Synthesis of Imidazoles, 2-Pyrrolines and Pyrrolidines via Phospha-Münchnone Cycloadditions

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Abstract

This thesis describes the use of a new class of dipole, phospha-Münchnones, in 1,3-dipolar cycloaddition reactions. Phospha-Münchnones can be readily prepared from imines, acid chlorides and the catechyl-substituted phosphonite PhP(2-catechyl). Coupling the multicomponent formation of these dipoles with subsequent cycloaddition has provided modular, one-pot syntheses of a number of heterocycles. In Chapter 1, an overview of the utility of imines in 1,3-dipolar cycloaddition reactions is provided. This includes their use in the synthesis of aromatic nitrogen-containing heterocycles such as of pyrroles, oxadiazoline, imidazoles, triazoles and their reduced analogues.

In Chapter 2, research towards the synthesis of imidazoles through the cycloaddition of electron deficient *N*-nosyl imines with phosha-Münchnones is described. This transformation allows the direct generation of densely substituted imidazoles in a one-pot fashion, and with high regioselectivity. The methodology is also modular, where the substitution pattern can be altered by simple variation of the building blocks (imine, acid chloride and *N*-nosyl imine). Alternatively, *N*-nosyl substituted imines can be replaced by nitriles in intramolecular cycloaddition reactions. This allows the synthesis of polycyclic imidazoles from nitrile-tethered imines and acid chlorides. To the best of our knowledge, this is the first report of intamolecular nitrile dipolar cycloaddition reactions in imidazole synthesis.

Chapter 3 focuses on the intramolecular cycloaddition of phospha-Münchnones with olefins. The resulting polycyclic 2-pyrrolines are prepared in good yields with high diastereo- and regio-selectivity from olefin-tethered imines, acid chlorides and phosphonites. Further reactions of these *N*-heterocycles are also investigated, including the formation of substituted pyrrolidines under reductive conditions.

Résumé

Cette thèse décrit l'utilisation d'une nouvelle classe de 1,3-dipôle, le phospha-Münchnone, dans la préparation d'hétérocycles azotés. Le phospha-Münchnone peut être facilement préparé à partir d'imines, de chlorures d'acides et de composés organophosphorés (2-catechyl)PhP. Le couplage sélectif de ces composés suivi d'une réaction de cycloaddition permettent la synthèse d'une variété de composés hétérocycliques de façon modulaire et rapide. Dans le Chapitre 1, un aperçu est présenté en ce qui a trait à l'utilité des imines dans les réactions de cycloadditions 1,3-dipolaires. Cela inclut également leur rôle dans la synthèse d'hétérocycles aromatiques contenant un azote tels que les pyrroles, les imidazoles, les oxadiazolines, les triazoles et leurs analogues réduits.

Dans le Chapitre 2, la synthèse d'imidazoles par cycloaddition d'imines électrons pauvres avec le phospha-Münchnone est décrite. Cette réaction permet la formation directe d'imidazoles hautement substitués de façon « one-pot », et avec une grande régiosélectivité. La méthode est également modulaire, où le modèle de substitution peut être modifiée par simple variation des briques moléculaires (imine, chlorure d'acide et imine N-nosyl). D'autre part, les imines substituées N-nosyl peuvent être remplacées par des nitriles lors des cycloadditions intramoléculaires. Cela permet la synthèse d'imidazoles polycycliques avec des imines contenant un nitrile et des chlorures d'acides. À notre connaissance, cela représente le premier exemple de réaction de cycloaddition intramoléculaire à partir de nitriles non-électrons pauvres dans la synthèse d'imidazole.

Le Chapitre 3 se concentre sur la cycloaddition intramoléculaire du phospha-Münchnone avec des oléfines. Les 2-pyrrolines polycycliques qui en résultent sont préparées de façon efficace avec une grande diastéréo- et régiosélectivité à partir d'imines contenant un alcène, de chlorures d'acides et de phosphonites. D'autres synthèses de N-hétérocycles sont également étudiées, y compris la formation de pyrrolidines substituées dans des conditions réductrices.

Acknowledgements

First and foremost, I would like to thank Allah for granting me this opportunity and providing me with the strength to complete this degree amidst my hard times.

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The contributions from the support staff including Georges Kopp, Chantal Marotte Dr. Fred Morin, Claude Perryman, Rick Rossi, Nadim Saade, Dr. Sean Wahba, and Weihua Wang is greatly appreciated as their help was essential for the completion of my degree.

Lastly, I'd like to thank my family and friends for enduring me these last three years, each and every one of you provided me with immeasurable aid in the completion of this degree, and for that, I dedicate this thesis to you.

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List of Abbreviations

Ac – Acetate

Ar – Aryl

Bn – Benzyl

°C – Degrees Celsius

Catechyl (cat) – *o*-$O_2C_6H_4$

Cy – Cyclohexyl

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

DCCI – Dicyclohexylcarbodiimide

DMF – Dimethylformamide

d – doublet

eq – Equivalents

Et – Ethyl

EWG – Electron withdrawing group

FMO – Frontier molecular orbital

h – Hour (s)

Hex – Hexyl

HOMO – Highest occupied molecular orbital

HRMS – High resolution mass spectrometry

Hz – Hertz

J – coupling constant

L.A – Lewis Acid

LDA – Lithium diisopropulamide

LiHMDS – Lithium hexamethyldisilazane

LUMO – Lowest occupied molecular orbital

m – multiplet

MAO – Methylaluminoxane

Me – Methyl

min – Minute(s)

MS – Mass spectrum

NBS – N-Bromosuccinimide

n-BuLi – n-ButylLithium

NMR – Nuclear magnetic resonance

Ns – Nosyl

PG – Protecting group

Ph – Phenyl

Ph – Phenyl

PMP – *p*-$CH_3OC_6H_4$

ppm – Parts per million

p-Tol – *p*-$CH_3C_6H_4$

q – Quartet

rt – Room temperature

s – singlet

t – triplet

t-BuOK – Potassium tert-butoxide

TFA –Trifluoroacetic Acid

THF – Tetrahydrofuran

TMS – Trimethyl silane

TMSOTf – Trimethylsilyl trifluoromethanesulfonate

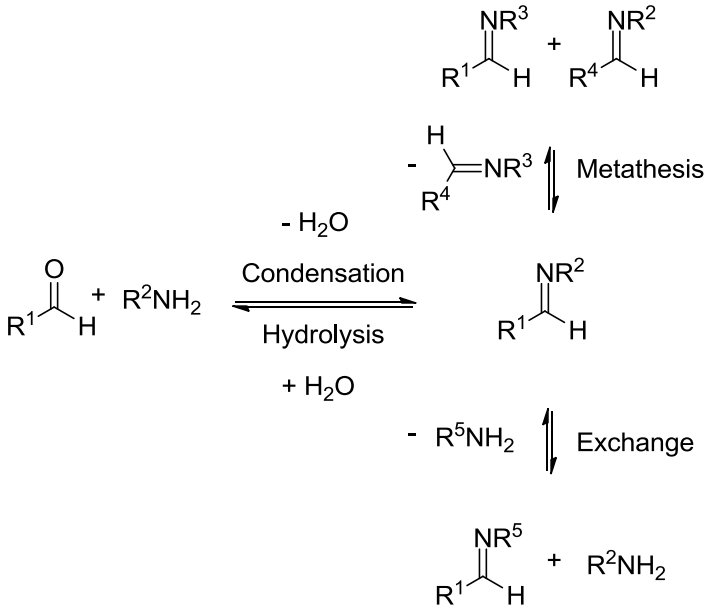
Ts – Tosyl

CHAPTER ONE

Introduction: Characteristics and 1,3-Dipolar Cycloaddition of Imines

1.1 Perspective

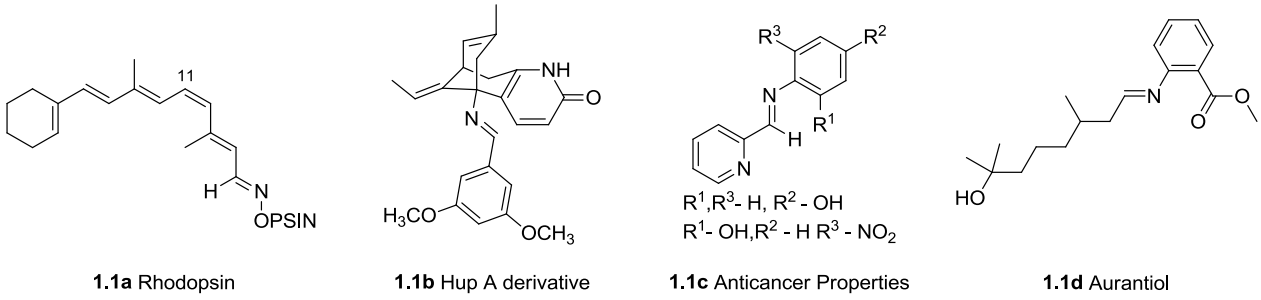
Imines are a useful class of building blocks in organic synthesis.[1] An important feature of imines is the ease of their synthesis. This is typically performed by the simple condensation of primary amines with aldehydes and ketones (Scheme 1.1). Since these substrates are commercially available in multiple forms, a diverse range of imines can be generated by this reaction. The synthesis of imines was first discovered by German chemist, Hugo Schiff, in the 19th century.[2] As such, these products are often referred to as Schiff's bases. Other names include azomethines, anils, and the more widely accepted imines.



Scheme 1.1 Imines: Preparation and Exchange Reactions

The condensation reaction to form imines is driven forward by the reversible liberation of water. This reversibility allows access to equilibrium-controlled reactions, including hydrolysis to give starting aldehyde and amine, metathesis, and exchange reactions.

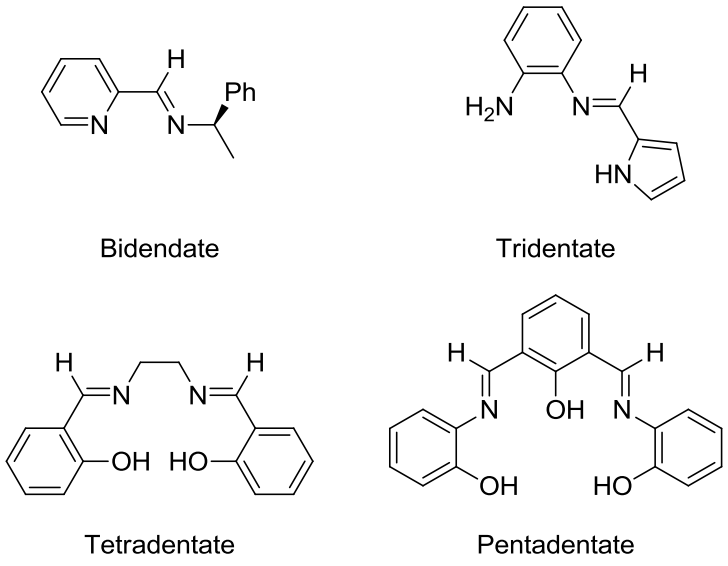
Imine products have found utility in a wide range of areas. For example, they are components in a variety of biologically active compounds (Fig. 1.1). Illustrative examples include rhodopsin **1.2a**,[3] found in the biological system of retinal (vitamin A aldehyde), as well as Huperzine *A*[4] **1.2b** and substituted imines[5] **1.2c**, have been proven important in medicinal chemistry. In addition, imines are equally important in chemistry of fragrances **1.2d**.[6]



1.1a Rhodopsin **1.1b** Hup A derivative **1.1c** Anticancer Properties **1.1d** Aurantiol

Figure 1.1 Imine Containing Compounds in Pharmaceuticals and Fragrances

Due to the coordinating ability of the nitrogen atom, imines are also commonly used as metal-bonding ligands. These are often within chelates, where neighboring coordinating groups can help associate these substrates to metals (Figure 1.2).[7] These metal complexes have found utility in many venues,[8] including as biologically active molecules,[9] optically active materials,[10] and catalysts.[7b] Representative examples are shown in Figure 1.3.



Bidendate Tridentate

Tetradentate Pentadentate

Figure 1.2 Examples of Chelating Schiff Base Ligands

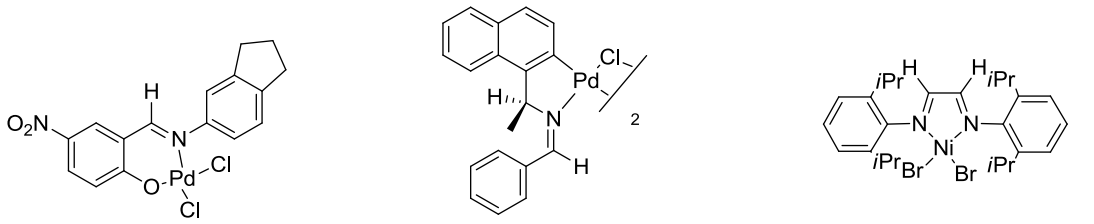


Figure 1.3 Uses of Imine Based Metal Complexes

Likely the most important current application of imines is as synthetic build blocks. The combination of the electronegative nitrogen atom and the electron deficient carbon gives imines a diverse reactivity profile (Figure 1.4).

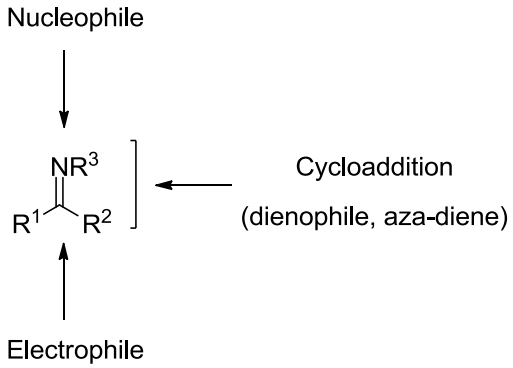
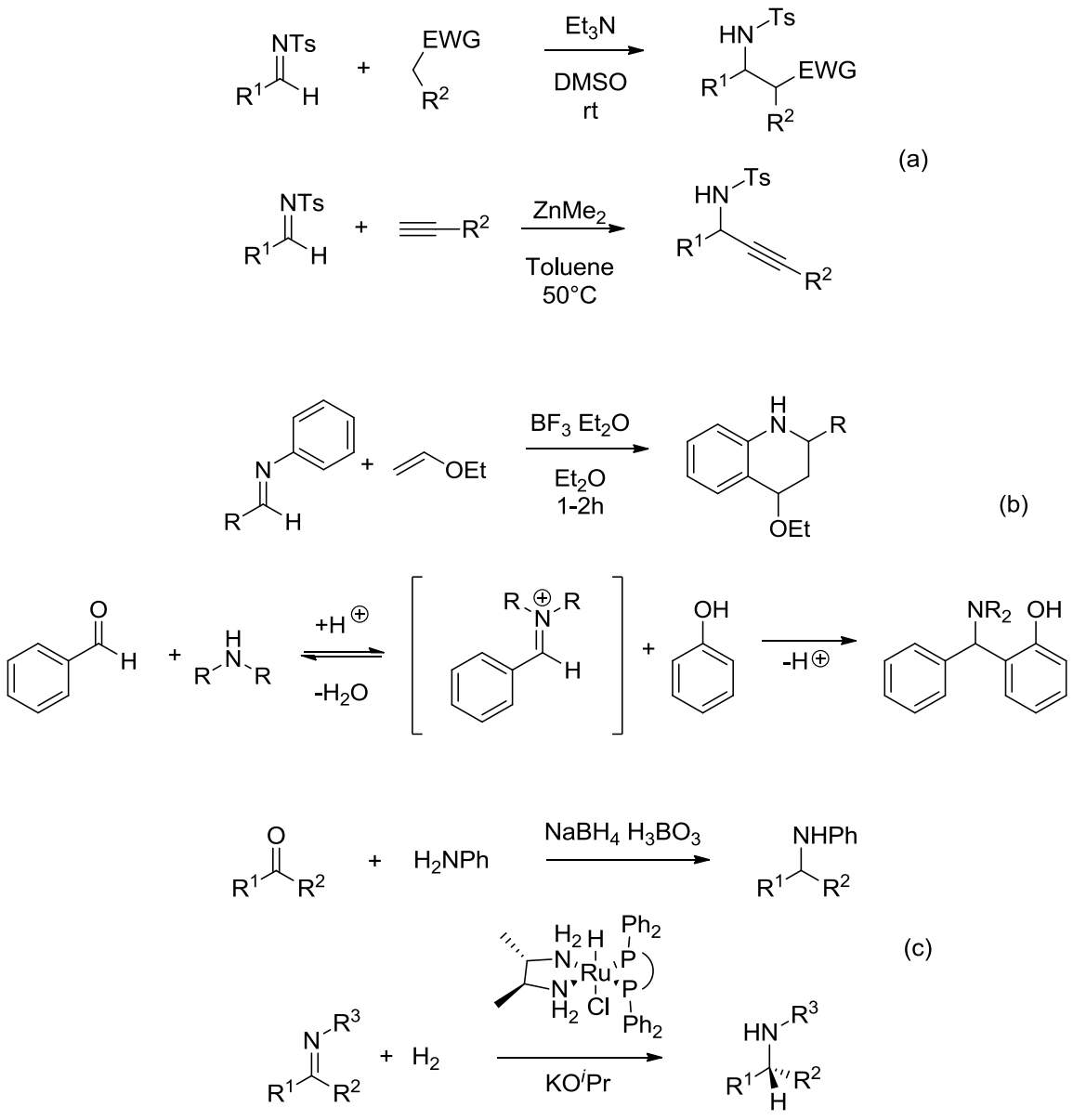


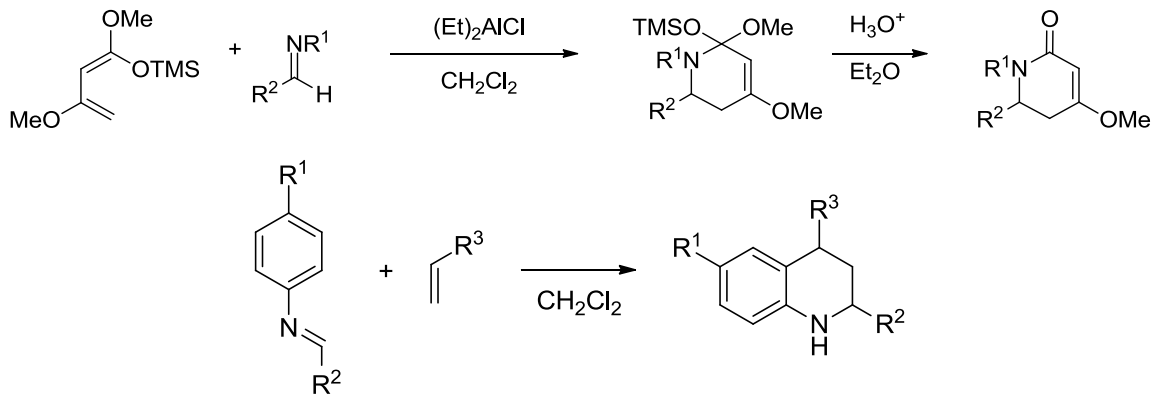
Figure 1.4 General Reactivity Profile of Imines

A common application of imines is as electrophiles in nucleophilic attack reactions.[11] Simple *N*-alkyl or *N*-aryl imines are not highly electrophilic. However, their reactivity can be enhanced by electron withdrawing nitrogen substituents (Scheme 1.2a)[12] or the use of acidic catalysts (Scheme 1.2b).[13] Imines can also be readily reduced (Scheme 1.2c),[14] often by exploiting the polarized C=N bond.



Scheme 1.2 Reactivity of Imines

Alternatively, imines possess a π-bond that has made them useful substrates in cycloaddition reactions. A common use of imines is in hetero Diels-Alder reactions (Scheme 1.3).[15] When coupled with the range of available imines, this has provided a general platform to assemble 6-membered ring heterocycles.

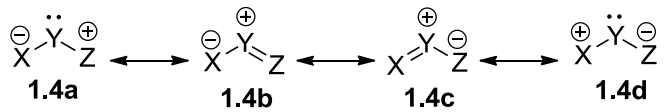


Scheme 1.3 Cycloaddition Reactions of Imines

Another transformation of imines is 1,3-dipolar cycloaddition. This reaction can provide an efficient method to generate 5-membered ring nitrogen-containing heterocycles; which are a classic structure in pharmaceutical design. The latter reactivity will be the subject of Chapter 1 of this thesis.

1.2 General Features of 1,3-Dipolar Cycloaddition

1,3-dipolar cycloaddition reactions provide an atom economical approach to prepare 5-membered ring products.[16] 1,3-dipoles are typically comprised of a four π-electron system delocalized over the three atoms (X-Y-Z). The formed positive and negative charges are spread amongst these atoms through various resonance structures. Notably, non-radical resonance structures cannot be drawn that eliminate the charges **1.4a-1.4d** (Scheme 1.4). The reactive behavior of dipoles is typically attributed to their ambiphilic behavior, as they behave as both nucleophiles and electrophiles.



X, Z = CR_2, NR, O
Y= NR, S, O

Scheme 1.4 Valence Bond Resonance Structures on 1,3-Dipoles

Mechanistically, cycloaddition of the dipole with a dipolarophile occurs in a six π-electron [$_{\pi}4_s$ + $_{\pi}2_s$] fashion by a thermally allowed suprafacial process. The reaction often proceeds via a concerted mechanism, although both bonds may not be formed equally in the transition state.

1.2.1 Reactivity

The reactivity of 1,3-dipoles, much like simple unsaturated substrates, is often explained using frontier molecular orbital (FMO) theory. FMO theory explains reactivity based upon interactions between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the substrates. The theory stipulates that the most rapid cycloaddition will occur between reactants that have the smallest HOMO (substrate 1) – LUMO (substrate 2) energy difference, as this leads to significant overlap in the transition state.[17]

With this as a basis, three possible scenarios can occur during cycloaddition. These are referred to as Sustmann-type interactions (Figure 1.5).[18] Reactions of electron rich dipoles (high HOMO energy) with electron-poor and low energy LUMO dipolarophiles are often called Sustmann type I cycloadditions ($HOMO_{dipole}$-$LUMO_{dipolarophile}$). Alternatively, cycloadditions between a low LUMO energy dipole and high HOMO energy dipolarophile are type III ($HOMO_{dipolarophile}$-$LUMO_{dipole}$). Reactions with similar HOMO-LUMO energy gaps are called type II cycloadditions.

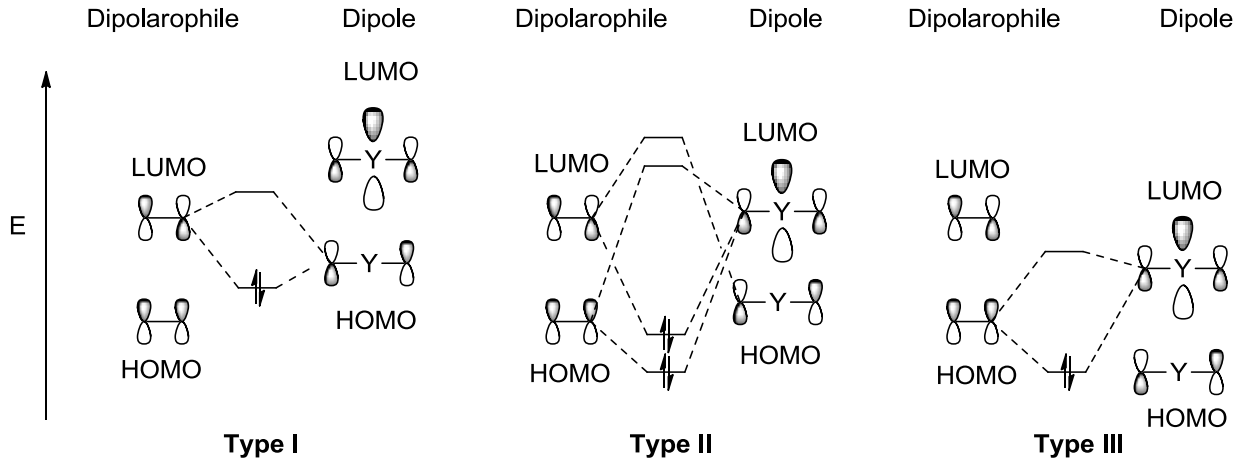
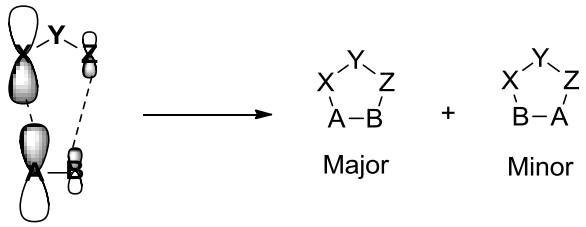


Figure 1.5 Sustmann's Classification of 1,3-Dipolar Cycloaddition Reactions

The relative HOMO-LUMO energies, and thus their reactivity, depend on the nature of the dipole and dipolarophile. For example, azomethine ylides (vide infra) are typically electron rich dipoles, and react via Sustmann Type I cycloaddition.[19] Alternatively, more heteroatom rich dipoles such as nitrile oxides and azides have low LUMO energies, and generally react most rapidly with electron rich dipolarophiles.[20] A range of dipoles display type II behavior.[16]

1.2.2 Regioselectivity

FMO theory is also useful to interpret the regioselectivity of 1,3-dipolar cycloaddition reactions. Reactions of unsymmetrical 1,3-dipoles and dipolarophiles can lead to regioisomeric products. The regiochemical outcome of these reactions is highly dependent on the substrates, and is controlled by both electronic and steric factors.[20] FMO theory rationalizes the electronic influences on regioselectivity based upon the combination of atoms with large orbital coefficients in the 1,3-dipole and dipolarophile.[21] A general example of this is shown in Scheme 1.5.



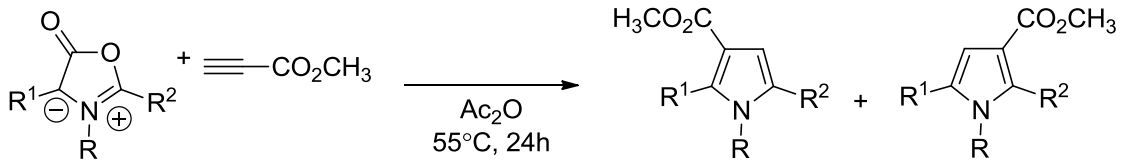
Scheme 1.5 Regiochemistry of 1,3-Dipolar Cycloaddition Reactions

The relative coefficients in the FMOs are influenced by the atoms in the dipole, dipolarophile, and the substituents. The latter can also be used to tune reactivity. For example, an electron-withdrawing group on the dipolarophile can enhance their reactivity with electron rich dipoles (Type I cycloaddition) and increase regioselectivity, by creating a more biased LUMO orbital.

However, it is not always straightforward to predict product regioselectivity. A major complicating issue can be steric effects. These can either cooperate or compete with electronic effects, and in some cases override the electronic preference. This behavior is illustrated in the

cycloaddition of mesoionic compounds such as 1,3-oxazolium-5-olates (Münchnones) with alkynes. Münchnones are electron rich dipoles, and display Type I Sustmann reactivity behavior. Based upon orbital coefficients, these reactions are expected to lead to regioisomeric products where the alkyne electron withdrawing unit is directed away from R^1 (Table 1.1). However, Trost has demonstrated that the regiochemistry in these reactions are more influence by steric interaction than FMO effects, and proceed via an unsymmetrical transition state.[22] These reactions often lead to the favored formation of the pyrrole isomer where the two smallest units are cis, regardless of electronic influences.

Table 1.1 Münchnone Cycloadditions with Methyl Propiolate

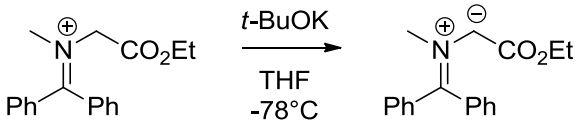


Entry	R^1	R^2	R	Isomer Ratio	
1	H	$(CH_3)_2CH$	CH_3	25	75
2	H	Ph	CH_3CH_2	25	75
3	Ph	H	CH_3CH_2	86	14
4	CH_3	H	CH_3CH_2	84	16

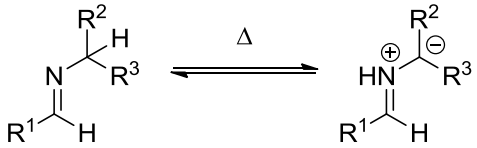
1.3 Imines in 1,3-Dipolar Cycloaddition

1.3.1 Imine-Based in 1,3-Dipoles

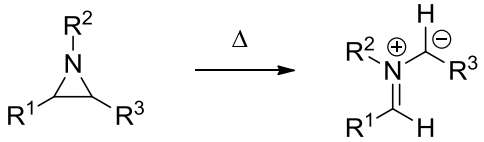
Imines have found utility as precursors to a number of 1,3-dipoles. Likely the most commonly employed imine-based 1,3-dipole is azomethine ylides (Scheme 1.6). A number of methods have been developed to access these dipoles. One of the simplest is through either the deprotonation of iminum salts (Scheme 1.6a),[23] or the tautomerization of imines (Scheme 1.6b).[24] Both of these reactions are facilitated by electron withdrawing units on the α-carbon to the imine nitrogen. Other routes to these dipoles include the ring-opening of aziridines (Scheme 1.6c),[25] nucleophilic additions to oxazolium salts (Scheme 1.6d),[26] the decarboxylation of amino acids (Scheme 1.6e)[27] as well as silicon-based protocols (Scheme 1.6f).[28] Together, these methods can be used to generate a variety of azomethine ylides.



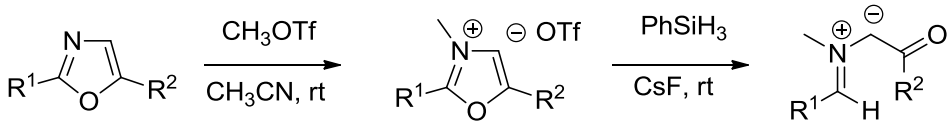
(a) Deprotonation of Iminium Salts



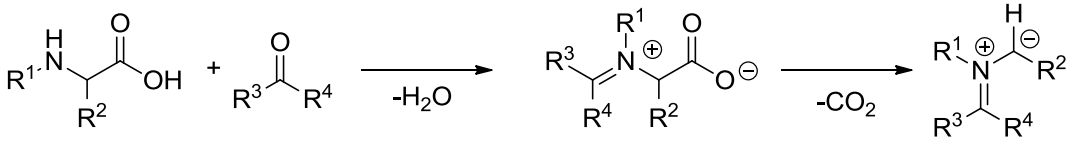
(b) Tautomerization of Imines



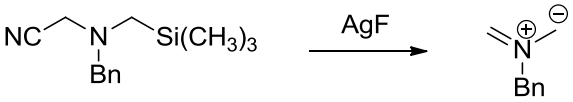
(c) Ring Opening of Aziridines



(d) Nucleophilic Addition to Oxazolium Salts



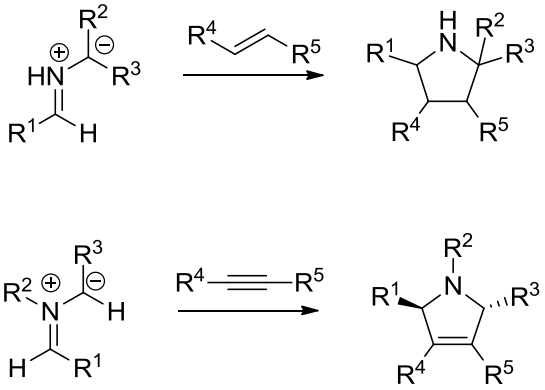
(e) Decarboxylation of Amino Acids



(f) Desilylation Reactions

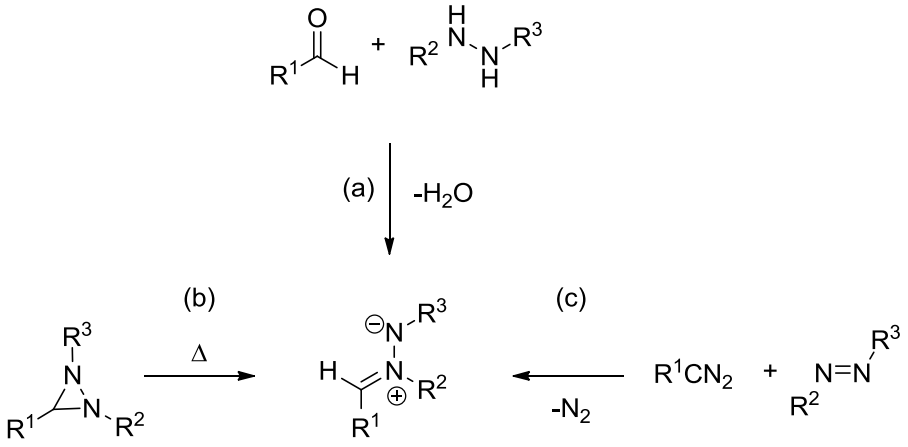
Scheme 1.6 Synthesis of Azomethine Ylides

Due to their high reactivity, azomethine ylides are usually prepared and used *in situ* for 1,3-dipolar cycloaddition reactions. Electron poor dipolarophiles such as alkenes and alkynes are typically employed in these reactions, and yield pyrrolidines and pyrrolines, respectively (Scheme 1.7).[29]

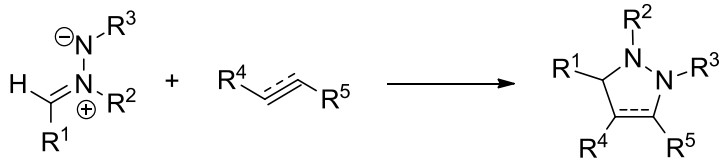


Scheme 1.7 Synthesis of Highly Functionalized Pyrrolidines and Pyrrolines from Azomethine Ylides

In addition to azomethine ylides, azomethine imines is another type of imine-based 1,3-dipole.[30] A classic synthesis of these dipoles is via the condensation of aldehydes with 1,2-disubstituted hydrazines (Scheme 1.8a).[31] Other routes to these 1,3-dipoles include the thermal ring-opening of diaziridines (Scheme 1.8b)[32] and the reaction of diazoalkanes with azo compounds (Scheme 1.8c).[30] These 1,3-dipoles readily undergo cycloaddition with alkenes and alkynes to give pyrazolidines and pyrazolines, respectively (Scheme 1.9)

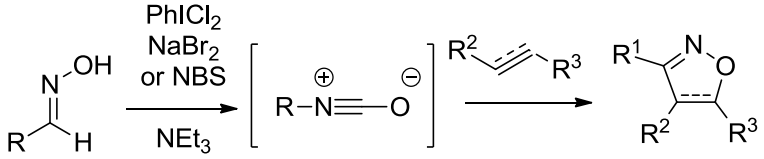


Scheme 1.8 Synthesis of Azomethine Imines



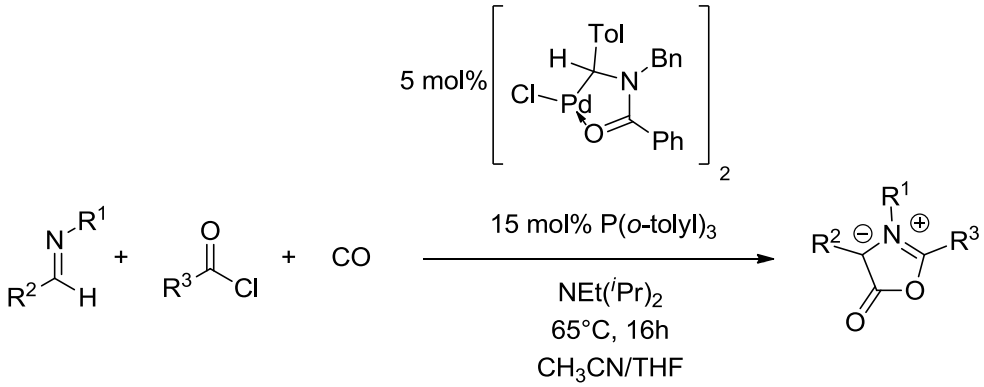
Scheme 1.9 Synthesis of Pyrazolidines and Pyrazolines from Azomethine Imines

Nitrile oxides are another example of imine-based 1,3-dipole. Many methods have been developed to generate these 1,3-dipoles. The most common approach is the oxidation of oximes (Scheme 1.10).[33] These 1,3-dipoles commonly undergo cycloaddition with alkenes and alkynes to give isoxazolines and isoxazoles (Scheme 1.10).

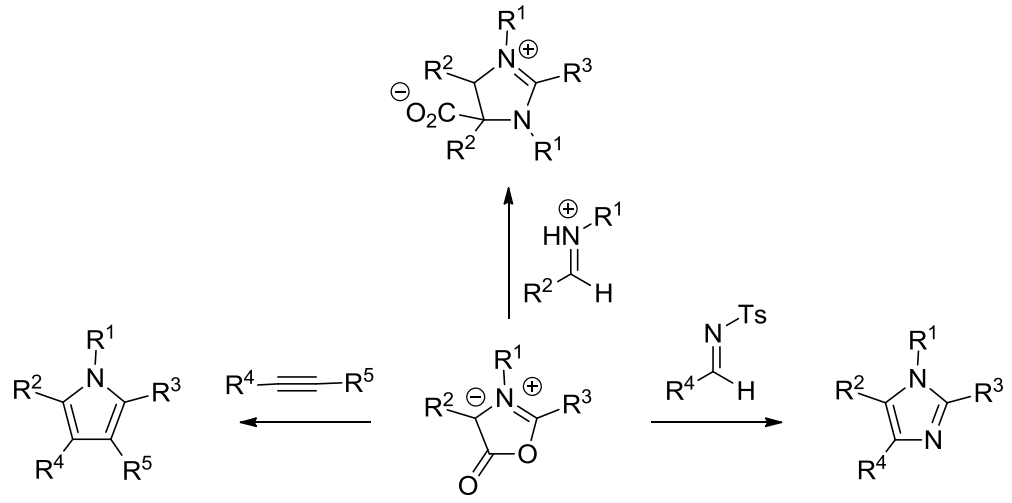


Scheme 1.10 Synthesis of Isoxazolines and Isoxazoles from Cycloaddition of Nitrile Oxides with Alkenes and Alkynes

Our group has reported that Münchnones can be generated via the palladium-catalyzed multicomponent coupling of imines, acid chloride and carbon monoxide (Scheme 1.11).[34] When coupled with cycloaddition, this transformation can provide modular syntheses of nitrogen containing heterocycles from imines, acid chlorides and dipolarophile (Scheme 1.12).

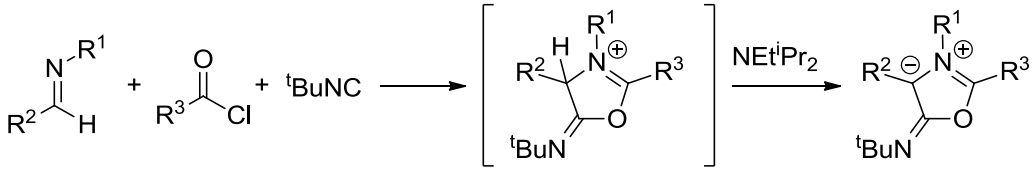


Scheme 1.11 Paladium-Catalyzed Synthesis of Münchnones

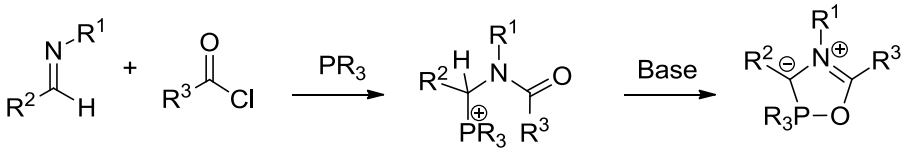


Scheme 1.12 Synthesis of Nitrogen-Containing Heterocycles via Münchnone Cycloaddition

More recently, we have reported that Münchnone imines (Scheme 1.13), and a new class of 1,3-dipole: phospha-Münchnones (Scheme 1.14), can be generated from the coupling of imines with acid chlorides and either isonitriles or phosphonites.[35] These dipoles display similar reactivity to Münchnones, and provide non-palladium catalyzed routes to pyrroles from the same building blocks as above. Notably, the latter reaction with phospha-Münchnones is much more general than that with Münchnones, shows high regioselectivity, and uses stable, relatively inexpensive reagents.



Scheme 1.13 Synthesis of Münchnone Imines



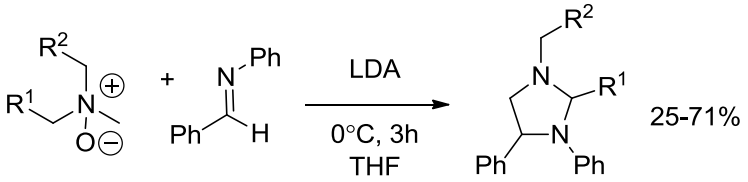
Scheme 1.14 Synthesis of Phospha-Münchones

1.4 Imines as Dipolarophiles

In addition to generating reactive dipoles, imines can also serve as dipolarophiles in 1,3-dipolar cycloaddition reactions. A range of 1,3-dipoles have been reported to participate in cycloaddition reactions with imines. Examples of these are presented below.

1.4.1 Azomethine Ylides Cycloaddition

Azomethine ylides undergo cycloaddition reactions with imines to generate imidazolidines. For example, azomethine ylides generated from tertiary amine N-oxide **1.15a** has been reported to react with unactivated imine dipolarophiles (Scheme 1.15).[29a] This transformation provides a route to imidazolidines **1.15b** in good yields and diastereoselectivity.

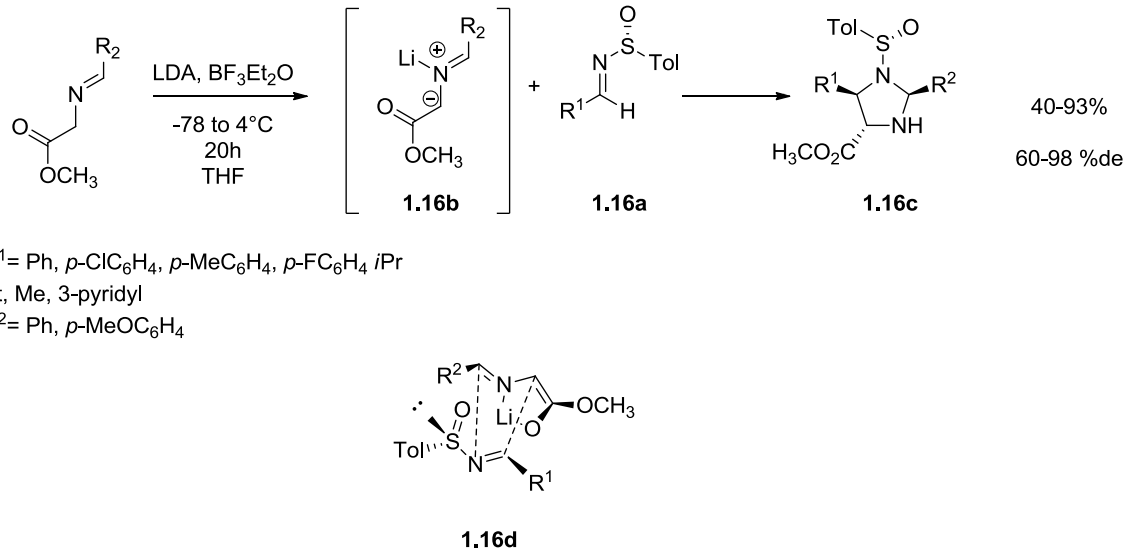


1.15a **1.15b**

R^1, R^2= H, CH_3, $(CH_2)_3$

Scheme 1.15 Imidazolidine Synthesis Using Nonstabilized Azomethine Ylides

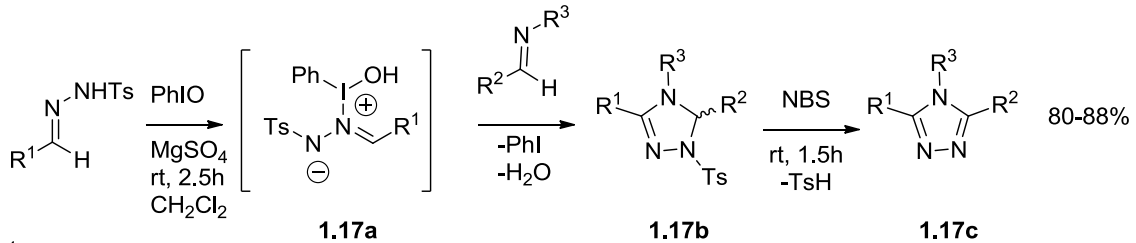
Azomethine ylides can also undergo diastereoselective 1,3-dipolar cycloaddition reactions with imines. Viso *et al.* have reported that chiral sulfimines **1.16a** reacts with azomethine ylide **1.16b** with high diastereoselectivity, leading to the formation of 1,3-imidazolidine **1.16c** (Scheme 1.16).[36] The stereoselectivity in this reaction is rationalized based upon transition state **1.16d**, where the chelated iminoester enolate adds to the less sterically hindered face of the sulfinimine.



Scheme 1.16 Disastereoselective Synthesis of Imidazolidines via Chiral Sulfimine Cycloaddition

1.4.2 Azomethine Imines

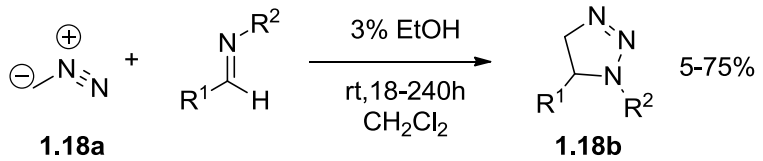
Azomethine imines **1.17a** also undergo cycloaddition reactions with imines, in this case leading to the formation of triazole products. As shown in Scheme 1.17, electron-poor *N*-tosyl imine derived from **1.17a** reacts with various imines to generate substituted 1,2,4-triazolines **1.17b**. Treatment of the later with NBS results in 1,2,4-triazoles **1.17c** upon removal of the tosyl group.[37]



Scheme 1.17 1,2,4-Triazoline Synthesis

1.4.3 Diazomethane

Diazoalkanes are well-established carbene precursors.[38] However, these compounds are also 1,3-dipoles and can participate in cycloaddition reactions to form heterocycles.[39] For example, Kadaba *et al.* have reported that the reaction of diazomethane with substituted imines leads to the formation of 1,2,3-triazolines **1.18b** (Scheme 1.18).[40] This reaction is catalyzed by ethanol, and proceeds in moderate yields.



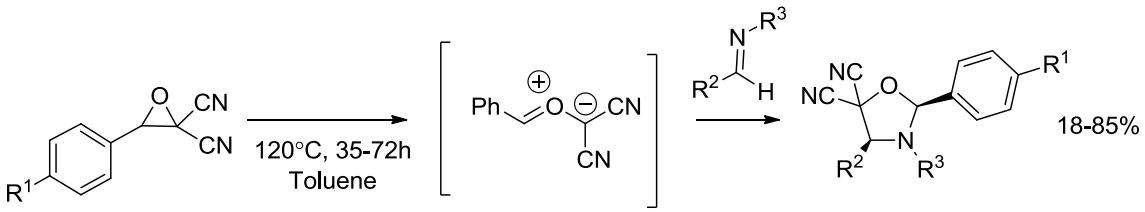
1.18a **1.18b**

R^1, R^2= Ph, *p*-NO_2-C_6H_4, *p*-Cl-C_6H_4, *p*-OMe-C_6H_4

Scheme 1.18 1,2,3-Triazoline Synthesis via 1,3-Dipolar Cycloaddition of Azomethane and Imines

1.4.4 Carbonyl Ylides

Imines can also react with oxygen-containing 1,3-dipoles. For example, the addition of various imines to carbonyl ylides **1.19b** (Scheme 1.19), generated from the ring-opening of epoxides **1.19a**,[41] provides a route to prepare substituted oxazolidines **1.19c** in moderate yields.



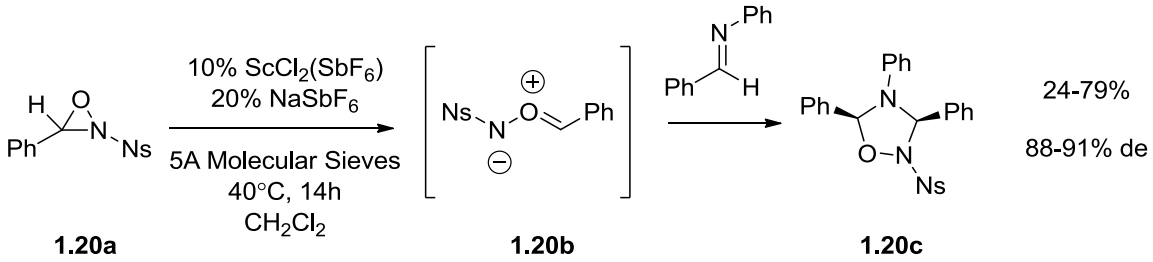
1.19a **1.19b** **1.19c**

R^1= H, Cl, OMe, NO_2
R^2= Ph,
R^3=Me, Pr, Bu, Bn

Scheme 1.19 Carbonyl Dipoles in Oxazolidine Synthesis

1.4.5 Carbonyl Imines

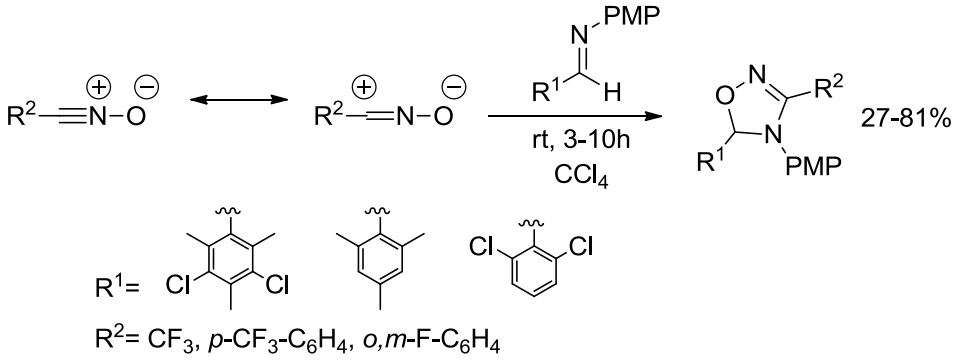
Carbonyl imines **1.20b** are a less commonly employed 1,3-dipole. These have been reported to react with imines to form oxadiazolidines.[42] **1.20b** is generated in situ via the Lewis acid catalyzed rearrangement of oxaziridines (Scheme 1.20). The cycloaddition is forms **1.20c** with good diastereoselectivity.



Scheme 1.20 Stereoselective Synthesis of Oxadiazolidine

1.4.6 Nitrile Oxides

Imines have been reported to react with nitrile oxides to generate 1,2,4-oxadiazolines. An example of this is shown below with fluoro-substituted imines (Scheme 1.21).

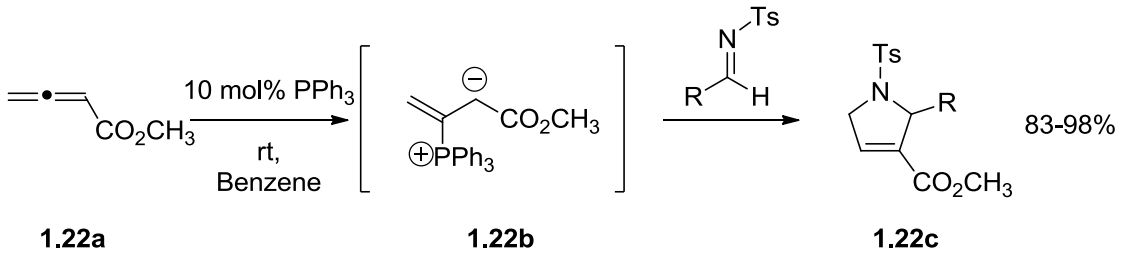


Scheme 1.21 Synthesis of 1,2,4-Oxadiazolines

1.4.7 Carbon 1,3-Dipoles

All carbon 1,3-dipoles **1.22b** (Scheme 1.22), generated *in situ* from the reaction of allenes **1.22a** with phosphine catalysts, are effective in 1,3-dipolar cycloaddition reactions with activated

imines. The reactivity is easily tuned by altering the phosphine source, and provides a route to generate substituted 3-pyrrolines **1.22c** in high yields.[43]

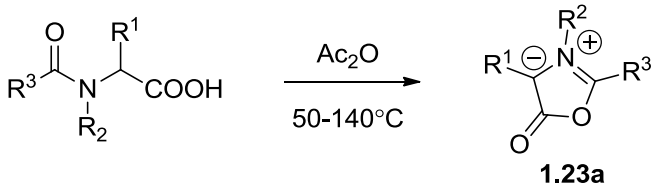


R= Ph, *o*-OMe-C_6H_4,*p*-OMe-C_6H_4,*p*-Cl-C_6H_4,*p*-NO_2-C_6H_4,1-napthyl, piperonyl, cinnamyl, 2-furyl, 2-methyl-4-pentenyl

Scheme 1.22 Cycloaddition of Carbon-Based 1,3-Dipoles with Imines

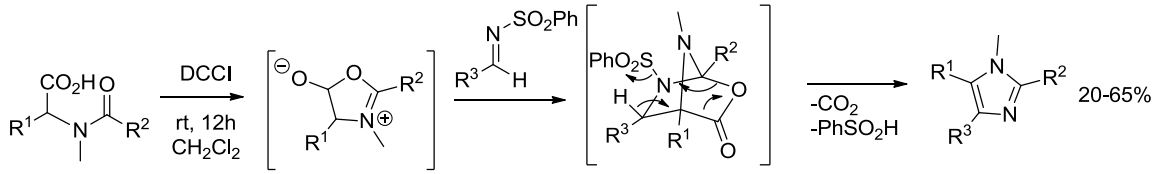
1.4.8 Münchnones

Münchnones have also been employed in 1,3-dipolar cycloaddition reactions with imines. These dipoles are a special class of azomethine ylide, where the 1,3-dipole is integrated in an oxazolium heterocycle **1.23a** (Scheme 1.23). As with many 1,3-dipoles, Münchnones are usually prepared and used *in situ* in 1,3-dipolar cycloaddition reactions. The most common method is through the dehydration of α-amido acids (Scheme 1.23)



Scheme 1.23 Synthesis of Münchnones from Dehydration of α-Amido Acids

Münchnones were first reported to participate in 1,3-dipolar cycloaddition reactions with imines by Consonni *et al*.[44] The reaction of **1.24b** (Scheme 1.24) with N-tosyl substituted imines leads to the rapid generation of an unstable bicyclic adduct **1.24c** that expels carbon dioxide, benzenesulfinic acid and aromatizes to form imidazoles.[45]

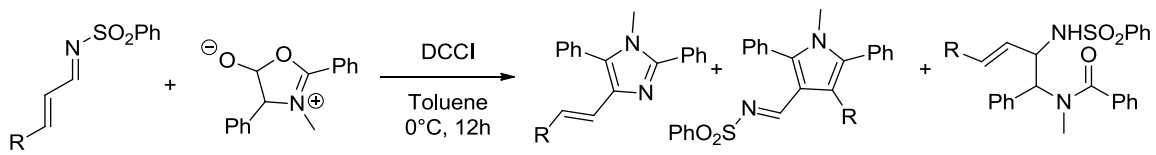


1.24a **1.24b** **1.24c** **1.24d**

R^1=CH_3, Ph
R^2=CH_3, Ph, H
R^3=Ph, *p*-CH_3O-C_6H_4, *p*-NO_2-C_6H_4

Scheme 1.24 Münchnone-Mediated Synthesis of Substituted Imidazoles

α,β unsaturated imines gives rise to a number of products when reacted with Münchnones. Since both the alkene and the imine can react with the 1,3-dipole, imidazoles **1.25c**, pyrrole **1.25d**, and open chain products **1.25e** are all obtained in this reaction (Scheme 1.25).[46]

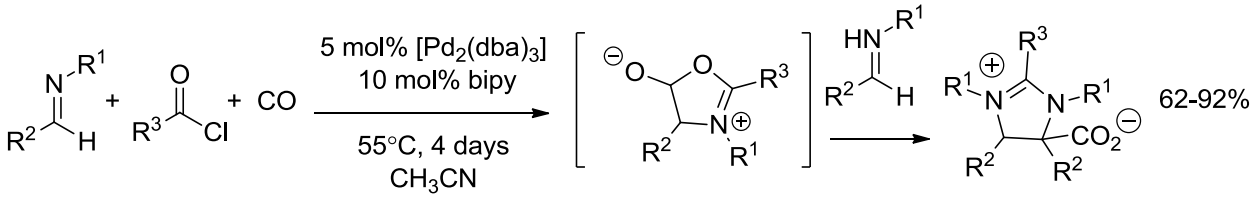


1.25a **1.25b** **1.25c** **1.25d** **1.25e**

R= Ph, *m*-propyl-C_6H_4, *p*-NO_2-C_6H_4, *p*-CH_3O-C_6H_4, 30-38% 8-13% 6-9%

Scheme 1.25 Cycloaddition Reactions of N-Phenylsulfonyl Unsaturated Imines

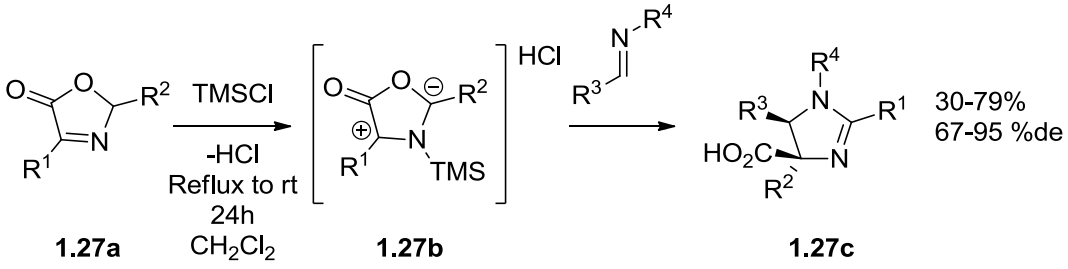
N-alkyl and N-aryl imines can also undergo cycloaddition with Münchnones. As Münchnones are electron rich dipoles, these reactions require acid catalysis, and it is postulated that the protonated imine is the reactive dipolarophile. Our lab reported that protonated imines undergo cycloaddition with in situ generated Münchnones to lead to the formation of imidazolium carboxylate salts (Scheme 1.26).[47]



R^1= Bn, CH_3, $CH_2CH_2OCH_3$, Ph
R^2= Tol, *p*-Me-C_6H_4, *p*-$CH_3SC_6H_4$, *p*-Cl-C_6H_4, *p*-NO_2-C_6H_4
R^3= CH_3, Ph

Scheme 1.26 Palladium-Catalyzed Synthesis of Imidazolines

In a similar approach, Tepe has found that TMSCl addition to azlactones in the presence of imines leads to cycloaddition to form neutral imidazolines **1.27c** (Scheme 1.27).[48]

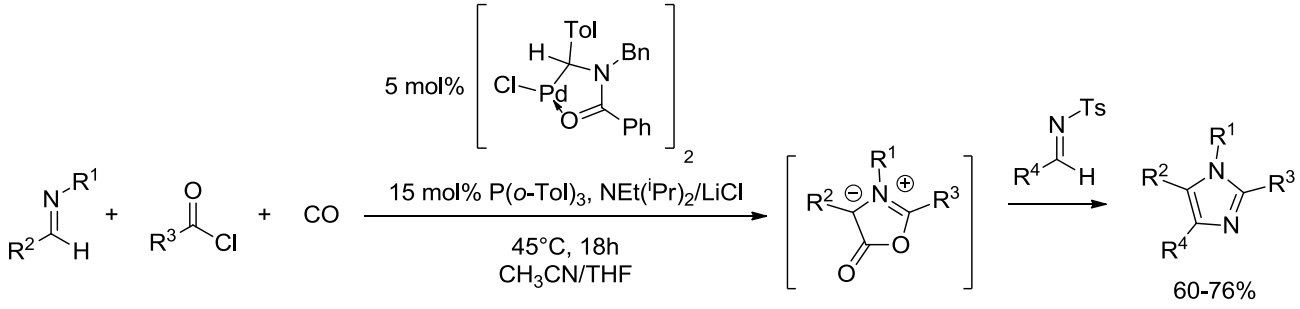


1.27a **1.27b** **1.27c**

R^1= Ph, Bn
R^2= Me, Ph, indolyl-3-methyl, $CH_2CH_2CO_2CH_3$
R^3= Ph, *p*-MeO-C_6H_4, 4-pyridinyl, CO_2Et
R^4= H, Bn, *p*-F-C_6H_4, $CH_2CO_2CH_3$, $CH(CH_3)CO_2CH_3$

Scheme 1.27 Silicon Mediated 1,3-Dipolar Cycloaddition Reactions

Finally, our lab has reported that the palladium catalyzed multicomponent synthesis of Münchnones can be coupled with N-tosyl imine cycloaddition (Scheme 1.28). This provides a general route to imidazoles from three simple units: imines, acid chlorides and N-tosyl imines.



R^1= Et, *p*-OCH_3-C_6H_4, Bn, hexyl
R^2=, *t*-Bu, Tol, *p*-CH_3S-C_6H_4
R^3= Ph, 2-furyl, 3-pyridine, cyclohexyl, pentyl

Scheme 1.28 Modular Catalytic Synthesis of Tetra-Substituted Imidazoles

1.5 Overview of Thesis

Due to the importance of nitrogen containing heterocycles in the fields of chemistry and biology, a range of synthetic methodologies have been developed to generate these products. As described above, one of the most convergent approaches is via 1,3-dipolar cycloaddition reactions with imines. Notably, imines are readily available from amines and aldehydes (or ketones), making these building blocks both accessible and easily generalized.

One important class of heterocycles is imidazoles. As discussed in Section 1.4 (Scheme 1.24), imidazoles can be synthesized by the cycloaddition reaction of Münchnones with electron poor N-tosyl imines. This method is limited by the need to first generate the poly-substituted Münchnone dipole. Our lab has shown that this can be avoided by using palladium catalysis to assemble Münchnones from imines, acid chlorides and carbon monoxide (Scheme 1.28). However, the latter reaction shows limited scope, and typically only proceeds in high yields with aryl- or heteroaryl-substituted imines and acid chlorides.

As an alternative to Münchnones, the Arndtsen group has recently described a new class of 1,3-dipole: phospha-Münchnones (Section 1.3). These dipoles are easily prepared from imines, acid chlorides and phosphonites, and undergo cycloadditions with alkynes in a fashion similar to Münchnones. In light of this reactivity, we have undertaken a study of the potential utility of these dipoles in imidazole synthesis. Chapter 2 of this thesis describes the preparation of tetra-substituted imidazoles through 1,3-dipolar cycloaddition reactions of electron deficient *N*-nosyl imines with phospha-Münchnones. The reactivity was further extended to nitrile-tethered imines, which undergo intramolecular cycloaddition to form polycyclic imidazoles.

In Chapter 3, we examine the cycloaddition of these phospha-Münchnones with alkenes. These studies were initiated by a PhD student in our group, Marie Morin. We show that the use of olefin-tethered imines in the generation of the phospha-Münchnones results in spontaneous alkene cycloaddition. This provides an efficient route to generate polycyclic 2-pyrrolines and pyrrolidines in one pot reactions from alkene-tethered imines and acid chlorides.

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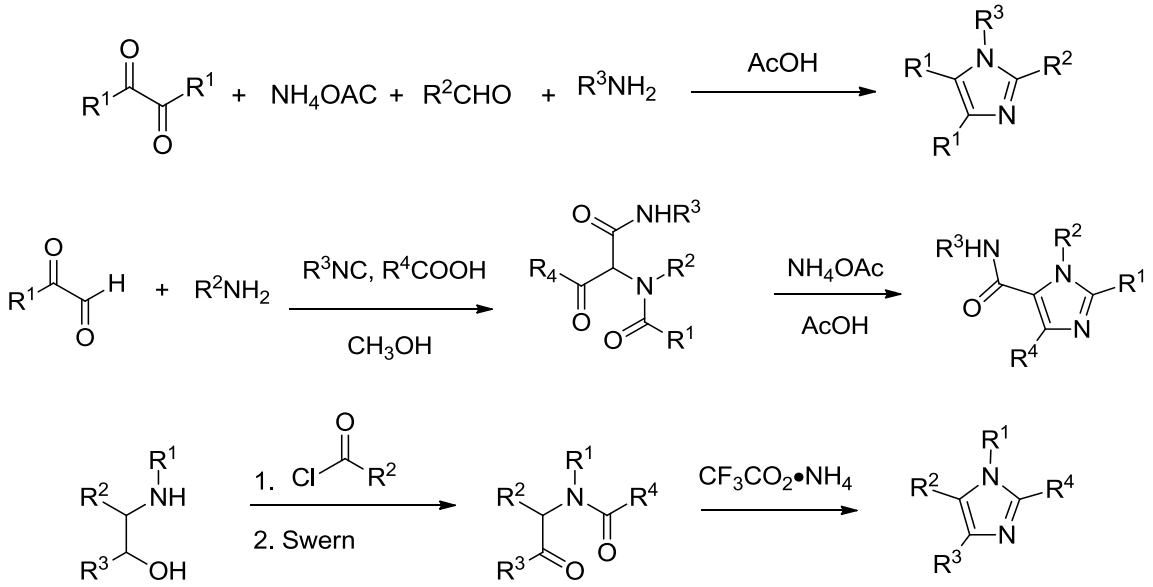
CHAPTER TWO

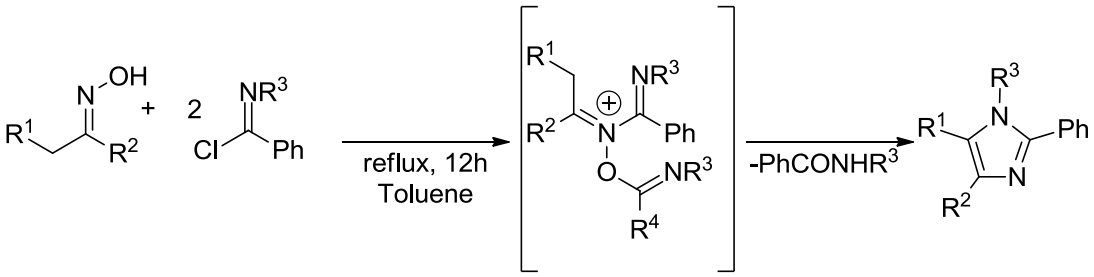
Synthesis of Highly Substituted and Fused-Ring Imidazoles via Phospha-Münchnone Cycloaddition

2.1 Introduction

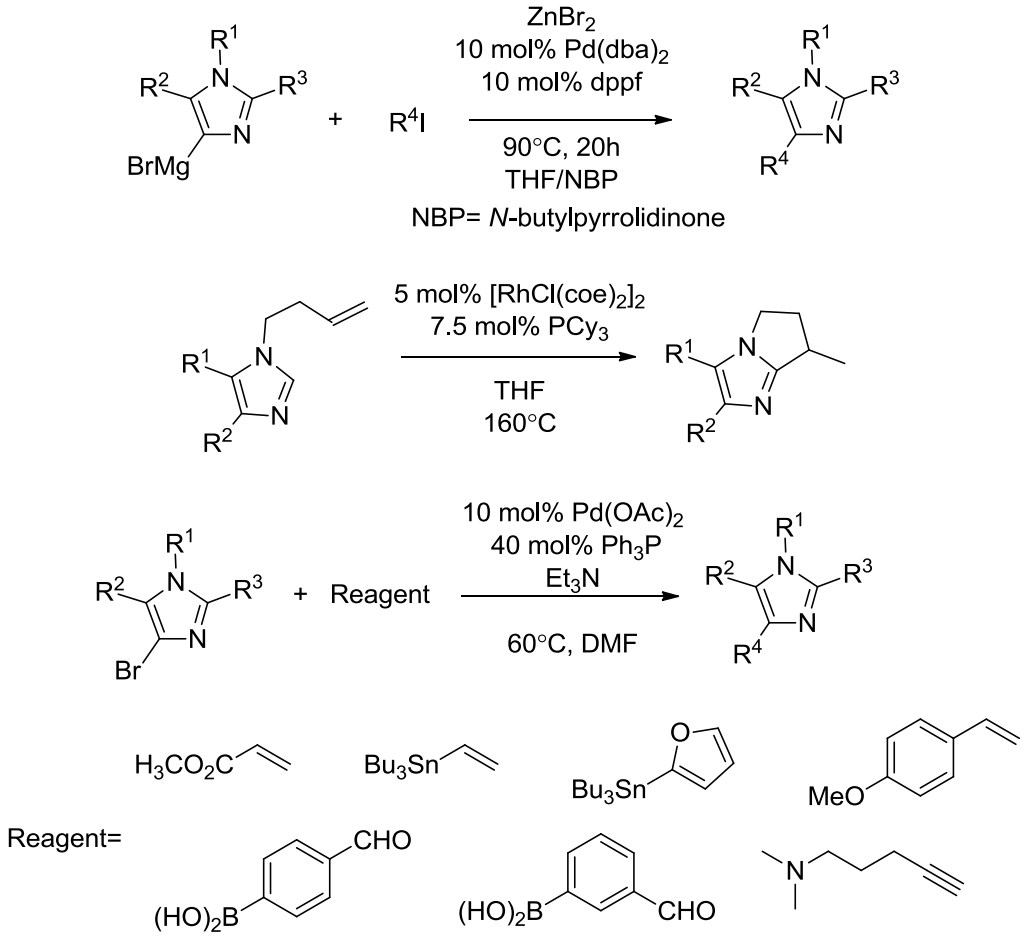
Imidazoles are an important general class of nitrogen containing heterocycle. These structures represent the core unit in a diverse range of pharmaceutical agents[1] and natural products,[2] including the angiotensin II inhibitor, olmesartan,[3] and the antitumor agent, clathridine A.[4] Imidazoles have also been incorporated into ionic liquids,[5] metal-coordinating ligands[6] and functional polymers.[7] Due to their importance, a variety of methods have been developed to construct these heterocycles.[8] However, only a few give access to tetra-substituted imidazoles. These include cyclocondensation reactions (Scheme 2.1),[9] hetero-cope rearrangements (Scheme 2.2),[10] or substitution reactions on pre-synthesized imidazoles (Scheme 2.3).[11] While effective, these methods typically require the non-trivial, multistep synthesis of the starting materials, generate waste, and/or suffer from the lack of regiocontrol.



Scheme 2.1 Cyclocondensation Approaches to Imidazoles



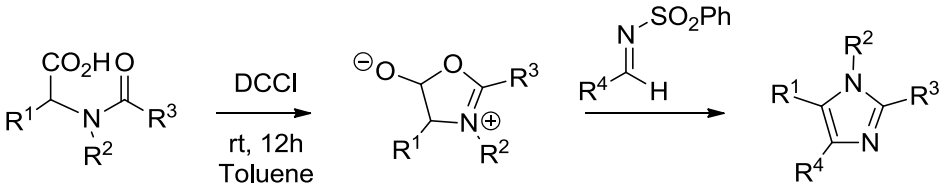
Scheme 2.2 Imidazole Synthesis via Hetero-Cope Rearrangement



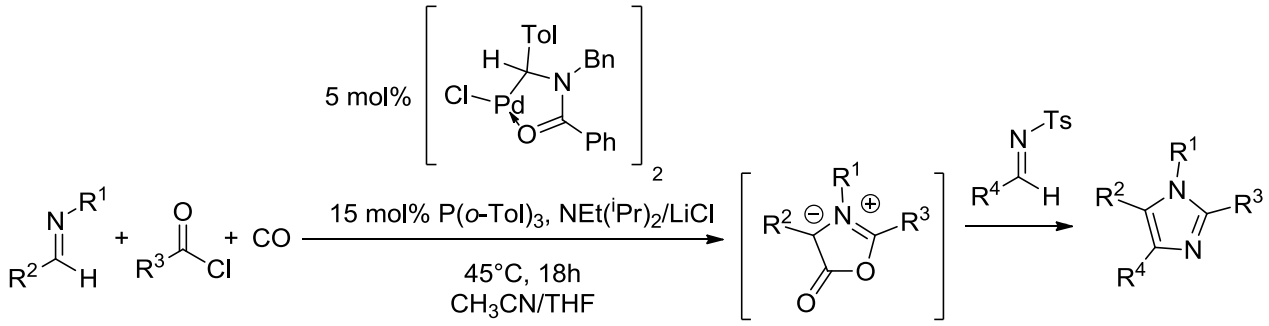
Scheme 2.3 Substitution Reactions on Pre-Synthesized Imidazoles

A convergent approach to imidazoles is via the 1,3-dipolar cycloaddition of *N*-phenylsulfonyl-substituted imines with 1,3-oxazolium-5-oxides (Münchnones) (Scheme 2.4). This reaction was first reported by Consonni *et al*,[12a] and allows regioselective formation of

tetra-substituted imidazoles via cycloaddition followed by spontaneous CO_2 and benzenesulfinic acid loss.[13] More recently, we have shown that Münchnones can be generated via the palladium-catalyzed coupling of imines, acid chlorides and carbon monoxide,[14] which, when coupled with *N*-tosyl imine cycloaddition, provides an efficient synthesis of imidazoles from imines, acid chlorides and *N*-tosyl imines (Scheme 2.5).[15] A challenge with these cycloaddition approaches is the scope of products readily available, as palladium catalysis typically requires the use of stable C-aryl substituted imines, and more traditional approaches to Münchnones involve the initial multistep build up of an α-amido acid precursor.[16] In addition, both of these cycloaddition reactions require the use of sensitive *N*-tosyl imines.



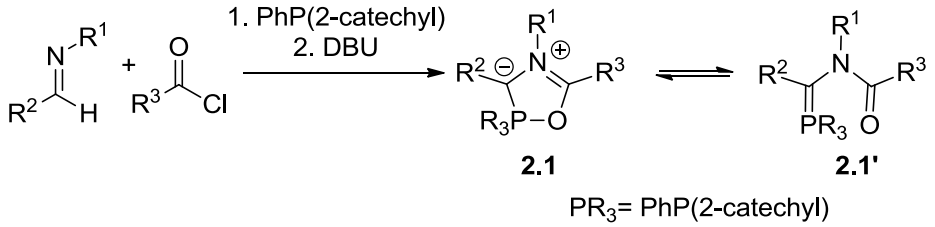
Scheme 2.4 Münchnone-Mediated Synthesis of Imidazoles



Scheme 2.5 Palladium-Catalyzed, Multicomponent Synthesis of Imidazoles

We have recently reported a new type of dipole that suggests an alternative to the above methods, phospha-Münchnones **2.1** (Scheme 2.6). The latter is readily prepared from imines, acid chlorides and catechyl-substituted phosphonites, and undergoes cycloaddition with alkynes and alkenes in a direct analogy to Münchnones.[17] In light of the facile generation of **2.1**, we became interested in the use of these substrates in cycloadditions to generate imidazoles. As described below, this can allow the mild, regioselective and general synthesis of tetra-substituted imidazoles. In addition, the high reactivity of these dipoles has opened the potential of replacing

N-tosyl imines with nitriles, providing a novel synthesis of polycyclic imidazole products from nitrile-tethered imines and acid chlorides.

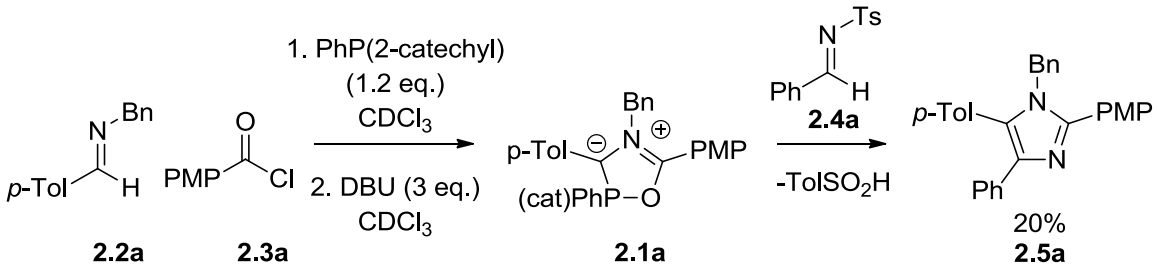


Scheme 2.6 Modular Design of Phosphorus Based 1,3-Dipole

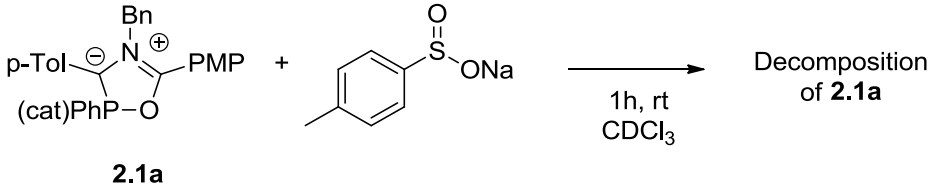
2.2 Results and Discussion

2.2.1 Imine Cycloaddition with Phospha-Münchnone

Our initial work probed the reaction of phospha-Münchnone **2.1a** with *N*-tosyl benzaldimine. As shown in Scheme 2.7, the *in situ* formation of **2.1a** from imine **2.2a**, acid chloride **2.3a** and PhP(2-catechyl) followed by the addition of *N*-tosyl imine **2.4a** leads to the complete consumption of the dipole over the course of 2 h, and the formation of imidazole **2.5a**.[12b] However, the yield of **2.5a** is very low (20%). In situ ^{1}H and ^{31}P NMR analysis of the reaction mixture show that the dipole has decomposed to a number of unidentifiable side products, together with the near quantitative formation of phosphine oxide. Control experiments suggest that the toluene sulfinate leaving group generated as a byproduct of imidazole formation is non-innocent in this reaction. The addition of sodium *p*-toluene sulfinate to phospha-Münchnone **2.1a** results in the rapid decomposition of the 1,3-dipole within 1 h, at ambient temperature (Scheme 2.8), generating a complex mixture of products.[18]



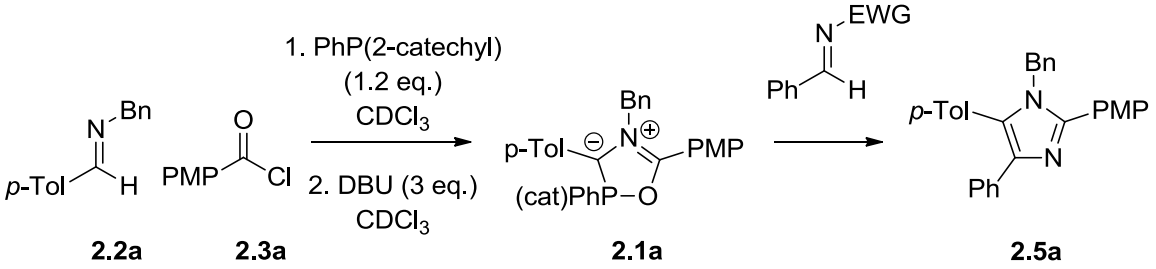
Scheme 2.7 Phospha-Münchnone Mediated Synthesis of Imidazole

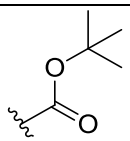
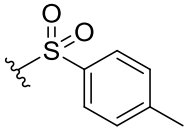
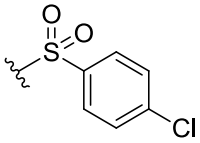
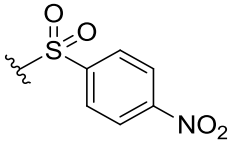
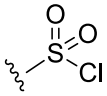


Scheme 2.8 Control Experiment of Phospha-Münchnone and *p*-Toluene Sulfinate

In an attempt to improve the efficiency of this reaction, both the imine dipolarophile and phosphine used in the reaction were optimized (Tables 2.1 and 2.2). Firstly, since the arylsulfonyl unit on the imine is lost upon cycloaddition, we probed the potential of other *N*-substituted imines to increase the yield of this reaction. As shown in Table 2.1, a number of other electron deficient imines can undergo cycloaddition with *in situ* generated **2.1a**. **2.1a** reacts most efficiently with electron poor dipolarophiles. Thus, the more electron rich *N*-Boc substituted imine does not react with **2.1a**, while the use of the *p*-chloroaryl sulfonyl imine leads to a slight increase in yield (entry 3) Moving to the even more electron deficient *N*-nosyl imine leads to the formation of **2.5a** in a useful 65% yield (entry 4). More electron poor *N*-SO_2Cl substituted imine does not further increase the reaction yield, and only 10% (entry 5) of the imidazole was formed, together with decomposition of the dipole.

Table 2.1 Screening of Electron Deficient Imines[a]



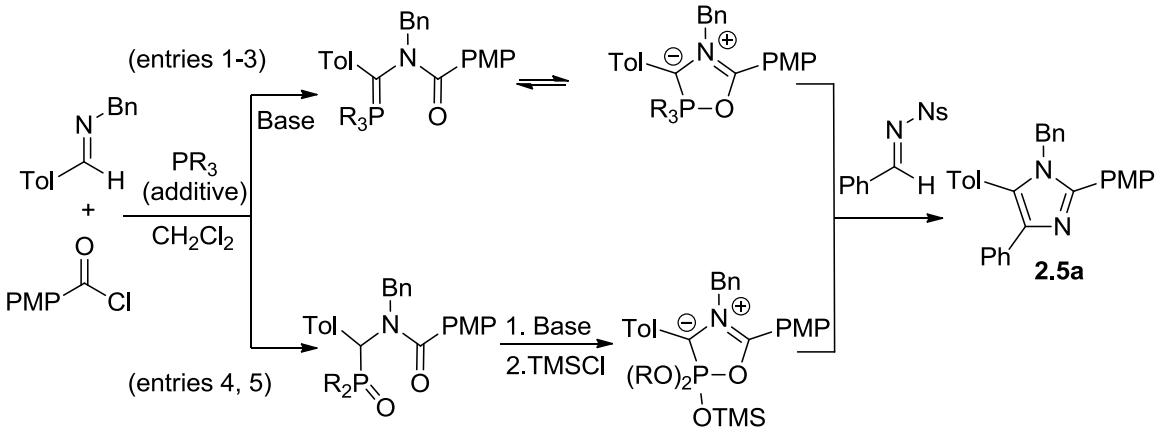
Entry	EWG	Yield (%)
1[b]		0
2		20
3		25
4		65
5		10

[a] **2.1a** (42 mg, 0.2 mmol), **2.2a (**38mg, 0.22 mmol),0.5 mL $CDCl_3$, 30 min. rt; then PhP(2-catechyl)(48 mg, 0.22 mmol) 30 min. rt; DBU (91 mg, 0.6 mmol); **2.5** (87 mg, 0.3 mmol), 2h. rt.[b] 50°C

Various phosphorus sources were also examined in this reaction. Consistent with previous reports, trialkyl phosphines do not mediate cycloaddition presumably due to the electron rich phosphine that does not cyclize to form the 1,3-dipole (Table 2.2, entry 1). Triphenylphosphite (entry 3) and tris(trifluoroethyl)phosphite (entry 2) do mediate the formation of imidazole, but in moderate yield. Amido-substituted Horner-Wadsworth-Emmons reagents have been previously reported to be precursors to 1,3-dipoles in the presence of TMSCl.[19] As

shown in entries 4 and 5, the generation of these dipoles from imines, acid chloride and phosphite does result in cycloaddition with N-nosyl imine, but in lower yields. Overall, these studies suggest that PhP(2-catechyl) in concert with N-nosyl imine provides the most efficient system for cycloaddition to form imidazole in good yield, at ambient temperature and without the use of any additives.

Table 2.2 Development of Phosphine Mediated Synthesis of Imidazoles[a]



Entry	PR_3	Base	Additive	Time	Yield (%)
1	$P(Cy)_3$	LiHMDS[b]		18h	0
2	$P(OCH_2CF_3)_3$	DBU		3h	18
3	$P(OPh)_3$	LiHMDS[b]	TMSOTf	18h	40
4	(Catechyl)POTMS[c]	LiHMDS[b]	TMSOTf	4h	47
5	$P(OEt)_3$ [c]	LiHMDS[b]		18h	19

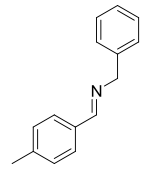
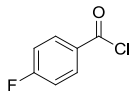
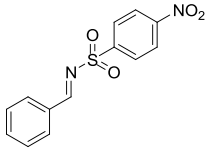
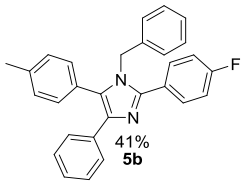
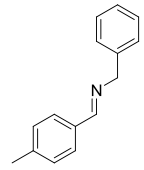
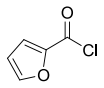
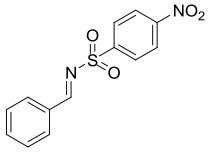
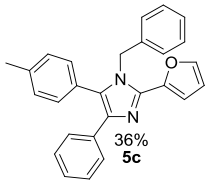
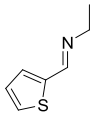
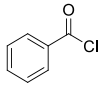
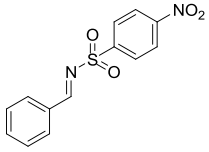
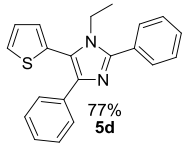
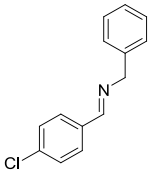
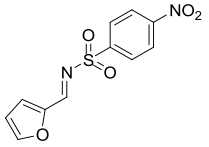
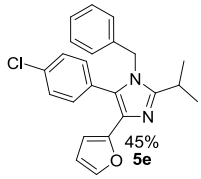
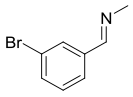
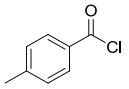
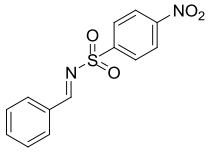
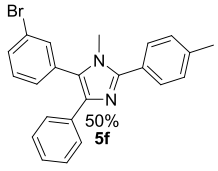
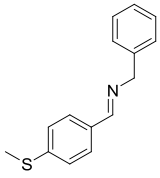
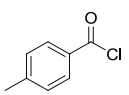
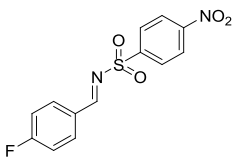
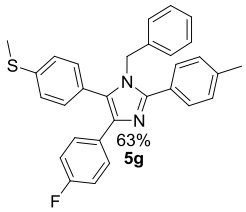
[a] Table 2.1 procedure [b] Added at -78°C. [c] (0.2 mmol TMSCl)

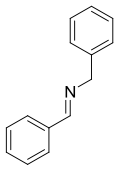
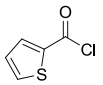
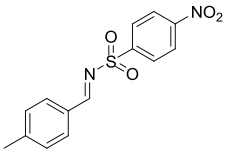
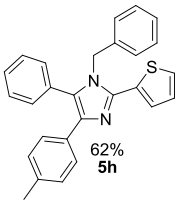
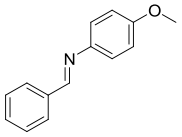
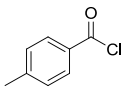
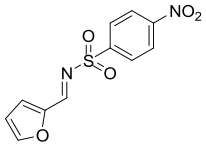
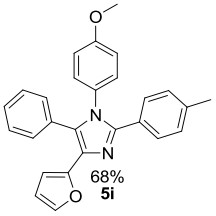
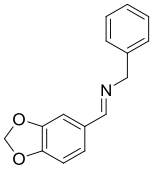
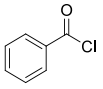
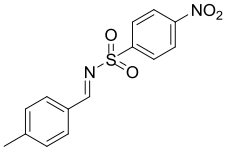
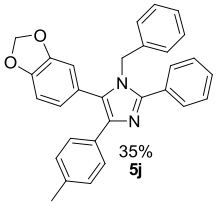
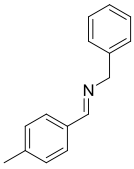
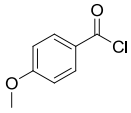
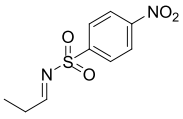
2.2.2 Scope of Substituted Imidazoles

With the optimized reaction conditions, we turned our attention to the substrate scope. A useful feature of the phosphorus-based 1,3-dipole **2.1** is its modular formation from PhP(2-catechyl), imines, and acid chlorides. Thus, it is straightforward to tune any of the three dipole substituents. This is illustrated in Table 2.3. The reaction proceeds with various *C*-aryl and *C*-heteroaryl substituted imines, as well as those with *N*-alkyl, *N*-benzyl or *N*-aryl substituents. Similarly, a variety of acid chlorides can be employed. These include not only substituted

benzoyl chloride, but also heteroaryl (entries 2 and 7) and alkyl acid chlorides (entry 4). The *N*-nosyl substituted imine can also be modulated with a range of aryl and heteroaryl substituents. However, aliphatic *N*-nosyl imines do not undergo cycloaddition, but instead leads to decomposition of the dipole (entry 10). Overall, this reaction can allow the buildup of a range of substituted imidazoles from two imines, and acid chloride, where each of the four substituents can be systematically modulated with perfect regiocontrol.

Table 2.3 Scope of Tetra-Substituted Imidazole

Entry	Imine	Acid Chloride	Imine	Product (% yield)
1				 41% **5b**
2				 36% **5c**
3				 77% **5d**
4				 45% **5e**
5				 50% **5f**
6				 63% **5g**

7				 62% **5h**
8				 68% **5i**
9				 35% **5j**
10				0%

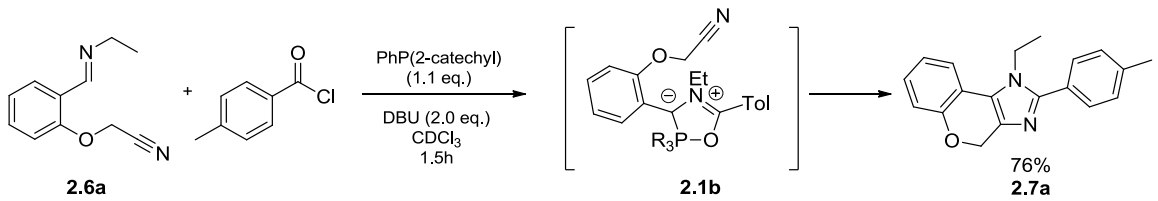
[a] Table 2.1 procedure

2.2.3 Synthesis of Polycyclic Imidazoles

With the synthesis of polysubstituted imidazoles in hand, we next turned our attention to a potentially more atom economical approach to these products: nitrile cycloaddition. Nitriles are readily available and stable units, and would obviate the need to generate *N*-tosyl imines. In addition, their cycloaddition leads to no waste from the C=N fragment. Unfortunately, nitriles are also poor cycloaddition substrates with Münchnones. Previous results have shown that only electron poor nitriles (e.g. ethyl cyanoformate) are sufficiently reactive to cycloadd to Münchnones, and do so in low yield.[20] As an alternative, since the phospha-Münchnone is generated from imines and acid chlorides, we postulated that it should be straightforward to incorporate simple, unactivated nitriles into **2.1** from nitrile-tethered imines. This would allow a more favorable intramolecular cycloaddition reaction to assemble polycyclic imidazoles.

Nitrile-linked imines are easily generated from aldehyde precursors. For example, imine **2.6a** can be generated from salicylaldehyde and bromoacetonitrile, followed by condensation

with ethylamine.[21] The reaction of **2.6a** with *p*-toluoyl chloride and PhP(2-catechyl) in $CDCl_3$ followed by the addition of DBU leads to a spontaneous cycloaddition of **2.1b** to generate polycyclic imidazole **2.7a** (Scheme 2.7) in 76% isolated yield.



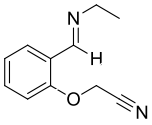
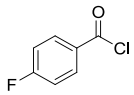
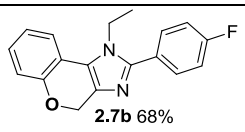
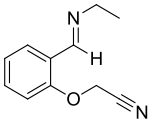
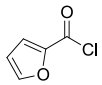
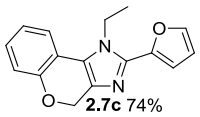
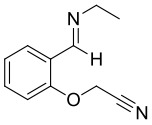
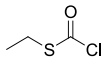
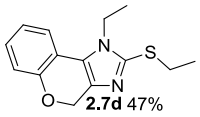
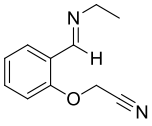
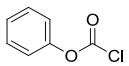
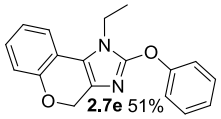
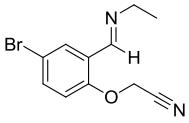
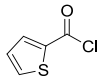
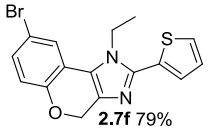
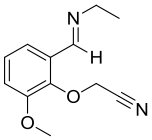
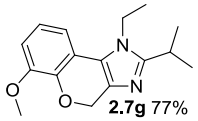
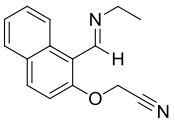
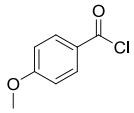
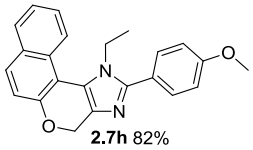
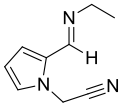
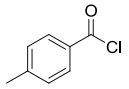
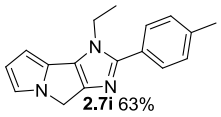
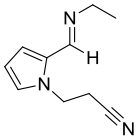
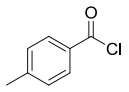
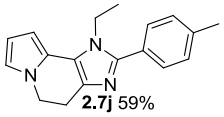
2.6a **2.1b** **2.7a**

Scheme 2.9 Phosphorus Mediated Intramolecular Cycloaddition Reaction

Similar to that shown in Section 2.2.2, this reaction is also easily generalized. A number of imines can be used in this imidazole synthesis (Table 2.4), including aryl- (entries 5 and 6), napthyl- (entry 7) and pyrrole-based (entries 8 and 9) imines. The nitrile tether can be also varied, with oxygen- or nitrogen-tethered nitriles generating imidazole in good yields (entries 1, 8), while 6,6-, 6,5- and 5,5-fused ring products can be formed at equal ease (entries 7-9).[22]

The acid chloride can similarly be modulated in this transformation. Various aryl-, heteroaryl- (entries 2, 5), and even alkyl- (entry 6) substituted acid chlorides lead to imidazoles in high yields. In addition, this chemistry can be expanded beyond acid chlorides. Chloroformates and chlorothioformates are also established to react with imines to form iminium salts. The use of the latter in this reaction provides efficient access to 2-thioalkyl (entry 4) and 2-phenoxy- (entry 3) substituted products in moderate to good yield. Overall, considering the availability of these substrates, this reaction provides a very efficient approach to prepare polycyclic imidazoles, where these products can be assembled in one pot, from nitrile-tethered imines and acid chlorides and with good substrate diversity.

Table 2.4 Scope of Polycyclic Imidazoles

Entry	Substrate	Acid Chloride	Product (% yield)
1			 **2.7b** 68%
2			 **2.7c** 74%
3			 **2.7d** 47%
4			 **2.7e** 51%
5			 **2.7f** 79%
6			 **2.7g** 77%
7			 **2.7h** 82%
8[b]			 **2.7i** 63%
9[b]			 **2.7j** 59%

[a] imine (0.2 mmol), acid chloride (0.22 mmol), 0.5 mL $CDCl_3$, 30 min. rt; then PhP(2-catechyl) (0.22 mmol) 30 min. rt; DBU (0.4 mmol) [b] CD_3CN

2.3 Conclusions

In conclusion, phospha-Münchnones have been found to participate in 1,3-dipolar cycloaddition reaction electron deficient imines and tethered nitriles to generate imidazoles. These reactions are modular, easily generalized, and allow access to highly substituted or polycyclic imidazoles in one pot from available substrates. These represent new multicomponent routes to polysubstituted imidazoles.

2.4 Experimental

2.4.1 General Procedures

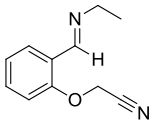
All reactions were performed in a Vacuum Atmospheres 553-2 dry box. All reagents were purchased from commercial sources and used as received. PCy_3 was dried by heating at 120°C under high vacuum. Liquid $P(OCH_2CF_3)_3$ and $P(OPh)_3$ were dried over 4Å molecular sieves. PhP(2-catechyl),[22] (catechyl)POTMS[19] and aldehyde precursors to imines[23] were prepared as described in the literature. Deuterated $CDCl_3$ was distilled from CaH_2 under nitrogen. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 and 400 MHz instruments. HRMS were obtained from the McGill University mass spectra facilities.

2.4.2 Typical Nitrile-Tethered Imine Synthesis

2-(2-formylphenoxy)acetonitrile was prepared in anology to literature reports[21.] To salicylaldehyde (500 mg, 4.09 mmol) in DMF (15mL), was added K_2CO_3 (848 mg, 6.15 mmol and stirred at room temperature for 15 min. Bromoacetonitrile (0.589 mg, 4.92 mmol) was added and stirred at room temperature for 18h. Reaction mixture was filtered, diluted with EtOAc (100mL), washed with water (3x100mL), brine (2x10mL) and dried over Na_2SO_4. The solvent was evaporated and the crude residue was purified by column chromatography with a solvent gradient of EtOAc/Hexanes 0-40% to give 2-(2-formylphenoxy)acetonitrile, as pale yellow solid (84%). To a solution of 2-(2-formylphenoxy)acetonitrile (500 mg, 3.1 mmol) in dichloromethane (15 mL) was added $MgSO_4$ and ethyl amine (2.0 M in THF, 1.7 mL, 3.41 mmol). The heterogeneous mixture was stirred at room temperature for 18h. The reaction mixture was filtered, and the solvent and excess amine was evaporated *in vacuo* to provide imine **2.6a** as a dark orange oil in quantitative yield.

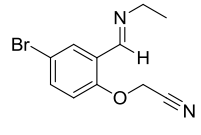
2.4.3 Spectroscopic Data

(E)-2-(2-((ethylimino)methyl)phenoxy)acetonitrile



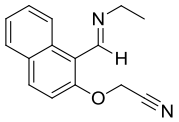
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 6.9 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 4.84 (s, 2H), 3.66 (q, J = 6.2 Hz, 2H), 1.30 (t, J = 7.3 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.22, 131.73, 128.11, 125.94, 123.36, 114.90, 112.39, 56.21, 54.00, 16.32. **HRMS** (ESI^+) for $C_{11}H_{13}N_2O^+$; calculated: 189.10224, found: 189.10225.

(E)-2-(4-bromo-2-((ethylimino)methyl)phenoxy)acetonitrile



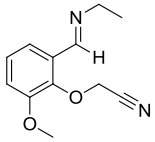
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.13 (d, J = 2.5 Hz, 1H), 7.52 (dd, J = 8.8, 2.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 4.82 (s, 2H), 3.66 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.37, 153.80, 134.19, 130.88, 127.76, 116.48, 114.20, 56.16, 54.17, 16.21. **HRMS** (ESI^+) for $C_{11}H_{12}N_2OBr^+$; calculated: 267.0128, found: 267.0116.

(E)-2-((1-((ethylimino)methyl)naphthalen-2-yl)oxy)acetonitrile



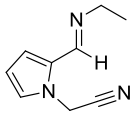
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 – 8.81 (m, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.35 – 7.20 (m, 1H), 4.92 (s, 1H), 3.81 (qd, *J* = 7.3, 1.4 Hz, 1H), 1.43 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.70, 154.22, 132.34, 131.96, 130.56, 128.22, 128.19, 125.70, 125.29, 120.78, 114.31, 77.43, 77.00, 76.58, 57.42, 55.75, 16.63. **HRMS** (ESI^+) for $C_{15}H_{15}N_2O^+$; calculated: 239.1179, found: 239.1175.

(E)-2-(2-((ethylimino)methyl)-6-methoxyphenoxy)acetonitrile



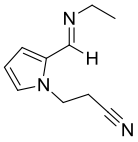
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 116H), 7.57 (dd, *J* = 7.9, 1.4 Hz, 118H), 7.16 (t, *J* = 8.0 Hz, 125H), 6.99 (dd, *J* = 8.2, 1.4 Hz, 126H), 4.87 (s, 1H), 3.90 (s, 13H), 3.69 (qd, *J* = 7.3, 1.3 Hz, 240H), 1.31 (t, *J* = 7.3 Hz, 372H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.50, 151.82, 130.46, 125.69, 119.21, 115.50, 114.04, 57.70, 56.24, 55.87, 16.17. **HRMS** (ESI^+) for $C_{12}H_{15}N_2O_2^+$; calculated: 219.1128, found: 219.1122.

(E)-2-(2-((ethylimino)methyl)-1H-pyrrol-1-yl)acetonitrile



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.82 (s, 1H), 6.45 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.23 (dd, *J* = 3.7, 2.9 Hz, 1H), 5.57 (s, 2H), 3.53 (q, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, CD_3CN) δ 151.62, 127.23, 125.01, 117.31, 109.60, 55.47, 36.74, 15.98. **HRMS** (ESI^+) for $C_9H_{12}N_3^+$; calculated: 162.1026, found: 162.1026

(E)-3-(2-((ethylimino)methyl)-1H-pyrrol-1-yl)propanenitrile



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 6.87 – 6.72 (m, 1H), 6.47 (d, *J* = 2.0 Hz, 1H), 6.17 (dd, *J* = 3.7, 2.8 Hz, 1H), 4.59 (t, *J* = 6.6 Hz, 2H), 3.51 (q, *J* = 7.3 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.45, 128.88, 127.37, 117.87, 108.69, 56.06, 44.81, 19.81, 16.74 **HRMS** (ESI^+) for $C_{10}H_{14}N_3^+$; calculated: 176.1182, found: 176.1187.

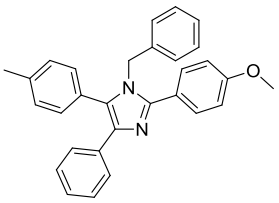
Reaction of 2.2a with NaO_2STol

In a glovebox, imine **2.2a** (0.2 mmol) and acid chloride **2.2b** (0.22 mmol) were mixed in $CDCl_3$ (ca. 0.5 mL) and allowed to stand at room temperature for 30 min. PhP(2-catechyl) (0.22 mmol) was added, and after 30 min DBU (0.6 mmol) was added as a solution in $CDCl_3$, followed by addition of sodium *p*-toluene sulfinate as a suspension in $CDCl_3$. Reaction color changed from a deep red to a pale yellow within 1h. ^{1}H and ^{31}P NMR showed decomposition of the dipole. The presence of H_2O decomposes the 1,3-dipole within minutes to the hydrolyzed phospha-Müchnone, PhP(2-catechyl)CH(Tol)N(Bn)COPh (Laure Kayser's unpublished results)

2.4.4 Synthesis of Tetra-Substituted Imidazoles 2.5

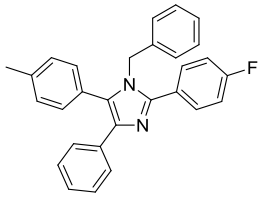
In a glovebox, imine (0.2 mmol) and acid chloride (0.22 mmol) were mixed in $CDCl_3$ (ca. 0.5 mL) and allowed to stand at room temperature for 30 min. PhP(2-catechyl) (0.22 mmol) was added, and after 30 min DBU (0.6 mmol) was added as a solution in $CDCl_3$, followed by the addition of *N*-nosyl substituted imine (0.3 mmol). The reaction was complete within 3h. The crude solution was concentrated in vacuo and purified by column chromatography on a 4g column of Silica Gel 60 using a ethyl acetate:hexanes gradient (0-40%) on a Combi-Flash system, giving pure product as an off-white powder.

1-benzyl-2-(4-methoxyphenyl)-4-phenyl-5-(*p*-tolyl)-1*H*-imidazole (**2.5a**)



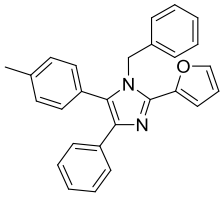
Isolated yield: 65%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (t, *J* = 9.3 Hz, 4H), 7.26 – 7.23 (m, 5H), 7.17 – 7.04 (m, 5H), 6.90 (d, *J* = 6.6 Hz, 2H), 6.83 (d, *J* = 6.3 Hz, 2H), 5.07 (s, 2H), 3.81 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.10, 147.74, 138.47, 137.71, 130.88, 130.42, 129.84, 129.53, 128.58, 128.04, 127.84, 127.29, 126.75, 126.27, 125.94, 113.98, 55.30, 48.12, 21.37. **HRMS** (ESI^+) for $C_{30}H_{27}N_2O^+$; calculated: 206.09980,found: 206.09928.

1-benzyl-2-(4-fluorophenyl)-4-phenyl-5-(*p*-tolyl)-1*H*-imidazole(**2.5b**)



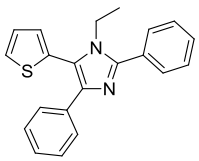
Isolated yield: 41%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 4H), 7.23 – 7.20 (m, 5H), 7.14 – 7.04 (m, 7H), 6.82 (d, *J* = 6.9 Hz, 2H), 5.06 (s, 2H), 2.37 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.07, 130.96, 130.84, 130.22, 129.63, 128.68, 128.11, 127.47, 126.76, 126.51, 125.85, 115.81, 115.52,48.14, 21.38.**HRMS** (ESI+) for $C_{29}H_{24}N_2F$+; calculated: 419.19180, found: 419.19102.

1-benzyl-2-(furan-2-yl)-4-phenyl-5-(*p*-tolyl)-1*H*-imidazole (**2.5c**)



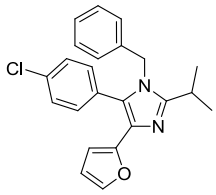
Isolated yield: 36%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.3 Hz, 2H), 7.46 (d, *J* = 1.0 Hz, 1H), 7.28 – 7.18 (m, 6H), 7.15 (dd, *J* = 7.4, 4.8 Hz, 3H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 6.8 Hz, 2H), 6.72 (s, 1H), 6.43 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.25 (s, 2H), 2.38 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.85, 138.83, 137.33, 130.88, 130.37, 129.65, 128.64, 128.04, 127.34, 126.92, 126.54, 125.92, 111.46, 48.27, 21.39. **HRMS** (ESI+) for $C_{27}H_{23}ON_2$+; calculated: 391.18049, found: 391.17957.

1-ethyl-2,4-diphenyl-5-(thiophen-2-yl)-1*H*-imidazole (**2.5d**)



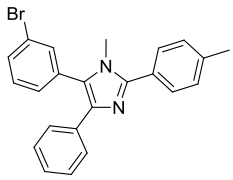
Isolated yield: 77%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.65 – 7.57 (m, 2H), 7.54 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.26 – 7.22 (m, 2H), 7.19 – 7.14 (m, 3H), 3.99 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.09, 131.39, 130.44, 129.12, 129.06, 128.65, 128.52, 128.09, 127.69, 126.82, 126.65, 126.33, 124.44, 121.14, 39.80, 16.60. **HRMS** (ESI+) for $C_{21}H_{19}N_2S$+; calculated: 331.12635, found: 331.12554.

1-benzyl-5-(4-chlorophenyl)-4-(furan-2-yl)-2-isopropyl-1*H*-imidazole (**2.5e**)



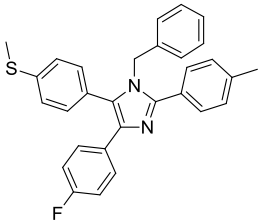
Isolated yield: 45%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.7 Hz, 2H), 7.30 – 7.24 (m, 5H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 7.0 Hz, 2H), 6.28 (s, 1H), 6.06 (d, *J* = 3.0 Hz, 1H), 4.97 (s, 2H), 1.34 (d, *J* = 6.7 Hz, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.13, 149.47, 141.07, 136.96, 134.68, 132.19, 130.21, 128.88, 128.85, 128.74, 127.64, 126.80, 125.53, 110.73, 105.10, 46.73, 26.65, 21.76. **HRMS** (ESI+) for $C_{23}H_{22}ON_2Cl$+; calculated: 377.14152, found: 377.14112.

5-(3-bromophenyl)-1-methyl-4-phenyl-2-(*p*-tolyl)-1*H*-imidazole (**2.5f**)



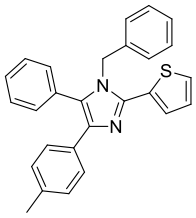
Isolated yield: 50%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68 – 7.50 (m, 6H), 7.36 – 7.27 (m, 4H), 7.27 – 7.13 (m, 3H), 3.50 (s, 3H), 2.42 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.43, 138.86, 138.16, 134.30, 133.47, 131.58, 130.53, 129.67, 129.29, 128.95, 128.57, 128.16, 127.80, 127.02, 126.54, 124.44, 122.86, 33.23, 21.40. **HRMS** (ESI^+) for $C_{23}H_{20}N_2Br^+$; calculated: 403.08044, found: 403.08010.

1-benzyl-4-(4-fluorophenyl)-5-(4-(methylthio)phenyl)-2-(*p*-tolyl)-1*H*-imidazole (**2.5g**)



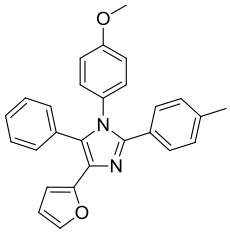
Isolated yield: 63%. **^{1}H NMR** (400 MHz, $CDCl_3$ 7.61 – 7.47 (m, 4H), 7.29 – 7.12 (m, 7H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.90 (t, *J* = 8.8 Hz, 2H), 6.85 – 6.78 (m, 2H), 5.08 (s, 2H), 2.48 (s, 3H), 2.36 (s, 3H).**HRMS** (ESI+) for $C_{30}H_{26}N_2FS$+; calculated: 465.17952, found: 465.17798.

1-benzyl-5-phenyl-2-(thiophen-2-yl)-4-(*p*-tolyl)-1*H*-imidazole (**2.5h**)



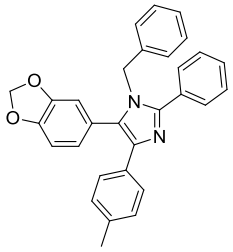
Isolated yield: 62%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.15 (m, 10H), 7.12 (d, *J* = 2.8 Hz, 1H), 7.07 – 6.89 (m, 4H), 5.19 (s, 2H), 2.29 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.93, 138.34, 137.29, 136.09, 131.30, 130.98, 130.69, 130.08, 128.81, 128.79, 128.69, 127.43, 127.41, 126.85, 126.76, 126.35, 126.09, 125.76, 124.44, 48.22, 21.16. **HRMS** (ESI+) for $C_{27}H_{23}N_2S$+; calculated: 407.1576, found: 407.1587.

4-(furan-2-yl)-1-(4-methoxyphenyl)-5-phenyl-2-(*p*-tolyl)-1*H*-imidazole (**2.5i**)



Isolated yield: 68%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 0.9 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.24 (m, 3H), 7.20 (dt, *J* = 7.5, 3.7 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96 – 6.91 (m, 2H), 6.78 – 6.72 (m, 2H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.27 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.08, 149.41, 147.53, 141.26, 138.19, 131.02, 130.64, 129.92, 129.67, 129.32, 128.82, 128.75, 128.05, 128.02, 127.37, 114.21, 110.81, 105.70, 55.34, 21.29.**HRMS** (ESI+) for $C_{27}H_{23}O_2N_2$+; calculated: 407.17540, found: 407.17426.

5-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-2-phenyl-4-(*p*-tolyl)-1*H*-imidazole (**2.5j**)

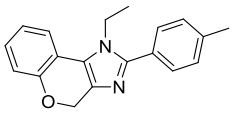


Isolated yield: 35%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 - 7.63 (m, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.36 (m, 3H), 7.28 – 7.15 (m, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.72 – 6.67 (m, 1H), 6.64 (d, *J* = 1.4 Hz, 1H), 5.97 (s, 2H), 5.10 (s, 2H), 2.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.86, 147.82, 147.75, 138.12, 137.63, 135.93, 131.55, 130.97, 129.07, 129.02, 128.82, 128.59, 128.56, 127.36, 126.60, 125.97, 125.12, 124.43, 111.28, 108.67, 101.25, 48.16, 21.18. **HRMS** (ESI^+) for $C_{30}H_{25}N_2O_2^+$; calculated: 445.19105, found: 445.18969.

2.4.5 Synthesis of Polycyclic Imidazoles 2.7

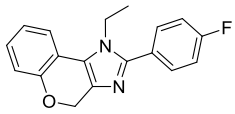
In a glovebox, imine (0.2 mmol) and acid chloride (0.22 mmol) were mixed in $CDCl_3$ (0.5 mL) and allowed to stand at room temperature for 30 min. PhP(2-catechyl) (0.22 mmol) was added, and after 30 min DBU (0.6 mmol) was added as a solution in $CDCl_3$. The reaction was complete within 5 min. The crude solution was concentrated in vacuo and purified by column chromatography on a 4g column of Silica Gel 60 using a ethyl acetate:hexanes gradient (0-40%) on a Combi-Flash system giving pure product as a pale yellow powder.

1-ethyl-2-(*p*-tolyl)-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7a**)



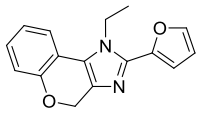
Isolated yield: 76%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 8.0 Hz, 2H), 6.30 (d, *J* = 7.9 Hz, 1H), 6.22 (d, *J* = 7.9 Hz, 2H), 6.12 – 6.00 (m, 1H), 5.94 - 5.90 (m, 2H), 4.30 (s, 2H), 3.22 (q, *J* = 7.2 Hz, 2H), 1.36 (s, 3H), 0.39 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.94, 149.51, 139.11, 134.21, 129.36, 128.97, 127.54, 127.45, 122.16, 121.74, 119.68, 117.95, 117.41, 66.38, 40.74, 21.37, 16.36. **HRMS** (ESI+) for $C_{19}H_{19}ON_2$+; calculated: 291.14919, found: 291.14903.

1-ethyl-2-(4-fluorophenyl)-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7b**)



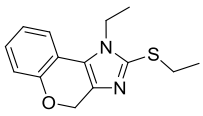
Isolated yield: 68%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 2H), 7.46 – 7.32 (m, 1H), 7.26 – 7.13 (m, 3H), 7.05 – 6.95 (m, 2H), 6.80 – 6.65 (m, 3H), 5.33 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (**75 MHz, $CDCl_3$) δ 164.89, 161.58, 152.99, 148.27, 144.72, 134.06, 131.13, 131.01, 127.76, 126.42, 122.46, 121.83, 120.12, 119.77, 117.66, 117.54, 116.02, 115.73, 114.98, 66.14, 40.81, 16.34. **HRMS** (ESI+) for $C_{18}H_{16}ON_2F$+; calculated: 295.12412, found: 295.12322.

1-ethyl-2-(furan-2-yl)-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7c**)



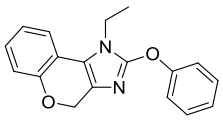
Isolated yield: 74%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.19 – 7.08 (m, 1H), 7.03 - 6.94 (m, 2H), 6.89 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.54 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.31 (s, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 1.59 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.15, 145.27, 142.93, 140.04, 134.44, 127.85, 122.63, 121.89, 119.83, 117.58, 115.01, 111.73, 110.16, 66.06, 41.19, 16.19. **HRMS** (ESI+) for $C_{16}H_{15}O_2N_2$+; calculated: 296.11280, found: 267.11204.

1-ethyl-2-(ethylthio)-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7d**)



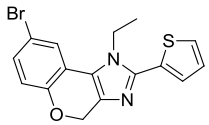
Isolated yield: 47%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 1H), 7.17 – 7.04 (m, 1H), 6.99 – 6.92 (m, 2H), 5.29 (s, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.11 (q, *J* = 7.4 Hz, 2H), 1.47 – 1.32 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.69, 143.16, 134.70, 127.55, 122.83, 121.77, 119.43, 117.61, 117.43, 66.31, 40.68, 28.96, 15.76, 15.08. **HRMS** (ESI+) for $C_{14}H_{17}ON_2S^+$; calculated: 261.10561, found: 261.10477.

1-ethyl-2-phenoxy-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7e**)



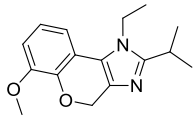
Isolated yield: 51%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 - 7.36 (m, 2H), 7.29 – 7.14 (m, 4H), 7.14 – 7.04 (m, 1H), 6.99 - 6.93 (m, 2H), 5.24 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.86, 152.49, 151.19, 129.81, 128.76, 127.00, 124.75, 121.69, 118.75, 118.71, 117.97, 117.69, 117.22, 66.11, 38.88, 15.73. **HRMS** (ESI^+) for $C_{18}H_{17}N_2O_2^+$; calculated: 293.12845, found: 293.12827.

8-bromo-1-ethyl-2-(thiophen-2-yl)-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7f**)



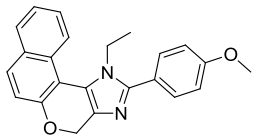
Isolated yield: 79%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.4 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.22 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 5.35 (s, 2H), 4.42 (q, *J* = 7.3 Hz, 2H), 1.61 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.02, 143.70, 135.16, 131.96, 130.16, 127.71, 127.42, 126.28, 122.14, 121.88, 119.36, 119.11, 114.06, 66.29, 40.88, 16.15. **HRMS** (ESI+) for $C_{16}H_{14}ON_2BrS^+$; calculated: 361.00047, found: 361.00023.

1-ethyl-2-isopropyl-6-methoxy-1,4-dihydrochromeno[3,4-*d*]imidazole (**2.7g**)



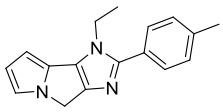
Isolated yield: 77%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.96 – 6.89 (m, 2H), 6.82 – 6.66 (m, 1H), 5.35 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.01 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.43, 149.03, 141.35, 132.94, 121.50, 120.58, 118.89, 111.94, 110.32, 66.87, 56.02, 39.22, 25.90, 22.11, 16.35. **HRMS** (ESI+) for $C_{16}H_{21}O_2N_2^+$; calculated: 273.15975, found: 273.15885.

1-ethyl-2-(4-methoxyphenyl)-1,4-dihydrobenzo[5,6]chromeno[3,4-*d*]imidazole (**2.7h**)



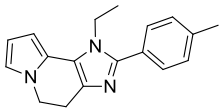
Isolated yield: 82%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.70 (t, *J* = 8.1 Hz, 3H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 5.24 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 0.66 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.19, 152.62, 152.20, 135.73, 130.15, 130.13, 128.64, 128.32, 127.72, 126.14, 125.11, 124.73, 124.01, 123.61, 118.74, 114.19, 112.69, 66.59, 55.37, 43.54, 15.25.**HRMS** (ESI+) for $C_{23}H_{21}O_2N_2^+$; calculated: 357.15975, found: 357.15891.

1-ethyl-2-(p-tolyl)-1,4-dihydroimidazo[4,5-a]pyrrolizine (**2.7i**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.30 – 6.21 (m, 1H), 6.01 (d, *J* = 3.1 Hz, 1H), 4.74 (s, 2H), 4.19 (q, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 1.54 (t, *J* = 7.3 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.07, 144.85, 138.53, 130.33, 129.35, 129.18, 128.41, 127.95, 117.96, 110.43, 95.65, 47.05, 41.58, 21.34, 15.83. **HRMS** (ESI^+) for $C_{17}H_{18}N_3^+$; calculated: 264.14952, found: 264.14953.

1-ethyl-2-(*p*-tolyl)-4,5-dihydro-1*H*-imidazo[4,5-*g*]indolizine (**2.7k**)



Isolated yield: 63%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.86 – 6.64 (m, 1H), 6.29 – 6.16 (m, 2H), 4.29 – 4.11 (m, 4H), 3.15 (t, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.45, 145.02, 138.67, 129.32, 128.59, 123.33, 121.14, 119.88, 114.98, 108.12, 101.34, 45.67, 40.45, 24.20, 21.34, 15.94.**HRMS** (ESI+) for $C_{18}H_{20}N_2$+; calculated: 278.1652, found: 278.1641.

2.5 References

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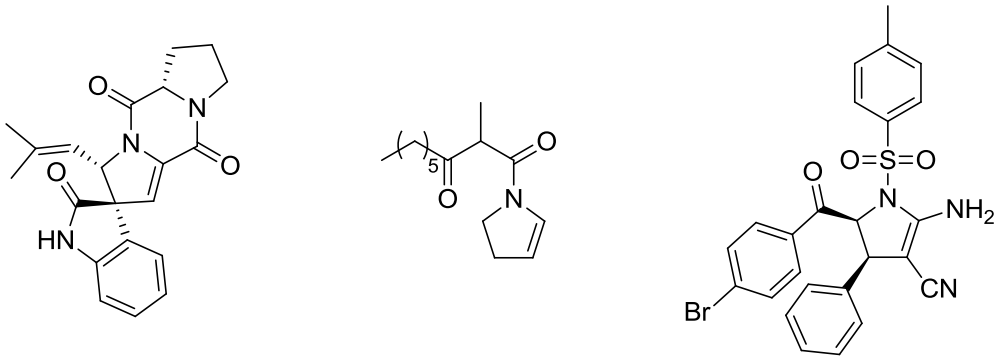
CHAPTER THREE

Synthesis of Polycyclic 2-Pyrrolines via Phospha-Münchnone Cycloaddition

3.1 Introduction

2-pyrrolines are important heterocyclic motifs in a variety of natural and synthetic products of biological importance.[1] Examples of these include Spirotryprostatin B **1.1** (Figure 3.1),[2] insecticides (**1.2**)[3] and anticancer agents (**1.3**).[4] Furthermore, these heterocycles can be used as intermediates in the synthesis of pyrrolidines (via reduction)[5] or pyrroles (via oxidation).[1a,6]



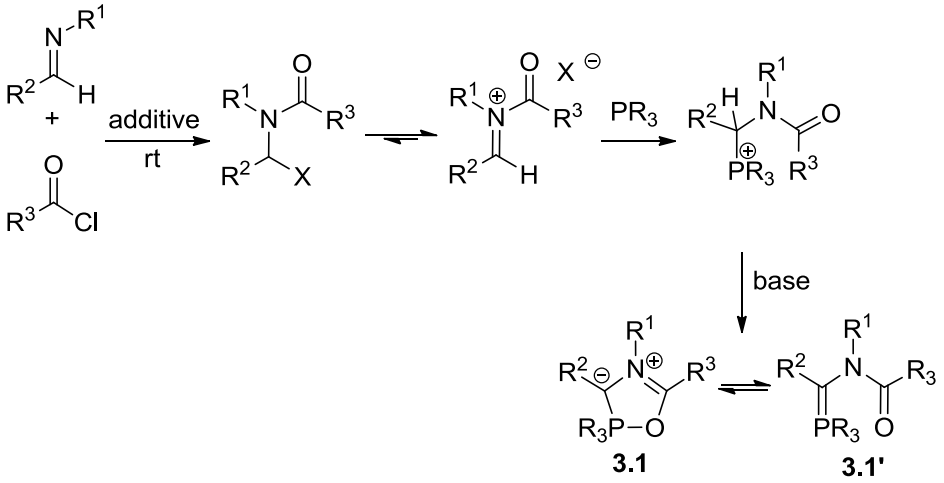
1.1 Spirotryprostatin B **1.2** Insecticide **1.3** Anti-cancer properties

Figure 3.1 Structure of Natural and Biologically Active 2-Pyrrolines

While a range of methods have been developed to synthesize 2-pyrrolines (e.g. hydroamination reactions,[7] cyclizations,[4,8] ring-closing metathesis,[9] isomerization of 3,4-dihydropyrroles,[10] and others[11]), one of the most convergent is the 1,3-dipolar cycloaddition of alkenes and Münchnones. This transformation was first noted by Huisgen *et al.* in 1964,[12] and has since been used in the preparation of a range of 2-pyrroline derivatives.[13] While effective, a major limitation of this approach is the need to first synthesize the Münchnone. The latter can require multiple steps, especially for highly substituted products, generates significant waste, and limits the overall efficiency of these syntheses.

As discussed in Chapter 2, we have recently reported in our laboratory a new class of 1,3-dipole, phospha-Münchnone **3.1** (Scheme 3.1). This dipole can be easily generated in one pot from imines, acid chlorides and phosphorus reagents, and undergoes cycloaddition reactions in

direct analogy to Münchnones. This includes alkyne cycloaddition to synthesize pyrroles,[14] and as described in Chapter 2, cycloaddition with N-nosyl imines or tethered nitriles to form imidazoles.

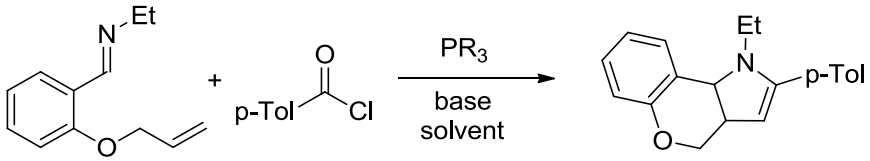


Scheme 3.1 Assembly of Phospha-Münchnone

Considering the accessibility of phospha-Münchnone **3.1**, **w**e were interested in applying these dipoles to the synthesis of 2-pyrrolines. Initial studies by Marie Morin, a PhD student in our group, demonstrated that the intramolecular cycloaddition of tethered alkenes can occur, and provides an overall synthesis of polycyclic 2-pyrrolines (Table 3.1). The reactivity of phospha-Münchnone **3.1** is highly dependent on the electronic nature of the phosphorus reagent. Thus, the reaction of the imine, acid chloride and triphenylphosphine followed by deprotonation forms the acyclic phosphorus ylide **3.1'**, which under no explored conditions undergo 1,3-dipolar cycloaddition (entry 1).[14] The cycloaddition is presumably inhibited due to the electron-rich phosphine preventing chelation with the carbonyl oxygen to form the 1,3-dipole **3.1**. Similar results were observed PCy_3 and $P(NMe_2)_3$. More electron poor phosphites slowly form the fused cyclic pyrroline at moderate yield (entries 4 and 5). The addition of TMSOTf increases reaction yield, while decreasing the reaction time, presumably by favoring the equilibrium formation of the ionic N-acyliminium salt (Scheme 1, X = OTf), which is more susceptible to nucleophilic attack of the phosphite (entries 6, 7). In contrast, the moderately electron rich phosphonite PhP(2-catechyl) is sufficiently nucleophilic to react with the iminium salt without additives, yet

it can still accept chelation of the oxygen from the former acid chloride to form **3.1**, and allows the high yield formation of pyrroline within 2 h at ambient temperature.

Table 3.1. Development of PR_3 Mediated Pyrroline Synthesis



3.2a **3.3a**

Entry	PR_3	Base	Additive	Time	Yield[b]
1	PPh_3	LiHMDS[c]	/		0%
2	PCy_3	LiHMDS[c]	/		0%
3	$P(NMe_2)_3$	LiHMDS[c]	/		0%
4	$(PhO)_3P$	DBU	/	24h	46%
5	$(CF_3CH_2O)_3P$	DBU	/	10h	46%
6	$(PhO)_3P$	DBU	TMSOTf	5h	80%
7	$(CF_3CH_2O)_3P$	DBU	TMSOTf	2h	67%
8	PhP(2-catechyl)	$Et(^iPr)_2N$	/	6h[d]	36%
9	PhP(2-catechyl)	Et_3N	/	6h[d]	66%
10	PhP(2-catechyl)	DBU	/	2h	85%

[a] Procedure: Imine (0.2 mmol), acid chloride (0.22 mmol), 0.5 mL of $CDCl_3$ or CH_2Cl_2, 30 min; followed by PR_3 (0.22 mmol), 1h, base (0.36-0.5 mmol), rt. [b] NMR yield. [c] Added at -78˚C and warmed to rt. [d] 65˚C.

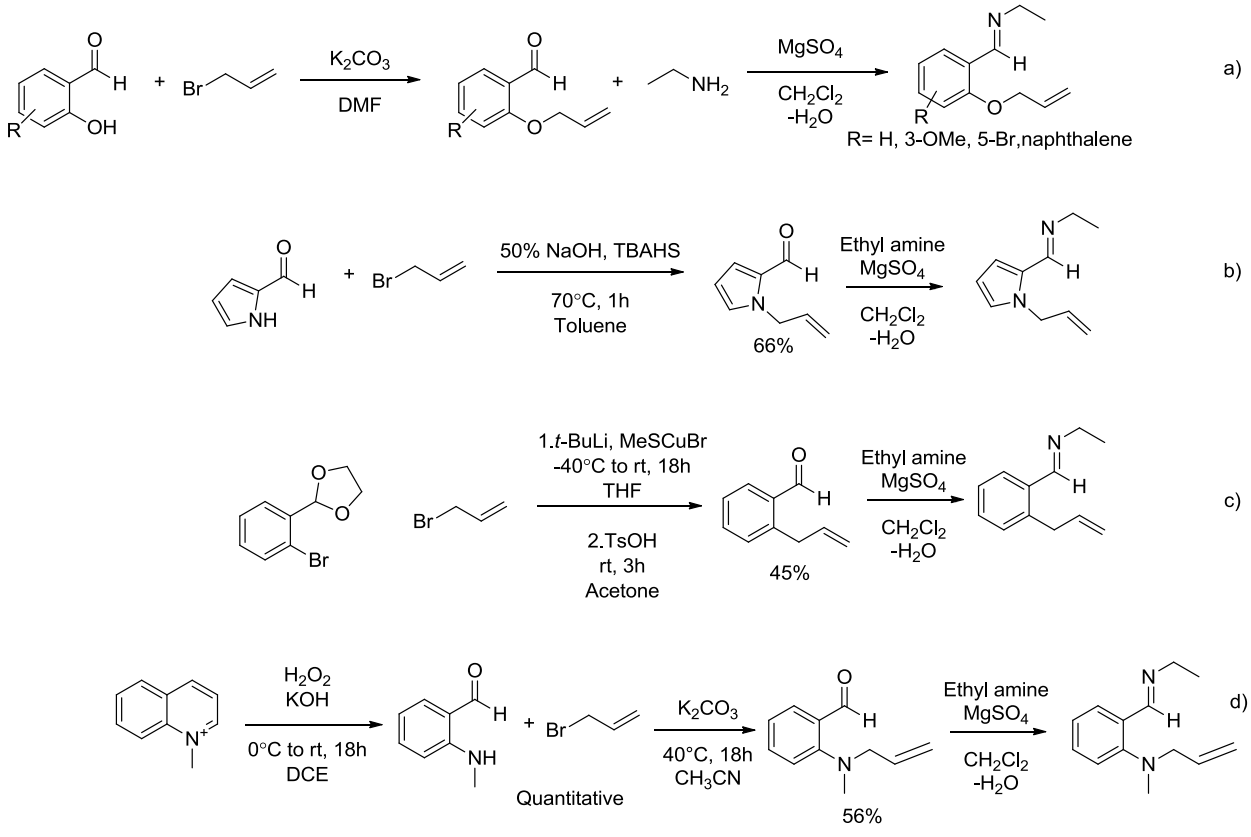
In light of the efficiency of this transformation, I undertook a study for the product diversity available from this approach. These results are described below.

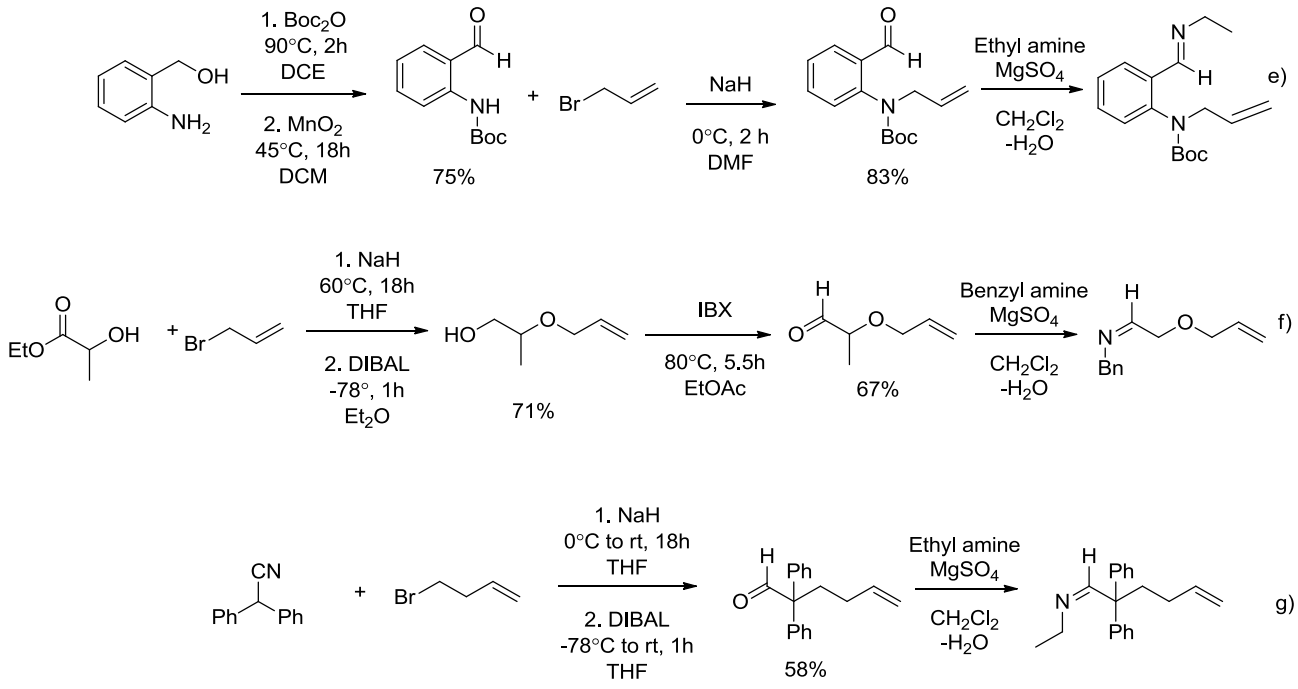
3.2 Results and Discussion

3.2.1 Alkene-Tethered Imine Synthesis

In order to probe the scope of the reaction in Table 3.1, we first synthesized a number of new alkene-tethered imines. These imines can be easily prepared from known aldehydes in quantitative yields.[16] For example, imines **3.2a, 3.2b** and **3.2g-j** are generated from salicyladehyde derivatives in a two-step protocol involving initial allylation,[16e] followed by condensation with a primary amine (Scheme 3.2a). A similar approach was used to prepare the

pyrrole-based **3.2f** (Scheme 3.2b) with the substitution of K_2CO_3 for a solution of NaOH and tertbutylammonium hydrogen sulfate (TBAHS).[16a] The carbon-linked imine **3.2c** can be generated by the allylation of the protected aldehyde (Scheme 3.2c)[16h] followed by deprotection and amine condensation. Alternatively, nitrogen-linked alkenes can be synthesized via oxidative ring opening of quinolium salts (for imine **3.2d**), or alkylation and oxidation of 2-aminobenzyl alcohol (for imine **2c)**, followed by *N*-allylation and condensation (Scheme 3.2 d and e).[16b,16g] These imines are generally formed in high yields, and isolated by simply evaporating the excess amine and solvent. Finally, the aldehyde precursors to non-aromatic imines[16c,16f] **3.2h-3.2k** can be prepared via previously reported procedures (Scheme 3.2f, 3.2g). These aldehydes also undergo similar condensation reactions with primary amines. In the case of these latter imines they are used soon after completion to avoid decomposition.



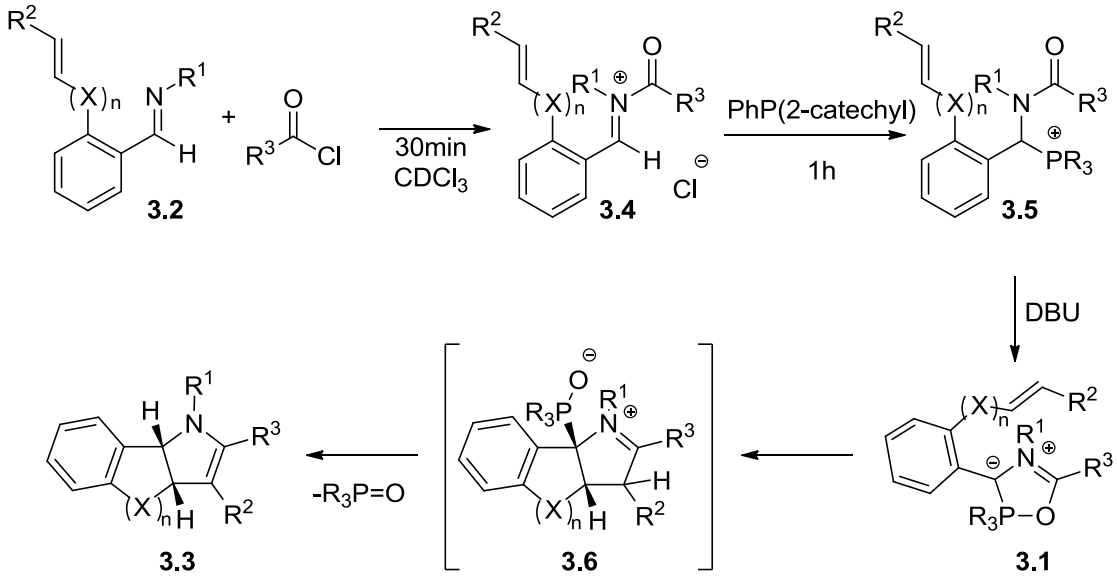


Scheme 3.2 Synthesis of Olefin-Tethered Imine and Imine Precursors

3.2.2 Scope of Polycyclic 2-Pyrroline Synthesis

With these imines in hand, we examined the scope of their phosphonite mediated coupling with acid chlorides to generate 2-pyrrolines. The procedure generally involves the addition of acid chloride to **3.2** to generate an N-acyl iminium salt **3.4** (Scheme 3.3), followed by PhP(2-catechyl) and deprotonation by DBU to form the 1,3-dipole. For most of the substrates employed, cycloaddition of alkene occurs spontaneously to generate 2-pyrrolines with 10 min at ambient temperature.

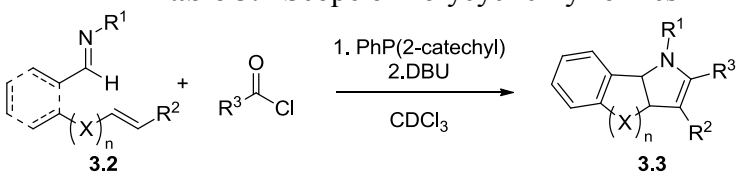
These steps can each be monitored by in situ ^{1}H and ^{31}P NMR. For example, the reaction of N-alkyl imine **3.2c** with toluoyl chloride leads to the formation of iminium salt within 30 min **3.4** (Scheme 3.3), as evidenced disappearance of the imine C(H) signal at 8.41 ppm, and an upfield NCH_2R resonance at 2.43 ppm in the ^{1}H NMR spectra. The addition of PhP(2-catechyl) results in the rapid generation of the phosphonium salt **3.5** (^{31}P NMR: 0.51, 0.19 ppm), within 30 min, and subsequent deprotonation with DBU results in the disappearance of **3.5** and the rapid generation of 2-pyrroline, together with the phosphine oxide (36.91 ppm).[15]



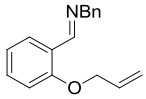
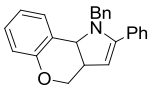
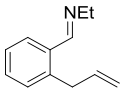
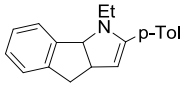
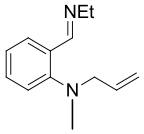
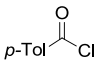
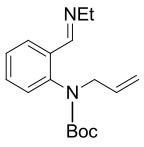
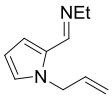
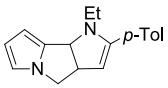
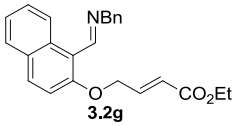
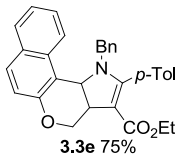
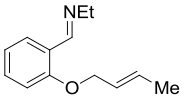
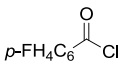
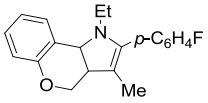
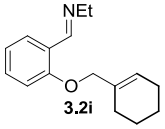
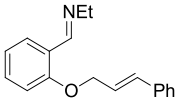
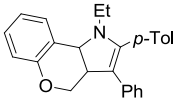
Scheme 3.3 Reaction Mechanism of Polycyclic Pyrrolines

As illustrated in Table 3.2, many of the imines and acid chlorides investigated lead to the formation of polycyclic 2-pyrrolines in high yields.These include imines with oxygen-tethered alkenes, carbon linkers (e.g. entry 2), and even the pyrrole-based imine **3.2f** (entry 5). In addition, to 6,5-fused ring products, 5,5-polycyclic pyrrolines can also be generated. The latter contrasts with previous results employing Münchnones, where short tethers are not tolerated.[17] Each of these products is formed as a single diastereomer, and with a *cis*-fused ring, as demonstrated by NOE experiments performed by Marie Morin that confirm the assignment shown.[18] Due to the sensitivity of the partially reduced pyrrolines, these products were all isolated using a small pipette column of alumina, as detailed in the experimental section. Internal alkenes were also tolerated in this reaction (entry 6), and even internal unactivated alkenes (entries 7, 9). However, the more sterically hindered cyclohexene-linked imine **3.2i** does not undergo cycloaddition (entry 8). Nitrogen tethers were also not suitable under these conditions (entries 3 and 4). In situ ^{1}H NMR analysis shows that these latter imines do not lead to the clean formation of N-acyl iminium salts, presumably due to the steric bulk near the imine unit.

Table 3.2 Scope of Polycyclic Pyrrolines[a]

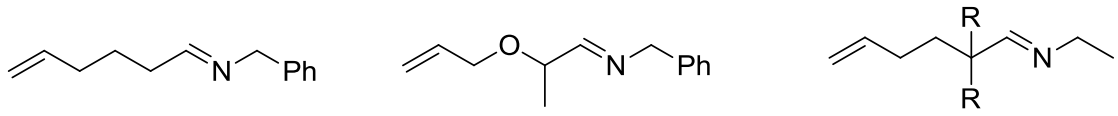


3.2 3.3

Entry	Substrate	Acid Chloride	Product (% yield)
1	 **3.2b**		 **3.3b** 85%
2	 **3.2c**		 **3.3c** 74%
3	 **3.2d**		0%
4	 **3.2e**		0%
5	 **3.2f**		 **3.3d** 76%
6	 **3.2g**		 **3.3e** 75%
7[b]	 **3.2h**		 **3.3f** 88%
8	 **3.2i**		0%
9[b]	 **3.2j**		 **3.3g** 91%

[a] Procedure: Imine (0.2 mmol), acid chloride (0.20-0.22 mmol), 0.5 mL of $CDCl_3$ or CD_3CN, 30 min; then PhP(2-catechyl) (0.22 mmol), 1h, added DBU (0.30 mmol), 10 min, rt [b]cycloaddition at 60˚C for 1h.

Attempts to expand the scope of this transformation to non-aromatic imines have to date not been successful. In the case of imines **3.2j** and **3.2k**, the steric bulk near the imine carbon appears to inhibit phosphonium salt generation (for imine **3.2k**) or deprotonation (for imine **3.2j**). For aliphatic enolizable imines (**3.2h** and **3.2i**), we observe the rapid formation of enamides upon the addition of acid chloride.

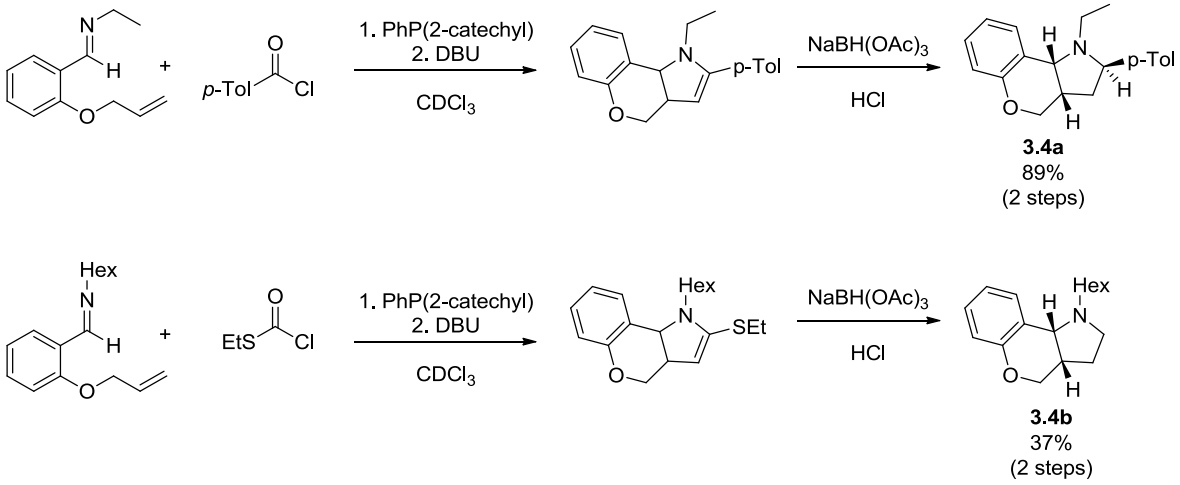


3.2h **3.2i** **3.2j** R=CH_3 **3.2k** R=Ph

Scheme 3.4 Aliphatic Olefin-Tethered Imines

3.2.3 Reduction of 2-Pyrrolines to Pyrrolidines

The above transformation provides a straightforward method to generate polycyclic 2-pyrrolines. In addition to their own utility, as previously stated, 2-pyrrolines are reactive heterocycles that can serve as intermediates to pyrrolidines under reductive conditions. We were therefore interested in probing the potential of this method to access these latter heterocycles. As shown in Scheme 3.5, the phosphonite mediated synthesis of 2-pyrroline can be coupled with subsequent reduction with $NaBH(OAc)_3$ to generate polycyclic pyrrolidine **3.4a** (Scheme 3.5) in a one pot, and in high yield. A similar reaction can be performed using chlorothioformate. In this case, reduction appears to also lead to dethiolation **3.4b**. The latter provides a route generate 5-unsubstituted heterocycles: a structure not directly available from the use of acid chlorides.



Scheme 3.5 Transformations of Reactive 2-Pyrrolines

3.3 Conclusions

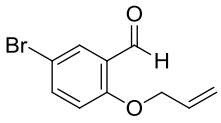
In conclusion, a range of tethered alkenes have been found to undergo rapid cycloaddition reactions with phospha-Münchnones to generate 2-pyrrolines. These transformations occur with high stereocontrol, and can be coupled with subsequent reduction to allow the synthesis of pyrrolidines. Considering the facile synthesis of phospha-Münchnones from imines, acid chlorides and PhP(2-catechyl), as well as the availability of alkene tethered imines, this provides an attractive to generate a range of polycyclic pyrrolines directly from simple building blocks.

3.4 Experimental

3.4.1 General Procedures

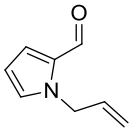
All reactions were performed in a Vacuum Atmospheres 553-2 dry box or using Schlenk techniques. All reagents were purchased from commercial sources and used as received. Aldehyde precursors to the imines were prepared by literature procedures.[16] Deuterated $CDCl_3$ and CD_3CN were distilled from CaH_2 under nitrogen. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 and 400 MHz instruments. HRMS were obtained from the McGill University mass spectra facilities.

3.4.2 Synthesis of Olefin-Tethered Aldehydes



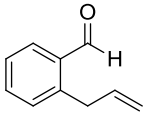
2-(allyloxy)-5-bromobenzaldehyde

To a solution of 5-bromo-2-hydroxybenzaldehyde (1.0 equiv) in DMF was added K_2CO_3 (1.5 equiv), and stirred at room temperature for 15 min. Allyl bromide (1.2 equiv.) was added and stirred at room temperature for 18h. The reaction mixture was filtered, diluted with water and extracted with EtOAc (3x), dried of $MgSO_4$ and concentrated in vacuo. The residue was purified through column chromatography with solvent gradient of EtOAc:Hexanes 0-30% to give pure 2-(allyloxy)-5-bromobenzaldehyde 79%



1-allyl-1H-pyrrole-2-carbaldehyde

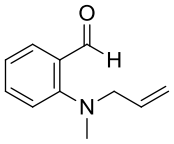
To a stirred mixture of 50% aqueous NaOH solution, 2-formylpyrrole (1.0 equiv) and tetra-butylammonium hydrogen sulfate (0.1 equiv) in toluene was allyl bromide (1.03 equiv.) The mixture was then heated at 70°C, with vigorous stirring for 1 h. The cooled mixture was diluted with water and extracted with ether (3x). The combined organic extracts were washed with water (3x), dried over Na_2SO_4 and concentrated in vacuo to give 1-allyl-1H-pyrrole-2-carbaldehyde 66%.



2-allylbenzaldehyde

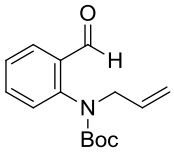
To a solution of 2-(2-bromophenyl)-1,3-dioxolane (1.0 equiv.) in THF was cannula transferred a 1.76 M solution of tBuLi (2.5 equiv.) in n-pentane at -40 °C under N_2. The mixture was stirred for 2 h and CuBr · Me_2S (0.5 equiv.) was added at -40 °C. The mixture was then warmed to 0 °C over 2 h and allyl bromide (1.2 equiv.) was added. After being stirred for 2.5 h at room temperature, the reaction was quenched by sat. NH_4Cl aq. The precipitate was filtrated through a pad of celite and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography with a solvent gradient of EtOAc:Hexanes 0-20% to give pure product. To a solution of the allylated (1.0 equiv.) in acetone was added TsOH · H_2O (0.1 equiv.) and the mixture was stirred for 3 h at room temperature. The solvent was evaporated under vacuo and the residue was added solution of $NaHCO_3$.The aqueous layer was extracted with EtOAc (3x) and washed with water (3x) and brine (1x), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography with a solvent gradient of EtOAc:Hexanes 0-40% to give pure 2-allylbenzaldehyde 45%

2-(allyl(methyl)amino)benzaldehyde



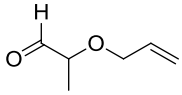
To a solution of quinoline (1.0 equiv.) in acetone was added MeI (1.4 equiv.) and stirred for 1h at 60°C until yellow crystals crashed out. The resulting filtrates was filtered, washed and recrystallized from acetone to give methylated quinoline. To a stirred mixture of potassium hydroxide (10 equiv.) in water and DCE at 0°C was added hydrogen peroxide (5.0 equiv) in water. 1-Methylquinolinium iodide (1.0 equiv.) in water was added dropwise over 45 min to this vigorously stirred mixture at 0°C, which was then warmed to room temperature and stirred for 72h. Thiodiethanol (0.3 equiv.) was added and after 5 min stirring the layers were separated and the aqueous phase extracted with DCM, washed with water (3x) and sodium sulfite solution (10%) (1x), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography with a solvent gradient of EtOAc:Hexanes 0-40% to give pure 2-(allyl(methyl)amino)benzaldehyde 56%.

tert-butyl allyl(2-formylphenyl)carbamate



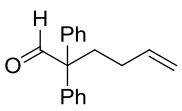
A solution of 2-aminobenzyl alcohol (1.0 equiv) in DCE, to it was added Boc_2O (1.1 equiv.) and heated at 90°C for 2h. Excess solvent was evaporated and reaction mixture was then dissolved in DCM, to it was added MnO_2 (10.0 equiv.) and refluxed for 18h. The cooled reaction mixture was filtered over a pad of celite, concentrated and the residue was purified through column chromatography with solvent gradient of EtOAc: Hexanes 0-5% to give the pure product. A cooled to 0°C solution of tert-butyl (2-formylphenyl)carbamate (1.0 equiv.) and allyl bromide (1.5 equiv.) in DMF was added to a suspension of NaH cooled in DMF. The reaction mixture was stirred at 0°C for 2h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3x) and washed with water (3x) and brine (1x), died over $MgSO_4$ and concentrated in vacuo. The residue was purified through column chromatography with solvent gradient of EtOAc:Hexanes 0-30% to give pure *tert*-butyl allyl(2-formylphenyl)carbamate 83%.

2-(allyloxy)propanal



To a suspension of NaH (1.2 equiv.) in THF was added ethyl 2-hydroxypropanoate (1.0 equiv.) and heated to 60°C for 30 min. After cooling to room temperature, allylbromide (1.1 equiv.) was slowly added and the reaction mixture was stirred for 18 h at 60°C. The solvent was evaporated under vacuo and replaced with Et_2O. The salt was filtered and the solvent was dried over $MgSO_4$, and concentrated. To cooled a to -78°C solution of the allylated product, ethyl 2-(allyloxy)propanoate (1.0 equiv.), in Et_2O was slowly added DIBAL (1M in THF) (1.5 equiv.) and stirred at -78°C for 1 hour. The reaction was worked up with water, extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated in vacuo to give 2-(allyloxy)propan-1-ol. To a suspension of IBX (2.0 equiv.) in EtOAc was added 2-(allyloxy)propan-1-ol (1.0 equiv.) and heated to 80°C for 5.5 h. The reaction was filtered, concentrated in vacuo and purified through column chromatography with solvent gradient of EtOAc:Hexanes 0-20% to give pure 2-(allyloxy)propanal 67%.

2,2-diphenylhex-5-enal



A suspension of NaH (1.1 equiv) in THF was cooled to 0 °C. Diphenylacetonitrile (1.0 equiv) was added dropwise over 10 min, and the reaction was allowed to stir for 45 min at 0 °C. Allyl bromide (1.1 equiv) was

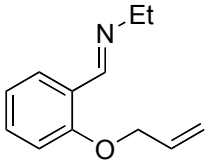
added dropwise, and then the reaction mixture was allowed to warm to 25 °C and stirred for 18 h. The reaction mixture was cooled to 0°C and water was slowly added to quench excess NaH. The reaction was diluted 1:1 with Et_2O and washed with water (3×) and brine (1×) and dried over Na_2SO_4 and concentrated in vacuo. To the resulting 2,2-diphenylhex-5-enenitrile (1.0 equiv.), in THF was slowly added DIBAL (1M in THF) (1.5 equiv.) and stirred at -78°C to room temperature for 1 hour. The reaction was worked up with water, extracted with EtOAc (3x), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography with a solvent gradient of EtOAc:Hexanes 0-40% to give pure 2,2-diphenylhex-5-enal 58%

3.4.3 Typical Synthesis of Imines 3.2

To a solution of 2-(allyloxy)benzaldehyde (2.5 mmol) in dichloromethane (10 mL) was added $MgSO_4$ and ethylamine (2.0 M in THF) (2.75 mmol). The heterogeneous mixture was stirred at room temperature for 18h. The reaction mixture was filtered, and the solvent and excess amine were evaporated *in vacuo* to provide the imine as a clear oil. In the preparation of **2b, 2e** and **2e** imines, exactly 1.0 equivalent of amine was added.

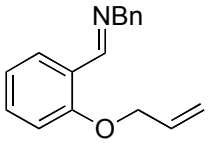
3.4.4 Spectroscopic Data

(*E*)-N-(2-(allyloxy)benzylidene)ethanamine **3.2a**



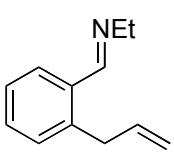
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 7.96 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.34-7.29 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.86 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 6.11-6.01 (m, 1H), 5.41 (dt, *J* = 17.3 Hz, 1.6 Hz, 1H), 5.29 (dt, *J* = 10.6 Hz, 1.5 Hz, 1H), 4.58-4.55 (m, 2H), 3.65 (qd, *J* = 7.3 Hz, 1.3 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz; $CDCl_3$): δ 157.6, 156.3, 133.0, 131.5, 127.3, 125.1, 121.0, 117.5, 112.3, 69.0, 56.2, 16.5. **HRMS** (ESI^+) for $C_{12}H_{16}NO^+$; calculated: 190.12264, found: 190.12231.

(*E*)-*N*-(2-(allyloxy)benzylidene)-1-phenylmethanamine **3.2b**



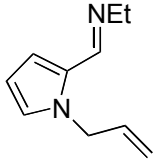
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.06 (dd, *J* = 7.7 Hz, 1.8 Hz, 1H), 7.37-7.35 (m, 5H), 7.30-7.25 (m, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.15-6.05 (m, 1H), 5.44 (dd, *J* = 17.3 Hz, 1.5 Hz, 1H), 5.34-5.31 (m, 1H), 4.86 (s, 2H), 4.62 (d, *J* = 5.1 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.9_4, 157.8_6, 139.7, 133.0, 131.9, 128.4, 128.0, 127.5, 126.8, 124.9, 121.0, 117.6, 112.3, 69.1, 65.5 **HRMS** (ESI^+) for $C_{17}H_{18}NO^+$; calculated: 252.13829, found: 252.13766.

N-(2-allylbenzylidene)ethanamine **3.2c**



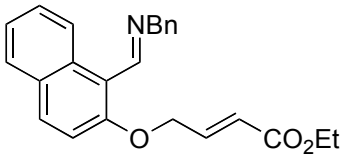
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.00-5.92 (m, 1H), 5.03 (d, *J* = 9.0 Hz, 1H), 4.92 (d, *J* = 17.0 Hz, 1H), 3.63-3.57 (m, 4H), 1.27 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 158.8, 139.0, 137.2, 134.4, 130.3, 130.2, 127.5, 126.8, 116.1, 56.4, 36.9, 16.5. **HRMS** ($APCI^+$) for $C_{12}H_{16}N^+$; calculated: 174.12773, found: 174.12772.

(*E*)-*N*-((1-allyl-1*H*-pyrrol-2-yl)methylene)ethanamine **3.2d**



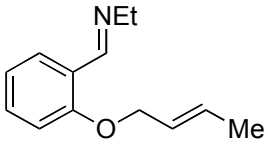
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 6.75 (t, *J* = 2.2 Hz, 1H), 6.50 (dd, *J* = 3.7 Hz, 1.8 Hz, 1H), 6.17 (dd, *J* = 3.7 Hz, 2.7 Hz, 1H), 6.03-5.94 (m, 1H), 5.14-5.11 (m, 1H), 5.04-4.96 (m, 3H), 3.51 (qd, *J* = 7.3 Hz, 1.2 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz; $CDCl_3$): δ 151.5, 135.1, 129.4, 126.2, 116.4, 115.8, 108.3, 56.3, 50.6, 16.7. **HRMS** ($APCI^+$) for $C_{10}H_{15}N_2^+$; calculated: 163.12298, found: 163.12271.

(*E*)-ethyl 4-((1-((*E*)-(benzylimino)methyl)naphthalen-2-yl)oxy)but-2-enoate **3.2e**



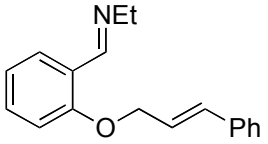
^{1}H NMR (400 MHz; $CDCl_3$): δ 9.25 (d, *J* = 8.7 Hz, 1H), 9.20 (t, *J* = 1.4 Hz, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.53 (ddd, *J* = 8.6 Hz, 6.9 Hz, 1.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.41-7.35 (m, 2H), 7.31-7.26 (m, 2H), 7.19-7.11 (m, 2H), 6.23 (dt, *J* = 15.7 Hz, 2.0 Hz, 1H), 4.99 (s, 2H), 4.88 (dd, *J* = 4.0 Hz, 2.0 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz; $CDCl_3$): δ 166.0, 159.4, 156.5, 142.1, 139.7, 132.6, 132.1, 129.5, 128.5, 128.2, 128.1, 126.9, 125.9, 124.4, 122.3, 118.2, 113.6, 68.0, 66.8, 60.7, 14.3. **HRMS** (ESI^+) for $C_{24}H_{24}NO_3^+$; calculated: 374.17507, found: 374.17396.

N-(2-((*E*)-but-2-en-1-yloxy)benzylidene)ethanamine **3.2f**



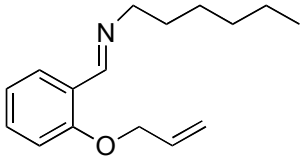
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75-8.74 (m, 1H), 7.93 (dd, *J* = 7.7 Hz, 1.8 Hz, 1H), 7.34 (ddd, *J* = 8.3 Hz, 7.3 Hz, 1.8 Hz, 1H), 6.98-6.97 (m, 1H), 6.91-6.88 (m, 1H), 5.90-5.83 (m, 1H), 5.79-5.71 (m, 1H), 4.64-4.48 (m, 2H), 3.67-3.62 (m, 2H), 1.78-1.74 (m, 3H), 1.29 (td, *J* = 7.3 Hz, 1.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$), with rotamers: δ 157.8, 156.5, 131.5, 130.3, 128.6, 127.2, 125.9, 125.5, 125.0, 120.9, 120.8, 112.4, 112.2, 69.1, 64.2, 56.1, 17.9, 16.4, 13.4. **HRMS** (ESI^+) for $C_{13}H_{18}NO^+$; calculated: 204.13829, found: 204.13784.

(*E*)-*N*-(2-(cinnamyloxy)benzylidene)ethanamine **3.2g**



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.00 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.45-7.43 (m, 2H), 7.39-7.34 (m, 3H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.03-6.95 (m, 2H), 6.75 (d, *J* = 16.0 Hz, 1H), 6.45 (dt, *J* = 16.0 Hz, 5.8 Hz, 1H), 4.76 (dd, *J* = 5.8 Hz, 1.1 Hz, 2H), 3.68 (qd, *J* = 7.3 Hz, 1.3 Hz, 2H), 1.33 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.7, 156.4, 136.3, 133.1, 131.6, 128.7, 128.0, 127.4, 126.6, 125.1, 124.2, 121.1, 112.4, 69.1, 56.2, 16.5. **HRMS** (ESI^+) for $C_{18}H_{20}NO^+$; calculated: 266.15394, found: 266.15345.

(*E*)-*N*-(2-(allyloxy)benzylidene)hexan-1-amine **3.2h**

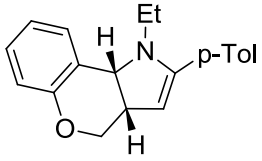


^{1}H NMR (400 MHz; $CDCl_3$): δ 8.74 (s, 1H), 7.96 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.35-7.31 (m, 1H), 6.98 (t, *J* = 7,5 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.12-6.03 (m, 1H), 5.43 (dd, *J* = 17.3 Hz, 1.6 Hz, 1H), 5.30 (dt, *J* = 10.6 Hz, 1.3 Hz, 1H), 4.59 (td, *J* = 3.4 Hz, 1.7 Hz, 2H), 3.62 (td, *J* = 7.1 Hz, 1.1 Hz, 2H), 1.70 (quintet, *J* = 7.3 Hz, 2H), 1.39-1.30 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz; $CDCl_3$): δ 157.6, 156.6, 133.1, 131.5, 127.3, 125.2, 121.0, 117.5, 112.3, 69.1, 62.1, 31.7, 31.0, 27.1, 22.6, 14.1. **HRMS** (ESI^+) for $C_{16}H_{24}NO^+$; calculated: 246.18524, found: 246.18461.

3.4.5 Synthesis of Pyrrolines 3.3

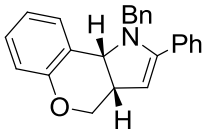
In a glovebox, imine **2** (0.2 mmol) and acid chloride (0.22 mmol) were mixed in $CDCl_3$ (ca. 0.5 mL) and allowed to stand at room temperature for 30 min. PhP(2-catechyl) (0.22 mmol) was added, and after 1h, DBU (0.3 mmol) was added as a solution in $CDCl_3$. The reaction was complete within 10min at room temperature. The crude solution was concentrated in vacuo and purified by dissolving the residue in minimal amount of DCM. The product is purified in a glovebox with small pipette column of alumina using diethyl ether as eluent for **3a-3d** and **3f-3g** or by column chromatography on silica gel using hexanes/diethyl ether 95/5 as eluent for **3e** affording **3** as a pure a light yellow oil

(3aS,9bR)-1-ethyl-2-(p-tolyl)-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole **3.3a**



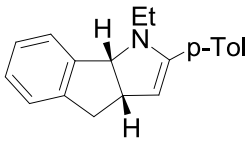
Isolated yield: 85%.**^{1}H NMR**: (500 MHz, $CDCl_3$) δ 7.31ppm (d, *J* = 7.5 Hz, 1H), 7.26-7.21 (m, 3H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.98-6.93 (m, 2H), 4.79 (d, *J* = 2.0 Hz, 1H), 4.35 (d, *J* = 8.0 Hz, 1H), 4.06 (dd, *J* = 10.5 Hz, 4.5 Hz, 1 H), 3.83 (t, *J* = 10.5 Hz, 1H), 3.32-3.21 (m, 2H), 3.09-3.04 (m, 1H), 2.36 (s, 3H), 0.98 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR**: (125.7 MHz, $CDCl_3$) δ 155.5, 155.0, 137.8, 131.3, 130.9, 128.9, 128.7, 127.2, 122.0, 120.4, 117.2, 101.0, 66.3, 57.4, 40.4, 38.6, 21.2, 10.1. **HRMS** (ESI^+) for $C_{20}H_{22}NO^+$; calculated: 292.16959, found: 292.16908.

(3aS,9bR)-1-benzyl-2-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole **3.3b**



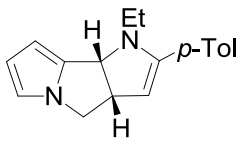
Isolated yield: 85%. **^{1}H NMR**: (500 MHz, CD_3CN) δ 7.49 (dd, *J* = 8.2 Hz, 1.4 Hz, 2H), 7.40-7.31 (m, 7H), 7.27 (td, *J* = 6.2 Hz, 3.04 Hz, 1H), 7.17-7.12 (m, 2H), 6.85-6.81 (m, 2H), 5.08 (d, *J* = 2.3 Hz, 1H), 4.41 (d, *J* = 8.3 Hz, 1H), 4.32 (d, *J* = 15.9 Hz, 1H), 4.27 (d, *J* = 15.9 Hz, 1H), 4.05 (dd, *J* = 11.0 Hz, 4.2 Hz, 1H), 3.95 (dd, *J* = 11.0 Hz, 7.6 Hz, 1H), 3.23-3.19 (m, 1H). **^{13}C NMR**: (125.7 MHz, CD_3CN) δ 161.0, 159.8, 144.2, 138.9, 136.3, 133.8, 133.7, 133.6, 132.4, 132.2, 128.5, 125.9, 122.0, 109.3, 71.6, 63.9, 57.3, 45.3. **HRMS** (ESI^+) for $C_{24}H_{22}NO^+$; calculated: 340.16959, found: 340.16954.

(3aS,8bR)-1-ethyl-2-(p-tolyl)-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole **3.3c**



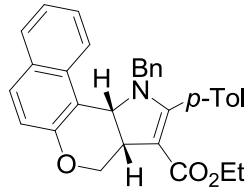
Isolated yield: 74%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51–7.47 (m, 1H), 7.35–7.31 (m, 2H), 7.29–7.18 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.05 (d, *J* = 2.1 Hz, 1H), 4.79 (d, *J* = 8.3 Hz, 1H), 4.04 (t, *J* = 8.3 Hz, 1H), 3.26 (dd, *J* = 16.2 Hz, 8.3 Hz, 1H), 3.19–3.05 (m, 1H), 2.98 (ddd, *J* = 17.4 Hz, 11.0 Hz, 4.3 Hz, 2H), 2.31 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}CNMR** (75 MHz, $CDCl_3$) δ 151.2, 145.4, 142.0, 137.5, 131.2, 128.8, 127.6, 127.0, 126.5, 125.5, 124.9, 109.6, 72.7, 46.3, 45.9, 38.3, 21.3, 14.3. **HRMS** (ESI^+) for $C_{20}H_{22}N^+$: calculated: 276.17468, found: 276.17430.

(3aR,8bR)-1-ethyl-2-(p-tolyl)-1,3a,4,8b-tetrahydropyrrolo[2,3-a]pyrrolizine **3.3d**



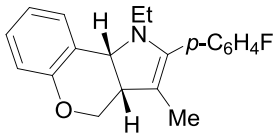
CD_3CN was used as solvent. Isolated yield: 76%.**^{1}H NMR** (400 MHz, C_6D_6) δ 7.29 (d, *J* = 6.4 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 2H), 6.57–6.47 (m, 1H), 6.38 (dd, *J* = 2.6 Hz, 1.3 Hz, 1H), 6.22 (dd, *J* = 3.5 Hz, 1.2 Hz, 1H), 4.66 (d, *J* = 2.3 Hz, 1H), 4.52 (d, *J* = 9.5 Hz, 1H), 3.87–3.71 (m, 1H), 3.51 (dd, *J* = 10.1 Hz, 8.2 Hz, 1H), 3.42 (dd, *J* = 10.1 Hz, 4.1 Hz, 1H), 3.11 (dq, *J* = 14.5 Hz, 7.2 Hz, 1H), 2.71 (dq, *J* = 13.9 Hz, 7.0 Hz, 1H), 2.02 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, C_6D_6) δ 153.1, 138.4, 137.5, 131.4, 128.8, 113.6, 113.5, 103.0, 100.7, 65.6, 52.3, 50.1, 45.2, 20.8, 13.8. **HRMS** ($APCI^+$) for $C_{18}H_{21}N_2^+$; calculated: 265.16993, found: 265.16930.

(3aS,11cR)-ethyl 1-benzyl-2-(p-tolyl)-1,3a,4,11c-tetrahydrobenzo[5,6]chromeno[4,3-b]pyrrole-3-carboxylate **3.3e**



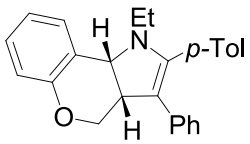
Isolated yield: 75%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79–7.60 (m, 3H), 7.37–7.17 (m, 4H), 7.17–7.07 (m, 6H), 6.69–6.59 (m, 2H), 5.69 (d, *J* = 9.4 Hz, 1H), 4.20–4.10 (m, 3H), 4.07–3.91 (m, 3H), 3.66 (dt, *J* = 9.3 Hz, 5.9 Hz, 1H), 2.33 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.9, 163.6, 156.1, 138.9, 138.4, 133.7, 130.1, 129.2, 128.8, 128.7, 128.0, 126.7, 126.5, 123.5, 122.0, 119.3, 112.3, 98.9, 67.3, 58.6, 55.6, 48.1, 40.3, 21.4, 14.3, 14.1. **HRMS** ($APCI^+$) for $C_{32}H_{30}NO_3^+$; calculated: 476.22202, found: 476.22177.

(3aS,9bR)-1-ethyl-2-(4-fluorophenyl)-3-methyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole **3.3f**



Cycloaddition required 1h at 60°C. Isolated yield: 88%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 4H), 7.04 (m, 2H), 7.00–6.88 (m, 2H), 4.25 (d, *J* = 8.0 Hz, 1H), 4.20 (dd, *J* = 10.8 Hz, 4.4 Hz, 1H), 3.93 (t, *J* = 10.3 Hz, 1H), 3.20–2.95 (m, 3H), 1.71 (s, 3H), 0.95 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.9 (d, $^{1}J_{C\text{-}F}$ = 237.5 Hz), 155.5, 145.4, 130.9, 130.4 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 128.7 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 128.6, 122.4, 120.5, 117.1, 115.1 (d, $^{2}J_{C\text{-}F}$ = 15.0 Hz), 110.0, 64.8, 56.1, 42.9, 40.8, 11.8, 10.0. **HRMS** ($APCI^+$) for $C_{20}H_{21}NOF^+$; calculated: 310.16017, found: 310.16097.

(3aS,9bR)-1-ethyl-3-phenyl-2-(p-tolyl)-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole **3.3g**

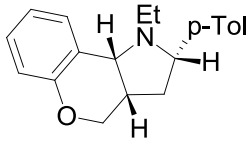


Cycloaddition required 1h at 60˚C**.** Isolated yield: 91%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.15 (m, 6H), 7.09 (t, *J* = 7.7 Hz, 2H), 7.00-6.94 (m, 5H), 4.50 (d, *J* = 7.9 Hz, 1H), 4.18 (dd, *J* = 10.9 Hz, 4.8 Hz, 1H), 3.91 (t, *J* = 11.0 Hz, 1H), 3.33-3.56 (m, 1H), 3.24–3.04 (m, 2H), 2.41 (s, 3H), 1.01 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.7, 148.7, 138.0, 135.7, 131.1$_3$, 131.0$_8$, 129.6, 129.1, 129.0, 128.1, 126.0, 124.2, 120.7, 120.3, 117.3, 110.6, 65.0, 56.1, 39.9, 38.9, 21.4, 10.5. **HRMS** (APCI$^+$) for $C_{26}H_{26}NO^+$; calculated: 368.20089, found: 368.19963.

3.4.6 Synthesis of Pyrrolidines

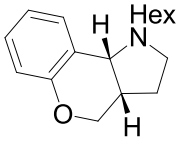
In a glovebox, imine **2** (0.2 mmol) and acid chloride (0.22 mmol) were mixed in $CDCl_3$ (ca. 0.5 mL) and allowed to stand at room temperature for 30 min. PhP(2-catechyl) (0.22 mmol) was added, and after 1h, DBU (0.3 mmol) was added as a solution in $CDCl_3$. The reaction was complete within 10min at room temperature. To the crude reaction mixture in a 25 mL round bottom flask was added $NaBH(OAc)_3$ (0.4 mmol) followed by HCl, 1M in Et_2O (0.4 mmol). The solution is stirred at rt for 18h and then quenched with 4 mL of 2N NaOH. The product is extracted with dichloromethane, washed with water, then dried on $MgSO_4$, filtered and concentrated. The product is purified by flash column chromatography on silica using petroleum ether/diethyl ether as eluent 90/10, affording **4** as a white foam.

1-ethyl-2-(*p*-tolyl)-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole**, 3.4a**



4a was prepared according to the same procedure as **4c**. Isolated yield: 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26-7.20 (m, 4H), 7.12 (d, *J* = 8 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 2H), 4.18 (t, *J* = 10.5 Hz, 1H), 4.05 (dd, *J* = 10.5 Hz, 4.5 Hz, 1H), 3.83 (t, *J* = 8.5 Hz, 1H), 3.70 (d, *J* = 5.5 Hz, 1H), 2.87 (dt, *J* = 14.5 Hz, 7.0 Hz, 1H), 2.74 (dt, *J* = 14.5 Hz, 7.0 Hz, 1H), 2.51-2.45 (m, 1H), 2.42-2.35 (m, 1H), 2.33 (s, 3H) 1.31-1.26 (m, 1H), 0.95 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 155.2, 141.1, 136.5, 131.4, 129.1, 128.6, 127.3, 122.2, 119.9, 116.9, 67.4, 64.1, 57.4, 41.2, 36.1, 33.3, 21.1, 8.2. **HRMS** (ESI$^+$) for $C_{20}H_{24}NO^+$; calculated: 294.18524, found: 294.18454.

(3aS,9bR)-1-hexyl-1,2,3,3a,4,9b-hexahydrochromeno[4,3-b]pyrrole **3.4b**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.16 (m, 2H), 6.91–6.87 (m, 2H), 4.05–3.91 (m, 2H), 3.17-3.13 (m, 1H), 3.08-2.98 (m, 2H), 2.41-2.34 (m, 1H), 2.23-2.19 (m, 2H), 2.08-2.01 (m, 1H), 1.54–1.35 (m, 3H), 1.27-1.24 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.2, 131.9, 128.6, 121.7, 119.6, 116.8, 67.6, 61.5, 53.3, 50.9, 34.3, 31.8, 28.4, 27.3, 24.6, 22.6, 14.1. **HRMS** (APCI$^+$) for $C_{17}H_{26}NO^+$; calculated: 260.20131, found: 260.20199

3.5 References

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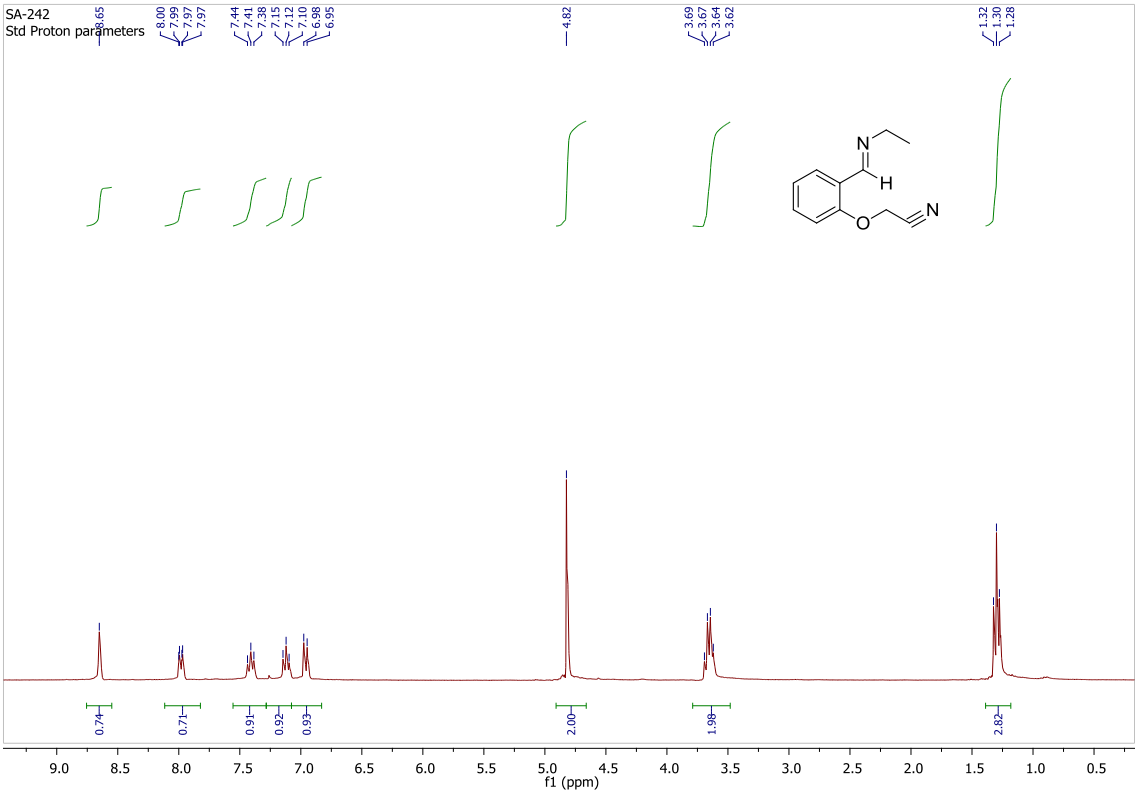
CONCLUSIONS

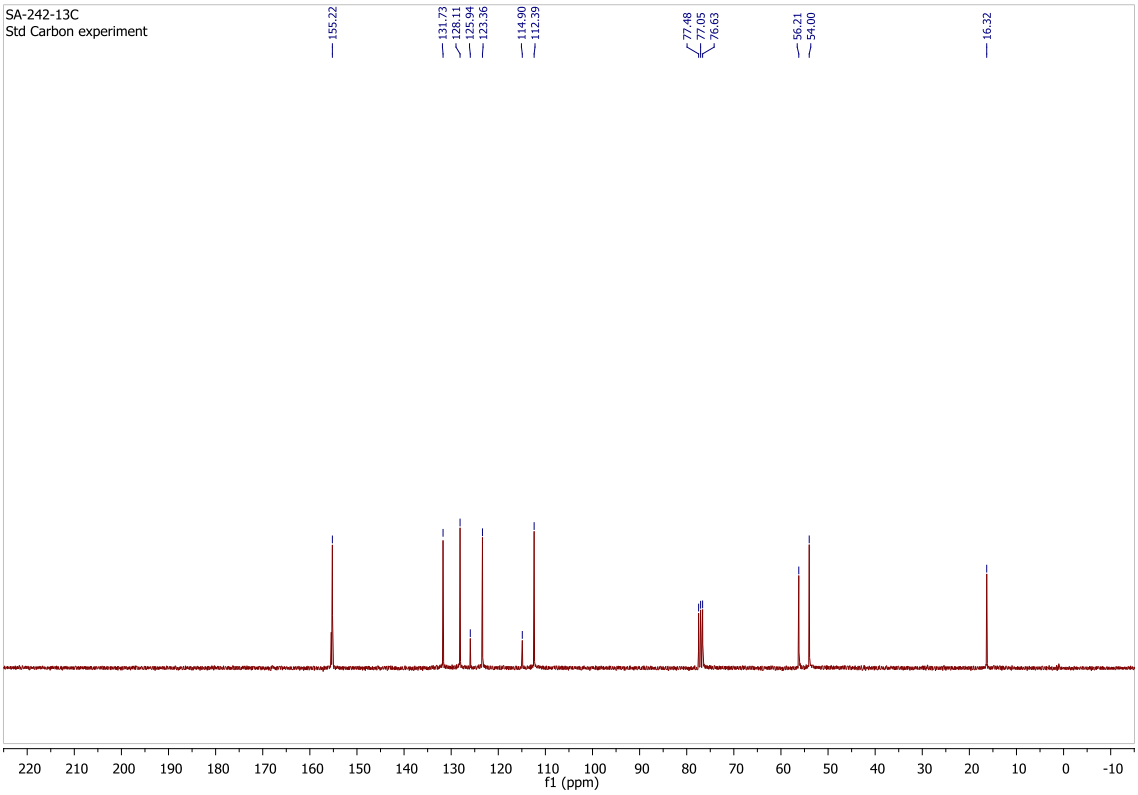
1,3-Dipolar cycloaddition reactions represent an important general approach to prepare five-membered ring heterocycles. This thesis explored two new variants of this transformation with a 1,3-dipole developed in our laboratory: phospha-Münchnones. Chapter 2 describes how electron deficient *N*-nosyl substituted imines, and tethered-nitriles, can undergo cycloaddition reactions with phospha-Münchnones to generate imidazoles. Considering that these dipoles are generated in one pot reactions of imines, acid chlorides and phosphonites, these provide efficient routes to construct polysubstituted imidazoles from simple and available building blocks.

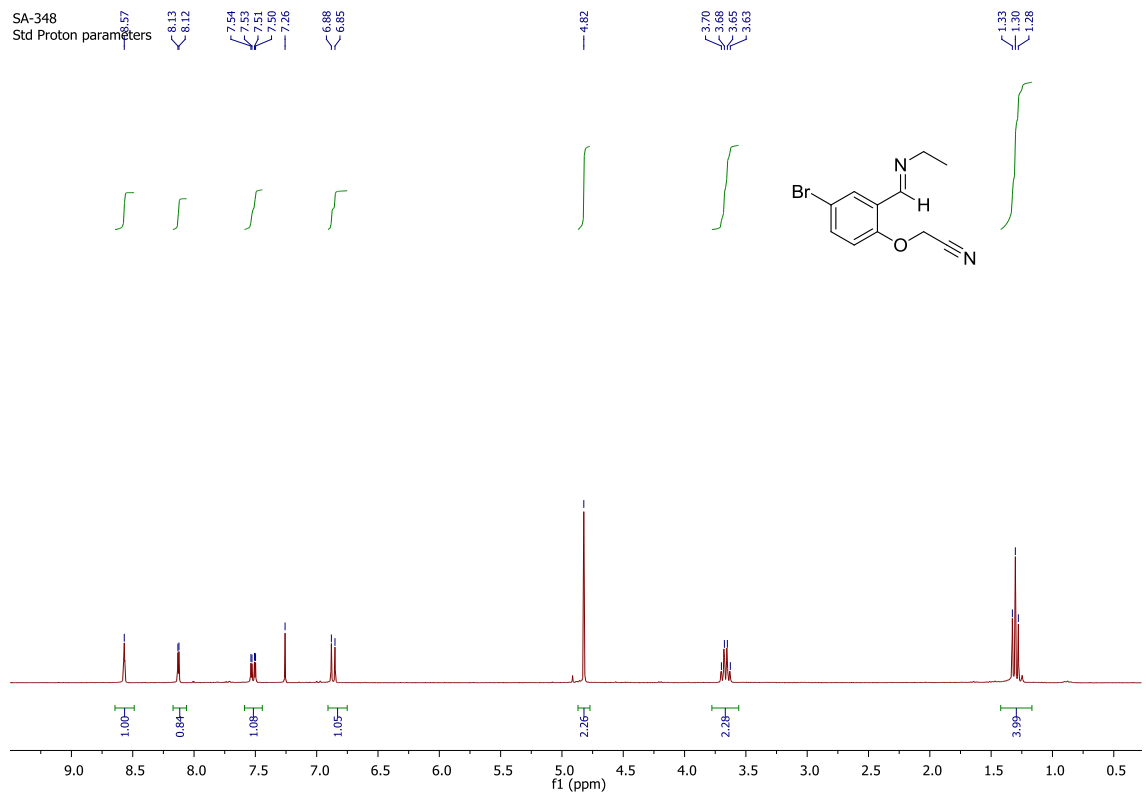
In light of the successful synthesis of imidazoles, olefin-tethered imines were investigated in the synthesis of polycyclic 2-pyrrolines in Chapter 3. Phosphonites again proved to be effective for the formation of reactive phospha-Münchnones from imines and acid chlorides. When coupled with intramolecular alkene cycloaddition, this allows the preparation of 2-pyrrolines in high yields and with facile access to product diversity.

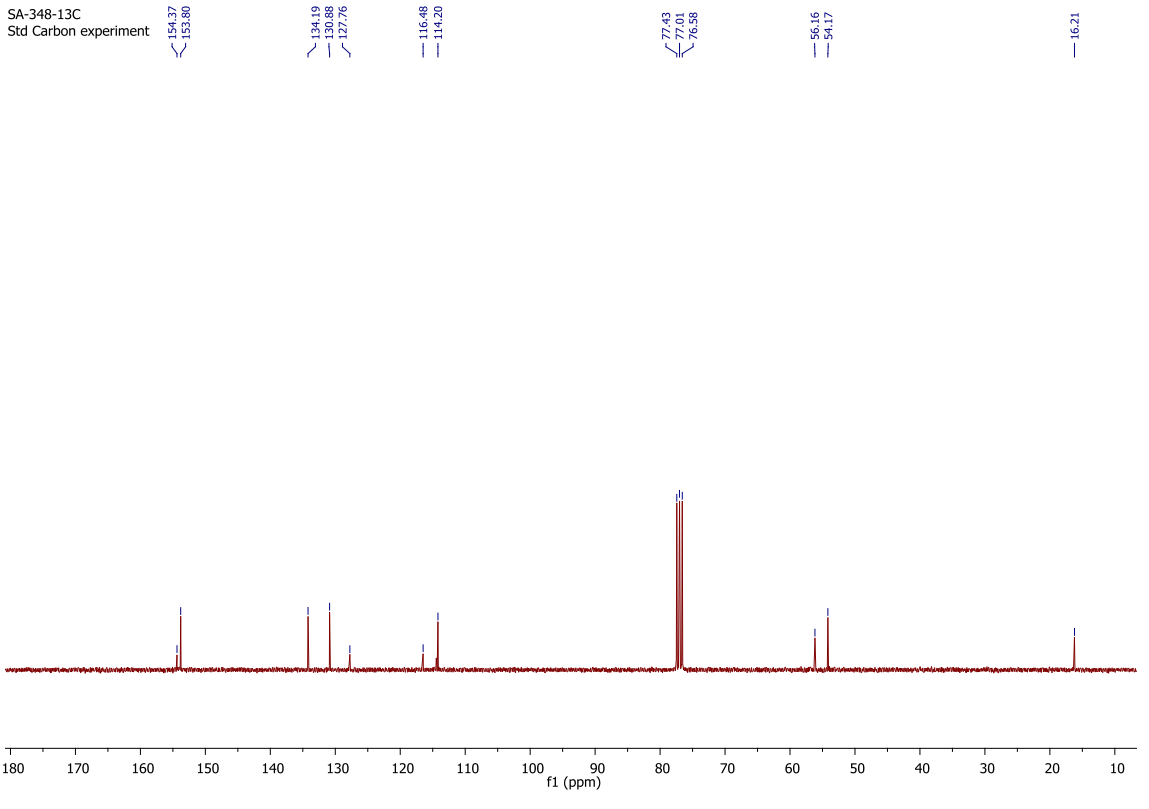
In conclusion, phosphonite-mediated 1,3-dipolar cycloaddition reactions provide an efficient approach to generate structurally complex nitrogen-containing heterocycles that would be difficult to prepare using traditional, often multistep, methods.

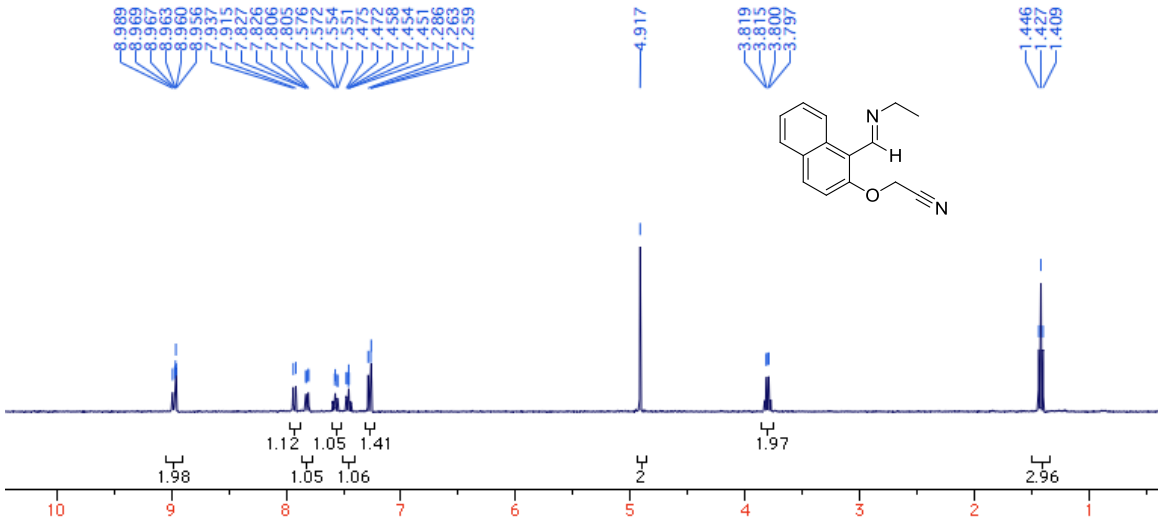
APPENDIX A ^{1}HNMR and ^{13}CNMR Spectra of Nitrile Tethered Imines and Imidazoles






SA-348
Std Proton parameters
8.57
8.13
8.12
7.54
7.53
7.51
7.50
7.26
6.88
6.85
4.82
3.70
3.68
3.65
3.63
1.33
1.30
1.28
Br
N
H
O
N
1.00
0.84
1.08
1.05
2.26
2.28
3.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


SA-348-13C
Std Carbon experiment
154.37
153.80
134.19
130.88
127.76
116.48
114.20
77.43
77.01
76.58
56.16
54.17
16.21
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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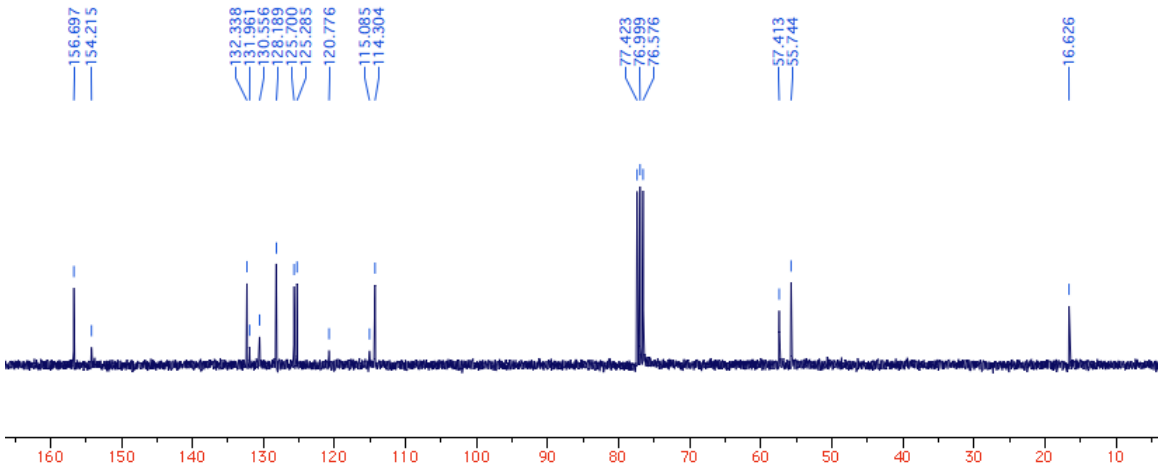
8.969
8.967
8.963
8.960
8.956
7.937
7.915
7.827
7.826
7.806
7.805
7.576
7.572
7.554
7.551
7.475
7.472
7.458
7.454
7.451
7.286
7.263
7.259
4.917
3.819
3.815
3.800
3.797
1.446
1.427
1.409
N
H
O
N
1.12
1.05
1.41
1.97
1.98
1.05
1.06
2
2.96
10
9
8
7
6
5
4
3
2
1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132.338
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130.556
128.189
125.700
125.285
120.776
115.085
114.304
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76.999
76.576
57.413
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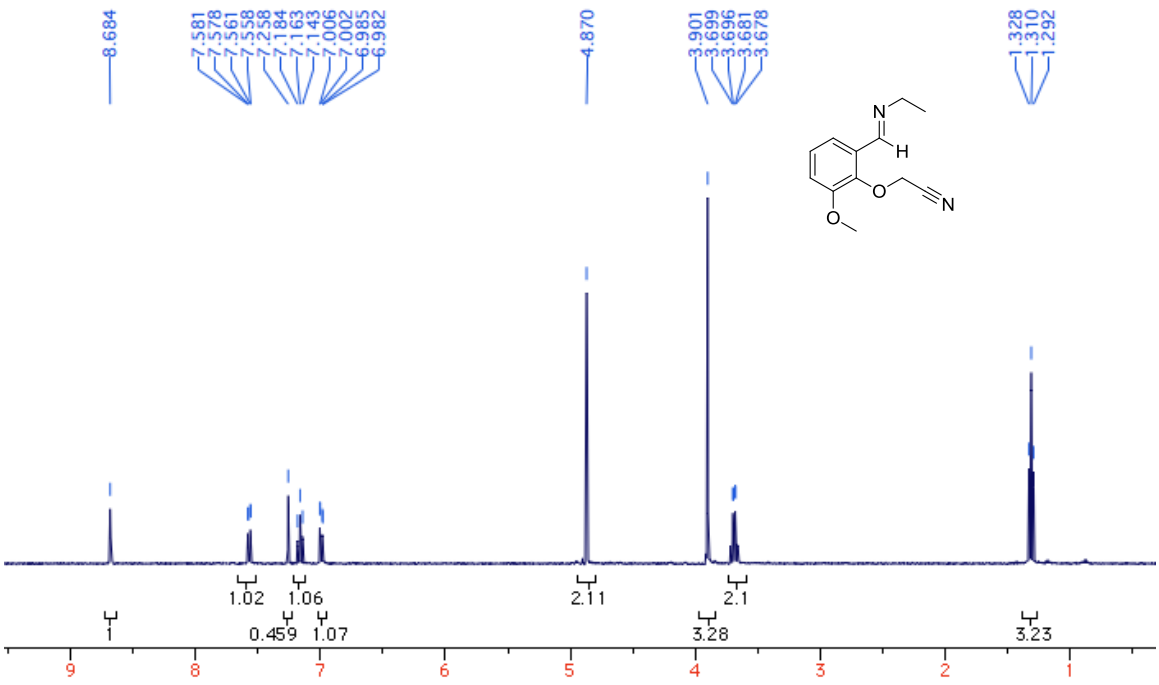
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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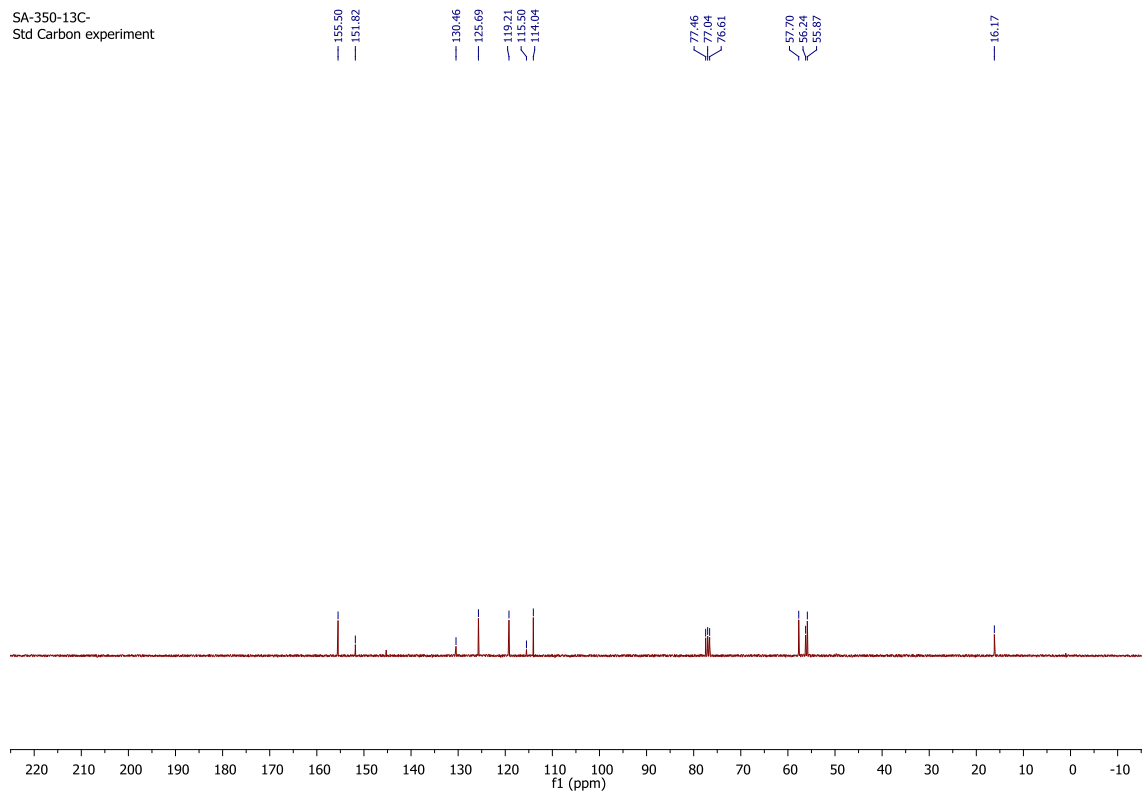
7.143
7.006
7.002
6.985
6.982
4.870
3.901
3.699
3.696
3.681
3.678
1.328
1.310
1.292
N
H
O
O
N
1.02
1.06
2.11
2.1
1
0.459
1.07
3.28
3.23
9
8
7
6
5
4
3
2
1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Std Carbon experiment
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130.46
125.69
119.21
115.50
114.04
77.46
77.04
76.61
57.70
56.24
55.87
16.17
220
210
200
190
180
170
160
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110
100
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30
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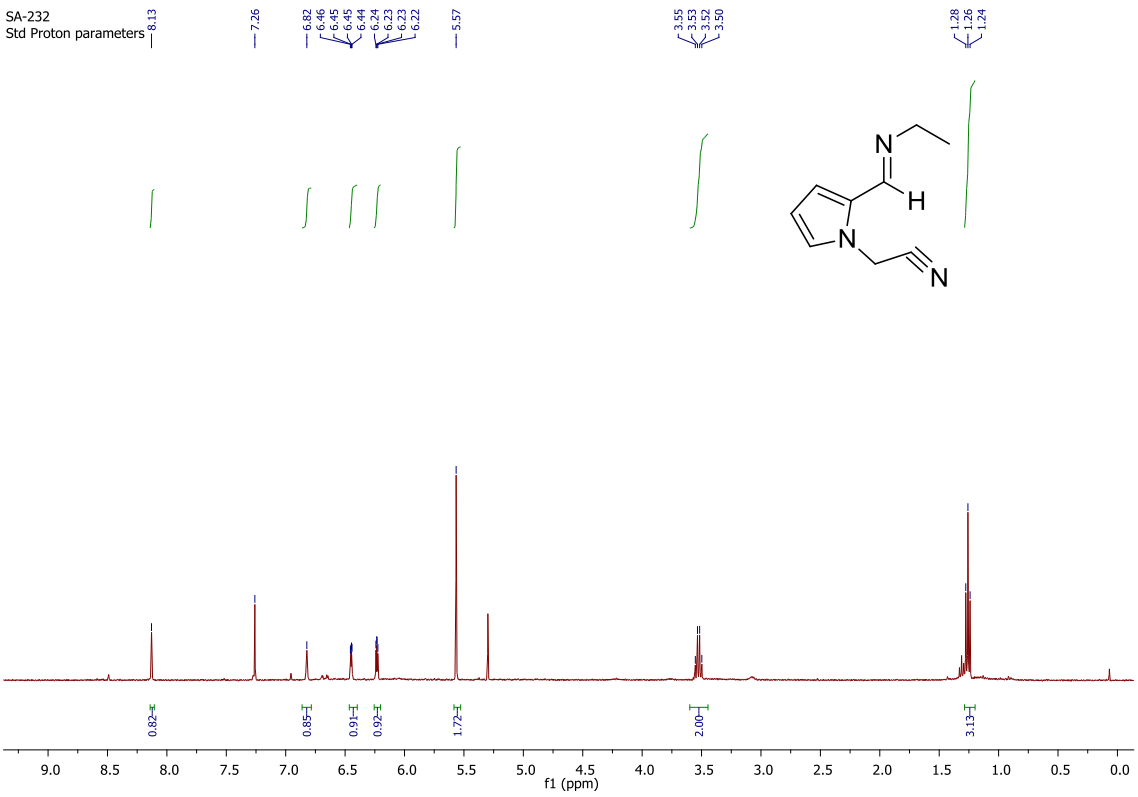
-10
f1 (ppm)


SA-232
Std Proton parameters
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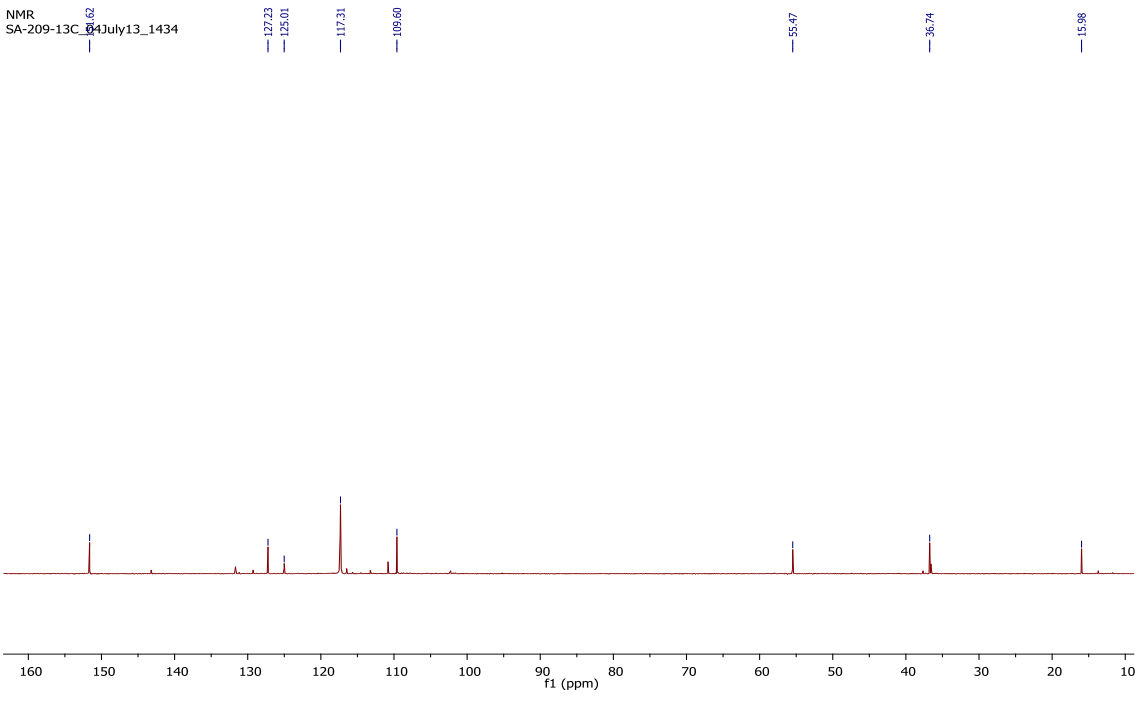
6.46
6.45
6.45
6.44
6.44
6.24
6.23
6.22
5.57
3.55
3.53
3.52
3.50
1.28
1.26
1.24
N
H
N
N
0.82
0.85
0.91
0.92
1.72
2.00
3.13
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


NMR
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125.01
117.31
109.60
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36.74
15.98
160
150
140
130
120
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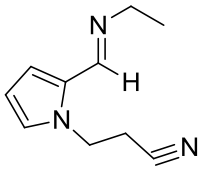
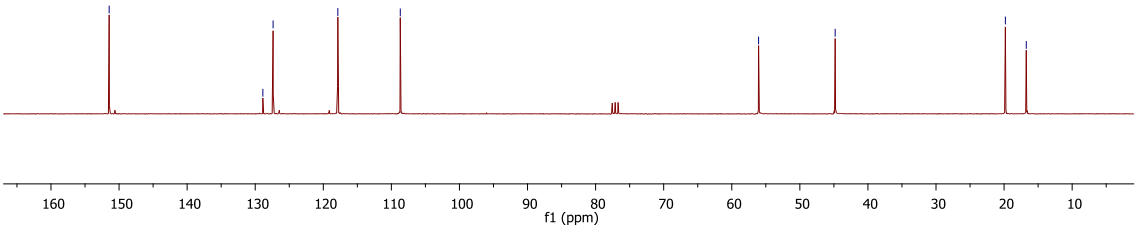
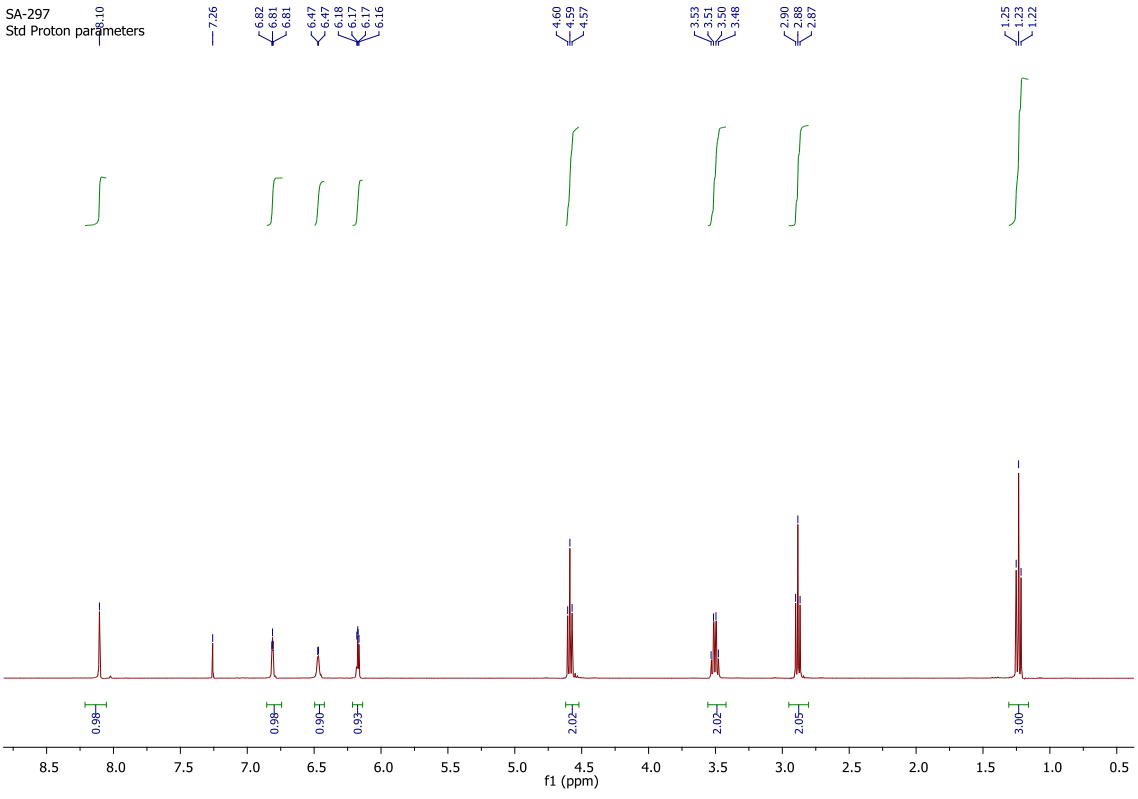
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

SA-270-13C_CARBON_01

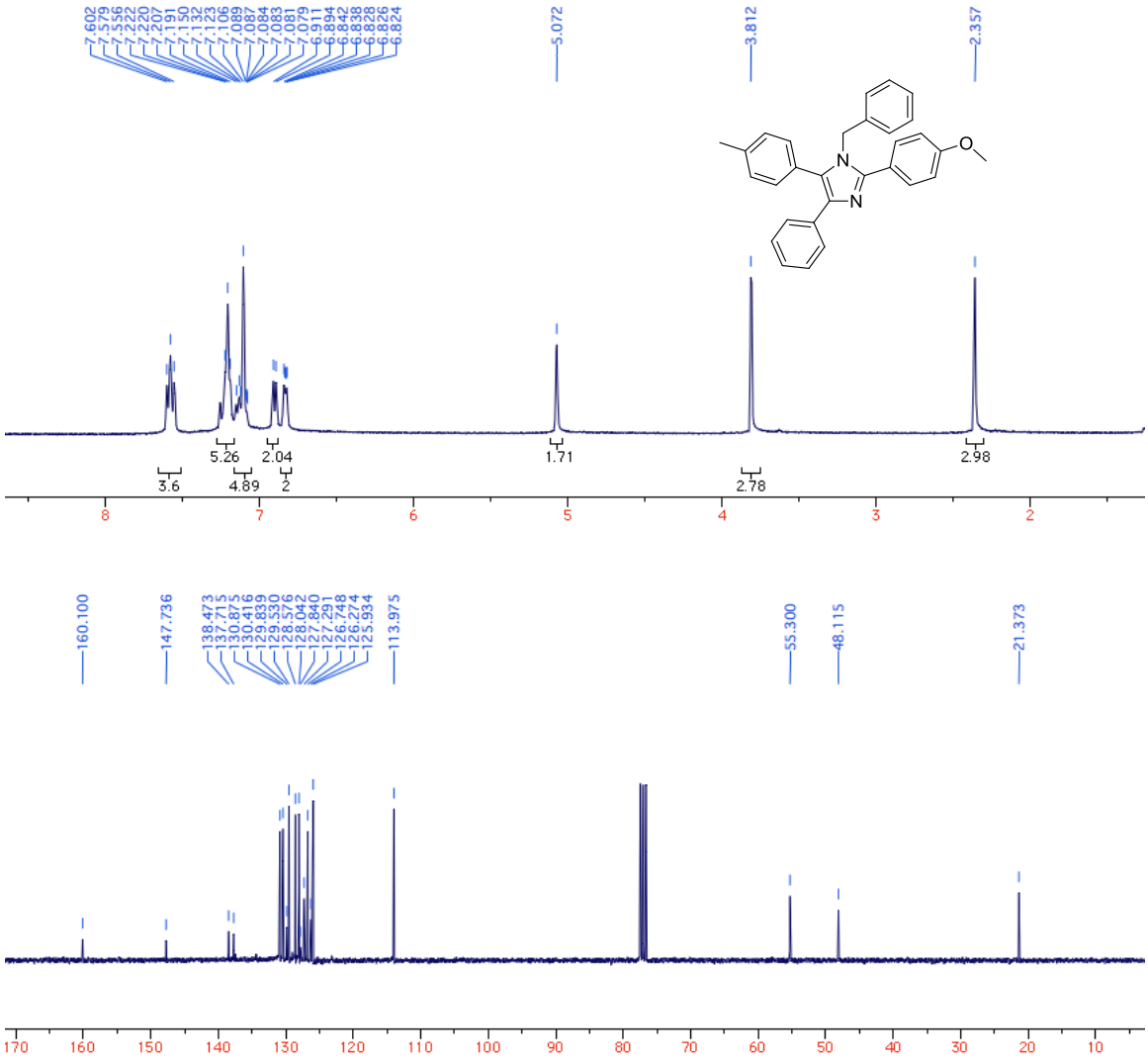




SA-297
Std Proton parameters



2.5a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7.132
7.123
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7.084
7.083
7.081
7.079
6.911
6.894
6.842
6.838
6.828
6.826
6.824
5.072
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2.357
O
N
N
5.26
2.04
3.6
4.89
2
1.71
2.78
2.98
8
7
6
5
4
3
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129.839
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127.291
126.748
126.274
125.934
113.975
55.300
48.115
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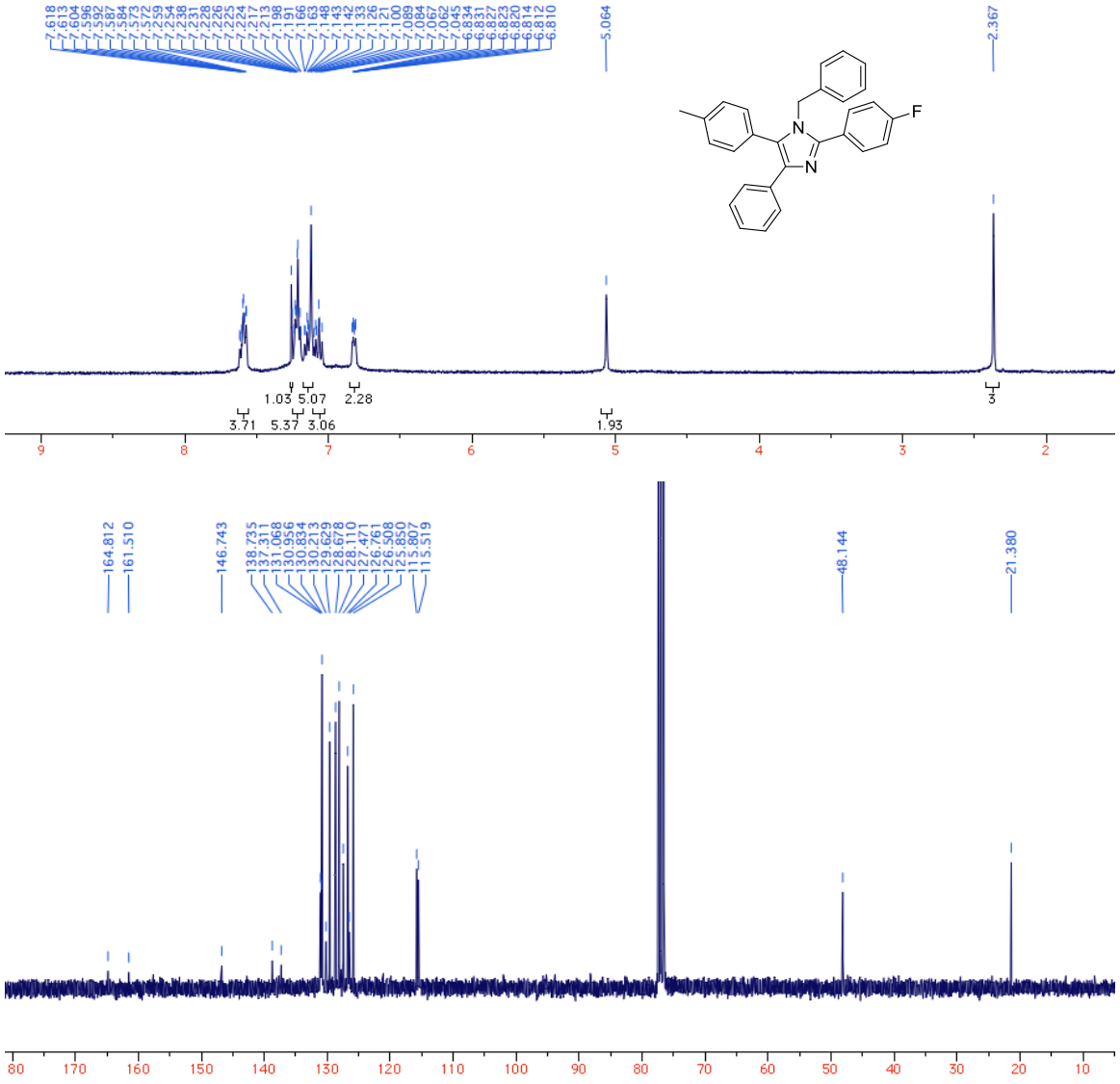
30
20
10

2.5b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7.524
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7.491
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7.163
7.148
7.143
7.142
7.133
7.126
7.121
7.100
7.089
7.084
7.067
7.062
7.045
6.834
6.831
6.827
6.823
6.820
6.814
6.812
6.810
5.064
2.367
F
N
N
1.03
5.07
2.28
3.71
5.37
3.06
1.93
3
9
8
7
6
5
4
3
2
164.812
161.510
146.743
138.735
137.311
131.068
130.956
130.834
130.713
130.623
128.678
128.110
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126.508
125.850
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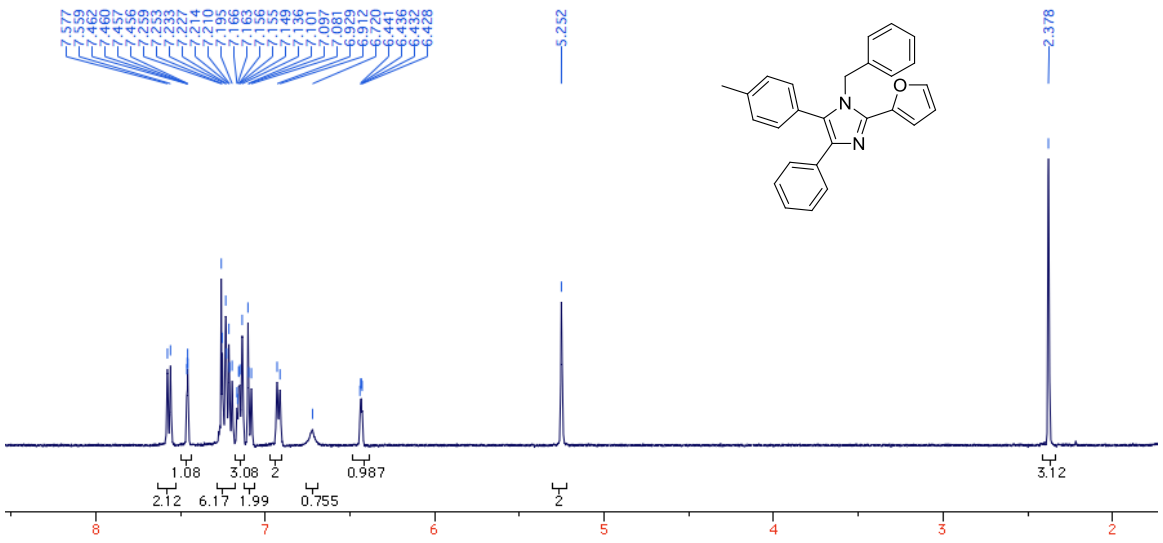
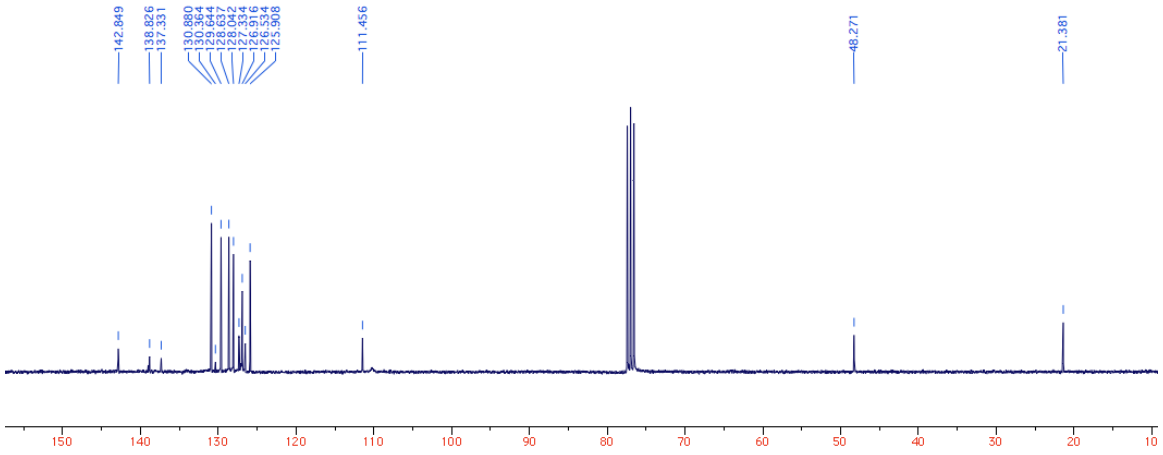
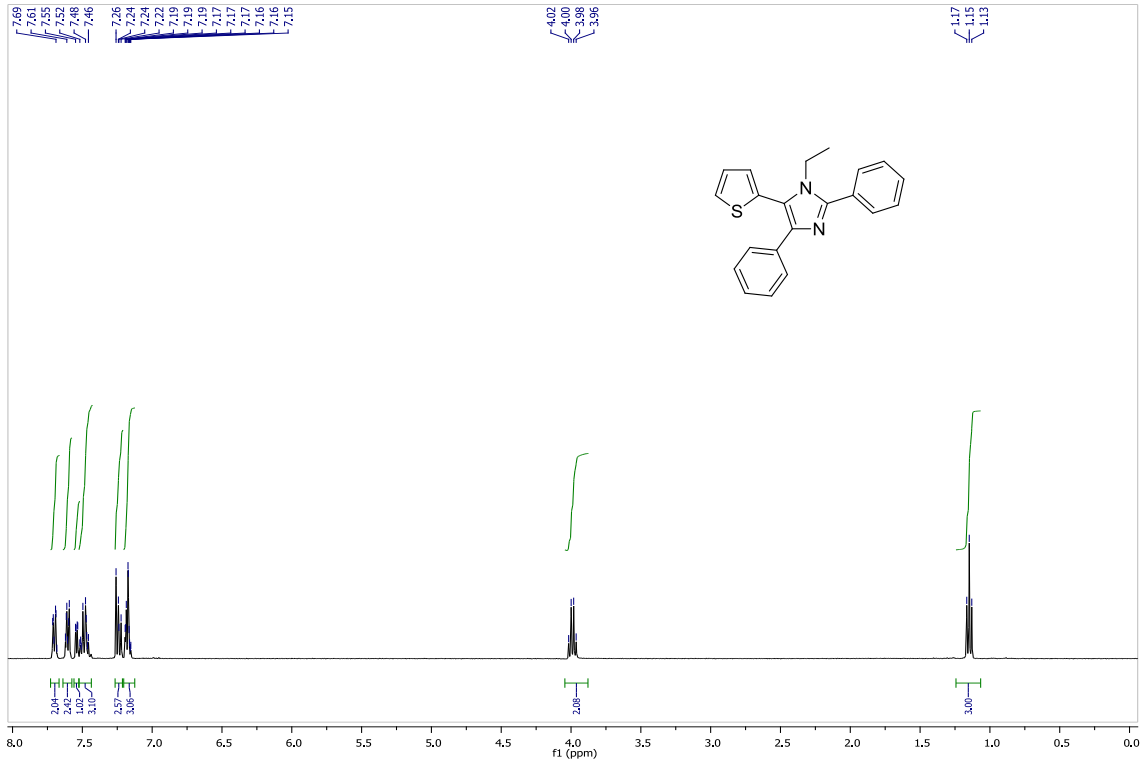
115.519
48.144
21.380
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

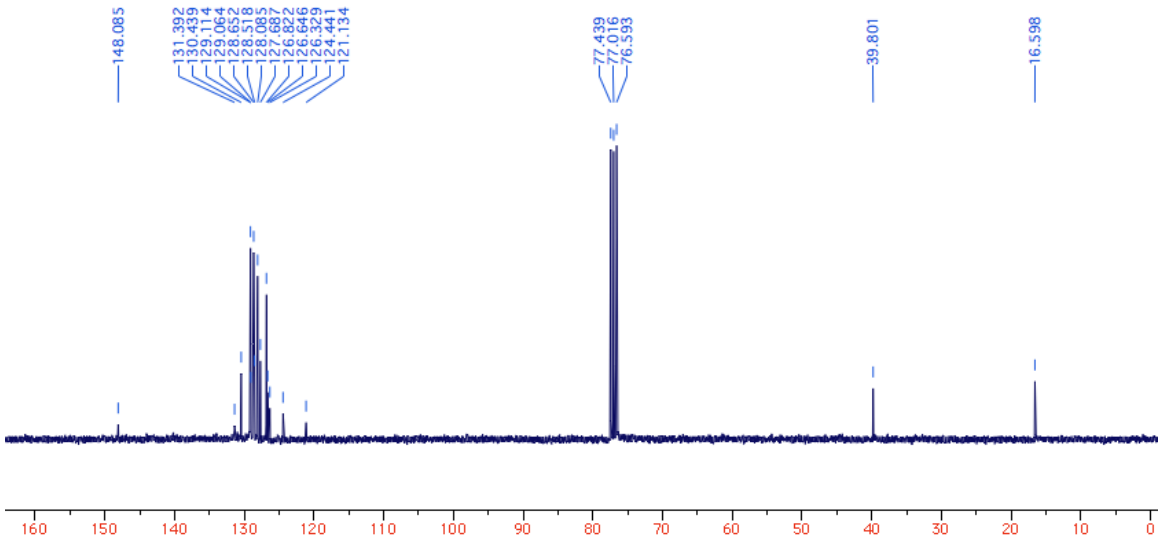
2.5c


7.577
7.559
7.462
7.460
7.457
7.456
7.239
7.233
7.227
7.214
7.210
7.195
7.166
7.163
7.156
7.155
7.149
7.136
7.101
7.097
7.081
6.929
6.912
6.720
6.441
6.436
6.432
6.428
5.252
2.378
N
O
N
1.08
3.08
2
0.987
3.12
2.12
6.17
1.99
0.755
2
8
7
6
5
4
3
2

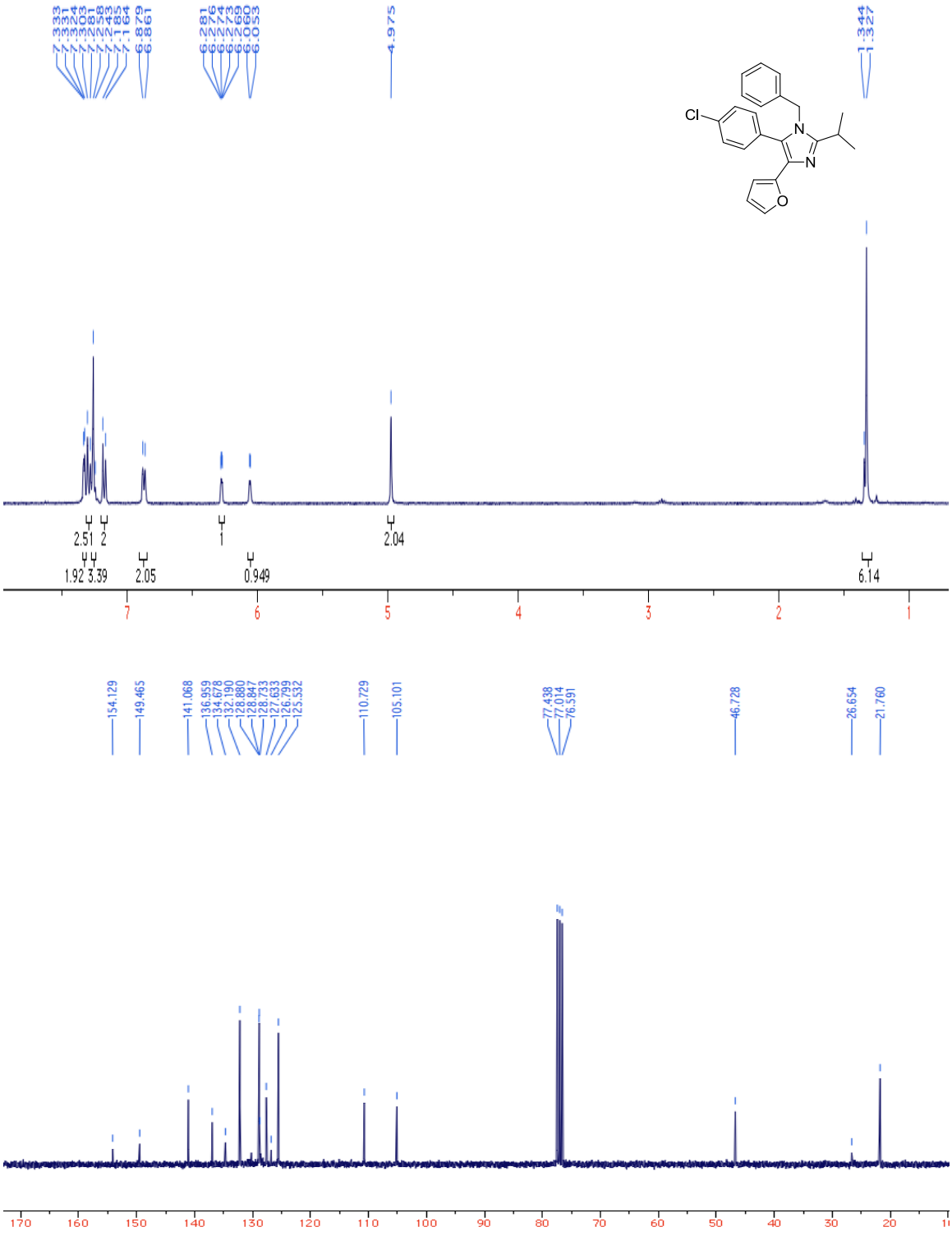

142.849
138.826
137.331
130.880
130.364
129.644
128.637
128.042
127.314
127.316
126.534
125.908
111.456
48.271
21.381
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

2.5d


7.69
7.61
7.55
7.52
7.48
7.46
7.26
7.24
7.24
7.22
7.19
7.19
7.19
7.17
7.17
7.17
7.16
7.16
7.15
4.02
4.00
3.98
3.96
1.17
1.15
1.13
S
N
N
2.04
2.42
1.02
3.10
2.57
3.06
2.08
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


148.085
131.392
130.439
129.114
129.064
128.652
128.518
128.085
127.687
126.822
126.646
126.329
124.441
121.134
77.439
77.016
76.593
39.801
16.598
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

2.5e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7.331
7.324
7.303
7.281
7.258
7.243
7.185
7.164
6.879
6.861
6.281
6.276
6.274
6.273
6.269
6.060
6.053
4.975
1.344
1.327
Cl
N
N
O
2.51
2
1
2.04
1.92
3.39
2.05
0.949
6.14
7
6
5
4
3
2
1
154.129
149.465
141.068
136.959
134.678
132.190
128.880
128.847
128.733
127.633
126.799
125.532
110.729
105.101
77.438
77.014
76.591
46.728
26.654
21.760
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160
150
140
130
120
110
100
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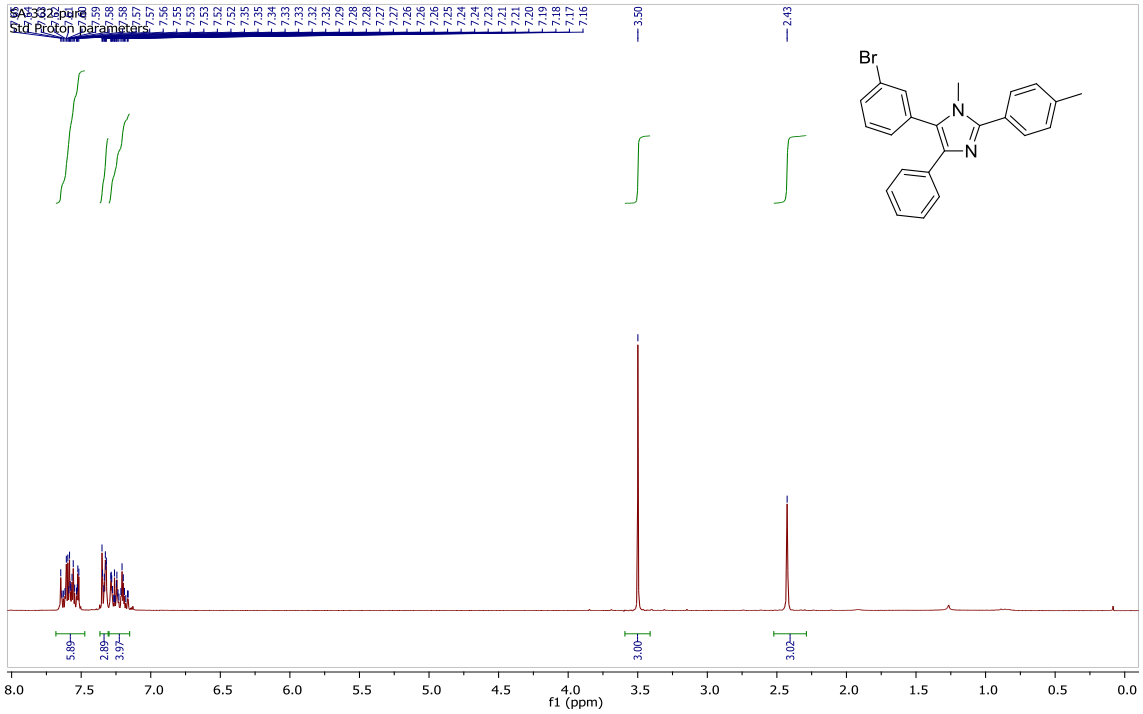
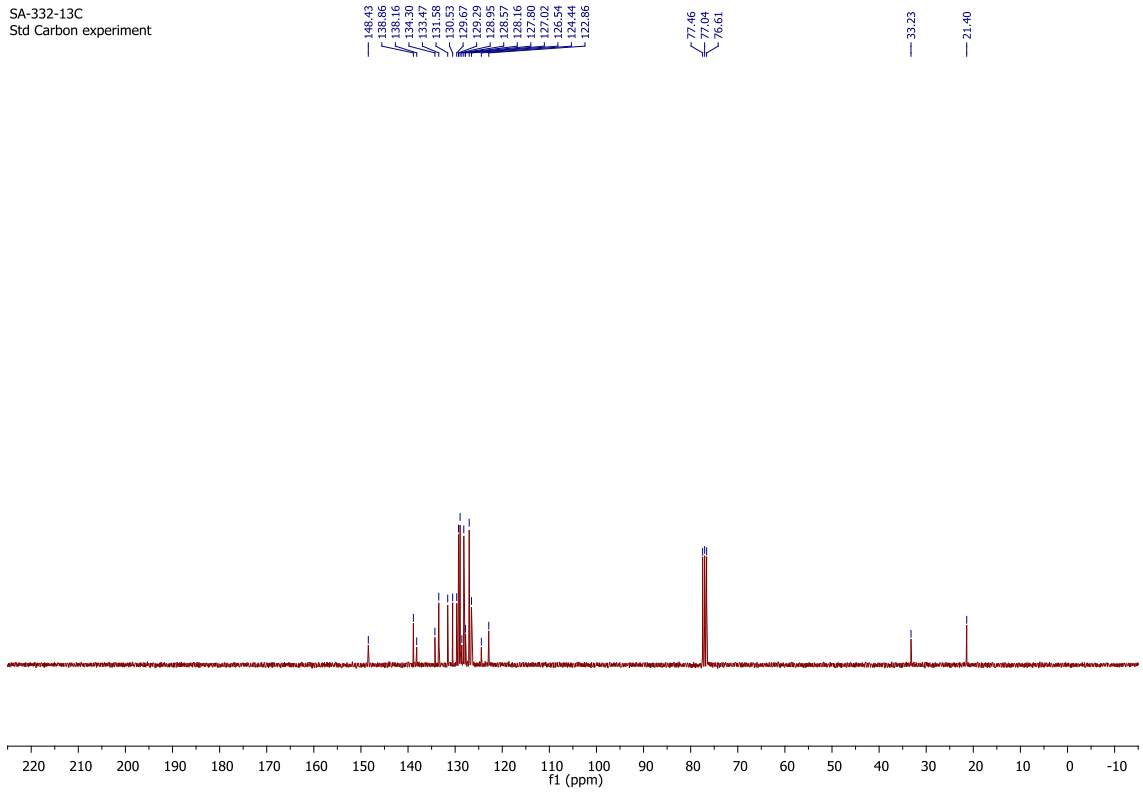
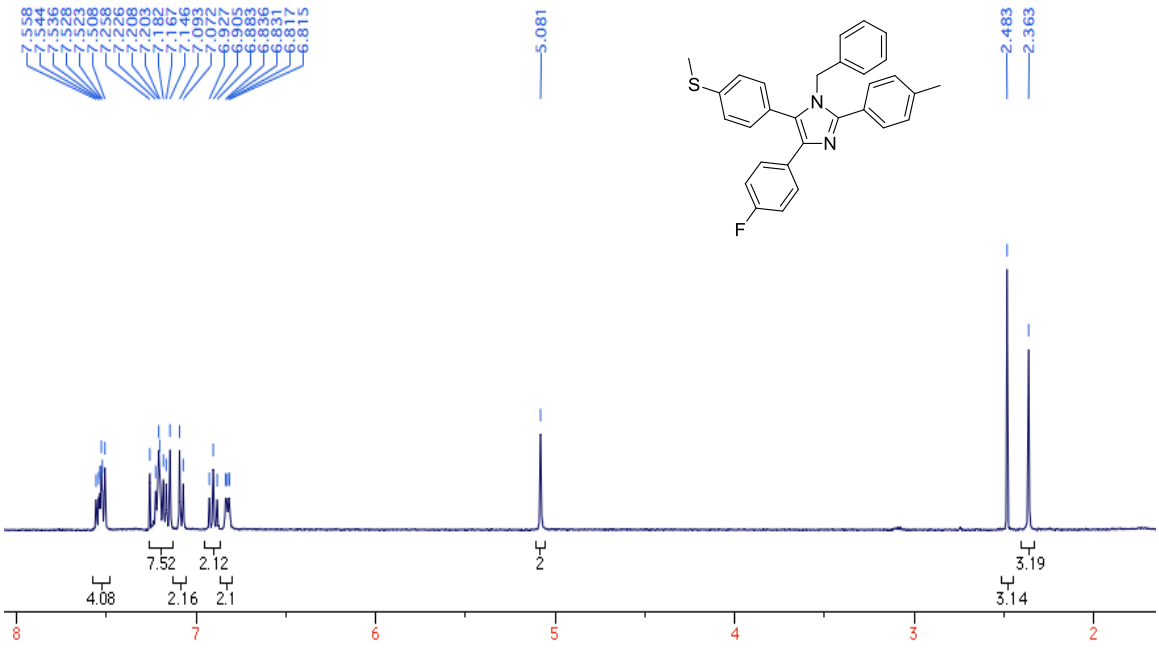
70
60
50
40
30
20

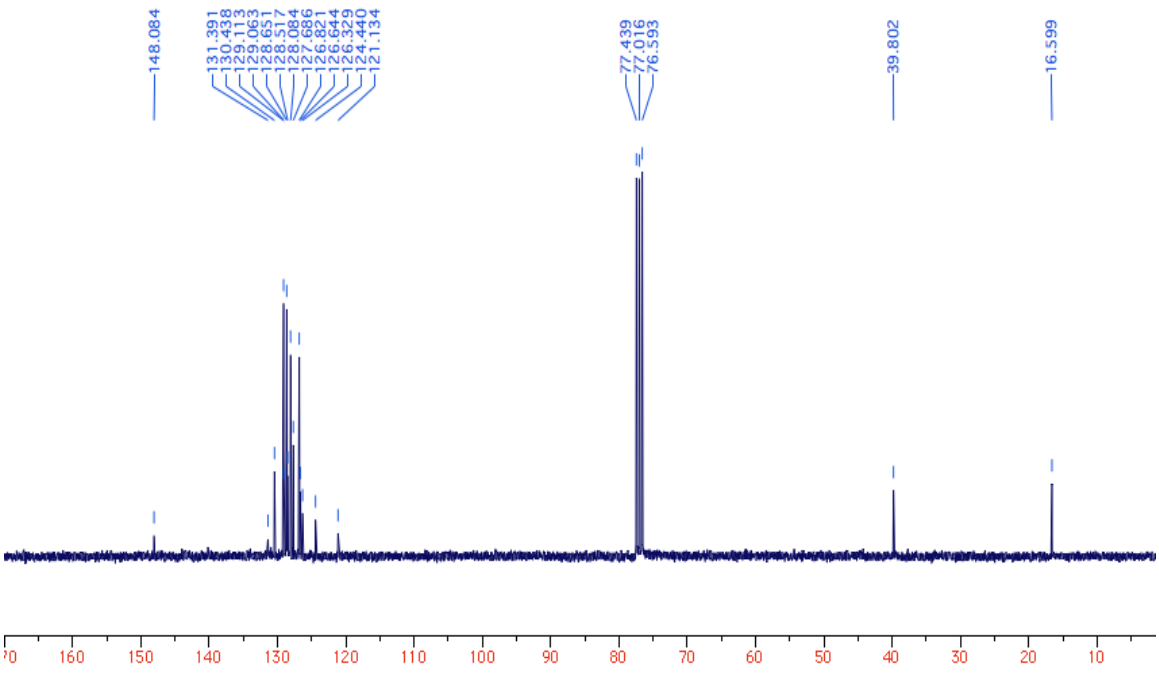
2.5f


SA-332.pa
Std Proton parameters
Br
N
N
3.50
2.43
5.89
2.89
3.97
3.00
3.02
f1 (ppm)

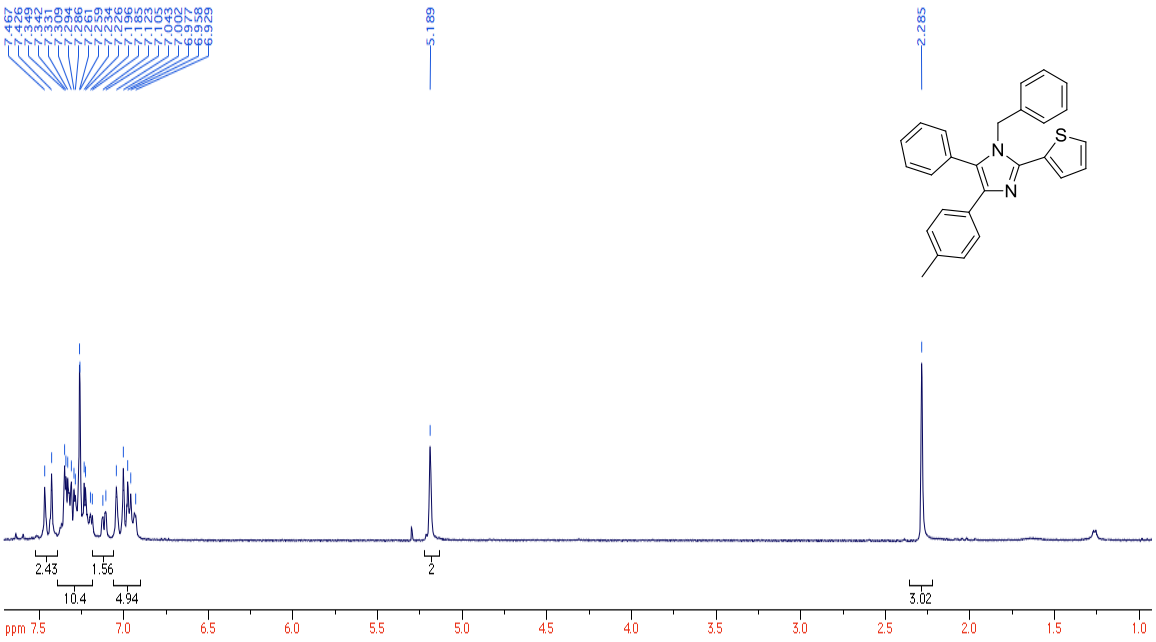

SA-332-13C
Std Carbon experiment
148.43
138.86
138.16
134.30
133.47
131.58
130.53
129.67
129.29
128.95
128.57
128.16
127.80
127.02
126.54
124.44
122.86
77.46
77.04
76.61
33.23
21.40
f1 (ppm)

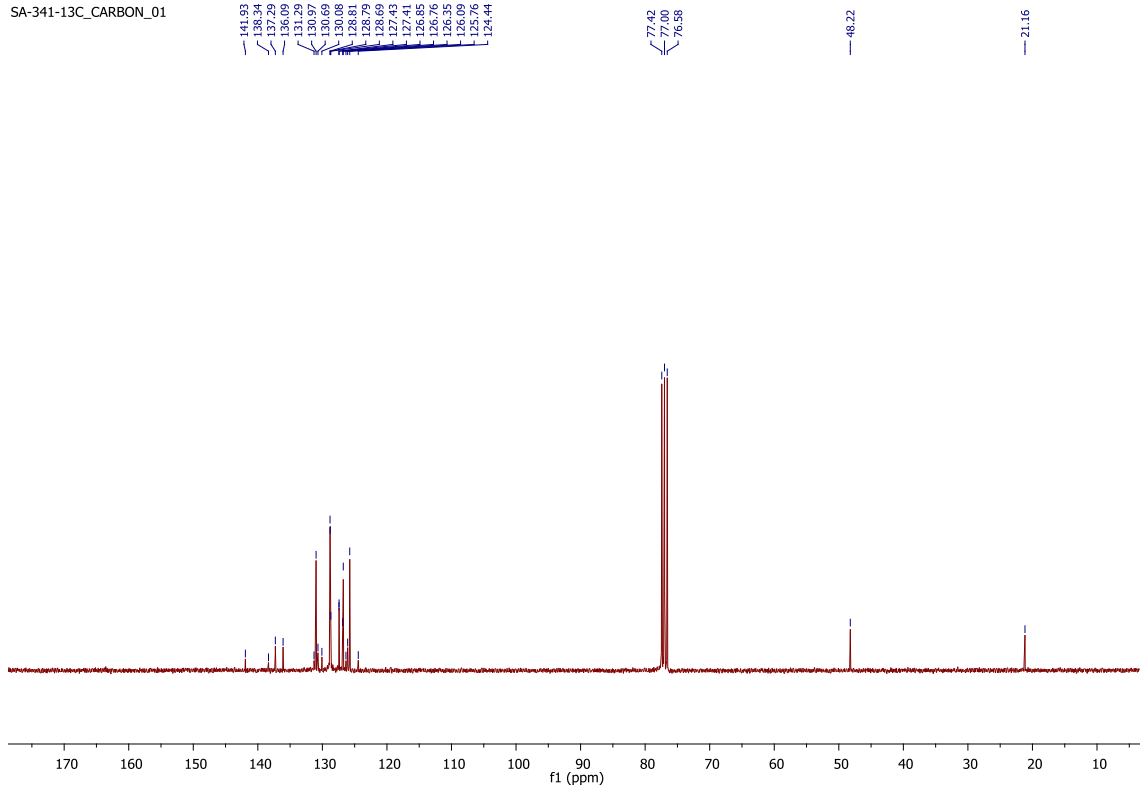
2.5g


7.558
7.544
7.536
7.528
7.523
7.508
7.258
7.226
7.208
7.203
7.182
7.167
7.146
7.093
7.072
6.927
6.905
6.883
6.836
6.831
6.817
6.815
5.081
2.483
2.363
S
N
N
F
7.52
2.12
2
3.19
4.08
2.16
2.1
3.14
8
7
6
5
4
3
2

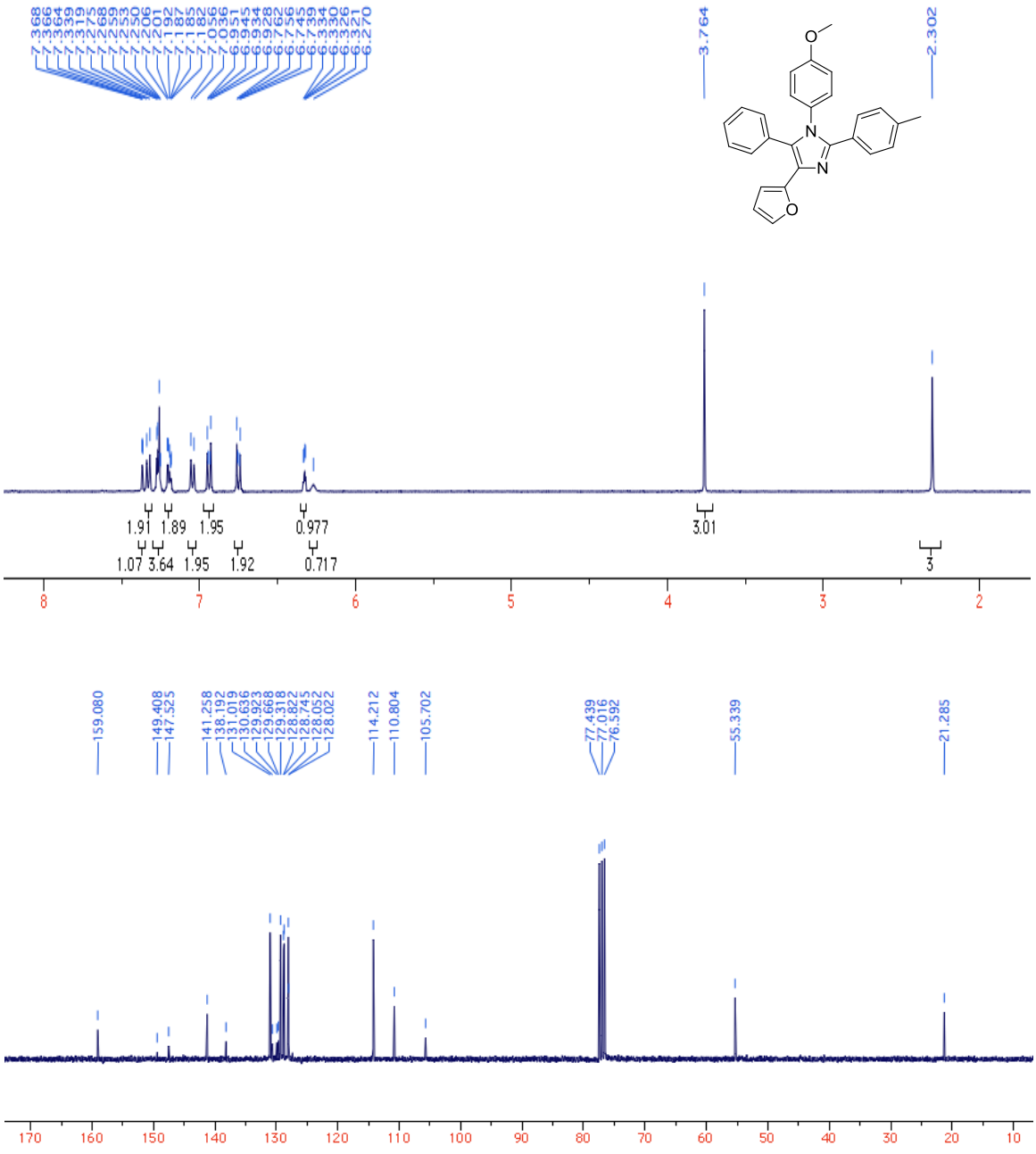

148.084
131.391
130.438
129.113
129.063
128.651
128.517
128.084
127.686
126.821
126.644
126.329
124.440
121.134
77.439
77.016
76.593
39.802
16.599
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

2.5h

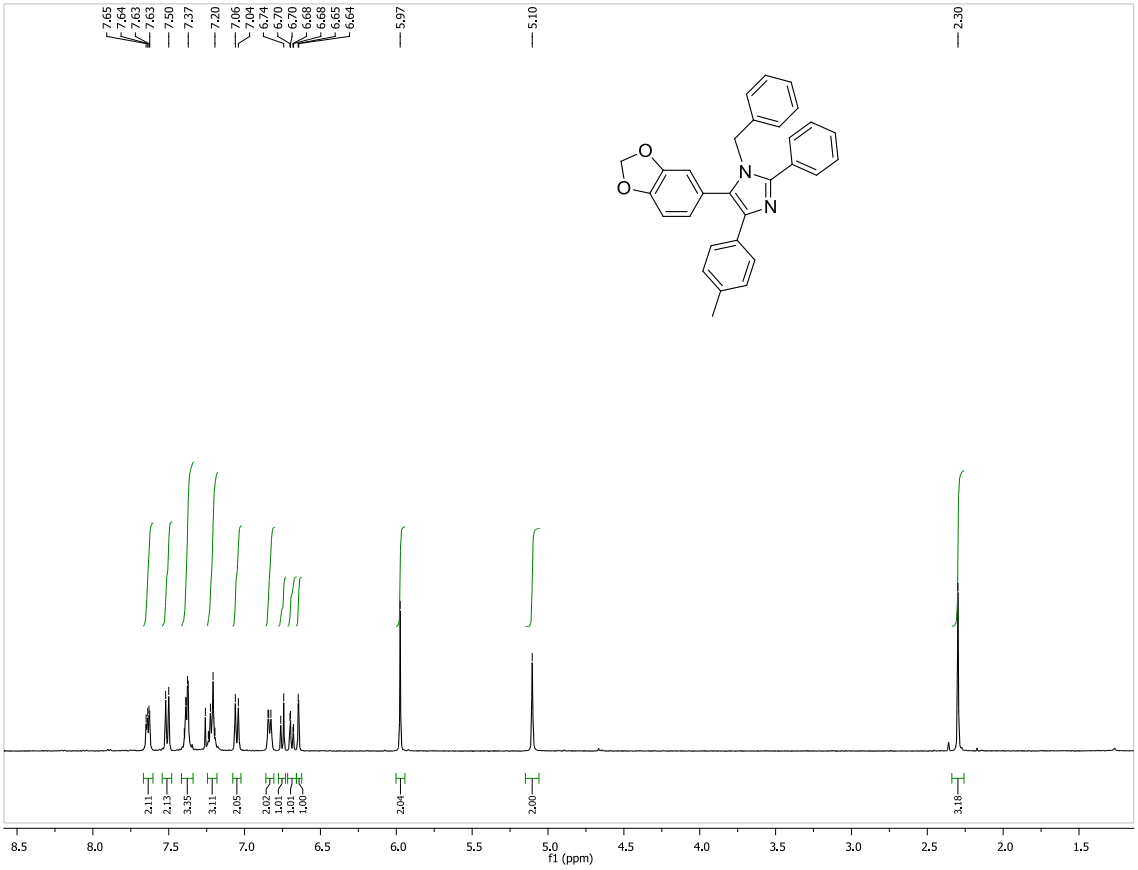

7.467
7.426
7.349
7.342
7.331
7.309
7.294
7.286
7.261
7.253
7.234
7.226
7.186
7.123
7.105
7.043
7.002
6.977
6.958
6.929
5.189
2.285
S
N
N
2.43
1.56
10.4
4.94
2
3.02
ppm 7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

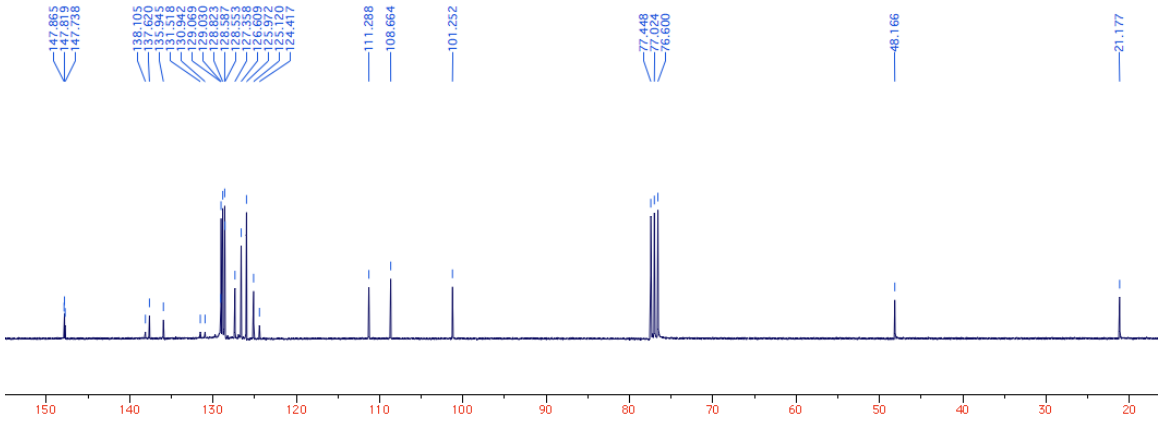

SA-341-13C_CARBON_01
141.93
138.34
137.29
136.09
131.29
130.97
130.69
130.08
128.81
128.79
128.69
127.43
127.41
126.85
126.76
126.35
126.09
125.76
124.44
77.42
77.00
76.58
48.22
21.16
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2.5i

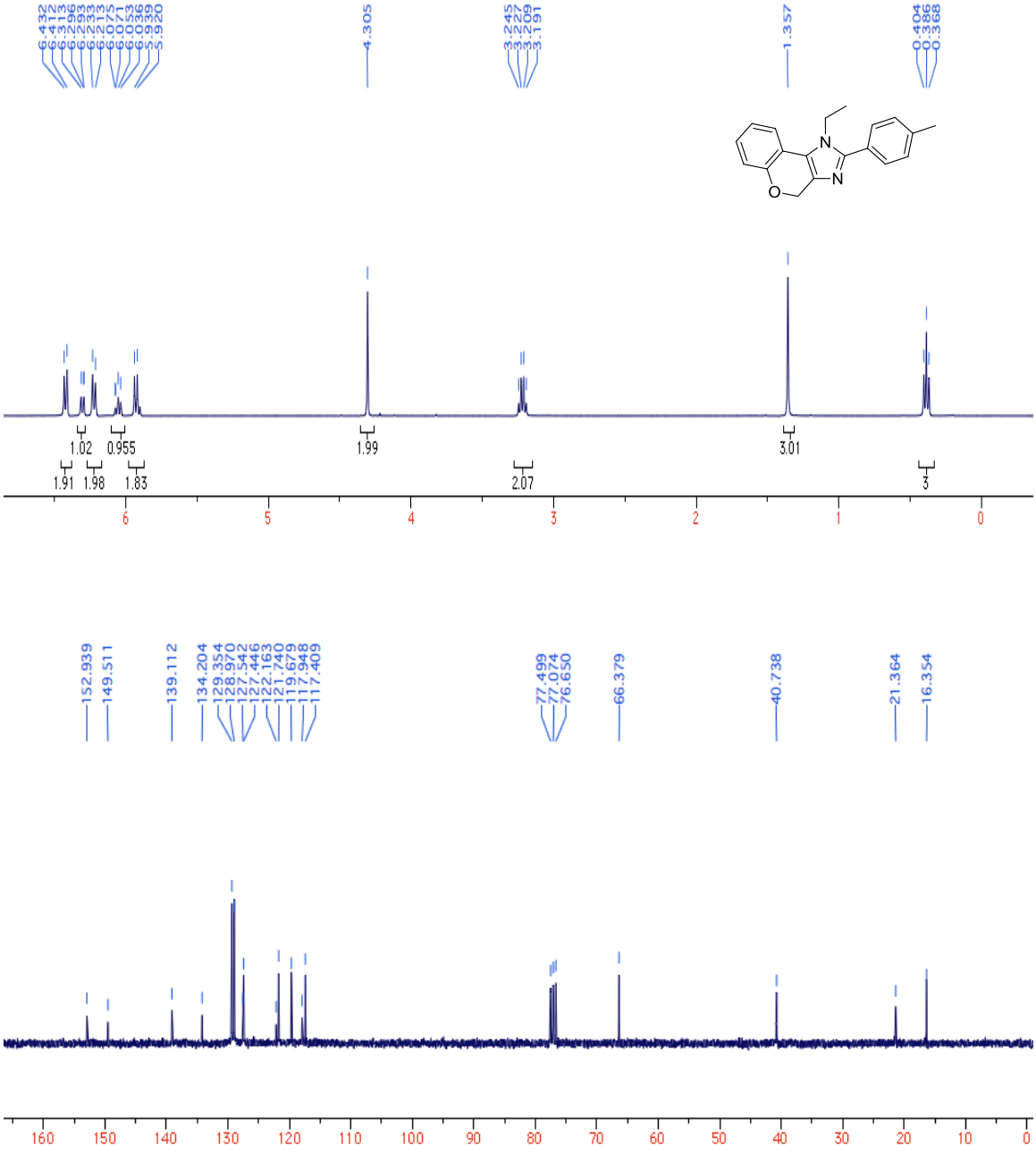

7.368
7.366
7.364
7.339
7.315
7.268
7.233
7.230
7.206
7.201
7.192
7.187
7.185
7.056
7.036
6.951
6.945
6.934
6.928
6.762
6.744
6.739
6.334
6.330
6.326
6.321
6.270
3.764
2.302
1.91
1.89
1.95
0.977
3.01
1.07
3.64
1.95
1.92
0.717
3
159.080
149.408
147.525
141.258
138.192
131.019
130.636
129.923
129.668
129.318
128.822
128.745
128.052
128.022
114.212
110.804
105.702
77.439
77.016
76.592
55.339
21.285

2.5j

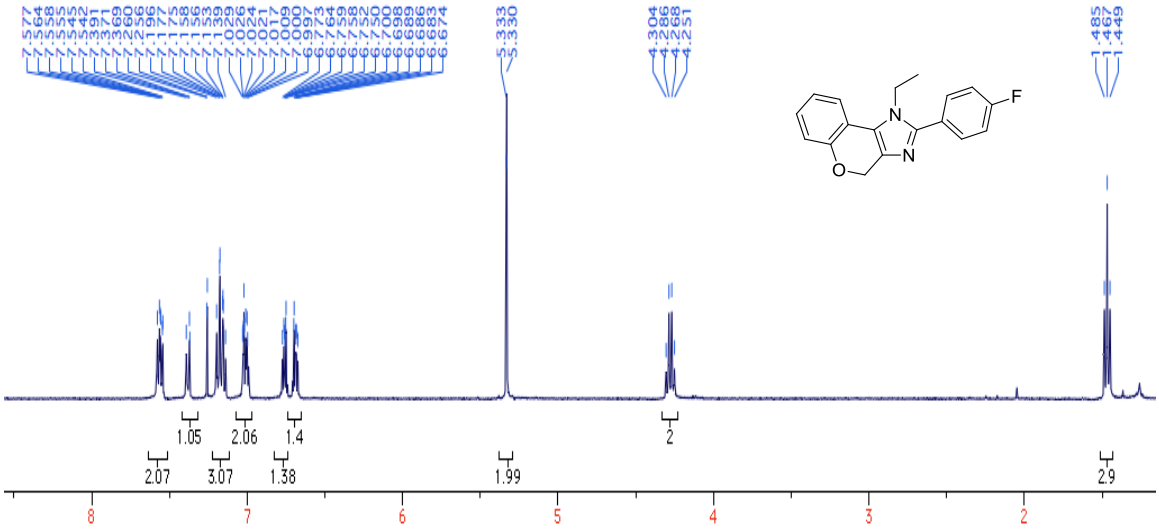

7.65
7.64
7.63
7.63
7.50
7.37
7.20
7.06
7.04
6.74
6.70
6.70
6.68
6.68
6.65
6.64
5.97
5.10
2.30
O
O
N
N
2.11
2.13
3.35
3.11
2.05
2.02
1.01
1.01
1.00
2.04
2.00
3.18
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

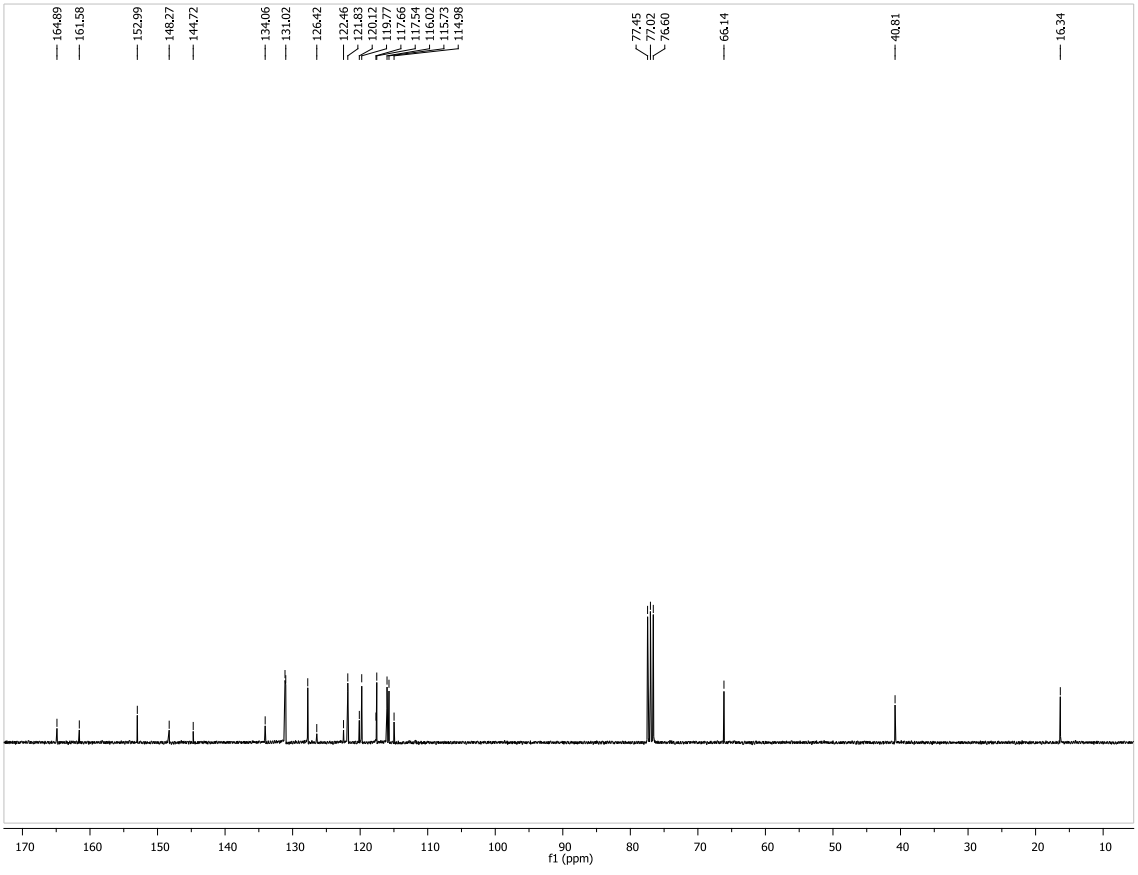

147.865
147.819
147.738
138.105
137.620
133.545
131.348
130.942
129.069
129.010
128.893
128.587
128.553
127.358
126.609
126.077
125.120
124.417
111.288
108.664
101.252
77.448
77.024
76.600
48.166
21.177
150
140
130
120
110
100
90
80
70
60
50
40
30
20

2.7a

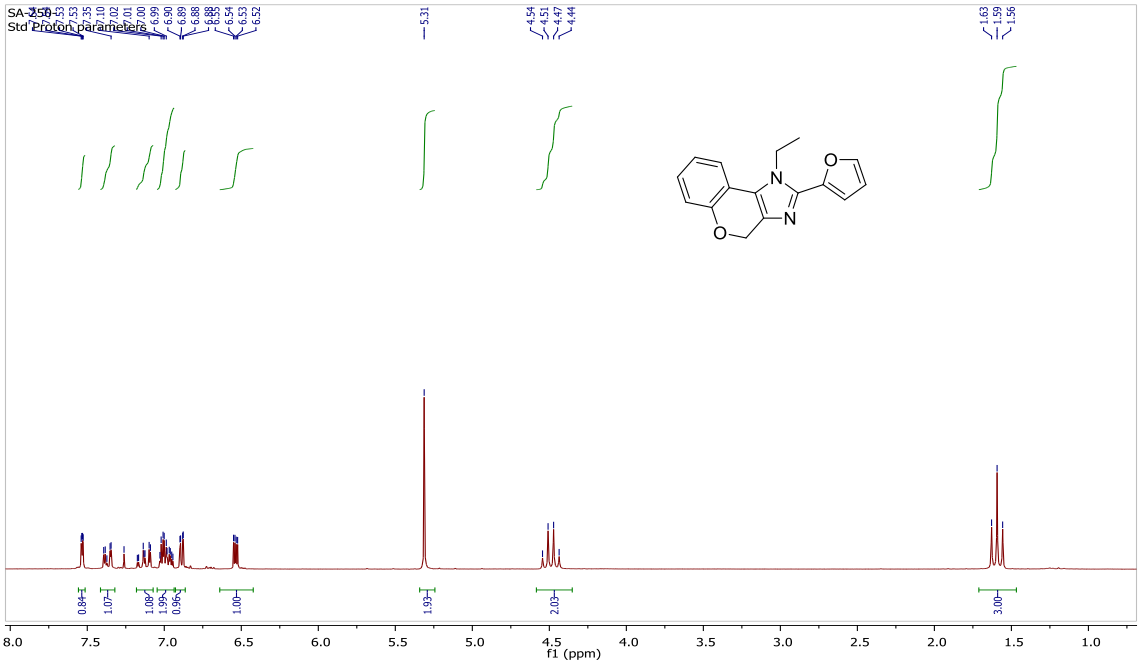

6.432
6.313
6.296
6.293
6.233
6.177
6.075
6.071
6.036
6.033
5.999
5.920
4.305
3.245
3.227
3.209
3.191
1.357
0.404
0.386
0.368
1.02
0.955
1.99
3.01
1.91
1.98
1.83
2.07
3
152.939
149.511
139.112
134.204
129.354
128.970
127.542
127.446
122.163
121.747
121.470
119.679
117.488
117.409
77.499
77.074
76.650
66.379
40.738
21.364
16.354

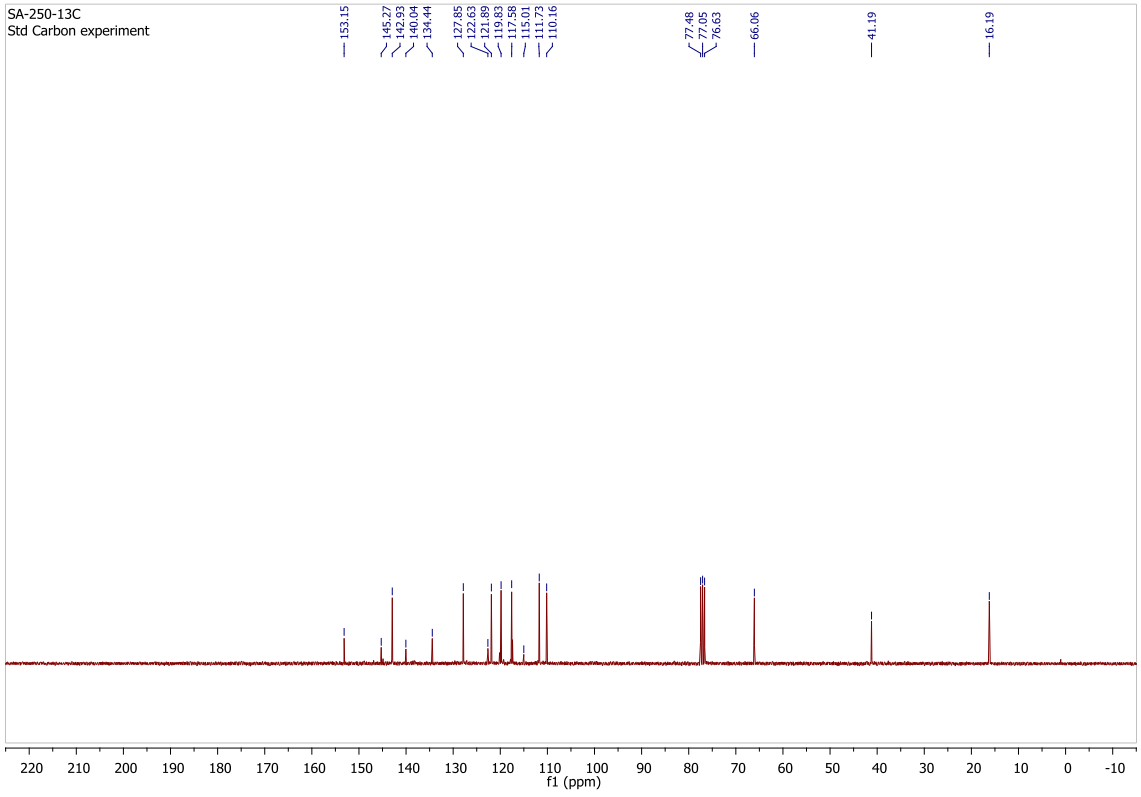
2.7b


7.577
7.564
7.558
7.545
7.442
7.431
7.421
7.391
7.369
7.360
7.256
7.196
7.177
7.158
7.156
7.139
7.029
7.026
7.024
7.021
7.017
7.009
7.009
6.997
6.973
6.764
6.759
6.758
6.732
6.730
6.700
6.698
6.688
6.686
6.683
6.674
5.333
5.330
4.304
4.286
4.268
4.251
1.485
1.467
1.449
N
N
O
F
1.05
2.06
1.4
2
2.07
3.07
1.38
1.99
2.9
8
7
6
5
4
3
2

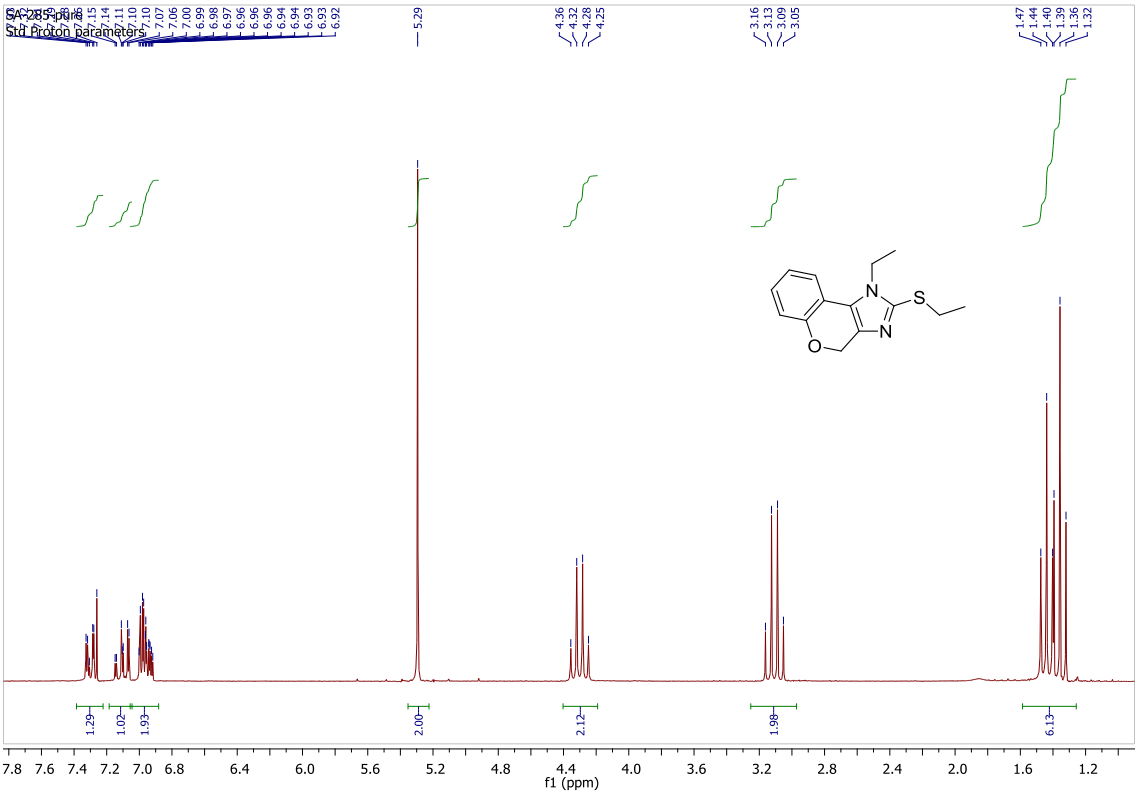

164.89
161.58
152.99
148.27
144.72
134.06
131.02
126.42
122.46
121.83
120.12
119.77
117.66
117.54
116.02
115.73
114.98
77.45
77.02
76.60
66.14
40.81
16.34
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

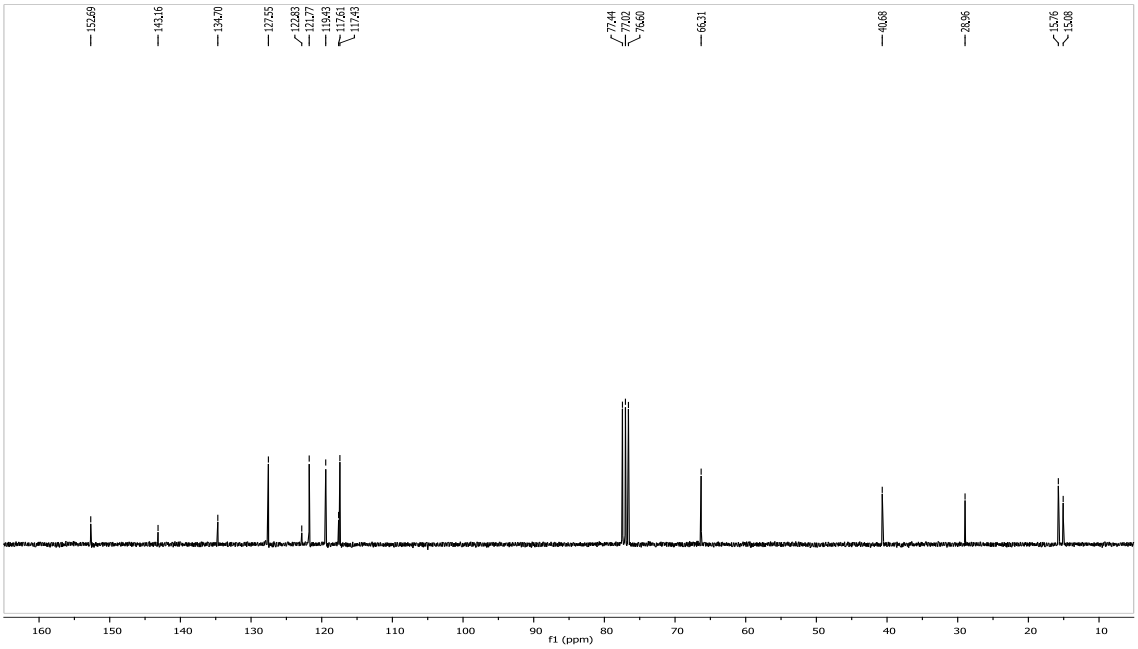
2.7c


SA-250
Std Proton parameters
5.31
4.54
4.51
4.47
4.44
1.63
1.59
1.56
0.84
1.07
1.08
1.99
0.96
1.00
1.93
2.03
3.00
f1 (ppm)

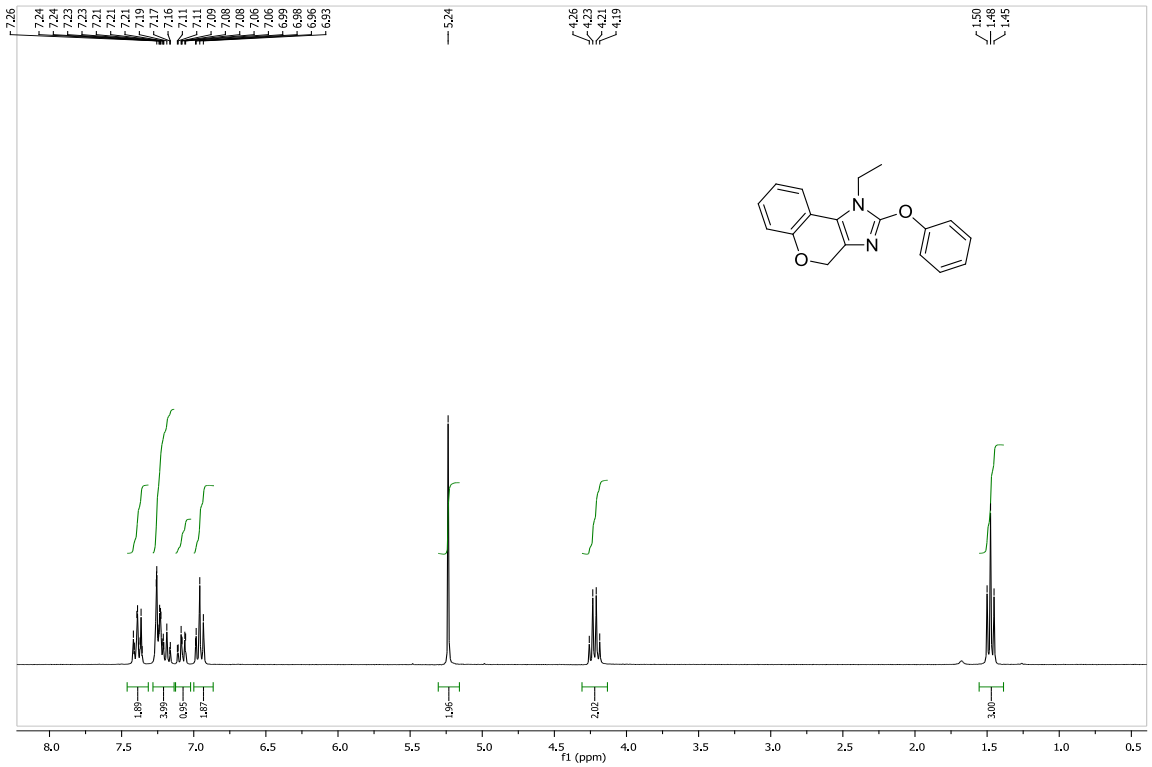

SA-250-13C
Std Carbon experiment
153.15
145.27
142.93
140.04
134.44
127.85
122.63
121.89
119.83
117.58
115.01
111.73
110.16
77.48
77.05
76.63
66.06
41.19
16.19
f1 (ppm)

2.7d


SA-285-proton
Std Proton parameters
5.29
4.36
4.32
4.28
4.25
3.16
3.13
3.09
3.05
1.47
1.44
1.40
1.39
1.36
1.32
1.29
1.02
1.93
2.00
2.12
1.98
6.13
f1 (ppm)


152.69
143.16
134.20
127.55
122.83
121.77
119.43
117.61
117.43
77.44
77.02
76.60
66.31
40.68
28.96
15.76
15.08
f1 (ppm)

2.7e


7.26
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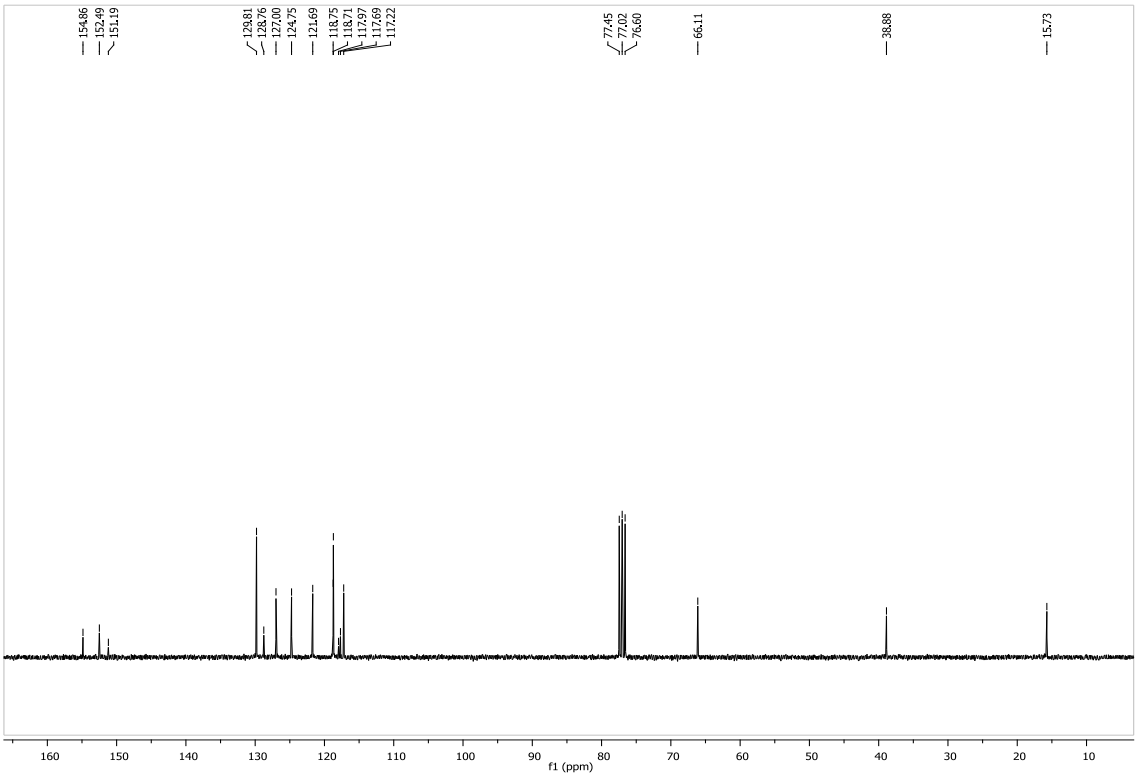
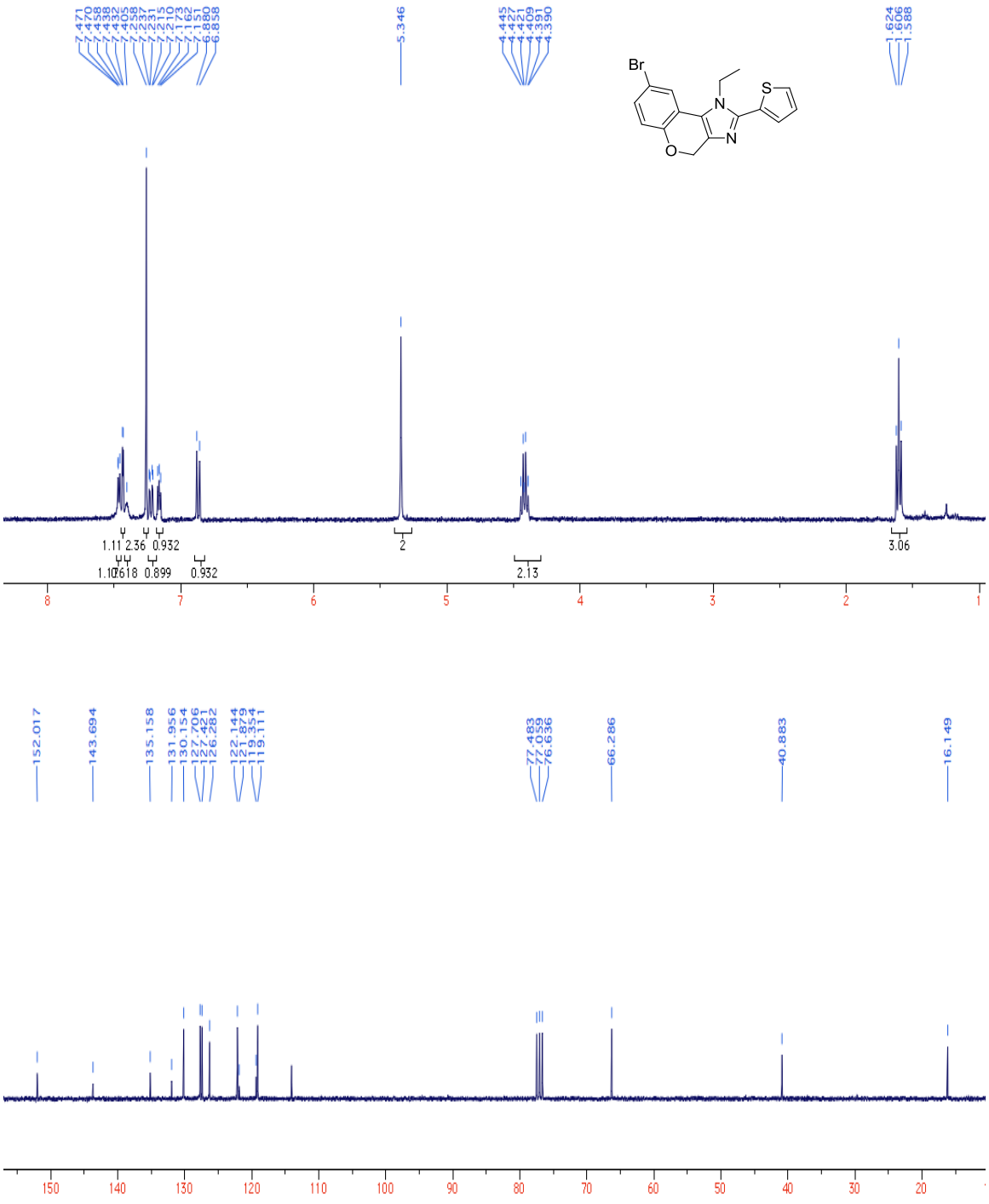
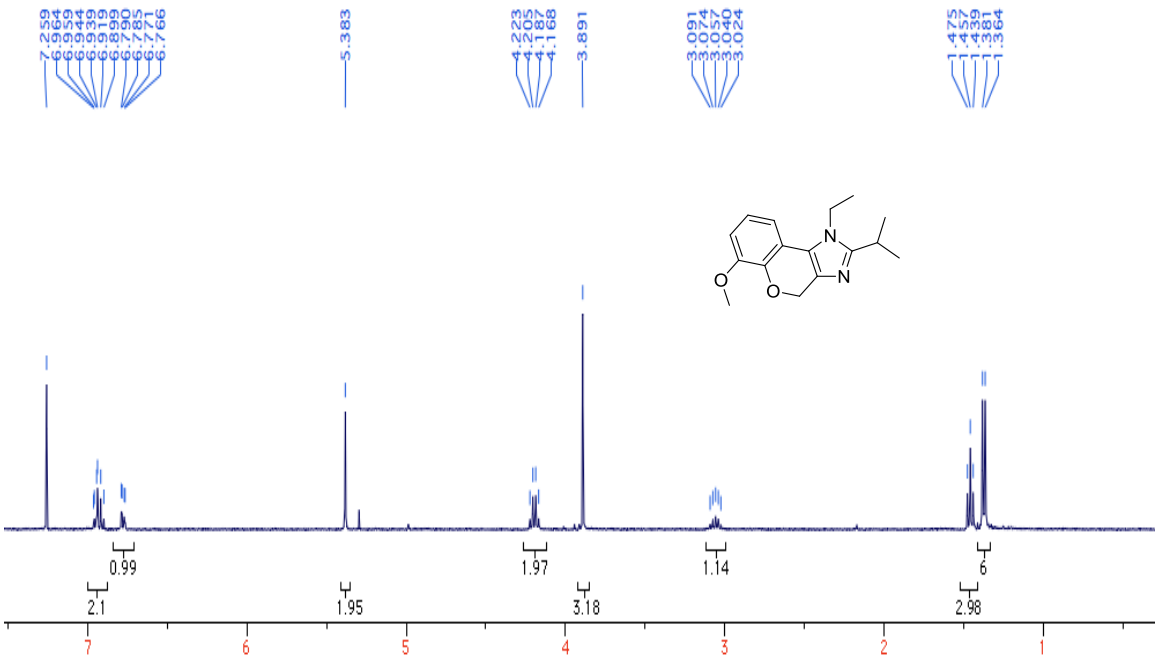
7.24
7.23
7.23
7.21
7.21
7.21
7.19
7.17
7.16
7.11
7.11
7.09
7.08
7.08
7.06
7.06
6.99
6.98
6.96
6.93
5.24
4.26
4.23
4.21
4.19
1.50
1.48
1.45
N
O
N
O
1.89
3.99
0.95
1.87
1.96
2.02
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

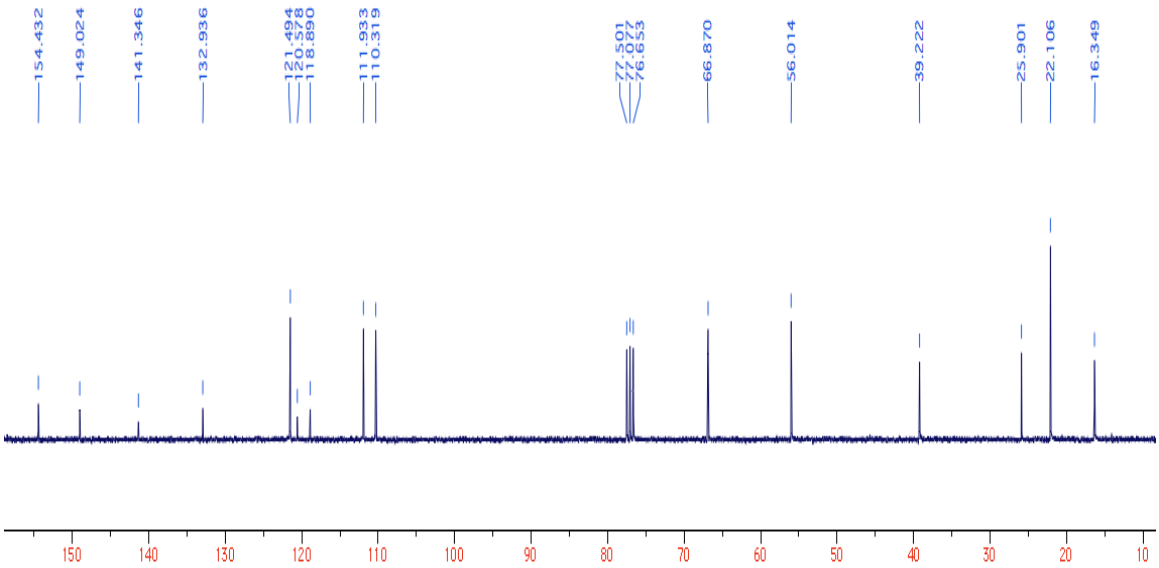

154.86
152.49
151.19
129.81
128.76
127.00
124.75
121.69
118.75
118.71
117.97
117.69
117.22
77.45
77.02
76.60
66.11
38.88
15.73
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2. 7f

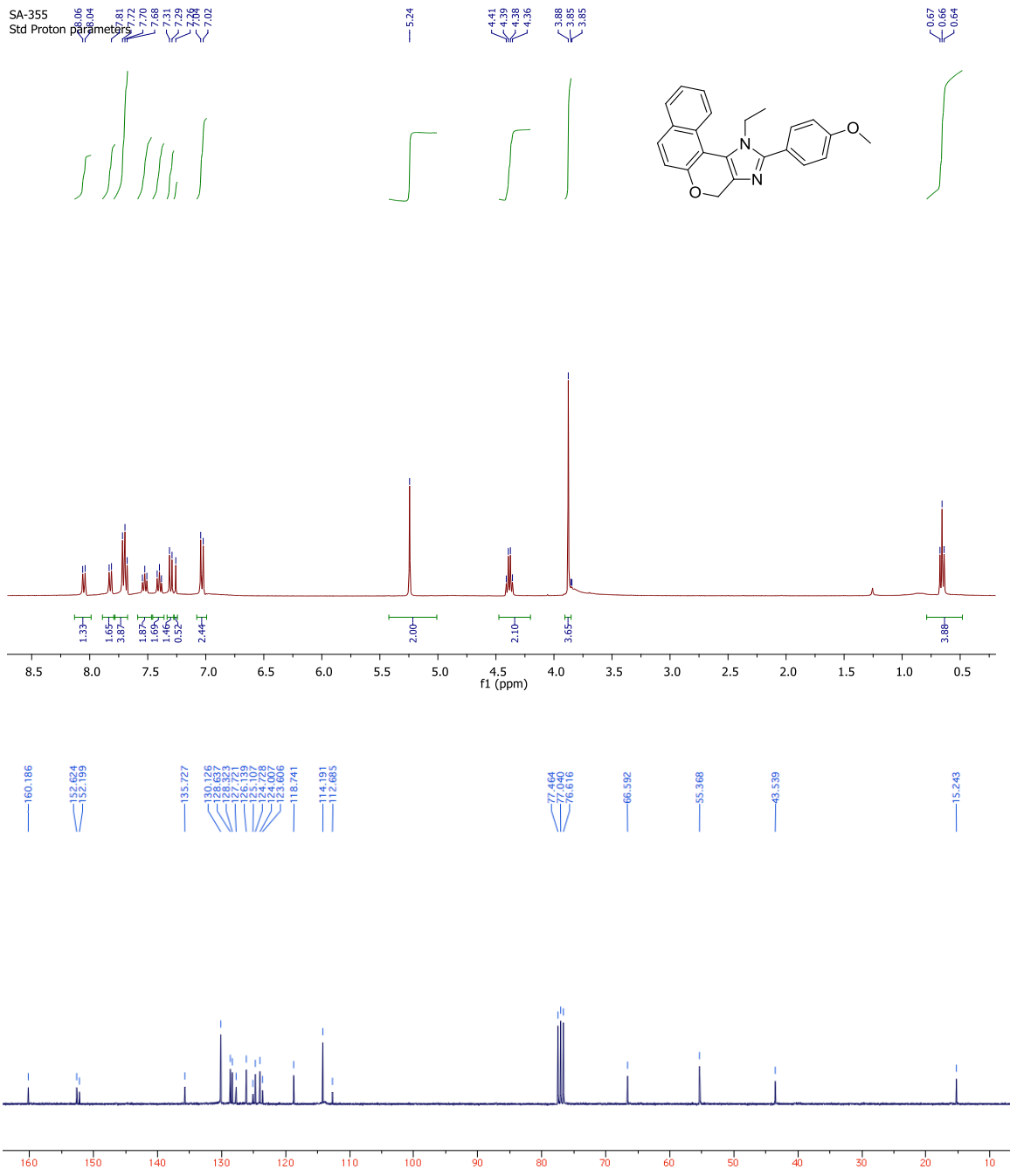

7.471
7.420
7.438
7.432
7.405
7.238
7.237
7.215
7.210
7.173
7.162
7.151
6.880
6.858
5.346
4.445
4.427
4.421
4.409
4.390
1.624
1.606
1.588
Br
S
N
N
O
1.11
2.36
0.932
1.107
0.618
0.899
0.932
2
2.13
3.06
8
7
6
5
4
3
2
1
152.017
143.694
135.158
131.956
130.154
127.406
127.216
126.282
122.144
121.829
119.554
119.111
77.483
77.059
76.636
66.286
40.883
16.149
150
140
130
120
110
100
90
80
70
60
50
40
30
20

2.7g

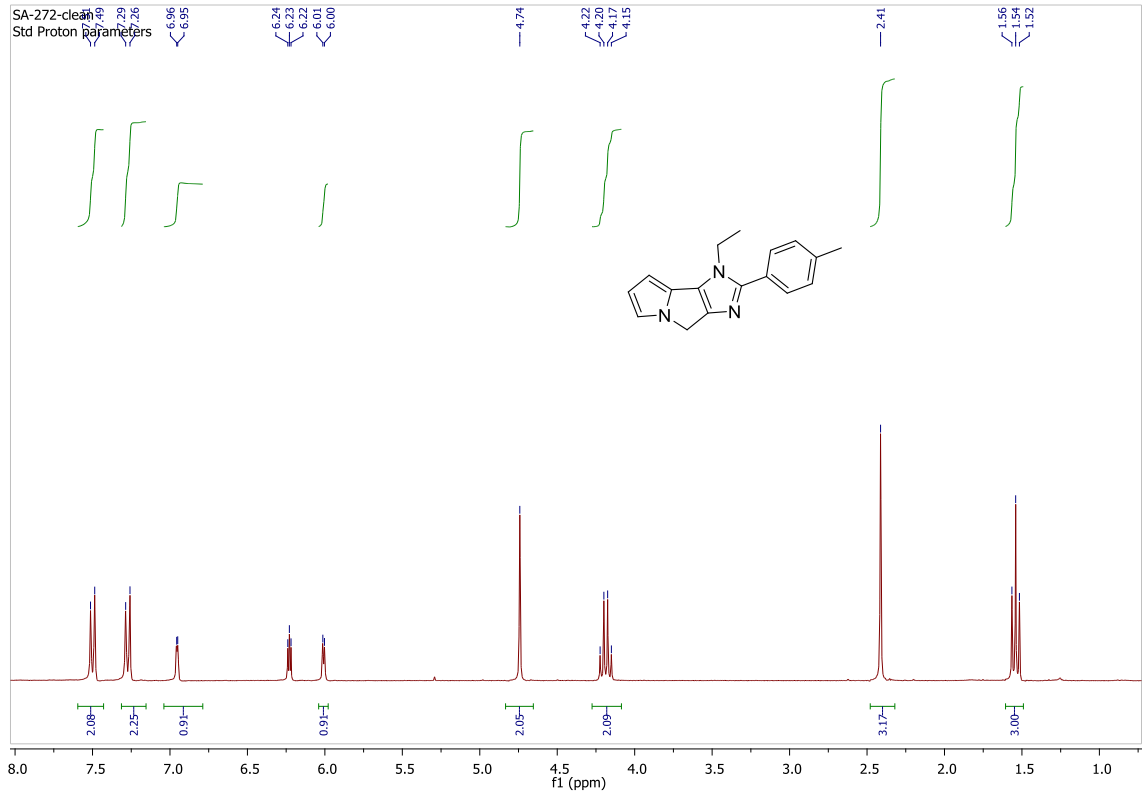

7.259
6.964
6.959
6.944
6.939
6.899
6.790
6.785
6.771
6.766
5.383
4.223
4.205
4.187
4.168
3.891
3.091
3.074
3.057
3.040
3.024
1.475
1.457
1.439
1.381
1.364
0.99
1.97
1.14
6
2.1
1.95
3.18
2.98

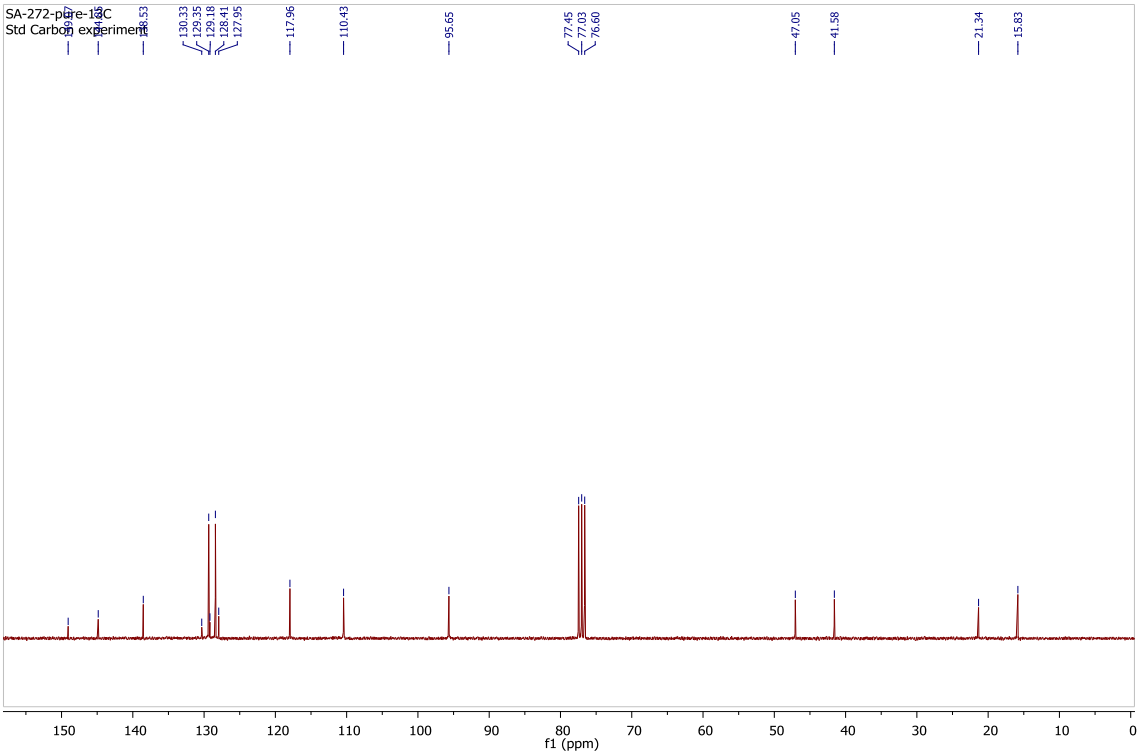

154.432
149.024
141.346
132.936
121.494
120.558
118.890
111.933
110.319
77.501
77.077
76.653
66.870
56.014
39.222
25.901
22.106
16.349

2.7h

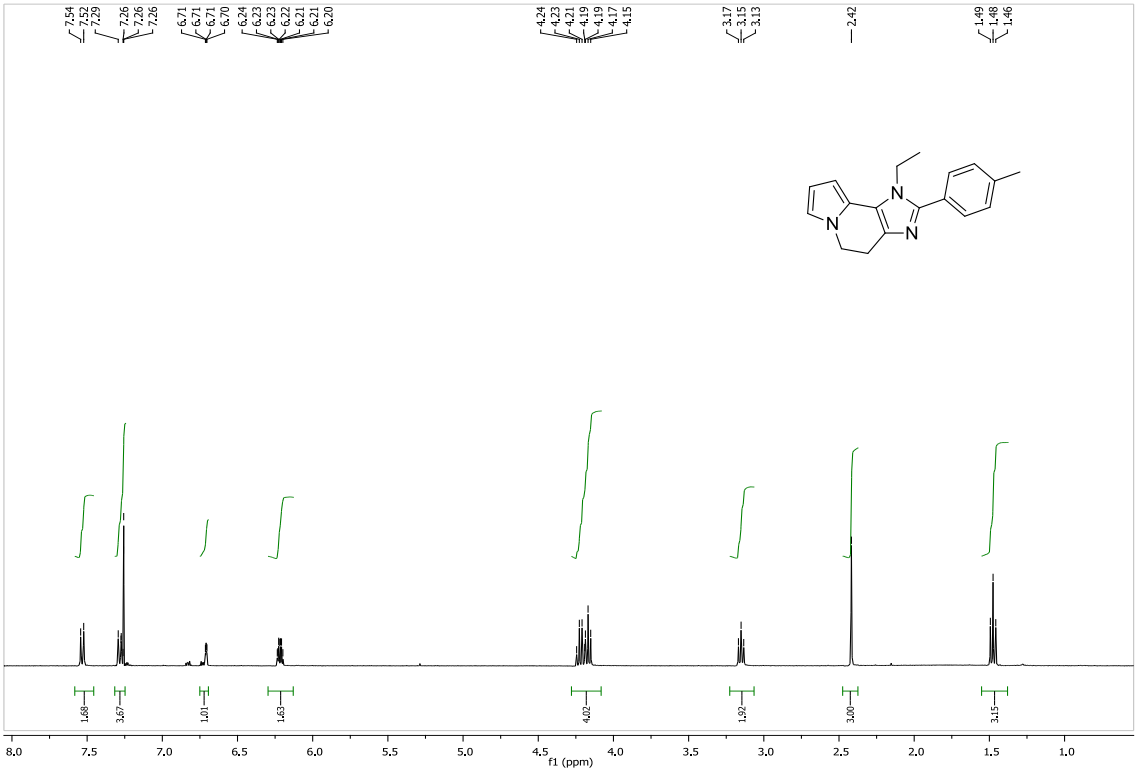

SA-355
Std Proton parameters
8.06
8.04
7.81
7.72
7.70
7.68
7.31
7.29
7.02
5.24
4.41
4.39
4.38
4.36
3.88
3.85
3.85
0.67
0.66
0.64
1.33
1.65
3.87
1.87
1.69
1.46
0.52
2.44
2.00
2.10
3.65
3.88
f1 (ppm)
160.186
152.624
152.199
135.727
130.126
128.637
128.323
128.171
126.139
125.107
124.728
124.007
123.606
118.741
114.191
112.685
77.464
77.040
76.616
66.592
55.368
43.539
15.243

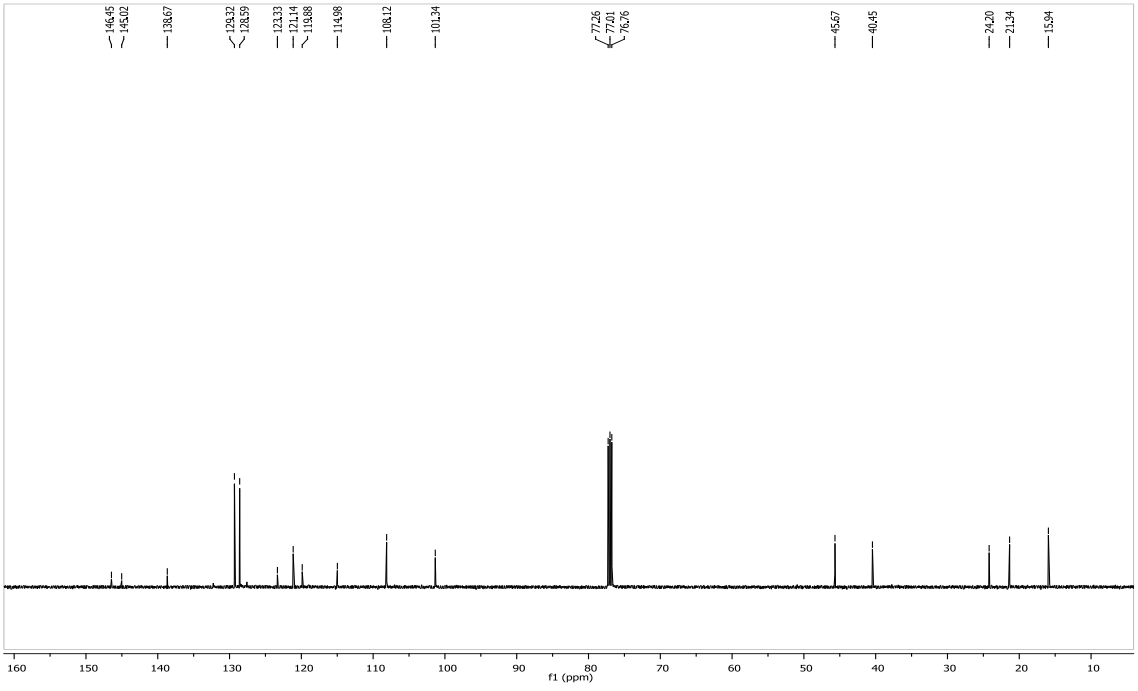
2.7i


SA-272-clean
Std Proton parameters
7.49
7.29
7.26
6.96
6.95
6.24
6.23
6.22
6.01
6.00
4.74
4.22
4.20
4.17
4.15
2.41
1.56
1.54
1.52
2.08
2.25
0.91
0.91
2.05
2.09
3.17
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


SA-272-pure-13C
Std Carbon experiment
130.33
129.35
129.18
128.41
127.95
117.96
110.43
95.65
77.45
77.03
76.60
47.05
41.58
21.34
15.83
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

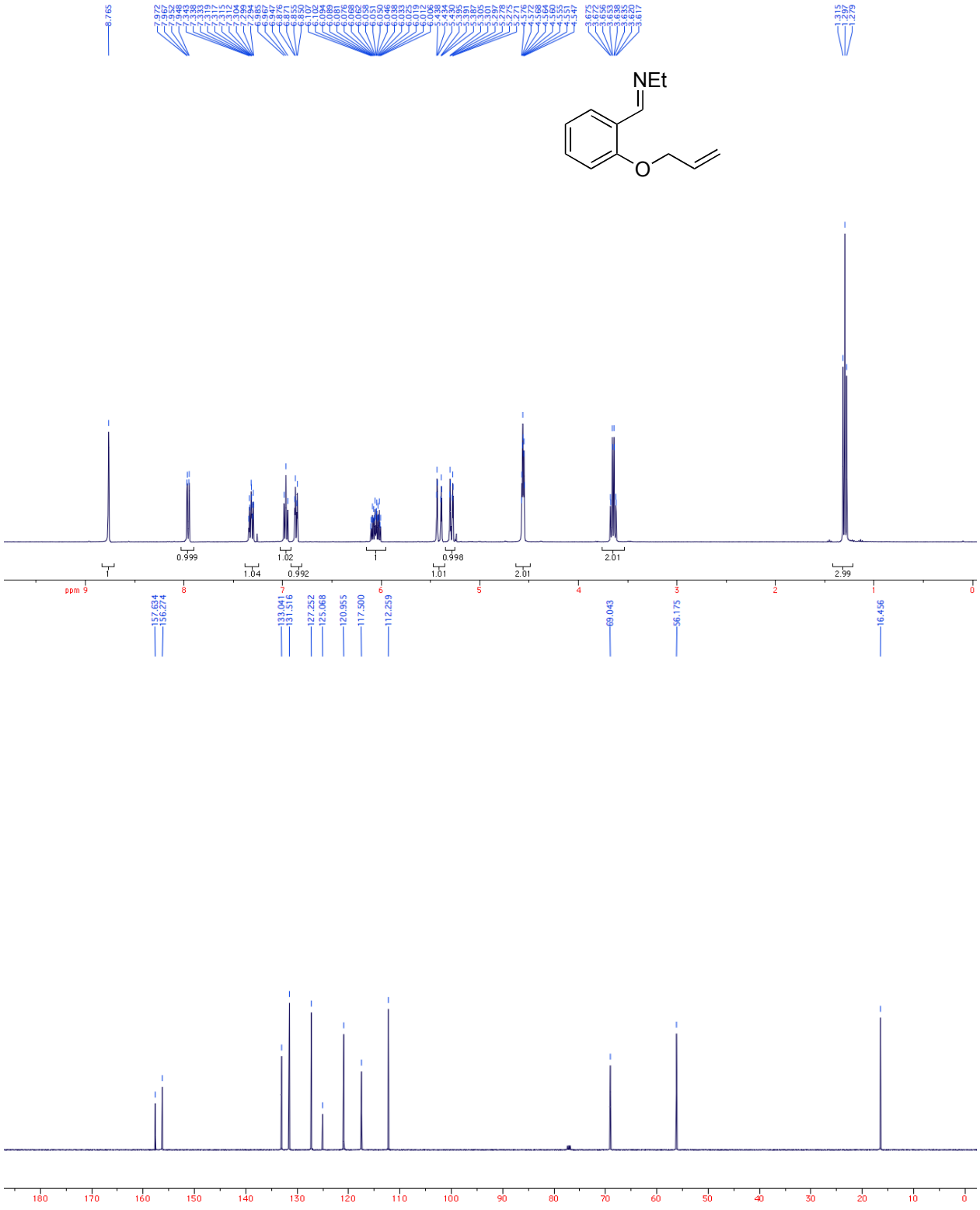
2.7j


7.54
7.52
7.29
7.26
7.26
7.26
6.71
6.71
6.71
6.70
6.24
6.23
6.23
6.22
6.21
6.21
6.20
4.24
4.23
4.21
4.19
4.19
4.17
4.15
3.17
3.15
3.13
2.42
1.49
1.48
1.46
N
N
N
1.68
3.67
1.01
1.63
4.02
1.92
3.00
3.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

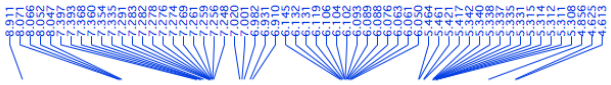

146.45
145.02
138.67
129.32
128.59
122.33
121.14
119.88
114.98
108.12
101.34
77.26
77.01
76.76
45.67
40.45
24.20
21.34
15.94
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

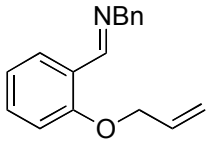
APPENDIX B ^{1}H and ^{13}C NMR Spectra of Olefin-Tethered Imines and 2-Pyrrolines

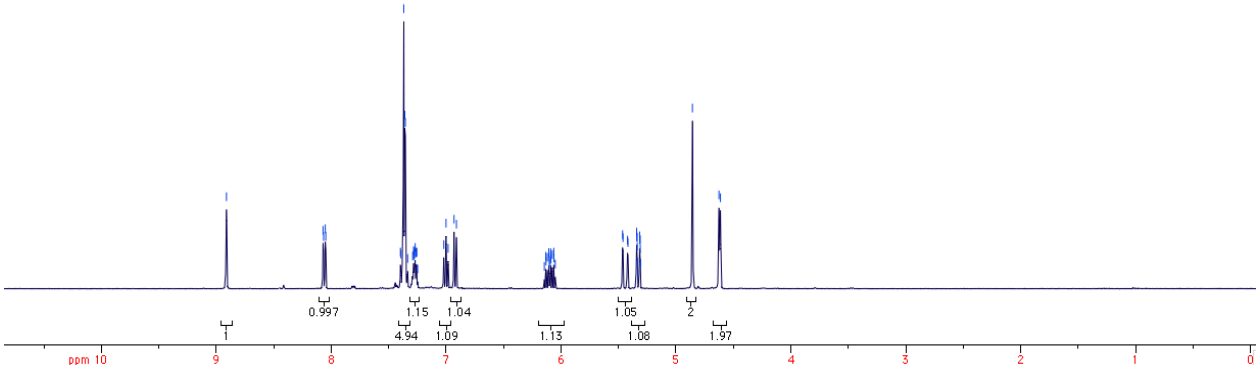
3.2a



3.2b




NBn
O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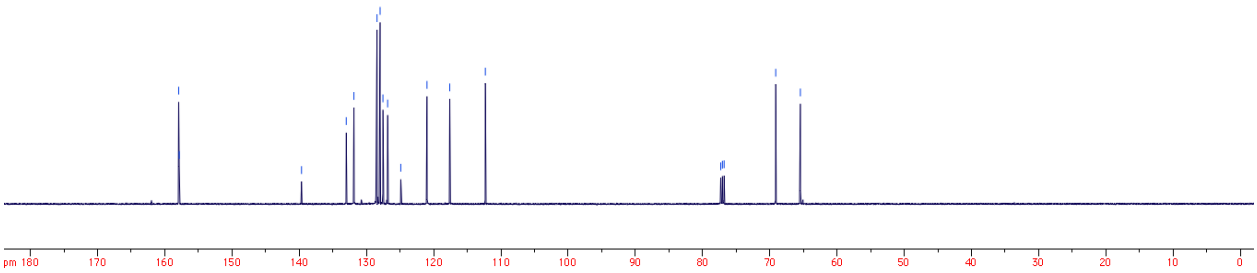
1.04
1.05
2
1
4.94
1.09
1.13
1.08
1.97
ppm 10
9
8
7
6
5
4
3
2
1
0


157.935
157.838
139.660
133.008
131.869
131.441
127.971
127.548
126.648
124.893
120.999
117.614
112.314
77.302
77.048
76.793
69.118
65.454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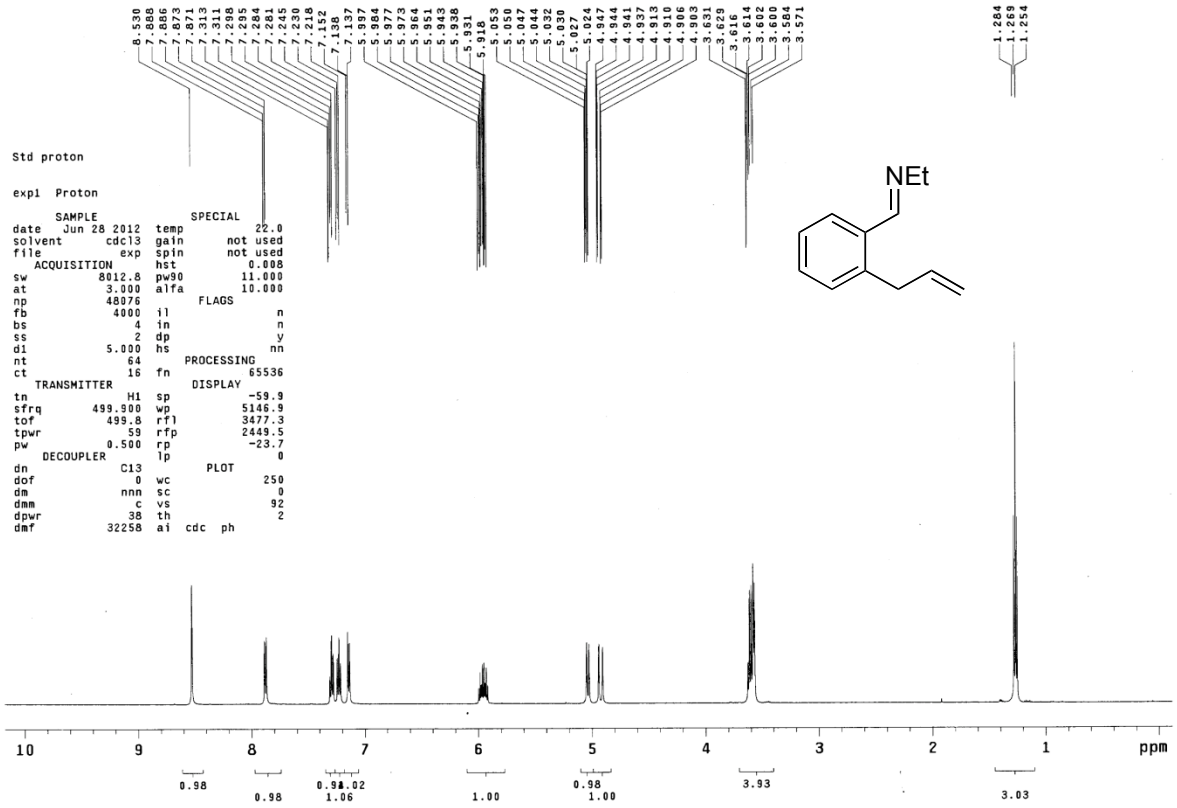
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

3.2c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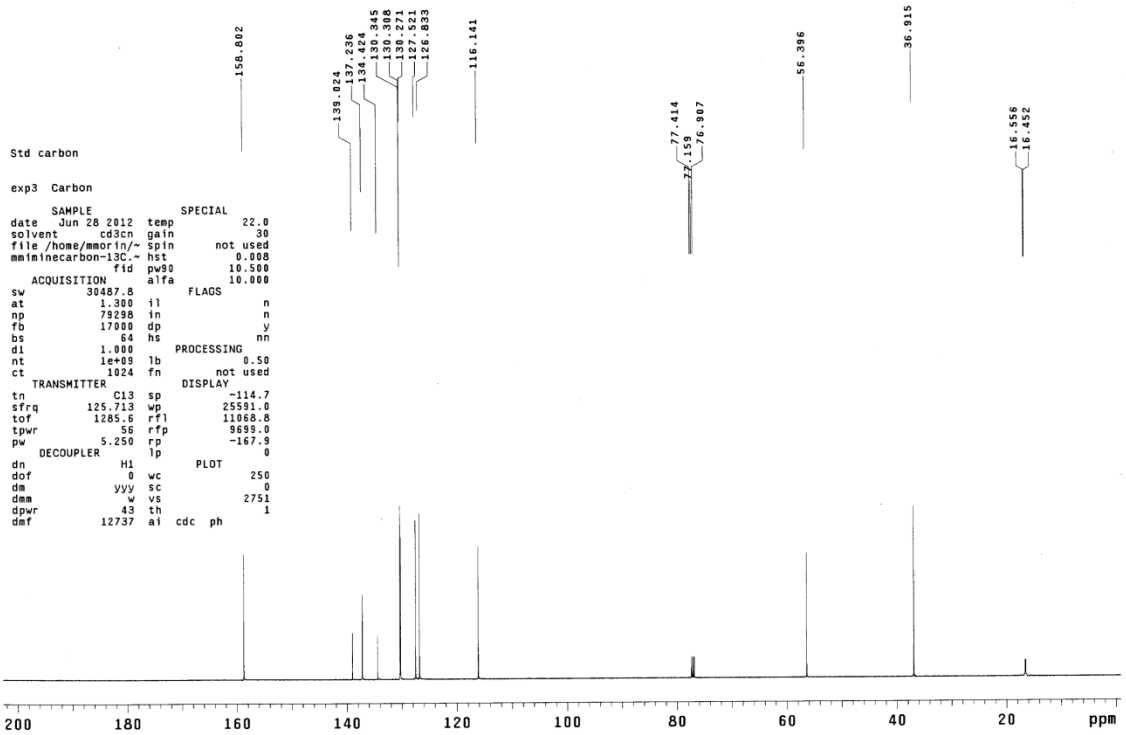
7.888
7.856
7.873
7.871
7.313
7.311
7.298
7.295
7.284
7.281
7.245
7.230
7.218
7.152
7.138
7.137
5.997
5.984
5.977
5.973
5.964
5.951
5.943
5.938
5.931
5.918
5.053
5.050
5.047
5.044
5.032
5.030
5.027
5.024
4.947
4.944
4.941
4.937
4.913
4.910
4.906
4.903
3.631
3.629
3.616
3.614
3.602
3.600
3.584
3.571
1.284
1.269
1.254
NEt
Std proton
exp1 Proton
SAMPLE
date Jun 28 2012
solvent cdcl3
file exp
ACQUISITION
sw 8012.8
at 3.000
np 48076
fb 4000
bs 4
ss 2
d1 5.000
nt 64
ct 16
TRANSMITTER
tn H1
sfrq 499.900
tof 499.8
tpwr 59
pw 0.500
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 38
dmf 32258
SPECIAL
temp 22.0
gain not used
spin not used
hst 0.008
pw90 11.000
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn 65536
DISPLAY
sp -59.9
wp 5146.9
rfl 3477.3
rfp 2449.5
rp -23.7
lp 0
PLOT
wc 250
sc 0
vs 92
th 2
ai cdc ph
10
9
8
7
6
5
4
3
2
1
ppm
0.98
0.98
0.98
1.02
1.06
1.00
0.98
1.00
3.93
3.03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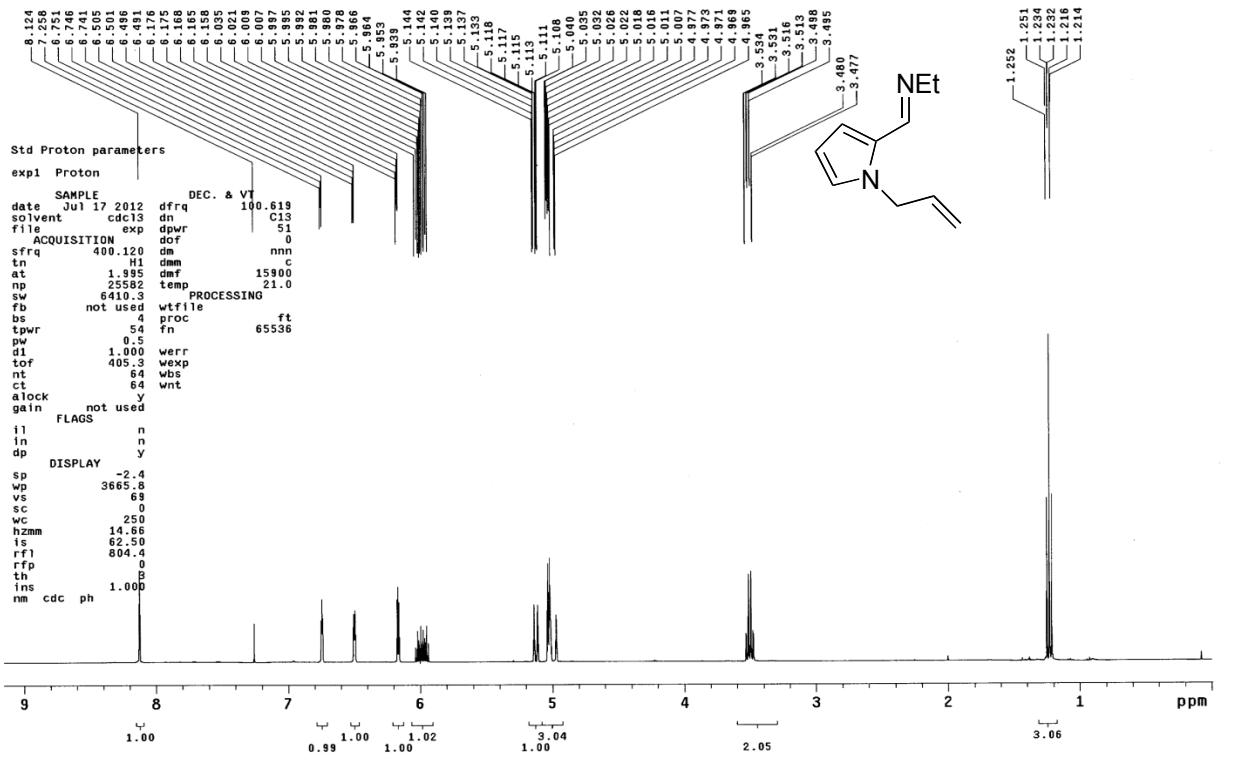
137.236
134.424
130.345
130.306
130.271
127.521
126.833
116.141
77.414
77.159
76.907
56.396
36.915
16.556
16.452
Std carbon
exp3 Carbon
SAMPLE
date Jun 28 2012
solvent cd3cn
file /home/mmorin/~
mmiminecarbon-13C.~
fid
ACQUISITION
sw 30487.8
at 1.300
np 79298
fb 17000
bs 64
d1 1.000
nt 1e+09
ct 1024
TRANSMITTER
tn C13
sfrq 125.713
tof 1285.6
tpwr 56
pw 5.250
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 43
dmf 12737
SPECIAL
temp 22.0
gain 30
spin not used
hst 0.008
pw90 10.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -114.7
wp 25591.0
rfl 11068.8
rfp 9699.0
rp -167.9
lp 0
PLOT
wc 250
sc 0
vs 2751
th 1
ai cdc ph
200
180
160
140
120
100
80
60
40
20
ppm

3.2d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6.751
6.746
6.741
6.505
6.501
6.496
6.491
6.176
6.175
6.168
6.165
6.158
6.035
6.021
6.009
6.007
5.997
5.995
5.992
5.981
5.980
5.978
5.966
5.964
5.953
5.939
5.144
5.142
5.140
5.139
5.137
5.133
5.116
5.117
5.115
5.113
5.111
5.108
5.040
5.035
5.032
5.026
5.022
5.018
5.016
5.011
5.007
4.977
4.973
4.971
4.969
4.965
3.534
3.531
3.516
3.513
3.498
3.495
3.480
3.477
1.252
1.251
1.234
1.232
1.216
1.214
NEt
N
Std Proton parameters
exp1 Proton
SAMPLE
date Jul 17 2012
solvent cdcl3
file exp
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tn H1
at 1.995
np 25582
sw 6410.3
fb not used
bs 4
tpwr 54
pw 0.5
d1 1.000
tof 405.3
nt 64
ct 64
alock y
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -2.4
wp 3665.8
vs 69
sc 0
wc 250
hzmm 14.66
is 62.50
rfl 804.4
rfp 0
th 8
ins 1.000
nm cdc ph
DEC. & VT
dfrq 100.619
dn C13
dpwr 51
dof 0
dm nnn
dmm c
dmf 15900
temp 21.0
PROCESSING
wtfile
proc ft
fn 65536
werr
wexp
wbs
wnt
9
8
7
6
5
4
3
2
1
ppm
1.00
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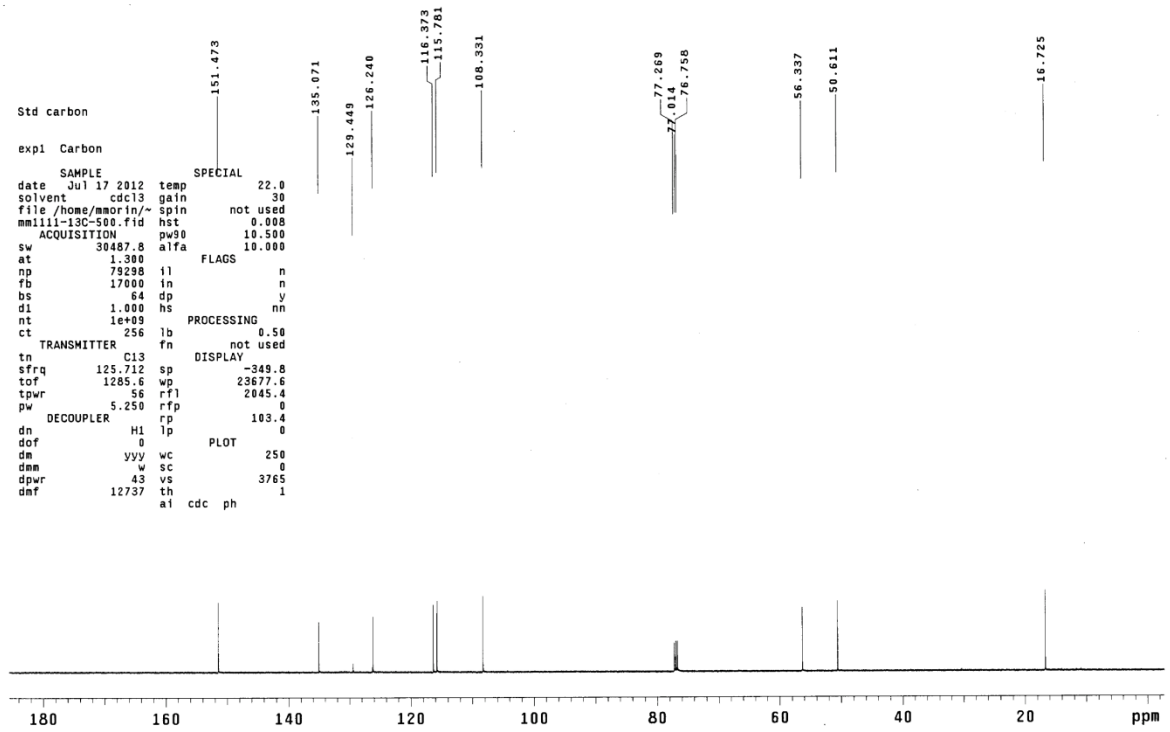
1.00
1.00
1.02
1.00
3.04
2.05
3.06


151.473
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129.449
126.240
116.373
115.781
108.331
77.269
77.014
76.758
56.337
50.611
16.725
Std carbon
exp1 Carbon
SAMPLE
date Jul 17 2012
solvent cdcl3
file /home/mmorin/~
mm1111-13C-500.fid
ACQUISITION
sw 30487.8
at 1.300
np 79298
fb 17000
bs 64
d1 1.000
nt 1e+09
ct 256
TRANSMITTER
tn C13
sfrq 125.712
tof 1285.6
tpwr 56
pw 5.250
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 43
dmf 12737
SPECIAL
temp 22.0
gain 30
spin not used
hst 0.008
pw90 10.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -349.8
wp 23677.6
rfl 2045.4
rfp 0
rp 103.4
lp 0
PLOT
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sc 0
vs 3765
th 1
ai cdc ph
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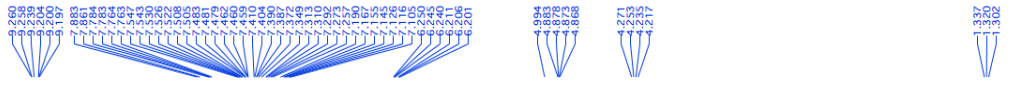
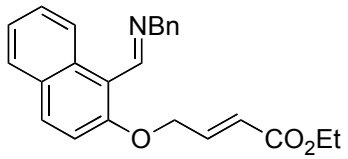
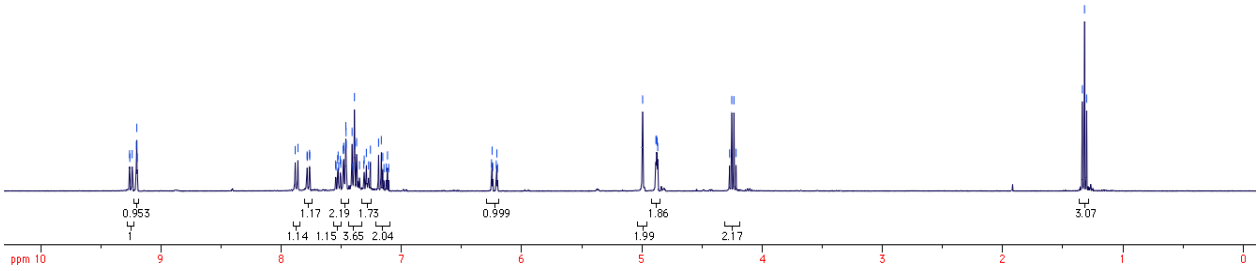
160
140
120
100
80
60
40
20
ppm

3.3e




NBn
O
CO2Et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0.999
1.86
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1.14
1.15
3.65
2.04
1.99
2.17
ppm 10
9
8
7
6
5
4
3
2
1
0


165.964
159.368
156.470
142.133
139.709
132.591
129.479
128.509
128.176
128.091
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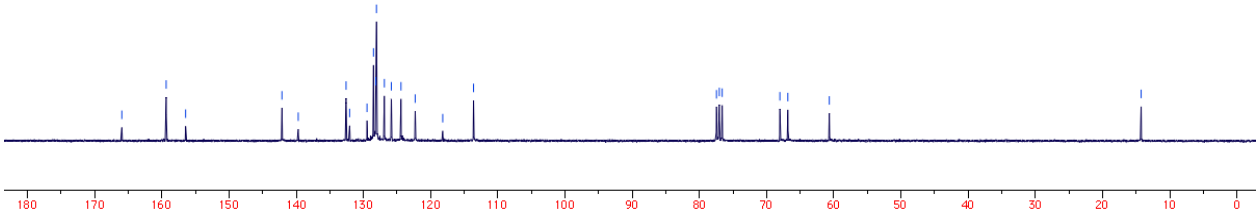
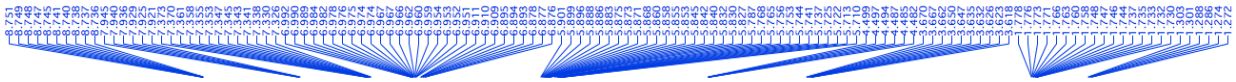
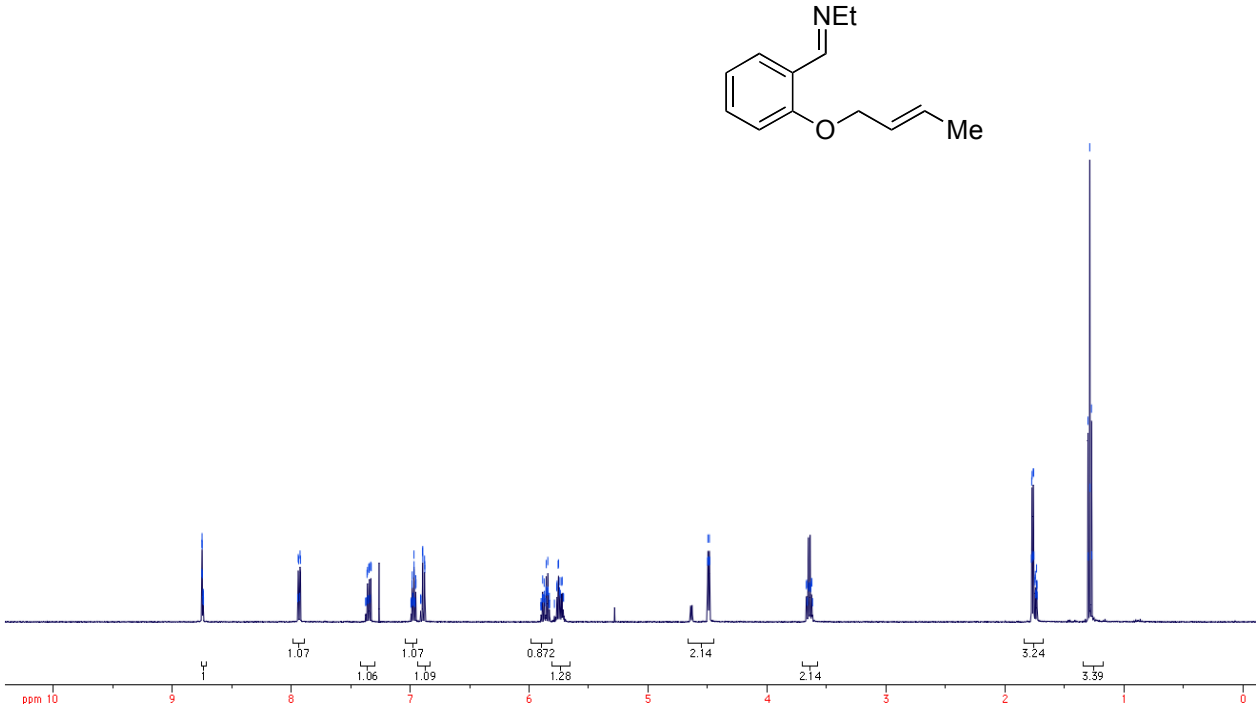
118.201
113.615
77.457
77.014
76.610
68.020
66.837
60.666
14.253


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

3.2f




NEt
O
Me
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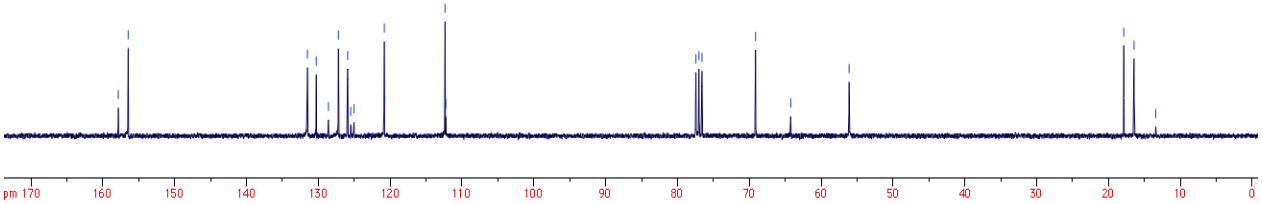
1.07
0.872
2.14
3.24
1
1.06
1.09
1.28
2.14
3.39
ppm 10
9
8
7
6
5
4
3
2
1
0


157.842
156.463
131.513
130.287
130.266
127.199
125.909
125.680
125.025
120.856
120.809
112.357
112.250
77.437
77.014
76.590
69.138
64.234
56.113
17.878
16.450
13.424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120
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100
90
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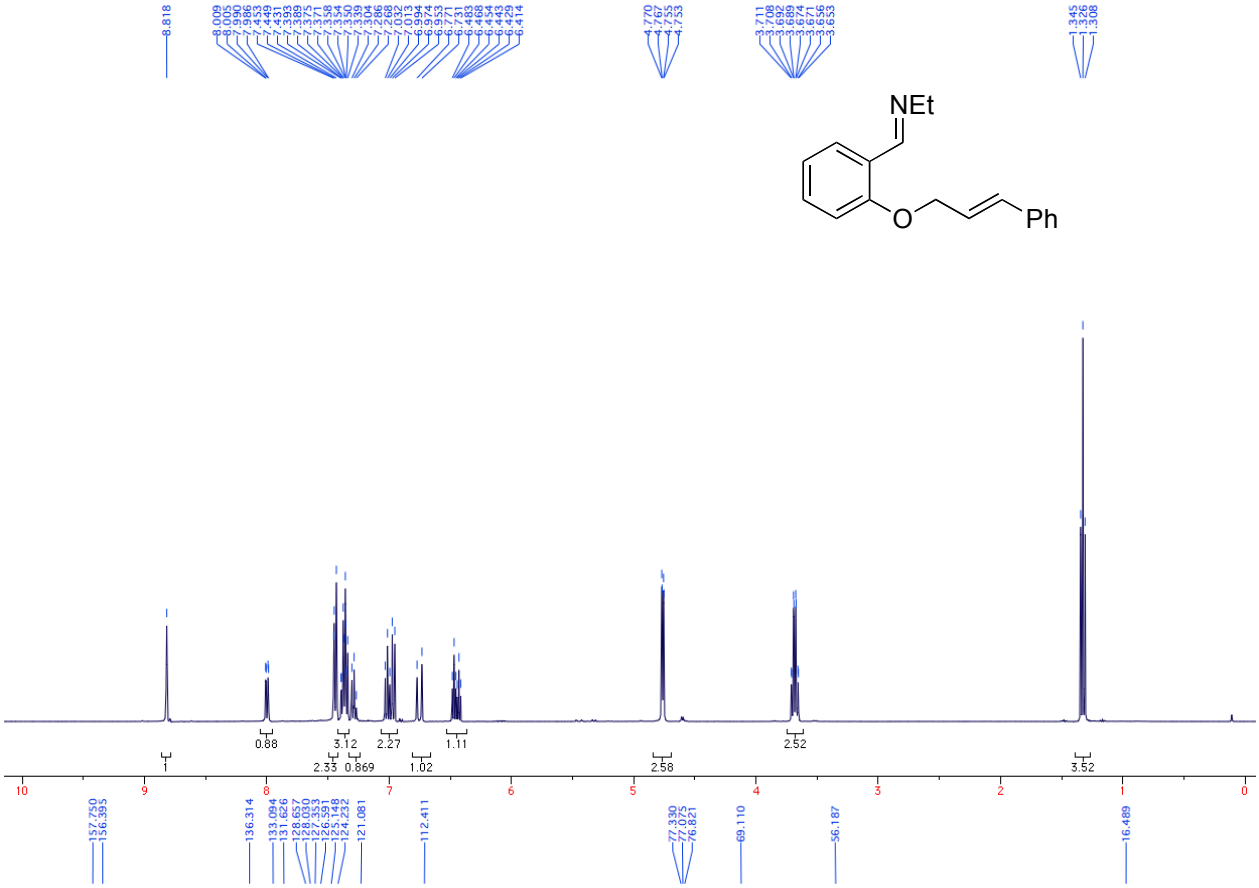
70
60
50
40
30
20
10
0

3.2g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8.009
8.005
7.990
7.986
7.453
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7.431
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7.389
7.375
7.371
7.354
7.350
7.339
7.304
7.286
7.268
7.032
7.013
6.994
6.974
6.753
6.751
6.731
6.488
6.468
6.454
6.443
6.429
6.414
4.770
4.767
4.755
4.753
3.711
3.708
3.692
3.689
3.674
3.671
3.656
3.653
1.345
1.326
1.308
NEt
O
Ph
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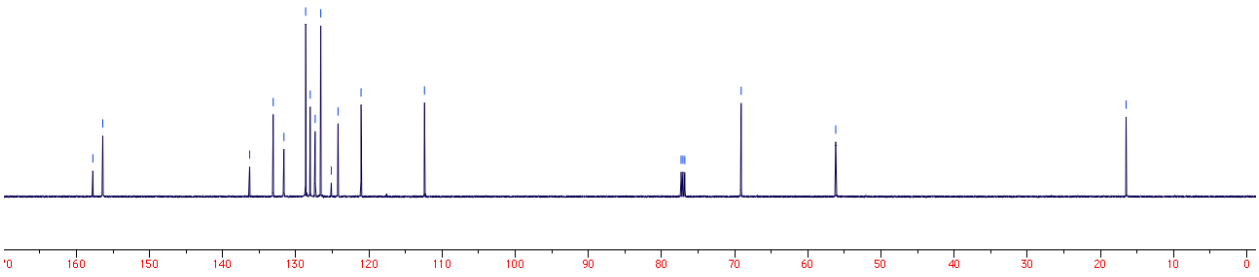
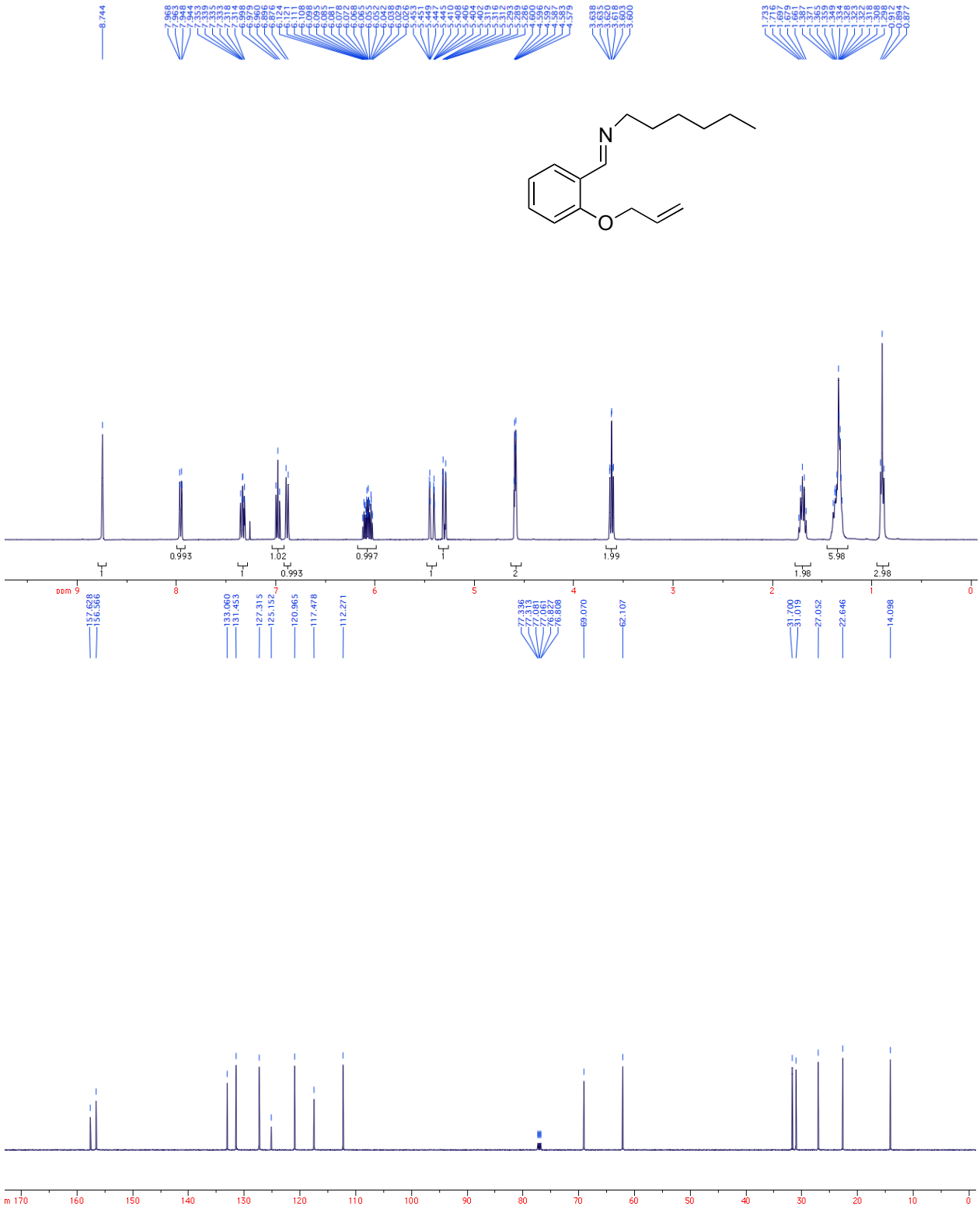
3.12
2.27
1.11
1
2.33
0.869
1.02
2.58
2.52
3.52


157.750
156.395
136.314
133.094
131.626
128.657
128.030
127.353
127.091
125.148
124.232
121.081
112.411
77.330
77.075
76.821
69.110
56.187
16.489

3.2h


N
O
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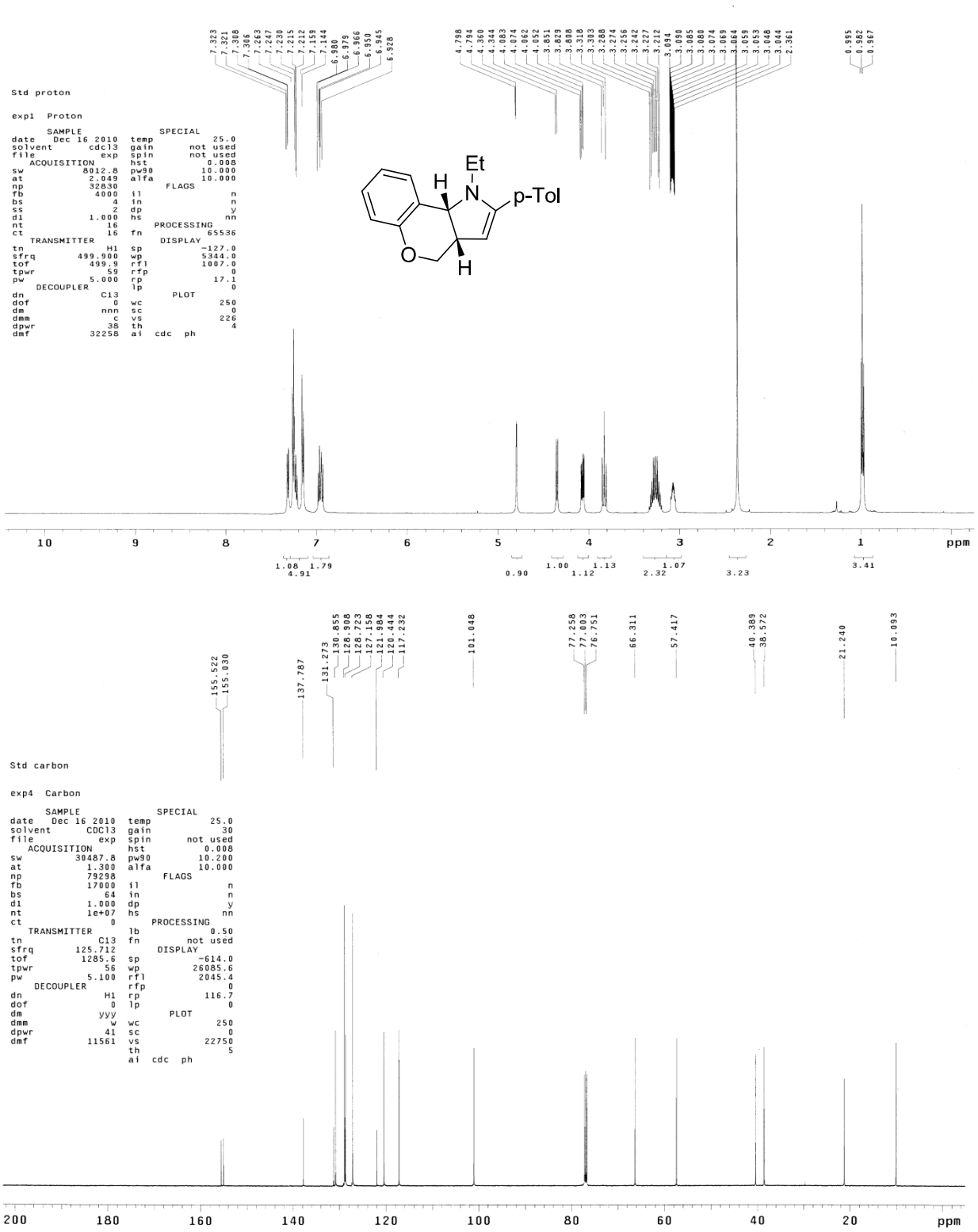
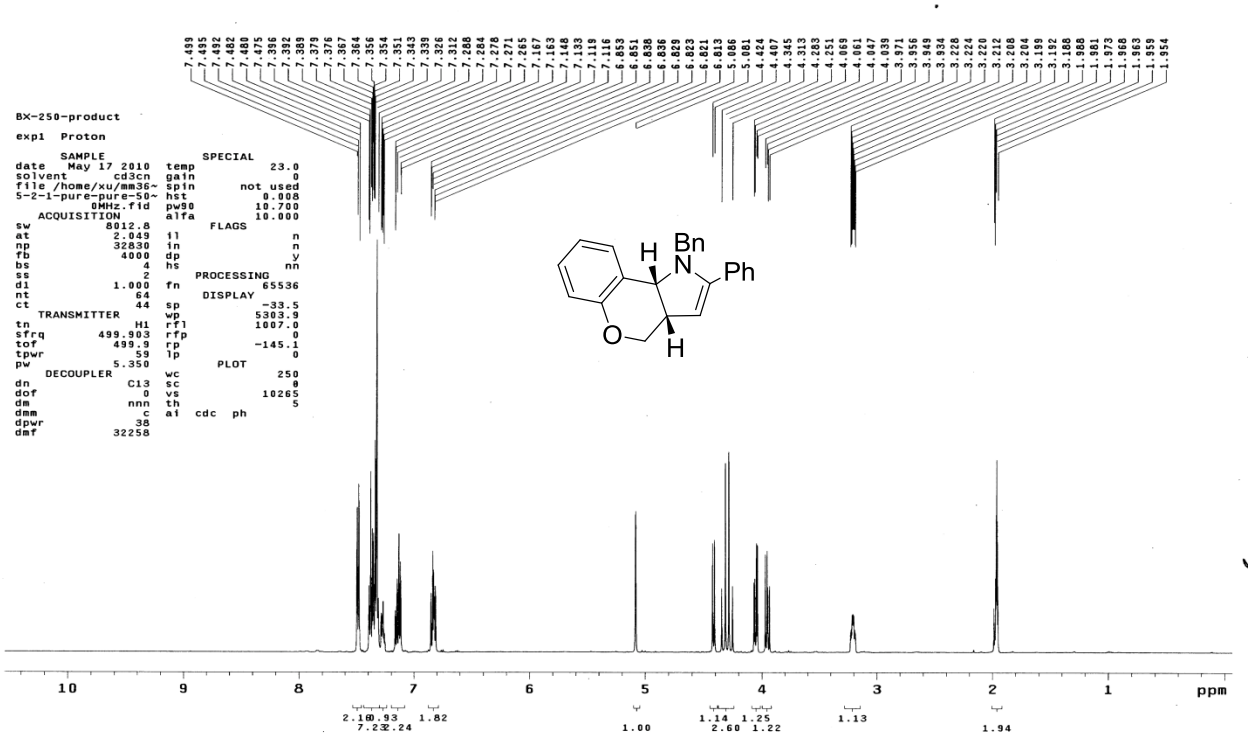
1.02
0.997
0.993
1.99
5.98
1.98
2.98
157.628
156.566
133.060
131.453
127.315
125.152
120.965
117.478
112.271
77.336
77.213
77.081
77.061
76.827
76.808
69.070
62.107
31.700
31.019
27.052
22.646
14.098

3.3a


Std proton
exp1 Proton
Et
H
N
p-Tol
O
H
ppm
Std carbon
exp4 Carbon
ppm

3.3b


BX-250-product
exp1 Proton
SAMPLE
date May 17 2010
solvent cd3cn
file /home/xu/mm36~
5-2-1-pure-pure-50~
0MHz.fid
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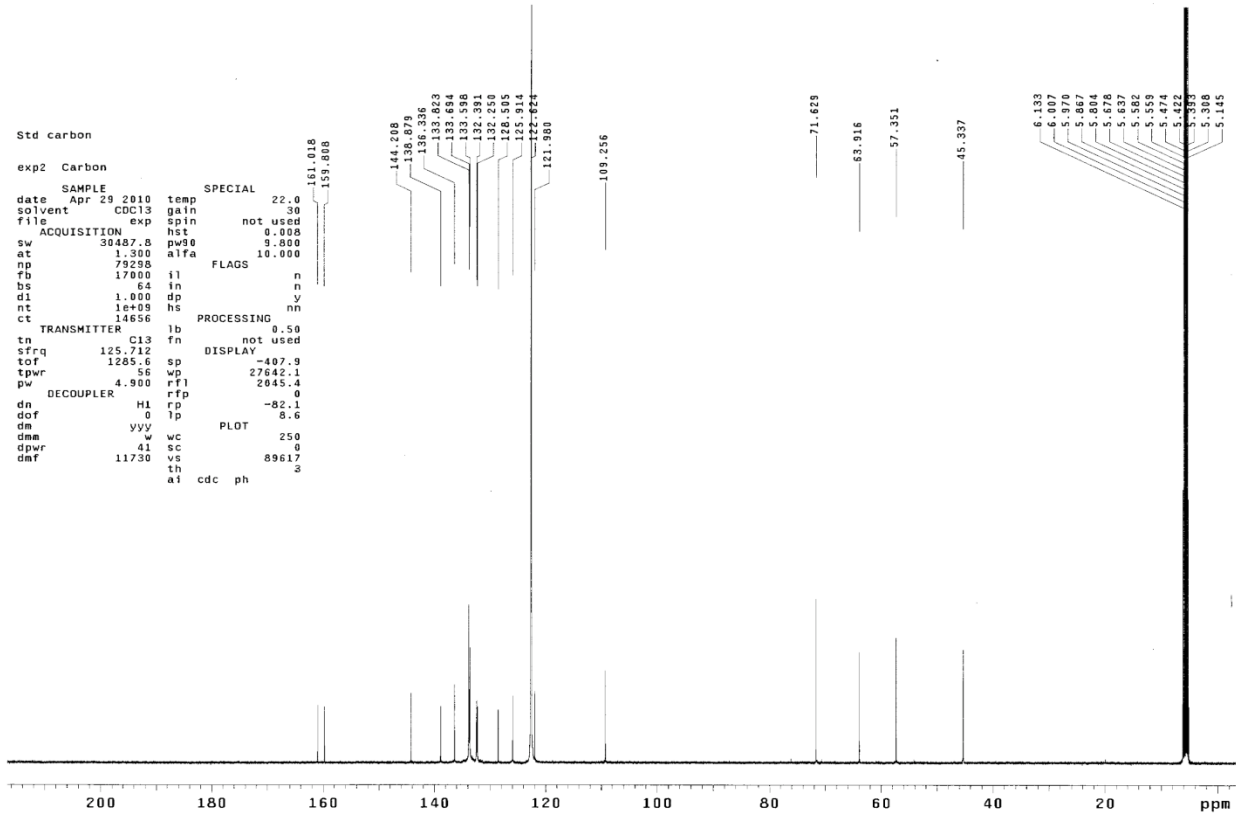
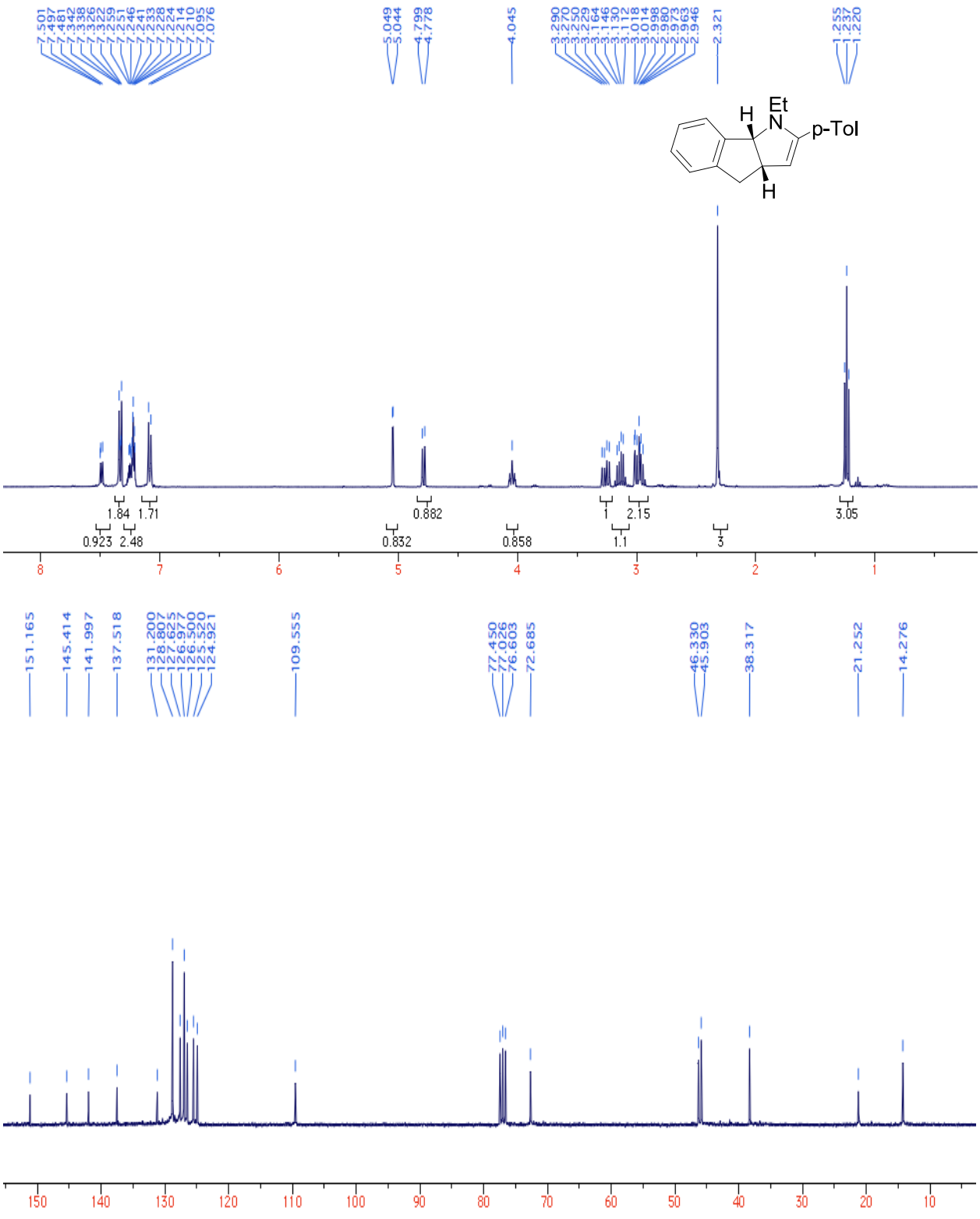
sw 8012.8
at 2.049
np 32830
fb 4000
bs 4
ss 2
d1 1.000
nt 64
ct 44
TRANSMITTER
tn H1
sfrq 499.903
tof 499.9
tpwr 59
pw 5.350
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 38
dmf 32258
SPECIAL
temp 23.0
gain 0
spin not used
hst 0.008
pw90 10.700
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn 65536
DISPLAY
sp -33.5
wp 5303.9
rfl 1007.0
rfp 0
rp -145.1
lp 0
PLOT
wc 250
sc 0
vs 10265
th 5
ai cdc ph
H
Bn
N
Ph
O
H
ppm


Std carbon
exp2 Carbon
SAMPLE
date Apr 29 2010
solvent CDCl3
file exp
ACQUISITION
sw 30487.8
at 1.300
np 79298
fb 17000
bs 64
d1 1.000
nt 1e+09
ct 14656
TRANSMITTER
tn C13
sfrq 125.712
tof 1285.6
tpwr 56
pw 4.900
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 41
dmf 11730
SPECIAL
temp 22.0
gain 30
spin not used
hst 0.008
pw90 9.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -407.9
wp 27642.1
rfl 2045.4
rfp 0
rp -82.1
lp 8.6
PLOT
wc 250
sc 0
vs 89617
th 3
ai cdc ph
ppm

3.3c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7.322
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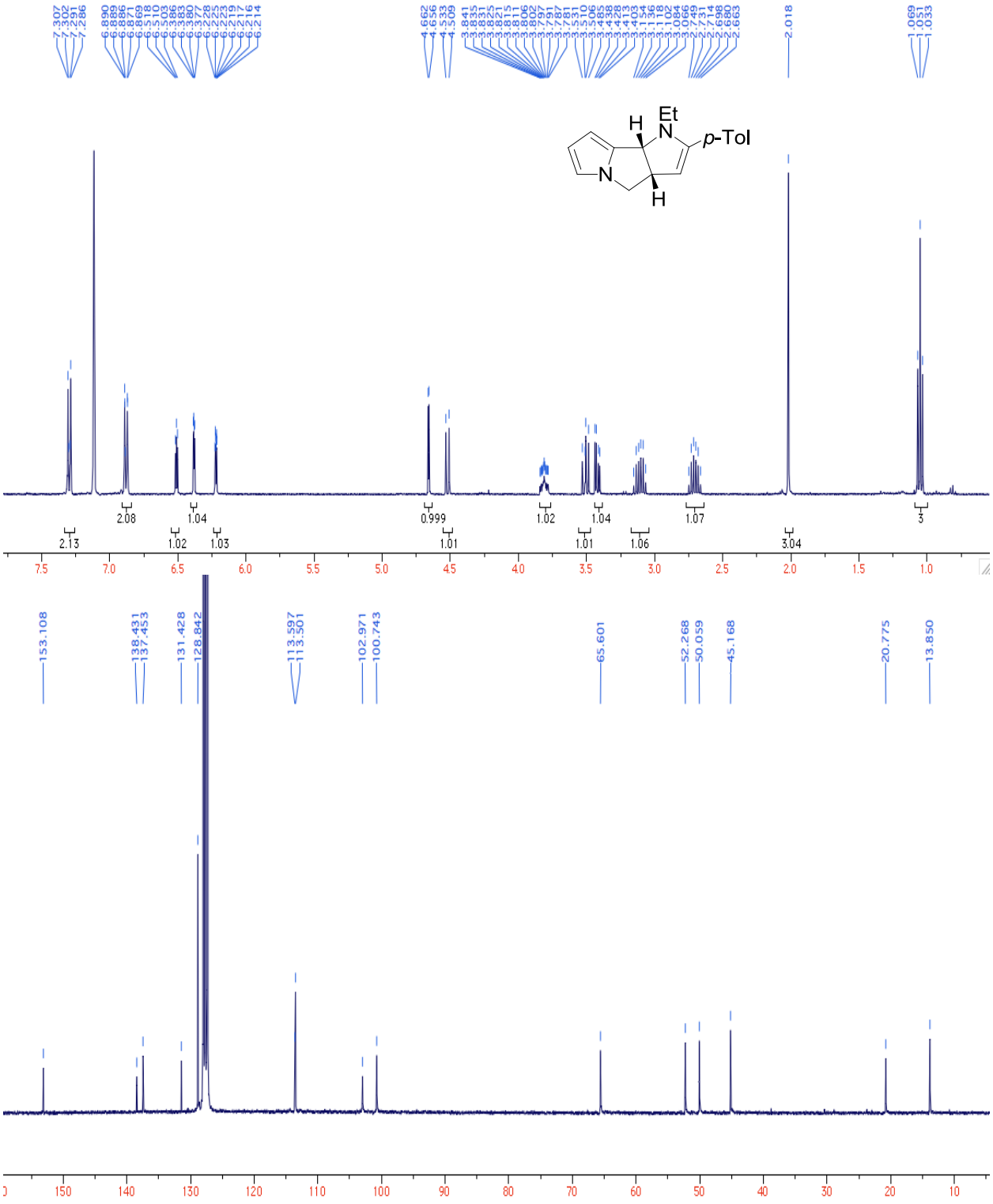
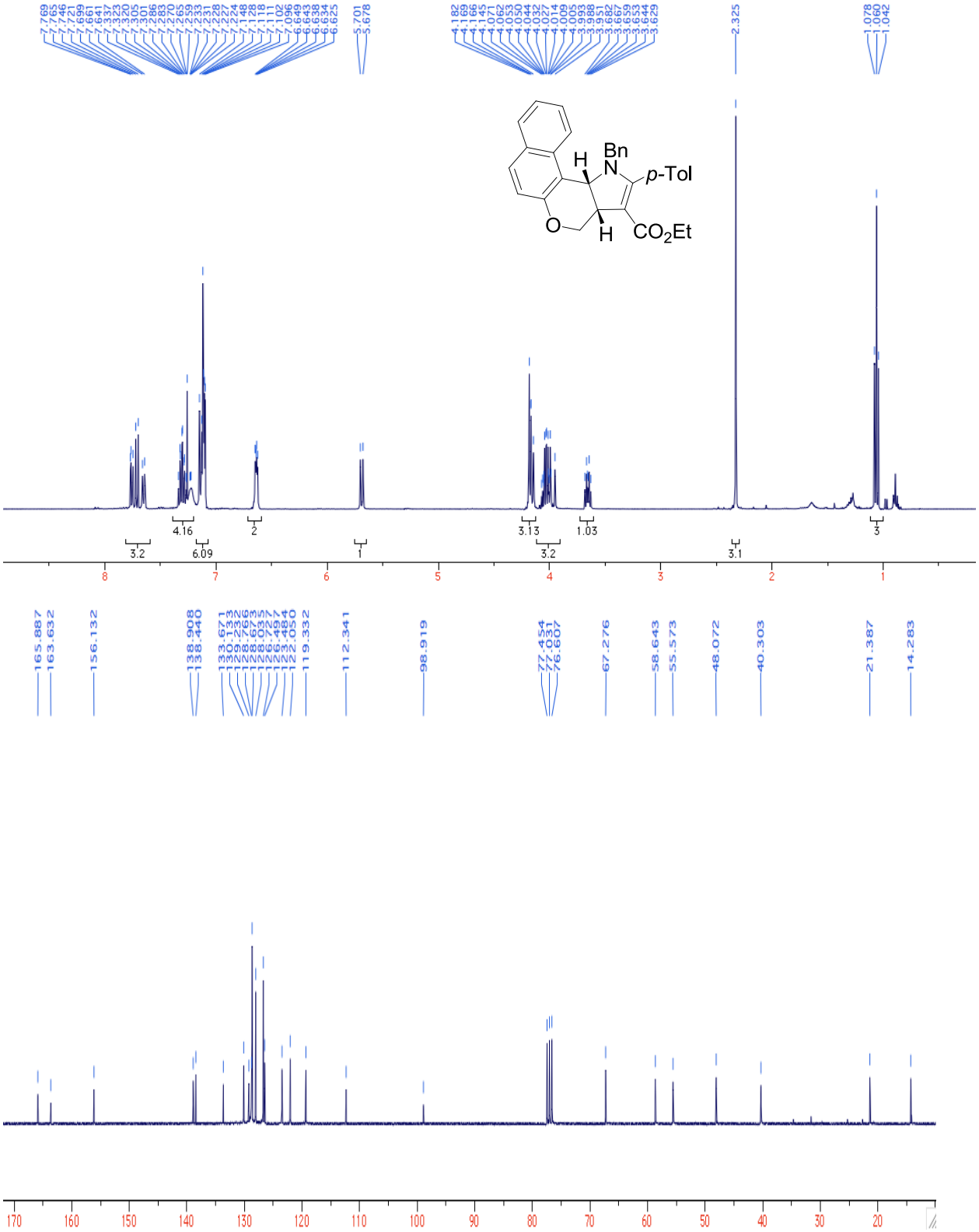
7.233
7.228
7.224
7.214
7.210
7.095
7.076
5.049
5.044
4.799
4.778
4.045
3.290
3.270
3.250
3.229
3.164
3.146
3.130
3.102
3.018
3.014
2.998
2.980
2.973
2.963
2.946
2.321
1.255
1.237
1.220
Et
H
N
p-Tol
H
1.84
1.71
0.923
2.48
0.882
0.832
0.858
1
2.15
1.1
3
3.05
151.165
145.414
141.997
137.518
131.200
128.807
127.625
126.977
126.500
125.520
124.921
109.555
77.450
77.026
76.603
72.685
46.330
45.903
38.317
21.252
14.276

3.3d



3. 3e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7.283
7.270
7.265
7.239
7.233
7.231
7.228
7.227
7.224
7.148
7.118
7.111
7.102
7.096
6.649
6.643
6.638
6.634
6.625
5.701
5.678
4.182
4.169
4.166
4.145
4.071
4.062
4.053
4.050
4.044
4.027
4.022
4.014
4.009
4.005
3.998
3.988
3.951
3.682
3.667
3.659
3.653
3.644
3.629
2.325
1.078
1.060
1.042
Bn
H
N
p-Tol
O
H
CO2Et
4.16
2
3.13
1.03
3
3.2
6.09
1
3.2
3.1
8
7
6
5
4
3
2
1
165.887
163.632
156.132
138.908
138.440
133.671
130.133
129.232
128.767
128.033
126.727
126.494
122.050
119.332
112.341
98.919
77.454
77.031
76.807
67.276
58.643
55.573
48.072
40.303
21.387
14.283
170
160
150
140
130
120
110
100
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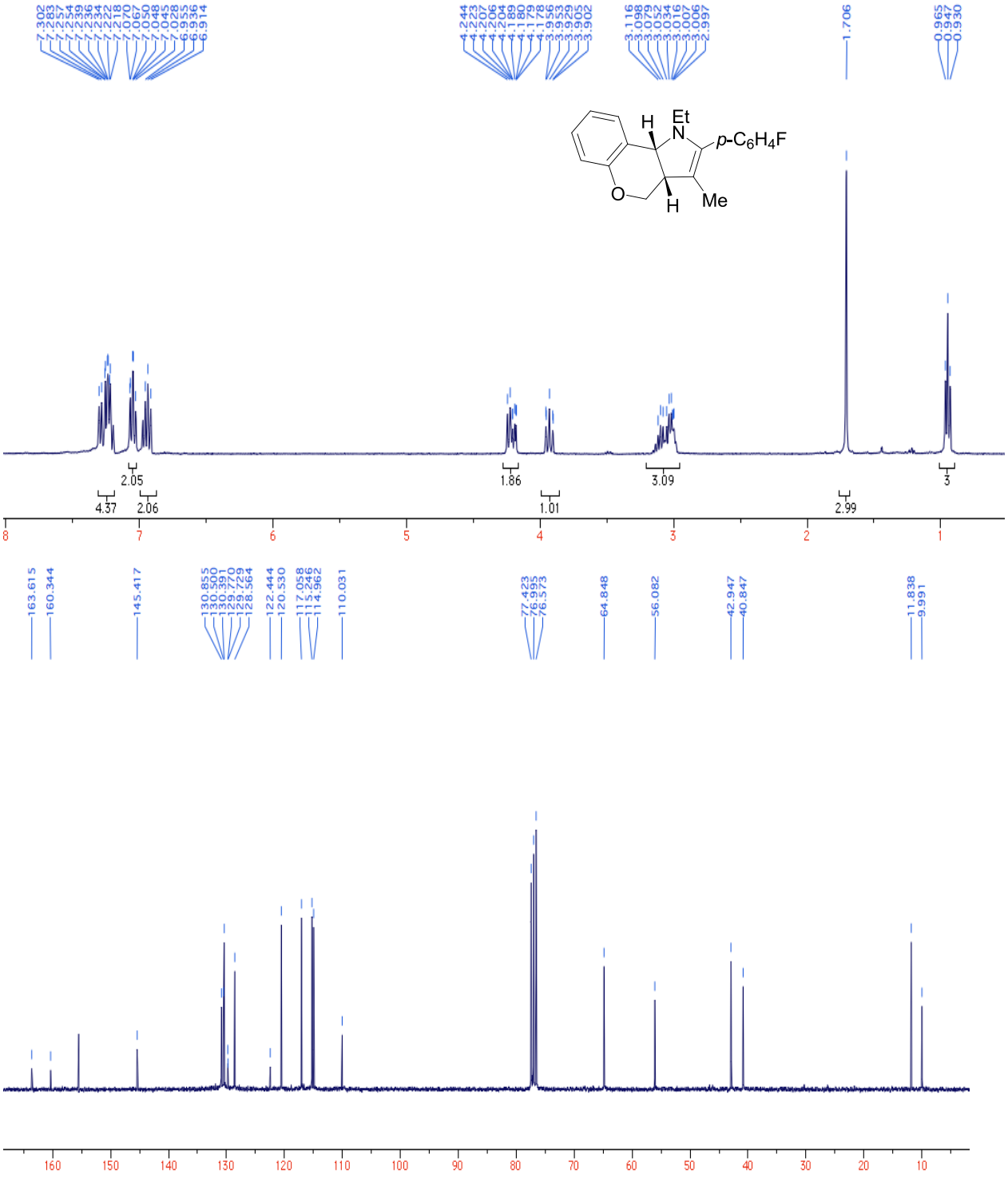
70
60
50
40
30
20

3.3f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7.234
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7.070
7.067
7.050
7.048
7.045
7.028
6.955
6.936
6.914
4.244
4.223
4.207
4.206
4.204
4.189
4.180
4.179
4.178
4.156
3.953
3.929
3.905
3.902
3.116
3.098
3.079
3.052
3.034
3.016
3.007
3.006
2.997
1.706
0.965
0.947
0.930
H
Et
N
p-C6H4F
O
H
Me
2.05
4.37
2.06
1.86
1.01
3.09
2.99
3
8
7
6
5
4
3
2
1
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130.855
130.500
130.391
129.770
129.729
128.564
122.444
120.530
117.058
115.246
114.962
110.031
77.423
76.995
76.573
64.848
56.082
42.947
40.847
11.838
9.991
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130
120
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100
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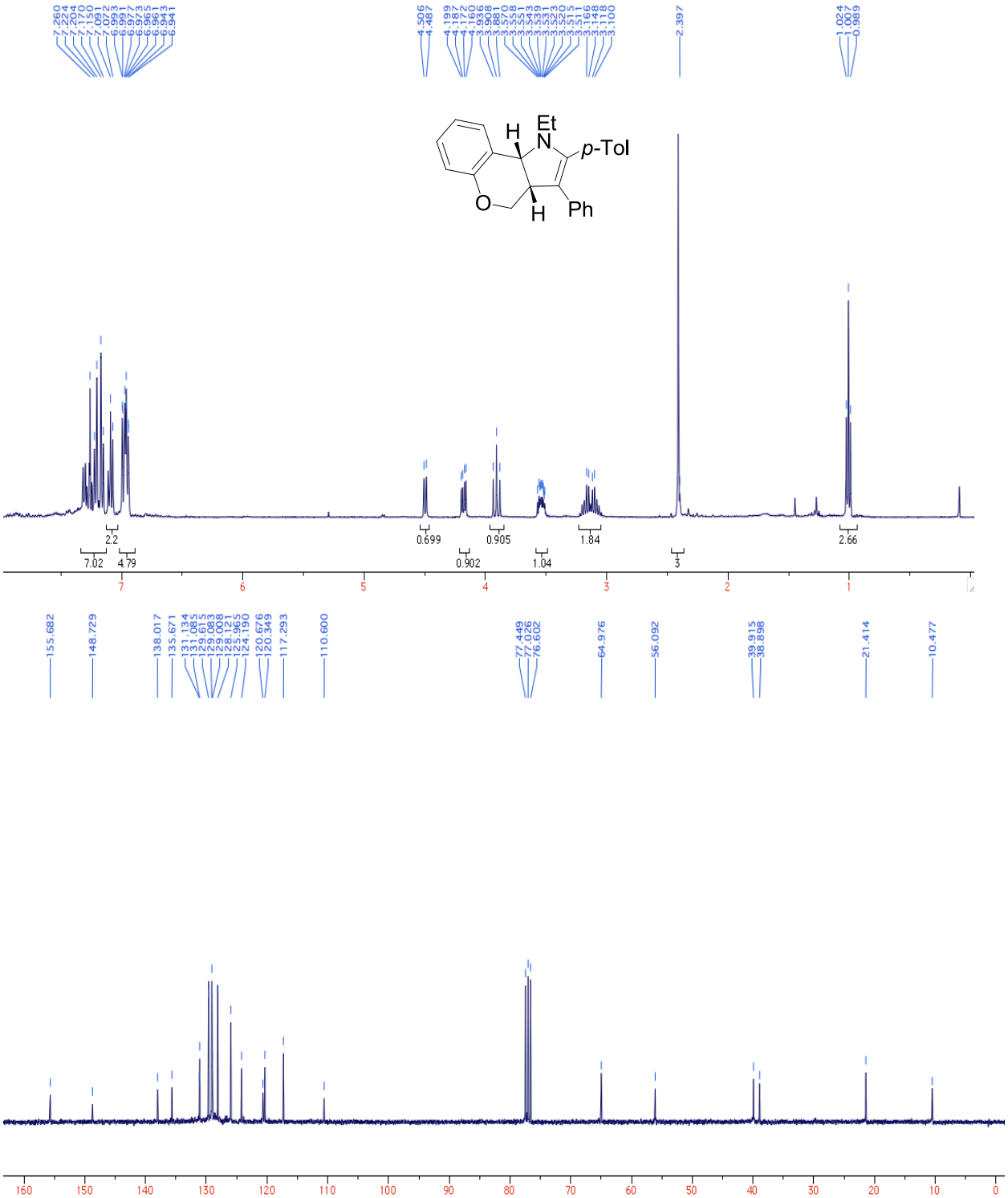
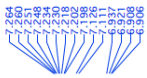
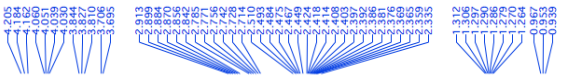
30
20
10

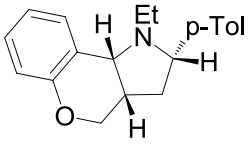
3.3g



3.4a



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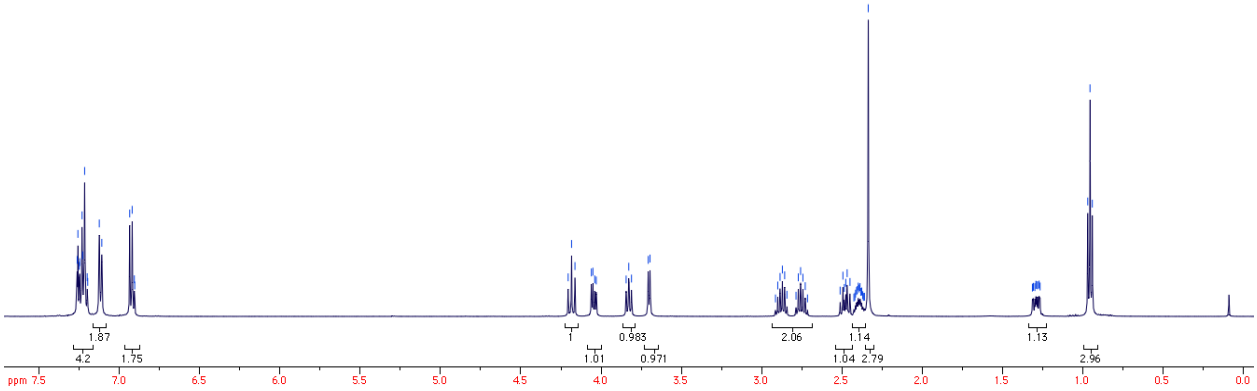
Et
N
p-Tol
H
O
H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1.13
2.96
ppm 7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


155.168
141.091
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131.431
129.015
128.613
127.338
122.142
119.860
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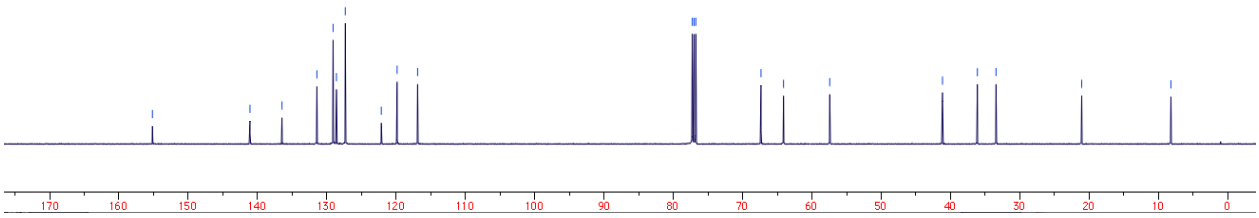
8.197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70
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50
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10
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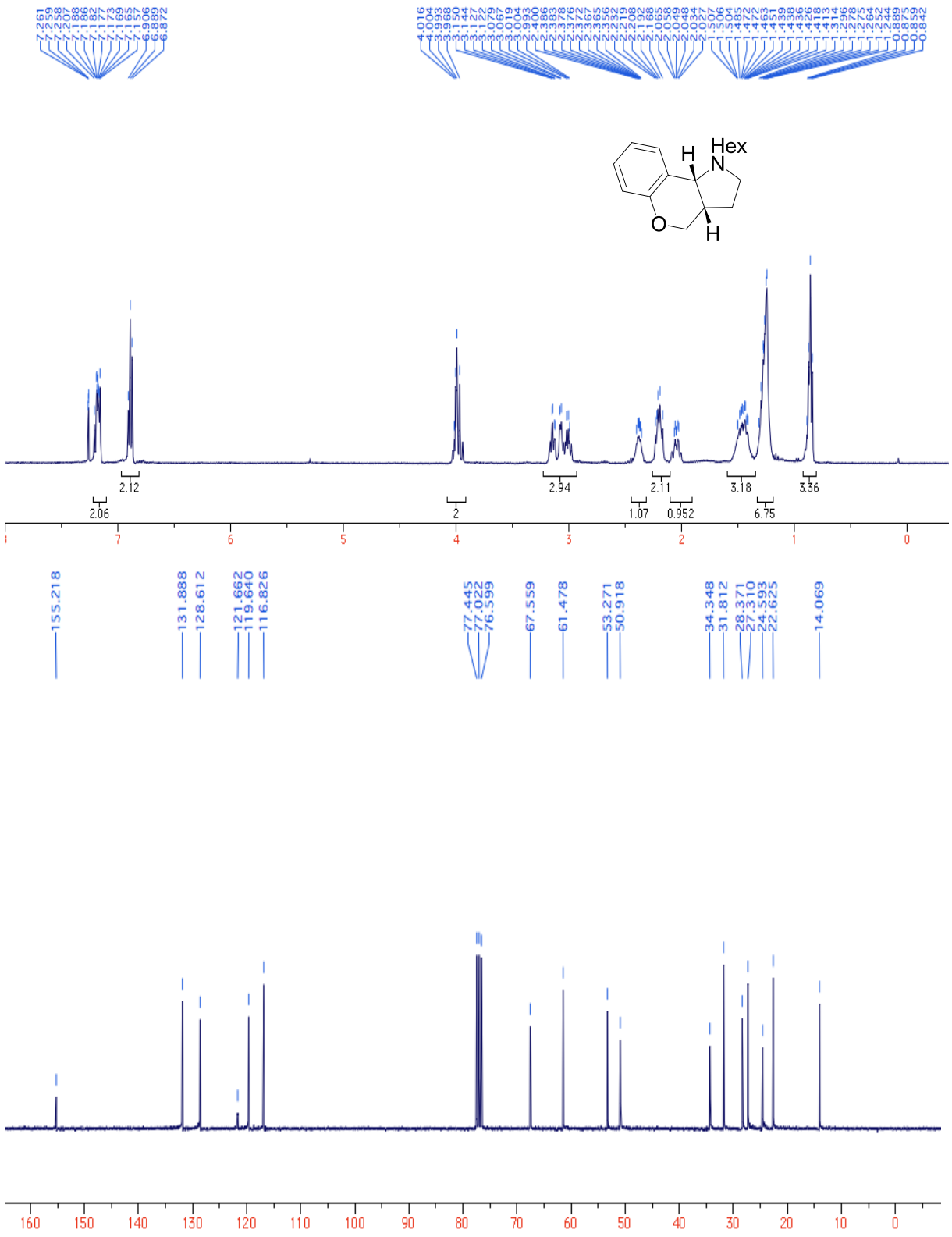
3.4b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61.478
53.271
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27.310
24.593
22.625
14.069