

Applications of New Phosphorus-Based 1,3-Dipolar Cycloaddition Reagents in Nitrogen Heterocycle Synthesis

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*À ma famille,
Le chemin a été long et difficile mais
Votre précieux soutien m'a permis d'avancer
Toujours plus loin*

Abstract

This thesis describes the study of phospho-Münchnones, a new class of 1,3-dipole. These 1,3-dipoles have been previously demonstrated to be accessible in a one-pot reaction of imines, acid chlorides and organophosphorus reagents, and participate in 1,3-dipolar cycloaddition reactions. The objective of the research described in this thesis is to both understand the reactivity of these dipoles, and exploit their cycloaddition with alkynes and alkenes to synthesize pyrroles and 2-pyrrolines with high regio-, diastereo- and enantioselectivity.

Chapter 2 focuses on understanding the factors that control regioselectivity in 1,3-dipolar cycloaddition reactions of phospho-Münchnones with alkynes, as well as the related mesoionic heterocycles Münchnones and Münchnone-imines. While each of the dipoles are established to participate in 1,3-dipolar cycloaddition reactions, until now, no general rules regarding the factors that control regioselectivity have been described. Cycloaddition reactions of the above mentioned dipoles are examined with a range of unsymmetrical electron poor and electron rich alkynes, and by comparing the behavior of these related dipoles, trends are observed in regioselectivity that relates to the alkyne ionization potential. In conjunction with Prof. Houk and Dr. Krenske at UCLA, DFT calculations were performed that provides a rational for the different behaviors of each of these dipoles. Importantly, these 1,3-dipoles display divergent regioselectivity, which can be exploited to synthesize a variety of pyrroles with high selectivity through the use of the appropriate reactant. Similarly, the rational on regioselectivity also allows the prediction of regioselectivity for a wide scope of alkynes.

In Chapter 3 we explore the effect of the organophosphorus unit in phospho-Münchnones on their structure, reactivity and regioselectivity. X-ray crystallographic studies demonstrate the significant role of the PR_3 unit on the ground state structure of these dipoles and their reactivity. In addition, the results of the theoretical investigation of Chapter 2 are exploited to show how changes in

the phosphorus substituents can be used to fine tune regioselectivity of alkyne cycloadditions without modifying the substituents on the final product.

In Chapter 4, phospho-Münchnone cycloaddition with alkenes is explored. Different phosphites and phosphonites are tested for their ability to mediate intramolecular cycloaddition with alkenes, and optimum results are obtained with (2-catechyl)PPh. Polycyclic 2-pyrrolines are generated in rapid cycloaddition reactions, in a modular fashion from easily accessible starting materials: olefin-tethered imines, acid chlorides and phosphonites. In addition, the reaction proceeds with high diastereo- and regioselectivity. The utility of this reaction has been extended to other products, including *in situ* reduction of the 2-pyrroline to pyrrolidines, or oxidation to form pyrroles.

In Chapter 5, a new way to control the enantioselectivity in 1,3-dipolar cycloaddition reactions is described. By the use of (R)-BINOL-based phosphites, a phospho-Münchnone can be prepared that is easily accessible, modular, yet requires no additional steps to install or remove the chiral fragment. As such, this provides a straightforward approach to control chirality in 1,3-dipolar cycloaddition reactions. This has been used to generate polycyclic pyrrolines and pyrrolidines with three or four stereogenic centers in one pot, and up to 99% ee.

Résumé

Cette thèse décrit l'étude du phospho-Münchnone, une nouvelle classe de 1,3-dipôle. Il a été démontré précédemment que ces 1,3-dipôles peuvent être facilement générés à partir des imines, des chlorures d'acides et de composés organophosphorés et peuvent être utilisés dans des réactions de cycloadditions 1,3-dipolaires. Le but de cette recherche est à la fois de comprendre la réactivité de ces dipôles et de les exploiter dans des réactions de cycloadditions avec des alcynes et des alcènes pour synthétiser des pyrroles et des 2-pyrrolines de façon hautement régio-, diastéréo- et énantiosélective.

Le Chapitre 2 focalise sur la compréhension des facteurs qui contrôlent la régiosélectivité des réactions de cycloadditions 1,3-dipolaires avec les phospho-Münchnones et les alcynes ainsi qu'avec des hétérocycles mésoioniques analogues, les Münchnones et les Münchnones-imines. Malgré que chacun de ces 1,3-dipôles soit reconnu pour sa participation aux réactions de cycloadditions 1,3-dipolaires, aucune règle générale concernant les facteurs qui contrôlent la régiosélectivité n'a été encore établie jusqu'à maintenant. Grâce à l'étude des cycloadditions de ces trois 1,3-dipôles avec une gamme d'alcynes asymétriques électron pauvres et électron riches, et par la comparaison des comportements de ces 1,3-dipôles, des tendances au niveau de la régiosélectivité en fonction du potentiel d'ionisation de l'alcyne ont pu être observées. Conjointement avec le Pr. Houk et le Dr. Krenke à L'UCLA, des calculs DFT ont été réalisés et fournissent une explication logique sur les différents comportements de ces dipôles. De plus, ces 1,3-dipôles présentent des régiosélectivités divergentes qui peuvent être exploitées pour la synthèse d'une variété de pyrroles avec de hautes sélectivités grâce au choix du réactif approprié. Cette étude permet également la prédiction de la régiosélectivité pour une large gamme d'alcynes.

Dans le Chapitre 3, l'effet de l'unité organophosphorée sur la structure, la réactivité et la régiosélectivité du phospho-Münchnone est étudié. Les études aux rayons-X cristallographiques démontrent le rôle important de l'unité PR_3 sur l'état

fondamental et la réactivité de ces 1,3-dipôles. De plus, les résultats de l'étude théorique du Chapitre 2 sont exploités pour varier de façon logique les substituants du phosphore afin d'améliorer la régiosélectivité des cycloadditions d'alcynes sans modifier les substituants du produit final.

Dans le Chapitre 4, la cycloaddition du phospho-Münchnone avec des alcènes est explorée. Différents phosphites et phosphonites sont testés pour leur capacité à participer aux cycloadditions intramoléculaires d'alcènes, et les résultats optimaux sont obtenus avec le (2-catechyl)PPh. Les 2-pyrrolines polycycliques sont générées dans des réactions de cycloadditions rapides, de façon modulaires et à partir de réactifs facilement accessibles : des imines contenant un alcène, des chlorures d'acyles et des phosphonites. De plus, la réaction procède avec une haute régio- et diastéréosélectivité. L'utilité de cette réaction a été étendue à d'autres produits, avec la réduction *in situ* des 2-pyrrolines en pyrrolidines, et avec l'oxydation en pyrroles.

Dans le Chapitre 5, une nouvelle façon de contrôler l'énantiosélectivité des réactions de cycloadditions 1,3-dipolaires est décrite. Grâce à l'utilisation d'un phosphite substitué par un groupement (R)-BINOL, un nouveau phospho-Münchnone peut être synthétisé avec l'avantage d'être facilement accessible, modulaire, et ne requiert aucune étape supplémentaire pour installer ou enlever le fragment chiral. Cela offre une approche simple pour contrôler la chiralité des réactions de cycloadditions 1,3-dipolaires et générer des pyrrolines et des pyrrolidines polycycliques avec trois ou quatre centres stéréogènes de façon « one-pot » et jusqu'à 99% ee.

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Contributions of Co-Authors

The main body of this Thesis consists of four chapters (Chapter 2 to 5), with a general introduction to this work in the first chapter and conclusions in the sixth chapter. Chapter 4 has been published, while Chapters 2 and 5 will be submitted. All the work described in these manuscripts was carried out as part of my research for the degree of Doctor of Philosophy in chemistry. Dr. Arndtsen was my supervisor throughout my doctoral degree. He is a co-author for each manuscript and assisted me in their writing. I performed all experiments reported with the following exceptions:

Chapters 2 and 3: Dr. Elizabeth Krenske performed DFT calculations to establish theoretical understanding on Münchnone and phospho-Münchnone reactivities and regioselectivities in cycloaddition reactions.

Chapter 4: Sara Aly synthesized the pyrrolines in Table 4.2, entries 4, 5, 7, 10 and 11. She also prepared the pyrrolidine **4.4m** of Scheme 4.2.

Chapters 3 and 5: X-Ray structure analyses were performed by Françoise Bélanger and Michel Simard.

Appendix G reports examples of intramolecular alkene cycloadditions that did not work with the approach developed in Chapters 4 and 5. This shows the limitations of the research and the areas that can be explored further.

The Appendices H and I include two co-authors papers that I equally contributed with former Ph-D students: Dr. Daniel St-Cyr and Dr. Yingdong Lu.

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List of Abbreviations

Ac	acetate
Ar	aryl
n-BuLi	n-butyl lithium
Bn	benzyl
bs	broad singlet
Bz	benzoyl
catechyl	<i>o</i> -O ₂ C ₆ H ₄
COSY	correlation spectroscopy
δ	chemical shift
Dabco	1,4-diazabicyclo[2,2,2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<i>de</i>	diastereomeric excess
DFT	density functional theory
DIEA	diisopropylethylamine (Hünigs base)
DMAD	dimethyl acetylene dicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulphoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>Ee</i>	enantiomeric excess
Et	ethyl
ESI-MS	electrospray ionization mass spectrometry
EtOAc	ethyl acetate
FMO	frontier molecular orbital
HMQC	heteronuclear multiple quantum correlation spectroscopy
HMBC	heteronuclear multiple bond correlation spectroscopy
HOMO	Highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
IP	ionization potential

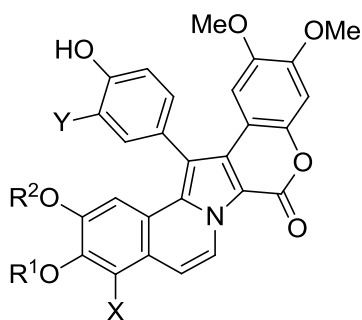
LiHMDS	Lithium hexamethyldisilazane (Lithium bis(trimethylsilyl)amide)
<i>J</i>	coupling constant
LUMO	lowest unoccupied molecular orbital
m	multiplet
Me	methyl
MS	mass spectrum
<i>m/z</i>	mass-to-charge ratio
NMR	nuclear magnetic resonance
Nu	nucleophile
pH	negative logarithm of hydrogen ion concentration
Ph	phenyl
pKa	negative logarithm of equilibrium constant for association
PMP	para-methoxyphenyl
ppm	parts per million
Py	pyridine
q	quartet
R _f	the retention factor, is defined as the distance traveled by the compound divided by the distance traveled by the solvent
rt	room temperature
s	singlet
t	triplet
<i>p</i> -Tol	para-tolyl
<i>t</i> -Bu	<i>tert</i> -butyl
TBDMS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TLC	thinlayer chromatography
TsCl	toluenesulfonyl chloride

CHAPTER 1

Introduction: Synthesis of Pyrroles via 1,3-Dipolar Cycloaddition with Mesoionic Heterocycles

1.1 Perspective

Pyrroles are found in a wide variety of molecules with attractive properties. Pyrroles have been extensively studied as components in biologically relevant molecules, including natural and non-naturally occurring compounds.^{1,2} For example, several pyrrole-containing marine alkaloid lamellarins (Figure 1.1) have been found to be cytotoxic to cancer lines (e.g., lamellarin K, D and M, **1.1a-c**).³ They also display antibiotic activity (lamellatin O and P, **1.1d,e**),⁴ and can inhibit cell division (lamellarin D, **1.1a**).⁵

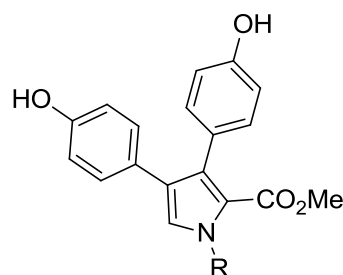


Lamellarin:

1.1a D: R¹ = X = H; R² = Me; Y = OMe

1.1b K: R¹ = R² = Me; X = OH; Y = H

1.1c M: R¹ = R² = Me; X = OH; Y = OMe



Lamellarin:

1.1d O: R = 4-(MeO)C₆H₄COCH₂

1.1e P: R = 2-(OH),4-(MeO)C₆H₄COCH₂

Figure 1.1: Pyrrole Containing Marine Alkaloids

Highly functionalized pyrroles are also found in the natural products storniamides A-D (**1.2a-d**), potent antibiotics,⁶ as well as in the polycitone A (**1.3**), a general inhibitor of DNA polymerase (Figure 1.2).⁷ Pyrroles are also key constituents in natural pigments of crucial importance in living systems, such as hemoglobin, chlorophyll, vitamin B12 and bile pigments.

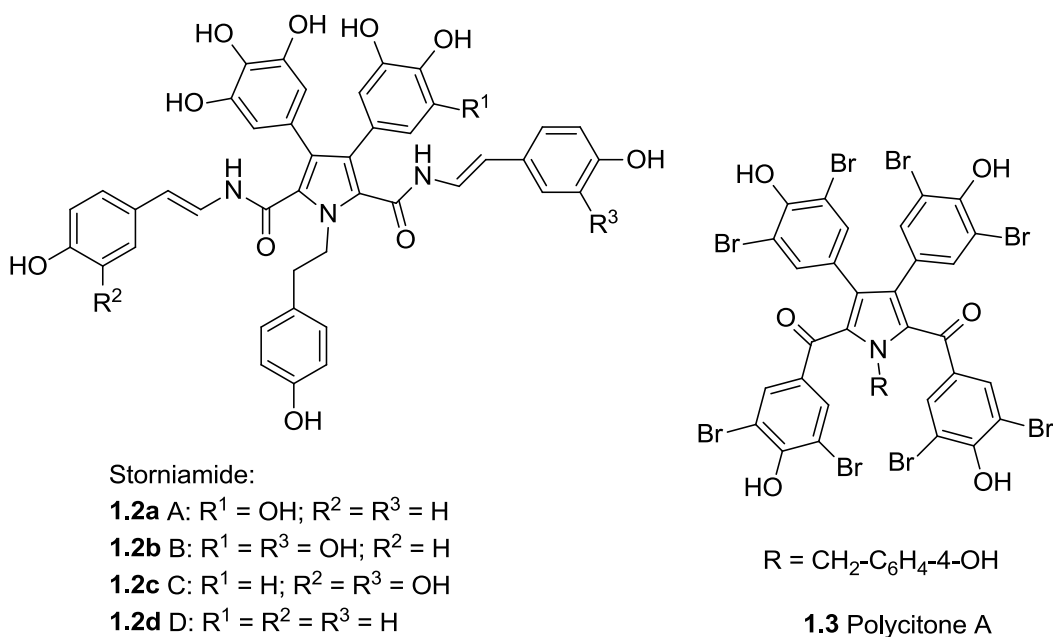


Figure 1.2: Pyrrole-Containing Biomolecules

In addition to naturally occurring compounds, pyrroles are found in many synthetic biologically active molecules. The most important example is the blockbuster drug Atorvastatin (**1.4**) (marketed as Lipitor),⁸ used to lower cholesterol levels. Other examples include the pyrrole BM212 (**1.5**), an anti-mycobacterial agent;⁹ CS-706 (**1.6**), an anti-inflammatory substance;¹⁰ pyrrole **1.7**, an active species against hyperglycemic activity;¹¹ and pyrrole **1.8**, a potent inhibitor of the p38 kinase involved in immunological disorders such as rheumatoid arthritis (Figure 1.3).¹²

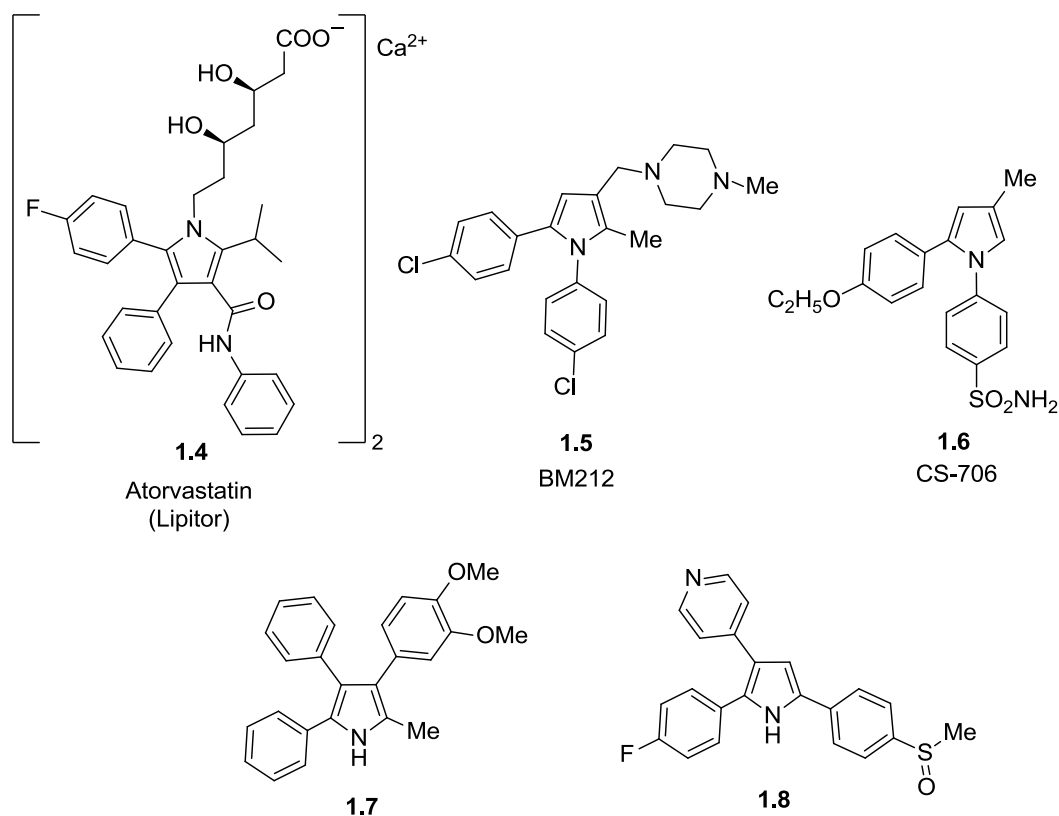


Figure 1.3: Representative Non-Natural Pyrrole Therapeutics

The former list is far from exhaustive; a wide spectrum of other biologically active pyrroles have also been reported.²

Pyrroles have also garnered interest in other areas, such as fluorescent spectroscopy. A typical example of this is 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene dye **1.9** (BODIPY).¹³ The fluorescent properties of this complex make it a powerful tool in many areas, including biological staining,¹⁴ fluorescent switches,¹⁵ and laser dyes.¹⁶

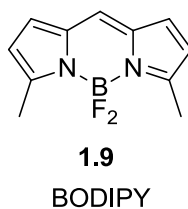
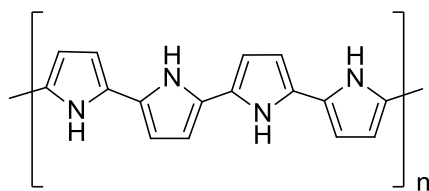


Figure 1.4: Fluorescent Pyrrole-Containing Molecule

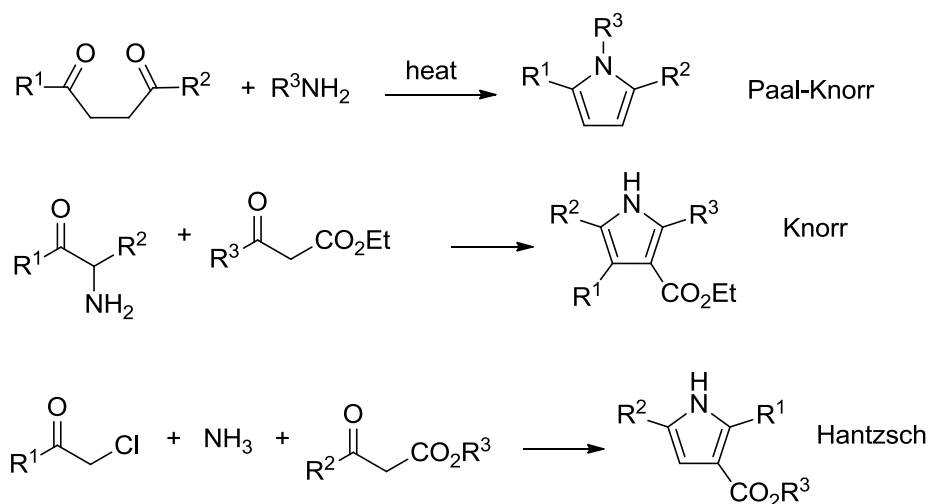
Pyrroles are also employed in polymer chemistry,¹⁷ where polypyrrole-based conjugated polymers **1.10** display high conductivity and stability. Their versatile properties, in combination with their facile synthesis by electropolymerization, have led to a variety of applications in the field of material science, especially as biosensors.¹⁸ Polypyrroles can also behave as gas,¹⁹ immuno-²⁰ and optical²¹ sensors, polymer electrodes,²² electrochemically switchable cation exchangers for water purification,²³ or as a coating material for solid phase microextraction.²⁴



1.10

Figure 1.5: Pyrrole-Based Conjugated Polymer

In light of the broad utility of pyrroles, the development of efficient methods for their synthesis has become a significant topic in research. Classical methods to prepare pyrroles include Paal-Knorr,²⁵ Knorr²⁶ and Hantzsch²⁷ syntheses (Scheme 1.1). While effective, these typically require the multistep preparation of the polysubstituted precursor(s), and have stimulated interest in more convergent synthetic approaches.



Scheme 1.1: Classic Approaches to Pyrrole Synthesis.

Among the many methods to prepare pyrroles, (3+2) cycloaddition reactions of 1,3-dipole containing heterocycles (e.g., mesoionic heterocycles) with alkenes or alkynes is an interesting approach. This reaction creates two new bonds in a single step, thereby providing a convergent and a diversifiable route to these products. A number of mesoionic heterocycles have been found to undergo [3+2] cycloaddition to generate pyrroles. In this chapter, we will briefly summarize these systems. The development and the applications of a new type of mesoionic heterocycle is the subject of the research in this thesis.

1.2 Mesoionic Heterocycles

Mesoionic compounds are an important class of synthetic building blocks. They are defined as cyclic conjugated molecules that cannot be drawn with a single neutral resonance structure; instead, they contain formal positive and negative charges in any one resonance structure. These molecules can often be depicted with a formal positive charge associated with a 5-membered ring, and a formal negative charge associated with the exocyclic atom or group of atoms.²⁸ Since their first discovery over 75 years ago, a large number of mesoionic heterocycles have been developed. Some examples are shown in Figure 1.6.²⁹

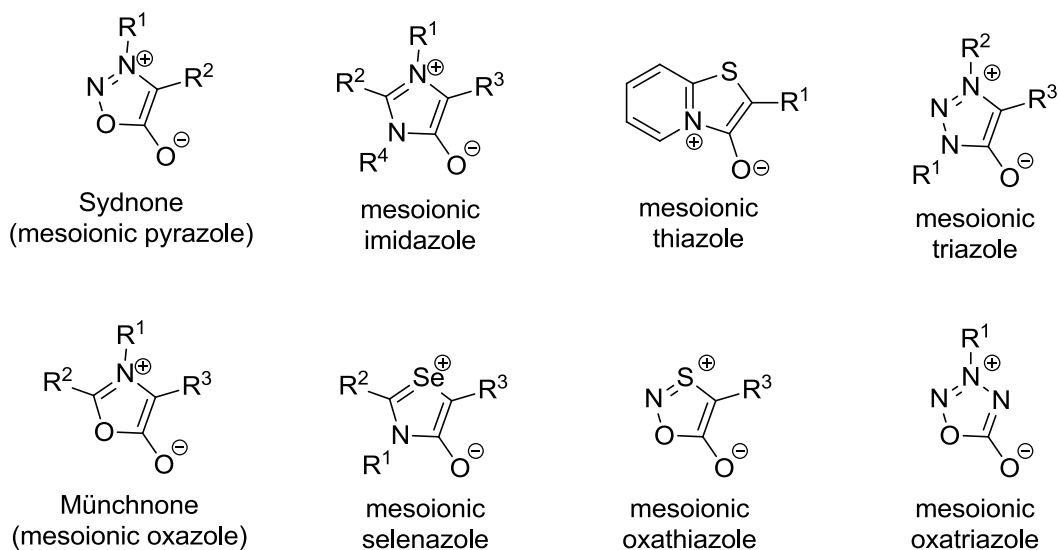
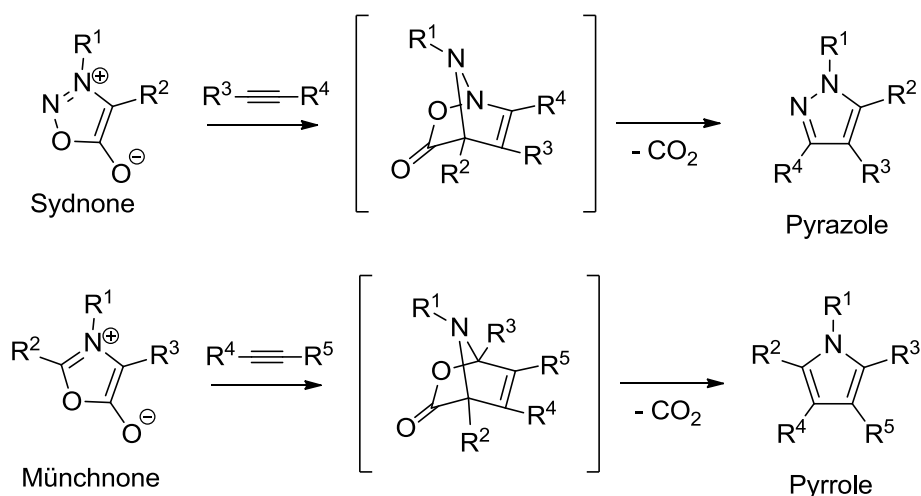


Figure 1.6: Representative Examples of Mesoionic Heterocycles

Developed in 1935, Sydnone was one of the first mesoionic molecules synthesized.³⁰ However, it was not until 1962 that their major synthetic use was discovered. Most mesoionic molecules possess a masked 1,3-dipole resonance structure, and can therefore undergo (3+2) cycloaddition reactions. The first examples, described by Huisgen and co-workers, showed the cycloadditions of alkynes with Sydnone³¹ and 1,3-oxazolium 5-oxides,³² called Münchnone. These reactions lead to pyrazoles and pyrroles, respectively, after the extrusion of CO₂ (Scheme 1.2).



Scheme 1.2: Pyrazole and Pyrrole Synthesis by 1,3-Dipolar Cycloaddition

Considering the broad utility of nitrogen-containing heterocycles, the application of the mesoionic rings in heterocyclic synthesis has increased considerably over the last several decades. Notably, many new systems capable of undergoing 1,3-dipolar cycloaddition have been developed, and led to the recognition of the mesoionic compounds as a useful tool in drug discovery.³³

1.3 Pyrrole Synthesis via 1,3-Dipolar Cycloaddition with Mesoionic Compounds

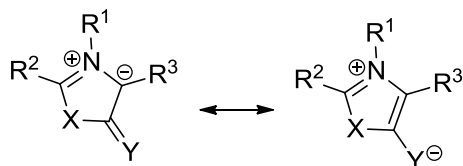


Figure 1.7: General Structure of Mesoionic Rings Containing an Azomethine Ylide Moiety

The general structure of mesoionic heterocycles that undergo 1,3-dipolar cycloaddition to form pyrroles are represented in Figure 1.7. This scaffold contains an azomethine ylide unit, and a fragment X-C-Y that is eliminated upon the cycloaddition. A number of different heteroatoms X and Y (oxygen, nitrogen or sulfur) can be incorporated into the mesoionic structures. However, not all combinations of heteroatoms in the mesoionic ring can lead to 1,3-dipolar cycloaddition reactivity. For example, no cycloaddition has been reported for Y=S.^{34,35} In this section, we will summarize the synthesis and reactivity of common variants of these mesoionic compounds that can undergo cycloaddition to afford pyrroles.

1.3.1 Münchnones (1,3-oxazolium-5-olates)

Among the variety of mesoionic heterocycles, Münchnones **1.11** (1,3-oxazolium-5-olates, Figure 1.8) are a prominent substrate. This is likely due to the combination of their accessibility (from α -amido acid derivatives, *vide infra*) and their high activity in 1,3-dipolar cycloadditions. Münchnones were first reported by Lawson and Miles³⁶ in 1958. However, it was in 1964 that their 1,3-dipolar reactivity was noted in the synthesis of pyrroles by the Huisgen group (performed in their Munich laboratory; Münchnones are named for the city München).³² Münchnones are a classic example of mesoionic rings, and cannot be represented by only one resonance structure. Figure 1.8 shows several possible resonance

structures. Crystallographic data suggest that **1.11a** is the most representative of the ground state structure.

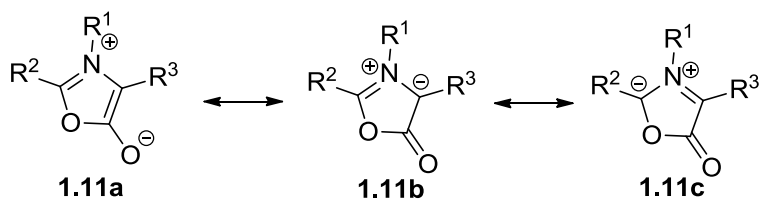
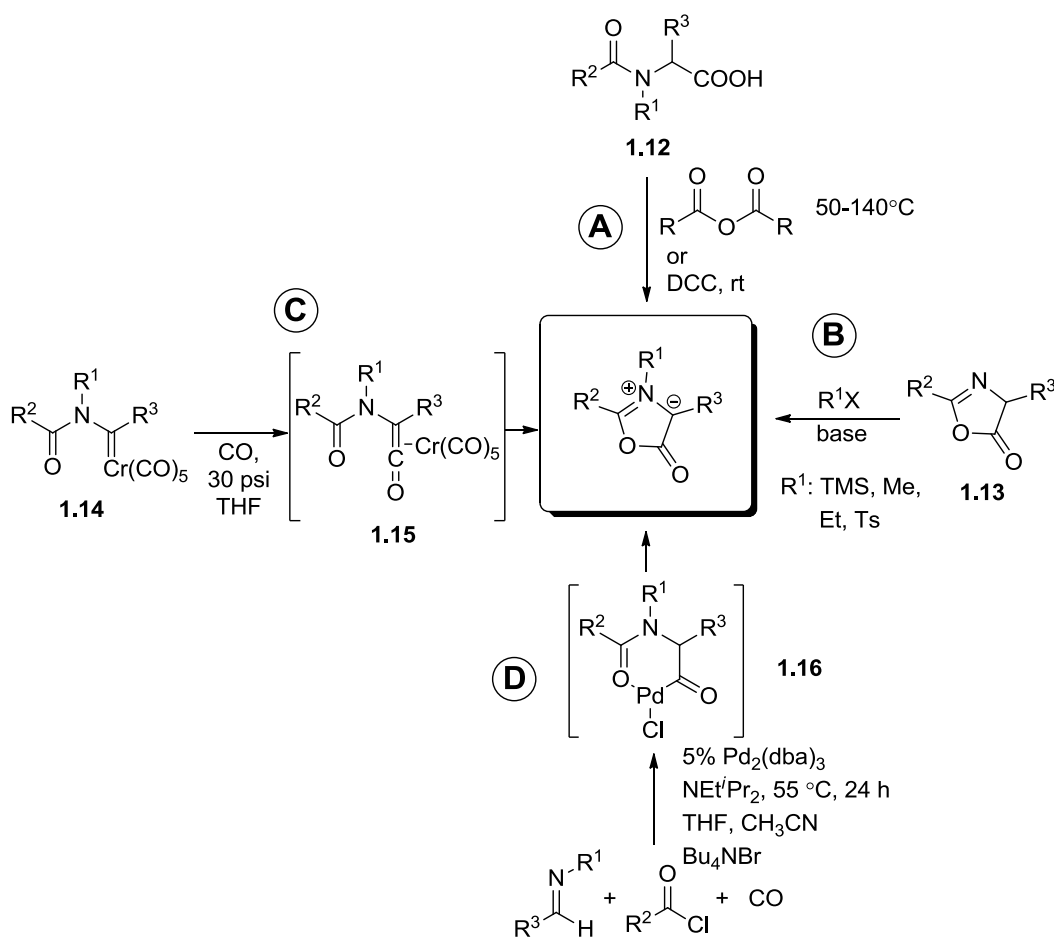


Figure 1.8: Resonance Structures of Münchnones

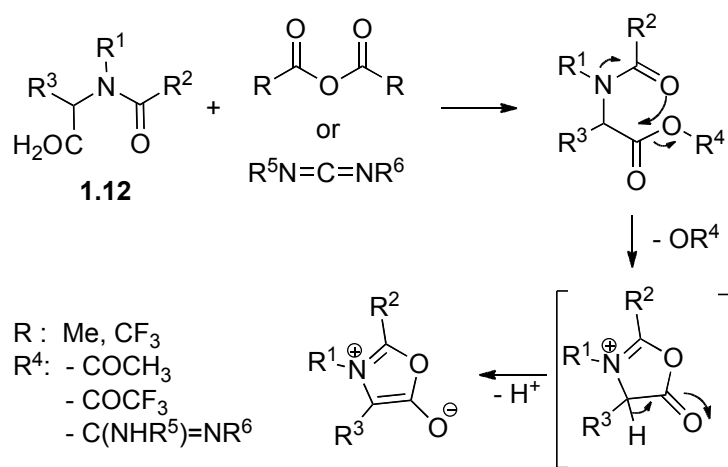
1.3.1.1 Münchnone Synthesis

Several synthetic strategies have been developed to form Münchnones. These are summarized in Scheme 1.3.



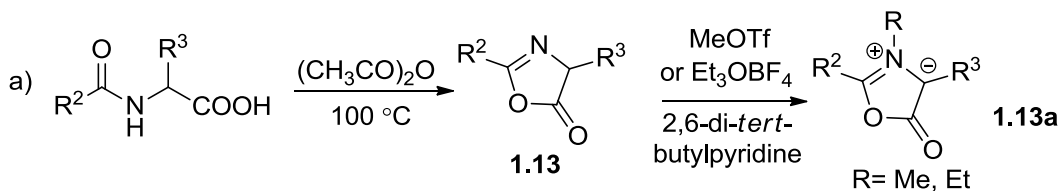
Scheme 1.3: General Methods for Münchnone Synthesis.

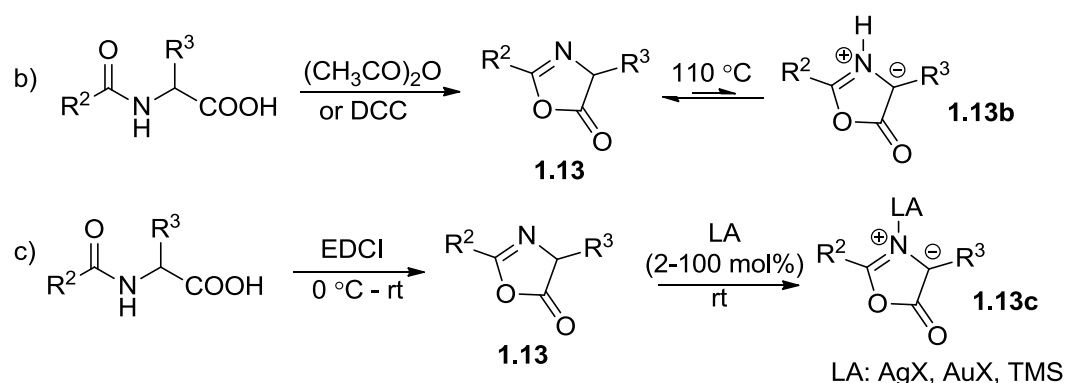
The most common route to form Münchnones involves the cyclodehydration of *N*-acylated α -amino acids **1.12**. This is usually performed with acetic- or trifluoroacetic anhydride at elevated temperature. The formation of Münchnones can also occur at room temperature in presence of a carboxylic acid activating reagent, such as *N,N'*-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).³⁷ These reactions are believed to involve the nucleophilic attack of the amide oxygen on the activated carboxylic acid. The resulting oxazolium ion is deprotonated by the leaving group (R^4O^-) to afford the Münchnone (Scheme 1.4).



Scheme 1.4: Mechanism of Cyclodehydration to form Münchnones.

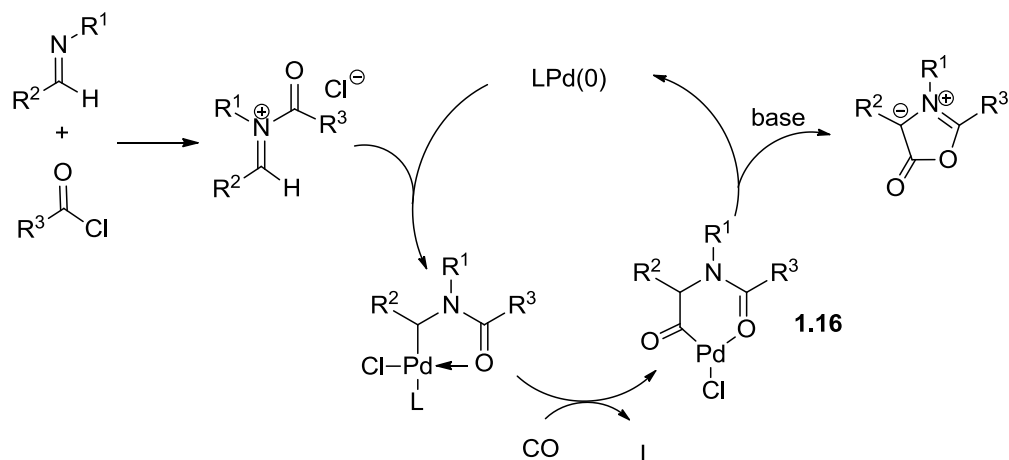
Münchnones can also be generated from oxazolones **1.13** in presence of an electrophile and base (Scheme 1.5a).³⁸ As oxazolones are themselves typically generated from α -amino acids, this represents an alternative to that shown in Scheme 1.4. The quaternization of the nitrogen can also occur by tautomerization of the oxazolone to its mesoionic form **1.13b** upon heating³⁹ or by the addition of a Lewis acid (**1.13c**, Scheme 1.5).^{40,41}





Scheme 1.5: Generation of Münchnones from Oxazolones.

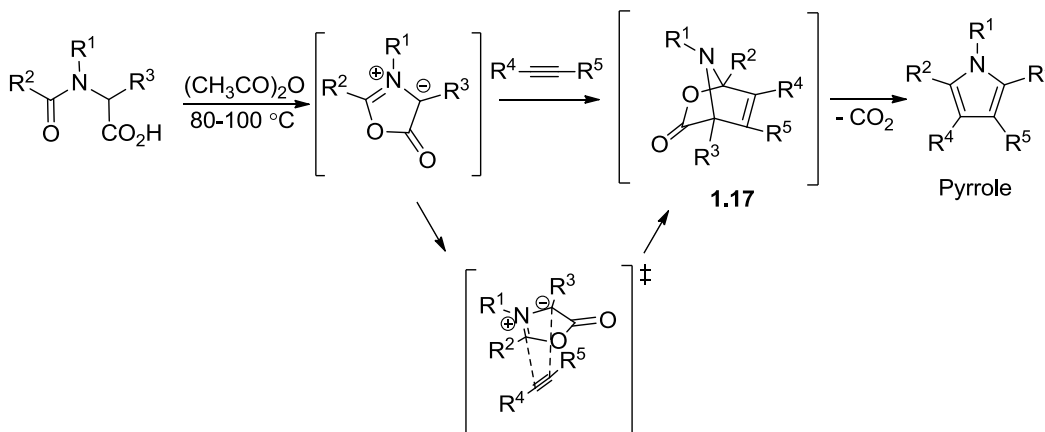
Chromium carbene complexes (**1.14**) have also been reported to behave as precursors to Münchnones (Scheme 1.3C). In these reactions, the insertion of CO is postulated to generate the metal-bound ketene **1.15**. The latter can cyclize to form Münchnone.⁴² A similar reaction has also been described with an iron complex.⁴³ Our research group reported the first transition metal catalyzed synthesis of Münchnones.⁴⁴ This involves the palladium-catalyzed multicomponent coupling of imines, acid chlorides and carbon monoxide (Scheme 1.3D). This reaction is postulated to proceed via the initial formation of an *N*-acyl iminium ion, followed by oxidative addition to palladium, and carbonylation to form intermediate **1.16**. The latter can undergo cyclization to form Münchnone and regenerate the palladium catalyst (Scheme 1.6). As imines, acid chlorides and carbon monoxide are readily available, this provides a modular synthesis of Münchnones.



Scheme 1.6: Mechanism of Palladium-Catalyzed Münchnone Synthesis

1.3.1.2 Pyrrole Formation from Münchnones

Münchnones are highly reactive 1,3-dipoles. While these compounds have been isolated, they easily revert back to α -amido acids in the presence of water. Due to their high reactivity, Münchnones are typically generated and used *in situ* in cycloaddition reactions. Münchnones can undergo cycloaddition with various dipolarophiles,⁴⁵ including: alkynes, alkenes, aldehydes, imines, thioketones, nitriles, phosphalkynes, heterocumulenes, nitroso-, nitro-, and aza-compounds. Among these, cycloadditions with alkynes, and to a lesser extent to alkenes, to form pyrroles is by far the most common. The reaction involves a concerted $[\pi^4s + \pi^2s]$ cycloaddition, where the 1,3-dipole approaches the dipolarophile in a plane orientation as illustrated in Scheme 1.7. The resulting cycloadduct **1.17** is usually not observed, and spontaneously rearranges to a pyrrole by elimination of CO_2 .



Scheme 1.7: Cycloaddition with Acetylenic Dipolarophile.

Münchnones react most rapidly with electron poor alkynes. Dimethyl acetylenedicarboxylate (DMAD) is a common alkyne used to trap these mesoionic compounds. In addition to DMAD, a broad scope of pyrroles can be obtained by reaction with different alkynes. A decrease in reactivity is observed from electron poor to electron rich alkynes (Figure 1.9).⁴⁶

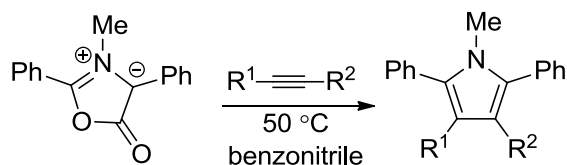
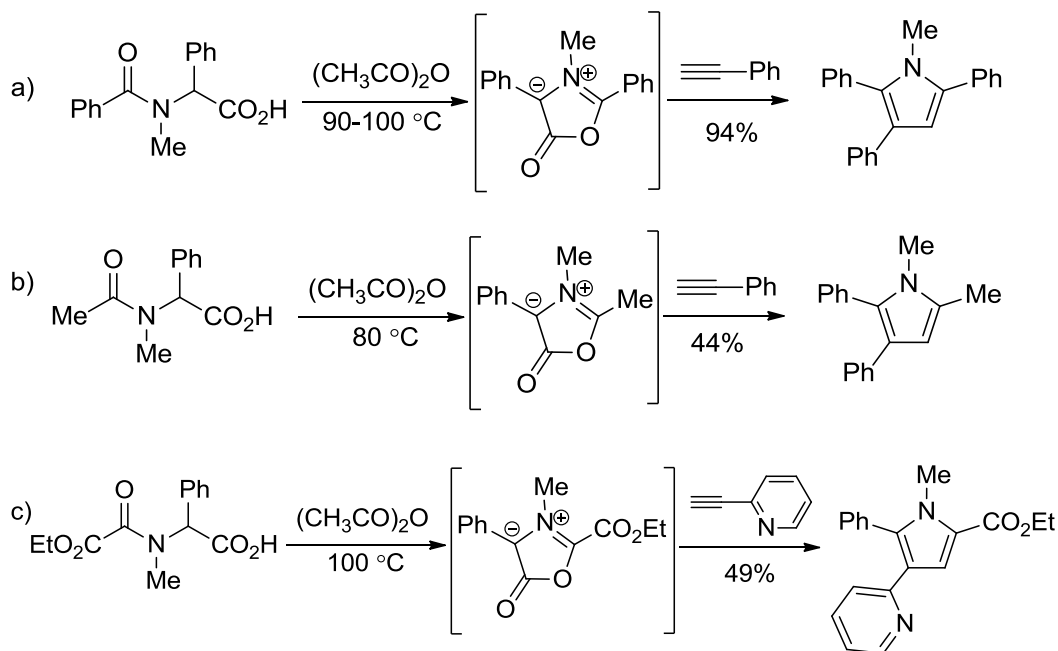
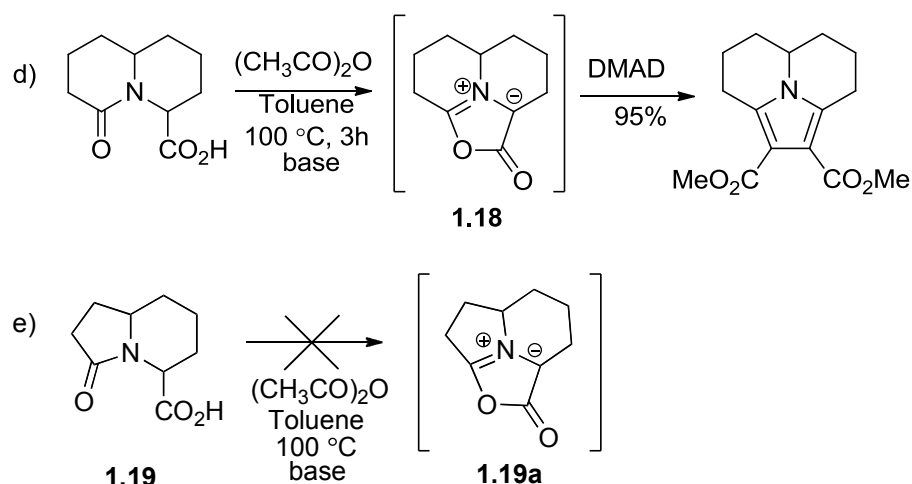


Figure 1.9: Reactivity Order of Alkynes in Cycloaddition with Münchnone
(From the most reactive to the least reactive alkynes)

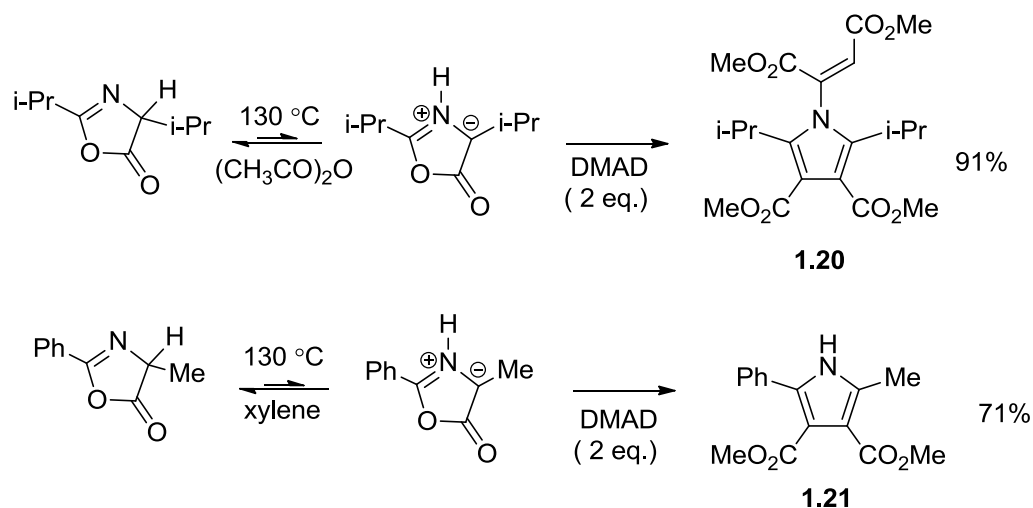
Numerous substitution variants ($\text{R}^1\text{-R}^3$) on Münchnones are possible. These ring substituents can influence both the stability of the 1,3-dipole, and its reactivity. Münchnones with aryl substituents at the C2 and C4 positions usually undergo cycloaddition to afford pyrroles in high yields.^{32,44a,47} Replacement of this substituent for other groups, such as hydrogen, methyl or esters, leads to a decrease in cycloaddition yields with arylacetylenes (Scheme 1.8a-c).^{47a,48,49} Fused-ring Münchnones have also been exploited in cycloadditions with high efficiency,⁵⁰ and even tricyclic Münchnones (**1.18**) have been successfully used in cycloaddition. However, the 5-membered ring homologue to **1.18** cannot be formed due to the excessive ring strain in cyclization of **1.19** (Scheme 1.8e).⁵¹





Scheme 1.8: Substituent effects on Münchnone Formation and Reactivity.

In the case of NH-substituted Münchnones, substituent influences are complicated by the reactivity of the pyrrole products. For example, when the Münchnone substituents at C2 and C4 are alkyl groups, the resulting pyrrole undergoes Michael addition to DMAD to afford the product **1.20**.⁵² To avoid this side reaction, one of two substituents must be an aryl group to decrease the nucleophilic character of the nitrogen. (Scheme 1.9).⁵³

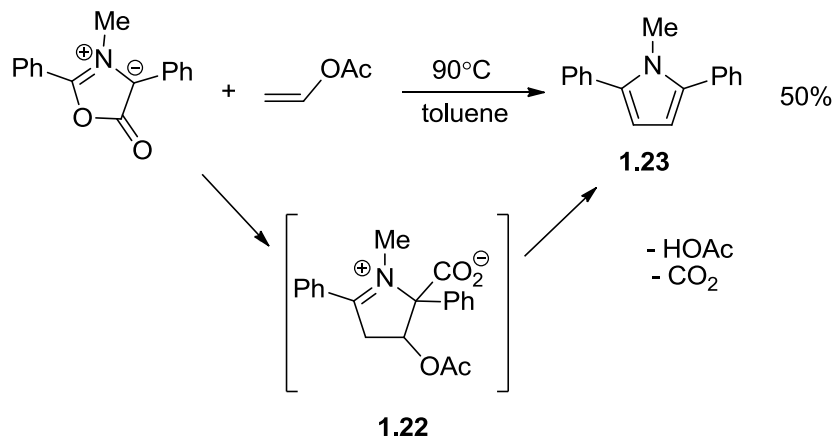


Scheme 1.9: 1,3-Dipolar Cycloaddition of Oxazolones.

The 3- and 4-substituents on the pyrrole products are derived from the alkyne. A variety of substituents can be introduced into these positions, including

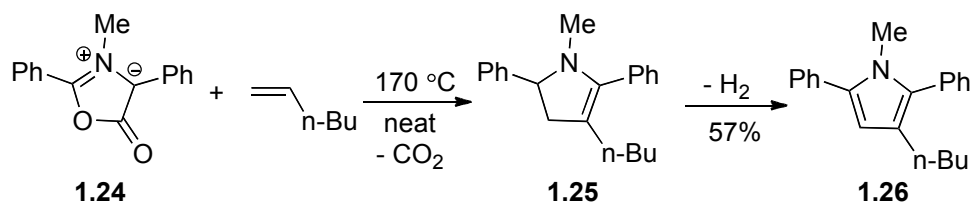
electron withdrawing units (e.g., CO₂R, CO₂H, CONHR, COR, SO₂CF₃, SO₂Ar), aromatics (arylacetylene derivatives), heteroaromatic alkynes and benzyne.⁵⁴ Electron rich alkynes with aliphatic substituents (*n*-butyl), and simple acetylene, also undergo cycloaddition, although these usually require more pressing reaction conditions.^{47a}

In addition to alkynes, alkene cycloadditions can also lead to pyrrole formation. These typically involve alkenes with electron-withdrawing leaving groups CH₂=CHX (X= OAc,⁵⁵ Cl,^{50c,47b,56} NO₂,^{55,57} CN⁵⁸ and PPh₃⁺Br⁻⁵⁹). This reaction is postulated to proceed via the formation of **1.22**, which eliminates HX and CO₂ to give the pyrrole product **1.23** (Scheme 1.10).



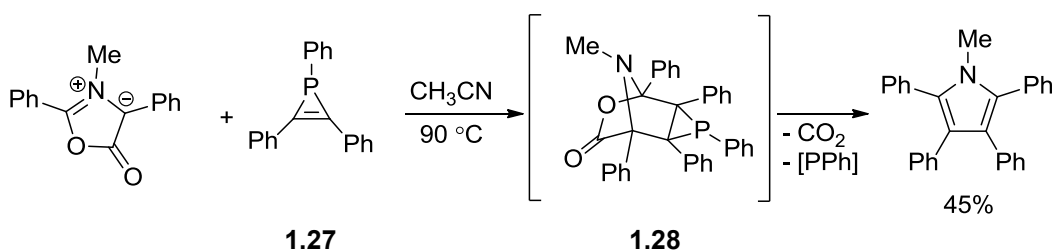
Scheme 1.10: Olefin Cycloaddition in Pyrrole Synthesis.

Electron rich alkenes undergo cycloaddition with Münchnones to generate pyrrolines. These alkenes are less prone to react with Münchnones, and require elevated reaction temperatures, which often lead to spontaneous oxidation to generate a pyrrole. For example, the cycloaddition of 1-hexene with Münchnone **1.24** at 170 °C results spontaneous oxidation to form the corresponding pyrrole **1.26** (Scheme 1.11).⁵⁵ Similar reactions to form pyrroles were observed with styrene⁵⁵ and acenaphthylene.⁶⁰



Scheme 1.11: Alkene Cycloaddition Followed by Oxidation to Pyrrole

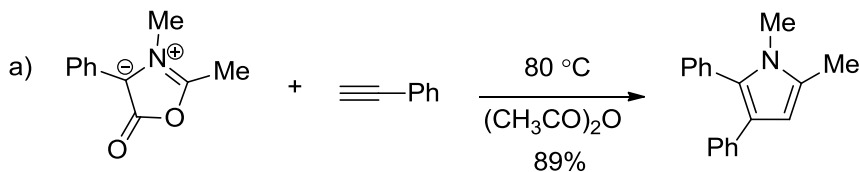
More unusual dipolarophiles have also been found to react with Münchnones to form pyrroles. For example, the higher reactivity of the strained olefin **1.27** has been exploited to form **1.28**, which eliminates phosphinidene [PPh] and carbon dioxide to form pyrrole (Scheme 1.12).⁶¹

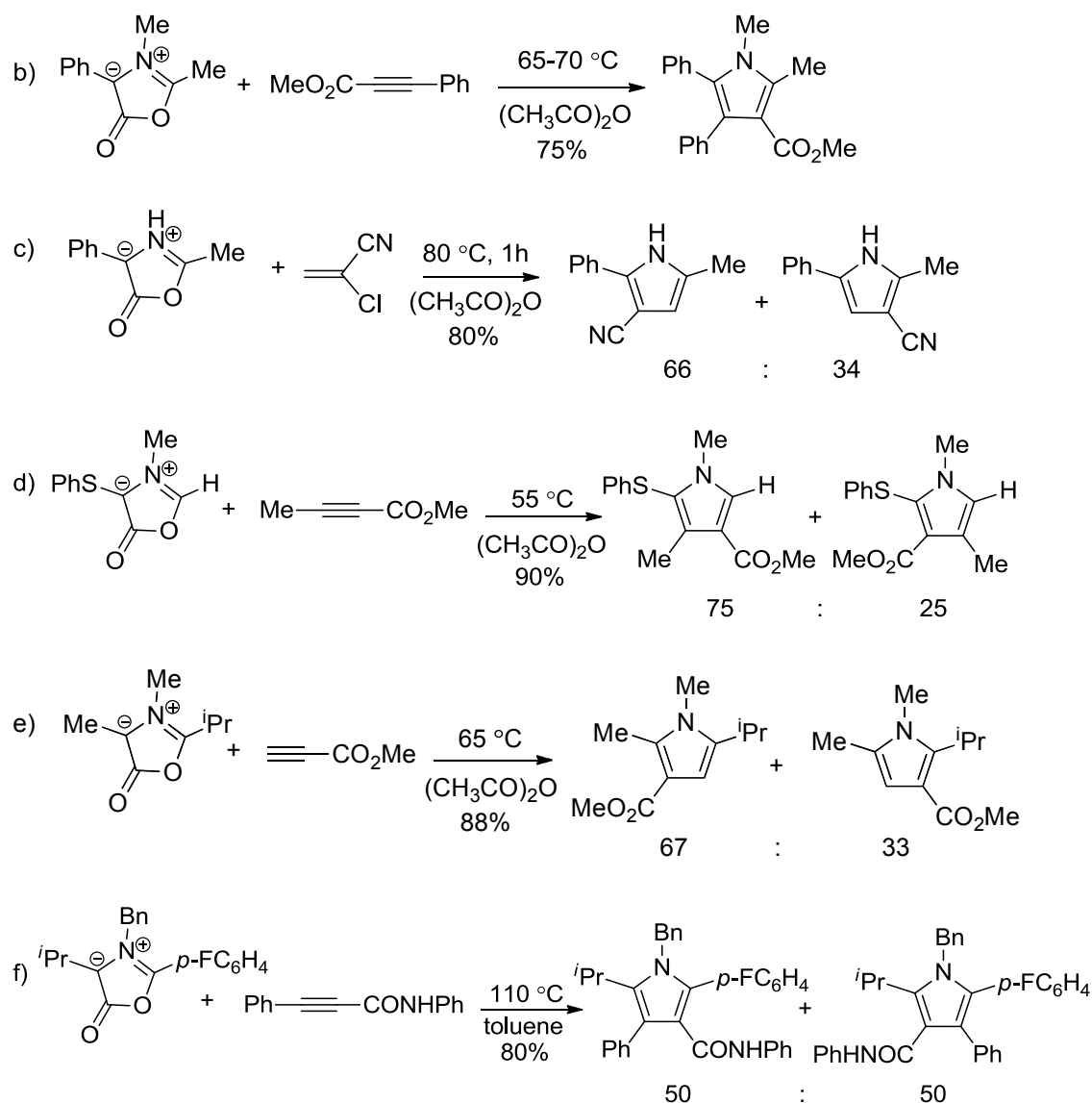


Scheme 1.12: Cycloaddition of Münchnones and Phosphirene

1.3.1.3 Regioselectivity

The cycloaddition of symmetrical Münchnones or dipolarophiles leads to only a single pyrrole product. However, reactions of unsymmetrical substrates raise the problem of regioselectivity. While some Münchnone cycloadditions are regioselective^{47a,48,57,62,59,63,64} (e.g., Scheme 1.13a,b), reactions with unsymmetrical electron poor alkynes or alkenes usually afford a mixture of regioisomers (Scheme 1.13c-g).^{33g,47b,48,50c,64,65}





Scheme 1.13: Cycloaddition with Unsymmetrical Substrates

The rapid cycloaddition of Münchnones with electron deficient dipolarophiles suggests they should display “type I” Sustmann behavior, where the HOMO-Münchnone and LUMO-dipolarophile is the controlling interaction (Figure 1.10).

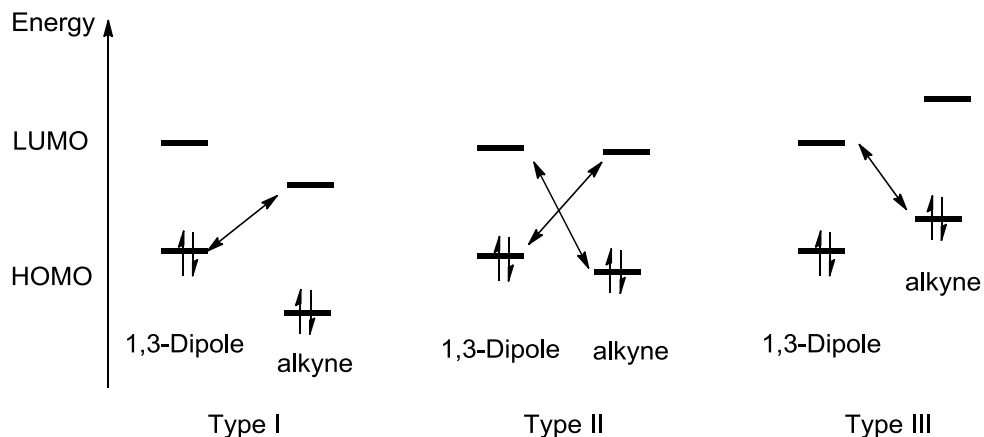


Figure 1.10: Sustmann's Classification for 1,3-Dipolar Cycloaddition Reactions

Frontier molecular orbital theory stipulates that cycloaddition should occur with the preferential combination of the atoms with larger orbital coefficients.⁶⁶ Since Münchnones have a high HOMO orbital contribution at C4 (i.e., where the negative charge is stabilized by the carbonyl),^{57,65a,65e,67} cycloadditions with electron poor alkynes should be regioselective, and strongly favor the formation of pyrrole A (Figure 1.11).

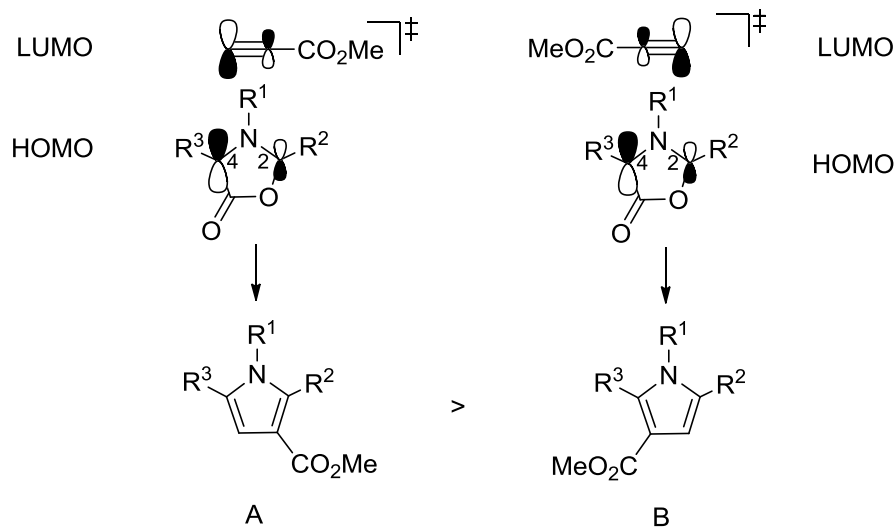
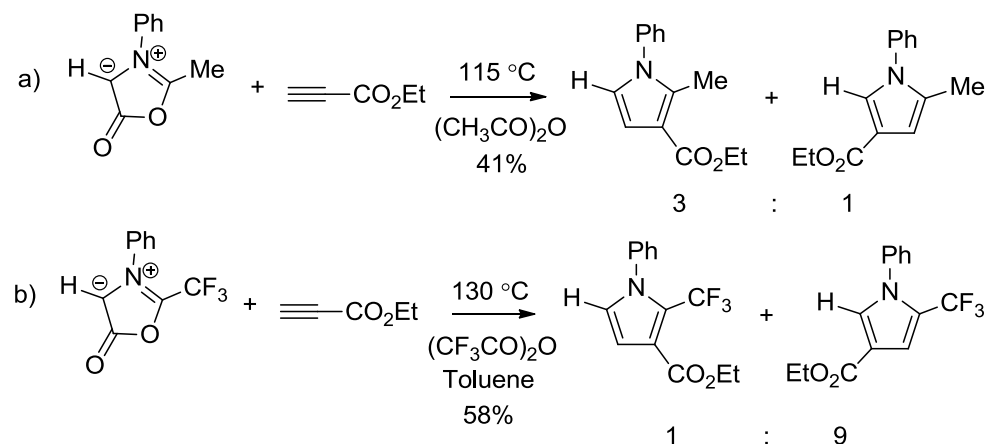


Figure 1.11: Frontier Orbital Analysis of Münchnone Cycloadditions.

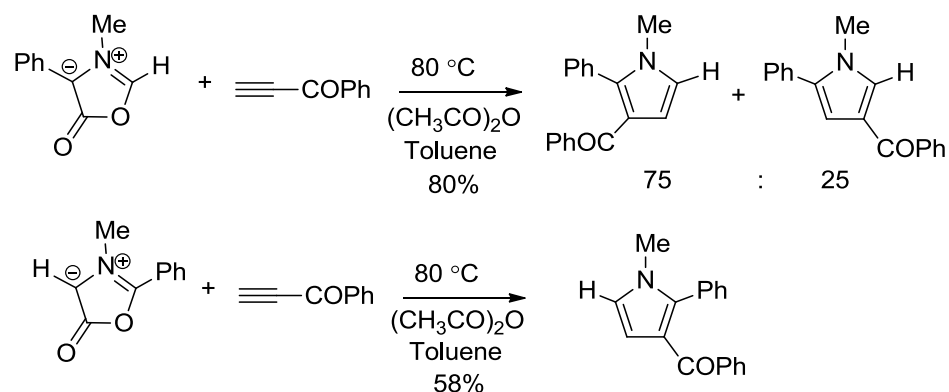
However, cycloadditions with Münchnones show low and sometimes even the opposite selectivity to that predicted by FMO theory. To probe these puzzling

results, a number of research groups have examined the influence of substituents on Münchnone cycloadditions. For example, Padwa and co-workers investigated in detail the reaction of Münchnones with methyl propiolate. They noted that the replacement of $R^2 = \text{Me}$ for $R^2 = \text{CF}_3$ results in a complete switch in pyrrole product distribution, where Münchnone substituted by a CF_3 group gives the opposite regioselectivity to that predicted by FMO analysis (Scheme 1.14).^{65e}



Scheme 1.14: Substituent Effects on Regioselectivity

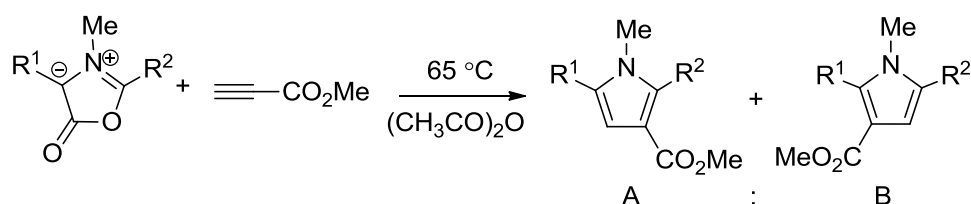
Similar cases have been reported by La Rosa (Scheme 1.15).⁴⁸ These authors came to the conclusion that the C2 and C4 substituents of the Münchnone change its HOMO polarization, leading to a change in the C2 and C4 orbital coefficients. This rational was based on experimental results, and calculations to support the theory were not performed.



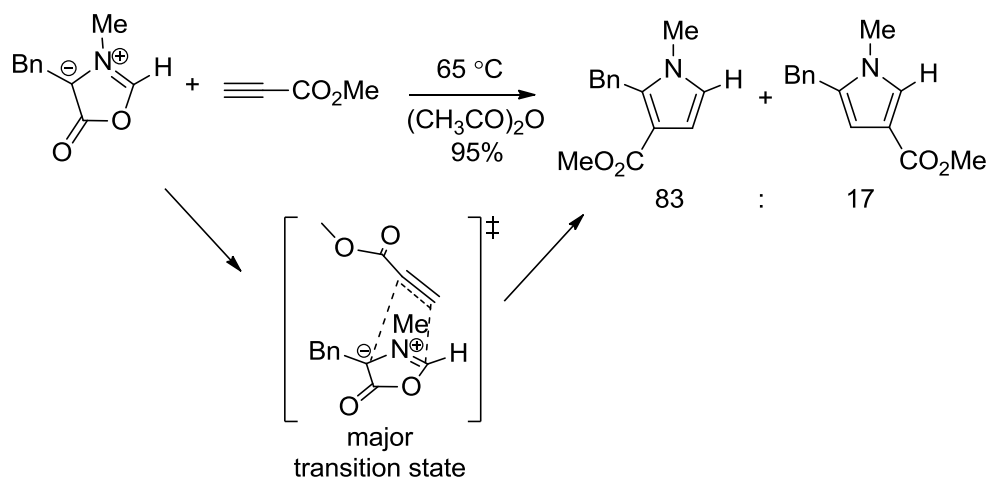
Scheme 1.15: Regioselectivity with Terminal Alkynes and Di-Substituted Münchnones

Elegant studies by Trost and co-workers illustrate the challenge of understanding and controlling M $\ddot{u}$ nchnone regioselectivity.⁶⁴ These researchers used nearly symmetrical M $\ddot{u}$ nchnones that differ only in the position of the isotopic label (C13), and obtained almost an equal mixture of the 2 regioisomers (Table 1.1, entry 1). The authors suggest that this reflects a lack of a strong electronic bias in M $\ddot{u}$ nchnones. Instead, they suggest steric influences are the controlling factor in cycloaddition, where bond formation between the two least substituted atoms leads to a favored asynchronous transition state. This affords the more sterically encumbered pyrrole as the major product (Scheme 1.16).

Table 1.1: Regioselectivity of Cycloadditions with Methyl Propiolate

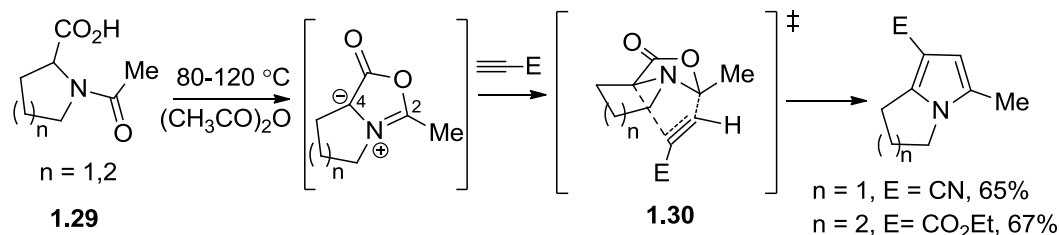


Entry	R ¹	R ²	Yield	A : B ratio
1	¹³ CH ₃	CH ₃	80%	47 : 53
2	Me	Et	64%	45 : 55
3	H	ⁱ Pr	92%	75 : 25
4	^t Bu	H	53%	33 : 67
5	ⁱ Pr	Me	84%	77 : 23



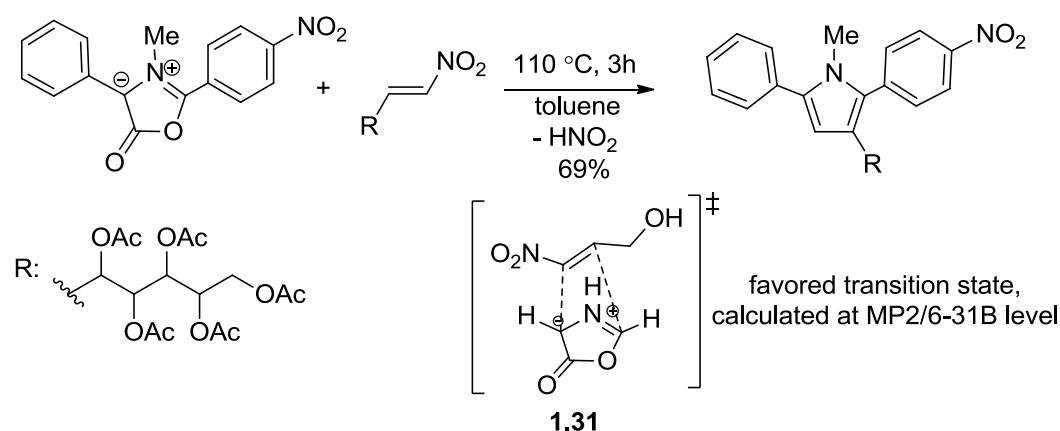
Scheme 1.16: Transition State Structures for H-Substituted M $\ddot{u}$ nchnone and Methyl Propiolate.

Coppola and co-workers suggested a related rationale for regioselectivity in cycloadditions with Münchnone **1.29** (Scheme 1.17).^{47b,50a,50d,68} In this system, the untethered C2 center can more easily pyramidalize in the transition state (**1.30**). They suggest this results in a favored asynchronous bond formation between the β -carbon of methyl propiolate and C2, the opposite product to that predicted from FMO analysis.



Scheme 1.17: Asynchronous Concerted Cycloaddition

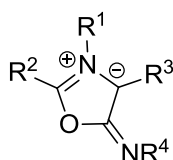
The group of Jimenez reported that the cycloaddition of Münchnone with nitroalkenes generates only a single pyrrole product after elimination of HNO_2 , but with completely “anti-FMO” selectivity.⁵⁷ High level molecular orbital calculations (MP2/6-31B) agree with the experimental results, and suggest a slightly asynchronous concerted cycloaddition pathway **1.31** (Scheme 1.18).



Scheme 1.18: Regioselectivity of Cycloadditions Between Nitroalkenes and Münchnones.

Overall, these studies have led to the conclusion that FMO theory does not accurately predict the regioselectivity outcome of Münchnone cycloadditions. Instead, factors such as sterics, geometry of the transition state, or interactions between substituents, can play a more important role in determining the product distribution. These aspects have made it difficult to predict and control regioselectivity in alkyne and alkene cycloaddition reactions.

1.3.2 Münchnone Imines (1,3-Oxazolium 5-imines)



1.32

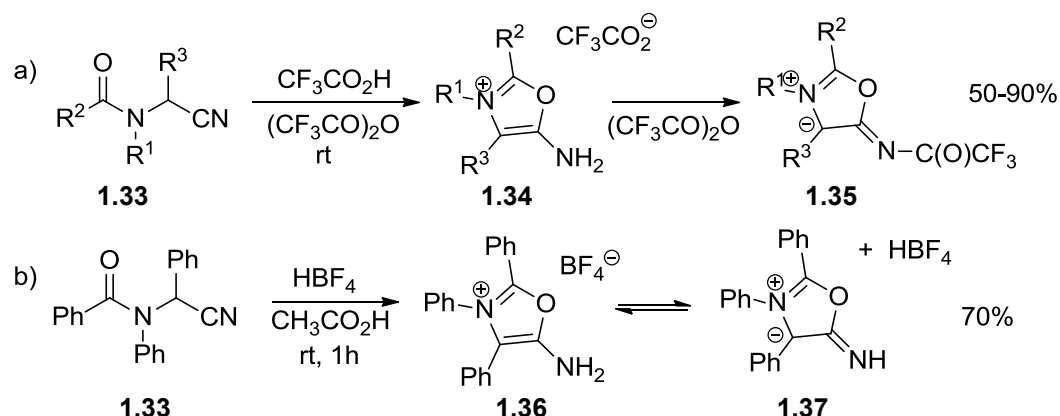
Figure 1.12: Münchnone Imine

The replacement of the exocyclic oxygen of Münchnones by a nitrogen creates a new mesoionic molecule **1.32**, commonly referred to as a Münchnone imine (Figure 1.12). As with Münchnones, these substrates can also undergo 1,3-dipolar cycloaddition reactions.

1.3.2.1 Synthesis

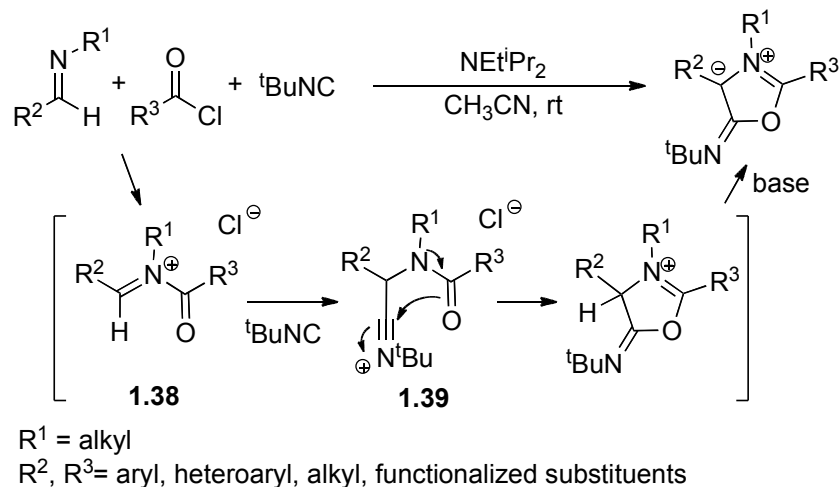
The most common synthetic precursor to Münchnone imines are α -acylaminonitriles (**1.33**). These compounds cyclize under acidic conditions (e.g., with $\text{CF}_3\text{CO}_2\text{H}$, $\text{CH}_3\text{CO}_2\text{H}$, ClSO_3H , or HCl) to form the salt **1.34** via intramolecular nucleophilic attack of the carbonyl oxygen to the nitrile carbon. Subsequent treatment of **1.34** with acid anhydride provides the Münchnone imine **1.35**.⁶⁹ The cyclization of **1.33** to **1.35** can also occur in a one pot process in the presence of trifluoroacetic acid and trifluoroacetic anhydride mixture (Scheme 1.19a).^{69d} This approach generates only N-acylated Münchnone imines, which

are isolable and stable molecules. A similar approach involves the treatment of **1.33** with hydrofluoroboric acid to form the corresponding oxazolium salt **1.36**, which exists in equilibrium with the mesoionic structure **1.37** (Scheme 1.19b).⁷⁰ The use of the strong acid HBF₄ allows the isolation of **1.36** as a stable salt.



Scheme 1.19: Münchnone-Imine Synthesis

More recently, it has been reported by our group that Münchnone imines can be formed from a three component reaction of acid chlorides, imines and isocyanides (Scheme 1.20).⁷¹ The reaction involves the *in situ* formation of the *N*-acyliminium salts **1.38**, which react with the isocyanide to form the nitrilium chloride **1.39**. This intermediate undergoes ring closure and deprotonation to form Münchnone imines. Various substituted Münchnone imines can be generated by this method.

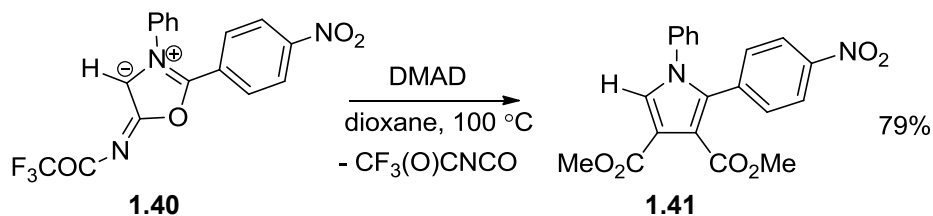


Scheme 1.20: Isocyanide-Mediated Synthesis of Münchnone Imines.

1.3.2.2 Cycloaddition Reactions to Form Pyrroles

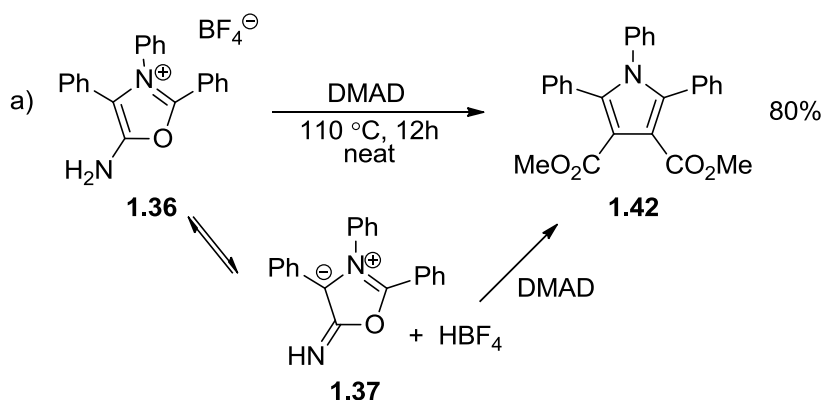
In comparison with Münchnones, Münchnone imines have been less intensively studied in cycloaddition reactions. Nevertheless, reports have demonstrated that these 1,3-dipoles can undergo cycloaddition with alkynes to form pyrroles. As with Münchnones, cycloaddition is most rapid with electron deficient dipolarophiles.

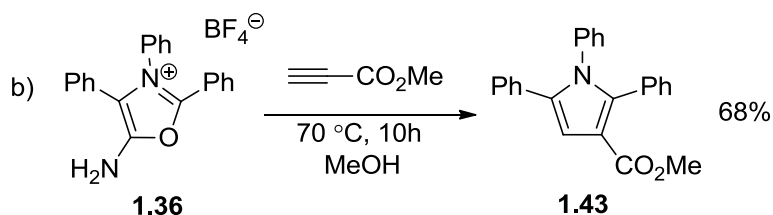
As mentioned above, *N*-acylated Münchnone imines are stable molecules and can be isolated. Treatment of the isolated Münchnone imine **1.40** with DMAD in refluxing dioxane produces the pyrrole **1.41** together with trifluoroacetyl isocyanate in very good yield.^{69d}



Scheme 1.21: Pyrrole Synthesis from Isolated Münchnone Imine.

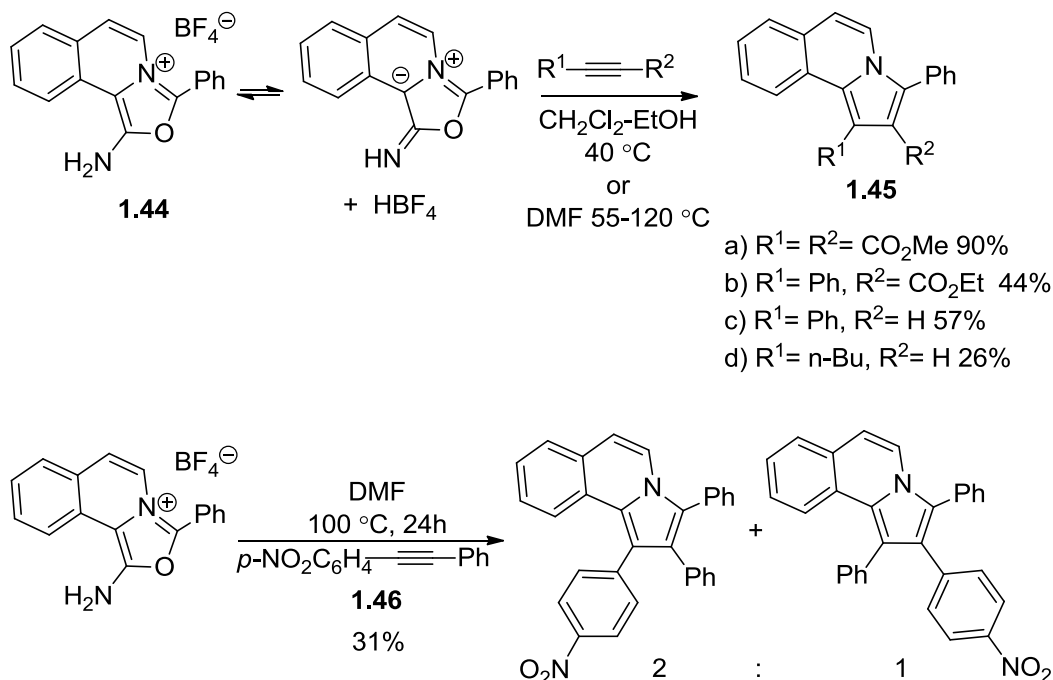
Pyrroles can also be obtained from the oxazolium salt **1.36** (Scheme 1.19b). Thermolysis of the latter is believed to generate *in situ* Münchnone imine **1.37**, which is trapped by reaction with DMAD or methyl propiolate to yield pyrroles **1.42** and **1.43** respectively (Scheme 1.22).⁷⁰





Scheme 1.22: Pyrrole Synthesis from Tautomeric Intermediate

The easily synthesized isoquinoline-derived Reissert compounds can also serve as precursors to Münchnone imines, and undergo cycloaddition reactions. Thus, the treatment of **1.44** with alkyne leads to the formation of polycyclic pyrroles (Scheme 1.23).⁷² Cycloaddition with unsymmetrical alkynes shows similar regioselectivity trends to that observed with Münchnones, where a single regioisomer product is obtained upon cycloaddition with phenyl propiolate,^{72a,72b} phenyl acetylene,^{72d} and 1-hexyne^{72e} (products **1.45a-d**, Scheme 1.23). However, more electron poor alkynes such as **1.46** produce a mixture of regioisomers.^{72c}



Scheme 1.23: Pyrrole Diversity from the Reaction of Reissert Salt with Alkynes

Reissert compounds can be prepared from a variety of heterocycles. This provides an attractive approach to create a range of polycyclic pyrroles.^{72e,73} Examples are shown in Figure 1.13:

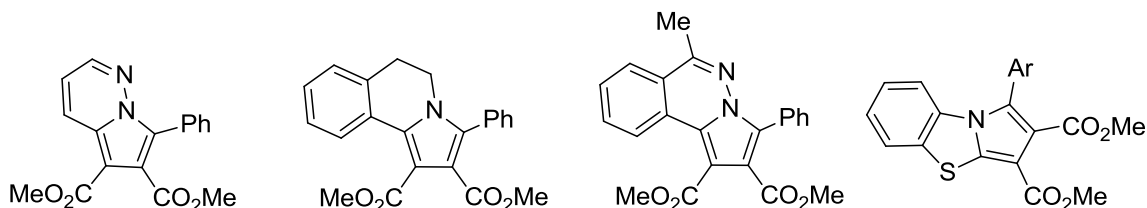


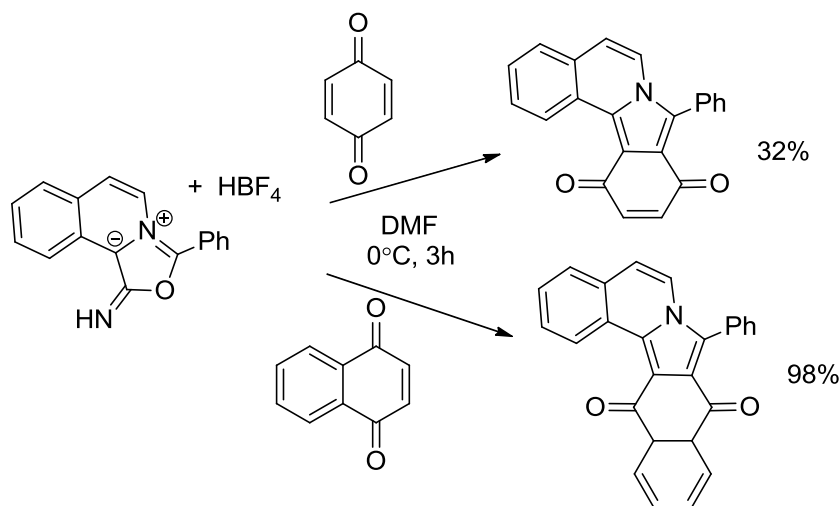
Figure 1.13: Fused-Ring Pyrroles

The multicomponent generation of Münchnone imines from imines, acid chlorides and isocyanides can be coupled with alkyne cycloaddition to form pyrroles in a one pot process (Table 1.2).⁷¹ A range of imines and acid chlorides can be incorporated into this reaction. However, only electron poor alkynes were observed to undergo cycloaddition.

Table 1.2: Diversity of Pyrroles from Imines, Acid Chlorides and Alkynes.

$ \begin{array}{c} \text{R}^1 \\ \text{N} \\ \text{R}^2 \text{C}=\text{H} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^3 \text{C}-\text{Cl} \end{array} + \text{R}^4-\text{C}\equiv\text{C}-\text{EWG} \xrightarrow[\text{CH}_3\text{CN, rt, 19h}]{\text{tBuNC, NEtPr}_2} \begin{array}{c} \text{R}^1 \\ \text{N} \\ \text{R}^2 \text{C}=\text{C}(\text{R}^3)-\text{C}(\text{R}^4)-\text{EWG} \end{array} $						
#	R ¹	R ²	R ³	EWG	R ⁴	Yield (%)
1	Bn	4-MeC ₆ H ₄	Ph	CO ₂ Me	CO ₂ Me	85
2	Allyl	4-MeOC ₆ H ₄	4-IC ₆ H ₄	CO ₂ Me	CO ₂ Me	80
3	Hexyl	4-MeC ₆ H ₄	4-MeC ₆ H ₄	CO ₂ Me	CO ₂ Me	71
4	propargyl	4-MeC ₆ H ₄	4-MeC ₆ H ₄	CO ₂ Me	CO ₂ Me	57
5	Et	thiophenyl	Ph	CO ₂ Me	CO ₂ Me	67
6	Bn	isopropyl	Ph	CO ₂ Me	CO ₂ Me	72
7	allyl	4-FC ₆ H ₄	thiophenyl	CO ₂ Me	CO ₂ Me	65
8	Bn	4-MeC ₆ H ₄	3-methylbutyl	CO ₂ Me	CO ₂ Me	81
9	Bn	4-MeC ₆ H ₄	4-MeC ₆ H ₄	CO ₂ Me	H	65
10	Bn	4-MeC ₆ H ₄	4-MeC ₆ H ₄	COPh	COPh	61
11	Bn	4-ClC ₆ H ₄	4-ClC ₆ H ₄	COPh	COPh	49

Only two examples of alkene cycloadditions to Münchnone imines have been reported. These involve the reaction with benzoquinone and 1,4-naphthoquinone, and leads to pyrroles in 32% and 98% yield respectively (Scheme 1.24).⁷⁴



Scheme 1.24: Alkene Cycloaddition with Münchnone Imine to Form Pyrroles

1.3.3 Other Mesoionic Heterocycles used in Pyrrole Synthesis

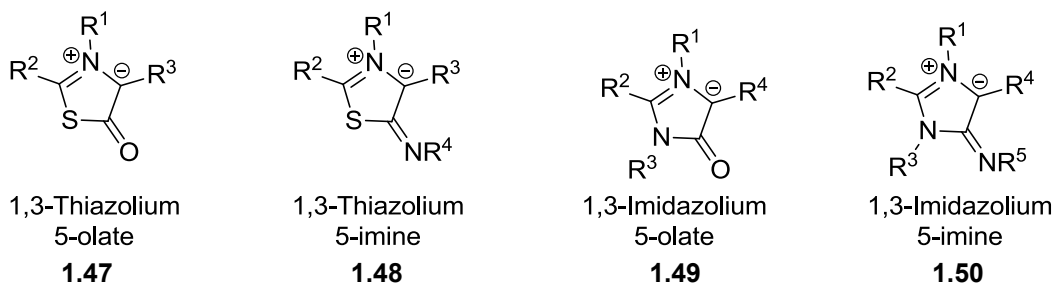


Figure 1.14: Structure of Other Mesoionic Heterocycles

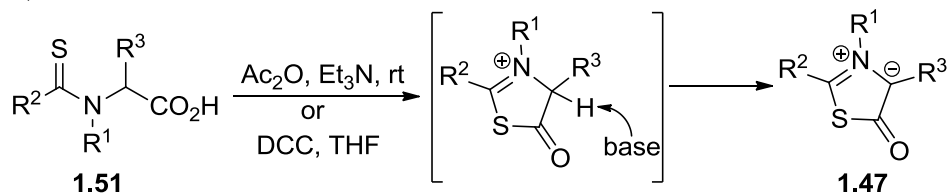
Münchnones and Münchnone imines are the most common mesoionic heterocycles employed in pyrrole synthesis. Nevertheless, a number of other variants of these 1,3-dipoles have been developed. The most common examples are thiazolium- and imidazolium-based mesoionic heterocycles (Figure 1.14), where the oxygen atom in the oxazole ring of Münchnones is exchanged for sulfur or nitrogen atoms. These dipoles are often less reactive in 1,3-dipolar

cycloaddition reactions, and/or more challenging to prepare than Münchnones. Thus, they have been less studied in pyrrole synthesis.

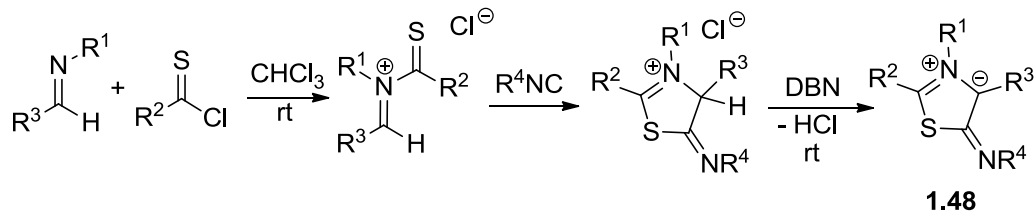
1.3.3.1 Syntheses

The common routes used to synthesize **1.47-1.50** are represented in Scheme 1.25. These reactions are similar to those reported for the formation of Münchnones or Münchnone imines. For example, the addition of acetic anhydride or DCC to **1.51** has been used to prepare a series of 1,3-thiazolium 5-olate derivatives **1.47** (Scheme 1.25a).⁷⁵ The mesoionic compound **1.48** can be generated by a three component reaction of imines, chlorothioformate and isocyanide under basic conditions (Scheme 1.25b).⁷⁶ The assembly of the precursors to imidazolium mesoionic heterocycles is more complex, and typically involves the condensation of benzamide **1.52** with bromoacetylchloride **1.53**^{77,78,79} or bromoacetonitrile **1.54**,^{80,81} which undergo cyclization under basic conditions (Scheme 1.25c, d).

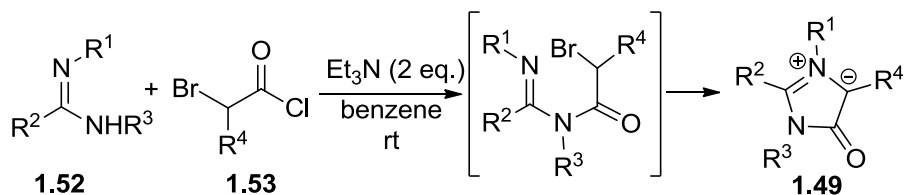
a) 1,3-Thiazolium 5-olate



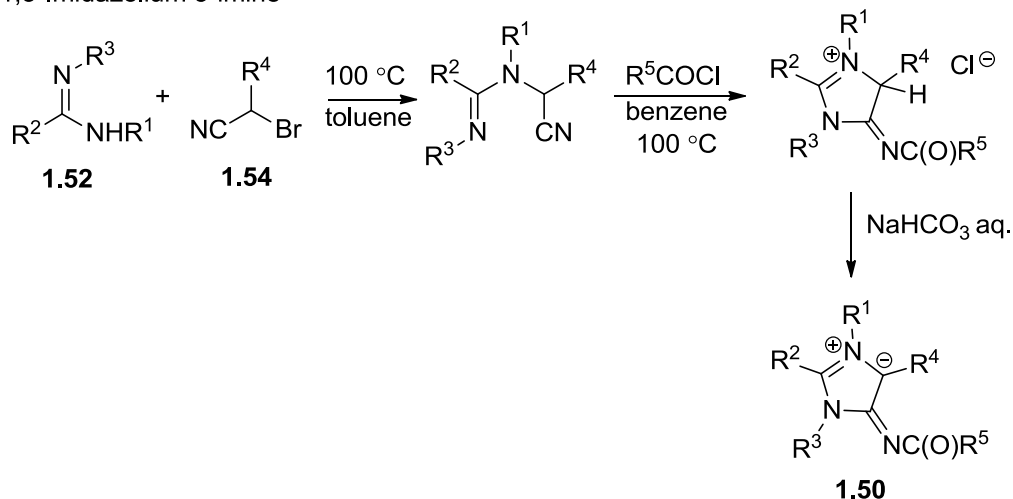
b) 1,3-Thiazolium 5-imine



c) 1,3-Imidazolium 5-oate



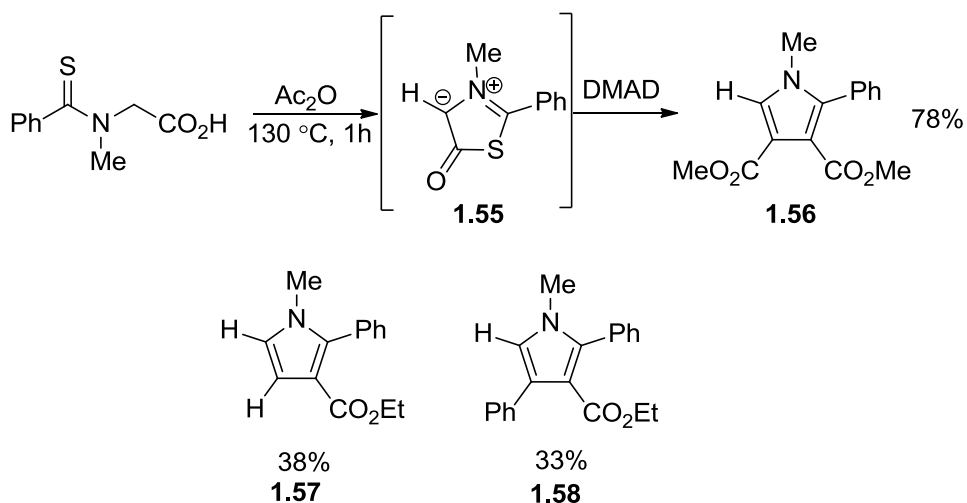
d) 1,3-Imidazolium 5-imine



Scheme 1.25: Syntheses of Thiazolium- and Imidazolium-based Mesoionic Heterocycles

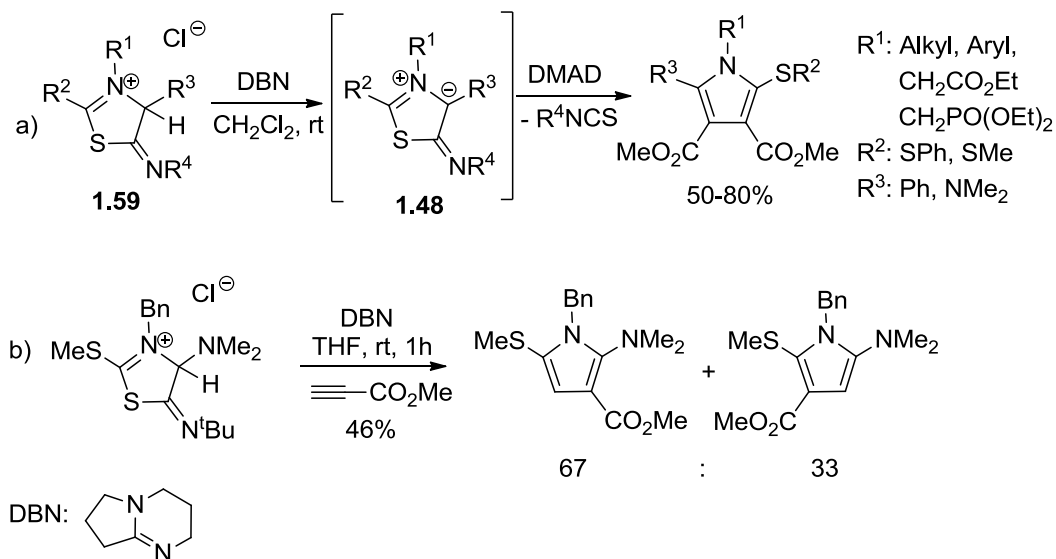
1.3.3.2 Syntheses of Pyrroles

The mesoionics **1.47-1.50** can all react with dipolarophiles (alkynes and alkenes) to generate pyrroles. **1.47** and **1.48** are reactive dipoles, and difficult to isolate. However, these can be used *in situ* in cycloaddition reactions. For example, the formation of 1,3-thiazolium 5-olate **1.55** in the presence of DMAD leads to the synthesis of pyrrole **1.56** in good yield. This reaction can also be performed with other alkynes (e.g., ethyl propiolate or ethyl phenylpropiolate), each yielding single pyrrole regioisomers **1.57** and **1.58**.⁸²



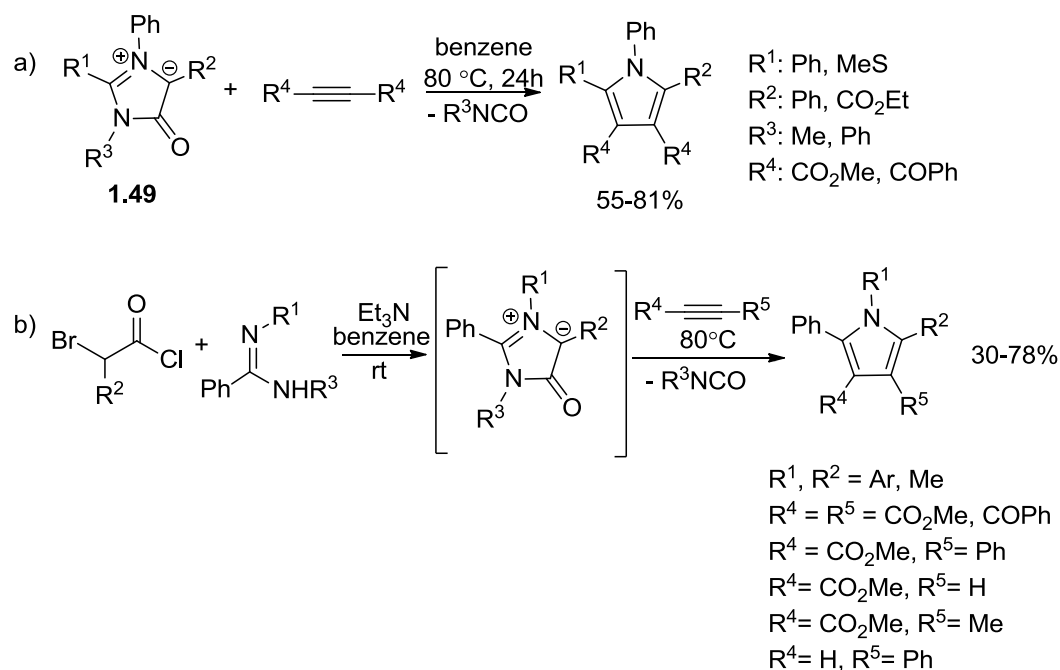
Scheme 1.26: 1,3-Dipolar Cycloaddition of 1,3-Thiazolium 5-olate

1,3-Thiazolium 5-imines **1.48** also undergo 1,3-dipolar cycloadditions with electron poor dipolarophiles.^{83,84} Their reactivity has been investigated with the salts **1.59** and the standard alkyne, DMAD, in the presence of base (Scheme 1.27a).⁸⁴ The reactions proceed very quickly with elimination of the isothiocyanate and formation of pyrroles in good yields. The unsymmetrical alkyne, methyl propiolate was also employed as a dipolarophile resulting in a mixture of pyrrole regioisomers similar to Münchnone cycloadditions (Scheme 1.27b).



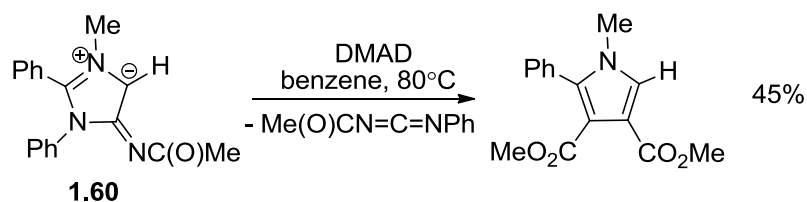
Scheme 1.27: 1,3-Dipolar Cycloaddition of 1,3-Thiazolium 5-imines.

The 1,3-imidazolium 5-olates **1.49-1.50** (Figure 1.14) are more stable mesoionic heterocycles, and in some cases can be isolated and stored at 0 °C without decomposition. Cycloaddition reactions with the isolated⁷⁸ or the *in situ* generated⁷⁷ imidazolium 5-olates **1.49** and electron poor alkynes gives pyrroles in good yields (Scheme 1.28). A useful feature of this mesoionic ring is that the nitrogen substituent of the leaving group isocyanide can be modulated to improve the reactivity of the 1,3-dipole. For example, in cycloaddition reaction with DMAD, the elimination of methyl isocyanate ($R^3 = \text{Me}$) instead of phenyl isocyanate ($R^3 = \text{Ph}$) increases the yield from 55% to 72%.⁷⁸



Scheme 1.28: 1,3-Dipolar Cycloaddition of 1,3-Imidazolium 5-olates

The reactivity of the 1,3-imidazolium 5-imine **1.50** appears lower than the previous mesoionic rings. Only one example of this reaction has been reported, where the cycloaddition of isolated 1,3-imidazolium 5-imines **1.60** with DMAD provides pyrrole in moderate yield (Scheme 1.29).⁸¹

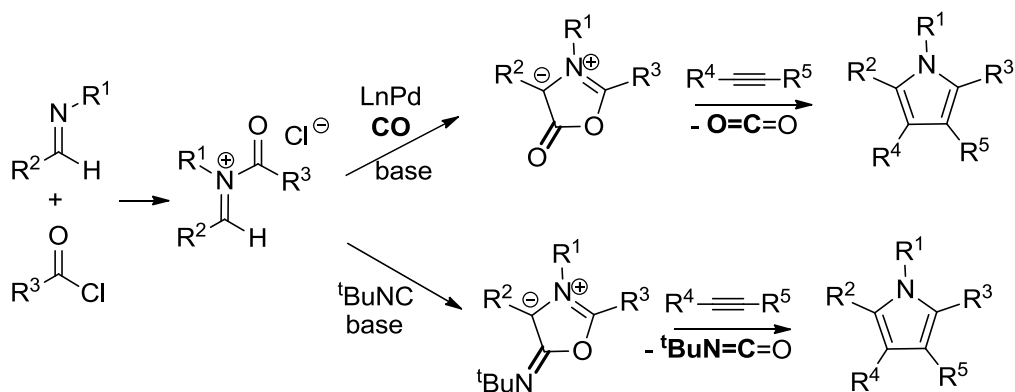


Scheme 1.29: 1,3-Dipolar Cycloaddition of 1,3-Imidazolium 5-Imine

1.3.4 Phospha-Münchnones

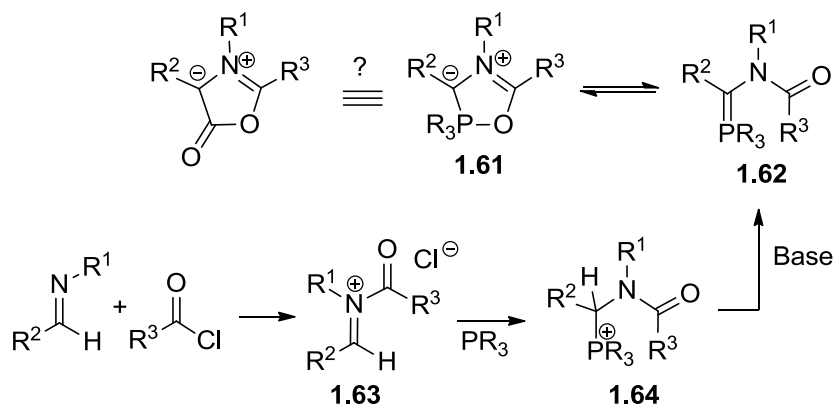
As described in the previous sections, 1,3-dipolar cycloaddition with mesoionic heterocycles can provide an attractive approach to synthesize pyrroles. However, several challenges remain in these reactions. Firstly, the generation of diversely substituted 1,3-dipoles can be an involved, multistep process. Some exceptions to this exist, such as the synthesis of Münchnones by cyclodehydration of α -amido acids (Scheme 1.4), or by palladium-catalyzed multicomponent reactions of imines, acid chlorides and carbon monoxide (Scheme 1.6). However, the scope of these approaches is limited to available naturally occurring α -amino acids, or aryl- and tertiary-alkyl substituted imine and acid chloride reagents, respectively. Secondly, cycloadditions of the mesoionic heterocycles described above with unsymmetrical alkynes often lead to a mixture of regioisomers.

Our research group has recently become interested in developing a new type of 1,3-dipole that would overcome these limitations. We noted from the palladium-catalyzed multicomponent Münchnone synthesis, and the isocyanide-mediated Münchnone imine formation (Scheme 1.30), that CO or isocyanide are not incorporated into the final pyrrole molecule, and are instead eliminated in their oxidized form, CO₂ and RN=C=O, respectively. As such, another reagent capable of undergoing oxidation could replace those units.



Scheme 1.30: Multicomponent Münchnone and Münchnone Imine Syntheses

Phosphine PR_3 reagents are very prone to form phosphine oxides $\text{R}_3\text{P}=\text{O}$. The replacement of the exocyclic $\text{C}=\text{O}$ or $\text{C}=\text{N}^t\text{Bu}$ in the mesoionic ring by a PR_3 unit gives the new organophosphorus heterocycles **1.61**. While appearing complicated, **1.61** is an isomeric form of an amido-substituted Wittig-type reagent **1.62** (Scheme 1.31). The former can be obtained in similar approach to Münchnones and Münchnone imines in a simple, three component reaction of imines, acid chlorides and a PR_3 reagent.



Scheme 1.31: General Pathway to Phospha-Münchnone

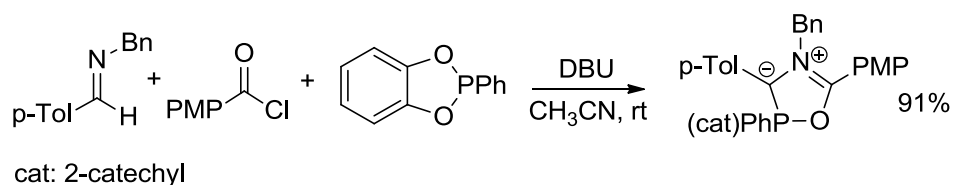
This reaction was tested first with Ph_3P . While **1.62** can be formed in quantitative yield with PPh_3 , no cycloaddition was observed in the presence of chloroacrylonitrile (Table 1.3, entry 1).⁸⁵ The lack of cycloaddition reactivity was postulated to arise from the electron rich phosphine, which could prevent chelation with the oxygen to form the 1,3-dipole **1.61**. To address this, more

electron poor phosphonites and phosphites were examined. As shown in entries 3-6, these do indeed allow cycloaddition to occur, leading to the formation of pyrrole in good to excellent yields.

Table 1.3: Effect of PR₃ reagent on Cycloaddition

#	PR ₃	Temperature	Time	Yield (%)
1	PPh ₃	80 °C	-	0
2	Ph ₂ P(OPh)	80 °C	-	0
3	PhP(OPh) ₂	65 °C	48 h	80
4	PhP(O- <i>p</i> -CNC ₆ H ₄) ₂	50 °C	11 h	81
5	P(OPh) ₃	23 °C	15 h	53
6	PhP(2-catechyl)	23 °C	1 h	95

Various phosphorus reagents were examined and (2-catechyl)PPh was found to be the most effective at mediating cycloaddition. This was attributed to the electronic nature of the phosphorus, which was sufficiently electron rich to react with the *in situ* generated N-acyl iminium salt, while being electron poor enough to allow cyclization to form **1.61**. In addition, the geometrical constraint of the catechyl ring helps to favor the trigonal bipyramidal **1.61** as a reactive intermediate.⁸⁶ The (2-catechyl)PPh-based **1.61** can be prepared and isolated (Scheme 1.32), and has been characterized by ³¹P NMR,⁸⁵ theoretical calculations,⁸⁷ and more recently X-ray crystallography (Chapter 3). All of these show that **1.61** can be considered as a new class of 1,3-dipole, a phosphamünchnone.

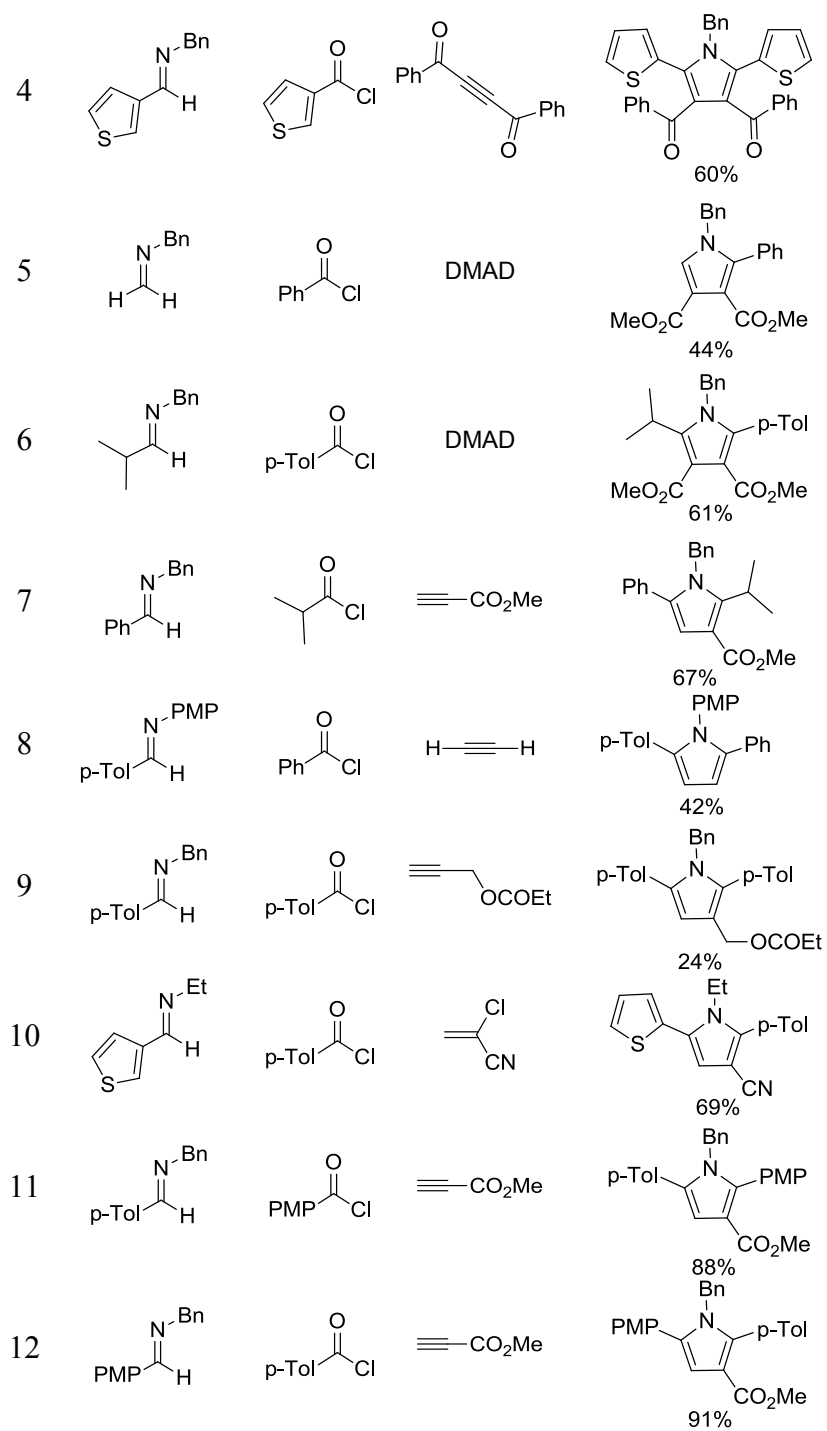


Scheme 1.32: Phospha-Münchnone Synthesis

Phospha-Münchnone **1.61** is readily generated in a modular fashion (Table 1.4). Moreover, it is formed much more rapidly than our previously reported multicomponent synthesis of Münchnones, often within minutes at ambient temperature. As a result, less stable reagents can be used, including enolizable imines (entry 6), formaldimines (entry 5), or acidic acid chlorides (entry 7). In addition, and in contrast to the reactivity of the mesoionic heterocycles described above, cycloadditions with unsymmetrical alkynes/alkenes (entries 2, 3, 7 and 9-12) proceed with the total control of regioselectivity. This is attributed to the PR_3 unit, and was postulated to result from a higher electronic bias across the 1,3-dipole. With the modular synthetic pathway and high regioselectivity, this approach gives facile access to a diverse variety of substituted pyrroles.

Table 1.4: Pyrrole Diversity through Phospha-Münchnone Cycloadditions

$ \begin{array}{c} \text{R}^2\text{C}=\text{N}^+\text{R}^1 + \text{R}^3\text{C}(=\text{O})\text{Cl} + \text{Ph-O-P(Ph)-O-Ph} \\ \xrightarrow[\text{rt}]{\text{DBU, CHCl}_3} \left[\text{R}^2\text{C}^-\text{N}^+\text{R}^1\text{C}(\text{R}^3)\text{O-P(Ph)-O-Ph} \right] \\ \xrightarrow[\text{-(cat)PhP=O}]{\text{R}^4\text{C}\equiv\text{C}\text{R}^5} \text{Pyrrole} \end{array} $				
#	Imine	Acid Chloride	Alkyne	Pyrrole
1			DMAD	 85%
2				 89%
3				 74%



1.4 Overview of Thesis

Cycloaddition reactions of Münchnones and their derivatives provide a convergent synthesis of pyrroles. Each of the mesoionic heterocycles highlighted in this chapter have their own strengths and weaknesses. Frequent issues with these systems arise from the multistep synthesis of the precursors, and the lack of regioselectivity in cycloaddition. In this regard, the results obtained with phosphamünchnones (section 1.3.4) are promising. These dipoles are formed from readily available starting materials, where they exhibit similar and even superior reactivity to Münchnones (e.g., high regioselectivity).

In light of these results, we have investigated in more detail (Chapter 2) the regioselectivity of phosphamünchnone cycloaddition and compared this to related mesoionic systems (Münchnones and Münchnone imines). Cycloaddition reactions were performed with a broad scope of unsymmetrical electron poor and electron rich alkynes, and the results were analyzed by DFT calculations in collaboration with Dr. Krenke and Pr. Houk (UCLA). These studies provide a rationale for the different behavior of Münchnones, Münchnone imines and phosphamünchnones in cycloaddition, as well as suggest factors that appear to control regioselectivity.

In Chapter 3, we examine the influence of the PR_3 unit on both cycloaddition reactivity and regioselectivity. These demonstrate how the phosphorus substituents can influence the ground state structure of the 1,3-dipole. This feature, together with the rules for regioselectivity that emerged from Chapter 2, were exploited to adjust the electronic nature of the phosphamünchnone such that the regioselectivity of alkyne cycloaddition can be finely tuned.

Chapter 4 describes how these phosphamünchnones can also be employed in alkene cycloaddition. By employing alkene-tethered imines, intramolecular cycloaddition occurs readily, and provides an efficient overall approach to prepare polycyclic 2-pyrrolines. This transformation occurs with high

regio- and stereoselectivity, and proceeds with a range of substituents on the imine, alkene and acid chloride.

A useful feature of the phospho-Münchnone dipole is the variety of PR_3 units that can be incorporated into the core. In Chapter 5, we show how this can be extended to chiral phosphites. This provides a new approach to enantioselective 1,3-dipolar cycloaddition, where the chiral phosphite is incorporated into the dipole in one step, leaves upon cycloaddition, yet is rigidly incorporated into the dipole. This has been employed to synthesize a range of chiral polycyclic 2-pyrrolines and pyrrolidines with high enantioselectivity.

1.5 References

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CHAPTER 2

Modular Mesoionics: Understanding and Controlling Regioselectivity in 1,3-Dipolar Cycloadditions of Münchnone Derivatives¹

2.0 Preface

As mentioned in the introduction, Münchnone cycloadditions with unsymmetrical alkynes often demonstrate poor regioselectivity, while phosphamünchnone cycloadditions proceed with high regiocontrol. To better understand and control this difference of behavior, the reactivities and regioselectivities of 1,3-dipolar cycloadditions between alkynes and three types of mesoionic 1,3-dipoles (Münchnones, imino-Münchnones, and phosphamünchnones) were investigated in this chapter. The structural analogy between the 1,3-dipoles affords a new approach to study the regioselectivity as function of the dipole electronics, and independent of the substituents incorporated into the product. Competition kinetic measurements reveal that these are nucleophilic 1,3-dipoles that react most rapidly with electron-poor alkynes. However, the regioselectivity of cycloaddition is found to undergo an inversion in selectivity as a function of alkyne ionization potential and the dipole employed. The origins of the regioselectivities were examined by means of competition reactions and density functional theory (DFT) calculations (by Dr. Krenske and Prof. Ken Houk (UCLA)). These provide a rationale for cycloaddition behavior, and reveal that problems of low regioselectivity can be overcome by choice of the proper mesoionic heterocycle.

2.1 Introduction

The 1,3-dipolar cycloadditions of Münchnones (1,3-oxazolium-5-oxides) (**2.1**), imino-Münchnones (**2.2**), and phospho-Münchnones (**2.3**) (Figure 2.1) with alkynes provide convenient access to pyrroles. Despite sharing a common azomethine ylide motif, these three classes of mesoionic 1,3-dipoles display varied reactivities and regioselectivities, which have not, until now, been systematized or explained. Here we report experimental and theoretical investigations of cycloadditions between Münchnone derivatives and alkynes that delineate the differences in behavior between the three classes of 1,3-dipoles.

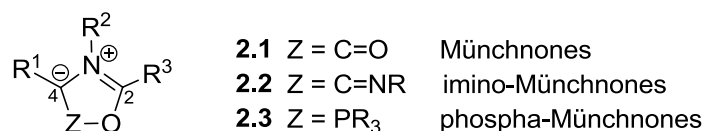
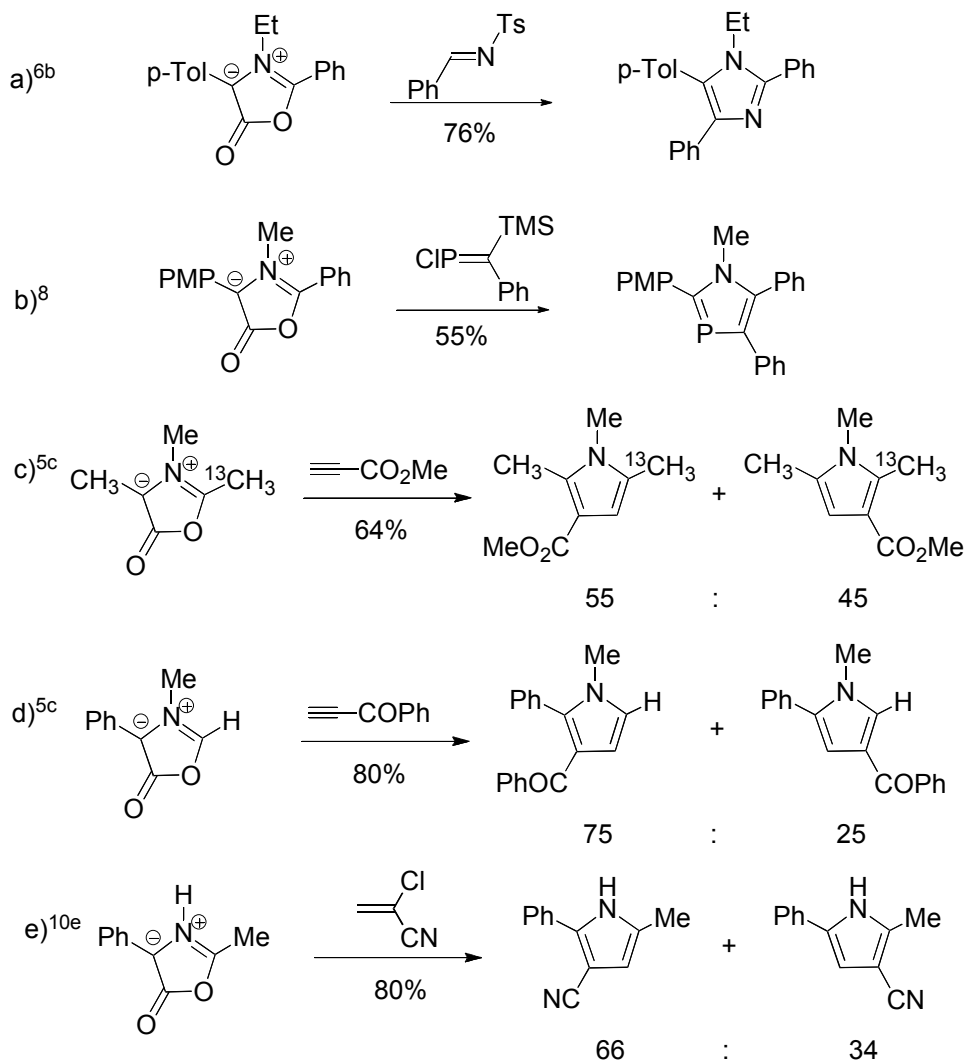


Figure 2.1: Mesoionic 1,3-dipoles: Münchnones (**2.1**), imino-Münchnones (**2.2**) and phospho-Münchnones (**2.3**).

Münchnones were first reported in 1964 by Huisgen to participate in 1,3-dipolar cycloadditions with alkynes to generate pyrroles (after CO_2 loss).² Subsequent studies extended the scope of the cycloaddition to include many other dipolarophiles, providing attractive routes to pyrrolines, imidazoles, imidazolines, and other heterocycles.³ Münchnones react most rapidly with electron-poor dipolarophiles. This “Type I” Sustmann behavior (Figure 1.10) suggests a predominant frontier molecular orbital interaction between HOMO-(Münchnone) and LUMO-(dipolarophile),⁴ and FMO calculations predict that regioselectivity should favor bond formation between C4 of the Münchnone and the electrophilic terminus of the dipolarophile.⁵ However, regioselectivity is often poor. While cycloadditions of Münchnones with electronically-biased dipolarophiles such as imines,⁶ aldehydes⁷ and phosphoalkenes⁸ give the predicted cycloadduct with high selectivity (e.g., Scheme 2.1a,b), cycloadditions with polarized alkynes^{5b,c,9} and alkenes^{5d,10} frequently lead to mixtures of regioisomers (e.g., Scheme 2.1c-e). A number of attempts have been made to understand this selectivity,^{5,11} and in some

instances it has been attributed to steric influences and asynchronous cycloadditions.^{5c,11d} Nevertheless, it remains generally unclear why Münchnones do not react with alkynes with the same degree of selectivity as they do with other electronically-biased dipolarophiles.



Scheme 2.1: Examples of Münchnone Regioselectivity in Cycloaddition Reactions.

Substituent effects at positions R¹ and R³ in Münchnones are frequently small and/or complicated by steric effects, and are not generally useful for controlling cycloaddition regioselectivities as they can only be used to generate one regioisomeric product. A better alternative is to tune the group “Z” (Figure 2.1). Imino-Münchnones (**2.2**, Z = C=NR) were first reported in 1968.¹² We

recently developed a third type of Münchnone derivative in which the carbonyl fragment is replaced by PR_3 (**2.3**).¹³ Phospha-Münchnones have reactivity profiles quite different from Münchnones and imino-Münchnones. These have also been called “Montréalones” in light of their discovery in Montréal, as Huisgen named Münchnones after München, and Earl¹⁴ named “Sydnones” after Sydney where they were developed. The efficiencies of cycloadditions of phospha-Münchnones with alkenes¹⁵ and alkynes^{13a,b,d} depend strongly on the identity of PR_3 . While PPh_3 is not effective, a $\text{PPh}(\text{catechyl})$ unit leads to rapid and high-yielding cycloadditions. Münchnones, imino-Münchnones, and phospha-Münchnones can each be synthesized by a one-pot multicomponent procedure, starting from an imine ($\text{R}^1\text{HC}=\text{NR}^2$), an acid chloride (R^3COCl), and either CO/Pd (for **2.1**),¹⁶ RNC (for **2.2**),¹⁷ or PR_3 (for **2.3**).^{13a,b}

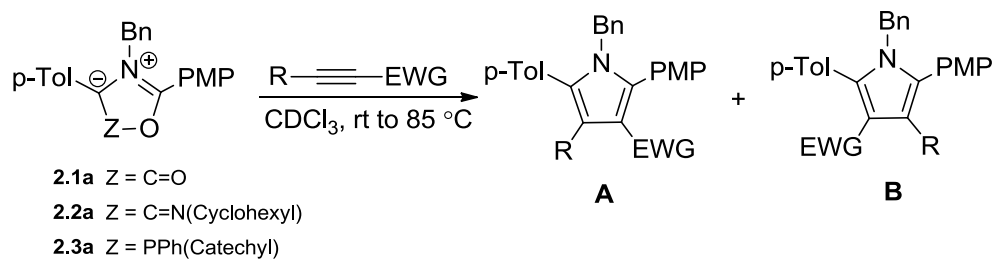
Here we have used the modular assembly routes to prepare Münchnone derivatives differing only in the group Z and have investigated their 1,3-dipolar cycloadditions with electron-poor and electron-rich alkynes. The origins of the reactivities and selectivities are examined by means of density functional theory calculations. We find that modulating the Z group from $\text{C}=\text{O}$ (or $\text{C}=\text{NR}$) to PR_3 opens access to regioselective cycloadditions with electron-poor alkynes, and vice versa for electron-rich alkynes.

2.2 Results and Discussion

2.2.1 Experimental Measurements of Cycloaddition Regioselectivities and Reactivities.

We prepared three 1,3-dipoles: Münchnone **2.1a**, imino-Münchnone **2.2a**, and phospha-Münchnone **2.3a**, from (*p*-tolyl) $\text{HC}=\text{NBn}$, *p*- $\text{MeOC}_6\text{H}_4\text{COCl}$, and the appropriate “ Z ” unit.¹⁸ The *p*-tolyl and *p*-methoxyphenyl groups were chosen to minimize the regiochemical influences of the C2 and C4 substituents.¹⁹ The regioselectivities of 1,3-dipolar cycloadditions of **2.1a–2.3a** with alkynes were measured by *in situ* ^1H NMR spectroscopy and by isolation and full characterization of the pyrrole products. The results are given in Tables 2.1 and 2.2.

Table 2.1: Cycloadditions of Mesoionic 1,3-Dipoles with Electron-Poor Alkynes.^a

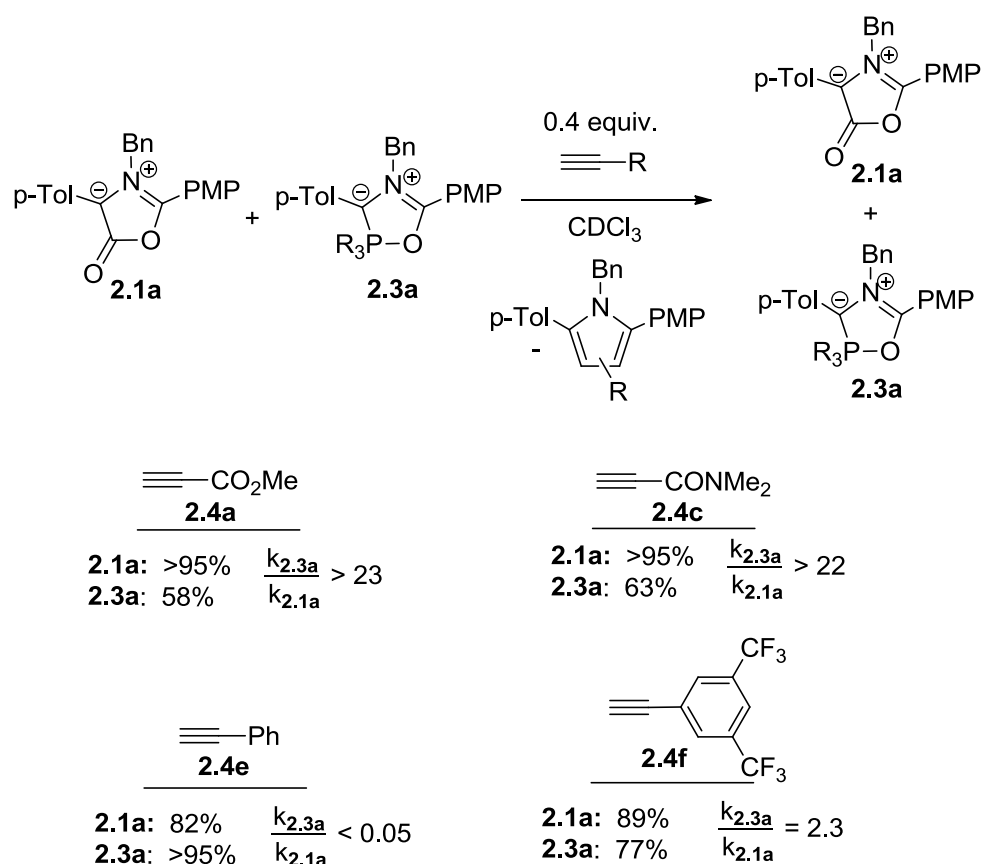


Entry	Alkyne	1,3-Dipole	Yield ^b	Ratio ^c A : B
1	$\equiv$ -CO ₂ Me 2.4a	2.1a	65 %	73 : 27
2	$\equiv$ -CO ₂ Me 2.4a	2.2a	85 %	88 : 12
3	$\equiv$ -CO ₂ Me 2.4a	2.3a	91 %	> 95 : 5
4 ^d	$\text{---}\equiv$ -CO ₂ Me 2.4b	2.1a	63 %	91 : 9
5 ^d	$\text{---}\equiv$ -CO ₂ Me 2.4b	2.2a	21 %	87 : 13
6 ^d	$\text{---}\equiv$ -CO ₂ Me 2.4b	2.3a	45 %	> 95 : 5
7	$\equiv$ -C(=O)NMe ₂ 2.4c	2.1a	95 %	69 : 31
8	$\equiv$ -C(=O)NMe ₂ 2.4c	2.2a	35 %	89 : 11
9	$\equiv$ -C(=O)NMe ₂ 2.4c	2.3a	98 %	> 95 : 5
10	$\equiv$ -C(=O)O-C ₆ H ₄ -CF ₃ 2.4d	2.1a	76 %	88 : 12
11	$\equiv$ -C(=O)O-C ₆ H ₄ -CF ₃ 2.4d	2.2a	84 %	93 : 7
12	$\equiv$ -C(=O)O-C ₆ H ₄ -CF ₃ 2.4d	2.3a	99 %	> 95 : 5

^a **2.1a** or **2.3a** (0.1 mmol), alkyne (0.2 mmol), CDCl₃ (1 mL), rt, 10 min to 2 days; **2.2a** (in situ, 0.2 mmol), alkyne (0.6 mmol), CDCl₃ (1.5 mL), rt, 1-15 days. ^b NMR yield. ^c Determined by ¹H NMR of crude reaction mixture. ^d 85 °C.

Table 2.1 summarizes cycloadditions of the 1,3-dipoles with electron-poor alkynes (**2.4a–2.4d**). The reactions of Münchnone **2.1a** and imino-Münchnone **2.2a** with alkynes **2.4a–2.4d** gave regioisomeric mixtures, favoring pyrrole A (69:31–93:7). Reactions of phospho-Münchnone **2.3a**, on the other hand, gave pyrrole A as the only observable regioisomer (>95:5). Münchnone **2.1a** usually gave lower selectivities than imino-Münchnone **2.2a**. For example, cycloaddition of **2.1a** with methyl propiolate (**2.4a**) yielded a 73:27 mixture of A and B (entry 1), while **2.2a** gave an 88:12 mixture (entry 2). Changing to the internal alkyne **2.4b** (entries 4–6) led to either an increase in selectivity (**2.1a**) or to no change in selectivity (**2.2a** and **2.3a**). This rules out the possibility that the regioselectivities obtained with the terminal alkyne were due simply to a sterically based preference for addition of C4 to the unsubstituted alkyne carbon. The less electron-poor alkyne **2.4c** gave lower selectivity with the Münchnone but no changes in selectivity for the imino- or phospho-Münchnone (entries 7–9). Conversely, the more electron-poor alkyne **2.4d** gave the highest selectivities overall (entries 10–12). In this case, even the Münchnone gave synthetically useful regioselectivity.

The general trend in the cycloadditions with electron-poor alkynes is towards higher selectivity in the order **2.1a** < **2.2a** < **2.3a**. Replacing the carbonyl group by PPh(catechyl) appears to generate a more electron-rich or electronically biased dipole. Experimental evidence for greater nucleophilicity in the phosphorus-containing dipole was obtained from the competition experiments shown in Scheme 2.2. Treatment of a 1:1 mixture of **2.1a** and **2.3a** with 0.4 equivalents of either methyl propiolate (**2.4a**) or dimethyl propiolamide (**2.4c**) led to consumption of only phospho-Münchnone **2.3a** based on ¹H NMR analysis. These results imply that the phospho-Münchnone is >20 times more reactive than the Münchnone toward **2.4a** and **2.4c**.

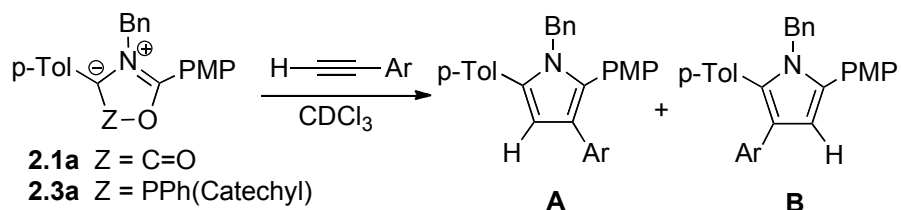


Scheme 2.2: Competition Reactions of Münchnone **2.1a** and Phospha-Münchnone **2.3a** with Alkynes. Data show the amounts of each 1,3-dipole remaining after treatment of an equimolar mixture with 0.4 equiv. alkyne. Relative rates were calculated as reported by Huisgen.²⁰

Cycloadditions with arylacetylene derivatives **2.4e-2.4h** displayed quite different regioselectivities (Table 2.2). As Münchnone **2.1a** and phospha-Münchnone **3a** displayed the most divergent selectivities toward electron-poor alkynes (Table 2.1), we employed these two dipoles in our investigations with electron-rich aryl-substituted alkynes. The cycloadditions of Münchnone **2.1a** with the arylacetylenes displayed consistently high regioselectivities, favoring pyrrole B (A:B <5:95). The regioselectivities obtained with phospha-Münchnone **2.3a**, on the other hand, were variable. While reaction with phenylacetylene (**2.4e**) gave a ca. 1:1 mixture of A and B (entry 2), reaction with the less electron-rich arylacetylene **2.4f** gave exclusively pyrrole A (entry 4) and the more electron-rich

alkynes **2.4g** and **2.4h** gave predominantly pyrrole B (entries 6 and 8). Interestingly, the Münchnone and phospho-Münchnone show opposite selectivities toward electron-poor alkyne **2.4f**.

Table 2.2: Cycloadditions of Mesoionic 1,3-Dipoles with Arylacetylenes.^a



Entry	Alkyne	1,3-Dipole	T [°C]	Yield ^b	Ratio ^c A : B
1	$\equiv$ -Ph 2.4e	2.1a	rt	40 %	< 5 : 95
2	$\equiv$ -Ph 2.4e	2.3a	70	58 %	48 : 52
3	2.4f	2.1a	rt	64 %	< 5 : 95
4	2.4f	2.3a	rt	86 %	> 95 : 5
5	2.4g	2.1a	rt	38%	< 5 : 95
6	2.4g	2.3a	70	36 %	35 : 65
7	2.4h	2.1a	rt	30 %	< 5 : 95
8	2.4h	2.3a	70	28 %	16 : 84

^a Conditions of Table 2.1. ^b Isolated yield. ^c Determined by ¹H NMR of crude reaction mixture.

Competition studies (Scheme 2.2) indicated that phospho-Münchnone **2.3a** reacted faster than Münchnone **2.1a** with the electron-poor arylacetylene **2.4f**,

although the relative reactivities of the two 1,3-dipoles in this case (2.3:1) were less dissimilar than those observed with alkynes **2.4a** and **2.4c** (>20:1). Phosphamünchnone **2.3a** reacted at least 20 times slower than Münchnone **2.1a** with the more electron-rich arylacetylene, **2.4e**. These data are consistent with the greater electrophilicity (lower LUMO energy) of Münchnones.

2.2.2 Reactivity/Selectivity Relationships

To quantify reactivity/selectivity relationships for dipoles **2.1a** and **2.3a**, we measured the kinetics of cycloadditions with alkynes **2.4a,c-h** by means of competition reactions. Relative rate constants are listed in Table 2.3, and reactivity/selectivity data are plotted in Figure 2.2 as a function of alkyne ionization potential (calculated from the π -HOMO energies).²¹

Table 2.3: Relative Rate Constants of 1,3-Dipolar Cycloadditions of **2.1a** and **2.3a** with Alkynes, Measured by Competition Reactions.^a

Alkyne	k _{rel} of cycloaddition with 2.1a	k _{rel} of cycloaddition with 2.3a
4-(Me) ₂ NC ₆ H ₄ —≡ 2.4h	1	1
4-MeOC ₆ H ₄ —≡ 2.4g	1.2	4.4
Ph—≡ 2.4e	1.8	14
3,5-(CF ₃) ₂ C ₆ H ₄ —≡ 2.4f	17	653
≡—CONMe ₂ 2.4c	107	1.39 x 10 ⁵
≡—CO ₂ Me 2.4a	1550	49.4 x 10 ⁵
≡—CO ₂ -4-CF ₃ C ₆ H ₄ 2.4d	3.2 x 10 ⁴	390 x 10 ⁵

^a Determined by reaction of **2.1a** or **2.3a** (0.1 mmol) with two different alkynes (0.5 mmol to 2.0 mmol) and ¹H NMR analysis of the resulting pyrroles.

For both 1,3-dipoles, reactivity increases linearly with alkyne ionization potential, as expected for a nucleophilic 1,3-dipole.²² However, regioselectivity displays an inversion within each series, favoring B at low alkyne IPs and A at high alkyne IPs. The regioisomer predicted for a nucleophilic dipole (A) is

favored for a larger range of alkynes by phosphamünchnone **2.3a** than by Münchnone **2.1a**. In contrast to FMO theory expectations, a coincidence of inversion in reactivity and regioselectivity was not observed.²³ Nevertheless, these data clearly shows that alkyne cycloaddition regioselectivity with Münchnone and phosphamünchnone is indeed predictable as function of alkyne ionization potential and the dipole. The ionization potential of selectivity inversion is different for Münchnones (ca. 10.7 eV) and phosphamünchnones (ca. 8.6 eV). This can be used to selectively synthesize pyrroles with any of the alkynes examined. For alkyne **2.4f**, the ionization potential (ca. 9.5 eV) lies outside both of the mixture-producing regions, yet on complementary sides of the A→B regioisomeric transition points. Consequently, both the isomeric pyrroles can be generated in >95% regioisomeric purity.

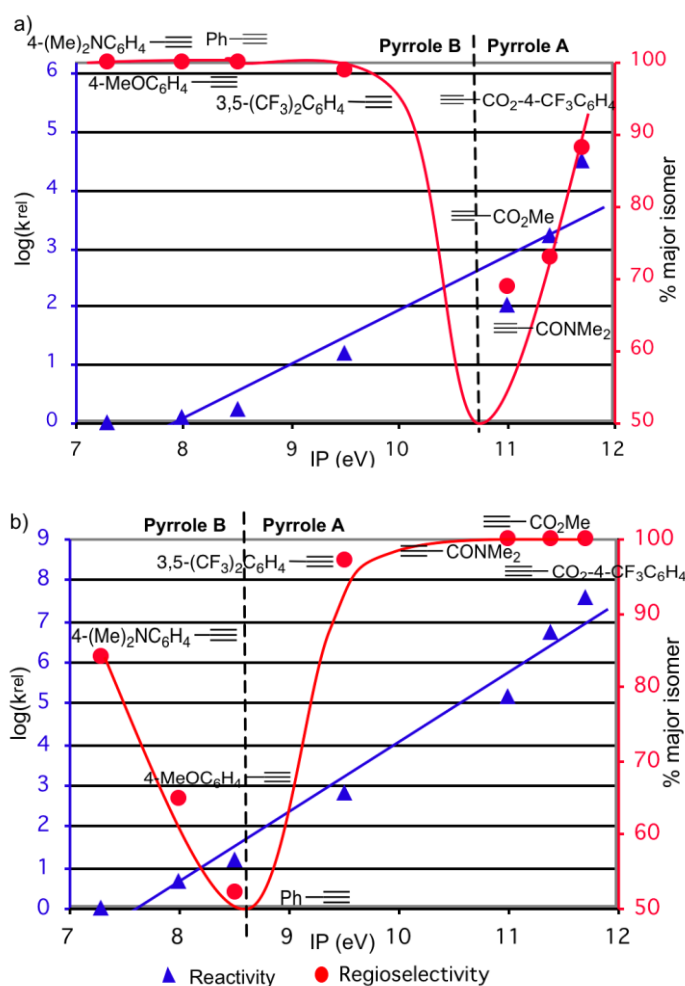


Figure 2.2. Reactivity and Selectivity of Cycloadditions of a) **2.1a** and b) **2.3a** with Alkynes, as a Function of Alkyne Ionization Potential.

2.2.3 Computational Studies of Regioselectivity and Reactivity.

FMO Analysis. We conducted density functional theory calculations to establish a theoretical rationale for the mesoionic 1,3-dipoles' reactivities and regioselectivities. Computations were performed at the B3LYP/6-31+G(d) level of theory, which we have previously been used^{13b,c} to characterize phosphamünchnone structures and reactivities. Figure 2.3 shows the FMO energies and π coefficients of model 1,3-dipoles **2.1b–2.3b** and of selected alkynes.

Methyl propiolate (**2.4a**) was used as a representative electron-poor alkyne. As has been previously noted with Münchnone,^{5b,c,9a} the FMO picture correctly predicts some, but not all, of the experimental observations for this type of dipolarophile. The dominant FMO interaction is HOMO(dipole)–LUMO(**2.4a**). As the HOMO orbital coefficients for all 1,3-dipoles are biased towards C4, and the LUMO(alkyne) has its major coefficient on the alkyne terminus, this data is consistent with the observed selectivity for pyrrole A in cycloadditions with electron-poor alkynes **2.4a–2.4d** (Table 2.1). However, the FMOs fail to predict that pyrrole B will be nearly competitive with the electron rich Münchnone and imino-Münchnone. The HOMO energies also fail to predict that a phosphamünchnone reacts faster than Münchnone with electron-poor alkynes (Scheme 2.2, Table 2.3).

Frontier molecular orbital considerations also give qualitatively inaccurate predictions of regioselectivity for the more electron-rich alkynes **2.4e**, **2.4f**, and **2.4h**. For example, the FMO energies suggest that the dominant orbital interaction with Münchnones should be HOMO(Münchnone)–LUMO(alkyne) for all but the most electron rich alkyne (**2.4h**). Considering the dominant orbital coefficients, this should strongly favor the formation of pyrrole A, or, in the case of **2.4h**, yield mixtures of pyrroles A and B. However, the Münchnone consistently favors pyrrole B experimentally while the phosphamünchnone is “ambiphilic”.

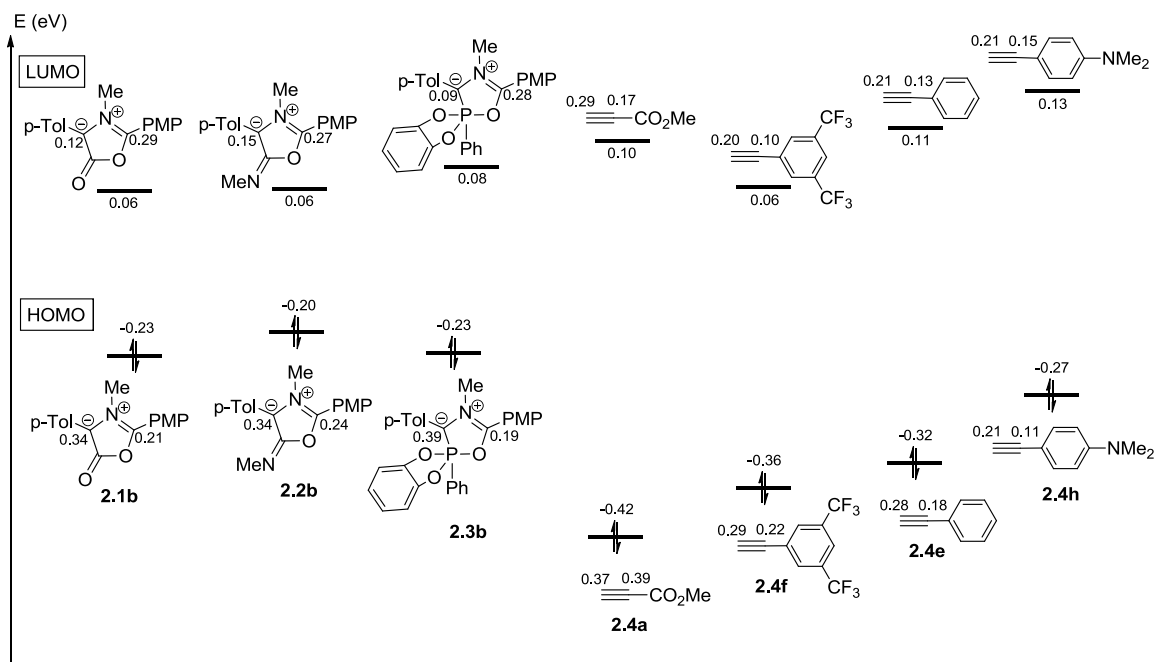


Figure 2.3: Frontier molecular orbital diagram for 1,3-dipoles **2.1b**–**2.3b** and selected alkyne dipolarophiles. Orbital energies (eV) and coefficients at the reacting termini were computed at the HF/6-31G//B3LYP/6-31+G(d) level.

Interaction/Distortion Models. Simple FMO considerations are not generally useful for comparing the reactivities and selectivities of cycloadditions involving these mesoionic 1,3-dipoles. We therefore computed transition states for the 1,3-dipolar cycloadditions of model mesoionic 1,3-dipoles with the four alkynes. Figure 2.4 shows the transition states for cycloadditions of model 1,3-dipoles **2.1c**–**2.3c** with methyl propiolate. Activation barriers for these reactions are listed in Table 2.4. Activation barriers for the cycloadditions of arylacetylenes with 1,3-dipoles **2.1d** and **2.3d** (which lack the N-Me group of **2.1c** and **2.3c**) are given in Table 2.5. The Tables list the values of $\Delta H^\ddagger$ and $\Delta G^\ddagger$ in the gas phase, as well as solution-phase values of $\Delta G^\ddagger$ in chloroform, which incorporate SMD solvation energies.

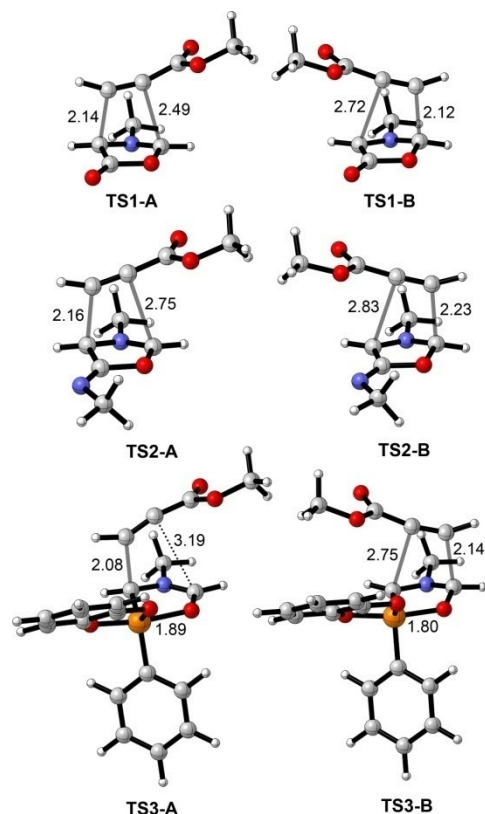
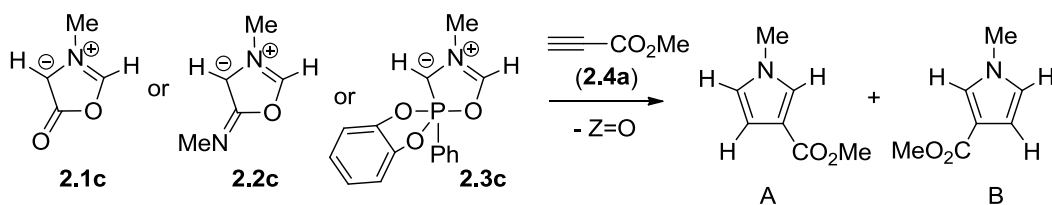


Figure 2.4 Transition structures for 1,3-dipolar cycloadditions of **2.1c–2.3c** with methyl propiolate, calculated at the B3LYP/6-31+G(d) level. Distances in Å.

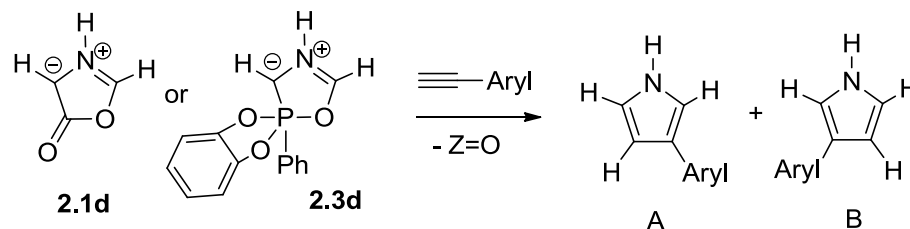
Table 2.4: Computed Activation Barriers and Distortion/Interaction Analyses for 1,3-Dipolar Cycloadditions of **2.1c–2.3c** with Methyl Propiolate.^a

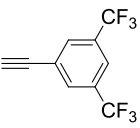
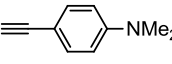


1,3-Dipole	Exptal ^b A:B	$\Delta H^\ddagger$ (gas)		$\Delta G^\ddagger$ (gas)		$\Delta G^\ddagger$ (soln)		ΔE_{dist}		ΔE_{int}	
		A	B	A	B	A	B	A	B	A	B
2.1c	73:27	10.1	10.4	24.7	25.0	27.5	26.7	21.7	18.6	-12.5	-9.1
2.2c	88:12	3.7	4.5	17.9	19.0	20.3	21.1	13.8	11.9	-11.2	-8.4
2.3c	>95:5	8.4	12.2	22.8	28.1	22.4	29.7	15.7	21.3	-8.2	-9.9

^a B3LYP/6-31+G(d), 298.15 K, 1 mol/L, kcal/mol. Solution values incorporate SMD solvation energies in chloroform. ^b Experimental regioisomer ratios for reactions of **2.1a–2.3a** (from Table 2.1).

Table 2.5: Computed Activation Barriers and Distortion/Interaction Analyses for 1,3-Dipolar Cycloadditions of **2.1d** and **2.3d** with Arylacetylenes.^a



Alkyne and 1,3-Dipole	Exptal ^b A:B	$\Delta H^\ddagger$ (gas)		$\Delta G^\ddagger$ (gas)		$\Delta G^\ddagger$ (soln)		ΔE_{dist}		ΔE_{int}	
		A	B	A	B	A	B	A	B	A	B
$\equiv\text{-Ph}$ 2.4e											
2.1d	<5:95	16.9	14.5	31.2	28.8	34.7	31.6	24.8	20.0	-8.9	-6.4
2.3d	48:52	18.4	18.6	32.7	33.4	35.7	36.0	24.9	23.1	-7.3	-5.2
 2.4f											
2.1d	<5:95	15.9	13.6	30.2	28.7	33.2	31.1	23.8	19.8	-8.9	-7.1
2.3d	>95:5	14.6	16.9	28.7	32.6	29.6	34.9	18.0	23.1	-4.2	-6.8
 2.4h											
2.1d	<5:95	17.7	14.3	32.7	28.7	36.6	31.7	25.3	19.4	-8.6	-6.0
2.3d	16:84	20.1	18.6	35.4	33.8	38.9	36.5	26.7	22.5	-7.4	-4.6

^a B3LYP/6-31+G(d), 298.15 K, 1 mol/L, kcal/mol. Solution values incorporate SMD solvation energies in chloroform. ^b Experimental regioisomer ratios for reactions of **2.1a** and **2.3a** (from Table 2.2).

For cycloadditions involving methyl propiolate (Table 2.4), the gas-phase values of $\Delta H^\ddagger$ and $\Delta G^\ddagger$ predict the correct sense and degree of regioselectivity (a preference for pyrrole A, which increases in the order **2.1** < **2.2** < **2.3**) and the correct relative rates of cycloaddition (**2.1** < **2.3**).²⁴ Theory also predicts the correct regioselectivities for cycloadditions involving arylacetylenes (Table 2.5). Experimentally, cycloadditions of Münchnone **2.1a** with arylacetylenes

consistently favored pyrroles B (>95:5), and the calculations on the model Münchnone **2.1d** predict pyrroles B to be favored by 2.3–3.4 kcal/mol ($\Delta\Delta H^\ddagger$). Experimentally, phospho-Münchnone **2.3a** was ambiphilic toward the arylacetylenes; and the computed barriers mirror this result by showing a strong preference for pyrrole A with alkyne **2.4f** ($\Delta\Delta H^\ddagger = 2.3$ kcal/mol), a preference for pyrrole B with **2.4h** ($\Delta\Delta H^\ddagger = 1.5$ kcal/mol), and low selectivity with **2.4e** ($\Delta\Delta H^\ddagger = 0.2$ kcal/mol).

The calculations appear to underestimate the reactivity of the phospho-Münchnone **2.3d** (relative to Münchnone **2.1d**) in cycloadditions with arylacetylenes. This is likely to be a hidden feature present in the reaction of **2.3c** with methyl propiolate as well, and it stems from the absence of substituents on the carbon and nitrogen atoms. We showed previously^{13b,c} that the activation energies for concerted cycloadditions of phospho-Münchnones correlate with the length of the P–O bond in the reactant; a longer P–O bond is associated with a higher activation energy because this bond must shorten more before the transition state is reached. The absence of *N*-alkyl and *C*-aryl substituents in the model phospho-Münchnone **2.3d** lengthens the P–O bond by about 0.13 Å compared with the more highly-substituted **2.3b** (1.97 Å vs. 1.84 Å), and this artificially raises the activation energies for the phospho-Münchnone.

We also computed activation barriers at the M06-2X/6-311+G(d,p)//B3LYP/6-311+G(d) level of theory. The M06-2X calculations agreed quite closely with experiment for methyl propiolate, but gave incorrect predictions of regioselectivity for all but one of the arylacetylene cycloadditions.

To analyze the variations in rates and regioselectivities, we applied the distortion/interaction model²⁵ of reactivity to the B3LYP transition states. Tables 2.4 and 2.5 show the total energy required to distort the 1,3-dipole and alkyne to their TS geometries (ΔE_{dist}) and the energy associated with interaction between the distorted reactants in the TS (ΔE_{int}).

The regioselectivities of Münchnone and imino-Münchnone cycloadditions with methyl propiolate (Table 2.4) are controlled by transition-state interaction energies. Although the favored transition states (leading to A) for

these two dipoles both have larger distortion energies than the TSs leading to B, they are stabilized by a stronger interaction between reactants that reflects the nucleophilic character of the 1,3-dipole. The greater distortion energies in the A transition states are due to greater *cis*-bending of the alkyne and out-of-plane bending of the dipole. The regioselectivity observed in the reaction of the phospho-Münchnone, on the other hand, is derived not from interaction energy but from distortion energy. The TS leading to A has a smaller distortion energy because of the less shortened P–O bond and the more favorable *trans*-bending of the alkyne. The small distortion energy is also responsible for the higher reactivity of **2.3** compared with **2.1** toward electron-poor alkynes.

The regioselectivities of arylacetylene cycloadditions (Table 2.5) are controlled by distortion energies. Münchnone TSs leading to pyrrole B have 4–6 kcal/mol smaller distortion energies than those leading to pyrrole A, which offset their 2–3 kcal/mol weaker interaction energies. In the phospho-Münchnone cycloadditions, small distortion energies favor formation of pyrrole A with alkyne **2.4f** and pyrrole B with alkyne **2.4h**. Only in the unselective reaction of the phospho-Münchnone with phenylacetylene does the correlation of selectivity with E_{dist} break down; here E_{dist} favors B by 1.8 kcal/mol, while E_{int} favors A by 1.9 kcal/mol.

Correlation of Calculations with Experimental Data. These findings have useful implications in the understanding of cycloaddition regioselectivities with Münchnones and the related phospho-Münchnones. FMO theory suggests the dominant orbital interaction with Münchnone is between the HOMO(Münchnone) and LUMO(alkyne). Considering the relative orbital coefficients, this Sustmann type I behavior should lead to pyrrole A. Experimentally, however, the opposite regioselectivity is always competitive. As shown in Table 2.5, this is due to the lower distortion energy brought on by a highly asynchronous cycloaddition to form pyrrole B. This cycloaddition correlates with the higher electronic bias in the LUMO(Münchnone) orbital coefficients towards C2, which can interact with the alkyne HOMO. The low distortion cycloaddition becomes increasingly dominant as alkyne ionization potential is decreased, which is clearly borne out by the

experimental data (Figure 2.2b), where selectivity undergoes a smooth inversion at a relatively high ionization potential.

For phosphamünchnones, cycloaddition regioselectivity matches more closely FMO predictions. However, this does not appear to result from a more electron rich dipole (i.e. a higher HOMO energy). Instead selectivity is driven by distortion energy differences in both directions. Phospha-Münchnones can undergo a low distortion, asynchronous cycloaddition with electron poor alkynes (TS2.3-A), where P-O bond compression is not required. In order to proceed via TS2.3-B (a similar transition state to TS2.1-B with Münchnones), the dipole itself must undergo P-O bond compression. This creates a greater barrier to this regioisomeric product than that with Münchnones, and requires more electron rich alkynes to be favorable. The latter is consistent with the lower ionization potential for selectivity inversion with phosphamünchnones. These influences are summarized in Figure 2.5.

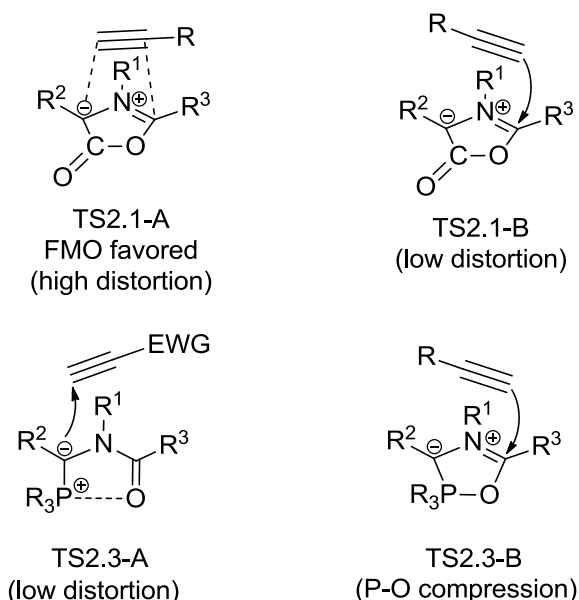


Figure 2.5. Electronic Influences on Transition States in Münchnone and Phospha-Münchnone Alkyne Cycloadditions.

2.3 Conclusions

The experiments and calculations reported here provide new insights into the reactivities and selectivities of 1,3-dipolar cycloadditions involving mesoionic 1,3-dipoles. Both Münchnones and phospho-Münchnones demonstrate clear trends in alkyne cycloaddition regioselectivity. These correlate with alkyne ionization potential, and can be used to predict not only the relative reactivity of these alkynes, but also the regioselectivity outcome with a diverse variety of dipolarophiles. Frontier molecular orbital considerations do not provide a useful rationale for these selectivities or reactivities. However, we found that the experimental results are reliably predicted by B3LYP calculations and can be interpreted in terms of the transition-state distortion and interaction energies.

To the best of our knowledge, this is the first demonstration that cycloadditions involving cyclic azomethine ylides can be performed regioselectively with electron-rich and electron-poor alkynes without varying the C- and N-substituents (R^1 – R^3). Phospha-Münchnones afford regioselective cycloadditions with electron-poor alkynes that react unselectively with Münchnones, which alternatively give better selectivities with electron-rich alkynes. These tunable selectivities suggest avenues for fruitful application to a range of other dipolarophiles, and experiments in this direction are currently underway.

2.4 Experimental Section

2.4.1 General Procedure

Experiments were conducted in a Vacuum Atmospheres dry glovebox or by using standard Schlenk techniques. All reagents were purchased from commercial sources and used as received. $CDCl_3$ and CD_3CN were distilled from CaH_2 under nitrogen. Acetonitrile, dichloromethane and diethyl ether were dried with solvent purification system. Imines were prepared as per standard literature procedures.²⁶ Alkyne **2.4c**²⁷ was synthesized by literature procedure. Pyrroles of

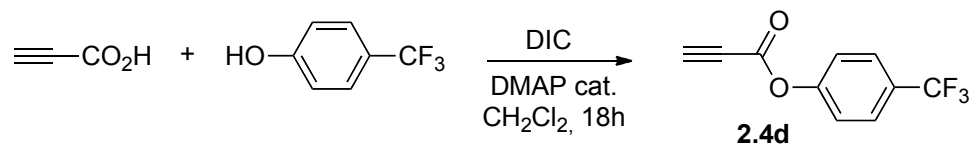
alkynes **2.4a** and **2.4b** and proof of their regiochemistry have been previously reported in the literature.^{13b} ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300, 400 MHz, and Unity 500 MHz spectrometers and are reported in Appendix A. Mass spectra were acquired by electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI), and obtained from the McGill University mass spectral facilities.

2.4.2 Synthesis of Starting Materials

Synthesis of PPh(2-catechyl)^{13b}

A modified version of a literature procedure was followed.²⁸ To catechol (11.01 g, 100 mmol) under nitrogen in a 500 mL Schlenk flask was added Et_2O (100 mL) followed by pyridine (16.2 mL, 200 mmol). The mixture was cooled to 0 °C and PhPCl_2 (13.6 mL, 100 mmol) was added dropwise over 15 min with vigorous stirring, then stirred at ambient temperature for 2 h. The flask was fitted to an air-free filtration assembly for the removal of the pyridine hydrochloride precipitate. The filtrate was concentrated *in vacuo* without exposure to air, and distilled (84 – 88 °C, 115 mTorr) to afford 12.9 g (60%) of a clear colorless oil, which was stored in the glovebox freezer at -35 °C. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.62-7.56 (m, 2H), 7.48-7.35 (m, 3H), 7.18-7.11 (m, 2H), 7.03-6.97 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 146.5 (d, J_{CP} = 6.8 Hz), 141.7 (d, J_{CP} = 49.0 Hz), 131.7, 128.5 (d, J_{CP} = 22.6 Hz), 128.4 (d, J_{CP} = 5.1 Hz), 122.7 (d, J_{CP} = 0.5 Hz), 113.0 (d, J_{CP} = 0.8 Hz). ^{31}P NMR (81 MHz, CDCl_3): δ (ppm) 180.1. ^{31}P NMR (81 MHz, CD_2Cl_2): δ (ppm) 174.2. HRMS (ESI^+) for $\text{C}_{12}\text{H}_{10}\text{O}_2\text{P}^+$; calculated: 217.04129, found: 217.04192.

Synthesis of Alkyne **2.4d**:



To a solution of 4-(trifluoromethyl)phenol (900 mg, 5.55 mmol) in 25 mL of dichloromethane was added propiolic acid (440 mL, 7.2 mmol), *N,N'*-diisopropylcarbodiimide (1 mL, 6.66 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol). The solution was stirred at room temperature for 18 h. The crude mixture was filtered and the product was purified by flash chromatography using hexanes/diethyl ether as eluent to afford the alkyne **2.4d** as a clear liquid (618 mg, 52% yield). The product is volatile, so the solvents were carefully removed in vacuo.

^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.68 (d, $J = 9.0$ Hz, 2H), 7.29 (d, $J = 9.0$ Hz, 2H), 3.13 (s, 1H). **^{13}C NMR** (125.7 MHz, CDCl_3) δ (ppm): 152.3, 150.3, 129.0 (q, $^2J_{\text{C-F}} = 32.8$ Hz), 127.1 (q, $^3J_{\text{C-F}} = 3.6$ Hz), 123.8 (q, $^1J_{\text{C-F}} = 272.1$ Hz), 122.0, 77.7, 73.9. **HRMS** (APCI $^+$) for $\text{C}_{10}\text{H}_6\text{O}_2\text{F}_3^+$; calculated: 215.03144, found: 215.03095.

Synthesis of Münchnone **2.1a**:

A modified version of a literature procedure was followed.²⁹ In the glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (138 mg, 0.66 mmol) and 4-methoxybenzoyl chloride (124 mg, 0.73 mmol) were mixed in 1 mL acetonitrile and allowed to stand for 30 min. The solution was transferred to a 50 mL reaction bomb followed by Pd(^tBu₃P)₂ (34.6 mg, 10 mol%), LiBr (57.2 mg, 0.66 mmol) and *N,N*-diisopropylethylamine (119 mg, 0.92 mmol). CO (4 atm) was added to the reaction bomb and the solution was heated at 45 °C for 16 h. After removing CO, the solution was stirred with 3 g of K₃PO₄ for 7 h in the glovebox. The solution was filtered through a small pad of celite and concentrated to dryness. 5 mL of Et₂O followed by 2.5 mL of acetonitrile were added and the solution was left in a -35 °C freezer for 18 h. The precipitate was collected and re-crystallized with 5 mL dichloromethane and 15 mL of pentane. Solution was stored in a -35 °C freezer for 1 day and 103 mg of pure Münchnone **2.1a** was collected (42% yield).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.51 (d, *J* = 6.5 Hz, 2H), 7.42-7.34 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 7.0 Hz, 2H), 5.35 (s, 2H), 3.80 (s, 3H), 2.26 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 161.7, 160.8, 143.3, 136.0, 134.6, 129.6, 129.5, 129.1, 128.6, 127.7, 125.7, 125.6, 115.3, 114.9, 95.9, 55.6, 50.6, 21.2. **HRMS** (APCI⁺) for C₂₄H₂₂O₃N⁺; calculated: 372.15942, found: 372.115955.

Synthesis of Münchnone-Imine **2.2a**:

A modified version of a literature procedure was followed.¹⁷ In the glovebox, a solution of (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (209 mg, 1.00 mmol) and *p*-methoxybenzoyl chloride (171 mg, 1.00 mmol) in 1.5 mL acetonitrile was prepared. After 30 min at room temperature, cyclohexyl isocyanide (109.2 mg, 1.00 mmol) was added and the solution was stirred for 1 h. K₃PO₄ (500 mg, 2.3 mmol) was added followed by an additional 16 h stirring at room temperature. The solution was filtered and concentrated in vacuo. The product was purified by several washes with pentane to obtain 294 mg of pure product (65% yield).

¹H NMR (500 MHz, CDCl₃, -14 °C) δ (ppm): 7.55 (d, *J* = 9.0 Hz, 2H), 7.34-7.27 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 5.80 (d, *J* = 14.5 Hz, 1H), 3.96 (d, *J* = 14.1 Hz, 1H), 3.74 (s, 3H), 2.74-2.69 (m, 1H), 2.37 (s, 3H), 1.54-1.40 (m, 5H), 1.02-0.77 (5H, m). **¹³C NMR** (125.7 MHz, CDCl₃, 10 °C) δ (ppm): 185.1, 172.1, 161.1, 137.9, 135.1, 130.6, 130.0, 129.3, 129.2, 128.4, 127.9, 127.5, 122.6, 113.1, 85.6, 62.3, 55.2, 50.2, 33.4, 24.9, 24.6, 21.1. **HRMS** (APCI⁺) for C₃₀H₃₃O₂N₂⁺; calculated: 453.25365, found: 453.25280.

Synthesis of Phospha-Münchnone **2.3a**:^{13b}

In the glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (209 mg, 1.00 mmol) and 4-methoxybenzoyl chloride (179 mg, 1.05 mmol) were mixed in ca. 1 mL acetonitrile and allowed to stand for 30 min. An acetonitrile solution (ca. 2 mL) of PhP(catechyl) (237 mg, 1.1 mmol) was added followed by DBU (274 mg, 1.8 mmol) after 1 h, the mixture was diluted with acetonitrile to ca. 8 mL total volume and cooled at ca. -40 °C overnight to improve product precipitation. Filtration, washing with cold acetonitrile, and removal of trace solvent residues *in vacuo* for ca. 12 h provides 430 mg product (77% yield).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.66 (dd, *J* = 8.5 Hz, 17.5 Hz, 2H), 7.44 (d, *J* = 6.5 Hz, 2H), 7.35-7.31 (m, 2H), 7.29-7.24 (m, 4H), 7.04-7.03 (m, 3H), 6.99-6.97 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.72 (dd, *J* = 3.0 Hz, 5.5 Hz, 2H), 6.45 (broad s, 1H), 5.03 (d, *J* = 15.5 Hz, 1H), 4.92 (d, *J* = 15.5 Hz, 1H), 3.79 (s, 3H), 2.28 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 161.0, 149.3, 148.1, 145.8, 143.0 (d, ¹*J*_{C-P} = 226.5 Hz), 135.8, 135.4 (d, ⁴*J*_{C-P} = 1.4 Hz), 135.2 (d, ³*J*_{C-P} = 6.1 Hz), 132.3 (d, ²*J*_{C-P} = 17.6 Hz), 129.7, 128.7, 128.6 (d, ² or ³*J*_{C-P} = 3.8 Hz), 128.1 (d, ² or ³*J*_{C-P} = 4.6 Hz), 128.0, 127.9, 127.6, 126.3, 121.8, 119.4, 119.0, 114.2, 110.9 (broad d, ²*J*_{C-P} = 10.7 Hz), 110.7 (broad s), 73.2 (d, ¹*J*_{C-P} = 221.8 Hz), 55.5, 51.0 (d, ³*J*_{C-P} = 8.3 Hz), 21.3 (d, ⁶*J*_{C-P} = 2.4 Hz). **HRMS** (APCI⁺) for C₃₅H₃₁O₄NP⁺; calculated: 560.19852, found: 560.19901.

2.4.3 Synthesis and Characterization of Pyrroles A and B

NMR spectra of pyrroles and proof of their regiochemistry are provided in Appendix A.

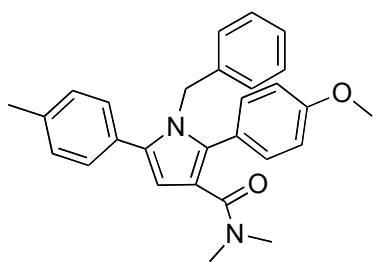
Pyrroles of Alkynes **2.4c**, **2.4d** and **2.4f**:^{13b}

In a glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (42.0 mg, 0.20 mmol) and *p*-methoxybenzoyl chloride (37.5 mg, 0.22 mmol) were mixed in 0.5 mL CD₃CN and allowed to stand for 30 min. PhP(catechyl) (47.5 mg, 0.22 mmol) was added. After 1 h, DBU (60.8 mg, 0.40 mmol) and the alkyne **2.4c** (58.3 mg, 0.6 mmol) were added as solutions in CD₃CN with a final volume of 1.5 mL. The reaction was complete within 2 h. The solution was concentrated in vacuo followed by column chromatography purification with toluene/acetone (9/1) as eluent to afford pyrrole **A** (74.6 mg, 88% yield). Pyrrole **B** was formed by the same procedure with (4-OMe-C₆H₄)HC=NCH₂C₆H₅ (45.0 mg, 0.20 mmol) and *p*-toluoyl chloride (34.0 mg, 0.22 mmol). Pyrrole regioisomers were distinguished by a combination of NMR experiments (NOE, COSY, NOESY-2D).

Pyrroles with alkyne **2.4d** required two flash chromatography columns, first with hexanes/ethyl acetate (9/1), and a second column with toluene/ethyl acetate (9/1) as eluent. The regioselectivity of these pyrroles was determined with the analogous N-ethyl substituted products, as these were not complicated by overlapping peaks in the ¹H NMR spectra.

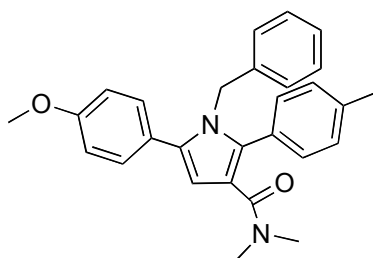
Pyrrole with alkyne **2.4f** required 18 h for cycloaddition, and flash chromatography column with hexanes/ethyl acetate (9/1) as eluent.

1-benzyl-2-(4-methoxyphenyl)-N,N-dimethyl-5-(p-tolyl)-1H-pyrrole-3-
carboxamide



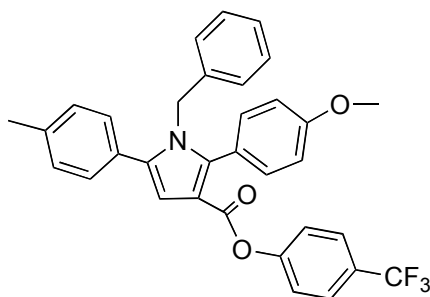
Isolated yield: 88%. **¹H NMR** (400 MHz, CDCl₃) δ (ppm): 7.24 (d, J = 9.6 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.12-7.10 (m, 5H), 6.81 (d, J = 8.4 Hz, 2H), 6.66-6.64 (m, 2H), 6.44 (s, 1H), 5.11 (s, 2H), 3.79 (s, 3H), 2.89 (br, 3H), 2.67 (br, 3H), 2.33 (s, 3H). **¹³C NMR** (75.5 MHz, CDCl₃) δ (ppm): 168.8, 159.1, 138.8, 137.1, 135.5, 133.8, 131.1, 130.1, 129.1, 129.0, 128.3, 126.9, 125.9, 124.6, 118.4, 113.8, 109.5, 55.2, 48.5, 38.8, 34.9, 21.2. **HRMS** (ESI⁺) for C₂₈H₂₉O₂N₂⁺; calculated: 425.22235, found: 425.22082.

1-benzyl-2-(4-methoxyphenyl)-N,N-dimethyl-5-(p-tolyl)-1H-pyrrole-3-
carboxamide



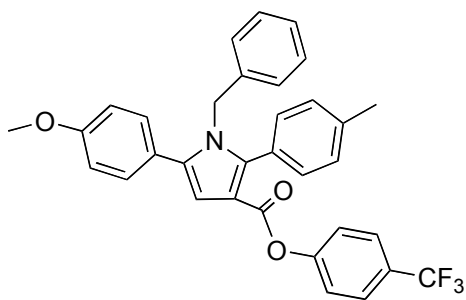
Isolated yield: 58%. **¹H NMR** (500 MHz, CDCl₃) δ (ppm): 7.25 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.12-7.08 (m, 5H), 6.83 (d, J = 8.5 Hz, 2H), 6.66-6.64 (m, 2H), 6.41 (s, 1H), 5.10 (s, 2H), 3.79 (s, 3H), 2.89 (br, 3H), 2.65 (br, 3H), 2.32 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 168.8, 159.0, 138.8, 137.4, 135.4, 133.8, 130.5, 129.6, 129.3, 129.1, 128.3, 126.8, 125.9, 125.5, 118.4, 113.8, 109.5, 55.2, 48.5, 38.7, 34.9, 21.2. **HRMS** (ESI⁺) for C₂₈H₂₉O₂N₂⁺; calculated: 425.22235, found: 425.22089.

4-(trifluoromethyl)phenyl 1-benzyl-2-(4-methoxyphenyl)-5-(p-tolyl)-1H-pyrrole-3-carboxylate



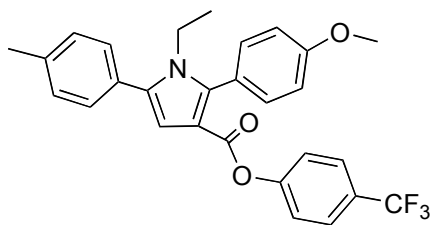
Isolated yield: 54%. **¹H NMR** (500 MHz, CDCl₃) δ (ppm): 7.58 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.0 Hz, 2H), 7.17-7.15 (m, 7H), 6.92 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.69-6.67 (m, 2H), 5.08 (s, 2H), 3.78 (s, 3H), 2.36 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 162.4, 159.7, 153.6, 141.4, 138.0, 137.8, 135.6, 131.8, 129.3, 129.2, 128.4, 127.2 (q, ²*J*_{C-F} = 32.8 Hz), 127.1, 126.4 (q, ³*J*_{C-F} = 3.7 Hz), 125.9, 124.0 (q, ¹*J*_{C-F} = 270.0 Hz), 123.6, 122.3, 113.5, 112.2, 110.8, 55.2, 48.5, 21.2. **HRMS** (ESI⁺) for C₃₃H₂₇O₃NF₃⁺; calculated: 542.19375, found: 542.19361.

4-(trifluoromethyl)phenyl 1-benzyl-5-(4-methoxyphenyl)-2-(p-tolyl)-1H-pyrrole-3-carboxylate



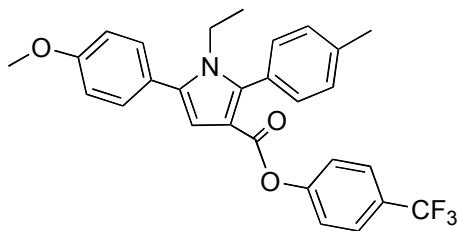
Isolated yield: 44%. **¹H NMR** (500 MHz, CDCl₃) δ (ppm): 7.58 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 6.5 Hz, 2H), 7.20 (t, *J* = 6.0 Hz, 2H), 7.18-7.13 (m, 7H), 6.89 (s, 1H), 6.87 (d, *J* = 7.0 Hz, 2H), 6.69-6.67 (m, 2H), 5.06 (s, 2H), 3.81 (s, 3H), 2.33 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 162.3, 159.4, 153.6, 141.4, 138.4, 138.0, 135.3, 130.7, 130.4, 128.8, 128.4₃, 128.3₈, 127.2 (q, ²*J*_{C-F} = 32.6 Hz), 127.1, 126.4 (q, ³*J*_{C-F} = 3.7 Hz), 125.9, 124.6, 124.0 (q, ¹*J*_{C-F} = 271.8 Hz), 122.3, 113.9, 112.1, 110.7, 55.3, 48.5, 21.4. **HRMS** (ESI⁺) for C₃₃H₂₇O₃NF₃⁺; calculated: 542.19375, found: 542.19269.

4-(trifluoromethyl)phenyl 1-ethyl-2-(4-methoxyphenyl)-5-(p-tolyl)-1H-pyrrole-3-carboxylate



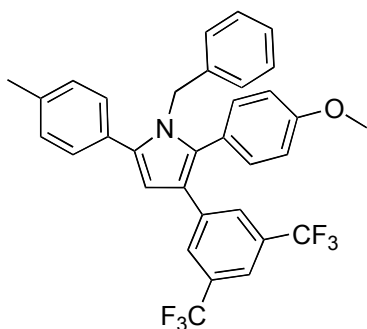
Isolated yield: 41%. **¹H NMR** (400 MHz, CDCl₃) δ (ppm): 7.58 (d, *J* = 8.8 Hz, 2H), 7.41-7.37 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 2.43 (s, 3H), 0.93 (t, *J* = 7.6 Hz, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 162.4, 159.8, 153.7, 140.6, 137.9, 134.6, 131.8, 129.8, 129.34, 128.29, 127.2 (q, ²*J*_{C-F} = 32.3 Hz), 126.4 (q, ³*J*_{C-F} = 4.1 Hz), 124.0 (q, ¹*J*_{C-F} = 270.3 Hz), 124.0, 122.3, 113.7, 111.7, 110.7, 55.2, 39.9, 21.3, 16.2. **HRMS** (ESI⁺) for C₂₈H₂₅O₃NF₃⁺; calculated: 480.17810, found: 480.17751.

4-(trifluoromethyl)phenyl 1-ethyl-5-(4-methoxyphenyl)-2-(p-tolyl)-1H-pyrrole-3-carboxylate



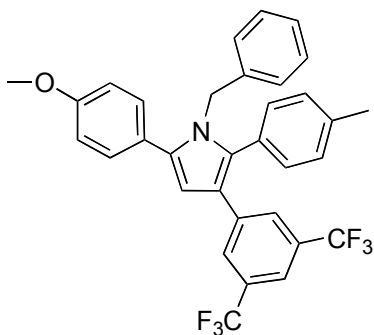
Isolated yield: 55%. **¹H NMR** (500 MHz, CDCl₃) δ (ppm): 7.56 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 6.5 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 6.5 Hz, 2H), 6.78 (s, 1H), 3.89 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 2.40 (s, 3H), 0.93 (t, *J* = 7.0 Hz, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 162.4, 159.4, 153.7, 140.6, 138.4, 134.3, 130.7, 130.4, 128.9₃, 128.9₀, 127.1 (q, ²*J*_{C-F} = 32.9 Hz), 126.3 (q, ³*J*_{C-F} = 3.7 Hz), 125.0, 124.0 (q, ¹*J*_{C-F} = 271.5 Hz), 122.3, 114.0, 111.6, 110.5, 55.3, 39.8, 21.4, 16.2. **HRMS** (ESI⁺) for C₂₈H₂₅O₃NF₃⁺; calculated: 480.17810, found: 480.17825.

1-benzyl-3-(3,5-bis(trifluoromethyl)phenyl)-2-(4-methoxyphenyl)-5-p-tolyl-1H-pyrrole



Isolated yield: 86%. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.60 (s, 2H), 7.52 (s, 1H), 7.31 (d, $J = 7.6$ Hz, 2H), 7.17-7.15 (m, 5H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.83 (d, $J = 9.2$ Hz, 2H), 6.71 (m, 2H), 6.59 (s, 1H), 5.10 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H). ^{13}C $\{^1\text{H}, ^{19}\text{F}\}$ NMR (100.6 MHz, CDCl_3) δ (ppm): 159.9, 138.9, 138.6, 137.5, 136.1, 133.2, 132.4, 131.2, 130.0, 129.3, 129.1, 128.4, 127.0, 126.0, 124.2, 123.6₁, 123.5₉, 120.4, 118.2, 114.4, 108.3, 55.4, 48.5, 21.3. ^{13}C $\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ (ppm): 159.8, 138.8, 138.5, 137.4, 136.0, 133.0, 132.3, 131.4, 131.2, 130.9, 130.7, 129.9, 129.2, 129.0, 128.3, 126.9, 125.9, 124.6, 124.1, 122.4, 120.3, 118.1₆, 118.1₃, 118.1₀, 118.0₇, 114.3, 108.1₉, 55.3, 48.4, 21.2. HRMS (ESI^+) for $\text{C}_{33}\text{H}_{26}\text{F}_6\text{NO}^+$; calculated: 566.1913, found: 566.1911.

1-benzyl-3-(3,5-bis(trifluoromethyl)phenyl)-5-(4-methoxyphenyl)-2-p-tolyl-1H-pyrrole



Isolated yield: 62%. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.58 (s, 2H), 7.51 (s, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.16-7.14 (m, 3H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.06 (d, $J = 8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.70 (m, 2H), 6.55 (s, 1H), 5.08 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H). ^{13}C $\{^1\text{H}, ^{19}\text{F}\}$ NMR (100.6 MHz, CDCl_3) δ (ppm): 159.2, 138.9, 138.6, 138.5, 135.8, 133.2, 131.1, 130.9, 130.6, 129.6, 129.0, 128.4, 127.1, 127.0, 126.0, 125.4, 123.6, 120.2, 118.2, 114.0, 108.2, 55.4, 48.4, 21.3. ^{13}C $\{^1\text{H}\}$ NMR (125.7 MHz, CDCl_3) δ (ppm): 159.1, 138.8, 138.5, 138.4, 135.7, 133.1, 132.3, 131.4, 131.1, 130.9, 130.8, 130.6, 130.5, 129.5, 129.2, 129.0, 128.9, 128.3, 127.0, 126.9₅, 126.9₂, 126.7, 125.9, 125.3, 124.6, 122.4, 120.2, 120.1, 118.1₄, 118.1₁, 118.0₈,

118.05, 114.3, 113.9, 108.1, 55.3, 48.4, 21.2. **HRMS** (ESI⁺) for C₃₃H₂₆F₆NO⁺; calculated: 566.1913, found: 566.1911.

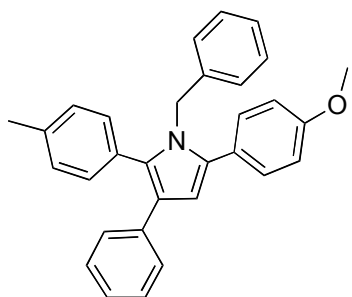
Pyrroles of alkynes **2.4e**, **2.4g** and **2.4h**.³⁰

In a glovebox, (4-OMeC₆H₄)HC=NCH₂C₆H₅ (112.6 mg, 0.50 mmol) and *p*-toluoyl chloride (85.0 mg, 0.55 mmol) were mixed in 1 mL CH₃CN and allowed to stand for 30 min. This solution was added to [Pd(allyl)Cl]₂ (13 mg, 7 mol%) and P(*o*-tolyl)₃ (23 mg, 15 mol%) in 5 mL of CH₃CN. The reaction mixture was transferred to a 50 mL reaction bomb, and *N,N*-diisopropylethylamine (90 mg, 0.70 mmol) in 5 mL of THF was added. The solution was evacuated, carbon monoxide (4 atm) added, and the solution stirred at 45 °C for 16 h. Carbon monoxide was removed and alkyne **2.4e** (153 mg, 1.5 mmol) was added. The solution was heated at 55 °C for 2 days. The solution was concentrated in vacuo and the product was purified by flash chromatography with hexanes/ethyl acetate (9/1) as eluent to afford pyrrole **A** (85.8 mg, 40% of yield). Pyrrole **B** was formed by the same procedure with (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (104.6 mg, 0.50 mmol) and *p*-methoxybenzoyl chloride (93.8 mg, 0.55 mmol). Pyrrole regioisomers were distinguished by a combination of NMR experiments (NOE, COSY, NOESY-2D).

Reaction with alkyne **2.4g** required 3 days at room temperature for cycloaddition, and was purified by two flash chromatography columns, first with hexanes/ethyl acetate (9/1) and a second column with toluene/ethyl acetate (9/1) as eluent.

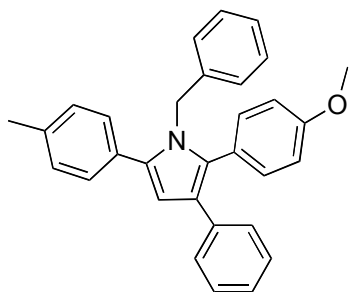
Pyrroles with alkyne **2.4f** required 3 days at room temperature for cycloaddition.

1-benzyl-5-(4-methoxyphenyl)-3-phenyl-2-(p-tolyl)-1H-pyrrole



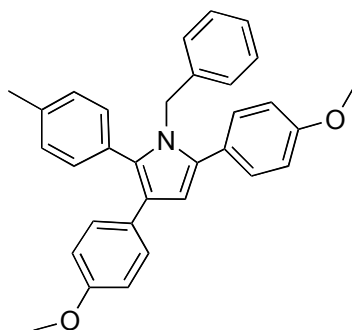
Isolated yield: 40%. **¹H NMR** (400 MHz, CDCl₃) δ (ppm): 7.30 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.18-7.04 (m, 10H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 7.6 Hz, 2H), 6.51 (s, 1H), 5.05 (s, 2H), 3.80 (s, 3H), 2.32 (s, 3H). **¹³C NMR** (75.5 MHz, CDCl₃) δ (ppm): 159.1, 139.6, 137.5, 136.6, 135.3, 132.0, 131.4, 130.6, 130.4, 129.3, 128.4, 128.2, 127.7, 126.9, 126.3, 126.2, 125.2, 123.0, 114.0, 109.1, 55.5, 48.4, 21.5. **HRMS** (ESI⁺) for C₃₁H₂₈NO⁺; calculated: 430.2165, found: 430.2168.

1-benzyl-2-(4-methoxyphenyl)-3-phenyl-5-(p-tolyl)-1H-pyrrole



Isolated yield: 43%. **¹H NMR** (400 MHz, CDCl₃) δ (ppm): 7.31 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.19-7.07 (m, 10H), 6.78 (d, *J* = 7.2 Hz, 2H), 6.72 (d, *J* = 6.4 Hz, 2H), 6.56 (s, 1H), 5.07 (s, 2H), 3.79 (s, 3H), 2.35 (s, 3H). **¹³C NMR** (75.5 MHz, CDCl₃) δ (ppm): 159.3, 139.6, 137.1, 136.6, 135.5, 132.7, 132.0, 130.8, 129.3, 129.2, 128.4, 128.3, 127.7, 126.9, 126.2, 125.7, 125.2, 123.1, 114.0, 109.1, 55.4, 48.5, 21.4. **HRMS** (ESI⁺) for C₃₁H₂₈NO⁺; calculated: 430.2165, found: 430.2168.

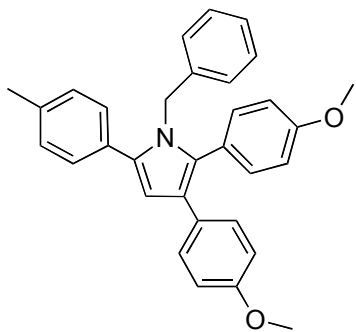
1-benzyl-3,5-bis(4-methoxyphenyl)-2-(p-tolyl)-1H-pyrrole



Isolated yield: 38%. **¹H NMR** (500 MHz, CDCl₃) δ (ppm): 7.30 (d, *J* = 7.0 Hz, 2H), 7.17-7.04 (m, 9H), 6.85 (d, *J* = 6.5 Hz, 2H), 6.73 (d, *J* = 7.0 Hz, 2H), 6.69 (d, *J* = 6.5 Hz, 2H), 6.46 (s, 1H), 5.04 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 2.32 (s, 3H). **¹³C NMR**

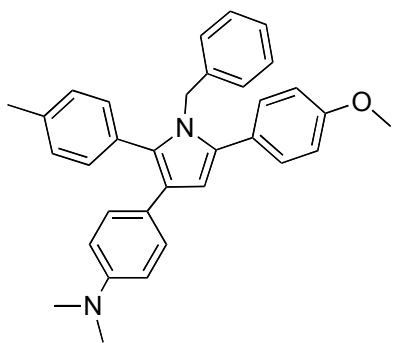
(125.7 MHz, CDCl₃) δ (ppm): 158.8, 157.2, 139.5, 137.1, 134.9, 131.2, 130.3, 130.2, 129.0₉, 129.0₆, 128.5, 128.2, 126.6, 126.1, 126.0, 122.4, 113.7, 113.5, 108.7, 55.2, 55.1, 48.2, 21.3. **HRMS** (APCI⁺) for C₃₂H₃₀O₂N⁺; calculated: 460.22711, found: 460.22613.

1-benzyl-2,3-bis(4-methoxyphenyl)-5-(*p*-tolyl)-1*H*-pyrrole



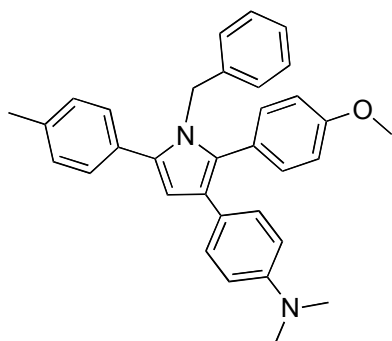
Isolated yield: 40%. **¹H NMR** (400 MHz, CDCl₃) δ (ppm): 7.34 (d, *J* = 8.0 Hz, 2H), 7.22-7.13 (m, 9H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.78-6.74 (m, 4H), 6.55 (s, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 2.37 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 159.0, 157.3, 139.5, 136.8, 135.2, 132.6, 131.1, 130.7, 129.1₃, 129.0₇, 128.9, 128.5, 128.2, 126.7, 126.0, 125.6, 122.6, 113.8, 113.6, 108.8, 55.2, 55.1, 48.2, 21.3. **HRMS** (APCI⁺) for C₃₂H₃₀O₂N⁺; calculated: 460.22711, found: 460.22623.

4-(1-benzyl-5-(4-methoxyphenyl)-2-*p*-tolyl-1*H*-pyrrol-3-yl)-*N,N*-dimethylaniline



Isolated yield: 30%. **¹H NMR** (400 MHz, CDCl₃) δ (ppm): 7.33 (d, *J* = 8.5 Hz, 2H), 7.17-7.10 (m, 7H), 7.07 (d, *J* = 8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 6.5 Hz, 2H), 6.66-6.63 (br, 2H), 6.49 (s, 1H), 5.07 (s, 2H), 3.81 (s, 3H), 3.07-2.91 (br, 6H), 2.34 (s, 3H). **¹³C NMR** (125.7 MHz, CDCl₃) δ (ppm): 158.7, 139.6, 137.0, 134.8, 131.3, 130.6, 130.5, 130.3, 129.0, 128.2₃, 128.1₇, 126.6, 126.3, 126.0, 122.9, 113.7, 112.7, 110.6, 108.7, 55.2, 48.2, 40.8, 21.3. **HRMS** (ESI⁺) for C₃₃H₃₃N₂O⁺; calculated: 473.25874, found: 473.25912.

4-(1-benzyl-2-(4-methoxyphenyl)-5-*p*-tolyl-1*H*-pyrrol-3-yl)-*N,N*-dimethylaniline



Isolated yield: 40%. ¹H NMR (500 MHz, CDCl₃)

δ (ppm): 7.33 (d, *J* = 8.0 Hz, 2H), 7.17-7.12 (m, 9H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 7 Hz, 2H), 6.66-6.63 (br, 2H), 6.54 (s, 1H), 5.09 (s, 2H), 3.80 (s, 3H), 2.99-2.90 (br, 6H), 2.36 (s, 3H). ¹³C

NMR (125.7 MHz, CDCl₃) δ (ppm): 158.9, 139.6, 136.6, 135.03, 132.6, 130.9, 130.8, 130.5,

129.1, 128.9, 128.2, 126.6, 126.0, 125.9, 123.0, 113.7, 112.8, 110.6, 108.7, 55.1, 48.3, 40.8, 21.2. HRMS (ESI⁺) for C₃₃H₃₃N₂O⁺; calculated: 473.25874, found: 473.25915.

2.4.4 Tables 2.1 and 2.2

Each entry of the tables is the average value of the experiment repeated a minimum of two times.

Regioselectivity study with Münchnone 2.1a: In a screw cap NMR tube containing Münchnone **2.1a** (37.1 mg, 0.1 mmol) in 1 mL of CDCl₃ with an internal standard (benzyl benzoate) was added the alkyne (0.2 mmol). The reaction was followed by ¹H NMR analysis for 1 to 6 days, depending on the alkyne. The ratio of the regioisomers was determined by ¹H NMR spectra of the crude reaction mixture related to the internal standard.

Regioselectivity study with Münchnone Imine 2.2a: A solution of (4-CH₃C₆H₄)HC=N(CH₂C₆H₅) (42.0 mg, 0.2 mmol) and *p*-methoxybenzoyl chloride (40.9 mg, 0.24 mmol) in 0.3 mL CDCl₃ was prepared in a glovebox with an internal standard (benzyl benzoate) and allowed to stand for 30 min. Cyclohexyl isocyanide (24.0 mg, 0.22 mmol) was added, and after 1 h K₃PO₄ (128 mg, 0.6 mmol) was added. The solution was stirred for 1 h and then transferred to a screw cap NMR tube with the alkyne (0.6 mmol) and the final volume of CDCl₃ was

adjusted to 1.8 mL. The reaction was followed by ^1H NMR analysis for 1 to 15 days. The ratio of the regioisomers was determined by ^1H NMR spectra of the crude reaction mixture related to the internal standard.

Regioselectivity study with phospho-Münchnone 2.3a: In a screw cap NMR tube containing phospho-Münchnone **2.3a** (55.9 mg, 0.1 mmol) in 1 mL of CDCl_3 with an internal standard (benzyl benzoate) was added the alkyne (0.2-0.5 mmol). The reaction was followed by ^1H NMR analysis for 1 to 2 days. The ratio of the regioisomers was determined by ^1H NMR spectra of the crude reaction mixture related to the internal standard.

2.4.5 Table 2.3

To a CDCl_3 solution of two alkynes in 1:1 ratio (0.5 mmol) in a screw cap NMR tube with an internal standard (benzyl benzoate) was added Münchnone **2.1a** (37.2 mg, 0.1 mmol), and the final volume of CDCl_3 adjusted to 1.5 mL. The reaction was followed by ^1H NMR analysis for 1 to 6 days. The ratio of alkynes reacted was determined by ^1H NMR spectra of the crude reaction mixture related to the internal standard.

Competition experiment between alkynes **2.4c** and **2.4f** was set up in a 1:9 ratio respectively.

Competition experiments with phospho-Münchnone **2.3a** followed the same procedure as Münchnone **2.1a**.

2.4.6 Computational Methods

Density functional theory calculations were performed using the Gaussian 03³¹ and Gaussian 09³² software. Geometry optimizations, conformational searching, and vibrational frequency calculations were conducted at the B3LYP/6-31+G(d) level.³³ The nature of each stationary point was ascertained by vibrational frequency analysis, and transition states were further verified by IRC calculations³⁴ where appropriate. Enthalpies and free energies were obtained from the unscaled B3LYP frequencies and are quoted at 298.15 K and 1 mol/L. Solvation energies in chloroform were calculated with the SMD model.³⁵ Single-point electronic energy calculations were also performed at the M06-2X/6-311+G(d,p) level,³⁶ for comparison to the B3LYP data. The M06-2X results are provided in the Supporting Information.

2.5 References

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CHAPTER 3

Tunable Phosphorus-Based 1,3-Dipoles: Effect of PR_3 on Structure, Reactivity and Regioselectivity in Alkyne Cycloadditions

3.0 Preface

Chapter 2 described how the regioselectivity of alkyne cycloadditions with Münchnones, Münchnone imines, and phospho-Münchnones can vary with the nature of the eliminating unit in the mesoionic ring. In this chapter, we show how changes to the PR_3 unit in phospho-Münchnones can be used to modulate not only their ground state structure, but also reactivity and selectivity in alkyne cycloaddition. These changes can provide a novel route to fine tune regioselectivity in the reaction of unsymmetrical alkynes with phospho-Münchnones.

3.1 Introduction

Our laboratory has recently reported the one-pot synthesis of a new 1,3-dipole, phospho-Münchnone **3.1**, by the multicomponent coupling of imines, acid chlorides and the catechyl-substituted phosphonite $\text{PPh}(2\text{-catechyl})$ (Figure 3.1).¹ Phospho-Münchnone **3.1** is the valence tautomer of an amido-substituted phosphorus ylide (**3.2**, Scheme 3.1) and can be generated by deprotonation of an *in situ* generated phosphorus salt **3.3**, formed by addition of a phosphonite to an α -chloroamide **3.4**. The modular formation of **3.1**, coupled with its 1,3-dipolar cycloaddition reactions with alkynes, allows the synthesis of a variety of pyrroles by the systematic variation of the imine, the acid chloride and the alkyne units.

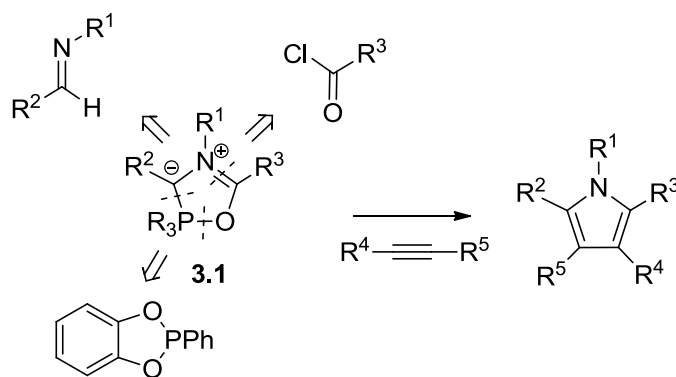
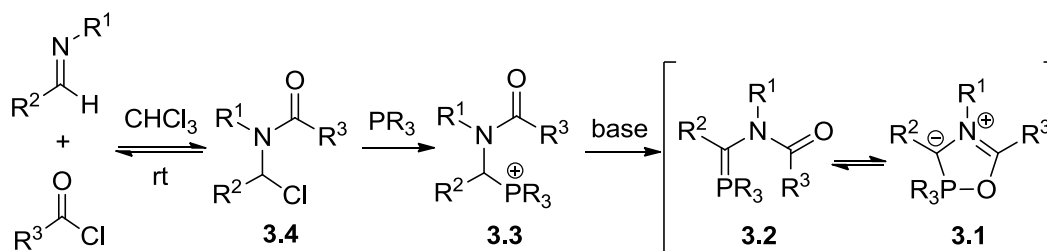


Figure 3.1: Modular Approach to Phospha-Münchnones **3.1**

Initial studies on this reaction showed that the nature of the PR_3 unit can have a significant influence on cycloaddition reactivity.¹⁻² Alkyne cycloaddition is most rapid with the phosphonite $\text{PPh}(\text{2-catechyl})$, while simple phosphines (e.g., PPh_3 , PCy_3 , PMe_3) do not mediate alkyne cycloaddition, and phosphites (e.g., P(OPh)_3 , $\text{P(OCH}_2\text{CF}_3)_3$) provide pyrroles in low yields. This was postulated to arise from the electronic features of the phosphorus reagent. With PPh_3 , the lack of cycloaddition reactivity was attributed to the disfavored chelation of the amide oxygen to the electron-rich phosphorus center, and the generation of an acyclic phosphonium ylide reagent **3.2** rather than **3.1**. Consistent with this analysis, the ^{31}P NMR chemical shift of this molecule (δ : 11.0 ppm, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Ph}$) is in the typical region of Wittig reagents (δ : +40 to -9 ppm).³ On the other hand, electron poor phosphites are more prone to cyclize to generate **3.1**, and display ^{31}P NMR signals in the range of five coordinated phosphorus (δ : -20 to -40 ppm).³ However, the poor nucleophilicity of phosphites limits the formation of the phosphorus salt **3.3** and only low yields of pyrrole are obtained.



Scheme 3.1: One-Pot Synthesis of 1,3-Dipole **3.1**

The efficiency of the phosphonite PPh(2-catechyl) in mediating pyrrole formation is believed to arise from a balance in the phosphorus center, which has sufficient nucleophilicity to attack the *in situ* generated α -chloroamide **3.4**, yet is also sufficiently electron poor to accept chelation of the former amide oxygen to generate the 1,3-dipole **3.1**. Insights into the structure of PPh(2-catechyl) derived **3.1** were revealed by the crystal structure of the molecule (Figure 3.2).² This confirmed the cyclic form of **3.1a**, where the phosphorus adopts a pseudo-trigonal bipyramidal structure and has a strong interaction between the phosphorus and the former amide oxygen (P–O(3) = 1.7894(18) Å). The catechyl unit has a O(1)–P–O(2) bond angle of 90.71(9)° in **3.1a**, which is postulated to further favor the cyclization of the molecule through the relief of the ring strain of the catechyl ring in the tetracoordinate phosphorus **3.2**.

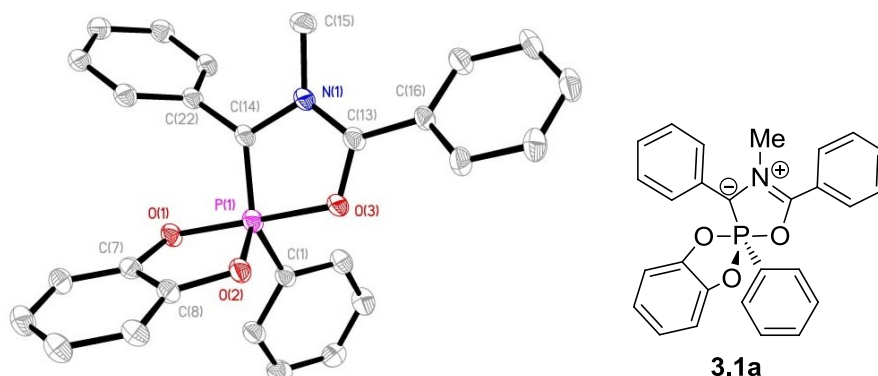


Figure 3.2: X-Ray Crystal Structure of PPh(2-catechyl)-Based 1,3-Dipole **3.1a**.

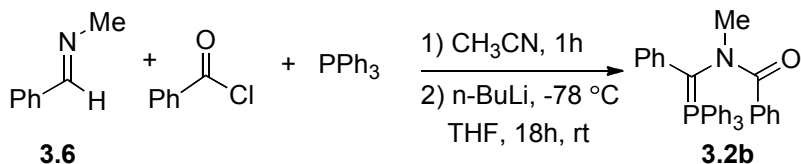
Selected bond lengths (Å) and angles (deg); P(1)–O(2): 1.6772(19), P(1)–C(14): 1.706(3), P(1)–O(1): 1.7281(18), P(1)–O(3): 1.7894(18), P(1)–C(1): 1.824(3), O(3)–C(13): 1.317(3), N(1)–C(13): 1.316(3), N(1)–C(14): 1.434(3), O(2)–P(1)–C(14): 126.90(12), O(2)–P(1)–O(1): 90.71(9), C(14)–P(1)–O(1): 93.09(11), O(2)–P(1)–O(3): 85.77(9), C(14)–P(1)–O(3): 86.78(11), O(1)–P(1)–O(3): 175.48(9), O(2)–P(1)–C(1): 105.66(12), O(1)–P(1)–C(1): 92.85(11), C(13)–O(3)–P(1): 114.86(17), C(13)–N(1)–C(14): 113.8(3), N(1)–C(13)–O(3): 112.5(2), N(1)–C(14)–P(1): 111.9(2).

A useful feature of these dipoles **3.1** is their modularity, where a range of phosphines can be incorporated into **3.1** by their reaction with imines and acid chlorides. This provides the opportunity to more closely probe the influence of the PR_3 unit on both the structure of **3.1/3.2**, and its reactivity with alkynes. These studies are the subject of this chapter.

3.2 Influence of PR_3 on Dipole Structure and Reactivity

3.2.1. Structure of PPh_3 Containing Wittig-Ylide

In order to more clearly understand the lack of cycloaddition with PPh_3 derived **3.2** as mentioned above, we have isolated and examined its structure. **3.2b** can be prepared by reaction of imine **3.6**, benzoyl chloride and PPh_3 in acetonitrile (forming the phosphonium salt **3.3b**), followed by deprotonation with BuLi (Scheme 3.2). The phosphorus ylide **3.2b** is generated quantitatively and isolated in 82% yield by precipitation in Et_2O . ^{13}C NMR analysis of **3.2b** reveals a signal at 176.1 ppm for the carbonyl unit derived from the acid chloride. This is in the typical region of simple amides, and it shows no perturbation as expected for P-O interaction in the cyclic 1,3-dipole. In addition, as previously noted, the ^{31}P NMR signal of **3.2b** (δ : 11.0 ppm) is in a region typical of PPh_3 -based Wittig reagents. These data imply that **3.2b** exists as an acyclic structure.



Scheme 3.2: Synthesis of PPh_3 -Based Wittig Reagent **3.2b**

To further confirm the structure, crystals were grown by slow diffusion of Et_2O into a saturated benzene solution of **3.2b**. The X-Ray crystal structure of **3.2b** was obtained, and the resulting ORTEP is shown in Figure 3.3. As it can be seen, the amide carbonyl oxygen in **3.2b** is oriented away from the phosphorus, which places O(3) well beyond bonding distance to P(1) (4.443(1) Å). The

carbonyl and C(13)-N(1) bond lengths and angles are typical of simple amides (C(13)–O(3): 1.2286(18) Å, N(1)–C(13): 1.3660(18) Å).⁴ The C(13)–N(1)–C(14)–P(1) torsion of 78.3° places the nitrogen lone pair nearly perpendicular to the P(1)–C(14) bond, which would minimize any destabilizing interaction between N(1) lone pair and the formal carbanion at C(14). The P(1)–C(14) bond length of 1.7189(14) Å and the pseudo tetrahedral configuration at phosphorus are both similar to other structurally characterized phosphorus ylides.^{3b,5} Overall, these data clearly demonstrate that **3.2b** exists in its acyclic, Wittig-type form in the ground state, with no interaction between the phosphorus and the amide oxygen.

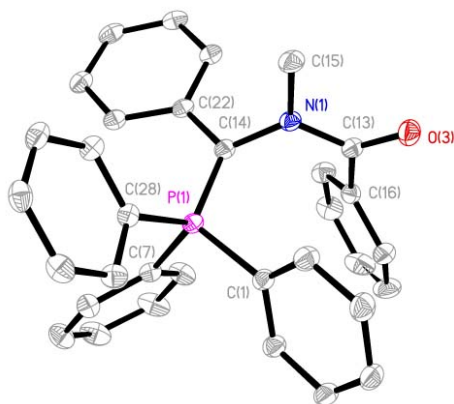


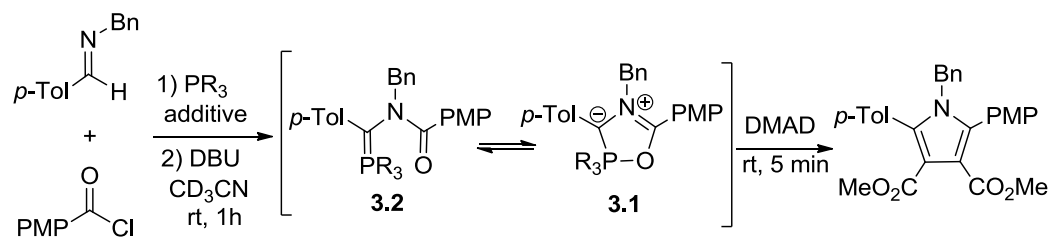
Figure 3.3: X-Ray Crystal Structure of PPh₃-Based **3.2b**. Selected bond (Å) and angles (deg): P(1)–C(14), 1.7189(14); P(1)–C(1), 1.8101(14); N(1)–C(13), 1.3660(18); N(1)–C(14), 1.4356(18); N(1)–C(15), 1.4652(18); O(3)–C(13), 1.2286(18); C(13)–C(16), 1.501(2); C(14)–P(1)–C(1), 112.55(7); C(14)–P(1)–C(7), 109.36(7); C(1)–P(1)–C(7), 106.98(7); C(13)–N(1)–C(14), 123.89(12), O(3)–C(13)–N(1), 121.87(13); N(1)–C(13)–C(16), 117.89(12); N(1)–C(14)–C(22), 118.25(12); N(1)–C(14)–P(1), 118.12(10).

3.2.2. Synthesis and Reactivity of Phosphite Derived 1,3-Dipoles

Our previous studies demonstrated that phosphite derived phosphamünchnones **3.1** are also reactive towards 1,3-dipolar cycloaddition. However, triarylphosphites are limited by their poor nucleophilicity, and react slowly with

α -chloroamide **3.4**, leading to low yields of pyrroles (Table 3.1, entry 3). In the case of trialkylphosphites, the absence of pyrrole formation results from the inability to produce phosphonium salt intermediate **3.3** due to the phosphine dealkylation to produce the corresponding phosphonate via a Michaelis-Arbuzov rearrangement (Table 3.1, entry 4).⁶

Table 3.1: Effect of PR₃ on Pyrrole Synthesis.^a



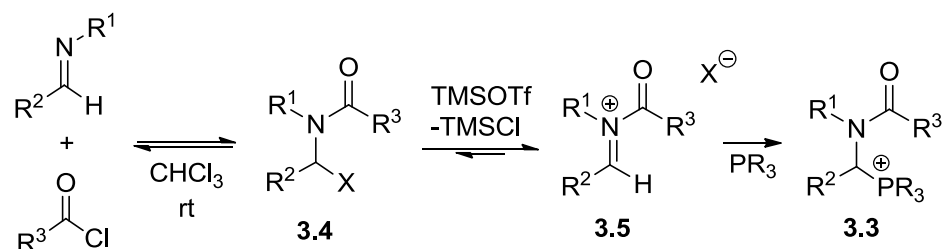
PMP: *p*-MeOC₆H₄

entry	PR ₃	³¹ P of 3.2 / 3.1 (ppm)	additive	yield ^b
1	PPh ₃	10.2	—	0
2	PPh(2-catechyl)	— 16.9	—	85%
3	P(OPh) ₃	30.2/ - 44.0 (1.2/1)	—	25%
4	P(OEt) ₃	— ^c	—	—
5	P(OPh) ₃	30.2/ - 44.0 (1.2/1)	TMSOTf	94%
6	P(OEt) ₃	44.4	TMSOTf	0
7	P(OCH ₂ CF ₃) ₃	47.0/ -21.3 (1.8/1)	TMSOTf	92%
8	PF(2-catechyl)	— 22.0 ^d	TMSOTf	61%

^a Imine (41.9 mg, 0.20 mmol), acid chloride (34.1 mg, 0.20 mmol), 0.5 mL CD₃CN, rt, 30 min; followed by additive (0.20 mmol), PR₃ (0.20 mmol), rt, 1h; DBU (60 mg, 0.40 mmol), DMAD (74 μ L, 0.60 mmol), rt, 5 min. ^b Isolated. ^c Arbuzov product obtained. ^d ¹J_{PF} = 1296.2 Hz.

While the yield of pyrrole is very low with P(OPh)₃, this reagent is an interesting potential alternative to PPh(2-catechyl). In contrast to PPh(2-catechyl), P(OPh)₃ is commercially available, inexpensive and more air and moisture stable.

One way to improve the formation of the phosphonium salt **3.3** with phosphites (Scheme 3.1) would be to activate the α -chloroamide **3.4** towards nucleophilic attack. It is known that α -chloroamides exist in equilibrium with the *N*-acyliminium salt **3.5** (Scheme 3.3).⁷ This equilibrium is shifted towards the covalent isomer **3.4** in organic solvents. We postulated that exchanging the chloride with less coordinating anions X^- would shift this equilibrium towards the more reactive iminium salt **3.5** and allow phosphites to be used in this chemistry. This can be addressed by the addition of TMSOTf, which is known to trap the chloride ion by forming the stable TMSCl, and generate the more electrophilic *N*-acyliminium triflate salt ($X = \text{OTf}$).⁸



Scheme 3.3: Formation of Phosphorus Salt **3.3**.

This approach was tested with $(\text{PhO})_3\text{P}$, which in the presence of TMSOTf results in the quantitative formation of the phosphonium salt **3.3** within 30 min at ambient temperature. This intermediate can be deprotonated with DBU base, and undergoes cycloaddition with DMAD to form pyrrole in very good yield (Table 3.1, entry 5). This approach can also be adapted to other commercially available phosphites, such as $\text{P}(\text{OCH}_2\text{CF}_3)_3$ as well as the weakly nucleophilic $\text{PF}(\text{2-catechyl})$ (entries 7, 8). However the more electron rich $\text{P}(\text{OEt})_3$ did not undergo cycloaddition (entry 6).

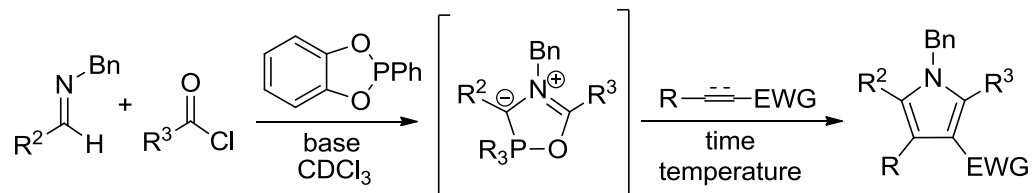
As mentioned above, insights into the structure of the *in situ* generated **3.1/3.2** in Table 3.1 can be obtained by monitoring the reaction by ^{31}P NMR spectroscopy. As shown in the table, there is a strong correlation between the ^{31}P NMR data of intermediates **3.1/3.2** and their reactivity with DMAD. In general, intermediates that are unreactive towards alkynes (entries 1 and 6) have ^{31}P NMR

resonances in a similar region to those often observed in related Wittig-type reagents. On the other hand, intermediates with upfield ^{31}P NMR resonances (δ : -16.9 to -22.0; entries 2 and 8), correlating with the five-coordinate **3.1**, can react with alkynes to form pyrroles. Interestingly, two different signals are observed with $\text{P}(\text{OPh})_3$ and $\text{P}(\text{OCH}_2\text{CF}_3)_3$, implying that the two structures, **3.1** and **3.2**, are present in solution (entries 5 and 7).⁹ This suggests that the phosphites are less able to stabilize the cyclic form relative to the catechyl substituted $\text{PPh}(\text{2-catechyl})$. This is presumably due to the angle strain of the catechyl in the acyclic **3.2**, imparting “strain release Lewis acidity”^{10,11} to the PR_3 unit. This favors the formation of the five coordinate P(V) compound, where the catechyl unit can adopt a 90.71° O(1)-P-O(2) bond angle in the product (cf. Figure 3.2).

3.3 Influence of PR_3 on Regioselectivity

The above section demonstrates that the electronic and steric features of the PR_3 unit can significantly influence the ground state structure of **3.1/3.2**. Based upon this, we became interested in the ability of the PR_3 to also influence regioselectivity in cycloaddition reactions. As shown in Chapter 2, (2-catechyl) PPh -based 1,3-dipoles undergo regioselective cycloadditions with electron poor alkynes, while Münchnones give a mixture of regioisomers. Examples of these are shown in Table 3.2. Each of the reactions yields only one observable regioisomer, where the electron withdrawing alkyne/alkene substituent directed away from the phosphorus-bound carbon.

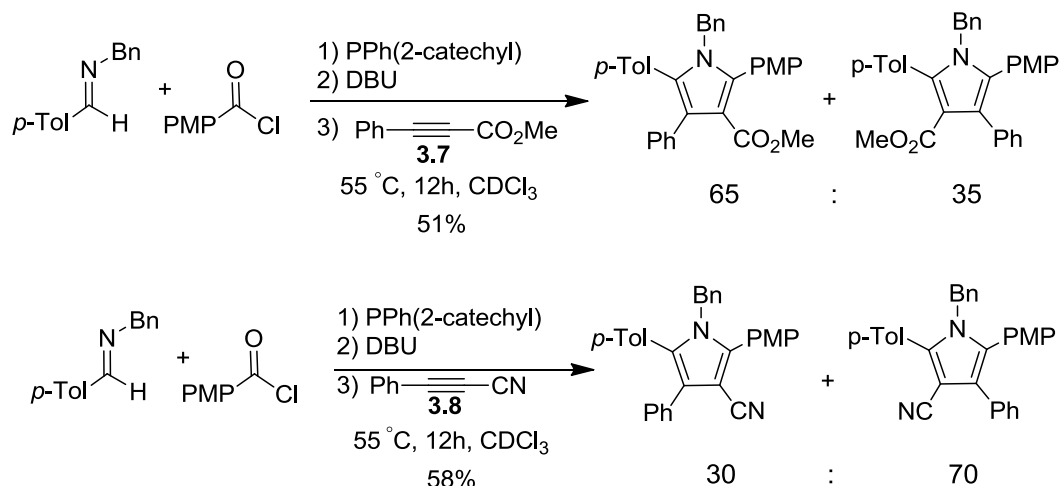
Table 3.2: Cycloaddition Regioselectivity with PPh(2-catechyl)-Based 1,3-Dipole^a



Entry	R ²	R ³	Alkyne	base	time	temp.	Yield (%)
1	<i>p</i> -Tol	PMP		DBU	5 min	rt	92
2	<i>p</i> -Tol	PMP	Me—C≡C—CO ₂ Me	DBU	17 h	rt	52
3 ^b	<i>p</i> -Tol	PMP	<i>n</i> -Bu—C≡C—CO ₂ Me	LiHMDS	8 h	45 °C	50
4	PMP	<i>p</i> -Tol		DBU	5 min	rt	92
5	PMP	<i>p</i> -Tol	Me—C≡C—CO ₂ Me	DBU	17 h	rt	47
6 ^b	PMP	<i>p</i> -Tol	<i>n</i> -Bu—C≡C—CO ₂ Me	LiHMDS	8 h	45 °C	50

^a Procedure described in Table 3.1. ^b in CH₂Cl₂.

With less electron poor alkynes, however, cycloadditions are not regioselective with the PPh(2-catechyl)-based 1,3-dipole. For example, reactions with methyl phenylpropiolate (**3.7**) and phenylpropynenitrile (**3.8**) lead to a mixture of regioisomers (Scheme 3.4). In light of the data in Chapter 2, the lack of selectivity with these alkynes is not surprising. Methyl phenylpropiolate (**3.7**) has an ionization potential of 8.9 eV, which would place it in the intermediate, unselective region of the plot in Figure 2.2 (Chapter 2).



Scheme 3.4: Non-selective Cycloadditions with Alkynes **3.7** and **3.8**.

Considering the ability to vary the phosphorus unit in the 1,3-dipole without changing the product, we became interested in the influence of the PR_3 unit on regioselectivity. The results of theoretical investigations in Chapter 2 suggest that the degree of P-O bonding can have an influence on cycloaddition. In general, cycloadditions to form pyrroles with the alkyne electron-withdrawing unit away from the phosphorus-bound carbon (pyrrole A of Chapter two) proceed most rapidly via a stepwise rather than concerted cycloaddition, where there is little P-O bond compression in the transition state. This could be considered as a nucleophilic attack of the C2 on the electrophilic alkyne (Figure 3.4a). Conversely, cycloaddition to form the opposite pyrrole isomer (pyrrole B in Chapter 2) involves significant compression of the P-O bond in the transition state, with a shorter bond length of almost 0.1 Å in the most selective cycloadditions. While the reason for this is still under investigation, one possibility is that this creates a more electrophilic C3 for a nucleophilic attack of the alkyne (Figure 3.4b).

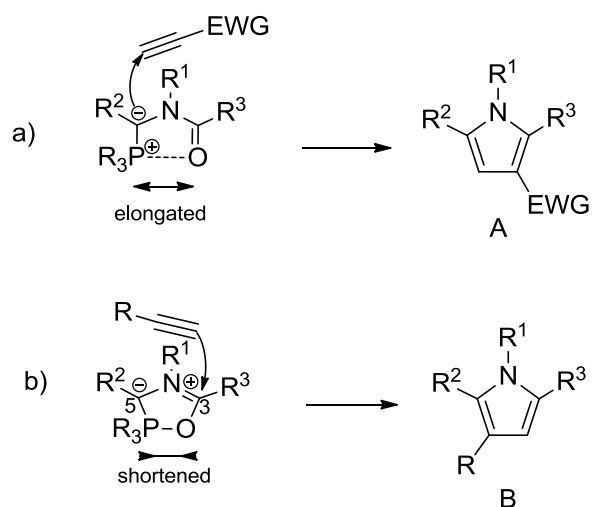
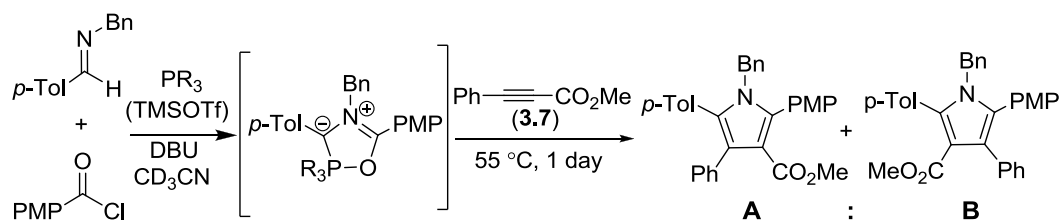


Figure 3.4: Transition States of PR_3 -Based 1,3-Dipoles in Alkyne Cycloadditions.

These data suggest that selectivity might be controlled by the ability of the phosphamünchnone to modulate the $\text{P}-\text{O}$ bond. A weakened $\text{P}-\text{O}$ bond in the ground state would presumably favor the top pathway in Figure 3.4, while phosphamünchnones that have an even stronger $\text{P}-\text{O}$ bonding interaction should favor the opposite isomer. As shown in sections 3.2 above, the nature of the PR_3 unit can influence the ability of the carbonyl oxygen to bond to phosphorus, with open phosphorus-ylides, cyclic 1,3-dipoles, and equilibrium between these all observed above. These features should therefore also affect regioselectivity. This was investigated with different phosphonite and phosphite reagents in cycloaddition with methyl phenylpropiolate **3.7** and phenyl propynenitrile **3.8**. The results are summarized in Tables 3.3 and 3.4.

Table 3.3: Cycloaddition Reactions with Methyl Phenylpropiolate **3.7**^a

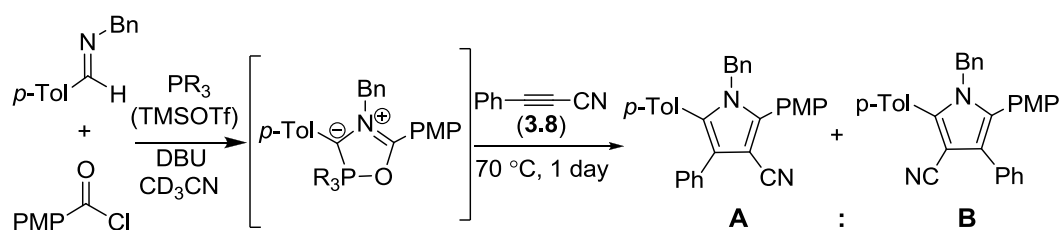
Entry	PR_3	ratio A : B	^{31}P of 3.1 / 3.2	Yield
1		58 : 42	-25.7 ppm	52 %
2		60 : 40	-25.3 ppm	64%
3		65 : 35	-17 ppm	51%
4		67 : 33	-27 ppm	55%
5		68 : 32	-20.5 ppm	55%
6 ^b		92 : 8	30.2 / -44 ppm 1.2 / 1 ratio	50%
7		96 : 4	47 / -21.3 ppm 1.8 / 1 ratio	30%

^a Table 3.1 procedure, cycloaddition at 55°C for 1 day. ^b MeLi in CH_2Cl_2 at -78°C

As shown in Table 3.3, catechyl-substituted phosphorus 1,3-dipoles were found to give the highest yields of pyrrole **B** with phenylpropiolate **3.7** (entries 1-5). The selectivity is slightly influenced by the third group on the phosphorus, but these effects are not large (from 58:42 to 68:32). However, the use of phosphites that lack the ring strain of the catechyl, and therefore disfavor cyclization, leads to

a shift in regioselectivity towards the formation of the opposite pyrrole A isomer. In the case of the trialkyl substituted phosphite $(\text{CF}_3\text{CH}_2\text{O})_3\text{P}$, there is almost total regioselectivity for pyrrole A (96:4, entry 7).

Table 3.4: Cycloaddition Reactions with Methyl Phenylpropiolate **3.8**^a



Entry	PR ₃	ratio A:B	³¹ P of 3.1/3.2	Yield
1		30 : 70	-17 ppm	58 %
2		34 : 66	-20.5 ppm	60%
3		35 : 65	-25.3 ppm	23%
4		40 : 60	-25.7 ppm	36%
5 ^b		55 : 45	30.2 / -44 ppm 1.2/1 ratio	50%
6		65 : 35	47 / -21.3 ppm 1.8/1 ratio	27%

^a Table 3.1 procedure, cycloaddition at 70 °C for 1 day. ^b MeLi in CH_2Cl_2 at -78 °C

A nearly identical trend in regioselectivity is observed with alkyne **3.8** (Table 3.4). In general, catechyl-substituted phosphonites and phosphites favor

pyrrole B (entries 1-4), and phosphites lead to more pyrrole A, including a reversal in selectivity to generate pyrrole A with $(\text{CF}_3\text{CH}_2\text{O})_3\text{P}$ (entry 6).

These data show that the PR_3 unit can be used to influence alkyne cycloaddition regioselectivity. These effects are also predictable. The ^{31}P NMR data for the catechyl-substituted phosphorus 1,3-dipoles all show a single upfield signal (δ : -17 to -27 ppm), as expected for a cyclic **3.1** structure. This presumably results from the presence of the strained catechyl unit, which is expected to favor cyclization to five coordinate **3.1** (Figure 3.5). As mentioned above, the strong P-O bond interaction in these dipoles is expected to favor pyrrole B (Figure 3.4). This is observed with both alkynes. Conversely, the non-catechyl containing phosphites examined all show two ^{31}P NMR signals, suggesting an equilibrium between the cyclic **3.1** and acyclic **3.2** structures. In the case of $(\text{CF}_3\text{CH}_2\text{O})_3\text{P}$, the open structure is formed in a 2/3 ratio. This data implies that there is a weaker P-O bond, which, as predicted by the theoretical model in Figure 3.4, favors a more nucleophilic 1,3-dipole and the generation of pyrrole A.

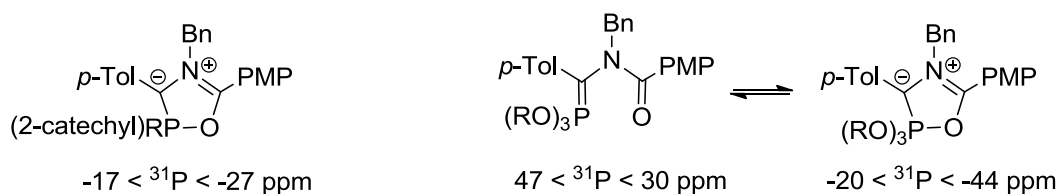


Figure 3.5: Cyclic vs. Acyclic 1,3-Dipoles

These results suggest that the ability of the phosphorus unit to fine tune regioselectivity in alkyne cycloadditions arises from influencing the degree of P-O bonding in the ground state. To confirm these important features, DFT calculations were carried out by Dr. Elizabeth Krenske and Prof. Ken Houk at UCLA.

3.4 Computational Studies of Geometries and Cycloaddition Barriers

3.4.1. Calculated Structures of Catechyl- and Non-Catechyl-Substituted 1,3-Dipoles

1,3-Dipoles with different phosphorus substituents were modeled by density functional theory calculations at the B3LYP/6-31+G(d) level in Gaussian 03¹² (Figure 3.6, cat = 2-catechyl). These models confirm that the catechyl substituent creates a P-O bond significantly shorter than in the dipole derived from (PhO)₃P (2.11 Å). They also show that regardless of the third group X in PX(2-catechyl), the P-O bond remains short (1.97 to 1.89 Å), and the catechyl unit has a geometrical preference to occupy an equatorial/axial arrangement (where it can have a preferred ca. 90° O-P-O bond angle).

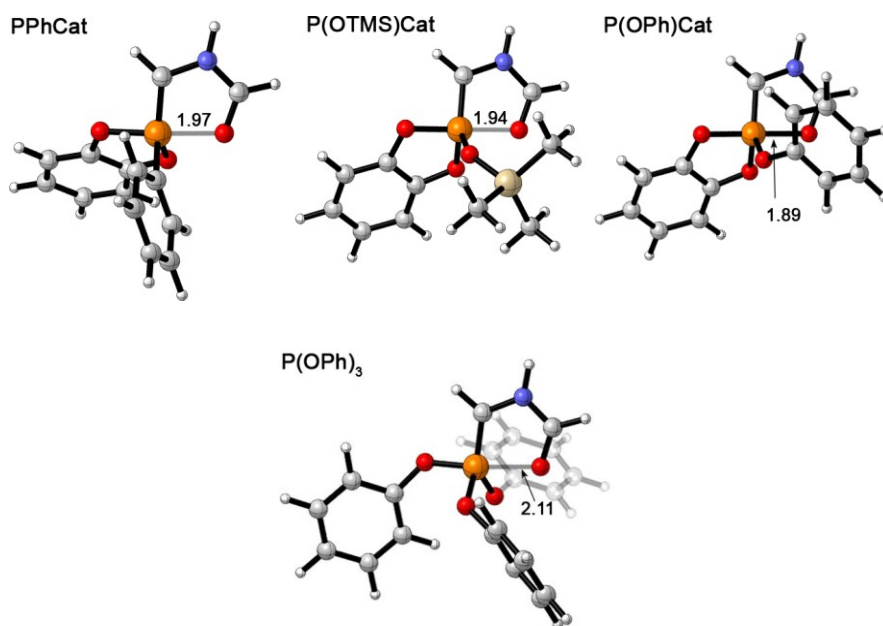
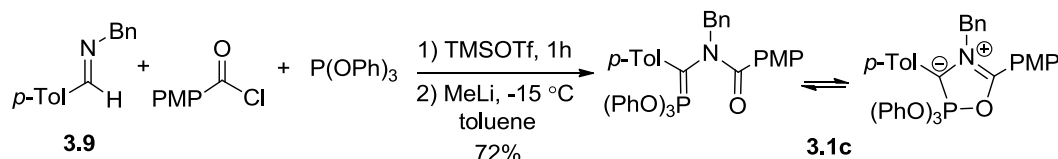


Figure 3.6: Geometries of Catechyl and Non-Catechyl Substituted Phosphorus 1,3-Dipoles

3.4.2. X-Ray Crystal Structure of (PhO)₃P-Based 1,3-Dipole

To better confirm the model for the (PhO)₃P-based 1,3-dipole, (PhO)₃P derived **3.1c** was synthesized by the reaction of imine **3.9**, (4-MeOC₆H₄)COCl and P(OPh)₃, followed by the addition of MeLi (Scheme 3.5). **3.1c** can be isolated in 72% yield by precipitation in a toluene/pentane solution. Single crystals of **3.1c** were obtained by slow diffusion of pentane into a saturated THF solution of **3.1c** at -35 °C. The X-ray crystal structure of **3.1c** is shown in Figure 3.8.



Scheme 3.5: Synthesis of (PhO)₃P-Based 1,3-Dipole **3.1c**.

Despite the ³¹P NMR data with P(OPh)₃, which shows both open and closed forms in solution (³¹P NMR: δ 30.2 and -44.0 ppm, 1.2:1 ratio), **3.1c** is observed only in the closed form in the solid state. Similarly to the catechyl-substituted **3.1a**, the phosphorus adopts a pseudo-trigonal bipyramidal geometry in **3.1c**. However, the bond between the phosphorus and the amide oxygen in **3.1c** (P-O(1) = 1.8052(10) Å) is slightly longer than with (2-catechyl)PPh-based 1,3-dipole **3.1a** (P-O(3) = 1.7894(18) Å). In addition the C-P (1.6963(14) Å) and the amide C-O (1.3068(17) Å) bonds are shorter. Each of these data is consistent with a moderately weakened P-O bond, and a resonance structure closer to **II** in **3.1c** (Figure 3.7), similar to the calculated structure.¹³

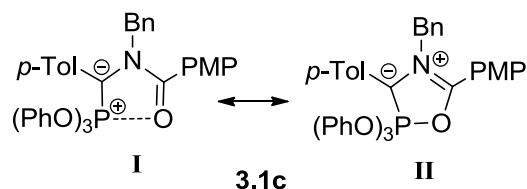


Figure 3.7: Resonance Structure of (PhO)₃P-Based 1,3-Dipole (**3.1c**).

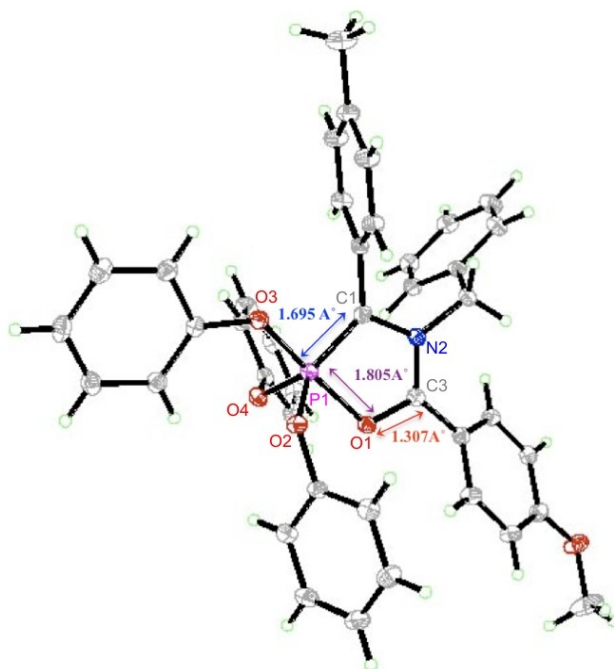


Figure 3.8: X-Ray Crystal Structure of (PhO)₃P-Based 1,3-Dipole (**3.1c**). Selected bond lengths (Å) and angles (deg): P(1)-O(1), 1.8052(10); P(1)-O(2), 1.6305(9); P(1)-O(3), 1.660(9); P(1)-O(4), 1.6342(10); P(1)-C(1), 1.6963(14); C(1)-N(2), 1.4234(18); N(2)-C(3), 1.3175(16); O(1)-C(3), 1.3068(17); O(2)-P(1)-O(3), 90.06(5); O(4)-P(1)-O(3), 95.77(5); O(2)-P(1)-C(1), 134.68(6); O(4)-P(1)-C(1), 124.10(6); O(3)-P(1)-O(1), 175.25; C(1)-P(1)-O(1), 85.73(6).

3.4.3. Transition State Structures for Alkyne Cycloaddition

The influence of the PR₃ unit on alkyne cycloaddition regioselectivity was further studied by calculating the transition state structures and energies for cycloaddition with phenylpropynenitrile (**3.8**) and the P(PhO)₃- or PPh(2-catechyl)-containing 1,3-dipoles (Figure 3.9). For the P(OPh)₃ derivative, calculations show a 3.5 kcal/mol preference for pyrrole isomer A. This barrier is 3.2 kcal/mol lower than that with PPh(2-catechyl)-substituted dipole for pyrrole A. As postulated above, the lower-energy transition state for (PhO)₃P, TS1-A, appears to result from a stepwise mechanism with a weak P-O interaction (2.24

Å). In contrast, there is a significantly shorter P-O bond with PPh(2-catechyl) in TS2-A. This leads to a higher barrier, more concerted cycloaddition to form both regioisomers A and B and with roughly similar barriers. These calculations suggest that the difference in regioselectivity between the 1,3-dipoles results from two different mechanistic pathways, and correlate with the different degree of P-O bonds in their ground state, and transition state, structures. Thus, there is a substantial geometrical effect exerted by the non-catechyl substituted phosphite P(OR)₃, which shifts the 1,3-dipole towards a more phosphorus ylide type structure, and leads to a low barrier stepwise cycloaddition.

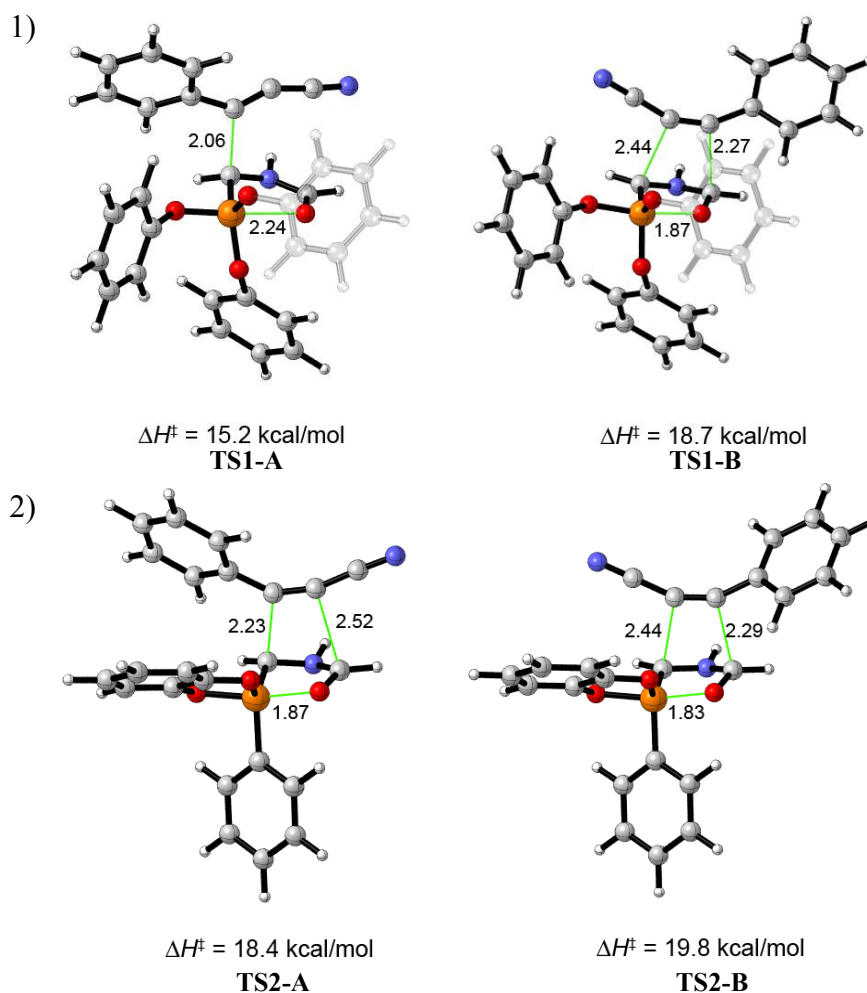


Figure 3.9: Transition Structures for Cycloaddition of Phenylpropynitrile with
1) (PhO)₃P-based 1,3-Dipole and 2) PPh(2-catechyl)-based 1,3-Dipole.

3.5 Conclusions

In this chapter, we have studied the effects of the PR_3 unit on cycloaddition reactivity and regioselectivity. It was found that non-catechyl-substituted phosphines and phosphites are less able to stabilize the closed form of the 1,3-dipole, and lead to shift its ground state structure towards either an acyclic form (phosphines), or an equilibrium between cyclic and acyclic structures (phosphites). This results in a weaker P-O interaction that directly influences the reactivity of the 1,3-dipole. This feature, together with the ability to tune the PR_3 unit without changing the structure of the cycloaddition product, were exploited to systematically modulate alkyne cycloaddition regioselectivity. The modification of the PR_3 fragment in **3.1** provides a new way to affect selectivity in cycloadditions, and should prove useful as a tool to achieve selective pyrrole syntheses with a diverse range of unsymmetrical dipoles and alkyne dipolarophiles.

3.6 Experimental Section

3.6.1 General Procedures

All reactions were performed in a Vacuum Atmospheres dry glovebox or using standard Schlenk techniques. Reagents were purchased from commercial sources and used as received. Solid PPh_3 was dried by heating under high vacuum. Liquid $\text{P}(\text{OEt})_3$, $\text{P}(\text{OCH}_2\text{CF}_3)_3$, and $\text{P}(\text{OPh})_3$ were dried over 4 Å molecular sieves. Dichloromethane, diethyl ether and acetonitrile were dried by using the solvent purification system. CDCl_3 , CD_2Cl_2 and CD_3CN were distilled from CaH_2 under nitrogen. Imines were prepared as per standard literature procedures.¹⁴ $\text{PPh}(\text{2-catechyl})$ was prepared as reported in Chapter 2. The pyrroles of Table 3.2 entries 1, 2, 4, 5 and proof of their regiochemistry were described in the literature.² NMR spectra (^1H , ^{13}C , and ^{31}P) were recorded on Varian Mercury 200, 300, 400 MHz, Unity 500 MHz and are reported in Appendix A. Mass spectra were obtained from the McGill facilities. X-ray structures were

determined by Franine B langer at the University of Montreal facilities and data are reported in Appendices B and C. Pyrrole regioisomers were distinguished by a combination of NMR experiments (nOe, NOESY 2D, COSY).

3.6.2 Synthesis of (2-Catechyl)-Substituted Phosphites

Synthesis of PF(2-catechyl)²

To dry NaF (3.05 g, 50 mmol) in a 50 mL flask under nitrogen was added neat (2-catechyl)PCl (2.38 mL, 20 mmol) and 15-crown-5 (0.40 mL, 2.0 mmol). The reaction was complete after 3 h. The product is very volatile, and can be selectively distilled from the 15-crown-5 by vacuum transfer: the crude was frozen (liquid N₂) and placed under static high vacuum. It was allowed to warm to room temperature without additional heating with collection into a liquid nitrogen-cooled flask. The product was obtained as an oil (1.76 g, 56% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.26-7.19 (m, 2H), 7.15-7.05 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 143.8 (d, *J*_{CP} = 6.9 Hz), 123.7, 113.3. ³¹P NMR (202 MHz, CDCl₃): δ (ppm) 124.7 (d, *J*_{PF} = 1306.6 Hz). ³¹P NMR (81 MHz, CD₃CN): δ (ppm) 124.8 (d, *J*_{PF} = 1296.2 Hz).

Synthesis of (2-catechyl)POPh

To phenol (1.882 g, 20 mmol) in a 250 mL round bottom flask was added Et₂O (100 mL) followed by Et₃N (2.024 g, 20 mmol). The mixture was cooled at 0 C and (2-catechyl)PCl (2.380 mL, 20 mmol) was added dropwise over 10 min. The solution was stirred at 0 C for 1h30, then 1h at rt. The solution was filtered through a coarse frit with celite and washed once with Et₂O. The filtrate was concentrated *in vacuo* to dryness to afford 4.3 g (93%) of a clear colorless oil. The product was used without further purification and stored under nitrogen. ¹H NMR (400 MHz; CDCl₃): δ 7.22 (t, *J* = 7.8 Hz, 2H), 7.08-7.00 (m, 5H), 6.96-6.93 (m, 2H); ¹³C NMR (126 MHz; CDCl₃): δ 150.2, 144.9 (d, *J*_{CP} = 7.4 Hz), 129.6, 124.8, 123.0, 121.1 (d, *J*_{CP} = 5.7 Hz), 112.6. ³¹P (80.9 MHz, CDCl₃): δ 125.7 ppm. HRMS (APCI⁺): for C₁₂H₁₀O₃P⁺; calculated: 233.03621 found: 233.03652.

Synthesis of (2-catechyl)PO(*p*-C₆H₄CN)

(2-catechyl)PO-*p*-CNC₆H₄ was prepared according to the same procedure as (2-catechyl)POPh. Yield: 82%. ¹H NMR (500 MHz; CDCl₃): δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.04-7.02 (m, 4H), 6.93 (dd, *J* = 6.0 Hz, 3.4 Hz, 2H); ¹³C NMR (126 MHz; CDCl₃): δ 153.9, 144.42 (d, *J*_{CP} = 7.5 Hz), 133.8, 123.4, 121.8 (d, *J*_{CP} = 5.5 Hz), 118.2, 112.66 (d, *J*_{CP} = 0.9 Hz), 108.44 (d, *J*_{CP} = 0.9 Hz). ³¹P (80.9 MHz, CDCl₃): δ 121.0 ppm. HRMS (APCI⁺): for C₁₃H₉O₃NP⁺; calculated: 258.03146 found: 258.03140.

Synthesis of (2-catechyl)POCH₂CF₃

(2-catechyl)POCH₂CF₃ was prepared according to the same procedure as (2-catechyl)POPh. Yield: 70%. ¹H NMR (400 MHz; CDCl₃): δ 7.17-7.13 (m, 2H), 7.07-7.03 (m, 2H), 3.85 (quintet, *J* = 8.2 Hz, 2H); ¹³C NMR (75 MHz; CDCl₃): δ 144.8 (d, *J*_{CP} = 7.6 Hz), 123.3 (d, *J*_{CP} = 0.5 Hz), 122.5 (qd, *J*_{CF} = 275.9 Hz, *J*_{CP} = 3.4 Hz), 122.2 (d, *J*_{CP} = 1.1 Hz), 60.3 (q, *J*_{CF} = 37.1 Hz). ³¹P (80.9 MHz, CDCl₃): δ 127.1 (q, *J*_{PF} = 2.3 Hz) ppm. HRMS (APCI): for C₈H₅O₃F₃P⁺; calculated: 236.99339 found: 236.99362.

3.6.3 Synthesis and X-Ray Crystallographic Studies of 3.1 and 3.2

Synthesis of 3.2b

In a glovebox, PhHC=NMe (1.19 g, 10.0 mmol) and benzoyl chloride (1.41 g, 10.0 mmol) were mixed in 3 mL acetonitrile and allowed to stand for 30 min. Triphenylphosphine (2.63 g, 10.0 mmol) was added as a CH₂Cl₂ (5 mL) solution. The solvent was removed *in vacuo*, the crude re-evaporated from THF, and dissolved in THF (100 mL). Outside the glovebox, *n*-BuLi (4.1 mL, 10.3 mmol, as 2.5 M hexanes solution) was added dropwise at -78 °C. Stirring overnight at room temperature and concentration *in vacuo* yields 4.0 g solid product (82%). *Crystallization conditions*: In the glovebox, a benzene solution of **3.2b** (100 mg) was concentrated until viscous, partially precipitated with Et₂O, and gravity filtered through dry celite. Et₂O was slowly diffused into the resulting saturated

solution of **3.2b** by the vial-in vial technique (base bath, water, acetone cleaned vials), yielding crystals suitable for X-ray analysis.

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.97–7.83 (very broad s, 2H), 7.60–6.85 (m, 20H), 6.73–6.50 (m, 3H), 3.28 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 176.1, 145.8 (d, $^1J_{\text{C-P}} = 28.7$ Hz), 138.2, 133.9, 133.8, 132.2 (d, $^4J_{\text{C-P}} = 2.9$ Hz), 129.1 (d, 2 or $^3J_{\text{C-P}} = 12.0$ Hz), 128.8 (d, $J_{\text{C-P}} = 6.9$ Hz), 128.4 (broad s), 127.3, 126.9, 118.7 (d, $J_{\text{C-P}} = 6.6$ Hz), 115.7, 56.2 (d, $^1J_{\text{C-P}} = 144.5$ Hz), 39.6. ^{31}P NMR (81 MHz, CDCl_3): δ (ppm) 11.0. ^{31}P NMR (121 MHz, solid state): δ (ppm) 12.2. HRMS (ESI $^+$) for $\text{C}_{33}\text{H}_{29}\text{NOP}^+$; calculated: 486.19813, found: 486.19744 (error $m/z = 1.4$ ppm).

Synthesis of **3.1c**

In a glovebox, (4- $\text{CH}_3\text{C}_6\text{H}_4$)HC=NCH $_2\text{C}_6\text{H}_5$ (209.3 mg, 1.00 mmol) and *p*-MeOC $_6\text{H}_4\text{COCl}$ (170.6 mg, 1.00 mmol) were mixed in 2 mL toluene and allowed to stand for 30 min. Outside the glovebox, (PhO) $_3\text{P}$ (262 μL , 1.00 mmol) and TMSOTf (182 μL , 1.00 mmol) were added to the solution and left at rt for 1h. MeLi (1.53 mL, 2.00 mmol as 1.3 M solution in Et $_2\text{O}$) was added dropwise to the mixture at -15 $^\circ\text{C}$ and then warmed up to rt. The solution was concentrated down *in vacuo* and precipitated in a toluene/pentane 1/3 solution to afford 470.6 mg of **3.1c** (72% yield). *Crystallization conditions*: In the glovebox, a THF solution of **3.1c** (50 mg) was concentrated until viscous, partially precipitated with pentane, and gravity filtered through dry celite. Pentane was slowly diffused into the resulting saturated solution of **3.1c** by the vial-in vial technique in a -35 $^\circ\text{C}$ freezer, yielding crystals suitable for X-ray analysis.

X-Ray Crystallographic Studies of **3.2b** and **3.1c**

X-ray crystallographic data were collected from a single crystal sample, which was mounted on a loop fiber. Data were collected using a Bruker Platform diffractometer, equipped with a Bruker SMART 4K Charged-Coupled Device (CCD) Area Detector using the program APEX2 and a Nonius FR591 rotating anode equipped with a Montel 200 optics. Upon isolation, the crystals were

covered in paratone-N and placed under a 150°K N₂ stream on the goniometer head of a Bruker microstar area detector system (graphite-monochromated Cu KR radiation, $\lambda = 1.54178 \text{ \AA}$). The structures were solved by direct methods (SHELXL). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were treated as idealized contributions (Riding model). The data are provided in Appendices B and C.

3.6.4 General Procedure for PR₃ Screening (Table 3.1)

In the glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (41.9 mg, 0.20 mmol) and *p*-MeOC₆H₄COCl (34.1 mg, 0.20 mmol) were mixed in 0.5 mL CD₃CN and allowed to stand for 30 min. TMSOTf (44.4 mg, 0.20 mmol) and PR₃ (0.20 mmol) were added with 0.5 mL of CD₃CN. After 1 h at rt, DBU (60 mg, 0.40 mmol) was added and the solution was transferred into a septum-sealed NMR tube. ¹H and ³¹P NMR data on **3.1/3.2** were obtained. The addition of dimethyl acetylene dicarboxylate (74 μ L, 0.60 mmol) was immediately followed by ¹H NMR analysis, showing complete conversion in all reactive dipoles within 1-5 min. The pyrrole product was isolated by column chromatography (ethyl acetate/hexanes eluent).

3.6.5 Pyrrole Synthesis (Table 3.2)

In a glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (42.0 mg, 0.20 mmol) and *p*-MeOC₆H₄COCl (37.5 mg, 0.22 mmol) were mixed in 0.5 mL CDCl₃ for 30 min. PhP(2-catechyl) (47.5 mg, 0.22 mmol) was added and after 1 h at rt, DBU (91.3 mg, 0.6 mmol), and 2-chloroacrylonitrile (37 μ L, 0.6 mmol) were added in order as solutions in chloroform, bringing the final volume to 1.5 mL. The reaction was complete within 5 min (for entries 3 and 6, LiHMDS (220 μ L, 0.22 mmol as 1M solution in hexanes) was injected at -78 °C, followed by the addition of methyl 2-heptynoate (84 mg, 0.6 mmol) and heating to 45°C for 8h) The solution was concentrated *in vacuo* followed by purification by column chromatography (ethyl

acetate/hexanes as eluent) to afford pyrrole of Table 3.2 entry 1 as a white solid (69.5 mg, 92%)

Pyrroles of Table 3.2 entries 2 and 5 required 17 h for cycloaddition.

3.6.6 Pyrrole Synthesis (Scheme 3.4)

In a glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (42.0 mg, 0.20 mmol) and *p*-MeOC₆H₄COCl (37.5 mg, 0.22 mmol) were mixed in 0.5 mL CDCl₃ for 30 min. PhP(2-catechyl) (47.5 mg, 0.22 mmol) was added and after 1h at rt, DBU (91.3 mg, 0.6 mmol), and methyl phenylpropiolate **3.7** (88 μL, 0.6 mmol) were added in order as solutions in chloroform, bringing the final volume to 1.5 mL. The reaction was complete after 12 h at 55 °C. The solution was concentrated *in vacuo* followed by purification by column chromatography (ethyl acetate/hexanes as eluent) to afford pyrrole as a white solid (49.7 mg, 51%). The ratios of the two regioisomers were determined by ¹H NMR analysis of the purified mixture. Reaction with phenylpropynenitrile **3.8** follows the same procedure.

3.6.7 General Procedure for Tables 3.3 and 3.4

In the glovebox, (4-CH₃C₆H₄)HC=NCH₂C₆H₅ (42.0 mg, 0.20 mmol) and *p*-MeOC₆H₄COCl (37.5 mg, 0.22 mmol) were mixed in 0.5 mL CD₃CN and allowed to stand for 30 min. PR₃ (0.22 mmol) and TMSOTf (44.4 mg, 0.20 mmol) were added and after 1h at rt, DBU (60.8 mg, 0.4 mmol) was added followed by methyl phenylpropiolate **3.7** (88 μL, 0.6 mmol). The reaction was complete after 24 h at 55°C. The solution was concentrated *in vacuo* followed by purification by column chromatography (ethyl acetate/hexanes as eluent). Ratios were determined by ¹H NMR analysis of the purified mixture of the two regioisomers. Reactions with (PhO)₃P (Table 3.3, entry 6 and Table 3.4, entry 5) were performed in dichloromethane with MeLi (614 μL, 0.8 mmol) as a base, injected at -78°C. Reactions with phenylpropynenitrile **3.8** required 24 h at 70 °C for cycloaddition.

3.6.8 Spectroscopic Data for Pyrroles

^1H , ^{13}C and NOE 1D NMR spectra of pyrroles of Table 3.2 entries 1, 2, 4 and 5 were reported in previous communication.² NMR spectra of pyrroles of Table 3.2 entries 3, 6 and Scheme 3.4 and proof of their regiochemistry are provided in Appendix A.

Table 3.2, entry 1: Isolated yield: 92%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.30 (d, $J = 9.0$ Hz, 2H), 7.22-7.11 (m, 7H), 6.91 (d, $J = 9.0$ Hz, 2H), 6.70-6.61 (m, 2H), 6.54 (s, 1H), 5.13 (s, 2H), 3.81 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 160.1, 142.5, 138.1, 137.7, 136.3, 131.0, 129.2, 128.6, 128.5, 127.3, 125.7, 121.9, 117.4, 114.2, 111.5, 92.8, 55.2, 48.8, 21.2. HRMS (ESI^+) for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}^+$; calculated: 379.18049, found: 379.18019.

Table 3.2, entry 2: Isolated yield: 52%. ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.20-7.07 (m, 9H), 6.85 (d, $J = 8.5$ Hz, 2H), 6.62-6.66 (m, 2H), 4.88 (s, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 2.36 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) 166.2, 159.2, 138.9, 138.4, 137.4, 132.3, 131.7, 130.8, 128.9, 128.1, 126.7, 125.9, 124.8, 118.6, 113.2, 112.7, 55.1, 50.4, 48.2, 21.2, 11.8. HRMS (ESI^+) for $\text{C}_{28}\text{H}_{28}\text{NO}_3^+$; calculated: 426.20637, found: 426.20605.

Table 3.2, entry 3: Isolated yield: 50%. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.16 (d, 2H), 7.14-7.06 (m, 7H), 6.83 (d, 2H), 6.56-6.53 (m, 2H), 4.81 (s, 2H), 3.79 (s, 3H), 3.61 (s, 3H), 2.60-2.56 (t, 2H), 2.34 (s, 3H), 1.55-1.47 (m, 2H), 1.27-1.23 (m, 2H), 0.87-0.80 (t, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 166.4, 159.4, 139.1, 138.7, 137.7, 132.5, 132.0, 131.2, 129.3, 129.1, 128.3, 126.9, 126.2, 125.2, 124.2, 113.4, 112.2, 55.3, 50.7, 48.4, 34.4, 25.7, 23.0, 21.5, 14.2. HRMS (ESI^+) for $\text{C}_{31}\text{H}_{33}\text{NO}_3\text{Na}^+$; calculated: 490.2353, found: 490.2361.

Table 3.2, entry 4: Isolated yield: 92%. ^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.31-7.17 (m, 2H), 7.23-7.13 (m, 7H), 6.84 (d, $J = 8.5$ Hz, 2H), 6.68-6.60 (m, 2H), 6.51 (s, 1H), 5.11 (s, 2H), 2.80 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 159.5, 142.5, 139.0, 137.6, 136.0, 130.7, 129.4₄, 129.4₃, 128.4,

127.2, 126.7, 125.7, 123.8, 117.4, 113.9, 111.5, 92.7, 55.2, 48.8, 21.2. HRMS (ESI⁺) for C₂₆H₂₂N₂O⁺; calculated: 379.18049, found: 379.18024.

Table 3.2, entry 5: Isolated yield: 47%. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.21-7.08 (m, 9H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.63-6.55 (m, 2H), 4.87 (s, 2H), 3.80 (s, 3H), 3.64 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 166.2, 159.0, 139.0, 138.3, 137.6, 132.2, 132.0, 130.4, 129.6, 128.5, 128.0, 126.7, 125.9, 124.1, 118.7, 113.6, 112.5, 55.1, 50.4, 48.1, 21.3, 11.7. HRMS (ESI⁺) for C₂₈H₂₈NO₃⁺; calculated: 426.20637, found: 426.20627.

Table 3.2, entry 6: Isolated yield: 50%. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.16-7.06 (m, 9H), 6.81 (d, 2H), 6.56-6.54 (m, 2H), 4.79 (s, 2H), 3.80 (s, 3H), 3.61 (s, 3H), 2.59-2.55 (t, 2H), 2.34 (s, 3H), 1.47 (m, 2H), 1.25-1.23 (m, 2H), 0.83-0.79 (t, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 166.3, 159.3, 139.3, 138.7, 137.8, 132.6, 132.1, 130.6, 130.0, 128.7, 128.3, 126.9, 126.2, 124.5, 124.4, 113.7, 112.0, 55.4, 50.6, 48.3, 34.3, 25.6, 23.0, 21.5, 14.2. HRMS (ESI⁺) for C₃₁H₃₃NO₃Na⁺; calculated: 490.2353, found: 490.2352.

Scheme 3.4, pyrroles of alkyne 3.7: Isolated yield: 51%. Isomer A (major isomer): ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.25-7.12 (m, 10H), 6.86 (s, 4H), 6.85 (d, *J* = 6.8 Hz, 2H), 6.65-6.62 (m, 2H), 4.93 (s, 2H), 3.81 (s, 3H), 3.44 (s, 3H), 2.25 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 166.1, 159.7, 138.7, 138.5, 137.6, 135.7, 132.9, 132.2, 131.4, 130.8, 129.0, 128.9, 128.4, 127.4, 127.1, 126.3, 126.0, 124.6, 124.4, 113.5, 113.3, 55.4, 50.8, 48.6, 21.4. HRMS (ESI⁺) for C₃₃H₃₀NO₃⁺; calculated: 488.22202, found: 488.22230.

Isomer B (minor isomer): ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.26-7.12 (m, 12H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.66-6.63 (m, 2H), 4.93 (s, 2H), 3.73 (s, 3H), 3.44 (s, 2H), 2.36 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.1, 159.2, 139.0, 138.5, 138.2, 135.6, 132.8, 132.7, 130.8₂, 130.8₀, 129.3, 128.9, 128.5, 127.4, 127.2, 126.3, 126.0, 124.5, 124.1, 113.7, 113.1, 55.3, 50.9, 48.6, 21.6. HRMS (ESI⁺) for C₃₃H₃₀NO₃⁺; calculated: 488.22202, found: 488.22218.

Scheme 3.4, pyrroles of alkyne 3.8: Isolated yield: 58%. Isomer A (minor Isomer): ^1H NMR (400 MHz; CDCl_3): δ (ppm) 7.39 (d, $J = 8.7$ Hz, 2H), 7.32 (d, $J = 7.2$ Hz, 2H), 7.24 (t, $J = 8.0$ Hz, 2H), 7.19-7.16 (m, 4H), 7.04 (q, $J = 6.7$ Hz, 4H), 6.94 (d, $J = 8.7$ Hz, 2H), 6.66 (dd, $J = 6.5$ Hz, 2.6 Hz, 2H), 5.06 (s, 2H), 3.82 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz; CDCl_3): δ 160.4, 142.7, 138.5, 137.8, 133.1, 132.7, 131.3₅, 131.2₉, 129.5, 129.2, 128.7, 128.4, 128.2, 127.5, 126.8, 126.2, 125.2, 122.1, 117.8, 114.6, 93.3, 55.6, 49.1, 21.6. HRMS (ESI^+) for $\text{C}_{32}\text{H}_{26}\text{N}_2\text{ONa}^+$; calculated: 477.1937, found: 477.1940.

Isomer B (Major Isomer): ^1H NMR (500 MHz; CDCl_3): δ 7.38 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 7.3$ Hz, 2H), 7.24 (t, $J = 8.0$ Hz, 4H), 7.19-7.16 (m, 4H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 6.66 (dd, $J = 6.4$ Hz, 2.5 Hz, 2H), 5.07 (s, 2H), 3.77 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (126 MHz; CDCl_3): δ 159.5, 142.5, 139.2, 137.6, 132.9, 132.5, 132.3, 129.6₁, 129.5₉, 129.0, 128.5, 128.2, 127.3, 126.67, 126.57, 126.0, 125.1, 123.1, 117.5, 114.0, 93.0, 55.2, 48.9, 21.4. HRMS (ESI^+) for $\text{C}_{32}\text{H}_{26}\text{N}_2\text{ONa}^+$; calculated: 477.1937, found: 477.1948.

3.6.9 Computational Methods

Density functional theory calculations were performed using the Gaussian 03¹⁶ and Gaussian 09¹⁷ software. Geometry optimizations, conformational searching, and vibrational frequency calculations were conducted at the B3LYP/6-31+G(d) level.¹⁸ The nature of each stationary point was ascertained by vibrational frequency analysis, and transition states were further verified by IRC calculations¹⁹ where appropriate. Enthalpies and free energies were obtained from the unscaled B3LYP frequencies and are quoted at 298.15 K and 1 mol/L.

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CHAPTER 4

Phosphonite Mediated 1,3-Dipolar Cycloaddition: A Route to Polycyclic 2-Pyrrolines from Imines, Acid Chlorides and Alkenes¹

4.0 Preface

The studies in chapters 2 and 3 demonstrate that the cycloaddition of phospho-Münchnones with alkynes can provide an efficient approach to generate pyrroles. We describe in this chapter the extension of this approach to alkene cycloaddition to synthesize pyrrolines. This has led to the development of a straightforward method to synthesize polycyclic 2-pyrrolines by the PhP(2-catechyl) mediated coupling of alkene-tethered imines and acid chlorides. The modularity of this reaction can be used to assemble a range of polysubstituted pyrrolines in one pot transformations.

4.1 Introduction

2-Pyrrolines, and their fully reduced counterpart pyrrolidines, are common structural motifs in biologically relevant products. Examples of these range from natural products,² structures of pharmaceutical utility³ (e.g. anti-cancer agents,⁴ antibiotics,⁵ hepatitis C inhibitors⁶ or antitubercular agents⁷), amino acid derivatives,⁸ and others. One challenge in the use of pyrrolines is their synthesis. A common approach to 2-pyrrolines is via the cyclization of amine-containing precursors, such as hydroamination,⁹ iodoamination,¹⁰ ring expansion,¹¹ or catalytic cyclization¹² reactions. While effective, these require the preparation of the correctly substituted substrate for subsequent cyclization.

A more convergent approach to 2-pyrrolines is via (4+1)¹³ or (3+2)¹⁴ cycloaddition reactions. The latter has been exploited with 1,3-oxazolium-5-oxides (Münchnones),¹⁵ metallated azomethine ylides,¹⁶ isocyanoesters,¹⁷ and aziridines¹⁸ in reactions with alkenes or alkynes. While alkenes and alkynes are readily available, a requirement in this case is the generation of the polysubstituted 1,3-dipole or dipole precursor. As an alternative, we have recently reported a modular approach to phosphorus-dipoles of the form **4.1** (i.e. phosphamünchnones). **4.1** is generated via the equilibrium of amide-substituted Wittig ylides (Figure 4.1). By coupling the multicomponent generation of **4.1'** with spontaneous cyclization, **4.1** can be formed in one pot with imines, acid chlorides and phosphines as the building blocks.¹⁹

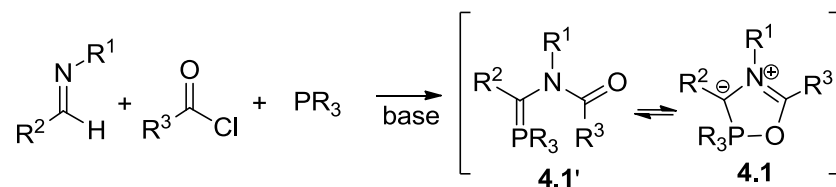


Figure 4.1: Multicomponent Assembly of Phospha-Münchnones.

Considering their ease of synthesis, we became interested in the potential utility of **4.1** in pyrroline synthesis. We describe the results of these studies below. These show that the correctly substituted dipole **4.1** can participate in alkene cycloaddition with high selectivity. This has allowed the design of a general approach to assemble polycyclic 2-pyrrolines directly from olefin-tethered imines and acid chlorides (Figure 4.2).

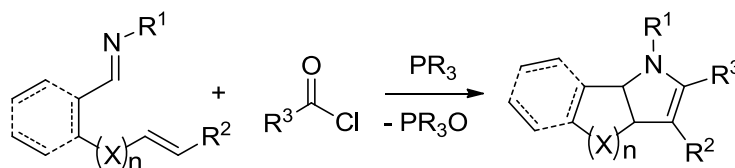
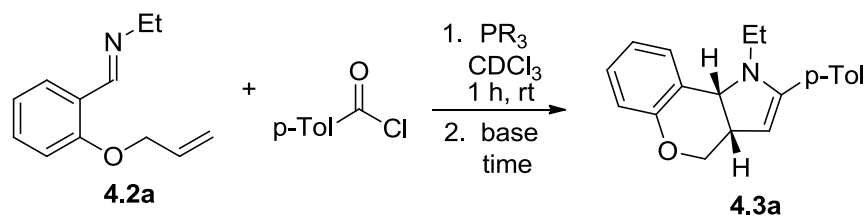


Figure 4.2: Phosphine Mediate Approach to Pyrrolines.

4.2 Results and Discussion

Our initial studies examined the reaction of the imine **4.2a** (Table 4.1). **4.2a** is readily accessible from salicylaldehyde, and alkene cycloaddition would provide a route to polycyclic pyrrolines² uncomplicated by the multiple alkene cycloadditions sometimes observed with Münchnones¹⁴ and phospho-Münchnones (cf. Appendix G). PPh₃ can react with **4.2a**, toluoyl chloride followed by base to form **4.1/4.1'**. However no cycloaddition is observed, and this compound simply decomposes at high temperatures (entry 1). Similar behaviour is observed with PCy₃ and P(NMe₂)₃ (entries 2, 3). We have previously noted that electron rich phosphines do not favor the amide chelation necessary for cyclization of the acyclic Wittig-type structure **4.1'** to its 1,3-dipole form (Figure 4.1),^{19b} which could slow cycloaddition to the unactivated alkene in **4.2a**. Consistent with this, the more electron poor phosphite P(OPh)₃ reacts with these same substrates to both generate **4.1**, and undergo cycloaddition to form 2-pyrroline **4.3a** in a 46% yield (entry 4). A similar reaction occurs with P(OCH₂CF₃)₃ (entry 5). The moderate yield of **4.3a** under these conditions arises from the poor nucleophilicity of phosphites, which reacts slowly with the *in situ* generated α -chloroamide **4.4** (Scheme 4.1). The latter can be enhanced by the addition of TMSOTf to activate **4.4** towards nucleophilic attack (X = OTf, entries 6, 7). Alternatively, the more nucleophilic phosphonite PhP(2-catechyl) avoids the need for this additive, and with DBU base leads to the high yield, rapid formation of **4.3a** (entry 10).

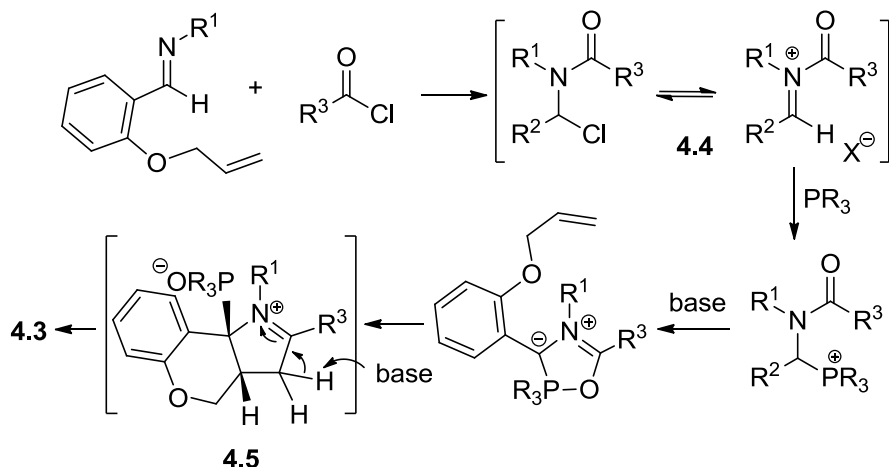
Table 4.1 Development of PR₃ Mediated Pyrroline Synthesis^a

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) ₃ P	DBU	/	24h	46%
5	(CF ₃ CH ₂ O) ₃ P	DBU	/	10h	46%
6	(PhO) ₃ P	DBU	TMSOTf	5h	80%
7	(CF ₃ CH ₂ O) ₃ P	DBU	TMSOTf	2h	67%
8	PhP(2-catechyl)	Et ₃ N	/	6h ^d	66%
9	PhP(2-catechyl)	Et(ⁱ Pr) ₂ N	/	6h ^d	36%
10	PhP(2-catechyl)	DBU	/	2h	85%

^a **4.2a** (38 mg, 0.2 mmol), TolCOCl (34 mg, 0.22 mmol), 0.5 mL CDCl₃, 30 min; then PR₃ (0.22 mmol), 1h; base (0.36 mmol), rt.

^b NMR yield. ^c added at -78 °C. ^d 65 °C.

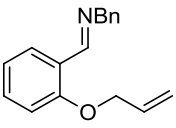
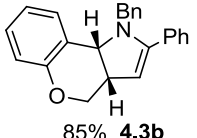
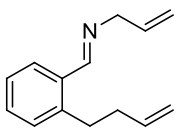
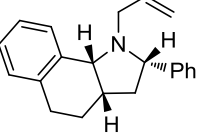
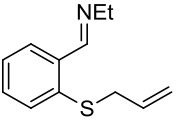
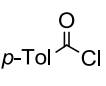
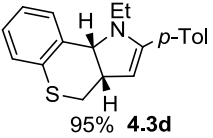
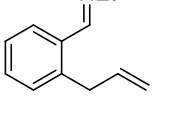
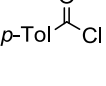
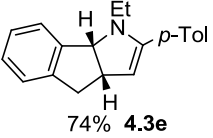
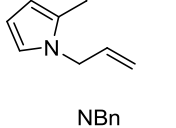
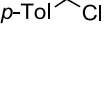
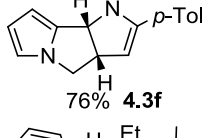
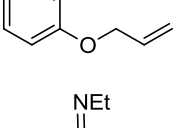
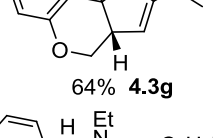
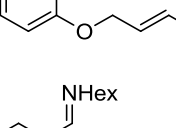
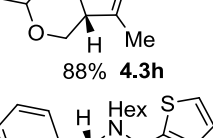
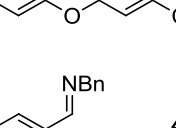
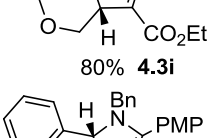
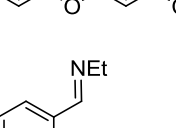
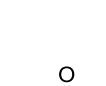
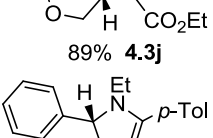
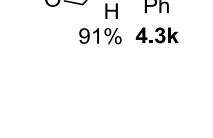
Pyrroline **4.3a** is formed as a single observable diastereomer and alkene regioisomer. In considering the reaction mechanism, these both likely arise from to the generation of the phosphorus-bound intermediate **4.5** (Scheme 4.1). The large steric profile of the PR₃ unit presumably favors the cis-ring fusion upon alkene cyclization, while slow phosphine oxide loss from **4.5** would allow the selective deprotonation at C4, and lead to a single pyrroline alkene isomer.

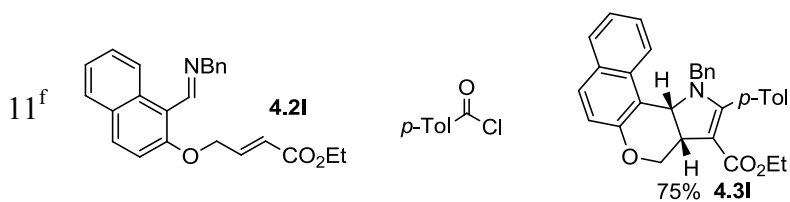


Scheme 4.1: Mechanism of **4.3** Formation.

In addition to generating **4.3a**, since this reaction relies upon imines and acid chlorides, it is straightforward to diversify these products. As shown in Table 4.2, a number of *N*-alkyl substituents can be employed in the reaction, including common protecting groups (entries 2, 9, 11). Carbon-, sulfur- and oxygen-containing tethers can all be employed in this chemistry (entries 1-3), as can various aromatic spacers, including simple phenyl, naphthyl (entry 11) and even pyrrole units (entry 5). However, amine tethered variants of **4.2b** are not compatible with these conditions. The alkene can be similarly diversified, with terminal and internal olefins both affording pyrrolines in good yields, and with similar selectivity (entries 7-11). This includes electron poor (entries 8, 9), styrenyl (entry 10) and even weakly donating alkyl-substituted alkenes (entry 7). 5,5-Fused ring products are also accessible (entries 4, 5). The acid chloride unit can be similarly varied to form a number of 5-aryl, -thiophenyl and even -tertiary alkyl substituted products (entries 5-9). Overall, this provides a modular route to prepare polycyclic 2-pyrrolines from accessible alkene-tethered imines and acid chlorides, where in one pot each substituent tuned by choice of the appropriate building blocks.

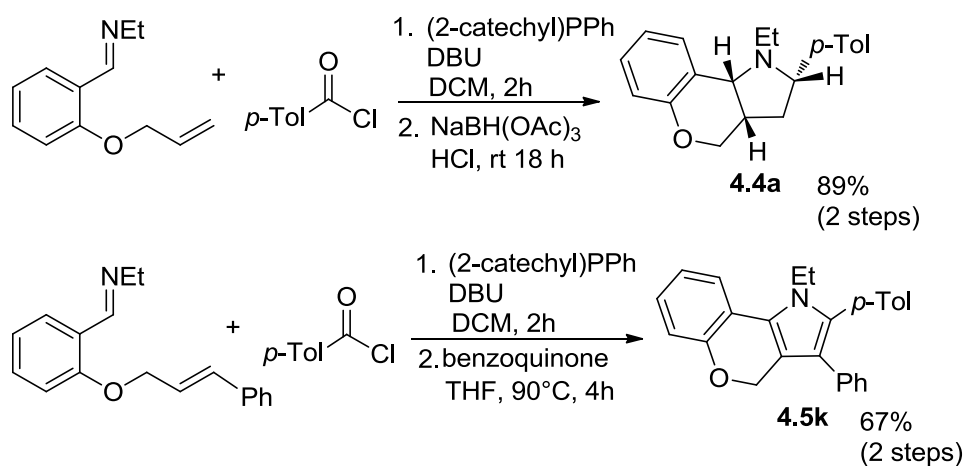
Table 4.2 Diversity of One Pot Pyrroline Polycyclic Synthesis^a

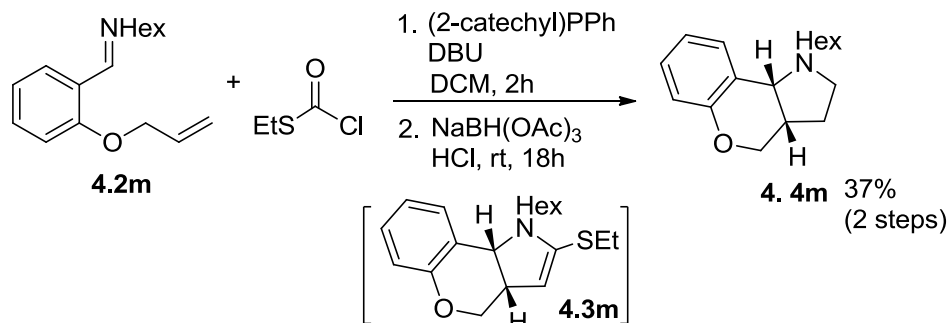
Entry	Imine	Acid Chloride	Product (% yield)
1	 4.2b		 85% 4.3b
2 ^b	 4.2c		 75% 4.4c
3 ^c	 4.2d		 95% 4.3d
4	 4.2e		 74% 4.3e
5 ^d	 4.2f		 76% 4.3f
6	 4.2b		 64% 4.3g
7 ^e	 4.2h		 88% 4.3h
8 ^f	 4.2i		 80% 4.3i
9 ^f	 4.2j		 89% 4.3j
10 ^e	 4.2k		 91% 4.3k



^a imine (0.20 mmol), acid chloride (0.21 mmol), 0.5 mL CHCl₃, 30 min; (2-catechyl)PPh (47.5 mg, 0.22 mmol), 1 h; DBU (45.7 mg, 0.30 mmol), rt, 10 min. ^b Reduced with NaBH(OAc)₃ (0.30 mmol), 1M HCl/ether (0.40 mmol), 18 h. ^c 2 h. ^d CD₃CN ^e 60°C, 1 h. ^f 0.40 mmol DBU.

Pyrrolines have been demonstrated to serve as useful building blocks for a variety of products. For example, coupling the generation of **4.3** with *in situ* reduction with NaBH(OAc)₃ results in a stereoselective route to prepare pyrrolidine **4.4a**, with five separate bonds generated in one pot (Scheme 4.2). Alternatively, the generation of **4.3** with subsequent benzoquinone oxidation allows the overall synthesis of polycyclic pyrrole **4.5k**. This reaction platform can also be expanded to chlorothioformates. In this case, cycloaddition and subsequent reduction leads to dethiolated product **4.4m**. The dethiolation presumably occurs upon reduction of **4.3m**,²⁰ and allows the assembly of 5-unsubstituted pyrrolidines: a structure unavailable from normal acid chloride chemistry.





Scheme 4.2: One-Pot Synthesis of Pyrrolidines and Pyrroles.

4.3 Conclusions

In conclusion, alkene-tethered imines and acid chlorides can undergo phosphonite mediated cyclization to generate polycyclic pyrrolines with high regio- and stereoselectivity. This reaction exploits the modular formation of phosphorus-containing dipoles **4.1**, which undergo rapid cycloaddition with alkenes. When coupled with the reactivity of the 2-pyrroline core itself, this can allow the synthesis of a range of heterocycles (pyrrolines, pyrroles, pyrrolidines) in efficient, one pot reactions.

4.4 Experimental Section

4.4.1 General Procedures

All reactions were performed under inert nitrogen atmosphere either in a Vacuum Atmospheres 553-2 dry box or using Schlenk technique. Reagents were purchased from commercial sources and used as received. Solid PPh_3 and PCy_3 were dried by heating at 120°C under high vacuum. Liquid $\text{P(OCH}_2\text{CF}_3)_3$, P(OPh)_3 and $\text{P(NMe}_2)_3$ were dried over 4 Å molecular sieves. PPh(2-catechyl) was prepared as reported in Chapter 2. Aldehyde precursors to the imines **4.2a,b,f-m**,²¹ **4.2c,e**²² and **4.2d**²³ were prepared by literature procedures, and purified by flash chromatography using hexanes/ ethyl acetate 9/1 as eluent. CDCl_3 and CD_3CN were distilled from CaH_2 under nitrogen. Dichloromethane and diethyl ether were dried with solvent purification system (MBraun SPS). ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 MHz, 400 MHz and

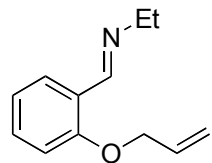
Unity 500 MHz spectrometers. ^1H and ^{13}C NMR spectra to show purity are available in the supporting information of the publication.¹ Pyrrolines were all formed as a single observable diastereoisomer. NoE experiments (**4.3a**, **4.3f**, **4.4a** and **4.4c**), and comparison to literature reported compounds,²⁴ confirm the assignments shown.

4.4.2 Synthesis and Spectroscopic Data of Imines

Typical Procedure²⁵

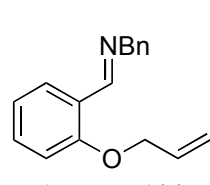
To a solution of 2-(allyloxy)benzaldehyde (405.4 mg, 2.5 mmol) in dichloromethane (10 mL) was added MgSO_4 and ethylamine (2.0 M in THF) (1.4 mL, 2.75 mmol). The heterogeneous mixture was stirred at room temperature for 18h. The reaction mixture was filtered, and the solvent and excess amine were evaporated *in vacuo* to provide imine **4.2a** as a clear oil (402 mg, 85%). In the case of imines **4.2b**, **4.2i**, **4.2j**, **4.2l** and **4.2m**, exactly 1.0 equivalent of amine was added.

(E)-N-(2-(allyloxy)benzylidene)ethanamine 4.2a

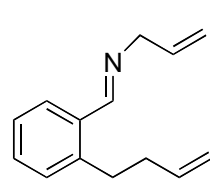


^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.77 (s, 1H), 7.96 (dd, J = 7.7 Hz, 1.7 Hz, 1H), 7.34-7.29 (m, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.86 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 6.11-6.01 (m, 1H), 5.41 (dt, J = 17.3 Hz, 1.6 Hz, 1H), 5.29 (dt, J = 10.6 Hz, 1.5 Hz, 1H), 4.58-4.55 (m, 2H), 3.65 (qd, J = 7.3 Hz, 1.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz; CDCl_3): δ (ppm) 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 $\text{C}_{12}\text{H}_{16}\text{NO}^+$; calculated: 190.12264, found: 190.12231.

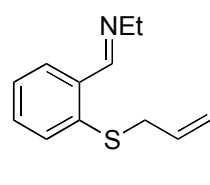
(E)-N-(2-(allyloxy)benzylidene)-1-phenylmethanamine 4.2b


¹H NMR (400 MHz, CDCl₃): δ (ppm) 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). **¹³C NMR** (126 MHz, CDCl₃): δ (ppm) 157.9₄, 157.8₆, 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 C₁₇H₁₈NO⁺; calculated: 252.13829, found: 252.13766.

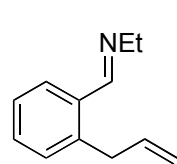
(E)-N-(2-(but-3-en-1-yl)benzylidene)prop-2-en-1-amine 4.2c


¹H NMR (400 MHz; CDCl₃): δ (ppm) 8.61 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.4 Hz, 1.5 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 6.10 (ddt, *J* = 17.1 Hz, 10.4 Hz, 5.6 Hz, 1H), 5.87 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.7 Hz, 1H), 5.28-5.15 (m, 2H), 5.08-4.99 (m, 2H), 4.29 (dq, *J* = 5.6 Hz, 1.5 Hz, 2H), 2.95 (t, *J* = 7.9 Hz, 2H), 2.35 (q, *J* = 6.8 Hz, 2H). **¹³C NMR** (126 MHz; CDCl₃): δ (ppm) 160.2, 141.5, 137.6, 136.0, 133.7, 130.3, 130.0, 127.7, 126.4, 115.9, 115.2, 64.0, 36.0, 32.1. **HRMS** (APCI⁺) for C₁₄H₁₈N⁺; calculated: 200.14287, found: 200.143338.

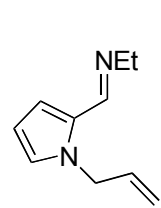
N-(2-(allylthio)benzylidene)ethanamine 4.2d


¹H NMR (400 MHz; CDCl₃): δ (ppm) 8.85 (s, 1H), 7.92 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.40 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.31 (td, *J* = 7.5 Hz, 1.7 Hz, 1H), 7.27-7.23 (m, 1H), 5.82 (ddt, *J* = 17.0 Hz, 10.0 Hz, 7.0 Hz, 1H), 5.07-5.01 (m, 2H), 3.67 (qd, *J* = 7.3 Hz, 1.4 Hz, 2H), 3.47 (dt, *J* = 7.0 Hz, 1.1 Hz, 2H), 1.31 (t, *J* = 7.3 Hz, 3H). **¹³C NMR** (126 MHz; CDCl₃): δ (ppm) 159.0, 136.6, 136.1, 133.1, 131.8, 130.3, 127.8, 127.1, 118.0, 56.0, 38.3, 16.4. **HRMS** (ESI⁺) for C₁₂H₁₆NS⁺; calculated: 206.09980, found: 206.09928.

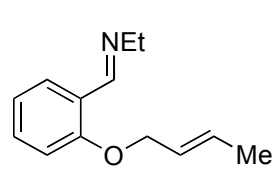
N-(2-allylbenzylidene)ethanamine 4.2e

¹H NMR (400 MHz, CDCl₃): δ (ppm) 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). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 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 C₁₂H₁₆N⁺; calculated: 174.12773, found: 174.12772.

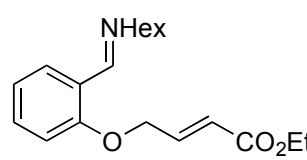
(*E*)-*N*-((1-allyl-1*H*-pyrrol-2-yl)methylene)ethanamine 4.2f

¹H NMR (400 MHz, CDCl₃): δ (ppm) 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). ¹³C NMR (126 MHz; CDCl₃): δ (ppm) 151.5, 135.1, 129.4, 126.2, 116.4, 115.8, 108.3, 56.3, 50.6, 16.7. HRMS (APCI⁺) for C₁₀H₁₅N₂⁺; calculated: 163.12298, found: 163.12271.

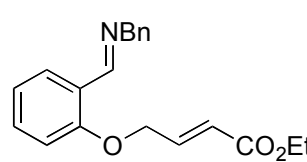
N-(2-((*E*)-but-2-en-1-yloxy)benzylidene)ethanamine 4.2h

¹H NMR (500 MHz, CDCl₃): δ (ppm) 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). ¹³C NMR (75 MHz, CDCl₃), with rotamers: δ (ppm) 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 C₁₃H₁₈NO⁺; calculated: 204.13829, found: 204.13784.

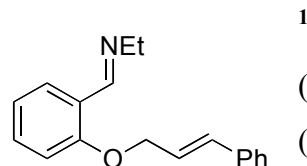
(E)-ethyl 4-(2-((E)-(hexylimino)methyl)phenoxy)but-2-enoate 4.2i

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.73 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.10 (dt, *J* = 4.0, 16.0 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 1H), 4.75 (d, *J* = 4.0 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.63 (t, *J* = 6.8 Hz, 2H), 1.72–1.66 (m, 2H), 1.39–1.29 (m, 9H), 0.89 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125.7 MHz, CDCl₃): δ (ppm) 166.0, 157.0, 156.2, 142.1, 131.5, 127.6, 125.3, 122.2, 121.5, 112.0, 66.8, 62.1, 60.6, 31.7, 31.0, 27.0, 22.6, 14.2, 14.1; HRMS (ESI⁺) for C₁₉H₂₈NO₃⁺; calculated: 318.20637, found: 318.20591.

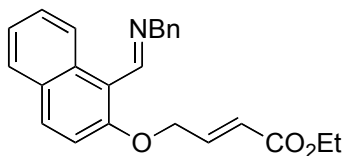
(E)-ethyl 4-(2-((E)-(benzylimino)methyl)phenoxy)but-2-enoate 4.2j

¹H NMR (400 MHz; CDCl₃): δ (ppm) 8.88 (s, 1H), 8.05 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.37–7.35 (m, 5H), 7.27–7.24 (m, 1H), 7.11 (dt, *J* = 15.8 Hz, 4.1 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.18 (dt, *J* = 15.8 Hz, 2.0 Hz, 1H), 4.86 (d, *J* = 1.2 Hz, 2H), 4.77 (dd, *J* = 4.1 Hz, 2.0 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ (ppm) 165.9, 157.4, 157.2, 142.0, 139.5, 131.9, 128.5, 128.0₁, 127.8₂, 126.9, 125.0, 122.2, 121.5, 112.1, 66.9, 65.4, 60.6, 14.3. HRMS (ESI⁺) for C₂₀H₂₂NO₃⁺; calculated: 324.15942, found: 324.15888.

(E)-N-(2-(cinnamyloxy)benzylidene)ethanamine 4.2k

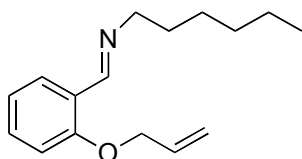
¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.82 (s, 1H), 8.00 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.45–7.43 (m, 2H), 7.39–7.34 (m, 3H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.03–6.95 (m, 2H), 6.75 (d, *J* = 16.0 Hz, 1H), 6.45 (dt, *J* = 16.0 Hz, 5.8 Hz, 1H), 4.76 (dd, *J* = 5.8 Hz, 1.1 Hz, 2H), 3.68 (qd, *J* = 7.3 Hz, 1.3 Hz, 2H), 1.33 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ (ppm) 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 C₁₈H₂₀NO⁺; calculated: 266.15394, found: 266.15345.

(E)-ethyl 4-((1-((E)-(benzylimino)methyl)naphthalen-2-yl)oxy)but-2-enoate 4.2l



¹H NMR (400 MHz; CDCl₃): δ (ppm) 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). **¹³C NMR** (75 MHz; CDCl₃): δ (ppm) 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 C₂₄H₂₄NO₃⁺; calculated: 374.17507, found: 374.17396.

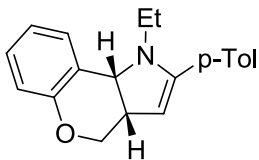
(E)-N-(2-(allyloxy)benzylidene)hexan-1-amine 4.2m



¹H NMR (400 MHz; CDCl₃): δ (ppm) 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). **¹³C NMR** (126 MHz; CDCl₃): δ (ppm) 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 C₁₆H₂₄NO⁺; calculated: 246.18524, found: 246.18461.

4.4.3 Synthesis and Spectroscopic Data of Pyrrolines 4.3

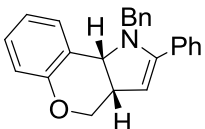
Synthesis and characterization of 4.3a.



In the glovebox, imine **4.2a** (37.8 mg, 0.2 mmol) and toluoyl chloride (32.5 mg, 0.21 mmol) were mixed in CDCl_3 (ca. 0.5 mL) and allowed to stand 30 min. (2-catechyl)PPh (47.5 mg, 0.22 mmol) was added and after 1h at room temperature, DBU (45.7 mg, 0.3 mmol) was added, and the volume of CDCl_3 adjusted to 1.5 mL. The reaction was complete within 10 min at room temperature. The solution was concentrated in vacuo, and the residue dissolved in minimum amount of CH_2Cl_2 . The product is purified in a glovebox with small pipette column of alumina using diethyl ether as eluent, affording **4.3a** as a light yellow oil (49.5 mg, 85%).

^1H NMR: (500 MHz, CDCl_3): δ (ppm) 7.31 (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 (ppm) 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 $\text{C}_{20}\text{H}_{22}\text{NO}^+$; calculated: 292.16959, found: 292.16908.

Synthesis and characterization of 4.3b



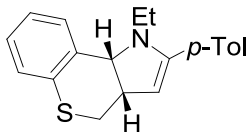
4.3b was prepared according to the same procedure as **4.3a**.

Isolated yield: 85%.

^1H NMR: (500 MHz, CD_3CN): δ (ppm) 7.49 (dd, $J = 8.15$ Hz, 1.42 Hz, 2H), 7.40-7.31 (m, 7H), 7.27 (td, $J = 6.16$ Hz, 3.04 Hz, 1H), 7.17-7.12 (m, 2H), 6.85-6.81 (m, 2H), 5.08 (d, $J = 2.25$ Hz, 1H), 4.41 (d, $J = 8.30$ Hz, 1H), 4.32 (d, $J = 15.91$ Hz, 1H), 4.27 (d, $J = 15.90$ Hz, 1H), 4.05 (dd, $J = 11.03$ Hz, 4.23 Hz, 1H), 3.95 (dd, $J = 11.02$ Hz, 7.63 Hz, 1H), 3.20 (dtd, $J = 10.21$ Hz, 5.03 Hz, 2.86 Hz, 1H). **^{13}C NMR:** (125.7 MHz, CD_3CN): δ (ppm) 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 $\text{C}_{24}\text{H}_{22}\text{NO}^+$; calculated: 340.16959, found: 340.16954.

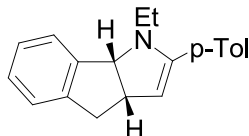
Synthesis and characterization of 4.3d



4.3d was prepared according to the same procedure as **4.3a**, except the cycloaddition required 2 h to go to completion. Isolated yield: 95%.

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.47–7.45 (m, 1H), 7.40–7.35 (m, 3H), 7.22–7.15 (m, 4H), 4.83 (s, 1H), 4.43 (d, $J = 10.4$ Hz, 1H), 3.83–3.78 (m, 1H), 3.15 (sx, $J = 7.2$ Hz, 1H), 2.97–2.88 (m, 2H), 2.58 (dd, $J = 6.8$ Hz, 12.8 Hz, 1H), 2.37 (s, 3H), 0.92 (t, $J = 7.2$ Hz, 3H). **^{13}C NMR** (75.5 MHz, CDCl_3): δ (ppm) 154.1, 137.9, 137.5, 136.9, 131.0, 130.1, 129.4, 129.0, 127.1, 127.0, 125.4, 104.8, 63.1, 45.8, 42.2, 34.0, 21.3, 10.8. **HRMS** (APCI^+) for $\text{C}_{20}\text{H}_{22}\text{NS}^+$; calculated: 308.14675, found: 308.14622.

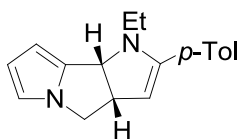
Synthesis and characterization of 4.3e



4.3e was prepared according to the same procedure as **4.3a**. Isolated yield: 74%.

^1H NMR (400 MHz, CDCl_3): δ (ppm) 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}C NMR** (75 MHz, CDCl_3): δ (ppm) 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 $\text{C}_{20}\text{H}_{22}\text{N}^+$; calculated: 276.17468, found: 276.17430.

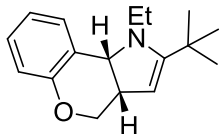
Synthesis and characterization of **4.3f**



4.3f was prepared according to the same procedure as **4.3a** with the exception that CD₃CN was used as solvent. Isolated yield: 76%.

¹H NMR (400 MHz, C₆D₆): δ (ppm) 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). **¹³C NMR** (75 MHz, C₆D₆): δ (ppm) 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 C₁₈H₂₁N₂⁺; calculated: 265.16993, found: 265.16930.

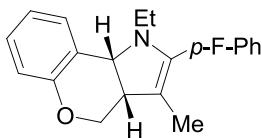
Synthesis and characterization of **4.3g**



In the glovebox, imine **4.2a** (37.8 mg, 0.2 mmol) and trimethylacetyl chloride (26.5 mg, 0.22 mmol) were mixed in CDCl₃ (ca. 0.5 mL) and allowed to stand 30 min. (2-catechyl)PPh (47.5 mg, 0.22 mmol) was added and after 18h at room temperature, DBU (45.7 mg, 0.3 mmol) was added, and the volume of CDCl₃ adjusted to 1.5 mL. The reaction was complete after 10 min at rt. The solution was concentrated in vacuo, and the residue dissolved in minimum amount of CH₂Cl₂. The product is purified in a glovebox with small pipette column of alumina using diethyl ether as eluent, affording **4.3g** as a light yellow oil (33 mg, 64%).

¹H NMR (400 MHz; CDCl₃): δ (ppm) 7.28 (dd, J = 7.6 Hz, 1.4 Hz, 1H), 7.19 (t, J = 8.4 Hz, 1H), 6.94–6.87 (m, 2H), 4.54 (d, J = 2.2 Hz, 1H), 4.21 (d, J = 7.7 Hz, 1H), 3.97 (dd, J = 10.7 Hz, 4.6 Hz, 1H), 3.66 (t, J = 10.0 Hz, 1H), 3.51–3.26 (m, 2H), 2.91–2.85 (m, 1H), 1.21 (t, J = 6.8 Hz, 3H), 1.16 (s, 9H). **¹³C NMR** (101 MHz; CDCl₃): δ (ppm) 161.4, 155.6, 130.9, 128.5, 121.8, 120.2, 117.0, 97.7, 66.3, 57.5, 40.7, 37.3, 30.0, 26.5, 11.4. **HRMS** (ESI⁺) for C₁₇H₂₄NO; calculated: 258.18524 found: 258.18491.

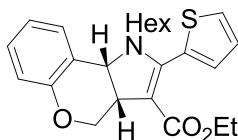
Synthesis and characterization of **4.3h**



4.3h was prepared according to the same procedure as **4.3a**, with the exception that cycloaddition required 1h at 60°C. Isolated yield: 88%.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 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). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 161.9 (d, ¹*J*_{C-F} = 237.5 Hz), 155.5, 145.4, 130.9, 130.4 (d, ³*J*_{C-F} = 7.5 Hz), 128.7 (d, ⁴*J*_{C-F} = 3.0 Hz), 128.6, 122.4, 120.5, 117.1, 115.1 (d, ²*J*_{C-F} = 15.0 Hz), 110.0, 64.8, 56.1, 42.9, 40.8, 11.8, 10.0. **HRMS** (APCI⁺) for C₂₀H₂₁NOF⁺; calculated: 310.16017, found: 310.16097.

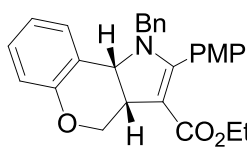
Synthesis and characterization of **4.3i**



In the glovebox, imine **4.2i** (63.5 mg, 0.2 mmol) and 2-thiophenecarbonyl chloride (32.2 mg, 0.22 mmol) were mixed in CDCl₃ (ca. 0.5 mL) and allowed to stand 30 min. (2-catechyl)PPh (47.5 mg, 0.22 mmol) was added and after 1h at room temperature, DBU (60.8 mg, 0.4 mmol) was added, and the volume of CDCl₃ adjusted to 1.5 mL. The reaction was complete within 10 min at room temperature. The product was purified by column chromatography on silica using hexanes/diethyl ether 95/5 as the eluent, affording **4.3i** as a light yellow oil (65.8 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.45 (d, *J* = 3.9 Hz, 1H), 7.29–7.22 (m, 2H), 7.08–7.03 (m, 2H), 6.98–6.94 (m, 2H), 4.68 (d, *J* = 8.4 Hz, 1H), 4.33 (dd, *J* = 4.8 Hz, 10.4 Hz, 1H), 4.05–3.96 (m, 2H), 3.82 (t, *J* = 10.8 Hz, 1H), 3.41–3.35 (m, 1H), 3.07 (t, *J* = 8.4 Hz, 2H), 1.72–1.65 (m, 1H), 1.31–1.06 (m, 10H), 0.83 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (75.5 MHz, CDCl₃): δ (ppm) 165.2, 156.2, 155.6, 131.1, 131.0, 129.6, 128.7, 127.2, 126.7, 120.5, 118.4, 117.8, 101.4, 65.0, 58.8, 58.5, 44.2, 37.9, 31.2, 27.4, 26.3, 22.4, 14.2, 13.9; **HRMS** (ESI⁺) for C₂₄H₃₀NO₃S⁺; calculated: 412.19409 found: 412.19430.

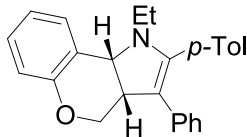
Synthesis and characterization of **4.3j**



Pyrroline **4.3j** was prepared according to the same procedure as **4.3i**. Isolated yield: 89%.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.37 (t, *J* = 7.6 Hz, 3H), 7.29-7.21 (m, 3H), 7.17 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.94-6.88 (m, 3H), 6.83 (t, *J* = 7.2 Hz, 1H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.48 (d, *J* = 16.8 Hz, 1H), 4.37 (dd, *J* = 4.8 Hz, 11.2 Hz, 1H), 4.20 (d, *J* = 16.8 Hz, 1H), 4.11-4.01 (m, 2H), 3.96 (t, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.56-3.50 (m, 1H), 1.12 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (75.5 MHz, CDCl₃): δ (ppm) 165.7, 163.4, 160.1, 156.5, 137.1, 131.3, 130.1, 129.5, 128.8, 127.2, 127.0, 123.6, 120.4, 118.5, 117.7, 113.5, 98.6, 65.9, 58.8, 57.6, 55.2, 47.5, 38.5, 14.4. **HRMS** (ESI⁺) for C₂₈H₂₈NO₄⁺; calculated: 442.20128, found: 442.20053.

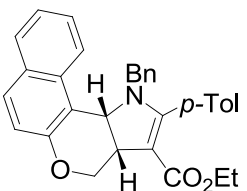
Synthesis and characterization of **4.3k**



Pyrroline **4.3k** was prepared according to the same procedure as **4.3h**. Isolated yield: 91%.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 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). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 155.7, 148.7, 138.0, 135.7, 131.1₃, 131.0₈, 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 C₂₆H₂₆NO⁺; calculated: 368.20089, found: 368.19963.

Synthesis and characterization of **4.3l**



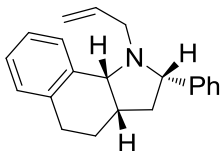
Pyrroline **4.3l** was prepared according to the same procedure as **4.3i**. Isolated yield: 75%.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 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). **¹³C NMR** (75 MHz,

CDCl₃): δ (ppm) 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 C₃₂H₃₀NO₃⁺; calculated: 476.22202, found: 476.22177.

4.4.4 Synthesis and Spectroscopic Data of Pyrrolidines 4.4

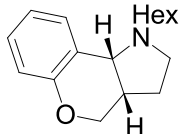
Synthesis and characterization of 4.4c



In the glovebox, imine **4.2c** (39.8 mg, 0.2 mmol) and benzoyl chloride (29.5 mg, 0.21 mmol) were mixed in CDCl₃ (ca. 0.5 mL) and allowed to stand 30 min. (2-catechyl)PPh (47.5 mg, 0.22 mmol) was added and after 1h at room temperature, DBU (45.7 mg, 0.3 mmol) was added, and the volume of CDCl₃ adjusted to 1.5 mL. The reaction was complete within 10 min at room temperature. To the crude reaction mixture in a 25 mL round bottom flask was added NaBH(OAc)₃ (64 mg, 0.3 mmol) followed by HCl, 1M in Et₂O (400 μ L, 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 with MgSO₄, filtered and concentrated. The product is purified by flash column chromatography on silica using petroleum ether/diethyl ether as eluent (90/10), affording **4.4c** as a white foam (43.4 mg, 75%).

¹H NMR (400 MHz; CDCl₃): δ (ppm) 7.39-7.36 (m, 2H), 7.32-7.28 (m, 3H), 7.26-7.22 (m, 4H), 6.03-5.92 (m, 1H), 5.13 (d, J = 10.2 Hz, 1H), 5.01 (d, J = 17.1 Hz, 1H), 3.90 (d, J = 8.8 Hz, 1H), 3.81 (dd, J = 9.9 Hz, 6.6 Hz, 1H), 3.20 (dd, J = 13.6 Hz, 6.4 Hz, 1H), 3.10-2.98 (m, 2H), 2.63-2.56 (m, 2H), 2.43 (ddd, J = 12.4 Hz, 8.5 Hz, 6.4 Hz, 1H), 1.74-1.70 (m, 2H), 1.61 (ddd, J = 12.3 Hz, 10.1 Hz, 8.4 Hz, 1H). **¹³C NMR** (126 MHz; CDCl₃): δ (ppm) 143.5, 141.1, 137.8, 132.9, 129.7, 128.3, 128.0, 127.6, 127.0, 126.7, 125.4, 118.2, 65.4, 62.2, 51.0, 41.9, 34.8, 30.4, 27.0. **HRMS** (APCI⁺) for C₂₁H₂₄N⁺; calculated: 290.19033, found: 290.18968.

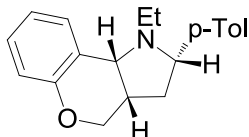
Synthesis and characterization of **4.4m**



In the glovebox, imine **4.2m** (49.1 mg, 0.2 mmol) and ethyl chlorothioformate (27.4 mg, 0.22 mmol) were mixed in CDCl_3 (ca. 0.5 mL) and allowed to stand 30 min at 50°C . (2-catechyl)PPh (47.5 mg, 0.22 mmol) was added and after 1h at 50°C , DBU (60.8 mg, 0.4 mmol) was added, and the volume of CDCl_3 adjusted to 1.5 mL. The reaction was complete within 10 min at room temperature. To the crude reaction mixture in a 25 mL round bottom flask was added $\text{NaBH}(\text{OAc})_3$ (85 mg, 0.4 mmol) followed by HCl, 1M in Et_2O (400 μl , 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 **4.4m** as a white foam (19.2 mg, 37%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 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 (ppm) 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 $\text{C}_{17}\text{H}_{26}\text{NO}^+$; calculated: 260.20131, found: 260.20199.

1-ethyl-2-(*p*-tolyl)-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole, **4.4a**



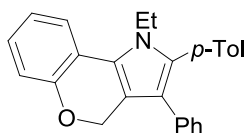
4.4a was prepared according to the same procedure as **4.4c**.

Isolated yield: 89%.

^1H NMR (500 MHz, CDCl_3) δ (ppm) 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 Hz, 1H), 2.74 (dt, $J = 14.5$ Hz, 7 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 (ppm) 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 C₂₀H₂₄NO⁺; calculated: 294.18524, found: 294.18454.

4.4.5 Synthesis and Spectroscopic Data of Pyrrole 4.5



The crude reaction mixture of pyrroline **4.3k** described above was dissolved in THF (5 mL). To this solution was added 1,4-benzoquinone (75 mg, 0.7 mmol). The solution is refluxed at 90 °C for 1 h, followed by the addition of more 1,4-benzoquinone (21.6 mg, 0.2 mmol). This solution was heated at 90 °C for 3 h. The product was purified by flash column chromatography on silica using hexanes/diethyl ether as eluent 90/10, affording **4.5k** as a white foam (48 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.48 (d, *J* = 7.6 Hz, 1H), 7.26-7.20 (m, 6H), 7.15-7.10 (m, 2H), 7.05-6.99 (m, 4H), 5.30 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (126 MHz; CDCl₃): δ (ppm) 153.6, 137.7, 134.8, 133.4, 131.3, 129.2, 129.1₇, 129.1, 128.1, 126.5, 125.4, 122.8, 121.7, 120.6, 119.8, 119.2, 117.4, 115.3, 65.1, 40.1, 21.4, 16.6. **HRMS** (APCI⁺) for C₂₆H₂₄NO⁺; calculated: 366.18524, found: 366.18440.

4.5 References

- (1) This chapter is a copy of a published communication and is reproduced with permission from The Royal Society of Chemistry, Marie S. T. Morin, Sara Aly, and Bruce A. Arndtsen, "Phosphonite mediated 1,3-dipolar cycloaddition: a route to polycyclic 2-pyrrolines from imines, acid chlorides and alkenes" *Chem. Commun.* **2013**, 49, 883-885.
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CHAPTER 5

Chiral Phosphorus-Based 1,3-Dipoles: A Modular Approach to Enantioselective 1,3-Dipolar Cycloaddition and 2-Pyrroline Synthesis¹

5.0 Preface

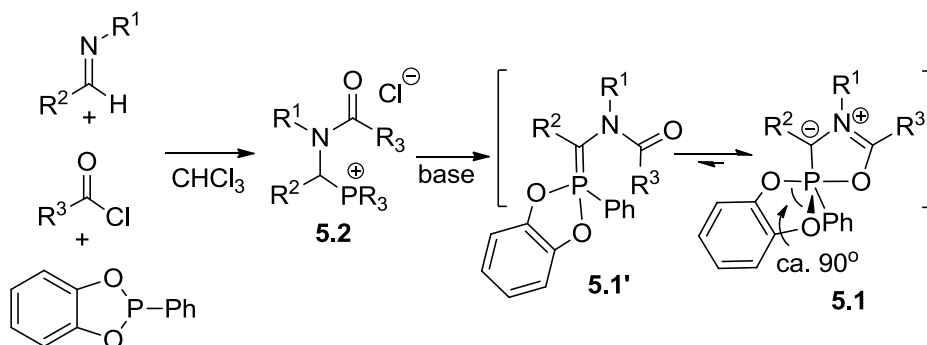
Chapter 4 describes the intramolecular cycloadditions of phosphamünchnones with alkenes to generate a polycyclic 2-pyrrolines. In addition to the control of the regio- and diastereoselectivity, we were next interested in the use of the phosphorus unit to control enantioselectivity. We describe herein the design of a new chiral 1,3-dipole, generated via the reaction of (R)-BINOL-based phosphites with imines and acid chlorides. These dipoles are easily formed, rigidly chiral, and undergo intramolecular alkene cycloaddition with high enantioselectivity, providing a straightforward approach to synthesize chiral polycyclic 2-pyrrolines and pyrrolidines.

5.1 Introduction

Enantioselective 1,3-dipolar cycloaddition reactions provide an efficient method to construct chiral heterocycles. An important example is the cycloaddition of 1,3-oxazolium-5-oxides (i.e., Münchnones) and their analogues with alkenes to form pyrrolines, or the fully reduced pyrrolidines. These latter are among the more common heterocyclic motifs found in biologically relevant compounds.² One challenge in this chemistry is the design of reliable methods to control enan-

tioreselectivity. A classic approach involves the use of chiral substituents on the dipole or dipolarophile.^{3,4} However, these typically require multiple synthetic steps to introduce, then subsequently remove, the chiral fragment. In addition, these substituents are often at potentially rotatable sites, and complex chiral units are often needed to achieve high selectivity. Chiral catalysts, such as chiral Lewis or Bronsted acids, provide a much more efficient method to control enantioselectivity in Münchnone cycloadditions.^{5,6} A challenge in this case is the scope of these transformations with any one chiral catalyst, perhaps due to their weak association to the substrate. Both of these methods also require the initial synthesis of the polysubstituted 1,3-dipole.

As an alternative, we have recently reported a new 1,3-dipole **5.1** (Scheme 5.1).^{7,8} **5.1** is easily generated in one step from imines, acid chlorides and phosphonites, and undergoes dipolar cycloaddition with alkynes or alkenes in analogy to Münchnones.⁹ Considering the generation of **5.1** from phosphines, and the availability of chiral phosphorus reagents, we became interested in the potential of using these dipoles in enantioselective 1,3-dipolar cycloadditions. The incorporation of chiral phosphines into **5.1** would generate a 1,3-dipole that is chiral, easily prepared (one step), and modular. In addition, the chiral unit would require no additional steps to introduce or remove, yet is rigidly associated into **5.1**. We describe our efforts towards the development of these 1,3-dipoles below. This has resulted in a straightforward and general platform to synthesize chiral polycyclic 2-pyrrolines and pyrrolidines in up to 99% enantioselectivity.



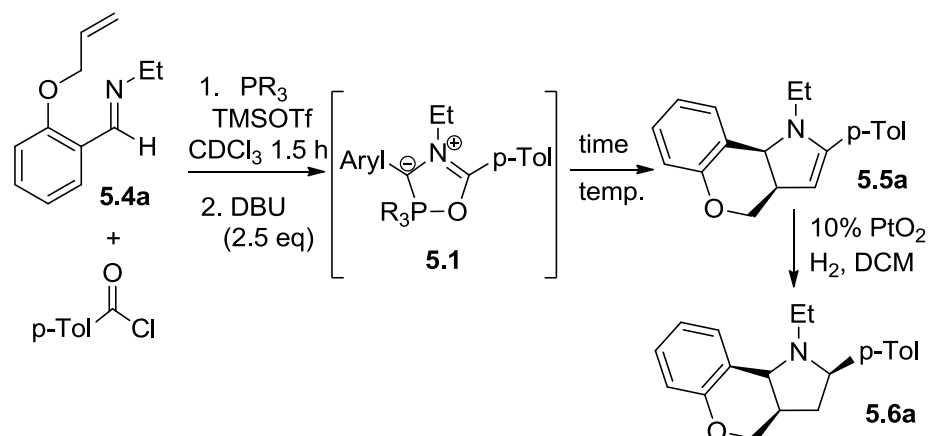
Scheme 5.1: Modular Generation of Phosphorus-Based 1,3-Dipole **5.1**.

5.2 Results and Discussion

Catechyl-based phosphonites of the form PhP(2-catechyl) are effective in generating the phosphorus-dipole **5.1**. These phosphonites provide a useful balance of nucleophilicity to generate **5.2** (Scheme 5.1), while retaining the phosphorus electrophilicity required to favor cyclization of the amide-substituted Wittiglide **5.1'** to its dipole form. We postulated that BINOL-based phosphonites might provide a similar electronic balance. (R)-BINOL derived **5.3a** (Table 5.1) can be prepared by reaction of PhPCl₂ with the commercially available diol.¹⁰ As shown in Table 5.1, the phosphonite **5.3a** can mediate the formation of 2-pyrroline **5.5a** from imine **5.4a** and *p*-toluoyl chloride in a similar fashion to PhP(2-catechyl), although it requires heating to 70 °C (entry 2). Chiral HPLC analysis of the more easily separable pyrrolidine **5.6a**, generated by hydrogenation of **5.5a** on PtO₂, shows this product is formed in a reasonable 60 % ee.

The elevated temperature needed to induce cycloaddition with phosphonite **5.3a** contrasts with the rapid reaction with PhP(2-catechyl), and presumably diminishes enantioselectivity. We postulated that this may result from the loss of angle strain in BINOL, and disfavored cyclization to generate the trigonal bipyramidal 1,3-dipole (with a ca. 90° O-P-O bond angle).^{7c,11} *In situ* ³¹P NMR analysis is consistent with this analysis, and show a downfield ³¹P NMR resonance (+76.0 ppm) in the typical region for Wittig-type reagents **5.1a'** rather than a 5-coordinate phosphorus (+10 to -90 ppm).¹² To help favor amide chelation, we turned to more electron poor phosphites. As shown in entry 3, the BINOL-derived phosphite **5.3b** allows the formation of the same pyrroline **5.2b** at now ambient temperature, and in significantly improved 86 % ee (entry 3). Since substituted phenols are readily available, it is easy to further tune the phosphite without modification of the BINOL (entries 3-6). The sterically encumbered 2,6-dimethylphenol (**5.3d**) or 2-*t*-butylphenol (**5.3e**) derived phosphites lead to cycloaddition in high enantioselectivity (97 and 98 % ee, entries 5, 6).

Table 5.1. Chiral Phosphites in Enantioselective 1,3-Dipolar Cycloaddition.^a



Entry	PR_3	temp.	time	Yield 5.5a ^b	ee ^c (O.R.)
1		rt	10 min	85%	/
2		70 °C	11 h	67 %	60 % (-)
3		rt	8 h	89 %	86 % (-)
4		rt	24 h	89 %	2 % (+)
5		rt	30 h	84 %	97 % (+)
6		rt	30 h	82 %	98 % (+)

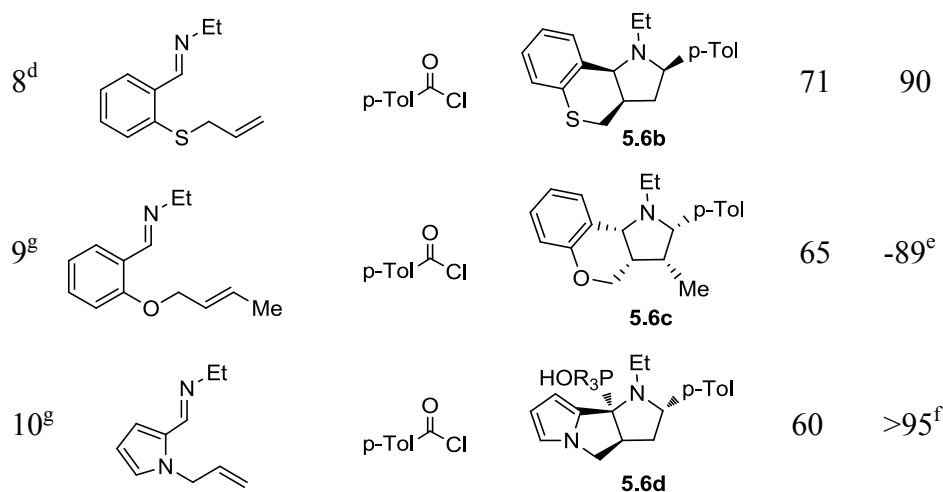
^a **5.4a** (38 mg, 0.2 mmol), *p*-toluoyl chloride (34 mg, 0.22 mmol), 0.5 mL CDCl_3 , 30 min; PR_3 (0.22 mmol) and TMSOTf (46.7 mg, 0.21

mmol), 90 min, DBU (76 mg, 0.5 mmol). ^b NMR yield. ^c **5.5a** reduced to **5.6a** for HPLC analysis. O.R. = optical rotation.

In addition to the cyclization of imine **5.4a** and *p*-toluoyl chloride, since these phosphorus 1,3-dipoles are modular (from imines, acid chlorides and phosphites), this can provide a general approach to synthesize chiral 2-pyrrolines. Examples are shown in Table 5.2. A range of aryl, functionalized aryl, heteroaryl, and alkyl-substituted acid chlorides can be used in this reaction (entries 1-7). Despite their varying steric profile, they each undergo cycloaddition to yield pyrrolines with high enantioselectivity (up to 99% ee). Both terminal and internal alkenes can be employed, including internal unactivated alkenes (entry 9), which upon heating with the less sterically encumbered phosphite **5.3b** lead to product in 89 % ee. A number of aromatic and even heteroaromatic spacers are also viable (entries 6, 7, 10), as are 5,5-fused ring products (entry 10). In this latter case, the phosphite unit does not eliminate upon cycloaddition, and generates the quaternary product with high enantioselectivity. As shown in entries 8-10, cycloaddition can be coupled with stereoselective reduction, allowing the formation of polycyclic pyrrolidines with three or four stereogenic centers as a single observable diastereomer.

Table 5.2. Generality of Enantioselective Cycloaddition.^a

#	Imine	Acid chloride	Product	Yield (%)	ee (%)
1				77	95
2				85	95 ^b
3				73	96
4				64	87
5 ^c				85	87 ^b
6 ^c				61	99
7				83	97



^a imine (0.2 mmol), acid chloride (0.22 mmol), 0.5 mL CH₂Cl₂, 30 min; **5.3d** (96 mg, 0.22 mmol), TMSOTf (46.7 mg, 0.21 mmol), 3h; DBU (76.1 mg, 0.50 mmol), rt, 3 h. ^b with **5.3e**. ^c 1.5 d. ^d 5 d, 45°C; H₂, PtO₂ (3.2 mg, 10%), DCM, 18h. ^e **5.3b**, AgOTf, 2h; LiHMDS at -78°C; 2 d, 50°C. ^f 3 days. ^g NaBH(OAc)₃, 1M HCl/ether reduction.

The cycloaddition of all of the substrates examined proceeds with good enantioselectivity. To probe the origin of this selectivity, crystals were grown of the chiral 1,3-dipole. The results of X-ray crystallographic analysis are shown in Figure 5.1 (see Appendix D). The (R)-BINOL unit adopts an axial-equatorial orientation in **5.1d** (O(52)-P(5)-O(53) = 94.00(16) Å) with a strong interaction between the phosphorus and the amide oxygen (P-O(51)=1.800(3) Å), similar to that noted with catechyl-substituted phosphonites.^{7c} The five-coordinate phosphorus in **5.1d** is itself a stereogenic center. Thus, the major stereochemical influence of the chiral BINOL appears to be to form **5.1d** as a single diastereomer. In this configuration, alkene cycloaddition is controlled by access to the face of the dipole. With a large 2,6-dimethylphenol, the bottom face of the dipole is blocked, and would be expected to result in selective cycloaddition syn to the BINOL unit, regardless of the alkene or dipole substituents. This is supported by X-ray structural analysis of the pyrrolidine product **5.6a**, which shows it to be formed as the (R,R,S)-enantiomer (see Appendix E).

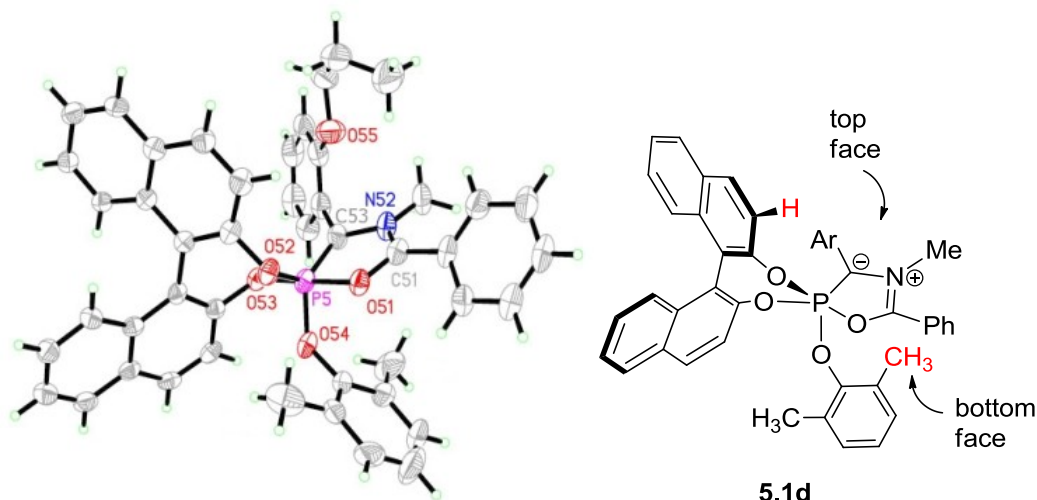
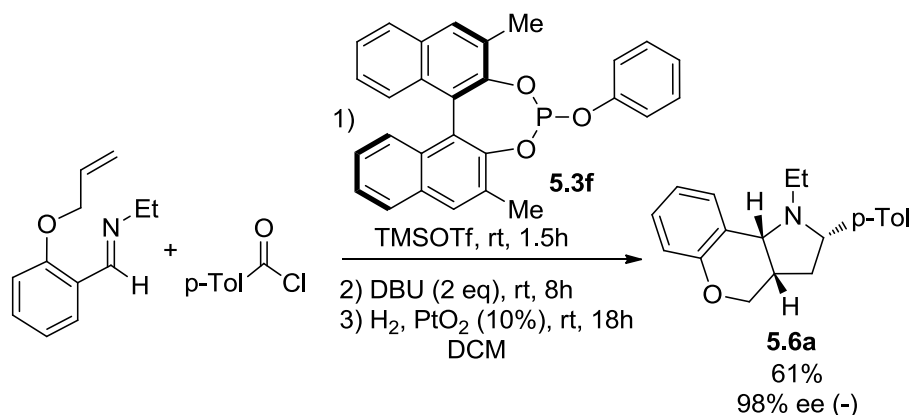


Figure 5.1. X-ray crystal structure of **5.1d** (ORTEP view). Ar = 2-(CH₃CH₂CH₂O)C₆H₄. The asymmetric unit contains two molecules which differ by the structural arrangement of the O-propyl chain (see Appendix D). Selected bond lengths (Å) and angles (deg.): P(5)-O(51), 1.800(3); P(5)-O(52), 1.646(3); P(5)-O(53), 1.667(3); P(5)-O(54), 1.621(4); P(5)-C(53), 1.702(5); O(51)-C(51), 1.313(6); C(51)-N(52), 1.303(6); N(52)-C(53), 1.426(6); O(54)-P(5)-O(53), 90.92(16); O(52)-P(5)-O(53), 94.00(16); O(54)-P(5)-C(53), 128.1(2); O(52)-P(5)-C(53), 128.7(2); O(53)-P(5)-O(51), 179.24(18); C(53)-P(5)-O(51), 86.48(19).

The model suggests that minimizing the steric profile of the phenol should favor the opposite pyrroline enantiomer. This is borne out in the screening Table 5.1: simple phenol derived **5.3b** provides pyrroline in good enantioselectivity (entry 3), but as the opposite enantiomer to that with larger phenols (- 86% ee). 2-Methylphenol appears to balance these factors, and leads to **5.5a** in nearly racemic form. These data suggest that increasing the steric profile of the BINOL unit should further favor the other enantiomer of **5.5a**. Indeed, as illustrated in Scheme 5.2, the (R)-3,3'-dimethyl-BINOL derived **5.3f** leads to **5.6a** is high enantioselectivity, yet as the (S,S,R)-enantiomer. This enantiomer change is obtained without modifying the chirality of the BINOL unit.



Scheme 5.2: (R)-3,3'-Dimethyl-BINOL Derived Phosphite **5.3f** in Enantioselective 1,3-Dipolar Cycloaddition.

5.3 Conclusions

In conclusion, we have reported a new class of chiral dipole for enantioselective 2-pyrroline synthesis. This phosphorus-based 1,3-dipole is readily generated from simple imines, acid chlorides and phosphites; employs an available chiral unit (BINOL) that is removed upon cycloaddition; is modular; and has chirality rigidly incorporated into the dipole for high and tunable enantioselectivity. As such, we feel this could provide a useful general platform for enantioselective cycloadditions to generate chiral heterocycles. Experiments directed towards the latter are currently underway.

5.4 Experimental Section

5.4.1 General Procedures

All reactions were carried out in a Vacuum Atmosphere dry glovebox or by using standard Schlenk-line techniques. All reagents were purchased from commercial sources and used as received. (2-catechyl)PPh and imines were prepared as reported in Chapter 2 and Chapter 4 respectively. (R)-3,3'-dimethyl-BINOL was synthesized according to literature procedure.¹³ CDCl₃ and CD₃CN were distilled from CaH₂ under nitrogen. Dichloromethane, tetrahydrofuran, pen-

tane were obtained dry from a solvent purification system. ^1H , ^{13}C , and ^{31}P NMR spectra were recorded on Varian Mercury 200, 300, 400 MHz, and Unity 500 MHz spectrometers and are reported in Appendix A. Mass spectra were acquired by electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI) and obtained from the McGill University mass spectral facilities. Optical rotations were measured on a digital polarimeter operating at the sodium D line with a 50 mm path cell. The cis-ring fusion in **5.5a-h** was determined by comparison to previously reported compounds.¹⁴ nOe studies were performed on **5.6a**, **5.6c** and **5.6d** to confirm stereochemistry and are reported in Appendix A. Enantiomeric excess was determined by HPLC analysis on chiral pak OD-H column using hexanes: isopropanol as eluent with a flow rate of 3 ml/min unless otherwise noticed. Racemic versions of **5.5a-h** and **5.6a-c** were prepared using (2-catechyl)PPh, and racemic **5.6d** was synthesized with ($\pm$)-BINOL derived **5.3d**. X-ray structures of compounds **5.1d** and **5.6a** were determined by Franine B langer and Michel Simard at the University of Montreal facilities. The data are provided in Appendices D and E.

5.4.2 Synthesis and Characterizations of 5.3a-f

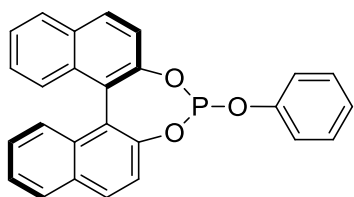
Synthesis of (R)-4-phenyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine, **5.3a**

A modified version of a literature procedure was followed.¹⁵ To (R)-BINOL (0.5 g, 1.75 mmol) in 10 mL of THF under nitrogen in a 50 mL Schlenk flask was added triethylamine (0.510 mL, 3.67 mmol). The mixture was cooled at 0  C and PhPCl_2 (0.236 mL, 1.75 mmol) was added dropwise with vigorous stirring. The solution was stirred at ambient temperature for 2 h and filtered through a medium frit in the glovebox. After concentration to dryness, the product **3a** was precipitated in dichloromethane to collect 365 mg (54%) of a white solid. The product was stored in a -35  C glovebox freezer to avoid decomposition. ^1H NMR spectroscopic data for the compound **5.3a** is consistent with that previously reported in the literature.¹⁶

Synthesis of Phosphites **5.3b-5.3f**

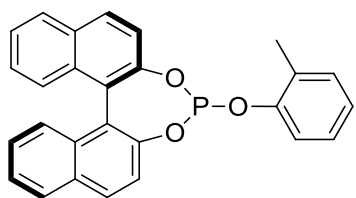
A modified version of a literature procedure was followed.¹⁷ Under nitrogen, (R)-BINOL (2.0 g, 7.0 mmol) was dissolved in 50 mL of THF in a 100 mL Schlenk flask and cooled at -40 °C. To this solution was added phosphorus trichloride (0.98 mL, 11.2 mmol) followed by triethylamine (1.95 mL, 14.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. The solution was filtered through a medium frit in a glovebox, and concentrated under reduced pressure. The mixture was diluted with THF (20 mL) followed by addition of triethylamine (780 mg, 7.7 mmol) and phenol (724 mg, 7.7 mmol). After 16 h, the mixture was filtered through a medium frit and concentrated to dryness. The product was purified by flash chromatography on silica gel (toluene/ethyl acetate, 9/1, dry loaded). The product was recrystallized in a glovebox with dichloromethane/pentane (1/2) in a -35 °C freezer for 1 day. The precipitate was collected by filtration to afford **5.3b** as pure white solid (1.972 g, 69%). The product was stored in a -35 °C glovebox freezer to avoid decomposition. **5.3c-5.3f** were prepared according to the same procedure.

(R)-4-phenoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine **5.3b**



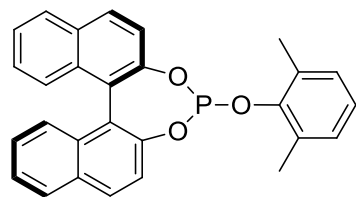
Isolated Yield: 69%. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.01 (d, *J* = 8.8 Hz, 1H), 7.96-7.91 (m, 3H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.48-7.34 (m, 7H), 7.31-7.26 (m, 2H), 7.21-7.15 (m, 3H). ¹³C NMR (126 MHz, CDCl₃): δ (ppm) 147.0 (d, *J* = 8.5 Hz), 142.7 (d, *J* = 4.4 Hz), 142.2 (d, *J* = 2.3 Hz), 129.0 (d, *J* = 1.2 Hz), 127.8 (d, *J* = 1.1 Hz), 126.9, 126.6, 125.8, 125.2, 125.1, 123.65 (d, *J* = 7.5 Hz), 122.30 (d, *J* = 11.7 Hz), 121.6 (d, *J* = 18.6 Hz), 120.4 (d, *J* = 26.4 Hz), 119.7, 119.6, 118.2 (d, *J* = 2.5 Hz), 116.9₄ (d, *J* = 1.6 Hz), 116.9₂, 115.6 (d, *J* = 8.0 Hz). ³¹P NMR (81 MHz, CDCl₃): δ (ppm) 144.1. HRMS (ESI⁺): for C₂₆H₁₈O₃P⁺; calculated: 409.09881, found: 409.09938.

(R)-4-(*o*-tolxyloxy)dinaphtho[2,1-*d'*:1',2'-*f'*][1,3,2]dioxaphosphepine 5.3c



Isolated yield: 65%. **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 8.01 (d, *J* = 8.8 Hz, 1H), 7.97-7.92 (m, 3H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.48-7.39 (m, 5H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 2.31 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 150.2 (d, *J* = 12.8 Hz), 147.7 (d, *J* = 9.8 Hz), 147.1 (d, *J* = 3.9 Hz), 132.8 (d, *J* = 2.6 Hz), 132.6 (d, *J* = 2.1 Hz), 131.7, 131.3, 131.2, 130.5, 129.8, 129.6 (d, *J* = 3.6 Hz), 128.3 (d, *J* = 8.0 Hz), 127.1, 126.9 (d, *J* = 6.8 Hz), 126.3 (d, *J* = 20.2 Hz), 125.1 (d, *J* = 27.1 Hz), 124.4 (d, *J* = 8.9 Hz), 124.3 (d, *J* = 1.7 Hz), 122.9 (d, *J* = 4.1 Hz), 121.8 (d, *J* = 2.9 Hz), 121.7, 119.7 (d, *J* = 20.0 Hz), 16.7 (d, *J* = 1.6 Hz). **³¹P NMR** (81 MHz, CDCl₃): δ (ppm) 145.7. **HRMS** (ESI⁺): for C₂₇H₂₀O₃P⁺; calculated: 423.11497 found: 423.11478.

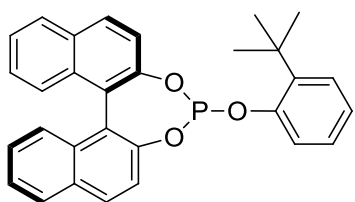
(R)-4-(2,6-dimethylphenoxy)dinaphtho[2,1-*d'*:1',2'-*f'*][1,3,2]dioxaphosphepine 5.3d



Isolated Yield : 75%. **¹H NMR** (500 MHz, CDCl₃): δ (ppm) 8.02 (t, *J* = 9.1 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.60 (dd, *J* = 16.6 Hz, 8.8 Hz, 2H), 7.50-7.47 (m, 4H), 7.35-7.31 (m, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 2.49 (s, 6H). **¹³C NMR** (126 MHz, CDCl₃): δ (ppm) 149.2 (d, *J* = 6.6 Hz), 147.9 (d, *J* = 5.7 Hz), 147.1 (d, *J* = 2.3 Hz), 132.9 (d, *J* = 1.4 Hz), 132.7 (d, *J* = 1.4 Hz), 131.7, 131.2, 130.5, 130.4, 129.9, 128.9 (d, *J* = 1.0 Hz), 128.4 (d, *J* = 8.8 Hz), 127.1 (d, *J* = 8.3 Hz), 126.3 (d, *J* = 20.1 Hz), 125.1 (d, *J* = 24.0 Hz), 124.6 (d, *J* = 1.4 Hz), 124.4 (d, *J* = 5.1 Hz), 122.9 (d, *J* = 2.5 Hz), 122.0, 121.8 (d, *J* = 1.5 Hz), 18.0 (d, *J* = 3.6 Hz). **³¹P NMR** (81 MHz, CDCl₃): δ (ppm) 148.3. **HRMS** (ESI⁺): for C₂₈H₂₂O₃P⁺; calculated: 437.13011 found: 437.13000.

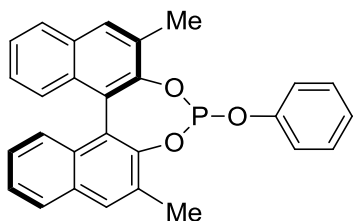
(R)-4-(2-(*tert*-butyl)phenoxy)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine

5.3e



Isolated yield: 67%. **¹H NMR** (500 MHz, CDCl₃): δ (ppm) 8.04 (d, *J* = 8.8 Hz, 1H), 7.99-7.94 (m, 3H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.50-7.41 (m, 5H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.34-7.29 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 1.42 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃): δ (ppm) 151.0 (d, *J* = 8.7 Hz), 148.0 (d, *J* = 4.8 Hz), 147.1 (d, *J* = 2.0 Hz), 140.4 (d, *J* = 2.3 Hz), 132.9, 132.6, 131.7, 131.3, 130.5, 129.8, 128.4 (d, *J* = 8.7 Hz), 127.5, 127.1 (d, *J* = 5.0 Hz), 127.0, 126.3 (d, *J* = 24.3 Hz), 125.1 (d, *J* = 31.0 Hz), 124.5 (d, *J* = 5.0 Hz), 124.0, 122.9 (d, *J* = 2.1 Hz), 121.8 (d, *J* = 21.7 Hz), 120.0 (d, *J* = 1.6 Hz), 34.8, 30.0. **³¹P NMR** (202.3 MHz, CDCl₃): δ (ppm) 144.9. **HRMS** (ESI⁺): for C₃₀H₂₆O₃P⁺; calculated: 465.16141 found: 465.16054.

(R)-2,6-dimethyl-4-phenoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 5.3f



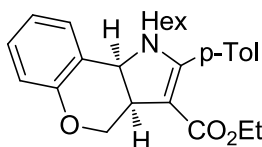
Isolated yield: 90%. **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.88-7.81 (m, 4H), 7.44-7.29 (m, 6H), 7.24-7.14 (m, 5H), 2.66 (d, *J* = 0.8 Hz, 3H), 2.58 (d, *J* = 0.7 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) 152.0 (d, *J* = 15.7 Hz), 147.4 (d, *J* = 8.9 Hz), 146.2 (d, *J* = 4.8 Hz), 131.7 (d, *J* = 2.9 Hz), 131.5, 131.4 (d, *J* = 2.5 Hz), 131.2, 130.1, 130.0, 129.9₈, 129.8, 129.7, 127.6 (d, *J* = 9.6 Hz), 127.0 (d, *J* = 3.1 Hz), 125.4, 125.1 (d, *J* = 33.0 Hz), 124.7 (d, *J* = 9.4 Hz), 124.1, 122.8 (d, *J* = 4.5 Hz), 119.8 (d, *J* = 15.5 Hz), 18.0, 17.5. **³¹P NMR** (81 MHz, CDCl₃): δ (ppm) 144.9. **HRMS** (ESI⁺): for C₂₈H₂₂O₃P⁺; calculated: 437.13011 found: 437.12951.

5.4.3 Synthesis and Characterization of Pyrrolines 5.5b-h

Typical Synthesis

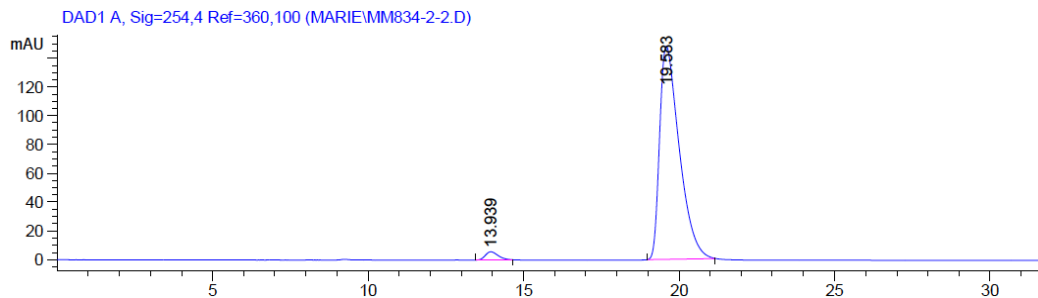
In a glovebox, (2-(EtO₂C(H)C=CHCH₂O)C₆H₄)HC=NH₂ (63.5 mg, 0.2 mmol) and toluoyl chloride (34.0 mg, 0.22 mmol) were mixed in 0.5 mL CH₂Cl₂ for 30 min. To the solution was added phosphite **5.3d** (96.0 mg, 0.22 mmol) and TMSOTf (46.7 mg, 0.21 mmol), and the mixture was left at rt for 3h. DBU (76.1 mg, 0.5 mmol) was added and the final volume of dichloromethane adjusted to 2 mL. The reaction was complete within 3 h (**5.5f**: 12 h; **5.5g**: 2 days). The solution was concentrated in vacuo and purified by flash chromatography on silica using hexanes/diethyl ether (9/1) as eluent to afford **5.5b** as light yellow oil (64.5 mg, 77%).

Pyrroline 5.5b



Isolated yield: 77%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.31-6.94 (m, 8H), 4.67 (d, $J = 8.7$ Hz, 1H), 4.34 (dd, $J = 4.8$ Hz, 10.8 Hz, 1H), 4.07-3.89 (m, 2H), 3.82 (t, $J = 10.5$ Hz, 1H), 3.42-3.34 (m, 1H), 3.09-2.92 (m, 2H), 2.39 (s, 3H), 1.71-1.59 (m, 1H), 1.26-1.00 (m, 10H), 0.81 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 165.5, 163.7, 156.3, 138.5, 131.2, 129.6, 129.2, 128.7, 127.7, 120.4, 118.6, 117.8, 98.7, 65.3, 58.5, 58.3, 43.8, 37.6, 31.1, 26.9, 26.2, 22.4, 21.4, 14.3, 13.9; **HRMS** (ESI^+) for $\text{C}_{27}\text{H}_{34}\text{NO}_3^+$; calculated: 420.25332, found: 420.25380; **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (99:1 Hexanes : iPrOH, 0.8 ml/min, 254 nm); major enantiomer $t_r = 19.6$ min, minor enantiomer $t_r = 13.9$ min; 95% ee; **Optical rotation**: $[\alpha]_D^{22} +2.8$ (c 1.0, CHCl_3).

- Chiral product HPLC:

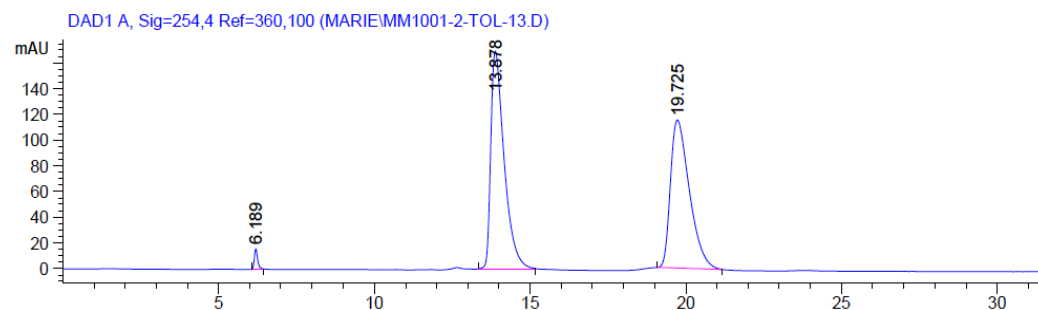


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

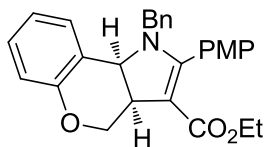
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.939	BB	0.4431	165.11320	5.71355	2.4684
2	19.583	BB	0.6647	6523.99414	148.44954	97.5316

Totals : 6689.10735 154.16309

- Racemic HPLC:



Pyrroline **5.5c**

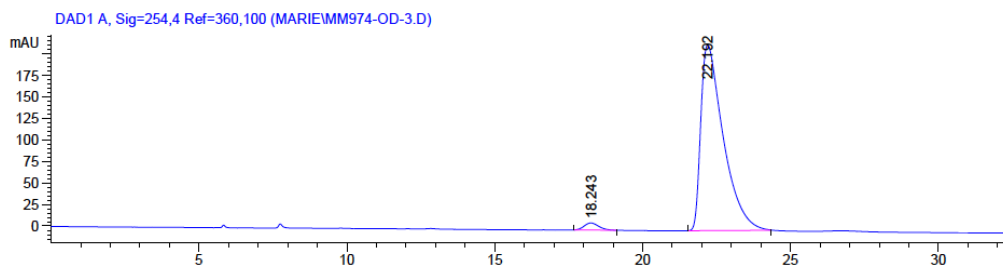


Isolated yield: 85%. ^1H NMR (400 MHz, CDCl_3): δ (ppm)

7.37 (t, $J = 7.6$ Hz, 3H), 7.29-7.21 (m, 3H), 7.17 (d, $J = 7.6$ Hz, 2H), 6.98 (d, $J = 7.6$ Hz, 1H), 6.94-6.88 (m, 3H), 6.83 (t, $J = 7.2$ Hz, 1H), 4.79 (d, $J = 8.8$ Hz, 1H), 4.48 (d, $J =$

16.8 Hz, 1H), 4.37 (dd, $J = 4.8$ Hz, 11.2 Hz, 1H), 4.20 (d, $J = 16.8$ Hz, 1H), 4.11-4.01 (m, 2H), 3.96 (t, $J = 10.8$ Hz, 1H), 3.79 (s, 3H), 3.56-3.50 (m, 1H), 1.12 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 165.7, 163.4, 160.1, 156.5, 137.1, 131.3, 130.1, 129.5, 128.8, 127.2, 127.0, 123.6, 120.4, 118.5, 117.7, 113.5, 98.6, 65.9, 58.8, 57.6, 55.2, 47.5, 38.5, 14.4. **HRMS** (ESI^+) for $\text{C}_{28}\text{H}_{28}\text{NO}_4^+$; calculated: 442.20128, found: 442.20053. **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (98:2 Hexanes : iPrOH, 0.6 ml/min, 254 nm); major enantiomer tr = 22.2 min, minor enantiomer tr = 18.2 min; 95% ee; **Optical rotation**: $[\alpha]_D^{22} +2.9$ (c 1.0, CHCl_3).

- Chiral product HPLC:

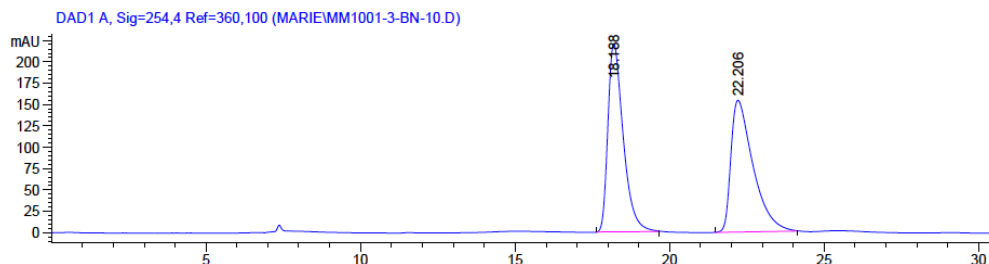


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

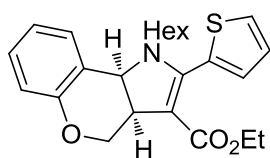
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.243	BB	0.5223	287.51434	8.33891	2.4622
2	22.192	BB	0.7818	1.13894e4	215.78615	97.5378

Totals : 1.16769e4 224.12506

- Racemic HPLC:

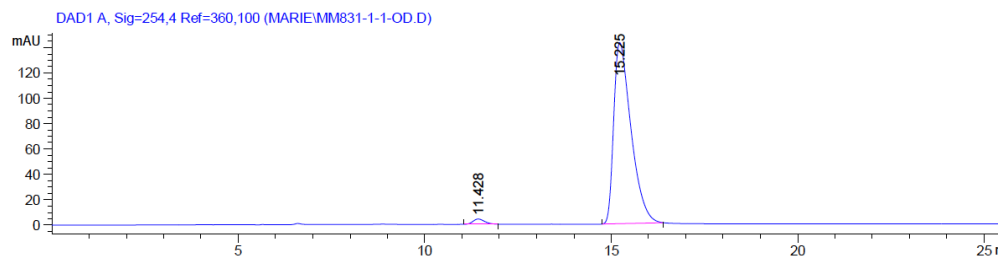


Pyrroline 5.5d



Isolated yield: 73%. **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 7.45 (d, *J* = 3.9 Hz, 1H), 7.29-7.22 (m, 2H), 7.08-7.03 (m, 2H), 6.98-6.94 (m, 2H), 4.68 (d, *J* = 8.4 Hz, 1H), 4.33 (dd, *J* = 4.8 Hz, 10.4 Hz, 1H), 4.05-3.96 (m, 2H), 3.82 (t, *J* = 10.8 Hz, 1H), 3.41-3.35 (m, 1H), 3.07 (t, *J* = 8.4 Hz, 2H), 1.72-1.65 (m, 1H), 1.31-1.06 (m, 10H), 0.83 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (75.5 MHz, CDCl₃): δ (ppm) 165.2, 156.2, 155.6, 131.1, 131.0, 129.6, 128.7, 127.2, 126.7, 120.5, 118.4, 117.8, 101.4, 65.0, 58.8, 58.5, 44.2, 37.9, 31.2, 27.4, 26.3, 22.4, 14.2, 13.9; **HRMS** (ESI⁺) for C₂₄H₃₀NO₃S⁺; calculated: 412.19409 found: 412.19430; **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (99:1 Hexanes : iPrOH, 0.8 ml/min, 254 nm); major enantiomer *t_r* = 15.2 min, minor enantiomer *t_r* = 11.4 min; 96% ee; **Optical rotation** [α]_D²⁵ +2.1 (c 1.0, CHCl₃).

- Chiral product HPLC:

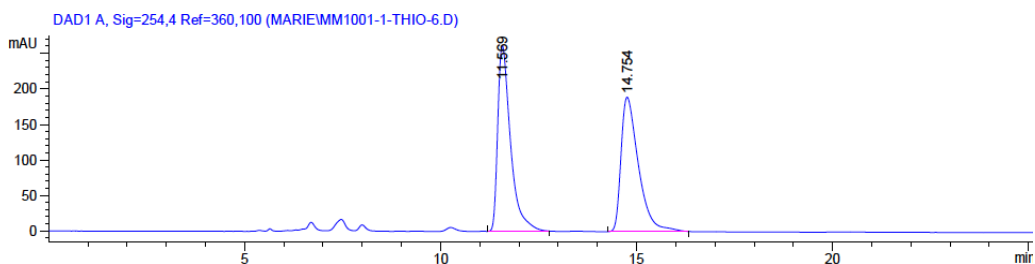


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

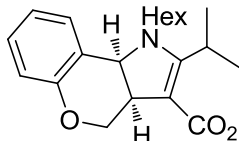
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.428	BB	0.3318	92.26884	4.17609	1.9568
2	15.225	BB	0.4891	4623.00195	143.00783	98.0432

Totals : 4715.27080 147.18391

- Racemic HPLC:

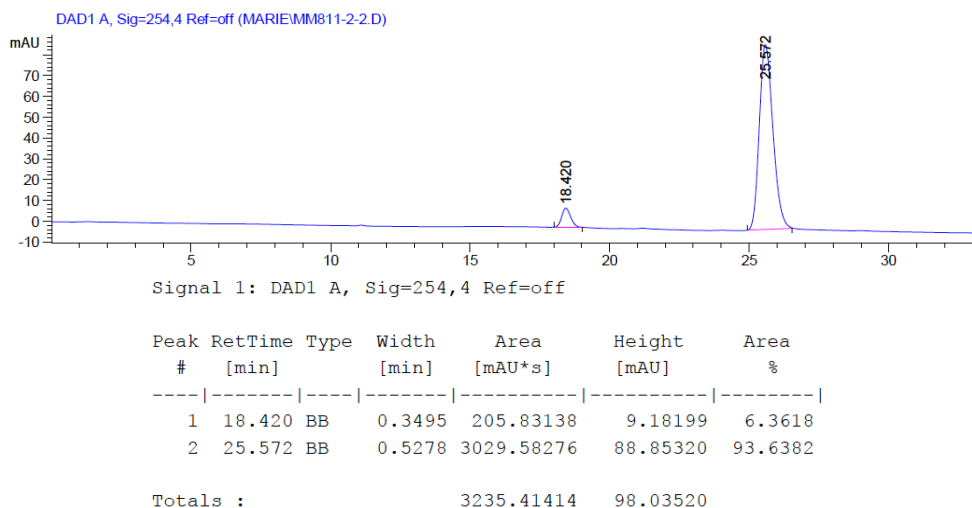


Pyrroline 5.5e

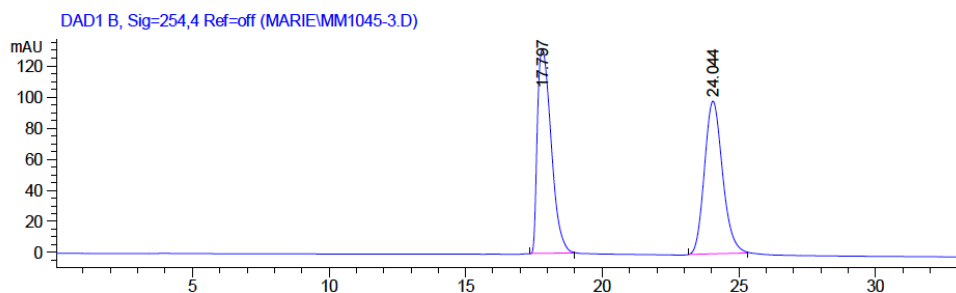


Isolated yield: 64%. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.27-7.23 (m, 1H), 7.20 (d, $J = 7.6$ Hz, 1H), 6.94 (t, $J = 8.4$ Hz, 2H), 4.43 (d, $J = 7.2$ Hz, 1H), 4.22 (dd, $J = 4.8, 10.8$ Hz, 1H), 4.13 (m, 2H), 3.50 (t, $J = 10.8$ Hz, 1H), 3.45 (broad s, 1H), 3.28-3.26 (m, 2H), 3.16-3.10 (m, 1H), 1.74-1.70 (m, 1H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.30-1.25 (m, 13H), 0.89 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 170.4, 165.7, 156.2, 131.5, 129.6, 120.2, 118.1, 117.6, 95.0, 65.2, 58.8, 58.5, 44.2, 36.8, 31.4, 28.0, 26.5, 26.0, 22.6, 19.1, 14.7, 14.0; HRMS (ESI $^+$) for $\text{C}_{23}\text{H}_{34}\text{NO}_3^+$; calculated: 372.25332, found: 372.25200; HPLC: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (99:1 Hexanes : iPrOH, 0.3 ml/min, 254 nm); major enantiomer tr = 25.6 min, minor enantiomer tr = 18.4 min; 87% ee; **Optical rotation**: $[\alpha]_D^{22} +2.5$ (c 1.0, CHCl_3).

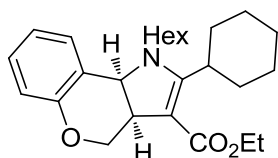
- Chiral product HPLC:



- Racemic HPLC:

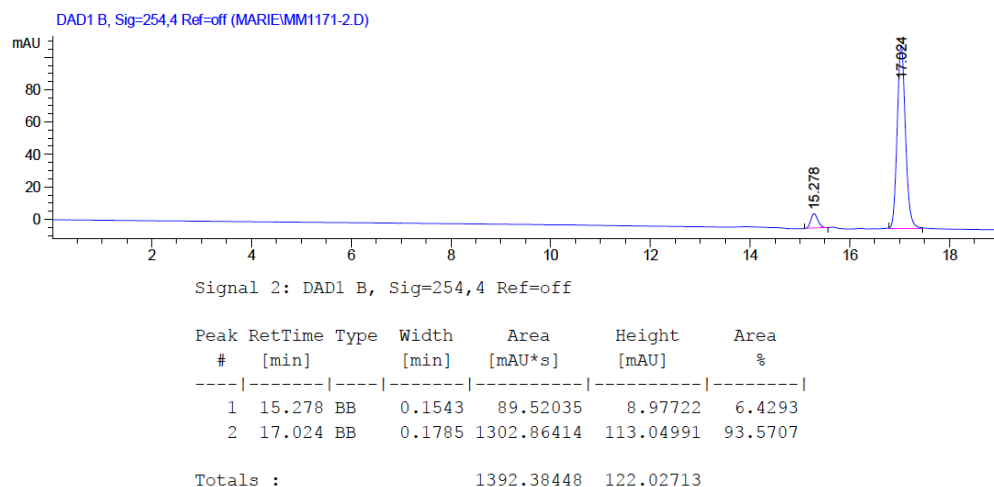


Pyrroline 5.5f

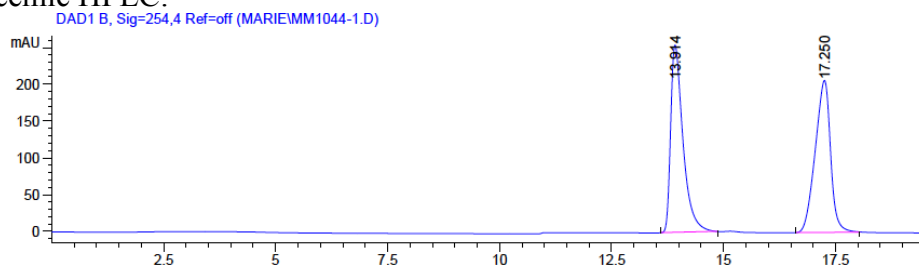


Isolated yield: 85%. **¹H NMR** (400 MHz, CDCl₃, 50°C): δ (ppm) 7.26–7.18 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 2H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.20 (dd, *J* = 5.2, 10.8 Hz, 1H), 4.19–4.11 (m, 2H), 3.51 (t, *J* = 10.4 Hz, 1H), 3.29–3.25 (m, 2H), 3.16–3.10 (m, 1H), 2.94 (br, 1H), 2.23 (br, 1H), 2.08 (br, 1H), 1.85–1.82 (m, 2H), 1.69–1.64 (m, 2H), 1.58–1.52 (m, 2H), 1.38–7.18 (m, 13H), 0.90 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (100.6 MHz, CDCl₃, 50°C): δ (ppm) 169.2, 165.6, 156.3, 131.5, 129.3, 120.1, 118.3, 117.6, 95.7, 65.4, 59.1, 58.4, 44.3, 37.5, 37.1, 31.3, 28.4, 28.3, 26.9, 26.8, 26.4, 25.4, 22.4, 14.6, 13.8. **HRMS** (ESI⁺) for C₂₆H₃₈NO₃⁺; calculated: 412.28462, found: 412.28281; **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (99:1 Hexanes: iPrOH, 0.3 ml/min, 254 nm); major enantiomer tr = 17.0 min, minor enantiomer tr = 15.2 min; 87% ee; **Optical rotation**: [α]_D²² +2.6 (c 1.0, CHCl₃).

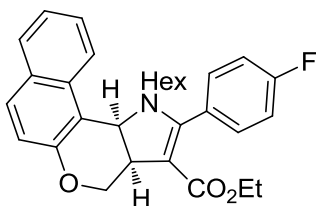
- Chiral product HPLC:



- Racemic HPLC:

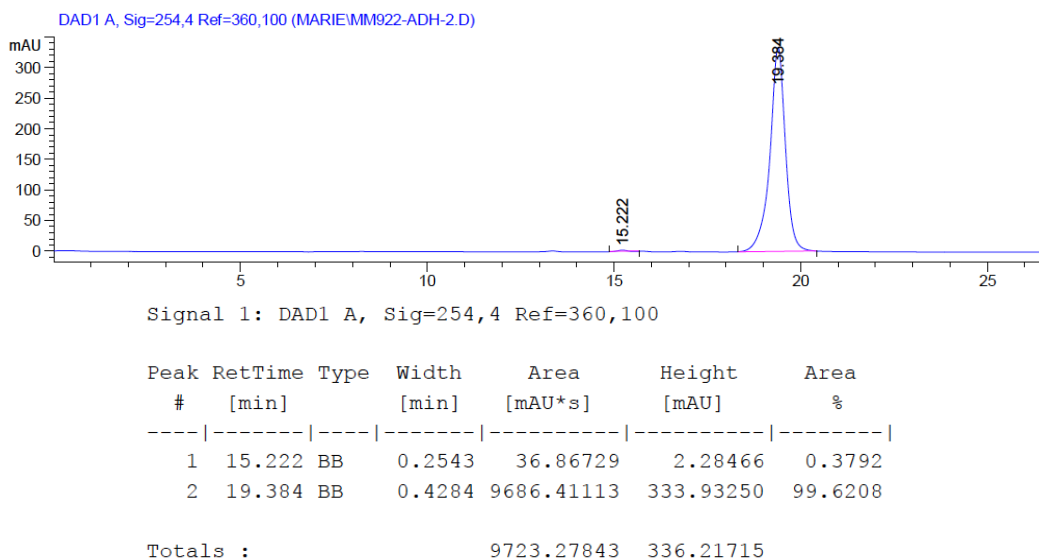


Pyrroline 5.5g

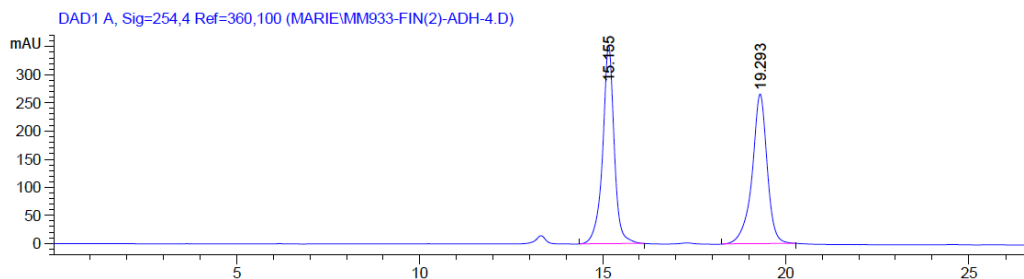


Isolated yield: 61%. **¹H NMR** (400 MHz, CDCl₃): δ (ppm) 8.01 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 6.4 Hz, 1H), 7.32 (br, 2H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.11 (t, *J* = 8.4 Hz, 2H), 5.58 (d, *J* = 8.0 Hz, 1H), 4.33 (dd, *J* = 4.4 Hz, 10.4 Hz, 1H), 4.12 (dd, *J* = 8.4 Hz, 10.8 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.44 (sex, *J* = 4.4 Hz, 1H), 2.96-2.76 (m, 2H), 1.11-1.03 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.90-0.83 (m, 2H), 0.76-0.53 (m, 8H); **¹³C NMR** (75.5 MHz, CDCl₃): δ (ppm) 165.8, 163.0 (d, ¹*J*_{C-F} = 248.4 Hz), 161.4, 155.4, 133.8, 130.7 (d, ³*J*_{C-F} = 8.3 Hz), 130.4, 129.3, 129.0, 128.1 (d, ⁴*J*_{C-F} = 3.9 Hz), 126.8, 123.5, 121.7, 119.3, 115.1 (d, ²*J*_{C-F} = 21.6 Hz), 111.4, 99.1, 66.5, 58.6, 56.3, 44.8, 39.0, 30.6, 29.8, 25.8, 22.0, 14.3, 13.7; **HRMS** (ESI⁺) for C₃₃H₃₃O₃NF⁺; calculated: 474.24390, found: 474.24338; **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak AD-H column (98:2 Hexanes : iPrOH, 0.5 ml/min, 254 nm); major enantiomer *t*_r = 19.4 min, minor enantiomer *t*_r = 15.2 min; 99% ee; **Optical rotation**: [α]_D²² +6.9 (c 1.0, CHCl₃).

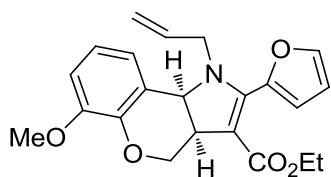
- Chiral product HPLC:



- Racemic HPLC:

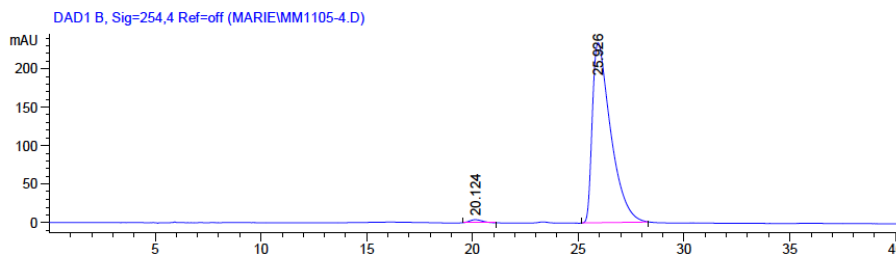


Pyrroline 5.5h



Isolated yield: 83%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.50 (s, 1H), 6.94 (m, 3H), 6.82 (d, *J* = 3.6 Hz, 1H), 6.47 (dd, *J* = 1.8 Hz, 3.3 Hz, 1H), 5.82-5.70 (m, 1H), 5.22 (dd, *J* = 10.8 Hz, 16.2 Hz, 2H), 4.69 (d, *J* = 8.1 Hz, 1H), 4.47 (dd, *J* = 5.1 Hz, 10.8 Hz, 1H), 4.13-4.02 (m, 2H), 3.96-3.81 (m, 5H), 3.73 (dd, *J* = 6.9 Hz, 17.4 Hz, 1H), 3.39-3.31 (m, 1H), 1.16 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 164.9, 151.3, 148.8, 145.7, 143.2, 143.1, 133.8, 123.1, 119.8, 118.4, 118.1, 114.3, 111.1, 111.0, 101.1, 65.1, 59.1, 58.4, 55.9, 46.9, 37.9, 14.3. HRMS (ESI⁺) for C₂₂H₂₄NO₅⁺; calculated: 382.16490, found: 382.16433. HPLC: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (92:8 Hexanes: iPrOH, 0.6 ml/min, 254 nm); major enantiomer tr = 25.9 min, minor enantiomer tr = 20.1 min; 97.5% ee; **Optical rotation:** [α]_D²² +4.2 (c 1.0, CHCl₃).

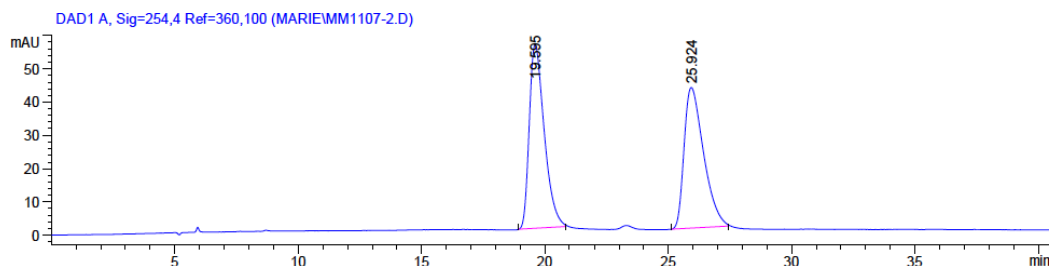
- Chiral product HPLC:



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.124	BB	0.5250	173.41827	4.07049	1.2085
2	25.926	BB	0.8899	1.41760e4	234.28856	98.7915

- Racemic HPLC:



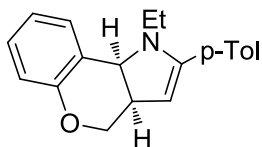
5.4.4 Synthesis and Characterization of Pyrrolidines 5.6a-5.6d

Pyrrolidine 5.6a

In a glovebox, (2-(CH₂=CHCH₂O)C₆H₄)HC=NEt (38.0 mg, 0.2 mmol) and *p*-toluoyl chloride (34.0 mg, 0.22 mmol) were mixed in 0.5 mL CDCl₃ for 30 min. Phosphite **5.3d** (96.0 mg, 0.22 mmol) and TMSOTf (46.7 mg, 0.21 mmol) were added to the solution. After 90 min., DBU (76.1 mg, 0.5 mmol) was added and the final volume of CDCl₃ adjusted to 1.5 mL. The reaction was complete after 30 h at room temperature. [Because of the instability of the enamine functionality in **5.5a**, the product cannot be purified by flash chromatography, however it can be partly purified by filtration on a small pad of alumina in a glovebox with diethyl ether, affording **5.5a** with a small amount phosphorus-containing side products.]

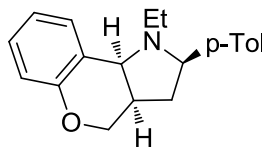
The crude reaction mixture of **5.5a** was transferred to a 25 ml round bottom flask followed by the addition of PtO₂ (3.2 mg, 10 mol%). The flask was connected to a H₂ balloon and the solution was stirred vigorously under 1 atm. H₂ for 18 h. The solution was filtered through celite and concentrated to dryness. The product was purified by flash chromatography using toluene/ethyl acetate (95/5) as eluent to afford product **5.6a** as a white foam (47 mg, 80% yield).

Pyrroline 5.5a



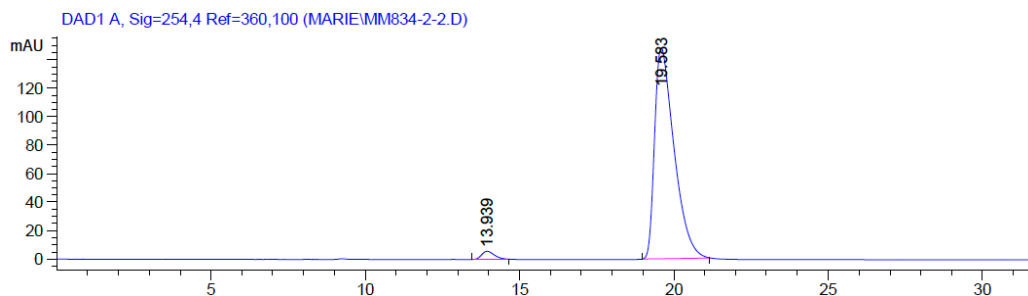
^1H NMR: (500 MHz, CDCl_3): δ (ppm) 7.31 (d, $J = 7.5$ Hz, 1H), 7.26-7.21 (m, 3H), 7.15 (d, $J = 7.5$ Hz, 2H), 6.98-6.93 (m, 2H), 4.79 (d, $J = 2$ Hz, 1H), 4.35 (d, $J = 8$ Hz, 1H), 4.06 (dd, $J = 10.5$ Hz, 4.5 Hz, 1H), 3.83 (t, $J = 10.5$ Hz, 1H), 3.32-3.21 (m, 2H), 3.09-3.04 (m, 1H), 2.36 (s, 3H), 0.98 (t, $J = 7$ Hz, 3H). **^{13}C NMR:** (125.7 MHz, CDCl_3): δ (ppm) 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 $\text{C}_{20}\text{H}_{22}\text{NO}^+$; calculated: 292.16959, found: 292.16908.

Pyrrolidine 5.6a



^1H NMR: (500 MHz, CDCl_3): δ (ppm) 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 Hz, 1H), 2.74 (dt, $J = 14.5$ Hz, 7 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 (ppm) 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 $\text{C}_{20}\text{H}_{24}\text{NO}^+$; calculated: 294.18524, found: 294.18454. **HPLC:** enantiomeric excess determined by HPLC with a Chiral pak OD-H column using hexanes: isopropanol 99 : 1 as eluent with a flow rate of 3 ml/min. **Optical rotation:** $[\alpha]_D^{22} +0.2$ (c 1.0, CHCl_3).

- Chiral product HPLC:

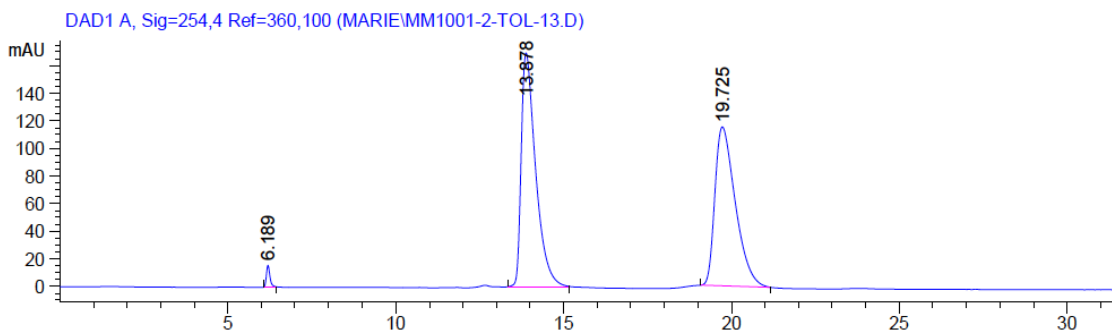


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.939	BB	0.4431	165.11320	5.71355	2.4684
2	19.583	BB	0.6647	6523.99414	148.44954	97.5316

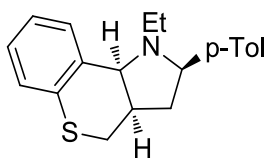
Totals : 6689.10735 154.16309

- Racemic HPLC:



Pyrrolidine **5.6b**

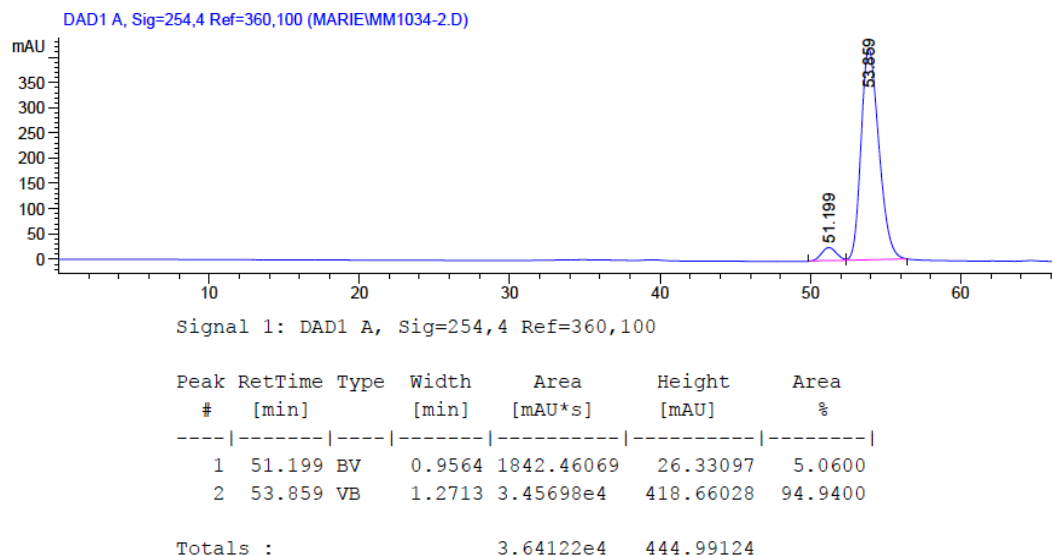
A similar procedure to above was followed, with DBU added after 5 h, and cycloaddition for 5 days at 45 °C. **5.6b** was purified by filtration through celite, and flash chromatography column using hexanes/toluene as eluent with 0% to 50% of toluene to afford **5.6b** as brown solid (44.1 mg, 71% yield).



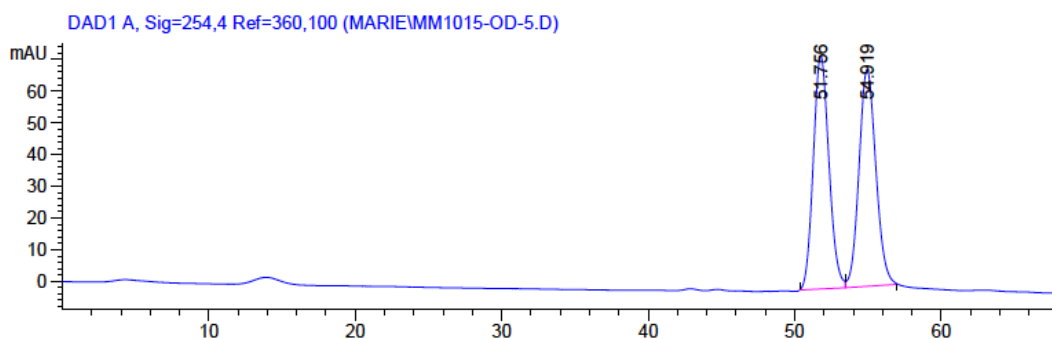
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.61 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.27–7.18 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.90 (dd, *J* = 10.0 Hz, 5.6 Hz, 1H), 3.82 (d, *J* = 9.2 Hz, 1H), 3.08–2.93 (m, 2H), 2.74–2.64 (m, 2H), 2.48 (dd, *J* = 12.4 Hz, 7.2 Hz, 1H), 2.36 (s, 3H), 2.33–2.27 (m, 1H), 1.70–1.62 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H). **¹³C NMR** (100.6 MHz, CDCl₃): δ (ppm) 141.1, 139.6, 136.8, 136.6, 129.9, 129.3, 129.0, 127.3, 126.4, 125.2, 67.0, 63.5, 44.9, 41.4, 41.2, 34.5, 21.2, 10.3. **HRMS** (ESI⁺) for C₂₀H₂₄NS⁺; calculated: 310.16240, found: 310.16172. **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (99.5:0.5 Hexanes :

iPrOH, 0.1 ml/min, 254 nm); major enantiomer tr = 53.8 min, minor enantiomer tr = 51.2 min; 90 % ee. **Optical rotation:** $[\alpha]_D^{22} +0.9$ (c 1.0, CHCl₃).

- Chiral product HPLC:



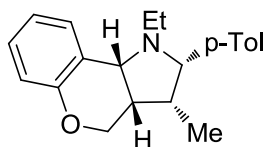
- Racemic HPLC:



Pyrrolidine **5.6c**

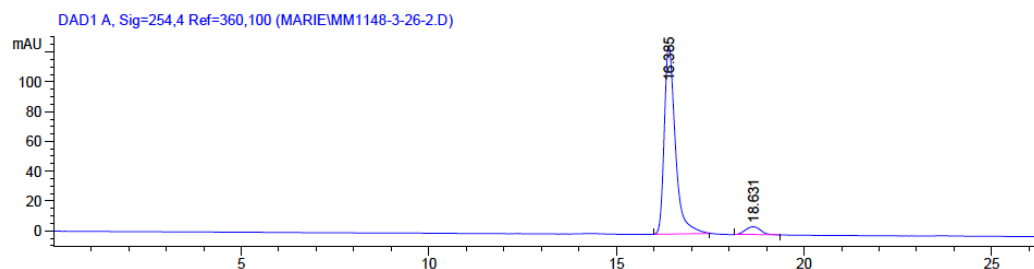
In a glovebox, (2-(CH₃(H)C=CHCH₂O)C₆H₄)HC=NEt (40.7 mg, 0.2 mmol) and *p*-toluoyl chloride (34.0 mg, 0.22 mmol) were mixed in 0.5 mL dichloromethane for 30 min. **5.3b** (90.0 mg, 0.22 mmol) was added and the solution was transferred to the vial containing AgOTf (51.4 mg, 0.20 mmol). The solution was left at rt for 2 h and filtered through a small pad of celite with a pipette column to remove AgCl. The solution was concentrated to 1.5 mL and transferred to a screw cap NMR tube with a septa top. Outside the glovebox, the solution was

cooled down to -78 °C and LiHMDS, 1M in THF (200 μ L, 0.2 mmol), was injected. The solution was warmed for 2 days at 50 °C. In a glovebox, the solution was filtered through a small pad of celite and concentrated in vacuo. The product was dissolved in 3 mL of dichloromethane and transferred to a 10 mL round bottom flask with NaBH(OAc)₃ (64.0 mg, 0.3 mmol). Outside the glovebox, HCl, 1M in Et₂O, (200 μ L, 0.2 mmol) was injected and the solution was stirred at rt for 18h. The mixture was concentrated, dissolved in EtOAc (5 mL) and quenched with 4 mL of 2N NaOH. The aqueous phase was extracted once with EtOAc and the combined organic phases were washed with water once. The solution was dried on MgSO₄, filtered and concentrated. The product was purified by flash chromatography column using toluene/ethyl acetate (95/5) as eluent to afford **5.6c** as a white foam (40 mg, 65% yield).



¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.24-7.19 (m, 4H), 7.09 (d, J = 8.0 Hz, 2H), 6.95-6.89 (m, 2H), 4.31 (t, J = 10.4 Hz, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.07 (dd, J = 10.4 Hz, 4.8 Hz, 1H), 3.71 (d, J = 4.4 Hz, 1H), 2.86 (q, J = 7.6 Hz, 2H), 2.82-2.77 (m, 1H), 2.40-2.33 (m, 1H), 2.33 (s, 3H), 0.93 (t, J = 7.2 Hz, 3H), 0.53 (d, J = 7.6 Hz, 3H). **¹³C NMR** (125.7 MHz, CDCl₃): δ (ppm) 155.1, 138.6, 136.1, 131.4, 128.7, 128.5, 122.0, 119.5, 116.7, 67.1, 65.0, 57.3, 42.2, 38.3, 36.7, 21.1, 12.5, 8.9. **HRMS** (ESI⁺) for C₂₁H₂₆NO⁺; calculated: 308.20089, found: 308.20147. **HPLC**: enantiomeric excess determined by HPLC with a Chiral pak OD-H column (99:1 Hexanes : iPrOH, 0.25 ml/min, 254 nm); major enantiomer tr = 16.4 min, minor enantiomer tr = 18.6 min; 89 % ee; **Optical rotation**: $[\alpha]_D^{22}$ -0.1 (c 1.0, CHCl₃).

- Chiral product HPLC:

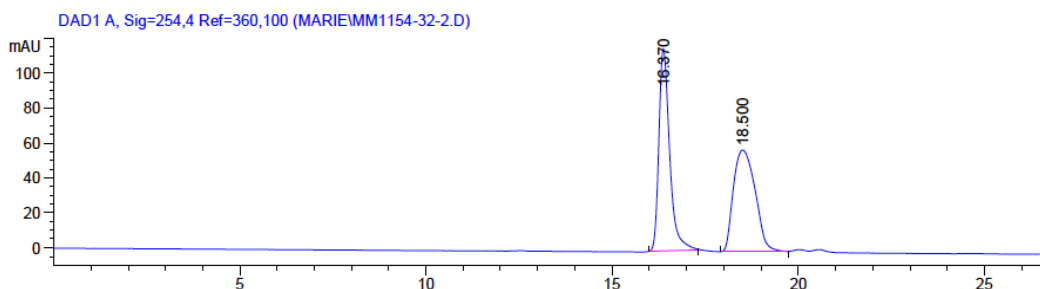


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.385	BB	0.3124	2601.91895	126.25430	94.4533
2	18.631	BB	0.4249	152.79681	5.35441	5.5467

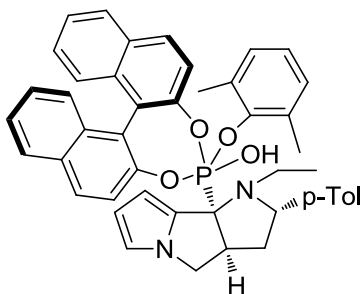
Totals : 2754.71576 131.60871

- Racemic HPLC:



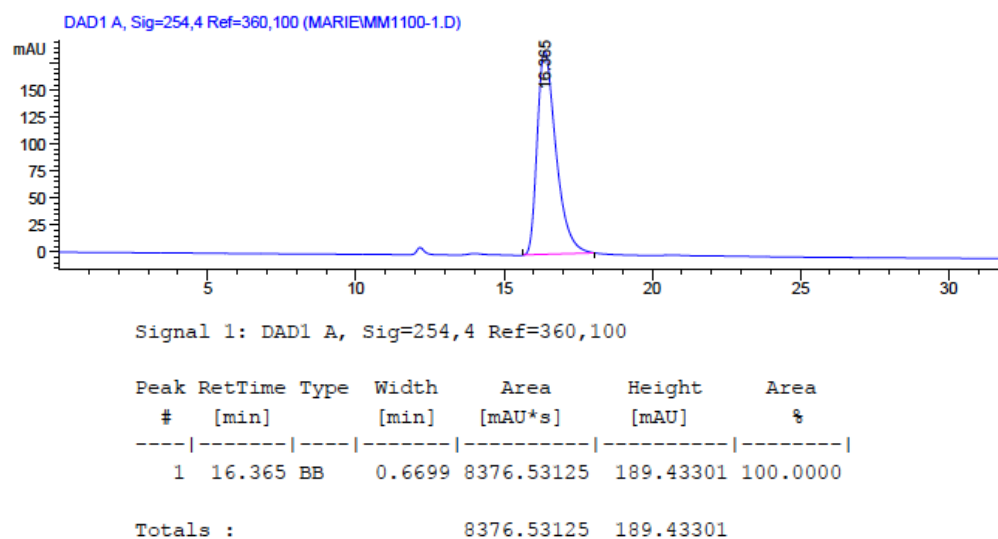
Pyrrolidine **5.6d**

In a glovebox, (1-(CH₂=CHCH₂O)C₄H₃N)HC=NEt (32.0 mg, 0.2 mmol) and *p*-toluoyl chloride (34.0 mg, 0.22 mmol) were mixed in 0.5 mL of dichloromethane and allowed to stand for 30 min. **5.3d** (96.0 mg, 0.22 mmol) and TMSOTf (46.7 mg, 0.21 mmol) were added and the solution was stirred for 10h. DBU (65 mg, 0.42 mmol) was added and the final volume of dichloromethane adjusted to 1.5 mL. The reaction was complete after 3 days at rt. The crude mixture was transferred to a 10 mL round bottom flask and NaBH(OAc)₃ (64.0 mg, 0.3 mmol) was added. Outside the glovebox, HCl, 1M in Et₂O (200 µl, 0.2 mmol) was injected and the solution was stirred at rt for 1 day. The mixture was quenched with 4 mL of 2N NaOH and extracted once with dichloromethane. The combined organic phases were washed once with brine, dried on MgSO₄, filtered and concentrated. The product was purified by flash chromatography column using toluene/ethyl acetate (95/5) as eluent to afford pyrrolidine **5.6d** as a white foam and as a single observable diastereomer by ¹H and ¹³C NMR (86 mg, 60% yield).

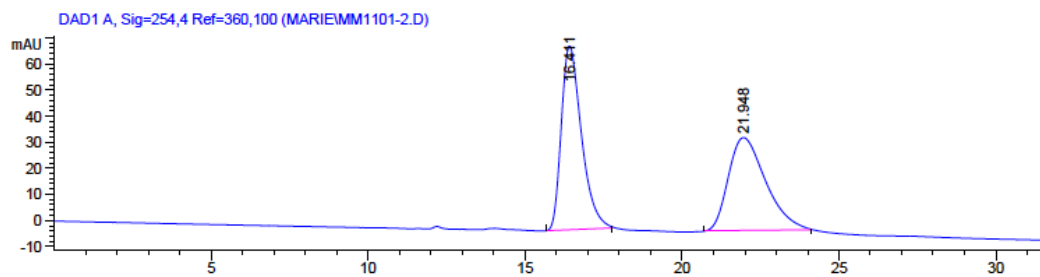


^1H NMR (400 MHz; CD_2Cl_2): δ (ppm) 7.90-7.82 (m, 4H), 7.52 (d, $J = 9.2$ Hz, 1H), 7.44 (t, $J = 6.9$ Hz, 1H), 7.32-7.26 (m, 5H), 7.12-7.08 (m, 2H), 7.02-6.97 (m, 5H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.38-6.38 (m, 1H), 6.04-6.03 (m, 1H), 5.97 (t, $J = 3.0$ Hz, 1H), 5.83 (br s, 1H), 3.98 (d, $J = 5.2$ Hz, 1H), 3.61 (t, $J = 9.8$ Hz, 1H), 3.50 (dd, $J = 10.3$ Hz, 6.7 Hz, 1H), 3.21-3.13 (m, 1H), 2.93-2.73 (m, 2H), 2.30 (s, 3H), 2.25-2.09 (m, 1H), 2.17 (s, 6H), 1.91 (dd, $J = 13.5$ Hz, 5.9 Hz, 1H), 0.35 (t, $J = 7.1$ Hz, 3H). **^{13}C NMR** (75.4 MHz; CDCl_3): δ (ppm) 151.3, 148.0 (d, $J = 7.7$ Hz), 147.0 (d, $J = 13.8$ Hz), 140.3, 136.8, 133.4 (d, $J = 3.8$ Hz), 131.6 (d, $J = 4.4$ Hz), 131.4 (d, $J = 4.4$ Hz), 131.0, 130.9 (d, $J = 3.3$ Hz), 130.3 (d, $J = 18.2$ Hz), 129.1, 129.0₇, 128.8, 127.9 (d, $J = 16.6$ Hz), 127.5, 127.3, 126.5, 125.4 (d, $J = 14.3$ Hz), 125.1, 124.7, 123.5, 120.8, 119.7 (d, $J = 7.7$ Hz), 117.7, 115.0 (d, $J = 10.5$ Hz), 112.2 (d, $J = 13.3$ Hz), 104.2, 71.3 (d, $J = 201.9$ Hz), 65.4 (d, $J = 11.0$ Hz), 50.5 (d, $J = 12.1$ Hz), 49.5, 43.2, 39.8 (d, $J = 22.6$ Hz), 21.1, 17.2, 12.2. **IR** ν_{max} (ATR) 3241 (O-H). **HRMS** (APCI⁺) for $\text{C}_{46}\text{H}_{44}\text{N}_2\text{O}_4\text{P}^+$; calculated: 719.30332, found: 719.30213. **HPLC**: HPLC with a Chiral pak OD-H column (97:3 Hexanes : iPrOH, 0.3 ml/min, 254 nm) shows the presence of only a single observable enantiomer; $t_r = 16.4$ min, > 95 % ee; Only one diastereoisomer was observed by ^1H NMR. **Optical rotation**: $[\alpha]_{\text{D}}^{22} -0.3$ (c 1.0, CHCl_3).

- Chiral product HPLC:



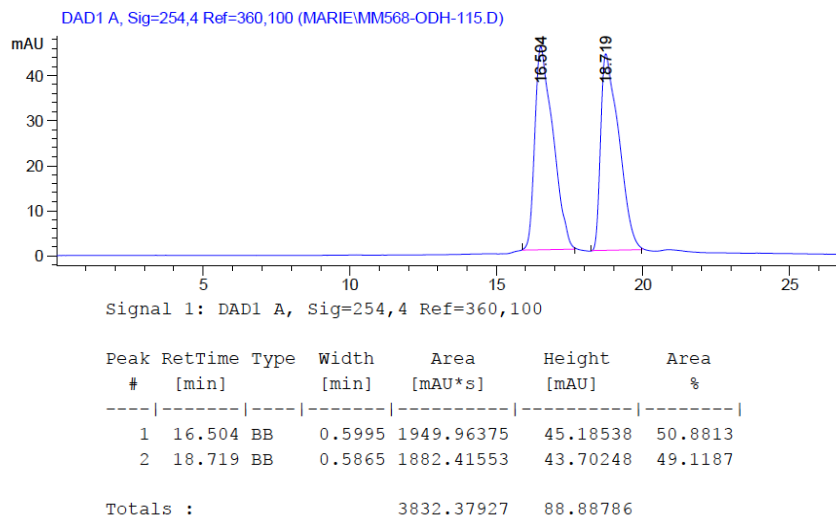
- From Racemic BINOL (HPLC):



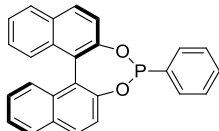
5.4.5 Table 5.1 Data

The enantiomeric excess **5.6a** were obtained on chiral pak OD-H column using hexanes: isopropanol 99 : 1 as eluent with a flow rate of 3 ml/min.

- PhP(2-catechyl): (racemic mixture)

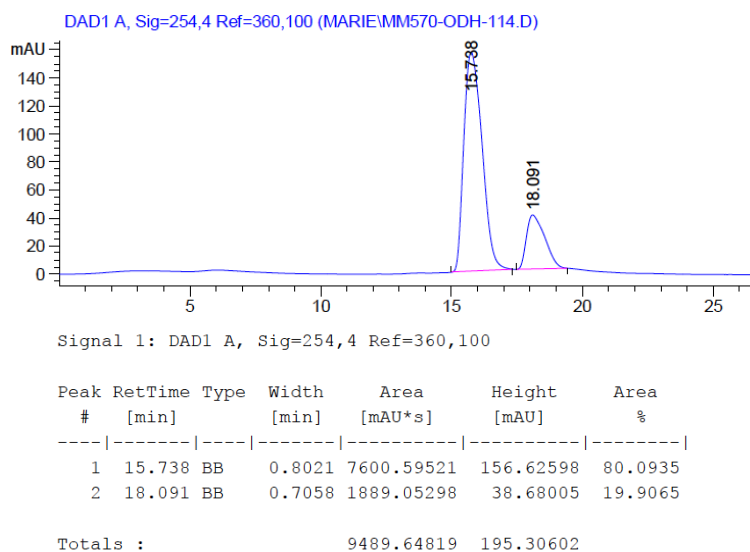


- **5.3a**

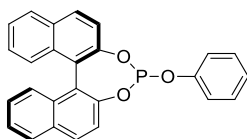


: t_r (major) 15.7 min, t_r (minor) 18.1 min; -60% ee.

Chiral product HPLC:

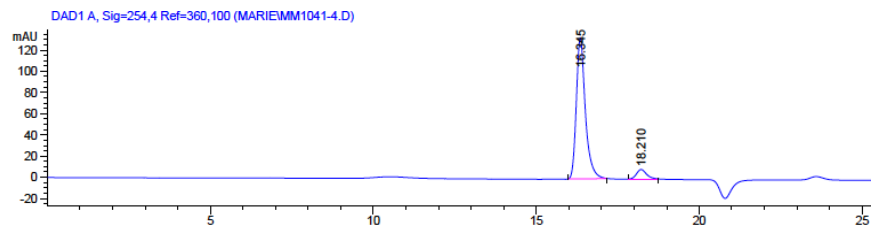


- **5.3b**



: t_r (major) 16.4 min, t_r (minor) 18.2 min; -86% ee.

Chiral product HPLC:

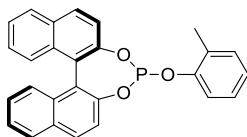


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.345	BB	0.2914	2571.52710	133.10008	92.9609
2	18.210	BB	0.3266	194.71753	9.06627	7.0391

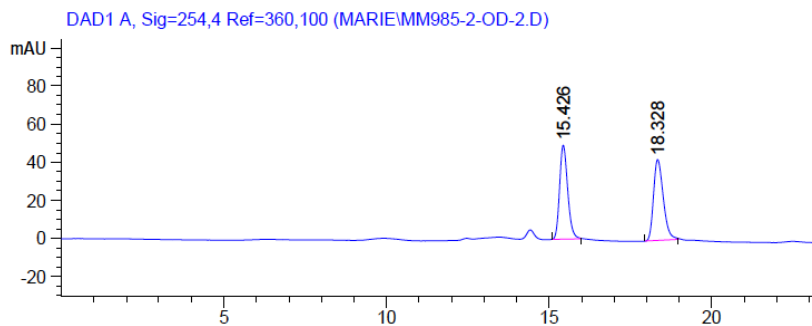
Totals : 2766.24463 142.16635

- **5.3c**



: t_r (major) 18.3 min, t_r (minor) 15.4 min; 2% ee.

Chiral product HPLC:

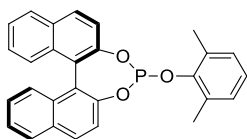


DAD1 A, Sig=254,4 Ref=360,100 (MARIE\MM985-2-OD-2.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.426	BB	0.2684	855.20825	49.30243	49.0446
2	18.328	BB	0.3239	888.52808	42.50585	50.9554

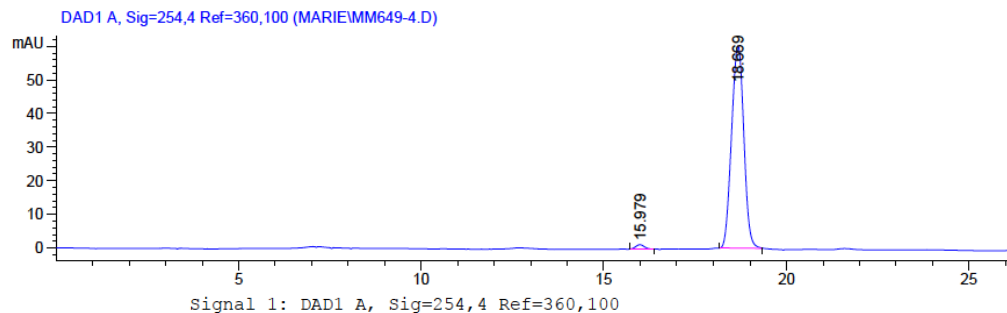
Totals : 1743.73633 91.80828

- **5.3d**



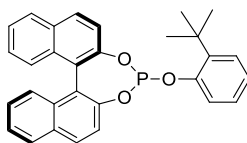
: t_r (major) 18.7 min, t_r (minor) 16.0 min; 97 % ee.

Chiral product HPLC:



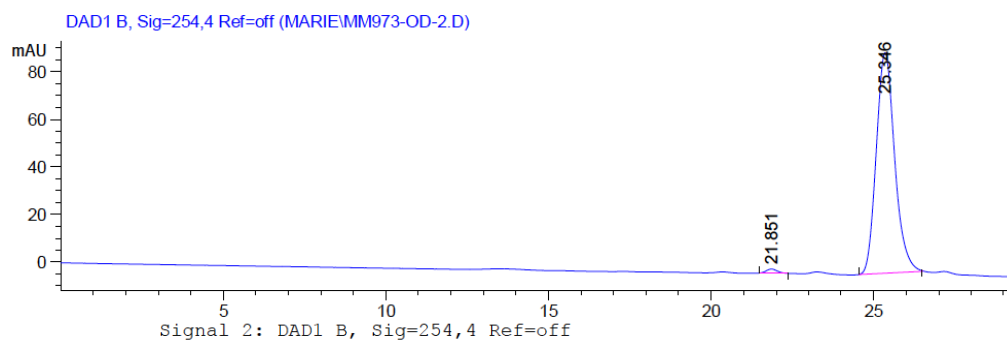
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.979	BB	0.2498	21.70612	1.32009	1.5147
2	18.669	BB	0.3709	1411.35010	60.33985	98.4853
Totals :				1433.05622	61.65994	

- **5.3e**



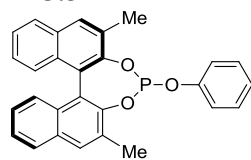
: t_r (major) 25.3 min, t_r (minor) 21.8 min; 98 % ee.

Chiral product HPLC:



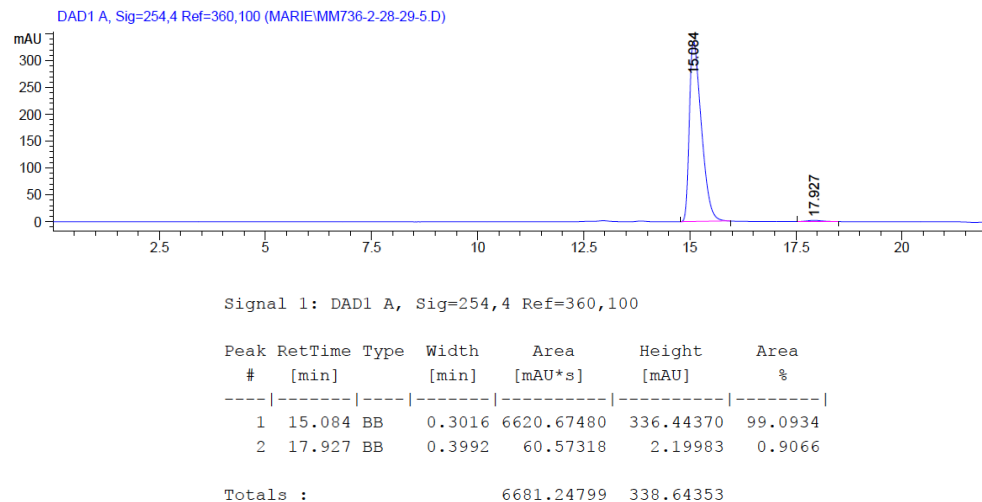
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.851	BB	0.3481	40.20749	1.71144	1.0859
2	25.346	BB	0.6162	3662.53882	92.85334	98.9141
Totals :				3702.74631	94.56478	

- **5.3f**



: t_r (major) 15.1 min, t_r (minor) 17.9 min; -98 % ee.

Chiral product HPLC:

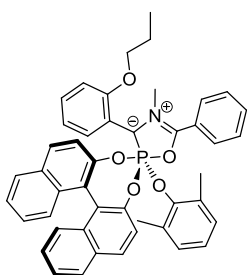


5.4.6 Synthesis and X-Ray Crystallographic Studies of 5.1d and 5.6a

Synthesis of **5.1d**

In a glovebox, (2-(CH₃CH₂CH₂O)C₆H₄)HC=NMe (106.3 mg, 0.66 mmol) and benzoyl chloride (88.5 mg, 0.63 mmol) were mixed in 0.5 mL acetonitrile and allowed to stand for 30 min. The solution was transferred to the vial containing **5.3d** (261.8 mg, 0.60 mmol) followed by the addition of AgOTf (154.1 mg, 0.60 mmol). The solution was left at rt for 2 h then filtered through a small pad of celite to remove AgCl. The solution was concentrated to 2.5 mL of acetonitrile and DBU (182.7 mg, 1.2 mmol) was added. After 2 h at rt, the solution was concentrated in vacuo, dissolved in 2 mL toluene, pentane (5 mL) was added, and the resultant oily precipitated (protonated DBU) was removed by filtration through a small pad of celite. The product solution was concentrated to dryness, and the

product isolated by precipitation from 2 mL of toluene and 10 mL of pentane in a -35 °C freezer for 1 day. The precipitate was collected by filtration in the glove-box yielded 150 mg of product (35%). For X-ray quality crystals, a toluene solution of **5.1d** isolated above was partially precipitated in pentane, filtered through celite, and then pentane was slowly diffused into the resulting saturated solution of **5.1d**, yielding crystal suitable for X-ray analysis.



¹H NMR (400 MHz; CDCl₃, 70°C): δ (ppm) 7.91-7.84 (m, 3H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 9.5 Hz, 2H), 7.42-7.22 (m, 10H), 7.03 (br, 2H), 6.96-6.88 (m, 4H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.36 (br, 1H), 3.93-3.67 (br, 2H), 3.31 (s, 3H), 2.42-1.79 (br, 8H), 1.07 (t, *J* = 7.4 Hz, 3H). **¹³C NMR** (126 MHz; CD₃CN, 84°C): δ (ppm) 159.1, 152.8 (d, ²*J*_{C-P} = 11.2 Hz), 151.8 (d, ²*J*_{C-P} = 14.9 Hz), 149.6 (d, ²*J*_{C-P} = 12.1 Hz), 145.9, 137.0, 132.5 (d, *J*_{C-P} = 3.6 Hz), 131.2, 130.8, 130.2, 129.8, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 128.3, 128.2, 127.8, 127.5, 127.3, 127.0, 126.8, 126.5, 126.4, 126.1, 126.0₁, 125.9₉, 125.9, 125.7, 125.3, 125.1, 125.0, 124.8, 124.7, 124.2, 124.1, 123.6₂, 123.5₉, 123.4, 123.3, 123.1, 123.0, 122.9, 122.8, 122.7, 122.4, 121.7, 119.3, 111.8 (d, *J*_{C-P} = 65.5 Hz), 111.1 (d, *J*_{C-P} = 68.5 Hz), 71.4 (d, ¹*J*_{C-P} = 322.1 Hz), 69.3, 35.1 (br), 22.5, 15.9, 10.1, 9.9. **HRMS** (ESI⁺) for C₄₆H₄₁O₅NP⁺; calculated: 718.27169, found: 718.26938.

Crystallization of **5.6a**

X-ray quality crystals of pyrrolidine **5.6a** were obtained by the slow diffusion of pentane into a dichloromethane (2 mL) solution of **5.6a** in a -30 °C freezer.

X-Ray Crystallographic Studies of **5.1d** and **5.6a**

All X-ray data were collected at T = 100 K and the structures were solved by direct method with ShelxS-97. All non-H atoms were refined by full matrix least-squares with anisotropic displacement parameters while hydrogen atoms

were placed in idealized position. X-ray crystallographic data were collected from single crystal sample, which was mounted on a loop fiber. The instrument is mounted on a three-circle platform and uses an APEX II CCD detector and a Bruker MX I μ S microsource (CuK α radiation). The data are provided in Appendices D and E.

5.5 References

- (1) This chapter is a copy of a communication that will be submitted. Spectroscopic data as proof of purity is provided in Appendix A.
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CHAPTER 6

Summary, Conclusions and Future Work

This chapter provides a brief summary of the results and the conclusions presented in this thesis as well as the contributions to original knowledge. Suggestions for future work are also reported.

6.1 Conclusions and Contributions to Knowledge

Previous research in our group has led to the generation of a new class of phosphorus-based 1,3-dipole, phosphamünchnones, which can be used in cycloaddition with alkynes to generate pyrroles. While this reactivity mirrors that reported for the more established Münchnones, one substantial difference is the ability of phosphamünchnones to undergo regioselective cycloadditions with electron poor, unsymmetrical alkynes. This provides routes to selectively generate a wide variety of substituted pyrroles.

In the initial studies of this thesis, we were able to rationalize the difference of regioselectivity observed between Münchnones, Münchnone imines and phosphamünchnones (Chapter 2). Among these 1,3-dipoles, experimental studies revealed a general trend in both regioselectivity and reactivity as function of the alkyne electronics. A clear inversion in selectivity is observed when proceeding from electron rich to electron poor alkynes with these dipoles. Importantly, the alkyne ionization potential at inversion is different for Münchnones and phosphamünchnones. From a synthetic standpoint, this can provide a route to generate various substituted pyrroles with high selectivity by varying the eliminating $O=X$ ($X = CO, PR_3$) unit. Computational studies on these systems support the experimental results and suggest the factors controlling the regioselectivity in each of the mesoionic heterocycles. In particular, distortion

energies were found to play a significant and previously underestimated role in controlling regioselectivity in cycloaddition, sometimes leading to the selective formation of the opposite product to that predicted from traditional FMO analysis. These studies allow the reactivity and regioselectivity to be reliably predicted for a range of dipolarophiles.

The findings in Chapter 2 provide important insights into the factors that influence phospho-Münchnone cycloadditions. This led us to probe the effect of specific phosphites and phosphonites on both the reactivity and cycloaddition regioselectivity with internal alkynes (Chapter 3). In contrast to Münchnones, the selectivity of phospho-Münchnone cycloadditions can be tuned without changing the structure of the cycloaddition product. This was achieved through the variation of the PR_3 unit, which behaves as a selective auxiliary and spontaneously eliminates during the reaction. Experimental results and DFT calculations demonstrated the ability of the phosphorus substituents to modulate regioselectivity results from changes in the degree of P-O bonding interactions.

In addition to alkynes, Münchnones are well established to undergo cycloaddition reactions with alkenes to generate pyrrolines. Considering the similarity between phospho-Münchnones and Münchnones, the use of alkene dipolarophiles was explored in Chapter 4. This led to the design of a new synthesis of polycyclic 2-pyrrolines by the one pot reaction of olefin-tethered imines with acid chlorides and (2-catechyl)PPh. The reaction proceeds via a highly regioselective cycloaddition of alkene to in situ generated phospho-Münchnones, and variation of the imine or the acid chloride units can be used to generate diversely substituted products. This represents an interesting alternative to other methods where a multistep synthesis of the 1,3-dipole (e.g., Münchnone) precursor is required.

Finally, in addition to influence reactivity and regioselectivity, we have found that the PR_3 unit can also be employed to achieve enantioselective 1,3-dipolar cycloadditions (Chapter 5). (R)-BINOL derived phosphites allow the formation of a new 1,3-dipole that is easily generated (one pot), modular, rigidly

chiral, yet the chiral unit leaves upon cycloaddition. This was used in the one pot synthesis of chiral 2-pyrrolines from olefin-tethered imines and acid chlorides with up to 99% enantioselectivity. In addition, the subsequent reduction of the pyrroline product affords a simple route to polysubstituted pyrrolidines with control of up to four chiral centers. Considering the prevalence of pyrrolidines in biological active molecules, this approach provides an interesting alternative approach to access those important molecules.

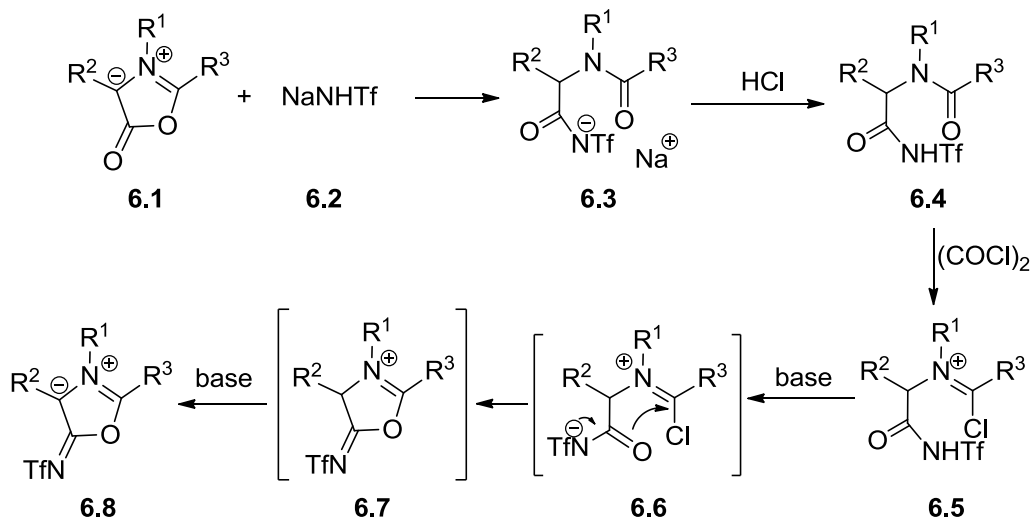
6.2 Suggestions for Future Work

We demonstrated in Chapters 2 and 3 that the regioselectivity of alkyne cycloadditions can be tuned with the nature of the leaving unit on the mesoionic heterocycles. While this can be used to achieve regioselective cycloadditions with a diverse array of alkynes, one challenge concerns reactivity. For example, although Münchnones undergo cycloadditions with electron rich alkynes with high selectivity, the reactivity drops dramatically when the electron donor ability of the alkyne increases (cf. Figure 2.2). As a result, these reactions often need elevated temperatures, long reaction times and many times do not proceed to completion. This lowers the synthetic utility of these reactions.

One potential alternative to improve the reactivity of Münchnone derivatives with more electron rich alkynes would be to create a more electrophilic 1,3-dipole, which would lower 1,3-dipole LUMO energy level and favor cycloadditions proceeding via TS2.1-B (Figure 2.5). This could involve replacing the exocyclic oxygen atom in Münchnones with a more electron withdrawing unit, such as trifluoromethanesulfonamide (N-Tf). It is well established that N-tosyl and N-triflyl substituted imines can be more electrophilic than the analogous aldehydes.¹ The incorporation of the N-Tf unit into a Münchnone would form the electrophilic Münchnone imine **6.8** (Scheme 6.1).

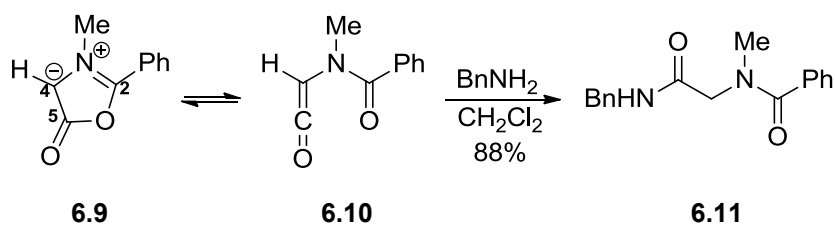
Dipole **6.8** should be accessible from a ring-opening/closing sequence with Münchnones as illustrated in Scheme 6.1. This involves an initial nucleophilic

addition of the trifluoromethanesulfonamide **6.2** to give the intermediate **6.3**, which, after neutralization, can undergo re-cyclization by treatment with a deoxygenating agent (e.g., oxalyl chloride) and a base.



Scheme 6.1: Synthesis of Electrophilic Münchnone imines.

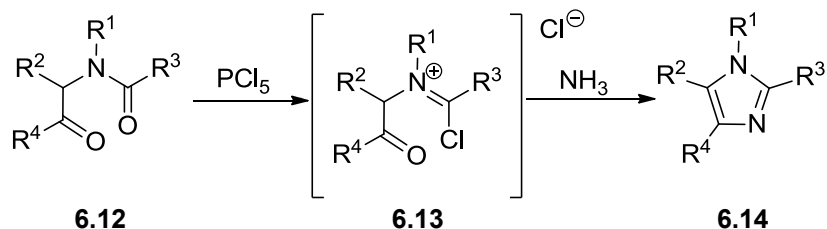
Literature precedent exists for this synthesis. It is well established that Münchnones can react with amine nucleophiles to generate ring-opened amides (e.g., Scheme 6.2).² This reaction can be considered to proceed via the Münchnone equilibration with its ketene tautomer **6.10**, which is trapped by the amine to form the amide **6.11**.^{2c} Based on this example, reaction between Münchnone **6.1** and the sulfonamide **6.2** might proceed via a similar pathway.



Scheme 6.2: Münchnone Aminolysis.

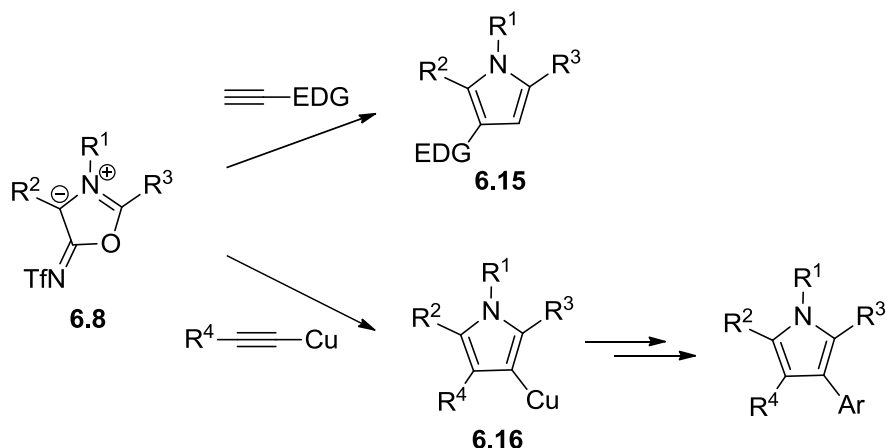
After the addition of the sulfonamide, the next step requires the ring closing of **6.4** to **6.7**. A similar reaction has been reported in imidazole synthesis (Scheme 6.3).³ In this example, the α -ketoamide **6.12** undergoes deoxygenation in

the presence of PCl_5 followed by condensation with ammonia to give the imidazole **6.14**. Based on the structural analogy between **6.12** and **6.4** (Scheme 6.1), the ring closing of the Münchnone imine could occur under similar conditions.



Scheme 6.3: Synthesis of Imidazoles from α -Ketoamides.

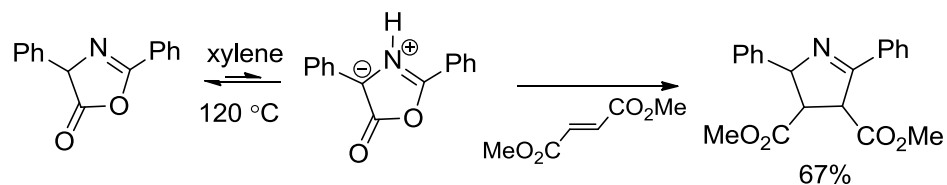
Once this new 1,3-dipole is formed, it would be expected to react more rapidly with electron rich dipolarophiles than other Münchnone derivatives. As an interesting variation, the cycloaddition of Münchnone imine **6.8** with electron rich copper-acetylides would give the pyrrole **6.16**, a versatile intermediate to access more complex structures by the subsequent cross coupling reactions (Scheme 6.4).



Scheme 6.4: Cycloaddition Reactions with Electrophilic Münchnone Imine **6.8**.

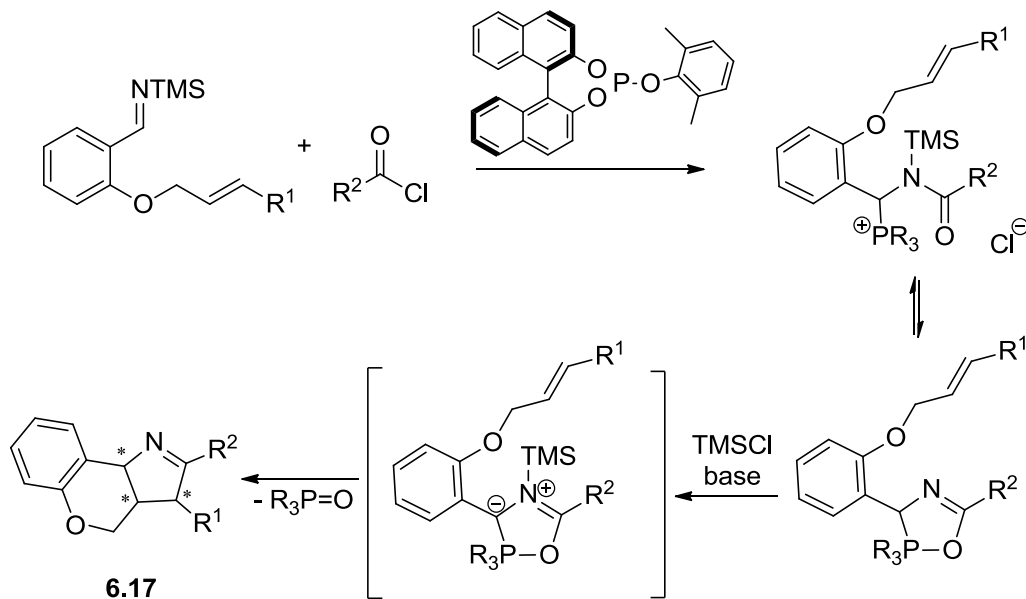
An alternative idea involves the use of the chiral phosphorus-based 1,3-dipole described in Chapter 5. This dipole has been demonstrated to be useful in the asymmetric synthesis of 2-pyrrolines. Considering the modular approach used to generate the 1,3-dipole, this new strategy could be extended to other substrates.

For example, it is well established in Münchnone chemistry that the reaction of N-H substituted Münchnones with alkynes provides a route to prepare 1-pyrrolines (Scheme 6.5).^{4,5}



Scheme 6.5: Münchnone/ Alkene Cycloaddition in 1-Pyrroline Synthesis.

The analogous reaction with the chiral phosphadipoles would allow the enantioselective formation of 1-pyrrolines with potential control of three stereocenters in a single step. Trimethylsilyl-substituted imines have been used as N-H imine equivalent in nucleophilic addition reactions,⁶ suggesting their potential efficiency to generate 1-pyrroline in this chemistry. A possible approach is represented in Scheme 6.6. Considering the biological importance of chiral pyrrolines and pyrrolidines, together with the reactivity of the imine unit in **6.17**, this could provide a useful general synthesis of these chiral heterocycles.



Scheme 6.6: Asymmetric Synthesis of 1-Pyrrolines.

6.3 References

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Appendix A

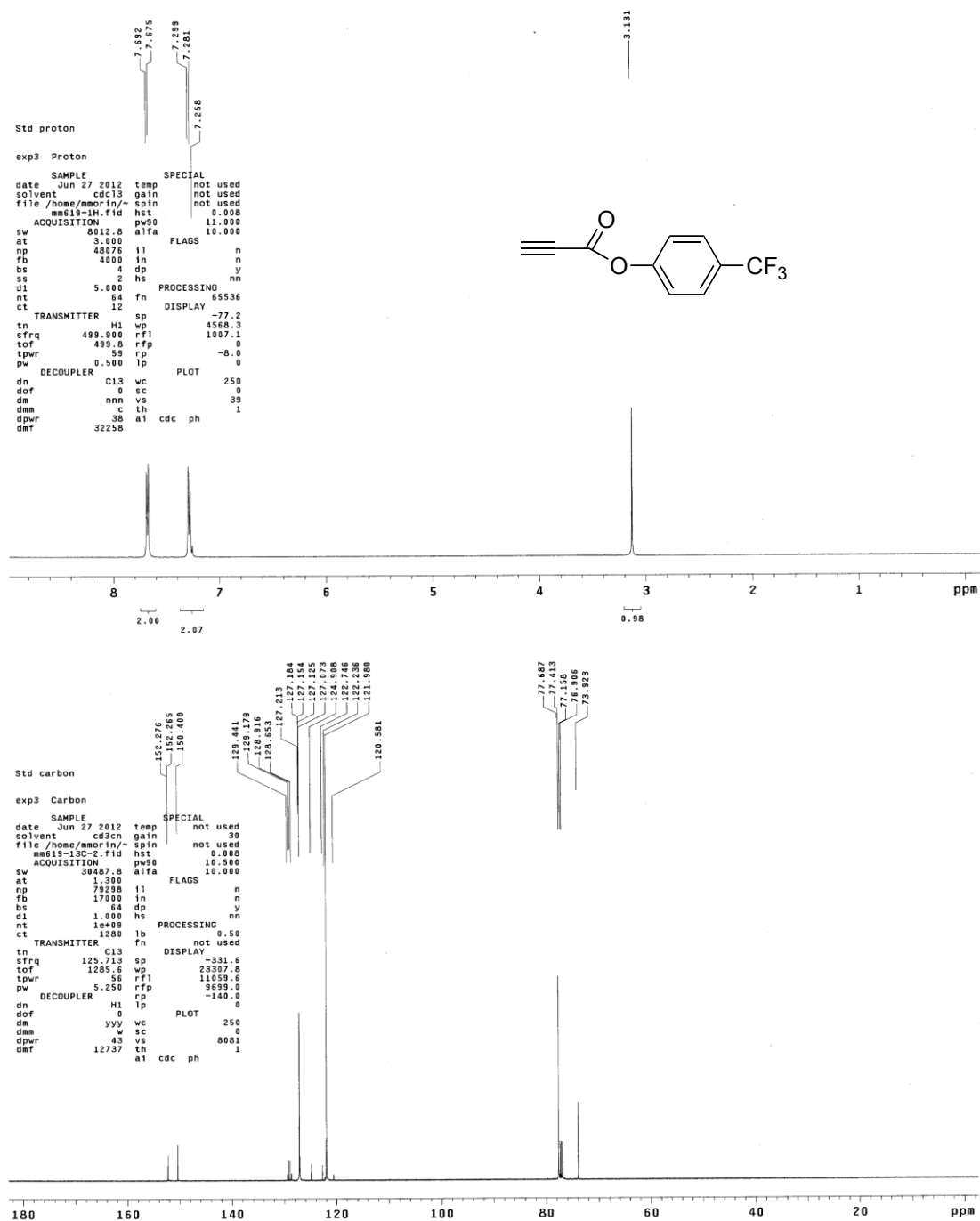
^1H , ^{13}C , NOE 1D and NOESY 2D Spectroscopic data as proof of purity and regiochemistry for unpublished chapters 2, 3 and 5 are provided below.

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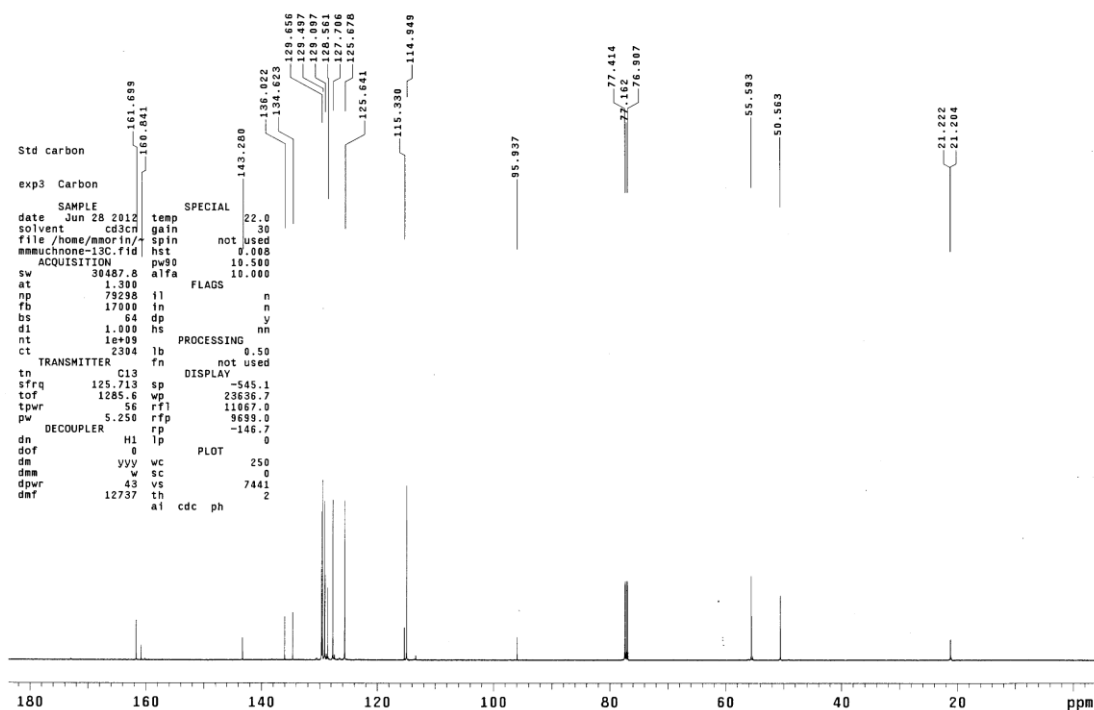
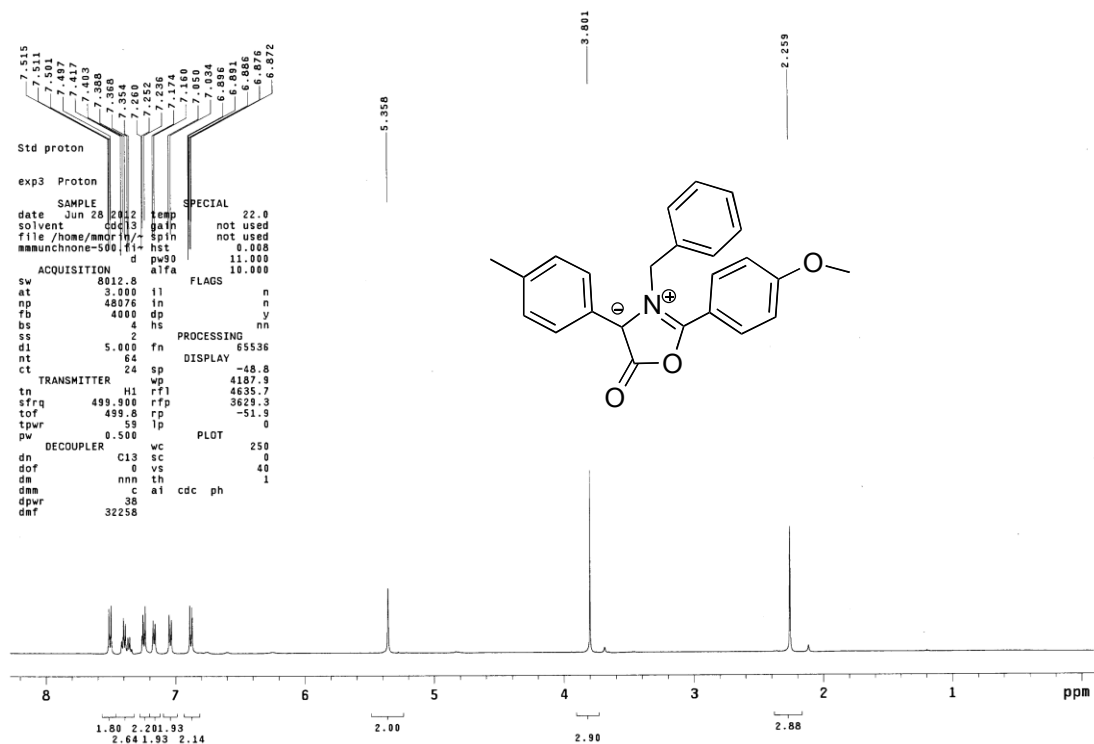
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Münchnone 2.1a	IV
Münchnone-Imine 2.2a	V
Phospha-Münchnone 2.3a	VI
Pyrrole A of alkyne 2.4c	VII
Pyrrole B of alkyne 2.4c	IX
Pyrrole A of alkyne 2.4d	XI
Pyrrole B of alkyne 2.4d	XII
Pyrrole A' of alkyne 2.4d	XIII
Pyrrole B' of alkyne 2.4d	XV
Pyrrole A of alkyne 2.4e	XVII
Pyrrole B of alkyne 2.4e	XIX
Pyrrole A of alkyne 2.4f	XXI
Pyrrole B of alkyne 2.4f	XXIII
Pyrrole A of alkyne 2.4g	XXV
Pyrrole B of alkyne 2.4g	XXVII
Pyrrole A of alkyne 2.4h	XXIX
Pyrrole B of alkyne 2.4h	XXXI
Table 3.2, entry 3	XXXIII
Table 3.2, entry 6.....	XXXV
Scheme 3.4, pyrrole of alkyne 3.7 (major isomer).....	XXXVII
Scheme 3.4, pyrrole of alkyne 3.7 (minor isomer)	XXXVIII
Scheme 3.4, pyrrole of alkyne 3.8 (minor isomer)	XLI
Scheme 3.4, pyrrole of alkyne 3.8 (major isomer).....	XLIII
Phosphite 5.3b	XLV
Phosphite 5.3c	XLVII

Phosphite 5.3d	XLVII
Phosphite 5.3e	XLVIII
Phosphite 5.3f	XLIX
Pyrroline 5.5a	L
Pyrroline 5.5b	LI
Pyrroline 5.5c	LII
Pyrroline 5.5d	LIII
Pyrroline 5.5e	LIV
Pyrroline 5.5f	LV
Pyrroline 5.5g	LVI
Pyrroline 5.5h	LVII
Pyrrolidine 5.6a	LVIII
Pyrrolidine 5.6b	LX
Pyrrolidine 5.6c	LXI
Pyrrolidine 5.6d	LXIII
1,3-Dipole 5.1d	LXV

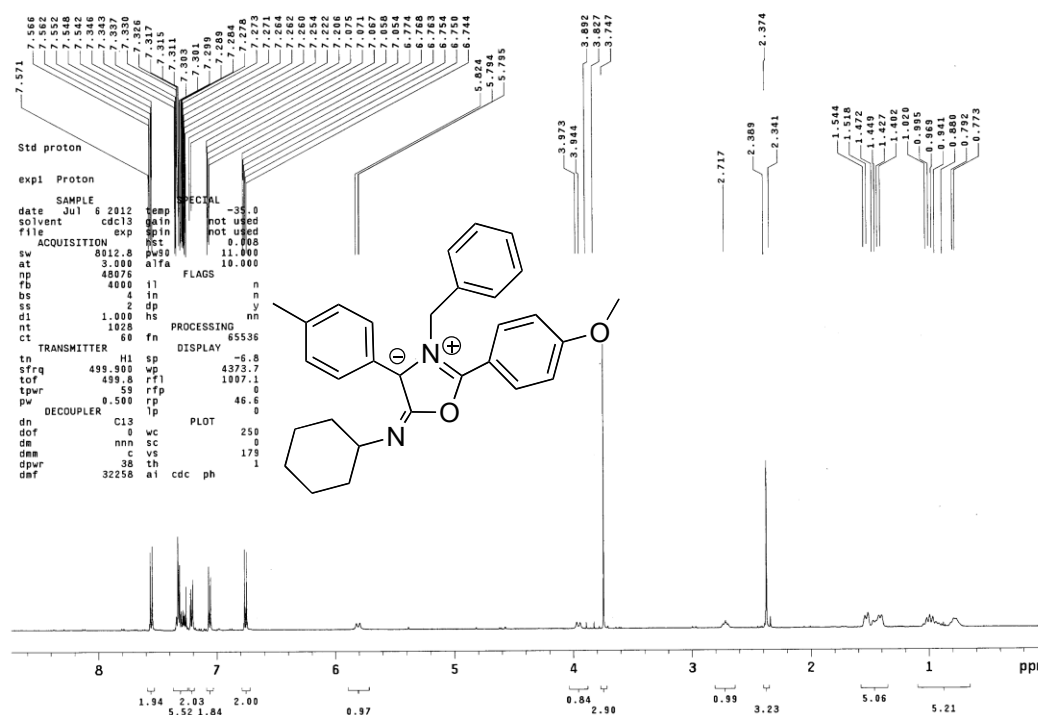
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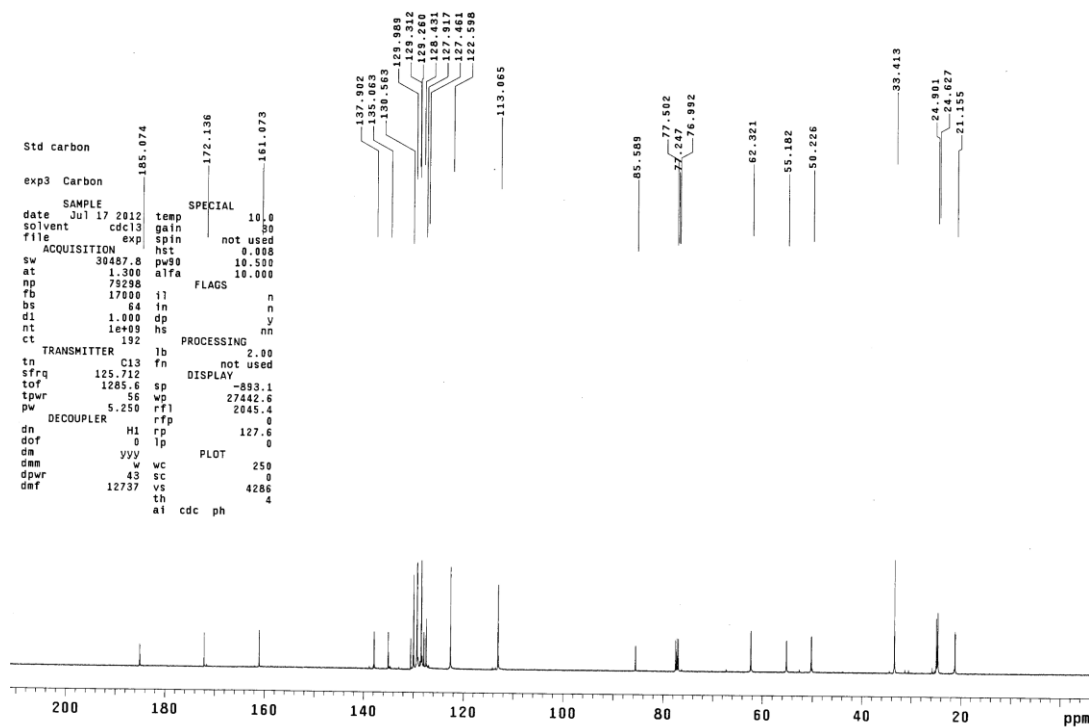
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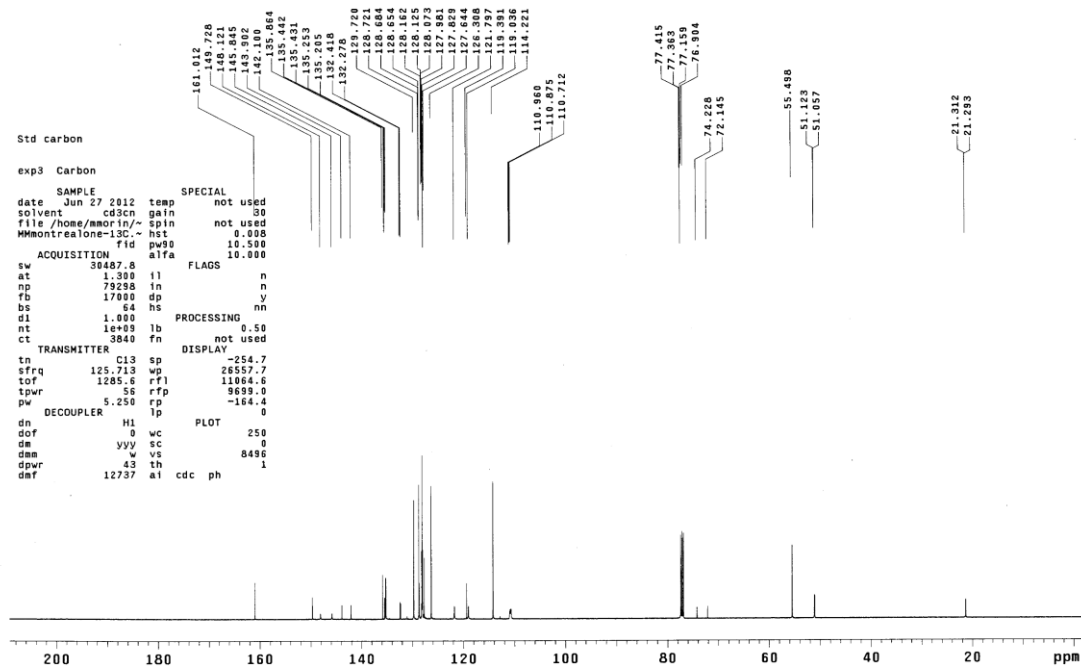
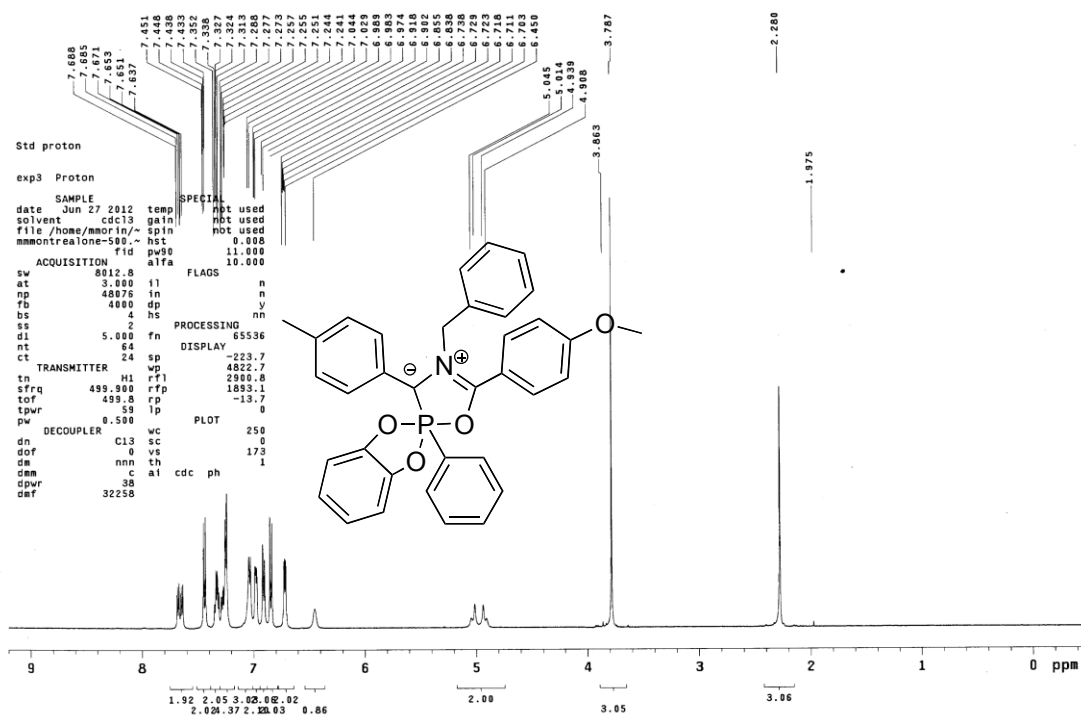
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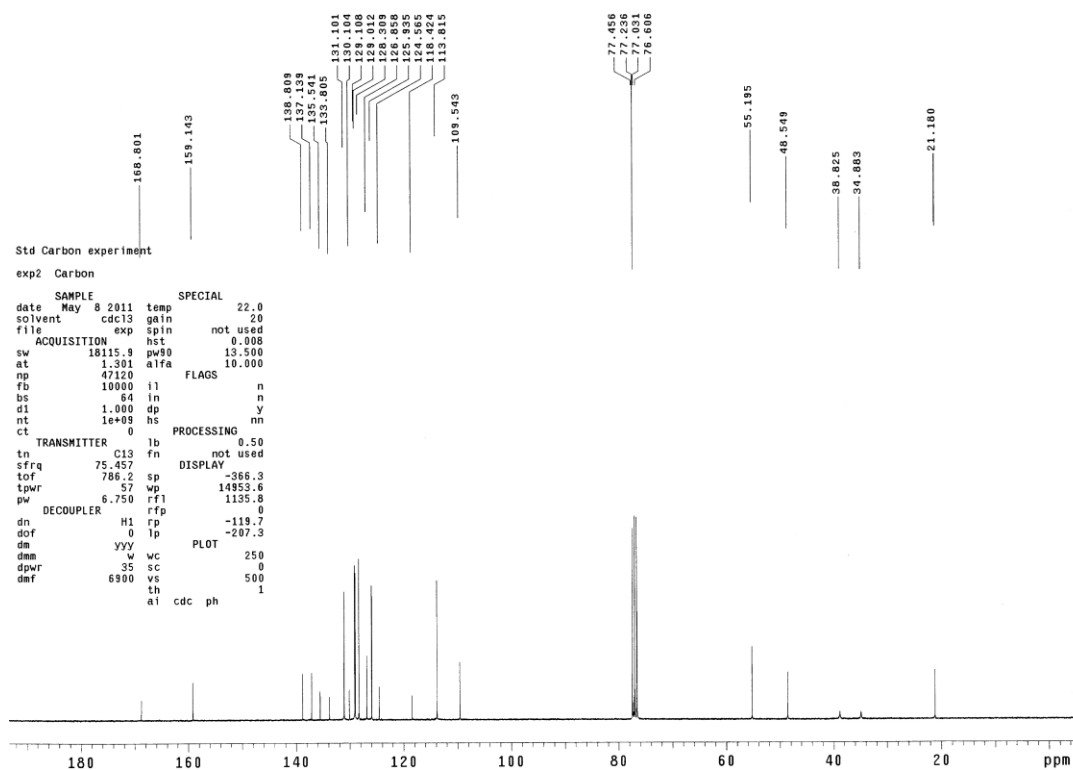
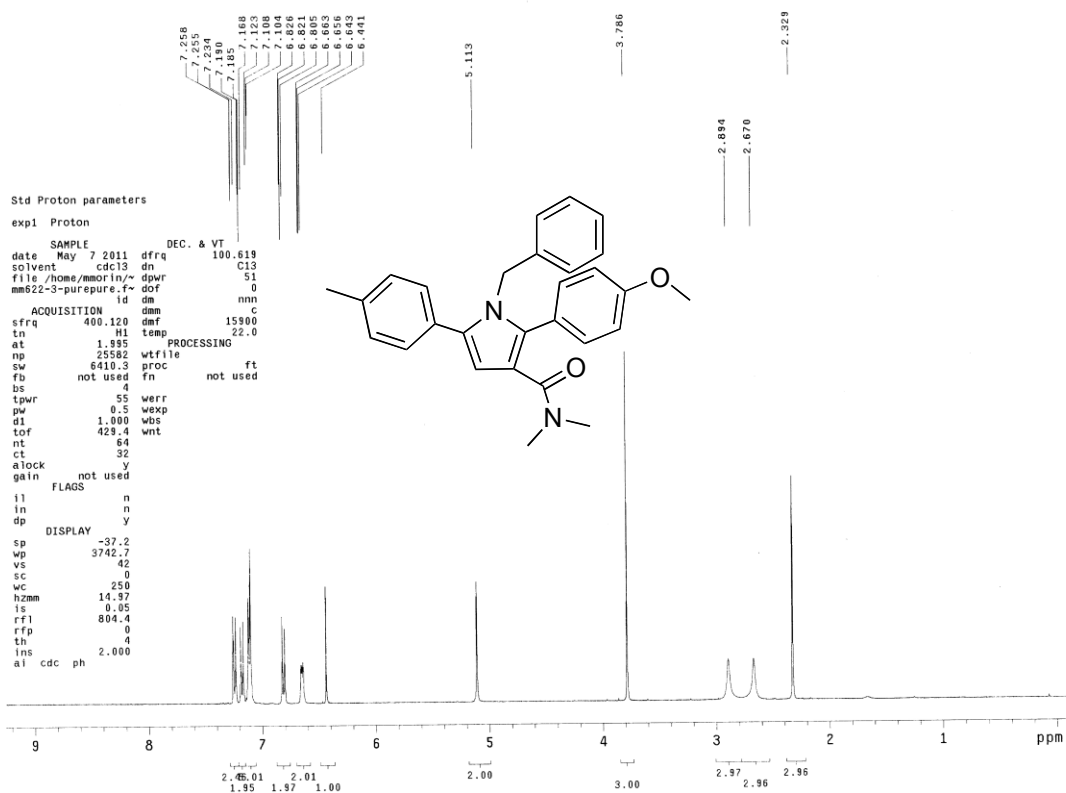
¹³C at +10°C in CDCl₃



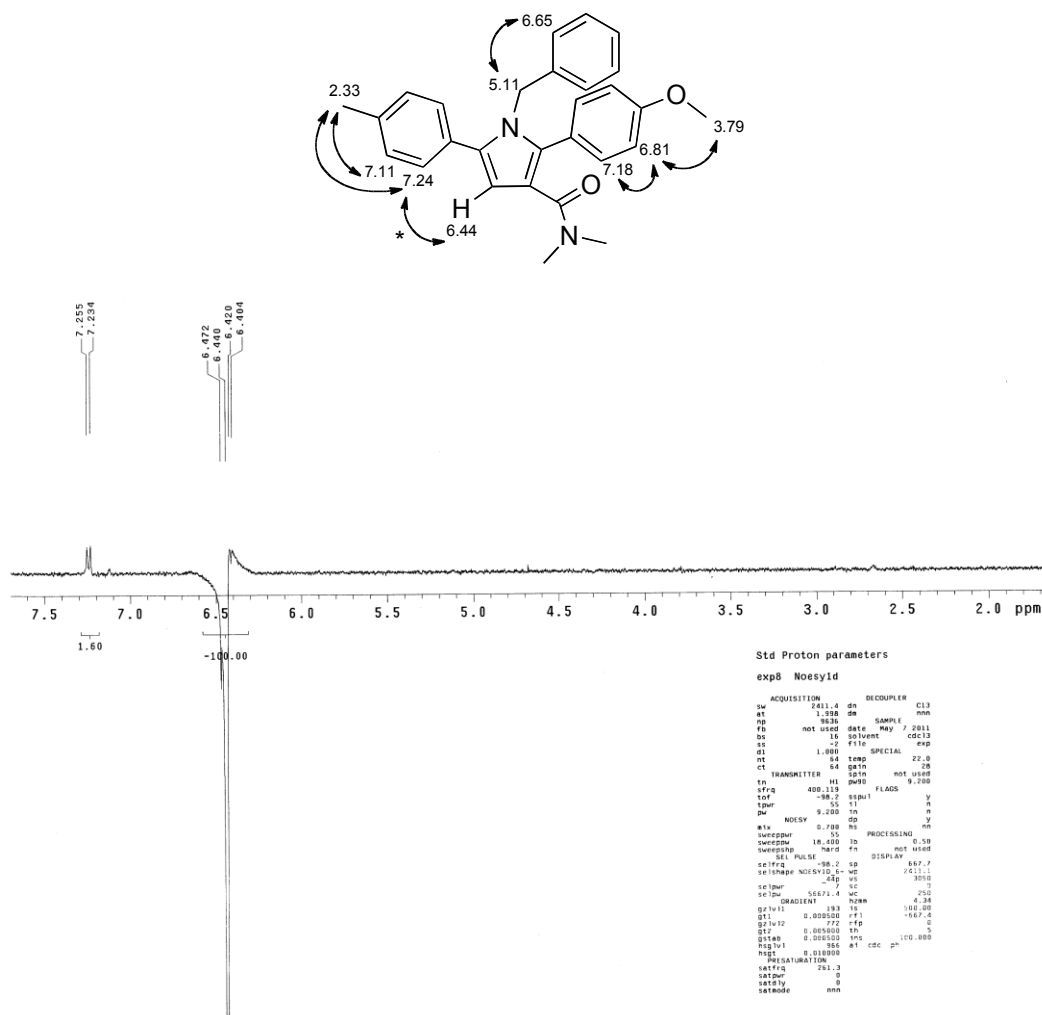
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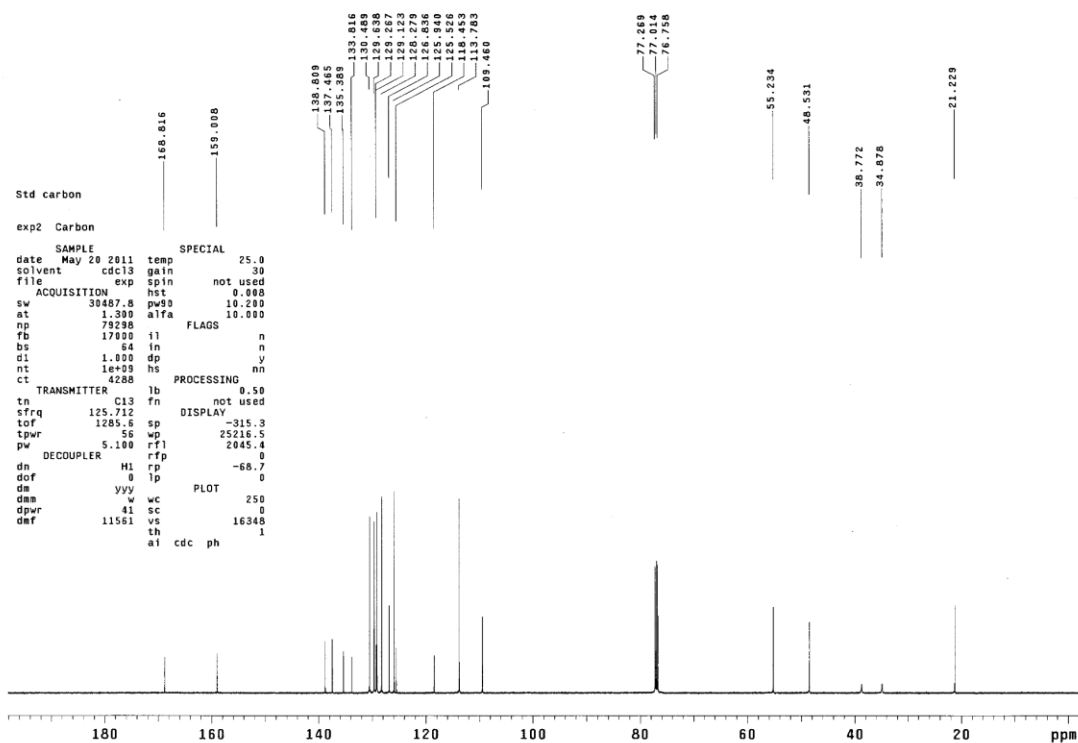
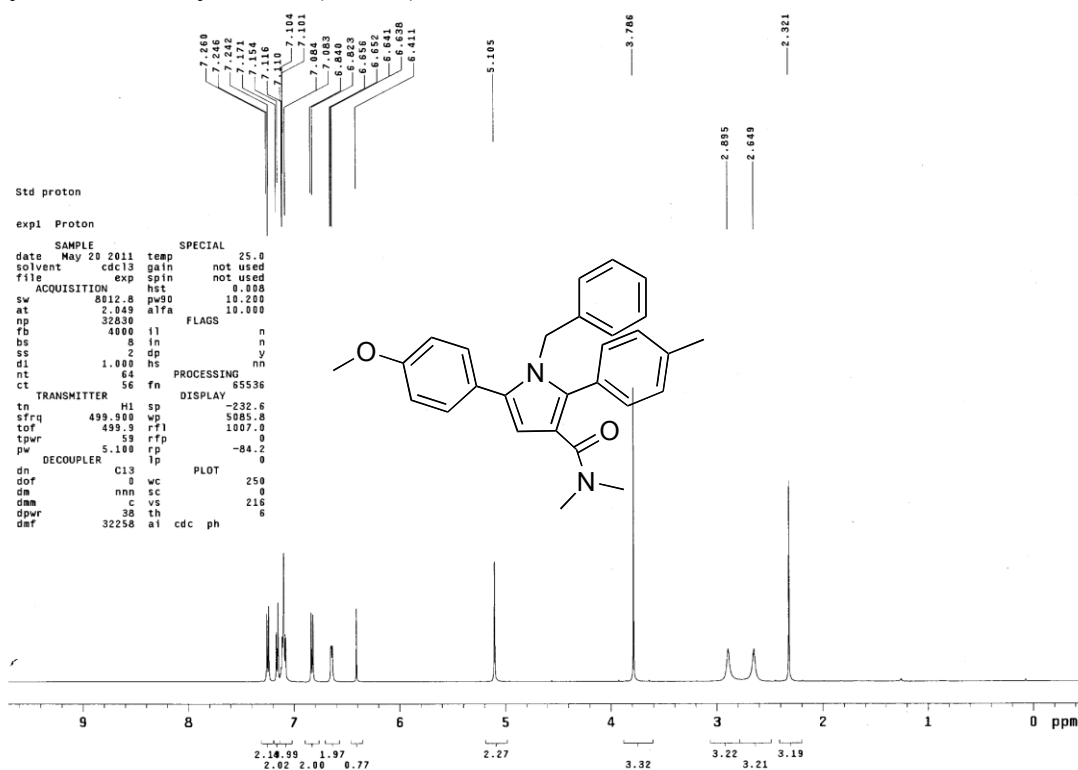
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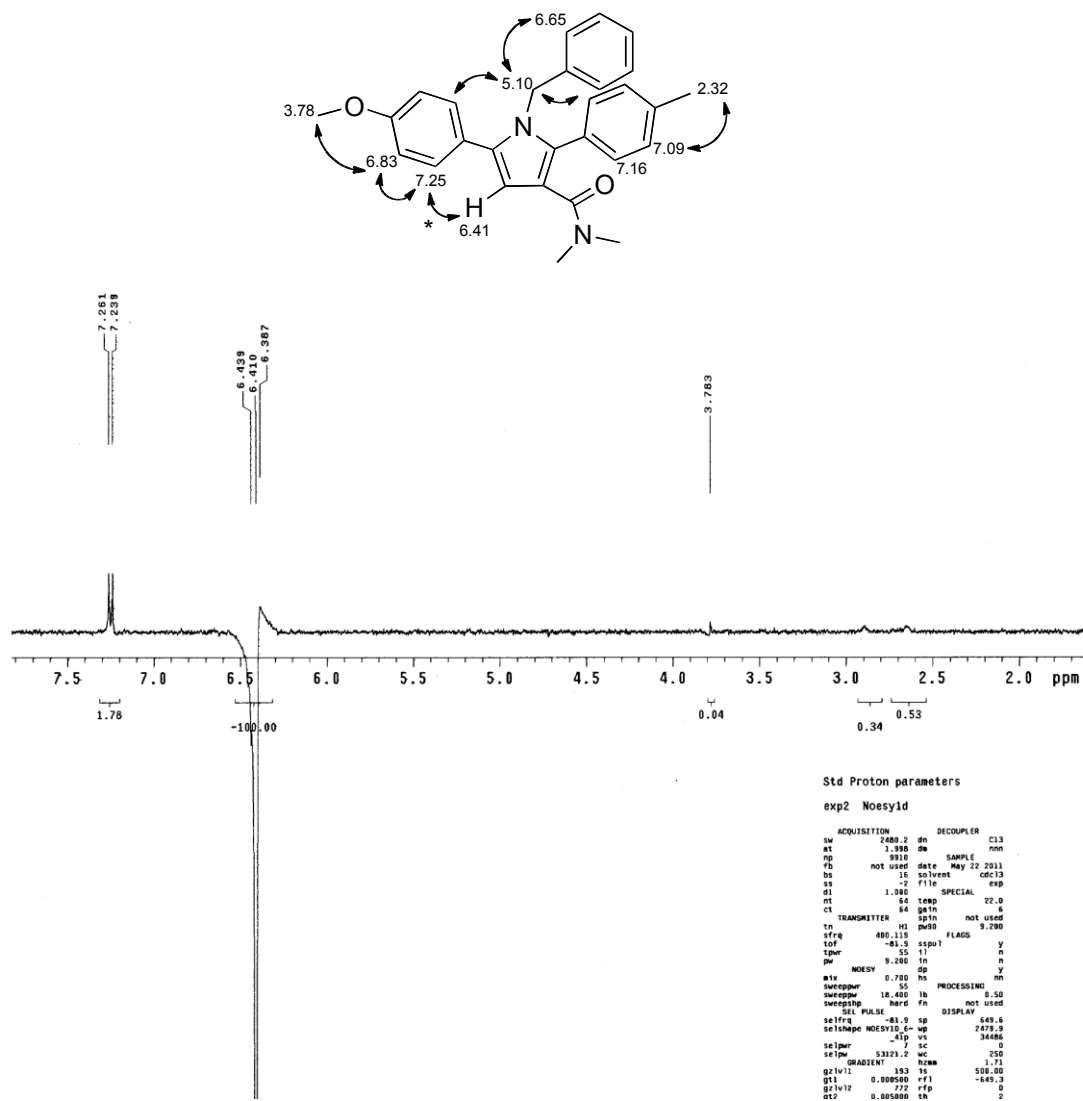
Summary of NOEs with spectrum of key correlation (*) provided



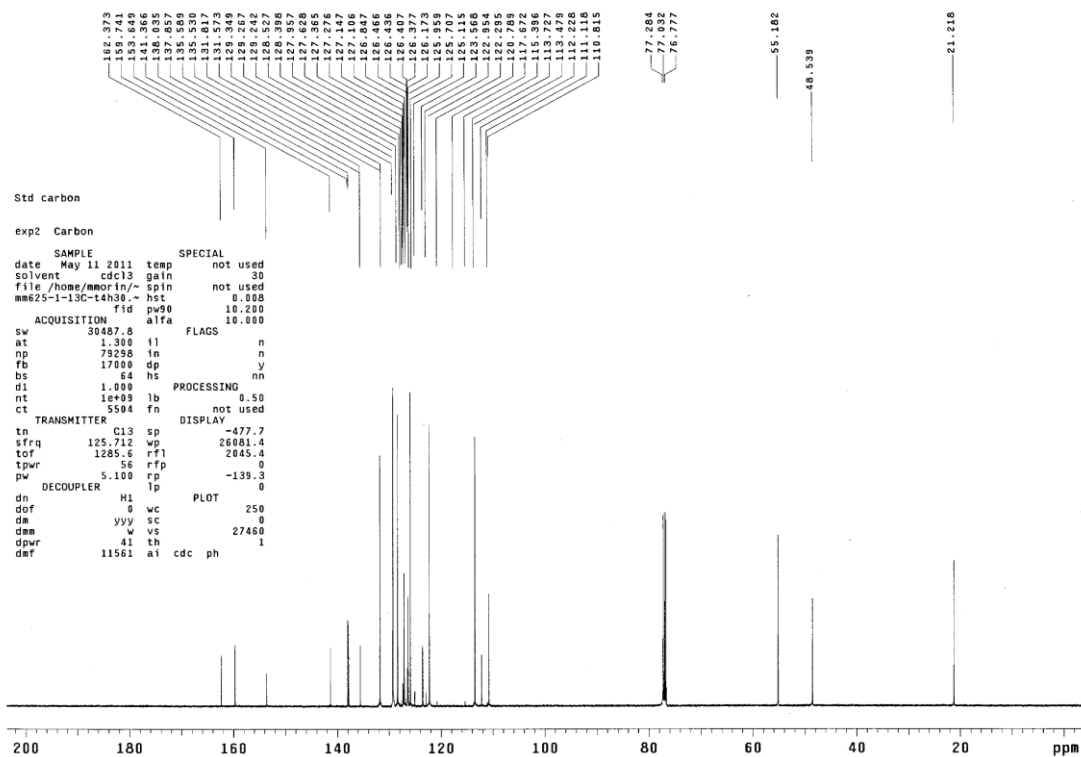
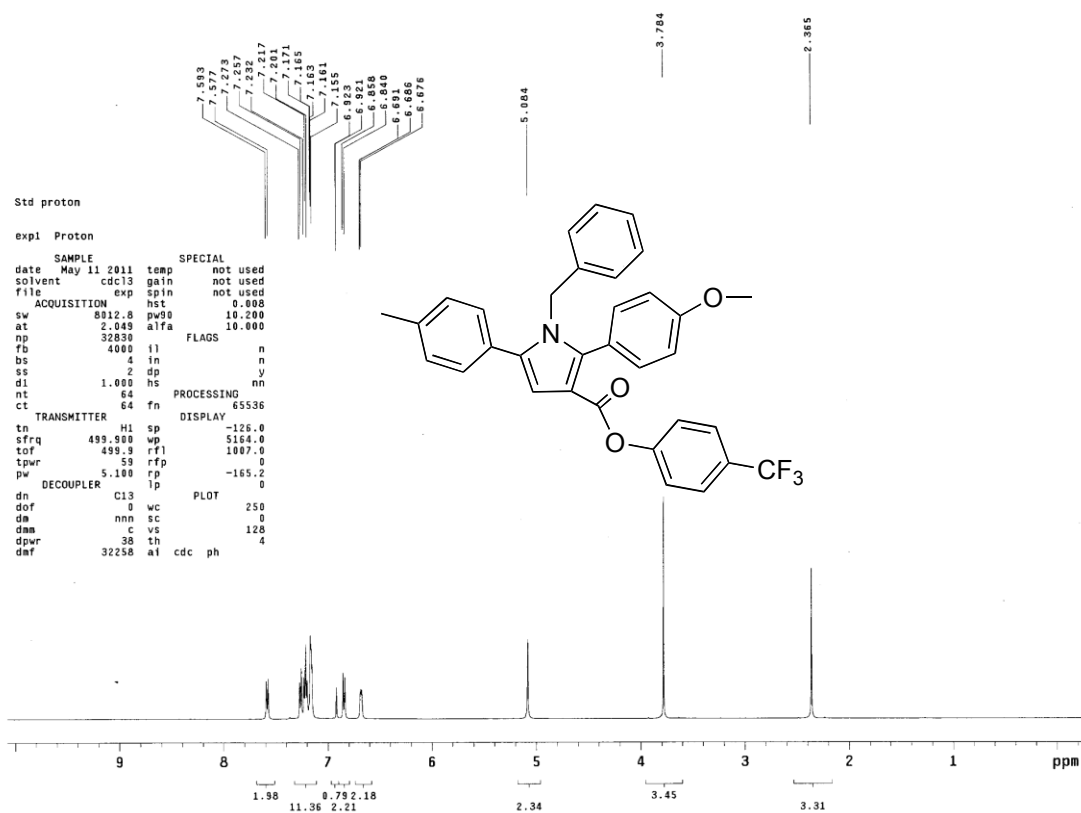
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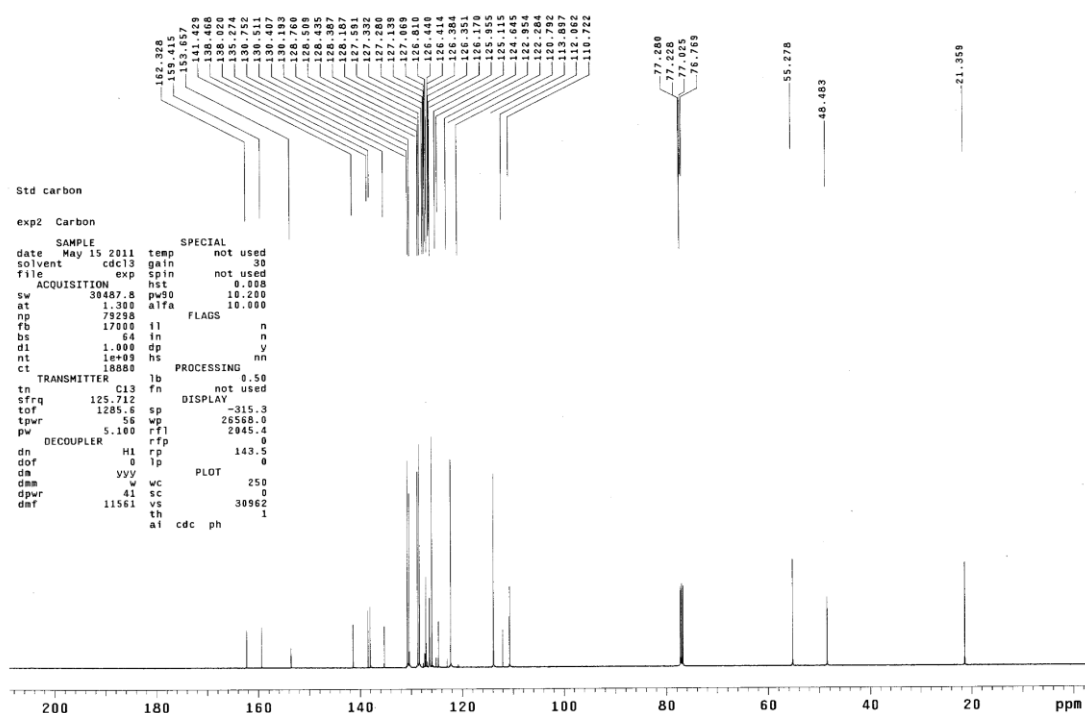
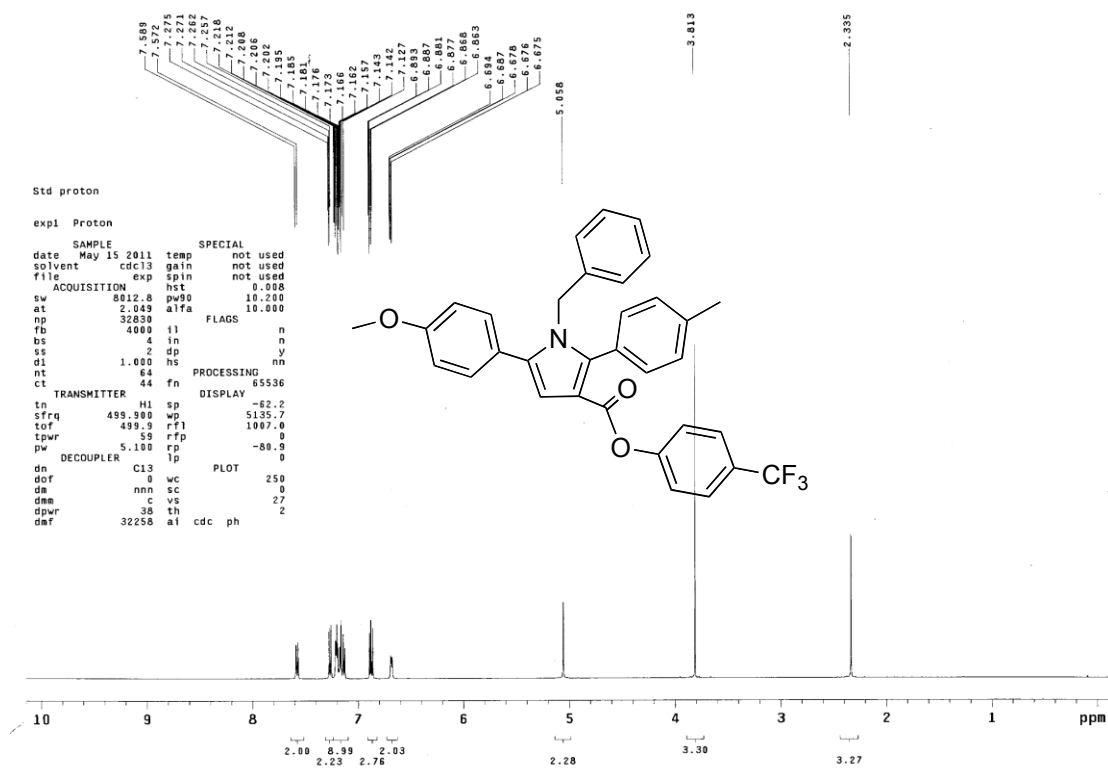
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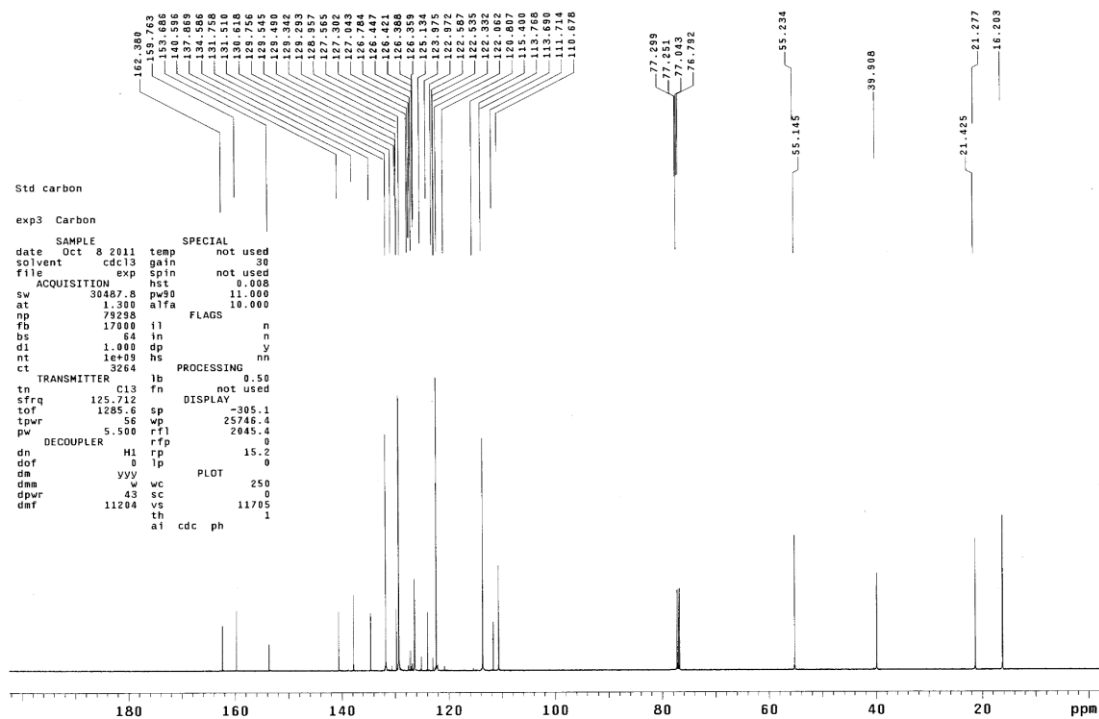
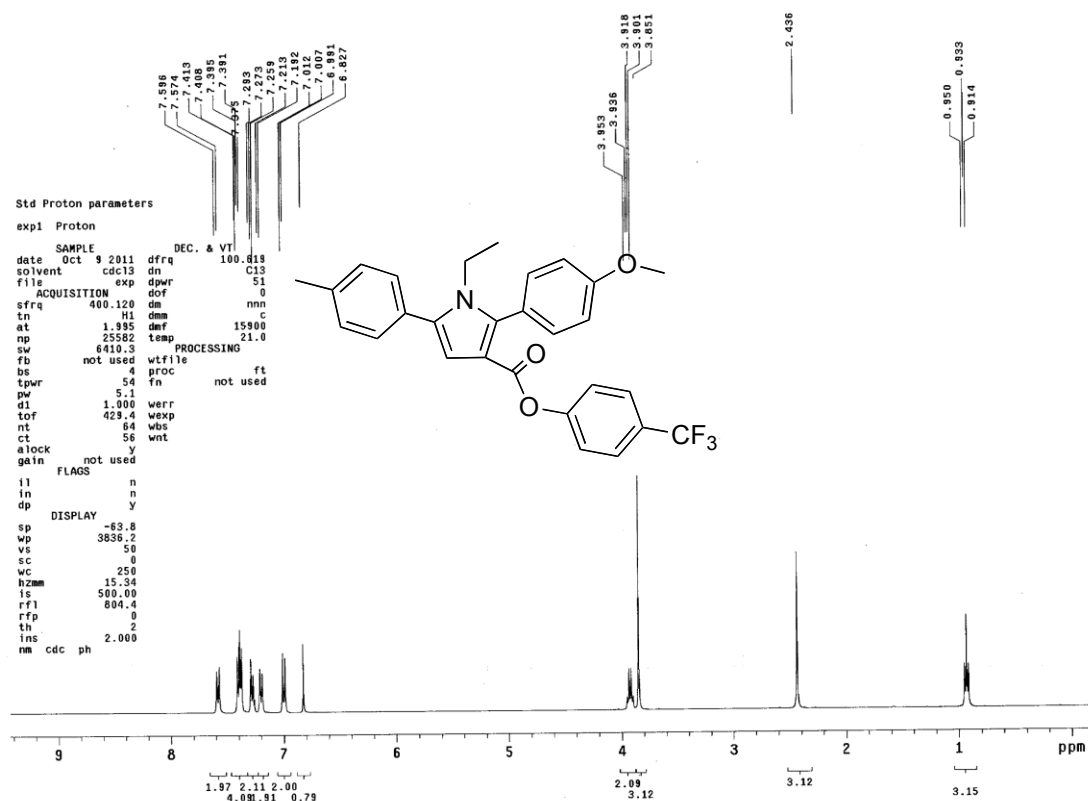
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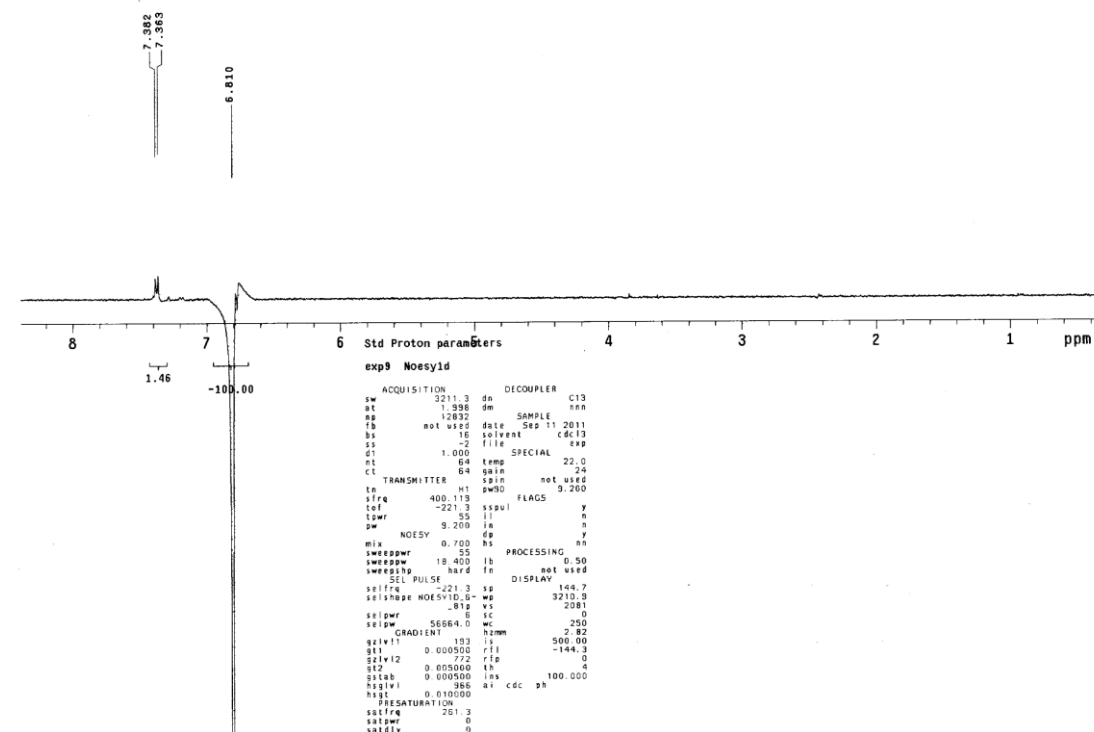
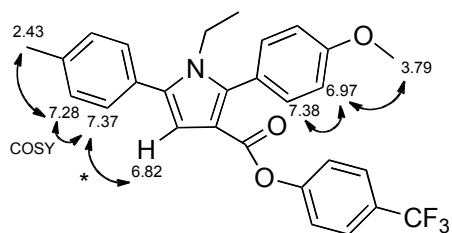
Pyrrole **B** of alkyne **2.4d** (CDCl₃)



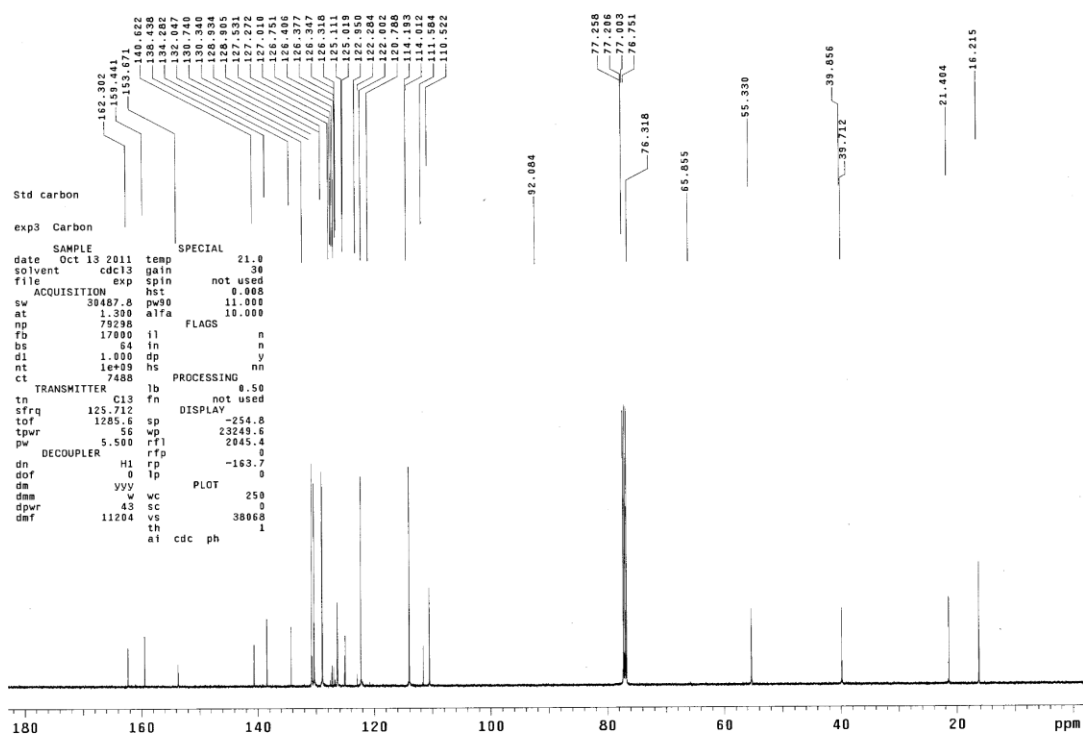
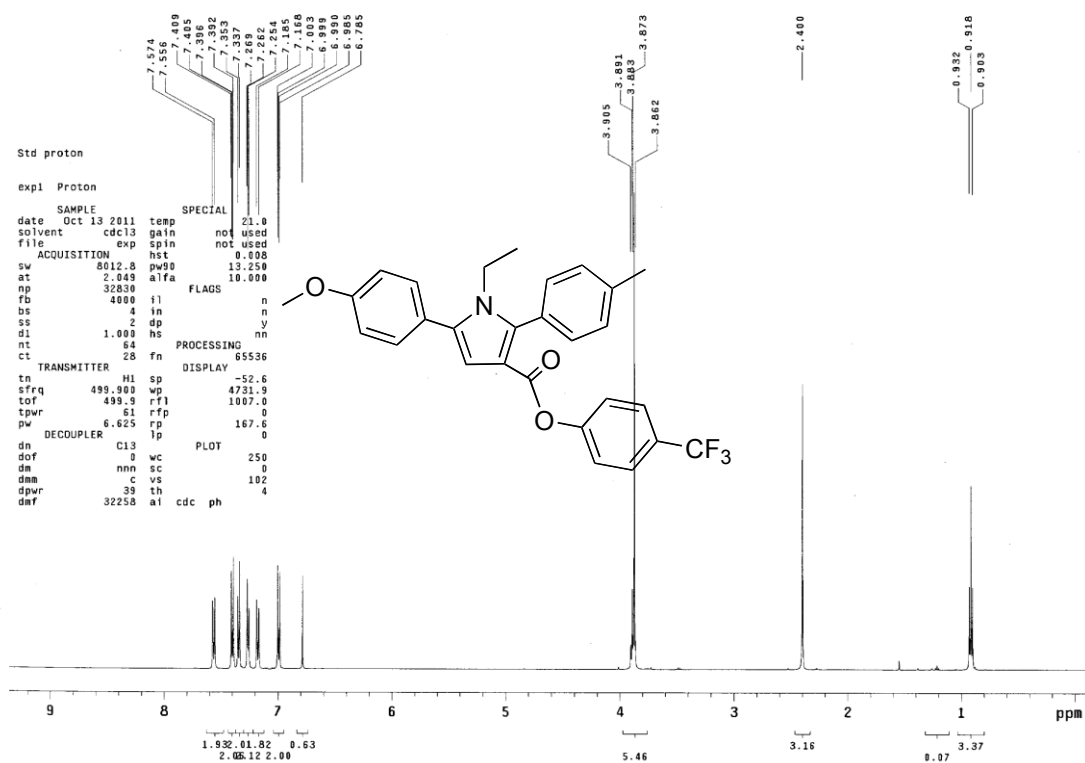
Pyrrole A' of alkyne **2.4d** (CDCl₃)



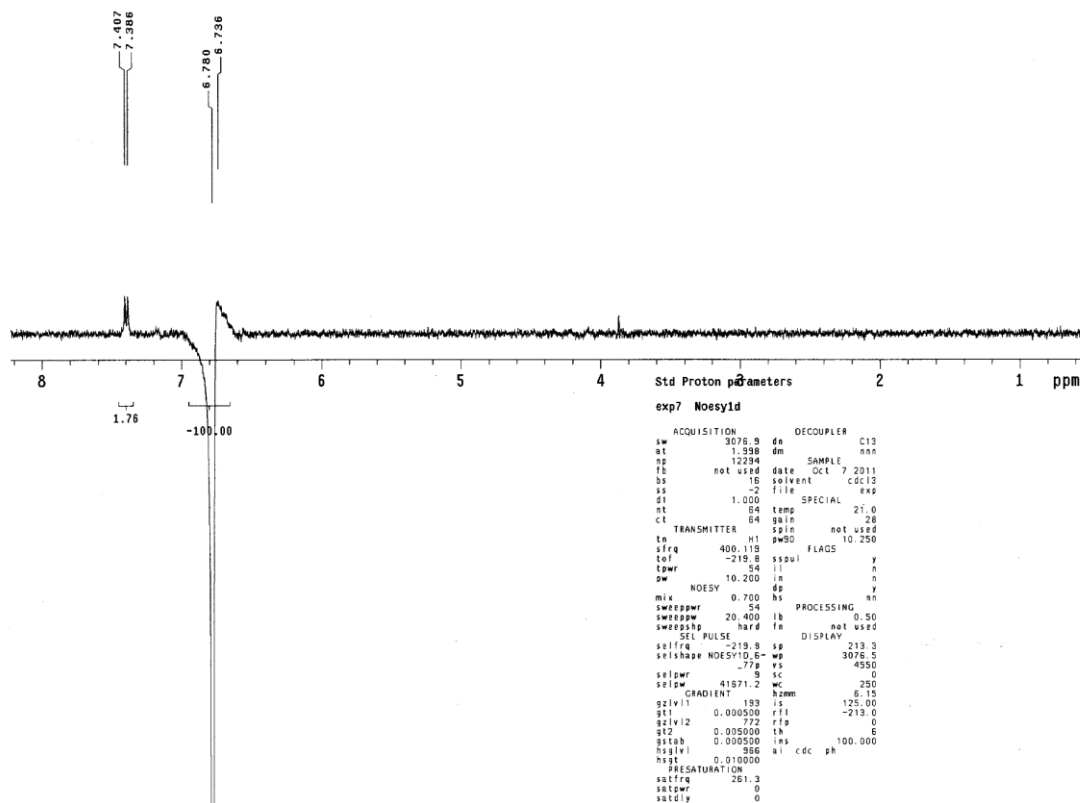
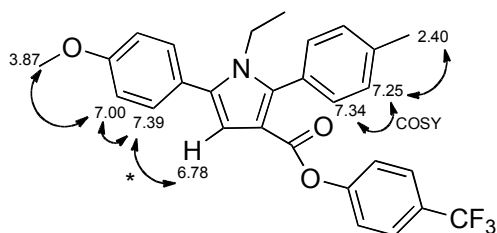
Summary of NOEs and COSY experiments
with spectrum of key correlation (*) provided



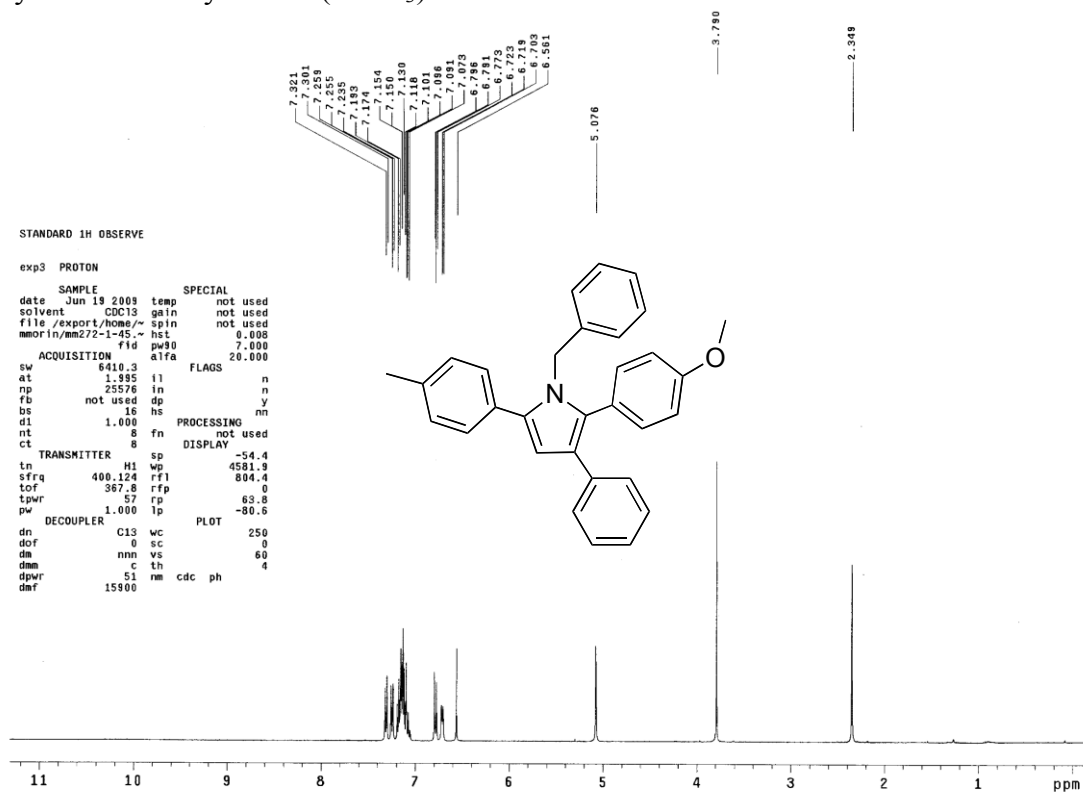
Pyrrole **B'** of alkyne **2.4d** (CDCl₃)



Summary of NOEs and COSY experiments
with spectrum of key correlation (*) provided



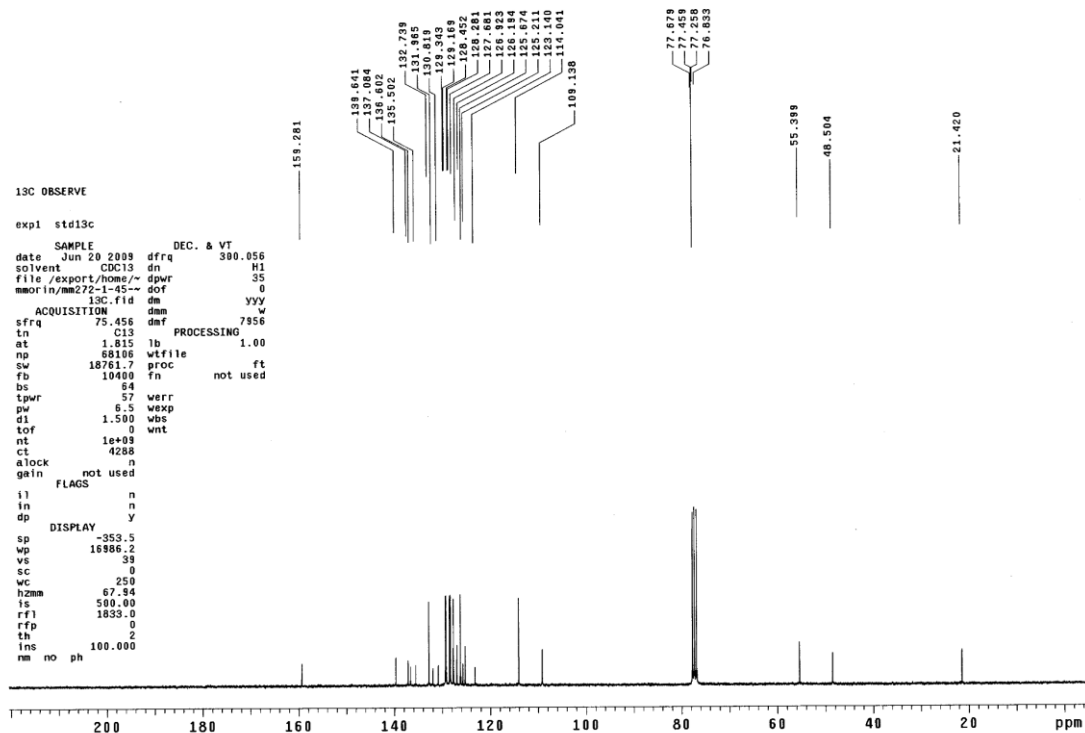
Pyrrole A of alkyne **2.4e** (CDCl₃)



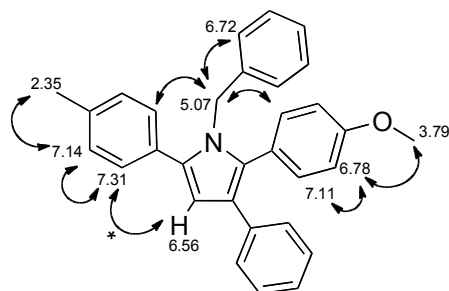
13C NMR

exp1 std13c

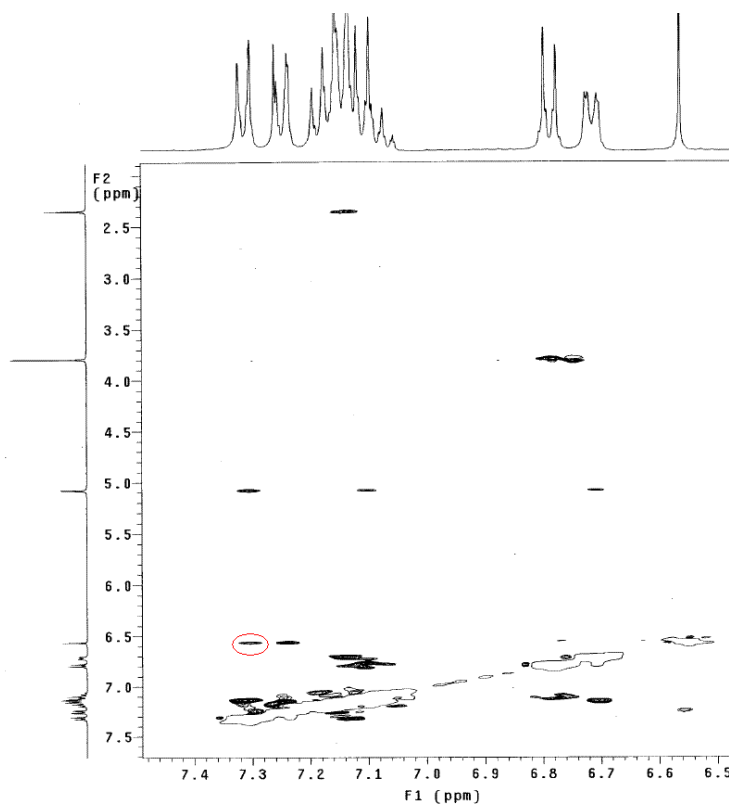
SAMPLE DEC. & VT
date Jun 20 2009 dfrq 300.056
solvent CDCl₃ dn H1
file /export/home/~ dpwr 35
morin/mm272-1-45~ dof 0
13C.fid dm yyy
ACQUISITION dam 7956
sfrq 75.458 dmf
tn C13 PROCESSING 1.00
at 1.515 lb wtfile
np 68106 proc ft
sw 18761.7 fn not used
fb 10400
bs 64
tpwr 57 verr
pw 6.5 wexp
dl 1.500 vbs
tof 0 wnt
nt 1e+09
ct 4288
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -353.5
wp 18986.2
vs 39
sc 9
wc 250
h2mm 67.94
ls 500.00
rfi 1833.0
rfp 0
th c
lms 100.000
nm no ph



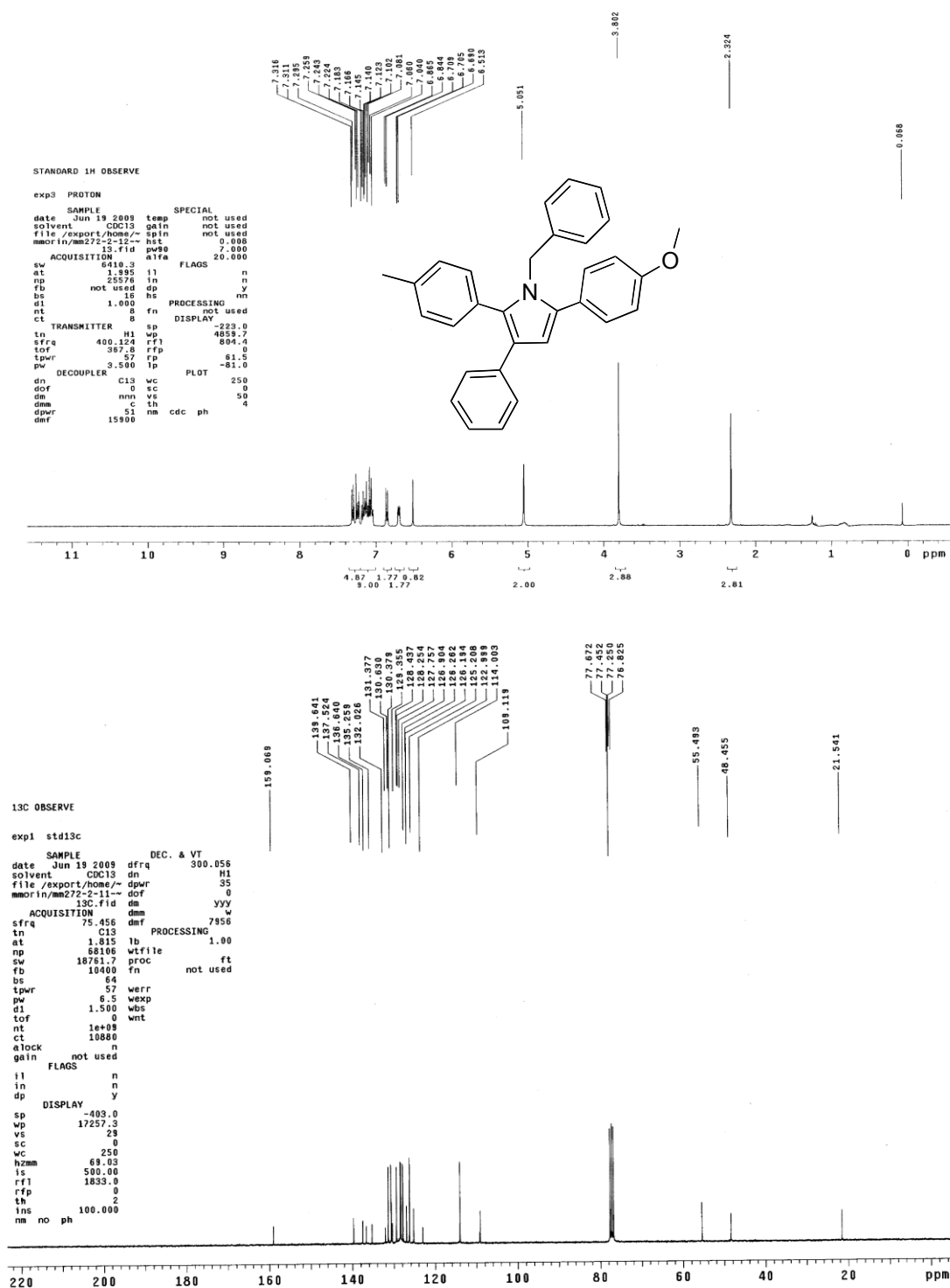
Summary of NOESY 2D with key correlation (*) circled on the spectrum



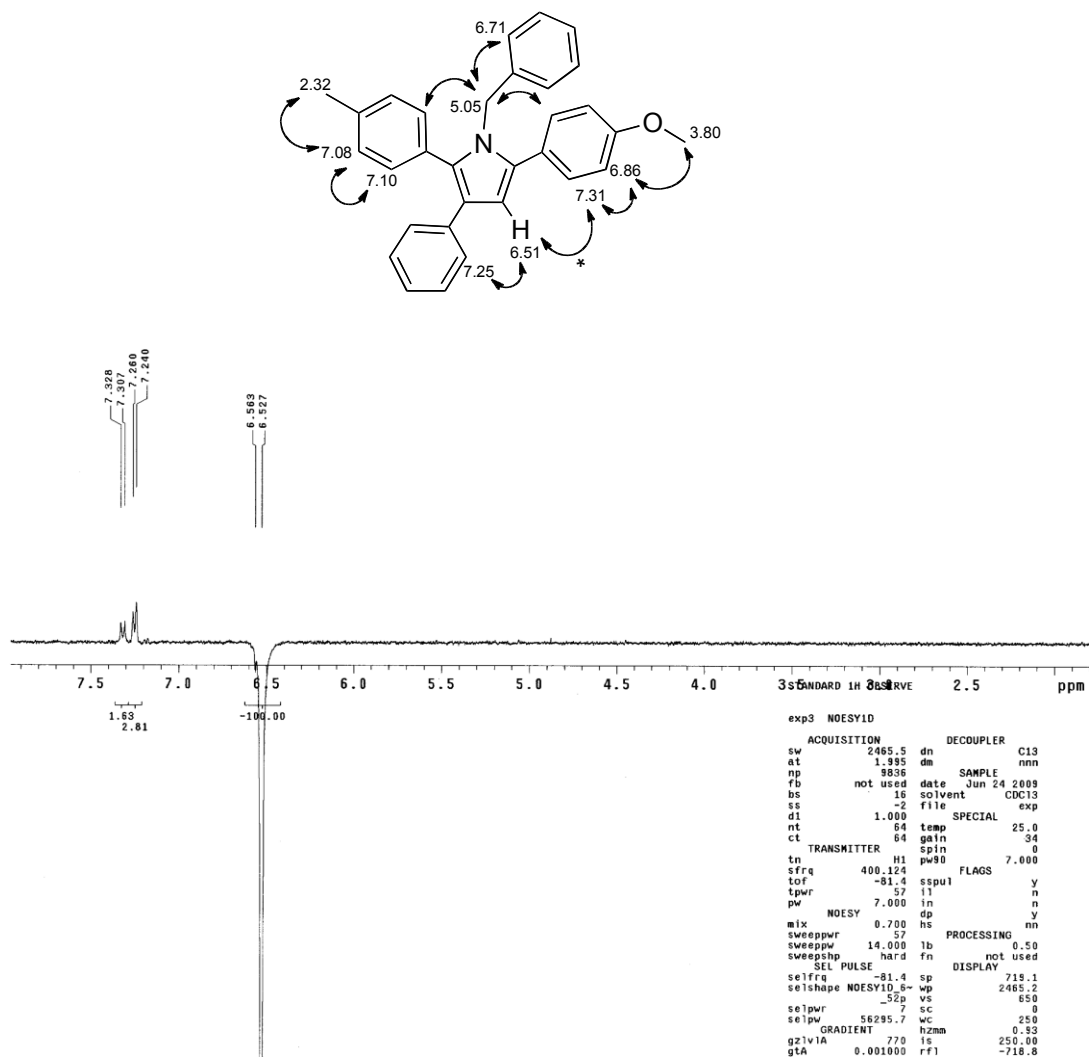
Data Collected on:
 m400-mercury400
 Archive directory:
 export/home/ammorin/vnmrsys/data
 Sample directory:
 File: NOESY
 Pulse Sequence: NOESY
 Solvent: CDCl3
 Relax. delay 1.000 sec
 Mixing 0.700 sec
 Acq. time 0.150 sec
 Width 2513.8 Hz
 2D Width 2513.8 Hz
 4 repetitions
 2 x 128 increments
 OBSERVE H1 400.1219604 MHz
 DATA PROCESSING
 Gauss apodization 0.069 sec
 F1 DATA PROCESSING
 Gauss apodization 0.073 sec
 FT size 2048 x 2048
 Total time 35 min



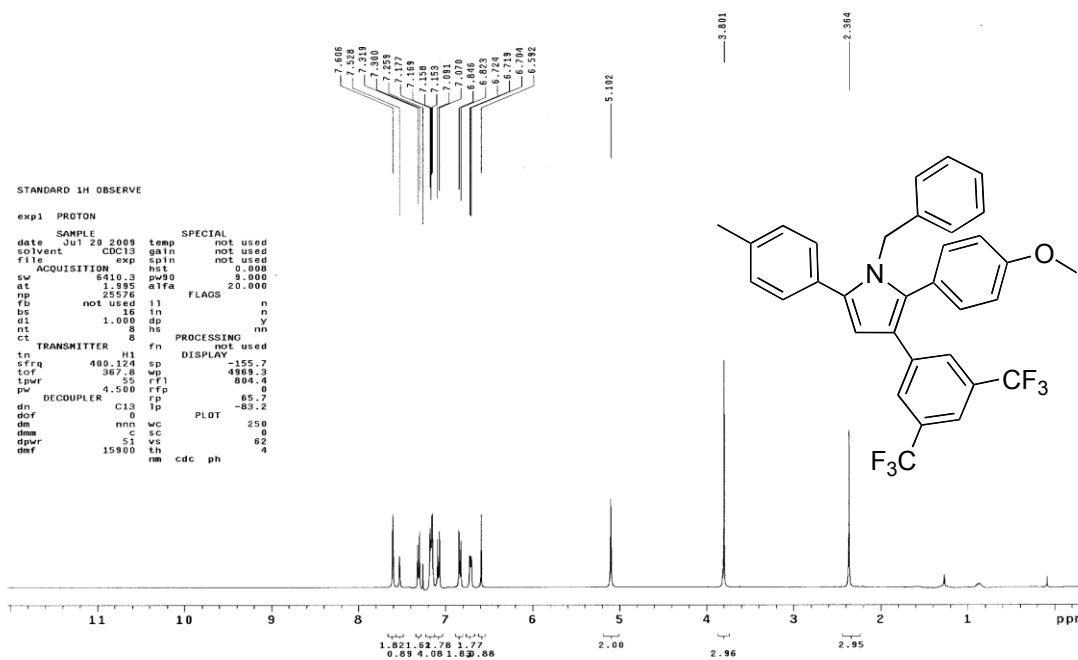
Pyrrole **B** of alkyne **2.4e** (CDCl₃)



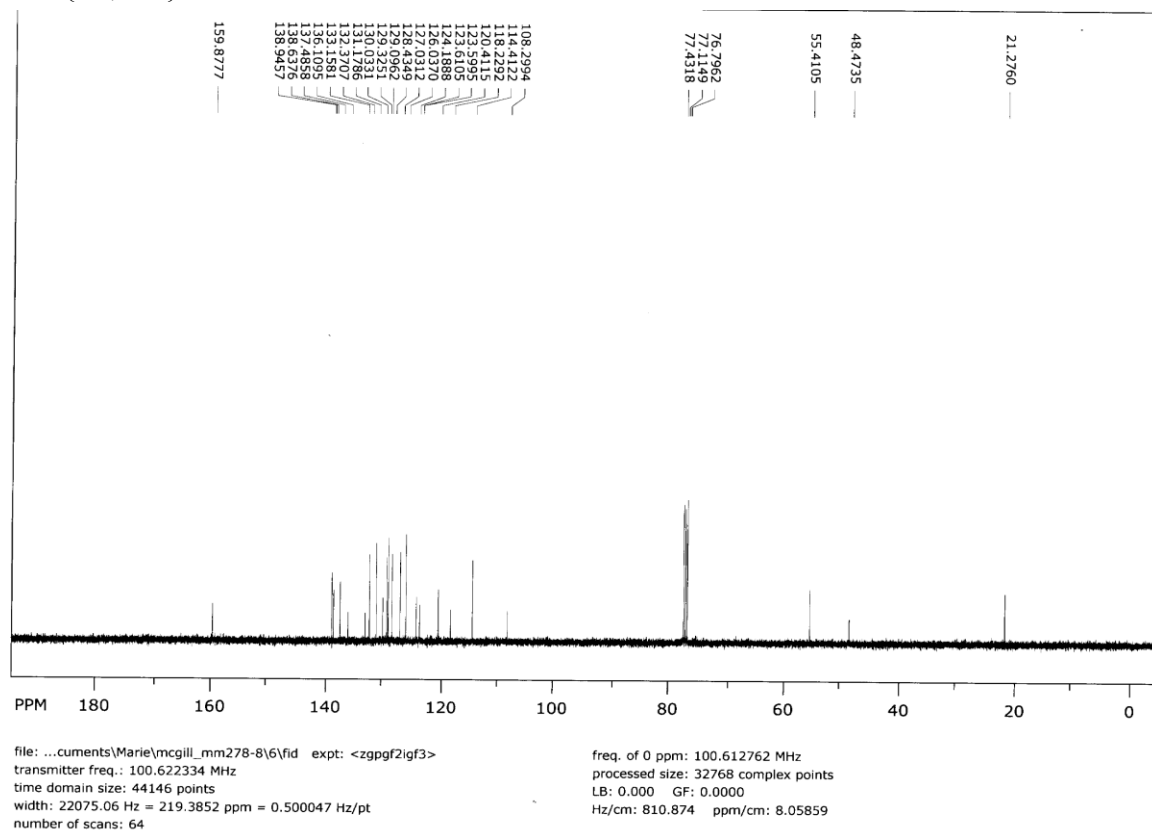
Summary of NOE 1D experiments with key correlation (*) provided



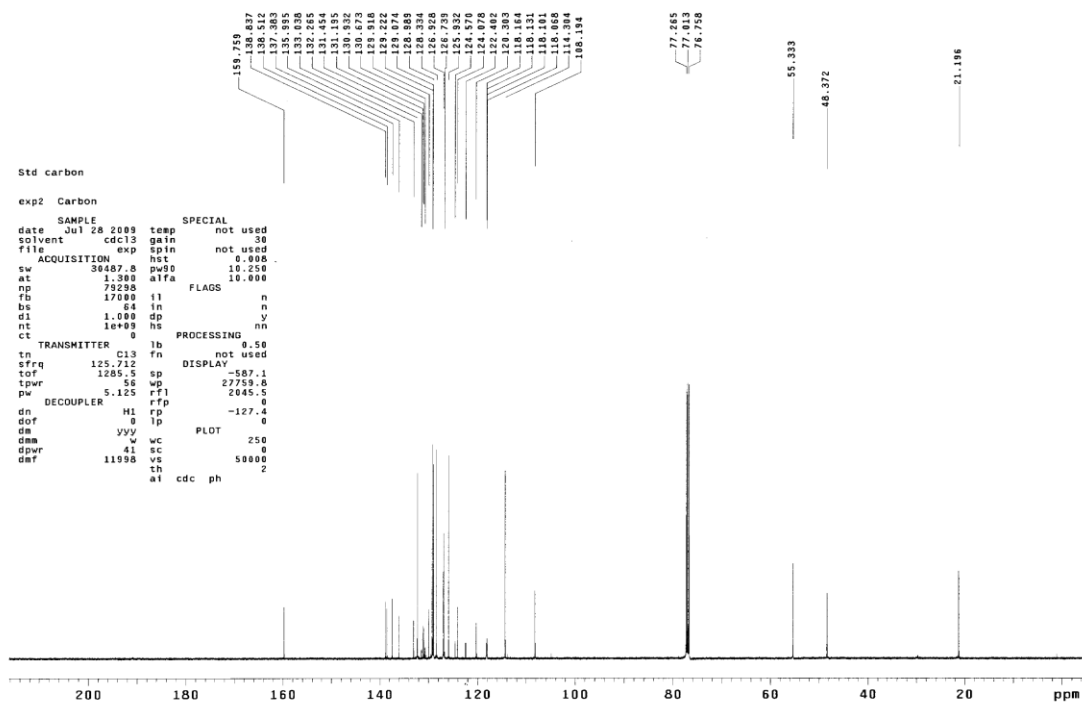
Pyrrole A of alkyne **2.4f** (CDCl₃)



¹³C {¹H, ¹⁹F} NMR



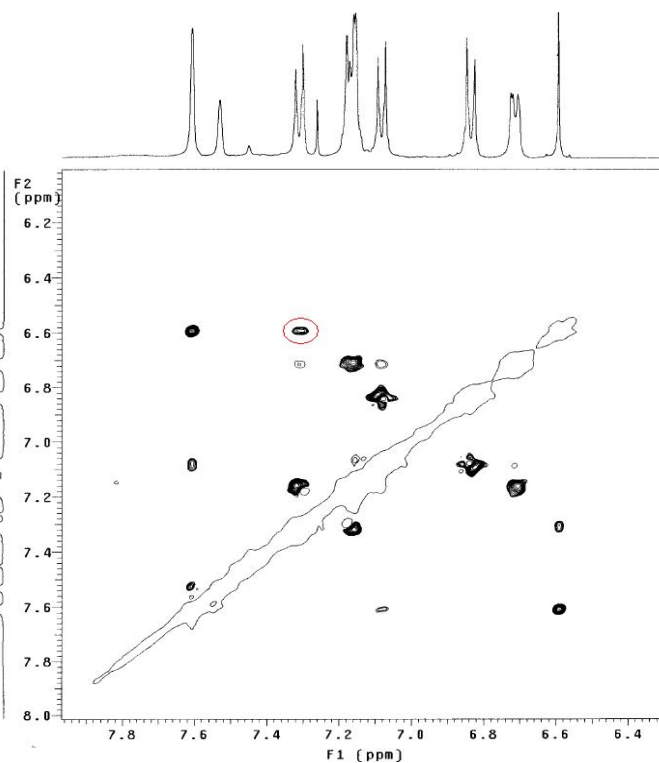
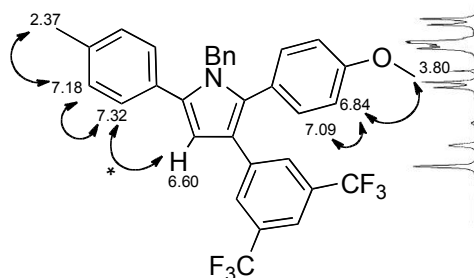
$^{13}\text{C} \{^1\text{H}\}$ NMR



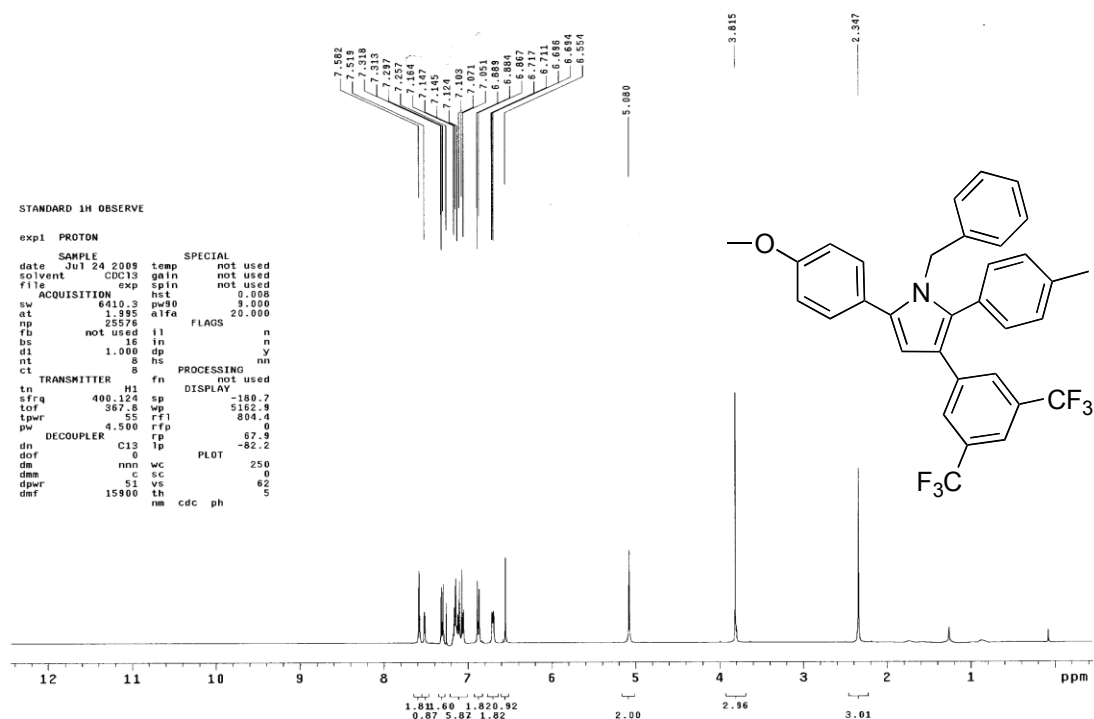
STANDARD 1H OBSERVE

Data Collected on:
 m400-mercury400
 Archive directory:
 export/home/mmorin/vnmr/sys/data
 Sample directory:
 File: NOESY
 Pulse Sequence: NOESY
 Solvent: CDCl3
 Temp: 25.0 C / 298.1 K
 Relax. delay 2.000 sec
 Mixing 0.700 sec
 Acq. time 0.150 sec
 Width 2471.0 Hz
 2D Width 2471.0 Hz
 4 repetitions
 2 x 256 increments
 OBSERVE H1 400.1219604 MHz
 DATA PROCESSING
 Gauss apodization 0.069 sec
 F1 DATA PROCESSING
 Gauss apodization 0.075 sec
 FI size 4096 x 4096
 Total time 1 hr, 44 min

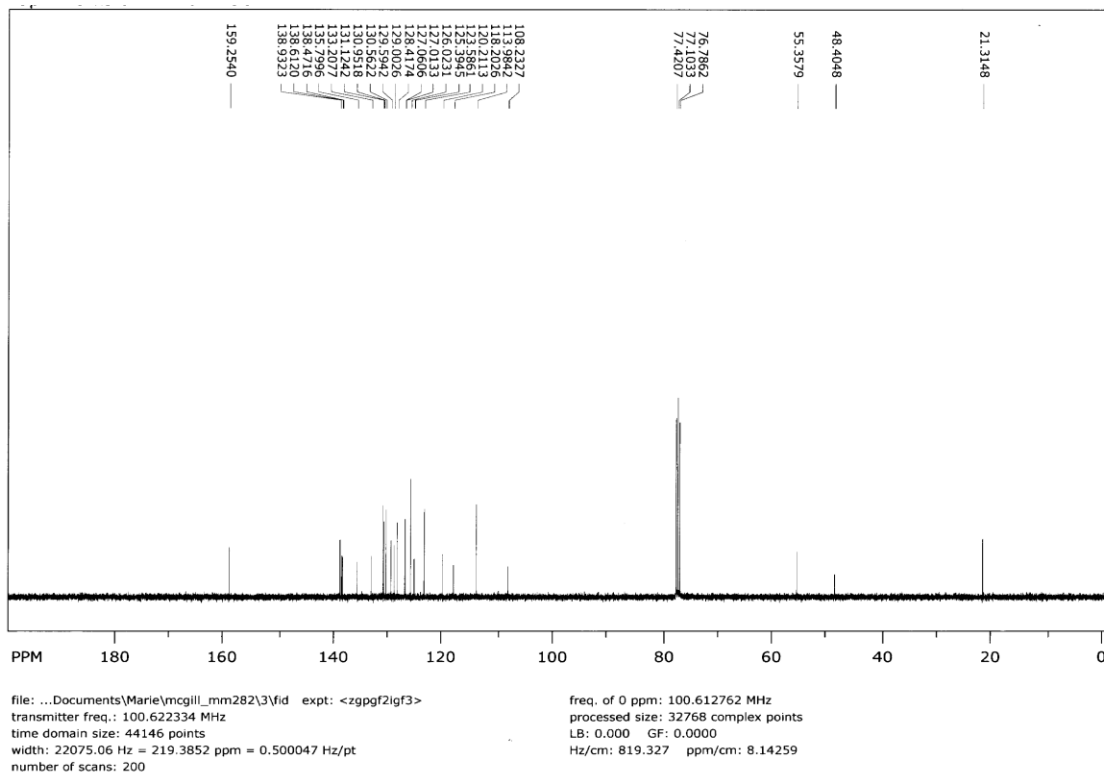
Summary of NOESY 2D with key correlation (*) circled on the spectrum



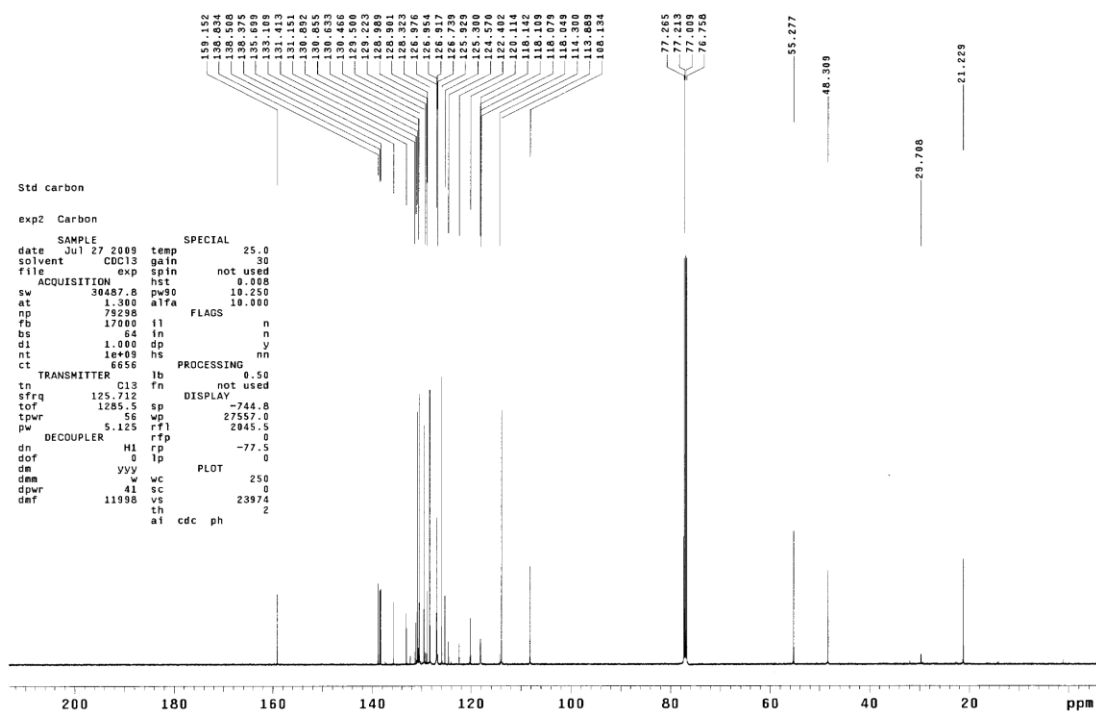
Pyrrole **B** of alkyne **2.4f** (CDCl₃)



¹³C {¹H, ¹⁹F} NMR :



$^{13}\text{C} \{^1\text{H}\}$ NMR:

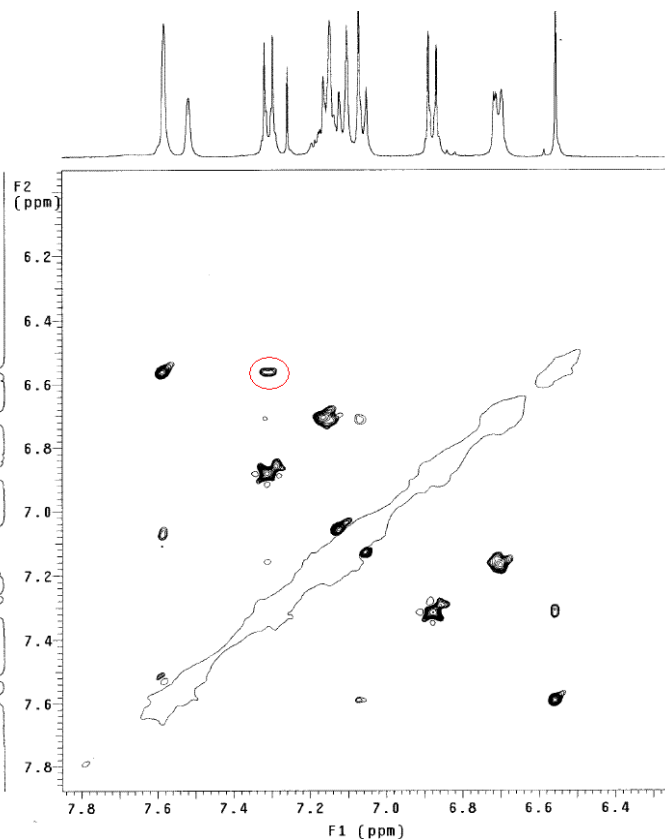
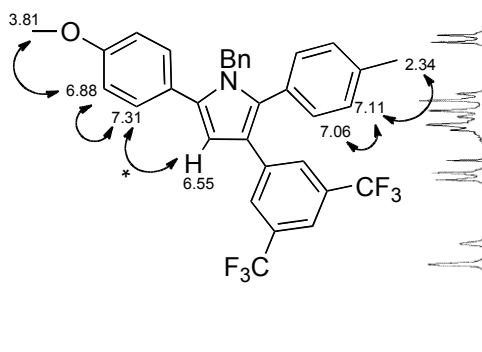


Data Collected on:
m400-mercury400
Archive directory:
/export/home/mmorin/vnmrsys/data
Sample directory:
File: NOESY

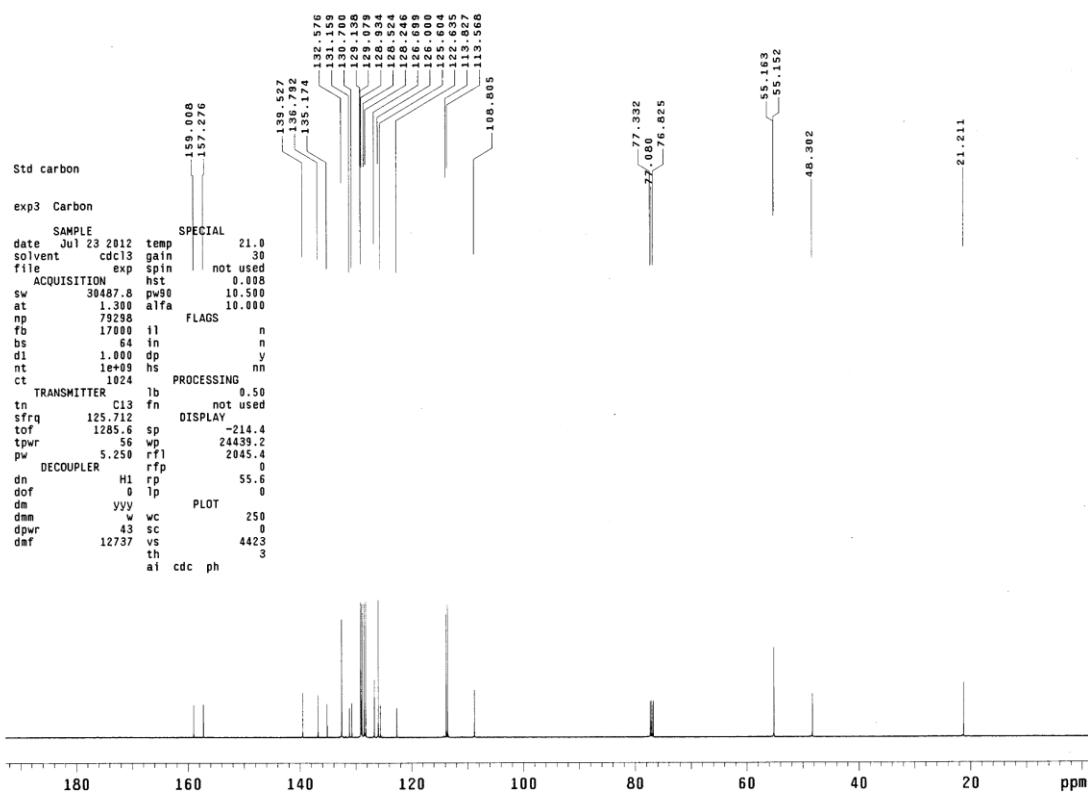
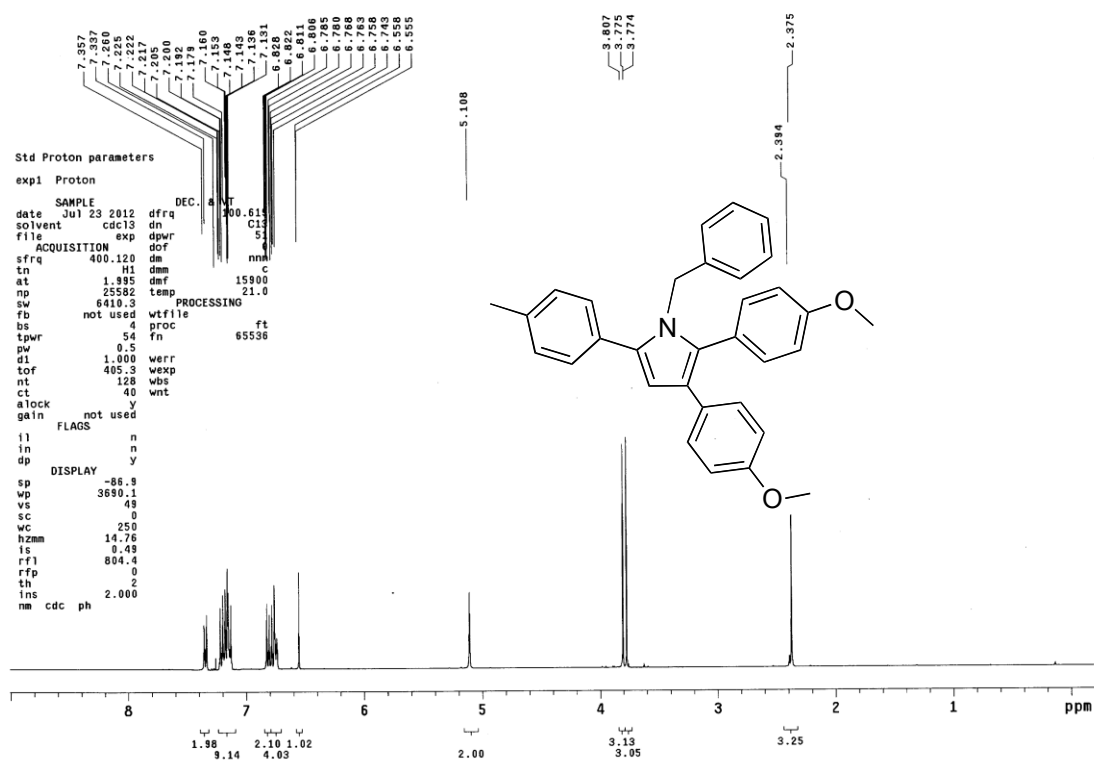
Pulse Sequence: NOESY
Solvent: CDCl3
Temp. 25.0 C / 298.1 K

Relax. delay 2.000 sec
Mixing 0.700 sec
Acq. time 0.150 sec
Width 2371.9 Hz
2D Width 2371.9 Hz
4 repetitions
2 x 256 increments
OBSERVE H1, 400.1219604 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.078 sec
FT size 4096 x 4096
Total time 1 hr, 44 min

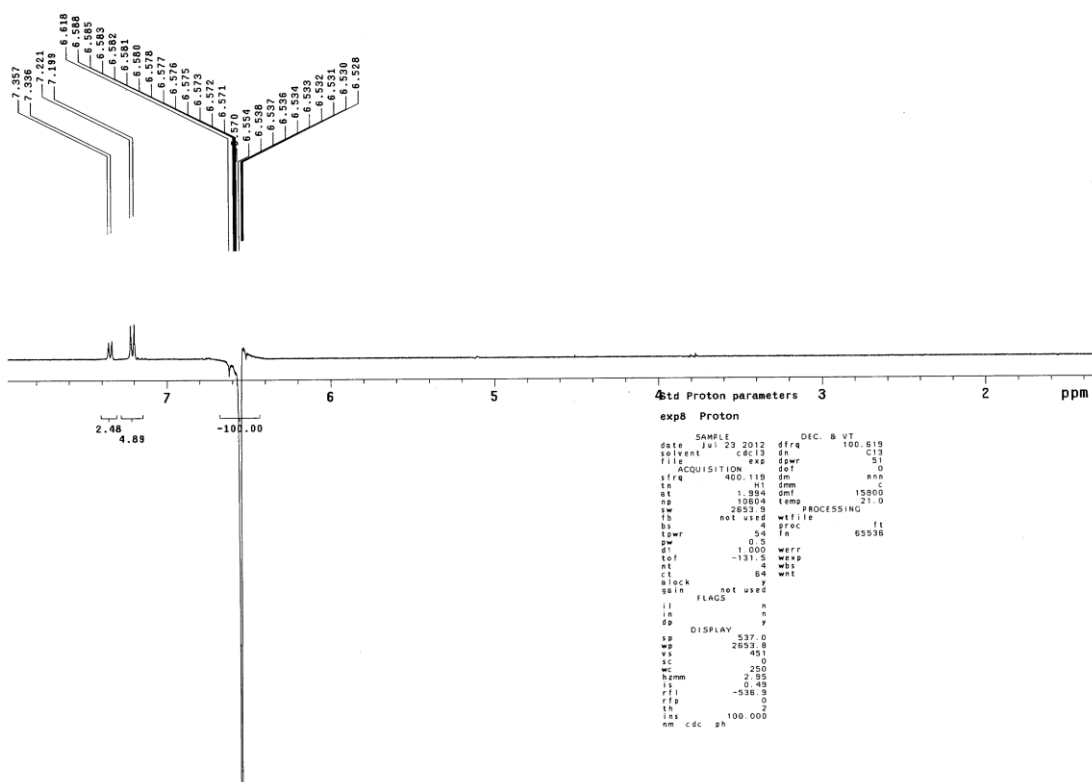
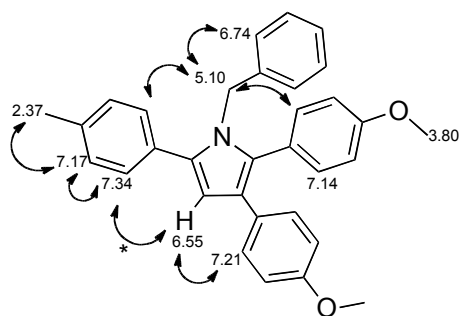
Summary of NOESY 2D with key correlation (*) circled on the spectrum



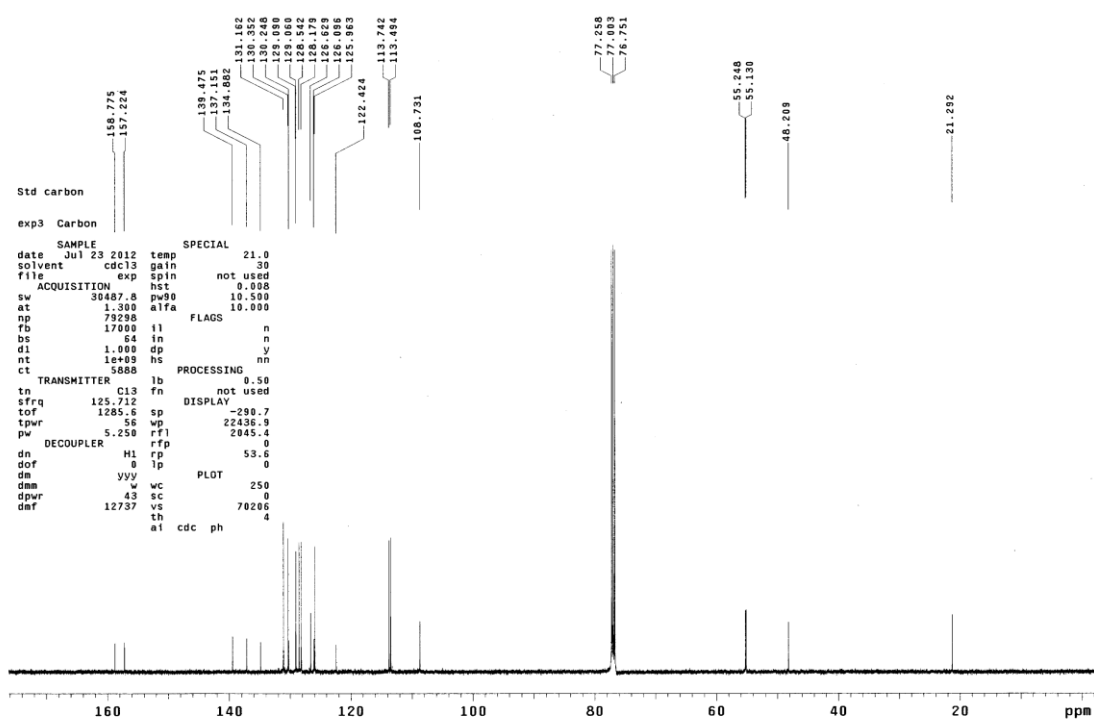
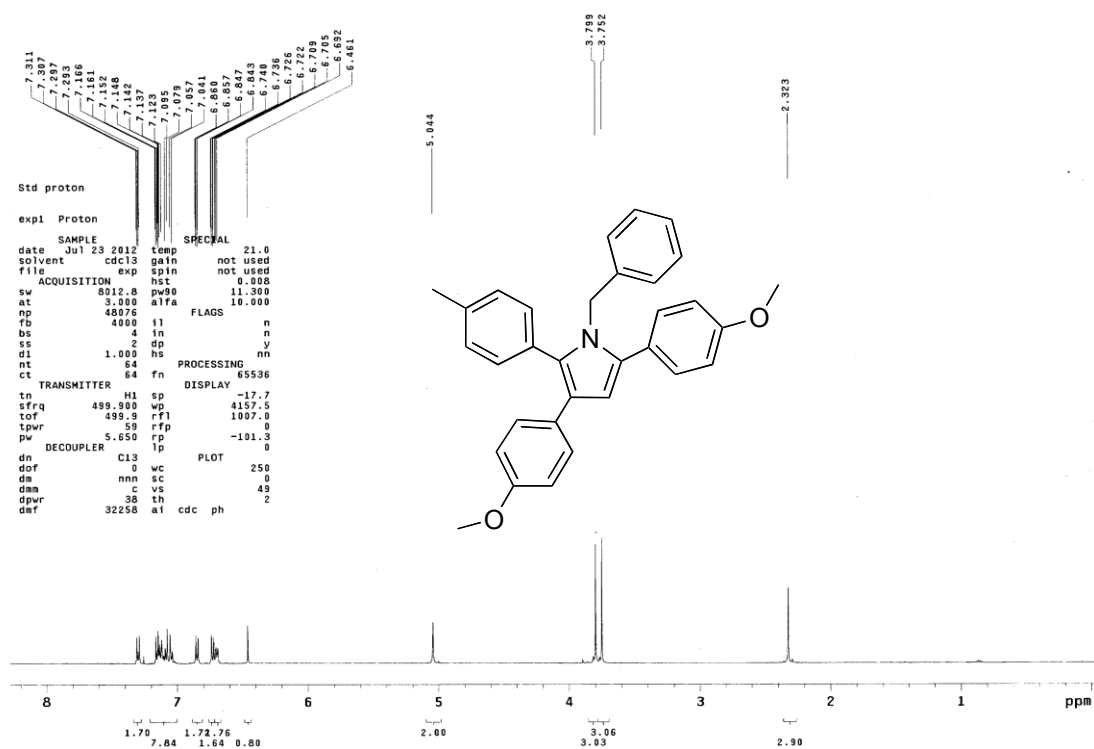
Pyrrole A of alkyne **2.4g** (CDCl₃)



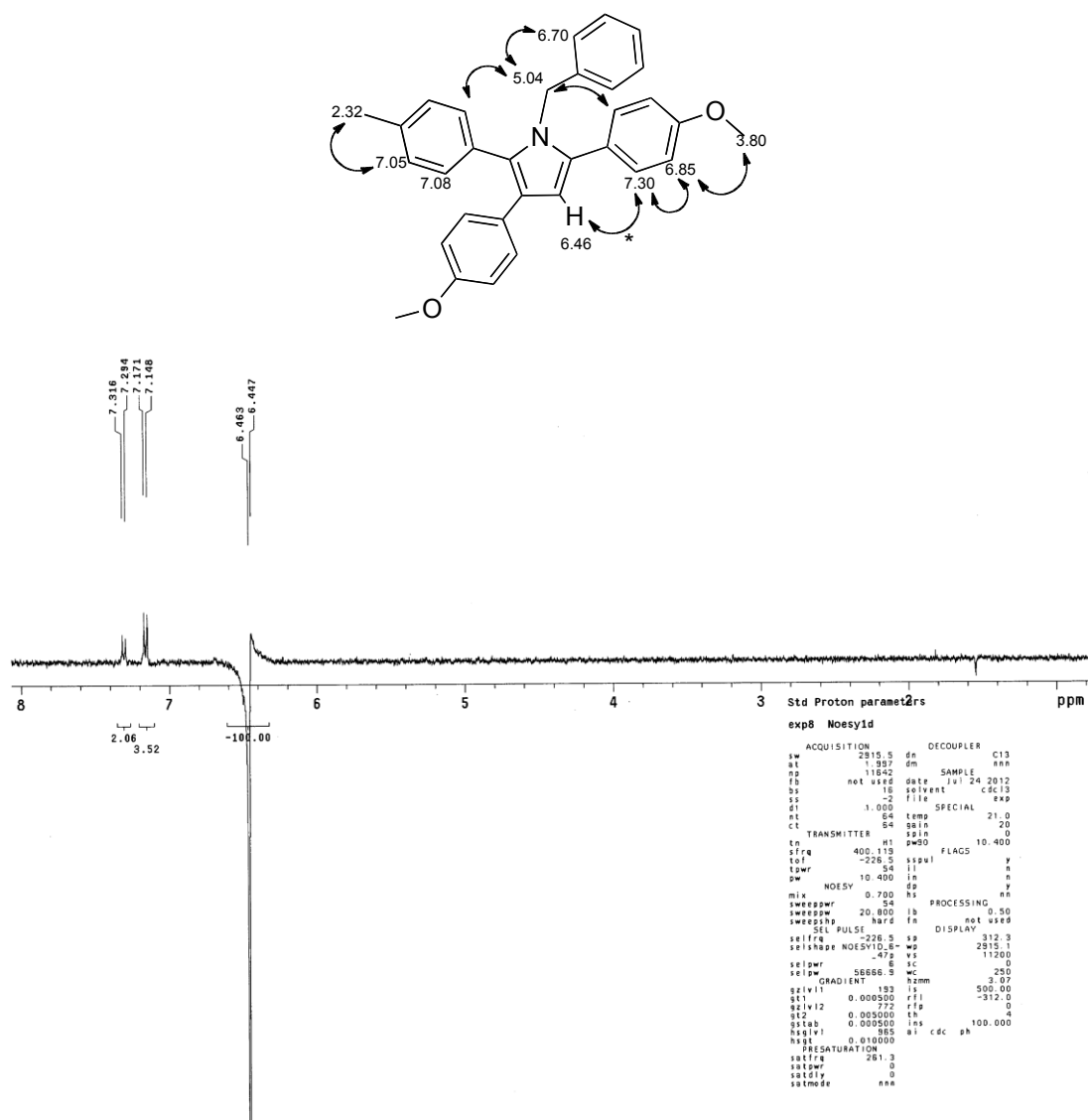
Summary of NOEs with spectra of key correlation (*) provided



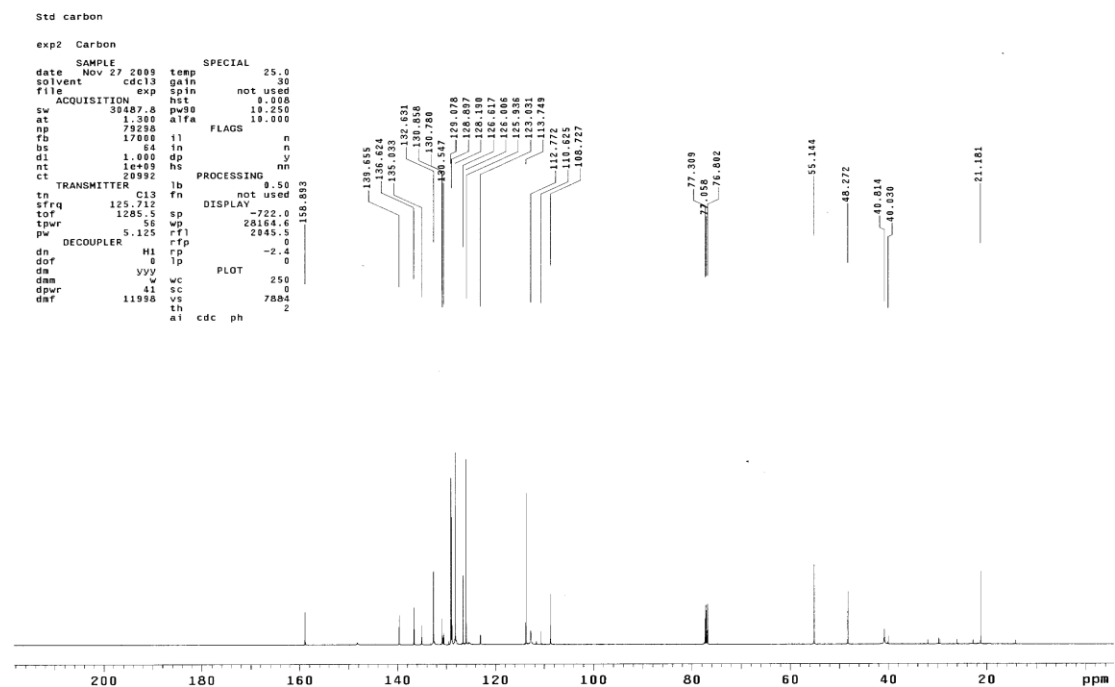
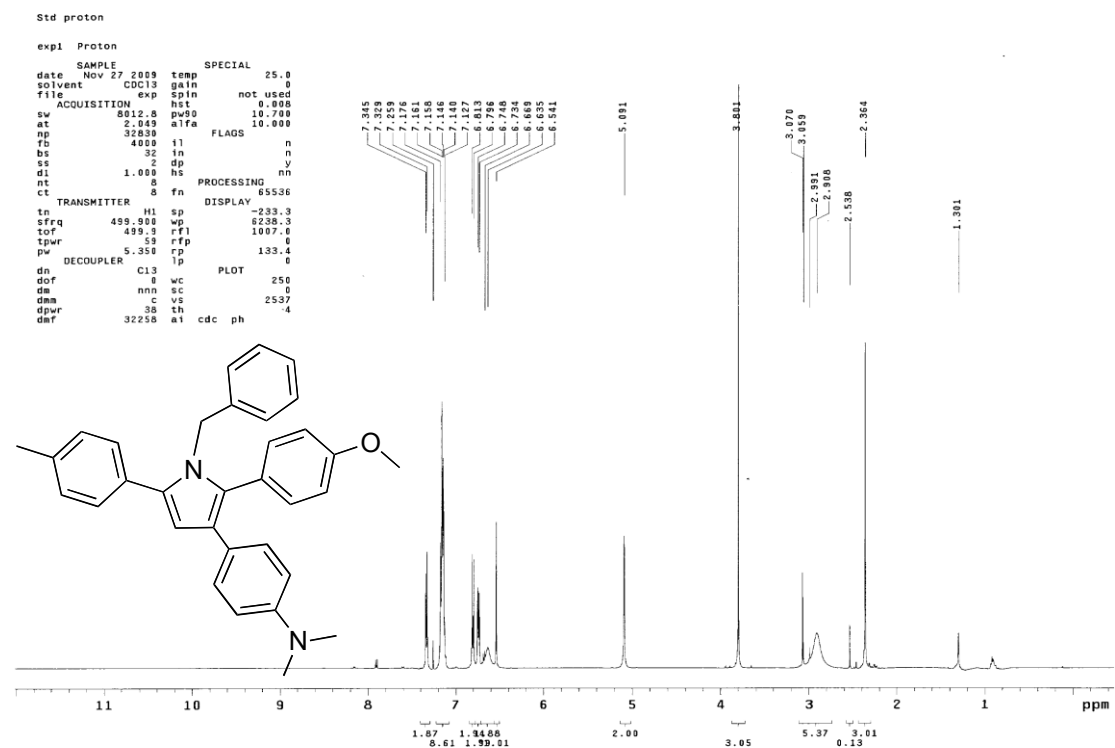
Pyrrole **B** of alkyne **2.4g** (CDCl₃)



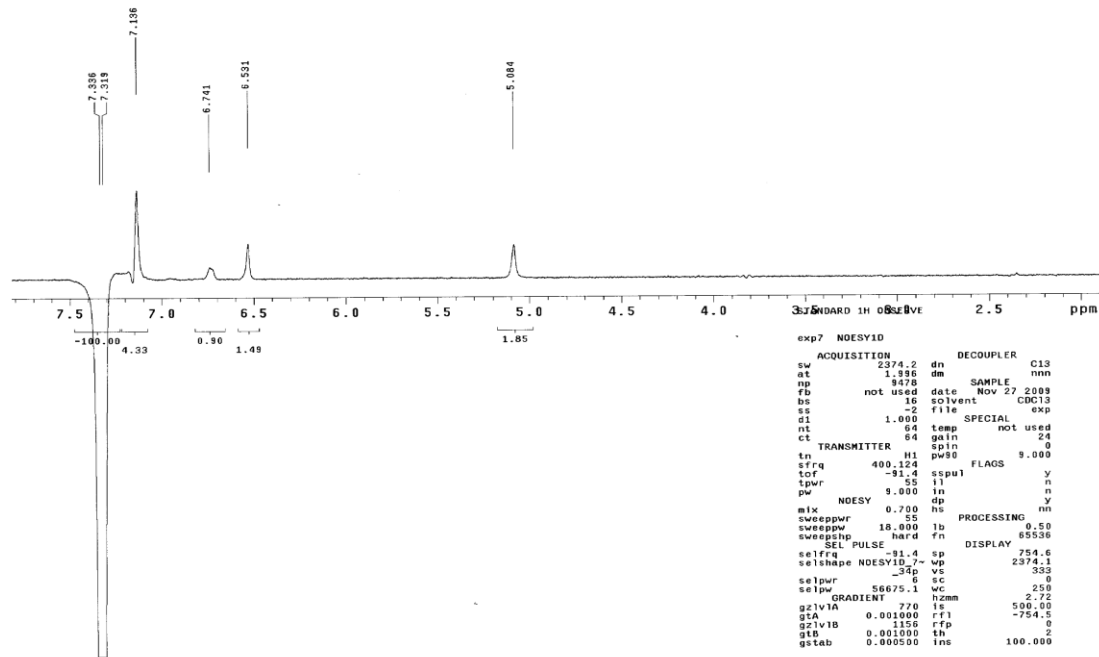
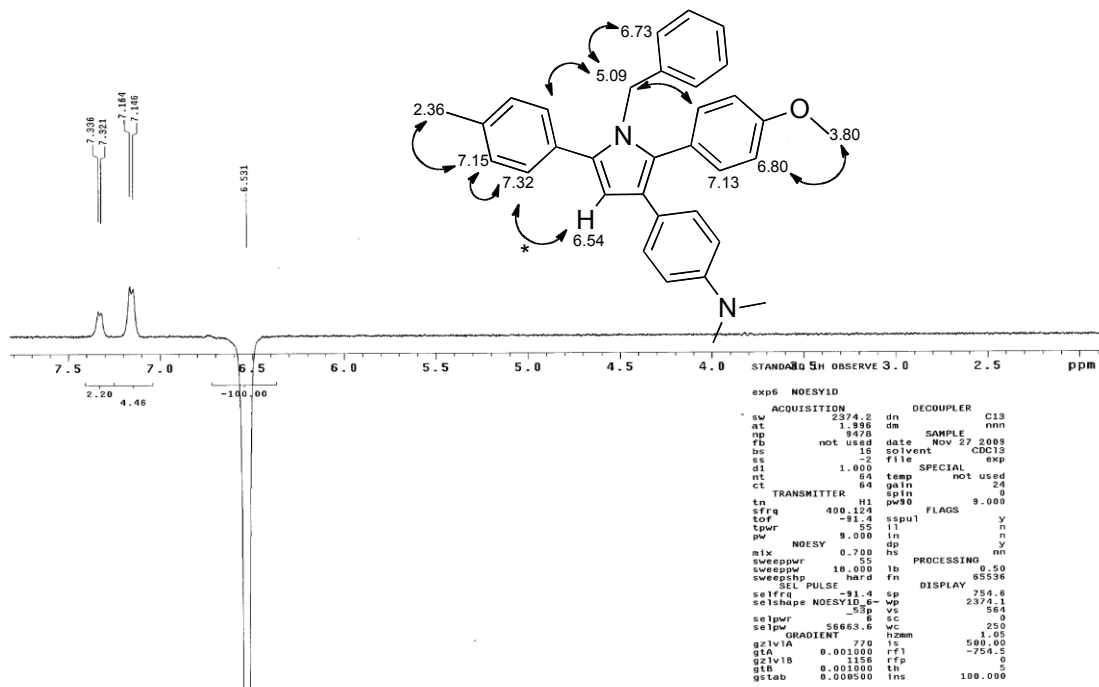
Summary of NOEs with spectra of key correlation (*) provided



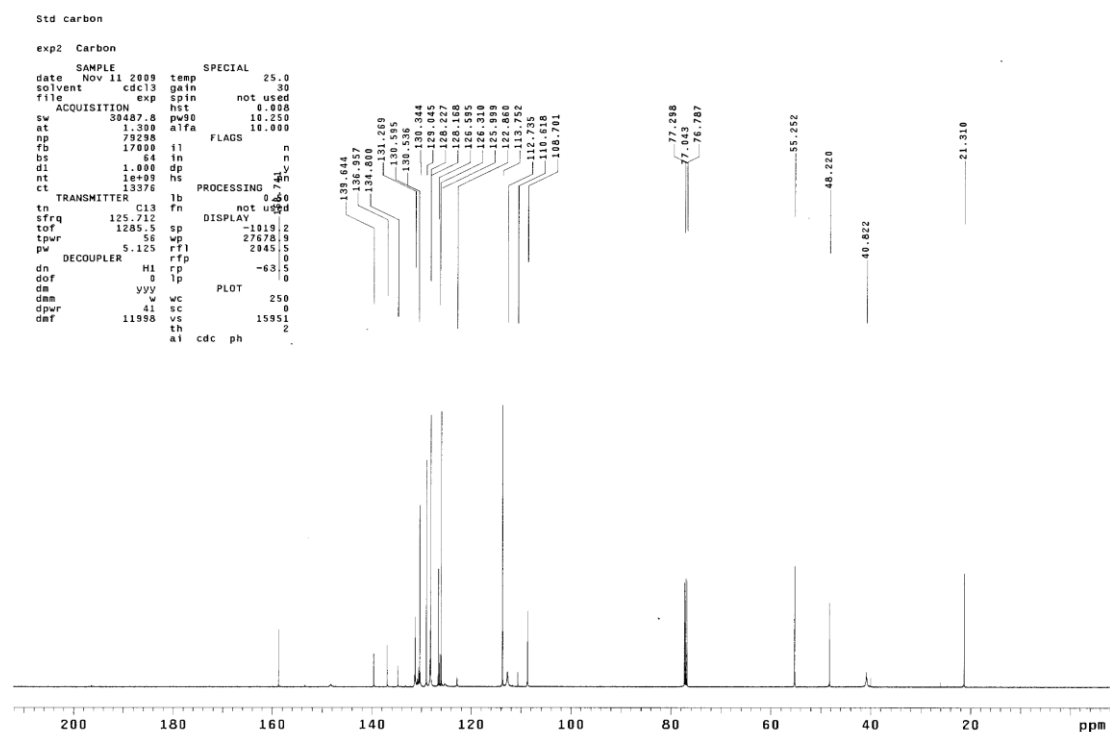
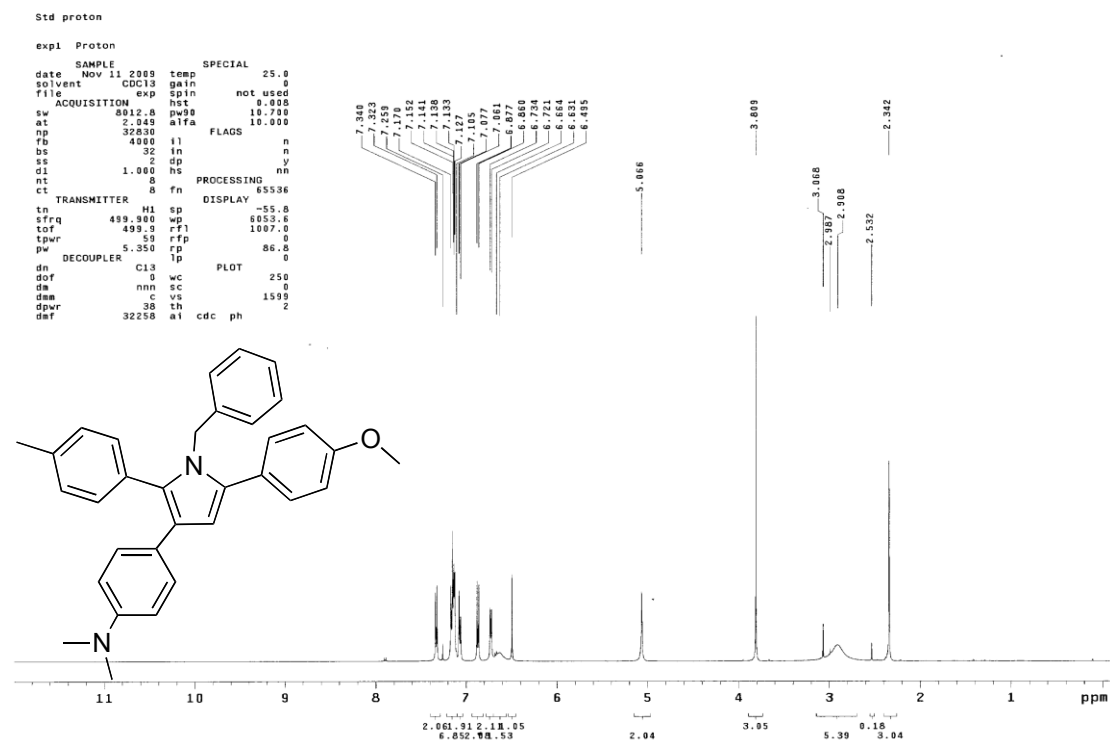
Pyrrole A of alkyne **2.4h** (CDCl₃)



Summary of NOEs with spectra of key correlation (*) provided



Pyrrole **B** of alkyne **2.4h** (CDCl₃)



Summary of NOEs with spectrum of key correlation (*) provided

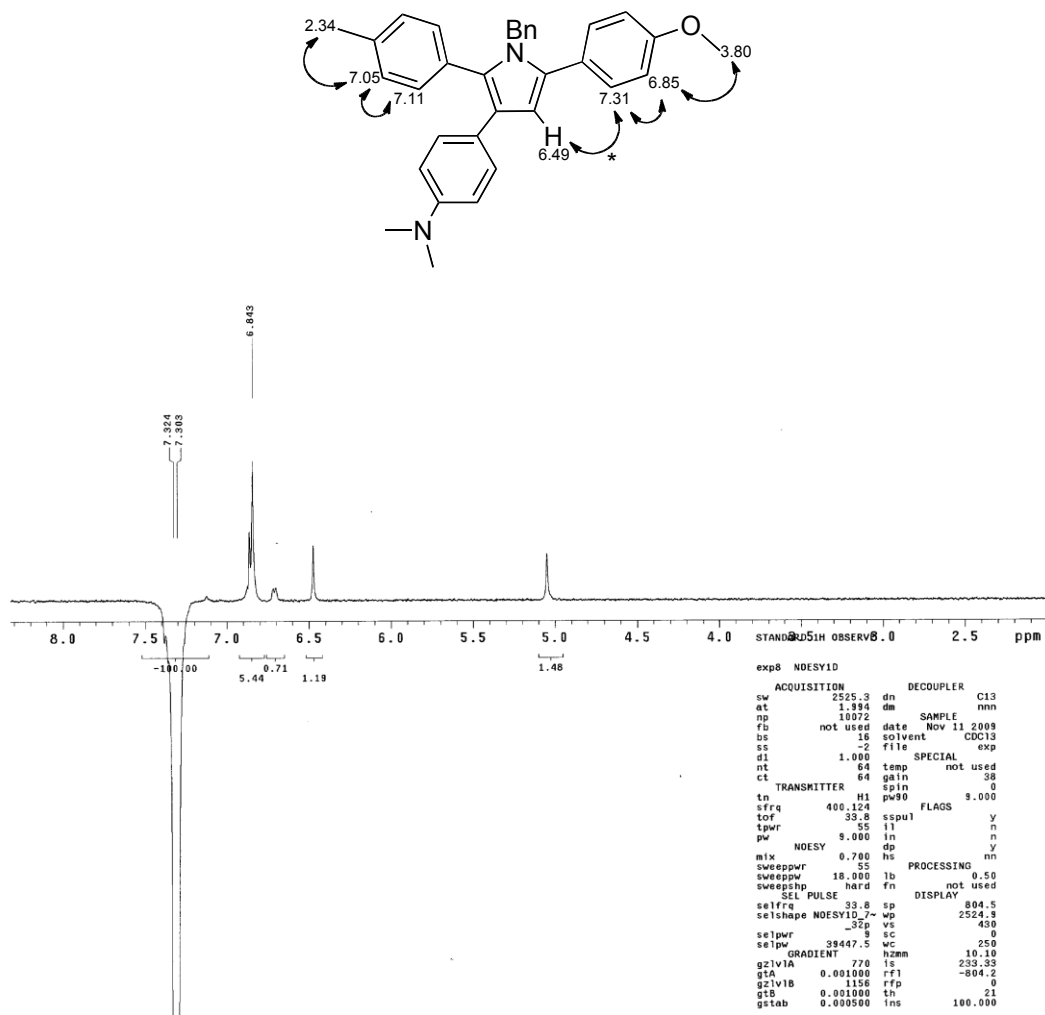
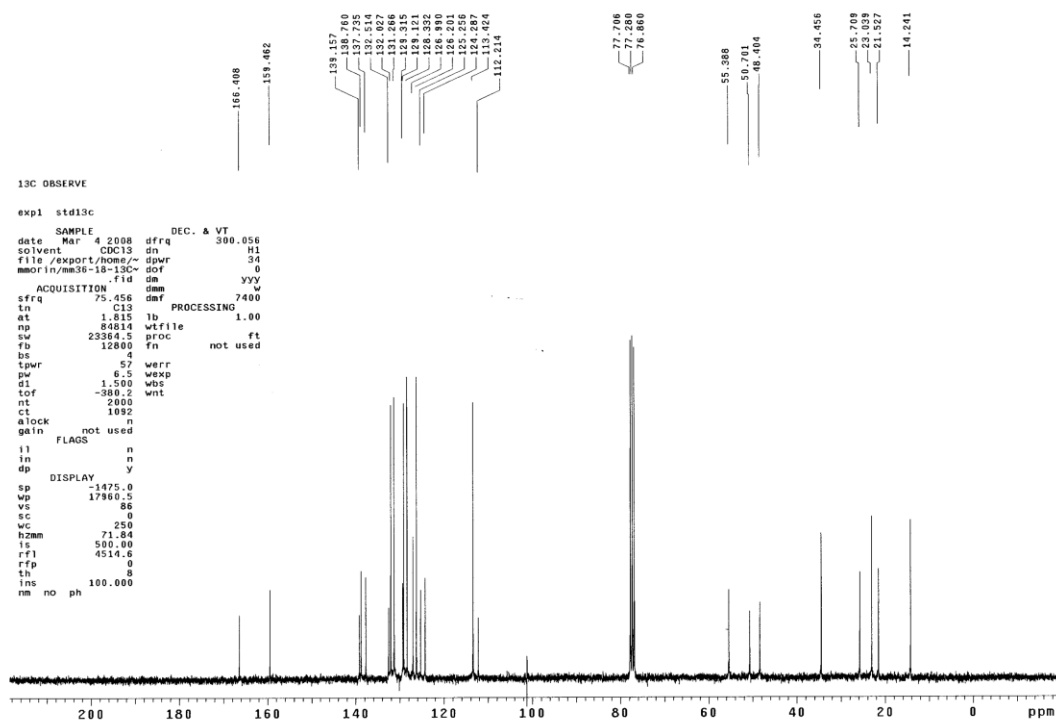
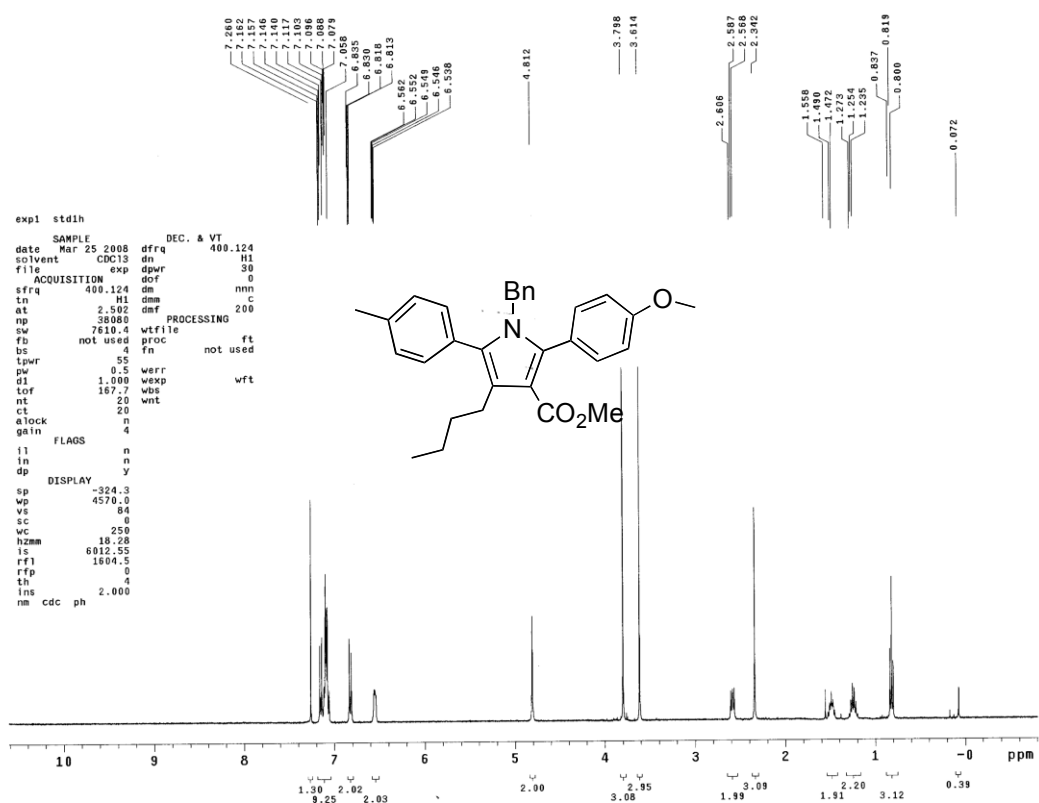


Table 3.2, entry 3



Summary of NOEs with spectrum of key correlation (*) provided

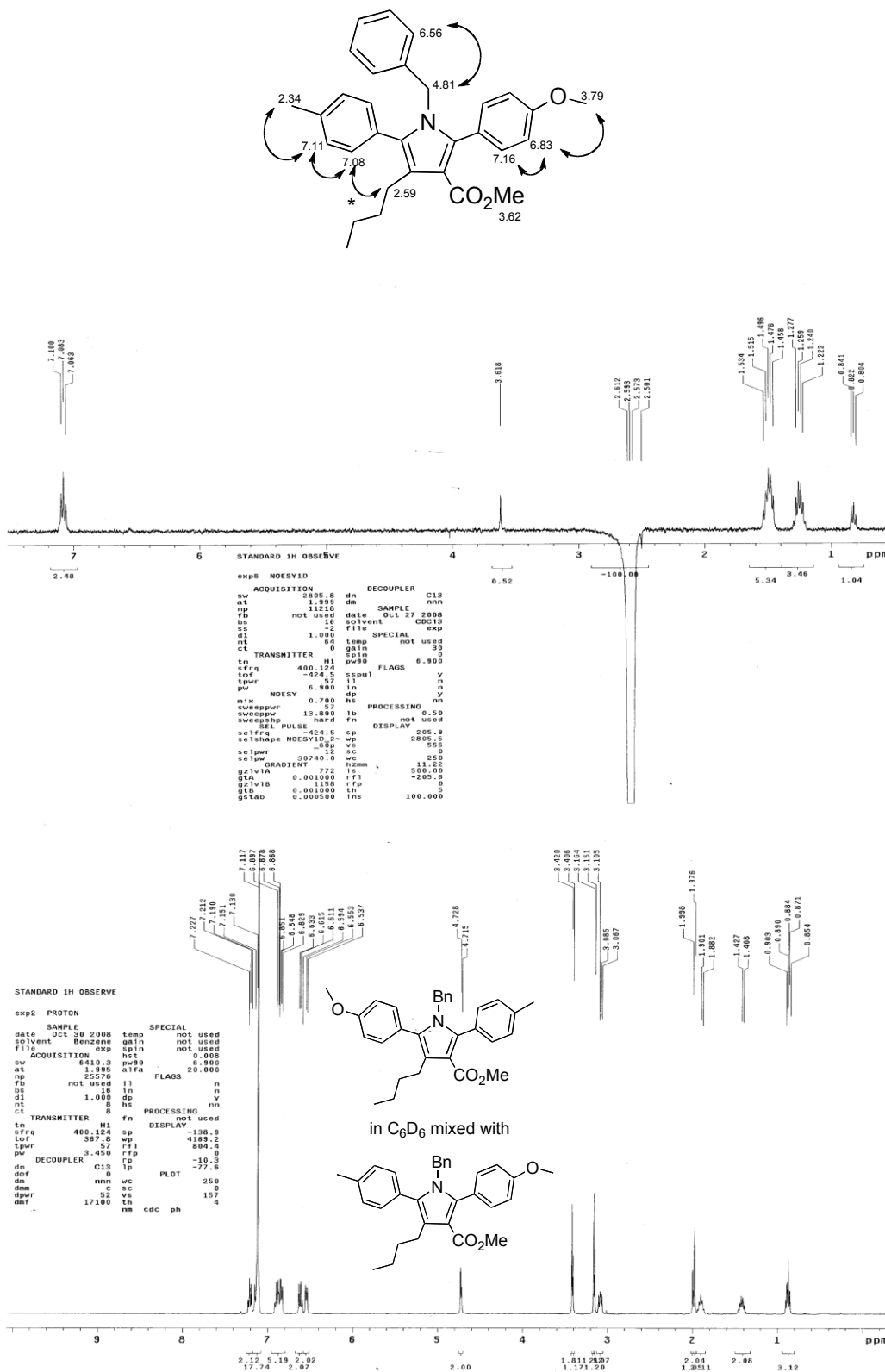
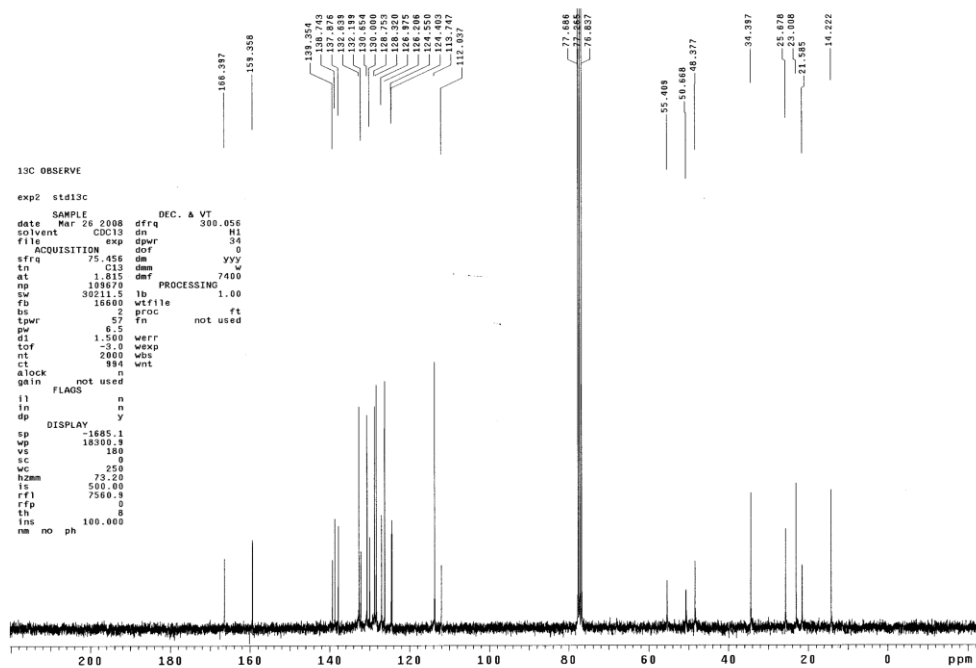
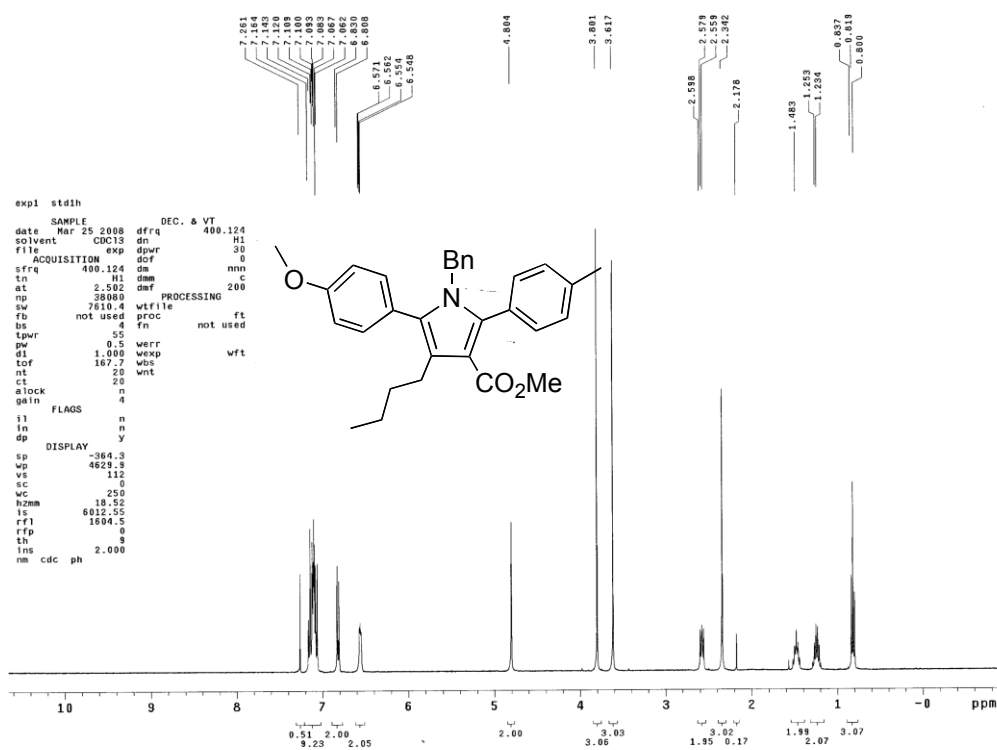
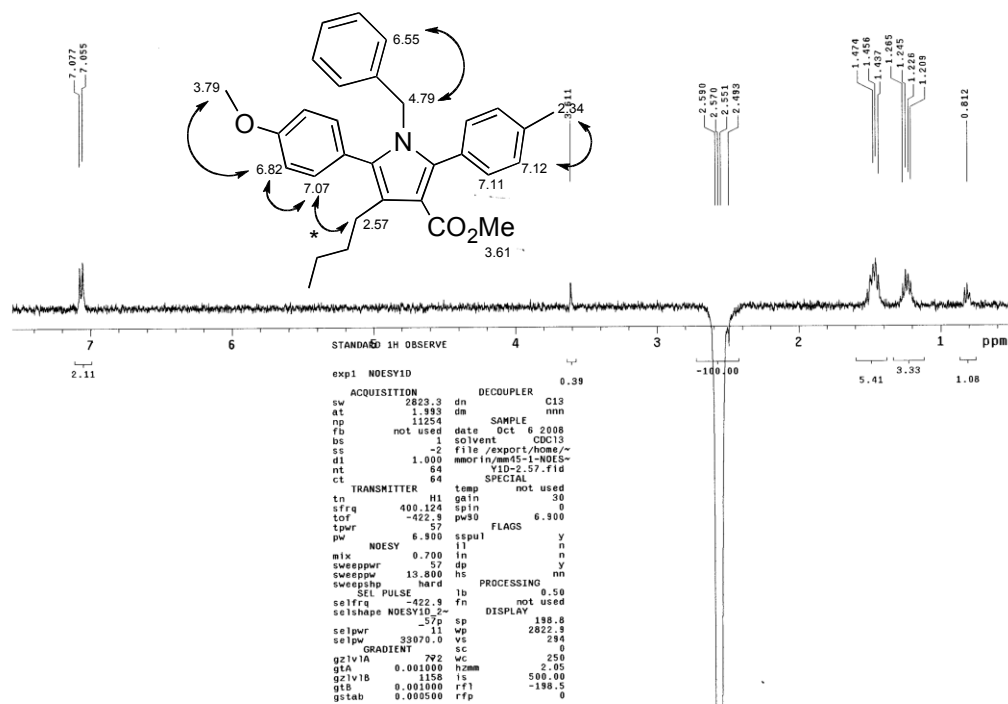


Table 3.2, entry 6



Summary of NOEs with spectrum of key correlation (*) provided



Chemical Structure: Methyl 2-(4-methoxyphenyl)-3-phenyl-5-(4-phenylphenyl)-1H-imidazole-4-carboxylate

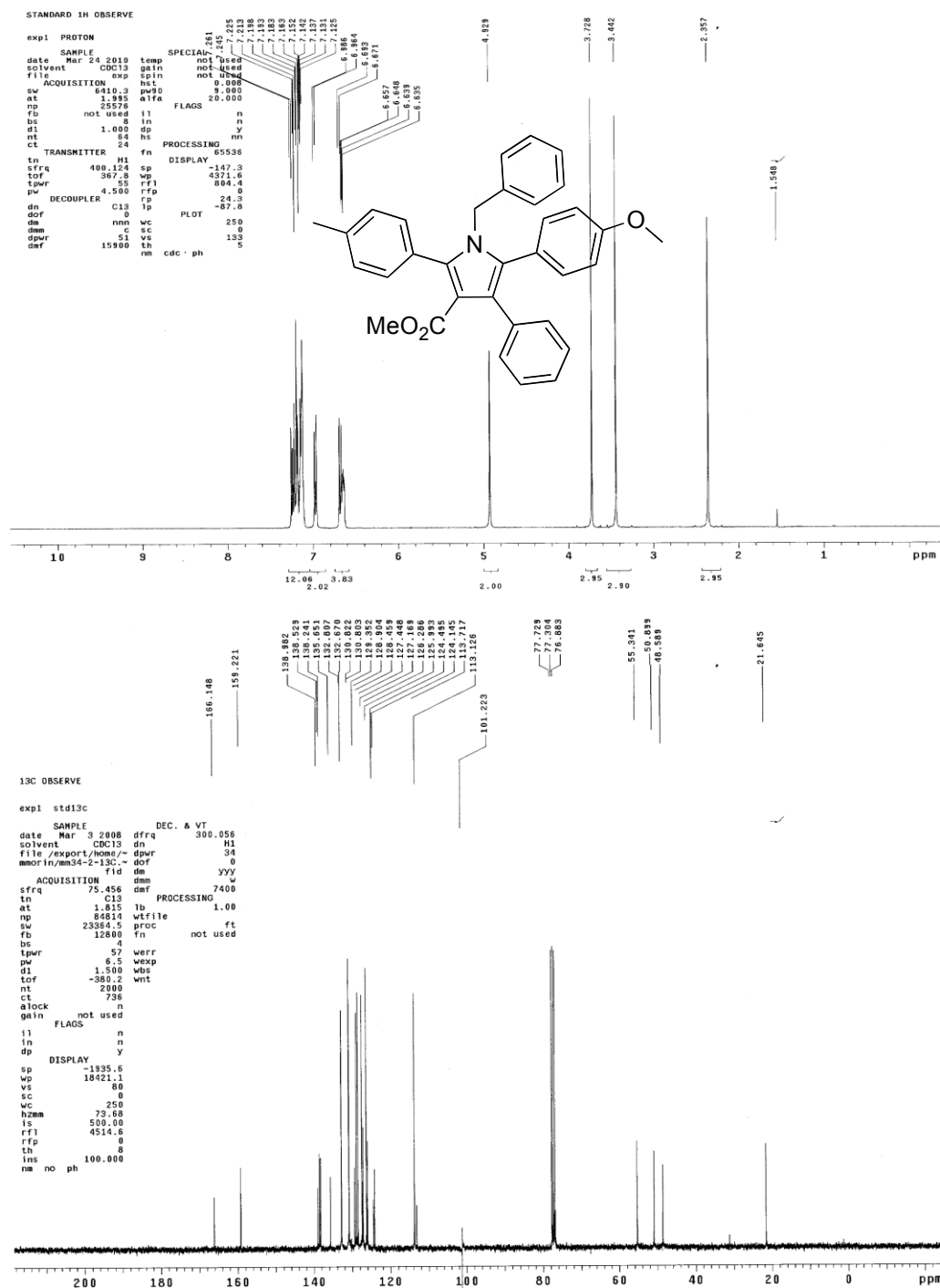
¹H NMR (400 MHz, CDCl₃):

Chemical Shift (ppm)	Integration
7.260, 7.248, 7.243, 7.240, 7.226, 7.194, 7.179, 7.143, 7.138, 7.130, 7.125, 7.120, 6.982, 6.967, 6.941, 6.908, 6.887, 6.868, 6.828, 6.822	11.28, 1.87, 3.70, 2.07
4.832	2.00
3.809, 3.436	2.89, 2.96
2.253	3.04

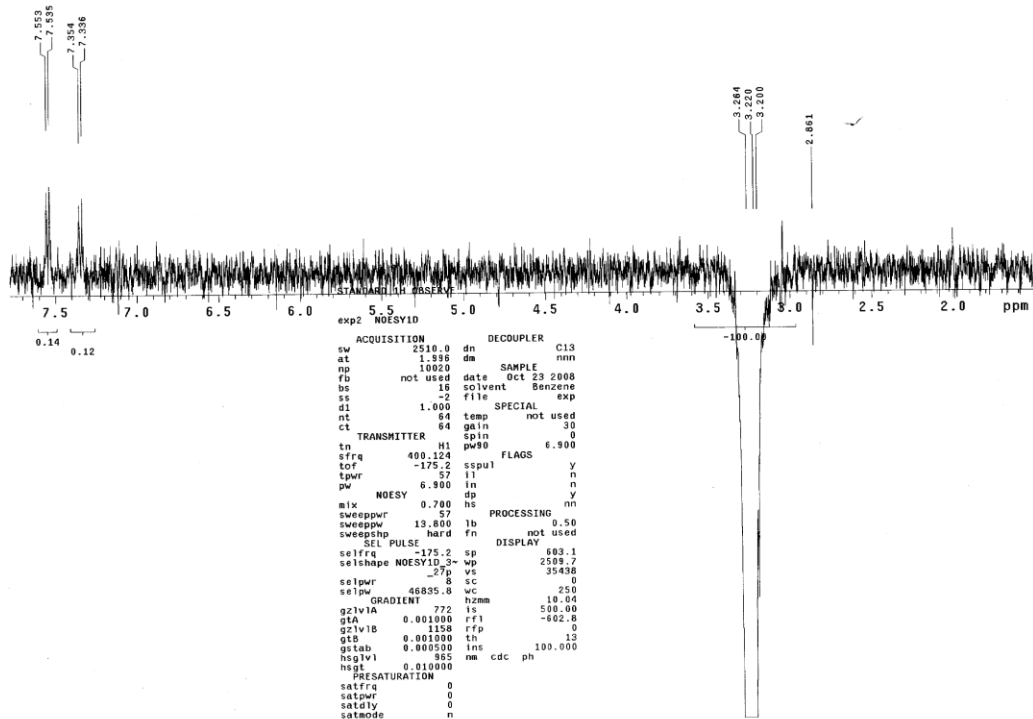
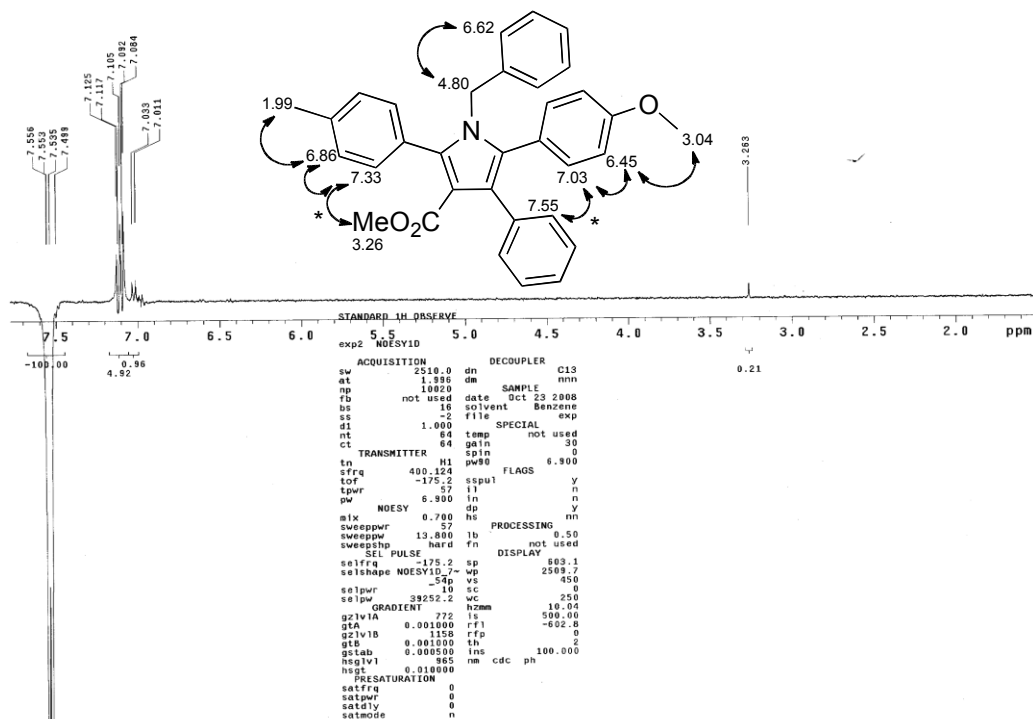
¹³C NMR (100 MHz, CDCl₃):

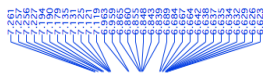
Chemical Shift (ppm)
166.094, 159.673
146.024, 145.994, 145.964, 145.934, 145.904, 145.874, 145.844, 145.814, 145.784, 145.754, 145.724, 145.694, 145.664, 145.634, 145.604, 145.574, 145.544, 145.514, 145.484, 145.454, 145.424, 145.394, 145.364, 145.334, 145.304, 145.274, 145.244, 145.214, 145.184, 145.154, 145.124, 145.094, 145.064, 145.034, 145.004, 144.974, 144.944, 144.914, 144.884, 144.854, 144.824, 144.794, 144.764, 144.734, 144.704, 144.674, 144.644, 144.614, 144.584, 144.554, 144.524, 144.494, 144.464, 144.434, 144.404, 144.374, 144.344, 144.314, 144.284, 144.254, 144.224, 144.194, 144.164, 144.134, 144.104, 144.074, 144.044, 144.014, 143.984, 143.954, 143.924, 143.894, 143.864, 143.834, 143.804, 143.774, 143.744, 143.714, 143.684, 143.654, 143.624, 143.594, 143.564, 143.534, 143.504, 143.474, 143.444, 143.414, 143.384, 143.354, 143.324, 143.294, 143.264, 143.234, 143.204, 143.174, 143.144, 143.114, 143.084, 143.054, 143.024, 142.994, 142.964, 142.934, 142.904, 142.874, 142.844, 142.814, 142.784, 142.754, 142.724, 142.694, 142.664, 142.634, 142.604, 142.574, 142.544, 142.514, 142.484, 142.454, 142.424, 142.394, 142.364, 142.334, 142.304, 142.274, 142.244, 142.214, 142.184, 142.154, 142.124, 142.094, 142.064, 142.034, 142.004, 141.974, 141.944, 141.914, 141.884, 141.854, 141.824, 141.794, 141.764, 141.734, 141.704, 141.674, 141.644, 141.614, 141.584, 141.554, 141.524, 141.494, 141.464, 141.434, 141.404, 141.374, 141.344, 141.314, 141.284, 141.254, 141.224, 141.194, 141.164, 141.134, 141.104, 141.074, 141.044, 141.014, 140.984, 140.954, 140.924, 140.894, 140.864, 140.834, 140.804, 140.774, 140.744, 140.714, 140.684, 140.654, 140.624, 140.594, 140.564, 140.534, 140.504, 140.474, 140.444, 140.414, 140.384, 140.354, 140.324, 140.294, 140.264, 140.234, 140.204, 140.174, 140.144, 140.114, 140.084, 140.054, 140.024, 140.004, 139.974, 139.944, 139.914, 139.884, 139.854, 139.824, 139.794, 139.764, 139.734, 139.704, 139.674, 139.644, 139.614, 139.584, 139.554, 139.524, 139.494, 139.464, 139.434, 139.404, 139.374, 139.344, 139.314, 139.284, 139.254, 139.224, 139.194, 139.164, 139.134, 139.104, 139.074, 139.044, 139.014, 138.984, 138.954, 138.924, 138.894, 138.864, 138.834, 138.804, 138.774, 138.744, 138.714, 138.684, 138.654, 138.624, 138.594, 138.564, 138.534, 138.504, 138.474, 138.444, 138.414, 138.384, 138.354, 138.324, 138.294, 138.264, 138.234, 138.204, 138.174, 138.144, 138.114, 138.084, 138.054, 138.024, 138.004, 137.974, 137.944, 137.914, 137.884, 137.854, 137.824, 137.794, 137.764, 137.734, 137.704, 137.674, 137.644, 137.614, 137.584, 137.554, 137.524, 137.494, 137.464, 137.434, 137.404, 137.374, 137.344, 137.314, 137.284, 137.254, 137.224, 137.194, 137.164, 137.134, 137.104, 137.074, 137.044, 137.014, 136.984, 136.954, 136.924, 136.894, 136.864, 136.834, 136.804, 136.774, 136.744, 136.714, 136.684, 136.654, 136.624, 136.594, 136.564, 136.534, 136.504, 136.474, 136.444, 136.414, 136.384, 136.354, 136.324, 136.294, 136.264, 136.234, 136.204, 136.174, 136.144, 136.114, 136.084, 136.054, 136.024, 136.004, 135.974, 135.944, 135.914, 135.884, 135.854, 135.824, 135.794, 135.764, 135.734, 135.704, 135.674, 135.644, 135.614, 135.584, 135.554, 135.524, 135.494, 135.464, 135.434, 135.404, 135.374, 135.344, 135.314, 135.284, 135.254, 135.224, 135.194, 135.164, 135.134, 135.104, 135.074, 135.044, 135.014, 135.004, 134.974, 134.944, 134.914, 134.884, 134.854, 134.824, 134.794, 134.764, 134.734, 134.704,

Scheme 3.4, pyrrole of alkyne **3.7** (Minor isomer) CDCl₃

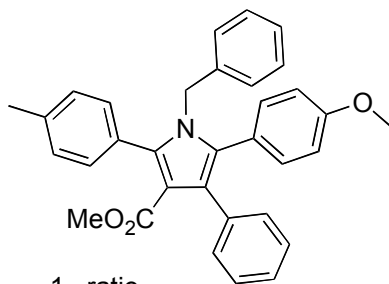
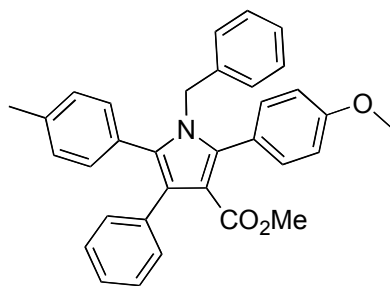


Summary of NOEs in C₆D₆ with spectra of key correlation (*) provided

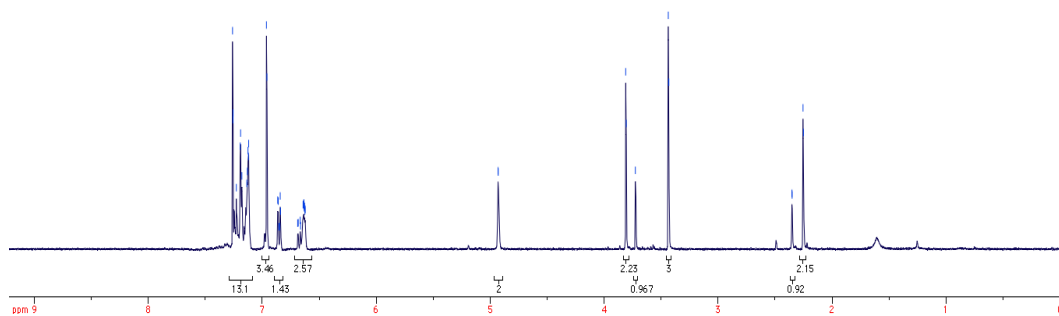




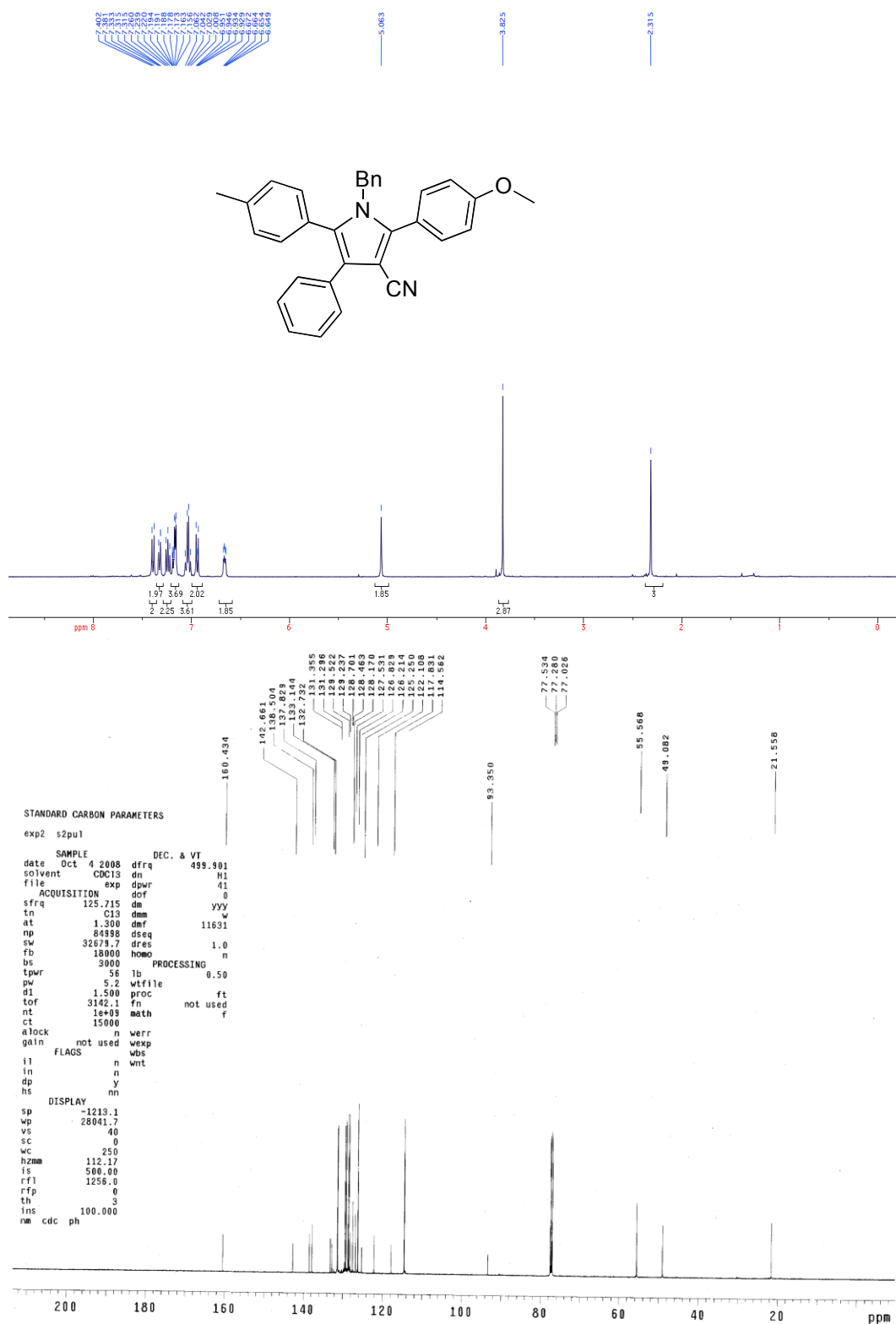
Mixed in CDCl₃



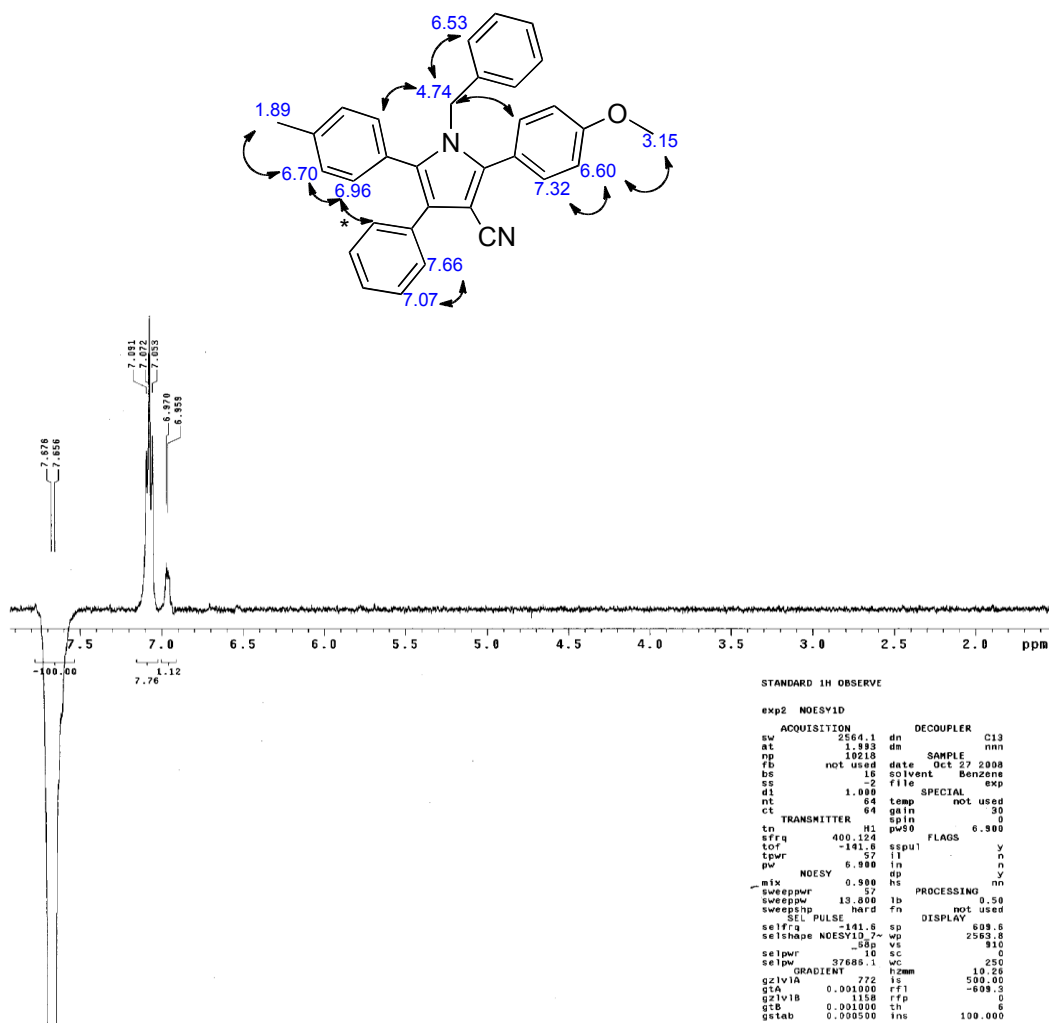
2 : 1 ratio



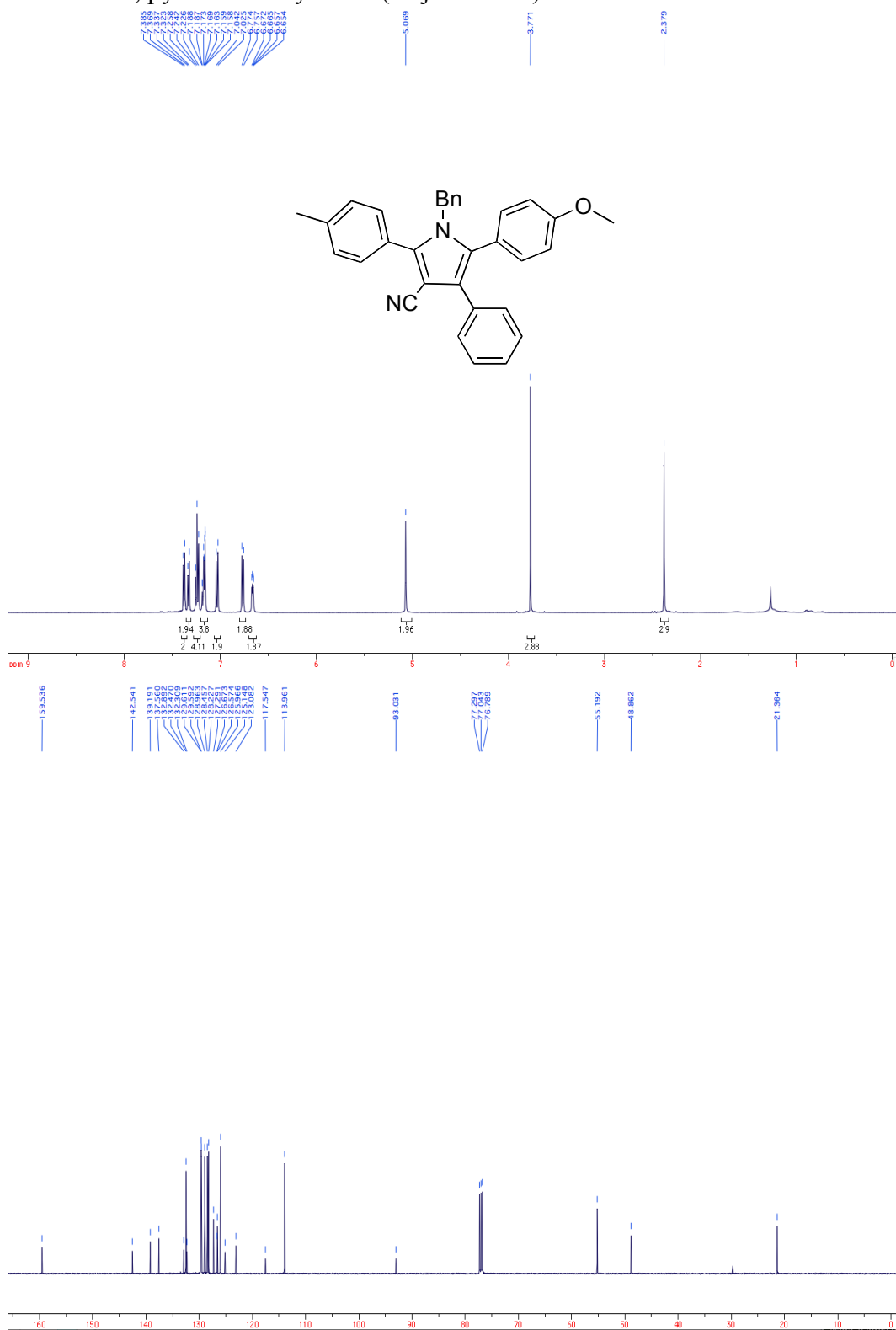
Scheme 3.4, pyrrole of alkyne **3.8** (minor isomer) CDCl₃



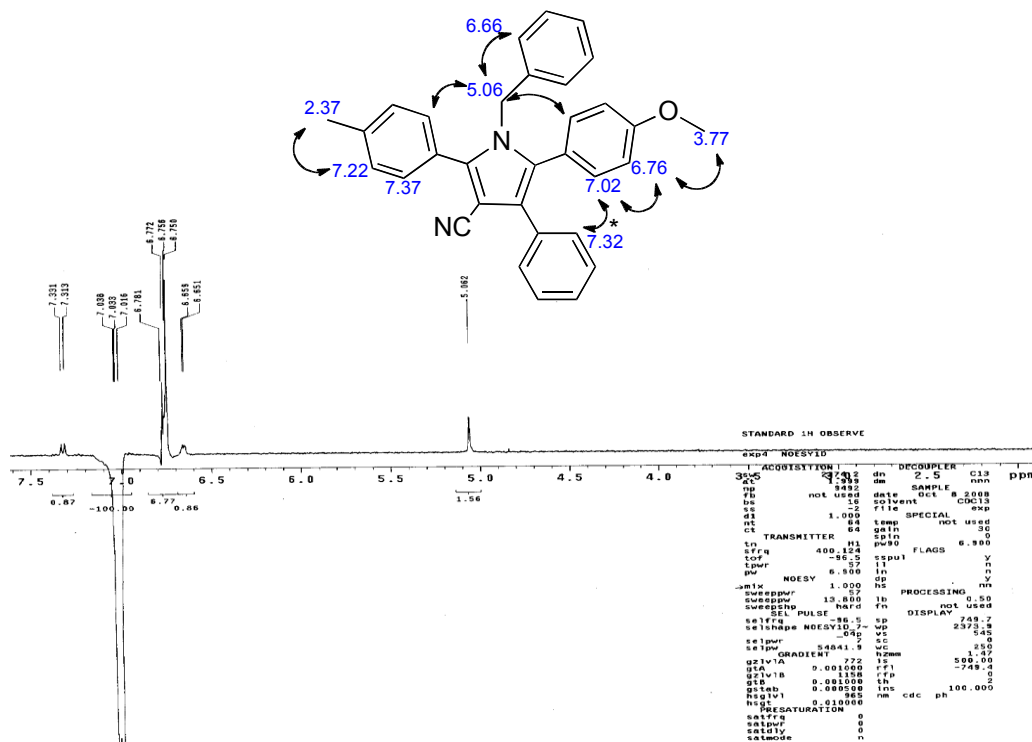
Summary of NOEs in C₆D₆ with spectrum of key correlation (*) provided



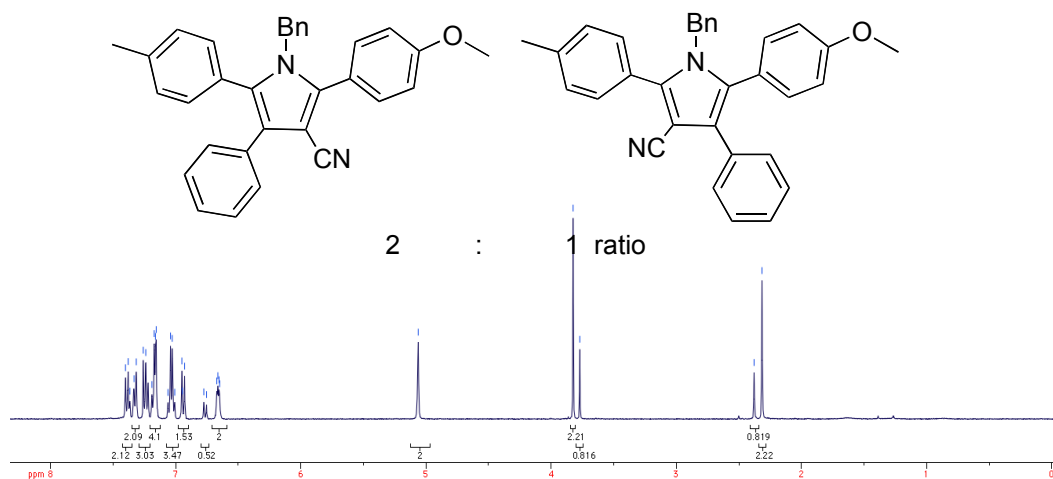
Scheme 3.4, pyrrole of alkyne **3.8** (major isomer)



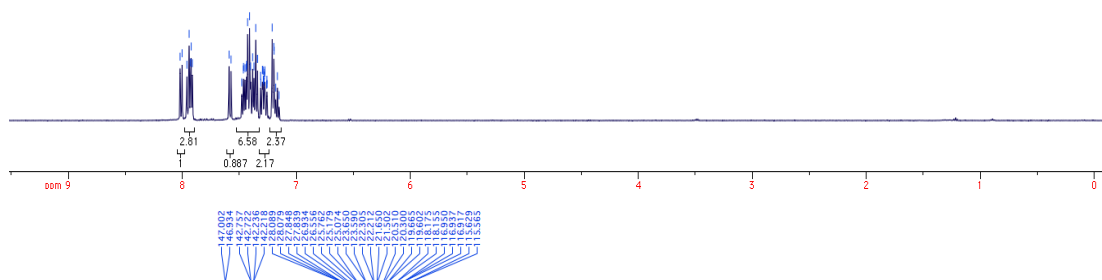
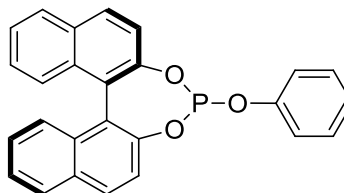
Summary of NOEs in CDCl₃ with spectrum of key correlation (*) provided



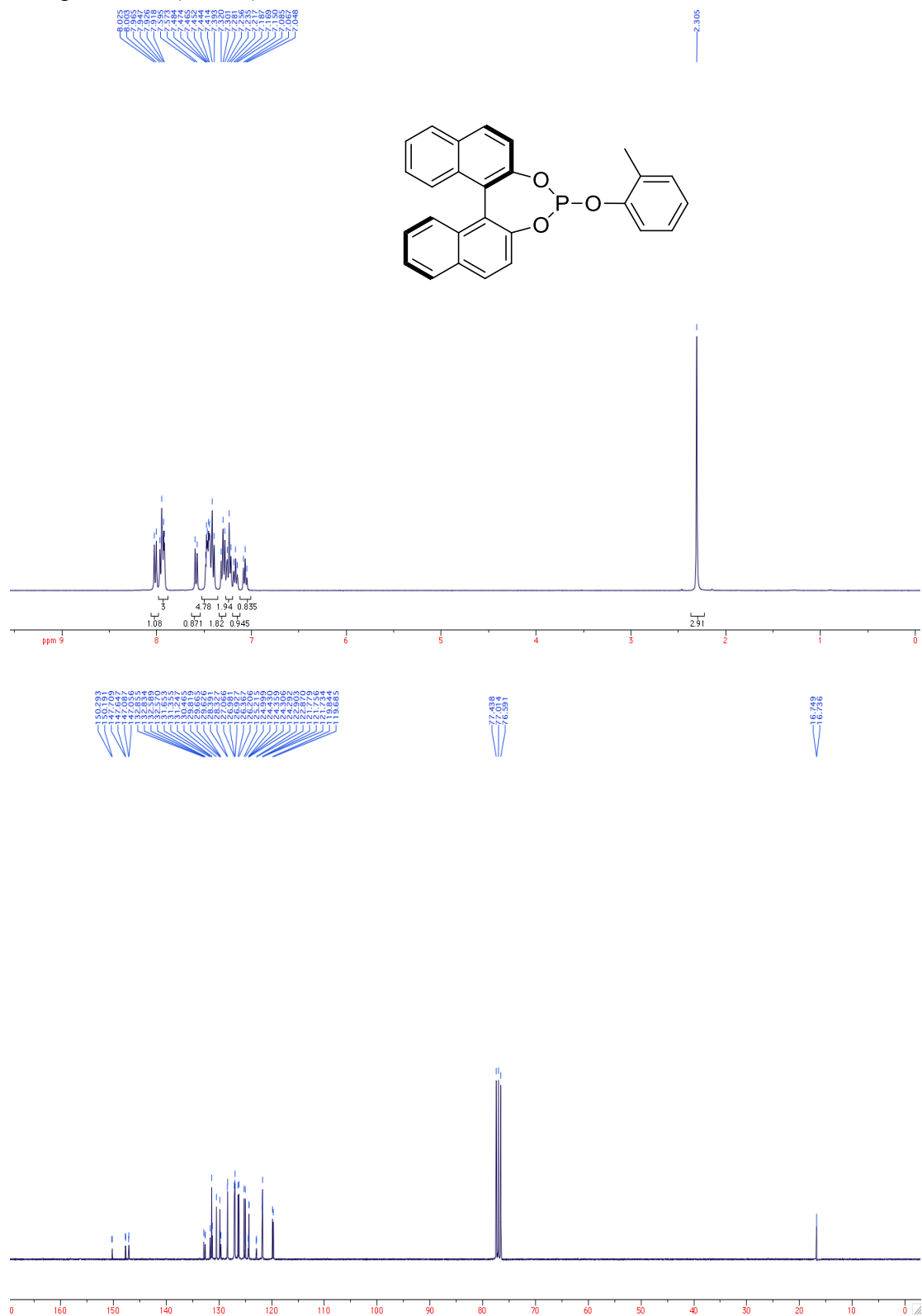
in CDCl₃, mixed



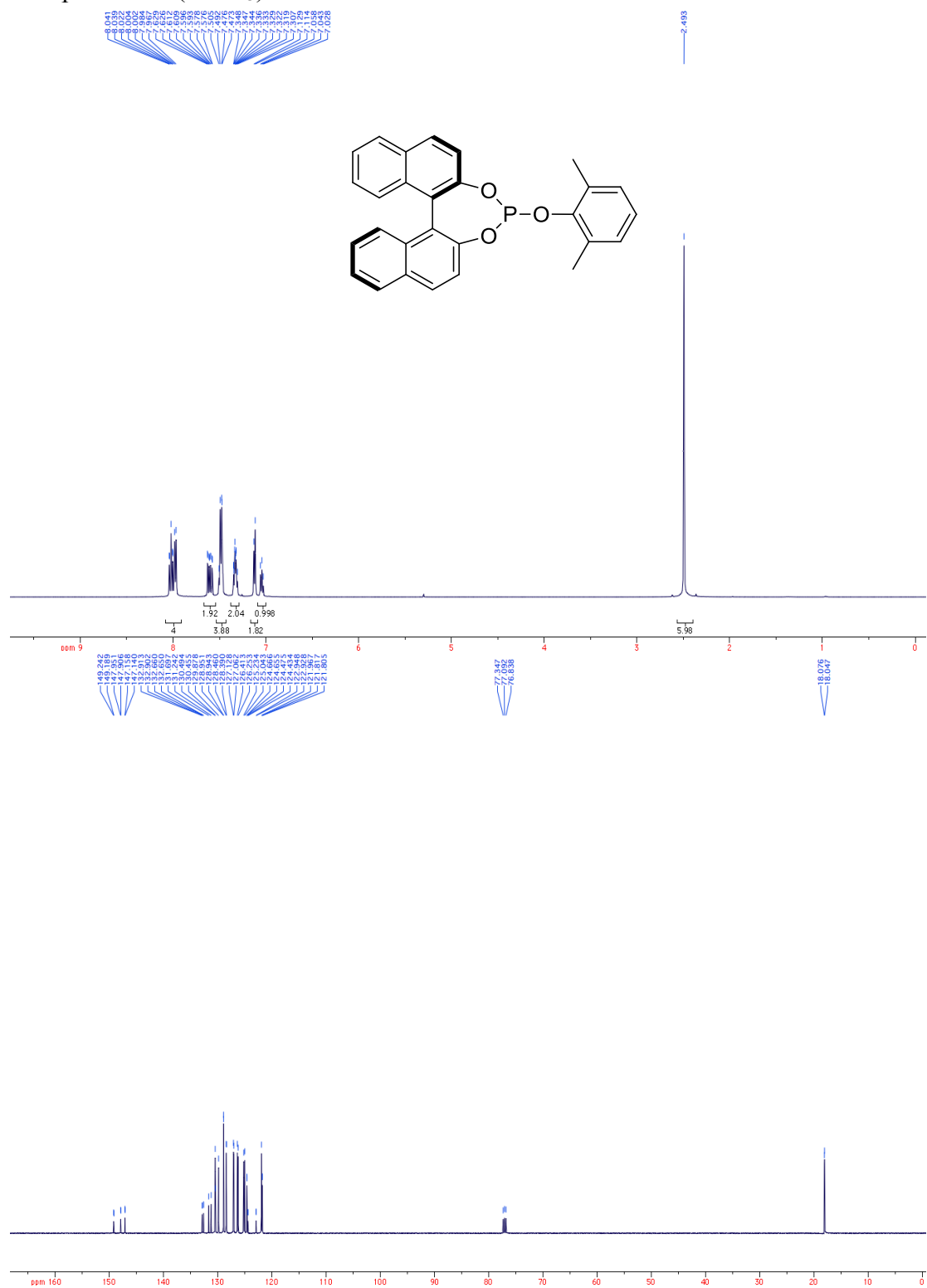
Phosphite **5.3b** (CDCl₃)



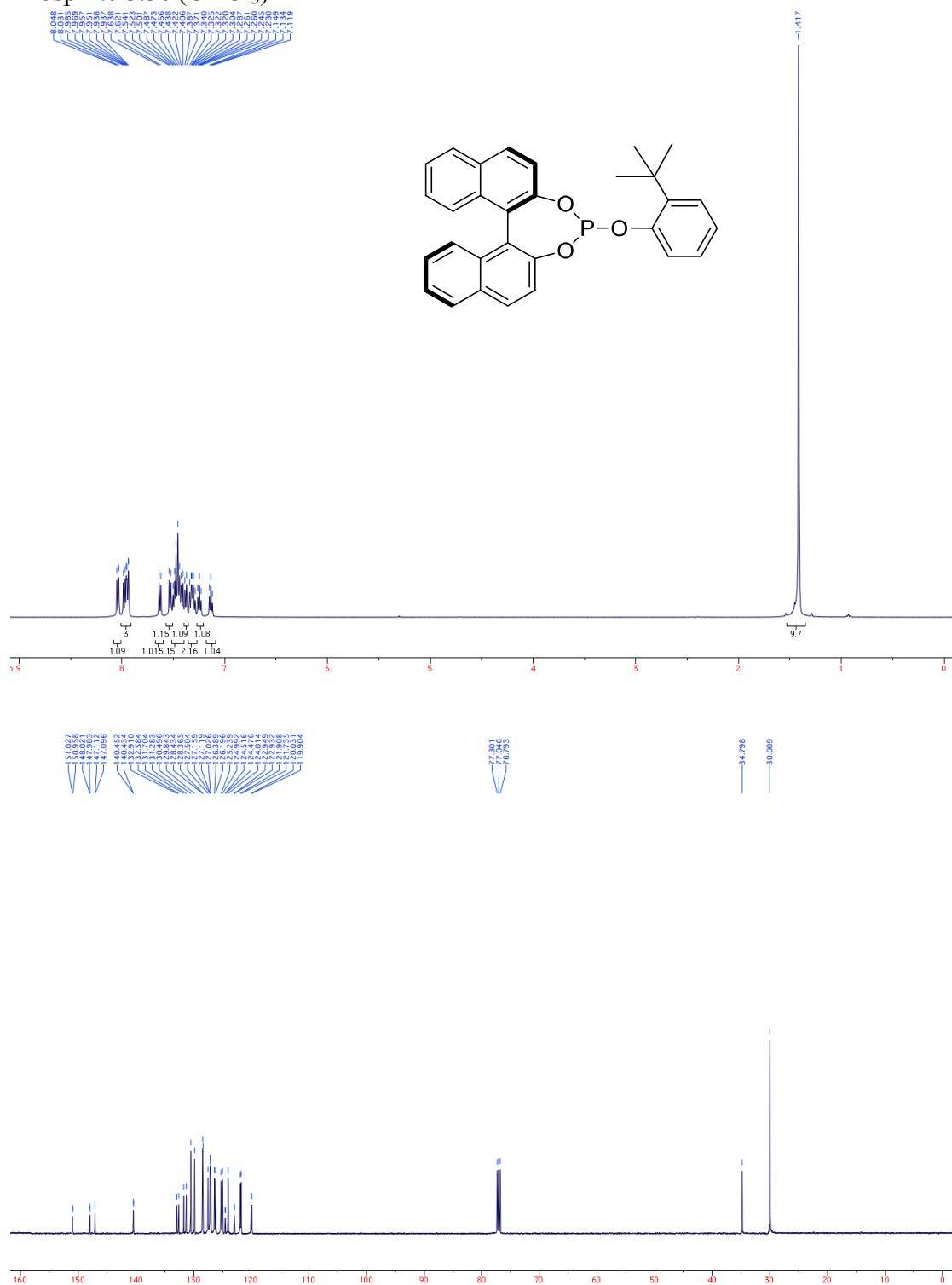
Phosphite **5.3c** (CDCl₃)



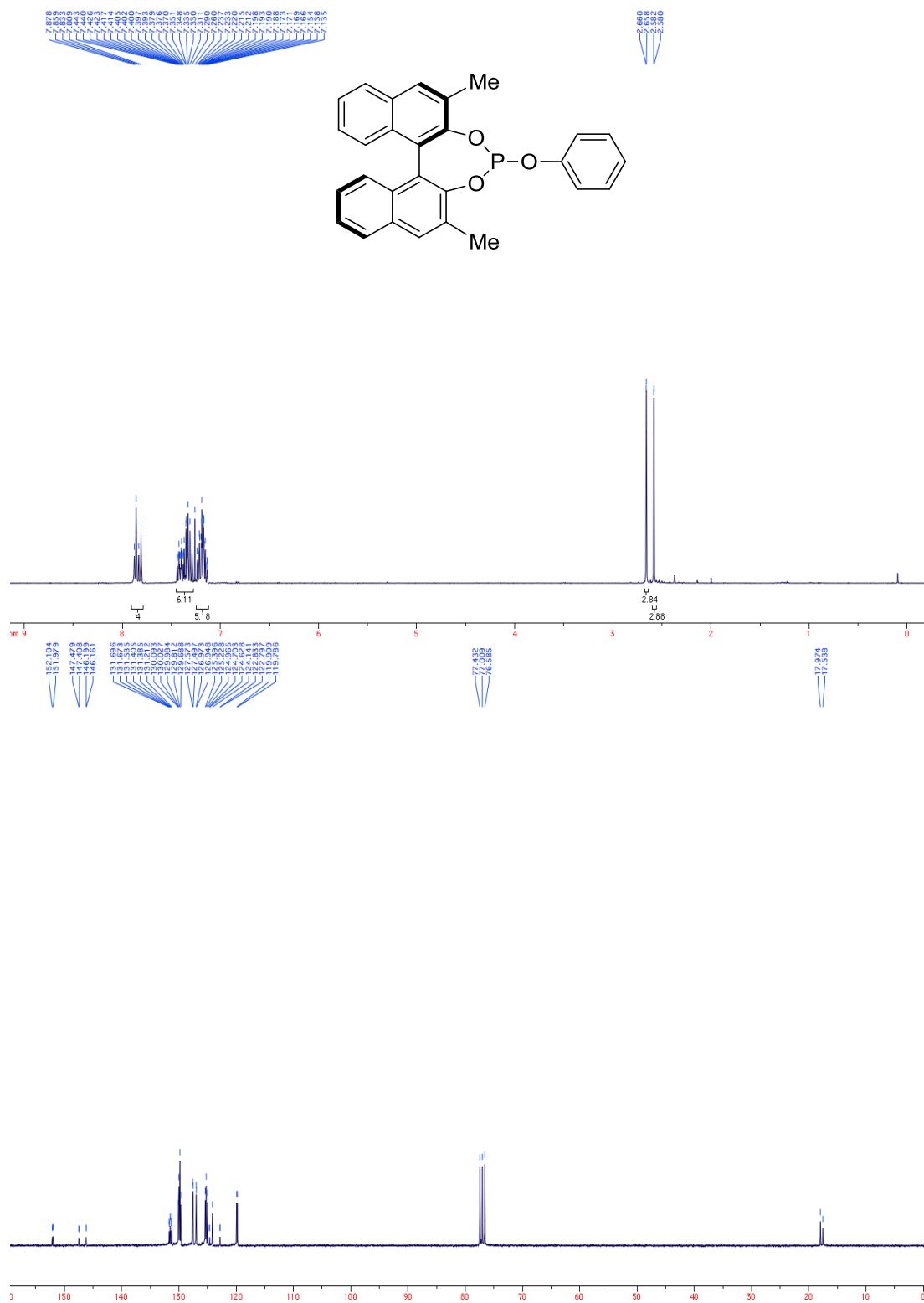
Phosphite **5.3d** (CDCl_3)



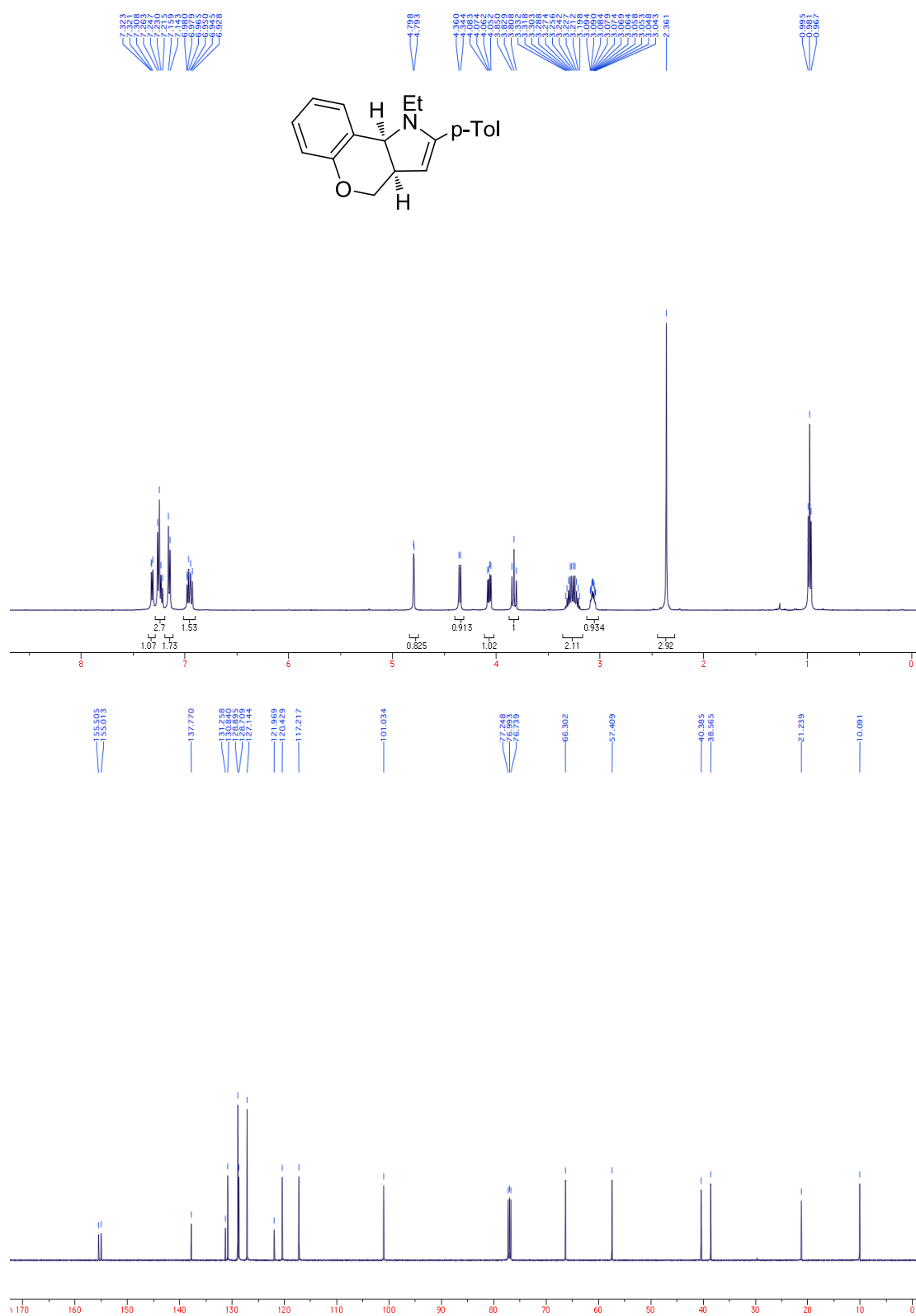
Phosphite **5.3e** (CDCl₃)



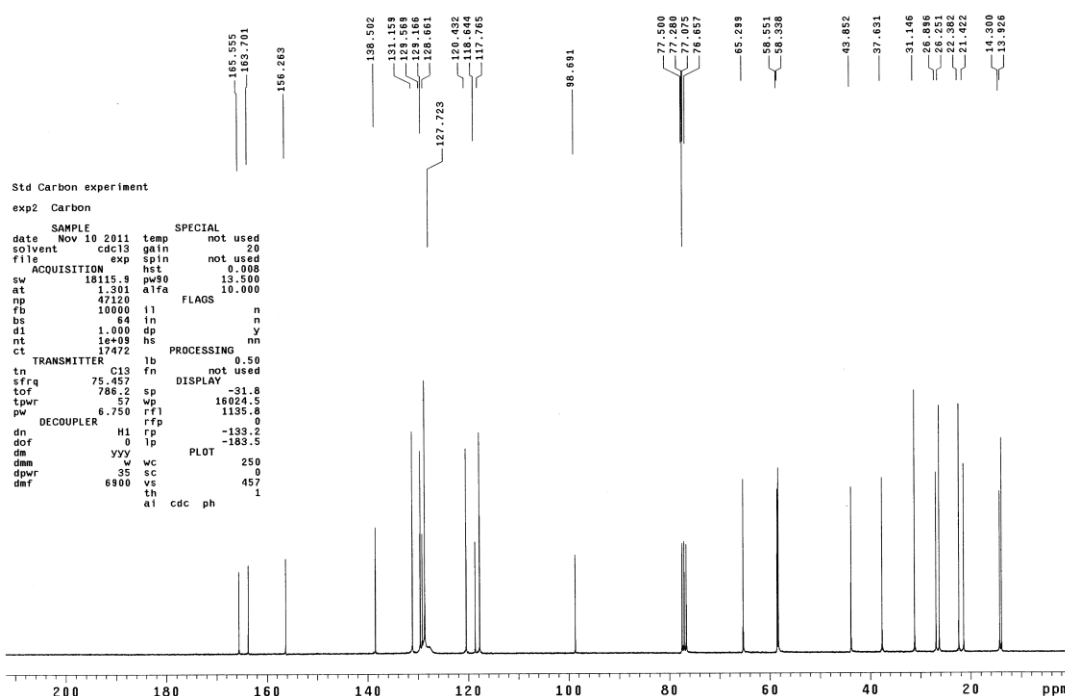
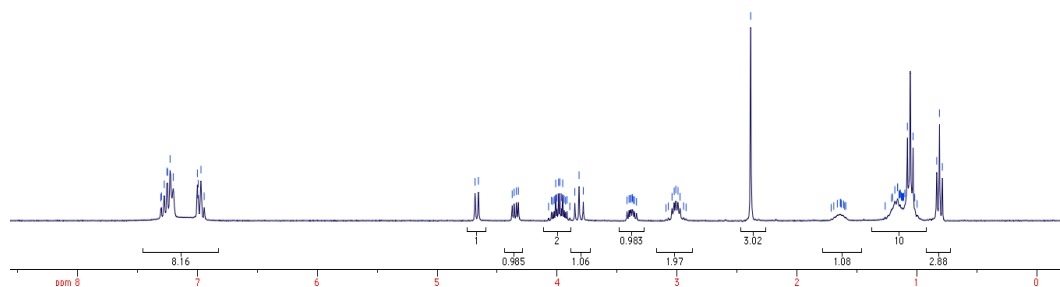
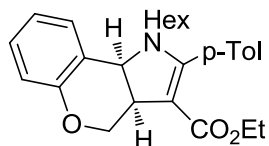
Phosphite **5.3f** (CDCl₃)



Pyrroline **5.5a** (CDCl₃)



Pyrroline **5.5b** (CDCl₃)



7.380
7.352
7.323
7.293
7.260
7.221
7.190
7.158
7.123
7.088
7.054
6.986
6.947
6.939
6.936
6.936
6.916
6.905
6.905
6.905
6.895
6.882
6.882
6.855
6.837
6.818
6.805
4.780
4.760
4.504
4.484
4.386
4.384
4.327
4.221
4.178
4.150
4.101
4.082
4.074
4.065
4.051
4.041
4.033
4.024
4.024
4.006
4.006
3.888
3.888
3.836
3.806
3.781
3.558
3.548
3.536
3.526
3.514
3.502

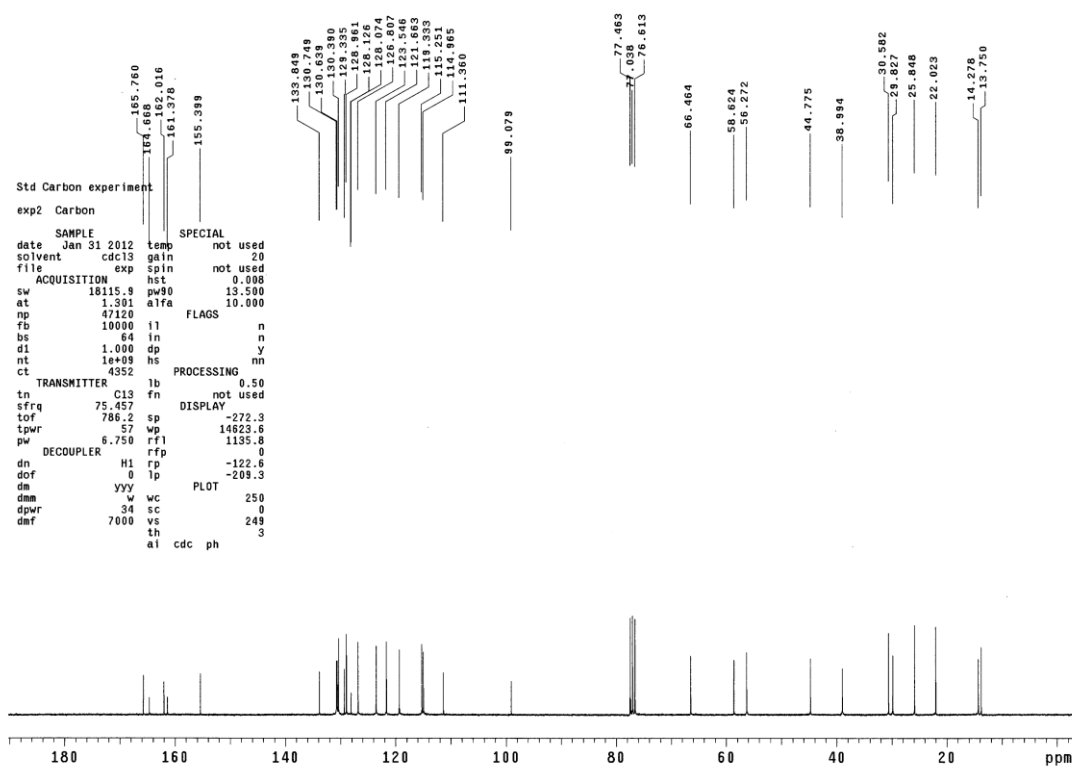
Std Proton parameters
exp2 Proton

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file 51
ACQUISITION
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tn H1 dmm C
at 1.995 dmf 15900
np 25582 temp 22.0
sw 6410.3 PROCESSING
fb not used wtfite ft
bs 4 proc 65536
tpwr 54 Fn
pw 0.5
dl 1.000 verr
tof 405.3 wexp
nt 512 vbs
ct 26 vnt
alock not used
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -86.7
vs 3524.2
vz 75
sc 0
wc 250
bzmm 14.10
ls 38.23
rf1 804.4
rfp 0
th 1
lms cdc ph 1.000

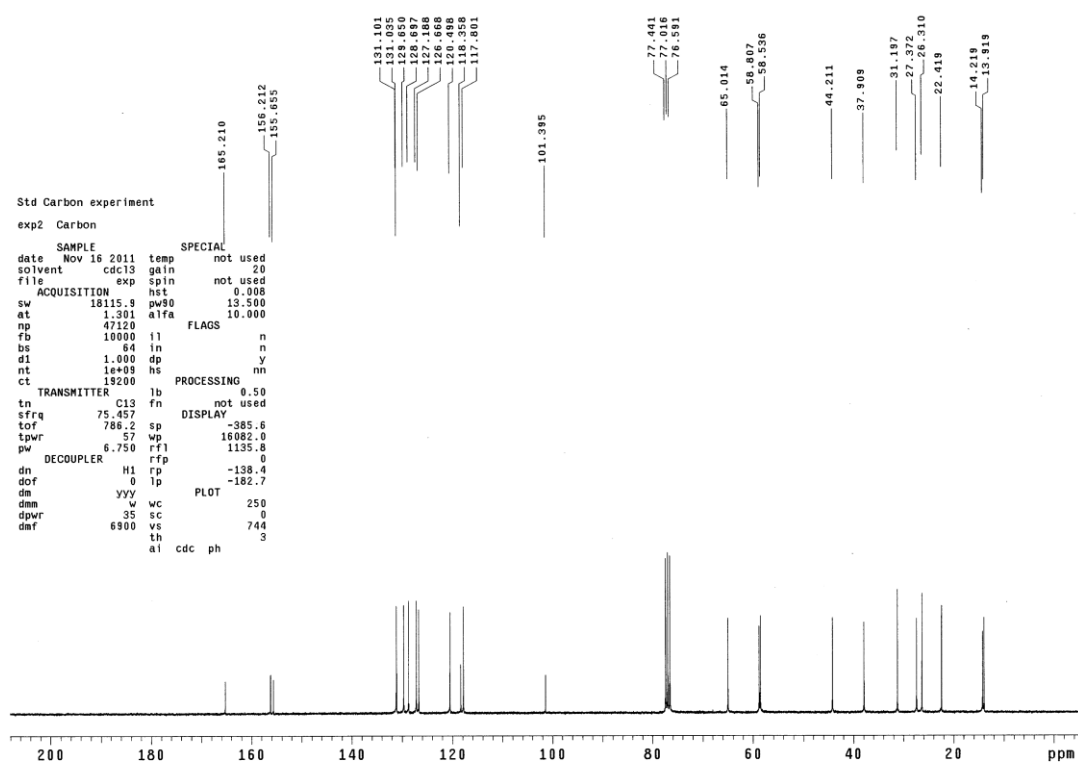
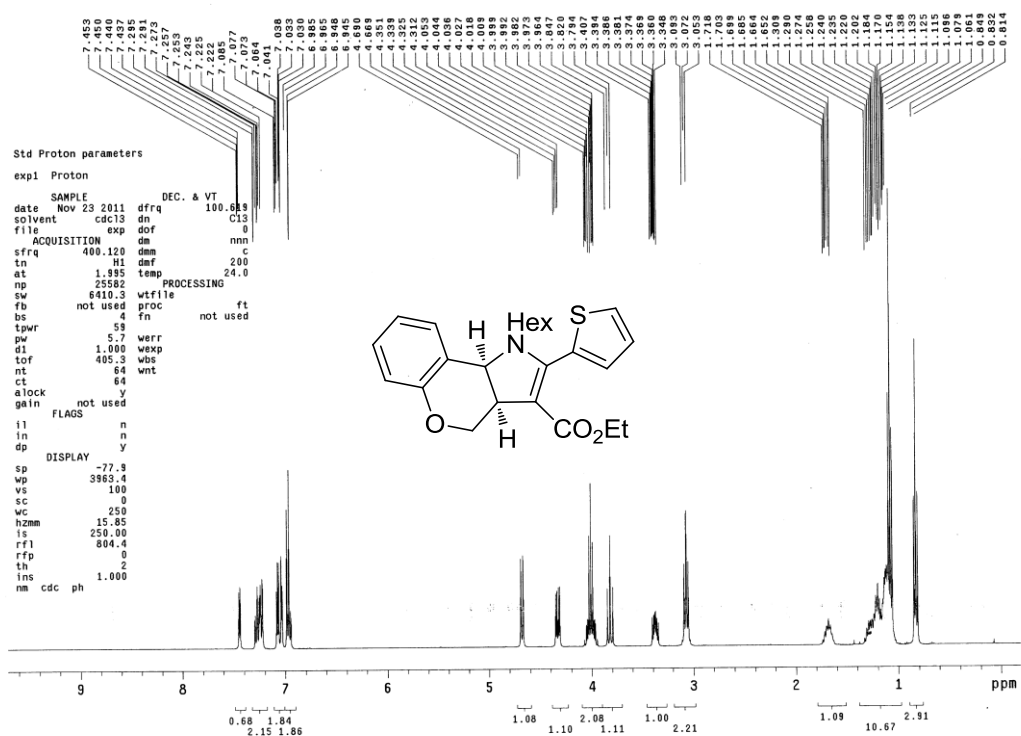
1.138
1.121
1.103

Chemical structure of PMP (1-benzyl-2-methoxy-3-methyl-4-oxo-5-phenyl-1,2,3,4-tetrahydropyridine-6-carboxylate) is shown. The structure includes a benzyl group (Bn), a methoxy group (OMe), a methyl group (Me), a carbonyl group (C=O), and a carboxylate group (CO₂Et).

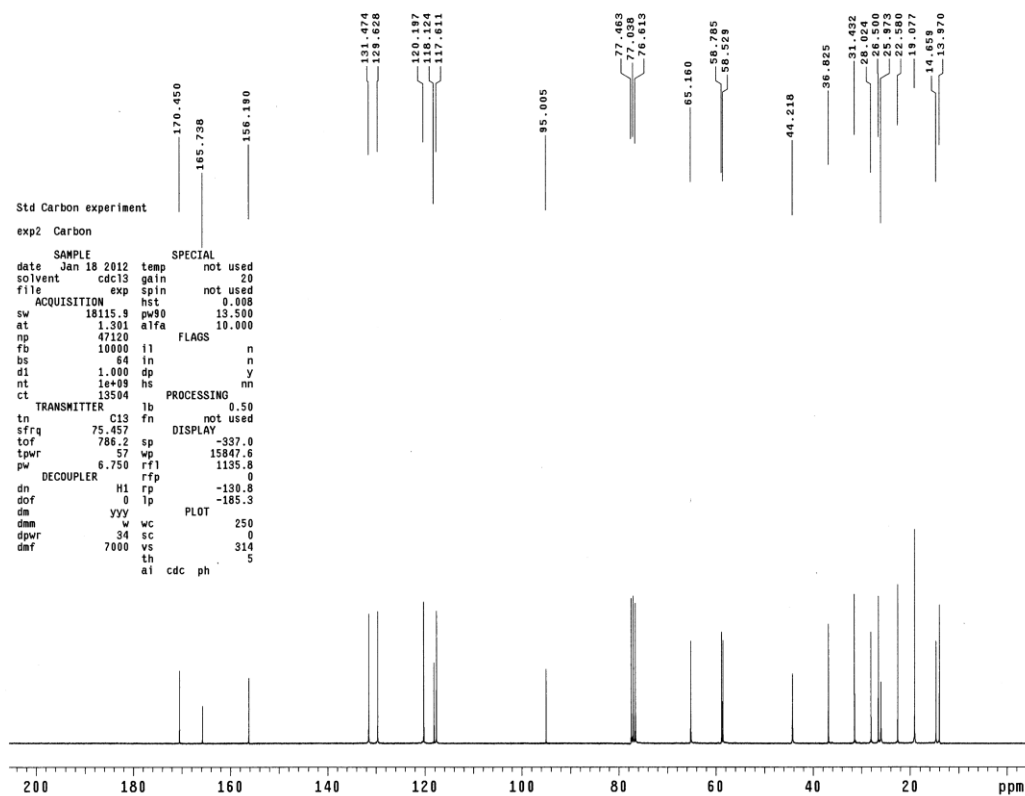
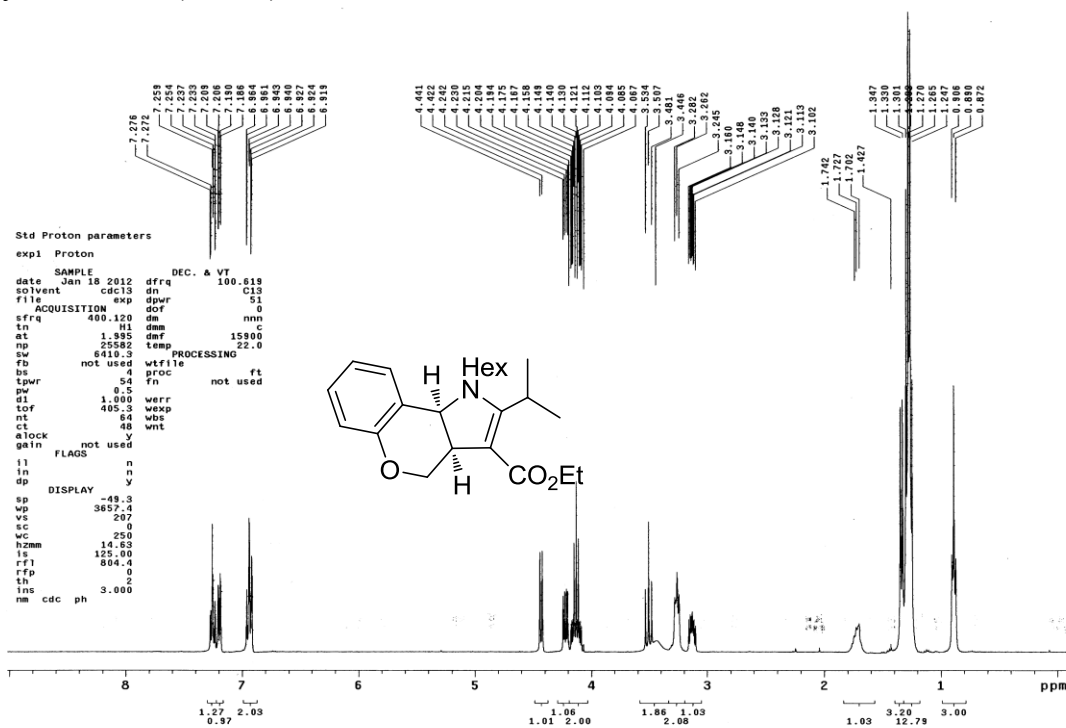
1.000
2.442 2.5 2.97
2.86 0.98.00
1.00 1.00 1.98 3.07
0.99 1.01 1.02 1.00
3.02



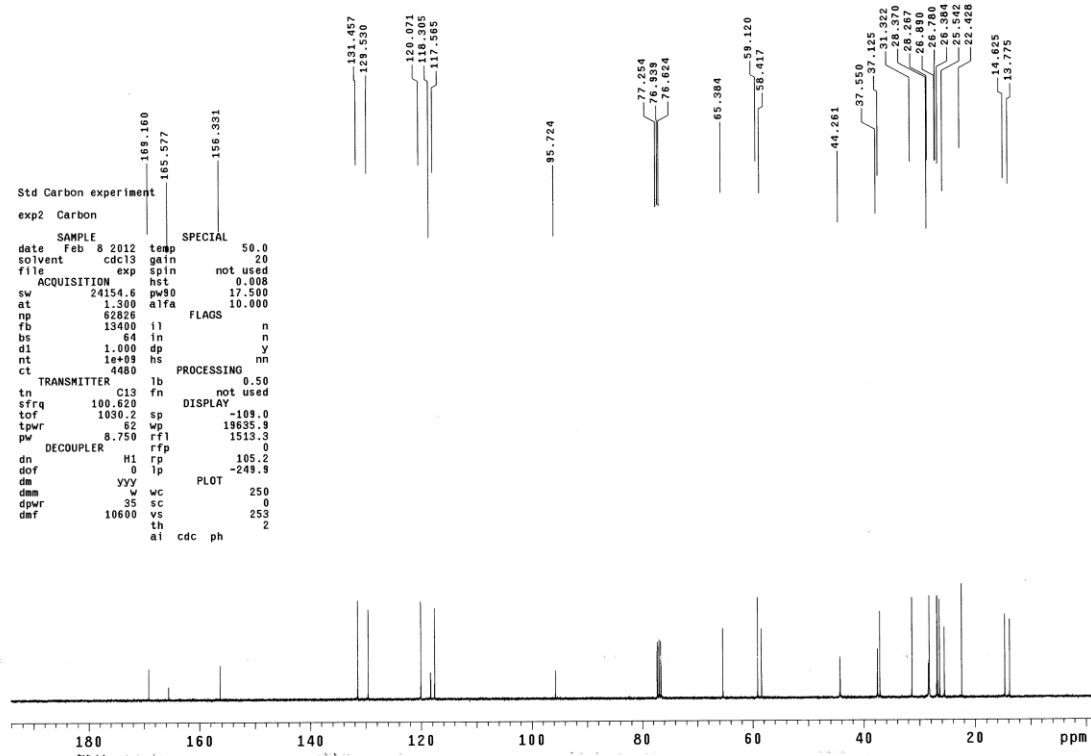
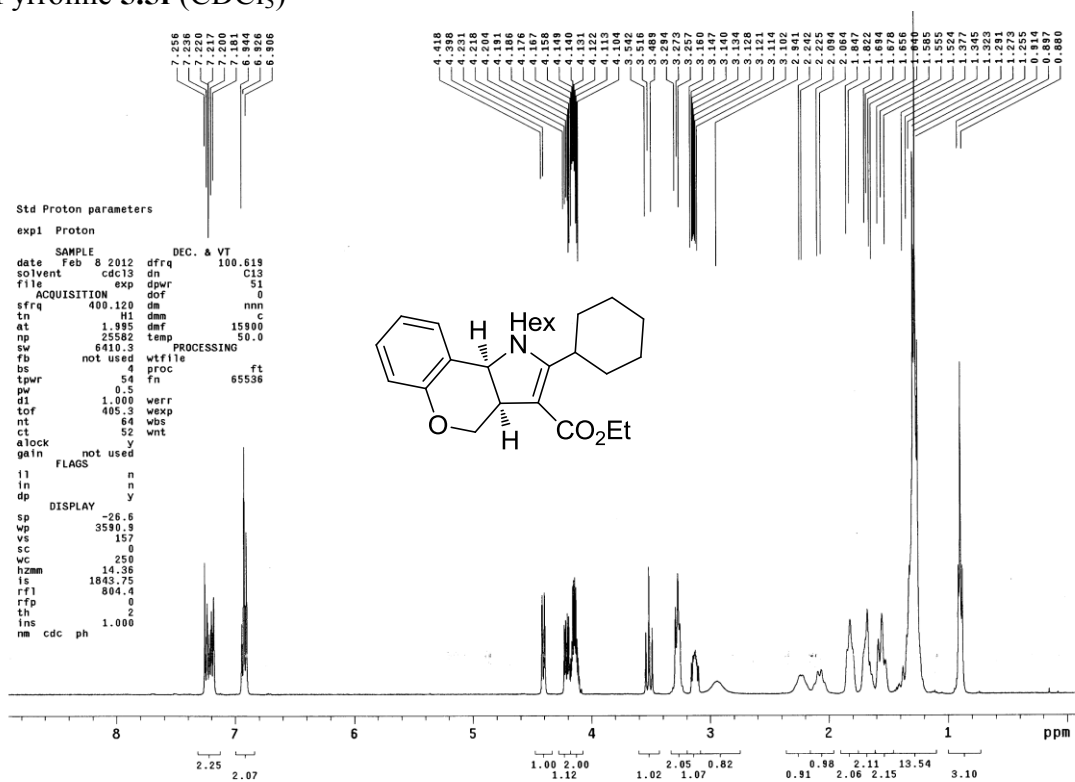
Pyrroline **5.5d** (CDCl₃)



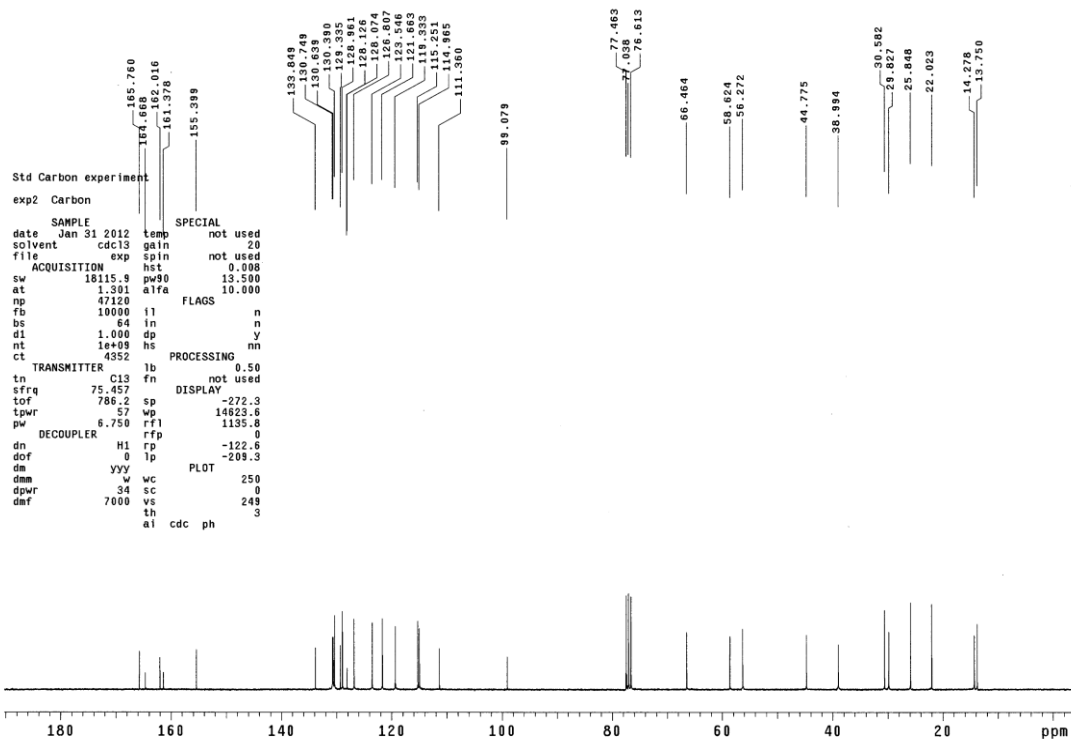
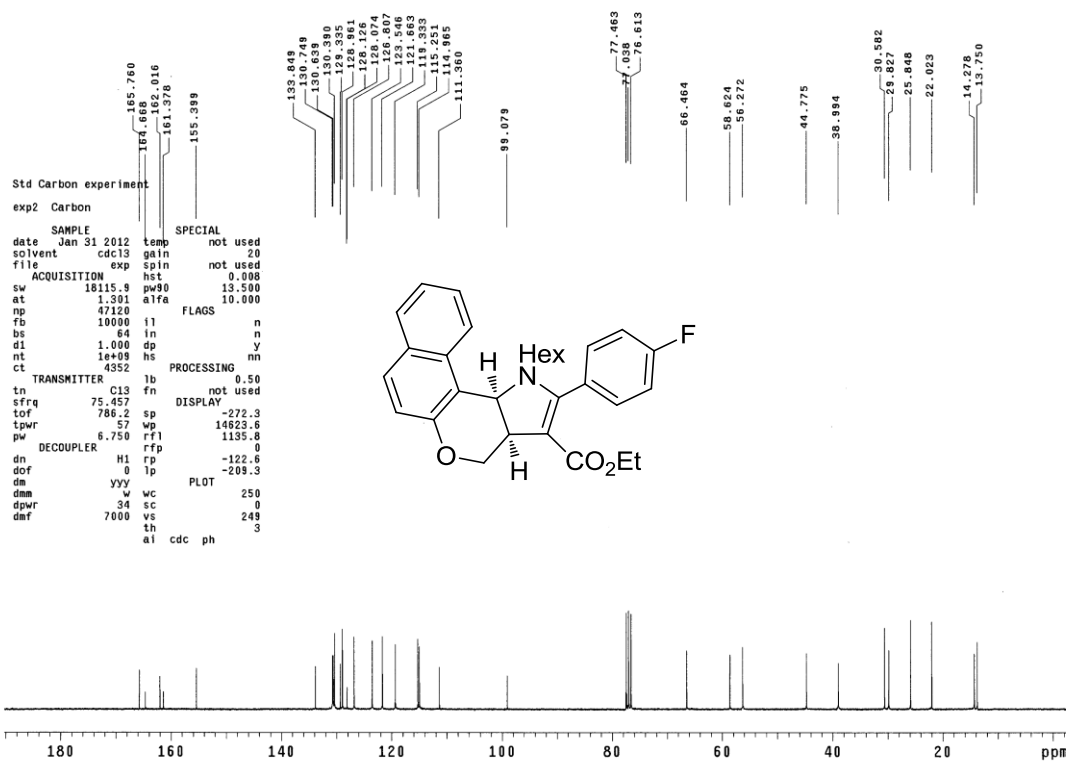
Pyrroline 5.5e (CDCl₃)



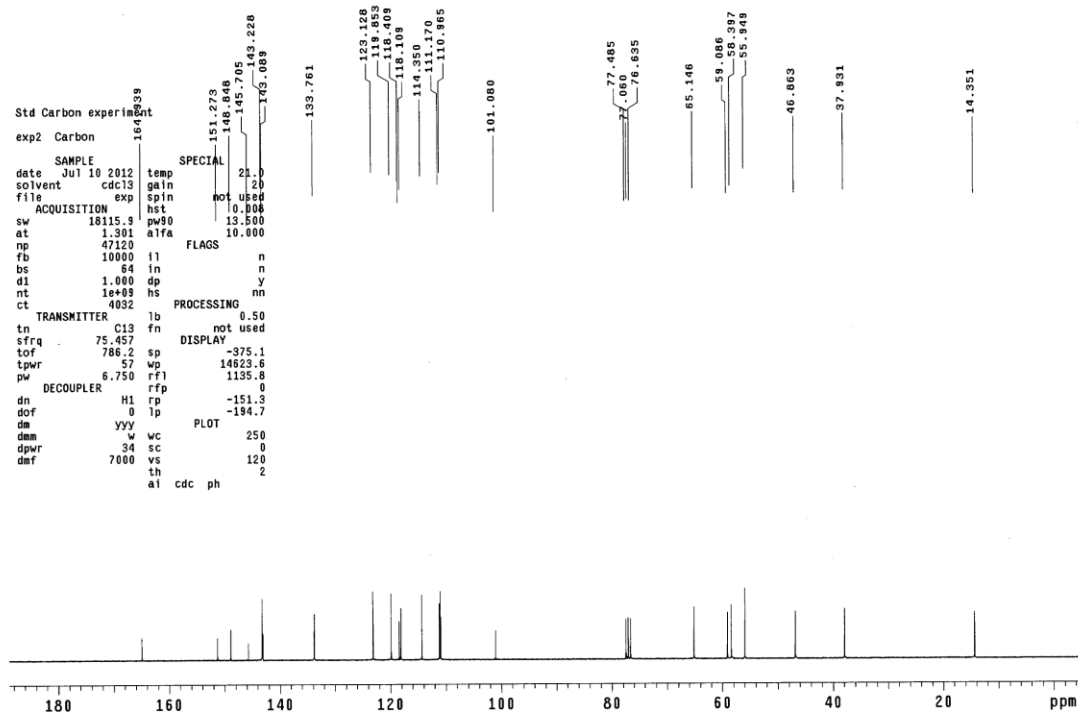
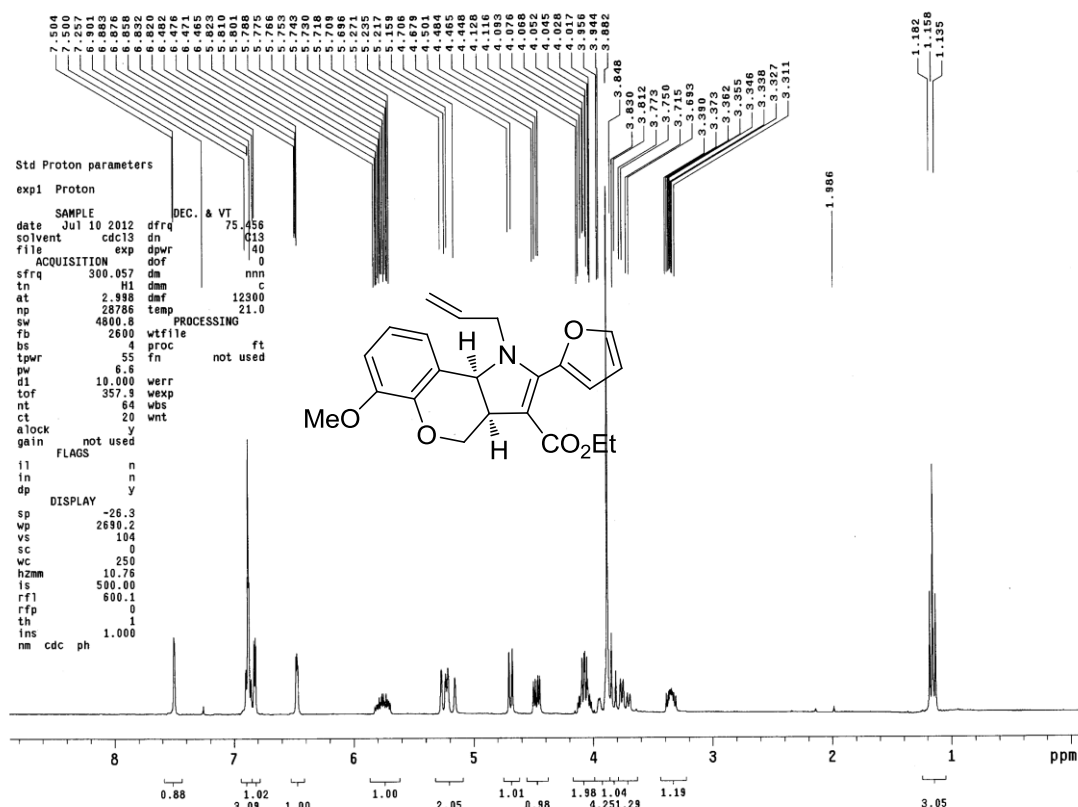
Pyrroline **5.5f** (CDCl₃)



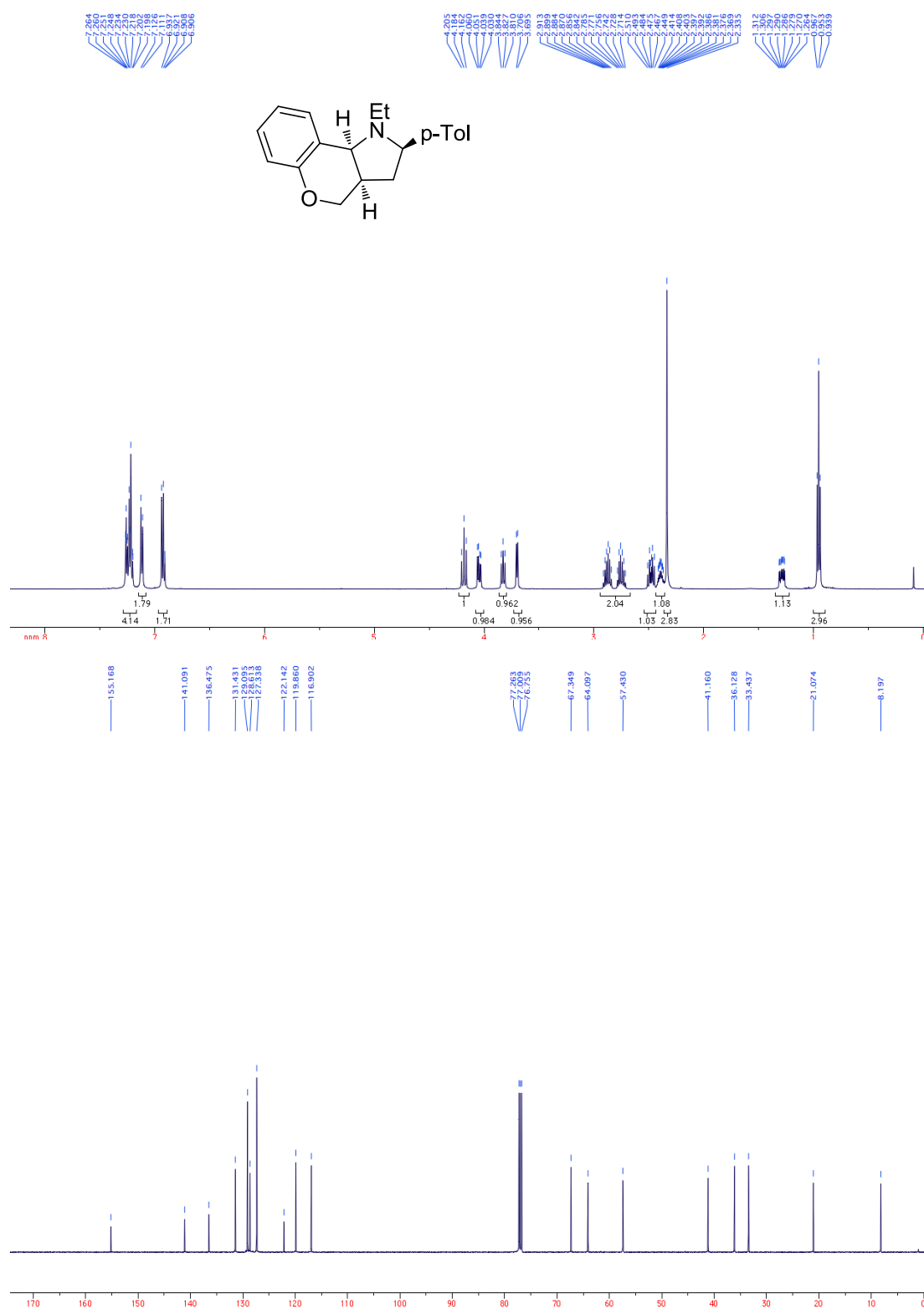
Pyrroline **5.5g** (CDCl₃)



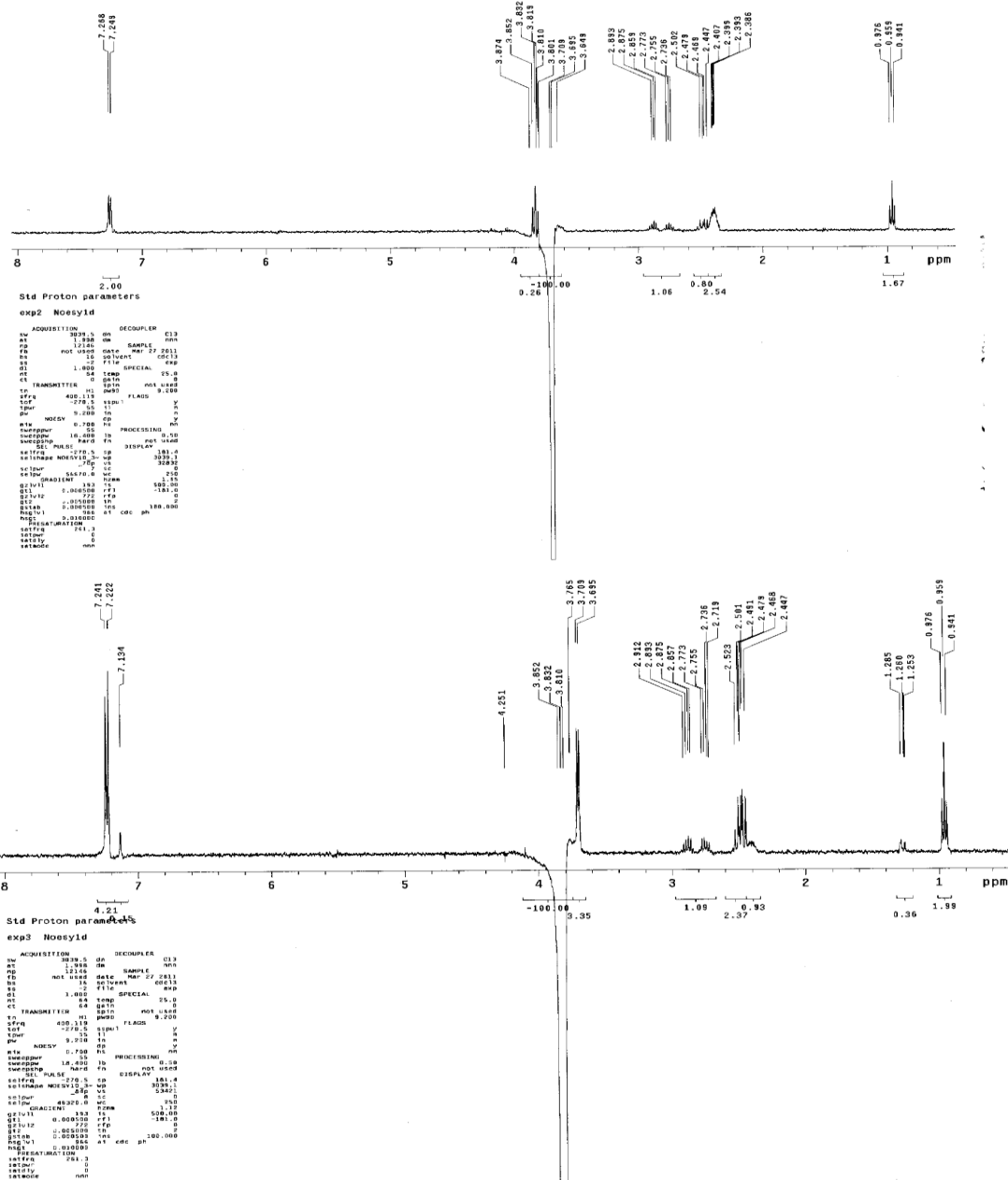
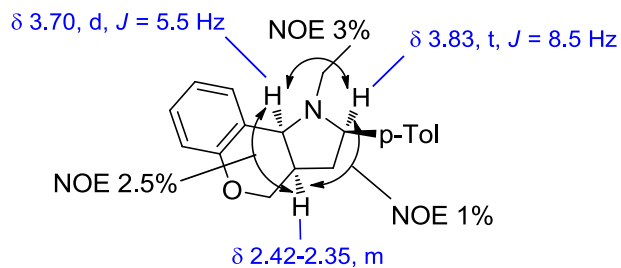
Pyrroline 5.5h (CDCl₃)



Pyrrolidine **5.6a** (CDCl₃)



NOEs of key correlations



7.628
7.610
7.426
7.411
7.407
7.374
7.354
7.272
7.260
7.250
7.254
7.250
7.232
7.228
7.223
7.218
7.213
7.205
7.201
7.186
7.183
7.168
7.138

3.915
3.901
3.890
3.878
3.865
3.855
3.824
3.819
3.801
2.982
2.967
2.951
2.931
2.740
2.723
2.706
2.681
2.669
2.674
2.640
2.630
2.595
2.487
2.465
2.359
2.329
2.286
2.282
2.275
1.794
1.784
1.679
1.675
1.650
1.625
1.412
1.412
0.889
0.871
0.105
0.111

expl Proton

SAMPLE
date May 9 2012
solvent cdc13
file exp
ACQUISITION
sfrq 400.120
tn H1
et 1.935
np 25582
sw 6410.3
fb not used
bs 4
tpwr 54
pw 5.2
d1 1.000
tof 405.3
128
32
alock y
gain not used

DEC A VT
dfrq 100.619
dh C13
exp S1
dpr dof 0
da nnn
dm 15900
wf file
proc ft
fn 65536

PROCESSING

FLAGS
il n
ln n
dp y

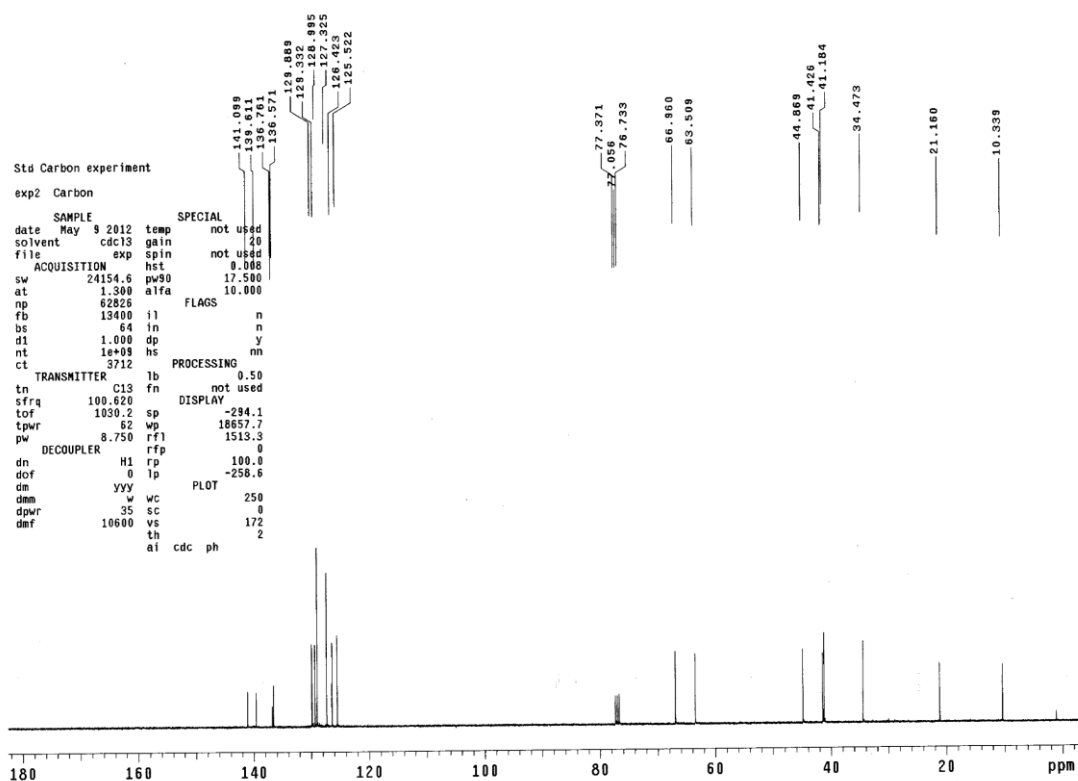
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wp 3618.9
vc 87
sc 0
wc 250
hzm 14.46
ls 250.00
rf1 804.4
rfp 0
th 2
ins 1.000
nm cdc ph

0.95 3.83
2.70
1.00 1.02
2.07 2.15 2.93 1.10 2.6
0.93
3.17

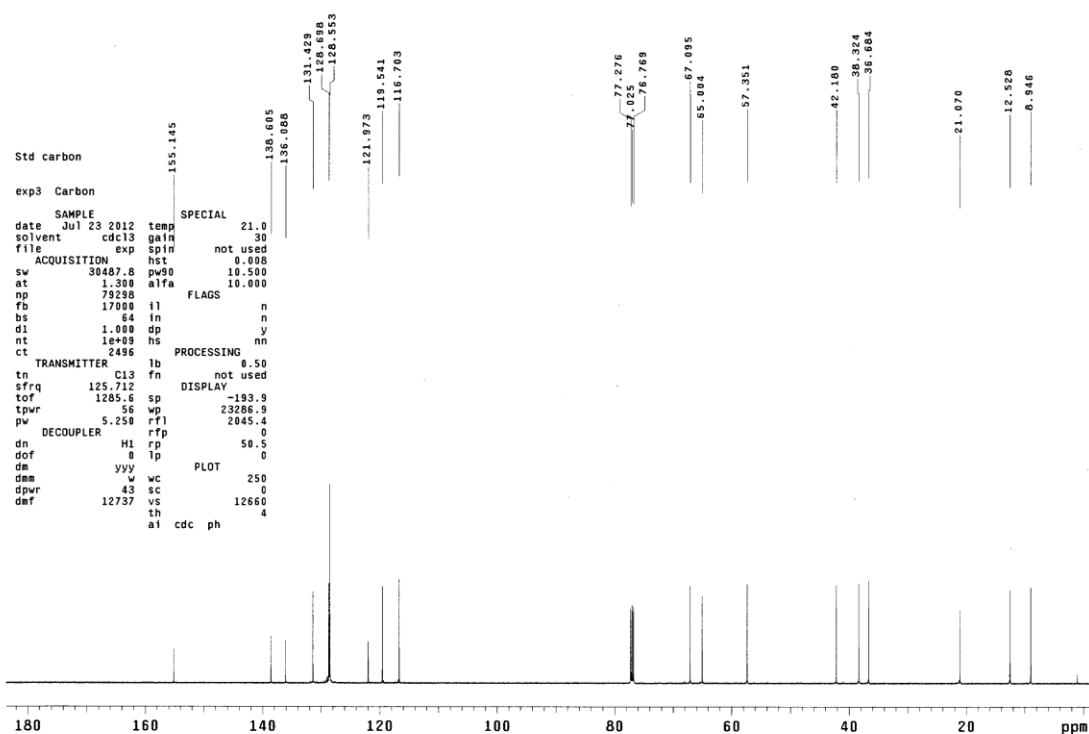
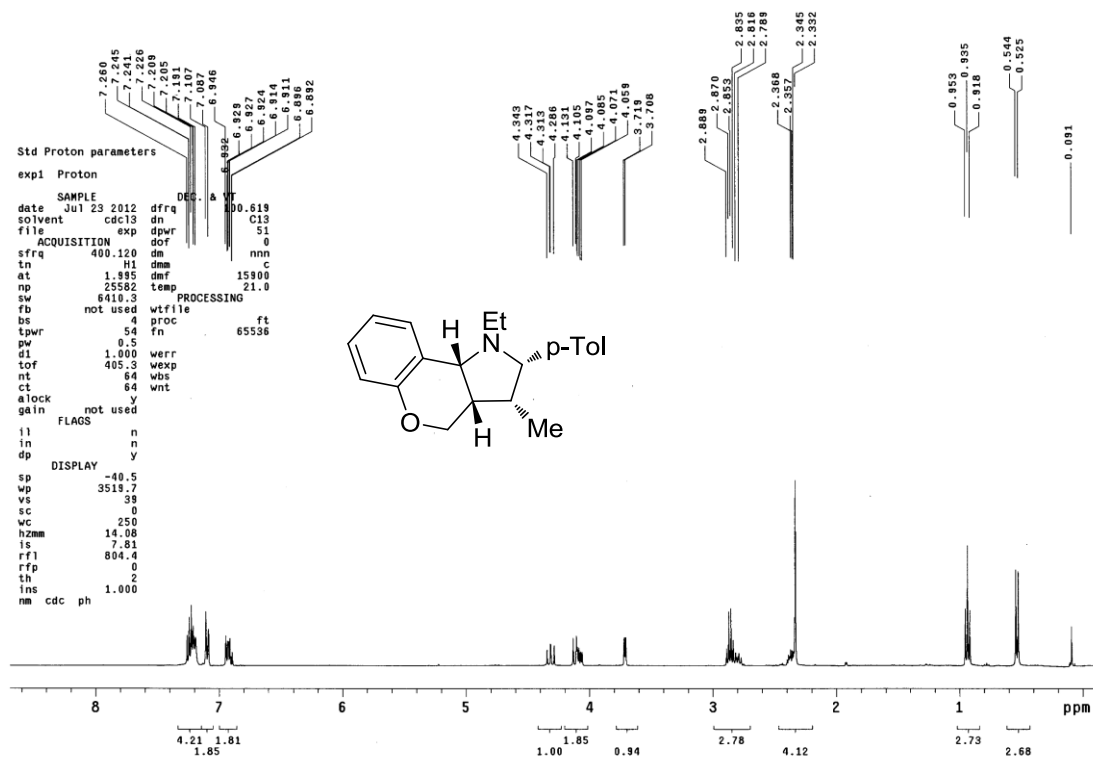
ppm

CC1(CCN1Cc2ccccc2)Cc3ccccc3

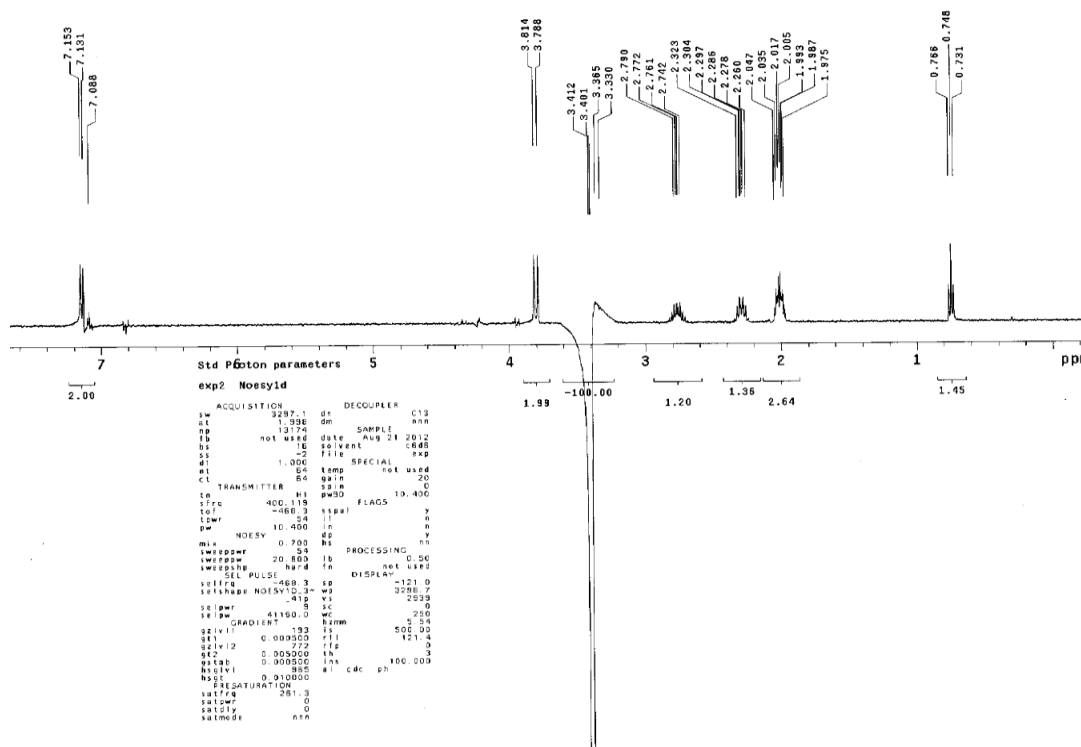
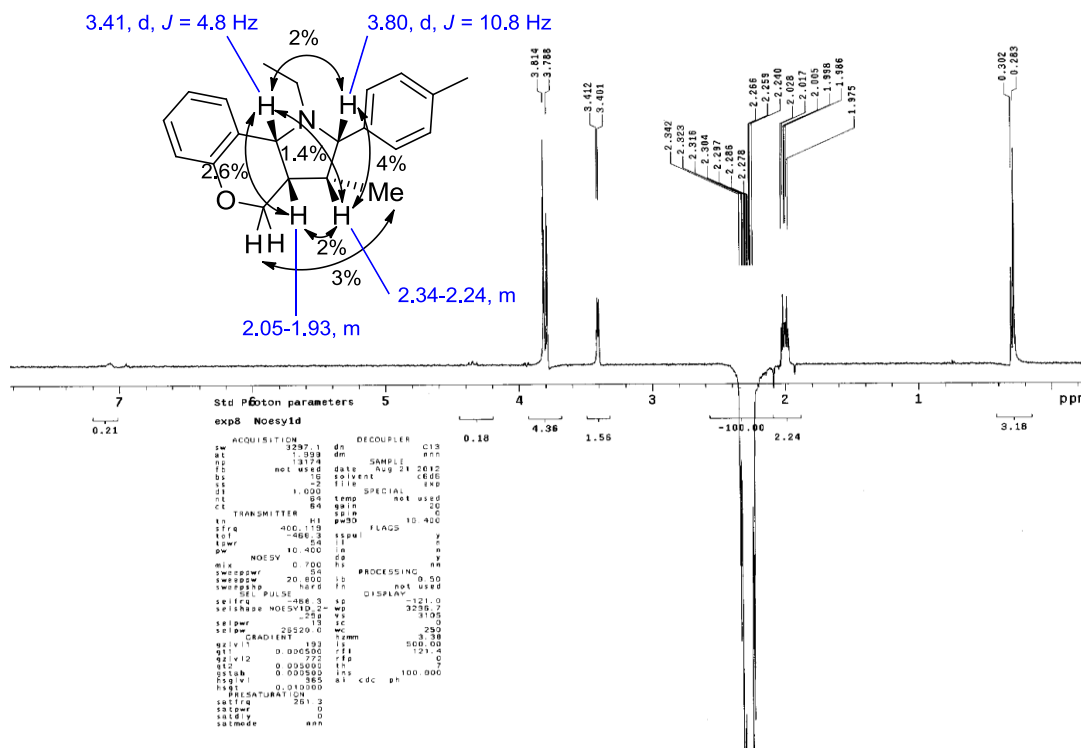
Et
p-Tol



Pyrrolidine **5.6c** (CDCl₃)



Summary of NOE experiments in C₆D₆



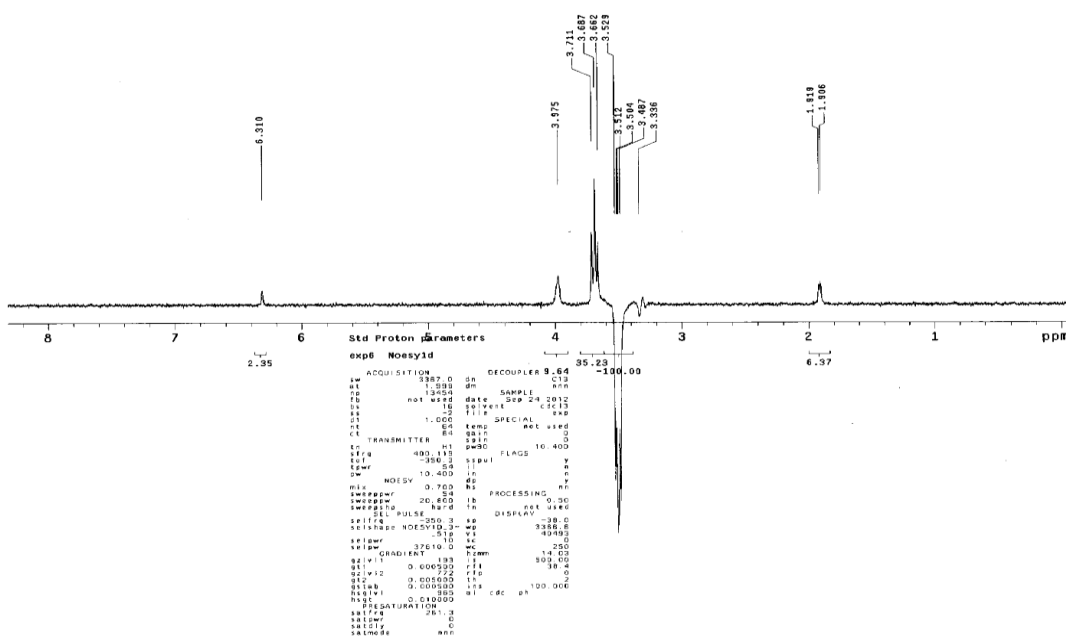
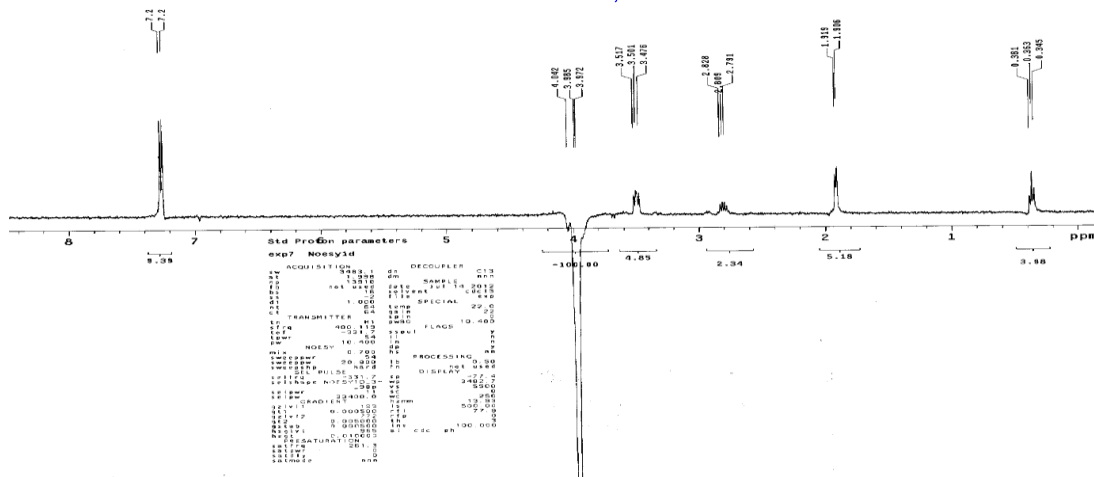
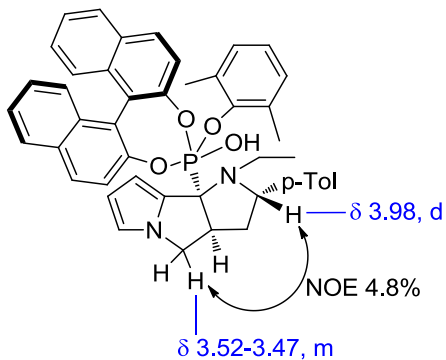
Chemical structure of compound 10 is shown above the spectrum. The structure is a complex polycyclic molecule featuring a phosphorus atom (P) bonded to two oxygen atoms (O) and a hydroxyl group (OH). It also contains a pyridine ring, a p-tolyl group (p-Tol), and a large polycyclic aromatic system.

¹H NMR spectrum (CDCl₃) of compound 10. The x-axis represents the chemical shift in ppm, ranging from 0 to 9. The spectrum shows several multiplets and singlets, with integration values provided below the baseline.

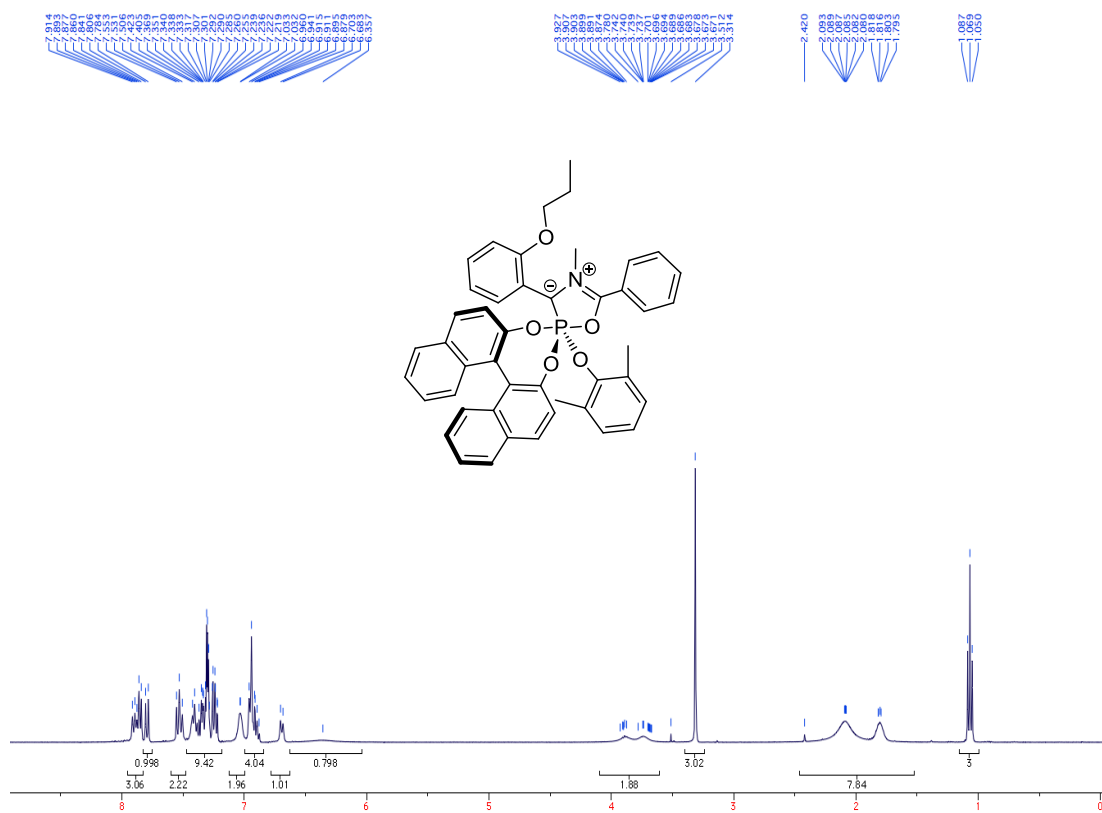
Integration values (from left to right): 4.00, 1.03, 5.12, 4.77, 0.806, 0.984, 0.996, 1.08, 1.04, 1.05, 1.12, 2.26, 6.27, 2.92, 0.87, 2.81.

[illegible]

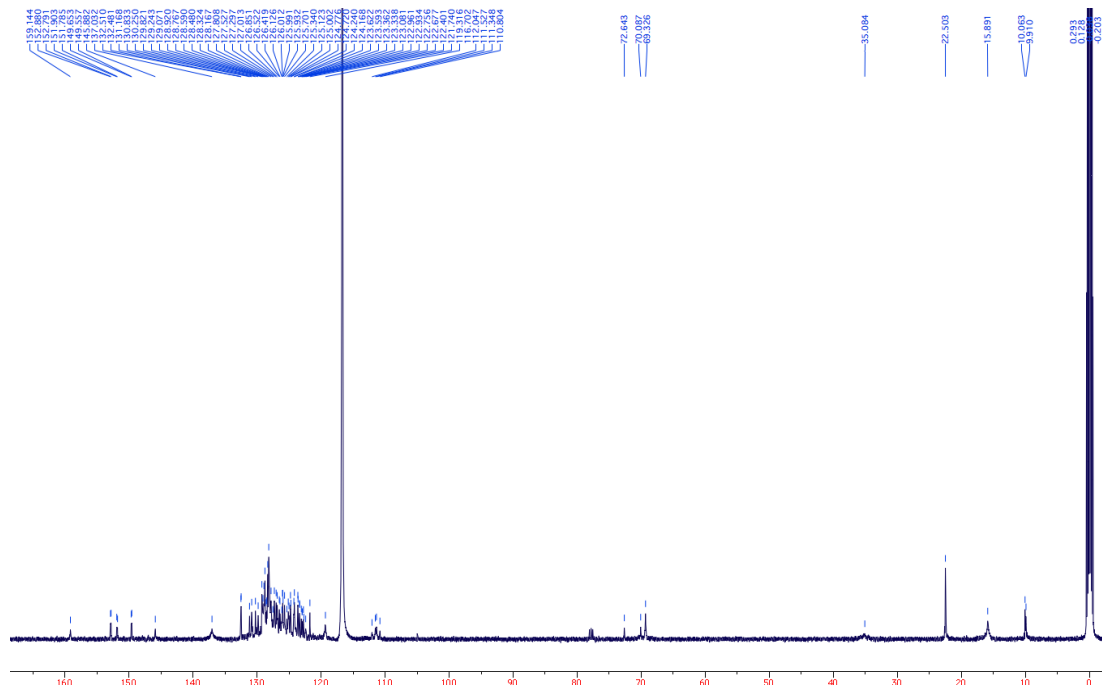
NOE of key correlation



1,3-Dipole **5.1d** ^1H NMR in CDCl_3 at 70°C

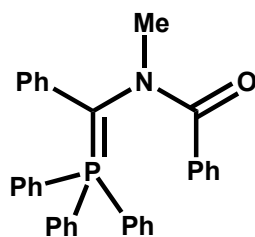


^{13}C NMR in CD_3CN , 84°C



Appendix B

X-Ray Structural Data for Compound 3.2b (Chapter 3)



Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Francine Bélanger.

ORTEP views of **3.2b** with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

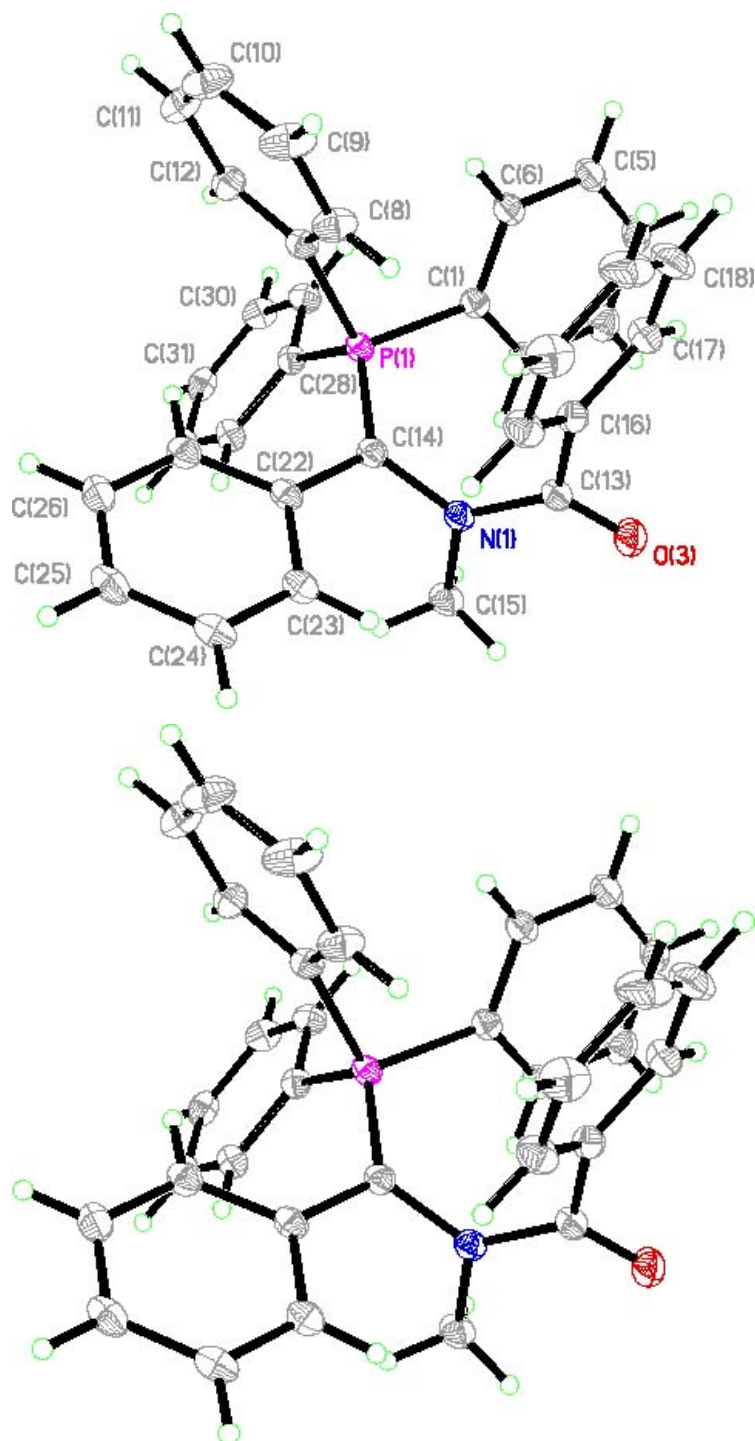


Table 1. Crystal data and structure refinement for **3.2b**.

Identification code	arst32
Empirical formula	C33 H28 N O P
Formula weight	485.53
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	$a = 9.8196(3) \text{ Å}$ $\alpha = 90^\circ$ $b = 17.4712(6) \text{ Å}$ $\beta = 96.005(2)^\circ$ $c = 14.7758(6) \text{ Å}$ $\gamma = 90^\circ$
Volume	$2521.03(15) \text{ Å}^3$
Z	4
Density (calculated)	1.279 g/cm^3
Absorption coefficient	1.165 mm^{-1}
F(000)	1024
Crystal size	0.10 x 0.05 x 0.05 mm
Theta range for data collection	3.93 to 67.76°
Index ranges	$-11 \leq h \leq 11$, $-20 \leq k \leq 20$, $-17 \leq l \leq 16$
Reflections collected	40492
Independent reflections	4511 [$R_{\text{int}} = 0.041$]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9434 and 0.7226
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4511 / 0 / 326
Goodness-of-fit on F^2	1.033
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0345$, $wR_2 = 0.0963$
R indices (all data)	$R_1 = 0.0392$, $wR_2 = 0.0992$
Largest diff. peak and hole	0.264 and -0.375 e/Å^3

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3.2b**.

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
P(1)	925(1)	309(1)	7294(1)	25(1)
N(1)	2611(1)	34(1)	8831(1)	28(1)
O(3)	4754(1)	-463(1)	8903(1)	42(1)
C(1)	2130(1)	-217(1)	6686(1)	28(1)
C(2)	2493(2)	-963(1)	6940(1)	36(1)
C(3)	3340(2)	-1388(1)	6440(1)	41(1)
C(4)	3814(2)	-1072(1)	5672(1)	42(1)
C(5)	3447(2)	-340(1)	5407(1)	39(1)
C(6)	2615(1)	92(1)	5915(1)	33(1)
C(7)	534(1)	1187(1)	6670(1)	29(1)
C(8)	1476(2)	1782(1)	6811(1)	41(1)
C(9)	1217(2)	2476(1)	6379(1)	51(1)
C(10)	24(2)	2591(1)	5820(1)	50(1)
C(11)	-900(2)	1998(1)	5659(1)	45(1)
C(12)	-646(2)	1294(1)	6077(1)	34(1)
C(13)	3956(1)	60(1)	8673(1)	31(1)
C(14)	1571(1)	525(1)	8391(1)	27(1)
C(15)	2191(2)	-583(1)	9413(1)	37(1)
C(16)	4456(1)	765(1)	8228(1)	31(1)
C(17)	5213(2)	687(1)	7491(1)	40(1)
C(18)	5793(2)	1330(1)	7129(1)	52(1)
C(19)	5641(2)	2043(1)	7510(1)	54(1)
C(20)	4902(2)	2118(1)	8246(1)	46(1)
C(21)	4303(2)	1485(1)	8598(1)	38(1)
C(22)	900(1)	1064(1)	8947(1)	28(1)
C(23)	1499(2)	1252(1)	9827(1)	32(1)
C(24)	911(2)	1785(1)	10359(1)	37(1)
C(25)	-312(2)	2143(1)	10059(1)	37(1)
C(26)	-950(2)	1950(1)	9211(1)	36(1)
C(27)	-362(1)	1425(1)	8666(1)	31(1)
C(28)	-603(1)	-295(1)	7120(1)	28(1)
C(29)	-936(2)	-696(1)	6310(1)	33(1)
C(30)	-2064(2)	-1179(1)	6218(1)	37(1)
C(31)	-2876(2)	-1253(1)	6925(1)	37(1)
C(32)	-2564(2)	-853(1)	7725(1)	36(1)
C(33)	-1417(2)	-381(1)	7827(1)	32(1)

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3.2b**.

	x	y	z	U _{eq}
H(2)	2157	-1183	7462	43
H(3)	3595	-1893	6622	49
H(4)	4395	-1363	5327	50
H(5)	3763	-129	4874	46
H(6)	2378	601	5735	40
H(8)	2296	1710	7204	49
H(9)	1869	2877	6469	61
H(10)	-164	3076	5545	60
H(11)	-1714	2072	5261	54
H(12)	-1277	885	5958	41
H(15A)	1928	-1033	9039	56
H(15B)	1410	-413	9723	56
H(15C)	2956	-716	9866	56
H(17)	5334	197	7234	47
H(18)	6296	1278	6618	63
H(19)	6046	2480	7265	65
H(20)	4804	2608	8512	55
H(21)	3779	1544	9099	45
H(23)	2326	1007	10060	39
H(24)	1356	1909	10942	44
H(25)	-703	2513	10427	45
H(26)	-1801	2179	9000	43
H(27)	-822	1305	8086	38
H(29)	-389	-639	5820	40
H(30)	-2279	-1459	5671	45
H(31)	-3652	-1581	6858	44
H(32)	-3131	-899	8205	43
H(33)	-1189	-115	8383	39

Table 4. Anisotropic parameters ($\text{\AA}^2 \times 10^3$) for **3.2b**.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
P(1)	26(1)	24(1)	26(1)	0(1)	6(1)	-2(1)
N(1)	29(1)	28(1)	28(1)	4(1)	7(1)	-1(1)
O(3)	38(1)	42(1)	49(1)	9(1)	12(1)	11(1)
C(1)	27(1)	31(1)	27(1)	-3(1)	4(1)	-2(1)
C(2)	40(1)	34(1)	35(1)	0(1)	9(1)	2(1)
C(3)	40(1)	37(1)	45(1)	-4(1)	5(1)	9(1)
C(4)	33(1)	55(1)	39(1)	-13(1)	6(1)	7(1)
C(5)	31(1)	53(1)	32(1)	-3(1)	9(1)	-2(1)
C(6)	31(1)	38(1)	32(1)	-1(1)	7(1)	-3(1)
C(7)	34(1)	27(1)	26(1)	-1(1)	7(1)	-1(1)
C(8)	49(1)	37(1)	36(1)	5(1)	-3(1)	-12(1)
C(9)	77(1)	34(1)	39(1)	5(1)	-5(1)	-21(1)
C(10)	80(1)	29(1)	40(1)	7(1)	-2(1)	1(1)
C(11)	52(1)	37(1)	43(1)	6(1)	-4(1)	6(1)
C(12)	36(1)	30(1)	37(1)	-1(1)	2(1)	0(1)
C(13)	31(1)	33(1)	28(1)	-1(1)	7(1)	1(1)
C(14)	28(1)	28(1)	27(1)	1(1)	6(1)	-1(1)
C(15)	42(1)	33(1)	39(1)	10(1)	14(1)	1(1)
C(16)	25(1)	38(1)	30(1)	3(1)	2(1)	-2(1)
C(17)	33(1)	51(1)	36(1)	2(1)	8(1)	0(1)
C(18)	42(1)	82(1)	35(1)	7(1)	13(1)	-16(1)
C(19)	56(1)	64(1)	41(1)	16(1)	-1(1)	-32(1)
C(20)	49(1)	41(1)	46(1)	2(1)	0(1)	-16(1)
C(21)	38(1)	40(1)	36(1)	-1(1)	7(1)	-10(1)
C(22)	31(1)	26(1)	28(1)	1(1)	10(1)	-4(1)
C(23)	34(1)	33(1)	31(1)	-1(1)	9(1)	-4(1)
C(24)	46(1)	36(1)	29(1)	-5(1)	12(1)	-8(1)
C(25)	49(1)	27(1)	40(1)	-3(1)	21(1)	-2(1)
C(26)	39(1)	27(1)	42(1)	5(1)	15(1)	3(1)
C(27)	35(1)	29(1)	31(1)	1(1)	8(1)	-1(1)
C(28)	28(1)	23(1)	33(1)	2(1)	5(1)	0(1)
C(29)	38(1)	30(1)	32(1)	0(1)	5(1)	-4(1)
C(30)	41(1)	31(1)	38(1)	0(1)	-3(1)	-7(1)
C(31)	28(1)	30(1)	51(1)	6(1)	-1(1)	-3(1)
C(32)	29(1)	35(1)	46(1)	5(1)	12(1)	1(1)
C(33)	32(1)	30(1)	36(1)	-1(1)	8(1)	-1(1)

Table 5. Bond lengths [Å] and angles [°] for **3.2b**.

P(1)-C(14)	1.7189(14)	C(14)-N(1)-C(15)	118.35(11)
P(1)-C(1)	1.8101(14)	C(6)-C(1)-C(2)	119.05(13)
P(1)-C(7)	1.8107(14)	C(6)-C(1)-P(1)	120.52(11)
P(1)-C(28)	1.8296(14)	C(2)-C(1)-P(1)	120.21(11)
N(1)-C(13)	1.3660(18)	C(3)-C(2)-C(1)	120.51(15)
N(1)-C(14)	1.4356(18)	C(2)-C(3)-C(4)	119.80(15)
N(1)-C(15)	1.4652(18)	C(5)-C(4)-C(3)	120.16(14)
O(3)-C(13)	1.2286(18)	C(4)-C(5)-C(6)	120.24(15)
C(1)-C(6)	1.390(2)	C(5)-C(6)-C(1)	120.21(15)
C(1)-C(2)	1.393(2)	C(12)-C(7)-C(8)	119.42(14)
C(2)-C(3)	1.384(2)	C(12)-C(7)-P(1)	123.55(11)
C(3)-C(4)	1.385(2)	C(8)-C(7)-P(1)	117.02(11)
C(4)-C(5)	1.375(2)	C(9)-C(8)-C(7)	119.89(15)
C(5)-C(6)	1.388(2)	C(10)-C(9)-C(8)	120.67(16)
C(7)-C(12)	1.391(2)	C(9)-C(10)-C(11)	119.73(15)
C(7)-C(8)	1.392(2)	C(10)-C(11)-C(12)	120.29(16)
C(8)-C(9)	1.381(2)	C(11)-C(12)-C(7)	119.92(14)
C(9)-C(10)	1.376(3)	O(3)-C(13)-N(1)	121.87(13)
C(10)-C(11)	1.381(3)	O(3)-C(13)-C(16)	120.21(13)
C(11)-C(12)	1.387(2)	N(1)-C(13)-C(16)	117.89(12)
C(13)-C(16)	1.501(2)	N(1)-C(14)-C(22)	118.25(12)
C(14)-C(22)	1.4529(19)	N(1)-C(14)-P(1)	118.12(10)
C(16)-C(21)	1.387(2)	C(22)-C(14)-P(1)	122.09(10)
C(16)-C(17)	1.388(2)	C(21)-C(16)-C(17)	119.07(14)
C(17)-C(18)	1.391(2)	C(21)-C(16)-C(13)	121.24(13)
C(18)-C(19)	1.381(3)	C(17)-C(16)-C(13)	119.34(14)
C(19)-C(20)	1.375(3)	C(16)-C(17)-C(18)	119.85(16)
C(20)-C(21)	1.380(2)	C(19)-C(18)-C(17)	120.38(16)
C(22)-C(23)	1.408(2)	C(20)-C(19)-C(18)	119.77(16)
C(22)-C(27)	1.414(2)	C(19)-C(20)-C(21)	120.16(17)
C(23)-C(24)	1.384(2)	C(20)-C(21)-C(16)	120.76(15)
C(24)-C(25)	1.385(2)	C(23)-C(22)-C(27)	115.80(13)
C(25)-C(26)	1.383(2)	C(23)-C(22)-C(14)	120.21(13)
C(26)-C(27)	1.385(2)	C(27)-C(22)-C(14)	124.00(13)
C(28)-C(33)	1.387(2)	C(24)-C(23)-C(22)	121.48(14)
C(28)-C(29)	1.397(2)	C(23)-C(24)-C(25)	121.48(15)
C(29)-C(30)	1.387(2)	C(26)-C(25)-C(24)	118.32(14)
C(30)-C(31)	1.385(2)	C(25)-C(26)-C(27)	120.81(14)
C(31)-C(32)	1.380(2)	C(26)-C(27)-C(22)	122.05(14)
C(32)-C(33)	1.392(2)	C(33)-C(28)-C(29)	119.31(13)
		C(33)-C(28)-P(1)	119.01(11)
C(14)-P(1)-C(1)	112.55(7)	C(29)-C(28)-P(1)	121.63(11)
C(14)-P(1)-C(7)	109.36(7)	C(30)-C(29)-C(28)	120.09(14)
C(1)-P(1)-C(7)	106.98(7)	C(31)-C(30)-C(29)	120.03(15)
C(14)-P(1)-C(28)	118.36(7)	C(32)-C(31)-C(30)	120.33(13)
C(1)-P(1)-C(28)	101.94(6)	C(31)-C(32)-C(33)	119.81(14)
C(7)-P(1)-C(28)	106.87(6)	C(28)-C(33)-C(32)	120.41(14)
C(13)-N(1)-C(14)	123.89(12)		
C(13)-N(1)-C(15)	117.45(12)		

Table 6. Torsion angles [$^{\circ}$] for **3.2b**.

C(14)-P(1)-C(1)-C(6)	-117.56(12)	C(13)-C(16)-C(21)-C(20)	172.49(14)
C(7)-P(1)-C(1)-C(6)	2.59(14)	N(1)-C(14)-C(22)-C(23)	17.50(19)
C(28)-P(1)-C(1)-C(6)	114.59(12)	P(1)-C(14)-C(22)-C(23)	-176.94(10)
C(14)-P(1)-C(1)-C(2)	67.82(13)	N(1)-C(14)-C(22)-C(27)	-162.11(12)
C(7)-P(1)-C(1)-C(2)	172.03(12)	P(1)-C(14)-C(22)-C(27)	3.45(19)
C(28)-P(1)-C(1)-C(2)	-60.03(13)	C(27)-C(22)-C(23)-C(24)	-2.9(2)
C(6)-C(1)-C(2)-C(3)	0.8(2)	C(14)-C(22)-C(23)-C(24)	177.45(13)
P(1)-C(1)-C(2)-C(3)	175.52(12)	C(22)-C(23)-C(24)-C(25)	1.7(2)
C(1)-C(2)-C(3)-C(4)	-1.0(2)	C(23)-C(24)-C(25)-C(26)	0.6(2)
C(2)-C(3)-C(4)-C(5)	0.1(2)	C(24)-C(25)-C(26)-C(27)	-1.6(2)
C(3)-C(4)-C(5)-C(6)	1.0(2)	C(25)-C(26)-C(27)-C(22)	0.3(2)
C(4)-C(5)-C(6)-C(1)	-1.1(2)	C(23)-C(22)-C(27)-C(26)	2.0(2)
C(2)-C(1)-C(6)-C(5)	0.2(2)	C(14)-C(22)-C(27)-C(26)	-178.42(13)
P(1)-C(1)-C(6)-C(5)	-174.48(11)	C(14)-P(1)-C(28)-C(33)	18.20(14)
C(14)-P(1)-C(7)-C(12)	-137.81(13)	C(1)-P(1)-C(28)-C(33)	142.24(11)
C(1)-P(1)-C(7)-C(12)	100.03(13)	C(7)-P(1)-C(28)-C(33)	-105.68(12)
C(28)-P(1)-C(7)-C(12)	-8.56(14)	C(14)-P(1)-C(28)-C(29)	-158.97(11)
C(14)-P(1)-C(7)-C(8)	41.50(14)	C(1)-P(1)-C(28)-C(29)	-34.93(13)
C(1)-P(1)-C(7)-C(8)	-80.67(13)	C(7)-P(1)-C(28)-C(29)	77.16(13)
C(28)-P(1)-C(7)-C(8)	170.75(12)	C(33)-C(28)-C(29)-C(30)	-0.4(2)
C(12)-C(7)-C(8)-C(9)	1.5(2)	P(1)-C(28)-C(29)-C(30)	176.72(11)
P(1)-C(7)-C(8)-C(9)	-177.84(14)	C(28)-C(29)-C(30)-C(31)	1.2(2)
C(7)-C(8)-C(9)-C(10)	1.0(3)	C(29)-C(30)-C(31)-C(32)	-0.5(2)
C(8)-C(9)-C(10)-C(11)	-2.6(3)	C(30)-C(31)-C(32)-C(33)	-0.9(2)
C(9)-C(10)-C(11)-C(12)	1.6(3)	C(29)-C(28)-C(33)-C(32)	-1.0(2)
C(10)-C(11)-C(12)-C(7)	1.0(3)	P(1)-C(28)-C(33)-C(32)	-178.19(11)
C(8)-C(7)-C(12)-C(11)	-2.5(2)	C(31)-C(32)-C(33)-C(28)	1.6(2)
P(1)-C(7)-C(12)-C(11)	176.82(13)		
C(14)-N(1)-C(13)-O(3)	-164.06(14)		
C(15)-N(1)-C(13)-O(3)	9.4(2)		
C(14)-N(1)-C(13)-C(16)	17.8(2)		
C(15)-N(1)-C(13)-C(16)	-168.81(13)		
C(13)-N(1)-C(14)-C(22)	-115.58(15)		
C(15)-N(1)-C(14)-C(22)	71.05(16)		
C(13)-N(1)-C(14)-P(1)	78.28(16)		
C(15)-N(1)-C(14)-P(1)	-95.08(14)		
C(1)-P(1)-C(14)-N(1)	-26.40(12)		
C(7)-P(1)-C(14)-N(1)	-145.16(10)		
C(28)-P(1)-C(14)-N(1)	92.21(11)		
C(1)-P(1)-C(14)-C(22)	168.02(11)		
C(7)-P(1)-C(14)-C(22)	49.27(13)		
C(28)-P(1)-C(14)-C(22)	-73.36(13)		
O(3)-C(13)-C(16)-C(21)	-122.57(16)		
N(1)-C(13)-C(16)-C(21)	55.63(19)		
O(3)-C(13)-C(16)-C(17)	50.5(2)		
N(1)-C(13)-C(16)-C(17)	-131.32(15)		
C(21)-C(16)-C(17)-C(18)	-0.6(2)		
C(13)-C(16)-C(17)-C(18)	-173.81(14)		
C(16)-C(17)-C(18)-C(19)	1.2(3)		
C(17)-C(18)-C(19)-C(20)	-0.6(3)		
C(18)-C(19)-C(20)-C(21)	-0.6(3)		
C(19)-C(20)-C(21)-C(16)	1.2(3)		
C(17)-C(16)-C(21)-C(20)	-0.6(2)		

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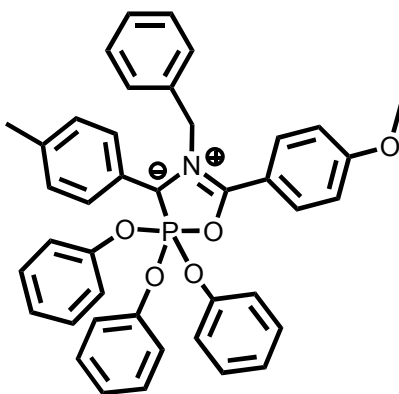
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Appendix C

X-Ray Structural Data for Compound 3.1c (Chapter 3)



Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Francine Bélanger.

ORTEP view of **3.1c** with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

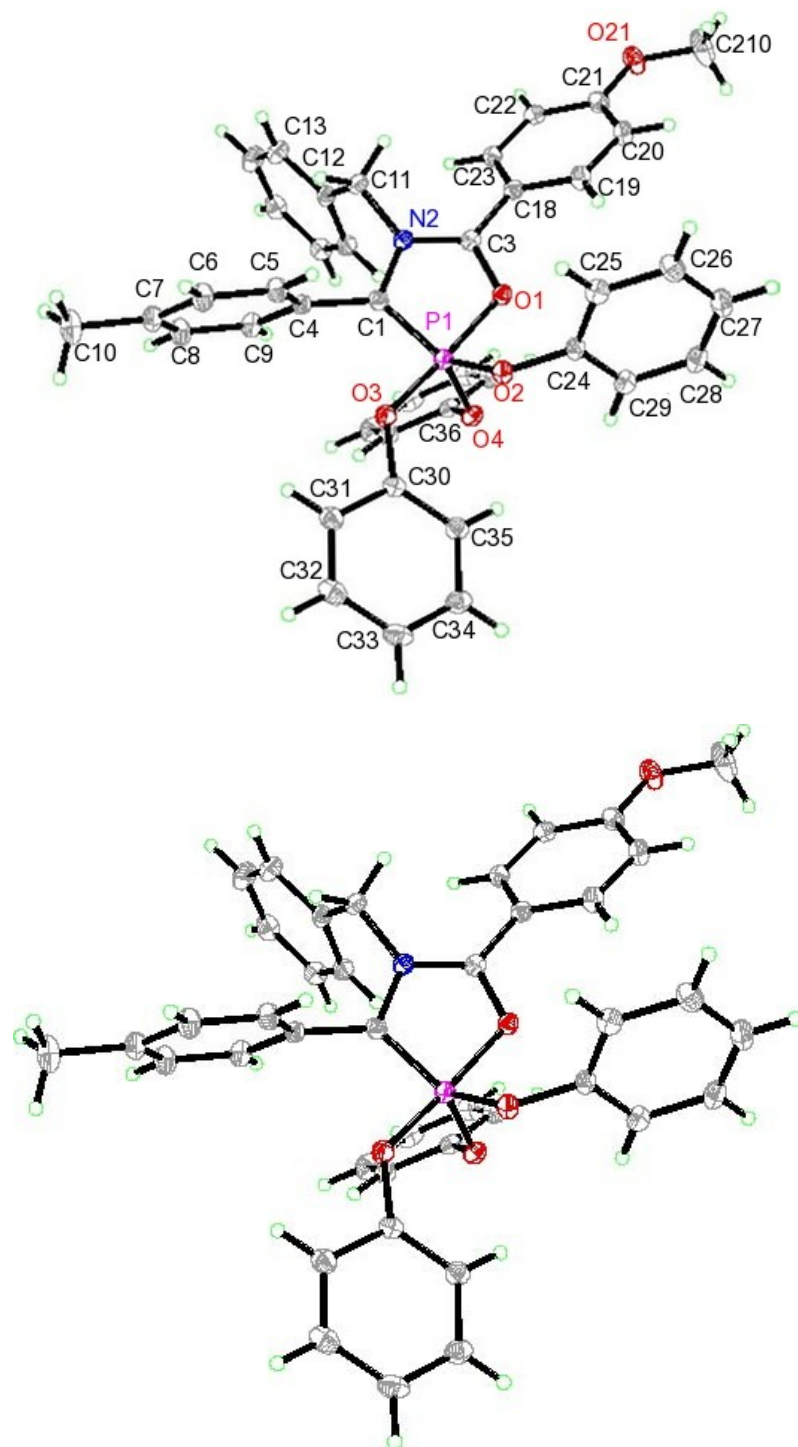


Table 1. Crystal data and structure refinement for **3.1c**

Identification code	arst36
Empirical formula	C41 H36 N O5 P
Formula weight	653.68
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	$a = 8.6691(2) \text{ Å}$ $\alpha = 90^\circ$ $b = 18.5176(3) \text{ Å}$ $\beta = 97.849(1)^\circ$ $c = 20.9175(3) \text{ Å}$ $\gamma = 90^\circ$
Volume	$3326.45(11) \text{ Å}^3$
Z	4
Density (calculated)	1.305 g/cm^3
Absorption coefficient	1.116 mm^{-1}
F(000)	1376
Crystal size	0.10 x 0.05 x 0.03 mm
Theta range for data collection	3.20 to 67.91°
Index ranges	$-8 \leq h \leq 9, -22 \leq k \leq 22, -25 \leq l \leq 25$
Reflections collected	53509
Independent reflections	5403 [$R_{\text{int}} = 0.043$]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9671 and 0.7656
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5403 / 0 / 435
Goodness-of-fit on F^2	1.037
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0318, wR_2 = 0.0879$
R indices (all data)	$R_1 = 0.0357, wR_2 = 0.0901$
Largest diff. peak and hole	0.282 and -0.347 e/Å^3

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3.1c**.

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
P (1)	273 (1)	6730 (1)	2197 (1)	22 (1)
O (1)	1564 (1)	7139 (1)	1693 (1)	24 (1)
O (2)	-144 (1)	6104 (1)	1653 (1)	25 (1)
O (3)	-795 (1)	6306 (1)	2682 (1)	27 (1)
O (4)	-1038 (1)	7337 (1)	1945 (1)	26 (1)
O (21)	6880 (2)	8752 (1)	480 (1)	41 (1)
C (210)	6922 (3)	8539 (1)	-168 (1)	62 (1)
C (1)	1734 (2)	6861 (1)	2813 (1)	24 (1)
N (2)	3039 (1)	7228 (1)	2622 (1)	23 (1)
C (3)	2882 (2)	7375 (1)	2000 (1)	24 (1)
C (4)	1803 (2)	6594 (1)	3488 (1)	24 (1)
C (5)	1514 (2)	7042 (1)	3993 (1)	30 (1)
C (6)	1520 (2)	6772 (1)	4614 (1)	35 (1)
C (7)	1811 (2)	6047 (1)	4754 (1)	33 (1)
C (8)	2097 (2)	5600 (1)	4251 (1)	34 (1)
C (9)	2099 (2)	5869 (1)	3634 (1)	30 (1)
C (10)	1802 (3)	5753 (1)	5425 (1)	49 (1)
C (11)	4442 (2)	7381 (1)	3074 (1)	26 (1)
C (12)	4392 (2)	8091 (1)	3431 (1)	26 (1)
C (13)	3264 (2)	8612 (1)	3263 (1)	29 (1)
C (14)	3342 (2)	9276 (1)	3578 (1)	34 (1)
C (15)	4532 (2)	9417 (1)	4070 (1)	37 (1)
C (16)	5645 (2)	8896 (1)	4251 (1)	41 (1)
C (17)	5579 (2)	8237 (1)	3930 (1)	35 (1)
C (18)	3974 (2)	7727 (1)	1623 (1)	25 (1)
C (19)	4017 (2)	7483 (1)	994 (1)	30 (1)
C (20)	4980 (2)	7803 (1)	598 (1)	33 (1)
C (21)	5898 (2)	8387 (1)	826 (1)	30 (1)
C (22)	5851 (2)	8642 (1)	1449 (1)	28 (1)
C (23)	4907 (2)	8317 (1)	1843 (1)	27 (1)
C (24)	179 (2)	6113 (1)	1020 (1)	25 (1)
C (25)	1288 (2)	5645 (1)	851 (1)	31 (1)
C (26)	1595 (2)	5630 (1)	216 (1)	38 (1)
C (27)	790 (2)	6080 (1)	-242 (1)	38 (1)
C (28)	-326 (2)	6539 (1)	-64 (1)	36 (1)
C (29)	-654 (2)	6560 (1)	565 (1)	31 (1)
C (30)	-2301 (2)	6067 (1)	2575 (1)	25 (1)
C (31)	-2778 (2)	5685 (1)	3088 (1)	31 (1)
C (32)	-4255 (2)	5397 (1)	3036 (1)	40 (1)
C (33)	-5293 (2)	5491 (1)	2476 (1)	38 (1)
C (34)	-4826 (2)	5887 (1)	1977 (1)	33 (1)
C (35)	-3345 (2)	6177 (1)	2019 (1)	29 (1)
C (36)	-827 (2)	8035 (1)	2190 (1)	25 (1)
C (37)	-232 (2)	8556 (1)	1821 (1)	31 (1)
C (38)	-96 (2)	9260 (1)	2051 (1)	38 (1)
C (39)	-560 (2)	9435 (1)	2637 (1)	39 (1)
C (40)	-1158 (2)	8905 (1)	3002 (1)	37 (1)
C (41)	-1287 (2)	8199 (1)	2780 (1)	30 (1)

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3.1c**

	x	y	z	U _{eq}
H(21A)	7242	8032	-179	94
H(21B)	7668	8841	-358	94
H(21C)	5885	8596	-415	94
H(5)	1310	7540	3912	36
H(6)	1321	7091	4949	42
H(8)	2296	5102	4331	40
H(9)	2307	5550	3300	36
H(10A)	729	5646	5493	73
H(10B)	2247	6112	5742	73
H(10C)	2424	5310	5477	73
H(11A)	5349	7387	2832	31
H(11B)	4604	6985	3393	31
H(13)	2430	8516	2930	35
H(14)	2572	9633	3455	41
H(15)	4587	9871	4283	45
H(16)	6456	8988	4594	50
H(17)	6355	7883	4054	42
H(19)	3374	7090	834	36
H(20)	5010	7625	175	39
H(22)	6475	9043	1604	33
H(23)	4888	8495	2268	32
H(25)	1838	5335	1165	37
H(26)	2361	5309	96	45
H(27)	1006	6072	-675	45
H(28)	-881	6847	-378	43
H(29)	-1434	6874	684	38
H(31)	-2081	5623	3476	37
H(32)	-4566	5133	3386	48
H(33)	-6306	5287	2436	46
H(34)	-5539	5962	1596	39
H(35)	-3046	6449	1670	34
H(37)	80	8436	1416	37
H(38)	318	9624	1803	45
H(39)	-469	9918	2790	47
H(40)	-1480	9026	3404	44
H(41)	-1686	7833	3030	36

Table 4. Anisotropic parameters ($\text{\AA}^2 \times 10^3$) for **3.1c**

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
P(1)	25(1)	21(1)	21(1)	0(1)	3(1)	-2(1)
O(1)	25(1)	24(1)	23(1)	0(1)	1(1)	-3(1)
O(2)	30(1)	23(1)	23(1)	0(1)	4(1)	-4(1)
O(3)	27(1)	30(1)	25(1)	2(1)	2(1)	-5(1)
O(4)	26(1)	22(1)	28(1)	-2(1)	0(1)	-2(1)
O(21)	53(1)	41(1)	35(1)	-2(1)	19(1)	-17(1)
C(210)	95(2)	58(1)	42(1)	-9(1)	37(1)	-30(1)
C(1)	26(1)	24(1)	23(1)	1(1)	4(1)	-2(1)
N(2)	22(1)	23(1)	24(1)	-1(1)	1(1)	-1(1)
C(3)	25(1)	21(1)	25(1)	-1(1)	1(1)	0(1)
C(4)	22(1)	26(1)	23(1)	1(1)	1(1)	-3(1)
C(5)	37(1)	25(1)	28(1)	-1(1)	3(1)	2(1)
C(6)	47(1)	34(1)	26(1)	-5(1)	6(1)	2(1)
C(7)	38(1)	35(1)	24(1)	2(1)	3(1)	-3(1)
C(8)	45(1)	26(1)	31(1)	4(1)	6(1)	2(1)
C(9)	37(1)	27(1)	27(1)	-1(1)	7(1)	1(1)
C(10)	74(2)	45(1)	28(1)	5(1)	11(1)	0(1)
C(11)	23(1)	28(1)	27(1)	1(1)	-1(1)	-1(1)
C(12)	29(1)	27(1)	22(1)	2(1)	4(1)	-6(1)
C(13)	28(1)	32(1)	28(1)	-1(1)	3(1)	-3(1)
C(14)	37(1)	31(1)	36(1)	-1(1)	8(1)	-1(1)
C(15)	46(1)	33(1)	35(1)	-8(1)	8(1)	-10(1)
C(16)	45(1)	42(1)	33(1)	-6(1)	-7(1)	-9(1)
C(17)	34(1)	36(1)	32(1)	0(1)	-4(1)	-2(1)
C(18)	25(1)	24(1)	26(1)	2(1)	3(1)	1(1)
C(19)	37(1)	25(1)	28(1)	-2(1)	3(1)	-6(1)
C(20)	42(1)	32(1)	25(1)	-3(1)	8(1)	-4(1)
C(21)	32(1)	28(1)	30(1)	3(1)	9(1)	-2(1)
C(22)	27(1)	25(1)	31(1)	0(1)	3(1)	-2(1)
C(23)	29(1)	26(1)	25(1)	-1(1)	3(1)	0(1)
C(24)	29(1)	23(1)	23(1)	-2(1)	2(1)	-6(1)
C(25)	34(1)	26(1)	32(1)	1(1)	4(1)	0(1)
C(26)	42(1)	36(1)	37(1)	-4(1)	13(1)	4(1)
C(27)	46(1)	41(1)	27(1)	-3(1)	8(1)	-5(1)
C(28)	41(1)	38(1)	26(1)	4(1)	-2(1)	-3(1)
C(29)	33(1)	31(1)	29(1)	0(1)	1(1)	1(1)
C(30)	25(1)	21(1)	30(1)	-3(1)	7(1)	-2(1)
C(31)	31(1)	31(1)	31(1)	3(1)	8(1)	1(1)
C(32)	39(1)	40(1)	45(1)	6(1)	16(1)	-7(1)
C(33)	28(1)	39(1)	50(1)	-6(1)	12(1)	-9(1)
C(34)	29(1)	31(1)	38(1)	-6(1)	3(1)	-1(1)
C(35)	28(1)	27(1)	31(1)	-1(1)	4(1)	-3(1)
C(36)	22(1)	22(1)	29(1)	-1(1)	-1(1)	2(1)
C(37)	29(1)	29(1)	35(1)	3(1)	6(1)	1(1)
C(38)	35(1)	25(1)	53(1)	6(1)	5(1)	-2(1)

C(39)	37(1)	25(1)	53(1)	-9(1)	-4(1)	3(1)
C(40)	39(1)	37(1)	33(1)	-8(1)	-1(1)	8(1)
C(41)	30(1)	31(1)	30(1)	2(1)	3(1)	2(1)

Table 5. Bond lengths [Å] and angles [°] for **3.1c**

P(1)-O(2)	1.6305(9)	C(32)-C(33)	1.388(2)
P(1)-O(4)	1.6342(10)	C(33)-C(34)	1.380(2)
P(1)-O(3)	1.6605(9)	C(34)-C(35)	1.383(2)
P(1)-C(1)	1.6963(14)	C(36)-C(37)	1.3796(19)
P(1)-O(1)	1.8052(10)	C(36)-C(41)	1.3809(19)
O(1)-C(3)	1.3068(17)	C(37)-C(38)	1.389(2)
O(2)-C(24)	1.3913(15)	C(38)-C(39)	1.378(2)
O(3)-C(30)	1.3678(18)	C(39)-C(40)	1.387(2)
O(4)-C(36)	1.3929(15)	C(40)-C(41)	1.386(2)
O(21)-C(21)	1.3687(17)		
O(21)-C(210)	1.4177(19)	O(2)-P(1)-O(4)	100.76(5)
C(1)-N(2)	1.4234(18)	O(2)-P(1)-O(3)	90.06(5)
C(1)-C(4)	1.4897(17)	O(4)-P(1)-O(3)	95.77(5)
N(2)-C(3)	1.3175(16)	O(2)-P(1)-C(1)	134.68(6)
N(2)-C(11)	1.4625(18)	O(4)-P(1)-C(1)	124.10(6)
C(3)-C(18)	1.4657(19)	O(3)-P(1)-C(1)	91.40(6)
C(4)-C(5)	1.3916(18)	O(2)-P(1)-O(1)	89.28(4)
C(4)-C(9)	1.3921(18)	O(4)-P(1)-O(1)	88.97(5)
C(5)-C(6)	1.3903(19)	O(3)-P(1)-O(1)	175.25(5)
C(6)-C(7)	1.390(2)	C(1)-P(1)-O(1)	85.73(6)
C(7)-C(8)	1.388(2)	C(3)-O(1)-P(1)	115.04(8)
C(7)-C(10)	1.5077(19)	C(24)-O(2)-P(1)	126.98(8)
C(8)-C(9)	1.3841(19)	C(30)-O(3)-P(1)	130.77(8)
C(11)-C(12)	1.5157(18)	C(36)-O(4)-P(1)	117.99(9)
C(12)-C(13)	1.385(2)	C(21)-O(21)-C(210)	117.86(12)
C(12)-C(17)	1.388(2)	N(2)-C(1)-C(4)	119.61(12)
C(13)-C(14)	1.393(2)	N(2)-C(1)-P(1)	113.25(9)
C(14)-C(15)	1.378(2)	C(4)-C(1)-P(1)	127.00(11)
C(15)-C(16)	1.380(2)	C(3)-N(2)-C(1)	113.34(12)
C(16)-C(17)	1.389(2)	C(3)-N(2)-C(11)	124.25(12)
C(18)-C(19)	1.3972(18)	C(1)-N(2)-C(11)	122.3(1)
C(18)-C(23)	1.3987(19)	O(1)-C(3)-N(2)	112.47(12)
C(19)-C(20)	1.385(2)	O(1)-C(3)-C(18)	118.05(11)
C(20)-C(21)	1.388(2)	N(2)-C(3)-C(18)	129.44(13)
C(21)-C(22)	1.3911(19)	C(5)-C(4)-C(9)	117.09(12)
C(22)-C(23)	1.376(2)	C(5)-C(4)-C(1)	122.24(11)
C(24)-C(25)	1.376(2)	C(9)-C(4)-C(1)	120.62(11)
C(24)-C(29)	1.386(2)	C(6)-C(5)-C(4)	121.12(12)
C(25)-C(26)	1.390(2)	C(7)-C(6)-C(5)	121.40(13)
C(26)-C(27)	1.384(2)	C(8)-C(7)-C(6)	117.54(12)
C(27)-C(28)	1.378(2)	C(8)-C(7)-C(10)	120.99(13)
C(28)-C(29)	1.384(2)	C(6)-C(7)-C(10)	121.47(13)
C(30)-C(35)	1.389(2)	C(9)-C(8)-C(7)	121.04(13)
C(30)-C(31)	1.3940(19)	C(8)-C(9)-C(4)	121.81(12)
C(31)-C(32)	1.377(2)		

N(2)-C(11)-C(12)	114.18(12)	C(27)-C(26)-C(25)	120.34(15)
C(13)-C(12)-C(17)	118.70(13)	C(28)-C(27)-C(26)	119.42(14)
C(13)-C(12)-C(11)	123.04(13)	C(27)-C(28)-C(29)	121.12(14)
C(17)-C(12)-C(11)	118.18(13)	C(28)-C(29)-C(24)	118.69(14)
C(12)-C(13)-C(14)	120.49(14)	O(3)-C(30)-C(35)	125.94(12)
C(15)-C(14)-C(13)	120.21(15)	O(3)-C(30)-C(31)	114.58(13)
C(14)-C(15)-C(16)	119.78(13)	C(35)-C(30)-C(31)	119.47(14)
C(15)-C(16)-C(17)	120.00(15)	C(32)-C(31)-C(30)	120.39(14)
C(12)-C(17)-C(16)	120.79(15)	C(31)-C(32)-C(33)	120.42(14)
C(19)-C(18)-C(23)	118.23(12)	C(34)-C(33)-C(32)	118.81(15)
C(19)-C(18)-C(3)	117.74(12)	C(33)-C(34)-C(35)	121.63(15)
C(23)-C(18)-C(3)	123.92(11)	C(34)-C(35)-C(30)	119.23(13)
C(20)-C(19)-C(18)	121.34(13)	C(37)-C(36)-C(41)	121.48(12)
C(19)-C(20)-C(21)	119.48(12)	C(37)-C(36)-O(4)	118.88(12)
O(21)-C(21)-C(20)	124.88(12)	C(41)-C(36)-O(4)	119.55(12)
O(21)-C(21)-C(22)	115.34(12)	C(36)-C(37)-C(38)	118.82(13)
C(20)-C(21)-C(22)	119.77(13)	C(39)-C(38)-C(37)	120.52(14)
C(23)-C(22)-C(21)	120.56(13)	C(38)-C(39)-C(40)	119.93(13)
C(22)-C(23)-C(18)	120.61(12)	C(41)-C(40)-C(39)	120.16(14)
C(25)-C(24)-C(29)	121.15(12)	C(36)-C(41)-C(40)	119.09(13)
C(25)-C(24)-O(2)	118.35(12)		
C(29)-C(24)-O(2)	120.43(13)		
C(24)-C(25)-C(26)	119.27(14)		

Table 6. Torsion angles [$^{\circ}$] for **3.1c**

O(2)-P(1)-O(1)-C(3)	-138.77(9)	C(4)-C(1)-N(2)-C(11)	-2.45(18)
O(4)-P(1)-O(1)-C(3)	120.45(9)	P(1)-C(1)-N(2)-C(11)	-178.51(9)
O(3)-P(1)-O(1)-C(3)	-56.7(6)	P(1)-O(1)-C(3)-N(2)	3.47(13)
C(1)-P(1)-O(1)-C(3)	-3.85(9)	P(1)-O(1)-C(3)-C(18)	-178.76(9)
O(4)-P(1)-O(2)-C(24)	74.77(12)	C(1)-N(2)-C(3)-O(1)	-0.96(15)
O(3)-P(1)-O(2)-C(24)	170.66(12)	C(11)-N(2)-C(3)-O(1)	175.39(10)
C(1)-P(1)-O(2)-C(24)	-97.30(13)	C(1)-N(2)-C(3)-C(18)	-178.42(12)
O(1)-P(1)-O(2)-C(24)	-14.04(12)	C(11)-N(2)-C(3)-C(18)	-2.1(2)
O(2)-P(1)-O(3)-C(30)	-52.47(11)	N(2)-C(1)-C(4)-C(5)	81.94(19)
O(4)-P(1)-O(3)-C(30)	48.35(11)	P(1)-C(1)-C(4)-C(5)	-102.60(16)
C(1)-P(1)-O(3)-C(30)	172.83(11)	N(2)-C(1)-C(4)-C(9)	-100.84(16)
O(1)-P(1)-O(3)-C(30)	-134.5(5)	P(1)-C(1)-C(4)-C(9)	74.62(19)
O(2)-P(1)-O(4)-C(36)	-164.16(9)	C(9)-C(4)-C(5)-C(6)	-0.1(2)
O(3)-P(1)-O(4)-C(36)	104.67(9)	C(1)-C(4)-C(5)-C(6)	177.19(15)
C(1)-P(1)-O(4)-C(36)	9.04(12)	C(4)-C(5)-C(6)-C(7)	-0.1(3)
O(1)-P(1)-O(4)-C(36)	-75.10(9)	C(5)-C(6)-C(7)-C(8)	0.0(3)
O(2)-P(1)-C(1)-N(2)	87.86(11)	C(5)-C(6)-C(7)-C(10)	-179.40(17)
O(4)-P(1)-C(1)-N(2)	-82.73(11)	C(6)-C(7)-C(8)-C(9)	0.3(3)
O(3)-P(1)-C(1)-N(2)	179.33(9)	C(10)-C(7)-C(8)-C(9)	179.70(17)
O(1)-P(1)-C(1)-N(2)	3.12(9)	C(7)-C(8)-C(9)-C(4)	-0.5(3)
O(2)-P(1)-C(1)-C(4)	-87.85(14)	C(5)-C(4)-C(9)-C(8)	0.4(2)
O(4)-P(1)-C(1)-C(4)	101.56(12)	C(1)-C(4)-C(9)-C(8)	-176.93(15)
O(3)-P(1)-C(1)-C(4)	3.63(12)	C(3)-N(2)-C(11)-C(12)	95.50(15)
O(1)-P(1)-C(1)-C(4)	-172.58(12)	C(1)-N(2)-C(11)-C(12)	-88.47(14)
C(4)-C(1)-N(2)-C(3)	173.98(11)	N(2)-C(11)-C(12)-C(13)	-11.65(18)
P(1)-C(1)-N(2)-C(3)	-2.08(14)	N(2)-C(11)-C(12)-C(17)	171.62(12)

C (17)-C (12)-C (13)-C (14)	1.5 (2)
C (11)-C (12)-C (13)-C (14)	-175.19 (13)
C (12)-C (13)-C (14)-C (15)	-1.1 (2)
C (13)-C (14)-C (15)-C (16)	-0.3 (2)
C (14)-C (15)-C (16)-C (17)	1.2 (2)
C (13)-C (12)-C (17)-C (16)	-0.6 (2)
C (11)-C (12)-C (17)-C (16)	176.23 (14)
C (15)-C (16)-C (17)-C (12)	-0.7 (2)
O (1)-C (3)-C (18)-C (19)	-32.96 (18)
N (2)-C (3)-C (18)-C (19)	144.38 (14)
O (1)-C (3)-C (18)-C (23)	143.28 (13)
N (2)-C (3)-C (18)-C (23)	-39.4 (2)
C (23)-C (18)-C (19)-C (20)	1.4 (2)
C (3)-C (18)-C (19)-C (20)	177.83 (14)
C (18)-C (19)-C (20)-C (21)	1.3 (2)
C (210)-O (21)-C (21)-C (20)	2.6 (2)
C (210)-O (21)-C (21)-C (22)	177.10 (16)
C (19)-C (20)-C (21)-O (21)	-179.31 (15)
C (19)-C (20)-C (21)-C (22)	0.4 (2)
O (21)-C (21)-C (22)-C (23)	-179.92 (13)
C (20)-C (21)-C (22)-C (23)	0.3 (2)
C (21)-C (22)-C (23)-C (18)	-0.2 (2)
C (19)-C (18)-C (23)-C (22)	-0.6 (2)
C (3)-C (18)-C (23)-C (22)	-176.84 (13)
P (1)-O (2)-C (24)-C (25)	110.42 (13)
P (1)-O (2)-C (24)-C (29)	-72.58 (17)
C (29)-C (24)-C (25)-C (26)	1.1 (2)
O (2)-C (24)-C (25)-C (26)	178.08 (13)
C (24)-C (25)-C (26)-C (27)	-0.2 (2)
C (25)-C (26)-C (27)-C (28)	-0.4 (2)
C (26)-C (27)-C (28)-C (29)	0.2 (2)
C (27)-C (28)-C (29)-C (24)	0.7 (2)
C (25)-C (24)-C (29)-C (28)	-1.4 (2)
O (2)-C (24)-C (29)-C (28)	-178.30 (13)
P (1)-O (3)-C (30)-C (35)	-4.90 (19)
P (1)-O (3)-C (30)-C (31)	175.71 (9)
O (3)-C (30)-C (31)-C (32)	-178.24 (12)
C (35)-C (30)-C (31)-C (32)	2.3 (2)
C (30)-C (31)-C (32)-C (33)	-0.8 (2)
C (31)-C (32)-C (33)-C (34)	-1.0 (2)
C (32)-C (33)-C (34)-C (35)	1.4 (2)
C (33)-C (34)-C (35)-C (30)	0.1 (2)
O (3)-C (30)-C (35)-C (34)	178.68 (12)
C (31)-C (30)-C (35)-C (34)	-1.95 (19)
P (1)-O (4)-C (36)-C (37)	100.32 (13)
P (1)-O (4)-C (36)-C (41)	-82.91 (15)
C (41)-C (36)-C (37)-C (38)	0.0 (2)
O (4)-C (36)-C (37)-C (38)	176.73 (14)
C (36)-C (37)-C (38)-C (39)	-0.5 (2)
C (37)-C (38)-C (39)-C (40)	0.4 (3)
C (38)-C (39)-C (40)-C (41)	0.2 (3)
C (37)-C (36)-C (41)-C (40)	0.5 (2)
O (4)-C (36)-C (41)-C (40)	-176.15 (14)
C (39)-C (40)-C (41)-C (36)	-0.7 (2)

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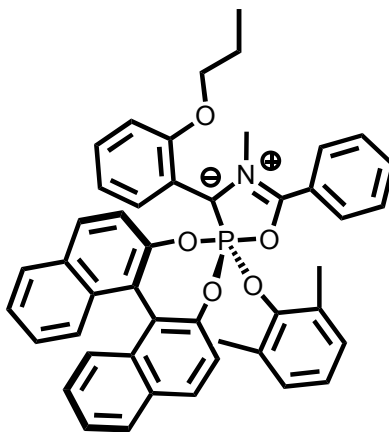
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Appendix D

X-Ray Structural Data for Compound 5.1d (Chapter 5)



Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Francine Bélanger.

ORTEP view of **5.1d** with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

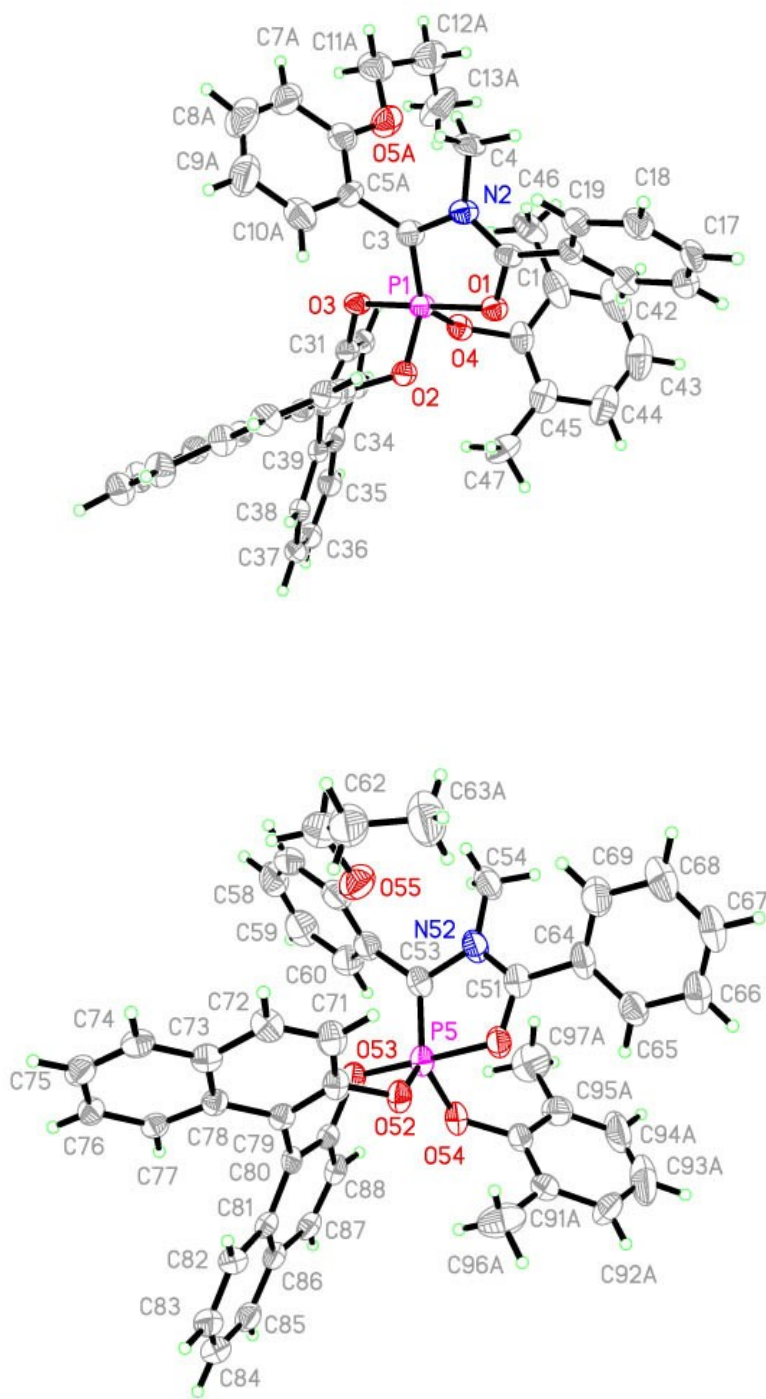


Table 1. Crystal data and structure refinement for **5.1d**

Identification code	arst37
Empirical formula	C ₄₆ H ₄₀ N O ₅ P
Formula weight	717.76
Temperature	100K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 11.4547(3) Å $\alpha = 90^\circ$ b = 13.3323(4) Å $\beta = 90^\circ$ c = 48.8967(14) Å $\gamma = 90^\circ$
Volume	7467.4(4) Å ³
Z	8
Density (calculated)	1.277 g/cm ³
Absorption coefficient	1.043 mm ⁻¹
F(000)	3024
Crystal size	0.06 x 0.04 x 0.02 mm
Theta range for data collection	1.81 to 71.10°
Index ranges	-13 ≤ h ≤ 14, -16 ≤ k ≤ 16, -57 ≤ l ≤ 59
Reflections collected	47212
Independent reflections	13792 [R _{int} = 0.095]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9794 and 0.7835
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	13792 / 73 / 997
Goodness-of-fit on F ²	1.018
Final R indices [I > 2sigma(I)]	R ₁ = 0.0685, wR ₂ = 0.1531
R indices (all data)	R ₁ = 0.0974, wR ₂ = 0.1694
Absolute structure parameter	0.03(3)
Largest diff. peak and hole	0.358 and -0.336 e/Å ³

Experimental details: The asymmetric unit contains two molecules

For the first molecule (around P1), the cycle with O-propyl is disordered over 2 positions.

The occupation factors were fixed to 0.75 and 0.25 in the last cycles while EADP constraints and SADI, SAME restraints were applied.

For the second molecule (around P5), the end of the propyl chain is disordered over two positions (occupation factors fixed to 0.50, EADP constraints and ISOR, SADI restraints were applied).

The O-dimethylphenyl is also disordered over two positions (occupation factors fixed to 0.50, EADP and AFIX 66 constraints and SADI restraints were applied).

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **5.1d**.

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	Occ.	x	y	z	U_{eq}
P(1)	1	9832(1)	4604(1)	4272(1)	28(1)
O(1)	1	10050(2)	3295(2)	4334(1)	29(1)
O(2)	1	11210(2)	4633(2)	4178(1)	29(1)
O(3)	1	9620(2)	5840(2)	4219(1)	30(1)
O(4)	1	9912(3)	4801(2)	4600(1)	32(1)
C(1)	1	9265(3)	2709(3)	4223(1)	29(1)
N(2)	1	8483(3)	3205(3)	4082(1)	31(1)
C(3)	1	8682(4)	4276(3)	4076(1)	35(1)
C(4)	1	7455(4)	2752(3)	3958(1)	36(1)
C(5A)	0.75	8053(5)	4842(4)	3851(1)	33(1)
C(6A)	0.75	6872(6)	5085(5)	3856(2)	44(2)
C(7A)	0.75	6322(11)	5505(11)	3613(2)	56(3)
C(8A)	0.75	6945(8)	5624(7)	3386(2)	66(2)
C(9A)	0.75	8103(9)	5460(7)	3374(2)	69(2)
C(10A)	0.75	8671(7)	5059(6)	3607(1)	50(2)
O(5A)	0.75	6313(4)	4902(4)	4086(1)	48(1)
C(11A)	0.75	5096(7)	5237(6)	4099(2)	56(2)
C(12A)	0.75	4618(7)	4943(7)	4374(2)	68(2)
C(13A)	0.75	5221(8)	5418(8)	4603(2)	82(3)
C(5B)	0.25	7584(12)	4847(12)	4030(3)	33(1)

C (6B)	0.25	7408 (16)	4929 (16)	3752 (3)	44 (2)
C (7B)	0.25	6270 (30)	5350 (40)	3671 (7)	56 (3)
C (8B)	0.25	5650 (20)	5790 (20)	3860 (4)	66 (2)
C (9B)	0.25	5800 (20)	5720 (20)	4140 (4)	69 (2)
C (10B)	0.25	6828 (16)	5265 (16)	4238 (4)	50 (2)
O (5B)	0.25	8112 (12)	4576 (11)	3567 (3)	48 (1)
C (11B)	0.25	8990 (19)	5266 (17)	3456 (5)	56 (2)
C (12B)	0.25	9574 (18)	4830 (20)	3210 (4)	68 (2)
C (13B)	0.25	8840 (20)	4610 (20)	2974 (4)	82 (3)
C (14)	1	9352 (3)	1621 (3)	4266 (1)	30 (1)
C (15)	1	9707 (4)	1268 (3)	4521 (1)	33 (1)
C (16)	1	9910 (4)	252 (4)	4557 (1)	41 (1)
C (17)	1	9755 (4)	-411 (3)	4341 (1)	41 (1)
C (18)	1	9382 (4)	-72 (4)	4089 (1)	40 (1)
C (19)	1	9181 (4)	948 (3)	4052 (1)	33 (1)
C (20)	1	11638 (4)	5248 (3)	3969 (1)	31 (1)
C (21)	1	11962 (4)	4750 (3)	3725 (1)	34 (1)
C (22)	1	12516 (4)	5269 (4)	3524 (1)	38 (1)
C (23)	1	12733 (4)	6299 (4)	3553 (1)	37 (1)
C (24)	1	13351 (5)	6845 (4)	3347 (1)	44 (1)
C (25)	1	13569 (5)	7845 (4)	3374 (1)	45 (1)
C (26)	1	13140 (4)	8369 (4)	3600 (1)	38 (1)
C (27)	1	12534 (4)	7874 (4)	3802 (1)	35 (1)
C (28)	1	12359 (4)	6818 (3)	3792 (1)	32 (1)
C (29)	1	11823 (4)	6255 (3)	4010 (1)	28 (1)
C (30)	1	11433 (3)	6719 (3)	4269 (1)	27 (1)
C (31)	1	10319 (4)	6493 (3)	4359 (1)	28 (1)
C (32)	1	9851 (4)	6937 (3)	4600 (1)	28 (1)
C (33)	1	10511 (4)	7558 (3)	4754 (1)	32 (1)
C (34)	1	11692 (4)	7787 (3)	4680 (1)	30 (1)
C (35)	1	12395 (4)	8425 (3)	4841 (1)	37 (1)
C (36)	1	13529 (4)	8606 (4)	4772 (1)	38 (1)
C (37)	1	14012 (4)	8129 (3)	4544 (1)	35 (1)
C (38)	1	13353 (4)	7510 (3)	4383 (1)	30 (1)
C (39)	1	12150 (4)	7338 (3)	4438 (1)	28 (1)
C (40)	1	10036 (4)	4110 (3)	4814 (1)	37 (1)
C (41)	1	9023 (5)	3710 (4)	4926 (1)	47 (1)
C (42)	1	9148 (7)	3084 (4)	5150 (1)	60 (2)
C (43)	1	10228 (7)	2886 (5)	5260 (1)	66 (2)
C (44)	1	11223 (6)	3298 (4)	5146 (1)	57 (2)
C (45)	1	11139 (5)	3928 (4)	4919 (1)	43 (1)
C (46)	1	7849 (5)	3971 (4)	4812 (1)	53 (2)
C (47)	1	12206 (5)	4397 (5)	4793 (1)	51 (1)
P (5)	1	1524 (1)	4340 (1)	6876 (1)	33 (1)
O (51)	1	1363 (3)	5062 (2)	7185 (1)	36 (1)
O (52)	1	799 (3)	5249 (2)	6724 (1)	35 (1)
O (53)	1	1691 (3)	3677 (2)	6589 (1)	32 (1)
O (54)	1	488 (3)	3599 (2)	6977 (1)	37 (1)
O (55)	1	4646 (3)	5551 (3)	6770 (1)	57 (1)
C (51)	1	2337 (4)	5166 (4)	7323 (1)	40 (1)
N (52)	1	3241 (4)	4758 (3)	7206 (1)	41 (1)
C (53)	1	2971 (4)	4282 (4)	6953 (1)	38 (1)
C (54)	1	4380 (5)	4609 (5)	7336 (1)	53 (2)
C (55)	1	3961 (4)	3922 (4)	6784 (1)	42 (1)
C (56)	1	4822 (4)	4585 (4)	6694 (1)	45 (1)
C (57)	1	5768 (4)	4230 (5)	6541 (1)	52 (2)
C (58)	1	5854 (5)	3238 (5)	6472 (1)	57 (2)

C (59)	1	4997 (5)	2587 (5)	6549 (1)	60 (2)
C (60)	1	4070 (4)	2915 (4)	6707 (1)	47 (1)
C (61)	1	5458 (6)	6285 (6)	6663 (1)	71 (2)
C (62)	1	5039 (7)	7315 (6)	6750 (1)	76 (2)
C (63A)	0.50	4800 (40)	7430 (30)	7050 (3)	96 (8)
C (63B)	0.50	5210 (40)	7510 (30)	7050 (3)	96 (8)
C (64)	1	2279 (5)	5706 (4)	7584 (1)	43 (1)
C (65)	1	1246 (5)	5642 (4)	7735 (1)	45 (1)
C (66)	1	1131 (6)	6193 (4)	7973 (1)	51 (1)
C (67)	1	1998 (6)	6817 (4)	8062 (1)	52 (2)
C (68)	1	3022 (6)	6895 (5)	7914 (1)	60 (2)
C (69)	1	3149 (6)	6346 (5)	7675 (1)	55 (2)
C (70)	1	1188 (4)	5652 (3)	6479 (1)	31 (1)
C (71)	1	1758 (4)	6577 (4)	6493 (1)	39 (1)
C (72)	1	2112 (4)	7042 (4)	6257 (1)	38 (1)
C (73)	1	1926 (4)	6591 (3)	5998 (1)	32 (1)
C (74)	1	2323 (4)	7044 (3)	5756 (1)	34 (1)
C (75)	1	2231 (4)	6572 (4)	5511 (1)	39 (1)
C (76)	1	1752 (4)	5594 (3)	5498 (1)	32 (1)
C (77)	1	1343 (3)	5142 (3)	5728 (1)	28 (1)
C (78)	1	1387 (4)	5620 (3)	5987 (1)	28 (1)
C (79)	1	956 (4)	5171 (3)	6237 (1)	28 (1)
C (80)	1	357 (4)	4174 (3)	6242 (1)	28 (1)
C (81)	1	-632 (4)	3931 (3)	6074 (1)	29 (1)
C (82)	1	-1212 (4)	4647 (4)	5906 (1)	34 (1)
C (83)	1	-2129 (4)	4376 (4)	5747 (1)	39 (1)
C (84)	1	-2533 (4)	3373 (4)	5742 (1)	43 (1)
C (85)	1	-2023 (4)	2681 (4)	5904 (1)	41 (1)
C (86)	1	-1078 (4)	2938 (3)	6077 (1)	32 (1)
C (87)	1	-584 (4)	2222 (4)	6258 (1)	34 (1)
C (88)	1	292 (4)	2492 (3)	6431 (1)	34 (1)
C (89)	1	752 (3)	3469 (3)	6422 (1)	28 (1)
C (90A)	0.50	-136 (9)	3579 (14)	7224 (2)	41 (2)
C (91A)	0.50	-1200 (8)	4070 (11)	7252 (2)	43 (3)
C (92A)	0.50	-1844 (7)	3963 (9)	7491 (2)	74 (4)
C (93A)	0.50	-1425 (9)	3366 (10)	7702 (2)	85 (5)
C (94A)	0.50	-361 (10)	2875 (10)	7675 (2)	77 (5)
C (95A)	0.50	283 (9)	2981 (12)	7436 (2)	49 (3)
C (96A)	0.50	-1670 (20)	4680 (20)	7017 (4)	71 (5)
C (97A)	0.50	1419 (16)	2424 (18)	7402 (4)	74 (5)
C (90B)	0.50	135 (10)	3423 (14)	7238 (2)	41 (2)
C (91B)	0.50	-884 (8)	3881 (11)	7329 (2)	43 (3)
C (92B)	0.50	-1328 (7)	3653 (9)	7586 (2)	74 (4)
C (93B)	0.50	-753 (9)	2968 (9)	7753 (2)	85 (5)
C (94B)	0.50	267 (10)	2511 (9)	7662 (2)	77 (5)
C (95B)	0.50	710 (9)	2738 (12)	7405 (2)	49 (3)
C (96B)	0.50	-1500 (20)	4590 (20)	7134 (4)	71 (5)
C (97B)	0.50	1770 (16)	2190 (18)	7298 (4)	74 (5)

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **5.1d**

	Occ.	x	y	z	U _{eq}
H(4A)	1	7556	2725	3759	55
H(4B)	1	6764	3155	4002	55
H(4C)	1	7352	2070	4029	55
H(7A)	0.75	5522	5693	3616	67
H(8A)	0.75	6555	5834	3224	79
H(9A)	0.75	8532	5610	3213	83
H(10A)	0.75	9487	4933	3600	61
H(11A)	0.75	4635	4916	3952	68
H(11B)	0.75	5053	5973	4075	68
H(12A)	0.75	3781	5124	4382	82
H(12B)	0.75	4676	4206	4394	82
H(13A)	0.75	6066	5345	4579	123
H(13B)	0.75	4982	5096	4774	123
H(13C)	0.75	5018	6132	4609	123
H(7B)	0.25	5992	5302	3488	67
H(8B)	0.25	5026	6208	3799	79
H(9B)	0.25	5225	5966	4263	83
H(10B)	0.25	7013	5236	4427	61
H(11C)	0.25	9583	5409	3599	68
H(11D)	0.25	8611	5907	3406	68
H(12C)	0.25	10191	5302	3151	82
H(12D)	0.25	9966	4201	3267	82
H(13D)	0.25	8258	5136	2951	123
H(13E)	0.25	8449	3961	3002	123
H(13F)	0.25	9331	4569	2809	123
H(15)	1	9810	1721	4669	40
H(16)	1	10155	8	4730	49
H(17)	1	9908	-1104	4367	49
H(18)	1	9264	-530	3943	48
H(19)	1	8924	1187	3879	39
H(21)	1	11793	4058	3702	41
H(22)	1	12757	4931	3362	45
H(24)	1	13615	6503	3188	53
H(25)	1	14013	8186	3239	54
H(26)	1	13268	9071	3615	46
H(27)	1	12225	8245	3951	42
H(32)	1	9070	6794	4653	34
H(33)	1	10186	7848	4915	38
H(35)	1	12075	8733	4999	45
H(36)	1	13988	9055	4878	46
H(37)	1	14811	8237	4500	42
H(38)	1	13706	7188	4230	36
H(42)	1	8475	2785	5229	72
H(43)	1	10291	2463	5415	80
H(44)	1	11966	3153	5223	68
H(46A)	1	7824	4688	4768	80
H(46B)	1	7245	3816	4947	80
H(46C)	1	7708	3580	4645	80
H(47A)	1	12341	4107	4612	77

H (47B)	1	12885	4267	4910	77
H (47C)	1	12089	5122	4776	77
H (54A)	1	4660	3929	7297	80
H (54B)	1	4305	4699	7534	80
H (54C)	1	4937	5099	7263	80
H (57)	1	6360	4685	6485	63
H (58)	1	6506	3005	6370	69
H (59)	1	5037	1904	6495	72
H (60)	1	3495	2447	6765	57
H (61A)	1	5489	6241	6461	85
H (61B)	1	6251	6159	6736	85
H (62A)	0.50	5633	7816	6695	91
H (62B)	0.50	4313	7472	6648	91
H (62C)	0.50	5468	7831	6644	91
H (62D)	0.50	4199	7381	6705	91
H (63A)	0.50	4514	8110	7086	145
H (63B)	0.50	5528	7320	7152	145
H (63C)	0.50	4217	6939	7107	145
H (63D)	0.50	4921	8180	7096	145
H (63E)	0.50	6041	7463	7095	145
H (63F)	0.50	4775	7008	7156	145
H (65)	1	627	5223	7675	54
H (66)	1	434	6137	8077	61
H (67)	1	1897	7196	8225	63
H (68)	1	3634	7320	7976	72
H (69)	1	3847	6410	7572	66
H (71)	1	1900	6882	6666	46
H (72)	1	2487	7676	6267	45
H (74)	1	2663	7694	5764	40
H (75)	1	2486	6896	5348	47
H (76)	1	1717	5252	5328	38
H (77)	1	1019	4488	5715	34
H (82)	1	-954	5324	5906	41
H (83)	1	-2505	4866	5636	47
H (84)	1	-3161	3189	5625	52
H (85)	1	-2302	2010	5902	49
H (87)	1	-865	1551	6258	41
H (88)	1	592	2020	6559	41
H (92A)	0.50	-2571	4299	7510	89
H (93A)	0.50	-1865	3293	7866	102
H (94A)	0.50	-74	2467	7819	93
H (96A)	0.50	-2491	4838	7050	107
H (96B)	0.50	-1597	4293	6847	107
H (96C)	0.50	-1221	5302	7001	107
H (97A)	0.50	1434	1850	7528	110
H (97B)	0.50	2071	2874	7445	110
H (97C)	0.50	1491	2185	7214	110
H (92B)	0.50	-2025	3966	7648	89
H (93B)	0.50	-1056	2813	7928	102
H (94B)	0.50	660	2042	7776	93
H (96D)	0.50	-2223	4828	7218	107
H (96E)	0.50	-1679	4234	6963	107
H (96F)	0.50	-989	5161	7094	107
H (97D)	0.50	2394	2674	7260	110
H (97E)	0.50	1565	1836	7129	110
H (97F)	0.50	2038	1706	7435	110

Table 4. Anisotropic parameters ($\text{\AA}^2 \times 10^3$) for **5.1d**.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
P(1)	26(1)	20(1)	38(1)	-3(1)	-2(1)	1(1)
O(1)	29(1)	23(1)	35(2)	-5(1)	-3(1)	-1(1)
O(2)	28(1)	21(2)	39(2)	0(1)	-2(1)	2(1)
O(3)	25(1)	24(1)	39(2)	-4(1)	-4(1)	-1(1)
O(4)	33(2)	22(1)	40(2)	-4(1)	2(1)	-1(1)
C(1)	26(2)	27(2)	33(2)	-6(2)	2(2)	-2(2)
N(2)	29(2)	23(2)	42(2)	-8(2)	-5(2)	0(1)
C(3)	34(2)	23(2)	47(3)	-3(2)	-4(2)	1(2)
C(4)	30(2)	28(2)	51(3)	-10(2)	-8(2)	-7(2)
C(5A)	39(3)	23(3)	37(3)	-2(3)	-14(3)	1(2)
C(6A)	40(4)	33(3)	59(5)	4(3)	-4(3)	-3(3)
C(7A)	63(4)	36(7)	69(6)	5(5)	-25(5)	-3(4)
C(8A)	86(6)	70(6)	42(4)	4(4)	-21(4)	-1(5)
C(9A)	89(6)	66(6)	51(5)	16(4)	-12(4)	-1(5)
C(10A)	54(4)	55(5)	43(4)	-1(3)	7(3)	-16(3)
O(5A)	45(2)	42(3)	58(3)	2(2)	-3(2)	14(2)
C(11A)	54(4)	47(4)	68(5)	-10(4)	-7(4)	-5(3)
C(12A)	53(4)	73(6)	78(6)	8(5)	4(4)	19(4)
C(13A)	63(5)	127(9)	57(5)	22(5)	2(4)	43(6)
C(5B)	39(3)	23(3)	37(3)	-2(3)	-14(3)	1(2)
C(6B)	40(4)	33(3)	59(5)	4(3)	-4(3)	-3(3)
C(7B)	63(4)	36(7)	69(6)	5(5)	-25(5)	-3(4)
C(8B)	86(6)	70(6)	42(4)	4(4)	-21(4)	-1(5)
C(9B)	89(6)	66(6)	51(5)	16(4)	-12(4)	-1(5)
C(10B)	54(4)	55(5)	43(4)	-1(3)	7(3)	-16(3)
O(5B)	45(2)	42(3)	58(3)	2(2)	-3(2)	14(2)
C(11B)	54(4)	47(4)	68(5)	-10(4)	-7(4)	-5(3)
C(12B)	53(4)	73(6)	78(6)	8(5)	4(4)	19(4)
C(13B)	63(5)	127(9)	57(5)	22(5)	2(4)	43(6)
C(14)	28(2)	29(2)	34(2)	2(2)	4(2)	-4(2)
C(15)	34(2)	30(2)	35(2)	-2(2)	6(2)	-4(2)
C(16)	38(2)	46(3)	40(3)	11(2)	-1(2)	-5(2)
C(17)	41(2)	22(2)	58(3)	7(2)	5(2)	-4(2)
C(18)	41(2)	29(2)	50(3)	-3(2)	3(2)	-4(2)
C(19)	36(2)	27(2)	35(2)	-3(2)	1(2)	-4(2)
C(20)	27(2)	27(2)	38(2)	-3(2)	-2(2)	5(2)
C(21)	32(2)	26(2)	45(3)	-9(2)	2(2)	5(2)
C(22)	41(2)	39(3)	34(2)	-8(2)	5(2)	5(2)
C(23)	42(2)	32(2)	36(3)	-3(2)	2(2)	2(2)
C(24)	49(3)	44(3)	40(3)	0(2)	10(2)	7(2)
C(25)	47(3)	46(3)	41(3)	4(2)	7(2)	-3(2)
C(26)	44(3)	33(3)	37(3)	2(2)	3(2)	-5(2)
C(27)	35(2)	33(2)	37(3)	-1(2)	0(2)	4(2)
C(28)	31(2)	31(2)	34(2)	2(2)	-3(2)	1(2)
C(29)	25(2)	25(2)	34(2)	-1(2)	-2(2)	4(2)
C(30)	29(2)	20(2)	33(2)	4(2)	0(2)	1(2)

C (31)	27 (2)	20 (2)	37 (2)	-1 (2)	-5 (2)	3 (2)
C (32)	30 (2)	19 (2)	36 (2)	2 (2)	4 (2)	5 (2)
C (33)	42 (2)	24 (2)	29 (2)	1 (2)	6 (2)	3 (2)
C (34)	42 (2)	20 (2)	30 (2)	4 (2)	-8 (2)	4 (2)
C (35)	48 (3)	28 (2)	35 (2)	-2 (2)	-7 (2)	-5 (2)
C (36)	44 (3)	29 (2)	41 (3)	2 (2)	-14 (2)	-9 (2)
C (37)	30 (2)	31 (2)	44 (3)	10 (2)	-8 (2)	-7 (2)
C (38)	28 (2)	26 (2)	36 (2)	9 (2)	-2 (2)	0 (2)
C (39)	29 (2)	24 (2)	31 (2)	6 (2)	-4 (2)	-2 (2)
C (40)	56 (3)	25 (2)	30 (2)	-3 (2)	2 (2)	-3 (2)
C (41)	72 (4)	23 (2)	45 (3)	-10 (2)	19 (3)	-7 (2)
C (42)	99 (5)	36 (3)	46 (3)	-11 (3)	21 (3)	-13 (3)
C (43)	118 (6)	43 (3)	39 (3)	4 (3)	0 (4)	2 (4)
C (44)	92 (5)	37 (3)	43 (3)	-4 (2)	-22 (3)	8 (3)
C (45)	60 (3)	34 (3)	34 (3)	-6 (2)	-2 (2)	7 (2)
C (46)	45 (3)	45 (3)	70 (4)	-9 (3)	21 (3)	-8 (2)
C (47)	47 (3)	59 (4)	48 (3)	-6 (3)	-18 (3)	11 (3)
P (5)	40 (1)	34 (1)	26 (1)	-2 (1)	3 (1)	4 (1)
O (51)	40 (2)	44 (2)	26 (2)	-3 (1)	1 (1)	5 (2)
O (52)	41 (2)	39 (2)	26 (2)	-2 (1)	5 (1)	8 (1)
O (53)	34 (2)	34 (2)	28 (2)	2 (1)	2 (1)	5 (1)
O (54)	49 (2)	38 (2)	23 (2)	1 (1)	4 (1)	4 (2)
O (55)	55 (2)	56 (2)	60 (2)	-2 (2)	12 (2)	-14 (2)
C (51)	48 (3)	41 (3)	32 (2)	0 (2)	1 (2)	3 (2)
N (52)	46 (2)	50 (3)	27 (2)	-4 (2)	-3 (2)	8 (2)
C (53)	46 (3)	38 (3)	30 (2)	-7 (2)	-2 (2)	1 (2)
C (54)	49 (3)	79 (4)	32 (3)	-12 (3)	-8 (2)	9 (3)
C (55)	33 (2)	58 (3)	34 (3)	-6 (2)	-3 (2)	12 (2)
C (56)	42 (3)	57 (3)	37 (3)	-11 (2)	-6 (2)	3 (2)
C (57)	32 (2)	83 (4)	43 (3)	-5 (3)	-3 (2)	2 (3)
C (58)	47 (3)	83 (5)	42 (3)	-15 (3)	3 (3)	22 (3)
C (59)	56 (3)	70 (4)	53 (3)	-10 (3)	-7 (3)	29 (3)
C (60)	39 (3)	53 (3)	49 (3)	2 (3)	-3 (2)	13 (2)
C (61)	70 (4)	84 (5)	59 (4)	-12 (4)	3 (3)	-29 (4)
C (62)	91 (5)	75 (5)	62 (4)	-5 (3)	8 (4)	-36 (4)
C (63A)	140 (20)	86 (7)	59 (4)	-11 (4)	13 (7)	-37 (12)
C (63B)	140 (20)	86 (7)	59 (4)	-11 (4)	13 (7)	-37 (12)
C (64)	54 (3)	51 (3)	24 (2)	-2 (2)	-1 (2)	16 (2)
C (65)	48 (3)	55 (3)	33 (2)	-2 (2)	-6 (2)	10 (2)
C (66)	66 (4)	56 (4)	32 (3)	0 (2)	1 (3)	23 (3)
C (67)	84 (4)	47 (3)	26 (3)	-2 (2)	-1 (3)	17 (3)
C (68)	89 (5)	56 (4)	34 (3)	-1 (3)	-8 (3)	-2 (3)
C (69)	69 (4)	58 (4)	39 (3)	-5 (3)	6 (3)	-6 (3)
C (70)	35 (2)	27 (2)	30 (2)	0 (2)	4 (2)	10 (2)
C (71)	48 (3)	33 (3)	36 (3)	-6 (2)	3 (2)	6 (2)
C (72)	45 (3)	27 (2)	41 (3)	-1 (2)	-4 (2)	0 (2)
C (73)	30 (2)	28 (2)	38 (2)	0 (2)	-1 (2)	4 (2)
C (74)	31 (2)	26 (2)	44 (3)	1 (2)	0 (2)	-2 (2)
C (75)	34 (2)	41 (3)	41 (3)	8 (2)	4 (2)	-2 (2)
C (76)	29 (2)	34 (2)	31 (2)	-1 (2)	3 (2)	2 (2)
C (77)	25 (2)	26 (2)	33 (2)	2 (2)	1 (2)	2 (2)
C (78)	26 (2)	29 (2)	31 (2)	1 (2)	2 (2)	4 (2)
C (79)	27 (2)	27 (2)	30 (2)	1 (2)	2 (2)	5 (2)
C (80)	30 (2)	33 (2)	21 (2)	-6 (2)	6 (2)	4 (2)
C (81)	26 (2)	33 (2)	28 (2)	-2 (2)	8 (2)	2 (2)
C (82)	30 (2)	35 (2)	37 (2)	0 (2)	0 (2)	-1 (2)
C (83)	32 (2)	48 (3)	38 (3)	5 (2)	0 (2)	3 (2)

C (84)	32 (2)	53 (3)	43 (3)	0 (3)	3 (2)	-5 (2)
C (85)	39 (3)	48 (3)	36 (3)	-1 (2)	10 (2)	-11 (2)
C (86)	32 (2)	34 (2)	29 (2)	0 (2)	9 (2)	-3 (2)
C (87)	35 (2)	32 (2)	36 (2)	-2 (2)	13 (2)	-6 (2)
C (88)	38 (2)	33 (2)	30 (2)	4 (2)	11 (2)	7 (2)
C (89)	26 (2)	34 (2)	25 (2)	-2 (2)	5 (2)	3 (2)
C (90A)	41 (6)	55 (6)	27 (3)	-4 (3)	1 (3)	-14 (4)
C (91A)	37 (6)	55 (7)	36 (6)	-8 (5)	-3 (5)	-9 (5)
C (92A)	41 (7)	122 (11)	58 (8)	-29 (7)	22 (5)	-25 (7)
C (93A)	128 (14)	93 (11)	34 (5)	-3 (6)	18 (7)	-23 (9)
C (94A)	97 (12)	109 (12)	27 (4)	3 (6)	2 (7)	-31 (9)
C (95A)	46 (9)	61 (9)	40 (4)	16 (5)	-5 (5)	-9 (6)
C (96A)	42 (7)	62 (7)	109 (17)	0 (11)	0 (10)	16 (5)
C (97A)	72 (11)	81 (11)	68 (12)	44 (10)	-2 (7)	3 (7)
C (90B)	41 (6)	55 (6)	27 (3)	-4 (3)	1 (3)	-14 (4)
C (91B)	37 (6)	55 (7)	36 (6)	-8 (5)	-3 (5)	-9 (5)
C (92B)	41 (7)	122 (11)	58 (8)	-29 (7)	22 (5)	-25 (7)
C (93B)	128 (14)	93 (11)	34 (5)	-3 (6)	18 (7)	-23 (9)
C (94B)	97 (12)	109 (12)	27 (4)	3 (6)	2 (7)	-31 (9)
C (95B)	46 (9)	61 (9)	40 (4)	16 (5)	-5 (5)	-9 (6)
C (96B)	42 (7)	62 (7)	109 (17)	0 (11)	0 (10)	16 (5)
C (97B)	72 (11)	81 (11)	68 (12)	44 (10)	-2 (7)	3 (7)

Table 5. Bond lengths [Å] and angles [°] for **5.1d**.

P (1) -O (4)	1.627 (3)	C (5b) -C (6b)	1.380 (16)
P (1) -O (2)	1.646 (3)	C (5b) -C (10b)	1.447 (17)
P (1) -O (3)	1.686 (3)	C (6b) -O (5b)	1.300 (15)
P (1) -C (3)	1.687 (5)	C (6b) -C (7b)	1.478 (18)
P (1) -O (1)	1.788 (3)	C (7b) -C (8b)	1.30 (3)
O (1) -C (1)	1.309 (5)	C (8b) -C (9b)	1.385 (19)
O (2) -C (20)	1.398 (5)	C (9b) -C (10b)	1.408 (19)
O (3) -C (31)	1.365 (5)	O (5b) -C (11b)	1.466 (17)
O (4) -C (40)	1.400 (5)	C (11b) -C (12b)	1.495 (19)
C (1) -N (2)	1.309 (5)	C (12b) -C (13b)	1.46 (2)
C (1) -C (14)	1.469 (6)	C (14) -C (19)	1.391 (6)
N (2) -C (3)	1.446 (5)	C (14) -C (15)	1.397 (6)
N (2) -C (4)	1.457 (5)	C (15) -C (16)	1.385 (6)
C (3) -C (5b)	1.488 (12)	C (16) -C (17)	1.389 (7)
C (3) -C (5a)	1.517 (7)	C (17) -C (18)	1.380 (7)
C (5a) -C (6a)	1.392 (8)	C (18) -C (19)	1.392 (6)
C (5a) -C (10a)	1.418 (9)	C (20) -C (29)	1.374 (6)
C (6a) -O (5a)	1.316 (8)	C (20) -C (21)	1.413 (6)
C (6a) -C (7a)	1.460 (10)	C (21) -C (22)	1.361 (7)
C (7a) -C (8a)	1.329 (17)	C (22) -C (23)	1.403 (6)
C (8a) -C (9a)	1.346 (12)	C (23) -C (28)	1.426 (6)
C (9a) -C (10a)	1.416 (10)	C (23) -C (24)	1.428 (7)
O (5a) -C (11a)	1.466 (9)	C (24) -C (25)	1.363 (7)
C (11a) -C (12a)	1.504 (11)	C (25) -C (26)	1.399 (7)
C (12a) -C (13a)	1.458 (12)	C (26) -C (27)	1.375 (6)

C(27)-C(28)	1.423(6)	C(72)-C(73)	1.417(7)
C(28)-C(29)	1.439(6)	C(73)-C(74)	1.405(6)
C(29)-C(30)	1.481(6)	C(73)-C(78)	1.436(6)
C(30)-C(31)	1.382(6)	C(74)-C(75)	1.359(7)
C(30)-C(39)	1.428(6)	C(75)-C(76)	1.415(6)
C(31)-C(32)	1.426(6)	C(76)-C(77)	1.358(6)
C(32)-C(33)	1.351(6)	C(77)-C(78)	1.421(6)
C(33)-C(34)	1.433(6)	C(78)-C(79)	1.449(6)
C(34)-C(35)	1.410(6)	C(79)-C(80)	1.496(6)
C(34)-C(39)	1.426(6)	C(80)-C(89)	1.366(6)
C(35)-C(36)	1.363(7)	C(80)-C(81)	1.435(6)
C(36)-C(37)	1.397(7)	C(81)-C(86)	1.420(6)
C(37)-C(38)	1.369(6)	C(81)-C(82)	1.424(6)
C(38)-C(39)	1.424(6)	C(82)-C(83)	1.358(6)
C(40)-C(45)	1.385(7)	C(83)-C(84)	1.415(7)
C(40)-C(41)	1.390(7)	C(84)-C(85)	1.350(7)
C(41)-C(42)	1.385(8)	C(85)-C(86)	1.416(6)
C(41)-C(46)	1.496(8)	C(86)-C(87)	1.419(6)
C(42)-C(43)	1.375(10)	C(87)-C(88)	1.363(6)
C(43)-C(44)	1.382(9)	C(88)-C(89)	1.405(6)
C(44)-C(45)	1.395(7)	C(90a)-C(91a)	1.3900
C(45)-C(47)	1.505(8)	C(90a)-C(95a)	1.3900
P(5)-O(54)	1.621(4)	C(91a)-C(92a)	1.3900
P(5)-O(52)	1.646(3)	C(91a)-C(96a)	1.506(12)
P(5)-O(53)	1.667(3)	C(92a)-C(93a)	1.3900
P(5)-C(53)	1.702(5)	C(93a)-C(94a)	1.3900
P(5)-O(51)	1.800(3)	C(94a)-C(95a)	1.3900
O(51)-C(51)	1.313(6)	C(95a)-C(97a)	1.507(12)
O(52)-C(70)	1.388(5)	C(90b)-C(91b)	1.3900
O(53)-C(89)	1.378(5)	C(90b)-C(95b)	1.3900
O(54)-C(90b)	1.362(7)	C(91b)-C(92b)	1.3900
O(54)-C(90a)	1.406(7)	C(91b)-C(96b)	1.514(12)
O(55)-C(56)	1.355(7)	C(92b)-C(93b)	1.3900
O(55)-C(61)	1.450(7)	C(93b)-C(94b)	1.3900
C(51)-N(52)	1.303(6)	C(94b)-C(95b)	1.3900
C(51)-C(64)	1.466(7)	C(95b)-C(97b)	1.510(12)
N(52)-C(53)	1.426(6)		
N(52)-C(54)	1.463(6)	O(4)-P(1)-O(2)	102.72(16)
C(53)-C(55)	1.483(6)	O(4)-P(1)-O(3)	90.12(15)
C(55)-C(56)	1.395(7)	O(2)-P(1)-O(3)	94.10(15)
C(55)-C(60)	1.400(7)	O(4)-P(1)-C(3)	130.2(2)
C(56)-C(57)	1.399(7)	O(2)-P(1)-C(3)	126.5(2)
C(57)-C(58)	1.370(9)	O(3)-P(1)-C(3)	93.06(19)
C(58)-C(59)	1.364(9)	O(4)-P(1)-O(1)	89.12(14)
C(59)-C(60)	1.384(7)	O(2)-P(1)-O(1)	86.36(14)
C(61)-C(62)	1.516(10)	O(3)-P(1)-O(1)	179.18(16)
C(62)-C(63a)	1.499(15)	C(3)-P(1)-O(1)	87.21(19)
C(62)-C(63b)	1.506(15)	C(1)-O(1)-P(1)	114.6(3)
C(64)-C(69)	1.385(8)	C(20)-O(2)-P(1)	123.8(3)
C(64)-C(65)	1.398(7)	C(31)-O(3)-P(1)	117.5(3)
C(65)-C(66)	1.382(7)	C(40)-O(4)-P(1)	129.4(3)
C(66)-C(67)	1.366(9)	O(1)-C(1)-N(2)	112.8(4)
C(67)-C(68)	1.381(9)	O(1)-C(1)-C(14)	118.9(4)
C(68)-C(69)	1.387(8)	N(2)-C(1)-C(14)	128.3(4)
C(70)-C(79)	1.369(6)	C(1)-N(2)-C(3)	113.6(4)
C(70)-C(71)	1.397(7)	C(1)-N(2)-C(4)	124.3(4)
C(71)-C(72)	1.373(7)	C(3)-N(2)-C(4)	121.9(4)

N (2) -C (3) -C (5B)	112.0 (8)	C (28) -C (29) -C (30)	123.0 (4)
N (2) -C (3) -C (5A)	115.5 (4)	C (31) -C (30) -C (39)	118.3 (4)
C (5B) -C (3) -C (5A)	39.9 (7)	C (31) -C (30) -C (29)	117.3 (4)
N (2) -C (3) -P (1)	111.6 (3)	C (39) -C (30) -C (29)	124.4 (4)
C (5B) -C (3) -P (1)	127.9 (7)	O (3) -C (31) -C (30)	121.5 (4)
C (5A) -C (3) -P (1)	130.9 (4)	O (3) -C (31) -C (32)	117.2 (4)
C (6A) -C (5A) -C (10A)	116.9 (6)	C (30) -C (31) -C (32)	121.3 (4)
C (6A) -C (5A) -C (3)	124.4 (6)	C (33) -C (32) -C (31)	120.4 (4)
C (10A) -C (5A) -C (3)	118.4 (5)	C (32) -C (33) -C (34)	121.2 (4)
O (5A) -C (6A) -C (5A)	116.4 (6)	C (35) -C (34) -C (39)	120.3 (4)
O (5A) -C (6A) -C (7A)	124.0 (8)	C (35) -C (34) -C (33)	121.9 (4)
C (5A) -C (6A) -C (7A)	119.6 (8)	C (39) -C (34) -C (33)	117.8 (4)
C (8A) -C (7A) -C (6A)	119.7 (10)	C (36) -C (35) -C (34)	120.9 (5)
C (7A) -C (8A) -C (9A)	123.0 (8)	C (35) -C (36) -C (37)	119.6 (4)
C (8A) -C (9A) -C (10A)	118.8 (8)	C (38) -C (37) -C (36)	121.0 (4)
C (9A) -C (10A) -C (5A)	121.7 (8)	C (37) -C (38) -C (39)	121.4 (4)
C (6A) -O (5A) -C (11A)	116.3 (6)	C (38) -C (39) -C (34)	116.6 (4)
O (5A) -C (11A) -C (12A)	107.8 (6)	C (38) -C (39) -C (30)	122.6 (4)
C (13A) -C (12A) -C (11A)	113.6 (8)	C (34) -C (39) -C (30)	120.8 (4)
C (6B) -C (5B) -C (10B)	125.1 (13)	C (45) -C (40) -C (41)	123.3 (5)
C (6B) -C (5B) -C (3)	108.3 (12)	C (45) -C (40) -O (4)	119.0 (4)
C (10B) -C (5B) -C (3)	126.6 (13)	C (41) -C (40) -O (4)	117.5 (5)
O (5B) -C (6B) -C (5B)	124.5 (16)	C (42) -C (41) -C (40)	117.1 (6)
O (5B) -C (6B) -C (7B)	120.1 (18)	C (42) -C (41) -C (46)	121.8 (6)
C (5B) -C (6B) -C (7B)	115.1 (17)	C (40) -C (41) -C (46)	121.0 (5)
C (8B) -C (7B) -C (6B)	118 (2)	C (43) -C (42) -C (41)	121.2 (6)
C (7B) -C (8B) -C (9B)	127 (2)	C (42) -C (43) -C (44)	120.5 (5)
C (8B) -C (9B) -C (10B)	118.3 (18)	C (43) -C (44) -C (45)	120.2 (6)
C (9B) -C (10B) -C (5B)	115.2 (16)	C (40) -C (45) -C (44)	117.6 (5)
C (6B) -O (5B) -C (11B)	117.0 (16)	C (40) -C (45) -C (47)	121.1 (4)
O (5B) -C (11B) -C (12B)	111.1 (17)	C (44) -C (45) -C (47)	121.3 (5)
C (13B) -C (12B) -C (11B)	117.4 (18)	O (54) -P (5) -O (52)	102.49 (18)
C (19) -C (14) -C (15)	119.7 (4)	O (54) -P (5) -O (53)	90.92 (16)
C (19) -C (14) -C (1)	121.4 (4)	O (52) -P (5) -O (53)	94.00 (16)
C (15) -C (14) -C (1)	118.7 (4)	O (54) -P (5) -C (53)	128.1 (2)
C (16) -C (15) -C (14)	119.5 (4)	O (52) -P (5) -C (53)	128.7 (2)
C (15) -C (16) -C (17)	120.3 (4)	O (53) -P (5) -C (53)	92.86 (19)
C (18) -C (17) -C (16)	120.7 (4)	O (54) -P (5) -O (51)	89.77 (16)
C (17) -C (18) -C (19)	119.2 (5)	O (52) -P (5) -O (51)	86.14 (16)
C (14) -C (19) -C (18)	120.6 (5)	O (53) -P (5) -O (51)	179.24 (18)
C (29) -C (20) -O (2)	121.4 (4)	C (53) -P (5) -O (51)	86.48 (19)
C (29) -C (20) -C (21)	122.8 (4)	C (51) -O (51) -P (5)	113.7 (3)
O (2) -C (20) -C (21)	115.6 (4)	C (70) -O (52) -P (5)	120.8 (3)
C (22) -C (21) -C (20)	119.6 (4)	C (89) -O (53) -P (5)	121.0 (3)
C (21) -C (22) -C (23)	120.5 (4)	C (90B) -O (54) -C (90A)	15.7 (8)
C (22) -C (23) -C (28)	120.3 (4)	C (90B) -O (54) -P (5)	127.4 (8)
C (22) -C (23) -C (24)	121.0 (5)	C (90A) -O (54) -P (5)	130.2 (8)
C (28) -C (23) -C (24)	118.7 (4)	C (56) -O (55) -C (61)	116.5 (5)
C (25) -C (24) -C (23)	121.5 (5)	N (52) -C (51) -O (51)	113.9 (4)
C (24) -C (25) -C (26)	120.0 (5)	N (52) -C (51) -C (64)	128.5 (5)
C (27) -C (26) -C (25)	120.3 (5)	O (51) -C (51) -C (64)	117.6 (4)
C (26) -C (27) -C (28)	121.5 (5)	C (51) -N (52) -C (53)	113.3 (4)
C (27) -C (28) -C (23)	117.7 (4)	C (51) -N (52) -C (54)	125.1 (4)
C (27) -C (28) -C (29)	123.4 (4)	C (53) -N (52) -C (54)	120.6 (4)
C (23) -C (28) -C (29)	118.8 (4)	N (52) -C (53) -C (55)	117.5 (4)
C (20) -C (29) -C (28)	117.9 (4)	N (52) -C (53) -P (5)	112.5 (3)
C (20) -C (29) -C (30)	119.1 (4)		

C(55)-C(53)-P(5)	129.5(3)	C(81)-C(80)-C(79)	123.6(4)
C(56)-C(55)-C(60)	117.4(5)	C(86)-C(81)-C(82)	117.6(4)
C(56)-C(55)-C(53)	120.7(5)	C(86)-C(81)-C(80)	119.2(4)
C(60)-C(55)-C(53)	121.8(5)	C(82)-C(81)-C(80)	123.2(4)
O(55)-C(56)-C(55)	114.2(5)	C(83)-C(82)-C(81)	120.9(5)
O(55)-C(56)-C(57)	125.7(5)	C(82)-C(83)-C(84)	121.0(5)
C(55)-C(56)-C(57)	120.1(5)	C(85)-C(84)-C(83)	119.7(5)
C(58)-C(57)-C(56)	121.0(6)	C(84)-C(85)-C(86)	121.1(5)
C(59)-C(58)-C(57)	119.5(5)	C(85)-C(86)-C(87)	121.0(4)
C(58)-C(59)-C(60)	120.5(6)	C(85)-C(86)-C(81)	119.7(4)
C(59)-C(60)-C(55)	121.4(6)	C(87)-C(86)-C(81)	119.4(4)
O(55)-C(61)-C(62)	107.9(5)	C(88)-C(87)-C(86)	120.2(4)
C(63A)-C(62)-C(63B)	18(3)	C(87)-C(88)-C(89)	120.1(4)
C(63A)-C(62)-C(61)	115.1(15)	C(80)-C(89)-O(53)	120.1(4)
C(63B)-C(62)-C(61)	112.8(15)	C(80)-C(89)-C(88)	122.2(4)
C(69)-C(64)-C(65)	118.4(5)	O(53)-C(89)-C(88)	117.4(4)
C(69)-C(64)-C(51)	123.3(5)	C(91A)-C(90A)-C(95A)	120.0
C(65)-C(64)-C(51)	117.9(5)	C(91A)-C(90A)-O(54)	121.4(6)
C(66)-C(65)-C(64)	119.6(5)	C(95A)-C(90A)-O(54)	118.4(7)
C(67)-C(66)-C(65)	121.4(6)	C(92A)-C(91A)-C(90A)	120.0
C(66)-C(67)-C(68)	119.9(5)	C(92A)-C(91A)-C(96A)	120.5(10)
C(67)-C(68)-C(69)	119.3(6)	C(90A)-C(91A)-C(96A)	119.5(10)
C(64)-C(69)-C(68)	121.3(6)	C(91A)-C(92A)-C(93A)	120.0
C(79)-C(70)-O(52)	120.1(4)	C(94A)-C(93A)-C(92A)	120.0
C(79)-C(70)-C(71)	123.2(4)	C(95A)-C(94A)-C(93A)	120.0
O(52)-C(70)-C(71)	116.6(4)	C(94A)-C(95A)-C(90A)	120.0
C(72)-C(71)-C(70)	119.6(4)	C(94A)-C(95A)-C(97A)	119.9(8)
C(71)-C(72)-C(73)	121.1(5)	C(90A)-C(95A)-C(97A)	120.1(8)
C(74)-C(73)-C(72)	121.5(4)	O(54)-C(90B)-C(91B)	118.2(7)
C(74)-C(73)-C(78)	119.7(4)	O(54)-C(90B)-C(95B)	121.6(7)
C(72)-C(73)-C(78)	118.7(4)	C(91B)-C(90B)-C(95B)	120.0
C(75)-C(74)-C(73)	121.3(4)	C(90B)-C(91B)-C(92B)	120.0
C(74)-C(75)-C(76)	119.7(4)	C(90B)-C(91B)-C(96B)	117.6(10)
C(77)-C(76)-C(75)	120.5(4)	C(92B)-C(91B)-C(96B)	122.4(10)
C(76)-C(77)-C(78)	121.8(4)	C(93B)-C(92B)-C(91B)	120.0
C(77)-C(78)-C(73)	116.9(4)	C(94B)-C(93B)-C(92B)	120.0
C(77)-C(78)-C(79)	123.8(4)	C(93B)-C(94B)-C(95B)	120.0
C(73)-C(78)-C(79)	119.2(4)	C(94B)-C(95B)-C(90B)	120.0
C(70)-C(79)-C(78)	117.9(4)	C(94B)-C(95B)-C(97B)	120.2(8)
C(70)-C(79)-C(80)	119.6(4)	C(90B)-C(95B)-C(97B)	119.7(8)
C(78)-C(79)-C(80)	122.4(4)		
C(89)-C(80)-C(81)	118.4(4)		
C(89)-C(80)-C(79)	117.9(4)		

Table 6. Torsion angles [$^{\circ}$] for **5.1d**.

O(4)-P(1)-O(1)-C(1)	127.2(3)	O(1)-P(1)-O(2)-C(20)	145.2(3)
O(2)-P(1)-O(1)-C(1)	-130.0(3)	O(4)-P(1)-O(3)-C(31)	44.8(3)
O(3)-P(1)-O(1)-C(1)	106(13)	O(2)-P(1)-O(3)-C(31)	-57.9(3)
C(3)-P(1)-O(1)-C(1)	-3.1(3)	C(3)-P(1)-O(3)-C(31)	175.1(3)
O(4)-P(1)-O(2)-C(20)	-126.5(3)	O(1)-P(1)-O(3)-C(31)	66(13)
O(3)-P(1)-O(2)-C(20)	-35.4(3)	O(2)-P(1)-O(4)-C(40)	-89.2(4)
C(3)-P(1)-O(2)-C(20)	61.4(4)	O(3)-P(1)-O(4)-C(40)	176.6(4)

C (3) -P (1) -O (4) -C (40)	82.5 (4)	O (5B) -C (6B) -C (7B) -C (8B)	-173 (4)
O (1) -P (1) -O (4) -C (40)	-3.1 (4)	C (5B) -C (6B) -C (7B) -C (8B)	14 (6)
P (1) -O (1) -C (1) -N (2)	1.5 (5)	C (6B) -C (7B) -C (8B) -C (9B)	-16 (8)
P (1) -O (1) -C (1) -C (14)	-178.8 (3)	C (7B) -C (8B) -C (9B) -C (10B)	12 (6)
O (1) -C (1) -N (2) -C (3)	1.3 (5)	C (8B) -C (9B) -C (10B) -C (5B)	-5 (4)
C (14) -C (1) -N (2) -C (3)	-178.2 (4)	C (6B) -C (5B) -C (10B) -C (9B)	5 (3)
O (1) -C (1) -N (2) -C (4)	-174.3 (4)	C (3) -C (5B) -C (10B) -C (9B)	-176.1 (19)
C (14) -C (1) -N (2) -C (4)	6.1 (7)	C (5B) -C (6B) -O (5B) -C (11B)	-94 (2)
C (1) -N (2) -C (3) -C (5B)	-154.5 (7)	C (7B) -C (6B) -O (5B) -C (11B)	93 (4)
C (4) -N (2) -C (3) -C (5B)	21.3 (8)	C (6B) -O (5B) -C (11B) -C (12B) -	
C (1) -N (2) -C (3) -C (5A)	161.8 (4)		168.8 (18)
C (4) -N (2) -C (3) -C (5A)	-22.4 (6)	O (5B) -C (11B) -C (12B) -C (13B)	61 (3)
C (1) -N (2) -C (3) -P (1)	-3.7 (5)	O (1) -C (1) -C (14) -C (19)	-136.4 (4)
C (4) -N (2) -C (3) -P (1)	172.0 (4)	N (2) -C (1) -C (14) -C (19)	43.1 (7)
O (4) -P (1) -C (3) -N (2)	-82.9 (4)	O (1) -C (1) -C (14) -C (15)	38.3 (6)
O (2) -P (1) -C (3) -N (2)	87.0 (4)	N (2) -C (1) -C (14) -C (15)	-142.1 (5)
O (3) -P (1) -C (3) -N (2)	-175.6 (3)	C (19) -C (14) -C (15) -C (16)	1.4 (7)
O (1) -P (1) -C (3) -N (2)	3.6 (3)	C (1) -C (14) -C (15) -C (16)	-173.4 (4)
O (4) -P (1) -C (3) -C (5B)	62.1 (9)	C (14) -C (15) -C (16) -C (17)	-0.3 (7)
O (2) -P (1) -C (3) -C (5B)	-128.0 (9)	C (15) -C (16) -C (17) -C (18)	-1.0 (7)
O (3) -P (1) -C (3) -C (5B)	-30.6 (9)	C (16) -C (17) -C (18) -C (19)	1.1 (7)
O (1) -P (1) -C (3) -C (5B)	148.6 (9)	C (15) -C (14) -C (19) -C (18)	-1.3 (7)
O (4) -P (1) -C (3) -C (5A)	114.4 (5)	C (1) -C (14) -C (19) -C (18)	173.4 (4)
O (2) -P (1) -C (3) -C (5A)	-75.7 (5)	C (17) -C (18) -C (19) -C (14)	0.0 (7)
O (3) -P (1) -C (3) -C (5A)	21.7 (5)	P (1) -O (2) -C (20) -C (29)	77.0 (5)
O (1) -P (1) -C (3) -C (5A)	-159.1 (5)	P (1) -O (2) -C (20) -C (21)	-108.5 (4)
N (2) -C (3) -C (5A) -C (6A)	77.1 (7)	C (29) -C (20) -C (21) -C (22)	2.3 (7)
C (5B) -C (3) -C (5A) -C (6A)	-17.4 (11)	O (2) -C (20) -C (21) -C (22)	-172.2 (4)
P (1) -C (3) -C (5A) -C (6A)	-120.7 (6)	C (20) -C (21) -C (22) -C (23)	-2.1 (7)
N (2) -C (3) -C (5A) -C (10A)	-96.7 (6)	C (21) -C (22) -C (23) -C (28)	-1.0 (7)
C (5B) -C (3) -C (5A) -C (10A)	168.9 (13)	C (21) -C (22) -C (23) -C (24)	177.7 (5)
P (1) -C (3) -C (5A) -C (10A)	65.5 (7)	C (22) -C (23) -C (24) -C (25)	-179.8 (5)
C (10A) -C (5A) -C (6A) -O (5A)	178.5 (6)	C (28) -C (23) -C (24) -C (25)	-1.1 (8)
C (3) -C (5A) -C (6A) -O (5A)	7.7 (9)	C (23) -C (24) -C (25) -C (26)	-2.9 (8)
C (10A) -C (5A) -C (6A) -C (7A)	2.5 (12)	C (24) -C (25) -C (26) -C (27)	2.4 (8)
C (3) -C (5A) -C (6A) -C (7A)	-171.4 (9)	C (25) -C (26) -C (27) -C (28)	2.2 (7)
O (5A) -C (6A) -C (7A) -C (8A)	-177.0 (10)	C (26) -C (27) -C (28) -C (23)	-6.0 (7)
C (5A) -C (6A) -C (7A) -C (8A)	2.0 (18)	C (26) -C (27) -C (28) -C (29)	174.2 (4)
C (6A) -C (7A) -C (8A) -C (9A)	-6 (2)	C (22) -C (23) -C (28) -C (27)	-175.9 (4)
C (7A) -C (8A) -C (9A) -C (10A)	5.7 (17)	C (24) -C (23) -C (28) -C (27)	5.4 (7)
C (8A) -C (9A) -C (10A) -C (5A)	-0.8 (13)	C (22) -C (23) -C (28) -C (29)	3.9 (7)
C (6A) -C (5A) -C (10A) -C (9A)	-3.1 (11)	C (24) -C (23) -C (28) -C (29)	-174.9 (4)
C (3) -C (5A) -C (10A) -C (9A)	171.2 (7)	O (2) -C (20) -C (29) -C (28)	174.8 (4)
C (5A) -C (6A) -O (5A) -C (11A)	175.0 (6)	C (21) -C (20) -C (29) -C (28)	0.6 (6)
C (7A) -C (6A) -O (5A) -C (11A)	-6.0 (12)	O (2) -C (20) -C (29) -C (30)	-7.1 (6)
C (6A) -O (5A) -C (11A) -C (12A)	179.2 (6)	C (21) -C (20) -C (29) -C (30)	178.7 (4)
O (5A) -C (11A) -C (12A) -C (13A)	62.2 (9)	C (27) -C (28) -C (29) -C (20)	176.1 (4)
N (2) -C (3) -C (5B) -C (6B)	-87.2 (15)	C (23) -C (28) -C (29) -C (20)	-3.6 (6)
C (5A) -C (3) -C (5B) -C (6B)	16.7 (11)	C (27) -C (28) -C (29) -C (30)	-2.0 (7)
P (1) -C (3) -C (5B) -C (6B)	127.9 (12)	C (23) -C (28) -C (29) -C (30)	178.3 (4)
N (2) -C (3) -C (5B) -C (10B)	93.8 (18)	C (20) -C (29) -C (30) -C (31)	-46.8 (6)
C (5A) -C (3) -C (5B) -C (10B)	-162 (2)	C (28) -C (29) -C (30) -C (31)	131.2 (4)
P (1) -C (3) -C (5B) -C (10B)	-51 (2)	C (20) -C (29) -C (30) -C (39)	130.0 (4)
C (10B) -C (5B) -C (6B) -O (5B)	178 (2)	C (28) -C (29) -C (30) -C (39)	-52.0 (6)
C (3) -C (5B) -C (6B) -O (5B)	-1 (3)	P (1) -O (3) -C (31) -C (30)	81.4 (5)
C (10B) -C (5B) -C (6B) -C (7B)	-9 (4)	P (1) -O (3) -C (31) -C (32)	-98.8 (4)
C (3) -C (5B) -C (6B) -C (7B)	172 (3)	C (39) -C (30) -C (31) -O (3)	-174.6 (4)

C (29) -C (30) -C (31) -O (3)	2.4 (6)	C (53) -P (5) -O (54) -C (90A)	80.8 (7)
C (39) -C (30) -C (31) -C (32)	5.6 (6)	O (51) -P (5) -O (54) -C (90A)	-4.5 (6)
C (29) -C (30) -C (31) -C (32)	-177.3 (4)	P (5) -O (51) -C (51) -N (52)	2.3 (6)
O (3) -C (31) -C (32) -C (33)	177.3 (4)	P (5) -O (51) -C (51) -C (64)	-177.3 (4)
C (30) -C (31) -C (32) -C (33)	-2.9 (6)	O (51) -C (51) -N (52) -C (53)	-0.3 (7)
C (31) -C (32) -C (33) -C (34)	-0.1 (6)	C (64) -C (51) -N (52) -C (53)	179.3 (5)
C (32) -C (33) -C (34) -C (35)	-179.3 (4)	O (51) -C (51) -N (52) -C (54)	-168.8 (5)
C (32) -C (33) -C (34) -C (39)	0.0 (6)	C (64) -C (51) -N (52) -C (54)	10.8 (9)
C (39) -C (34) -C (35) -C (36)	-1.5 (7)	C (51) -N (52) -C (53) -C (55)	171.4 (5)
C (33) -C (34) -C (35) -C (36)	177.8 (4)	C (54) -N (52) -C (53) -C (55)	-19.6 (7)
C (34) -C (35) -C (36) -C (37)	-2.0 (7)	C (51) -N (52) -C (53) -P (5)	-1.9 (6)
C (35) -C (36) -C (37) -C (38)	2.4 (7)	C (54) -N (52) -C (53) -P (5)	167.2 (4)
C (36) -C (37) -C (38) -C (39)	0.8 (7)	O (54) -P (5) -C (53) -N (52)	-84.4 (4)
C (37) -C (38) -C (39) -C (34)	-4.2 (6)	O (52) -P (5) -C (53) -N (52)	84.7 (4)
C (37) -C (38) -C (39) -C (30)	178.2 (4)	O (53) -P (5) -C (53) -N (52)	-177.9 (4)
C (35) -C (34) -C (39) -C (38)	4.5 (6)	O (51) -P (5) -C (53) -N (52)	2.5 (4)
C (33) -C (34) -C (39) -C (38)	-174.8 (4)	O (54) -P (5) -C (53) -C (55)	103.3 (5)
C (35) -C (34) -C (39) -C (30)	-177.8 (4)	O (52) -P (5) -C (53) -C (55)	-87.6 (5)
C (33) -C (34) -C (39) -C (30)	2.9 (6)	O (53) -P (5) -C (53) -C (55)	9.9 (5)
C (31) -C (30) -C (39) -C (38)	171.8 (4)	O (51) -P (5) -C (53) -C (55)	-169.8 (5)
C (29) -C (30) -C (39) -C (38)	-4.9 (6)	N (52) -C (53) -C (55) -C (56)	-58.4 (7)
C (31) -C (30) -C (39) -C (34)	-5.7 (6)	P (5) -C (53) -C (55) -C (56)	113.5 (5)
C (29) -C (30) -C (39) -C (34)	177.6 (4)	N (52) -C (53) -C (55) -C (60)	121.8 (5)
P (1) -O (4) -C (40) -C (45)	96.8 (5)	P (5) -C (53) -C (55) -C (60)	-66.2 (7)
P (1) -O (4) -C (40) -C (41)	-88.8 (5)	C (61) -O (55) -C (56) -C (55)	-174.8 (5)
C (45) -C (40) -C (41) -C (42)	-1.4 (7)	C (61) -O (55) -C (56) -C (57)	5.7 (8)
O (4) -C (40) -C (41) -C (42)	-175.5 (4)	C (60) -C (55) -C (56) -O (55)	178.4 (5)
C (45) -C (40) -C (41) -C (46)	177.1 (5)	C (53) -C (55) -C (56) -O (55)	-1.3 (7)
O (4) -C (40) -C (41) -C (46)	3.1 (7)	C (60) -C (55) -C (56) -C (57)	-2.0 (7)
C (40) -C (41) -C (42) -C (43)	1.5 (8)	C (53) -C (55) -C (56) -C (57)	178.2 (4)
C (46) -C (41) -C (42) -C (43)	-177.0 (5)	O (55) -C (56) -C (57) -C (58)	-179.0 (5)
C (41) -C (42) -C (43) -C (44)	-1.1 (9)	C (55) -C (56) -C (57) -C (58)	1.6 (8)
C (42) -C (43) -C (44) -C (45)	0.5 (9)	C (56) -C (57) -C (58) -C (59)	0.8 (8)
C (41) -C (40) -C (45) -C (44)	0.9 (7)	C (57) -C (58) -C (59) -C (60)	-2.7 (9)
O (4) -C (40) -C (45) -C (44)	174.9 (4)	C (58) -C (59) -C (60) -C (55)	2.2 (9)
C (41) -C (40) -C (45) -C (47)	-178.7 (5)	C (56) -C (55) -C (60) -C (59)	0.2 (8)
O (4) -C (40) -C (45) -C (47)	-4.8 (7)	C (53) -C (55) -C (60) -C (59)	180.0 (5)
C (43) -C (44) -C (45) -C (40)	-0.4 (8)	C (56) -O (55) -C (61) -C (62)	174.6 (5)
C (43) -C (44) -C (45) -C (47)	179.2 (5)	O (55) -C (61) -C (62) -C (63A)	52.0 (19)
O (54) -P (5) -O (51) -C (51)	125.5 (3)	O (55) -C (61) -C (62) -C (63B)	71.8 (18)
O (52) -P (5) -O (51) -C (51)	-132.0 (3)	N (52) -C (51) -C (64) -C (69)	37.9 (9)
O (53) -P (5) -O (51) -C (51)	-32 (14)	O (51) -C (51) -C (64) -C (69)	-142.5 (5)
C (53) -P (5) -O (51) -C (51)	-2.8 (4)	N (52) -C (51) -C (64) -C (65)	-148.3 (6)
O (54) -P (5) -O (52) -C (70)	-138.0 (3)	O (51) -C (51) -C (64) -C (65)	31.2 (7)
O (53) -P (5) -O (52) -C (70)	-46.2 (4)	C (69) -C (64) -C (65) -C (66)	-1.7 (8)
C (53) -P (5) -O (52) -C (70)	50.7 (4)	C (51) -C (64) -C (65) -C (66)	-175.7 (5)
O (51) -P (5) -O (52) -C (70)	133.1 (3)	C (64) -C (65) -C (66) -C (67)	1.3 (8)
O (54) -P (5) -O (53) -C (89)	52.5 (3)	C (65) -C (66) -C (67) -C (68)	-0.9 (9)
O (52) -P (5) -O (53) -C (89)	-50.1 (3)	C (66) -C (67) -C (68) -C (69)	0.9 (9)
C (53) -P (5) -O (53) -C (89)	-179.3 (3)	C (65) -C (64) -C (69) -C (68)	1.7 (9)
O (51) -P (5) -O (53) -C (89)	-150 (33)	C (51) -C (64) -C (69) -C (68)	175.4 (5)
O (52) -P (5) -O (54) -C (90B)	-110.3 (7)	C (67) -C (68) -C (69) -C (64)	-1.3 (9)
O (53) -P (5) -O (54) -C (90B)	155.4 (7)	P (5) -O (52) -C (70) -C (79)	81.1 (5)
C (53) -P (5) -O (54) -C (90B)	61.0 (7)	P (5) -O (52) -C (70) -C (71)	-102.2 (4)
O (51) -P (5) -O (54) -C (90B)	-24.3 (7)	C (79) -C (70) -C (71) -C (72)	0.0 (7)
O (52) -P (5) -O (54) -C (90A)	-90.5 (6)	O (52) -C (70) -C (71) -C (72)	-176.6 (4)
O (53) -P (5) -O (54) -C (90A)	175.2 (6)	C (70) -C (71) -C (72) -C (73)	-1.1 (7)

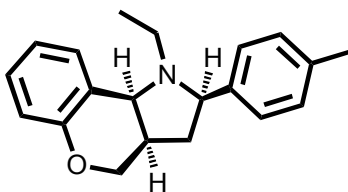
C(71)-C(72)-C(73)-C(74) -177.6(4) O(54)-C(90A)-C(91A)-C(92A)
C(71)-C(72)-C(73)-C(78) -1.7(7) 174.3(16)
C(72)-C(73)-C(74)-C(75) 174.4(4) C(95A)-C(90A)-C(91A)-C(9) -177(2)
C(78)-C(73)-C(74)-C(75) -1.4(7) O(54)-C(90A)-C(91A)-C(96A) 3.1(19)
C(73)-C(74)-C(75)-C(76) -1.6(7) C(90A)-C(91A)-C(92A)-C(93A) 0.0
C(74)-C(75)-C(76)-C(77) 2.6(7) C(96A)-C(91A)-C(92A)-C(93) 177(2)
C(75)-C(76)-C(77)-C(78) -0.6(6) C(91A)-C(92A)-C(93A)-C(94A) 0.0
C(76)-C(77)-C(78)-C(73) -2.3(6) C(92A)-C(93A)-C(94A)-C(95A) 0.0
C(76)-C(77)-C(78)-C(79) 179.7(4) C(93A)-C(94A)-C(95A)-C(90A) 0.0
C(74)-C(73)-C(78)-C(77) 3.3(6) C(93A)-C(94A)-C(95A)-C(9)
C(72)-C(73)-C(78)-C(77) -172.6(4) -178.2(19)
C(74)-C(73)-C(78)-C(79) -178.6(4) C(91A)-C(90A)-C(95A)-C(94A) 0.0
C(72)-C(73)-C(78)-C(79) 5.5(6) O(54)-C(90A)-C(95A)-C(94)
O(52)-C(70)-C(79)-C(78) -179.7(4) -174.5(15)
C(71)-C(70)-C(79)-C(78) 3.8(6) C(91A)-C(90A)-C(95A)-C(97)
O(52)-C(70)-C(79)-C(80) -4.4(6) 178.2(19)
C(71)-C(70)-C(79)-C(80) 179.1(4) O(54)-C(90A)-C(95A)-C(97A) 3.6(17)
C(77)-C(78)-C(79)-C(70) 171.5(4) C(90A)-O(54)-C(90B)-C(91B) -3(5)
C(73)-C(78)-C(79)-C(70) -6.4(6) P(5)-O(54)-C(90B)-C(91B) 103.0(8)
C(77)-C(78)-C(79)-C(80) -3.7(6) C(90A)-O(54)-C(90B)-C(95B) 171(7)
C(73)-C(78)-C(79)-C(80) 178.4(4) P(5)-O(54)-C(90B)-C(95B) -82.6(12)
C(70)-C(79)-C(80)-C(89) -46.4(5) O(54)-C(90B)-C(91B)-C(92B)
C(78)-C(79)-C(80)-C(89) 128.7(4) 174.5(16)
C(70)-C(79)-C(80)-C(81) 131.3(4) C(95B)-C(90B)-C(91B)-C(92B) 0.0
C(78)-C(79)-C(80)-C(81) -53.6(5) O(54)-C(90B)-C(91B)-C(96B)
C(89)-C(80)-C(81)-C(86) -7.4(6) -3.1(18)
C(79)-C(80)-C(81)-C(86) 174.9(4) C(95B)-C(90B)-C(91B)-C(9)
C(89)-C(80)-C(81)-C(82) 171.4(4) -177.6(19)
C(79)-C(80)-C(81)-C(82) -6.3(6) C(90B)-C(91B)-C(92B)-C(93B) 0.0
C(86)-C(81)-C(82)-C(83) -2.6(6) C(96B)-C(91B)-C(92B)-C(93) 177(2)
C(80)-C(81)-C(82)-C(83) 178.6(4) C(91B)-C(92B)-C(93B)-C(94B) 0.0
C(81)-C(82)-C(83)-C(84) -0.2(7) C(92B)-C(93B)-C(94B)-C(95B) 0.0
C(82)-C(83)-C(84)-C(85) 1.9(7) C(93B)-C(94B)-C(95B)-C(90B) 0.0
C(83)-C(84)-C(85)-C(86) -0.7(7) C(93B)-C(94B)-C(95B)-C(9)
C(84)-C(85)-C(86)-C(87) 176.6(4) -175.8(18)
C(84)-C(85)-C(86)-C(81) -2.2(7) O(54)-C(90B)-C(95B)-C(94)
C(82)-C(81)-C(86)-C(85) 3.7(6) -174.3(16)
C(80)-C(81)-C(86)-C(85) -177.4(4) C(91B)-C(90B)-C(95B)-C(94B) 0.0
C(82)-C(81)-C(86)-C(87) -175.0(4) O(54)-C(90B)-C(95B)-C(97B) 1.5(17)
C(80)-C(81)-C(86)-C(87) 3.9(6) C(91B)-C(90B)-C(95B)-C(97)
C(85)-C(86)-C(87)-C(88) -177.2(4) 175.8(18)
C(81)-C(86)-C(87)-C(88) 1.5(6)
C(86)-C(87)-C(88)-C(89) -3.3(6)
C(81)-C(80)-C(89)-O(53) -179.2(3)
C(79)-C(80)-C(89)-O(53) -1.4(6)
C(81)-C(80)-C(89)-C(88) 5.8(6)
C(79)-C(80)-C(89)-C(88) -176.3(4)
P(5)-O(53)-C(89)-C(80) 80.8(4)
P(5)-O(53)-C(89)-C(88) -104.0(4)
C(87)-C(88)-C(89)-C(80) -0.5(6)
C(87)-C(88)-C(89)-O(53) -175.6(4)
C(90B)-O(54)-C(90A)-C(91) -180(7)
P(5)-O(54)-C(90A)-C(91A) 94.3(10)
C(90B)-O(54)-C(90A)-C(95A) -5(5)
P(5)-O(54)-C(90A)-C(95A) 91.3(10)
C(95A)-C(90A)-C(91A)-C(92A) 0.0

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Appendix E

X-Ray Structural Data for Compound 5.6a (Chapter 5)



Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Michel Simard.

Identification code	ARST38
Empirical formula	C ₂₀ H ₂₃ N O
Formula weight	293.39
Temperature	100K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P2 ₁
Unit cell dimensions	$a = 15.7825(2) \text{ Å}$ $\alpha = 90^\circ$ $b = 5.8322(1) \text{ Å}$ $\beta = 113.102(1)^\circ$ $c = 18.8095(2) \text{ Å}$ $\gamma = 90^\circ$
Volume	1592.51(4) Å ³
Z	4
Density (calculated)	1.224 g/cm ³
Absorption coefficient	0.575 mm ⁻¹
(000)	632
Crystal size	0.20 x 0.16 x 0.06 mm
Theta range for data collection	2.55 to 71.16°
Index ranges	$-19 \leq h \leq 19, -7 \leq k \leq 7, -23 \leq \ell \leq 23$
Reflections collected	83998
Independent reflections	6071 [R _{int} = 0.020]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9661 and 0.8630
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6071 / 1 / 401
Goodness-of-fit on F ²	1.061
Final R indices [I>2sigma(I)]	R ₁ = 0.0280, wR ₂ = 0.0722
R indices (all data)	R ₁ = 0.0281, wR ₂ = 0.0723
Absolute structure parameter	0.09(14)
Largest diff. peak and hole	0.286 and -0.158 e/Å ³

ORTEP view of the **5.6a** with the numbering scheme adopted.
Ellipsoids drawn at 50% probability level.

Two molecules per asymmetric unit:

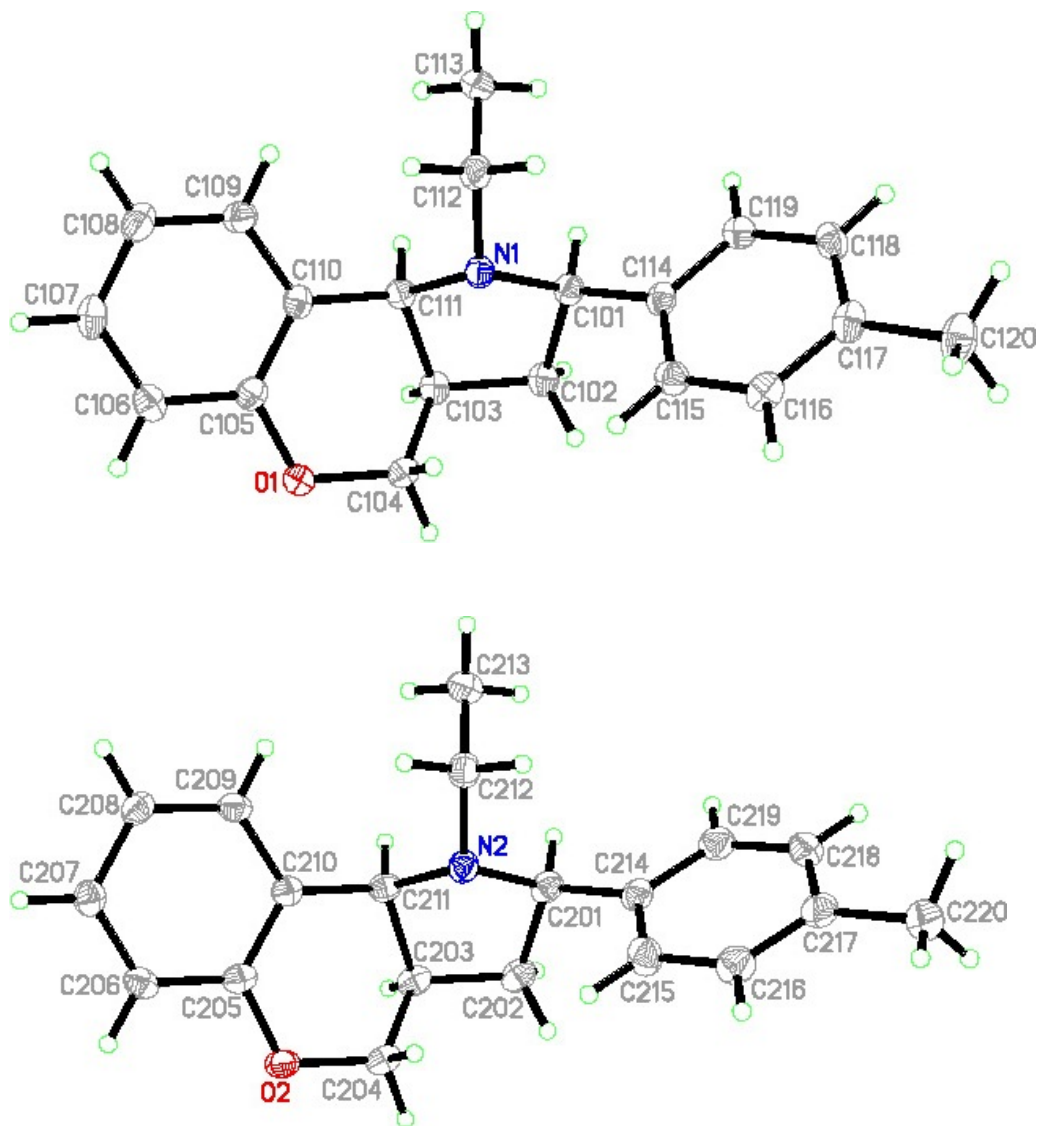


Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **5.6a**.

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O(1)	8072(1)	-504(2)	4316(1)	24(1)
N(1)	7406(1)	3460(2)	2590(1)	18(1)
C(101)	6651(1)	5005(2)	2552(1)	18(1)
C(102)	6531(1)	4515(2)	3317(1)	21(1)
C(103)	7427(1)	3281(2)	3835(1)	20(1)
C(104)	7245(1)	754(2)	3888(1)	23(1)
C(105)	8788(1)	-108(2)	4090(1)	19(1)
C(106)	9517(1)	-1663(2)	4369(1)	22(1)
C(107)	10277(1)	-1387(2)	4182(1)	24(1)
C(108)	10323(1)	473(2)	3736(1)	26(1)
C(109)	9605(1)	2030(2)	3480(1)	23(1)
C(110)	8815(1)	1771(2)	3641(1)	18(1)
C(111)	8065(1)	3569(2)	3404(1)	18(1)
C(112)	7787(1)	3940(2)	2009(1)	23(1)
C(113)	8231(1)	6292(2)	2046(1)	28(1)
C(114)	5797(1)	4600(2)	1823(1)	18(1)
C(115)	5356(1)	2474(2)	1689(1)	21(1)
C(116)	4563(1)	2105(2)	1036(1)	23(1)
C(117)	4184(1)	3841(2)	489(1)	22(1)
C(118)	4639(1)	5931(2)	612(1)	23(1)
C(119)	5434(1)	6307(2)	1274(1)	20(1)
C(120)	3296(1)	3449(3)	-203(1)	30(1)
O(2)	4813(1)	10144(2)	3479(1)	22(1)
N(2)	2502(1)	7271(2)	2429(1)	20(1)
C(201)	2584(1)	5256(2)	1987(1)	22(1)
C(202)	3637(1)	5063(2)	2217(1)	24(1)
C(203)	4072(1)	6453(2)	2967(1)	21(1)
C(204)	4467(1)	8671(2)	2812(1)	22(1)
C(205)	4220(1)	10478(2)	3844(1)	19(1)
C(206)	4456(1)	12234(2)	4391(1)	21(1)
C(207)	3896(1)	12715(2)	4781(1)	22(1)
C(208)	3108(1)	11409(2)	4646(1)	22(1)
C(209)	2911(1)	9591(2)	4134(1)	21(1)
C(210)	3449(1)	9092(2)	3712(1)	19(1)
C(211)	3261(1)	7015(2)	3194(1)	19(1)
C(212)	1580(1)	7601(2)	2424(1)	28(1)
C(213)	1207(1)	5707(3)	2786(1)	39(1)
C(214)	2027(1)	5566(2)	1130(1)	22(1)
C(215)	2114(1)	7539(2)	748(1)	26(1)
C(216)	1599(1)	7822(2)	-36(1)	27(1)
C(217)	984(1)	6154(2)	-468(1)	25(1)
C(218)	892(1)	4186(2)	-87(1)	28(1)
C(219)	1409(1)	3890(2)	702(1)	26(1)
C(220)	435(1)	6462(3)	-1322(1)	32(1)

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **5.6a**.

	x	y	z	U _{eq}
H(101)	6856	6629	2556	22
H(10A)	6453	5961	3561	25
H(10B)	5989	3525	3224	25
H(103)	7699	3996	4360	24
H(10C)	6805	565	4141	27
H(10D)	6956	111	3360	27
H(106)	9492	-2908	4685	26
H(107)	10767	-2468	4358	29
H(108)	10844	674	3608	31
H(109)	9648	3315	3186	28
H(111)	8353	5126	3514	21
H(11A)	7285	3770	1491	27
H(11B)	8254	2753	2055	27
H(11C)	7773	7495	1981	41
H(11D)	8459	6412	1632	41
H(11E)	8746	6475	2548	41
H(115)	5604	1265	2051	25
H(116)	4271	648	958	27
H(118)	4406	7120	240	27
H(119)	5732	7756	1350	24
H(12A)	2773	3647	-51	45
H(12B)	3290	1889	-398	45
H(12C)	3248	4556	-609	45
H(201)	2361	3864	2171	27
H(20A)	3837	3442	2305	29
H(20B)	3814	5707	1808	29
H(203)	4553	5539	3380	25
H(20C)	4973	8312	2644	26
H(20D)	3983	9495	2384	26
H(206)	5002	13099	4495	25
H(207)	4048	13940	5142	27
H(208)	2713	11762	4903	27
H(209)	2393	8650	4066	26
H(211)	3134	5666	3466	23
H(21A)	1144	7795	1880	33
H(21B)	1582	9053	2697	33
H(21C)	1192	4253	2520	58
H(21D)	582	6106	2735	58
H(21E)	1607	5552	3335	58
H(215)	2532	8705	1028	32
H(216)	1669	9186	-284	33
H(218)	471	3026	-368	34
H(219)	1339	2527	950	31
H(22A)	485	8055	-1466	48
H(22B)	-213	6092	-1443	48
H(22C)	676	5437	-1611	48

Table 4. Anisotropic parameters ($\text{\AA}^2 \times 10^3$) for **5.6a**.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
O(1)	21(1)	25(1)	28(1)	9(1)	11(1)	2(1)
N(1)	16(1)	19(1)	18(1)	1(1)	6(1)	1(1)
C(101)	18(1)	16(1)	21(1)	-1(1)	7(1)	1(1)
C(102)	20(1)	22(1)	20(1)	-2(1)	8(1)	2(1)
C(103)	20(1)	21(1)	18(1)	-2(1)	7(1)	2(1)
C(104)	18(1)	25(1)	27(1)	5(1)	11(1)	2(1)
C(105)	17(1)	20(1)	18(1)	-3(1)	5(1)	-2(1)
C(106)	23(1)	19(1)	18(1)	-1(1)	3(1)	0(1)
C(107)	20(1)	27(1)	21(1)	-4(1)	2(1)	5(1)
C(108)	19(1)	36(1)	23(1)	-1(1)	9(1)	2(1)
C(109)	20(1)	28(1)	21(1)	3(1)	8(1)	-1(1)
C(110)	17(1)	20(1)	15(1)	-2(1)	4(1)	0(1)
C(111)	18(1)	16(1)	18(1)	-1(1)	6(1)	-1(1)
C(112)	20(1)	29(1)	19(1)	2(1)	8(1)	3(1)
C(113)	23(1)	35(1)	24(1)	10(1)	9(1)	0(1)
C(114)	16(1)	21(1)	18(1)	-2(1)	8(1)	3(1)
C(115)	23(1)	18(1)	23(1)	1(1)	10(1)	3(1)
C(116)	21(1)	20(1)	27(1)	-5(1)	10(1)	-1(1)
C(117)	19(1)	29(1)	19(1)	-6(1)	8(1)	5(1)
C(118)	23(1)	26(1)	19(1)	3(1)	9(1)	7(1)
C(119)	21(1)	19(1)	22(1)	-1(1)	10(1)	1(1)
C(120)	23(1)	40(1)	23(1)	-8(1)	5(1)	4(1)
O(2)	20(1)	27(1)	23(1)	1(1)	11(1)	-2(1)
N(2)	20(1)	21(1)	20(1)	-2(1)	8(1)	2(1)
C(201)	28(1)	18(1)	24(1)	-2(1)	14(1)	1(1)
C(202)	28(1)	21(1)	27(1)	1(1)	15(1)	5(1)
C(203)	22(1)	22(1)	23(1)	5(1)	11(1)	6(1)
C(204)	23(1)	25(1)	22(1)	3(1)	13(1)	3(1)
C(205)	18(1)	23(1)	17(1)	6(1)	7(1)	4(1)
C(206)	17(1)	24(1)	20(1)	5(1)	4(1)	-2(1)
C(207)	24(1)	23(1)	17(1)	1(1)	6(1)	0(1)
C(208)	23(1)	27(1)	18(1)	1(1)	10(1)	2(1)
C(209)	18(1)	25(1)	21(1)	3(1)	8(1)	-2(1)
C(210)	18(1)	21(1)	16(1)	4(1)	6(1)	2(1)
C(211)	19(1)	19(1)	20(1)	3(1)	9(1)	2(1)
C(212)	19(1)	38(1)	24(1)	-9(1)	7(1)	2(1)
C(213)	29(1)	49(1)	45(1)	-20(1)	21(1)	-16(1)
C(214)	25(1)	21(1)	24(1)	-4(1)	13(1)	1(1)
C(215)	31(1)	21(1)	27(1)	-4(1)	11(1)	-3(1)
C(216)	31(1)	24(1)	28(1)	2(1)	13(1)	-1(1)
C(217)	22(1)	32(1)	25(1)	-1(1)	11(1)	3(1)
C(218)	26(1)	30(1)	30(1)	-7(1)	12(1)	-7(1)
C(219)	31(1)	22(1)	28(1)	-1(1)	16(1)	-4(1)
C(220)	27(1)	42(1)	26(1)	-2(1)	9(1)	-2(1)

Table 5. Bond lengths [Å] and angles [°] for **5.6a**.

O(1)-C(105)	1.3734 (13)	C(112)-N(1)-C(111)	115.91 (8)
O(1)-C(104)	1.4378 (14)	C(101)-N(1)-C(111)	104.52 (8)
N(1)-C(112)	1.4656 (14)	N(1)-C(101)-C(114)	111.28 (8)
N(1)-C(101)	1.4741 (14)	N(1)-C(101)-C(102)	103.49 (9)
N(1)-C(111)	1.4778 (13)	C(114)-C(101)-C(102)	114.98 (9)
C(101)-C(114)	1.5174 (14)	C(103)-C(102)-C(101)	104.91 (9)
C(101)-C(102)	1.5493 (15)	C(104)-C(103)-C(111)	108.88 (9)
C(102)-C(103)	1.5441 (15)	C(104)-C(103)-C(102)	110.18 (10)
C(103)-C(104)	1.5123 (17)	C(111)-C(103)-C(102)	104.19 (9)
C(103)-C(111)	1.5294 (15)	O(1)-C(104)-C(103)	112.33 (9)
C(105)-C(110)	1.3953 (16)	O(1)-C(105)-C(110)	123.02 (10)
C(105)-C(106)	1.3962 (16)	O(1)-C(105)-C(106)	115.59 (10)
C(106)-C(107)	1.3856 (17)	C(110)-C(105)-C(106)	121.33 (10)
C(107)-C(108)	1.3904 (19)	C(107)-C(106)-C(105)	119.88 (11)
C(108)-C(109)	1.3826 (17)	C(106)-C(107)-C(108)	119.90 (11)
C(109)-C(110)	1.4012 (15)	C(109)-C(108)-C(107)	119.54 (11)
C(110)-C(111)	1.5117 (15)	C(108)-C(109)-C(110)	122.07 (11)
C(112)-C(113)	1.5299 (18)	C(105)-C(110)-C(109)	117.23 (10)
C(114)-C(119)	1.3864 (16)	C(105)-C(110)-C(111)	121.04 (9)
C(114)-C(115)	1.3952 (16)	C(109)-C(110)-C(111)	121.47 (10)
C(115)-C(116)	1.3839 (16)	N(1)-C(111)-C(110)	115.24 (9)
C(116)-C(117)	1.3999 (17)	N(1)-C(111)-C(103)	101.67 (8)
C(117)-C(118)	1.3874 (18)	C(110)-C(111)-C(103)	111.77 (9)
C(117)-C(120)	1.5094 (15)	N(1)-C(112)-C(113)	116.91 (10)
C(118)-C(119)	1.3961 (16)	C(119)-C(114)-C(115)	118.25 (10)
O(2)-C(205)	1.3738 (13)	C(119)-C(114)-C(101)	121.45 (10)
O(2)-C(204)	1.4391 (15)	C(115)-C(114)-C(101)	120.30 (10)
N(2)-C(212)	1.4629 (14)	C(116)-C(115)-C(14)	120.76 (11)
N(2)-C(211)	1.4750 (13)	C(115)-C(116)-C(17)	121.12 (11)
N(2)-C(201)	1.4751 (15)	C(118)-C(117)-C(116)	117.99 (10)
C(201)-C(214)	1.5137 (16)	C(118)-C(117)-C(120)	121.41 (11)
C(201)-C(202)	1.5475 (16)	C(116)-C(117)-C(12)	120.59 (12)
C(202)-C(203)	1.5357 (16)	C(117)-C(118)-C(19)	120.80 (11)
C(203)-C(204)	1.5136 (17)	C(114)-C(119)-C(18)	121.02 (11)
C(203)-C(211)	1.5347 (14)	C(205)-O(2)-C(204)	114.87 (9)
C(205)-C(206)	1.3948 (17)	C(212)-N(2)-C(211)	116.41 (9)
C(205)-C(210)	1.4000 (16)	C(212)-N(2)-C(201)	114.10 (9)
C(206)-C(207)	1.3821 (16)	C(211)-N(2)-C(201)	104.58 (9)
C(207)-C(208)	1.3930 (17)	N(2)-C(201)-C(214)	111.22 (9)
C(208)-C(209)	1.3840 (17)	N(2)-C(201)-C(202)	102.86 (9)
C(209)-C(210)	1.4012 (15)	C(214)-C(201)-C(202)	114.77 (9)
C(210)-C(211)	1.5095 (15)	C(203)-C(202)-C(201)	105.24 (9)
C(212)-C(213)	1.532 (2)	C(204)-C(203)-C(211)	108.84 (9)
C(214)-C(215)	1.3917 (18)	C(204)-C(203)-C(202)	110.08 (9)
C(214)-C(219)	1.3923 (17)	C(211)-C(203)-C(202)	104.31 (9)
C(215)-C(216)	1.3873 (17)	O(2)-C(204)-C(203)	112.69 (9)
C(216)-C(217)	1.3892 (18)	O(2)-C(205)-C(206)	115.82 (10)
C(217)-C(218)	1.3898 (19)	O(2)-C(205)-C(210)	123.02 (10)
C(217)-C(220)	1.5068 (16)	C(206)-C(205)-C(210)	121.10 (10)
C(218)-C(219)	1.3956 (17)	C(207)-C(206)-C(205)	119.95 (10)
		C(206)-C(207)-C(208)	120.26 (11)
		C(209)-C(208)-C(207)	119.10 (10)
C(105)-O(1)-C(104)	114.64 (8)	C(208)-C(209)-C(210)	122.18 (10)
C(112)-N(1)-C(101)	114.06 (9)	C(205)-C(210)-C(209)	117.26 (10)

C(205)-C(210)-C(211)	120.96(10)	C(216)-C(215)-C(214)	120.82(12)
C(209)-C(210)-C(211)	121.53(10)	C(215)-C(216)-C(217)	121.41(12)
N(2)-C(211)-C(210)	115.27(9)	C(216)-C(217)-C(218)	117.92(11)
N(2)-C(211)-C(203)	101.37(8)	C(216)-C(217)-C(220)	121.12(12)
C(210)-C(211)-C(203)	112.14(9)	C(218)-C(217)-C(220)	120.96(11)
N(2)-C(212)-C(213)	117.21(12)	C(217)-C(218)-C(219)	120.91(11)
C(215)-C(214)-C(219)	118.05(11)	C(214)-C(219)-C(218)	120.89(12)
C(215)-C(214)-C(201)	120.97(11)		
C(219)-C(214)-C(201)	120.98(11)		

Table 6. Torsion angles [°] for **5.6a**.

C(112)-N(1)-C(101)-C(114)	68.39(12)	N(1)-C(101)-C(114)-C(119)	-
C(111)-N(1)-C(101)-C(114)	-164.03(9)	118.17(11)	
C(112)-N(1)-C(101)-C(102)	-167.59(9)	C(102)-C(101)-C(114)-C(119)	
C(111)-N(1)-C(101)-C(102)	-40.01(10)	124.61(11)	
N(1)-C(101)-C(102)-C(103)	17.08(11)	N(1)-C(101)-C(114)-C(115)	61.70(13)
C(114)-C(101)-C(102)-C(103)		C(102)-C(101)-C(114)-C(115)	-
138.64(10)		55.53(13)	
C(101)-C(102)-C(103)-C(104)		C(119)-C(114)-C(115)-C(116)	-
-105.86(10)		1.89(16)	
C(101)-C(102)-C(103)-C(111)	10.78(11)	C(101)-C(114)-C(115)-C(116)	
C(105)-O(1)-C(104)-C(103)	-49.72(13)	178.24(10)	
C(111)-C(103)-C(104)-O(1)	61.90(12)	C(114)-C(115)-C(116)-C(117)	
C(102)-C(103)-C(104)-O(1)	175.58(8)	0.53(17)	
C(104)-O(1)-C(105)-C(110)	16.63(15)	C(115)-C(116)-C(117)-C(118)	1.44(16)
C(104)-O(1)-C(105)-C(106)	-166.04(10)	C(115)-C(116)-C(117)-C(120)-	
O(1)-C(105)-C(106)-C(107)	-179.05(10)	177.38(10)	
C(110)-C(105)-C(106)-C(107)	-1.67(16)	C(116)-C(117)-C(118)-C(119)	-2.03(16)
C(105)-C(106)-C(107)-C(108)	1.82(17)	C(120)-C(117)-C(118)-C(119)	176.78(10)
C(106)-C(107)-C(108)-C(109)	-0.30(18)	C(115)-C(114)-C(119)-C(118)	1.30(16)
C(107)-C(108)-C(109)-C(110)	-1.43(18)	C(101)-C(114)-C(119)-C(118)	
O(1)-C(105)-C(110)-C(109)	177.18(10)	-178.84(10)	
C(106)-C(105)-C(110)-C(109)	0.00(15)	C(117)-C(118)-C(119)-C(114)	0.68(16)
O(1)-C(105)-C(110)-C(111)	3.00(16)	C(212)-N(2)-C(201)-C(214)	67.03(13)
C(106)-C(105)-C(110)-C(111)	-	C(211)-N(2)-C(201)-C(214)	-164.67(9)
174.18(10)		C(212)-N(2)-C(201)-C(202)	-169.64(10)
C(108)-C(109)-C(110)-C(105)	1.56(16)	C(211)-N(2)-C(201)-C(202)	-41.33(11)
C(108)-C(109)-C(110)-C(111)		N(2)-C(201)-C(202)-C(203)	18.77(12)
175.72(11)		C(214)-C(201)-C(202)-C(203)	139.70(10)
C(112)-N(1)-C(111)-C(110)	-65.50(13)	C(201)-C(202)-C(203)-C(204)	
C(101)-N(1)-C(111)-C(110)	168.06(9)	-107.46(10)	
C(112)-N(1)-C(111)-C(103)	173.43(10)	C(201)-C(202)-C(203)-C(211)	9.16(12)
C(101)-N(1)-C(111)-C(103)	46.99(10)	C(205)-O(2)-C(204)-C(203)	-48.91(13)
C(105)-C(110)-C(111)-N(1)	-104.84(11)	C(211)-C(203)-C(204)-O(2)	61.10(12)
C(109)-C(110)-C(111)-N(1)	81.23(13)	C(202)-C(203)-C(204)-O(2)	174.85(9)
C(105)-C(110)-C(111)-C(103)	10.57(14)	C(204)-O(2)-C(205)-C(206)	-167.73(10)
C(109)-C(110)-C(111)-C(103)	-	C(204)-O(2)-C(205)-C(210)	15.37(15)
163.36(10)		O(2)-C(205)-C(206)-C(207)	179.27(10)
C(104)-C(103)-C(111)-N(1)	82.95(11)	C(210)-C(205)-C(206)-C(207)	-3.77(16)
C(102)-C(103)-C(111)-N(1)	-34.60(11)	C(205)-C(206)-C(207)-C(208)	1.85(17)
C(104)-C(103)-C(111)-C(110)	-	C(206)-C(207)-C(208)-C(209)	1.75(17)
40.51(12)		C(207)-C(208)-C(209)-C(210)	-3.59(17)
C(102)-C(103)-C(111)-C(110)	-	O(2)-C(205)-C(210)-C(209)	178.73(10)
158.05(9)		C(206)-C(205)-C(210)-C(209)	1.99(15)
C(101)-N(1)-C(112)-C(113)	61.97(12)	O(2)-C(205)-C(210)-C(211)	4.39(16)
C(111)-N(1)-C(112)-C(113)	-59.51(13)	C(206)-C(205)-C(210)-C(211)	
		-172.34(10)	

C(208)-C(209)-C(210)-C(205)	1.71(16)	C(202)-C(201)-C(214)-C(215)	-65.39(15)
C(208)-C(209)-C(210)-C(211)	176.01(10)	N(2)-C(201)-C(214)-C(219)	-129.01(11)
C(212)-N(2)-C(211)-C(210)	-64.56(13)	C(202)-C(201)-C(214)-C(219)	114.76(12)
C(201)-N(2)-C(211)-C(210)	168.55(9)	C(219)-C(214)-C(215)-C(216)	0.13(18)
C(212)-N(2)-C(211)-C(203)	174.11(11)	C(201)-C(214)-C(215)-C(216)	
C(201)-N(2)-C(211)-C(203)	47.22(10)		-179.73(11)
C(205)-C(210)-C(211)-N(2)	-105.81(11)	C(214)-C(215)-C(216)-C(217)	-0.25(19)
C(209)-C(210)-C(211)-N(2)	80.10(12)	C(215)-C(216)-C(217)-C(218)	0.47(18)
C(205)-C(210)-C(211)-C(203)	9.49(14)	C(215)-C(216)-C(217)-C(220)	
C(209)-C(210)-C(211)-C(203)			-179.25(11)
	-164.60(10)	C(216)-C(217)-C(218)-C(219)	-0.57(17)
C(204)-C(203)-C(211)-N(2)	83.80(10)	C(220)-C(217)-C(218)-C(219)	179.14(12)
C(202)-C(203)-C(211)-N(2)	-33.67(11)	C(215)-C(214)-C(219)-C(218)	-0.23(17)
C(204)-C(203)-C(211)-C(210)	-39.69(12)	C(201)-C(214)-C(219)-C(218)	179.62(11)
C(202)-C(203)-C(211)-C(210)	-157.17(9)	C(217)-C(218)-C(219)-C(214)	0.47(18)
C(211)-N(2)-C(212)-C(213)	-59.58(14)		
C(201)-N(2)-C(212)-C(213)	62.43(13)		
N(2)-C(201)-C(214)-C(215)	50.84(14)		

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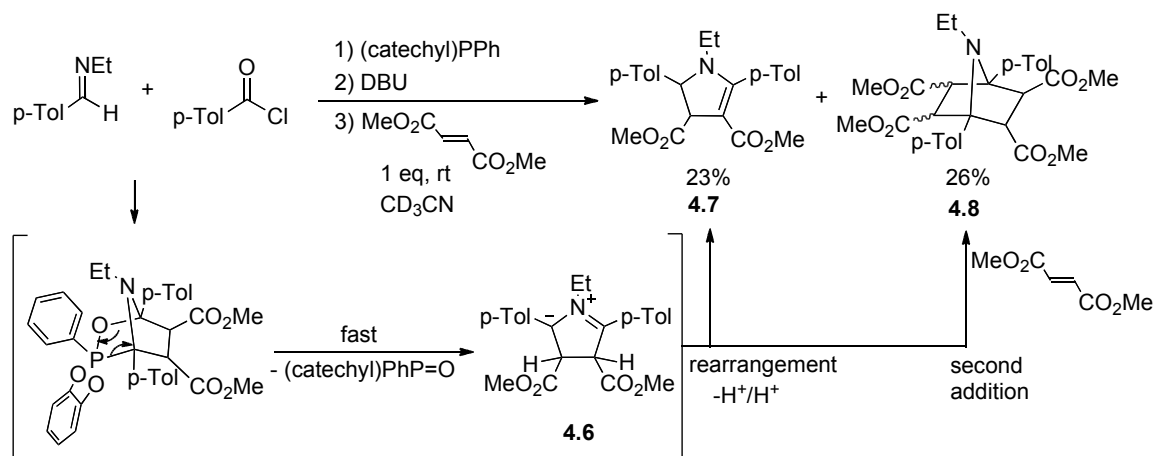
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Appendix G

Additional Results: Alkene Cycloaddition with Phospha-Münchnones

I. Chapter 4: Intermolecular Alkene Cycloaddition with Phospha-Münchnones

Alkene cycloadditions with phospha-Münchnones was first attempted in an intermolecular reaction with electron poor olefins to form 2-pyrrolines. As shown in Scheme 1, the reaction of dimethyl fumarate with a phospha-Münchnone resulted in low yield of the 2-pyrroline **4.7**. This results from the formation of the bicyclic **4.8**, which presumably forms due to the reactivity of the intermediate azomethine ylide **4.6**, which can either rearrange to form the 2-pyrroline **4.7** or add a second equivalent of alkene to generate **4.8**. These two processes are in competition, likely due to the rapid elimination of the sterically encumbered penta-coordinated phosphorus to generate the new 1,3-dipole **4.6**. The later is formed more rapidly than the consumption of one equivalent of alkene by cycloaddition with phospha-Münchnone and leads to the competitive formation of the bicyclic adduct **4.8**.



Scheme 1: Intermolecular Alkene Cycloaddition with Phospha-Münchnone.

Various reaction conditions have been explored to limit the formation of the bicyclic product **4.8** and increase the yield of 2-pyrroline (Table 1). Considering that the azomethine ylide **4.6** is formed more rapidly than the cycloaddition of one equivalent of alkene to the phospho-Münchnone, the rearrangement of **4.6** was favored by decreasing the concentration of alkene in solution. This was achieved by diluting the reaction mixture and the slow addition of alkene into the solution. Under these conditions, the yield of 2-pyrroline was improved from 23% to 57% (entry 3). However, these optimized conditions are dependant on the phospho-Münchnone substituents. With the more sterically encumbered N-benzyl substituted dipole, 2-pyrroline was only formed in 37% of yield upon the slow addition of alkene (entry 6). The reaction is therefore sensitive to substituents, which limits the scope of this approach. The intramolecular approach of alkene cycloaddition was therefore considered to overcome the problem of double cycloaddition. The proximity of the reacting species allows the more rapid cycloaddition of alkene on the phospho-Münchnone and disfavored the second addition on the resulting azomethine ylide (cf. Chapter 4).

Table 1: Optimization of Pyrroline Synthesis^a

Entry	R	Concentration	Condition	Pyrroline	Bicycle
1	Et	0.1 mol.L ⁻¹	rapid addition of alkene	23%	26%
2	Et	0.02 mol.L ⁻¹	rapid addition of alkene	43%	10%
3	Et	0.02 mol.L ⁻¹	alkene added over 6 h	57%	5%
4	Bn	0.02 mol.L ⁻¹	rapid addition of alkene	17%	20%
5	Bn	0.02 mol.L ⁻¹	alkene added over 3 h	32%	13%
6	Bn	0.02 mol.L ⁻¹	alkene added over 7 h	37%	8%

^aimine (0.2 mmol), TolCOCl (34 mg, 0.22 mmol), CD₃CN, 30 min; then (2-catechyl)PPh (47.5 mg, 0.22 mmol), 1h; DBU (55 mg, 0.36 mmol), dimethyl fumarate (28.8 mg, 0.2 mmol), rt.

II. Chapter 4: Limitations on Intramolecular Alkene Cycloadditions with Phospha-Münchnones

Chapter 4 reports the intramolecular alkene cycloaddition with the (2-catechyl)PPh-based 1,3-dipole, and the scope of the reaction is illustrated in Table 4.2. During the investigation of the variety of 2-pyrrolines that can be obtained with this approach, different alkene-tethered imines and acid chlorides were tested and only the successful examples have been reported in Table 4.2. Table 2 below shows the unsuccessful results of this method with different imines and acid chlorides. Examples include the attempts to obtain larger ring system (entry 2), nitrogen-containing tether unit (entry 5) or acyclic spacer (entry 6). All lead to low or no yield of 2-pyrroline either due to lack of reactivity (entries 2 and 5) or side product formation (entries 1, 3, 4 and 6). For entries 3, 4 and 6, the products we believed to have formed (based upon in situ ^1H NMR analysis, but not fully characterized), are provided.

Table 2: Intramolecular Alkene Cycloaddition Limitations^a

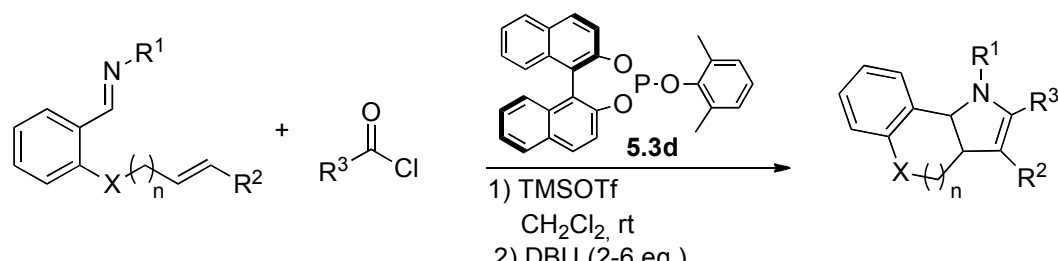
Entry	Imine	Acid Chloride	Product (% yield)
1			Low yield, side product formation
2			0% (decomposition upon heating)
3			potential two diastereoisomers formed, not selective cycloaddition.
4			50% (NMR yield), no pyrrole observed
5			0%
6			0% of pyrrole,^b decomposition to enamide (70% NMR yield)

^aimine (0.2 mmol), acid chloride (34 mg, 0.22 mmol), CDCl₃, 30 min; then (2-catechyl)PPh (47.5 mg, 0.22 mmol), 1h; DBU (60 mg, 0.4 mmol), rt. ^bimine/acid chloride at -78 °C, AgOTf (1 eq.), LiHMDS, at -78 °C, CH₂Cl₂.

III. Chapter 5: Limitations on Intramolecular Alkene Cycloaddition with Chiral Phosphorus-Based 1,3-Dipole

Similarly to Table 2, the following section describes the unsuccessful results in the enantioselective intramolecular alkene cycloadditions by the method developed in Chapter 5. The substrates used in Table 3 are not compatible with the optimized reaction conditions, and lead to low or no yield of 2-pyrroline. Further investigations of the reaction condition are necessary to successfully employ these substrates.

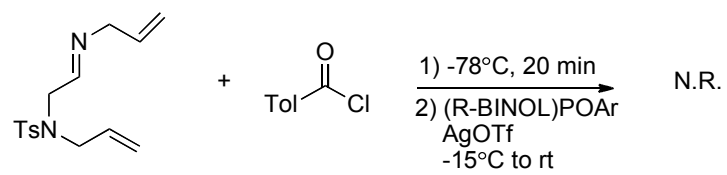
Table 3: Limitations on Alkene Cycloadditions with **5.3d**^a



Entry	R ¹	R ²	R ³	X	n	Product (% yield)
1	Bn	CO ₂ Et	OBn	O	1	0 %
2	Hex	CO ₂ Et	^t Bu	O	1	28% (2 isomers 5:1 ratio)
3	Bn	CO ₂ Et	<i>p</i> -NO ₂ C ₆ H ₄	O	1	30 %
4	Allyl	H	Ph	O	2	0%
5	Et	H	<i>p</i> -Tol	NBoc	1	0% ^b
6	Et	H	<i>p</i> -Tol	CH ₂	0	0% ^c
7	Et	H	<i>p</i> -Tol	CH ₂	1	0% ^c

^a imine (0.2 mmol), acid chloride (0.22 mmol), 0.5 mL CH₂Cl₂, 30 min; **5.3d** (96 mg, 0.22 mmol), TMSOTf (46.7 mg, 0.21 mmol), 3h; DBU (0.4-1.2 mmol), rt. ^bphosphorus salt not formed. ^cPhosphorus salt formed at 40-50% because of the formation of a side product non-identified.

A non-aromatic substituted alkene-tethered imine was also tested in this reaction. However, the corresponding 2-pyrroline was not formed, probably because of the low stability of the iminium salt intermediate that readily decomposes to form enamide (Scheme 2).



Scheme 2: Acyclic Imine Substrate in Pyrroline Synthesis

Appendix H

Horner-Wadsworth-Emmons Reagents as Azomethine Ylide Analogues: Pyrrole Synthesis via (3+2) Cycloaddition

This text below is a copy of a published paper that I equally contributed with Daniel J. St-Cyr. It is reproduced with permission from Marie S. T. Morin, Daniel J. St-Cyr and Bruce A. Arndtsen. "Horner-Wadsworth-Emmons Reagents as Azomethine Ylide Analogues: Pyrrole Synthesis via (3+2) Cycloaddition." Org. Lett. 2010, 12, 4916.

Introduction

1,3-Dipolar cycloaddition with azomethine ylides has found broad application in the synthesis of five-membered ring heterocycle.¹ There are a range of methods available to generate azomethine ylides, including the α -deprotonation of activated imine precursors,² the carbon-carbon ring opening of aziridines,³ or the desilylation of *in situ* generated *N*- α -silyliminium ions.⁴ While effective, these methods typically require the initial build up of a precursor with the correct substituents prior to creating the dipole or need specific activating groups to proceed in good yields (e.g. imines with electron withdrawing substituents). In addition, because of their symmetry, the regioselectivity of azomethine ylide cycloaddition is substituent dictated, and will result in mixtures unless there is a large electronic or steric bias between the two carbon-bound units.^{1,5}

A potential approach to address these issues of azomethine ylide generation and selectivity is to design synthetic equivalents.⁶ One commonly employed variant of azomethine ylides are Huisgen's 1,3-oxazolium-5-oxides (i.e. Münchnones, **2**, Figure 1),⁷ though these can also be challenging to prepare, unless they are derived from natural amino acids,^{8,9} or formed via catalysis.¹⁰ As

an alternative, we have recently reported that Wittig-type reagents **3** can serve as precursors to 1,3-dipoles via cyclization to form **4**.¹¹ These phosphorus-based dipoles can be synthesized in a modular fashion from simple imines, acid chlorides and phosphonites. In addition, the PR_3 unit creates a strong electronic bias across the dipole, providing a tool to control selectivity in cycloaddition reactions.^{11c}

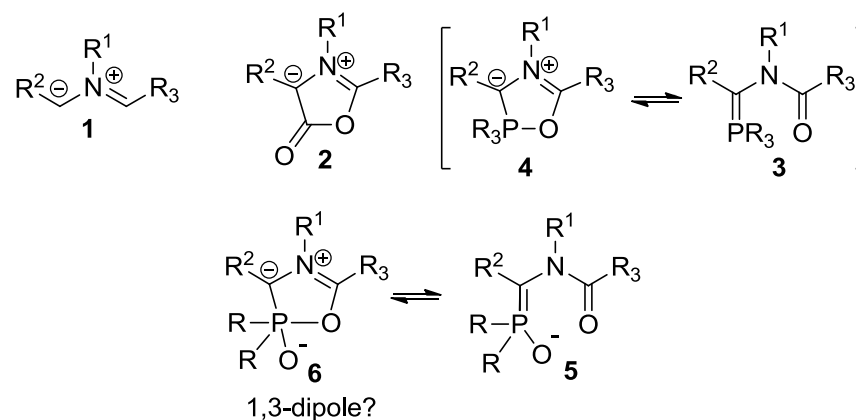


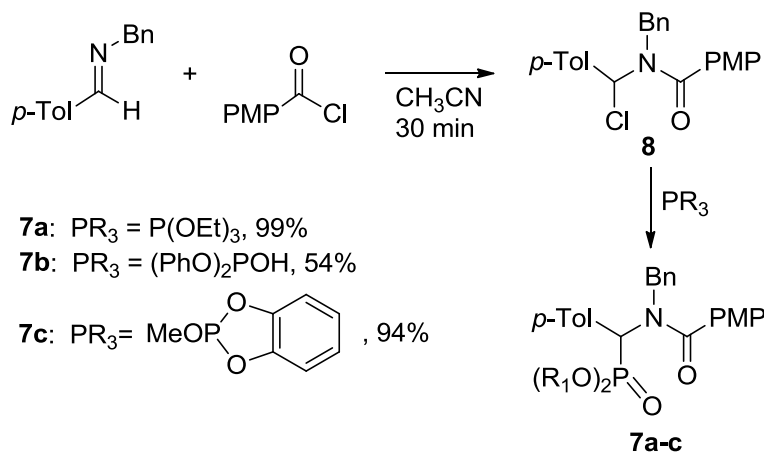
Figure 1. 1,3-Dipolar Cycloaddition Reagents.

A challenge in the use of **4** is that it is generated via the equilibrium reaction of imines, acid chlorides and (2-catechyl)PPh, thereby limiting the scope of dipoles available to those derived from stabilized precursors (e.g., R^2 or R^3 = aryl, alkyl).¹¹ In considering this issue, we became interested in the potential of Horner-Wadsworth-Emmons reagents such as **5** (Figure 1) to behave as 1,3-dipoles. Horner-Wadsworth-Emmons reagents have become useful alternatives to Wittig reagents in alkene synthesis due in large part to the stability and availability of their precursors: phosphonates (e.g., **7**, Scheme 1).¹² The latter are generated via the Arbuzov reaction of phosphites and electrophiles. As described below, amido-substituted Arbuzov products can serve as attractive precursors to 1,3-dipoles. These compounds are formed in a non-equilibrium reaction of imines, acid chlorides and phosphites, are air stable, and can be broadly diversified. In addition, the generation of dipole **6** can be coupled with cycloaddition, providing one pot access to pyrroles.

Results and Discussion

Amido-substituted phosphonates can be generated by the reaction of *in situ* formed α -chloroamides with phosphites.¹³ For example, the reaction of *p*-tolyl(H)C=N-Bn, and anisoyl chloride in acetonitrile leads to the formation of α -chloroamide **8** (Scheme 1). The subsequent addition of P(OEt)₃ results in a rapid Arbuzov reaction, generating phosphonate **7a** in near quantitative yield. Other phosphites can also participate in this reaction, yielding variously phosphorus-substituted products (**7b** and **7c**).

Scheme 1. Synthesis of Phosphonate Precursors **7a-c**.^{a-c}

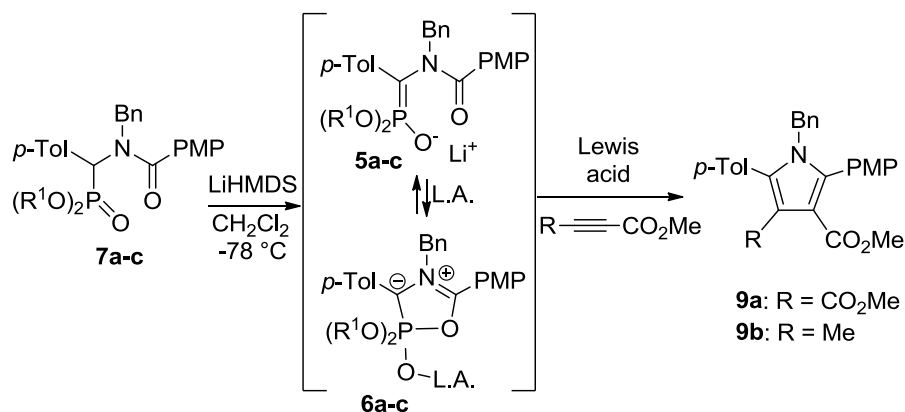


^a P(OEt)₃ at 0 °C, 5 min. ^b (PhO)₂POH in CH₂Cl₂ with 2,4,6-collidine, 0 °C → rt. ^c P(catechyl)OMe at rt, 15h.

Amido-substituted phosphonate **7a** can be deprotonated with LiHMDS base to generate the corresponding ylide **5a** (Table 1). This product has the potential to cyclize in a fashion similar to Wittig-type reagents **3** (Figure 1). However, *in situ* ³¹P and ¹³C NMR data suggests **5a** exists predominately in an acyclic ylide structure. For example, ³¹P NMR analysis reveals a signal at 34.4 ppm, which is typical of Wadsworth-Emmons structures,¹⁴ while the amide ¹³C NMR resonance (δ 176.8 ppm) is not perturbed as expected for the 1,3-dipole.¹¹ Despite these structural features, the addition of the alkyne DMAD to **5a** does result in a slow cycloaddition reaction to form pyrrole (Table 1).¹⁵ **5b** and **5c**

react in a similar fashion, with the less sterically encumbered catechyl-substituted **5c** leading to the rapid formation of pyrrole (< 5 min, entry 3).

Table 1. Phosphonates in Alkyne Cycloaddition and Pyrrole Synthesis.^a

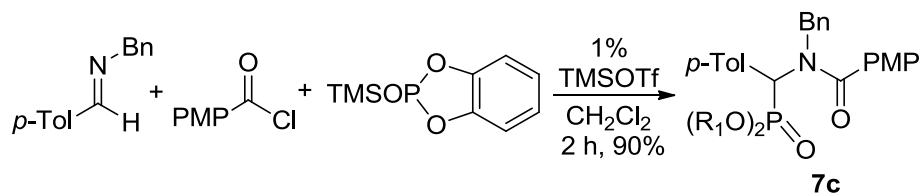


Entry	Compd	R	Lewis acid	Time (h)	Yield (%)
1	7a	CO ₂ Me	-	24	50
2	7b	CO ₂ Me	-	0.5	70
3	7c	CO ₂ Me	-	< 5 min	80
4	7c	Me	-		-
5	7c	Me	BF ₃ .Et ₂ O		-
6	7c	Me	TsCl		-
7	7c	Me	^t BuPh ₂ SiCl	17	73
8	7c	Me	SiCl ₄	17	56
9	7c	Me	TBSCl	17	68
10	7c	Me	TESCl	3	91
11	7c	Me	TMSCl	3	95

^a0.2 mmol **7** in 0.5 mL CH₂Cl₂, -78 °C, 0.2 mmol LiHMDS solution; then 0.22 mmol L.A. at rt, followed by 0.6 mmol alkyne.

While the reaction in Table 1 provides a method to generate pyrroles, there are several challenges in this approach. First, the most effective phosphonate precursor, the catechyl-substituted **7c**, is formed slowly from (2-catechyl)P(OMe) and **8**, making it difficult to diversify this reagent to other imines/acid chlorides. This can be addressed by the use of the slightly more nucleophilic P(2-catechyl)-

OTMS and addition of catalytic TMSOTf (Scheme 2). Under these conditions, **7c** is generated 2 h at ambient temperature, presumably via the *in situ* formation of a more electrophilic *N*-acyl iminium triflate salt intermediate. This approach can be readily adapted to less reactive imines and acid chlorides (*vide infra*).



Scheme 2. TMSOTf-Catalyzed One-Pot Multicomponent Synthesis of **7c**.

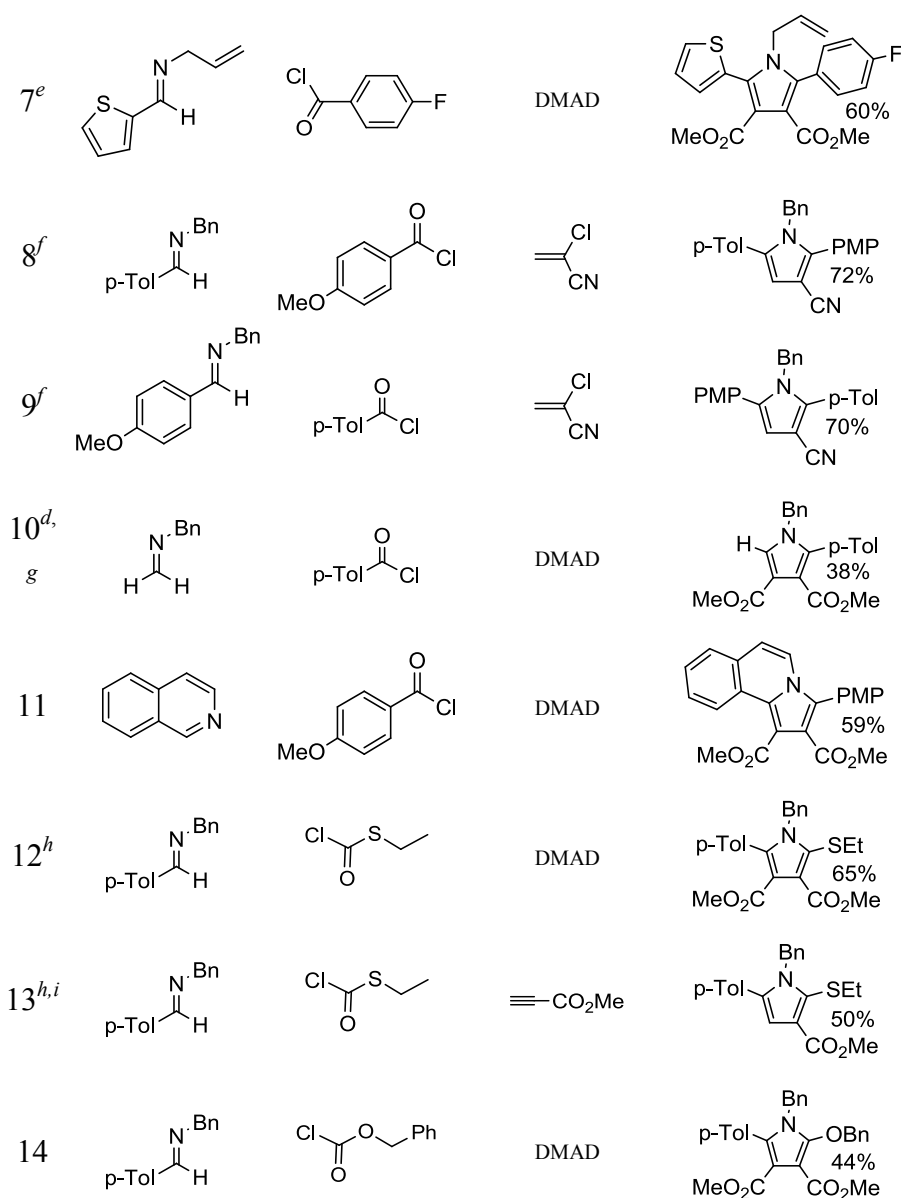
A second issue with **5c** is its inability to undergo cycloaddition with less activated dipolarophiles (e.g., Table 1, entry 4). The low reactivity presumably arises from the relatively electron rich phosphorus unit in **5**, which disfavors a P–O interaction to generate the dipole. One approach to favor cyclization of **5** is to neutralize the formal oxygen anionic charge. As shown in Table 1, a number of Lewis acids can serve this purpose (entries 7-11), with TMSCl proving to be the most effective.¹⁶ *In situ* NMR analysis is consistent with the Lewis acid favoring a dipolar form (**6c**). This shows a significant perturbation of the amide carbonyl resonance of **6c** in presence of TMSCl (at δ 146.8 ppm), as well as an upfield shift in the ³¹P NMR resonance (δ -28.2 ppm, relative to **5c** at 47.6 ppm). This latter is within the range expected for pentacoordinate organophosphorus structures¹⁷ and similar to crystallographically characterized phosphorus dipoles.¹¹

The coupling of these optimized conditions for phosphonate formation, deprotonation and dipolar cycloaddition allows for a series of very rapid and selective reactions, and the assembly of poly-substituted pyrroles within hours at ambient temperature (Table 2). Because of the stability of the phosphonate intermediates, this transformation is straightforward to generalize. A range of *C*-aryl, -functionalized aryl, and -heteroaryl-substituted imines can be used in this reaction (entries 1-7), as can various aryl-substituted acid chlorides. Electron poor dipolarophiles are the most reactive with **6**, though aryl-acetylenes are also viable substrates (entry 6). Alkynes can be replaced with electron deficient alkenes,

which undergo acid loss to generate pyrroles upon cycloaddition (entries 8 and 9). In addition to forming pyrroles, the cycloadditions with unsymmetrical alkynes typically results in a single isomeric product, where the electron withdrawing unit is directed away from the formerly phosphorus-bound carbon. This is consistent with a phosphorus-induced electronic bias in these dipoles controlling regioselectivity.^{11c}

Table 2. Scope of Three-Component Pyrrole Synthesis.^a

$ \begin{array}{c} \text{R}^2\text{C}=\text{N}^{\text{R}^1}\text{H} + \text{R}^3\text{C}(=\text{O})\text{Cl} + \text{Ph-O-POTMS} \\ \xrightarrow[\text{c) TMSCl (1 equiv.)}]{\text{a) 1\% TMSOTf, CH}_2\text{Cl}_2, \text{rt; b) LiHMDS, -78 }^\circ\text{C}} \\ \text{R}^4\text{C}\equiv\text{C}\text{R}^5 \end{array} \longrightarrow \begin{array}{c} \text{R}^1 \\ \\ \text{R}^3\text{C}-\text{N}-\text{C}-\text{R}^2 \\ \quad \\ \text{R}^4 \quad \text{R}^5 \end{array} $				
#	Imine	Acid chloride	Alkyne	Pyrrole (%)
1				
2				
3				
4 ^{b,c}				
5 ^d				
6				



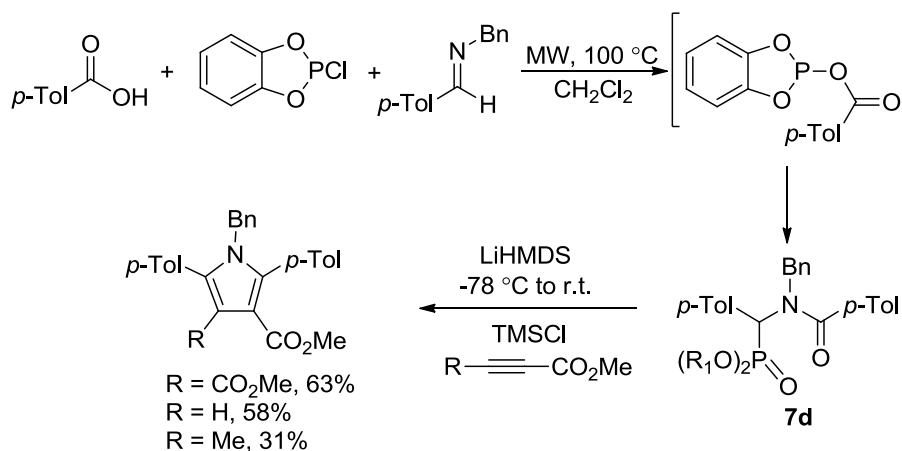
^aa) 0.20 mmol imine/ acid chloride, 0.5 h; TMSOP(2-catechyl) (0.22 mmol), TMSOTf (0.002 mmol), 2h; b) 0.20 mmol LiHMDS; c) TMSCl (0.20 mmol), alkyne (0.60 mmol). ^bc) 55 °C. ^c Major isomer (66:34 ratio). ^da) 24 h. ^e 5% TMSOTf. ^f 0.80 mmol LiHMDS. ^g 0.22 mmol TMSOTf, CH₃CN, DBU. ^ha) 12 h, 55 °C. ⁱc) 0.40 mmol TMSOTf.

The irreversibility of phosphonate formation can also allow the use of less stable imine/acid chloride reagents. For example, formaldimines can be employed in the coupling, followed by subsequent cyclization and dipolar addition to form 5-H substituted pyrroles (entry 10). Alternatively, imines can be

replaced with aromatic heterocycles such as isoquinoline, which can be efficiently trapped to yield a polycyclic pyrrole (entry 11).¹⁸ The acid chlorides can even be replaced with chloroformates and chlorothioformates. While these latter create less electrophilic analogues to **8**, their trapping can occur with P(2-catechyl)OTMS, providing a route to 2-heteroatom-substituted pyrroles (entries 12-14).

The Arbuzov intermediates in this reaction can be exploited to create alternative routes to these dipoles. Burnaeva and co-workers have reported that the reaction of imines with benzoate-substituted phosphonites leads to amido-substituted phosphonates.¹⁹ Performing this reaction with a catechyl-substituted phosphorus reagent can provide a single-step synthesis of **7d** from commercially available (2-catechyl)PCl, *p*-toluic acid, and imine (Scheme 3). Notably, this approach avoids both the need to generate (2-catechyl)P(OTMS), and the use of often sensitive acid chloride (and iminium salt) precursors. Coupling this synthesis with subsequent cycloaddition can allow the overall synthesis of pyrroles in one pot from carboxylic acids, imines and alkynes.

Scheme 3. Pyrrole Synthesis from Carboxylic Acids.^a



^a 0.2 mmol imine, 0.22 mmol carboxylic acid, 0.22 mmol (2-catechyl)PCl, 1 mL CH₂Cl₂, MW, 100 °C 2 h; 0.45 mmol LiHMDS solution, -78 °C to rt; 0.4 mmol TMSCl, 0.6 mmol alkyne, rt.

Conclusions

In conclusion, amido-substituted Horner-Wadsworth-Emmons reagents can serve as precursors to 1,3-dipoles, and participate in cycloaddition reactions with alkynes to form pyrroles. Coupling the generation of these reagents with cycloaddition can provide a modular method to construct pyrroles from available building blocks. Studies directed towards the reaction of these reagents with other dipolarophiles, and the development of alternative approaches to generate **6**, are under investigation.

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Appendix I

Copper-Catalyzed Petasis-Type Reaction: A General Route to α -Substituted Amides From Imines, Acid Chlorides and Organoboron Reagents

*This text below is a copy of a published paper that I equally contributed with Dr. Yingdong Lu. It is reproduced with permission from Marie S. T. Morin, Yingdong Lu, Daniel A. Black, and Bruce A. Arndtsen. "Copper-Catalyzed Petasis-Type Reaction: A General Route to α -Substituted Amides From Imines, Acid Chlorides and Organoboron Reagents" J. Org. Chem. **2012**, 77, 2013.*

Introduction

Because of their relevance in pharmaceuticals and other bio-active compounds, there is significant interest in the synthesis of α -substituted amines and amides.¹ One straightforward strategy is the nucleophilic addition of organometallic reagents to imines.² However, this approach can be limited by the poor electrophilicity of the C=N double bond and the instability of some imines towards reactive organometallic reagents (e.g., organolithium and organomagnesium compounds). Because of their low toxicity, stability to air and water, and functional group tolerance, organoboron reagents have become widely used in organic synthesis.³ This includes in carbon-carbon bond forming reactions with imines, via either transition metal catalyzed⁴ and noncatalytic pathways.⁵ Transition metal mediated variants of this reaction often employ rhodium or palladium catalysts and can be very effective, though they do generally require activated imines bearing electron-withdrawing groups on the nitrogen, such as *N*-sulfonyl, *N*-diphenylphosphinoyl, and *N*-sulfinyl imines.⁴ Alternatively, the non-metal catalyzed couplings with organoboranes often involve the use of *in situ*

generated iminium ions, i.e., the Petasis reaction.⁵ These typically require directing groups at α - or β -position to the iminium salt carbon (e.g., α -keto acids, α -hydroxy aldehydes, and salicylaldehydes). While there are exceptions to the latter,⁶ particularly with less sterically hindered aldehydes (e.g., paraformaldehyde), or reactive organoboranes (e.g., allylic boranes or 2-furylboranes), this can limit the scope of α -substituted amines available via this route.

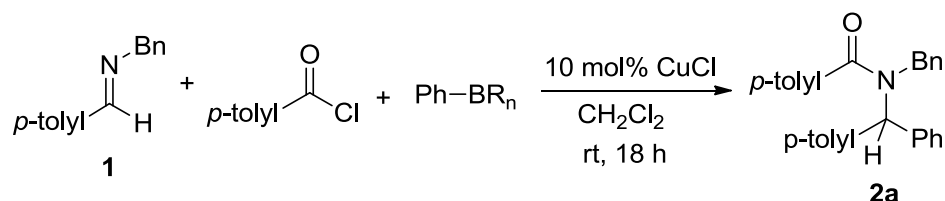
Considering the availability and stability of organoboron reagents, we became interested in the potential development of a general approach to employ these reagents in imine addition. We have recently demonstrated that palladium or copper complexes can catalyze the cross-coupling like reaction between in situ generated *N*-acyl iminium salts and organo-tin or -indium reagents.^{7,8} Similarly, Doyle has reported that heterocyclic ethoxy-substituted carbamates can undergo a nickel catalyzed Petasis-type coupling with aryl-boron reagents,⁹ while Li has found that rhodium complexes can catalyze aryl-borane reactions with α -amido sulfones.¹⁰ In addition, various research groups have found that copper salts can catalyze the addition of organometallic reagents to in situ generated iminium salts, in reactions that presumably proceed via the formation of organocopper intermediates from transmetallation.¹¹ We show herein how copper catalysis and the correct organoboron reagent can provide a novel method to assemble α -substituted amides from imines, acid chlorides and borates. Notably, this reaction does not require activated or specialized imines, and proceeds with a variety of organoboron reagents.

Results and Discussion

Our initial studies involved the CuCl-catalyzed reaction of the unactivated imine **1** with various phenyl-substituted organoboranes. As can be seen in Table 1, no amide product is observed either with or without acid chloride (entries 1, 2), nor in the presence of known organoborane activators (K_3PO_4 , F^- , entries 3, 4). Similar results were observed with other phenyl-substituted organoboranes

(entries 5, 6). Considering the cationic charge on the in situ generated iminium salts (vide infra), we postulated that negatively charged boron reagents might be better suited for this reaction, through initial ion pairing to the iminium unit. Indeed, the use of $\text{Na}^+\text{BPh}_4^-$ does result in the formation of trace amounts of **2a** (11 %, entry 8), along with significant decomposition. A similar decomposition is observed without copper catalysts present (though without **2a** formation), and presumably arises from the generation of an unstable, uncoordinated *N*-acyl iminium cation with BPh_4^- as the counterion.¹²

Table 1. Copper-Catalyzed Reaction of Imines and Organoboranes^a

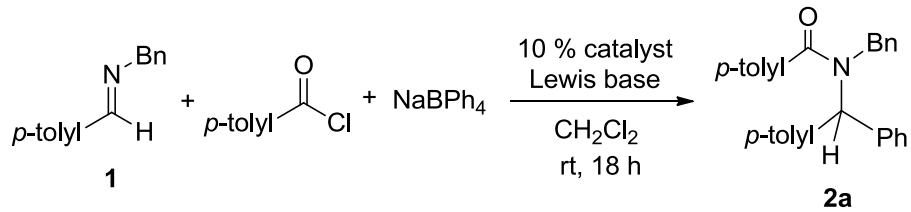


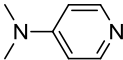
Entry	Organoborane	Additive	Yield 2a
1		-	-
2 ^b	“	-	-
3	“	K_3PO_4	-
4	“	F^-	-
5	$(\text{MeO})_2\text{B-Ph}$	F^-	-
6	$(\text{HO})_2\text{B-Ph}$	F^-	-
7	$\text{K}^+\text{F}_3\text{BPh}^-$	-	-
8	$\text{Na}^+\text{BPh}_4^-$	-	11%
9 ^c	$\text{Na}^+\text{BPh}_4^-$	-	-

^a *p*-tolyl(H)=NBn (41.8 mg, 0.20 mmol), *p*-toluoyl chloride (34 mg, 0.22 mmol), CuCl (2.0 mg, 0.02 mmol), organoborane (0.20 mmol), additive (0.30 mmol), CH_2Cl_2 , rt, 18h. ^b Without *p*-toluoyl chloride. ^c No CuCl.

It has been postulated in copper-catalyzed cross-coupling reactions that transmetalation of organic units from main group elements to copper(I) salts is reversible, and can be inhibited by the build-up of the organometallic-halide byproduct as the reaction proceeds.¹³ In our case, this byproduct is BPh₃. This product could in principle be trapped by Lewis bases. In addition, Lewis bases could coordinate to the *N*-acyl iminium salt, thereby lowering its background decomposition with BPh₄⁻. As shown in Table 2, the addition of a catalytic amount of pyridine base (10 mol%) increases the yield of **2a** to 14 %, while the use of stoichiometric pyridine leads to near quantitative **2a** formation (83%, entry 2). This coupling is extremely rapid, and proceeds to completion within 30 min at ambient temperature (entry 5). DMAP is also effective as the Lewis base additive (entry 8), while the more electron rich phosphines either slow (PPh₃, entry 7) or inhibit (PBU₃, entry 9) catalysis.

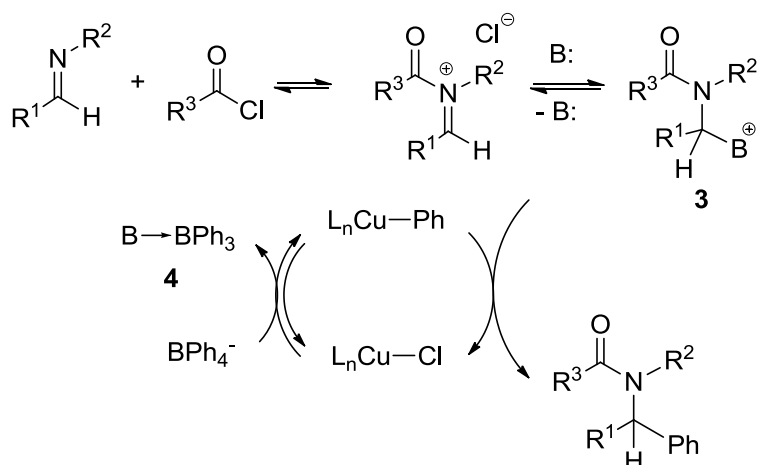
Table 2. Reaction Optimization with Lewis Base Additives^a

			
Entry	Catalyst	Lewis Base	Yield %
1	CuCl	 (10%)	14
2	CuCl		83
3	CuPF ₆		86
4	CuI		83
5 ^b	CuCl		80
6	Pd ₂ dba ₃		10

7 ^c	CuCl	PPh ₃	11
8	CuCl		43
9	CuCl	P(<i>n</i> -Bu) ₃	-

^a *p*-tolyl(H)=NBn (41.8 mg, 0.20 mmol), *p*-toluoyl chloride (34 mg, 0.22 mmol), NaBPh₄ (68.4 mg, 0.20 mmol), catalyst (0.02 mmol), and Lewis base (0.20 mmol), 2 mL CH₂Cl₂, rt, 18 h, yields determined by ¹H NMR. ^b 30 min, rt. ^c 60 °C

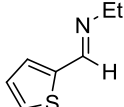
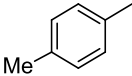
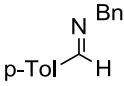
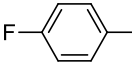
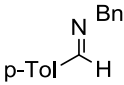
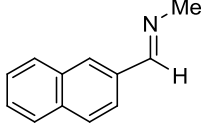
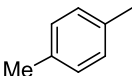
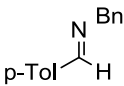
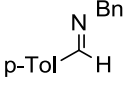
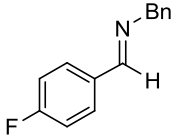
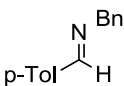
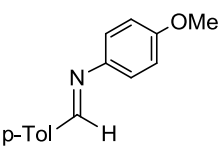
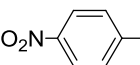
The role of Lewis bases in this transformation can be probed by monitoring the copper-catalyzed reaction by ¹H NMR spectroscopy. This shows the immediate formation of a pyridine-containing intermediate prior to the addition of the copper catalyst.¹⁴ This intermediate can be independently generated via the addition of pyridine to the *N*-acyl iminium salt, and has been characterized as the pyridinium salt **3** (Scheme 1; B = pyridine).¹⁵ The formation of **3** provides a rationale for the slower coupling reaction with DMAP relative to pyridine, or inhibition with phosphines, since these more Lewis basic units presumably undergo slower displacement by the in situ formed organocopper complex to form the product. Compound **3** appears to be a viable intermediate in the catalytic reaction. Warming of the solution of **3** in the presence of the copper catalyst and NaBPh₄ leads to its slow disappearance together with the formation of amide **2a**. In addition to **2a**, a new organoboron product is observed in similar yield to **2a**: the pyridine-BPh₃ adduct **4**.

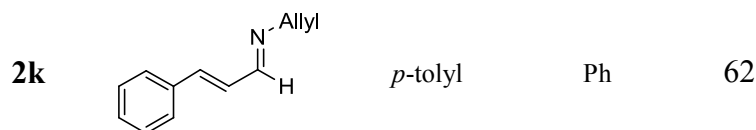


Scheme 1. Proposed Mechanism of the Copper-Catalyzed Coupling.

A useful feature of this catalytic coupling is that it does not require the use of specifically substituted imines or organoboranes. As such, it is easily diversified to assemble a range of α -substituted amides. For example, a number of simple imines can be used in this reaction. This includes *N*-benzyl-, -aryl and -alkyl imines, as well as imines derived from aryl- or heteroaryl-aldehydes (Table 3). Similarly, aryl-, alkyl-, and heteroaryl-acid chlorides provide amides in good yield (**2g-i**). The borate unit can also be easily tuned. In addition to simple phenyl-substituted borates, functionalized aryl- (**2b**, **2c**), heteroaryl- (**2d**), and even alkyl groups can be transferred to imines with good yields at room temperature (**2f**, **2g**). α,β -unsaturated imines can also be employed in this reaction, leading to the 1,2-addition product **2k**.

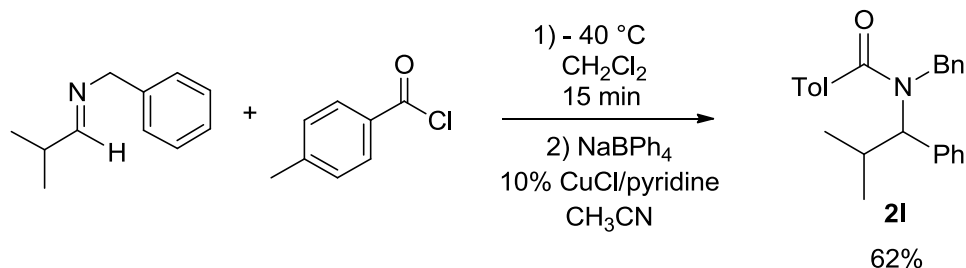
Table 3. Diversity of Copper-Catalyzed Multicomponent Coupling of Imines, Acid Chlorides and Organoboron Reagents.

$ \begin{array}{c} \text{R}^2\text{C}=\text{N}-\text{R}^1 \\ + \quad \text{R}^3\text{C}(=\text{O})\text{Cl} + \text{Na}^+ \text{BR}_4^- \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt, 18 h}]{10\% \text{ CuCl, Pyridine}} \\ \text{R}^3\text{C}(=\text{O})\text{N}(\text{R}^1)\text{CH}(\text{R}^2)\text{R} \\ \mathbf{2} \end{array} $				
Product	Imine	R ³	R	Yield %
2b		Ph		74
2c		Ph		90
2d^b				80
2e		Ph		71
2f		Ph	-CH ₂ Ph	71
2g		<i>p</i> -tolyl	Et	74
2h			Ph	70
2i			Ph	57
2j			Ph	83



^aImine (0.20 mmol), acid chloride (0.22 mmol), organoborane (0.20 mmol), CuCl (2.0 mg, 0.020 mmol), pyridine (15.8 mg, 0.20 mmol), 2 mL CH₂Cl₂, rt, 18 h. ^bWith KB(2-thiophenyl)₄.

The formation of the Lewis base coordinated intermediate **3** also allows the use of less stabilized imines in this chemistry. For example, due to their sensitivity to base, enolizable imines can be more challenging substrates for coupling with organometallic reagents, and their corresponding *N*-acyl iminium salts are very prone to enamide formation. The latter has precluded their use in similar copper-catalyzed coupling reactions with other organometallic reagents.¹⁶ However, because of the low basicity of organoborates, and the generation of a stabilized pyridinium salts **3**, these imines can also be employed in this copper catalyzed reaction, affording **2i** in good yield (Scheme 2).



Scheme 2. Coupling Reaction with Enolizable Imine.

Conclusions

In conclusion, we have developed a copper-catalyzed multicomponent synthesis of α -substituted amides from imines, acid chlorides and organoborane reagents. Considering the simplicity of the catalyst, the generality of the reaction, and the stability of these reagents, this provides a straightforward route to construct α -substituted amides. This approach does not require the use of activated

imines or the transfer of special units from the organoboranes. As such, it represents a useful generalization of Petasis-type coupling reactions of in situ generated iminium salts with organoboranes.

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- (12) The reaction of *p*-tolyl(H)C=NBn, *p*-tolylCOCl and NaBPh₄ in CH₂Cl₂ leads to a complex mixture of decomposition products within 3 h at ambient temperature, including *p*-tolylCON(Bn)H and (*p*-tolyl)H₂CN(Bn)CO(*p*-tolyl).
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- (14) The added pyridine presumably also coordinates to the copper catalyst, which may also influence catalytic activity. However, only a slight increase of yield is observed when a catalytic amount of pyridine is added (Table 2, entry 1).
- (15) The intermediate **3** is formed in equilibrium, and cannot be isolated in clean form. However, its in situ ¹H and ¹³C NMR data are consistent with its formation. See Supporting information for spectral data.
- (16) These *N*-acyl iminium salts cannot be employed in the copper catalyzed couplings with organotin and organoindium reagents.⁸