The Palladium-Catalyzed, Multicomponent Synthesis of Imidazoline Carboxylate Heterocycles

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Abstract

This thesis describes the development of palladium catalyzed, multicomponent synthetic routes to imidazoline carboxylates. Chapter 2 describes the design of an active catalyst for the multicomponent assembly of imidazoline carboxylates from two imines, acid chlorides and carbon monoxide. By modifying reaction conditions, two different imines can be selectively incorporated into the imidazoline core. This provides a method to assemble imidazolines in one pot, with independent control of five separate substituents. This approach has been used to assemble a diverse range of imidazoline carboxylates. In Chapter 3, a new, palladium catalyzed route to generate imidazoline carboxylates is described, via a five component coupling of two imines, two carbon monoxides and aryl-iodide. This process proceeds via a similar mechanism to that reported in Chapter 2, but replaces sensitive acid chlorides with an phenyl-iodide. Finally, Appendix A briefly describes methods to decarboxylate these products to imidazolinium and imidazolium salts.

Résumé

Cette thèse décrit le développement d'itinéraires synthétiques pour former des carboxylates d'imidazoline, catalysés par le palladium. Le chapitre 2 décrit la conception d'un catalyseur actif pour la synthèse de carboxylates d'imidazoline à partir de deux imines, de chlorures acides et d'oxyde de carbone. En modifiant les conditions réactionnelles, deux imines différentes peuvent être sélectivement incorporées au noyau d'imidazoline. Cette méthode permet d'assembler des imidazolines en un seul pot, avec la possibilité de varier les différents substituants. Cette approche a été employée pour la synthèse d'une large gamme une gamme de carboxylates d'imidazoline. En chapitre 3, une nouvelle synthèse catalysée par le palladium pour produire des carboxylates d'imidazoline est décrite, via le couplage de cinq composants, à savoir deux imines, deux oxydes de carbone et un iodure d'aryle. Ce processus procède par l'intermédiaire d'un mécanisme semblable à celui rapporté au chapitre 2, où le chlorure d'acide est remplacé par un iodure d'aryle. En conclusion, l'annexe A décrit brièvement différents méthodes pour décarboxyler ces produits en sels d'imidazolinium et d'imidazolium.

For Chip(s).

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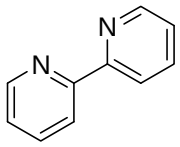
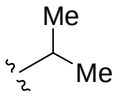
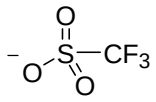
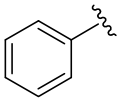
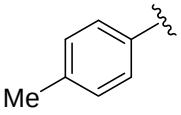
LIST OF ABBREVIATIONS

Ar	**Aryl**	
atm	**atmosphere**	
Bipy	**2,2'-bipyridyl**	
***t*Bu**	***tert*-butyl**	
CO	**carbon monoxide**	
CO_2	**carbon dioxide**	
d	**doublet**	
ESI-HRMS	**Electrospray Ionization-High resolution Mass Spectrometry**	
Et	**ethyl**	-CH_2CH_3
h	**hours**	
iPr	***iso*-propyl**	
m	**multiplet**	
min	**minutes**	
Me	**Methyl**	-CH_3
NHC	**N-heterocyclic carbene**	
NMR	**Nuclear Magnetic Resonance**	

OTf	**triflate, trifluoromethanesulfonate**	
Ph	**Phenyl**	
q	**quartet**	
s	**singlet**	
t	**triplet**	
***p*-Tol or Tol**	***para*-Toluyl**	

CHAPTER I: INTRODUCTION TO IMIDAZOLINES

1.1: PERSPECTIVE

Imidazolines are the 4,5-reduced counterpart of imidazoles. These structures are found in a diverse range of biologically relevant products. For example, imidazoline containing natural products (e.g. spongotine, topsentin C & D and nortopsentin) are sought after for their antiviral and antitumor properties.[1] Non-naturally occurring imidazolines have also been found to display important therapeutic properties. Since the early 1940s, the antihypertensive activity of 2-substituted imidazolines such as priscoline[2] (2-benzyl imidazoline) has been known. Since then, variously substituted imidazolines have been used to treat such conditions as high blood pressure,[3] arrhythmia,[4] diabetes,[5] depression,[6] and migraine.[7] The mode of action of these compounds derives from modulation of α-adrenoreceptors or specific imidazoline receptors. Some representative compounds and their uses are depicted in Figure 1.1.

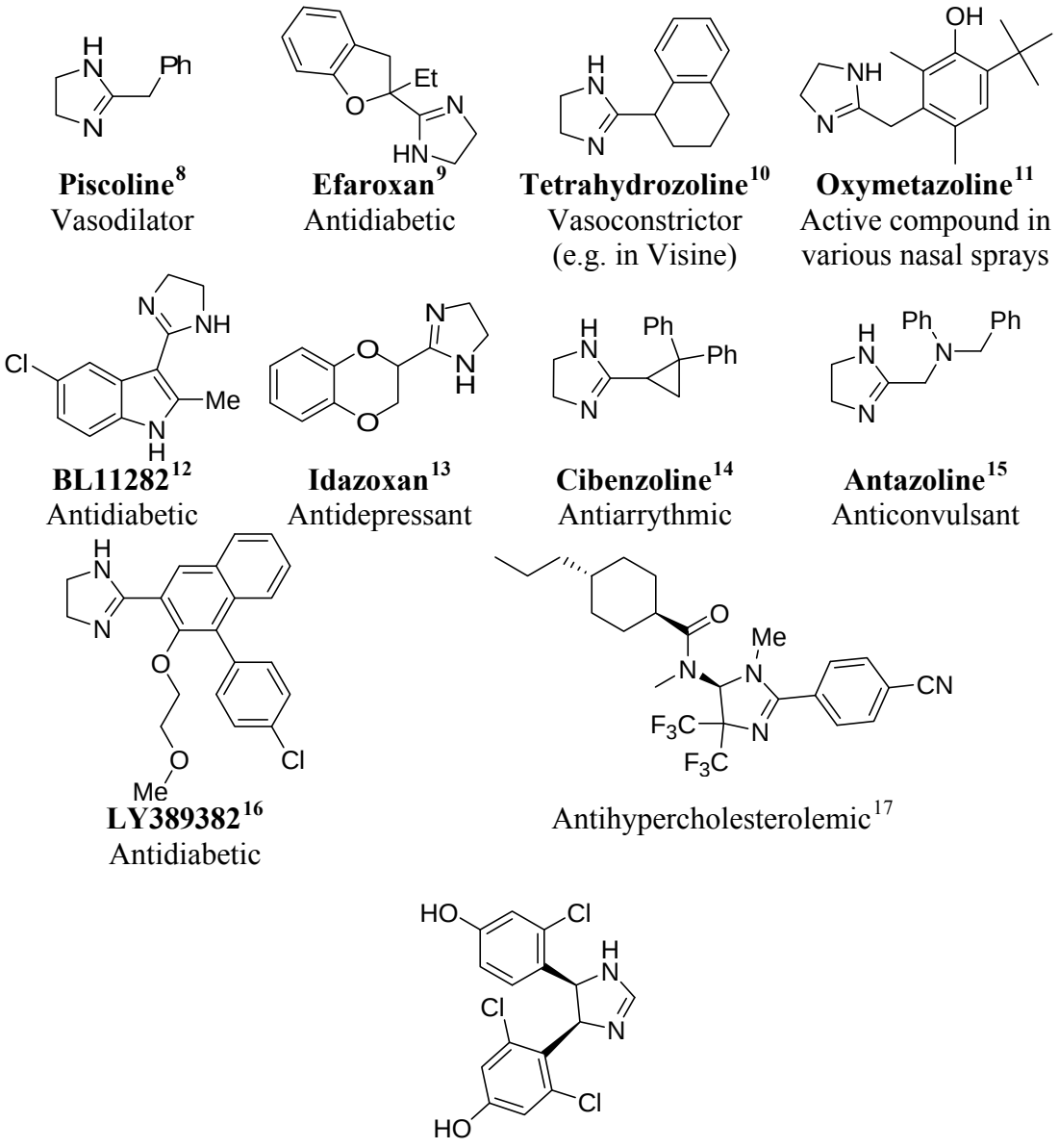


Figure 1.1: Representative Imidazoline Therapeutics

Other imidazoline-based therapeutics have been identified whose actions are not related to the aforementioned compounds. The highly-substituted Nutley inhibitors (or Nutlins, Fig. 1.2), are tetra-substituted *cis*-imidazolines that reactivate programmed cell death in certain cancers. This tumor suppression is effective in cell lines that display over expression of MGM2, a suppressor of p53-mediated apoptosis.[19] Structure variation of

the Nutlin core has provided submicromolar activity *in vitro*. Recently, a large library of these molecules has been patented by LaRoche.[20]

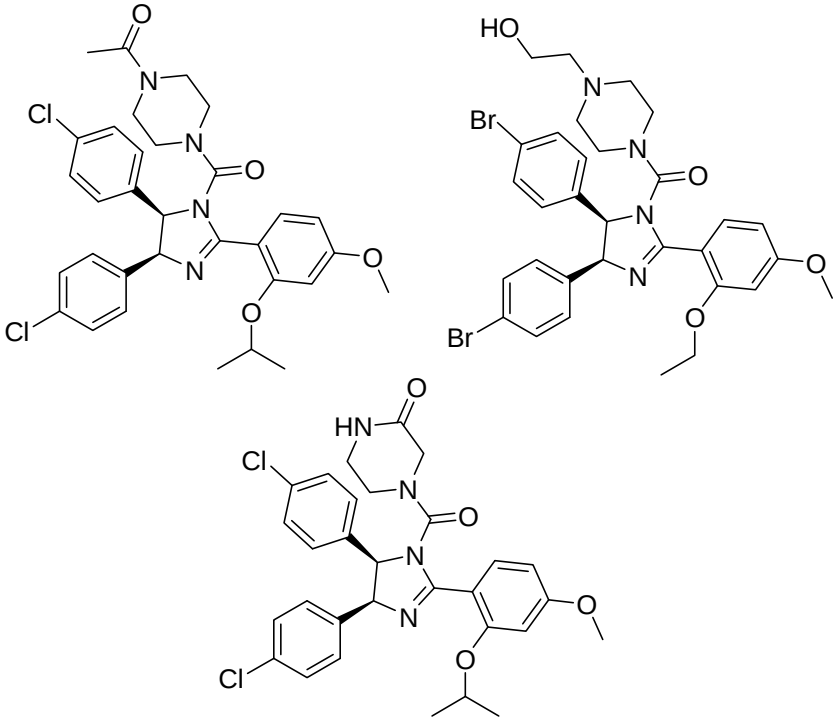


Figure 1.2: Representative Nutley Inhibitors

The utility of imidazolines also extends into the field of asymmetric catalysis, where they have been adopted as ligands. 2-unfunctionalized imidazolines can be N-alkylated and deprotonated to generate metal binding carbene ligands.[21] A notable entry in this class is the imidazolinium ligand of Grubbs' second generation olefin metathesis catalyst (Fig. 1.3).[22] Alternatively, imidazolines see use as N-donor ligands,[23] or as components of bidentate P-N ligands.[24]

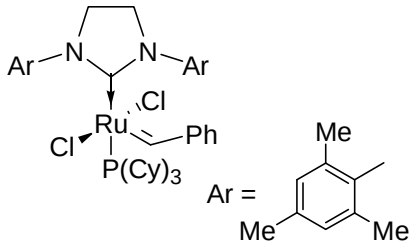


Figure 1.3: Grubbs' Second Generation Olefin Metathesis Catalyst

In synthesis, imidazoles can be readily formed via oxidation of imidazolines.[25] This is arguably the most commonly cited synthetic use for these molecules, though other sporadic reports have revealed alternative applications. Various heterocycles have been formed by manipulation of imidazolines, including pyrrolidines,[26] azapenams,[27] and piperidines.[28] Imidazolines have also been employed successfully as chiral auxiliary for the preparation of quaternary stereocenters.[29] Finally, there have been reports of the use of imidazolinium salts in the place of imidazolium salts in ionic solvents.[30]

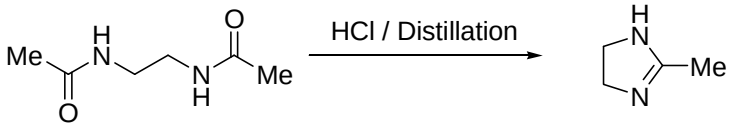
In light of this utility, the development of routes to synthesize imidazolines is an important goal. This chapter will provide a brief overview of the common synthetic routes to imidazolines. Focus will be placed specifically on the synthesis of 4-carboxylate substituted imidazolines, whose synthesis is the subject of this thesis.

1.2: SYNTHESIS OF IMIDAZOLINES

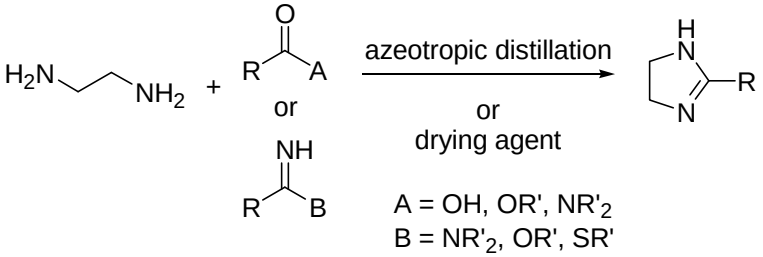
1.2.1: HISTORICALLY SIGNIFICANT ROUTES TO 2-IMIDAZOLINES[31]

The first reported synthesis of imidazolines was by Hofmann in 1888. In this initial report, diacetyl ethylene diamine was distilled under a stream of gaseous hydrochloric acid (Scheme 1.1a).[32] Unexpectedly, he collected 2-methyl-2-imidazoline. This presumably arose through cleavage of one amide group to an amine, followed by subsequent cyclization. Into the 1950s, many 2-imidazoline syntheses required similarly high temperatures or strong reducing agents (as a result, low yields were also commonly observed), though some mild routes did exist (e.g. with 1,2-diamines and imidates).[45] Scheme 1.1 shows a number of representative synthetic routes from this era. Although on paper these synthetic methods appear diverse, a fundamental trait unites them: the imidazoline products form through condensation of an intermediate β-amino amide (or β-amino imidate, as in Scheme 1.1b). Where these methods diverge is in the formation of this intermediate.

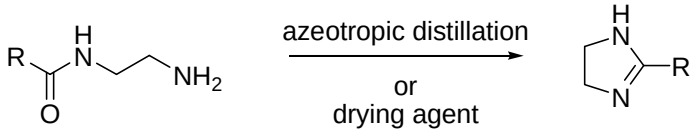
(a) Original Hofmann synthesis



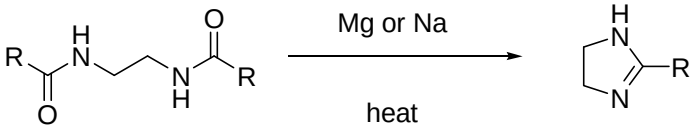
(b) Diamine Condensation[33]



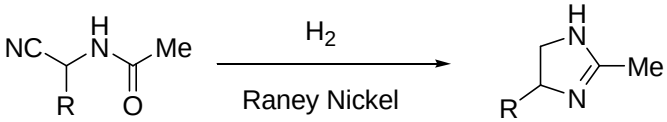
(c) β-amino amide-cyclization[34]



(d) Reductive diamide cyclization[35]



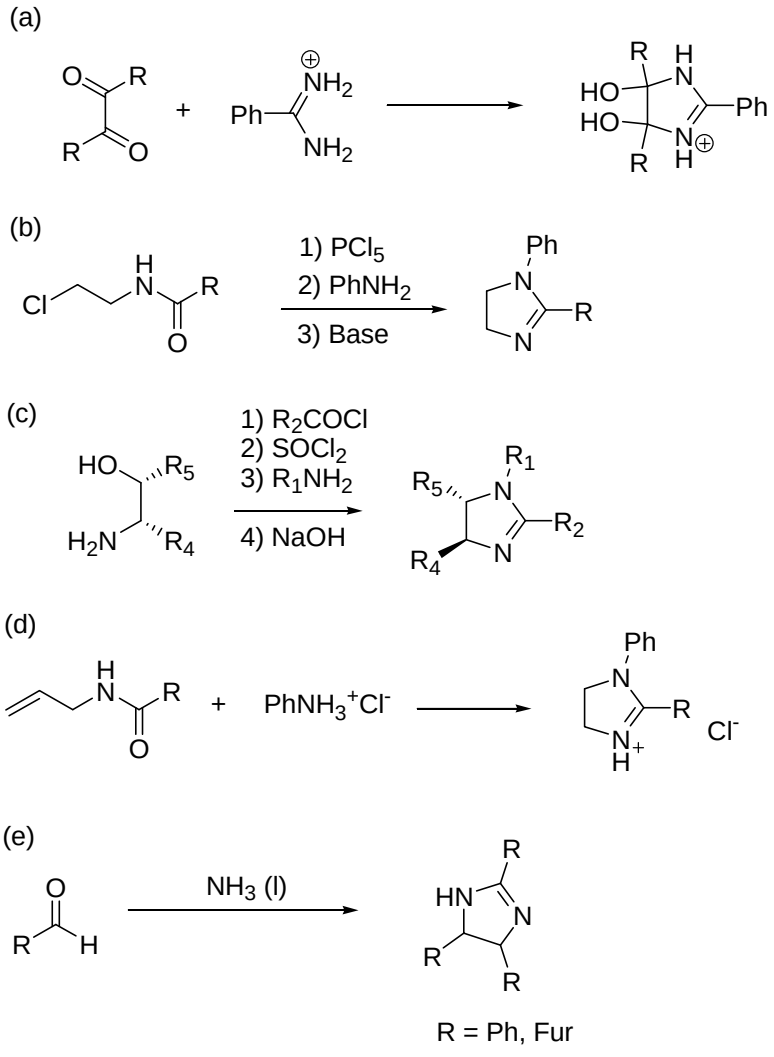
(e) Reductive α-cyano amide cyclization[36]



Scheme 1.1: Classic Diamine-Type Imidazoline Syntheses

In addition to the diamine based approaches above, three mechanistically distinct approaches also came about in this time period. The first of which is the reaction of glyoxals with amidines.[37] This method yields 4,5-dihydroxy imidazolines in good yields (Scheme 1.2a). This route stands apart in the fact that the 4,5-imidazoline carbons are derived from the electrophilic moiety. A second approach comes from an S_N2-ring closure, in which a ß-chloro amidine cyclizes when treated with base (Scheme 1.2b).[38]

The β-chloro amidine is formed by chlorination of β-chloro amide with PCl_5 followed by addition of aniline. The starting material for this reaction comes stepwise from β-chloro amide, though a more recent publication has reported a similar reaction utilizing β-amino alcohols (Scheme 1.2c).[39] Similarly, allyl amide has been transformed to imidazoline through a proposed ß-chloro amidine intermediate[40] (Scheme 1.2d). Finally, 2-imidazolines can be prepared by treating benzaldehyde[41] or furfural[42] with excess ammonia. This condensation incorporates three equivalents of aldehyde and two equivalents of ammonia, and proceeds in excellent yield, though the reaction takes place over 30-35 days with benzaldehyde (Scheme 1.2e).



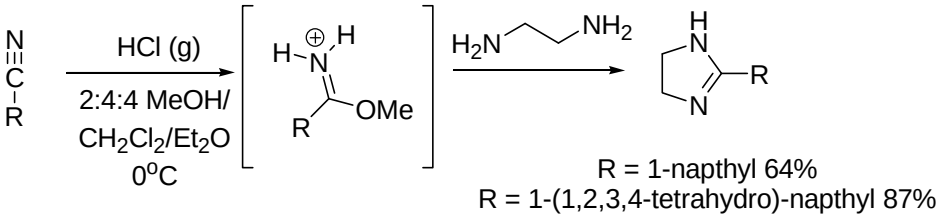
Scheme 1.2: Other Classic Approaches to Imidazoline

1.2.2: MORE RECENT SYNTHESES USING 1,2-DIAMINES

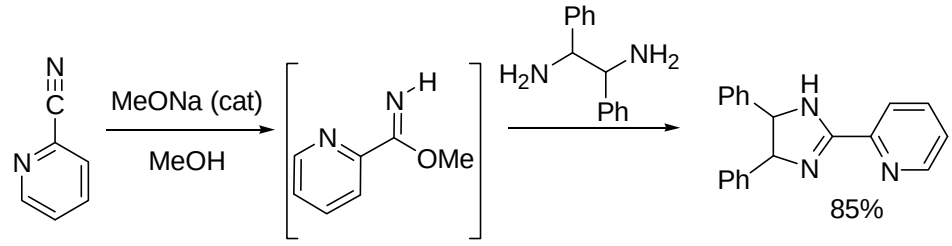
As mentioned, many of these early (pre-1960s) cyclocondensation reactions required harsh conditions to favor imidazoline formation. The cyclizations based on 1,2-diamines have since been significantly improved upon by modification of the reagents and reaction conditions. For example, the addition of trimethylaluminum to 1,2-ethylene diamine and esters can facilitate a reaction that previously required very high temperatures (Scheme 1.3).[43] While successful, the use of stoichiometric lewis acid is required.

Scheme 1.3: Trimethylaluminum-mediated synthesis of 2-imidazoline

The reaction of 1,2-diamines and nitriles typically requires reaction temperatures well above 200 °C,[44] while the use of imidates in the place of nitriles provides condensation products in excellent yields at 0 °C.[45] It was observed that the *in situ* conversion of nitriles to imidates was a viable alternative to harsh nitrile-diamine condensation. Using nitriles in alcoholic media, in the presence of catalytic acid (Scheme 1.4),[46] or base (Scheme 1.5)[47] provides a relatively general route to imidazolines at low temperatures.[48]

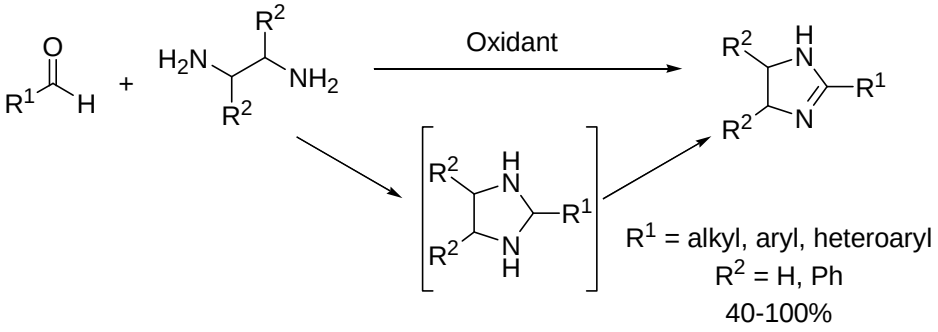


Scheme 1.4: Acid-Catalyzed Diamine-Nitrile Condensations



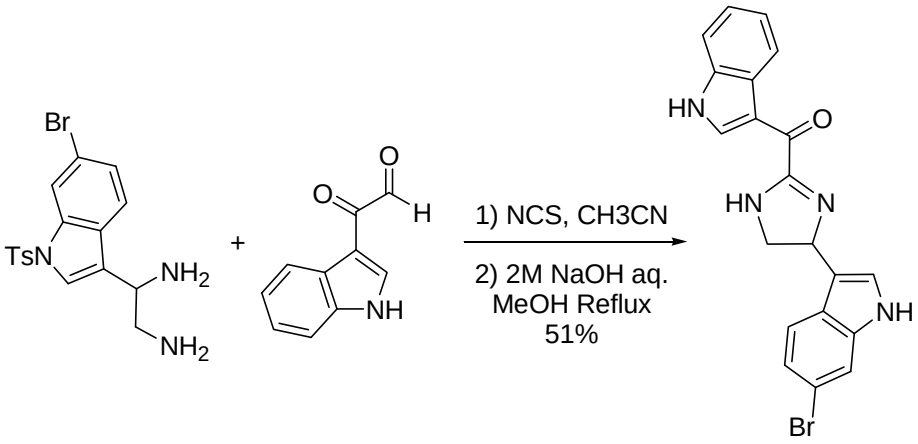
Scheme 1.5: Base-Catalyzed Diamine-Nitrile Condensations

Another notable condensation approach involves the reaction of aldehydes and diamines in the presence of a stoichiometric oxidant. When aldehydes are used as the electrophile, the initial product is an imidazolidine, in which the central carbon is reduced. Several techniques exist in which the N-C-N bond structure can be oxidized without leading to complete oxidation to imidazoles. The use of mild oxidants such as N-bromosuccinamide[49] (NBS), molecular iodine[50] (I_2), *tert*-butyl hypochlorite[51], and pyridinium hydrobromide[52] all lead to imidazolines (Scheme 1.6). While mild and effective, the use of a stoichiometric oxidant can be undesirable when applied to large scale syntheses.



Scheme 1.6: Aldehyde-Diamine Condensations with Oxidant

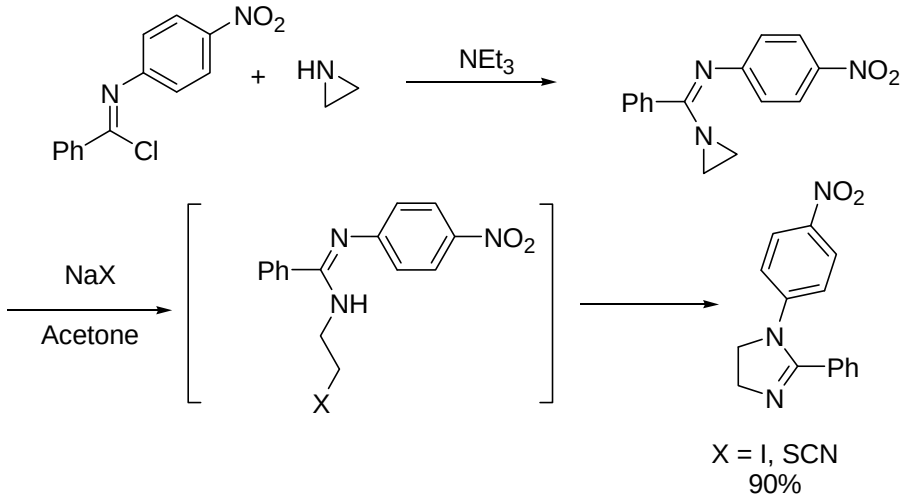
This condensation/oxidation method has been applied to the total synthesis of Spongotine A (Scheme 1.7).[53]



Scheme 1.7: The ultimate step in the total synthesis of Spongotine A

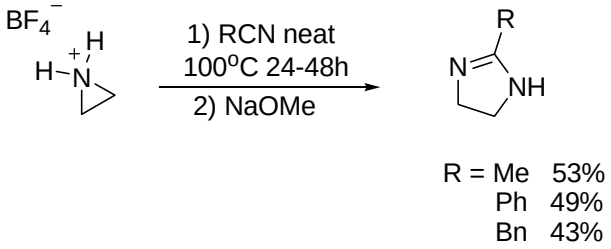
1.2.3: AZIRIDINE RING EXPANSION

Aziridines have also been employed as synthons for imidazolines. In 1960, Heine and Bender reported a rearrangement of 1-arylbenzimidoyl aziridines promoted by iodide or thiocyanide anions to generate imidazolines (Scheme 1.8).[54] It is proposed that the anion in solution opens the aziridine ring, which followed by S_N2 displacement of the pendant iodo- or thiocyano-group by the other nitrogen to generate the product. The proposed intermediate is analogous to the ß-chloro amidine in Figure 1.2 (b-d), though not observed.



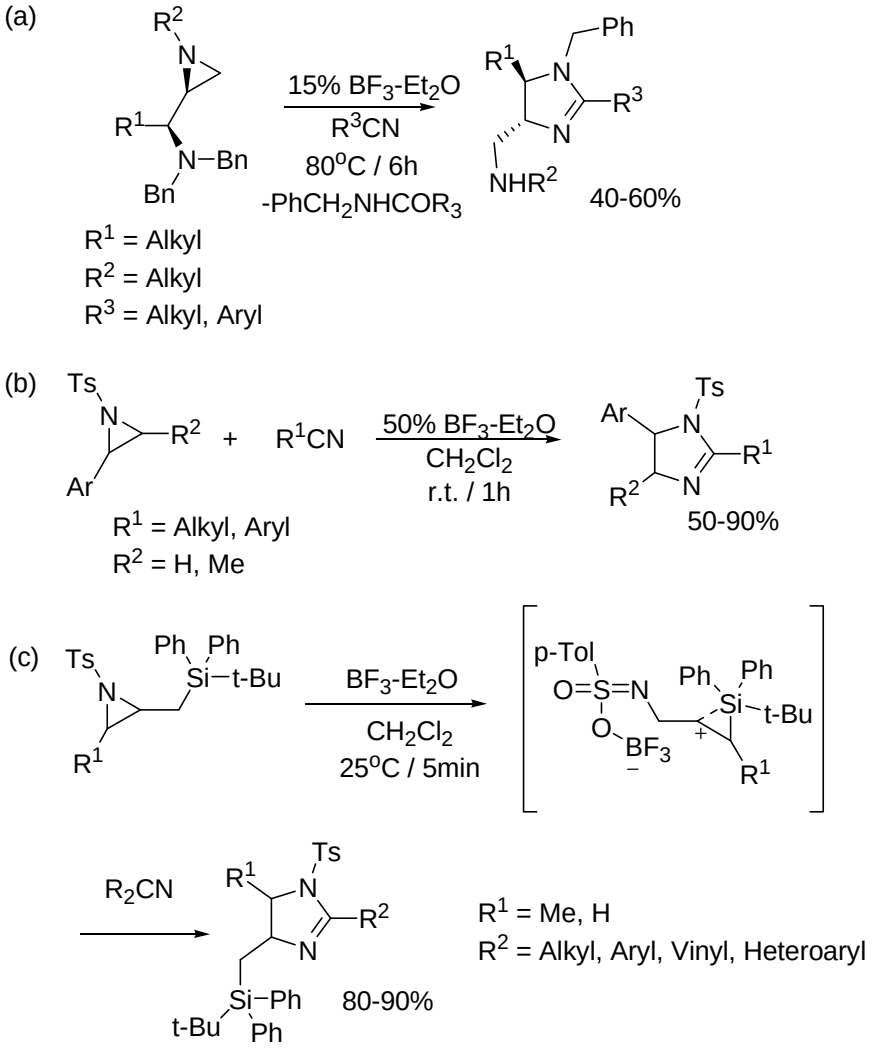
Scheme 1.8: Anion mediated rearrangement of 1-arylbenzimidoyl aziridines

In 1965, Pfeil and Harder reported a second type of aziridine ring expansion in which nitriles react with aziridinium tetrafluoroborate (Scheme 1.9).[55] In contrast to the previous approach, this reaction is thought of as a formal 1,3-dipolar cycloaddition, where the aziridine acts as a concealed azomethine ylide.



Scheme 1.9: Ring Expansion of Aziridinium Tetrafluoroborate with Nitriles

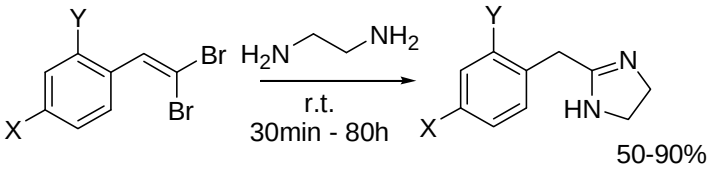
Since this observation, several groups have reported that Lewis acids catalyze the coupling of aziridines with nitriles to generate imidazolines. For example, Concellón and coworkers reported ring expansion of aziridine via a Ritter-type reaction with retention of the aziridine stereochemistry (Scheme 1.10a).[56] In 2007, Singh and coworkers report a similar reaction of N-tosyl aziridine with nitriles (Scheme 1.10b).[57] Finally, Yadav and Sriramurthy also report this reaction, but used the ß-effect of silicon to stabilize their intermediate ylides (Scheme 1.10c).[58] Notably, all three reports arrive at BF_3 as the most capable Lewis acid.



Scheme 1.10: Aziridine Ring Expansions with Nitriles

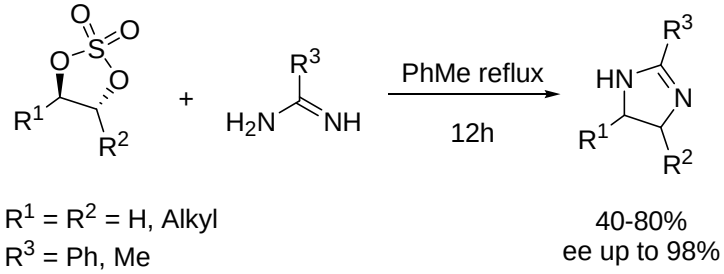
1.2.4: OTHER ROUTES TO IMIDAZOLINES

There are a number of published routes to imidazolines that fall beyond simple classification. In 2004, Kim and coworkers reported a synthesis of 2-imidazolines from 2-aryl-1,1-bromoethenes and 1,2-ethylene diamine.[59] This room temperature reaction yields 2-benzylic-2-imidazolines, however the starting material does limit its diversity (Scheme 1.11).



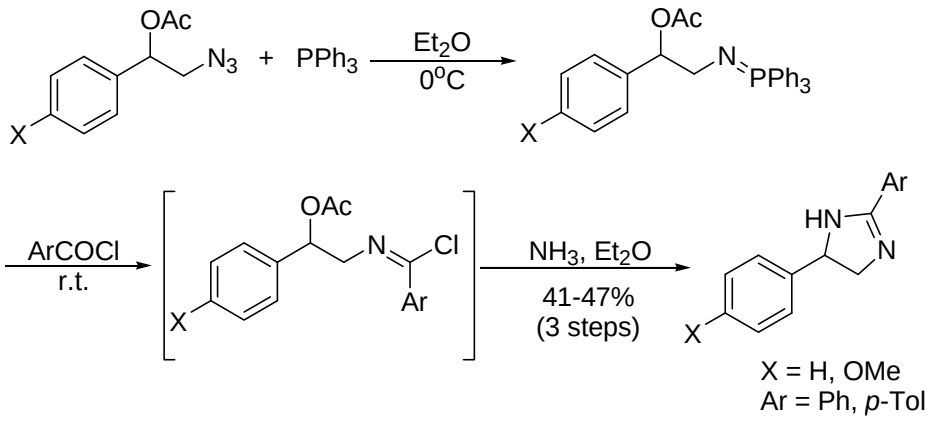
Scheme 1.11: 2-Aryl-1,1-Bromoethenes Reacted with Diamine

Similar to the approach depicted in Scheme 1.2a, Sharpless and Oi reported another synthetic route in which the 4,5-imidazoline carbons are derived from the electrophile.[60] Here, 1,2-cyclic sulfates react with amidines to generate imidazolines (Scheme 1.12). This stepwise sulfate displacement proceeds in excellent yields for the unsubstituted cyclic sulfate and in moderate yields when substituents are present.



Scheme 1.12: Sulfate-Displacement by Amidine

An aza-Wittig approach had been described that is analogous to the β-chloro amidine approach depicted in Scheme 1.2b. Here, a β-acetate subtituted amidine is formed from aroyl chloride, which is derived from an aza-Witig precursor (Scheme 1.13).[61]



Scheme 1.13: An Aza-Wittig Approach towards 2-Imidazolines

1.3: 4-CARBOXY IMIDAZOLINES

The research described in this thesis (Chapters 2 & 3 and Appendices) is directed towards the synthesis of 4-carboxylate substituted imidazolines. As such, a focus on the biological relevance and synthesis of these products is presented here.

1.3.1: UTILITY

1.3.1.1: Peptidomimetics

4-carboxy substituted imidazolines contains an amino acid equivalent incorporated into their heterocyclic core (Fig. 1.4). As such, these represent interesting structural analogues to proline, as well as other peptidomimetics. In this regard, there have been several reports in which imidazoline-based pseudodipeptides have been generated and introduced into proteins. For example, the cyclization of β-amino alanine has recently been reported both with the isolated unnatural amino acid, and when incorporated into a peptide.[62] Though no biological properties of these products are reported, this demonstrates that the ring closure of β-amino amides can occur under mild conditions (Fig. 1.5).

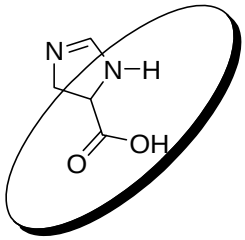


Figure 1.4: 4-Carboxy Imidazolines as Amino Acid Analogues

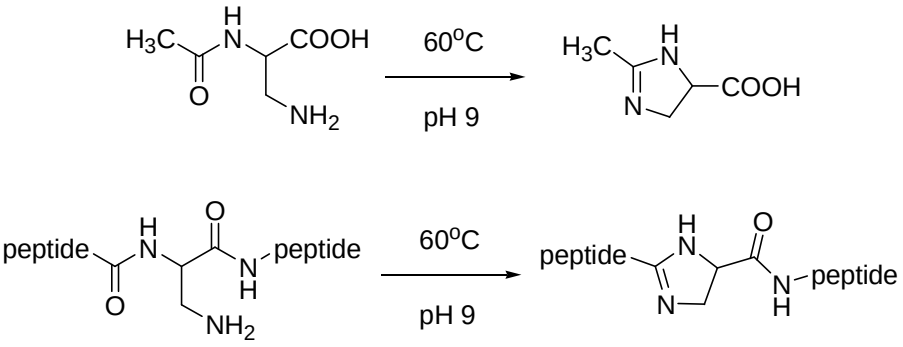


Figure 1.5: pH Controlled Cyclization of β -Amino Analine

Jones and Ward demonstrated that synthetic imidazolines can be incorporated into pseudopeptides.[63] In their publication, the authors developed an imidazoline to convey proteolytic stability to the pentapeptide enkephalin. They were able to integrate the imidazoline moiety to arrive at pseudoenkephalin (Fig. 1.6).

Enkephalin: Tyr-Gly-Gly-Phe-Leu

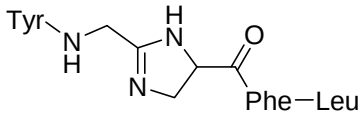


Figure 1.6: Enkephalin & Pseudoenkephalin

Shortly after this report, a similar pseudopeptide was described. This time, more functionality was incorporated into the imidazoline ring in an attempt to better model the replaced amino acids.[64] The pseudopeptide analog of CCK-4 was synthesized with retention of the tryptophan side chain (Fig. 1.7). Biological studies of pseudoenkephalin and pseudo-CCK-4 have not been published to date.

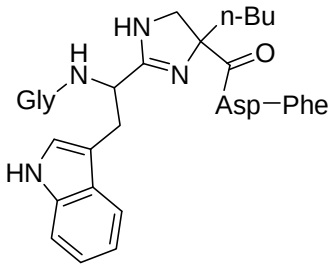


Figure 1.7: Pseudo-CCK-4

1.3.1.2: Therapeutic 4-Carboxy Imidazolines

As with other imidazolines, 4-carboxy imidazolines have been reported as potential therapeutics. Tepe and coworkers have shown that a highly substituted imidazoline (Fig. 1.8) displays important activity in sensitizing cancer cells towards other chemotherapeutics.[65] The authors have postulated that this noncytotoxic imidazoline modulates the NF-κB pathway, and helps to reinstate apoptosis, thus acting synergistically with drugs such as Campothecin. A variety of structurally similar products have been recently patented.[66]

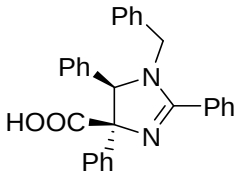
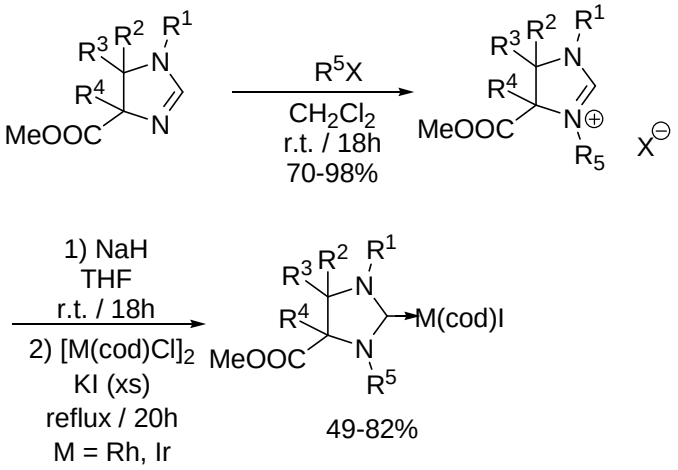


Figure 1.8: A Potential Imidazoline Therapeutic

1.3.1.3: Carboxy Imidazolines as N-Heterocyclic Carbene Ligands

4-carboxy imidazolines have also been employed as precursors to metal-binding carbene ligands. Orru and coworkers have demonstrated a new class of ligands that can be readily prepared from ester-substituted imidazolines.[67] Simple N-alkylation with various carbon electrophiles, deprotonation, then reaction with appropriate metal salts yields new metal complexes (Scheme 1.14). A range of rhodium-N-heterocyclic carbene (NHC) complexes were prepared using this methodology.



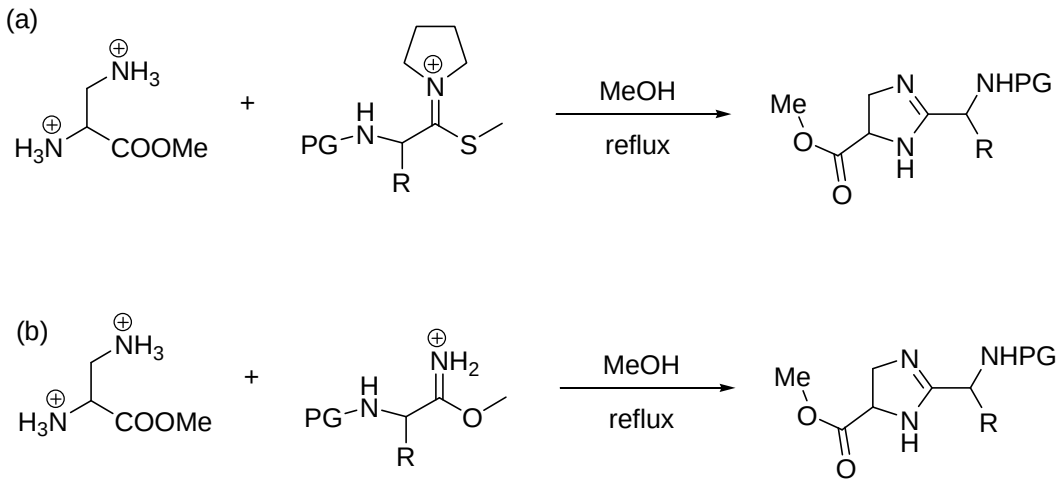
Scheme 1.14: 4-Carboxy Imidazoline based NHC-Complex

1.3.2: SYNTHESIS OF 4-CARBOXY IMIDAZOLINES

Similar to that described in section 1.2 for imidazolines, 4-carboxylate substituted imidazolines can also be generated via cyclization methodologies. In addition, a number of routes that are more specific to this class have also been described. An overview of synthetic routes to 4-carboxylate substituted 2-imidazolines is provided below.

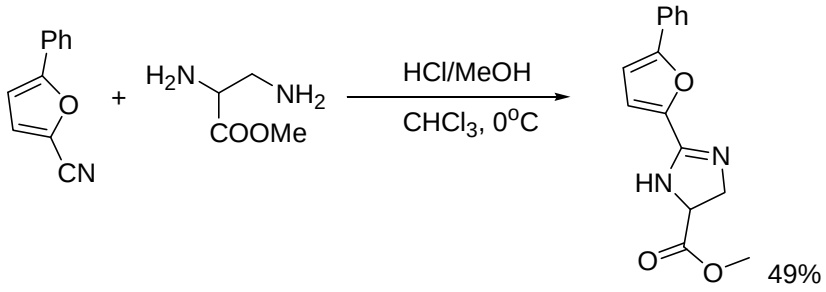
1.3.2.1: Cyclocondensation

The cyclocondensation of ester substituted 1,2-diamines provides a classic route to assemble 4-carboxylate substituted imidazolines. For example, a number of peptidomimetics have been prepared by the condensation of thioimidates (Scheme 1.15a) or imidates (Scheme 1.15b) with ester substituted 1,2-diamines.[63]



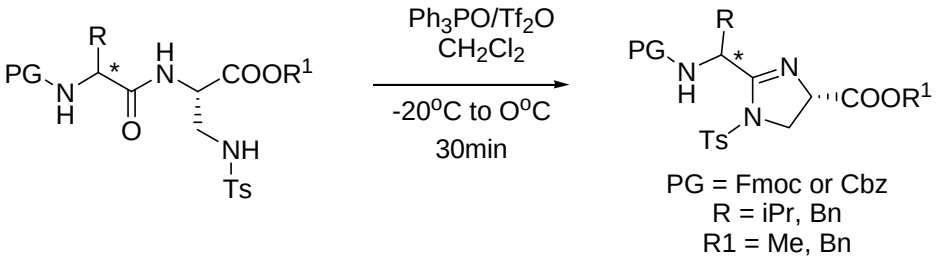
Scheme 1.15: Thioimidate and Imidate-Ester Substituted Diamine Condensations

Carboxy-substituted imidazolines can also be synthesized from simple condensations of ester substituted diamines with nitriles.[68] Again, this reaction proceeds through the imidate intermediate (Scheme 1.16). Here the authors were able to generate a library of potential monoamine oxidase (MAO) inhibitors. The depicted example was the only one with carboxylate substitution.



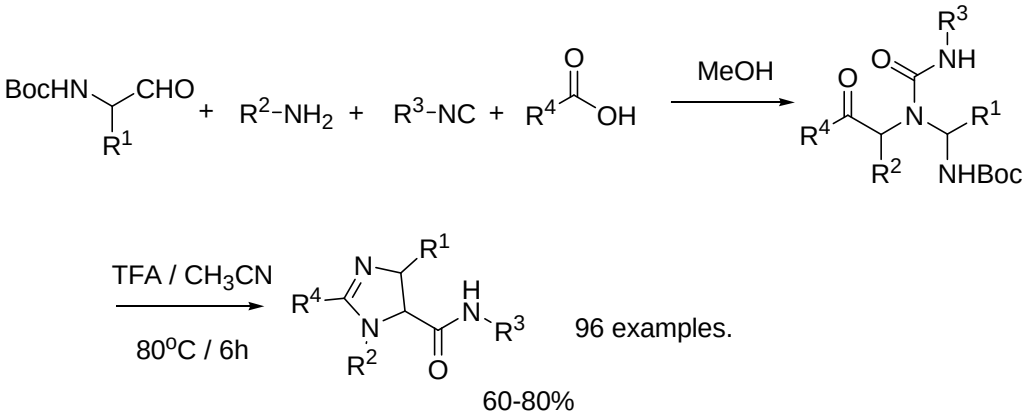
Scheme 1.16: Acid-Catalyzed Diamine-Nitrile Condensation

An alternate cyclocondensation involves the reaction of α,β-diamino acids with oxodiphosphonium-trifluoromethanesulfonate.[69] This latter reagent activates the amide carbonyl towards nucleophilic attack, providing a route to generate imidazolines from simple protected dipeptides (Scheme 1.17). These products contain the requisite end groups for integration into peptides, though the authors did not demonstrate imidazoline peptide mimicry. Instead, the oxidized imidazole was built into unnatural macrocyclic peptides.



Scheme 1.17: Ph_3PO/Tf_2O Promoted Cyclization of Dipeptide

This same cyclization can be coupled with the Ugi reaction to prepare 4-amido imidazolines. In this example, the highly substituted amino acid derivatives are found to undergo cyclization under acidic conditions, which allows selective cleavage of the Boc protecting group.[70] This Ugi/de-boc/cyclization process gives imidazolines in good yields, with ready access to diversification (Scheme 1.18). The authors have synthesized a 10,000 member product library using this approach.

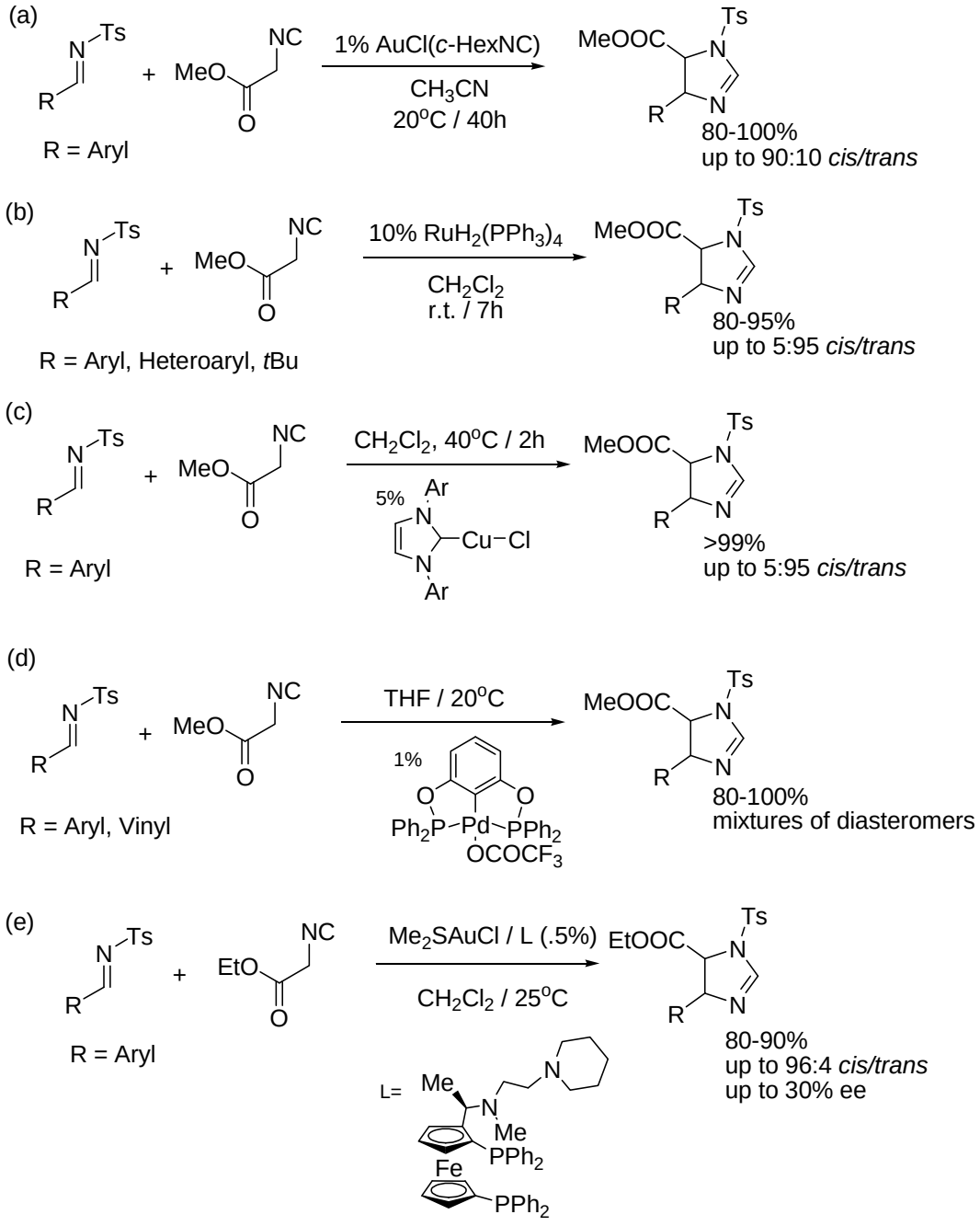


Scheme 1.18: Ugi/De-boc/Cyclization

1.3.2.2: Isocyanoacetate Building Blocks

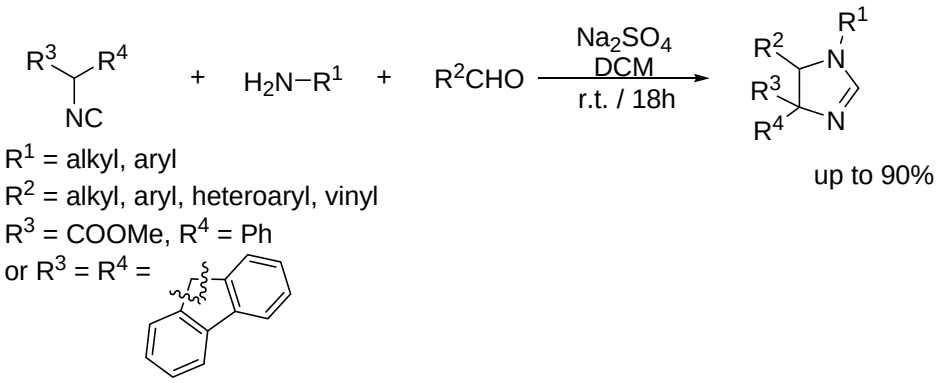
Isocyanides with acidic α-hydrogens can undergo deprotonation in the presence of Lewis acid catalysts to generate 1,3-dipoles. These isocyanides commonly possess an α-electron withdrawing functional group to increase the acidity of the α-proton. In most cases, this electron withdrawing group takes the form of an ester, providing a synthon for imidazoline carboxylates (Scheme 1.21). The *in situ* generated dipoles can undergo either cycloaddition or aldol condensation with imines to generate imidazolines. Early examples of this transformation used N-tosyl imines as the reacting partner. The electrophilic nature of the tosyl imine presumably helps the reaction to proceed. Various

catalysts have been reported reported to mediate this reaction, including those with gold (Scheme 1.19a),[71] ruthenium (b),[72] copper (c)[73] and palladium (d)[74] catalysts. In addition, an asymmetric synthesis has also been reported employing a gold catalyst with a chiral ferrocene ligand (Scheme 1.19e).[75]



Scheme 1.19: The Reaction of Isocyanides with N-Tosyl Imine

N-alkyl imines are also competent reagents for this transformation. In 2003, Orru and coworkers first demonstrated a multicomponent coupling reaction between isocyanoacetates, amines and aldehydes. This initial report did not include a Lewis acid catalyst, and the yields ranged from moderate to good (Scheme 1.20).[76]



Scheme 1.20: The Reaction of Isocyanides with Imines

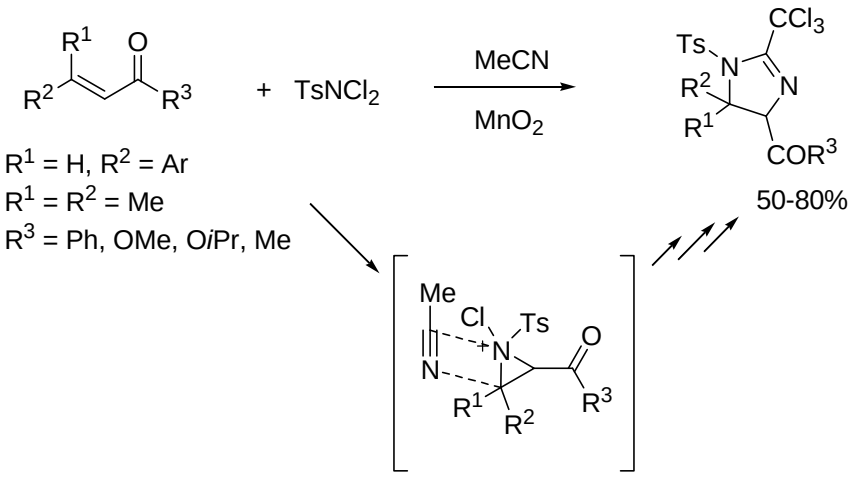
Introduction of 2% silver acetate to this reaction brought about notable yield and scope improvements.[77] Simple ketones could be used in the place of aldehydes, giving access to new imidazolines, bearing 5-dialkyl substitution. A number of reports have been published by this group detailing the optimization of solvents, conditions and catalysts.[78] Overall, these publications have provided a route to easily diversified 2-imidazolines. The N-heterocyclic carbene ligands described in section 1.3.3 are a direct application of this methodology.

1.3.2.3: Aziridines in 4-Carboxy Imidazoline Synthesis

A number of aziridine based routes to 4-carboxyl or 4-ketone substituted imidazolines have been published that, at first glance, lie outside of conventional disconnections. On closer inspection however, these methods are analogues to reactions previously described (Section 1.2.3).

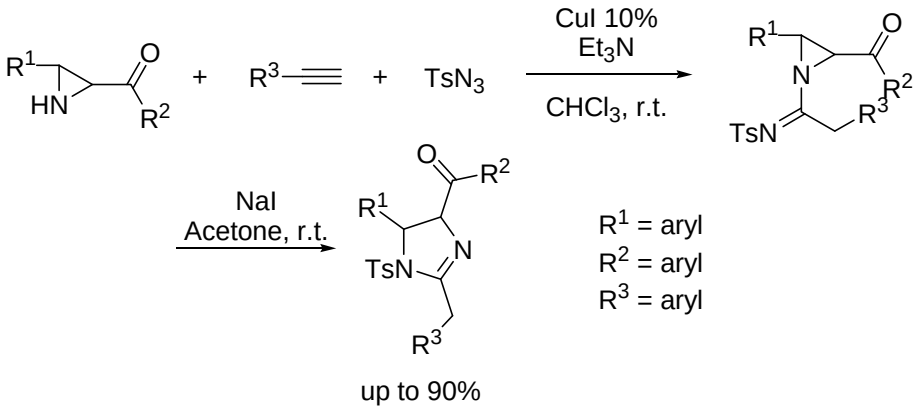
Manganese oxide has been found to catalyze diamination of α,β-unsaturated esters and ketones, with *N*,*N*-dichloro-*p*-toluenesulfonamide and acetonitrile as the halogen and nitrogen sources, respectively (Scheme 1.21).[79] This reaction is proposed to proceed through the formation of an N-tosyl aziridine which then ring-expands, incorporating an

equivalent of acetonitrile. Chlorination of the acetonitrile-derived 2-methyl substituent occurs to varying degrees without catalyst. If the reaction is allowed to progress for 24 hours in the presence of MnO_2, only the 2-trichloromethyl-2-imidazoline is produced. In this case, the electron withdrawing ester or ketone groups facilitate aziridine formation and govern regioselectivity.



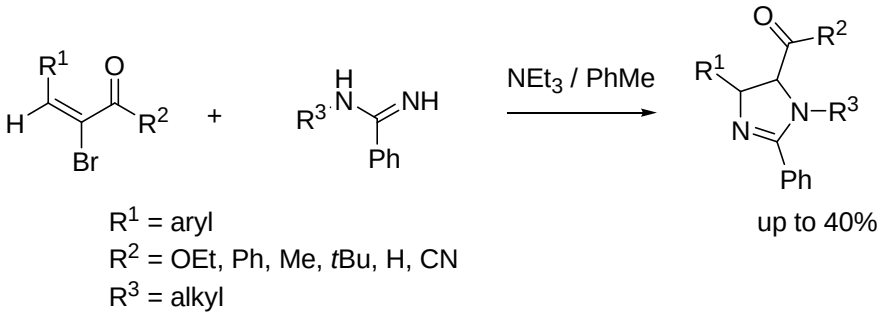
Scheme 1.21: The reaction of α,β-Unsaturated Esters and Ketones with $TsNCl_2$ and Acetonitrile

Terminal alkynes, sulfonyl azides, and N-unsubstituted aziridines can be coupled into 4-ketone imidazolines.[80] This reaction proceeds via the formation of an N-substituted aziridine directly analogous to 1-arylbenzimiloyl aziridine in Section 1.2.4. This step is achieved by the formation of ketenimine from sulfonyl azides and alkynes. The reactive ketenimine then reacts with the N-unsubstituted aziridine. Rearrangement, as in Section 1.2.4, is again induced by iodide ions (Scheme 1.22).



Scheme 1.22: Three-Component Coupling Reaction towards Imidazoline

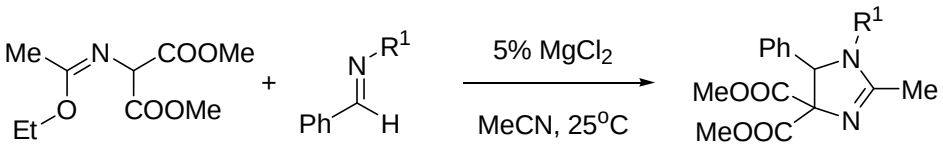
Finally, mono-substituted amidines can react with 2-bromo-2-alkenoic esters to give 4-ester imidazolines.[81] This reaction is believed to proceed via similar imidoyl aziridine intermediates. However, the aziridine intermediate is neither observed nor isolated in this case (Scheme 1.23).



Scheme 1.23: the Reaction of 2-Bromo-2-Alkenoic Esters with Amidines

1.3.2.4: Cycloaddition with Münchnones and Azomethine Ylides

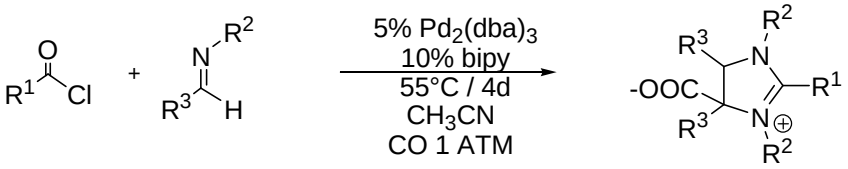
In addition to aziridine and isocyanide derived 1,3-dipoles, 1,3-oxazolium-5-oxides (i.e. Münchnones) and azomethine ylides are also viable precursors to imidazolines. The reaction of a Lewis acid-activated imidates with imines was reported in 2004 by Johnson and coworkers.[82] The specific imidate in this case possesses two ester groups, which is believed to form a metal coordinated azomethine ylide by sigmatropic rearrangement. Upon cycloaddition, imidazoline 4,4-biscarboxylates are observed in good to moderate yield (Scheme 1.24).



R^1 = Ts 80%
Aryl 93%
Benzyl 57%

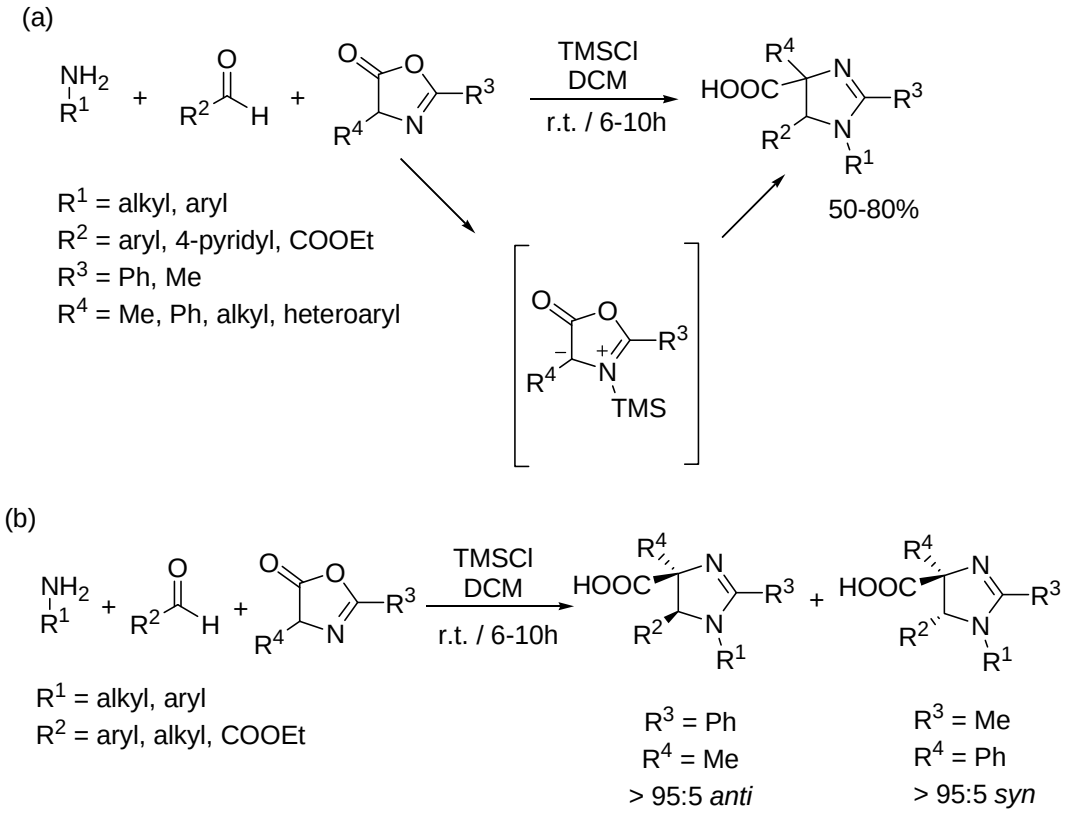
Scheme 1.24: Azomethine ylide-Imine Cycloaddition

Münchnones are also able to undergo cycloaddition with imines to yield 4-carboxy imidazolines. This was first demonstrated by our group, in 2001,[83] in the palladium catalysed coupling of imines, acid chlorides and carbon monoxide (CO) (Scheme 1.25). Mechanistically, this process is believed to proceed via the oxidative addition of an *in situ* generated N-acyl iminium salt to Pd(0), followed by CO insertion and ß-hydride elimination to form Münchnone intermediate (Scheme 1.26). The latter is rapidly consumed by protonated imine in a dipolar cycloaddition. This provides penta-substituted imidazoline carboxylates, in which two equivalents of identical imine are incorporated into the product.



Scheme 1.25: Palladium Catalyzed Imidazoline Synthesis

More recently,[84] azlactones prepared by EDCl dehydration of appropriately protected amino acids have been reported to undergo analogous TMS-Cl promoted cycloaddition with *in situ* generated imines (Scheme 1.26a). This method affords a range of tetra-substituted imidazoline carboxylic acids in moderate to good yields. Soon after their initial report, the authors demonstrated that either cis- or trans- products can be formed in this reaction, depending upon the steric bulk of R^4 relative to the carboxylate unit (Scheme 1.26b). [85]



Scheme 1.26: TMS-Cl Mediated Cycloaddition of Azlactone and Imine

1.4 : OVERVIEW OF THESIS

The one-pot synthesis of imidazoline carboxylates as described in our 2001 publication was the starting point for this research. At the outset, we saw significant potential in this process, owing to the efficiency of the reaction (one step), the simplicity of the building blocks (imines, acid chlorides and CO) and their atom-economical assembly into the product. As such, the potential utility of this reaction as a general approach to imidazoline derivatives is the subject of this thesis. This includes improving the catalyst for this reaction, probing and expanding its scope of the reaction, and further simplification of the building blocks employed. Overall, this has provided one-pot methods to directly assemble imidazoline carboxylates with independent control of the substituents.

In Chapter 2, the development of a highly active catalyst for imidazoline synthesis is described. This palladium-phosphine catalyst can allow the reaction to proceed within

hours, instead of the previous four days, and with expanded substrate scope. In addition, by modifying the reaction conditions, a method to selectively incorporate two different imines into the imidazoline core has been developed. This has allowed the preparation of a diverse range of substituted imidazoline products.

In Chapter 3, the preliminary observation of a new palladium catalyzed route to prepare imidazoline carboxylates from imines, phenyl iodide and carbon monoxide is reported. This procedure stems from the imidazoline synthesis in Chapter 2, and replaces acid chlorides with a simple aryl-iodide the latter undergoes carbonylation under the reaction conditions. Overall, this provides a route to prepare imidazoline carboxylates from five units: two imines, two carbon monoxides and an aryl-iodide.

Finally, Appendix A describes various observations that were made during the research that makes up Chapter 2. This includes routes to convert these imidazoline carboxylate products to decarboxylated imidazolinium salts or aromatized imidazolium salts.

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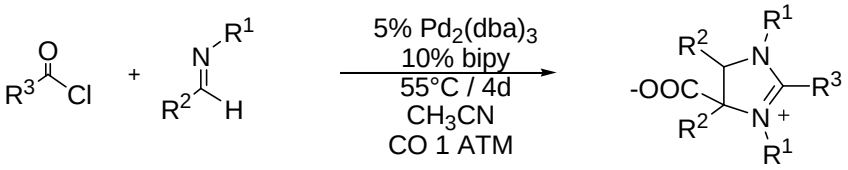
CHAPTER 2: THE PALLADIUM-CATALYZED, MULTICOMPONENT SYNTHESIS OF IMIDAZOLINE CARBOXYLATES FROM IMINES, ACID CHLORIDES AND CARBON MONOXIDE

2.1: INTRODUCTION

The imidazoline core is found in a diverse range of biologically relevant compounds. This includes synthetic imidazoline-based anticancer agents,[1] vasoregulators,[2] antidepressants,[3] antidiabetics,[4] components in peptidomimetics,[5] and a variety of bio-active natural products.[6] In addition to their biological activity, imidazolines have found significant use as metal coordinating ligands,[7] precursors to chiral N-heterocyclic carbenes,[8] and as building blocks in organic synthesis.[9] Considering their utility, many synthetic routes have been reported to generate imidazolines and their derivatives. These heterocycles have traditionally been prepared via the cyclization of substituted 1,2-diamines with various electrophiles (e.g. esters,[10] amides,[11] or imidates,[12] or aldehydes in concert with oxidants),[13] or the cyclization of ß-substituted amidines.[14] Nevertheless, these routes often require the initial multistep generation of the correctly substituted precursors prior to cyclization, and can suffer from poor regiocontrol when generating highly substituted products. More recently, a number of diversifiable syntheses of imidazolines have been reported based upon cycloaddition. These include the reaction of isocyanides with imines,[15] the ring expansion of aziridines with nitriles,[16] and the cycloaddition of imines with imidate derived azomethine ylides.[17]

An alternative to these approaches would be to assemble substituted imidazoline derivatives directly from several available building blocks. Towards this end, we reported in 2001 that the palladium catalyzed coupling of two imines, one acid chloride and carbon monoxide can provide a facile, one step route to generate imidazoline carboxylates (Scheme 2.1).[18] This reaction has been postulated to proceed via the formation of Münchnone intermediates, which undergo cycloaddition with protonated imines (Scheme 2.1). More recently, Tepe reported the synthesis of potent anti-cancer cell sensitizing imidazoline carboxylic acids via TMS-mediated cycloaddition of imines

with Münchnones.[19] In this case, the Münchnones are generated from pre-synthesized N-acyl amido acid derivatives.



Scheme 2.1: Palladium-Catalyzed Imidazoline Formation from Imines and Acid Chloride

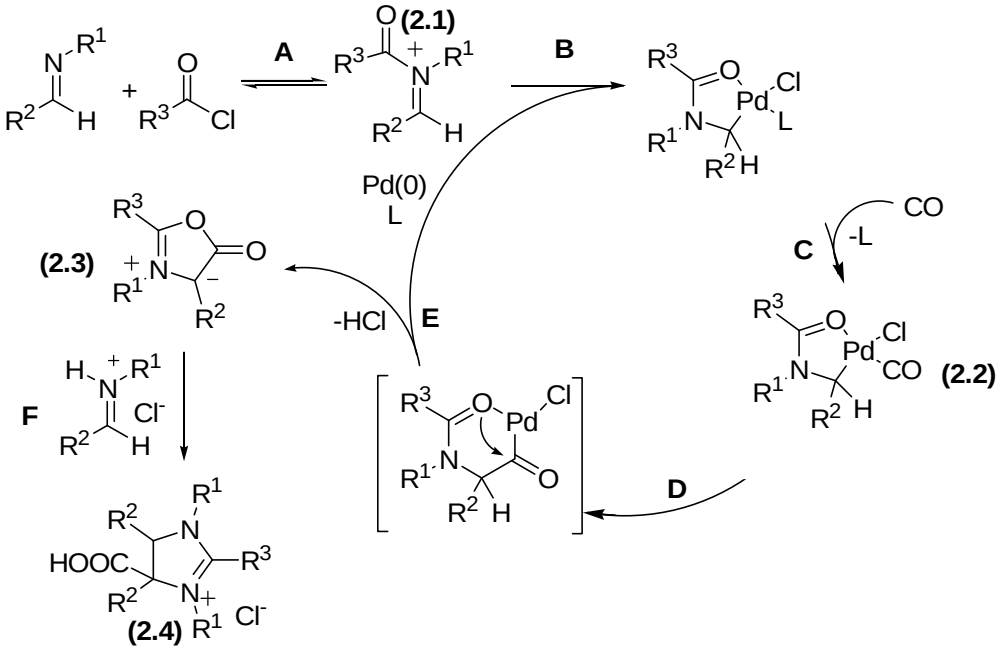
Considering the efficiency of the palladium catalyzed imidazoline synthesis in Scheme 2.1, as well as the utility of these products, we became interested in the potential of using this methodology as a general approach to form imidazolines. Notably, imines and acid chlorides are available from commercial sources, or easily generated from inexpensive substrates (e.g. aldehydes and primary amines or carboxylic acids), suggesting this could provide a synthesis that is directly amenable to diversification. However, our original report showed this reaction to be very sluggish, typically requiring 4 days for complete conversion, and the products generated showed limited scope (R^1 = Ph, Me; R^3 = *p*-tolyl). Perhaps most importantly, this procedure was limited to the formation of products containing two identical imines, and thus only generated symmetrically substituted imidazoline products.

To address these issues, we describe herein the development of a highly active palladium catalyst for this imidazoline synthesis, which can allow this coupling to proceed in hours under mild conditions. In addition, by modifying the reaction conditions, a diverse range of substituted imidazolines products can be generated. This includes the selective incorporation of two separate imine units into the heterocyclic core. Overall, this provides a straightforward route to form these products in a single step reaction, and with near perfect atom economy.

2.2: RESULTS AND DISCUSSION

2.2.1: CATALYST DEVELOPMENT

In order to develop a more active catalyst for this reaction, the postulated mechanism was examined more closely (Scheme 2.2). This mechanism is based upon other studies in our laboratory, where it was found that Münchnones **2.3** can be generated by a similar palladium catalyzed coupling of imines, acid chlorides and carbon monoxide in the presence of amine base.[20] The base is believed to block the generation of protonated imine, thereby inhibiting the dipolar cycloaddition step to generate imidazolines. Without this added base, imidazoline **2.4** is the only product observed, even with an equal molar ratio of imine to acid chloride. This suggests that the trapping of Münchnone by protonated imine is more rapid than its generation.



Scheme 2.2 Proposed Catalytic Cycle for Imidazoline Formation

In considering approaches to generate a more active catalyst, it was noted that the bidentate bipyridine ligand added to this reaction (Scheme 2.1) must eventually be displaced by either iminium salt oxidative addition (step B) or CO coordination (step C) during the catalytic cycle. This implies that the ligand may be inhibiting these steps, in analogy to that observed in the catalytic synthesis of Münchnones. Indeed, as shown in

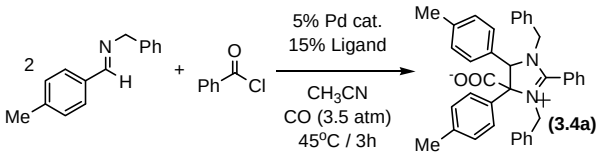
Table 1, performing this same coupling with only 5% $Pd_2dba_3 \cdot CHCl_3$ as catalyst leads to the generation of **2.4a** in 24 h (entry 2), in contrast to the 4 days under analogous conditions with bipyridine present. Similar results are observed using the palladacycle intermediate **2.6** as catalyst (generated by pretreating Pd_2dba_3 with imine and acid chloride) (Table 2.1, entry 4).

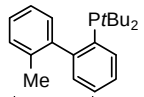
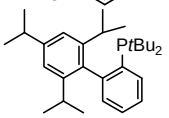
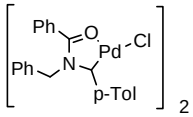
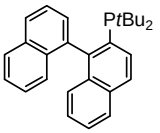
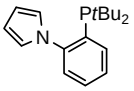
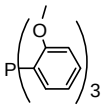
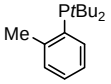
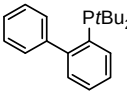
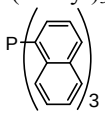
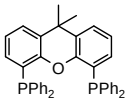
We have previously reported that the rate of iminium salt **2.1** carbonylation can be accelerated by the addition of bulky monodentate phosphine ligands, which can presumably coordinate to palladium to accelerate oxidative addition (step B), but retain sufficient lability to be displaced by CO (step C).[21] As shown in entries 6-10, the addition of smaller phosphines completely inhibits catalysis, presumably due to their strong coordination to palladium, which blocks carbonylation. Interestingly, bulkier triarylphosphines, while allowing catalysis to proceed, had little influence on the rate of imidazoline formation relative to that without ligand (entries 9, 10, 12). This includes P(*o*-tolyl)$_3$, which has been previously demonstrated to accelerate catalysis in related carbonylation reactions.[22] This may be due to the exceedingly poor coordinating ability of these ligands under these catalytic conditions. While these ligands are sterically bulky, they lack strong coordination ability. Therefore, several sterically encumbered and more strongly coordinating di-alkyl or tri-alkylphosphines were examined. As was hoped, these ligands were found to significantly accelerate catalysis. The di-*tert*-butyl-2-biphenyl phosphine **(2.7)** (entry 19) conveys the greatest rate enhancement of the phosphines screened, allowing imidazoline formation to proceed to completion within a matter of hours at 45 °C. Notably, the commercial $Pd_2(dba)_3 \cdot CHCl_3$ can also be employed with this ligand (entry 20), as can allylpalladium chloride dimer (entry 21).

In addition to enhancing the reaction rate, these catalyst systems proceed most rapidly with the 2:1 ratio of imine to acid chloride incorporated into the product, in contrast to the large excess acid chloride employed with bipyridine ligands.[18] As shown in entry 19, the reaction with ligand **2.7** actually proceeds slower with a 1:1 ratio of reagents. While the reason for this effect is as yet unclear, one hypothesis is that the second imine acts as a base to accelerate HCl elimination (step E). Overall, this provides

a both very rapid synthesis of imidazolines, as well as high atom economy. In addition, catalyst loadings can be dropped significantly (0.5% **2.6**) without loss in yield (entry 23).

Table 2.1: Catalyst Development for Imidazoline Carboxylate Synthesis



#	Pd catalyst	Ligand	Yield	#	Pd catalyst	Ligand	Yield
1	$Pd_2(dba)_3 \cdot CHCl_3$ **(2.5)**	bipy	<5% (82%)[a]	**13**	**2.6**	P*t*Bu$_3$	47%
2	**2.5**	-	21% (83%)[b]	**14**	**2.6**		33%
3	**2.5**	-	20%[c]	**15**	**2.6**		41%
4	 **(2.6)**	-	14% (90%)[b]	**16**	**2.6**		47%
5	**2.6**	-	5%[c]	**17**	**2.6**		72%
6	**2.6**		-	**18**	**2.6**		33%
7	**2.6**	PPh_3	-	**19**	**2.6**	 **(2.7)**	**84%** (34%)[c]
8	**2.6**	$P(OPh)_3$	-	**20**	**2.5**	**2.7**	62%
9	**2.6**	P(*o*Tolyl)$_3$	10%	**21**	$[Pd(C_3H_5)Cl]_2$	**2.7**	47%
10	**2.6**		14%	**22**	$PdCl_2$	**2.7**	-
11	**2.6**		15%	**23**	**2.6**	**2.7**	92%[d]
12	**2.6**	PCy_3	16%				

General: In a J-young NMR tube: Imine (52 mg, 0.25 mmol), benzoyl chloride (17 mg, 0.12 mmol), 5% Pd catalyst, 15% ligand (relative to acid chloride), 800 µL CD_3CN, 3.5 atm CO, 45 °C, 3 h. Yield based on ^{1}H-NMR comparison to internal standard.

[a] In a 100 mL reaction bomb: Imine (119 mg, 0.57 mmol), benzoyl chloride (80 mg, 0.57 mmol), 5% **2.5**, 10% bipy, 20 mL CH_3CN, 1 atm CO, 55 °C, 96 h. Isolated Yield.[18]

[b] 24 hours.

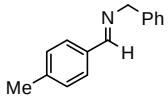
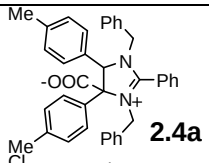
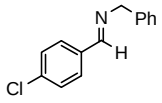
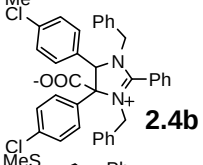
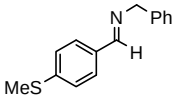
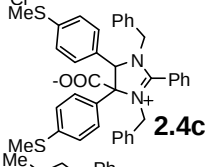
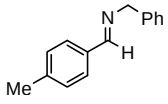
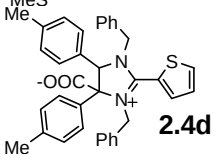
[c] 0.25 mmol benzoyl chloride (1:1).

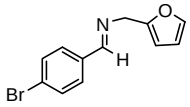
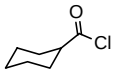
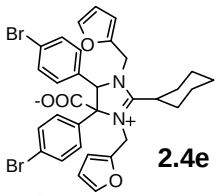
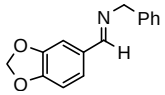
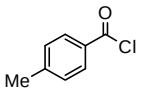
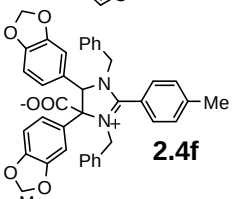
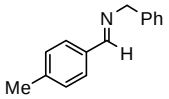
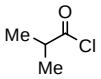
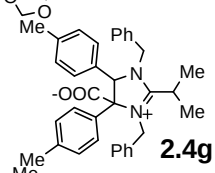
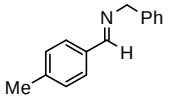
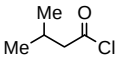
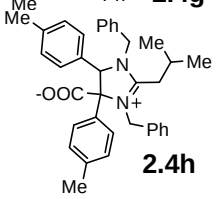
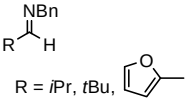
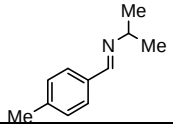
[d] 0.5% **2.6**, 1.5% **2.7**, 4 days.

2.2.2: PRODUCT DIVERSITY

With the more active catalyst, the diversity of imidazolines available via this reaction was probed. As shown in Table 2.2, a range of imines can be incorporated into this reaction. In general N-alkyl and C-aryl substituents are most applicable in this chemistry. This includes various functionalized C-aryl imines, as well as N-heteroaryl and N-protected substrates. Notably, C-alkyl or –heteroaryl imines, and bulky nitrogen substituents (entries 9, 10), are not compatible with the reaction, presumably due to the instability of these *in situ* formed iminium salts (e.g. enolizable imines) or Münchnone products.[23] A variety of substituents can be incorporated into the 2-position of the product from the acid chloride, with aryl **2.4f**, and heteroaryl **2.4d** groups all well tolerated. In addition, enolizable and bulky alkyl acid chlorides can be employed, though the yields are sometimes lower **2.4e,h**. Each of these products is formed in good yields and as single isomers, wherein the R^2 substituents are *trans* to one another. This is consistant with the results of our 2001 publication.[18]

Table 2.2: Substrate Diversity in Imidazoline Carboxylate Synthesis

entry[a]	Imine	Acid Chloride	Product	Yield
1			 **2.4a**	92%
2			 **2.4b**	73%
3			 **2.4c**	77%
4			 **2.4d**	86%

5			 **2.4e**	42%
6			 **2.4f**	70%
7			 **2.4g**	93%
8			 **2.4h**	49%
9			-	-
10			-	-

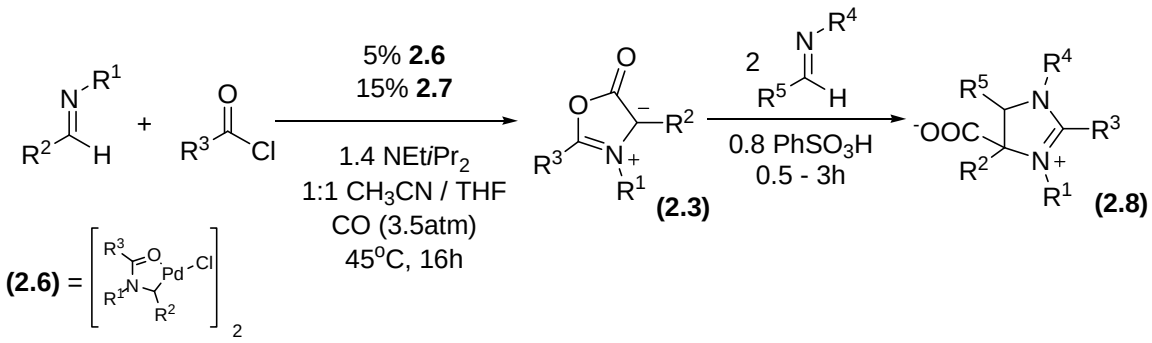
[a] In a reaction bomb. Imine (0.49 mmol), acid chloride (0.27 mmol), **2.5** (26 mg, 0.025 mmol), **2.7** (22 mg, 0.075 mmol), 15 mL CH_3CN, CO (3.5 atm). 45 °C, 16 h.

2.2.3: MORE DIVERSELY SUBSTITUTED IMIDAZOLINES

While, the reaction in Table 2.2 provides a route to directly generate imidazoline carboxylates, one limitation to this approach is that the products contain identical nitrogen (R^1) and R^2 substituents (e.g. Scheme 2.1). This arises from incorporation of the same imine in both sites in the product. Since many synthetically useful imidazolines have different substituents into these positions, we became interested in employing this same approach to selectively incorporate two different imines into the products.

In principle, these imidazolines could be formed by first catalytically generating Münchnones (steps A-E, Scheme 2.2), followed by the subsequent addition of a second imine. As shown in Table 2.3, the addition of NEt^iPr_2 base and the use of stoichiometric

imine in the palladium catalyzed reaction can allow the *in situ* formation of Münchnone **2.3a** in high yield (entry 1). However, the presence of the amine base completely blocks the subsequent dipolar cycloaddition of the second imine, presumably by removing the acid needed to generate the protonated dipolarophile. This can be circumvented by the addition catalytic amounts of benzene sulfonic acid, which allows the cycloaddition of imine to Münchnone to proceed within 3 hours at ambient temperature (entry 2). Under these conditions, small amounts of the inseperable homocoupled imidazoline product is generated, arising from the presence of residual imine after Münchnone formation. The use of slight excess of acid chloride in the initial Münchnone synthesis can inhibit the formation of this product, and allows the overall generation of the diversely substituted imidazoline **2.8a** in one pot and high yield (entry 3).

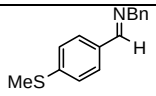
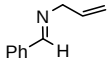
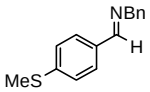
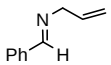
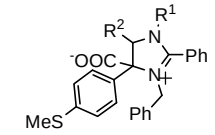
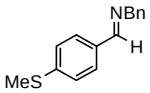
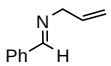
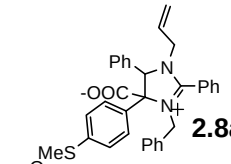
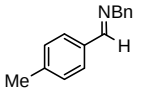
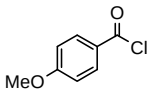
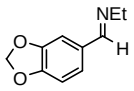
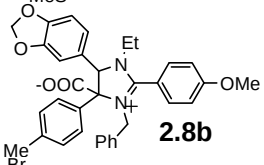
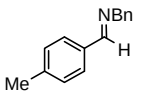
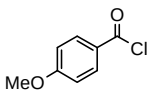
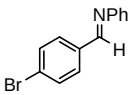
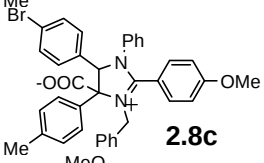
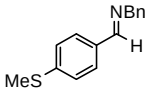
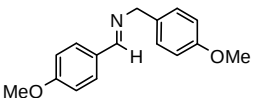
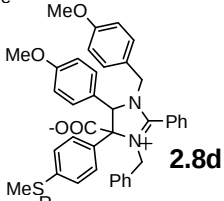
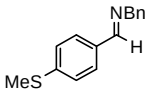
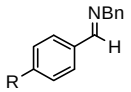
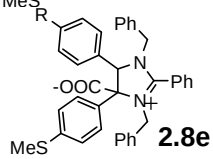
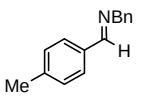
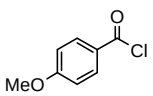
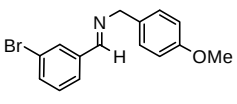
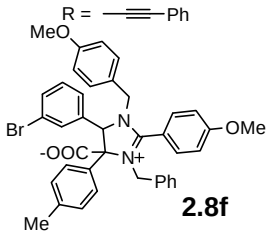


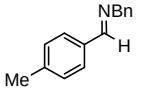
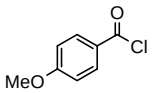
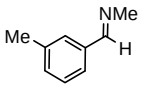
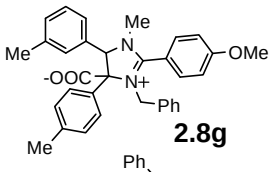
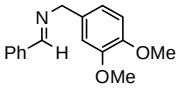
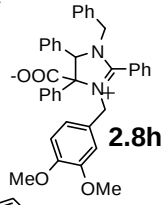
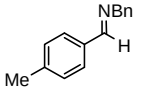
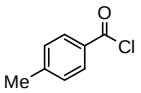
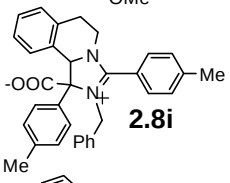
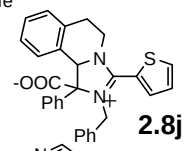
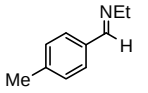
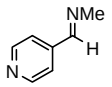
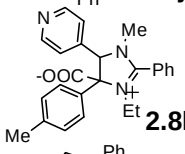
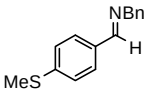
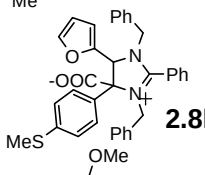
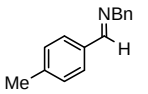
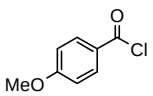
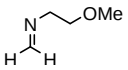
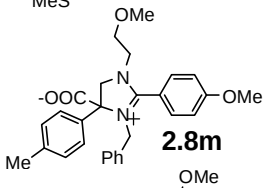
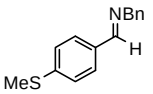
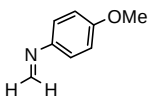
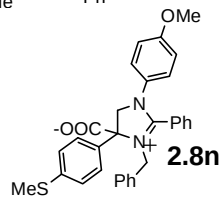
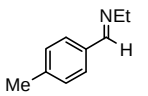
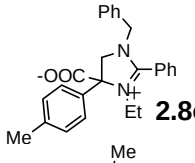
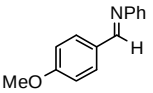
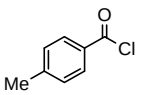
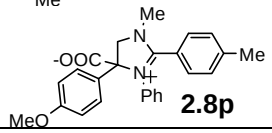
Scheme 2.3: Heterocoupled-Imidazoline Carboxylate Formation

As shown in Table 2.3, a wide range of imidazoline carboxylates can be prepared with this approach. This includes those derived from variously substituted C-aryl imines, such as, –ether (**2.8b-d)**, -halo (**2.8c,f)**, -thioether **(2.8a,e)**, and -alkynyl **(2.8e)** substituented reagents. In addition, a range of less stable imines can also be used in this method. For example, C-heteroaryl imines, which cannot be incorporated into homocoupled imidazolines, can be used to form pyridinyl **2.8k** and furanyl **2.8l** substituted imidazolines. Alternatively, cyclic imines can be employed (**2.8i,j**), allowing the selective generation of poly-cyclic imidazolines. Even less stable imines, such as formaldimines, are also compatible with this reaction **(2.8m-p)**. Overall, this provides a straightforward method to assemble a diverse range of imidazoline products, where each

substituent can be varied by simple changes in the imine and acid chloride building blocks employed.

Table 2.3: A Palladium Catalyzed Route to Diversely Substituted Imidazoline Carboxylates

Entry	Imine 1	Acid Chloride	Imine 2	Product	Yield
1[a,b]				-	-
2[a]				 **(2.8a) R^1 = -$CH_2CH{=}CH_2$ R^2 = Ph** **(2.4c) R^1 = -CH_2Ph R^2 = *p*SMePh**	62% **2.8a** 7% **2.4c**
3				 **2.8a**	75%
4				 **2.8b**	86%
5				 **2.8c**	67%
6				 **2.8d**	75%
7				 **2.8e**	95%
8				 **2.8f**	73%

9				 **2.8g**	87%
10				 **2.8h**	55%
11				 **2.8i**	93%
12				 **2.8j**	71%
13				 **2.8k**	77%
14				 **2.8l**	53%
15				 **2.8m**	93%
16				 **2.8n**	80%
17				 **2.8o**	80%
18				 **2.8p**	53%

General: Imine 1 (0.22 mmol), acid chloride (0.31 mmol)**,** 5% **2.6** (0.01 mmol), 15% **2.7** (10 mg, 0.03 mmol), 6 mL 1:1 THF/CH_3CN, NE*t*iPr_2 (55 µL, 0.31 mmol), CO (3.5 atm). 45 °C, 16 h. Imine 2 (0.44 mmol) and $PhSO_3H$ (28 mg, 0.18 mmol) in 2 mL CH_3CN. r.t. 3 h.

[a]Use of 0.22 mmol BnN=C(H)*p*SMePh, 0.20 mmol Ph(CO)Cl. Yield assessed from ^{1}H NMR.

[b] No $PhSO_3H$ added. Decomposition of Münchnone was observed over 3 hours.

2.3: CONCLUSION

These results demonstrate that the palladium catalyzed multicomponent reaction of imines, acid chlorides and carbon monoxide can provide a facile route to directly synthesize imidazoline carboxylates. Notably, palladium complexes in concert with the bulky, electron-rich di-*tert*-butyl-2-biphenyl phosphine provide a very active catalyst for this multicomponent coupling. In addition, by modifying the reaction conditions, this approach can also be used to generate a variety of diversely substituted imidazoline carboxylates, where each substituent can be independently varied. Considering the range of imidazolines found to be of utility, and the simplicity of these building blocks, this approach could prove useful in generating these targets, as well as new variants of these products. Experiments directed towards the latter are currently underway.

2.4: EXPERIMENTAL

2.4.1: GENERAL CONSIDERATIONS

All manipulations were carried out in Vacuum Atmosphere 553-2 glovebox under nitrogen atmosphere. Unless otherwise noted, all reagents were purchased from Aldrich and used without purification. Phosphine ligands were purchased from STREM chemicals. Carbon monoxide was supplied by MEGS (Matheson purity, 99.99%). All solvents were collected from an MBRAUN-SPS except acetonitrile which was distilled from CaH_2 and degassed. Once collected, solvents were stored under nitrogen over activated molecular sieves inside the glovebox. $Pd_2(dba)_3{\cdot}CHCl_3$ was prepared using literature techniques.[24] Aldimines were prepared from the condensation of aldehyde and amine using conc. Aqueous NaCl as drying agent, then distilled under vacuum. Formaldimines were prepared following literature procedures[25] or purchased as trisubstituted triazine from Aldrich. Pivaldehyde was purchased from Acros Organics. Amide-chelated palladacycle catalysts were prepared by pretreating $Pd_2(dba)_3{\cdot}CHCl_3$ with imine and acid chloride as previously reported.[20] Benzenesulfonic acid was purchased as the dry acid (not as the monohydrate) and dried under vacuum for 48 hours. Iminium salt (Imine · $PhSO_3H$) hydrolysis was tested by ^1H NMR to ensure dryness. Deuterated acetonitrile was stirred with CaH_2, vacuum transferred, degassed and stored over molecular sieves in the dry box.

Nuclear magnetic resonance (NMR) characterization was obtained on Varian Mercury 200 MHz, 300 MHz, 400 MHz and Varian Unity 500 MHz spectrometers. ^1H and ^{13}C NMR chemical shifts were referenced to residual solvent. Electrospray ionization-high resolution mass spectrometry (ESI-HRMS) analyses were performed by Dr. Alain Lesimple (Department of Medicine, Mass Spectrometry Unit, McGill University) and Dr. Alexandra Furtos (compound **2.8j**, Department of Chemistry, Université de Montréal). IR data for imidazolinium carboxylates was collected from a PIKE MIRacle ATR-equipped Perkin Elmer spectrum BX spectrometer at the Centre for Self Assembled Chemical Structures (CSACS, McGill University).

2.4.2: LIGAND SCREENING

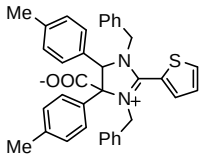
Reactions were set up in J. Young NMR tubes fitted with P.T.F.E. valves. BnN=(CH)Tol (52.3 mg, 0.25 mmol), Ph(CO)Cl (18.3 mg, 0.13 mmol), Palladium catalyst (0.007 mmol), ligand (0.018 mmol), and benzyl benzoate NMR standard (0.25 mmol) were combined in 800 μL CD_3CN, stirred until homogeneous, and transferred to the NMR tube. One freeze-pump-thaw cycle was carried out before pressurizing with 3.5 atm of CO. The conversion to imidazoline was determined by ^1H NMR analysis after 3 hours at 45 °C by comparison to the benzyl benzoate internal standard.

2.4.3: General Procedure for the Synthesis of Homocoupled Imidazoline Carboxylates (2.4)

In a 25-50 mL sealed glass reaction bomb (Kontes) equipped with a magnetic stir bar, imine (0.49 mmol), acid chloride (0.27 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ **2.5** (26 mg, 0.025 mmol), and di-*tert*-butyl-2-biphenyl phosphine **2.7** (22 mg, 0.75 mmol) were combined in 15 mL acetonitrile and stirred for 15 minutes, until homogeneous. One freeze-pump-thaw cycle was carried out before pressurizing with 3.5 atm of CO. The reactions were left for 16h at 45 °C, the solvent removed *in vacuo*, the residue dissolved in CH_2Cl_2, and filtered through celite.[26] The organic phase was washed sequentially with brine, 0.1 M HCl, and conc. Na_2CO_3. The organic phase was dried over Mg_2SO_4, filtered, concentrated to ca. 0.5mL then diethyl ether was added. Precipitation at -35 °C afforded the products as solid precipitates. Any modifications to this procedure are listed below.[27]

Compounds **2.4a-c** have been reported previously.[18]

1,3-Dibenzyl-2-thiophen-2-yl-4,5-di-p-tolyl-2-imidazolinium-4-carboxylate (2.4d):

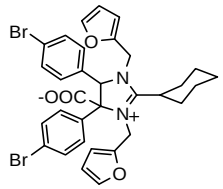


86% Yield. ^1H NMR (300 MHz, CD_3OD): δ 7.89 (d, 1H), 6.92-7.53 (m, 18H), 6.63 (d, 2H), 5.55 (s, 1H), 5.06 (d, 1H), 4.71 (d, 1H), 4.58 (d, 1H), 4.02 (d, 1H), 2.45 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 168.8, 160.5, 139.60, 139.5, 136.5, 135.3, 133.7, 133.1, 132.3, 130.6, 129.4, 129.3, 129.1, 128.8, 128.6, 128.3, 127.9, 127.7, 127.4,

127.0, 120.3, 83.0, 71.9, 50.6, 49.5, 20.0, 19.7. HRMS ($C_{36}H_{32}N_2O_2S$) calculated (M + 1): 557.22572 observed: 557.22555 IR ν_{CO}: 1637, 1533 (cm^{-1})

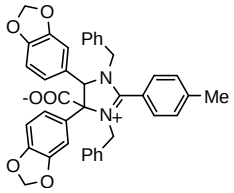
4,5-Bis-(4-bromo-phenyl)-2-cyclohexyl-1,3-bis-furan-2-ylmethyl-2-imidazolinium-4-carboxylate (2.4e):

Imine and acid chloride were each dissolved in 3mL of CH_3CN, and combined slowly, then stirred for 10 minutes before addition of catalyst. The product was precipitated from ethyl acetate with diethyl ether at room temperature.



42% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 6.95-7.6 (m, 8H), 6.35 (s, 1H), 6.1 (d, 2H), 5.4 (s, 1H), 5.1 (d, 1H), 3.98 (dd, 2H), 4.85, (s, 1H), 4.0 (d, 1H), 2.3 (m, 1H), 2.5 (m, 1H), 2.25 (m, 1H), 1.6-2.0 (m, 6H) 1.05-1.5 (m, 3H). ^{13}C NMR (125.71 MHz, CD_3OD): δ 169.7, 167.9, 148.5, 145.6, 144.2, 142.2, 139.2, 133.6, 131.6, 131.5_5, 129.7, 123.4, 123.0, 112.0, 111.0, 110.8, 110.5, 109.0, 81.3, 72.8, 42.6, 42.4, 37.4, 27.3, 27.0, 25.5(2 carbons), 24.6. HRMS ($C_{32}H_{30}Br_2N_2O_4$) calculated (M + 1): 665.06506 observed: 665.06524 IR ν_{CO}: 1630, 1568 (cm^{-1})

4,5-Bis-benzo[1,3]dioxol-5-yl-1,3-dibenzyl-2-p-tolyl-2-imidazolinium-4-carboxylate (2.4f):

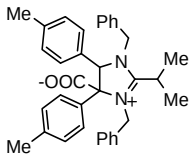


70% yield. ^1H NMR (400 MHz, CD_3OD): δ 7.41 (s, 2H), 6.61-7.35 (m, 18H), 6.05 (s, 2H), 5.95 (d, 2H), 5.45 (s, 1H) 4.89 (d, 1H), 4.45 (m, 2H), 4.05 (d, 1H), 2.40 (s, 3H). ^{13}C (100.62 MHz, DMSO): δ 165.7, 164.6, 148.2, 147.4_0, 147.3_5, 142.7, 136.3, 134.4, 133.5, 130.4, 130.3, 130.2_5, 128.8, 128.6, 129.4_8, 128.4_5, 128.0, 123.7_2, 123.6_8, 122.4, 120.6,

109.7, 109.3, 108.0, 101.6$_4$, 101.5$_7$, 73.7, 83.0, 50.3, 49.2, 21.5 HRMS ($C_{39}H_{32}N_2O_6$) calculated (M + 1): 625.23386 observed: 625.23338 IR ν_{CO}: 1639, 1556 (cm^{-1})

1,3-Dibenzyl-2-isopropyl-4,5-di-p-tolyl-2-imidazolinium-4-carboxylate (2.4g):

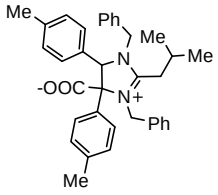
Imine and acid chloride were each dissolved in 3mL of acetonitrile, and combined slowly, then stirred for 10 minutes before addition of catalyst.



93% Yield. ^{1}H (300 MHz, $CDCl_3$): δ 7.00-7.50 (m, 16H), 6.69-6.92 (d, 2H), 5.20 (d, 1H), 5.17 (s, 1H), 4.95 (d, 1H), 3.90 (d, 1H), 4.05 (d, 1H), 3.25 (m, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 1.39-1.50 (d, 3H), 1.03-1.15 (d, 3H). ^{13}C (75.46 MHz, $CDCl_3$): δ 169.3, 166.6, 139.4, 138.8, 137.5, 136.9, 132.0, 131.3, 129.8, 129.7, 129.5, 129.1, 128.9, 128.5, 128.0, 127.4, 83.6, 72.7, 51.5, 49.3, 27.2, 21.7, 21.3, 18.3, 18.2. HRMS ($C_{35}H_{36}N_2O_2$) calculated (M + 1): 517.28550 observed: 517.28495. IR ν_{CO}: 1635, 1557 (cm^{-1})

1,3-Dibenzyl-2-isobutyl-4,5-di-p-tolyl-2-imidazolinium-4-carboxylate (2.4h):

Imine and acid chloride were each dissolved in 3mL of acetonitrile, and combined slowly, then stirred for 10 minutes before addition of catalyst.



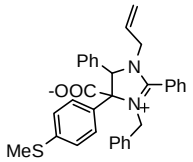
49% yield. ^{1}H (400 MHz, $CDCl_3$): δ 6.56-7.45 (m, 16H), 5.25 (s, 1H), 5.09 (d, 1H), 4.80 (d, 1H), 4.65 (d, 1H), 4.00 (d, 1H), 2.5 (m, 1H), 2.30-2.58 (dm, 2H), 2.29 (s, 3H), 2.23 (s, 3H), 1.50 (m, 1H) 1.05 (m, 6H), 1.03-1.15 (d, 3H). ^{13}C (100.62 MHz, $CDCl_3$): δ 20.9, 21.4, 22.6, 23.1, 27.5, 33.6, 48.9, 50.7, 72.9, 83.5, 126.7, 127.0, 127.8, 128.2, 128.6, 128.9, 129.1, 129.2, 129.4, 129.5, 131.1, 132.4, 135.4, 138.4, 139.0, 165.6, 166.1. HRMS

($C_{36}H_{38}N_2O_2$) calculated (M + 1): 531.29982 observed: 517.28495. IR ν_{CO}: 1637, 1566 (cm^{-1})

2.4.4: SYNTHESIS OF HETEROCOUPLED IMIDAZOLINE CARBOXYLATES (2.8B-P)

Inside a glovebox, in a 50 mL reaction bomb, imine (0.22 mmol) and acid chloride (0.31 mmol) were dissolved in 3 mL acetonitrile and stirred for ca. 10 minutes. The palladacyclic catalyst **2.6** (0.01 mmol) and P(*t*Bu)$_2$(2-biphenyl) **2.7** (10 mg, 0.03 mmol) were then added as a solution in 3mL THF and stirred for 5 minutes. Diisopropylethylamine (0.31 mmol) was added via microsyringe, and the reaction bomb was removed from the glovebox. One freeze-pump-thaw cycle was performed before pressurizing the vessel with 3.5 atm of CO. The reaction was allowed to stir at 45 °C for 16 h. CO was removed under vacuum, and the reaction bomb was brought back into the drybox. The second imine (0.44 mmol) and $PhSO_3H$ (28 mg, 0.18 mmol) were added as a solution in 2 mL acetonitrile. The reaction was stirred at room temperature until a color change from bright orange to pale yellow was observed (typically 3 h). The reaction progress was also monitored by ^1H NMR to confirm complete consumption of Münchnone. Products were purified as described above. Any modifications to the general procedure are noted below.

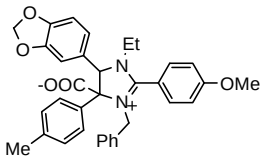
1-Allyl-3-benzyl-4-(4-methylsulfanyl-phenyl)-2,5-diphenyl-2-imidazolinium-4-carboxylate (2.8a):



75% yield. ^1H (400 MHz, CD_3OD): δ 7.69 (d, 2H), 7.35-7.59 (m, 12H), 7.14 (m, 1H), 6.97-7.17 (m, 1H), 6.85-6.93 (m, 2H), 6.47 (d, 2H), 5.90 (s ,1H), 5.73-5.85 (m, 1H), 5.25 (d, 1H), 4.83-5.000 (m, 2H), 4.25 (d, 1H), 3.78-3.89 (d, 1H), 3.44-3.53 (m, 1H), 2.49 (d, 1H), 2.50 (s, 3H). ^{13}C (100.62 MHz, CD_3OD): δ 168.7, 165.7, 141.2, 135.3, 135.1, 133.8, 132.1, 129.5, 129.3, 129.3, 129.1, 128.9, 128.5, 127.8, 127.7, 127.6, 127.2, 127.0, 126.1,

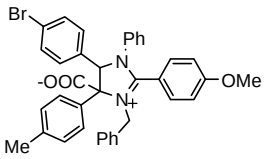
123.1, 121.3, 83.4, 72.8, 50.2, 13.8. HRMS ($C_{33}H_{30}N_2O_2S$) calculated (M + 1): 519.21062 observed: 519.20937 IR ν_{CO}: 1638, 1549 (cm^{-1})

5-Benzo[1,3]dioxol-5-yl-3-benzyl-1-ethyl-2-(4-methoxy-phenyl)-4-p-tolyl-2-imidazolinium-4-carboxylate (2.8b):



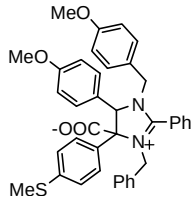
86% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.65 (d, 2H), 7.30 (d, 1H), 6.82-7.03 (m, 12H), 6.42 (d, 2H), 4.85 (d, 1H), 4.40 (d, 1H), 3.24-3.35 (m, 1H), 2.97-3.10 (m, 1H), 2.38 (s, 3H), 1.10-1.18 (m, 3H). ^{13}C NMR (100.62 MHz, CD_3OD): δ 169.5, 165.8, 162.8, 149.1, 148.3, 139.7, 136.8, 135.7, 129.7, 129.4, 129.0, 128.4, 128.0, 127.9, 127.8, 127.1, 123.2, 115.1, 115.0, 107.1, 101.7, 83.2, 72.3, 55.0, 50.3, 40.8, 20.0, 11.8. HRMS ($C_{34}H_{32}N_2O_5$) calculated (M + 1): 549.23895 observed: 549.23691 IR ν_{CO}: 1641, 1552 (cm^{-1})

3-Benzyl-5-(4-bromo-phenyl)-2-(4-methoxy-phenyl)-1-phenyl-4-p-tolyl-2-imidazolinium-4carboxylate (2.8c):



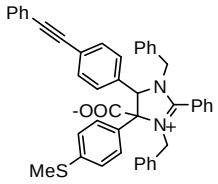
67% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.80-7.89 (d, 2H), 6.79-7.46 (m, 10H), 6.58-6.75 (s, 1H), 6.32-6.45 (d, 2H), 5.05 (d, 1H), 4.55 (d, 1H), 3.70 (s, 3H), 2.35 (s, 3H). ^{13}C (100.62 MHz, CD_3OD): δ 168.9, 165.3, 162.8, 139.9, 135.6, 134.9, 134.3, 133.3, 131.2, 130.9, 130.6, 129.8, 129.6, 129.2, 128.5, 127.8, 127.7, 127.1, 127.0, 123.0, 115.2, 114.6, 84.4, 75.5, 54.9, 50.3, 20.0. HRMS ($C_{37}H_{31}BrN_2O_3$) calculated (M + 1): 631.15963 observed: 631.15861 IR ν_{CO}: 1635, 1567 (cm^{-1})

3-Benzyl-1-(4-methoxy-benzyl)-5-(4-methoxy-phenyl)-4-(4-methylsulfanyl-phenyl)-2-phenyl-2-imidazolinium-4-carboxylate (2.8d):



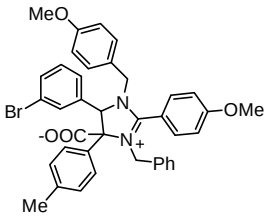
75% yield. ^{1}H (300 MHz, CD_3OD): δ 7.16-7.63 (m, 11H), 6.83-7.05 (m, 9H), 6.58-6.67 (d, 2H), 5.47 (s, 1H), 4.95 (d, 1H), 4.33-4.44 (m, 2H), 3.72-3.95 (m, 7H), 2.45 (s, 3H). ^{13}C (75.46 MHz, CD_3OD): δ 169.2, 165.2, 161.1, 160.7, 141.2, 136.3, 135.6, 132.3, 130.5, 129.9, 129.5, 128.4, 128.2, 128.1, 128.0, 127.4, 127.2, 126.3, 125.5, 124.1, 123.4, 114.5, 114.2, 83.0, 72.0, 54.7, 54.7, 54.7, 50.5, 48.8, 48.7. HRMS ($C_{39}H_{36}N_2O_4S$) calculated (M + 1): 629.24740 observed: 629.24726 IR ν_{CO}: 1638, 1547 (cm^{-1})

1,3-Dibenzyl-4-(4-methylsulfanyl-phenyl)-2-phenyl-5-(4-phenylethynyl-phenyl)-2-imidazolinium-4-carboxylate (2.8e):



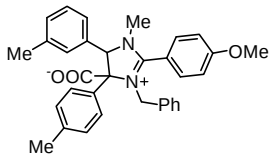
95% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.35-7.63 (m, 17H), 7.21-7.28 (m, 2H), 7.02-7.09 (m, 2H), 6.93-6.99 (m, 2H), 6.60 (m, 2H), 5.58 (s, H), 4.500 (d, 1H), 4.45 (d, 1H), (d, 1H), 4.02 (d, 1H), 2.47 (s, 3H). ^{13}C NMR (100.62 MHz, CD_3OD): δ 168.6, 165.8, 141.4, 135.8, 135.4, 134.0, 132.4, 132.3, 131.8, 131.4, 129.9, 129.6, 129.3, 129.1, 128.5, 128.4_7, 128.4, 128.2, 128.1, 127.5, 127.3, 126.3, 124.9, 123.2, 123.1, 90.3, 88.4, 83.5, 72.3, 53.6, 50.6, 49.7, 14.0. HRMS ($C_{45}H_{36}N_2O_2S$) calculated (M + 1): 669.25757 observed: 669.25677 IR ν_{CO}: 1637, 1567 (cm^{-1})

3-Benzyl-5-(3-bromo-phenyl)-1-(4-methoxy-benzyl)-2-(4-methoxy-phenyl)-4-p-tolyl-2-imidazolinium-4-carboxylate (2.8f):



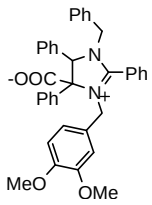
73% yield. ^{1}H NMR (200 MHz, CD_3OD): δ 7.53-7.62 (m, 2H), 6.83-7.50 (m, 21H), 6.65 (d, 2H), 5.55 (s, 1H), 5.01 (d, 1H), 4.49 (d, 1H), 4.36 (d, 1H), 3.91 (d, 1H) 3.73 (s, 3H), 3.72 (s, 3H), 2.36 (s, 3H) ^{13}C NMR (75.46 MHz, CD_3OD): δ 168.9, 165.7, 163.0, 160.7, 139.7, 139.1, 136.9, 136.8, 135.8, 132.6, 130.5, 129.9, 129.7, 129.2, 128.1, 128.0, 127.7, 127.2, 124.1, 122.5, 115.3, 115.1, 114.6, 114.5, 83.5, 71.2, 55.0, 54.7, 50.3, 49.1, 19.9. HRMS ($C_{39}H_{35}BrN_2O_4$) calculated (M + 1): 675.18530 observed: 675.18463 IR ν_{CO}: 1640, 1561 (cm^{-1})

3-Benzyl-2-(4-methoxy-phenyl)-1-methyl-5-m-tolyl-4-p-tolyl-2-imidazolinium-4-carboxylate (2.8g):



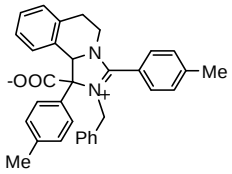
87% yield. ^{1}H NMR (200 MHz, CD_3OD): δ 7.68 (d, 2H), 7.17-1.33 (m, 8H), 6.83-7.00 (m, 3H), 6.43 (d, 2H) 5.90 (s, 1H), 5.86 (d, 1H), 4.40 (d, 1H), 3.80 (s, 3H), 2.79 (s, 3H), 2.35 (s, 6H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 169.5, 166.2, 162.8, 139.5, 139.1, 138.4, 136.1, 135.8, 134.3, 130.0, 129.6, 129.5, 128.9, 128.6, 127.8, 127.0, 125.6, 115.1, 114.9, 83.7, 74.9, 55.0, 50.2, 32.4, 20.3, 20.0. HRMS ($C_{33}H_{32}N_2O_3$) calculated (M + 1): 505.24912 observed: 505.24863 IR ν_{CO}: 1639, 1548 (cm^{-1})

1-Benzyl-3-(3,4-dimethoxy-benzyl)-2,4,5-2-imidazolinium-4-carboxylate (2.8h):



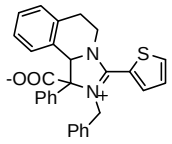
44% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.38-7.61 (m, 19H), 7.14 (d, 1H), 7.03 (m, 2H), 6.45 (d, 1H), 6.39 (s, 1H), 5.99 (d, 1H), 5.58 (s, 1H), 4.95 (d, 1H), 4.42 (d, 1H), 4.30 (d, 1H), 3.92(d, 1H), 3.71 (s, 3H), 3.61 (s, 3H). ^{13}C NMR (100.62 MHz, CD_3OD): δ 168.7 165.1 148.7 148.4 140.1 132.2 132.0 129.6 129.5 129.3 129.2 129.1 129.0 128.9_8 128.9_5 128.6 127.9 127.7 127.5 127.1 123.3 121.1 111.5 110.9 83.2 2.2 54.9_9, 54.9_8, 50.0, 49.1 HRMS ($C_{38}H_{34}N_2O_4$) calculated (M + 1): 583.25968 observed: 583.25969 IR ν_{CO}: 1642, 1551 (cm^{-1})

2-Benzyl-1,3-di-p-tolyl-1,5,6,10b-tetrahydro-imidazolinium-[5,1-a]isoquinoline-1-carboxylate (2.8i):



93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 1H), 7.99 (d, 2H), 7.45 (d, 1H), 6.83-7.15 (m, 10H), 6.40 (d, 1H), 6.05 (s, 1H), 4.75 (d, 1H), 4.20 (d, 1H), 3.65 (m, 1H), 3.18-3.41 (m, 2H), 2.63 (d, 1H), 2.41 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 166.0, 165.4, 143.4, 138.9, 135.8, 132.8, 132.2, 131.4, 129.9, 129.7, 129.4, 129.2, 129.0, 128.1, 128.0, 127.9, 127.8_9, 127.3, 126.9, 120.9, 86.8, 68.2, 49.6, 43.2, 29.9, 21.9, 21.3. HRMS ($C_{33}H_{30}N_2O_2$) calculated (M + 1): 487.23855 observed: 487.23824 IR ν_{CO}: 1616, 1545 (cm^{-1})

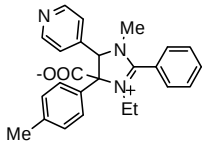
2-Benzyl-1-phenyl-3-thiophen-2-yl-1,5,6,10b-tetrahydro-imidazolinium[5,1-a]isoquinoline-1-carboxylate (2.8j):



71% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.09 (d, 2H), 7.71 (d 2H), 6.75-7.40 (m, 11H), 6.49 (d, 2H), 6.09 (s, 1H), 4.91 (d, 1H), 4.22 (d, 1H), 3.85 (m, 1H), 3.12-2.50 (m, 2H), 2.63 (d, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.0, 161.3, 135.1, 134.6, 134.0, 132.8, 132.7, 131.3, 129.3, 129.0, 128.8, 128.6, 128.2, 128.1, 127.8, 127.6, 127.5, 127.3,

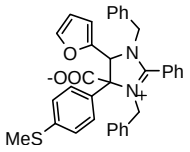
126.7, 121.1, 86.6, 68.0, 49.7, 43.6, 29.7. HRMS ($C_{29}H_{24}N_2O_2S$) calculated (M + 1): 465.16367 observed: 464.15585 IR ν_{CO}: 1639, 1555 (cm^{-1})

3-Ethyl-1-methyl-2-phenyl-5-pyridin-4-yl-4-p-tolyl-2-imidazolinium-4-carboxylate (2.8k):



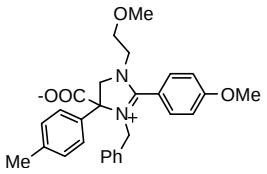
77% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (m, 2H), 7.52-7.85 (m, 8H), 7.18-7.34 (m, 8H), 5.44 (s, 1H), 3.58 (m, 2H), 2.74 (s, 3H), 2.36 (s, 3H), 0.54 (t, 3H). ^{13}C NMR (125.71 MHz, $CDCl_3$): δ 166.0, 164.8, 150.1, 143.7, 139.2, 136.4, 133.0, 130.1, 129.6, 129.3, 128.1, 123.6, 123.3, 84.8, 76.3, 43.0, 33.6, 21.0, 14.8. HRMS ($C_{25}H_{25}N_3O_2$) calculated (M + 1): 400.20250 observed: 400.20166

1,3-Dibenzyl-5-furan-2-yl-4-(4-methylsulfanyl-phenyl)-2-phenyl-2-imidazolinium-4-carboxylate (2.8l):



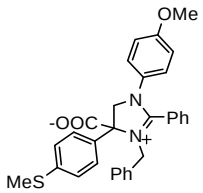
53% yield. ^{1}H NMR (500 Mhz, CD_3OD): δ 7.68 (s, 1H), 7.51-7.57 (m, 1H), 7.33-7.48 (m, 10H), 7.25 (d, 4H), 6.9-7.1 (m, 6H), 6.67 (m, 4H), 6.53 (s, 1H), 5.72 (s, 1H), 5.14 (d, 1H), 4.45 (d, 1H), 4.35 (d, 1H), 3.97 (d, 1H), 2.45 (3s, H). ^{13}C NMR (125.71 Mhz, CD_3OD): δ 167.7, 164.4, 145.1, 143.1, 140.0, 134.3, 134.2, 131.4, 131.0, 128.4, 128.2, 127.8, 127.7, 127.5, 126.8, 126.7, 126.6, 125.9, 125.0, 121.9, 112.1, 109.6, 79.3, 65.2, 49.0, 48.2, 12.7. HRMS ($C_{35}H_{30}N_2O_3S$) calculated (M + 1): 559.20554 observed: 559.20505 IR ν_{CO}: 1640, 1567 (cm^{-1})

3-Benzyl-1-(2-methoxy-ethyl)-2-(4-methoxy-phenyl)-4-p-tolyl-2-imidazolinium-4-carboxylate (2.8m):



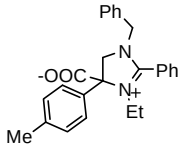
93% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 6.85-7.60 (m, 11H), 6.42-6.51 (d, 2H), 4.72-4.83 (m, 2H), 4.60 (d, 1H), 4.45 (d, 1H), 3.85 (s, 3H), 3.55 (m, 2H), 3.27-3.39 (m, 5H), 2.31 (s, 3H). ^{13}C NMR (100.62 MHz, CD_3OD): δ 174.0, 165.6, 162.9, 139.5, 135.8, 133.5, 130.3, 130.5, 129.4, 129.0, 127.8, 127.5, 127.0, 114.7, 77.6, 68.1, 59.5, 58.1, 55.0, 49.4, 48.4, 19.9. HRMS ($C_{28}H_{30}N_2O_4$) calculated (M + 1): 459.22838 observed: 459.22781 IR ν_{CO}: 1628, 1551 (cm^{-1})

3-Benzyl-1-(4-methoxy-phenyl)-4-(4-methylsulfanyl-phenyl)-2-phenyl-2-imidazolinium-4-carboxylate (2.8n):



80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 2H), 7.21-7.41 (m, 6H), 7.11 (d, 2H), 6.81-6.99 (m, 6H), 6.63 (d, 2H), 6.40 (d, 2H), 5.22 (d, 1H), 5.00 (d, 1H), 4.70-4.81 (m, 2H), 3.63 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125.71 MHz, $CDCl_3$): δ 170.9, 163.2, 159.6, 140.5 135.5, 132.3, 130.3, 129.5, 129.1, 128.9, 128.3, 128.1, 127.5, 126.8, 126.6, 126.5, 123.7, 115.0, 78.8, 64.5, 55.6, 50.6, 15.7. HRMS ($C_{31}H_{28}N_2O_3S$) calculated (M + 1): 509.18989 observed: 509.18976 IR ν_{CO}: 1633, 1555 (cm^{-1})

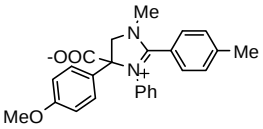
1-Benzyl-3-ethyl-2-phenyl-4-p-tolyl-2-imidazolinium-4-carboxylate (2.8o):



80% yield. ^{1}H (500 MHz, $CDCl_3$): δ 7.09-7.71 (m, 14H), 4.89 (d, 1H), 4.33-4.47 (dd, 4H), 4.09 (d, 1H), 3.67-3.76 (m, 1H), 3.49-3.57 (m, 1H), 2.28 (s, 3H), 0.48 (m, 3H). ^{13}C

(125.71 MHz, $CDCl_3$): δ 170.6, 163.4, 138.9, 135.2, 133.0, 132.9, 130.3, 130.0, 129.7, 129.6, 129.1, 128.9, 127.8, 123.4, 77.8, 61.2, 51.5, 42.1, 21.3, 15.4. HRMS ($C_{26}H_{26}N_2O_2$) calculated (M + 1): 399.20725 observed: 399.20625 IR ν_{CO}: 1628, 1568 (cm^{-1})

4-(4-Methoxy-phenyl)-1-methyl-3-phenyl-2-p-tolyl-2-imidazolinium-4-carboxylate (2.8p):



53% yield. ^1H NMR (300 MHz, DMSO): δ 7.50 (d, 2H), 7.41 (d, 2H), 7.24 (d, 4H), 6.95 (m, 3H), 6.72 (d, 2H), 4.70 (d, 1H), 4.45 (d, 1H), 3.62 (s, 3H), 3.15 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (125.71 MHz, D_2O): δ 176.1, 164.8, 159.5, 144.4, 135.7, 130.6, 129.9, 129.7, 129.5, 128.7, 128.6, 128.3, 119.5, 114.2, 78.8, 63.2, 55.5, 34.9, 20.9. HRMS ($C_{25}H_{24}N_2O_3$) calculated (M + 1): 401.18652 observed: 401.18563

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(23) For example, enolizable imines rapidly generate enamines from iminiium salts **2.1**, while heteroaromatic imines are prone to nucleophilic attack of imine onto iminium salt **2.1**. BnN=C(H)*t*Bu has been previously employed to generate Münchnones, but are presumably too bulky to allow subsequent dipolar cycloaddition.

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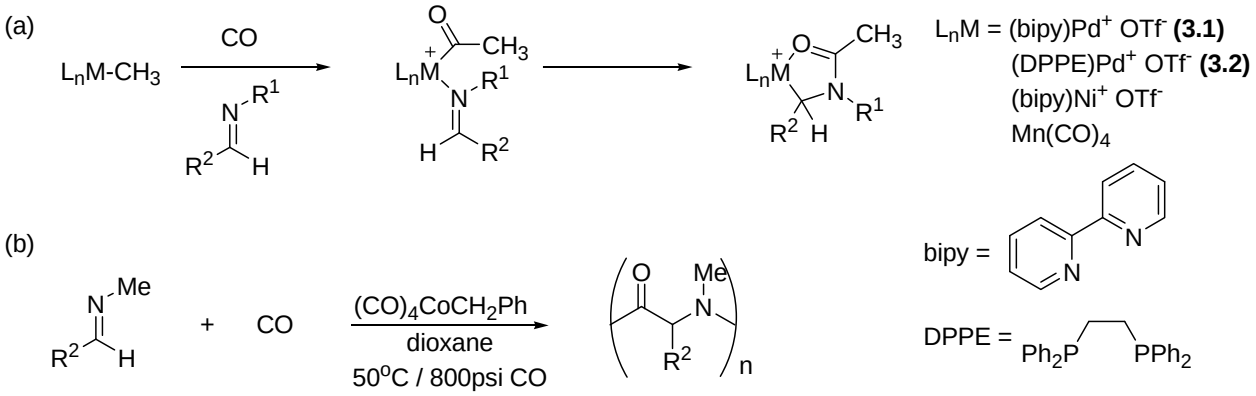
(26) Celite filtration was performed when palladium black formed in the crude solution. If the brine wash is neglected unidentified phosphine species contaminate the products, and are very difficult to remove.

(27) In order to ensure stability of these products during isolation, care must be taken to avoid prolonged contact with $CHCl_3$ or wet organic solvents. Decarboxylation to 4,5-dihydroimidazolinium salts is commonly observed when these precautions are not taken. Similarly, precipitation at -35°C, and collection of the precipitate should be carried out with care under a dry atmosphere as condensation of water vapor from the air can occasionally elicit the same decomposition.

CHAPTER 3: PALLADIUM CATALYZED SYNTHESIS OF IMIDAZOLINES FROM IMINES, ARYL-IODIDE AND CARBON MONOXIDE

3.1: INTRODUCTION

During the course of our investigation into the imidazoline carboxylate synthesis in Chapter 2, we were intrigued by related work by our lab[1] and others[2,3] on imine-insertion into metal-acyl bonds. This reaction has immense potential as a route to form copolymers of imine and CO. Nickel, cobalt, manganese and palladium complexes are all competent at imine insertion (Scheme 3.1a), though only cobalt carbonyl has permitted sequential insertion to provide amide polymers (Scheme 3.1b).[3] These processes are all believed to proceed via the reaction of the metal-acyl complex with a bound imine ligand (Scheme 3.1a). It is important to note that imine will not insert into metal-alkyl bonds, even at elevated temperatures.[1,2] This is postulated to arise from the thermodynamics of imine insertion, where amide bond formation and chelation provide a driving force for the reaction.[1,2] In addition, imine insertion is believed to proceed via an intramolecular nucleophilic attack of imine on the electrophilic acyl ligand.[1,2]

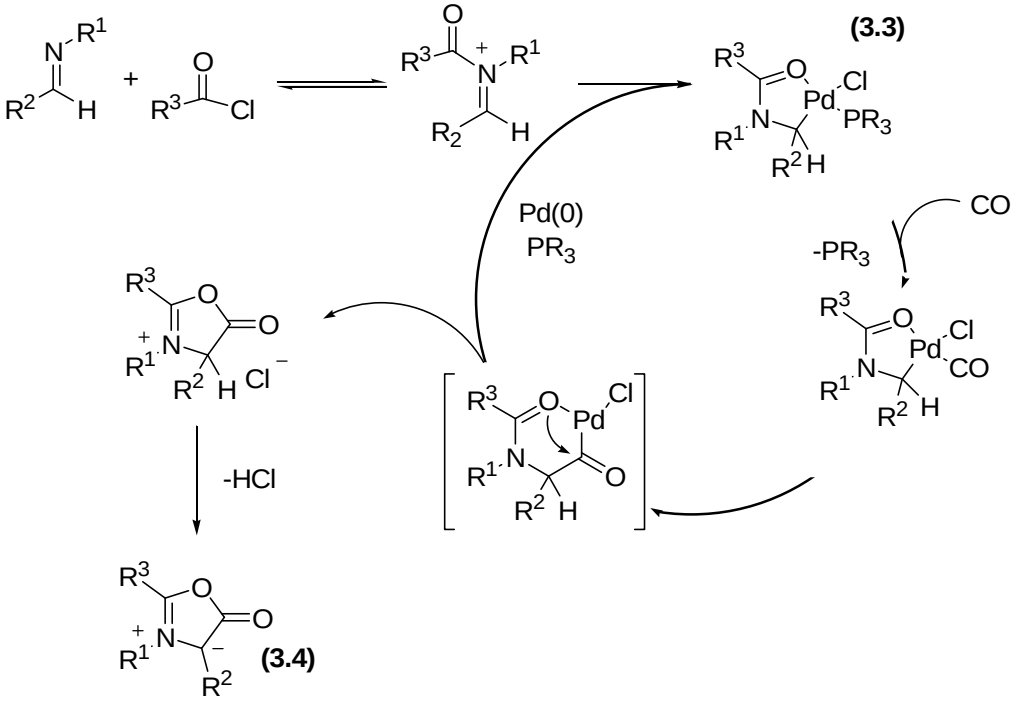


Scheme 3.1: Imine Insertion into Metal-Acyl Bonds

In 1998, we reported that imines can insert into cationic palladium-acyl bonds with with triflate as the anion **3.1**.[1] Shortly thereafter, Sen and coworkers demonstrated the same reaction with tetraflouroborate as counterion **3.2**.[2] The resultant amide chelated palladacycle permitted no further CO insertion, and thus in both cases, was the end

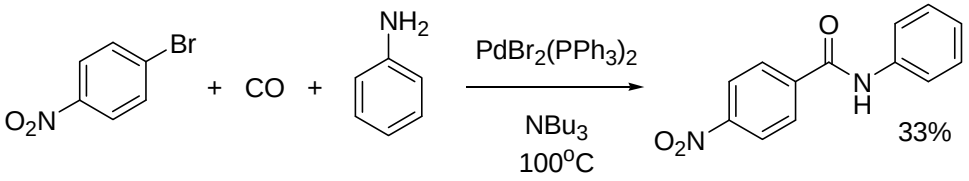
product. The stability of the amide chelate restricts access to the requisite coordination site, thus impeding further CO insertion. In both cases, N-alkyl and -aryl substituents were tolerated. Several other bidentate phosphine and amine ligands were used in the Sen publication, none of which facilitated subsequent CO insertion for **3.2**.

The catalytic synthesis of imidazolines from imines, acid chlorides and CO (Chapter 2) proceeds through strikingly similar intermediate metal complexes to those above (Scheme 3.2). In this case however, the chelated amide complex **3.3** is formed via the oxidative addition of an N-acyl iminium salt (formed from imine and acid chloride) to palladium (0). The product is a neutral palladium (II) metalacycle. This neutral variant is able to insert an additional CO since coordination sites are made available via dissociation of either the monodentate phosphine or halide. However, further insertion of imine does not occur into the palladium-acyl bond. Instead, formal reductive elimination and HCl elimination yields a Münchnone **3.4**.[4] In the absence of base, protonated imine will undergo 1,3-dipolar cycloaddition to yield imidazolinium carboxylate, as discussed in Chapter 2.

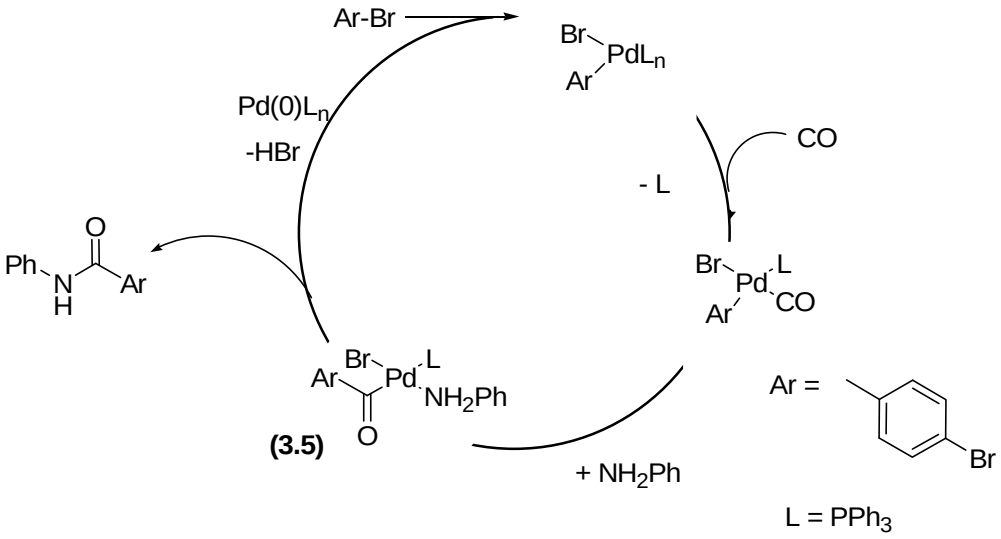


Scheme 3.2: Proposed Mechanism for Catalytic Münchnone Formation

A third reaction related to this chemistry is the palladium catalyzed aminocarbonylation of arenes. This is the process by which primary or secondary amines are coupled with CO and aryl halides to yield amides. The archetypical reaction by Heck is shown in Scheme 3.3.[5] The mechanism of this reaction is believed to involve the oxidative addition of the aryl halide to palladium, followed by CO insertion to yield a palladium-acyl complex **3.5** (Scheme 3.4). Finally, coordination of amine and reductive elimination of amide complete the catalytic cycle.



Scheme 3.3: Heck's Aminocarbonylation Reaction

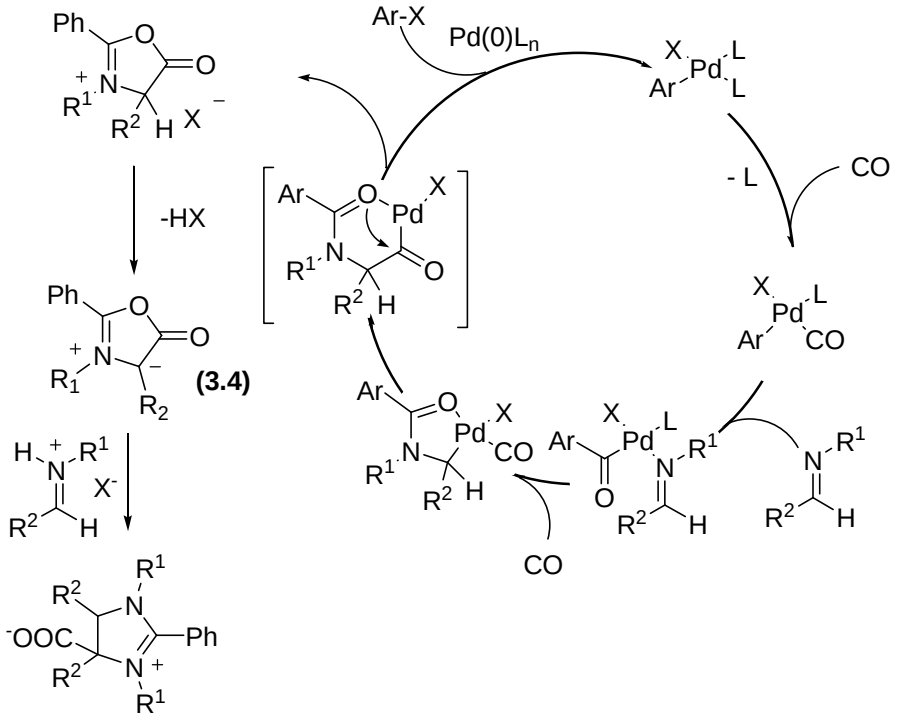


Scheme 3.4: The Proposed Mechanism for Arene Aminocarbonylation

3.2: CONCEPT

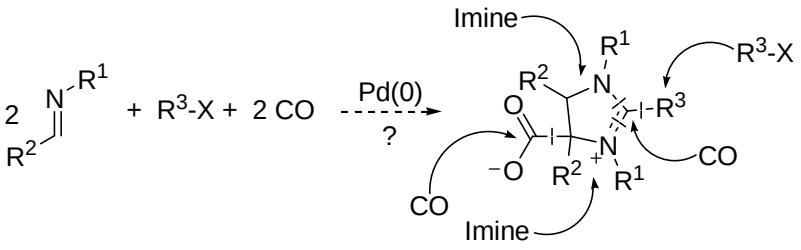
The mechanisms of imine-acyl insertion, catalytic Münchnone formation, and arene aminocarbonylation show significant overlap. Imine insertion and Münchnone synthesis both proceed through amide-chelated palladacycle intermediates (e.g. **3.1** and **3.3**), regardless of charge on the metal. Similarly, arene aminocarbonylation can be used

to generate *in situ* palladium-acyl complexes. Drawing on these three processes, we predicted that aryl halides could potentially replace acid chlorides in imidazoline carboxylate synthesis, as shown mechanistically in Scheme 3.5.



Scheme 3.5: The Proposed Mechanism for Catalytic Imidazoline Carboxylate Formation

Overall, this change from acid chlorides to aryl halides as building blocks has a number of appealing features. Firstly, it would eliminate the presence of large quantities of sensitive N-acyl iminum salts from the catalytic cycle, which often lead to significant scope limitations due to their high electrophilicity. In addition, it would obviate the need for pre-synthesized acid chlorides, and instead generate the equivalent *in situ* from simple aryl halides and CO. Overall, this would provide a simple method to generate imidazolines from five separate units: two imines, two carbon monoxides and an aryl halide, all coupled at once by palladium catalysis (Scheme 3.6). Experiments directed towards the development of this reaction are described herein.

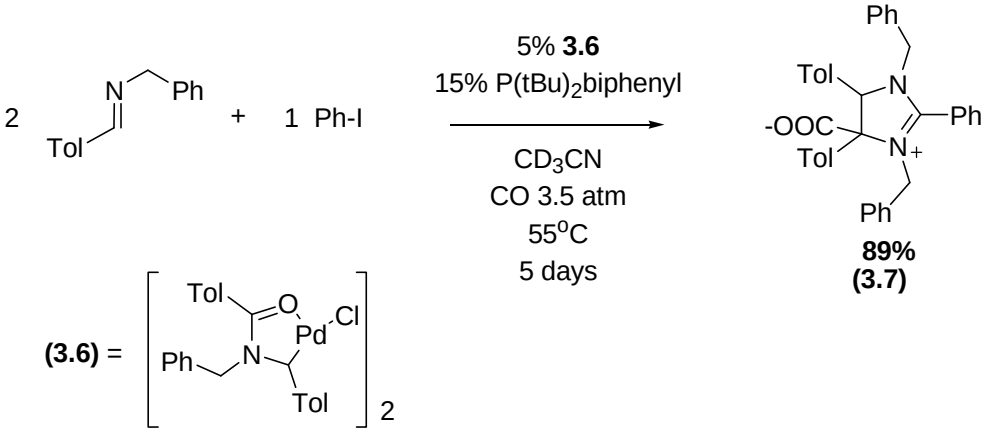


Scheme 3.6: Proposed Reaction

3.3: RESULTS AND DISCUSSION

3.3.1: A NEW SYNTHESIS OF IMIDAZOLINIUM CARBOXYLATE

The potential of this reaction was first probed as shown in Scheme 3.7. Upon mixing the reagents and palladium catalyst **3.6**, and charging the vessel with CO, palladium black precipitates from the mixture within 1 hour. ^{1}H-NMR analysis reveals only a trace of imidazoline **3.7** generated (ca. 10%). The latter likely arises from the amide ligand on the catalyst. Despite the precipitation of the catalyst, the reaction was continued at 55 °C. Gratifyingly, after 5 days, an 89% yield of imidazoline was formed.[6]



Scheme 3.7: Formation of 3.7

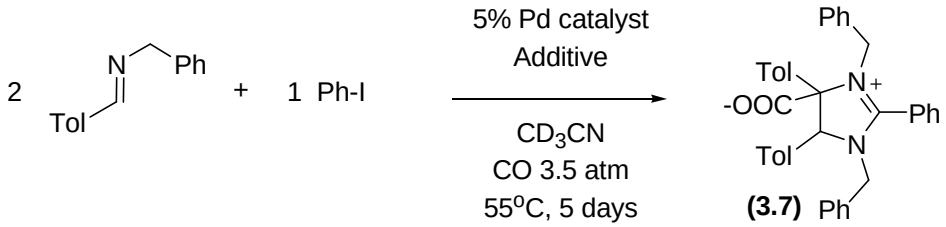
This initial result showed this reaction could indeed proceed as planned, though the nature of the palladium catalyst (a black precipitate) was very poorly defined. In principle, the reaction could be catalyzed by heterogeneous palladium, where the phosphine ligand would play no role. ^{31}P NMR analysis of the reaction showed that the

phosphine was completely converted to protonated phosphine after only one hour of heating. Thus, it appeared that phosphine was merely behaving as a base in catalysis.

3.3.2: OPTIMIZATION OF CONDITIONS

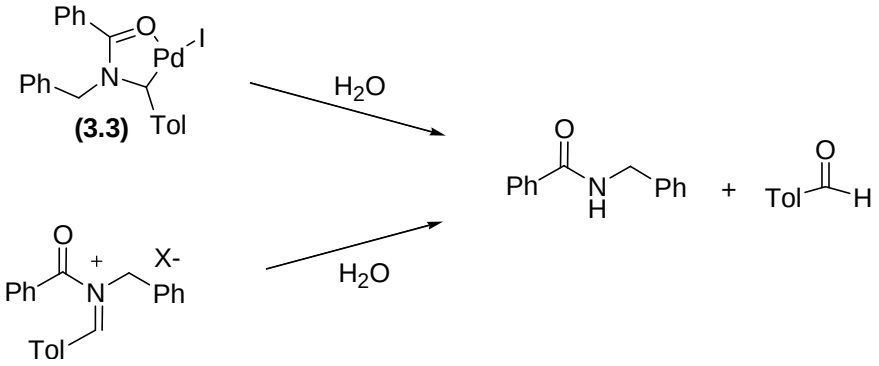
Based on this lead, various commercial heterogeneous palladium catalysts were examined, in this reaction. However, as shown in Table 3.1, none yielded imidazoline. Trace amounts of the amide Ph(CO)NHBn was observed with palladium on alumina (entry 3), suggesting that some carbonylation had occurred, followed by hydrolysis, perhaps of the palladium-amide intermediate **3.3** or an *in situ* formed iminium salt (Scheme 3.8).

Table 3.1: Trial of Heterogeneous Palladium Catalysts



entry[a]	Pd Catalyst	Additive	Yield 3.7
1	Pd Black	-	0%
2	Pd/C	-	0%
3	Pd/Al	-	0% (5% PhCONHBm)
4	Pd Black	15% $P(tBu)_2$biphenyl	0%
5[b]	Pd Black	15% $P(tBu)_2$biphenyl	0%

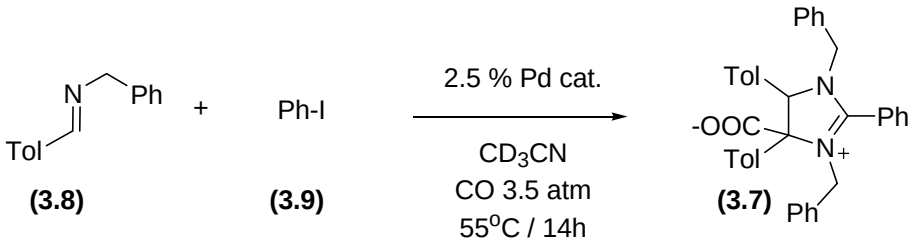
[a] In 15 mL reaction bomb: imine (50 mg, 0.24 mmol), Ph-I (24.5 mg, 0.12 mmol), 5% Pd catalyst, additive, CO (3.5 atm), 1 mL CH_3CN. 55 °C, 5 days. Yield determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] 85 °C.



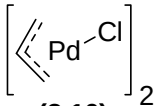
Scheme 3.8: Possible Routes for Amide Formation

The lack of imidazoline formation with heterogeneous palladium sources suggests that the active catalyst in the reaction of Scheme 3.7 may not actually be heterogeneous. Instead the palladium black precipitate may simply be inhibiting carbonylation by removing homogeneous catalyst from solution. Indeed, as shown in Table 3.2, by simply increasing the amount of Ph-I used, the palladium catalyst can be kept in solution. The excess Ph-I presumably leads to more favored oxidative addition to palladium (0), and competes with colloid formation.[7] Under these conditions, imidazoline formation is much more rapid, with 56% yield after only 14 hours at 55 °C, and 90% after 5 days (Table 3.2 entry 3). In addition, the commercially available allylpalladium complex **3.10** is also a viable catalyst for this reaction (Table 3.2, entry 6).[8]

Table 3.2: The Effect of Ph-I to Imine Ratio on Imidazoline Formation

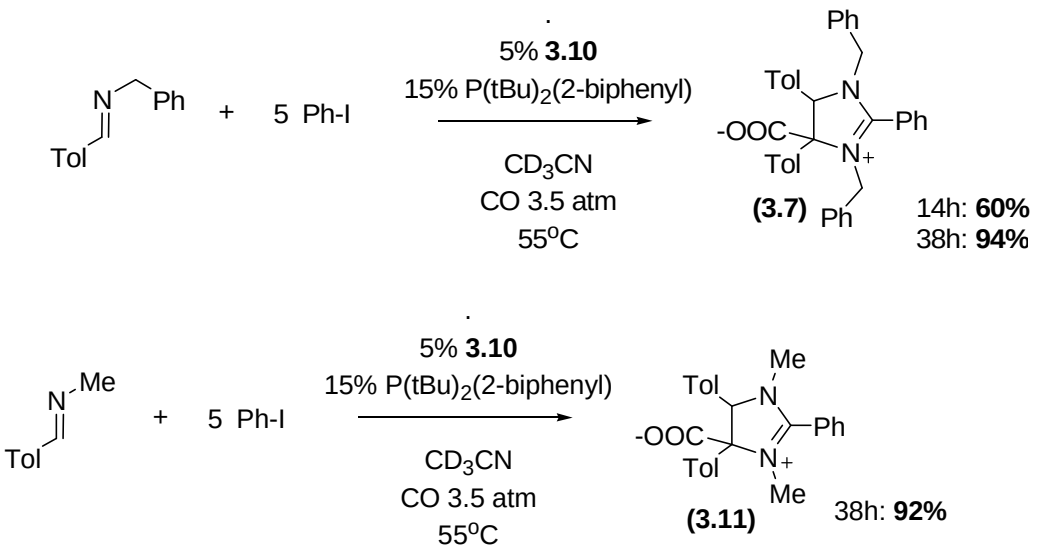


(3.8) **(3.9)** **(3.7)**

entry[a]	Pd cat.	3.8:3.9	% Yield 3.7	Observations
1	**3.6**	2:1	23	Pd black
2	**3.6**	1:1	31	Pd Black
3	**3.6**	1:5	56	Homogeneous
4	 **(3.10)**	2:1	23	Pd Black
5	**3.10**	1:1	32	Pd Black
6	**3.10**	1:5	55	Homogenous

[a] Reaction carried out in a J-Young NMR tube: imine **3.8** (21 mg, 0.1 mmol), 2.5% Pd catalyst, 800 µL CD_3CN, 3.5 atm CO. 55 °C, 14 h. Yield determined by i*n situ* ^{1}H-NMR.

The rate of catalysis can be further enhanced by the addition of electron rich phosphine ligands; these ligands presumably further inhibit the formation of palladium precipitate and/or colloids by coordination to Pd(0). Using the most active ligand from our previous ligand screening (Chapter 2), di-*tert*-butyl-2-biphenyl, it was found that imidazoline can be generated in only 38 hours in near quantitative yields (Scheme 3.7). Notably, ^{31}P NMR at the end of this experiment (Table 3.2, Entry 3) clearly showed the presence of a palladium-coordinated phosphine (δ 56.1ppm).[9] In addition to the N-methyl substituted imine, MeN=(CH)(H)Tol is also a viable reagent in this reaction, leading to the formation of imidazoline **3.11** in similarly high yield (Scheme 3.8). The effect of ligand addition at this time seems negligible since the reaction proceeds to 55% after 14h without additive (Table 3.2, Entry 6).



Scheme 3.9: The Syntheses of Imidazolines 3.7 and 3.11

3.4: CONCLUSIONS AND OUTLOOK

Overall these results demonstrate that acid chlorides can be replaced by available and stable aryl iodides in the palladium catalyzed synthesis of imidazoline carboxylates. This provides a 5-component coupling methodology to assemble theses products incorporating Ph-I, two equivalents of carbon monoxide and two equivalents of imine (Fig. 3.1). Considering the low reactivity of Ph-I relative to acid chlorides, this reaction holds the potential to access a range of substituted imidazoline products, as well as other Münchnone derivatives (e.g. pyrroles and imidazoles). The further development of this reaction is currently underway in the laboratory. It will be necessary to optimize a new Pd catalyst for this reaction.

3.5: EXPERIMENTAL

3.5.1: GENERAL CONSIDERATIONS

All manipulations were carried out in Vacuum Atmosphere 553-2 drybox under nitrogen atmosphere. Unless otherwise noted, all reagents were purchased from Aldrich and used without purification. Phosphine ligands were purchased from STREM chemicals. Carbon monoxide was supplied by MEGS (Matheson purity, 99.99%). All solvents were collected from an MBRAUN-SPS except acetonitrile which was distilled

from CaH_2 and degassed. Once collected, solvents were stored under nitrogen over activated molecular sieves inside the drybox. $Pd_2(dba)_3 \cdot CHCl_3$ was prepared using literature techniques.[10] Aldimines were prepared from the condensation of aldehyde and amine using brine as drying agent, then distilled under vacuum. Amide-chelated palladacycle catalysts were prepared by pretreating $Pd_2(dba)_3 \cdot CHCl_3$ with imine and acid chloride as previously reported.[11] Deuterated acetonitrile was stirred with CaH_2, vacuum transferred, degassed and stored over molecular sieves in the dry box. The products of these reactions, 3.6 and 3.11, have been previously reported.[6]

Nuclear magnetic resonance (NMR) characterization was obtained on Varian Mercury 200 MHz, 300 MHz, 400 MHz and Varian Unity 500 MHz spectrometers.

3.5.2: REACTION SETUP

All homogeneous catalyst reactions were set up in J-Young P.T.F.E. valve NMR tubes. Imidazoline products were characterized by *in situ* ^{1}H-NMR analysis in comparison to authentic material reported in chapter 2, at given time intervals. The reported yields were established in reference to benzyl benzoate which was included as internal standard. Quantities for J-Young reactions were measured as described in table footnotes. In general, reagents were combined in 800 μL CD_3CN, stirred until homogeneous, and transferred to the NMR tube. One freeze-pump-thaw cycle was carried out before pressurizing with 3.5 atm of CO.

The heterogeneous catalyst reactions (Table 2.1) were set up in 15 mL reaction bombs equipped with stirring in ca. 2 mL of acetonitrile. One freeze-pump-thaw cycle was carried out before pressurizing with 3.5 atm of CO. The NMR yield was again determined in reference to benzyl benzoate internal standard at given time points. The samples for yield analysis were prepared by removal of CO from the reaction by a freeze-pump-thaw cycle, transfer of the reaction to a drybox, then the solvent was removed *in vacuo*, and the residue was dissolved in CD_3CN.

---

(1) Dghaym, R. D.; Yaccato, K. J.; Arndtsen, B. A. *Organometallics* **1998**, *17,* 4.

(2) Kacker, S.; Kim, J. S.; Sen, A. *Angew. Chem. Int. Ed.* **1998,** *37,* 1251.

(3) Sun, H.; Zhang, J.; Liu, Q.; Yu, L.; Zhao, J. *Angew. Chem. Int. Ed.* **2007,** *46,* 6068.

(4) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004,** *126,* 468.

(5) Schoenberg, A.; Heck, F. F. *J. Org. Chem.,* **1974,** *39,* 3327.

(6) This and all yields for this appendix are assessed from ^{1}H NMR. The products reported herein are known. See: Dghaym, R. D.; Arndtsen, B. A. *Angew. Chem.* **2001,** *113,* 3328.

(7) In principle, a 2:1 ratio may still be feasible under highly concentrated conditions, assuming that the imine in solution plays no part in palladium black formation.

(8) While allylpalladium chloride dimer is a viable catalyst, its mode of activation is through allylation of the phosphine ligand, yielding Pd(0). Thus, if it is to be used as catalyst, a 4:1 ratio of phosphine to allylpalladium chloride dimer should be used. This is not suggested, however, since the byproduct phosphonium salt [^{31}P-NMR (CD_3CN): δ 46.6ppm] is difficult to remove from the product. For analogous allyl palladium chloride activation, see: Soheili, A.; Albanese-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4129.

(9) Protonated phosphine, δ 32.0 ppm was also observed.

(10) Ukai, T.; Kawazura, H.; Ishii, Y. *Journal of Organometallic Chemistry* **1974,** *65,* 253.

(11) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J Am. Chem. Soc.* **2003,** *125,* 1474.

APPENDIX A: REACTIVITY AND FUNCTIONALIZATION OF IMIDAZOLINIUM CARBOXYLATES

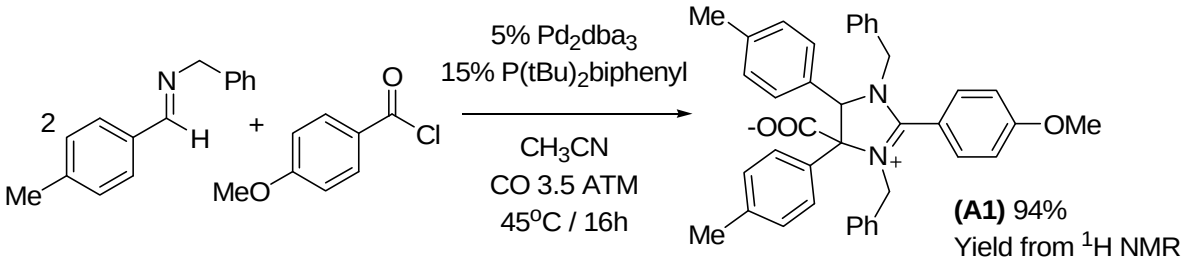
A.1: INTRODUCTION

During the course of the research that composes Chapter 2 of this thesis, a number of serendipitous discoveries were made involving the imidazolinium carboxylate products. Three of such observations will be discussed in this appendix. These involve the decarboxylation or aromatization of imidazolinium carboxylate, and the formation of imidazolinium derivatives. In addition, a new route to construct imidazolines directly from Münchnones is described.

A.2: DECARBOXYLATION AND AROMATIZATION OF IMIDAZOLINIUM CARBOXYLATES

A.2.1: INITIAL OBSERVATIONS

The imidazolinium carboxylate products reported in Chapter 2 are zwitterionic heterocycles (Scheme A.1). This results from the lack of CO_2 elimination upon the cycloaddition of protonated imines with Münchnones. Such decarboxylations are commonly seen with other dipolarophiles, such as alkynes, alkenes, or *N*-tosyl imines.[1] In the case of protonated imine cycloaddition, the products are neither neutral organic compounds, nor true salts. As such, their purification presents unusual challenges. In our original 2001 publication, the precipitation of these products from diethylether was reported as the sole method of purification. While this method works well for imidazolinium carboxylates where aromatic groups dominate the substituents, simple changes in structure can result in full or partial ether solubility. In addition, the phosphine ligand used to accelerate the formation of imidazoline carboxlates in Chapter 2 generates an unidentified phosphine derivative that precipitates with, or better than, the product.[2] While we eventually determined that washing of the crude reaction mixture with a saturated NaCl solution could convert this product into an ether soluble free phosphine, in the meantime, other purification protocols (e.g. column chromatography, product derivitization) were probed. These either failed outright or led to unexpected results described below.



Scheme A.1: The Synthesis of Imidazoline Carboxylate A1

In normal phase column chromatography with silica or alumina as the stationary phase, the extreme polarity of these molecules was problematic. For example, the use of pure methanol as elutant did allow the isolation of **A1** as analytically pure product, though in low yield.[3] Interestingly, the use of other elutants that could move the product on silica ($CHCl_3$ or 5% TFA in EtOAc), or water/methanol gradients on reverse phase C-18 silica, often led to the isolation of imidazolinium carboxylate with a second unknown compound. The same unknown compound was observed as a trace impurity in isolated **A1** samples that were allowed to stand in $CDCl_3$ solution for several days. This compound was eventually identified as the decarboxylated product **A2**.

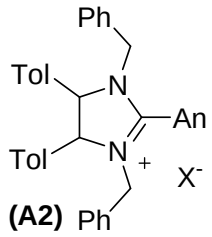
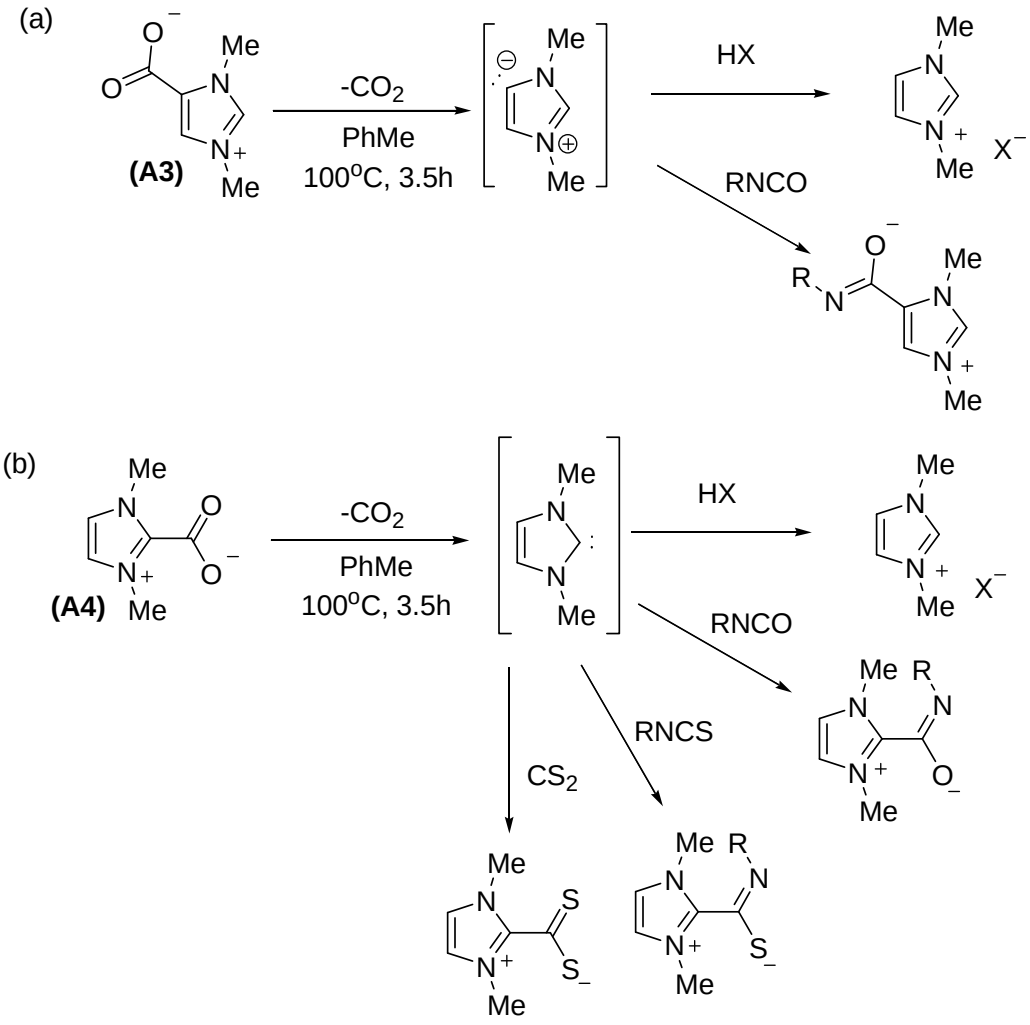


Figure A.1: The Structure of the Decarboxylated Product A2

A.2.2: LITERATURE PRECEDENCE FOR DECARBOXYLATION

While there is little precedence for imidazolinium carboxylates reported in Chapter 2, aside from our own work, reports do suggest that the analogous imidazolium carboxylates can undergo thermal decarboxylation under the correct conditions. Perhaps the most relevant of these is a report of transformations of norzooanemonine and a constitutional isomer thereof. Norzooanemonine **A3** is an alkaloid isolated from the marine sponge *Cacospongia scalaris*. It is an imidazolium 4-carboxylate that undergoes

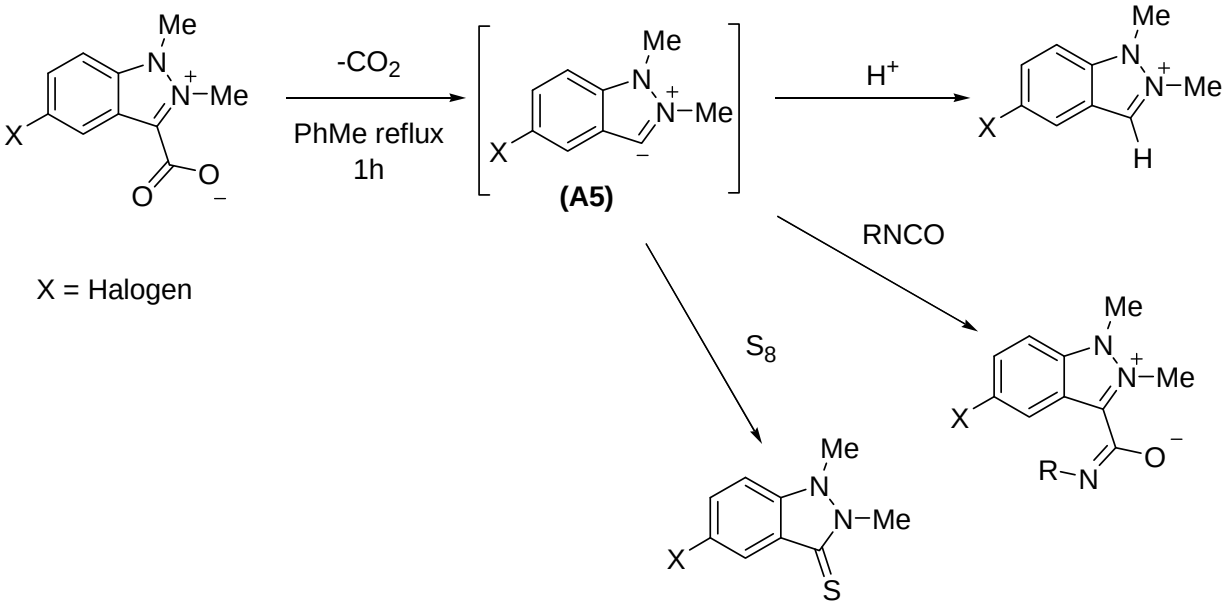
loss of CO_2 to yield an N-heterocyclic carbene upon heating to 100 °C in toluene (Scheme A.2a).[4] The 2-carboxylate isomer of Norzooanemonine, **A4**, has been demonstrated to undergo the same transformation (Scheme A.2b). These carbene products can be trapped with various electrophiles in good yields, including H^+, CS_2, thioisocyanate, and isocyanate (Scheme A.2).



Scheme A.2: (a) Decarbonylative trapping reactions of norzooanemonine. (b) Trapping of the carbene formed on thermal decomposition of imidazolium 2-carboxylate.

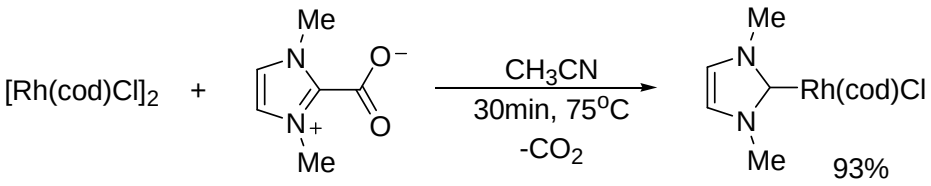
This carbon dioxide extrusion from mesoionic betaine molecules extends to other heterocycle cores. For example, CO_2 loss from various indazolium-3-carboxylates[5] leads

to the generation of **A5**, which can be trapped with acid, molecular sulfur, isocyanates (Scheme A.3).



Scheme A.3: Decarboxylation of indazolium carboxylates

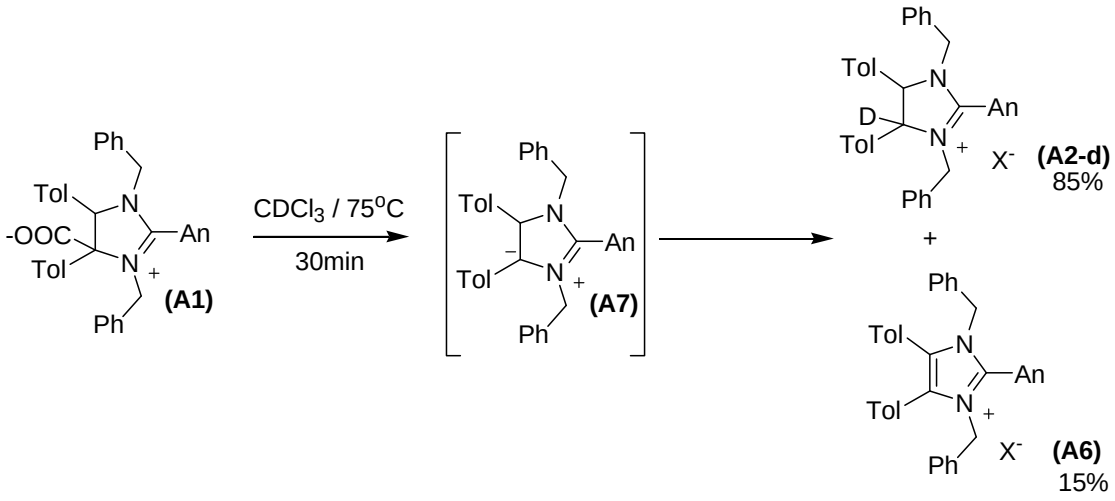
There also exists precedence for CO_2 loss from 2-imidazolium carboxylates in the orgamometallic literature. For example, both Crabtree[6] and Delaude[7] have demonstrated that metal N-heterocyclic carbene complexes can be synthesized from imidazolium 2-carboxylates and appropriate metal salts (Scheme A.4). These transformations are demonstrated to proceed under relatively mild conditions, without the need strong bases (which are typically needed to deprotonate N-heterocyclic carbene precursors). This diverges from the previously mentioned decarboxylations because here the imidazolium carboxylate is the active N-heterocyclic carbene (NHC) transferring reagent. The authors did not find evidence for a free NHC intermediate.



Scheme A.4: Decarboxylation and coordination to transition metal complexes

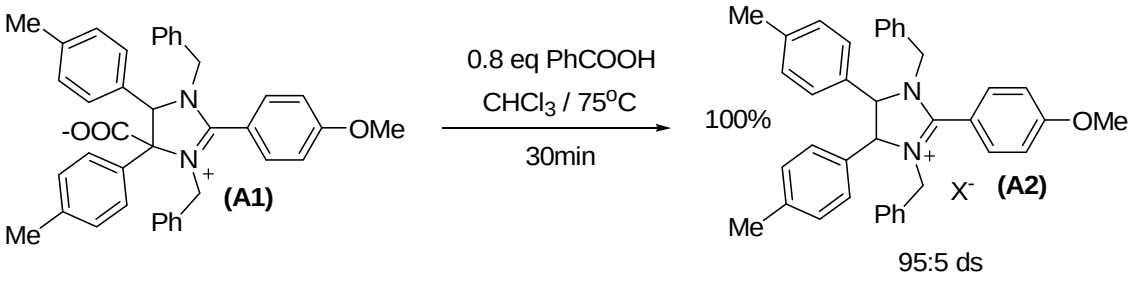
A.2.3: SYNTHESIS OF 4,5-DIHYDROIMIDAZOLINIUM SALT A2

Heating imidazolinium carboxylate **A1** in $CDCl_3$ leads to its quantitative decarboxylation (Scheme A.5). 4,5-Dihydroimidazolinium **A2-d** is the major product of this reaction along with traces of the aromatized product **A6**. Similar results are obtained when $CHCl_3$ is used, only **A2** is formed without deuterium incorporation. Interestingly, chloroform appears to be a relatively unique solvent for mediating this reaction. Heating of **A1** in CD_2Cl_2 at 50 °C results in only trace **A2**, while **A1** is completely stable when heated in D_2O, CD_3OD, or CD_3OD with stoichiometric trifluoroacetic acid.



Scheme A.5: Initial Decarboxylation Reaction

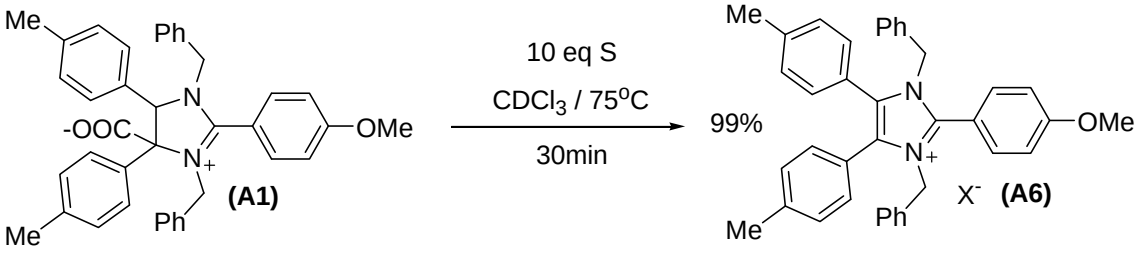
In considering potential mechanisms for this decarboxylation, it seems likely that thermal CO_2 loss leads to the formation of the azomethine ylide intermediate **A7**. Protonation of **A7** would lead to **A2** and suppress the formation of the aromatized product **A6**. To probe this effect, benzoic acid was added to the thermal decarboxylation reaction of **A1** (Scheme A.6). This leads to the quantitative formation of **A2** as a mixture if diastereomers (ca. 95:5, similar to in Scheme A.5). While steric demands suggest that protonation of the intermediate carbanion on **A7** would preferentially provide the *trans*-isomer, further studies are needed to confirm the identity of the major isomer.



Scheme A.6: The Synthesis of Imidazolinium Salt A2

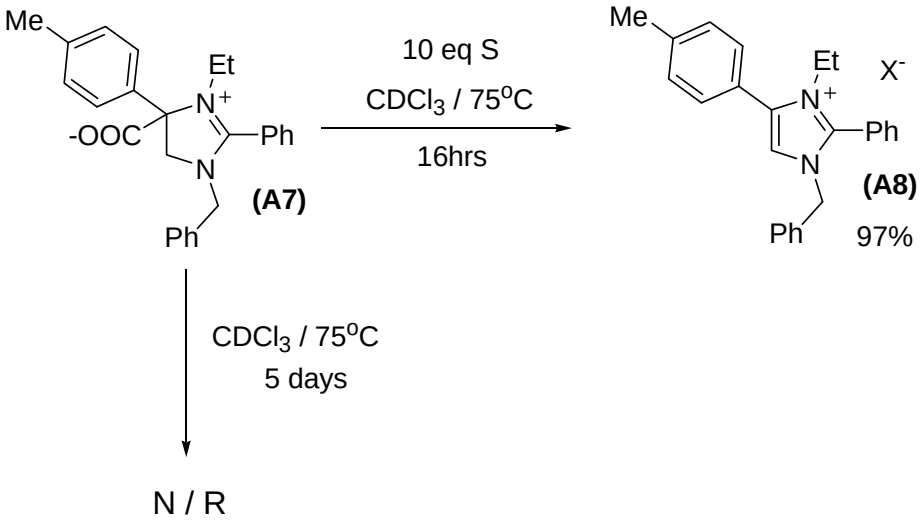
A.2.4: SYNTHESIS OF IMIDAZOLIUM SALT A6

In contrast to the above, the aromatized heterocycle **A6** can be obtained as the sole product by including a stoichiometric oxidant in the thermal decarboxylation of **A1** (Scheme A.7). Molecular sulfur was found to work well, providing near quantitative formation of **A6**. It is possible that decarboxylation is ensued by hydride abstraction by molecular sulfur to yield the aromatic heterocycle. SH_2 would be lost as byproduct.



Scheme A.7: The Synthesis of Imidazolium Salt A6

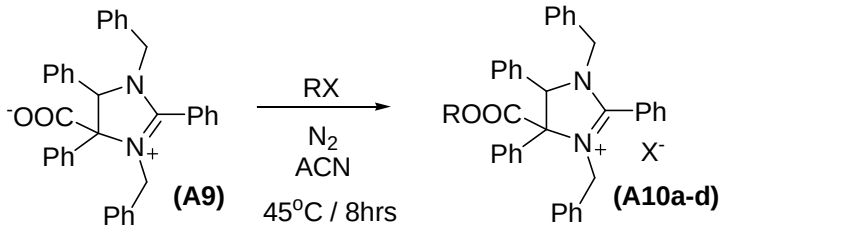
The scope, limitations and mechanism of this novel decarboxylation are presently unknown, though there are structural demands that will certainly dictate which imidazolinium carboxylates will undergo either decarboxylation or aromatization. As a brief example, imidazolinium **A7** is able to undergo aromatization to **A8** with sulfur, but will not form the dihydroimidazolium product, even on extended heating in chloroform (Scheme A.8). The reason for this observation is not known at present.



Scheme A.8: Successful Aromatization and Attempted Decarboxylation of A7

A.3: DERIVATIZATION OF IMIDAZOLINIUM CARBOXYLATES

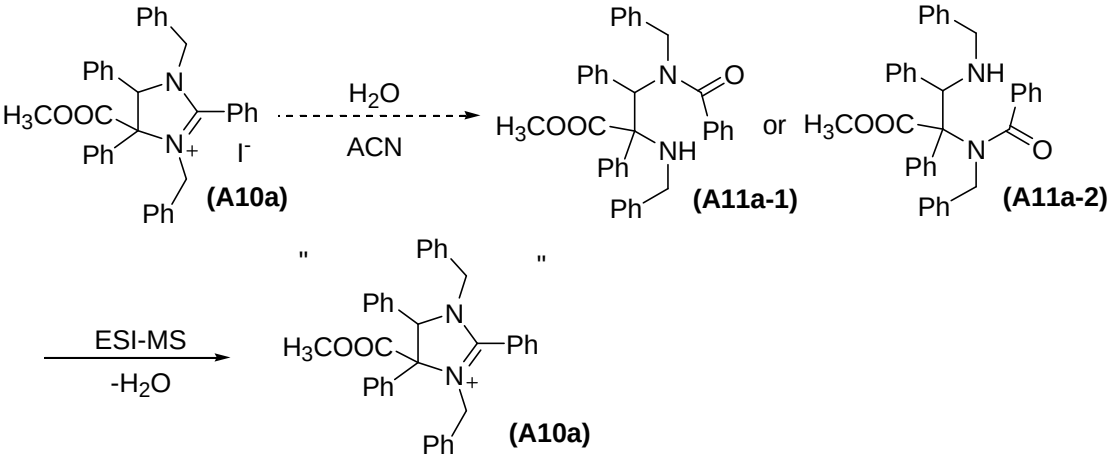
While probing the chemistry and isolation of the imidazolinium carboxylates, we also examined the conversion of these products to other derivatives. For example, esters of imidazoline carboxylate **A9** can be prepared by the simple addition of alkyl halides and heating at 45 °C in acetonitrile. Based on ^{1}H NMR data, **A9** was observed to react with methyl iodide, 1-propyl iodide, 2-propyl iodide, and benzyl bromide, providing esters **A10a-d** in 77-100% yield (Scheme A.9). Partial spectral data for these *in situ* observed products are tabulated in the experimental section.



A10a R = Me X = I 98%
A10b R = iPr X = I 77%
A10c R = nPr X = I 90%
A10d R = Bn X = Br 98%

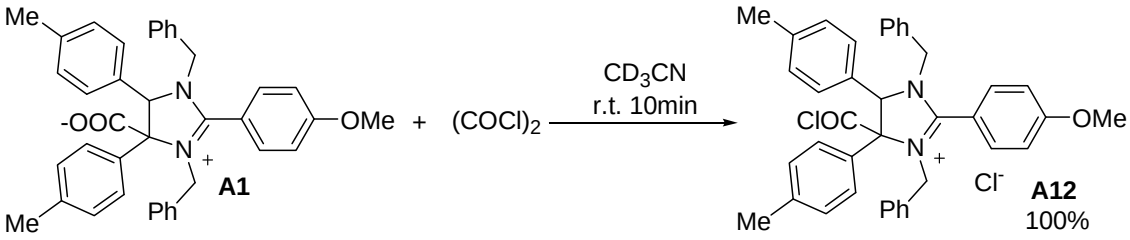
Scheme A.9: The Formation of Imidazolinium Esters

Interestingly, exposure of the **A10** products to atmospheric conditions resulted in dramatic changes in the ^{1}H NMR spectra. For example, the benzylic resonances of **A10a** [δ 5.80 (d, 1H), 4.45 (d, 1H)] shifts to [δ 4.71-4.80 (dd, 2H)], the methyl ester resonance shifts from δ3.48 (s, 3H) to δ3.34 (s, 3H), and the ring hydrogen moves from δ 5.85 to δ 6.55. One possibility is that exposure of **A10a** to air leads to hydrolysis of the amidinium N-C-N cationic structure to provide **A11a** (Scheme A.10). However, the data obtained from mass spectrometry did not support the putative assignment, and instead gives only the mass of the imidazolinium methyl ester. The expected hydrolysis product is not observed. While it is conceivable that loss of water is the mode of ionization in electrospray ionization, at present these ester products have not been fully characterized.



Scheme A.10: Possible Hydrolysis Product of A10a

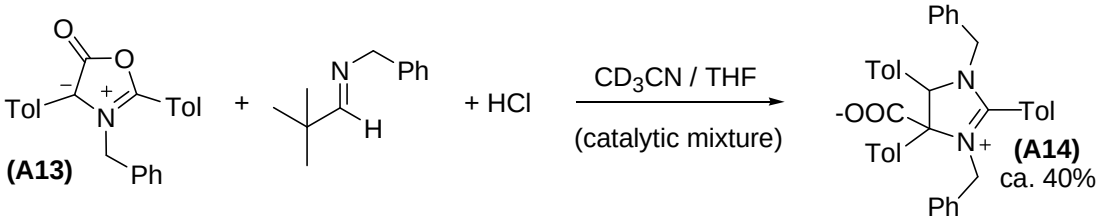
Finally, preliminary studies also suggest that the imidazolinium carboxylate **A1** can react readily with oxalyl chloride to yield the imidazolinium acid chloride **A12** (Scheme A.11). While the chemistry of **A12** has not been probed, this could provide an alternate route to generate esters, with substituents otherwise unavailable from alkyl electrophiles (e.g. phenyl or *tert*-butyl substitution). Alternatively, the acid chloride could be reacted with other nucleophiles to arrive at aldehyde, amide, or other functional groups (See Section A.5).



Scheme A.11: The Formation of Imidazolinium Acid Chloride A12

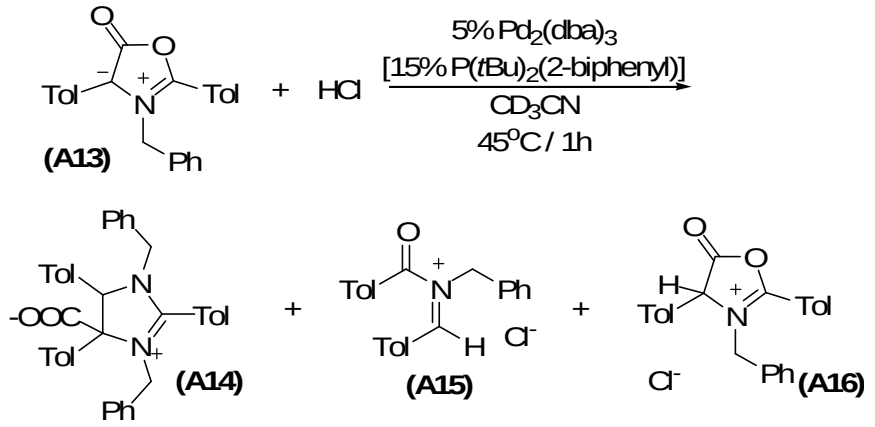
A.4: THE CONVERSION OF MÜNCHNONE TO IMIDAZOLINE CARBOXYLATE

During the course of trying to form imidazolines with less reactive, sterically encumbered imines (e.g. *i*PrN=C(H)Tol and EtN=C(H)*o*-BrPh), it was observed that small amounts (ca. 10-25%) of the homocoupled imidazoline carboxylate would form in the reaction. This occurred despite the fact that all of the first imine was consumed (as Münchnone) before adding the second imine with catalytic acid. In many cases, a mixture of hetero- and homo-coupled products would form in solution, however, in extreme cases (Scheme A.12) only the homocoupled product could be observed by *in situ* ^{1}H-NMR analysis.



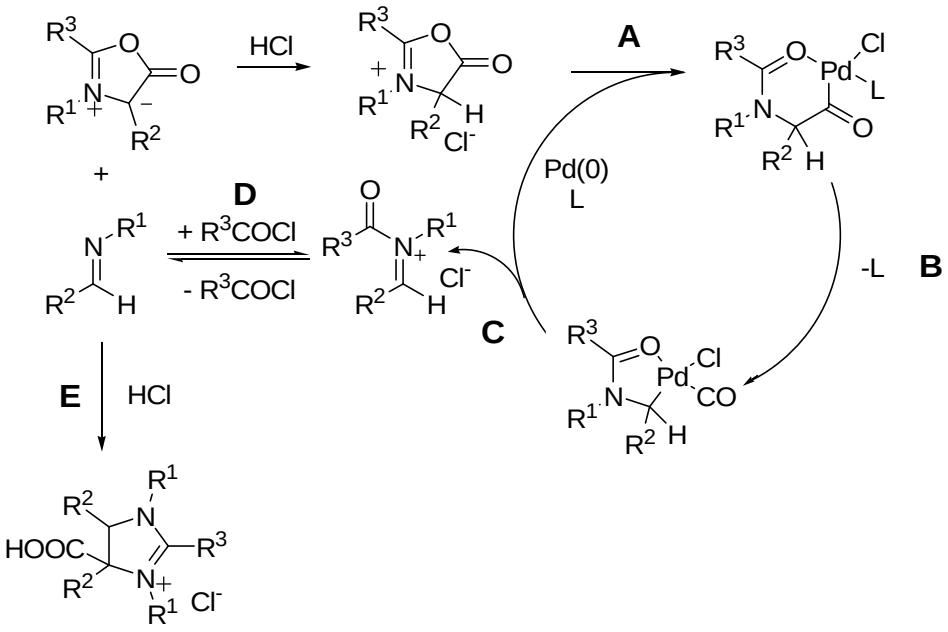
Scheme A.12: Formation of Homocoupled Imidazoline A14 in the Presence of Nonreactive Dipolarophile

In an attempt to determine the cause for this perplexing observation, a number of control reactions were carried out. The most relevant of which was the addition of catalytic acid to purified Münchnone in the presence of a Pd(0) catalyst (Scheme A.13).[8] It was observed that under these simulated cycloaddition conditions, in the absence of dipolarophile, Münchnone **A13** was converted to a mixture of imidazoline carboxylate **A14** and iminium salt **A15**.[9]



Scheme A.13: Decarbonylation of Münchnone A13

A postulated mechanism for the pathway leading to **A14-16** is shown in Scheme A.14. It is proposed that protonated Münchnone undergoes oxidative addition onto Pd(0) (step A), deinserts CO (step B), then reductively eliminates iminium salt (step C) (i.e. the microscopic reverse of catalytic Münchnone formation). Iminium salt then releases imine (step D) which can react with Münchnone to yield imidazoline carboxylate (step E).

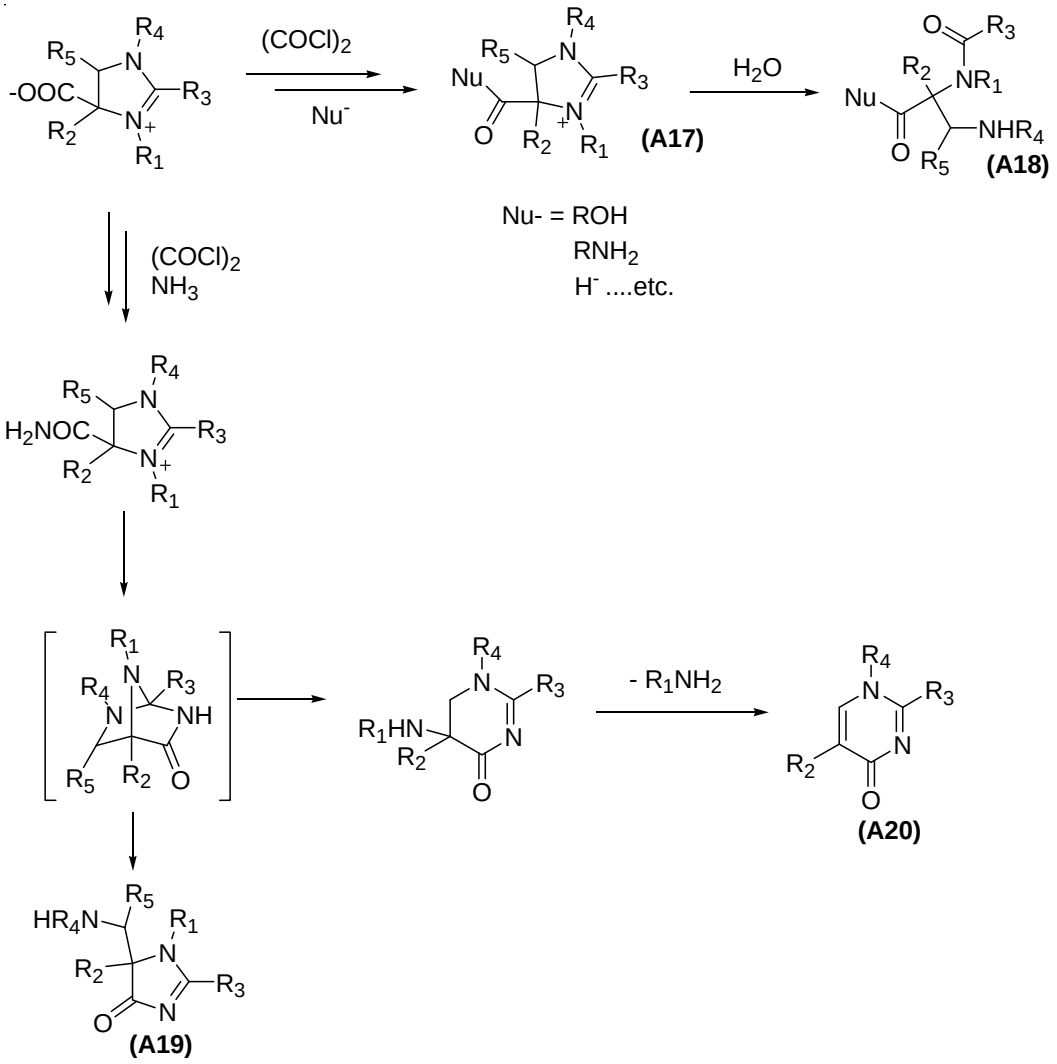


Scheme A.14: Postulated Mechanism for CO loss from Münchnones

Overall these data suggest that the palladium catalyzed formation of Münchnone is reversible, and, in the presence of acid and the absence of CO can lead back to imine, acid chloride and CO. From an imidazoline carboxylate synthesis perspective, this suggests that the removal of the palladium catalyst may be necessary to allow the cycloaddition of Münchnones with less reactive imine dipolarophiles.

A.5: OUTLOOK AND SUGGESTIONS FOR FUTURE WORK

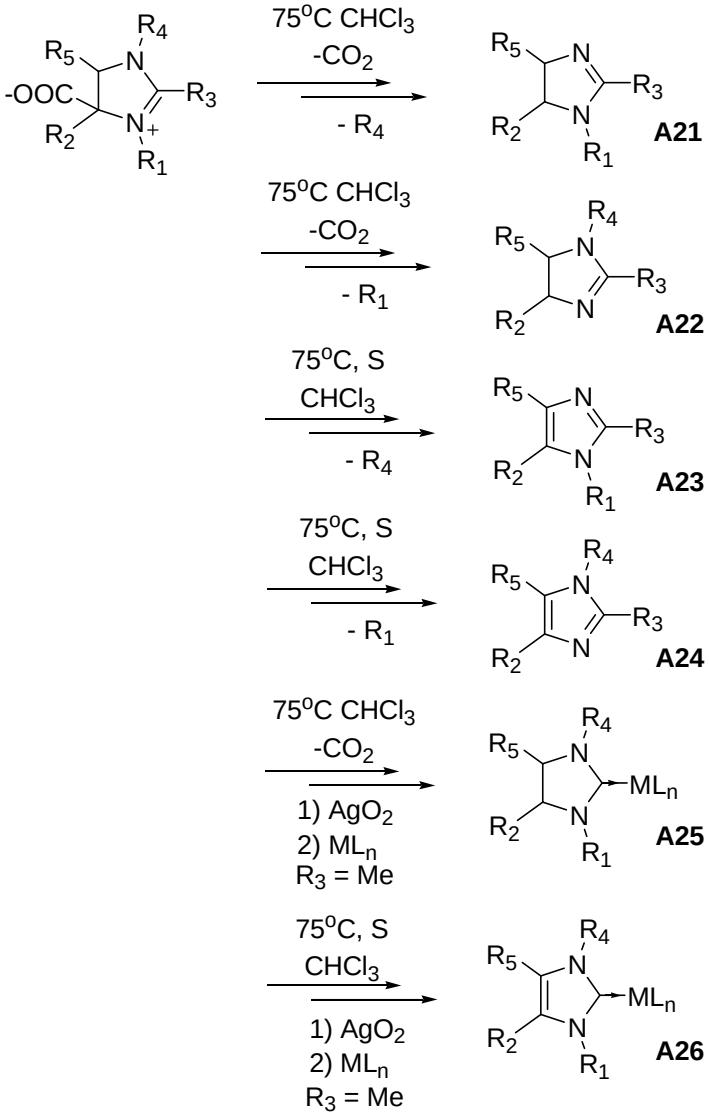
The above studies suggest that imidazolinium carboxylates can act as versatile building blocks for other products. Considering the ease with which these imidazolinium carboxylates are generated (via the Pd catalyzed coupling of imines, acid chlorides and carbon monoxide), these could provide efficient syntheses of a range of products. For example, in addition to imidazolinium esters, amides, and other derivatives of the form **A17**, hydrolysis of these products would provide an overall synthesis of ß-amino-α-amido carboxy products **A18** (Scheme A.15). Alternatively, the reaction of the imidazolinium acid chloride with ammonia or an ammonia equivalent (e.g. HMDS) would provide a nucleophilic primary amide. Literature precedent[10] suggests this amide would attack the electrophilic amidine moiety which could rearrange the imidazolinium core to provide highly substituted imidazolinones **A19** or pyrimidines **A20** (Scheme A.15)**.**



Scheme A.15: A Potential Route into Imidazoline Carboxylate Derivatives

In addition, observations made in section A.2 suggest that imidazolinium carboxylate can provide a route to generate imidazolines **A21** & **A22** and imidazoles **A23** & **A24** via deprotection of the imidazolinium and imidazolium products obtained from decarboxylation or decarboxylation-aromatization respectively (Scheme A.16). Alternatively, deprotection of the amidine central carbon instead of the pendant nitrogen groups as suggested by Crabtree (R = CH_3),[11] will provide a route to imidazolinium **A25** or imidazolium **A26** salts well suited for use as N-heterocyclic carbene ligands. As above, the coupling of these reactions with the initial multicomponent synthesis of

imidazolinium carboxylates like **A1** could provide both straightforward and easily diversified routes to each of these products.



Scheme A.16: Imidazoline Carboxylates as Building Blocks Imidazolines, Imidazoles, Imidazolinium Salts and Imidazolium Salts

A.6: EXPERIMENTAL

A.6.1: GENERAL CONSIDERATIONS

All manipulations were carried out in Vacuum Atmosphere 553-2 drybox under nitrogen atmosphere. **A1** and **A9** were prepared as described in Chapter 2. All decarboxylation, aromatization and derivitization reactions were performed in either Teflon septum equipped screw-cap NMR tubes or sealed 20mL scintillation vials with magnetic stirring. Heating was carried out outside the drybox in oil baths set to appropriate temperature. Spectroscopic data was obtained as described in Chapter 2, except low resolution ESI-MS which was collected on an Agilent LC-MS.

A.6.2: SYNTHESIS OF 4,5-DIHYDROIMIDAZOLINIUM SALT A2

Imidazolinium carboxylate **A1** (52 mg, 0.09 mmol) and benzoic acid (11 mg, 0.09 mmol) were dissolved in 5mL $CHCl_3$ and heated overnight at 75 °C. The solution was washed with concentrated sodium chloride, dried on $MgSO_4$, and the solvent removed *in vacuo*, providing **A2** in 100% yield as a 95:5 mixture of diastereomers.

A1 ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70-7.60 (m, 20H), 6.32-6.45 (d, 2H), 5.44 (s, 1H), 4.40 (d, 1H), 4.42 (d, 1H), 4.29 (d, 1H), 3.9 (d, 1H), 3.85 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100.62 MHz, CD_2Cl_2): δ 165.8, 165.2, 162.4, 139.1, 138.6, 137.5, 136.3, 132.6, 131.6, 129.7, 129.3, 129.2, 129.1, 128.9, 128.7, 128.5, 128.3, 128.0, 127.1, 115.3, 115.1, 114.9, 93.4, 72.3, 55.7, 50.8, 49.0, 21.2, 20.8.

A2 Major isomer, ^{1}H NMR, (500 MHz, $CDCl_3$): δ 8.15 (m, 2H), 7.06-7.39 (m, 10H), 6.80-7.0 (m, 4H), 4.91 (s, 2H), 4.71-4.82 (d, 2H), 4.21-4.31 (d, 2H), 3.95 (s, 3H) 2.33 (s, 6H). Minor isomer (ca. 5%): δ4.65 (d, 2H), 4.40 (d, 2H). ^{13}C NMR (125.71 MHz, $CDCl_3$): δ 167.3, 163.7, 140.4, 132.7, 131.9, 131.7, 130.7, 129.4, 129.1, 128.7, 128.3, 116.4, 113.3, 71.7, 56.3, 50.8, 21.5.

A.6.3: SYNTHESIS OF IMIDAZOLIUM SALT A6

Imidazolinium carboxylate **A1** (52 mg, 0.09 mmol) and sulfur (29 mg, 0.9 mmol) were combined in 5 mL $CHCl_3$ and heated overnight at 75 °C. The reaction mixture was cooled to room temperature, eliciting precipitation of sulfur. The mixture was filtered

through celite, dried over $MgSO_4$ and concentrated *in vacuo* to provide off white solid **A6** in 99% yield.

A6 ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, 2H), 7.34 (d, 4H), 7.25 (m, 4H), 7.02, (d, 4H), 6.93 (d, 2H), 6.73 (d, 4H), 5.25 (s, 4H), 3.75 (s, 3H), 2.21 (s, 6H). ^{13}C NMR (125.71 MHz, $CDCl_3$): δ 162.6, 145.6, 140.3, 134.6, 133.1, 132.9, 131.4, 129.7, 129.0, 128.4, 127.1, 122.8, 115.2, 113.9, 55.7, 50.72, 21.6.

A.6.4: SYNTHESIS OF IMIDAZOLIUM SALT A8

A8 was prepared in the same manner as **A6**. ^{1}H NMR (500 MHz, DMSO, 100 °C): δ 7.96 (s, 1H), 7.05-6.80 (m, 14H), 5.22 (s, 2H), 4.03 (q, 2H), 2.25 (s, 3H), 1.01 (t, 3H) HRMS Calculated (M+): 353.20122 Observed: 353.20104.

A.6.5: SYNTHESIS OF IMIDAZOLINIUM ESTERS A10A-D

Inside a glovebox, imidazolinium carboxylate **A9** (15.7 mg, 0.02 mmol) was dissolved in 800μL CD_3CN in a screw-cap NMR tube, and the electrophile (0.06 mmol) was added. The reaction was sealed and heated at 45 °C for 3 hours to afford the ester products. ^{1}H-NMR data is provided for the *in situ* observed esters below. On completion of the reaction, solvent was removed *in vacou,* and the residue washed with hexanes as to remove excess alkyl halide. The crude product was then redissolved in $CDCl_3$ outside of the glovebox. ^{1}H NMR analysis of these compounds after exposure to atmosphere gave unexpected results (**A11a-d)** as tabulated below.

A10a (Crude Yield 100%) ^{1}H NMR (300 MHz, CD_3CN): δ 7.34-7.65 (m, 19H), 7.01-7.08 (m, 4H), 6.60-6.65(d, 2H), 5.85 (s, 1H), 4.80 (d, 1H), 4.65 (d, 1H), 4.43 (d, 1H), 4.18 (d, 1H), 3.25 (s, 3H).

A11a ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, 1H), 7.78 (d, 2H), 7.62 (m, 1H), 7.33-7.59 (m, 6H), 7.15-7.32 (m, 8H), 6.98-7.08 (m, 3H), 6.88 (d, 2H), 6.65 (d, 2H), 6.55 (s, 1H), 4.65-4.82 (dd, 2H), 4.70 (d, 1H), 4.35 (d, 1H), 3.54 (s, 3H). Low Res MS calculated for **A10a**: 537.3 **A11a**: 554.3 Found **A10a**: 537.3 **A11a**: Not observed.

A10b (Crude Yield 77%) ^{1}H NMR (300MHz, CD_3CN): δ 7.02-7.65 (m, 23H), 7.70 (d, 2H), 5.82 (s, 1H), 4.93 (d, 1H), 4.60 (d, 1H), 4.45 (m, 1H), 4.42 (d, 1H), 4.09 (d, 1H), 1.05 (d, 3H), 0.62 (d, 3H).

A11b ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85-7.9 (m, 23H), 6.65 (d, 2H), 6.39 (s, 1H), 4.72-4.80 (dd, 2H), 4.63 (m, 1H), 4.55 (d, 1H), 4.35 (d, 1H), 1.10 (d, 3H), 0.58 (d, 3H).

A10c (Crude Yield 90%) ^{1}H NMR (300 MHz, CD_3CN): δ 7.00-7.65 (m, 23H), 6.65 (d, 2H), 5.86 (s, 1H), 4.8 (d, 1H), 4.65 (d, 1H), 4.42 (d, 1H), 4.15 (d, 1H), 3.87 (m, 1H), 3.24 (m, 1H), 1.25 (m, 2H), 0.69 (t, 3H).

A11c ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82-7.95 (m, 23H), 6.41 (s, 1H), 4.72 (d, 1H), 4.70 (d, 1H), 4.61 (d, 1H), 4.32 (d, 1H), 3.92 (m, 1H), 2.24 (m, 1H), 1.21 (m, 1H), 0.62 (t, 1H).

A10d (Crude Yield 100%) ^{1}H NMR (300 MHz, CD_3CN): δ 6.95-7.61 (m, undetermined due to excess BnBr), 6.62 (d, 2H), 5.95 (s, 1H), 5.05 (d, 1H), 4.79 (d, 1H), 4.60 (d, 1H), 4.40 (d, 1H), 4.35 (d, 1H), 4.14 (d, 1H).

A11d ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70-8.28 (m, 26H), 5.15 (d, 1H), 4.92 (d, 1H), 4.79 (d, 1H), 4.63 (d, 1H), 4.30-4.39 (dd, 2H), 4.24 (d, 1H).

A.6.6: SYNTHESIS OF IMIDAZOLINIUM ACID CHLORIDE A12

Imidazolinium carboxylate **A1** (30 mg, 0.05 mmol) was treated oxalyl chloride (4 mg, 0.06 mmol) in 2mL acetonitrile inside the glovebox. After 30 minutes, the solvent was removed *in vacuo*. ^{1}H-NMR analysis suggests the formation of imidazolinium acid chloride.

A12 ^{1}H NMR (500 MHz, CD_3CN): δ 6.76-7.58 (m, 20H), 6.63 (d, 2H), 6.25 (s, 1H), 4.87 (d, 1H), 4.70 (d, 1H), 4.45 (d, 1H), 4.25 (d, 1H), 3.82 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H).

A.6.7: DECOMPOSITION OF MÜNCHNONE A13

Munchnone **A13** was prepared and isolated as described elsewhere.[12] Inside a glovebox, Münchnone **A13 (**15 mg, 0.04 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.02 mg, 0.02 mmol) was dissolved in 800μL CD_3CN in a teflon septum equipped screw-cap NMR tube. Outside of the glovebox, via microsyringe, HCl was added as a 2M solution in

diethyl ether (20 μL, 0.04 mmol). ^{1}H-NMR was observed before addition of HCl, after 10 minutes and after 1 hour.[13] This reveals the formation of protonated Munchnone **A16** (ca. 40%), imidazoline carboxylate **A14** (ca. 30%) and iminium salt **A15** (ca. 30%).

---

(1) Gribble, G. W. *Chapter 4: Mesoionic Oxazoles. In* The Chemistry of Heterocyclic Compounds, Volume 600: Oxazoles: Synthesis, Reactions and Spectroscopy, Part A. **2003** John Wiley & Sons, Inc.

(2) This compound is likely P(*t*Bu)$_2$(2-biphenyl)Pd(COPh)Cl (^{31}P NMR (CD_3CN, 200MHz): δ 53.4ppm). The control reaction of $Pd_2(dba)_3$, Ph(CO)Cl and P(*t*Bu)$_2$(2-biphenyl) gives identical spectroscopic properties by ^{31}P NMR.

(3) Methanol as elutant resulted in considerable loss as the compounds generally elute very slowly from the solid support, over many fractions. 3-5% TFA in EtOAc eluted product from silica though loss of CO_2 was observed ranging from 40-50%. Reverse phase chromatography was tried on C-18 silica, but it too gave a complex mixture of decarboxylated and parent compound. $CHCl_3$ would slowly elute product from silica. Here too, the fractions collected gradually turned from the decarboxylated product to the parent compound, with considerable overlap. The most polar fractions were generally pure imidazoline carboxylate. Using this approach, 50% decarboxylation was typical.

(4) Schmidt, A.; Beutler, A.; Albrecht, M.; Snovydovych, B.; Ramírez, F. J. *Org. Biomol. Chem.* **2008,** *6,* 287.

(5) Schmidt, A.; Snovydovych, B.; Habeck, T.; Dröttboom, P.; Gjikaj, M.; Adam, A. *Eur. J. Org. Chem.* **2007,** 4909.

(6) Voutchkova, A. M.; Appelhans, L. N. ; Chianese, A. R.; Crabtree, R. H. *J. Am. Chem. Soc.* **2005,** *127,* 17624. Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2007,** *129,* 12834.

(7) Tudose, A.; Demonceau, A.; Delaude, L. *Journal of Organometallic Chemistry* **2006,** *691,* 5356.

(8) This process was observed to proceed in the presence and absence of phosphine ligand.

(9) Protonated Münchnone was prepared independently, and is stable in the absence of Palladium.

(10) Drabina, P.; Sedlák, M.; Růžička, A.; Malkov, A. V.; Kočovský, P. *Tetrahedron: Assymetry* **2008,** *19,* 384.

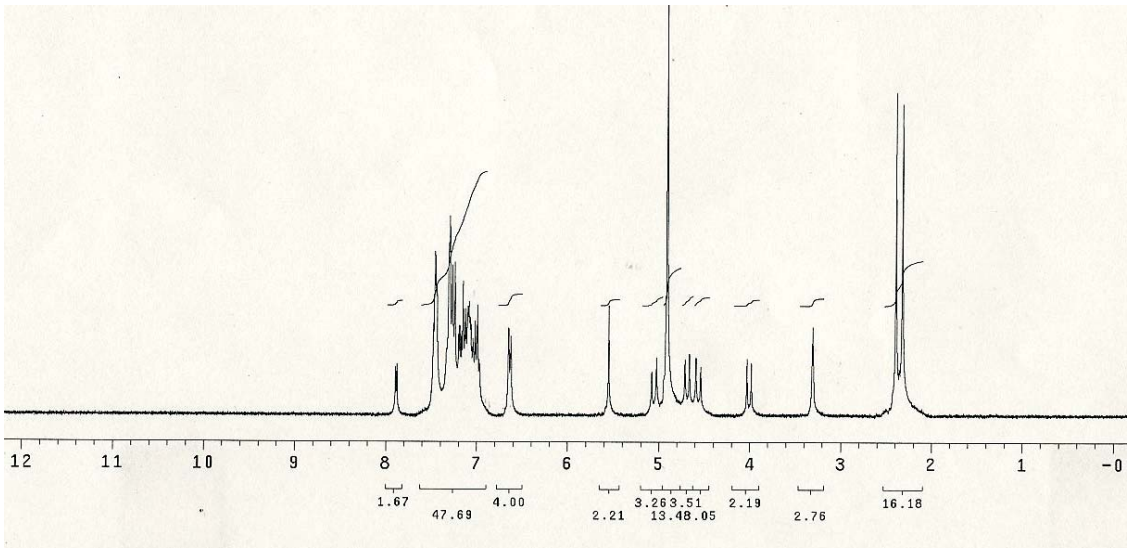
(11) Chianese, A. R.; Zeglis, B. M.; Crabtree, R. H. *Chem. Commun.* **2004,** 2167.

(12) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J Am. Chem. Soc.* **2003,** *125,* 1474.

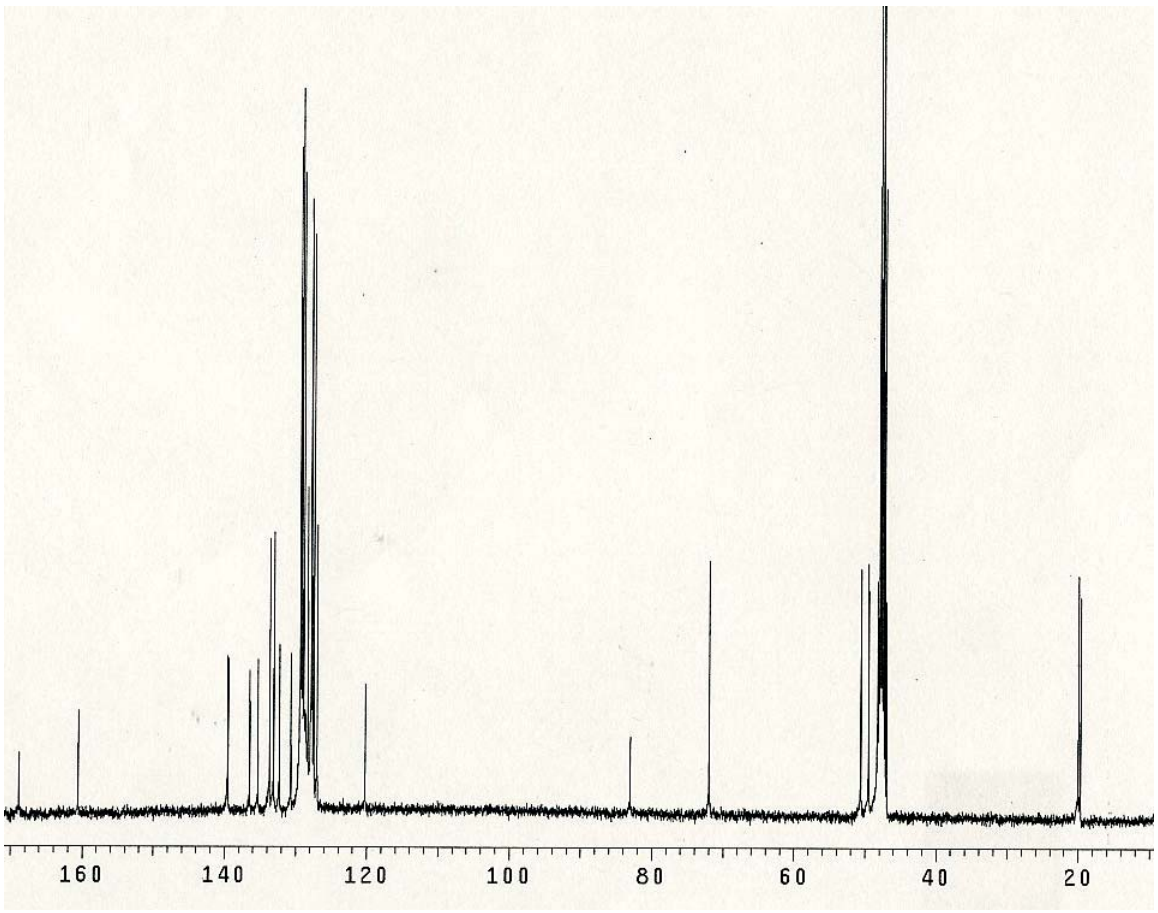
(13) Components **A14-16** were identified based on independently performed control reactions.

APPENDIX B: SPECTRA FOR COMPOUNDS FROM CHAPTER 2 AND APPENDIX A

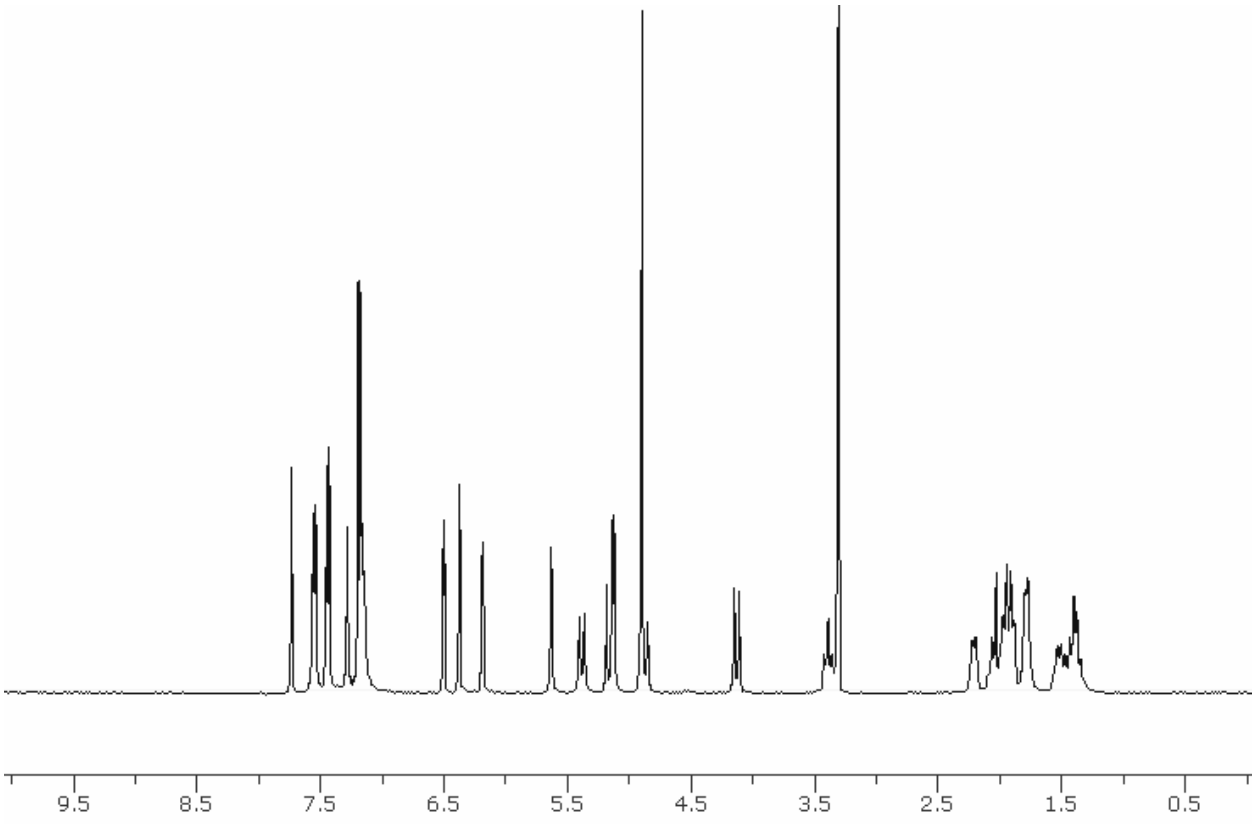
Compound 2.4d ^{1}H-NMR:



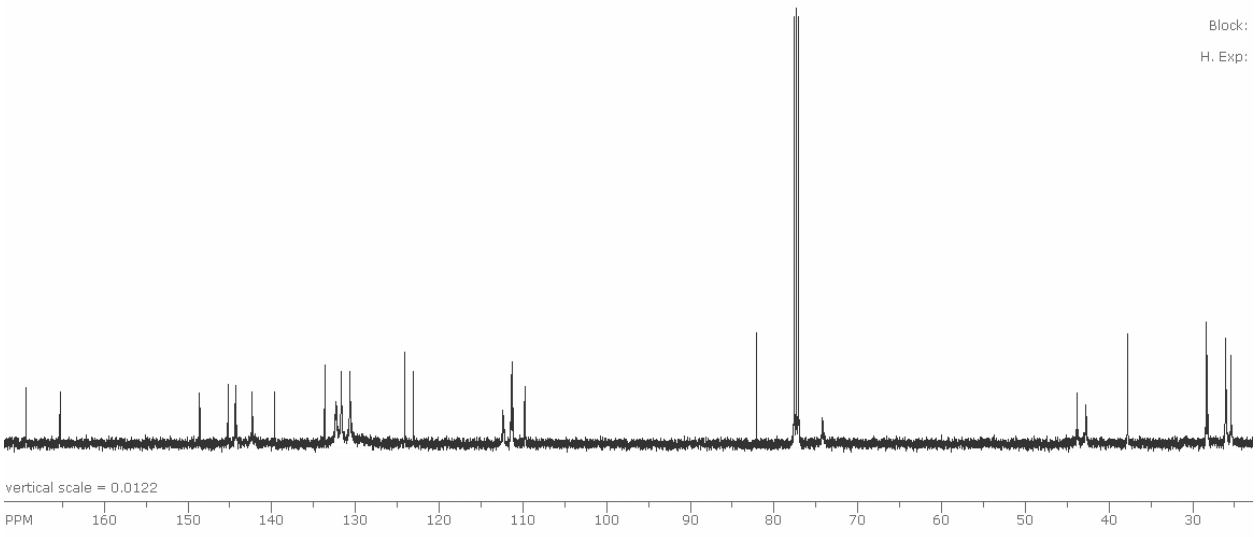
Compound 2.4d ^{13}C-NMR:



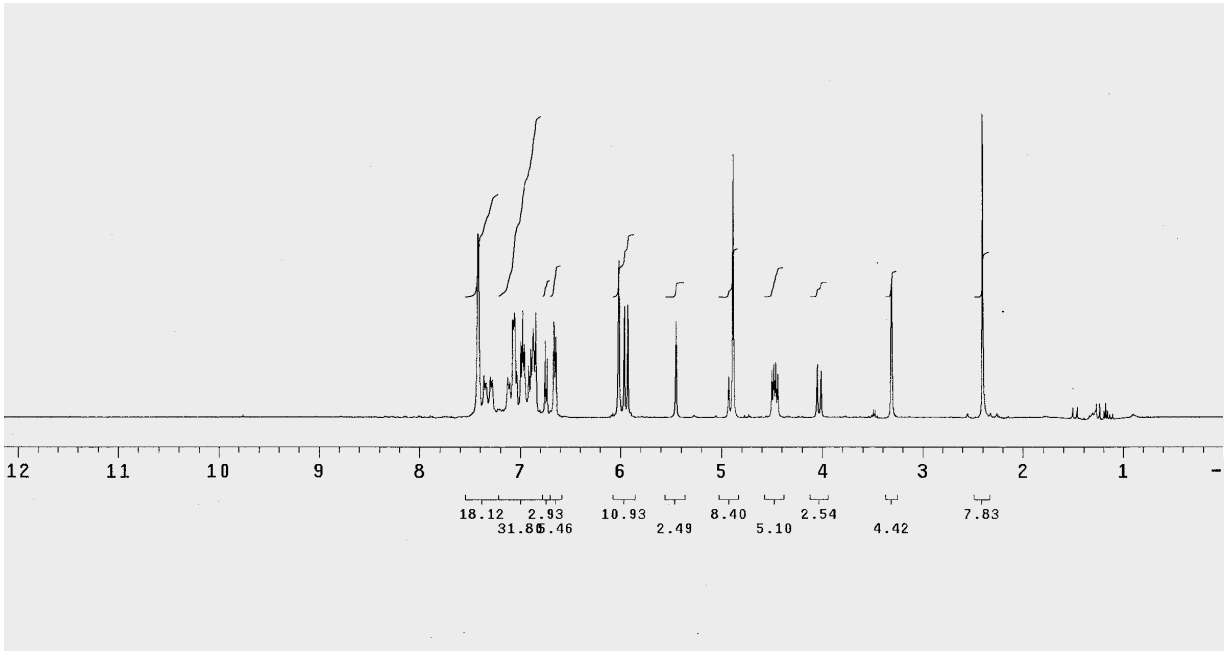
Compound 2.4e ^{1}H-NMR:



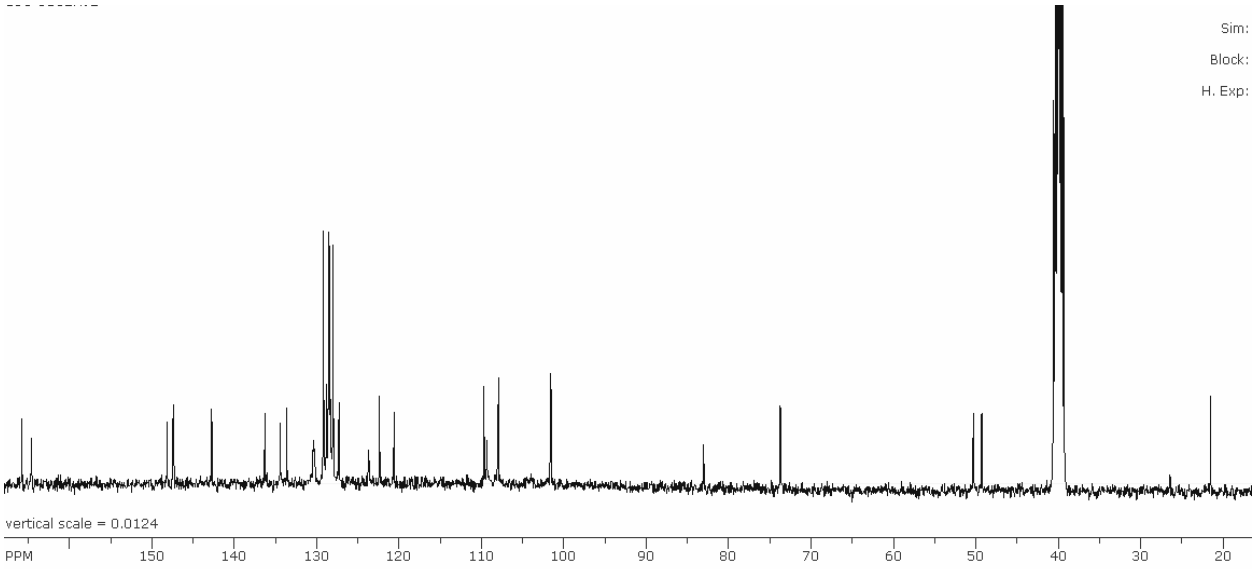
Compound 2.4e ^{13}C-NMR:



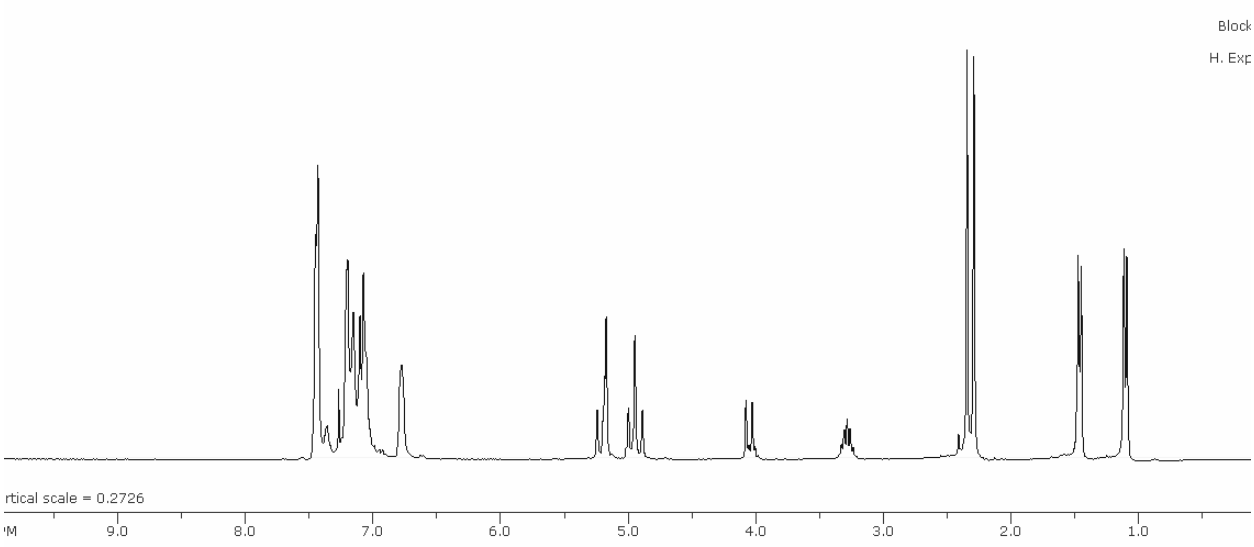
Compound 2.4f ^{1}H-NMR:



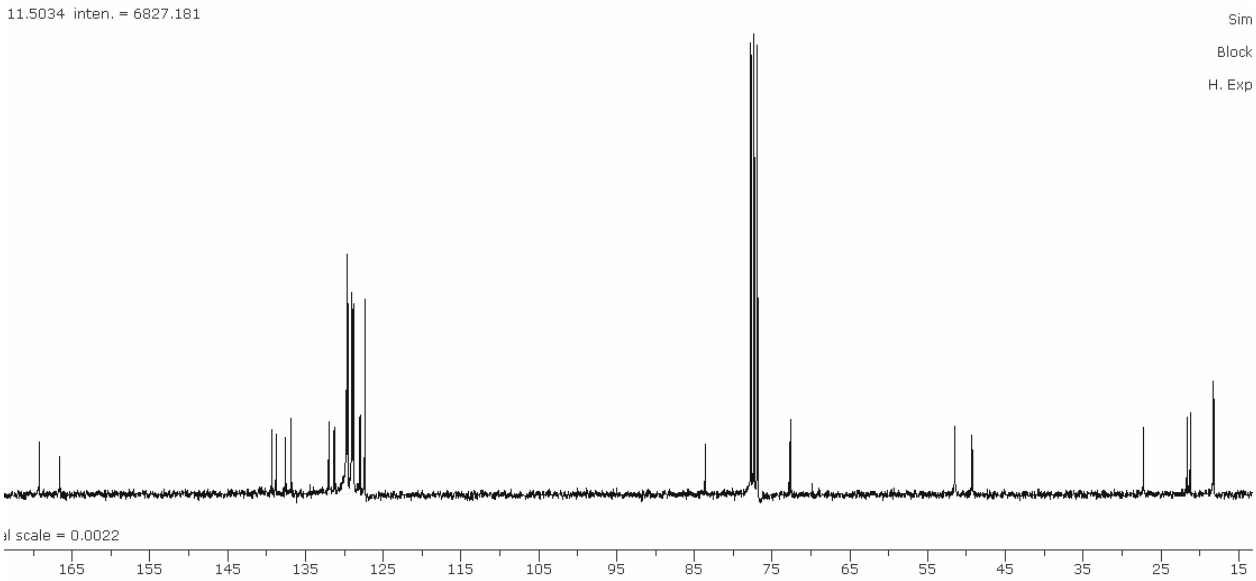
Compound 2.4f ^{13}C-NMR:



Compound 2.4g ^{1}H-NMR:



Compound 2.4g ^{13}C-NMR:



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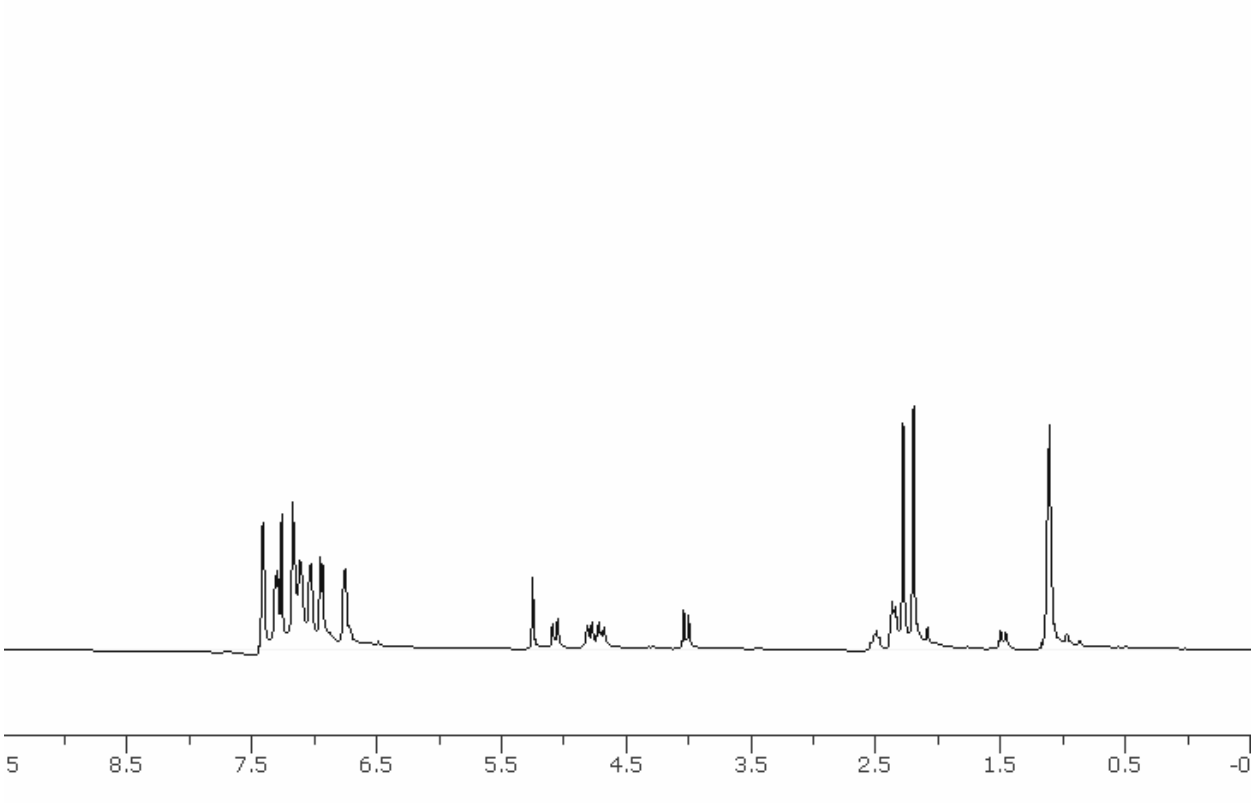

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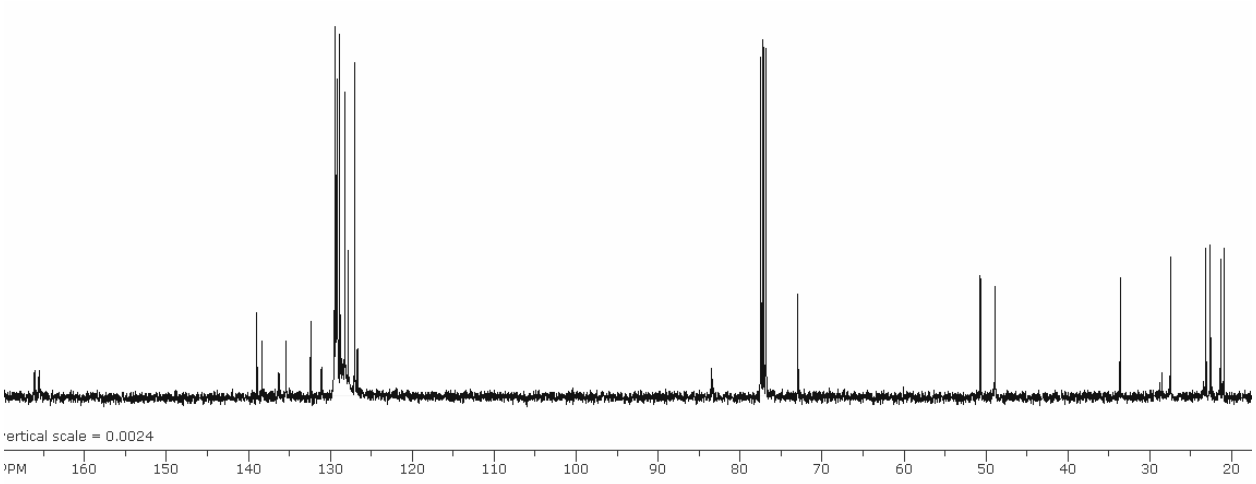

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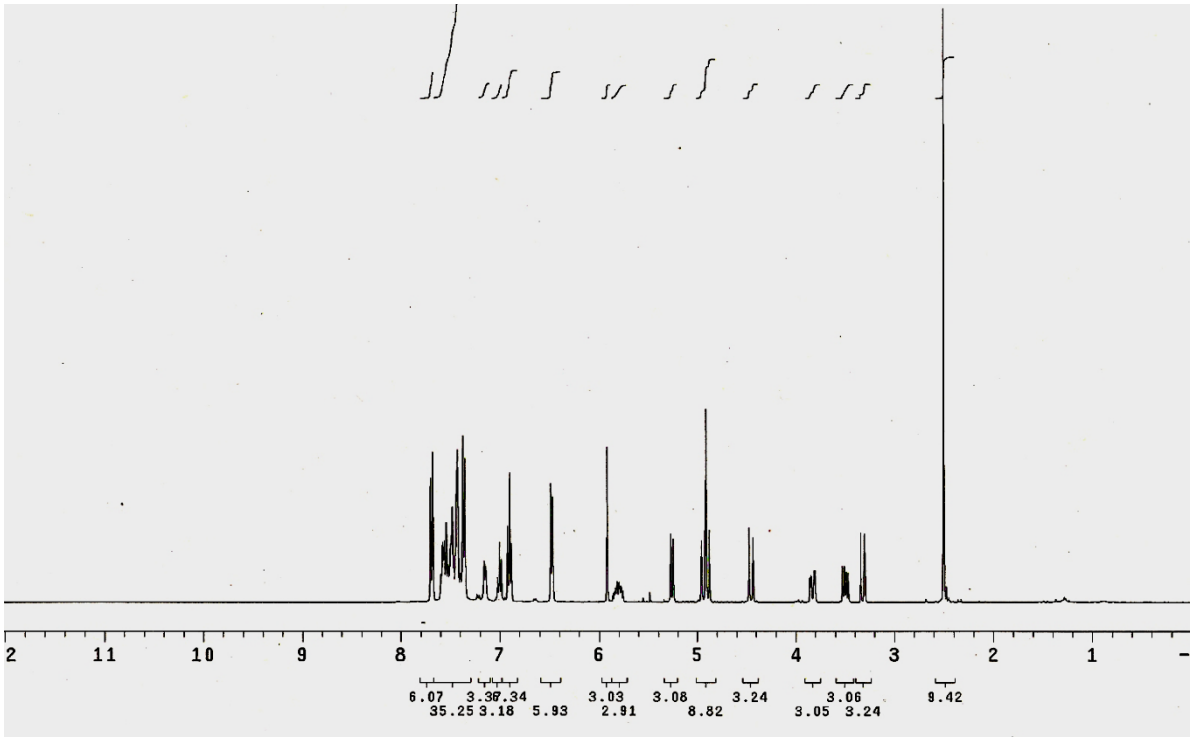

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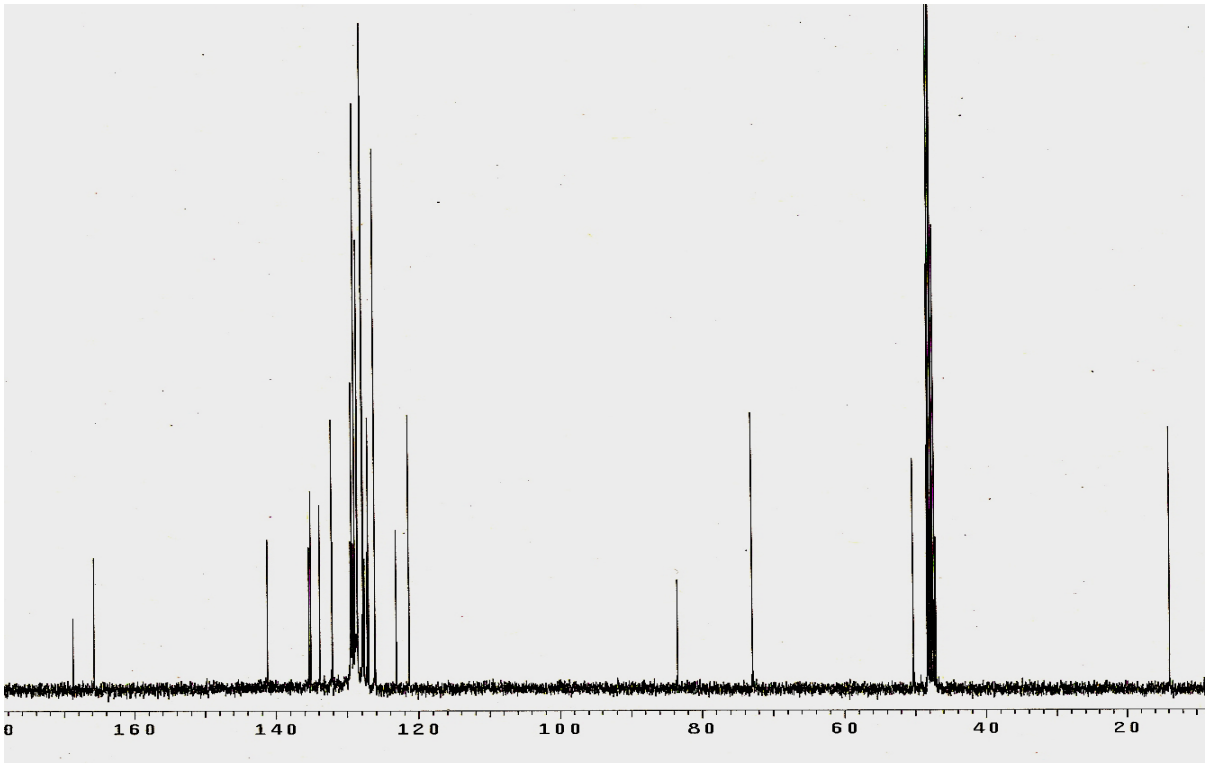
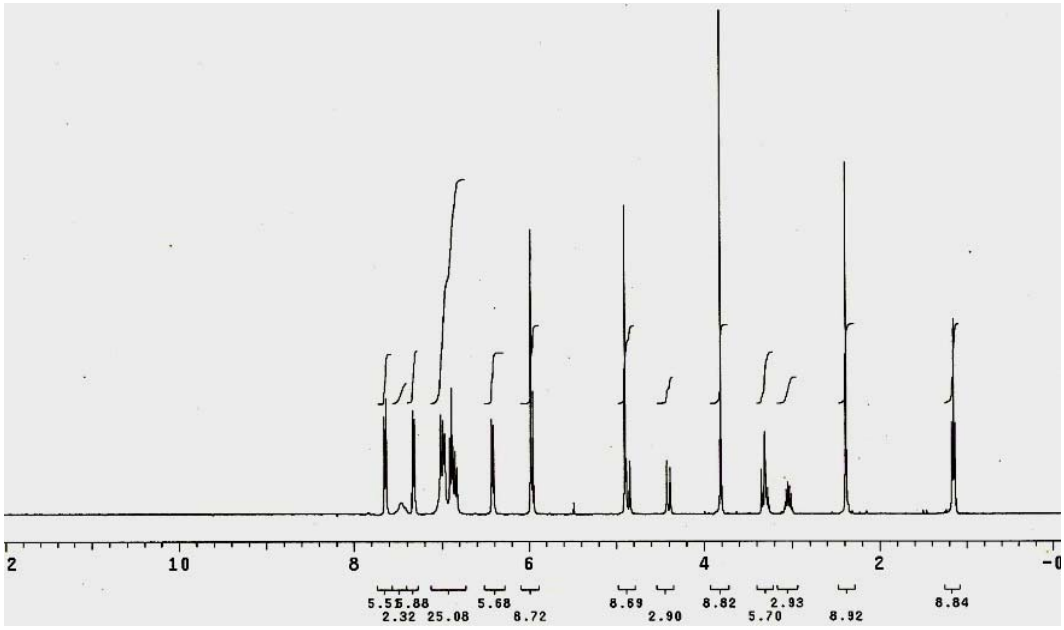


Compound 2.8b ^{1}H-NMR:



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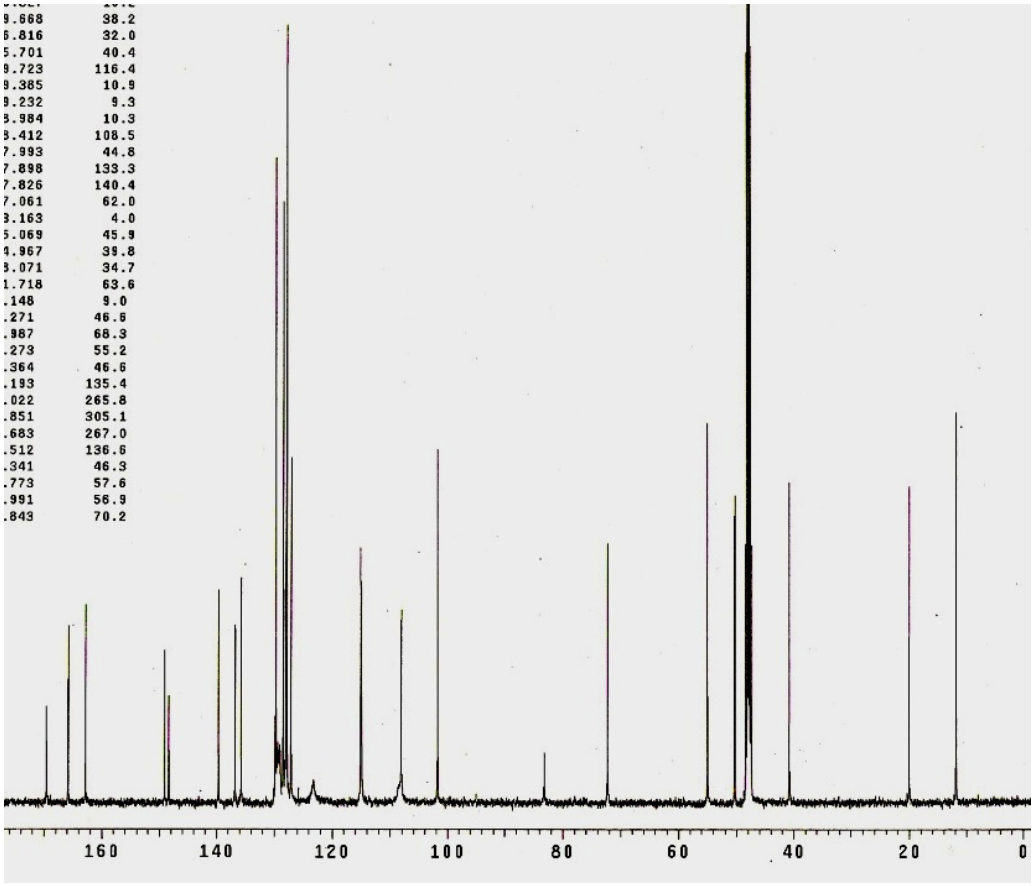

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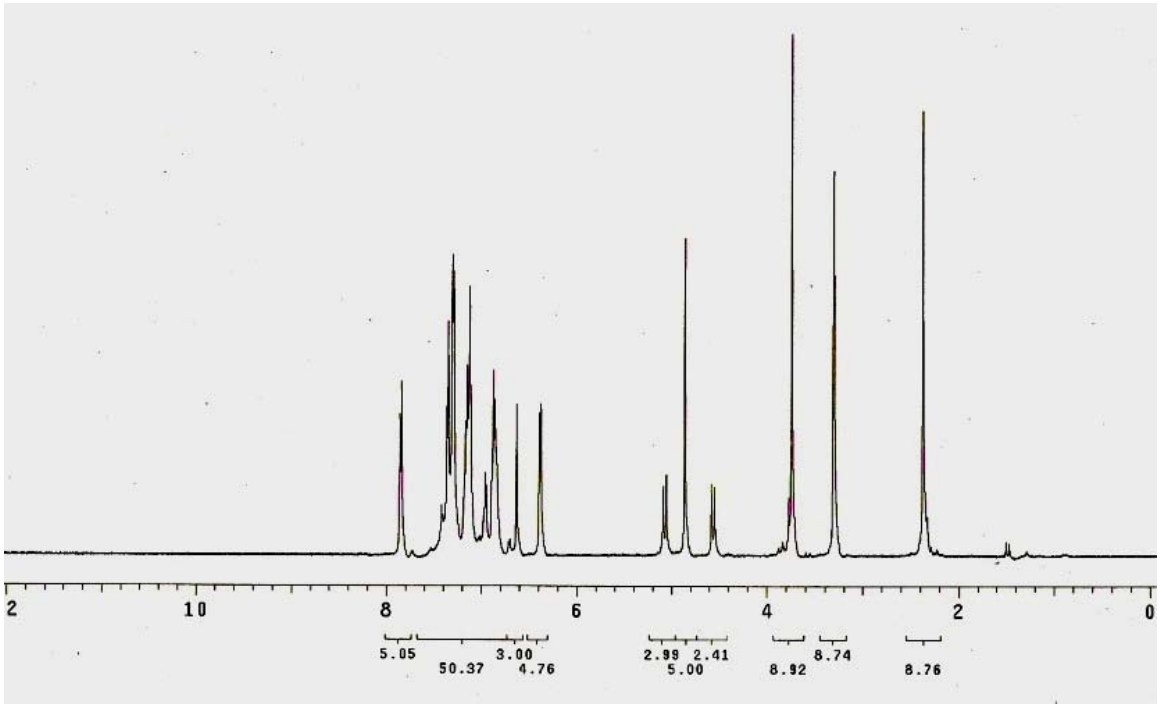
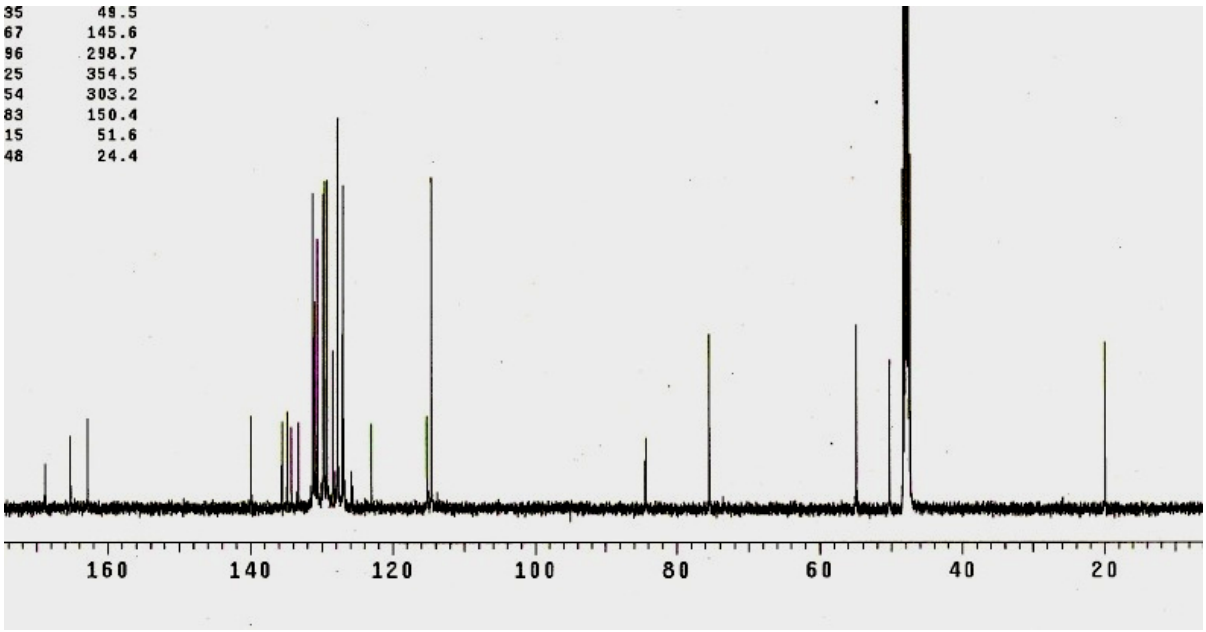
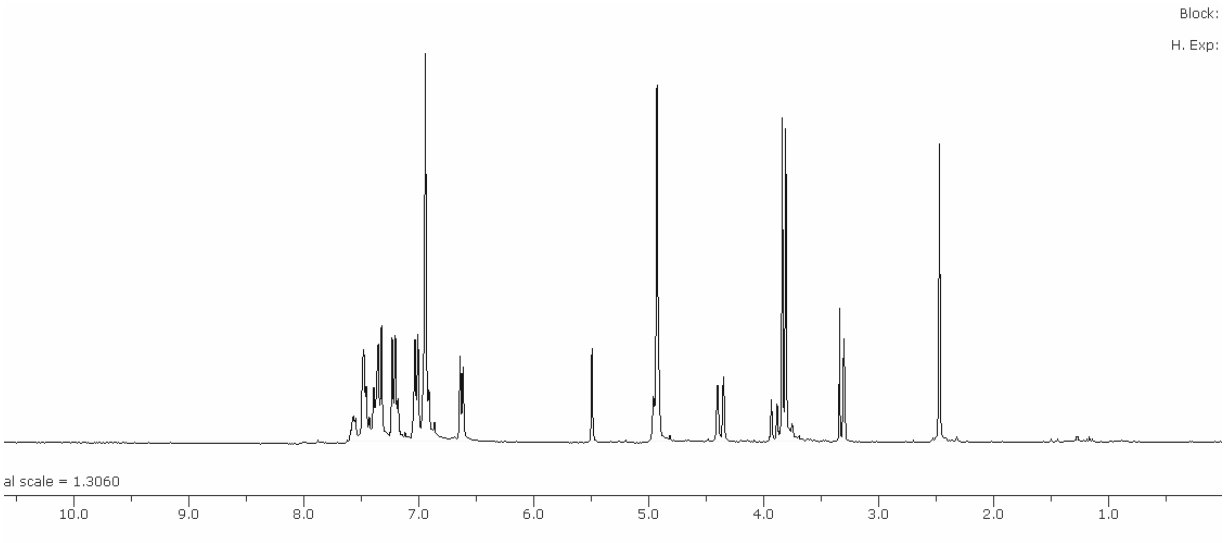


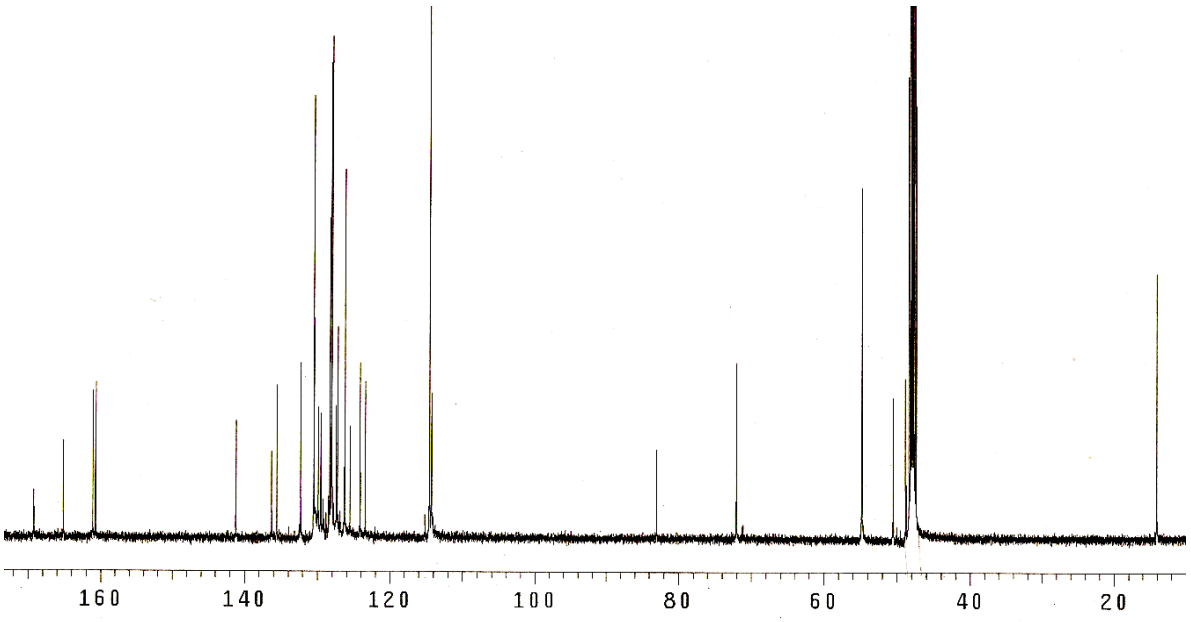
Compound 2.8c ^{13}C-NMR:



Compound 2.8d ^{1}H-NMR:



Compound 2.8d ^{13}C-NMR:



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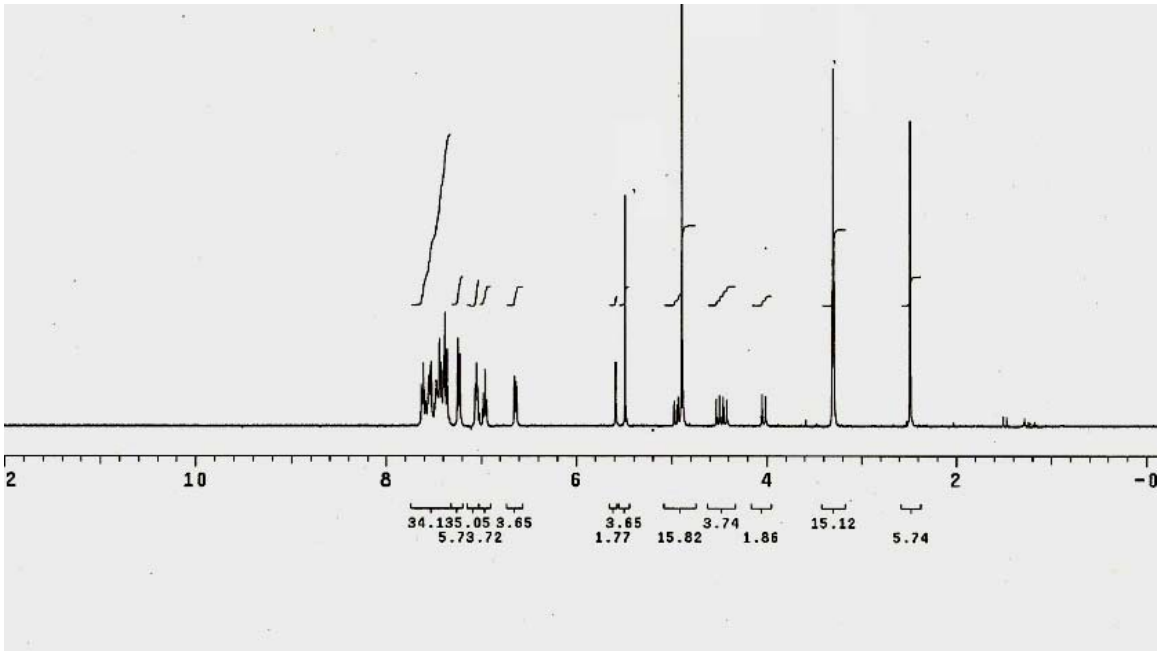
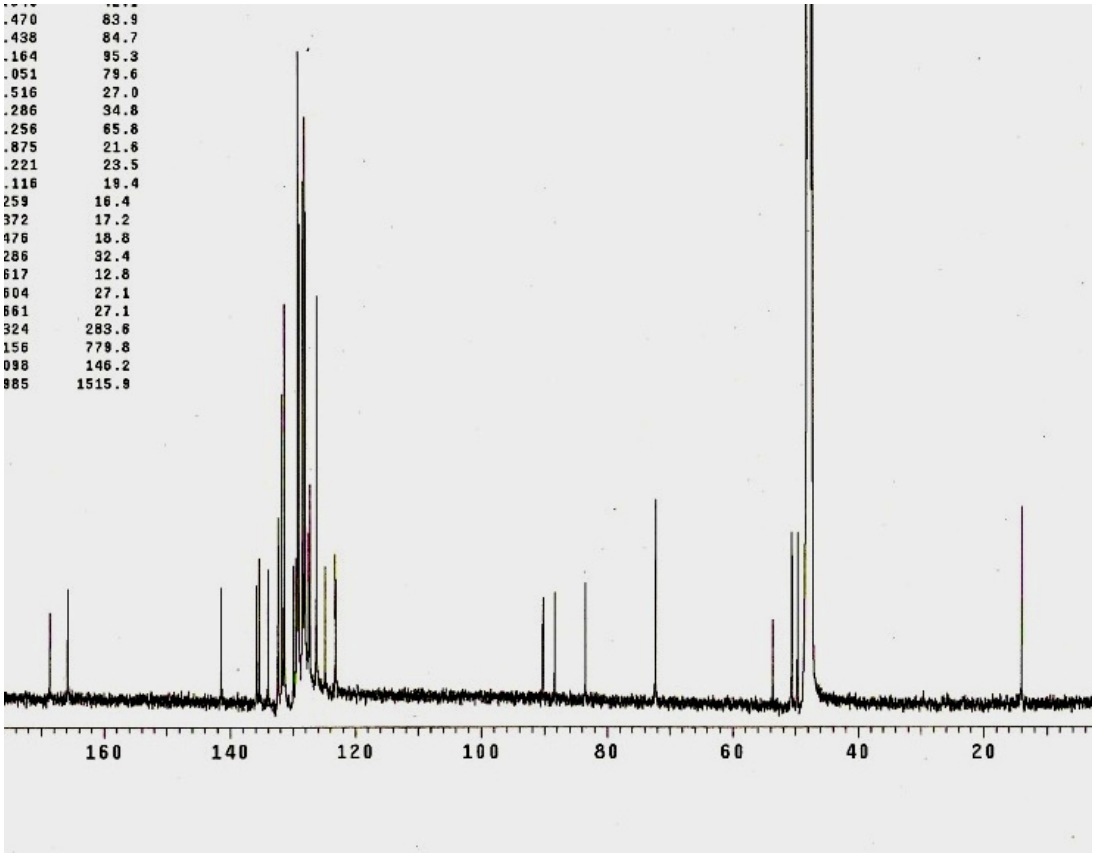


Compound 2.8e ^{13}C-NMR:



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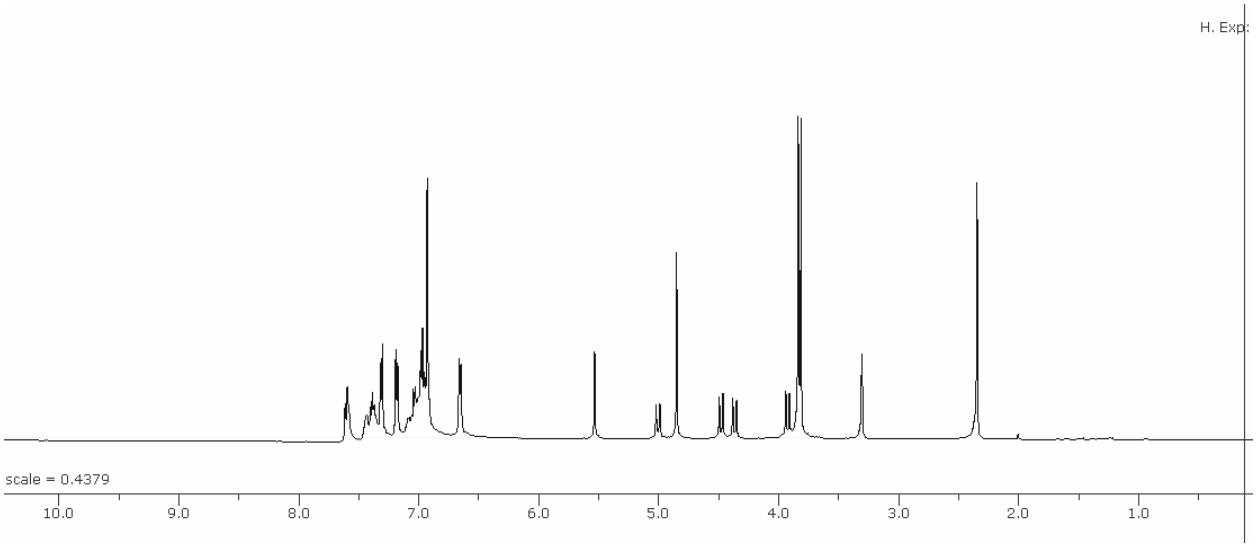
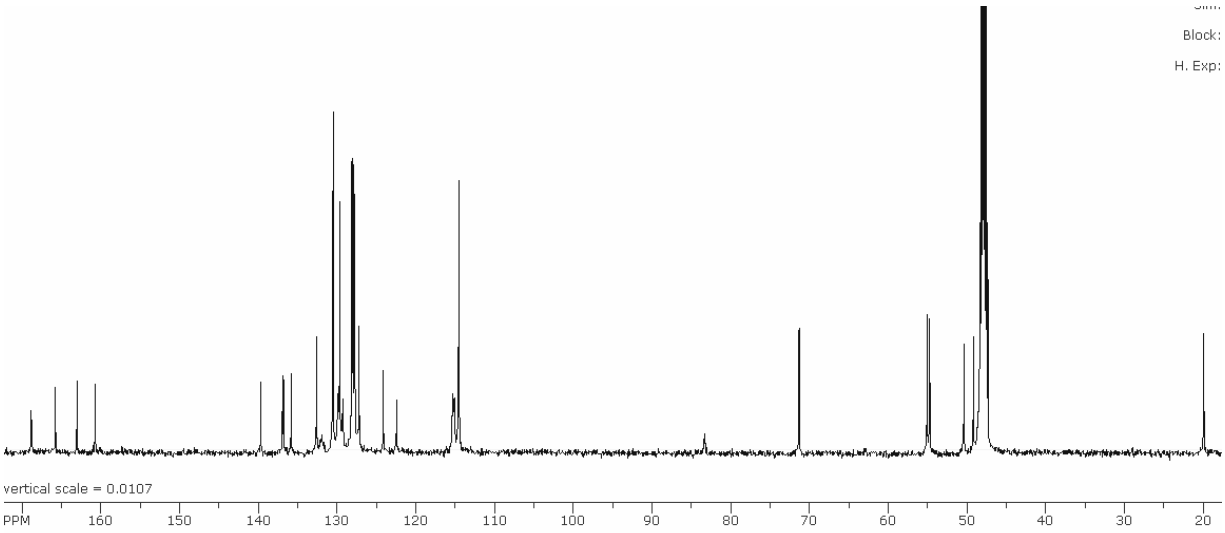
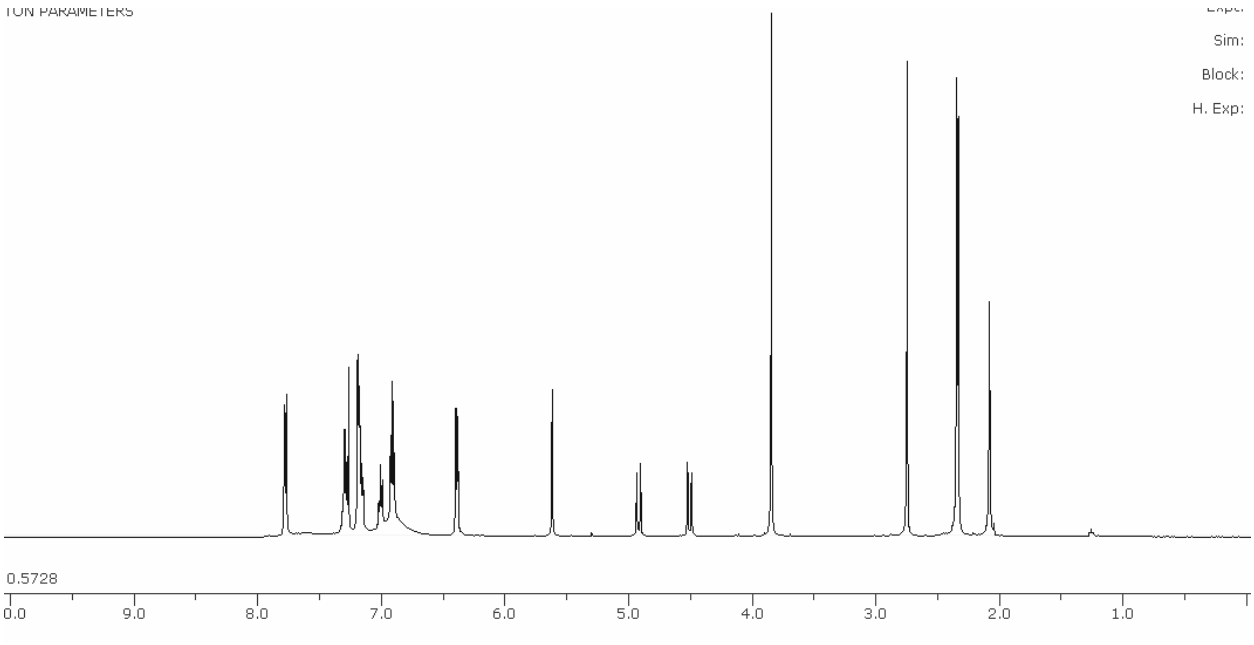


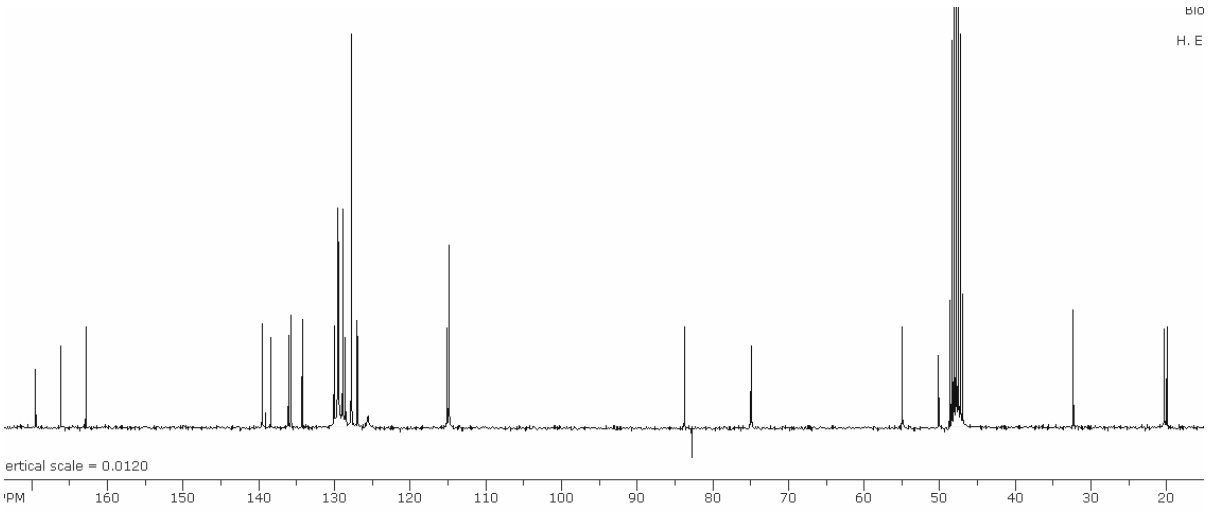
Compound 2.8f ^{13}C-NMR:



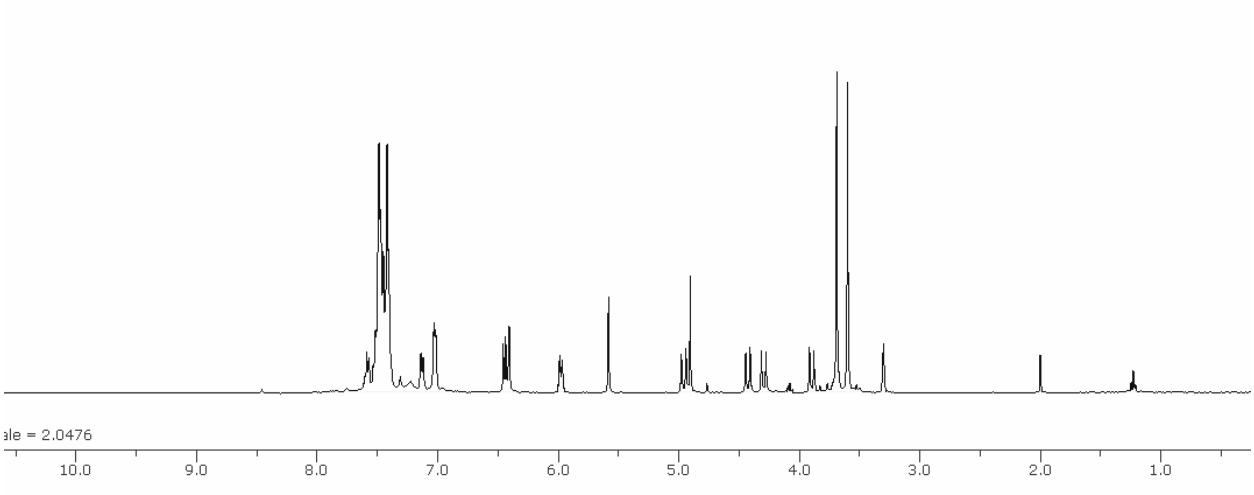
Compound 2.8g ^{1}H-NMR:



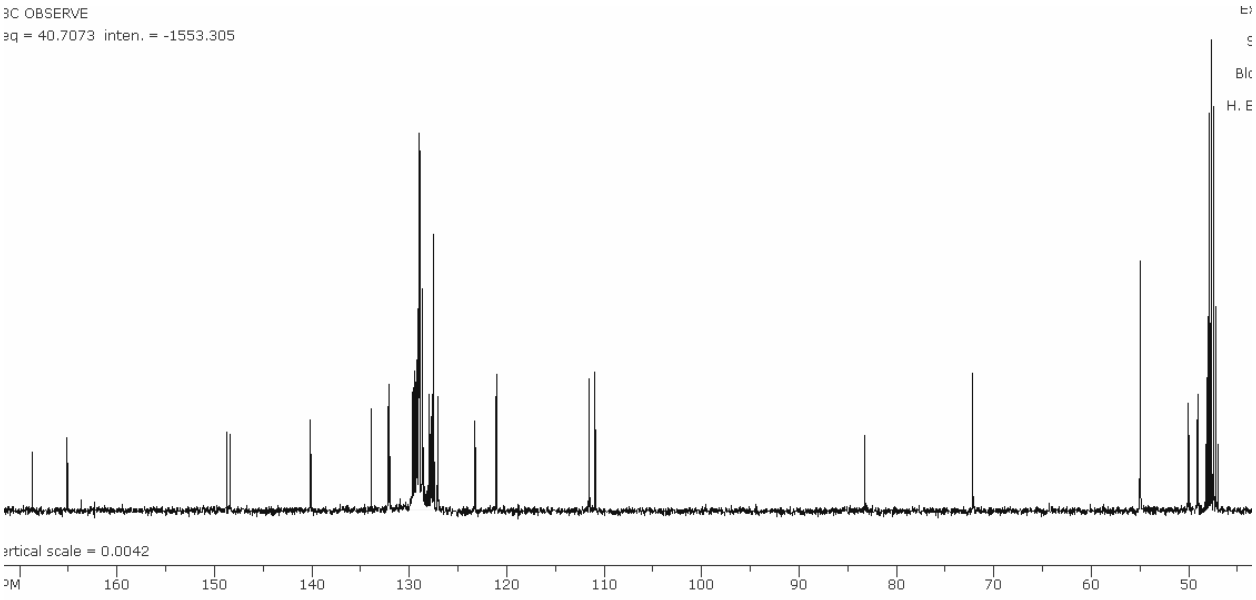
Compound 2.8g ^{13}C-NMR:



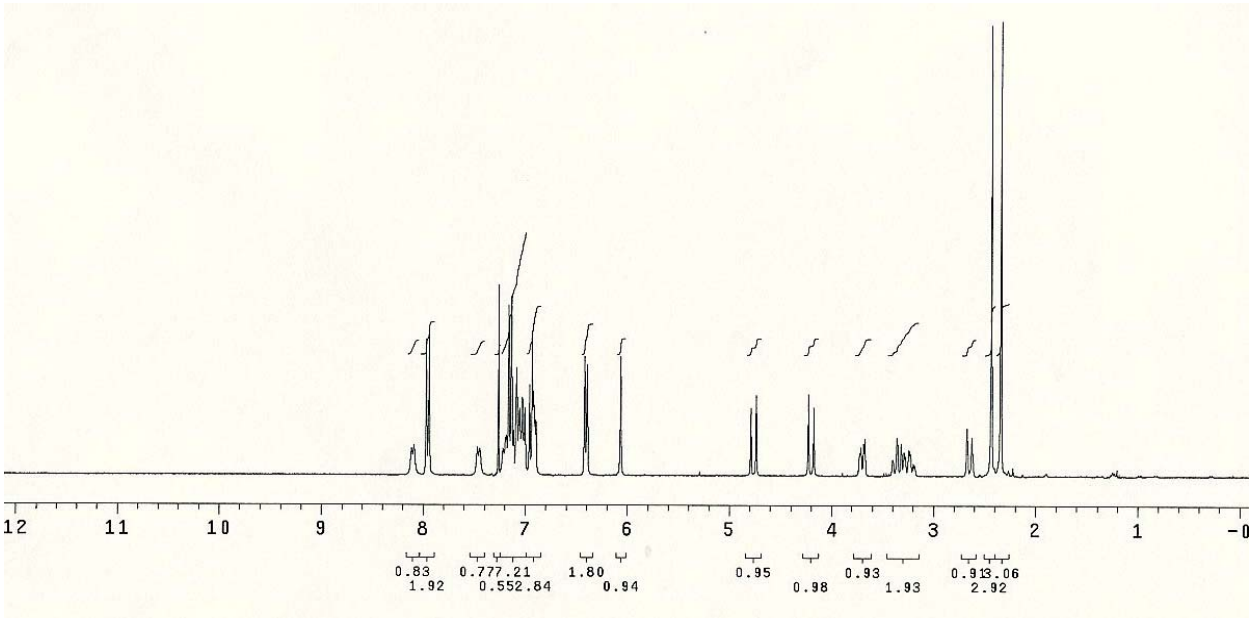
Compound 2.8h ^{1}H-NMR:



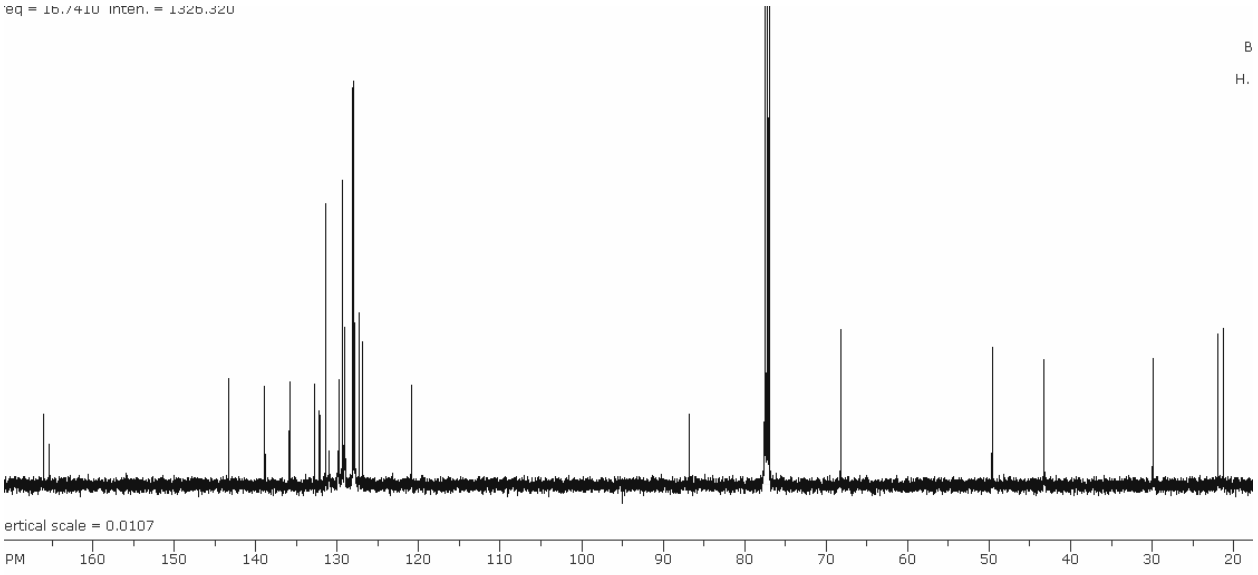
Compound 2.8h ^{13}C-NMR:



Compound 2.8i ^{1}H-NMR:



Compound 2.8i ^{13}C-NMR:



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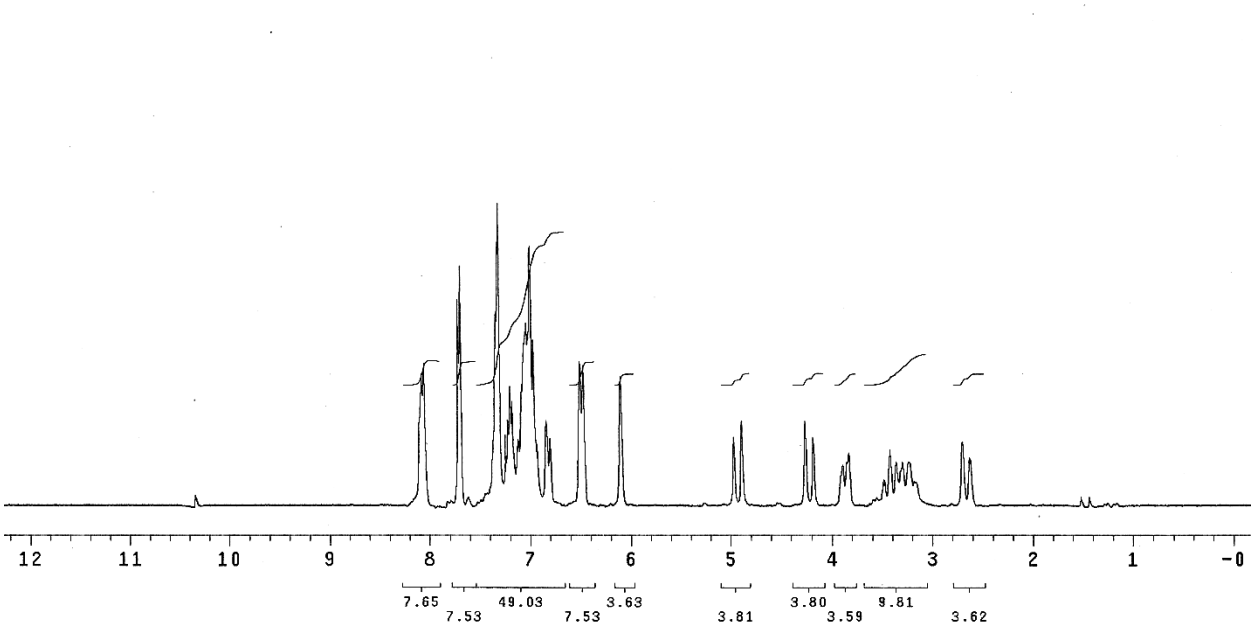

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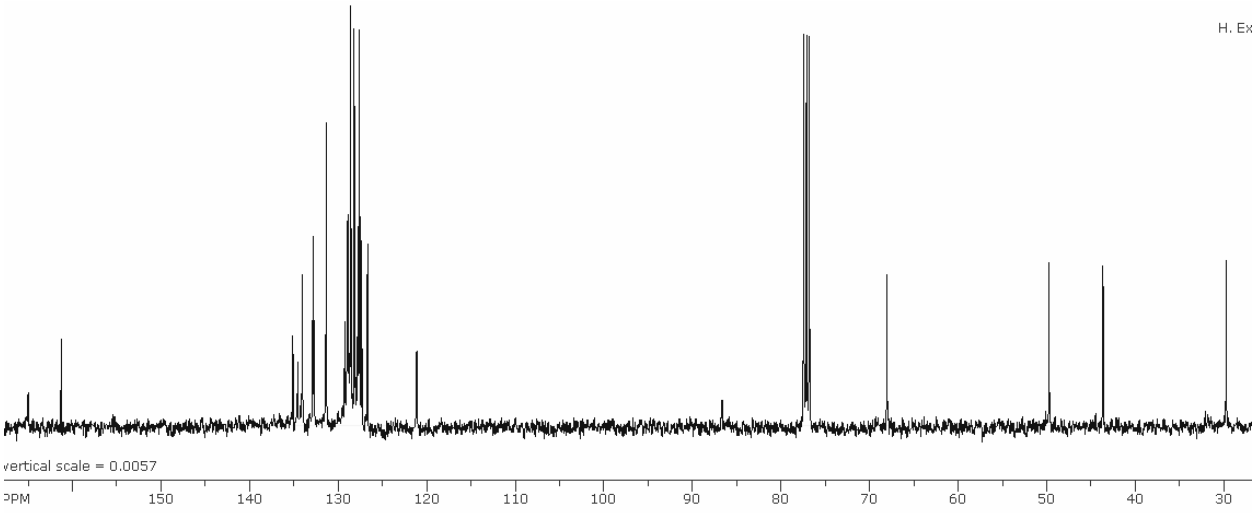
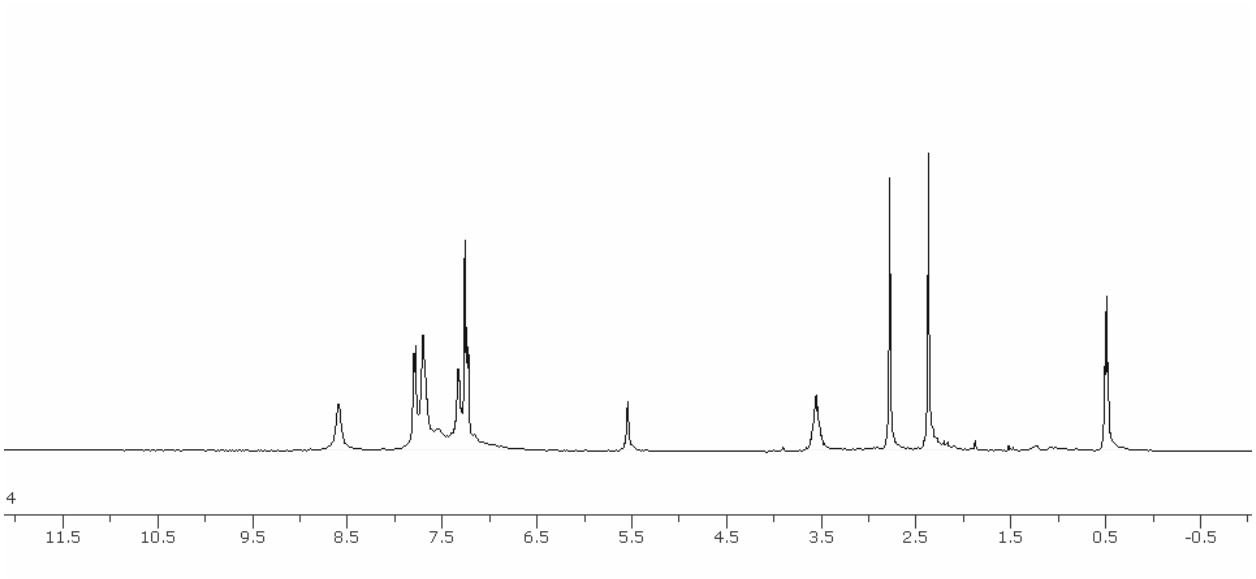
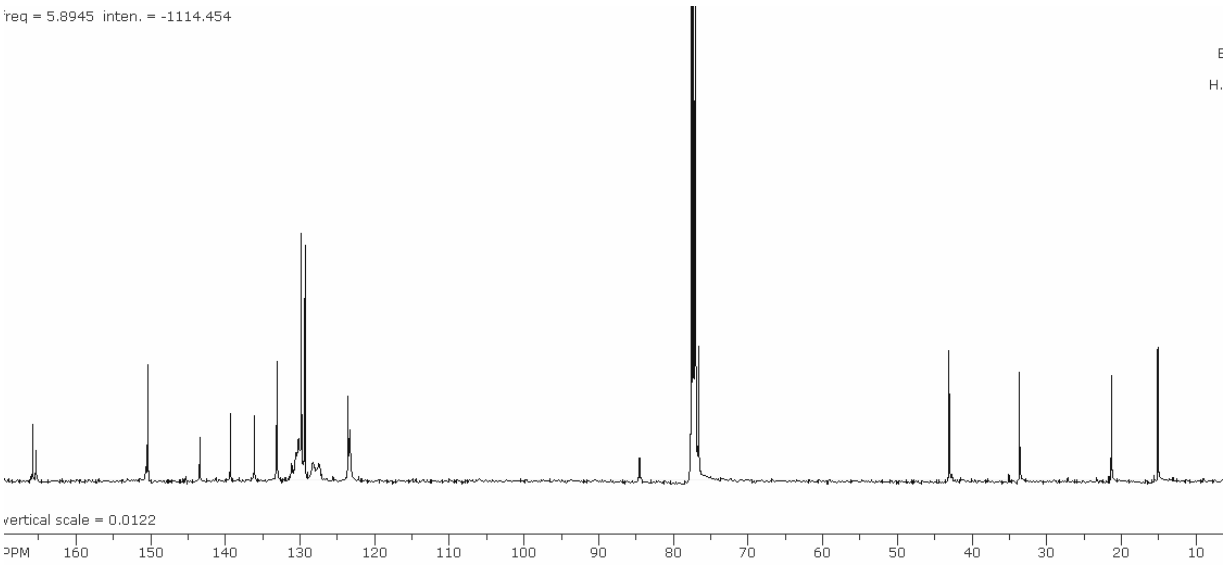


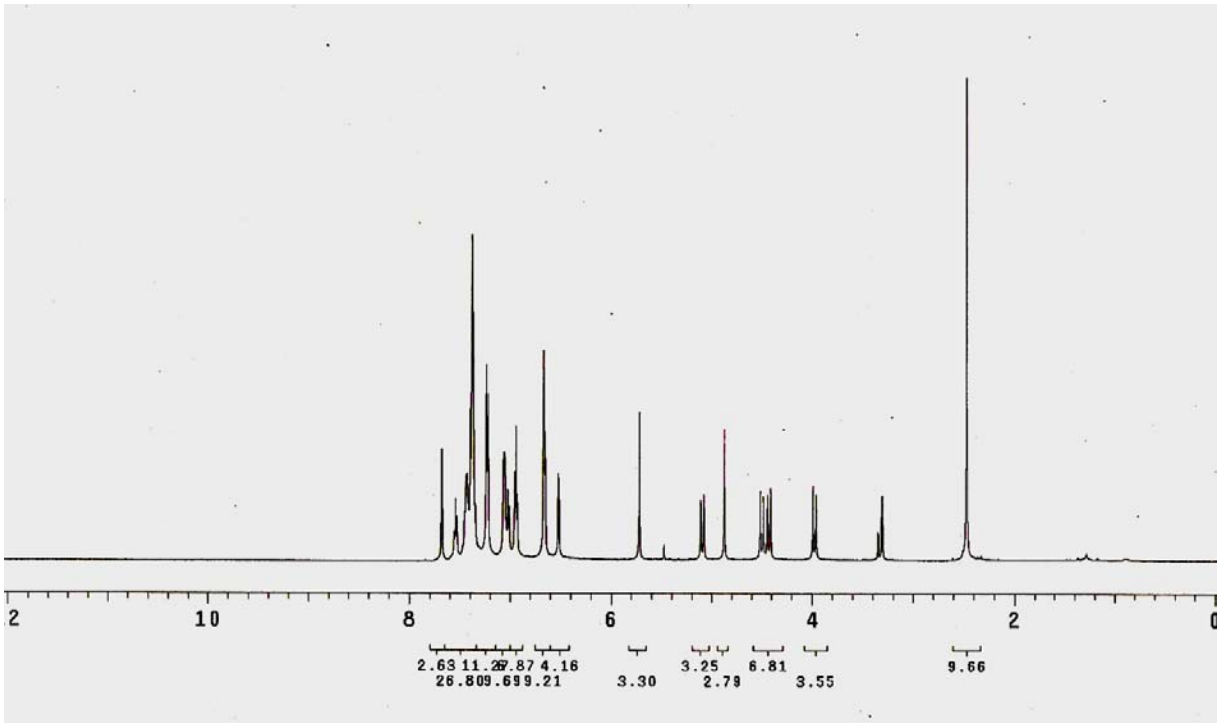
Compound 2.8k ^{1}H-NMR:



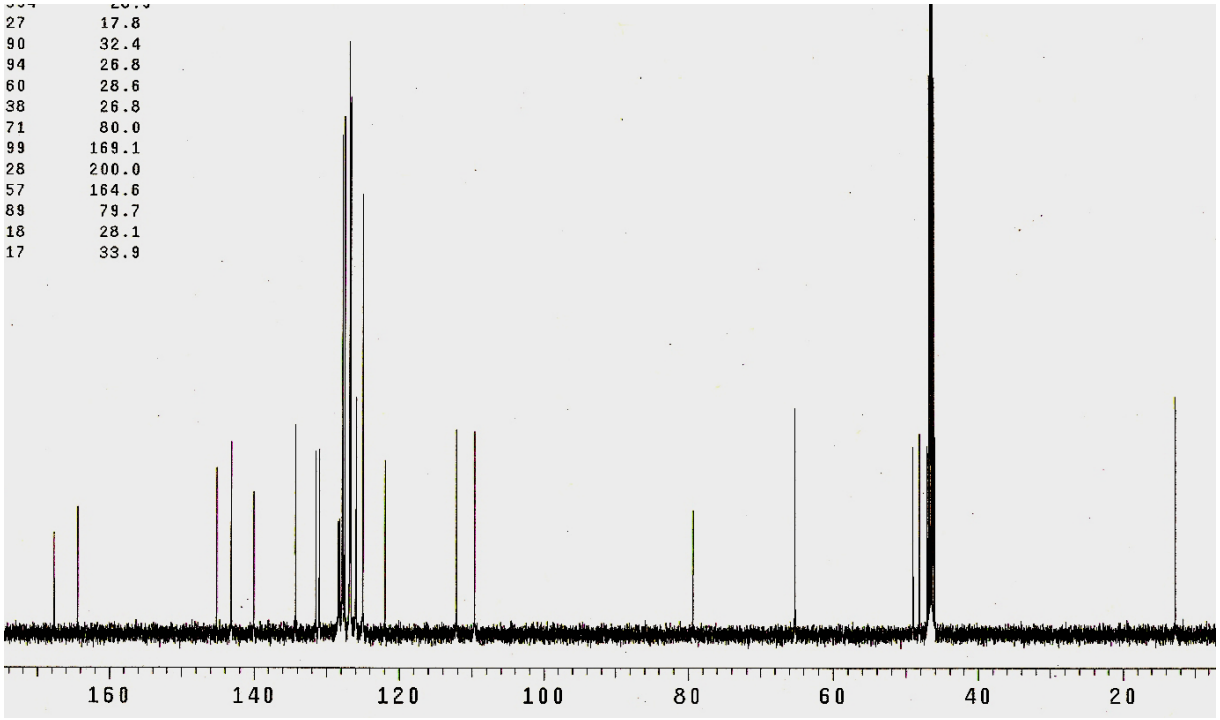
Compound 2.8k ^{13}C-NMR:



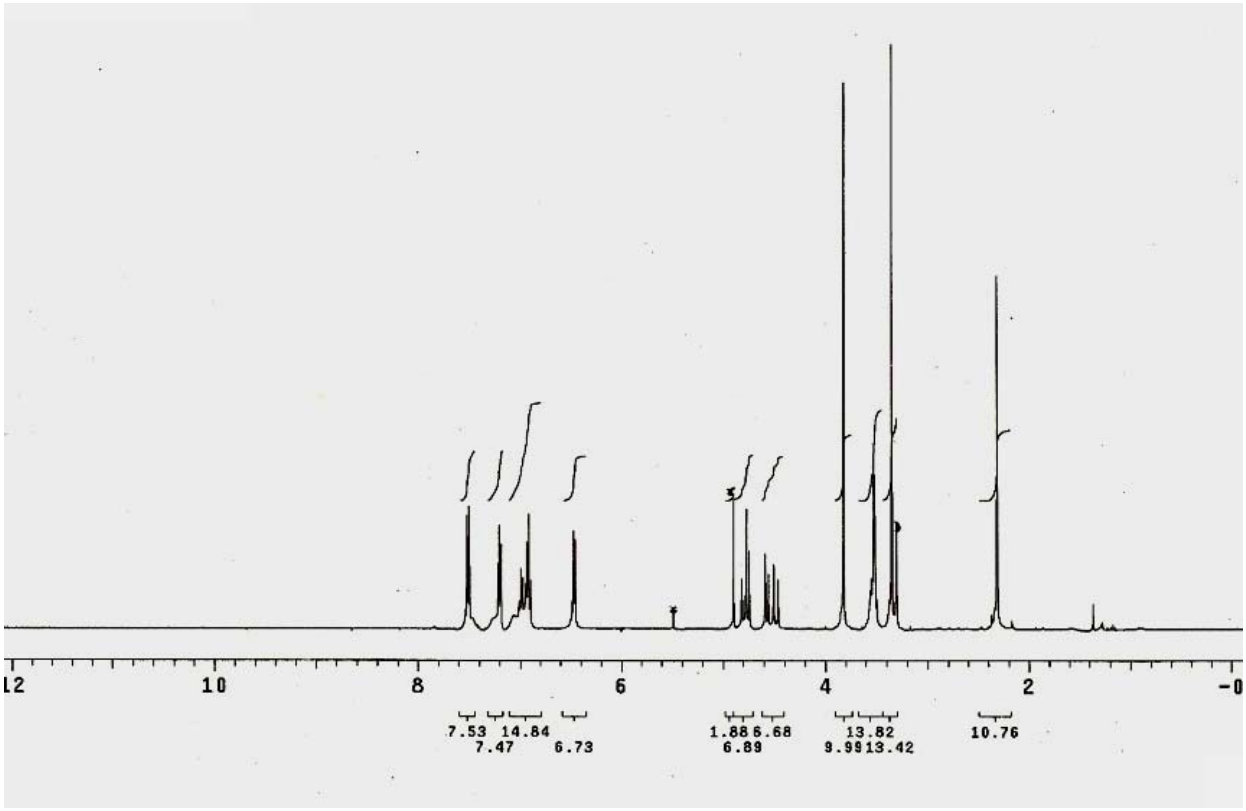
Compound 2.8l ^{1}H-NMR:



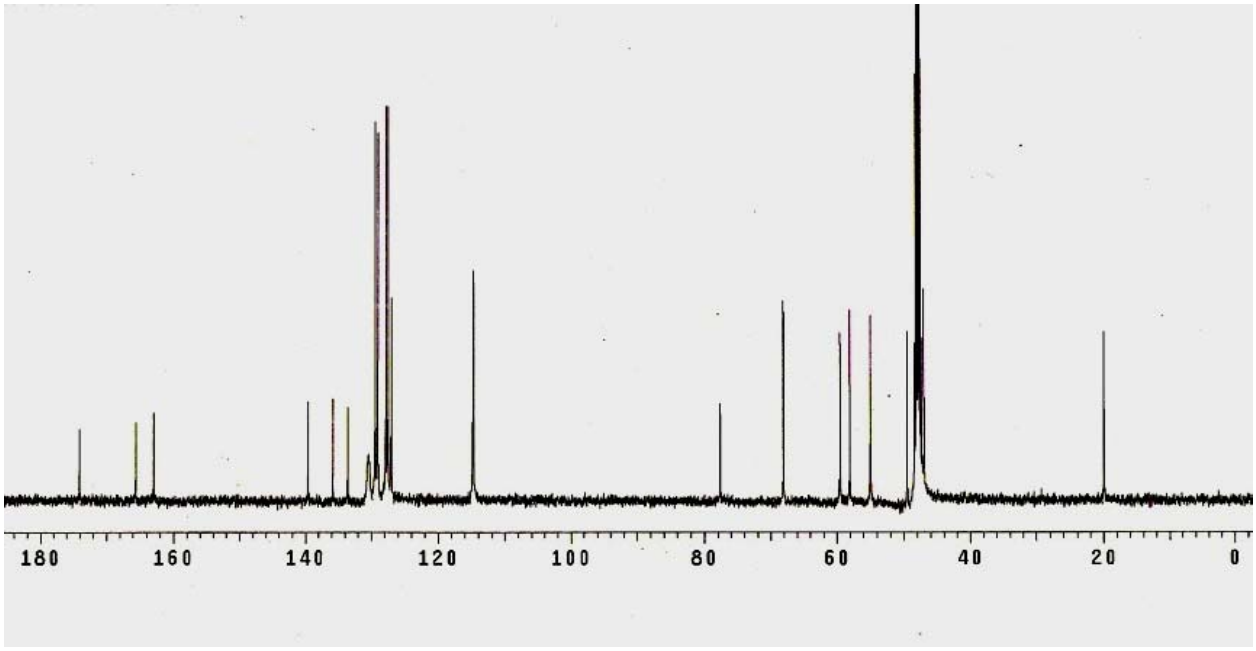
Compound 2.8l ^{13}C-NMR:



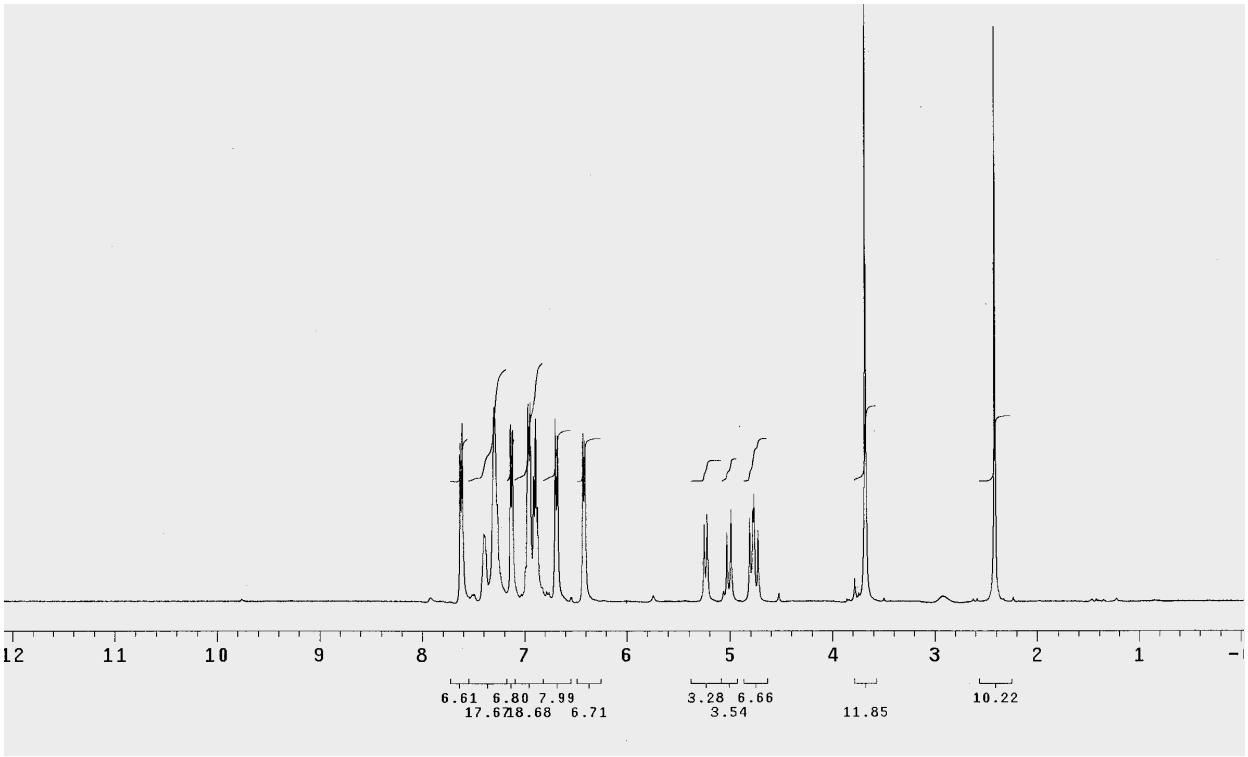
Compound 2.8m ^{1}H-NMR:



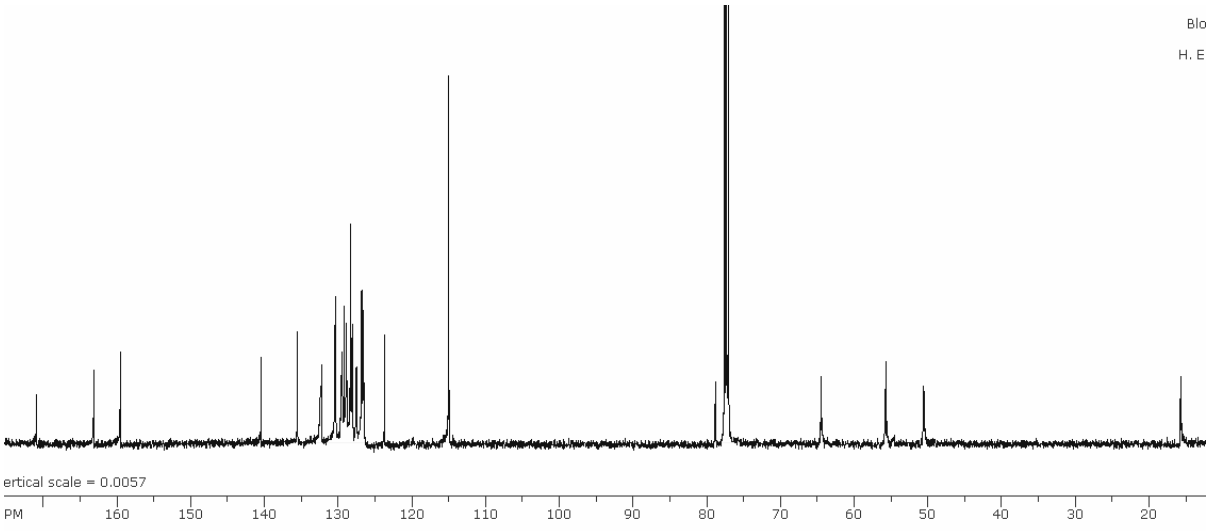
Compound 2.8m ^{13}C-NMR:



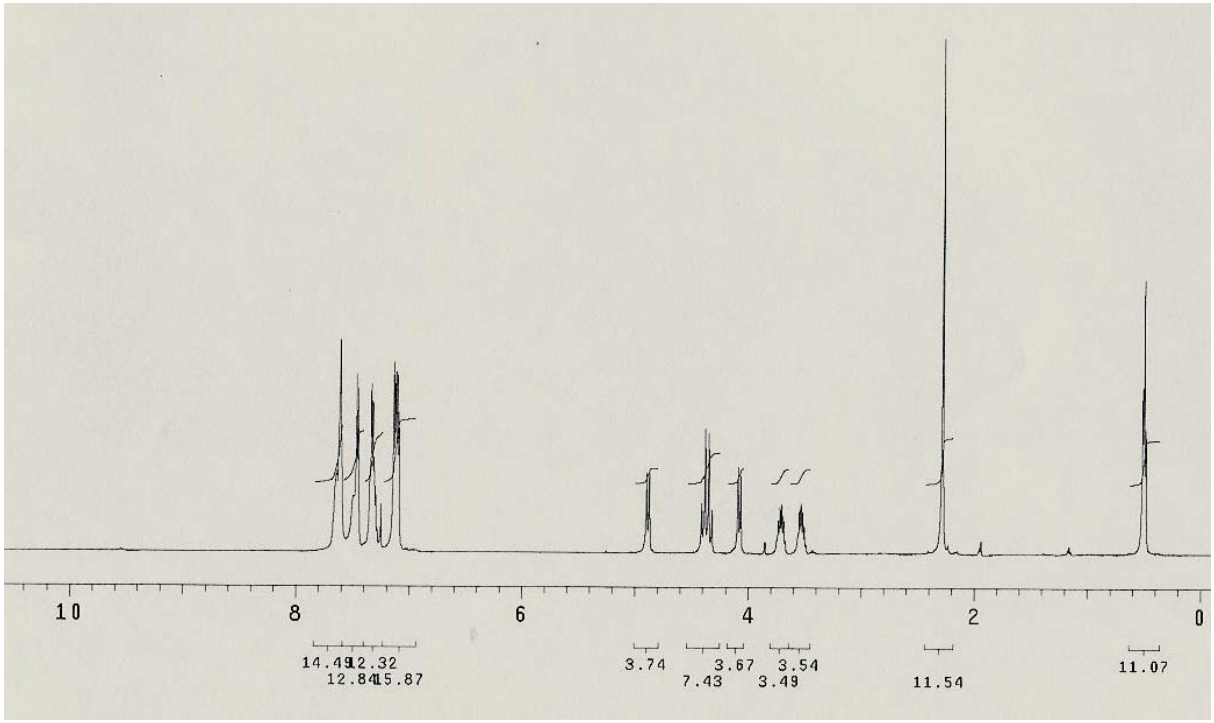
Compound 2.8n ^{1}H-NMR:



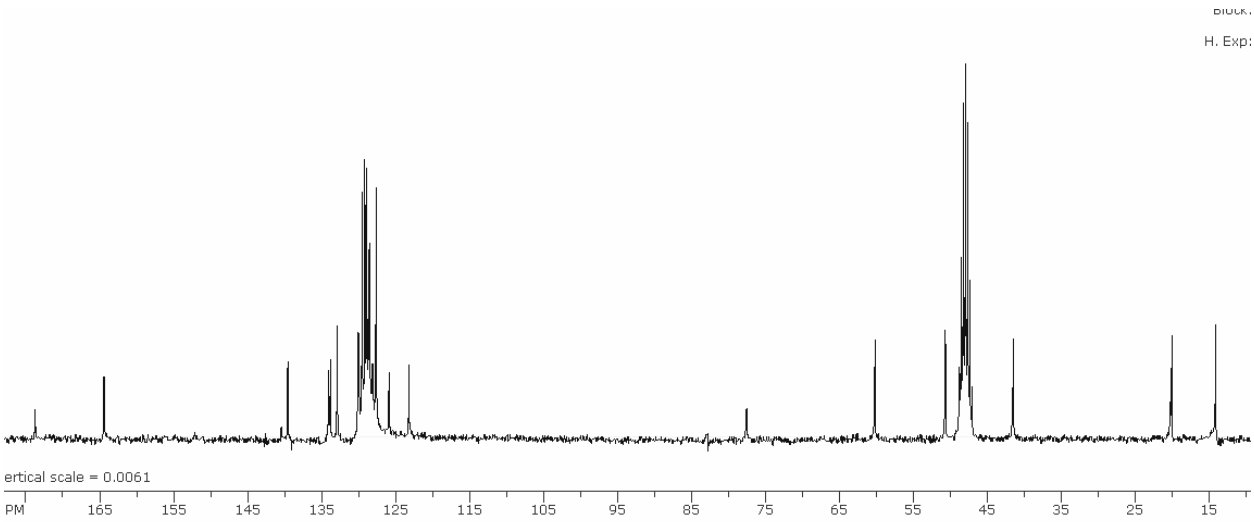
Compound 2.8n ^{13}C-NMR:



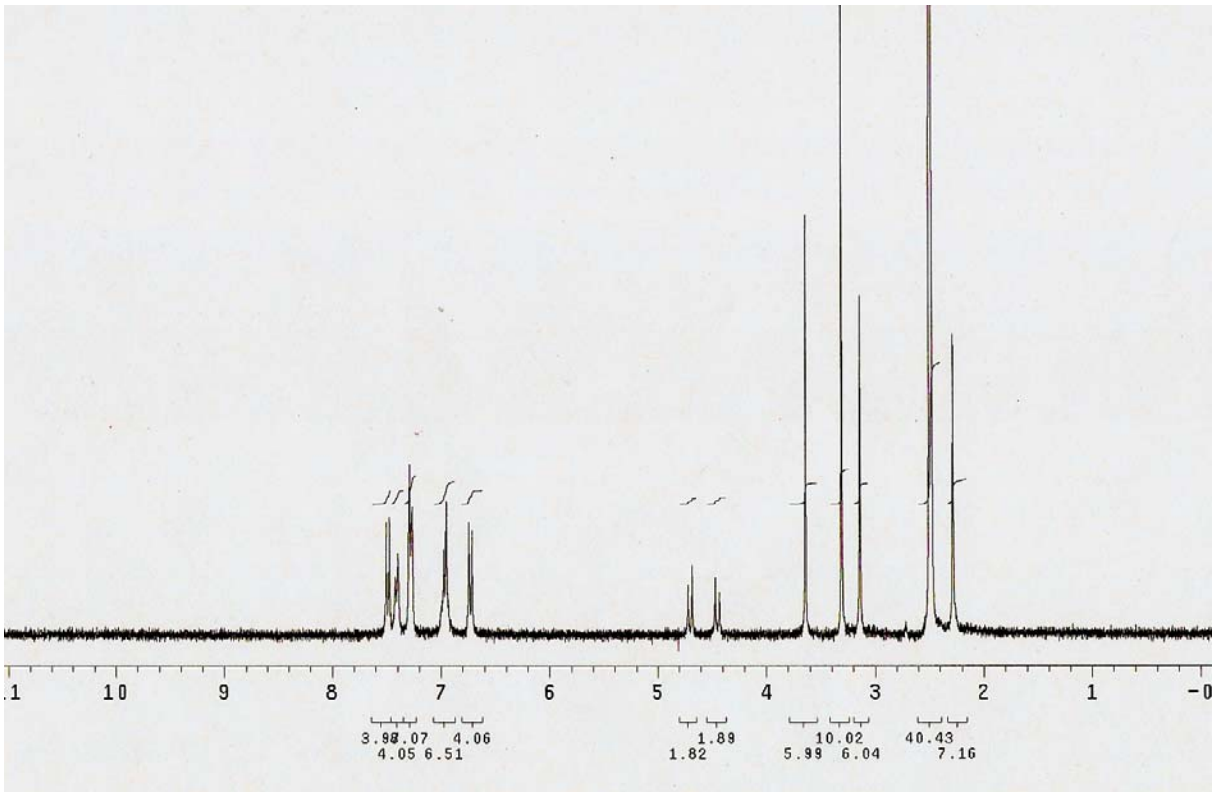
Compound 2.8o ^{1}H -NMR:



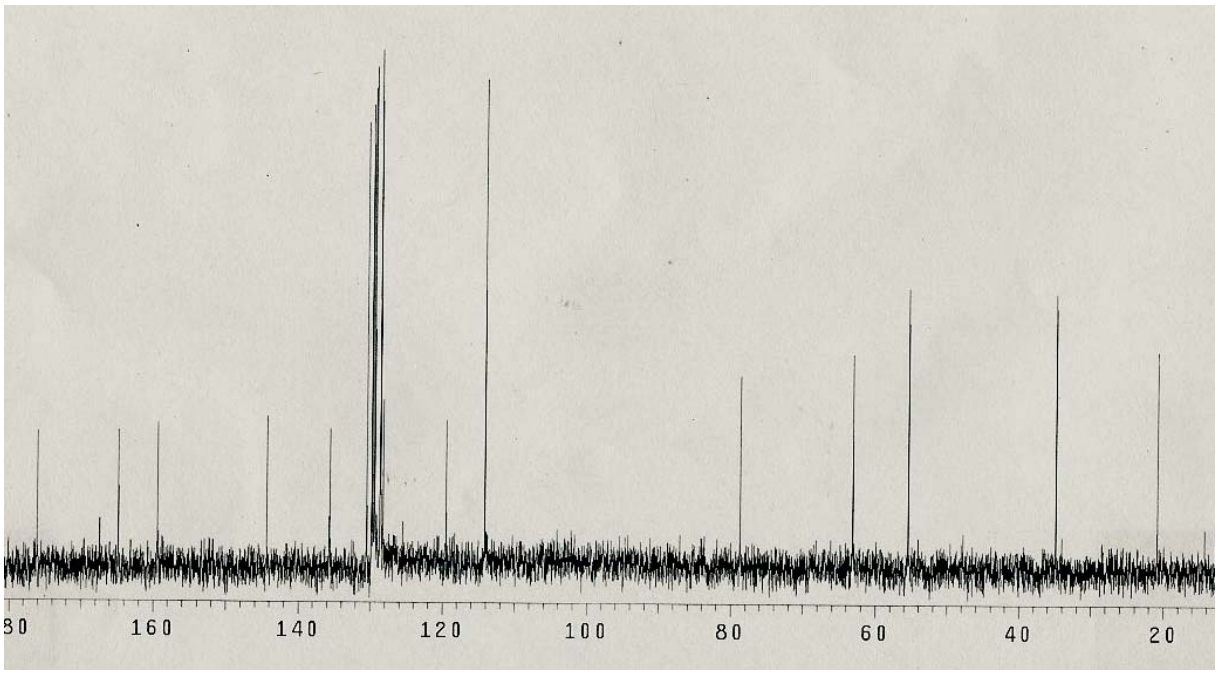
Compound 2.8o ^{13}C-NMR:



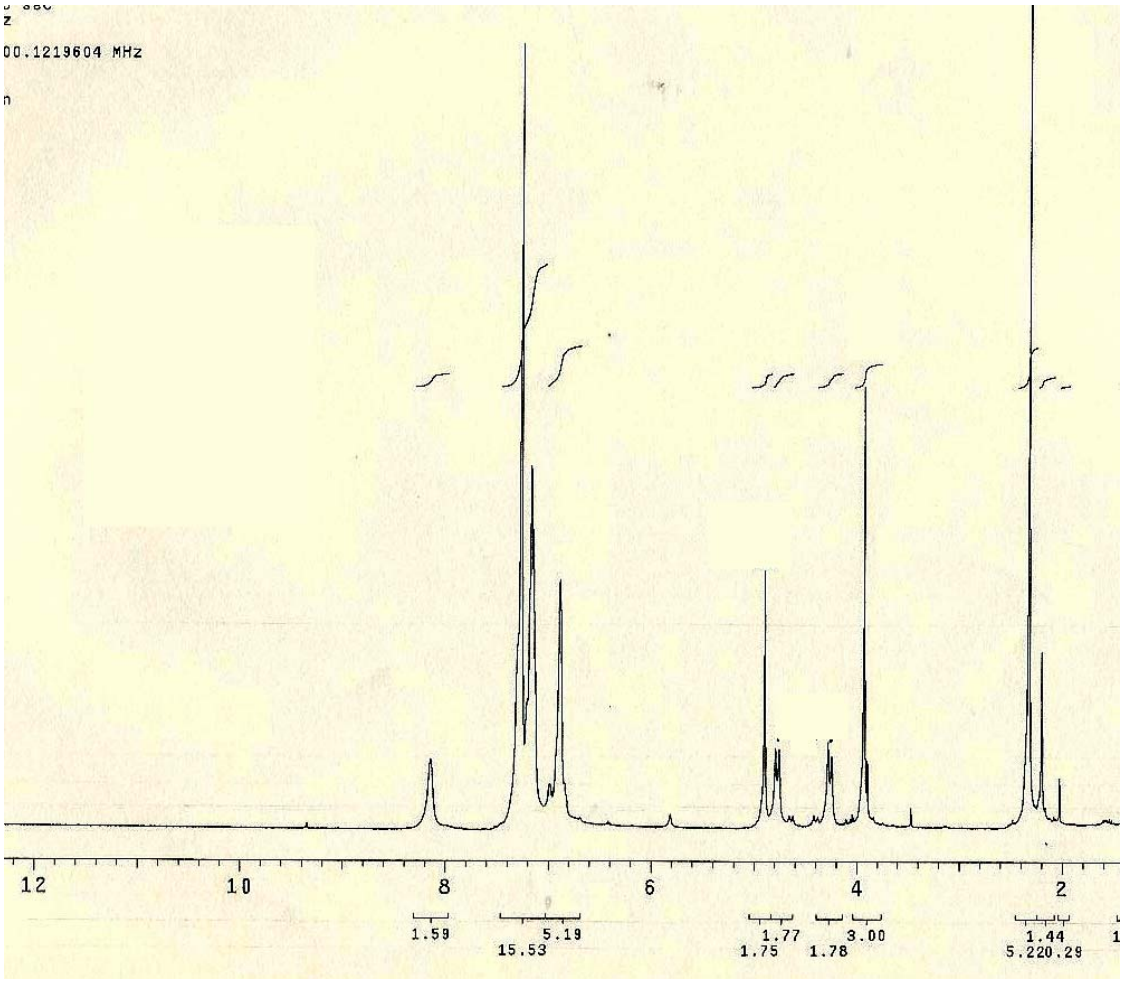
Compound 2.8p ^{1}H-NMR:



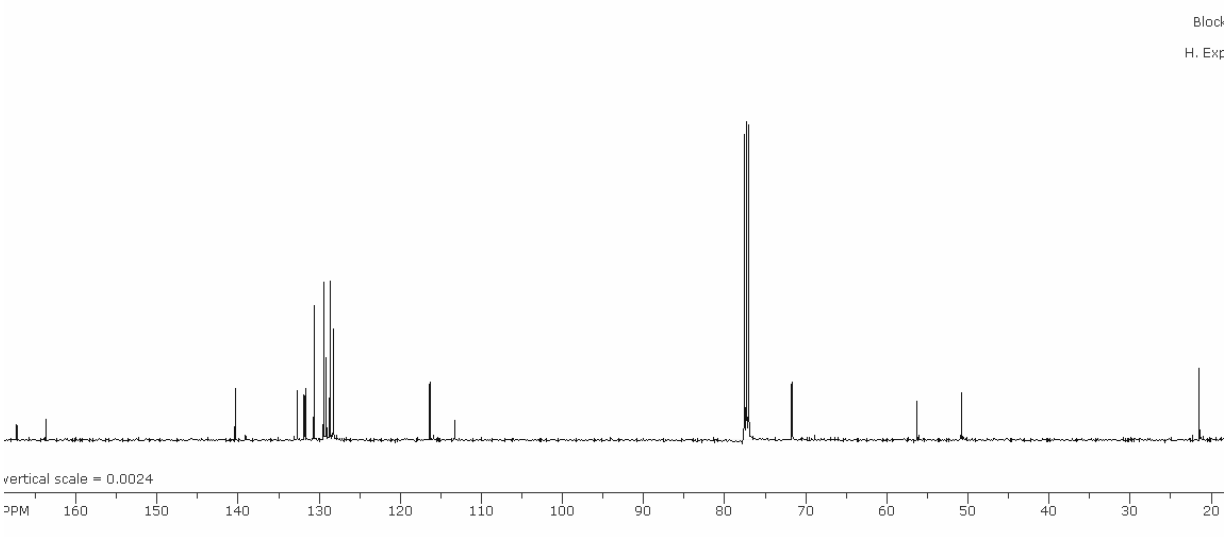
Compound 2.8p ^{13}C-NMR:



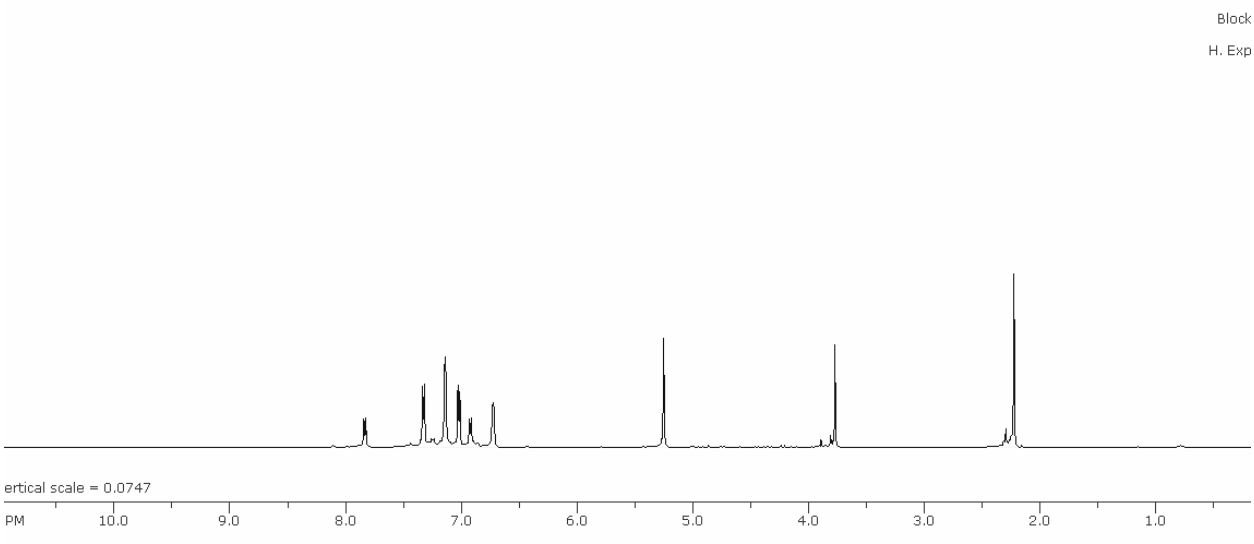
Compound A2 ^{1}H-NMR:



Compound A2 ^{13}C-NMR:



Compound A5 ^{1}H-NMR:



Compound A6 ^{13}C-NMR: