The Palladium Catalyzed Multicomponent Synthesis of Imidazoles and Imidazole-Containing π-Conjugated Polymers

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirement for the degree of Doctor of Philosophy

By

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Your file Votre référence
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I would like to dedicate this thesis to my wife and my daughter, Elham and Parya,

whom I love the most

ABSTRACT

The Palladium Catalyzed Multicomponent Synthesis of Imidazoles and Imidazole-Containing π-Conjugated Polymers

The primary goal of this study is to develop novel metal catalyzed multicomponent reaction methods to generate imidazoles and their derivatives. This is directed towards the assembly of poly-substituted imidazoles, imidazolones and imidazole-containing π-conjugated polymers. These products are generated in one-pot from such basic components as imines, acid chlorides, carbon monoxide, and/or organostannanes, via the use of palladium catalysis.

In Chapter 2, the design of a new palladium catalyzed synthesis of highly substituted imidazoles from imines and acid chlorides is described. This reaction involves the palladium catalyzed generation of 1, 3-oxazolium-5-oxides (Münchnones); which are trapped with *N*-tosyl substituted imines via a 1, 3 dipolar cycloaddition reaction to form the final products. Overall, this provides a one step method to assemble imidazoles from imines and acid chlorides with excellent regiochemical control. The versatility of this process is demonstrated by the assembly of diversely substituted imidazoles, including those with aryl, alkyl, heterocyclic and vinyl substituents.

Chapter 3 describes a new, palladium catalyzed, five component coupling of imines, chloroformates, organotin reagents, carbon monoxide and ammonium acetate to form imidazolones. The key step in this process is the efficient formation of ketocarbamates via the carbonylative cross coupling type reaction of imines,

chloroformates and organostannanes. These products can be easily converted into imidazolones via a cyclocondensation with ammonium acetate.

The synthesis of π-conjugated imidazole-containing polymers is described in Chapter 4. This process is designed based upon our previous studies on palladium catalyzed multicomponent synthesis of imidazoles, developed in Chapter 2. It is shown that bifunctional monomers such as di-imines, di-acid chlorides and di-*N*-tosylimines can be coupled together to assemble π-conjugated imidazole-containing oligomers and polymers utilizing this same palladium catalyzed reaction. This approach was used to create a novel library of conjugated imidazole polymers. By modifying the substituents on the polymer structures, the UV-vis absorbance and fluorescence excitation/emission spectra of these compounds are varied over a range of 150 nm.

In Chapter 5, the palladium catalyzed multicomponent polymerization is discussed in more detail. This includes the analysis of the end groups on the polymer backbone, as well as mechanistic studies into how the polymerization is terminated. These results suggest that the sulfinate anion liberated upon *N*-tosylimine cycloaddition may be non-innocent in this polymerization, and its presence could lead to termination of the growing polymer chain.

RESUME

Synthèse d'Imidazoles et d'Imidazoles contenant des unités Polymériques π-Conjugués par catalyse au Palladium.

Le but premier de cette étude est de développer des nouvelles méthodologies de synthèses multicomposés catalysées métalliquement pour générer des imidazoles et leurs dérivés. En particulier, l'étude est dirigée vers l'assemblage d'imidazoles et d'imidazoles polysubstituées ainsi qu'à des imidazoles contenant des unités polymeriques π-conjugués toutes générés en *one pot* à partir de composés simples comme des imines, des chlorures d'acides, du monoxyde de carbone et/ou des organostannanes *via* l'utilisation d'une catalyse au palladium.

Le second chapitre décrit le design d'une nouvelle synthèse catalysée au palladium d'imidazoles hautement substituées à partir d'imines et de chlorures d'acides. Cette réaction repose sur la génération par catalyse au palladium de 1,3-oxazolium-5-oxides (Münchnones), ceux-ci réagissent alors avec des imines *N*-tosylées *via* une cycloaddition 1,3 dipolaire pour fournir le produit final. Cette méthode a permis l'assemblage d'imidazoles en *one-pot* à partir de divers imines et chlorures d'acides avec une excellente régiosélectivité. La généralité du procédé est démontrée par l'assemblage d'une diversité d'imidazoles substituées par des unités aryliques, alkyliques, hétérocycliques ou encore vinyliques.

Le chapitre 3 décrit une nouvelle réaction à cinq composés catalysée au palladium. Les imidazolones sont obtenues à partir du couplage d'imines, de chloroformates, de

réactifs organostanniques, de monoxyde de carbone et d'acétate d'ammonium. L'étape clef du procédé repose sur la formation efficace d'un cetocarbamate, *via* une réaction de type couplage carbonique d'imines, de chloroformates et d'organostannanes. Celui ci peut alors être aisément convertis en imidazole *via* une réaction de cyclocondensation avec de l'acétate d'ammonium. Cette technologie permet l'élaboration d'un large éventail d'imidazoles à partir de réactifs basiques et faciles d'accès.

La synthèse d'imidazoles contenant des polymères π-conjugués est décrite dans le chapitre 4. Ce procédé est basé sur la méthode de synthèse d'imidazoles développée dans le chapitre 2. Des monomères bifonctionnels tels que des diimines, des diacides et des di-*N*-tosylimines peuvent être assemblés par la même technique de couplage reposant sur une catalyse au palladium pour générer des imidazoles contenant des polymères π-conjugués. Cette approche a été utilisée pour créer une nouvelle librairie de polymères imidazoliques conjugués. En modifiant simplement les substituants de la structure polymérique, le spectre d'absorbance UV visible ainsi que la longueur d'onde d'excitation/émission de fluorescence peut varier d'un ordre de 150 nm.

Dans le chapitre 5, la polymérisation par catalyse au palladium est examinée en plus grand détail. L'analyse des groupements terminaux du squelette polymérique est décrite ainsi qu'une étude du mécanisme de la réaction de terminaison de la polymérisation. Celle-ci suggère que l'anion sulfinate libéré lors de la cycloaddition des *N*-tosylimines joue un rôle dans la polymérisation et sa présence pourrait conduire à la terminaison de la croissance de la chaine polymérique.

Foreword

In accordance with guideline C of the "Guidelines for Thesis Preparation" (Faculty of Graduate Studies and Research), the following text is cited:

"As an alternative to the traditional thesis format, the dissertation can consist of a collection of papers that have a cohesive, unity character making them report of a single program of research. The structure for the manuscript-based thesis must conform to the following:

Candidates have the option of including, as part of the thesis, the text of one or more papers submitted, or to be submitted for publication, or the clearly duplicated text (not the reprints) of one or more published papers. These texts must conform to the "Guidelines for Thesis Preparation" with respect to font size, line spacing and margin sizes and must be bound together as an integral part of the thesis. (Reprints of published papers can be included in the appendices at the end of the thesis).

The thesis must be more than a collection of manuscripts. All components must be integrated into a cohesive unit with a logical progression from one chapter to the next. In order to ensure that the thesis has continuity, connecting texts that provide logical bridges between the different papers are mandatory.

As manuscript submitted for publication are frequently very concise documents, where appropriate, additional material must be provided (e.g. in appendices) in

sufficient detail to allow a clear and precise judgment to be made of the importance and originality of the research reported in the thesis.

In general, when co-authored papers are included in a thesis the candidate must have made a substantial contribution to all papers included in the thesis. In addition, the candidate is required to make an explicit statement as to who contributed to such work and to what extent. This statement should appear in a single section entitled "Contribution of Authors" as a preface to the thesis. The supervisor must attest the accuracy of this statement at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interests to clearly specify the responsibilities of all authored of the co-authored papers.

When previously published copyright material is presented in a thesis, the candidates must obtain, if necessary, signed waivers from the co-authors and publishers and submit these to the thesis office with the final deposition.

This dissertation is written in the form of three papers. The papers each comprise one chapter in the main body of the thesis (Chapter 2, 3, and 4) with general introduction to this work in the first chapter. An additional chapter elaborating on some unpublished results makes up the fifth chapter, and conclusions in the sixth chapter. Following normal procedures, the papers have either been published, or are to be submitted in scientific journals. A list of papers is given below:

Chapter 2: A Direct, One Step Synthesis of Imidazoles from Imines and Acid Chlorides: A Palladium Catalyzed Multicomponent Coupling Approach: Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050.

Chapter 3: Palladium-Catalyzed Carbonylative Cross-Coupling with Imines: A Multicomponent Synthesis of Imidazolones: Siamaki, A. R.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1135.

Chapter 4: Metal Catalyzed Multicomponent Polymerization: Design of a Basic Building Block Approach to π-Conjugated Imidazole-Containing Polymers: Siamaki, A. R.; Arndtsen, B. A. (to be submitted).

Contributions of the Authors

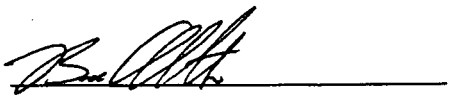
All these papers include the research director, Professor Bruce A. Arndtsen, as co-author as all research was performed under his direction. Chapter 3 includes Daniel A. Black, a colleague and Ph.D. Graduate of Dr. Arndtsen's laboratory, as co-author in acknowledgement of his contribution towards proposing the idea of ketocarbamate cyclization with ammonium acetate and performing a preliminary experiment on this work. Other than aforementioned contributions, all of the work presented in this dissertation was initiated and performed by the author.

I hereby give a copyright clearance for the inclusion of the following papers, of which I am co-author, in the dissertation of Ali Reza Siamaki.

"A Direct, One Step Synthesis of Imidazoles from Imines and Acid Chlorides: A Palladium Catalyzed Multicomponent Coupling Approach"

"Palladium-Catalyzed Carbonylative Cross-Coupling with Imines: A Multicomponent Synthesis of Imidazolones"

"Metal Catalyzed Multicomponent Polymerization: Design of a Basic Building Block Approach to π-Conjugated Imidazole-Containing Polymers"



Date: 8/28/08

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The Palladium Catalyzed Multicomponent Synthesis of Imidazole-Containing Macrocycles

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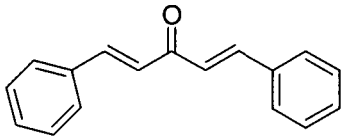
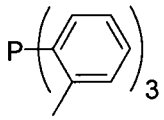
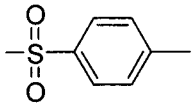
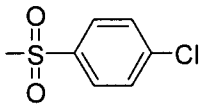
List of Abbreviations

An	-C_6H_4-4-OMe
Ar	-Aryl
Å	Angstrom
^{t}Bu	-$C(CH_3)_3$
Bu	-$CH_2CH_2CH_2CH_3$
Bn	-CH_2-C_6H_5
° C	Centrigrade
coe	Cyclooctene
COX 2	Cyclooxygenase-2
dba	
DMF	Dimethylformamide
DMAD	$H_3CO_2C—\equiv—CO_2CH_3$
Et	-CH_2CH_3
ESI	Electrospray Ionization
EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
GPC	Gel Permeation Chromatography
h	Hour
HSQC	Heteronuclear Single Quantum Coherence

HOMO	Highest Occupied Molecular Orbital
IR	Infrared Spectroscopy
*i*Pr	$-CH(CH_3)_2$
IL-1	Interleukin-1
LUMO	Lowest Unoccupied Molecular Orbital
Me	$-CH_3$
MS	Mass Spectrometry
M_n	Number Average Molecular Weight
M_w	Weight Average Molecular Weight
MALDI	Matrix-Assisted Laser Desorption/Ionization
M	$Mol.L^{-1}$
mg	Miligram
mmol	Milimole
min	Minute
MW	Microwave
NMR	Nuclear Magnetic Resonance Spectroscopy
nm	Nanometer
NOESY	Nuclear Overhauser Effect Spectroscopy
NCS	N-Chlorosuccinimide
OLED	Organic Light-Emitting Diods
Ph	$-C_6H_5$
Phen	1, 10-Phenanthroline
PDI	Polydispersity Index

P(*o*-tol)$_3$	
p38 MAP	Mitogen Activated Protein
Tol	-C_6H_4-4-CH_3
Ts	
TsCl	
THF	Tetrahydrofuran
TOF	Time of Flight Detector
TNF-α	Tumor Necrosis Factor Alfa
TGF-β	Transfering Factor-betas
TosMIC	Tosylmethylisocyanide
TMEDA	Tetramethylethylenediamine
UV-vis	Ultraviolet-Visible Spectroscopy

CHAPTER ONE

Introduction

1.0 Perspective

The past several decades have seen extensive efforts by chemists to design efficient synthetic routes to biologically relevant organic heterocycles. One particularly important class of these heterocycles are imidazoles. Imidazoles are components in a range of biomolecules, including the side chain in the amino acid histidine,[1] the neurotransmitter histamine,[1] and naturally occuring dipeptides, such as carnosine and anserine.[2] In addition, imidazoles are an essential part of numerous bio-active compounds, such as anti-inflammatory[5a] and anticancer agents,[5b] and a diverse array of natural products.[3] Alternatively, these heterocycles have found utility as components in polymers (e.g. conjugated materials),[15a, b] fluorescent materials,[15c,d] metal-coordinating ligands[13] and even ionic solvents.[12]

The utility of imidazoles has stimulated continuing efforts to design new reagents or reactions to assemble these heterocycles in an efficient fashion. Classical approaches to these products involve the cyclization of the appropriately substituted precursors, or performing substitution chemistry on simple imidazoles. However, a range of more recent methods have been developed to access these products, including those utilizing cycloaddition chemistry, transition metal catalysis, or multicomponent reactions.

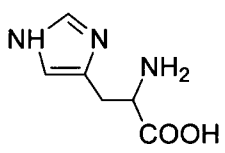
In this chapter, the general utility of imidazole containing molecules will be presented. This will be followed by an overview of the major synthetic approaches to these heterocycles. With this background, an outline of the thesis will be provided, which is directed towards developing efficient new routes to assemble highly substituted imidazoles.

1.1 Utility of Imidazoles

1.1.1 Biologically Relevant Imidazoles

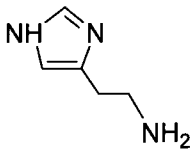
Prior to discussing the routes available to synthesize imidazoles, a brief overview of some of the main applications of these compounds will be given. Imidazoles are an essential part of a wide range of bio-molecules.[1] In addition to those mentioned in the previous section (amino acid histidine **1.1**, its decarboxylated derivative histamine **1.2**,[1] histidine containing dipeptides such as carnosine **1.3**, and anserine[2] **1.4** (Figure 1.1)), numerous imidazole containing natural products have been

Figure 1.1: Imidazole Containing Biomolecules



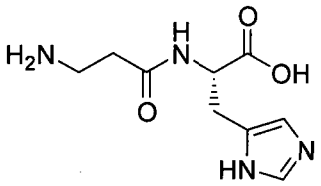
Histidine

1.1



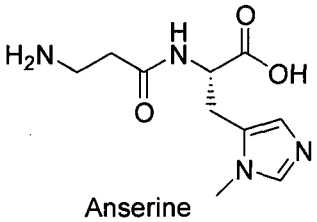
Histamine

1.2



Carnosine

1.3



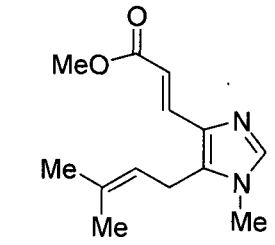
Anserine

1.4

isolated. For example, Fungirin **1.5** is a simple imidazole derivative that displays potent antifungal properties (Figure 1.2).[3a] Likewise, a range of pyrrole-imidazole

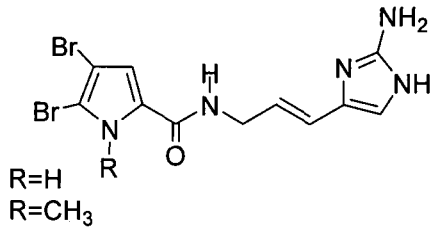
marine alkaloids has been isolated which demonstrate numerous biological properties. Some examples of these include oroidine **1.6**,[3b] phakelline **1.7**,[3c] cantharelline **1.8**,[3d] sceptrine **1.9**,[3e] and ageliferin **1.10**.[3f]

Figure 1.2: Representative Examples of Imidazole Containing Alkaloids



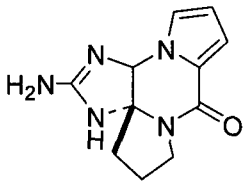
1.5

Fungerine



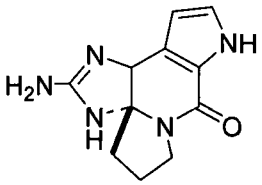
1.6

Oroidine-type alkaloids



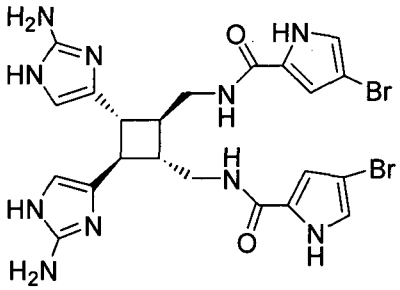
1.7

Phakelline



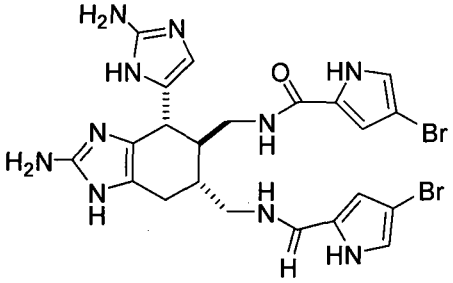
1.8

Cantharelline



1.9

Sceptrin



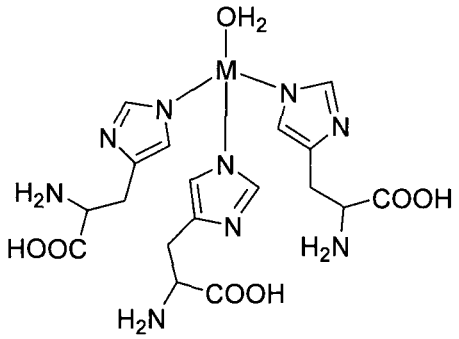
1.10

Ageliferin

Due to the presence of a basic nitrogen lone pair, imidazoles display an excellent metal binding ability in metalloenzymes.[4a] For example, the active sites of hemocyanin (Cu), nitrite reductase (Cu), and carbonic anhydrase (Zn) all contain

three imidazoles coordinated to one metal ion **1.11** (Figure 1.3). Likewise, the imidazole ring of histidine residues often form part of the metal-binding site in a range of other proteins.[4b, c]

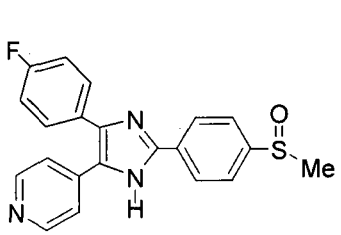
Figure 1.3: Example of Active Site Structure of the Copper-Containing Nitrite Reductase



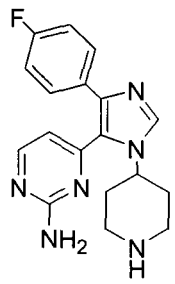
1.11

In addition to their presence in naturally occurring compounds, imidazoles are also key constituents in a range of synthetic bio-active molecules. For example, several aryl-substituted imidazoles, including 4,5- and 2,4,5-tri-aryl-1*H*-substituted imidazoles, exhibit potent anti-inflammatory[5a] and anti-cancer activity.[5b] Among these, inhibitors of p38 MAP (mitogen activated protein) kinase are perhaps the most well-known. These proteins are activated in response to pro-inflammatory cytokines, such as interleukin (IL-1) and tumor necrosis factor α (TNF-α) or by other environmental stress.[5a] A number of 1*H*-imidazoles containing a pyridine or pyrimidine at the 5-position, and a 4-fluorophenyl substituent on the 4-position, demonstrate strong anti-inflammatory activity by inhibiting this enzyme.[6] Compounds **1.12** (SB-203580),[7a, b] **1.13** (SB-220025),[7c] and **1.14** (SB-202190)[7d] are typical examples of this class of imidazoles (Figure 1.4).

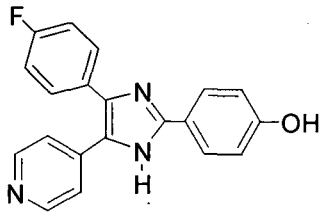
Figure 1.4: Inhibitors of p38 MAP Kinase



1.12 (SB-203580)



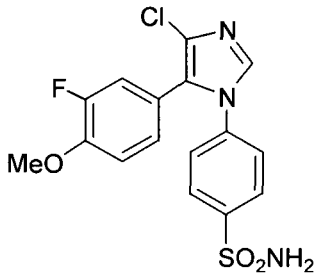
1.13 (SB-220025)



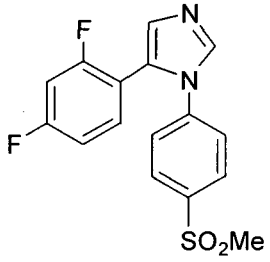
1.15 (SB-202190)

SB-203580 **1.12** also inhibits TGF-ß (transforming factor-betas);[8a] a family of cytokines which regulates a variety of physiological processes, including cell proliferation and differentiation.[8b] As such, these compounds can play a role in controlling tumor growth and fibrotic diseases. Similarly, aryl substituted imidazoles such as **1.15** and **1.16** have also been identified as highly selective inhibitors of cyclooxygenase-2 (COX 2), and demonstrate high potency in inflammation trials (Figure 1.5).[9a, b]

Figure 1.5: Structure of Two Inhibitors of Cyclooxygenase-2 (COX 2)



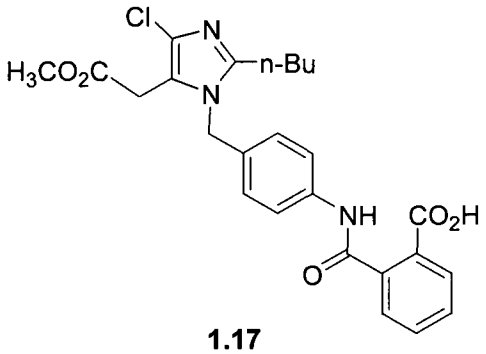
1.15



1.16

In addition, a series of novel *N*-(benzamidobenzyl)imidazoles have been identified as potent angiotensin II receptor antagonists.[10] Compound **1.17**, originally developed by DuPont, can regulate hypertension (high blood pressure) by blocking the activation of angiotensin II at the receptor level (Figure 1.6).[10]

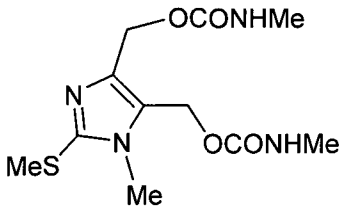
Figure 1.6: *N*-(benzamidobenzyl)imidazole **1.17** as Angiotensin II Receptor Antagonist



1.17

Substituted imidazoles have also been identified as potent alkylating agents capable of crosslinking DNA.[11] For example, **1.18** is a potent alkylating drug with high reactivity towards a variety of DNA-affinic carriers (Figure 1.7).[11]

Figure 1.7: A Potent Alkylating Agent **1.18**

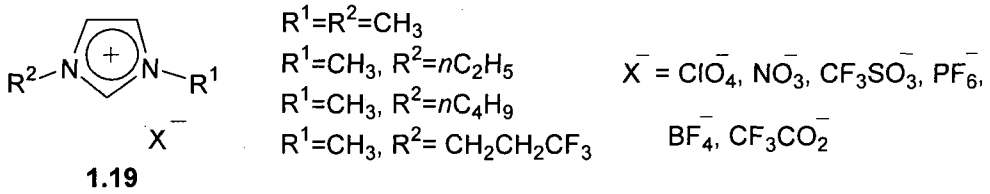


1.18

1.1.2 Imidazoles as Ionic Liquids

In addition to their biological relevance, imidazolium salts **1.19** have found major interest as ionic liquid solvents (Figure 1.8).[12a] Due to extremely low vapor pressures, excellent chemical and thermal stability, high ionic mobility, and a broad range of room temperature liquid compositions, these compounds are promising solvents for synthetic applications.[12b] Furthermore, these liquids have also been utilized as catalysts, electrolytes for batteries, photochemistry, electrosynthesis, and even advanced heat transfer fluids and lubricants.[12c]

Figure 1.8: Imidazolium Containing Ionic Liquid

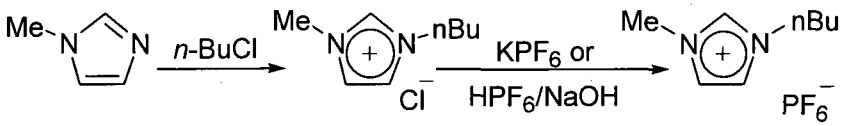


1.19

As shown in Figure 1.8, imidazolium ionic liquids are typically composed of bulky 1, 3-dialkylimidazolium cations and various anions, such as NO_3^-, ClO_4^-, $CF_3SO_3^-$, PF_6^-, BF_4^-, $(CF_3SO_2)_2N^-$, or $CF_3CO_2^-$. Among these, the imidazolium salts with fluorine-containing anions have dominated the field of ionic liquids.[12c] It is found that by tuning the anion or the substituents on the cation, a wide range of properties of these materials (e.g. viscosity, melting point, density, conductivity, solubility, thermal and hydrolytic stability) can be modified. The well-known 1-butyl-3-methylimidazolium ionic liquid (BMI)PF_6 **1.22** can be prepared by simple alkylation of the commercially available methylimidazole **1.20** with *N*-chlorobutane

followed by anion metathesis using potassium hexafluorophosphate KPF_6 (Scheme 1.1).[12a] This method has been utilized for the preparation of a variety of imidazolium ionic liquids.

Scheme 1.1: Preparation of 1-Butyl-3-methylimidazolium Ionic Liquid $(BMI)PF_6$

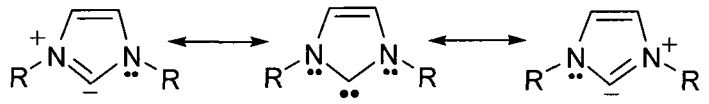


1.20 **1.21** **1.22**

1.1.3 Imidazoles as Ligands/Carbene Precursors

N-Heterocyclic carbenes derived from imidazolium salts were first used as a ligand for metal complexes by Wanzlick and Öfele in 1968.[13a, b] These compounds are electron-rich, nucleophilic, and neutral σ-donor ligands. Their resonance structures **1.23a-c** are illustrated in Figure 1.9.

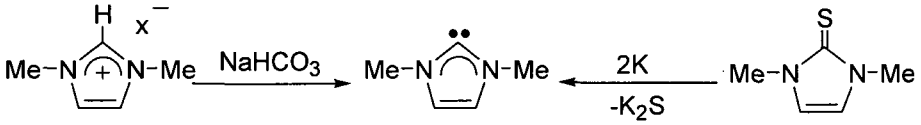
Figure 1.9: Resonance Structures of 1, 3-disubstituted imidazolin-2-ylidene



1.23a **1.23b** **1.23c**

As an example, the *N*-heterocyclic carbene **1.25** can be prepared by deprotonation of imidazolium salt **1.24** or by reductive desulfurization of imidazolin-2-thiones **1.26** (Scheme 1.2).[13c]

Scheme 1.2: Preparation of *N*-heterocyclic Carbene **1.25**

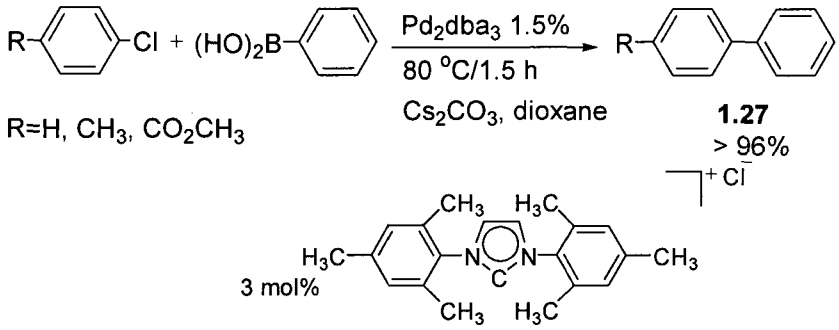


1.24 **1.25** **1.26**

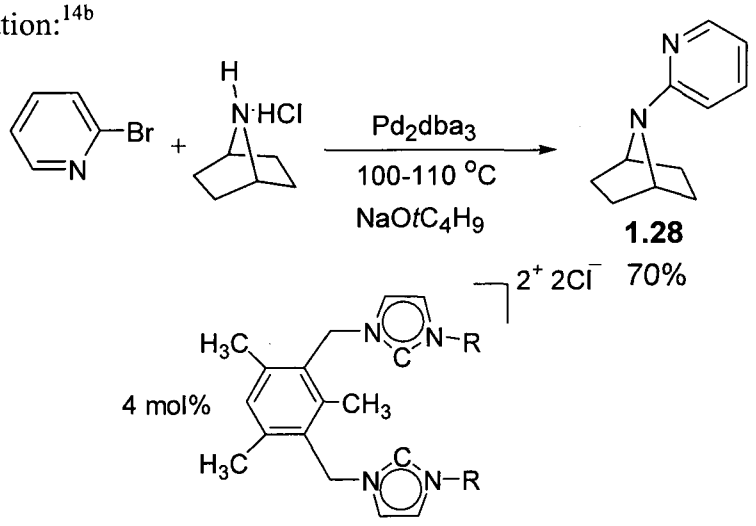
These ligands form stable bonds with many transition metals, and both stabilize and activate the metal center for a variety of catalytic reactions in organic synthesis. These include catalytic C-H bond activation, C-C, C-O, C-N bond formation, olefin metathesis and others. Representative examples of these approaches are shown in Scheme 1.3.[13d]

Scheme 1.3: Application of *N*-heterocyclic Carbene Ligands

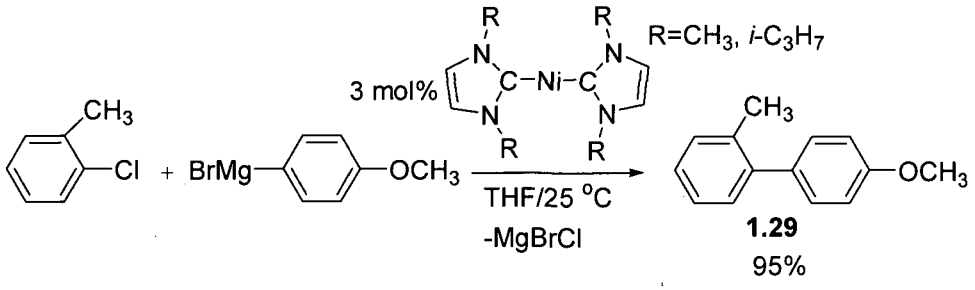
a) Suzuki Coupling:[14a]



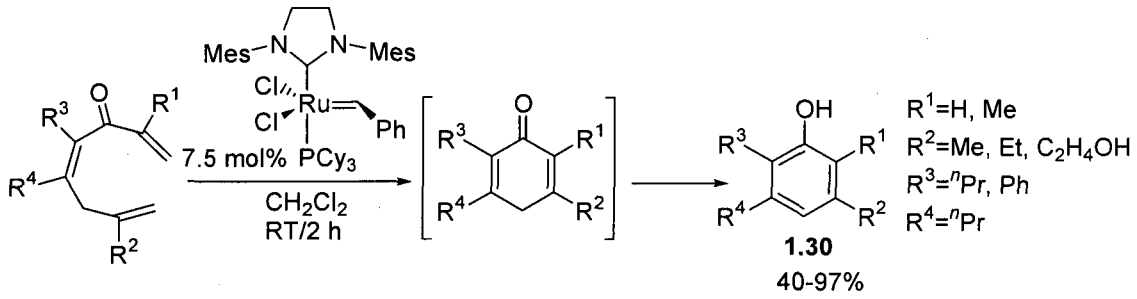
b) Aryl Amination:[14b]



c) Kumada Coupling:[14c]



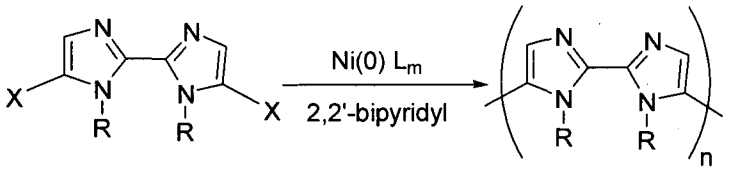
d) Ring Closing Metathesis: [14d]

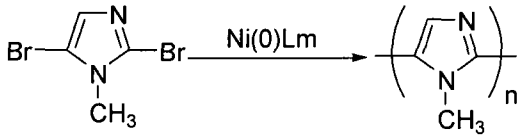


1.1.4 Imidazoles as Conjugated Materials

Imidazoles have also found utility in the field of material science. π-conjugated polymers containing imidazoles have attracted attention in the recent years due to their potential electronic and optical properties.[15a] A new class of polyimidazoles (**1.31** and **1.32**) was recently prepared by simple nickel mediated dehalogenative polycondensation. (Scheme 1.3).[15b] Alternatively, a significant number of imidazole tethered polymers have been prepared. For example, poly(*p*-phenylene) with cross

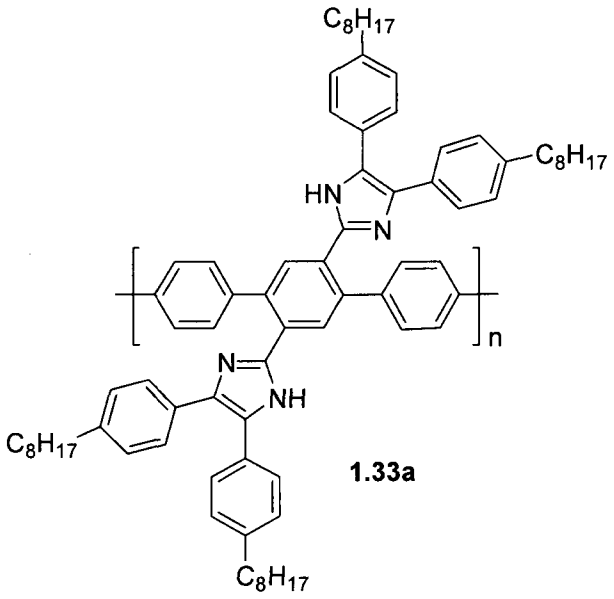
Scheme 1.3: Synthesis of Polyimidazoles



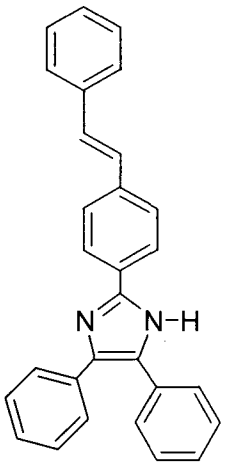


conjugated bis-imidazole base units **1.33a** has been found to be a blue-emitting material with potential application in organic light emitting diodes (OLEDs) (Figure 1.10).[15c] Notably, simple imidazoles when accompanied by aryl substituents on the ring, also exhibit photoluminescent properties with the emission peak in the blue region (**1.33b**) (Figure 1.10).[15d]

Figure 1.10: Structure of Blue-Emitting Materials



1.33a



1.33b

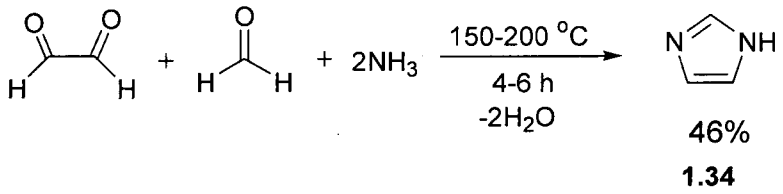
1.2 Synthetic Routes to Imidazoles

The utility of imidazoles has stimulated significant interest in the development of new and efficient methodologies of generating and functionalizing these compounds. In this section, an overview of some of the traditional and more recent approaches to these heterocycles is provided. In general, these include cyclocondensation reactions utilizing pre-synthesized substrates (e.g. with diketones, amidine derivatives, amidoketones, or tosylmethylisocyanides), or the stepwise functionalization of simple imidazoles. In addition, a number of more recent metal catalyzed methodologies will also be discussed.

1.2.1 Synthesis from 1,2-Diketones

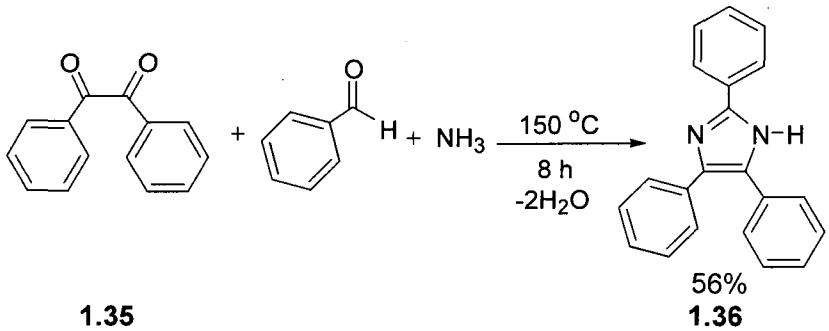
The first synthesis of simple unsubstituted imidazole **1.34** was reported in 1882 by both Japp and Radziszewski.[16a, b] This involved a multicomponent condensation of glyoxal, formaldehyde and ammonia and led to the formation of **1.34** in 46% yield (Scheme 1.4).

Scheme 1.4: Original Synthesis of Imidazole



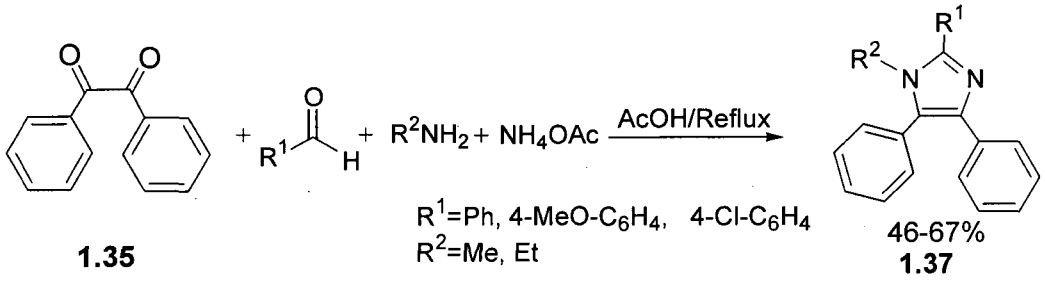
Since this observation, 1,2-diketones have been employed as synthetic building blocks for a range of diversely substituted imidazoles. As an illustrative example, the coupling of **1.35** with benzaldehyde and excess ammonia can be used to generate tri-substituted imidazole **1.36** (Scheme 1.5).[16b]

Scheme 1.5: Radziszewski Synthesis of Imidazoles



This approach can also be expanded to a four component coupling involving diketones, aldehydes, primary amines and ammonium actetate (Scheme 1.6).[16c]

Scheme 1.6: Four Component Coupling Cyclization of 1,2-Aryldiketone

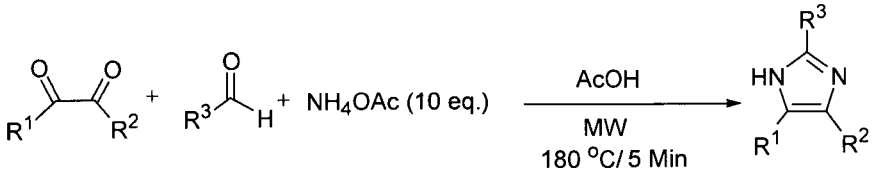


1.35 **1.37**

While these transformations provide an effective synthesis of polysubstituted imidazoles, they do suffer from low yields, harsh conditions and high reaction temperatures. A number of efforts have aimed on addressing these issues. For example, microwave irradiation and Lewis acid catalyzed reactions can be employed to increase product yields, lower reaction temperatures, and suppress side reactions. Some examples of these are shown in Scheme 1.7.

Scheme 1.7: Synthesis of Imidazoles Utilizing 1,2-Diketones

(a)[17a]

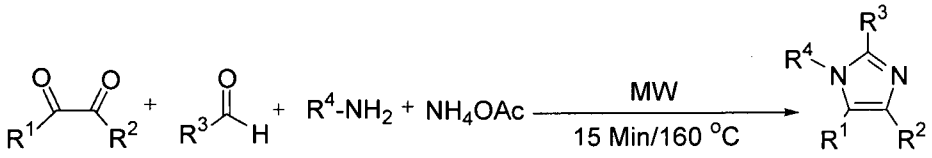


R^1, R^2=Ph, 4-$MeOC_6H_4$

R^3=Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-CNC_6H_4

80-99%

(b)[17b]

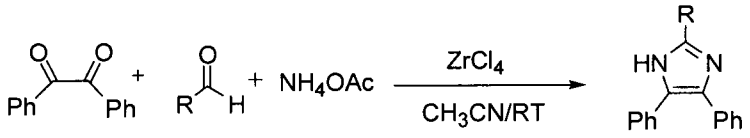


R^1, R^2=Ph, Me

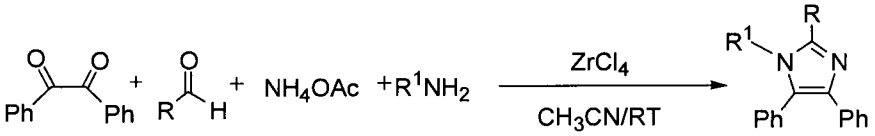
R^3, R^4=Ph, *i*Pr, Bn, H

20-90%

(c)[17c]

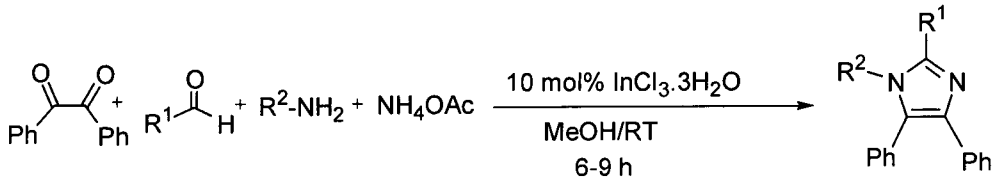


80-90%



80-90%

(d)[17d]

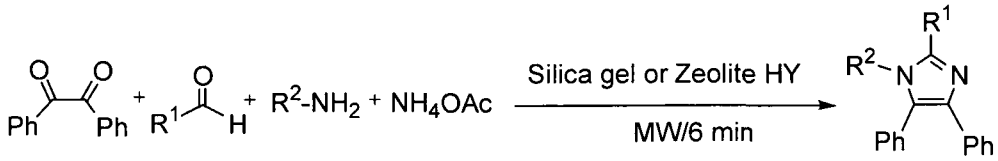


R^1=Ph, 4-MeC_6H_4, 4-BrC_6H_4

R^2=Ph, Me, Et

47-84%

(e)[17e]

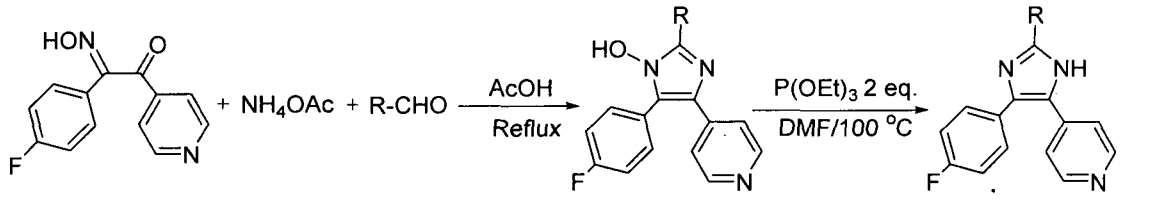


R^1=Ph, 4-$CH_3C_6H_4$, 4-BrC_6H_4
R^2=Me, Et, iso-C_3H_7, Ph-CH_2

42-85%

Another issue with this synthesis is in the use of unsymmetrical diketones, which can lead to the formation of a regioisomeric mixture of imidazole products. One approach to address this issue involves the use of keto-oximes such as **1.38**.[18] As shown in Scheme 1.8, the cyclocondensation of **1.38** in the presence of ammonium acetate and aldehyde in refluxing acetic acid leads to the regioselective formation of *N*-hydroxy substituted imidazoles **1.39.** Subsequent reduction of this product with triphenylphosphite in DMF generates series of corresponding 2,4,5-trisubstituted imidazole derivatives **1.40**. These compounds exhibit inhibitory effects on tumor necrosis factor α (TNF-α) and interleukin-1ß (IL-1ß). Nevertheless, this approach does require the selective synthesis of oxime **1.38**.

Scheme 1.8: Synthesis of Imidazoles from α-Keto-Oxime **1.39**



1.38

1.39

R=Ph$(CH_2)_2$ (71%)
R=Ph-CH=CH (41%)

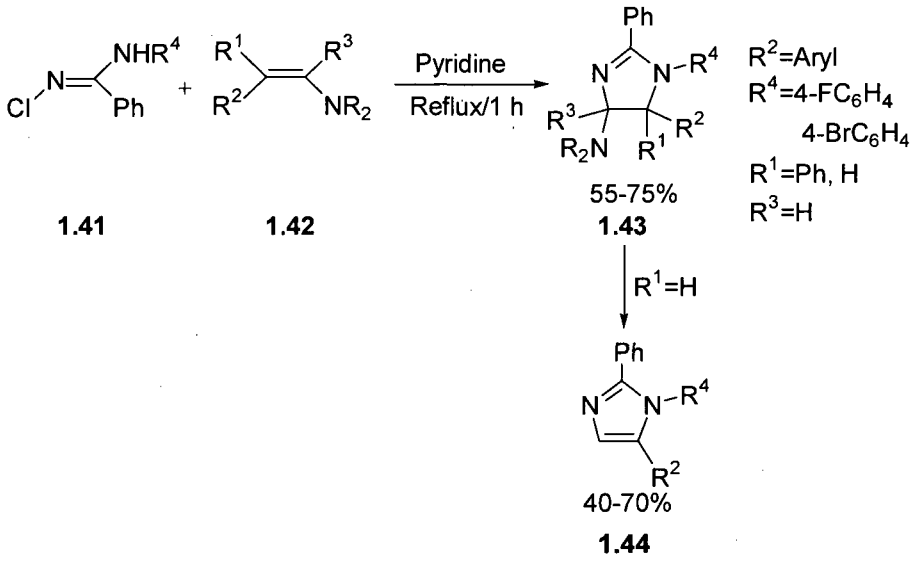
1.40

R=Ph$(CH_2)_2$ (25%)
R=Ph-CH=CH (52%)

1.2.2 Synthesis from Amidines

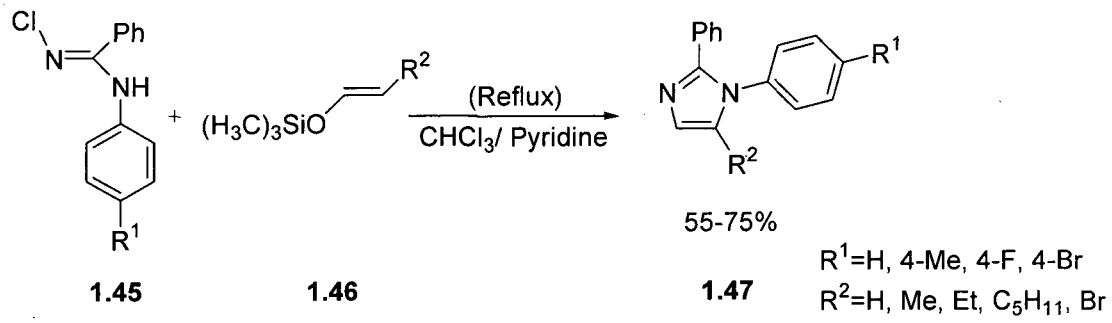
An alternative approach to imidazoles relies upon the use of amidine derivatives as building blocks. Early examples of this involved the reaction of *N*-chloro-*N'*-arylamidine **1.41** with enamine **1.42** to generate 4-aminoimidazoline intermediate **1.43** (Scheme 1.9). When R^1=H, amine elimination occurs to afford the tetrasubstituted imidazole **1.44**.[19]

Scheme 1.9: Synthesis of Imidazole Using Chloro-Substituted Amidine **1.41**



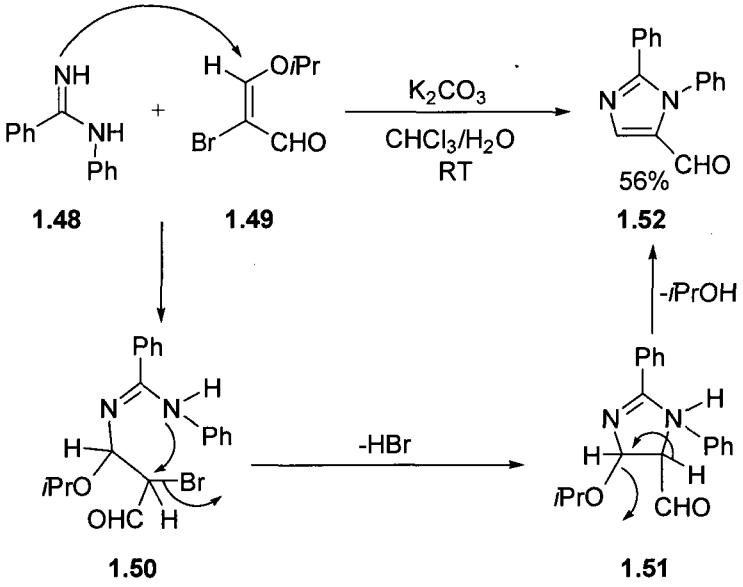
A similar reaction of *N*-chloro-*N'*-aryl-benzamidine **1.45** with silyl enol ethers **1.46** in refluxing chloroform can be used to generate 1-aryl-2-phenyl-1*H*-imidazoles **1.47** (Scheme 1.10).[20]

Scheme 1.10: Reaction of *N*-Chloroamidine **1.45** with Silyl enol ether **1.46**



As an alternative to *N*-chloro amidine, the reaction of simple monosubstituted amidines **1.48** with bromo enol ether **1.49** has been found to lead to the regioselective formation of imidazole carboxaldehyde **1.52**. The origin of regioselectivity can be explained from the mechanism of this transformation, in which the unsubstituted nitrogen of amidine is postulated to attack the ß-carbon bearing the alkoxy moiety. The subsequent cyclization of **1.50** with HBr elimination forms **1.51**, which upon loss of isopropanol generates imidazole **1.52** (Scheme 1.11).[21]

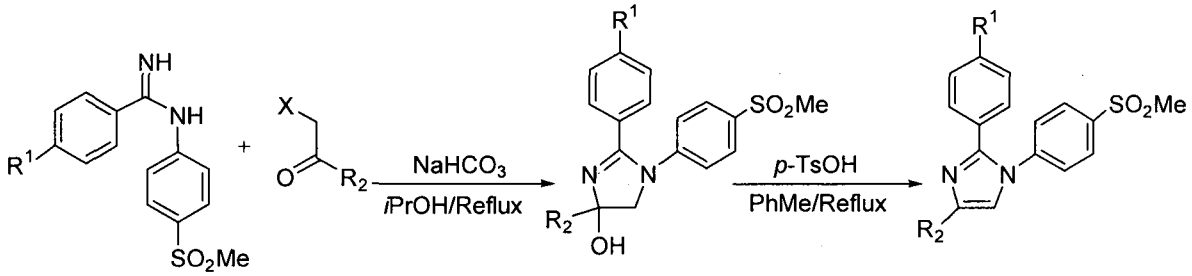
Scheme 1.11: Synthesis of Imidazole Carboxaldehyde **1.52**



One of the more common uses of amidines in imidazole synthesis involves their coupling with 2-haloketones. This strategy has been widely applied in the synthesis of 1, 2-diaryl-1*H*-imidazoles. One example of this approach is shown in Scheme 1.12, where the reaction of **1.53** with 2-halomethylketone **1.54** in the presence of

$NaHCO_3$ leads to the formation of hydroxyimidazoline **1.55**. The latter can undergo acid-catalyzed dehydration to generate imidazole **1.56**.[22]

Scheme 1.12: Synthesis of Imidazoles with α-Haloketones



1.53 **1.54** **1.55** **1.56**

40-70%

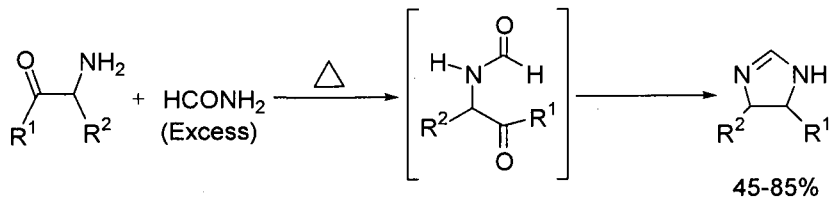
R^1=4-Me, 4-MeO

R^2=Me, CF_3, Ar, CO_2R, CH_2OAr

1.2.3 Synthesis from α-Aminoketones and α-Amidoketones

A third general approach to imidazoles involves the use of α-aminoketones. For example, Bredereck and Theilig have shown that both symmetrical and unsymmetrical 4,5-diaryl-1*H*-imidazoles can be prepared from the reaction of α-aminoketone **1.57** with an excess of formamide **1.58** (Scheme 1.13). It is believed that this reaction proceeds via the in situ formation of α-amidoketone **1.59**, which undergoes intramolecular cyclization in the presence of formamide to generate the corresponding imidazoles **1.60**.[23]

Scheme 1.13: Original Synthesis of Imidazole from α-Ketoamides



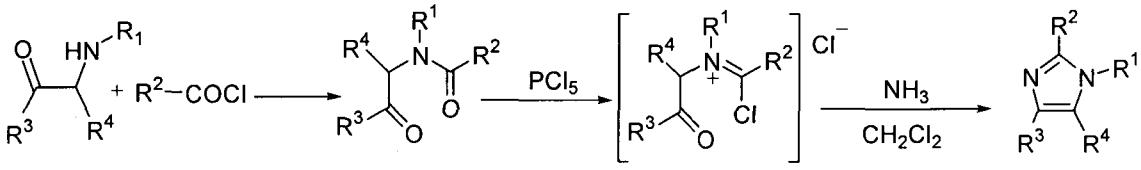
45-85%

1.57 **1.58** **1.59** **1.60**

R^1, R^2= Me, Et, *n*-propyl, *n*-butyl, *n*-hexyl

In a similar fashion, the in situ generated α-ketoamide **1.62**, resulting from the acylation of corresponding aminoketone **1.61,** can undergo cyclization upon treatment with PCl_5 and ammonia to generate a variety of substituted 1,2,4,5, tetraaryl-1*H*-imidazoles **1.64** (Scheme 1.14).[24]

Scheme 1.14: Synthesis of 1,2,4,5-Tetraaryl-Substituted Imidazoles from α-Ketoamide



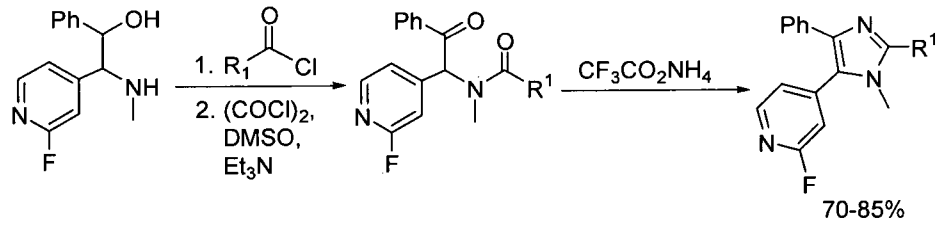
1.61 **1.62** **1.63** **1.64**

$R^1=R^2=R^3=R^4=Ph$
$R^1=R^3=R^4=Ph$, $R^2=4\text{-}MeOC_6H_4$
$R^1=R^3=R^4=Ph$, $R^2=4\text{-}ClC_6H_4$
$R^1=R^3=R^4=Ph$, $R^2=4\text{-}NO_2C_6H_4$
$R^1=R^3=R^4=Ph$, $R^2=4\text{-}Me_2NC_6H_4$

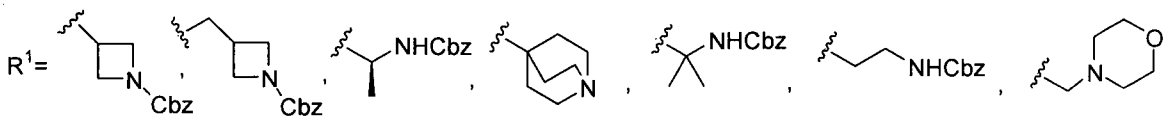
While the preparation of substituted α-ketoamides often requires multistep sequences, their facile cyclization with high regiocontrol has led to their significant use in imidazole synthesis. Some examples of these approaches are summarized in Scheme 1.15. As shown, this methodology has also allowed for direct access to small library of imidazoles using a solid phase synthetic protocol (Eq. a-c).

Scheme 1.15: Synthetic Application of α-Ketoamides

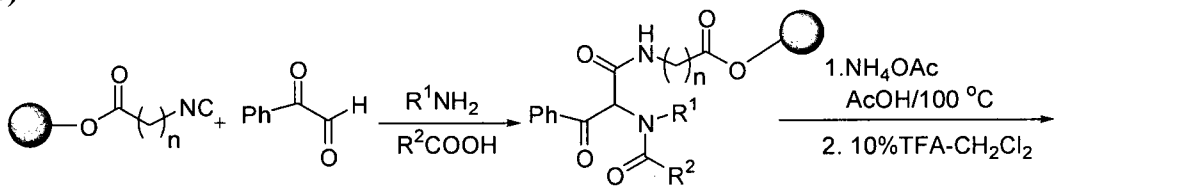
(a)[25a]



1.65 **1.66** **1.67**



(b)[25b]



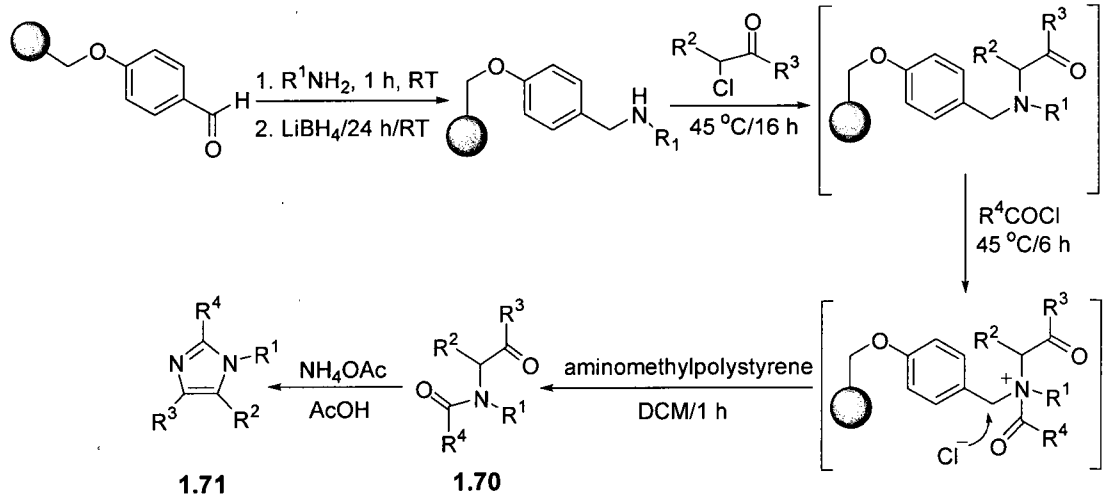
1.68

1.69

R^1=Ph, R^2=Ph (16%)

R^1=4-MeOC6H4, R^2=Ph (43%)

(c)[25c]



1.71

64-95%

R^1=n-C_4H_9, Ph, Bn

R^2=H, Me, Ph

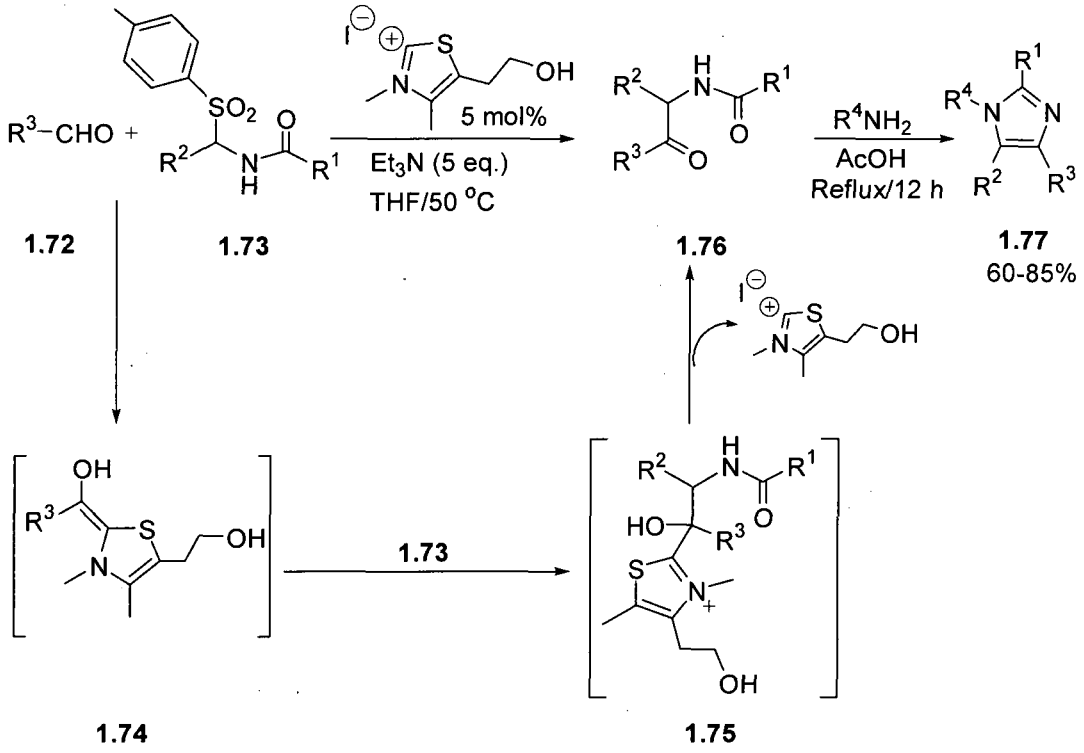
R^3=4-ClC_6H_4, 4-$MeOC_6H_4$

R^4=Me, CH_2OAC, COOEt,

1.70

Recently, a one–pot synthetic route to imidazoles has been developed employing aldehydes, α-sulfonylamides and amines. As shown in Scheme 1.16, this reaction involves the initial formation of α-ketoamides via the thiazolium catalyzed addition of aldehyde to **1.73**. This process presumably proceeds via the generation of thiozol-enamine **1.74**, which can be converted to intermediate **1.75** upon addition of **1.73**. Subsequent release of the thiazolium ylide generates α-ketoamide **1.76,** which can cyclize to imidazoles **1.77** in the presence of primary amines.[26]

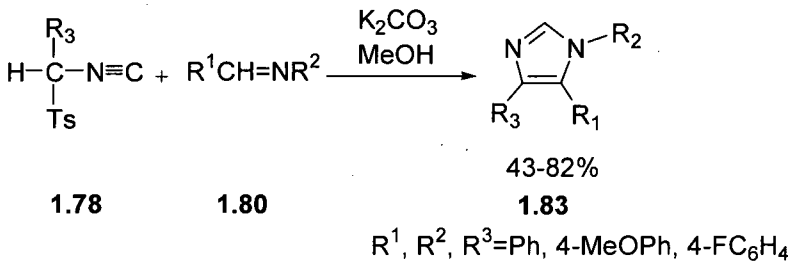
Scheme 1.16: Thiazolium Catalyzed Imidazole Synthesis



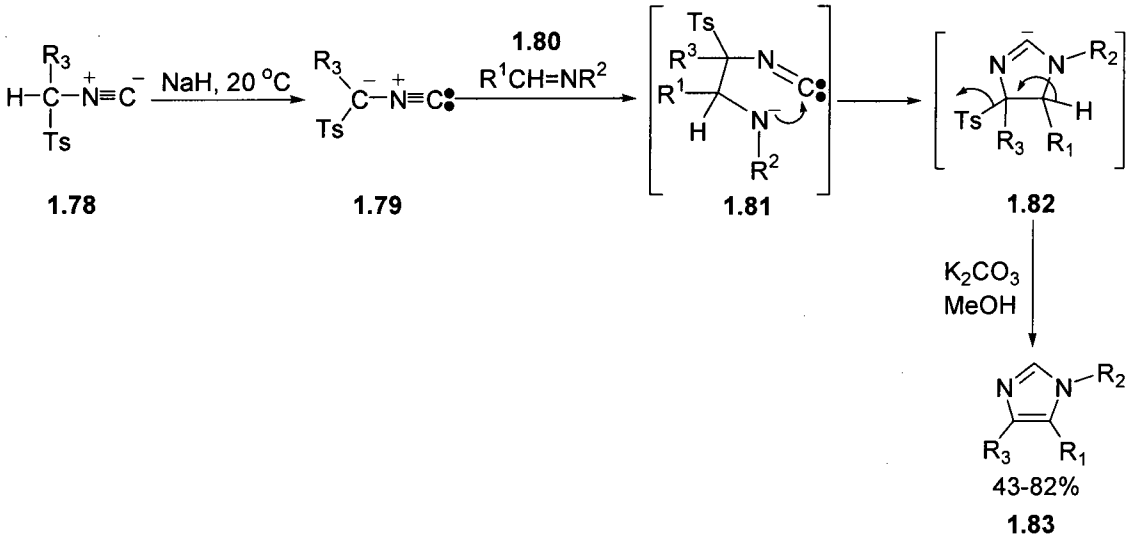
1.2.4 Synthesis from Tosylmethylisocyanides (TosMIC)

An alternative approach to imidazoles involves the based induced cycloaddition of tosylmethylisocyanide (TosMIC) with imines, developed by van Leusen in 1977 (Scheme 1.17). In this reaction, the carbanion **1.79**, generated in situ upon deprotonation with base, reacts with aldimine **1.80** in a protic solvent to form the postulated intermediate **1.81**. The latter can cyclize to **1.82**, which eliminates *p*-toluene sulfinic acid in the presence of base to form 1,4,5 trisubstituted imidazoles **1.83**.[27]

Scheme 1.17: Synthesis of Imidazoles from TosMIC and Aldimines



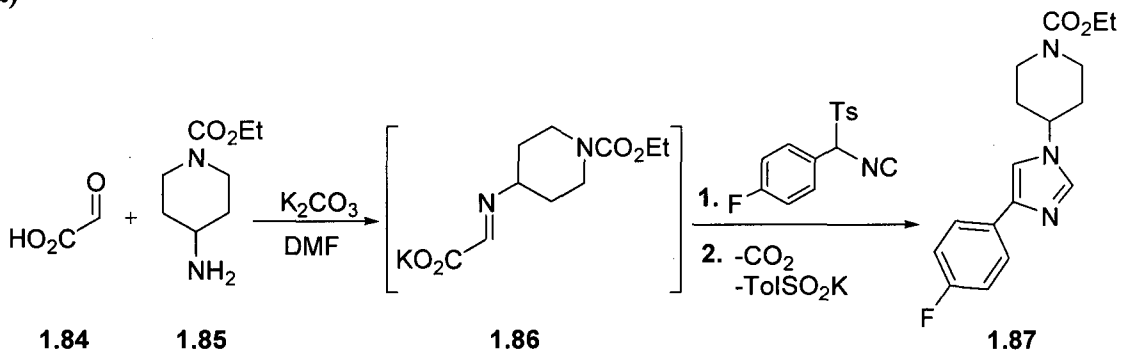
Mechanism:



Since its discovery, this approach has been widely employed in the synthesis of substituted imidazoles. For example, Sisko has reported an efficient multicomponent variant of this reaction by employing aryl-substituted tosylmethylisocyanide (TosMIC) reagents with imines generated in situ from the corresponding aldehydes and amines.[28a] This approach has since been applied to a broad range of amine and aldehyde building blocks. Examples include employing glyoxylic acid **1.84,** chiral amines such as **1.89**, α-amino acid **1.93,** or even using ammonium hydroxide **1.97** as an amine component (Scheme 1.18).[28b]

Scheme 1.18: Synthetic Utility of TosMIC Chemistry

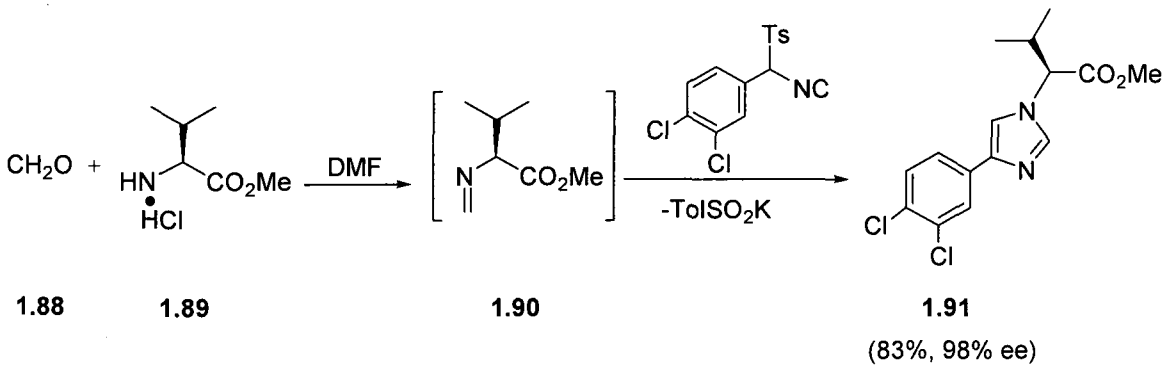
(a)[28b]



1.84 **1.85** **1.86** **1.87**

91%

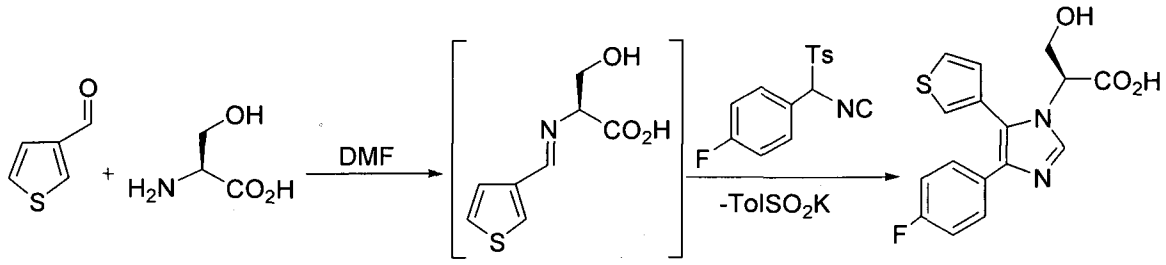
(b) [28b]



1.88 **1.89** **1.90** **1.91**

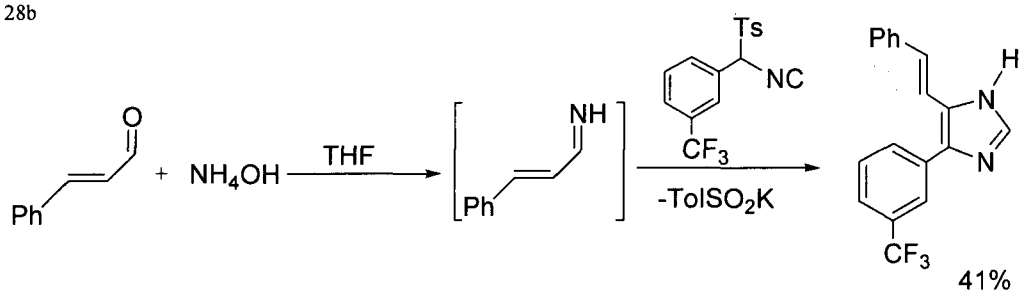
(83%, 98% ee)

(c) [28b]



1.92 **1.93** **1.94** **1.95**
(74%, 99% ee)

(d) [28b]

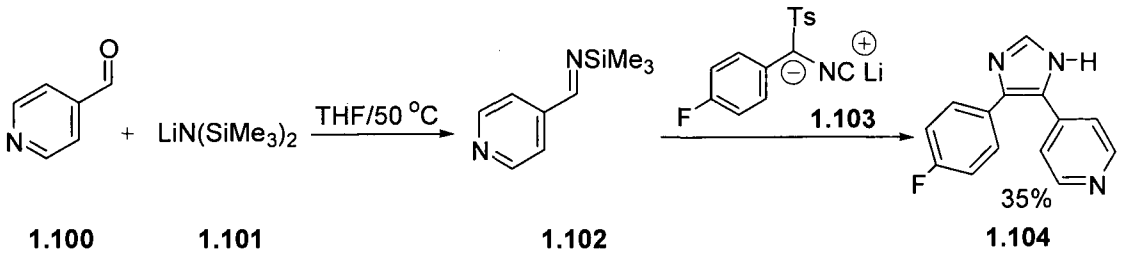


41%

1.96 **1.97** **1.98** **1.99**

The versatility of TosMIC chemistry has been further demonstrated in the synthesis of a series of 4-aryl-5-pyridinyl imidazoles derivatives, an essential core for a well known class of anti-inflammatory agents.[6] In one effort, pyridine-4-carboxaldehyde **1.100** was treated with lithium bis(trimethylsilyl)amide **1.101** in THF at -50 °C to generate imine **1.102,** which can undergo subsequent cyclization with the lithiated TosMIC derivative **1.103** to form the target imidazole **1.104** (Scheme 1.19).[29]

Scheme 1.19: Synthesis of an Anti-Inflammatory Core **1.104**

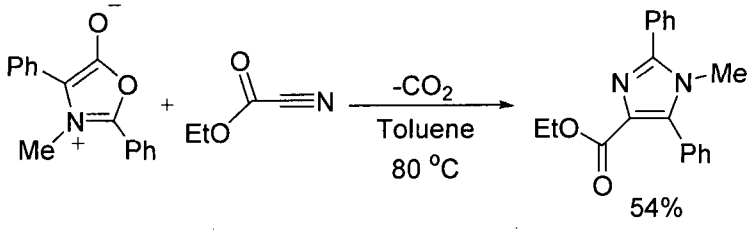


1.100 **1.101** **1.102** **1.104**

1.2.5 Synthesis from Mesoionic 1,3-Oxazolium-5-olates (Münchnones)

The mesoionic 1,3-oxazolium-5-olate, also known as a Münchnone, is a versatile 1,3-dipole, which can participate in a variety of cycloaddition reactions with dipolarophiles. This reactivity can be exploited to construct imidazoles. This was originally demonstrated by Hüisgen, who found that Münchnone **1.105** reacts with the electron deficient nitrile **1.106** to afford imidazole **1.107** (Scheme 1.20). However, the yield of this cycloaddition was low (54%), and limited to the use of highly electron deficient nitriles.[30]

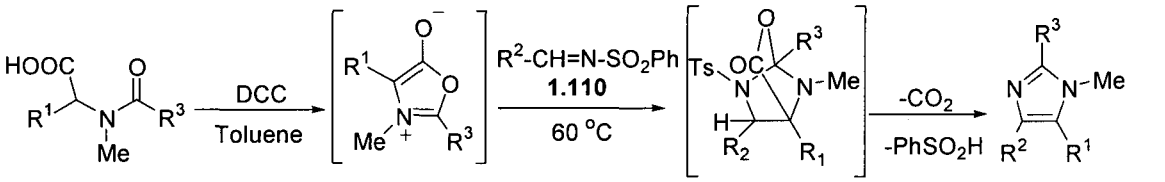
Scheme 1.20: Cycloaddition of Münchnones with Nitriles



1.105 **1.106** **1.107**

Alternatively, it was more recently demonstrated that Münchnones **1.109** generated from the dehydration of α-amido acid **1.108** can undergo cycloaddition with electron deficient *N*-tosyl-substituted imines **1.110** to afford imidazoles. It was envisaged that the reaction proceeds via the in situ formation of bicyclic intermediate **1.111,** which eliminates CO_2 and sulfinic acid to afford the products (Scheme 1.21).[31]

Scheme 1.21: Cycloaddition of Münchnone with *N*-Tosylimines

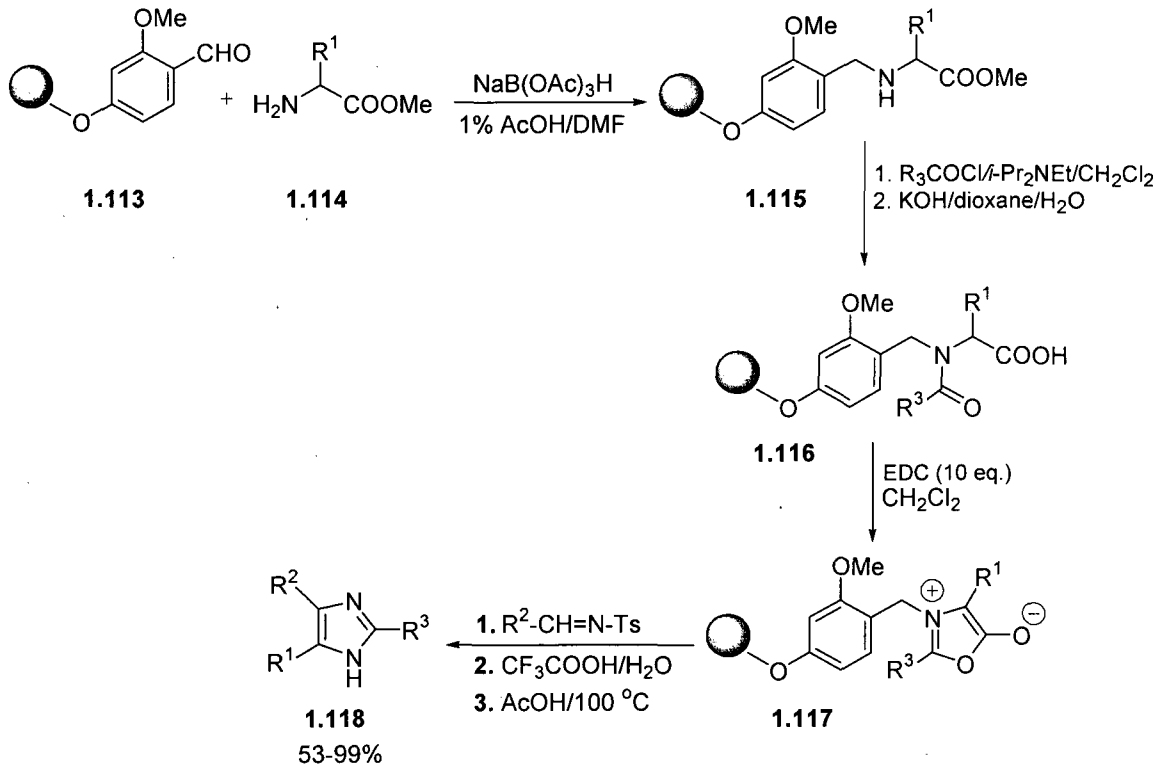


1.108 **1.109** **1.111** **1.112**

R_1=R_3=Ph, R_2=4-$NO_2C_6H_4$
R_1=R_3=Ph, R_2=4-$MeOC_6H_4$
R_1=R_2=R_3=Ph

Recently, Bilodeau and Cunningham have applied this approach to the solid phase synthesis of imidazoles. This protocol utilizes commercially available polystyrene-poly(ethylene glycol) graft copolymer resin **1.113**. Treatment of **1.113** with amino acid methyl ester **1.114** leads to the formation of compound **1.115**. Acylation of this product with acid chloride generates **1.116**, which is then converted to Münchnone **1.117** in the presence of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDC). Subsequent addition of the appropriate *N*-tosylimine affords imidazole **1.118** after the removal from the polymer-link with acid. A range of 2,4,5-triaryl-1*H* imidazoles have been prepared in high purity using this approach (Scheme 1.22).[32]

Scheme 1.22: A Solid Support Approach to Imidazoles



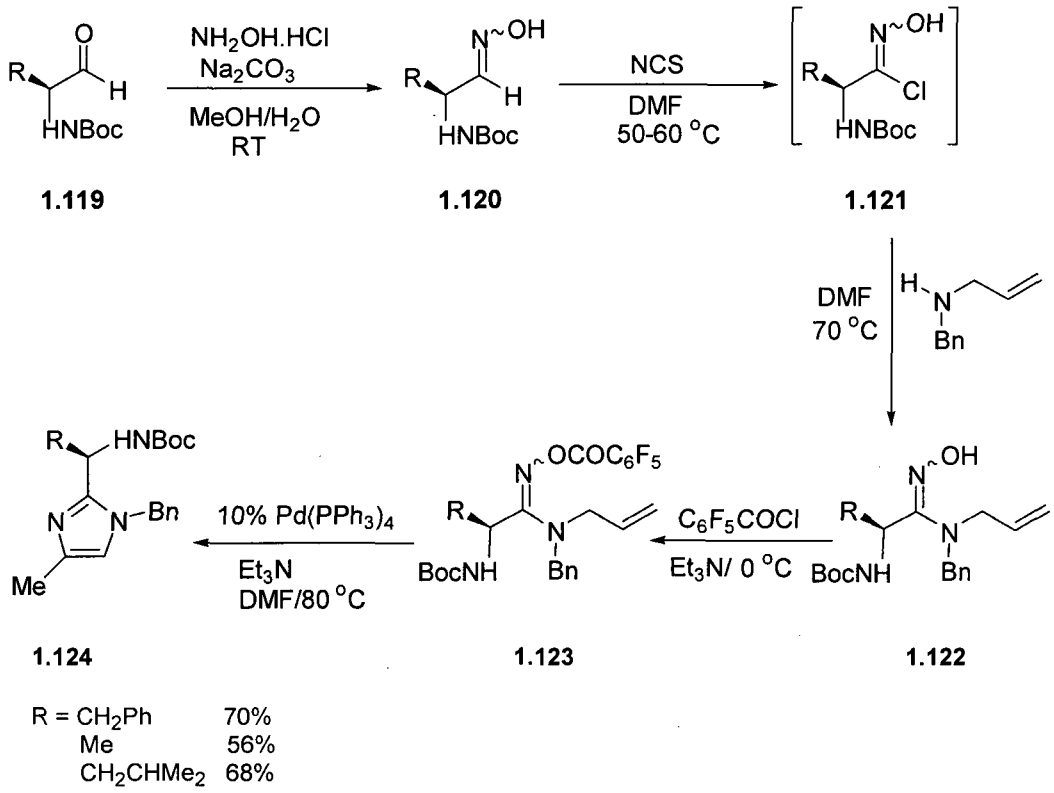
1.2.6 Metal Catalyzed Approaches to Imidazoles

In recent years, significant research efforts have been directed towards developing novel synthetic routes to imidazoles. In this context, a number of interesting transition metal cyclization approaches has been developed. These typically employ catalysts to mediate either a cyclization reaction, or the stepwise incorporation of substituents onto pre-synthesized imidazoles. An overview of these approaches is provided below.

1.2.6.1 Metal Catalyzed Cyclizations

A range of methods have been developed which employ metal catalysis to mediate cyclizations to form the imidazole core. For instance, a palladium catalyzed amino Heck reaction has been employed to synthesize 2-substituted imidazole derivatives.[33] As shown in Scheme 1.23, *N,O* pentafluorobenzoyloximes **1.123** can undergo intramolecular Heck cyclization in the presence of $Pd(PPh_3)_4$ and Et_3N to afford 1-benzyl-4-methylimidazole **1.124** with a number of substituents on the 2-position. Substrate **1.123** can be prepared via a multistep sequence, which involves the reaction of α-aminoaldehyde **1.119** with hydroxylamine hydrochloride in the presence of K_2CO_3 to form an E/Z mixture of aminoaldoxime **1.120**. Chlorination of the latter with *N*-chlorosuccinimide (NCS) affords hydroxyamoyl chloride **1.121**, which is treated in situ with allyl benzylamine to form amidooxime **1.122** (E/Z). Subsequent treatment with pentafluorobenzoyl chloride furnishes the starting amidoxime **1.123**.[33]

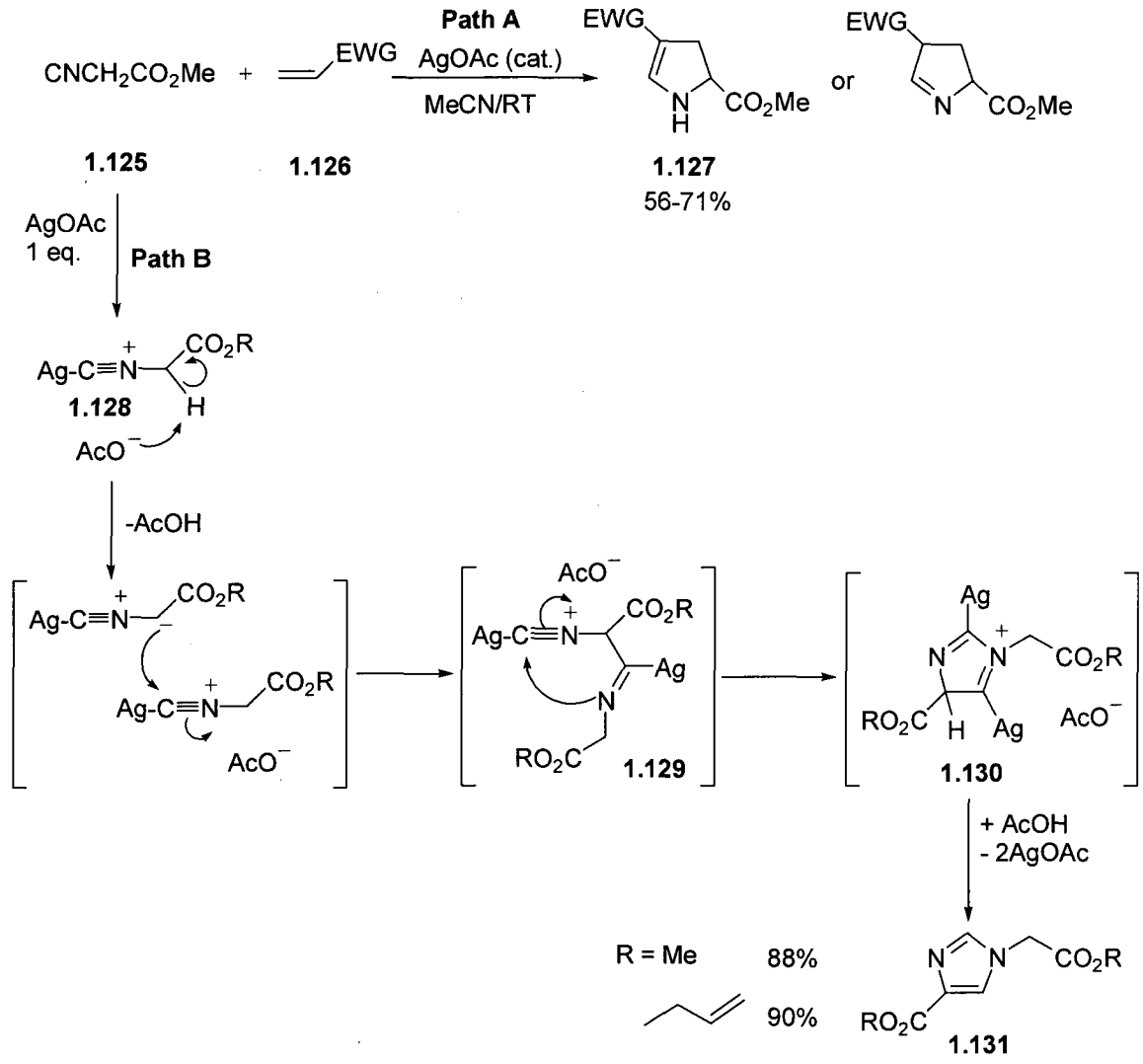
Scheme 1.23: Palladium Catalyzed Intramolecular Amino-Heck Cyclization



An interesting metal initiated cyclization was discovered while exploring the cycloaddition of methyl isocyanoacetate **1.125** with potential Michael acceptors, such as electron deficient alkenes **1.126**.[34] While this reaction was originally aimed at the synthesis of pyrroline derivatives **1.127** (Path A, Scheme 1.24), it was found that in the presence of stoichiometric silver acetate, and the absence of olefins, the reaction proceeds through the homodimerization of isocyanide to form imidazole derivatives **1.131** in high yield (Path B). It was postulated that this reaction involves the formation of a silver coordinated isocyanide **1.128**, which initiates a deprotonation of the α-hydrogen, followed by cyclization with a second equivalent

of **1.125**. Subsequent protonation by acetic acid can liberate the silver acetate, and form imidazoles **1.131**.[34]

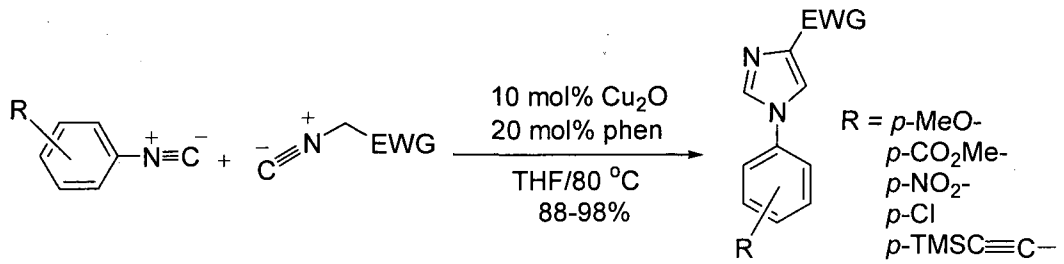
Scheme 1.24: Homodimerization of Isocyanoacetate **1.125** Initiated by AgOAc



A similar cyclodimerization has been developed using two electronically different isocyanides.[35] Aryl-substituted isocyanides such as **1.132** react with ethyl isocyanoacetate **1.133** in the presence of catalytic amount of Cu_2O to afford 1,4-disubstituted imidazole derivatives **1.138** (Scheme 1.25). The reaction is compatible

with various functional groups on the aryl substituent of **1.132**, including ester, cyano, nitro and chloro groups. The proposed catalytic cycle for this reaction is

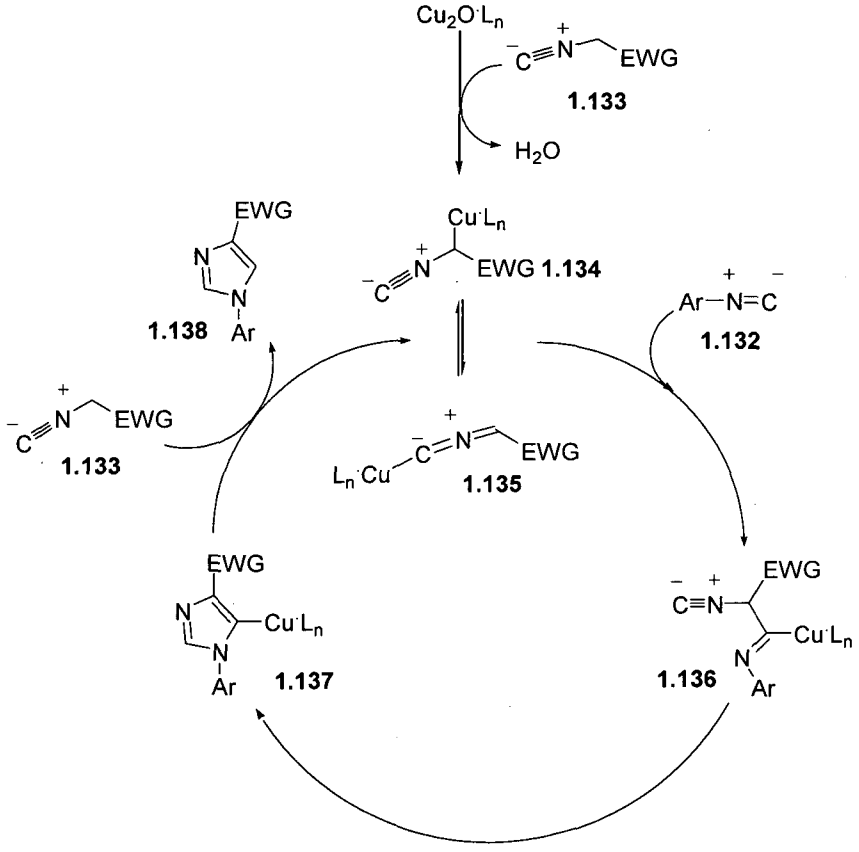
Scheme 1.25: Cross Cycloaddition of Isocyanides Catalyzed by Cu_2O



1.132 **1.133** **1.138**

similar to that in Scheme 1.24, and involves the initial C-H bond activation of the isocyanide by Cu_2O, to form α-cuprioisocyanide **1.134,** which is in equilibrium with its tautomeric form **1.135**. Subsequent nucleophilic attack of **1.135** on aryl-

Scheme 1.26: Proposed Mechanism for Cross Cycloaddition of Two Different Isocyanides



substituted isocyanide **1.132** generates intermediate **1.136,** which can undergo intramolecular cyclization followed by 1,3-hydrogen shift to provide cyclized adduct **1.137**. Protonation of **1.137** with excess **1.133** furnishes the product **1.138** and regenerates the active catalyst (Scheme 1.26).[35]

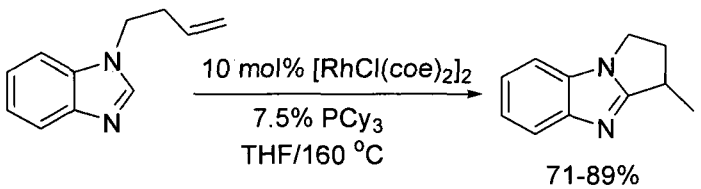
1.2.6.2 Metal Catalyzed Functionalization of Imidazoles

In addition to cyclization strategies, metal catalysis has also been employed to functionalize simple imidazoles. This can be achieved via a transition metal catalyzed C-H bond activation, metal catalyzed *N*-arylation, or cross coupling methods. Highlights of some of the main advances in these areas will be discussed below.

1.2.6.2.1 Transition Metal Catalyzed C-H Bond Activation

A number of metal catalyzed C-H bond activation strategies have recently been developed to functionalize imidazoles. One of the first examples of this involved *N*-homoallyl-benzimidazole **1.139.** This compound can undergo selective C-H bond activation at the α-position of the imidazole ring in the presence of 5% $[RhCl(coe)_2]_2$ and PCy_3, which initiates an intramolecular alkene insertion to form the fused imidazole skeleton **1.140** (Scheme 1.27). A wide range of di-, or tri-substituted alkenes can undergo cyclization, providing annulated products in good yields.[36]

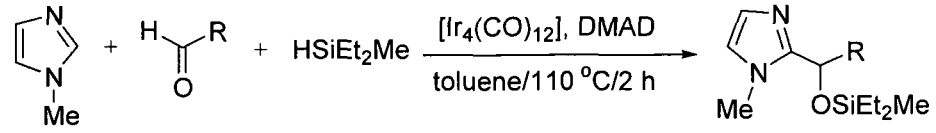
Scheme 1.27: Rhodium Catalyzed Intramolecular C-H Bond Activation



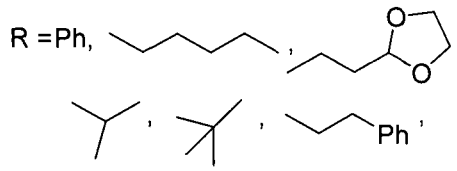
1.139 **1.140**

In another approach, $[Ir_4(CO)_{12}]$ was used to catalyze the intermolecular coupling of imidazole **1.141** with aldehyde **1.142** and hydrosilane **1.143,** affording 2-alkyl substituted imidazoles **1.148** (Scheme 1.28).[37] While the mechanistic details of this reaction are still under investigation, it was suggested that an in situ generated iridium silane complex **1.144** is the active catalyst, which undergoes a sequential insertion of aldehyde **1.142**, followed by imidazole **1.141**, to generate **1.146** (Scheme 1.29). ß-hydride elimination of this compound furnishes the product **1.148** along with Ir-H complex **1.147** which further reacts with **1.143** to regenerate the active catalyst **1.144**.[37] Nevertheless, an alternative mechanism involving direct C-H bond activation similar to that in Scheme 1.27 would also seem viable.

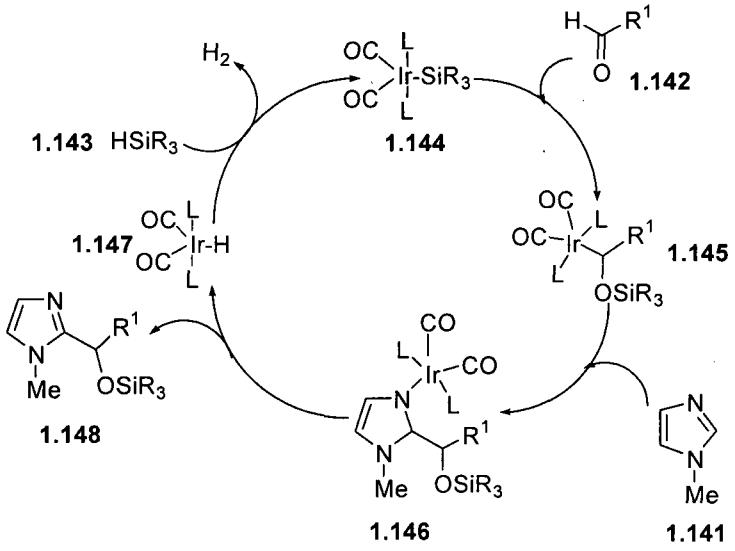
Scheme 1.28: Iridium Catalyzed Functionalization of Imidazoles



1.141 **1.142** **1.143** **1.148**



Scheme 1.29: Proposed Mechanism for Iridium Catalyzed Synthesis of 2-alkyl Substituted Imidazole **1.148**

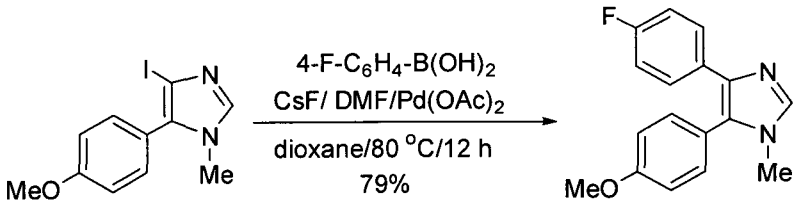


1.2.6.2.2 Cross Coupling Methods

A wide range of metal catalyzed cross coupling reactions has been employed to functionalize imidazoles. These include the use of Suzuki, Stille, Negishi, Sonogashira and Heck reactions. These approaches typically employ halogenated imidazoles as starting materials, though the use of imidazole as the organometallic coupling partner is also possible.[38] A brief summary of some of these reactions is shown in Scheme 1.30.

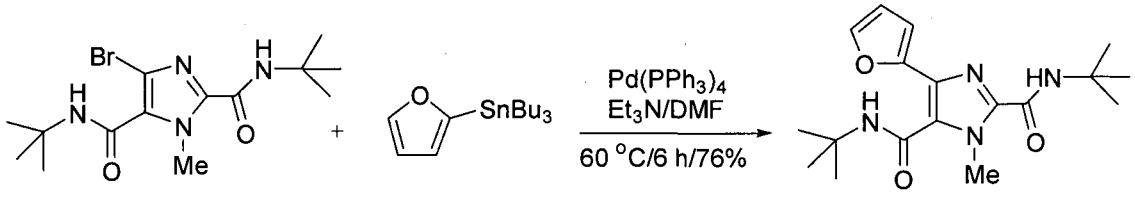
Scheme 1.30: Cross Coupling Approaches for Functionalization of Imidazoles

(a) Suzuki Coupling[39a]



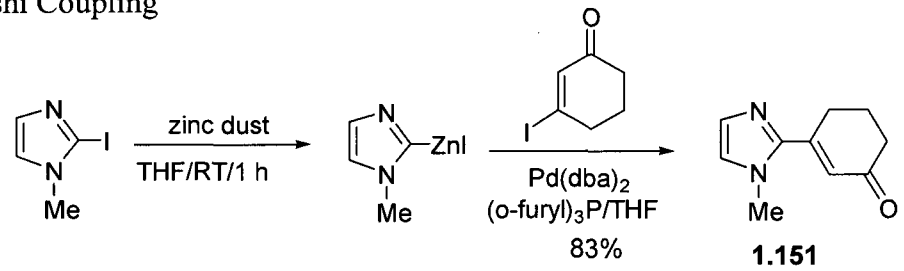
1.149

(b) Stille Coupling[39b]



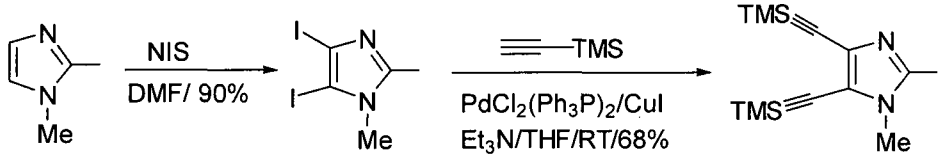
1.150

(c) Negishi Coupling[39c]



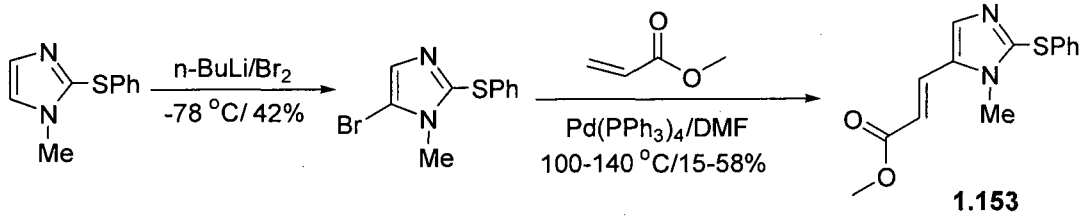
1.151

(d) Sonogashira Coupling[39d]



1.152

(e) Heck Coupling[39e]

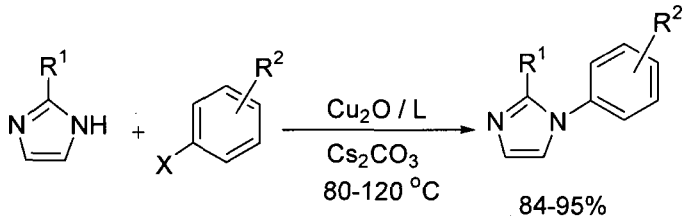


1.153

1.2.6.2.3 Metal Catalyzed *N*-Arylation

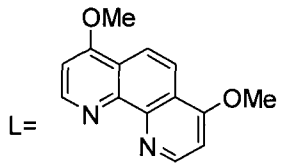
In addition to cross coupling reactions, metal catalyzed C-N bond forming reactions can be employed to directly functionalize the imidazole nitrogen. For example, *N*-arylated imidazoles **1.157** can be obtained from the reaction of imidazoles **1.154** with the aryl-halide **1.155** in the presence of Cu_2O catalyst with 4,7-dimethoxy-1,10-phenanthroline **1.156** as a ligand. Using this approach, sterically hindered 2,4-substituted imidazoles can easily undergo *N*-arylation in high yields (Scheme 1.31).[40]

Scheme 1.31: Cu_2O catalyzed *N*-arylation of imidazoles



1.154 **1.155** **1.157**

X = Br, I



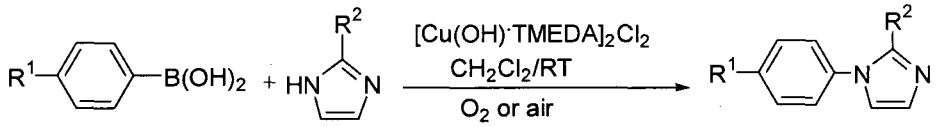
1.156

R^1 = H, Me

R^2 = 3, 5-Cl; 2-*i*-Pr; 2-CH_2OH; 4-F; 4-CO_2Et; 4-COMe

An alternative approach to these products involves the coupling of aryl boronic acids **1.158** with imidazoles **1.159** in the presence of copper catalyst $[Cu(OH)•TMEDA]_2Cl_2$ and an oxidant (Scheme 1.32). This reaction is compatible with a range of variously substituted arylboronic acids, and generates *N*-arylated imidazoles in moderate to excellent yields.[41]

Scheme 1.32: Synthesis of *N*-arylsubstituted imidazoles using $[Cu(OH)•TMEDA]_2Cl_2$



1.158 **1.159** **1.160**

58-98%

R^1= 4-Me- R^2= H
2-MeO- Me
3-MeO-
4-F-
4-Me-

1.3 Overview of the Thesis

As described in the previous section, a diverse range of methods have been developed to construct imidazoles. Together, these can provide access to a tremendous variety of substituted versions of these heterocycles, some of which have displayed interesting properties as bioactive molecules or in other applications. While these methods are all effective, they often require assembly of the correctly substituted precursors for cyclization, or the stepwise incorporation of substituents

onto simple imidazoles. As such, highly substituted imidazoles are often the product of a relatively involved, multistep synthesis. This can both limit the accessibility of products, and also complicate the structural modification of imidazoles to tune their properties, since this series of steps must often be repeated.

In principle, a more attractive route to these compounds would be to consider their structure as simply the product of basic, easily tunable, and readily available building blocks, brought together all at once. This would allow for a facile excess to imidazole derivatives, as well as access to a diverse range of differently substituted imidazoles by simple modulation of the basic building blocks employed. This thesis presents our efforts towards the development of such routes to imidazoles, via the use of transition metal catalysis. Chapter 2 of the thesis describes the design of a new, one step palladium catalyzed synthesis of imidazoles from imine and acid chloride building blocks. Considering the simplicity of these building blocks, this provides facile access to these products in a modular fashion. Chapter 3 describes the design of a palladium catalyzed four component coupling of imines, chloroformates, organotin reagents and carbon monoxide to generate ketocarbamates. The latter are amenable to cyclization in the presence of ammonium acetate to generate variously substituted imidazolones. Chapter 4 describes the development of a method to construct a diverse range of π-conjugated imidazole containing polymers, based upon a palladium catalyzed multicomponent coupling strategy developed in Chapter 2. The modularity of this approach has been used to generate a novel library of conjugated polymers. In Chapter 5, the results of

the mechanistic studies on the palladium catalyzed multicomponent synthesis of imidazole containing π-conjugated polymers will be discussed in detail.

1.4 References

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CHAPTER TWO

A Direct, One Step Synthesis of Imidazoles from Imines and Acid Chlorides: A Palladium Catalyzed Multicomponent Coupling Approach*

Preface

In this Chapter, an efficient palladium catalyzed one step synthesis of imidazoles from imines and acid chlorides is described. A plausible mechanism for this multicomponent reaction is provided, which explains the selective incorporation of two different imines into the final product with perfect regiocontrol. Overall, this catalytic process provides a modular method to prepare imidazoles directly from building blocks that are all either commercially available or readily generated.

2.0 Introduction

Imidazoles have found utility in a diverse range of areas,[1] with examples including drug cores (e.g. angiotensin II inhibitors,[2a] antiinflammatory,[2b] and anticancer[2c] agents), conjugated and functional polymers,[3a] natural products,[3b,c] and coordination complexes.[3d] Imidazoles are also important as ligands in metalloenzymes,[4] and, more recently, have been found to serve as precursors to

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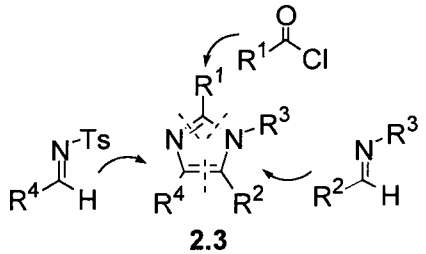
environmentally friendly ionic solvents[5] and carbene ligands.[6] In light of their wide use, many synthetic approaches have been developed to generate these heterocycles. This includes traditional cyclocondensation methods[1] (e.g. with pre-synthesized 1,2-diketones,[7a] α-sulfonylisocyanides[7b] or α-ketoamides[7c]) and a number of efficient recent cyclization routes.[8] In addition, imidazoles can be prepared via stepwise substitution reactions on simple imidazoles, including catalytic C-H activation,[9] cross coupling,[10] or aromatic substitution reactions.[1,11]

While all effective, these methods often require multiple steps to prepare diversely substituted imidazoles. An intriguing alternative approach to imidazoles could involve considering their structure as made up of multiple, simple and easily diversified reagents, put together all at once by metal catalysis (Figure 2.1). This can provide an attractive method to both easily generate products, and at the same time independently vary substituents, in a single step, as illustrated in the Pauson-Khand,[12] alkyne trimerization,[13] amidocarbonylation[14] and a range of more recent catalytic multicomponent syntheses.[15] We report herein the design of such a direct metal catalyzed synthesis of imidazoles, providing overall a highly modular, one step route to these heterocycles.

Figure 2.1: A Multicomponent Approach to Imidazole Synthesis



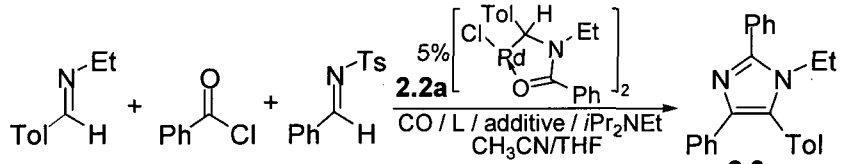
2.3

2.1 Results and Discussion

2.1.1 Method Development

Our approach to this synthesis involves considering the imidazole core as the product of two imines and an acid chloride (Figure 2.1), each of which are readily available in many forms. This is based upon our recently observed palladium catalyzed coupling of imine, acid chloride and carbon monoxide to generate 1,3-oxazolium-5-olates (Münchnones, **2.1**).[16] As such, we considered the possibility that performing this catalytic reaction in the presence of *N*-tosyl substituted imines, which can undergo *in situ* 1,3-dipolar cycloaddition with Münchnones,[8e] could provide a route to construct imidazoles. While mechanistically plausible (Scheme 1), this reaction would require the selective coupling of two similar imine substrates in a single reaction; a feature that has proven challenging for multicomponent reactions.[13] Nevertheless, our initial attempt towards this direct synthesis was encouraging. The reaction of (*p*-tolyl)HC=NEt, (Ph)HC=NTs, PhCOCl and CO in the presence of the previously developed catalyst **2.2a**[16] led to the consumption of starting materials over the course of 24h, and did form imidazole **2.3a**, though in low yield (28%, Table 2.1).

Table 2.1: A One Step Catalytic Synthesis of Imidazole **2.3a**.



Tol=-*p*-$C_6H_4CH_3$ Ts=-SO_2(*p*-$C_6H_4CH_3$)

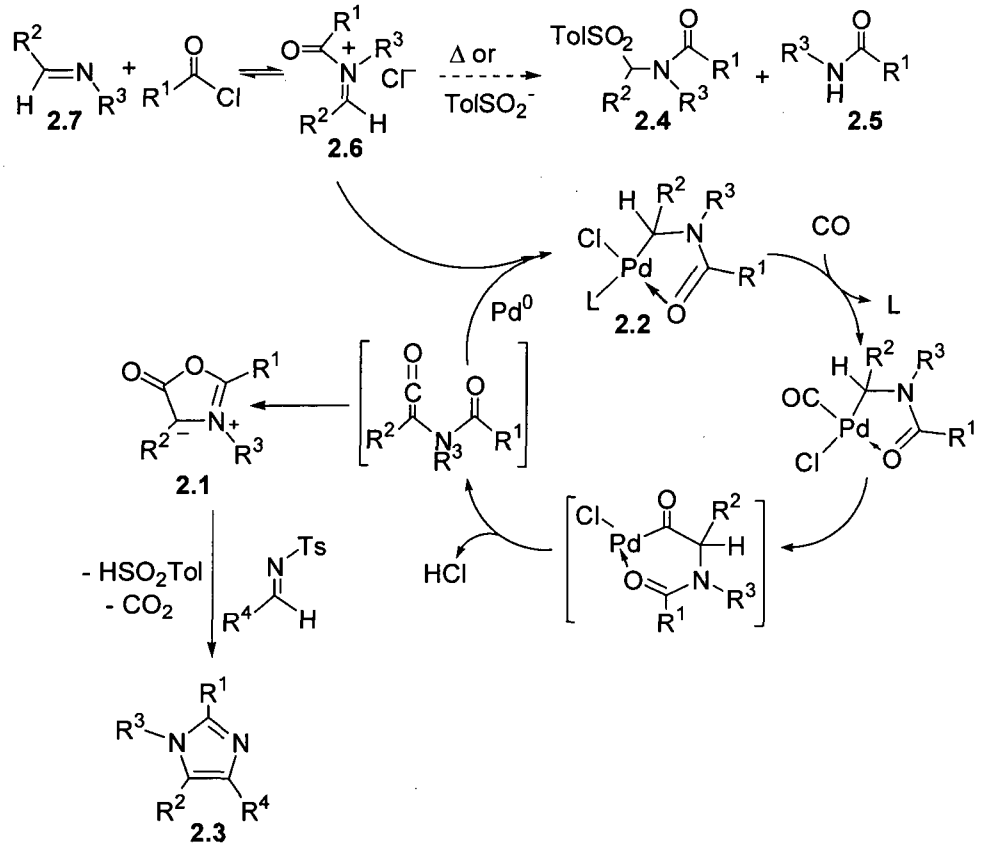
#	Temp	[CO][a]	Pd cat	L[b]	Additive[c]	%[d]
1	65 °C	1	**2.2a**	-	Bu_4NBr	28
2	45 °C	1	**2.2a**	-	Bu_4NBr	28
3	45 °C	4	**2.2a**	-	Bu_4NBr	43
4	45 °C	20	**2.2a**	-	Bu_4NBr	48
5	45 °C	4	**2.2a**	PPh_3	-	-
6	45 °C	4	**2.2a**	P^tBu_3	-	58
7	45 °C	4	**2.2a**	P(*o*Tol)$_3$[f]	-	60
8	45 °C	4	**2.2a**	P(*o*Tol)$_3$	Bu_4NCl	25
9	45 °C	4	**2.2a**	P(*o*Tol)$_3$	LiOTf	20
10	45 °C	4	**2.2a**	P(*o*Tol)$_3$	LiBr	54
11	45 °C	4	**2.2a**	P(*o*Tol)$_3$	LiCl	76
12	45 °C	4	Pd_2dba_3•$CHCl_3$	P(*o*Tol)$_3$	LiCl	68
13	45 °C	4	$Pd(PPh_3)_4$	P(*o*Tol)$_3$	LiCl	-
14	45 °C	4	**2.2a**	P(*o*Tol)$_3$	LiCl	79[e]

[a]atm. [b]15 mol%. [c]3 equiv. [d]NMR yield. [e]With Ph(H)C=N($SO_2C_6H_4Cl$). [f] *o*Tol=-*o*-$C_6H_4CH_3$

Closer examination of the reaction products shows the low imidazole yield is due to two competing processes, leading to the formation of an α-sulfonylamide **2.4** (25%) and amide **2.5** (46%) (Scheme 2.1). These products presumably arise from the *in situ* generated iminium salt **2.6**, via the either attack of the sulfonyl anion released by cycloaddition, or decomposition, respectively.[17] Based on this postulate, the efficiency of this reaction can be improved by inhibiting these steps. First, since iminium salt decomposition to **2.5** is a thermal process competing with catalysis, its role can be limited by lowering the temperature and accelerating the reaction with

CO pressure (entry 3). The addition of phosphine ligands can further accelerate catalysis, with the bulky P(oTol)$_3$ allowing imidazole formation in 60% yield. The inhibition of sulfonylamide **2.4** proved more challenging, since sulfonyl anion formation is part of the catalytic mechanism, and its attack on **2.6** is rapid.[17] However, experiments with an independently synthesized **2.4** demonstrate that the addition of LiCl can lead to the equilibrium regeneration of **2.6**. Similarly, while several salts inhibit the reaction,[17] LiCl completely suppresses **2.4**, and provides, overall, a very selective method to catalytically couple these three reagents directly into an imidazole (entry 11). Notably, commercially available Pd_2dba_3 is also an effective catalyst for this reaction.

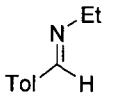
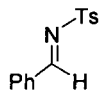
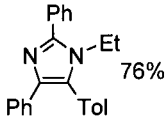
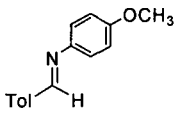
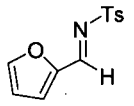
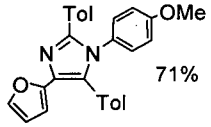
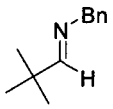
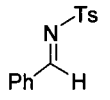
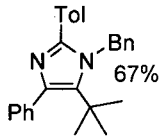
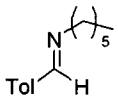
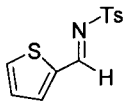
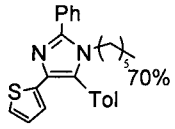
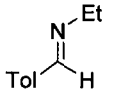
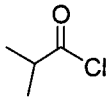
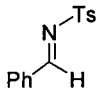
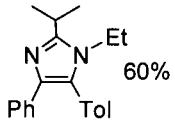
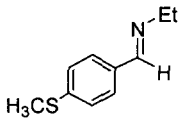
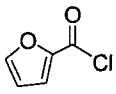
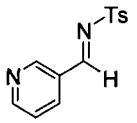
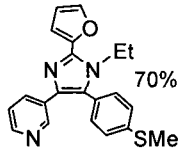
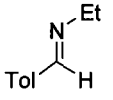
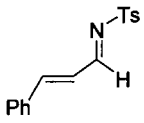
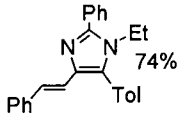
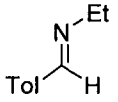
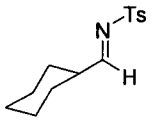
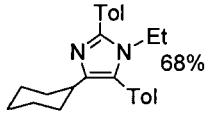
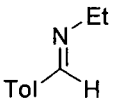
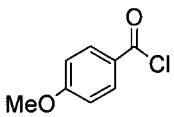
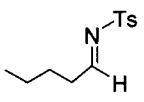
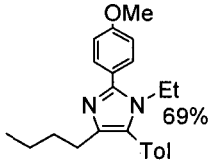
Scheme 2.1: Postulated Mechanism for Imidazole Synthesis.



2.1.2 Structural Diversity

As shown in Table 2.2, since the building blocks employed are all commercially available or readily prepared, this reaction can be directly applied to the one step synthesis of diversely substituted imidazoles. *N*-alkyl and *N*-aryl imines can be used

Table 2.2: A Modular Catalytic Synthesis of Imidazoles.

cpd	imine	acid chloride	tosyl imine	2.3 (% yield)
a		PhCOCl		 76%
b		TolCOCl		 71%
c		TolCOCl		 67%
d		PhCOCl		 70%
e				 60%
f				 70%
g		PhCOCl		 74%
h		TolCOCl		 68%
i				 69%

[a]Conditions: 0.68 mmol imine, 0.82 tosyl imine, 0.95 mmol acid chloride, 5 mol% **2.2**, 15 mol% P(*o*Tol)$_3$, 3 eq. NEt*i*Pr$_2$/LiCl, 4 atm CO, 45 °C, 18 h.

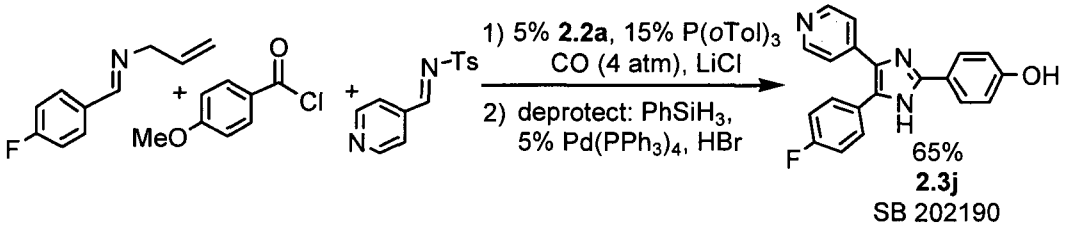
in this coupling, as can imines of aromatic and even nonenolizable alkyl (**2.3c**) aldehydes. Similarly, aryl, heteroaryl, and alkyl acid chlorides can all be employed. Even greater diversity can be achieved with the *N*-tosylimines, including aryl, alkyl, heterocyclic and α,ß-unsaturated substituents. While enolizable imines cannot be employed with *N*-alkyl substituted imines, they can be added via the *N*-tosylimine (**2.3h, i**). This reaction also displays good functional group compatibility, and even proceeds in the presence of coordinating functionalites (**2.3d, f**), all generating substituted imidazoles in good yield.

Interestingly, while this reaction involves the simultaneous coupling of different imines, no products incorporating two of the same imine are observed. This selectivity is believed to result from the catalytic mechanism (Scheme 2.1).[16] In particular, the *N*-tosylimine is not sufficiently nucleophilic to interact with the acid chloride, thus it is only imine **2.7** that is incorporated into iminium salt **2.6** and ultimately forms Münchnone **2.1**. However, once **2.1** is generated, it reacts exclusively with the more electron poor imine via cycloaddition. Consistent with this mechanism, the more electron deficient *p*-chlorosulfonylimine leads to higher imidazole yield (Table 2.1, #14).[18] Important from a synthetic perspective, this process provides complete regiochemical control of all the substituents about the ring, where each unit can be independently varied by choice of imine(s) and acid chloride reagents.

2.1.3 Direct Synthesis of SB 202190

We have begun to probe the utility of this reaction to provide access to imidazole targets. Compound **2.3j** has been demonstrated to be a potent p38 MAP kinase inhibitor and lead in the design of new anti-inflammatory agents.[2b] While the previously reported route to **2.3j** is a multistep process via 1,2-diketones, this catalytic coupling can allow the one-pot, regioselective assembly of **2.3j** directly from available imine and acid chloride substrates, after deprotection (Scheme 2.2).

Scheme 2.2: Synthesis of SB 202190



2.2 Conclusions

In conclusion, the palladium catalyzed coupling of imines and acid chlorides can be used to provide a new, one step method to synthesize imidazoles. Considering the efficiency of this reaction, and availability of the building blocks, this provides a very straightforward method to assemble these products. Experiments directed towards its application to other targets are underway.

2.3 Experimental Section

General Procedures

All reactions were carried out under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or using standard Schlenk techniques, unless otherwise indicated. Palladium catalysts (**2.2**) were prepared according to a previously reported procedure, by pretreating $Pd_2dba_3 \cdot CHCl_3$ with imine and acid chloride.[16] Carbon monoxide (99.99%) was purchased from Matheson and used as received. *N*-alkyl and -aryl imines, and *N*-tosylimines, were prepared according to the literature procedures.[19, 20] All other reagents were purchased from Aldrich® and used as received. Acetonitrile was freshly purified by distillation over CaH_2 under nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Deuterated solvents were dried over drying agents, transferred under vacuum and stored over 3 and 4 Å molecular sieves. ^1H and ^{13}C NMR were acquired on a Mercury 400 MHz spectrometer. Mass spectra were obtained from the McGill University Mass Spectral Facility.

General Procedure for the Catalytic Synthesis of Imidazoles 2.3

Imine (0.68 mmol) and acid chloride (0.98 mmol) in 5 mL of acetonitrile were added to a 50 mL reaction bomb, followed by the palladium catalyst (5 mol%) in 5 mL of acetonitrile, P(*o*Tol)$_3$ (31.3 mg, 0.102 mmol) in 5 mL of THF, EtN*i*Pr$_2$ (264 mg, 2.04 mmol) in 5 mL THF, *N*-tosyl imine (0.81 mmol) and LiCl (87 mg, 2.04 mmol). The entire solution was frozen in liquid nitrogen and evacuated, and carbon

monoxide (60 psi) added. The mixture was heated at 45 °C for 16-18 h. All imidazoles were purified by silica gel chromatography using hexane:ethyl acetate:triethylamine as eluent.

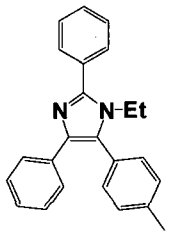
Synthesis of 4-[5-(4-Fluoro-phenyl)-4-pyridin-4-yl-1*H*-imidazol-2-yl]-phenol SB202190 (2.3j)

4-$FC_6H_4(H)C{=}N(CH_2CHCH_2)$ (111.5 mg, 0.68 mmol) and anisoyl chloride (348 mg, 2.04 mmol) in 5 mL acetonitrile were added to a 50 mL reaction bomb, followed by $[Pd(Cl)[\eta^2\text{-}CH(p\text{-tolyl})NEt(COPh)]_2$ (27 mg, 0.034 mmol) in acetonitrile (5 mL), P(*o*-tol)$_3$ (31.3 mg, 0.102 mmol) in 5 mL of THF, Et*i*Pr$_2$ (132 mg, 1.02 mmol) in 5 mL of THF and LiCl (29 mg, 0.68 mmol). 4-pyridyl(H)C=NTs (158.1 mg, 0.68 mmol) in 3 mL of THF was slowly added to the reaction solution over a 10 min period. Carbon monoxide (60 psi) was introduced into the reaction bomb as described previously, and the solution was heated at 55 °C for 28 h. The mixture was filtered through silica gel, redissolved in CH_2Cl_2 and transferred into a Schlenk tube under nitrogen, along with tetrakis(triphenylphosphine)palladium[21] (5 mol%) in 5 mL of CH_2Cl_2 and acetic acid (4 eq.). Phenylsilane (2 eq.) was added dropwise and the solution was stirred at room temperature and monitored by TLC until deallylation was completed (20 h). The solvent was evaporated and the brownish residue dissolved in HBr 48% (20 mL), NaI (2 eq.) was added and the mixture was heated at 120 °C for 24 h.[22] The mixture was then quenched with Na_2CO_3 and pH was adjusted to 7-8. The crude product was extracted with CH_2Cl_2

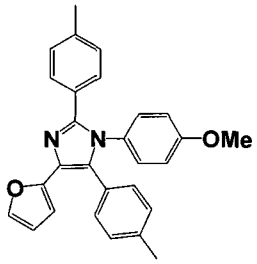
(5 × 50 mL), dried over anhydrous $MgSO_4$, and filtered. The product was purified by silica gel column chromatography using hexane:ethyl acetate:triethylamine:methanol (8:1.2:0.4:0.4).

Spectroscopic Data on 2.3

1-Ethyl-2,4-diphenyl-5-p-tolyl-1H-imidazole (2.3a) Yield: 76% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 2H), 7.57(d, 2H), 7.50-7.43 (m, 3H), 7.33-7.28 (m, 4H), 7.22-7.18 (t, 2H), 7.14-7.10 (t, 1H), 3.96 (q, 2H), 2.46 (s, 3H), 1.05 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 138.7, 137.7, 134.8, 131.6, 131.0, 129.9, 129.6, 129.3, 128.9, 128.7, 128.6, 128.1, 126.9, 126.3, 39.9, 21.8, 16.7. HRMS. Calculated for $C_{24}H_{22}N_2$: 338.17830; found: 338.17795.

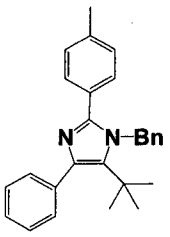


4-Furan-2-yl-1-(4-methoxy-phenyl)-2,5-di-p-tolyl-1H-imidazole (2.3b) Yield: 71% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 1H), 7.32-7.30 (d, 2H), 7.06 (s, 4H), 7.04-7.02 (d, 2H), 6.9-6.92 (d, 2H), 6.76-6.74(d, 2H), 6.33-6.26 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 149.6, 147.5, 141.3, 138.3, 137.9, 131.0, 130.9, 130.8, 129.9, 129.5, 129.0, 128.9, 127.6, 127.0, 114.4, 111.0, 105.8, 55.7, 21.8, 21.7. HRMS. Calculated for $C_{28}H_{24}N_2O_2$: 420.18378; found: 420.18436

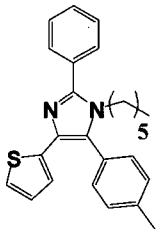


1-Benzyl-5-tert-butyl-4-phenyl-2-p-tolyl-1H-imidazole (2.3c) Yield: 67% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (m, 3H), 7.36-7.33 (m, 4H), 7.25-7.29 (t, 3H), 7.09(d, 2H), 6.83 (d, 2H), 5.59 (s, 2H), 2.35 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 145.0, 143.0, 138.9, 136.6, 135.6, 134.0, 131.5, 130.5, 130.1, 130.0, 129.6, 128.7, 128.5, 125.3, 51.0, 33.5, 31.8, 21.7

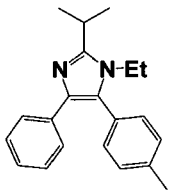
HRMS. Calculated for $C_{27}H_{28}N_2$: 380.22525; found: 380.22468



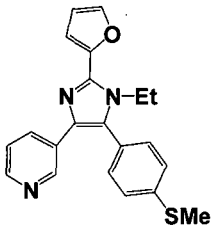
1-Hexyl-2-phenyl-4-thiophen-2-yl-5-p-tolyl-1H-imidazole (2.3d) Yield: 70% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 2H), 7.49-7.42 (m, 3H), 7.36-7.30 (m, 4H), 7.05-7.04 (m, 1H), 6.94-6.93 (d, 1H), 6.86-6.84 (m, 1H), 3.85 (t, 2H), 2.47 (s, 3H), 1.36 (m, 2H), 1.07 (m, 2H), 0.96 (m, 4H), 0.75 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 139.1, 138.5, 133.6, 131.4, 131.2, 129.9, 129.4, 129.0, 128.8, 128.7, 127.8, 127.1, 123.1, 122.5, 45.1, 31.1, 30.7, 26.2, 22.6, 22.0, 14.3. HRMS. Calculated for $C_{26}H_{28}N_2S$: 400.19732; found: 400.19706



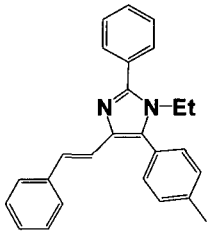
1-Ethyl-2-isopropyl-4-phenyl-5-p-tolyl-1H-imidazole (2.3e) Yield: 60% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.74 (d, 1H), 7.64-7.61 (m, 2H), 7.48-7.46 (d, 2H), 7.42-7.41 (m, 2H), 7.19-7.1 (m, 2H), 3.82-3.77 (q, 2H), 3.09-3.05 (m, 1H), 2.42 (s, 3H), 1.47-1.45 (d, 6H), 1.14-1.11 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 143.5, 135.0, 131.1, 130.7, 130.1, 129.2, 128.6, 128.4, 127.4, 125.6, 39.0, 26.7, 22.0, 21.6, 16.7. HRMS. Calculated for $C_{21}H_{24}N_2$: 304.19395; found: 304.19334



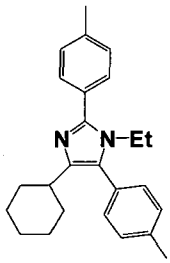
3-[1-Ethyl-2-furan-2-yl-5-(4-methylsulfanyl-phenyl)-1H-imidazol-4-yl]-pyridine (2.3f) Yield: 70% ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.34 (d, 1H), 7.86-7.84 (d, 1H), 7.52 (s, 1H), 7.32-7.30 (d, 2H), 7.26-7.24 (d, 2H), 7.14-7.11 (dd, 1H), 6.94-6.93 (d, 1H), 6.54-6.53 (m, 1H), 4.09 (q, 2H), 2.52 (s, 3H), 1.22 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.4, 145.6, 143.0, 140.6, 139.1, 135.5, 134.0, 131.3, 130.4, 130.2, 126.7, 126.3, 123.3, 111.8, 110.2, 40.3, 16.8, 15.6. HRMS. Calculated for $C_{21}H_{19}N_3OS$: 361.12488; found: 361.12452



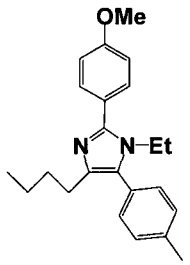
1-Ethyl-2-phenyl-4-styryl-5-p-tolyl-1H-imidazole (2.3g) Yield: 74% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.68 (d, 2H), 7.49-7.40 (m, 6H), 7.33 (s, 4H), 7.28-7.24 (t, 2H), 7.15 (t, 1H), 6.92-6.88 (d, 1H), 4.01 (q, 4H), 2.47 (s, 3H), 0.96 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 138.5, 138.3, 137.2, 132.0, 131.5, 130.6, 129.7, 129.4, 129.1, 128.8, 128.6, 127.2, 127.0, 126.8, 126.4, 119.7, 40.1, 21.8, 16.5. HRMS. Calculated for $C_{26}H_{24}N_2$: 364.19395; found: 364.19274



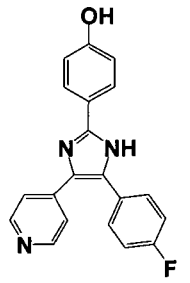
4-Cyclohexyl-1-ethyl-2,5-di-p-tolyl-1H-imidazole (2.3h) Yield: 68% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (d, 2H), 7.27-7.22 (m, 6H), 3.8 (q, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 1.74 (s, broad, 7H), 1.62 (s, broad, 1H), 1.25 (s, broad, 3H), 0.97 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.4, 144.6, 138.4, 138.0, 130.8, 129.3, 129.29, 129.27, 129.23, 128.7, 127.9, 39.8, 36.9, 33.5, 27.1, 26.3, 21.7, 16.6. HRMS. Calculated for $C_{25}H_{30}N_2$: 358.24090; found: 358.24040



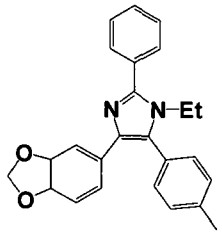
4-Butyl-1-ethyl-2-(4-methoxy-phenyl)-5-p-tolyl-1H-imidazole (2.3i) Yield: 69% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (d, 2H), 7.25-7.23 (m, 4H), 6.96-6.94 (d, 2H), 3.92 (q, 2H), 3.82 (s, 3H), 2.51 (t, 2H), 2.40 (s, 3H), 1.61 (m, 2H), 1.30 (m, 2H), 0.95 (t, 3H), 0.85 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 146.5, 139.6, 137.8, 130.52, 130.51, 129.4, 128.8, 128.3, 124.3, 114.0, 55.6, 39.9, 33.0, 27.5, 23.1, 21.7, 16.5, 14.3. HRMS. Calculated for $C_{23}H_{28}N_2O$: 348.22016; found: 348.22045



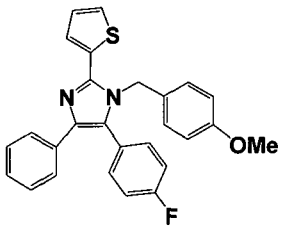
4-[5-(4-Fluoro-phenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-phenol (2.3j) Yield: 65% ^{1}H NMR (400 MHz, CD_3OD): δ 8.41 (s, broad, 2H), 7.83 (d, 2H), 7.51 (q, 4H), 7.2 (t, 2H), 6.88 (d, 2H), 3.34 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 164.9, 161.7, 158.8, 148.81, 148.80, 138.8, 130.9, 130.8, 127.5, 121.9, 121.03, 115.7, 115.5, 109.9. HRMS. Calculated for $C_{20}H_{14}FN_3O$: 331.11209; found: 331.11145



4-Benzo[1,3]dioxol-5-yl-1-ethyl-2-phenyl-5-p-tolyl-1H-imidazole (2.3k) Yield: 72% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 2H), 7.49-7.42 (m, 3H), 7.29 (s, 4H), 7.07 (d, 1H), 7.03 (s, 1H), 6.67 (d, 1H), 5.86 (s, 2H), 3.92 (q, 2H), 2.44 (s, 3H), 1.03 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 147.02, 146.06, 138.7, 137.5, 131.5, 131.08, 130.04, 129.3, 129.2, 128.9, 128.8, 128.7, 128.5, 120.6, 108.2, 107.7, 100.8, 39.9, 21.8, 16.7. HRMS. Calculated for $C_{25}H_{22}N_2O_2$: 382.16813; found: 382.16756

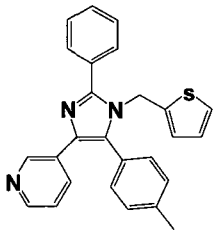


5-(4-Fluoro-phenyl)-1-(4-methoxy-benzyl)-4-phenyl-2-thiophen-2-yl-1H-imidazole (2.3l) Yield: 71% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.52 (d, 2H), 7.36-7.35 (d, 1H), 7.26-7.20 (m, 2H), 7.19-7.15 (m, 4H), 7.04-6.99 (m, 3H), 6.86-6.80 (m, 4H), 5.11 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 159.1, 142.4, 138.7, 134.3, 133.1, 133.0, 132.9, 129.2, 128.4, 127.7, 127.2, 127.1, 127.0, 126.8, 126.3, 116.4, 116.1, 114.5, 55.5, 47.9. HRMS. Calculated for $C_{27}H_{21}FN_2OS$: 440.13586; found: 440.13552

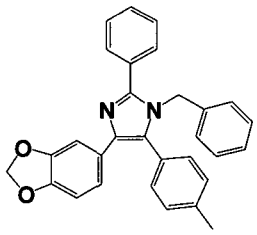


3-(2-Phenyl-1-thiophen-2-ylmethyl-5-p-tolyl-1H-imidazol-4-yl)-pyridine(2.3m)

Yield: 70% ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.38 (s, 1H), 8.16 (d, 1H), 7.69-7.66 (m, 2H), 7.48-7.46 (m, 2H), 7.33-7.30 (m, 2H), 7.26-7.24 (d, 2H), 7.19-7.17 (d, 2H), 7.13-7.11 (d, 1H), 6.79-6.77 (m, 1H), 6.40-6.39 (d, 1H), 5.22 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 139.9, 139.5, 136.2, 134.0, 131.8, 130.8, 130.69, 130.66, 130.4, 129.7, 129.6, 129.4, 129.3, 129.0, 126.9, 126.6, 125.9, 125.6, 124.2, 44.0, 21.7. HRMS. Calculated for $C_{26}H_{21}N_3S$: 407.14562; found: 407.14500

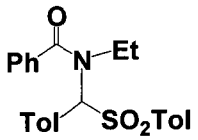


4-Benzo[1,3]dioxol-5-yl-1-benzyl-2-phenyl-5-p-tolyl-1H-imidazole (2.3n) Yield: 73% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.63 (m, 2H), 7.38-7.37 (m, 3H), 7.21-7.19(m, 3H), 7.16-7.11 (m, 3H), 7.09-7.07 (m, 3H), 6.82-6.80 (m, 2H), 6.70-6.68 (d, 1H), 5.87 (s, 2H), 5.08, (s, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.65, 147.56, 146.4, 138.8, 137.7, 131.3, 131.1, 129.8, 129.6, 129.5, 129.28, 129.23, 129.1, 128.8, 128.7, 127.6, 126.2, 120.8, 108.3, 107.7, 100.9, 48.5, 21.6. HRMS. Calculated for $C_{30}H_{24}N_2O_2$: 444.18378; found: 444.18324



Reaction of *N*-acyliminium salt 2.6 with $NaSO_2Tol$

p-tolylC_6H_4(H)C=NEt (40 mg, 0.272 mmol) and benzoyl chloride (53.5 mg, 0.38 mmol) were dissolved in 10 mL of acetonitrile and stirred at room temperature for 10 min. The formation of iminium salt **2.6** was confirmed by ^{1}H NMR spectroscopy. To this solution was added *p*-toluene sulfinic acid sodium salt (48.4 mg, 0.272 mmol), and the mixture was stirred at room temperature for 2 h. ^{1}H NMR shows the quantitative formation of 4-methylbenzenesulfinic acid (*N*-benzoyl-*N*-ethylamino)-*p*-tolyl-methyl ester **2.4**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (m, broad, 4H), 7.37-7.24 (m, 5H), 7.20-7.18 (d, 2H), 7.11-7.09 (d, 2H), 3.93-3.88 (m, 2H), 2.37 (s, broad, 3H), 2.35 (s, 3H), 0.672 (s, broad, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 145.1, 139.9, 135.9, 135.5, 130.3, 129.88, 129.86, 129.84, 129.2, 128.4, 127.6, 126.7, 78.6, 40.01, 21.94, 21.56, 14.9. Calculated for $C_{24}H_{25}NO_3S$: 407.53, ESI-MS: 429.7*m/z*



Thermal Decomposition of 2.6

p-TolC_6H_4(H)C=NEt (40 mg, 0.272 mmol) and benzoyl chloride (53.5 mg, 0.38 mmol) were dissolved in 10 mL of acetonitrile and stirred at room temperature for 10 min in a 50 mL reaction bomb. To this solution was added Et*i*Pr_2 (105.47 mg, 0.816 mmol) and the reaction solution was heated at 65 °C for 12 h. The formation of *N*-ethyl-benzamide **2.5** was confirmed by ^{1}H NMR spectroscopy (63%).

Reaction of 2.4 with LiCl

A solution of 4-Methyl-benzenesulfinic acid (benzoyl-ethyl-amino)-*p*-tolyl-methyl ester **2.4** was prepared according to the procedure described above. To this solution was added LiCl 3 eq. (34.68 mg, 0.816 mmol) and the mixture was stirred at room temperature for 30 min. Analysis of the reaction solution by ^{1}H NMR spectroscopy demonstrates the regeneration of **2.6** in 79 % yield.

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17. Warming **2.6** to 65°C with $NEtiPr_2$ leads to **2.5** (63%, 12 h). **2.6** reacts with $LiSO_2Tol$ form **2.4** in 5 min at r.t. The addition of LiCl (3 eq.) to **2.4** regenerates **2.6** in ½ hr (79%). Other salts in Table 2.1 do not react with **2.4**.

18. Münchnone **1** also decomposes under the catalytic conditions (ref. 16).

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CHAPTER THREE

Palladium-Catalyzed Carbonylative Cross-Coupling with Imines: A Multicomponent Synthesis of Imidazolones*

Preface

In this Chapter, we describe the palladium-catalyzed coupling of imines, chloroformates, organotin reagents, and carbon monoxide into ketocarbamates. These products can further be converted to highly substituted imidazolones via a cyclocondensation reaction. Overall, this methodology provides an alternative approach to imidazolones from five simple and readily available building blocks via a one pot, multicomponent process.

3.0 Introduction

Imidazolones are found in a range of biologically active compounds, including anti-inflammatory,[1a] anticancer,[1b] and cardioactive agents,[1c] angiotensin II receptor antagonists,[1d] and others.[1e-h] In addition, 2-imidazolones can serve as potential substrates for imidazole synthesis.[2] A variety of methods have been developed to generate and functionalize these heterocycles. These include the condensation of substituted ureas with carbonyl compounds,[3] the coupling of β-amino carbonyl reagents with isocyanates,[4] intramolecular iminium salt cyclizations,[5] as well as more recent metal catalyzed methods,[6-8] such as the rhodium catalyzed N-H

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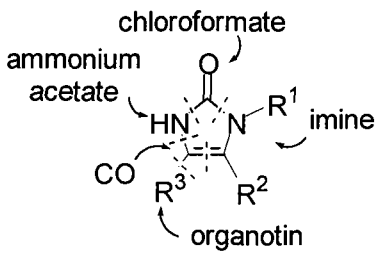
insertion of primary ureas with diazo carbonyl compounds,[2a, 6] or the ruthenium catalyzed reaction of substituted ureas with vicinal diols.[7, 8]

In principle, an attractive approach to imidazolones would be to assemble their core structure directly from multiple, available building blocks. Transition metal catalysis can be a powerful tool in developing such transformations, by activating what are often unreactive substrates towards coupling via metal-based reactions.[9] Towards this end, we have recently reported that imines can undergo a palladium catalyzed cross-coupling type reaction with organostannanes by the addition of acid chlorides or chloroformates, to generate α-substituted amides (or carbamates).[10] In addition, preliminary studies showed this reaction could proceed in concert with carbon monoxide insertion, allowing the synthesis of one example of a ketocarbamate. Considering that ketoamides are known to behave as precursors to imidazoles,[11] we became intrigued with the potential use of this ketocarbamate synthesis in an analogous fashion, to achieve the overall construction of imidazolones. As described below, this can provide a modular route to construct imidazolones from five separate and available building blocks, as shown in Figure 3.1.

Figure 3.1: A Multicomponent Approach to Imidazolones



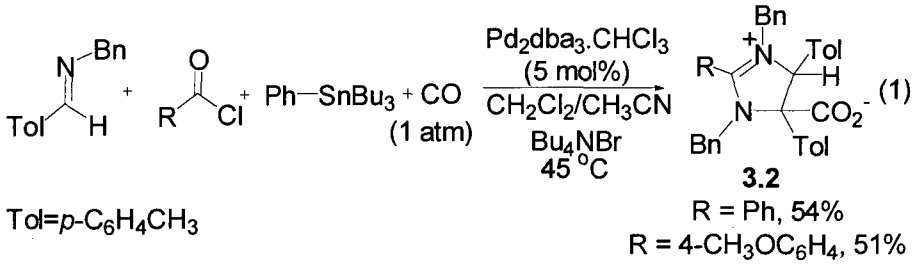
3.5

3.1 Method Development

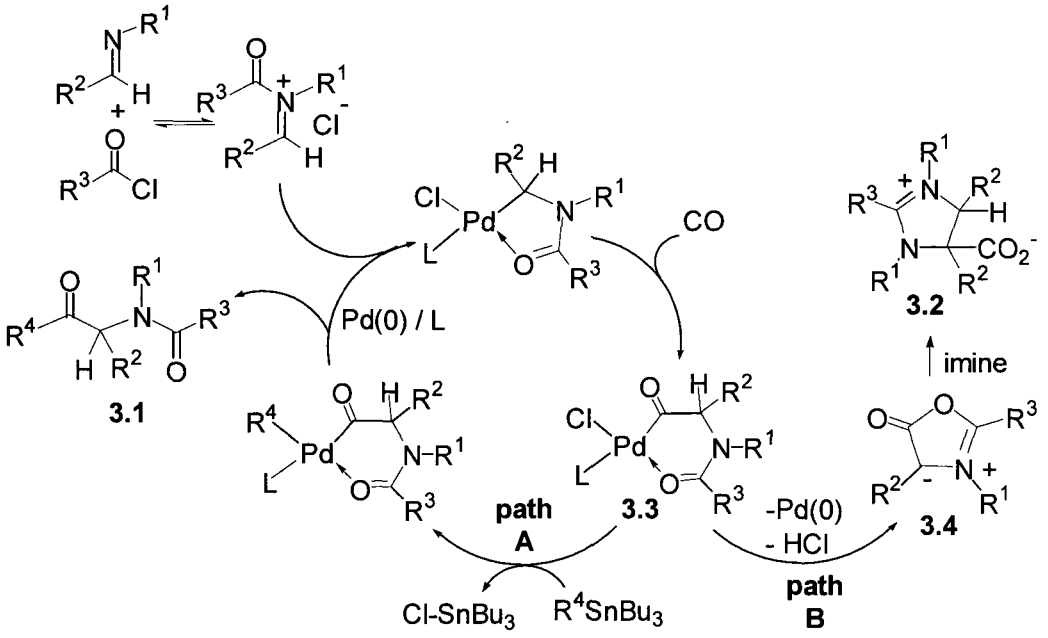
3.1.1 Synthesis of Ketocarbamates

Our initial efforts focused upon the palladium catalyzed carbonylative cross coupling reaction with imines. While we have shown that acid chlorides can activate imines toward cross coupling with organostannanes,[10] their use under carbonylative conditions leads instead to the formation of imidazolines **3.2** (Scheme 3.1, Tol = *p*-tolyl; Bn = benzyl). The latter presumably occurs via a mechanism involving the cyclization of the carbonylated palladium intermediate **3.3** to form 1,3-oxazolium-5-olate **3.4** (path B), followed by 1,3-dipolar cycloaddition of an imine (Scheme 3.2), a reaction we have previously reported.[12] In considering approaches to limit this pathway, we postulated that lowering the basicity of the carbonyl oxygen in intermediate **3.3** might disfavor cyclization to form **3.4**, and allow for competitive cross coupling to occur (path A). As shown in Table 3.1, replacement of the acid chloride with a chloroformate, leads to the carbonylative cross-coupling product **3.1a** in nearly quantitative yield at ambient temperature.[13]

Scheme 3.1: Formation of Imidazoline Carboxylate

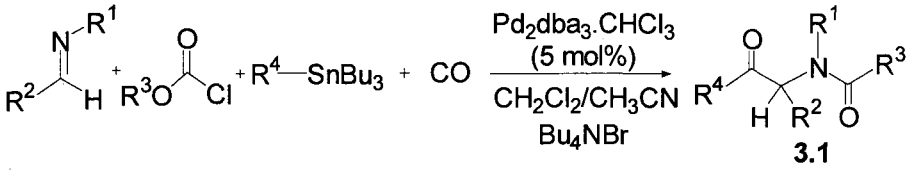


Scheme 3.2: Carbonylative Cross Coupling with Imines

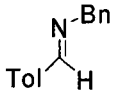
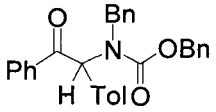
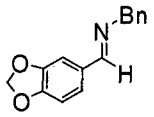
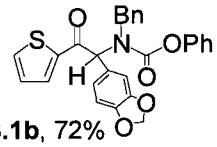
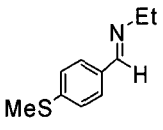
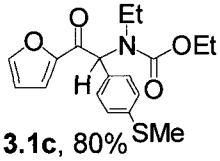
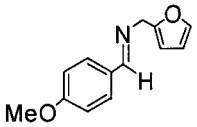
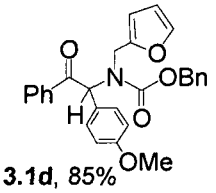
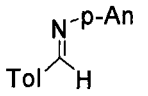
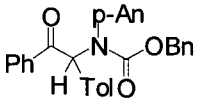
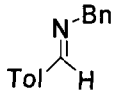
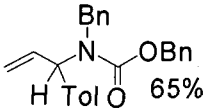


This palladium catalyzed carbonylative coupling is compatible with a number of chloroformates (entries 1-3). Both aromatic and heteroaromatic organostannanes can participate in the reaction, each providing ketocarbamates in good yields. An even greater variety of imines can participate in this reaction, including those of functionalized aryl-aldehydes (entries 2-4), and *N*-alkyl or *N*-aryl imines (entries 4, 5). There are certain limitations to this methodology. For example, more reactive transmetallating agents, such as vinyl-stannanes, appear to transmetallate more rapidly than carbonylation, leading instead to the formation of simple α-substituted carbamate (entry 6). Similarly, alkyl-substituted organostannanes are not sufficiently reactive to participate in this coupling, and enolizable imines lead to side reactions.

Table 3.1: Palladium Catalyzed Carbonylative Coupling of Imines, Chloroformates, CO, and Organostannanes.[a]



3.1

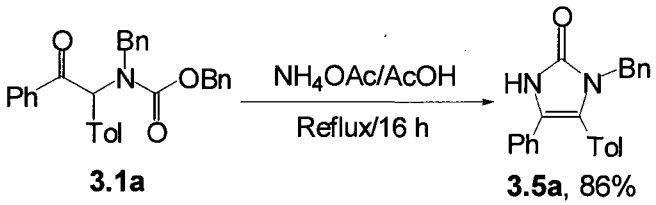
#	Imine	R^3	R^4	Product
1		-Bn	-Ph	 **3.1a**, 93%
2		-Ph		 **3.1b**, 72%
3		-Et		 **3.1c**, 80%
4		-Bn	-Ph	 **3.1d**, 85%
5[d]		-Bn	-Ph	 **3.1e**, 87%
6[b]		-Bn		 65%

[a] 0.48 mmol imine, 1.90 mmol chloroformate, 0.52 mmol organotin reagent, Pd_2dba_3•$CHCl_3$ (5%), 0.57 mmol Bu_4NBr and CO (1 atm) in CH_3CN/CH_2Cl_2 (2:1) at r.t. for 24-48h; *p*-An = 4-$CH_3OC_6H_4$.
[b] 50 atm CO.

3.1.2 Synthesis of Imidazolones

Ketoamides are well established to undergo ammonium acetate mediated cyclization to generate imidazoles.[11] However, to our knowledge ketocarbamates such as **3.1** have not been employed in similar cyclization reactions. As shown in Scheme 3.3, the addition of ammonium acetate to **3.1a** results in the clean cyclization, along with spontaneous removal of the former chloroformate substituent, leading to the synthesis of imidazolone **3.5a** in 86% yield.[14]

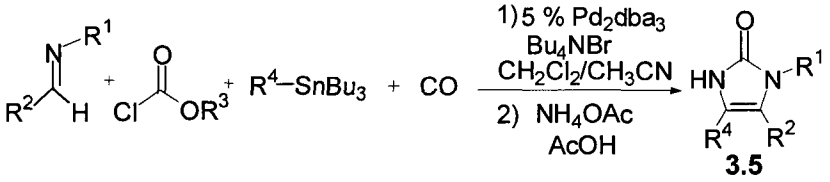
Scheme 3.3: Synthesis of Imidazolone from Ketocarbamate

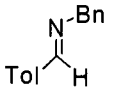
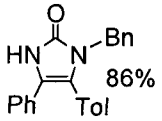
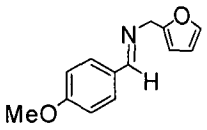
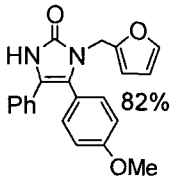
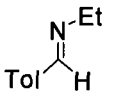
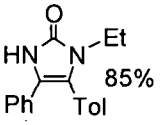
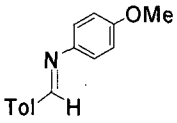
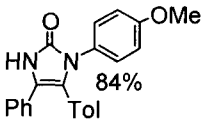
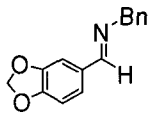
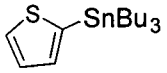
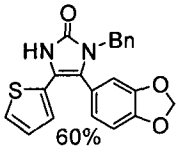
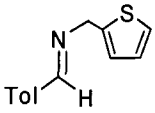
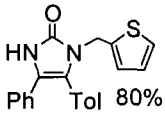
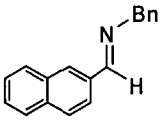
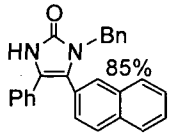
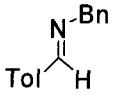
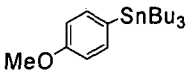
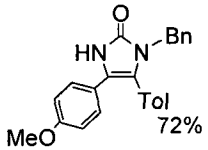
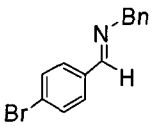
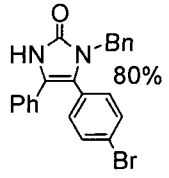


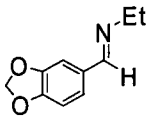
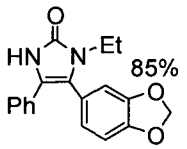
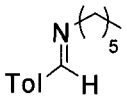
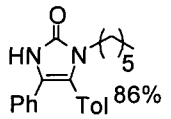
3.1a **3.5a**, 86%

Considering the high yield cyclization of **3.1a**, and the ability to access these substrates via carbonylative cross-coupling, we became interested in the potential coupling of these steps in a one pot format. As shown in Table 3.2, this can provide an efficient and high yield synthesis of imidazolones, where the products are assembled overall from five separate and readily available building blocks (imines, chloroformates, organostannanes, carbon monoxide and ammonium acetate). Notably, much of the same diversity noted in cross coupling chemistry can be incorporated into these imidazolone products, including the use of variously substituted and functionalized imines, as well as aryl- or heteroaryl-tin reagents. Overall, this allows access to a range of di- and tri-aryl substituted imidazolones with independent control over three substituents about the ring.

Table 3.2: A One-Pot Synthesis of Imidazolones[a]



Cpd	Imine	R^3	Tin Reagent	3.5 (% yield)
a		Bn-	Ph-$SnBu_3$	 86%
b		Bn-	Ph-$SnBu_3$	 82%
c		Et-	Ph-$SnBu_3$	 85%
d		Bn-	Ph-$SnBu_3$	 84%
e[b]		Ph-		 60%
f		Ph-	Ph-$SnBu_3$	 80%
g		Ph-	Ph-$SnBu_3$	 85%
h		Bn-		 72%
i		Bn-	Ph-$SnBu_3$	 80%

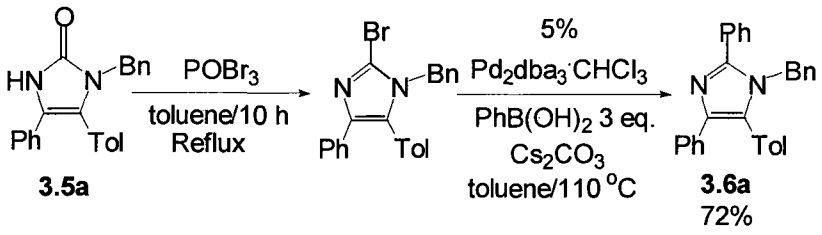
j		Ph-	$Ph\text{-}SnBu_3$	 85%
k		Bn-	$Ph\text{-}SnBu_3$	 86%

[a] Procedure of Table 1, followed by removal of solvent and addition of 15-20 equiv. NH_4OAc in AcOH, reflux 12-16h. [b]ketocarbamate was isolated and refluxed in NH_4OAc/AcOH solution for 5h.

3.1.3 Synthesis of Triarylimidazoles

Finally, this synthesis of imidazolones can also be used to access imidazoles. Tri-aryl substituted imidazoles have been found to display potent biological activity, including as selective p38 MAP kinase inhibitors.[15] As illustrated in Scheme 3.4, the coupling of the catalytic formation of imidazolones with the protocol developed by Janda for their bromination and use in palladium catalyzed cross coupling, provides access the tri-aryl substituted imidazole core in good yield.[2a] Notably, the four substituents in **3.6** arise overall from two separate cross coupling reactions (*e.g.* positions 2- and 4-) and from the imine building block (positions 1- and 5-).

Scheme 3.4: Synthesis of Triarylimidazoles



3.2 Conclusions

In conclusion, the palladium catalyzed four component cross-coupling of imines, chloroformates, organostannane reagents and carbon monoxide can be utilized to generate ketocarbamates, which are amenable to cyclization to generate imidazolones. Considering the mild conditions (1 atm of carbon monoxide, room temperature) and simple building blocks employed, this provides a straightforward access to these heterocycles. Experiments directed towards the use of this multicomponent reaction to generate other targets are underway.

3.3 Experimental Section

General Procedures

Unless otherwise noted all reactions were carried out under an inert atmosphere in a dry box or using standard Schlenk or vacuum line techniques. Tris(dibenzylideneacetone)dipalladium chloroform (Pd_2dba_3•$CHCl_3$) was prepared according to a literature reported procedure.[16] Carbon monoxide (99.99%) was purchased from Matheson and used as received. Imines were prepared and freshly distilled or recrystallized using literature procedures.[17] Tributylphenyltin as well as other organostannane reagents were prepared and freshly distilled according to literature procedure.[18] All other reagents were used as received from commercial suppliers.

Acetonitrile and methylene chloride were freshly purified by distillation over CaH_2 under nitrogen. Deuterated solvents were dried over drying agents, transferred under vacuum and stored over 3 and 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on 400 MHz and 500 MHz NMR spectrometers.

General Procedure for Ketocarbamate Synthesis

Imine (0.48 mmol) and chloroformate (1.91 mmol) were dissolved in acetonitrile (10 mL) and stirred for 15 min in a 50 mL reaction bomb. To this solution, Pd_2dba_3•$CHCl_3$ (25 mg, 0.024 mmol) was added and the mixture was stirred for 30 min until all Pd_2dba_3•$CHCl_3$ were completely dissolved. Tetrabutylammonium bromide (186 mg, 0.576 mmol) in 5 mL of methylene chloride, and tributylphenyltin (194 mg, 0.528 mmol) in 5 ml of methylene chloride, were added to the reaction

mixture. The solution was frozen in liquid nitrogen, degassed, and carbon monoxide (15 psi) was added. The mixture was stirred at room temperature for 24-48 h. After the reaction period was completed, solvents were removed *in vacuo* and the yellow-green oil was dissolved in 50 mL of ethyl acetate. In order to remove tributyltinchloride, 25 mL of saturated KF solution was added and the mixture was stirred for 5 h. This solution was then filtered over celite and extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, and solvent was evaporated under reduced pressure to give a yellow oil which was further purified by silica gel chromatography using hexane:ethyl acetate as eluent.

General Procedure for Imidazolone Synthesis

Imine (0.48 mmol) and chloroformate (1.91 mmol) were dissolved in acetonitrile (10 mL) and stirred for 15 min in a 50 mL reaction bomb. To this solution, $Pd_2dba_3 \cdot CHCl_3$ (25 mg, 0.024 mmol) was added and the mixture was stirred for 30 min until all $Pd_2dba_3 \cdot CHCl_3$ were completely dissolved. Tetrabutylammonium bromide (186 mg, 0.576 mmol) in 5 mL of methylene chloride, and tributylphenyltin (194 mg, 0.528 mmol) in 5 ml of methylene chloride, were added to the reaction mixture. The solution was frozen in liquid nitrogen, degassed, and carbon monoxide (15 psi) was added. The mixture was stirred at room temperature for 24-48 h. After the reaction period was completed, solvents were removed *in vacuo* to give yellow-greenish oil. To this oil were added 25 mL of acetic acid, 15-20 equiv. of ammonium acetate, and the mixture was refluxed for 16 h. The deep yellow solution was quenched with saturated Na_2CO_3 solution and pH was adjusted to 7-8 and

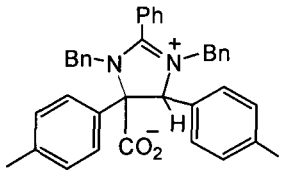
extracted with methylene chloride (3 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. All imidazolones were further purified by silica gel chromatography using hexane:ethyl acetate as eluent.

Spectroscopic Data of Products in Scheme 3.1 and Table 3.1

1,3-Dibenzyl-2-phenyl-4,5-di-*p*-tolyl-4,5-dihydro-3*H*-imidazole-4-carboxylate (Scheme 3.1) Yield: 55% ^{1}H NMR (400MHz, $CDCl_3$): δ 7.69 (s, br, 1H), 7.52-7.50 (d, 4H), 7.36-7.26 (m, 6H), 7.20-7.18 (d, 2H), 7.08-7.07 (d, 2H), 7.01-6.98 (t, 1H), 6.92-6.84 (m, 5H), 6.38-6.36 (d, 2H), 5.48 (s, 1H), 4.97-4.94 (d, 1H), 4.48-4.45 (d, 1H), 4.30-4.27 (d, 1H), 3.97-3.94 (d, 1H), 2.33 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.1, 165.1, 139.4, 138.8, 136.9, 136.0, 132.5, 132.2, 130.7, 130.1, 129.8, 129.6, 129.46, 129.40, 129.30, 129.2, 128.7, 128.5, 128.27, 128.2, 127.5, 127.3, 124.0, 84.5, 73.3, 51.4, 49.1, 21.6, 21.2.

IR (KBr): ν_{CO}: 1645 cm^{-1}, 1563 cm^{-1}

HRMS. Calculated for $C_{38}H_{35}N_2O_2^+$: 551.2698 found: 551.2693

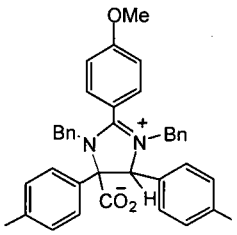


1,3-Dibenzyl-2-(4-methoxy-phenyl)-4,5-di-p-tolyl-4,5-dihydro-3*H*-imidazole-4-carboxylate (Scheme 3.1) Yield: 52% ^{1}H NMR (400MHz, $CDCl_3$): δ 7.59-7.58 (d, 1H), 7.49-7.47 (d, 2H), 7.37- 7.34 (m, 3H), 7.29 (s, br, 1H), 7.20-7.18 (d, 2H), 7.07-

7.00 (m, 4H), 6.94-6.90 (m, 4H), 6.7 (s, br, 1H), 6.41-6.39 (d, 2H), 5.46 (s, 1H), 4.96-4.92 (d, 1H), 4.52-4.48 (d, 1H), 4.38-4.34 (d, 1H), 3.98-3.95 (d, 1H), 3.83 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.1, 166.5, 162.4, 139.4, 138.7, 136.8, 136.3, 132.8, 130.7, 129.8, 129.5, 129.4, 129.3, 129.2, 128.7, 128.4, 128.2, 127.3, 115.6, 115.2, 115.1, 84.3, 73.1, 55.8, 51.5, 49.2, 21.6, 21.2.

IR (KBr): ν_{CO}: 1644 cm^{-1}, 1551 cm^{-1}

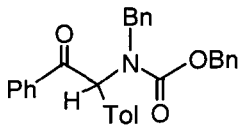
HRMS. Calculated for $C_{39}H_{37}N_2O_3^+$: 581.2821 found: 581.2798



Benzyl-(2-oxo-2-phenyl-1-*p*-tolyl-ethyl)-carbamic acid benzyl ester (entry 1, 3.1a) Yield: 93% ^1H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.8 (s, br, 2H), 7.47-7.43 (t, 1H), 7.34-7.27 (t, 2H), 7.27-7.25 (m, 3H), 7.18-7.15 (m, 4H), 7.13-7.11 (m, 4H), 7.04-7.02 (d, 2H), 6.92 (s, br, 2H), 5.25-5.16 (dd, 2H), 4.95-4.91 (d, 1H), 4.33-4.29 (d, 1H), 2.27 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 197.6, 157.6, 139.4, 138.9, 136.5, 135.8, 133.3, 131.1, 130.7, 129.9, 129.0, 128.7, 128.6, 128.4, 128.1, 128.0, 127.3, 126.6, 67.9, 65.9, 49.0, 21.3.

IR (KBr): ν_{CO}: 1703 cm^{-1}, 1698 cm^{-1}

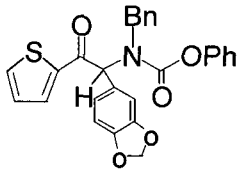
HRMS. Calculated for $C_{30}H_{28}NO_3^+$: 450.2069 found: 450.2063



(1-Benzo[1,3]dioxol-5-yl-2-oxo-2-thiophen-2-yl-ethyl)-benzyl-carbamic acid phenyl ester (entry 2, 3.1b) Yield: 72% ^{1}H NMR (400MHz, $CDCl_3$, 60 °C) δ 7.6 (s, br, 1H), 7.56-7.55 (d, 1H), 7.32-7.25 (q, 2H), 7.20-7.12 (m, 4H), 7.04-6.99 (m, 4H), 6.82-6.8 (m, 2H), 6.69-6.67 (d, 1H), 6.64 (s, br, 1H), 5.91-5.87 (d, 2H), 5.02-4.98 (d, 1H), 4.48-4.44 (1H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 188.3, 151.6, 148.5, 148.4, 142.3, 138.9, 133.9, 133.0, 129.3, 128.2, 128.1, 127.5, 127.3, 126.8, 125.5, 124.7, 121.7, 110.9, 108.7, 101.5, 66.6, 49.5.

IR (KBr): ν_{CO}: 1704 cm^{-1}, 1694 cm^{-1}

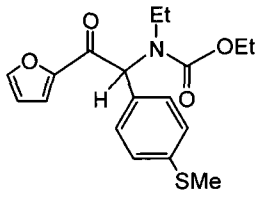
HRMS. Calculated for $C_{27}H_{22}NO_5S^+$: 472.1114 found: 472.1113



Ethyl-[2-furan-2-yl-1-(4-methylsulfanyl-phenyl)-2-oxo-ethyl]-carbamic acid ethyl ester (entry 3, 3.1c) Yield: 80% ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.40 (s, 1H), 7.24-7.22 (d, 2H), 7.16-7.14 (d, 2H), 6.5 (s, br, 1H), 6.36-6.34 (m, 1H), 6.2-6.1 (d, 1H), 4.21-4.16 (q, 2H), 3.38-3.35 (m, 1H), 3.26-3.19 (m, 1H), 2.46 (s, 3H), 1.28-1.23 (m, 3H), 0.85-0.79 (m, 3H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 172.3, 153.2, 142.3, 138.1, 135.7, 128.4, 127.07, 125.5, 110.5, 109.6, 61.5, 57.2, 40.1, 30.8, 16.1, 14.7.

IR (KBr): ν_{CO}: 1702 cm^{-1}, 1691 cm^{-1}

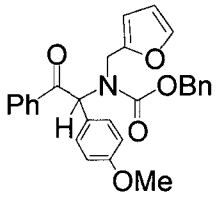
HRMS. Calculated for $C_{18}H_{22}NO_4S^+$: 348.1245 found: 348.1233



Furan-2-ylmethyl-[1-(4-methoxy-phenyl)-2-oxo-2-phenyl-ethyl]-carbamic acid benzyl ester (entry 4, 3.1d) Yield: 85% ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.85 (s, broad, 2H), 7.47-7.43 (t, 1H), 7.34-7.30 (t, 4H), 7.2 (s, broad, 4H), 7.19-7.15 (t, 3H), 6.82-6.80 (d, 2H), 6.14 (t, 1H), 5.7 (s, broad, 1H), 5.22-5.13 (q, 2H), 4.81-4.77 (d, 1H), 4.31-4.27 (d, 1H), 3.7 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 190.1, 160.2, 152.4, 141.2, 136.1, 133.0, 131.8, 128.8, 128.6, 128.5, 128.1, 128.05, 128.0, 126.1, 114.6, 110.5, 110.3, 107.2, 67.8, 65.2, 55.4, 42.3.

IR (KBr): ν_{CO}: 1704 cm^{-1}, 1695 cm^{-1}

HRMS. Calculated for $C_{28}H_{26}NO_5^+$: 456.2562 found: 456.2561

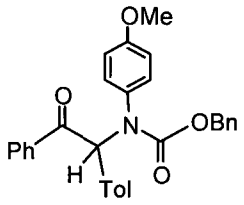


(4-Methoxy-phenyl)-(2-oxo-2-phenyl-1-*p*-tolyl-ethyl)-carbamic acid benzyl ester (entry 5, 3.1e) Yield: 87% ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.93-7.91 (d, 2H), 7.43-7.41 (t, 1H), 7.34-7.30 (t, 2H), 7.28-7.22 (m, 3H), 7.18-7.16 (m, 2H), 7.10-7.08 (d, 2H), 6.98-6.92 (q, 4H), 6.90 (br, 1H), 6.67-6.64 (d, 2H), 5.16-5.12 (d, 2H), 3.69 (s, 3H), 2.2 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 196.9, 158.6, 138.3,

137.0, 136.2, 132.9, 131.9, 130.9, 129.5, 129.3, 129.1, 128.9, 128.6, 128.4, 128.3, 127.8, 127.4, 113.6, 68.1, 67.5, 55.4, 21.1.

IR (KBr): ν_{CO}: 1703 cm^{-1}, 1691 cm^{-1}

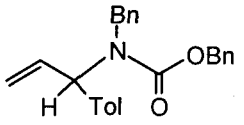
HRMS. Calculated for $C_{30}H_{28}NO_4^+$: 466.2013 found: 466.2012



Benzyl-(1-*p*-tolyl-allyl)-carbamic acid benzyl ester (entry 6) Yield: 65% ^1H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.36-7.30 (m, 4H), 7.28-7.22 (m, 4H), 7.18-7.11 (m, 4H), 7.07-7.02 (m, 2H), 6.19 (m, 1H), 5.82 (d, br, 1H), 5.34-5.25 (m, 2H), 4.68-4.64 (d, 1H), 4.55-4.51 (d, 1H), 2.36 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 155.7, 138.8, 137.5, 136.4, 135.8, 135.2, 130.5, 129.8, 129.5, 129.4, 128.1, 127.9, 127.8, 127.2, 118.4, 67.5, 63.4, 49.6, 21.1.

IR (KBr): ν_{CO}: 1699 cm^{-1}

HRMS. Calculated for $C_{25}H_{26}NO_2^+$: 372.1942 found: 372.1937

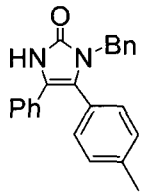


Spectroscopic Data of Imidazolones in Table 3.2

1-benzyl-4-phenyl-5-*p*-tolyl-1,3-dihydroimidazol-2-one (3.5a) Yield: 86% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.24 (s, 1H), 7.26 (s, 2H), 7.21-7.17 (m, 5H), 7.15-7.13 (m, 3H), 7.08-7.04 (m, 4H), 4.77 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 154.3, 138.8, 137.7, 130.9, 129.7, 129.5, 128.5, 128.3, 127.4, 127.1, 126.6, 126.4, 125.4, 121.9, 118.3, 44.7, 21.4.

IR (KBr): ν_{NH}: 3435 cm^{-1}, ν_{CO}: 1684 cm^{-1}

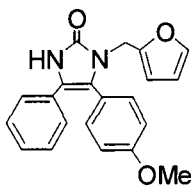
HRMS. Calculated for $C_{23}H_{21}N_2O^+$: 341.1648 found: 341.1648



1-furan-2-ylmethyl-5-(4-methoxyphenyl)-4-phenyl-1,3-dihydro-imidazol-2-one (3.5b) Yield: 82% ^{1}H NMR (400MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.27 (d, 1H), 7.26 (s, 1H), 7.22-7.21 (d, 1H), 7.20-7.18 (d, 4H), 7.16-7.13 (m, 1H), 6.94-6.92 (dd, 2H), 6.23 (d, 1H), 6.0 (d, 1H), 4.71 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 176, 160.0, 150.4, 141.9, 132.4, 129.6, 128.5, 126.7, 125.4, 121.3, 120.7, 118.3, 114.3, 110.3, 107.9, 55.2, 38.0.

IR (KBr): ν_{NH}: 3371 cm^{-1}, ν_{CO}: 1686 cm^{-1}

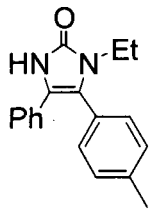
HRMS. Calculated for $C_{21}H_{19}N_2O_3^+$: 347.1212 found: 347.1212



1-ethyl-4-phenyl-5-*p*-tolyl-1,3-dihydro-imidazol-2-one (3.5c) Yield: 85% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.85 (s, 1H), 7.26-7.25 (m, 4H), 7.22 (d, 2H), 7.20-7.18 (d, 2H), 7.13-7.12 (t, 1H), 3.66-3.61 (q, 2H), 2.42 (s, 3H), 1.12-1.09 (t, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 154.0, 138.8, 130.7, 129.9, 129.8, 128.4, 126.9, 126.4, 125.4, 120.8, 118.2, 36.1, 21.4, 14.9.

IR (KBr): ν_{NH}: 3443 cm^{-1}, ν_{CO}: 1688 cm^{-1}

HRMS. Calculated for $C_{18}H_{19}N_2O^+$: 279.1492 found: 279.1491.

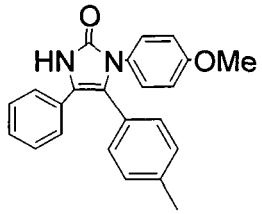


1-(4-methoxy-phenyl)-4-phenyl-5-*p*-tolyl-1,3-dihydro-imidazol-2-one (3.5d)

Yield: 84% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.0 (s, 1H), 7.27-7.24 (t, 3H), 7.22-7.17 (m, 2H), 7.07-7.05 (d, 2H), 7.02-6.96 (q, 4H), 6.81-6.79 (d, 2H), 3.77 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 158.5, 154.0, 137.9, 130.4, 129.6, 129.2, 128.9, 128.6, 127.7, 127.1, 126.3, 126.2, 121.4, 118.7, 114.0, 55.3, 21.3.

IR (KBr): ν_{NH}: 3353 cm^{-1}, ν_{CO}: 1692 cm^{-1}

HRMS. Calculated for $C_{23}H_{21}N_2O_2^+$: 357.1596 found: 357.1597

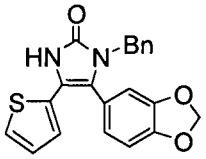


5-Benzo[1,3]dioxol-5-yl-1-benzyl-4-thiophen-2-yl-1,3-dihydro-imidazol-2-one

(3.5e) Yield: 60% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.4 (s, 1H), 7.26-7.24 (d, 3H), 7.10-7.05 (m, 4H), 6.93-6.91 (t, 1H), 6.86-6.84 (d, 1H), 6.73-6.72 (d, 1H), 6.64 (s, 1H), 6.04 (s, 2H), 4.6 (s, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 154.6, 149.5, 148.5, 136.2, 131.9, 129.5, 128.8, 128.1, 127.8, 127.4, 125.5, 124.9, 124.2, 121.9, 119.4, 110.9, 109.2, 101.9, 46.05.

IR (KBr): ν_{NH}: 3383 cm^{-1}, ν_{CO}: 1695 cm^{-1}

HRMS. Calculated for $C_{21}H_{17}N_2O_3S^+$: 377.0953 found: 377.0957

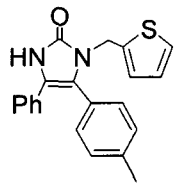


4-phenyl-1-thiophen-2-ylmethyl-5-*p*-tolyl-1,3-dihydro-imidazol-2-one (3.5f)

Yield: 80% ^{1}H NMR (400MHz, $CDCl_3$): δ 11.2 (s, 1H), 7.29-7.26 (t, 2H), 7.24-7.18 (m, 6H), 7.15-7.12 (t, 2H), 6.84-6.82 (t, 1H), 6.73-6.72 (d, 1H), 4.9 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 154.3, 139.9, 138.9, 131.1, 129.76, 129.73, 128.4, 126.6, 126.49, 126.43, 125.6, 125.2, 120.5, 118.8, 39.5, 21.4.

IR (KBr): ν_{NH}: 3350 cm^{-1}, ν_{CO}: 1696 cm^{-1}

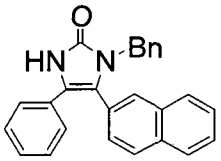
HRMS. Calculated for $C_{21}H_{19}N_2OS^+$: 347.1215 found: 347.1215



1-benzyl-5-naphthalen-2yl-4-phenyl-1,3-dihydro-imidazol-2-one (3.5g) Yield: 85% ^{1}H NMR (400MHz, $CDCl_3$): δ 11.2 (s, 1H), 7.88-7.86 (d, 1H), 7.82-7.80 (d, 1H), 7.70-7.66 (t, 2H), 7.55-7.50 (m, 2H), 7.27-7.24 (m, 3H), 7.21-7.19 (m, 3H), 7.17-7.11 (m, 3H), 7.11-7.07 (m, 2H), 4.85 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ 154.8, 137.8, 133.2, 133.1, 130.7, 130.6, 129.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.5, 127.2, 127.0, 126.8, 126.4, 125.6, 120.9, 119.1, 44.9.

IR (KBr): ν_{NH}: 3365 cm^{-1}, ν_{CO}: 1691 cm^{-1}

HRMS. Calculated for $C_{26}H_{21}N_2O^+$: 377.1647 found: 377.1648

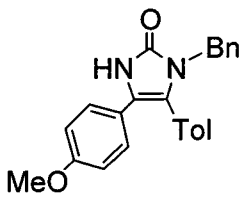


1-Benzyl-4-(4-methoxy-phenyl)-5-p-tolyl-1,3-dihydro-imidazol-2-one (3.5h)

Yield: 72% ^{1}H NMR (400MHz, $CDCl_3$): δ 9.3 (s, 1H), 7.79 (d, 1H), 7.22-7.20 (d, 2H), 7.1-7.09 (m, 3H), 7.07-7.01 (m, 3H), 6.95-6.93 (d, 2H), 6.74-6.71 (d, 2H), 4.75 (s, 2H), 3.74 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 162.9, 131.1, 129.9, 129.7, 129.5, 129.3, 128.8, 128.6, 128.5, 128.3, 127.4, 127.1, 125.6, 114.3, 114.02, 55.6, 44.9, 21.06.

IR (KBr): ν_{NH}: 3353 cm^{-1}, ν_{CO}: 1685 cm^{-1}

HRMS. Calculated for $C_{24}H_{23}N_2O_2^+$: 371.1724 found: 371.1726

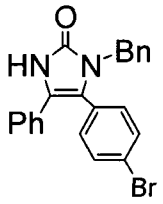


1-benzyl-5-(4-bromo-phenyl)-4-phenyl-1,3-dihydro-imidazol-2-one (3.5i)

Yield:80% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.9 (s, 1H), 7.47-7.45 (d, 2H), 7.22-7.15 (m, 7H), 7.08-7.06 (m, 2H), 7.03-7.01 (d, 2H), 4.7 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ 154.6, 137.5, 132.6, 132.1, 129.2, 128.68, 128.62, 128.4, 127.36, 127.32, 127.0, 125.6, 123.2, 119.6, 119.2, 44.8.

IR (KBr): ν_{NH}: 3371 cm^{-1}, ν_{CO}: 1693 cm^{-1}

HRMS. Calculated for $C_{22}H_{17}BrN_2ONa^{+}$: 427.0419 found: 427.0416

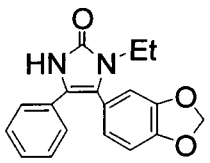


5-benzo[1,3]dioxol-5-yl-1-ethyl-4-phenyl-1,3-dihydro-imidazol-2-one (3.5j)

Yield: 85% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.6 (s, 1H), 7.26-7.22 (m, 4H), 7.16-7.12 (m, 1H), 6.87-6.81 (m, 3H), 6.05 (s, 2H), 3.6 (q, 2H), 1.12 (t, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 153.9, 148.19, 148.1, 129.7, 128.5, 126.5, 125.4, 124.9, 123.2, 120.2, 118.4, 111.0, 108.9, 101.4, 36.0, 14.9.

IR (KBr): ν_{NH}: 3447 cm^{-1}, ν_{CO}: 1689 cm^{-1}

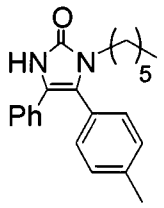
HRMS. Calculated for $C_{18}H_{17}N_2O_3^{+}$: 309.1237 found: 309.1233



1-hexyl-4-phenyl-5-*p*-tolyl-1,3-dihydro-imidazol-2-one (3.5k) Yield: 86% ^{1}H NMR (400MHz, $CDCl_3$): δ 10.9 (s, 1H), 7.24-7.21 (m, 7H), 7.19-7.17 (m, 1H), 7.13-7.11 (m, 1H), 3.5 (q, 2H), 2.4 (s, 3H), 1.4 (s, broad, 2H), 1.1 (s, broad, 6H), 0.80 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 158.2, 138.7, 130.8, 129.9, 129.7, 128.4, 126.9, 126.4, 125.4, 121.0, 118.2, 41.1, 31.1, 29.2, 26.1, 22.3, 21.4, 13.9.

IR (KBr): ν_{NH}: 3335 cm^{-1}, ν_{CO}: 1676 cm^{-1}

HRMS. Calculated for $C_{22}H_{27}N_2O^+$: 335.2121 found: 335.2117



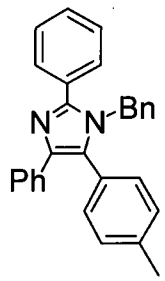
Synthesis of 1-Benzyl-2,4-diphenyl-5-*p*-tolyl-1*H*-imidazole (3.6)[19]

1-Benzyl-4-phenyl-5-*p*-tolyl-1,3-dihydro-imidazol-2-one (**3.5a**) (100 mg, 0.294 mmol) was dissolved in 30 mL of toluene in a round-bottom flask. To this solution was added phosphorus oxybromide (127 mg, 0.441 mmol) and the mixture was refluxed for 10 h under nitrogen and the progress of the reaction was monitored by TLC. After the reaction was completed, the yellow solution was washed with sodium hydrogen carbonate (50 mL) and further extracted with methylene chloride (3 × 50mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed and yellow oil was redissolved in dry toluene (5 mL) and transferred into a Schlenk tube under nitrogen. Pd_2dba_3•$CHCl_3$ (12.6 mg,

0.012 mmol), phenyl boronic acid (146 mg, 1.2 mmol), and Cs_2CO_3 (391 mg, 1.2 mmol) were added and the mixture was heated at 110 °C for 5 h. The mixture was then quenched with sodium hydrogen carbonate and extracted with methylene chloride (3 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The final product was purified by silica gel chromatography using hexane:ethyl acetate.

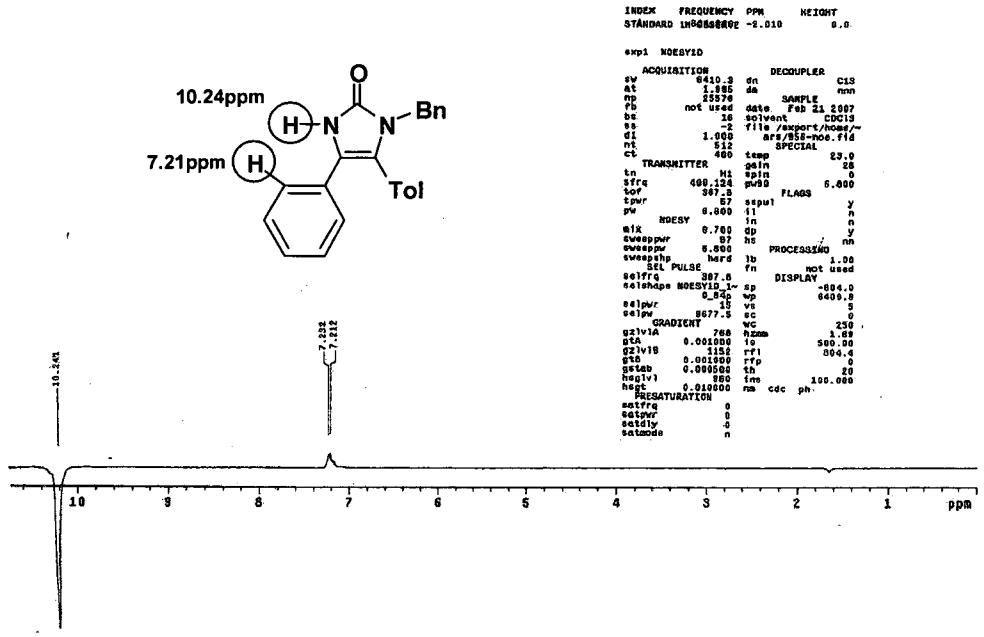
Yield: 72% ^{1}H NMR (400MHz, $CDCl_3$): δ 7.68-7.63 (m, 4H), 7.39-7.38 (m, 3H), 7.24-7.19 (m, 5H), 7.16(s, 5H), 6.85-6.83(d, 2H), 5.11 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 148.1, 138.7, 138.1, 137.9, 134.8, 131.2, 131.1, 130.4, 129.8, 129.29, 129.08, 128.8, 128.3, 128.1, 127.5, 127.0, 126.6, 126.5, 126.2, 48.4, 21.6.

HRMS. Calculated for $C_{29}H_{25}N_2^+$: 401.2015 found: 401.2012

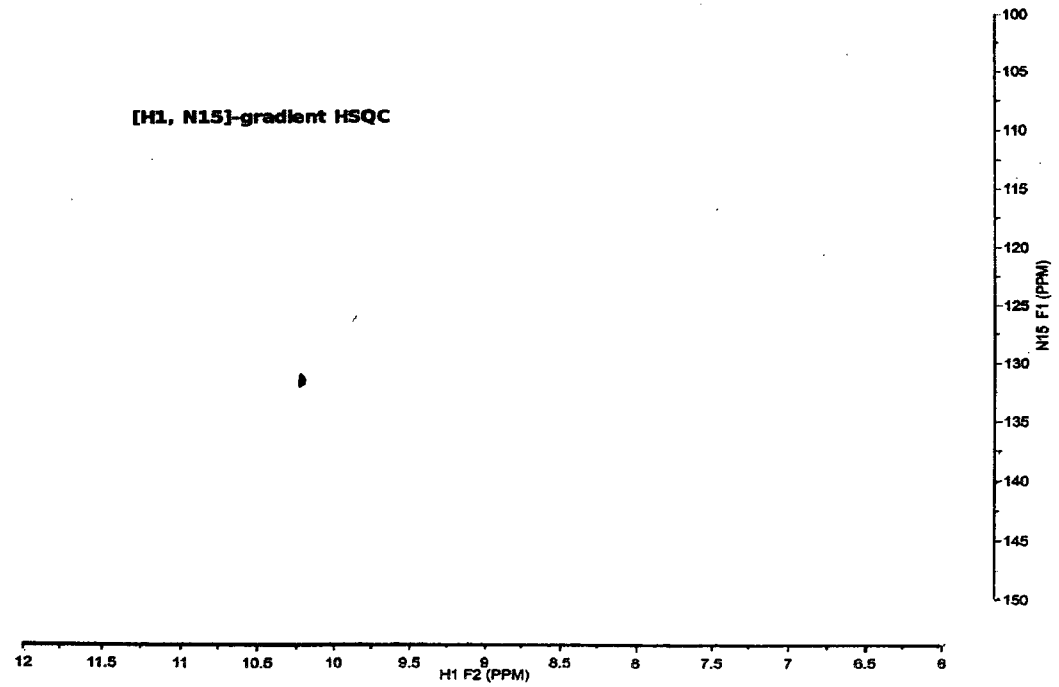


Structural Characterization of Imidazol-2-one (3.5a)

NOESY Experiment ($CDCl_3$): Irradiation of the signal at 10.24 ppm resulted in NOE effect at 7.21ppm, confirming the following structure.



HSQC Experiment ($CDCl_3$): HSQC Experiment was performed on a 500 MHz NMR Spectrometer. Only one cross peak was observed at 10.24 ppm ^{1}H and 132 ppm ^{15}N, corresponding to N-H coupling.



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4. For example: Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946**, *68*, 2350.
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14. The structure of **3.5a** was distinguished from its 1*H*-imidazol-2-ol tautomer by means of NOE, and HSQC NMR experiments, as well as IR spectral data, see supporting information for details.

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CHAPTER FOUR

Metal Catalyzed Multicomponent Polymerization: Design of a Basic Building Block Approach to π-Conjugated Oligomers and Polymers

Preface

π-Conjugated polymers have emerged over the past several decades as key materials for a range of applications, including n- and p-type semiconductors, molecular wires, sensors, light switchable transistors, and OLEDs. The construction of all but the simplest of these polymers often involves a multistep synthesis. This can limit both their accessibility to tune their properties, as well as the ultimate use of these materials on the scale often demanded for synthetic polymers. Described herein is an alternative approach to access complex and tunable π-conjugated imidazole containing polymers in a fashion similar to high demand polymers: by considering these structures to arise from simple, available monomers coupled together all at once by metal catalysis. This is based upon the palladium catalyzed synthesis of imidazoles from imines and acid chlorides described in Chapter 2.

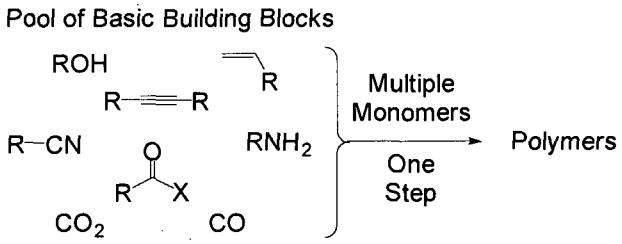
4.0 Introduction

A central tenet of polymer synthesis involves the ability to convert basic building blocks directly into useful materials. While a wide variety of interesting and potentially useful polymers that have been discovered (*e.g.* biopolymers such as proteins or DNA,[1] highly substituted materials,[2] etc.), their synthesis via traditional methods can be sufficiently involved to limit their accessibility, especially in the scale on which many polymers are desired. A prime example is in the field of π-conjugated polymers. The development of poly(heterocycles) (*e.g.* polypyrroles,[3] polythiophenes,[4] and others[5]) and their copolymers has sparked a renaissance in how scientists have considered constructing a host of formally metal-based devices, including conductors,[6] semi-conductors,[7] transistors,[8] components of optical devices (e.g. OLEDs),[9] and sensors.[10] These materials provide an intriguing combination of the processibility of polymers, the extended conjugation of metallic materials, and the tunability of organic structures. This tunability has elicited a significant body of research into generating new variants of these materials, since changes to polymer substituents, and alternating conjugated units, can influence the electronic features of the monomer unit, conjugation length, HOMO/LUMO gap, and chain/chain interactions.[11] While this diversity of properties is impressive, the preparation of all but the simplest conjugated polymers usually requires a multistep synthesis, whereby the appropriately substituted heterocycle is first generated. These are coupled typically via either electropolymerization[11a, 12] (for simple units), or by cross coupling chemistry[13] with the appropriately halogenated and metallated heterocycle. This introduces a significant number of steps to a hopefully scalable polymerization,

and also makes it difficult to modify their structure to modulate and discover new properties. Indeed, the synthesis of new variants of these polymers is often a research topic in itself.

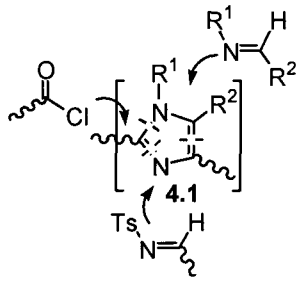
In principle, a more attractive approach to complex polymers such as substituted conjugated materials would be to assemble their structure in a fashion similar to high demand polymers: directly from simple, readily available building blocks. In this regard, transition metal catalysis can play a potentially useful role. The reactivity of metal complexes has become a valuable tool in polymer synthesis, by providing methods to convert available substrates into polymers. Prime examples of these include Ziegler-Natta polyolefin syntheses,[14] and the ring-opening metathesis polymerization of cyclic alkenes,[15] as well as more recent processes, such as the palladium catalyzed olefin/CO copolymerization,[16] and zinc catalyzed copolymerization of epoxide/CO_2.[17] Despite these and other significant advances, when one considers the types of building blocks that might be attractive precursors to polymers (*e.g.*, alkenes, alkynes, diamines, dialcohols, etc.), a wide variety of other materials might be considered. This would be especially true if one could assemble *multiple differing versions* of these units together to form a new and well-defined polymer structure (Figure 4.1). The challenge, however, is how to accomplish this in an efficient and selective fashion.

Figure 4.1: A One Step, Metal Catalyzed Synthesis of New Polymers.



We describe below the development of what is to our knowledge a novel method to construct conjugated materials, by considering their structure to be the product of multiple readily available building blocks, rather than as a series of linked heterocycles (Figure 4.2). This approach employs the reactivity of metal catalysts in two roles: to activate simple monomers towards reaction, and at the same time control how a number of these units come together at once (*i.e.* a metal catalyzed multicomponent polymerization). While this multicomponent approach has become of growing relevance in small molecule synthesis and library development,[18] it is significantly underexplored in the realm of polymer synthesis, a field for which it is arguably at least as relevant.[19] Overall, this provides access to new conjugated oligomers and polymers in one-pot reactions, and from monomers that are each easily generated and diversified, creating a unique platform to easily access and tune polymer properties.

Figure 4.2: A Basic Building Block Approach to Imidazole-Based Conjugated Polymers.



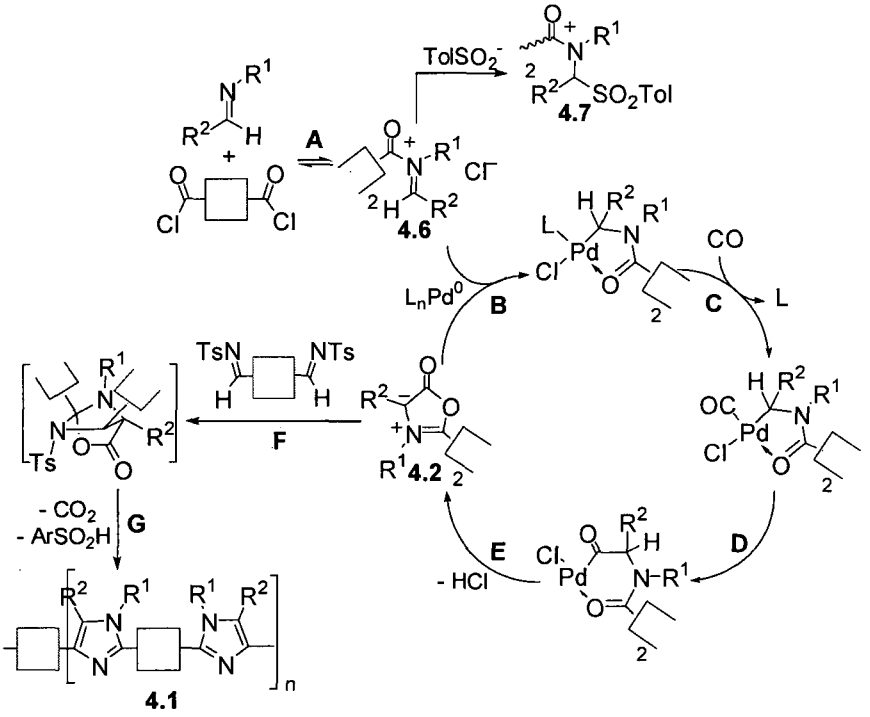
4.1 Results and Discussion

4.1.1 Method Development

Our approach to this synthesis is illustrated in Figure 4.2, and considers the structure of polymers to arise from simple diacid chloride and imine monomers. These building blocks are derivatives of those currently employed as polymerization monomers (e.g. dialdehydes, diamines, or diacids), or available from inexpensive substrates (simple aldehydes and amines). Transition metal catalysis can provide a potential pathway to mediate the selective coupling of these units, as illustrated in Scheme 4.1. This mechanism is based on the palladium catalyzed synthesis of small molecule heterocycles derived from mesoionic 1,3-oxazolium-5-oxides, commonly referred to as Münchnones **4.2** from imines, acid chlorides and CO (steps A-E).[20] By coupling this synthesis with the established ability of **4.2** to undergo 1, 3-dipolar cycloaddition with imines (step F), and subsequent aromatization (step G),[21] this would provide overall a route to selectively synthesize **4.1** directly from the three monomers in a single, palladium catalyzed operation.

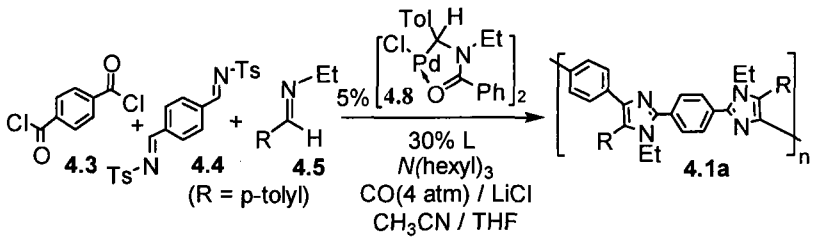
This palladium catalyzed reaction was first probed with commercial terephthaloyl dichloride **4.3**, imine **4.4** generated from terephthaldehyde and sulfonamide,[22] and the *p*-tolualdehyde-based **4.5**. As shown in Table 4.1, this does result in the formation of π-conjugated polymer **4.1a**, albeit in very low yield (25%). This illustrates a challenge the design of these transformations, where in this case four separate reagents, base and a catalyst are all required to selectively proceed through over eight separate (and sequential) steps. Examination of the reaction mixture shows a major product of the reaction is the iminium salt intermediate **4.6**

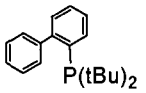
Scheme 4.1: Potential Palladium Catalyzed Mechanism for Polymerization.



implying that the oxidative addition of this substrate to palladium (Step B in the mechanism) may be a slow step in catalysis. Tuning of the palladium catalyst to facilitate this step by removing the dba ligand (entry 2), and adding bulky donor ligands (entries 3-4) can increase polymerization yields to 48%. In addition to polymer **4.1a**, α-sulfonylamide **4.7** is also observed as a byproduct, resulting from the reaction of $TolSO_2^-$ with the *in situ* generated iminium salt **4.6**. While our previous approaches have shown that the formation of **4.7** can be suppressed by the addition of LiCl,[21] the latter has little influence on this transformation (entry 5), perhaps due to the increased electrophilicity of the diiminium salt intermediate. However, by first generating **4.2**, then adding component, **4.4**, the formation of **4.7** is inhibited, allowing the generation of polymer **4.1a** in high isolated yield (entry 6).

Table 4.1: A Palladium Catalyzed, One Step Route to Imidazole-Based Polymers.[a]



Entry	Cat.	Ligand	Additive	Isolated Yield
1	Pd_2dba_3•$CHCl_3$	Bu_4NBr	-	25%
2	**4.8**	PPh_3	-	-
3	**4.8**	$P(oTol)_3$	-	48%
4[b]	**4.8**	$P(oTol)_3$	-	50%
5	**4.8**	$P(oTol)_3$	LiCl	51%
6[c]	**4.8**	$P(oTol)_3$	-	72%[d]
7[c]	**4.8**		-	70%

a. **4.3** (50 mg, 0.246 mmol), **4.4** (118 mg, 0.246mmol), **4.5** (72 mg, 0.492 mmol), 5 % of Pd catalyst, *N*(hexyl)$_3$ (199 mg, 0.738 mmol) and 30% of **L**, heated at 45°C for 16h. [b] 20 atm CO. [c] (85 mg, 0.177 mmol) of **4.4** added after carbonylation. Ts= $SO_2(p\text{-}C_6H_4Me)$ [d] M_n = 2.6×10^3, $M_w = 3.1 \times 10^3$, Polydispersity = 1.16.

The reaction in Table 4.1 represents what is to our knowledge the first example of the formation of these conjugated polymers from such available building blocks. Notably, while this product is referred to as a polymer, its molecular weight is low ($M_n = 2.6 \times 10^3$), suggesting it is best considered an oligomer, with approximately six repeating units. Imidazole-containing conjugated materials have attracted attention as intense blue-emitting materials with high quantum efficiency (*e.g.* for OLEDs) with potentially interesting conducting, fluorescence, non-linear optical and coordinative properties.[23] In contrast to previous approaches employing cross coupling chemistry of the parent heterocycle,[13a, 23a] this palladium catalyzed

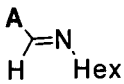
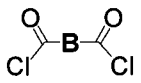
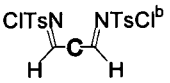
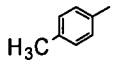
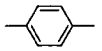
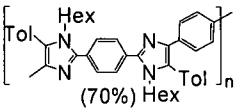
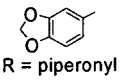
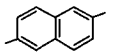
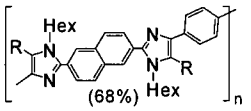
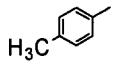
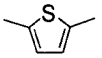
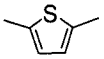
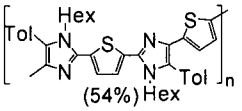
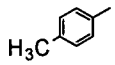
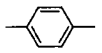
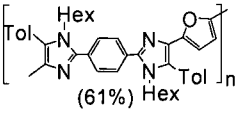
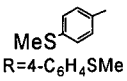
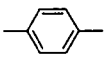
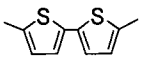
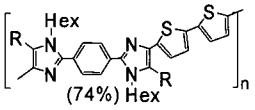
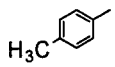
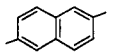
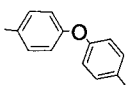
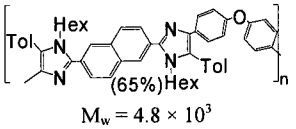
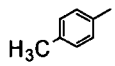
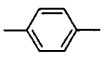
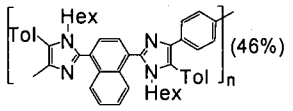
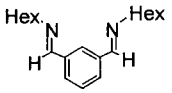
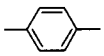
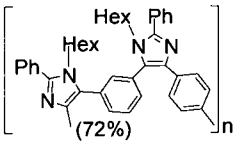
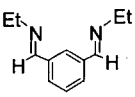
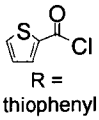
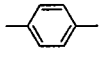
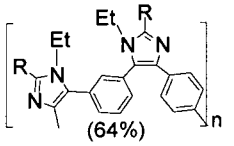
approach generates these materials directly from building blocks derived from accessible sources (imines, terephthalates, amides, CO).

4.1.2 Structural Diversity

A useful feature of this approach is its amenability to diversification. Since each of the building blocks employed in this synthesis can be modulated, this same synthetic approach can be used to access a range of synthetic products. This provides the potential to easily incorporate a range of desired substituents into these polymers (e.g. solubilizing groups, chromophores, sensors, etc.). For example, a series of imines can be incorporated into the reaction from available aldehydes and amines (Table 4.2). This includes the use of longer chain *N*-alkyl-substituted imines (**4.1b**), as well as those derived from variously substituted aromatic aldehydes. Similarly, the spacers between the imidazole units can be readily modified from the imine and acid chloride building blocks employed. This can allow significant changes to the connectivity between aromatic rings. The latter can include the use of heterocyclic units in the imine or acid chloride fragments (**4.1d, e**), or even using different combinations within a single polymer (**4.1f-h**).

Alternatively, changes in the actual backbone connectivity can also be readily accessed. For example, instead of using diacid chlorides, a combination of two different diimines leads to the generation of a novel class of 3,4-substituted polymers (**4.1i, j**). As far as we are aware, these materials have not been previously reported, likely due to the complexity of their synthesis via more classic routes.

Table 4.2: Diversity of Materials via Multicomponent Assembly.[a]

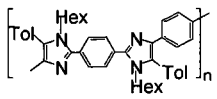
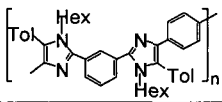
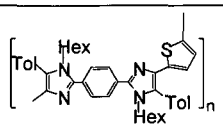
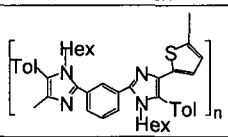
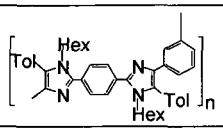
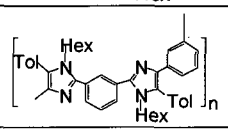
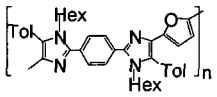
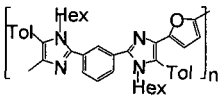
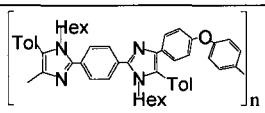
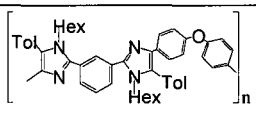
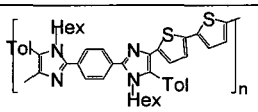
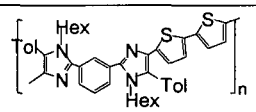
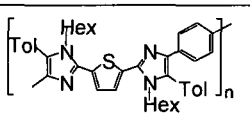
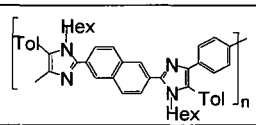
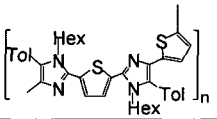
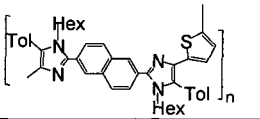
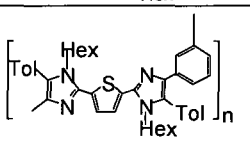
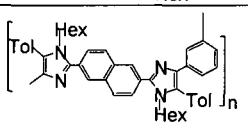
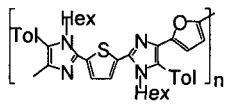
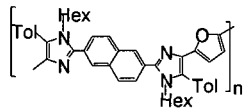
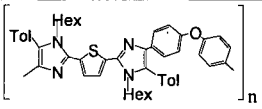
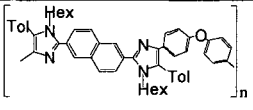
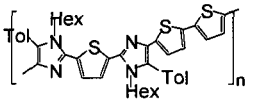
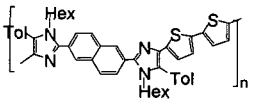
cpd				Polymer 4.1 (yield)[c]
b				 (70%) $M_w = 5.4 \times 10^3$
c	 R = piperonyl			 (68%) $M_w = 5.2 \times 10^3$
d				 (54%) $M_w = 5.5 \times 10^3$
e				 (61%) $M_w = 4.5 \times 10^3$
f	 R=4-C_6H_4SMe			 (74%) $M_w = 4.4 \times 10^3$
g				 (65%) $M_w = 4.8 \times 10^3$
h				 (46%) $M_w = 4.7 \times 10^3$
i	 Hex = -$(CH_2)_5CH_3$			 (72%) $M_w = 4.8 \times 10^3$
j		 R = thiophenyl		 (64%) $M_w = 4.5 \times 10^3$

a. Acid chloride (0.246 mmol), imine (0.493 mmol), $[Pd(\eta^2\text{- }C(H)TolNEtCOPh)Cl]_2$ **4.8** (9.6 mg, 0.123 mmol), $P(oTol)_3$ (22.6 mg, 0.074 mmol), N(hexyl)$_3$ (199 mg, 0.74mmol) in THF:CH_3CN (1:1, 20 mL) at 45 °C, 20h. *N*-tosylimine (80% relative to concentration of **4.2**) and *N*(hexyl)$_3$ (94 mg, 0.35mmol) added. 45°C, 20h. b. TsCl= $SO_2(p\text{-}C_6H_4Cl)$. c. Isolated.

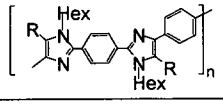
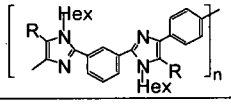
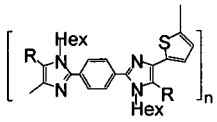
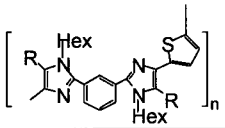
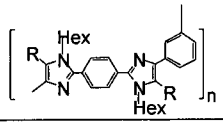
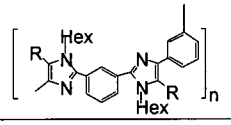
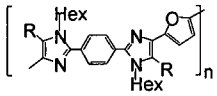
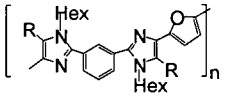
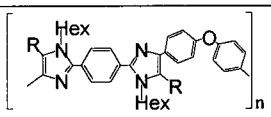
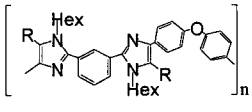
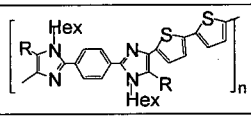
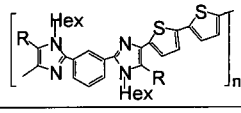
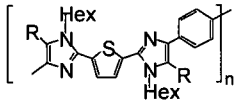
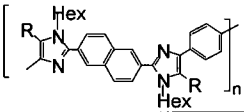
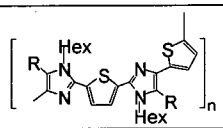
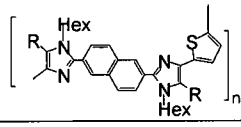
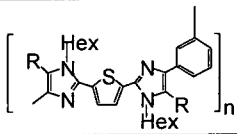
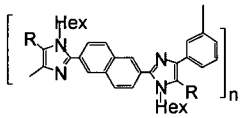
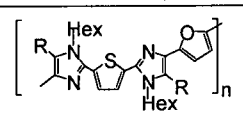
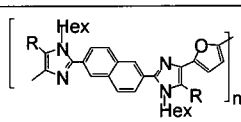
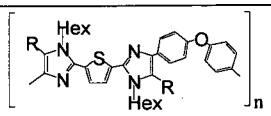
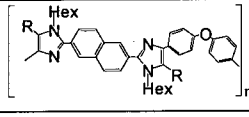
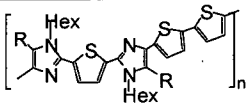
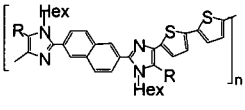
4.1.3 Development of a *Polymer* Library

From a product discovery standpoint, this amenability to diversity can be an important research tool. As an illustration of this feature, a simple pool of three imines, four diacids and six diimines has been used to create a novel library of 72 different conjugated imidazole containing polymers, each formed via this one step, palladium catalyzed reaction (Table 4.3). As mentioned above, modulating substituents on conjugated polymers can have a significant influence on their conjugation. This is illustrated in the UV/vis absorbance and fluorescence data of these materials, which can be systematically varied by over 150 nm by modulating the monomer units (Figure 4.3). The latter can provide an important level of structural control for the design of devices, where fine tuning polymer band gap is often required. For example, this has allowed the identification of the terpoly(imidazole-thiophene-4-phenylene) as a moderately low band gap material with intense blue fluoresence, which compares favorably to classic ladder-type poly(*p*-phenylene)s (LPPPs),[24] yet is soluble and can be modulated by changes in spacer, substituents and core connectivity. In general, these classes of donor-acceptor aromatic polymers have attracted significant interest as conjugated materials with tunable HOMO/LUMO gap.[25]

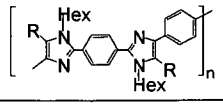
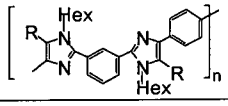
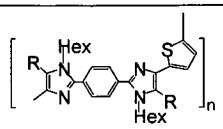
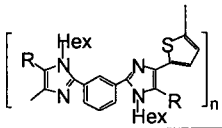
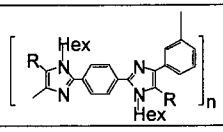
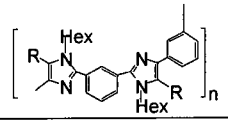
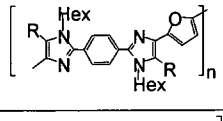
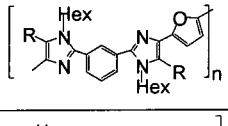
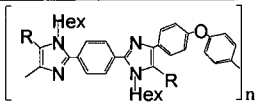
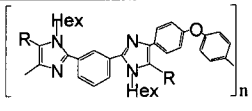
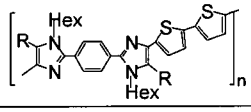
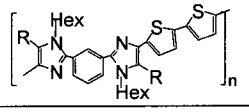
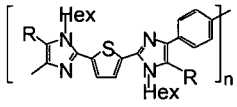
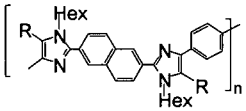
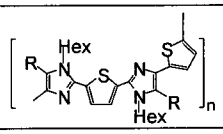
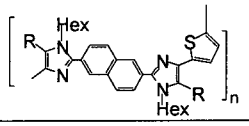
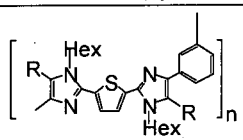
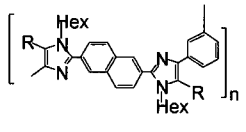
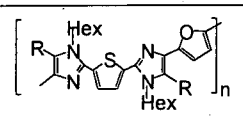
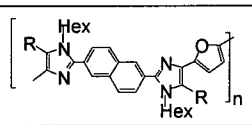
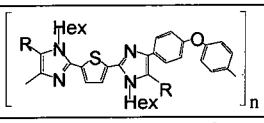
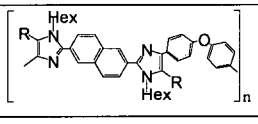
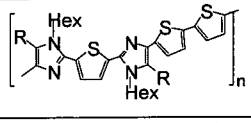
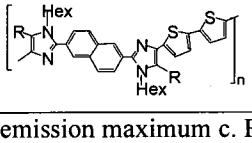
Table 4.3: UV-vis and Fluorescence Data of the Polymer Library

Polymers[c]	λ_{max}[a] (nm)	Fluorescence (nm)[b]		Polymers[c]	λ_{max}[a] (nm)	Fluorescence (nm)[b]	
		Exc.	Emis			Exc.	Emis
	324	363	465		336	354	461
	408	420	515		365	376	462
	286	335	430		290	328	420
	402	412	502		373	400	496
	290	337	452		286	334	417
	398	419	524		404	420	524
	365	366	461		336	363	464
	414	420	532		410	421	522
	343	367	456		323	362	454
	406	412	518		406	418	507
	353	369	459		312	360	461
	394	412	503		412	421	526

a. UV-vis maximum absorbance b. Fluorescence excitation/emission maximum c. Tol = 4-C_6H_4Me

Polymers[c]	λ_{max}[a] (nm)	Fluorescence (nm)[b]		Polymers[c]	λ_{max}[a] (nm)	Fluorescence (nm)[b]	
		Exc.	Emis			Exc.	Emis
	316	359	473		317	359	476
	361	382	476		361	380	474
	292	339	448		281	333	437
	412	400	517		351	367	457
	284	346	456		284	329	411
	404	420	528		400	420	526
	347	365	473		333	362	479
	367	377	474		369	380	476
	349	371	464		316	354	464
	347	373	467		357	369	457
	343	371	465		280	358	463
	381	420	530		394	420	530

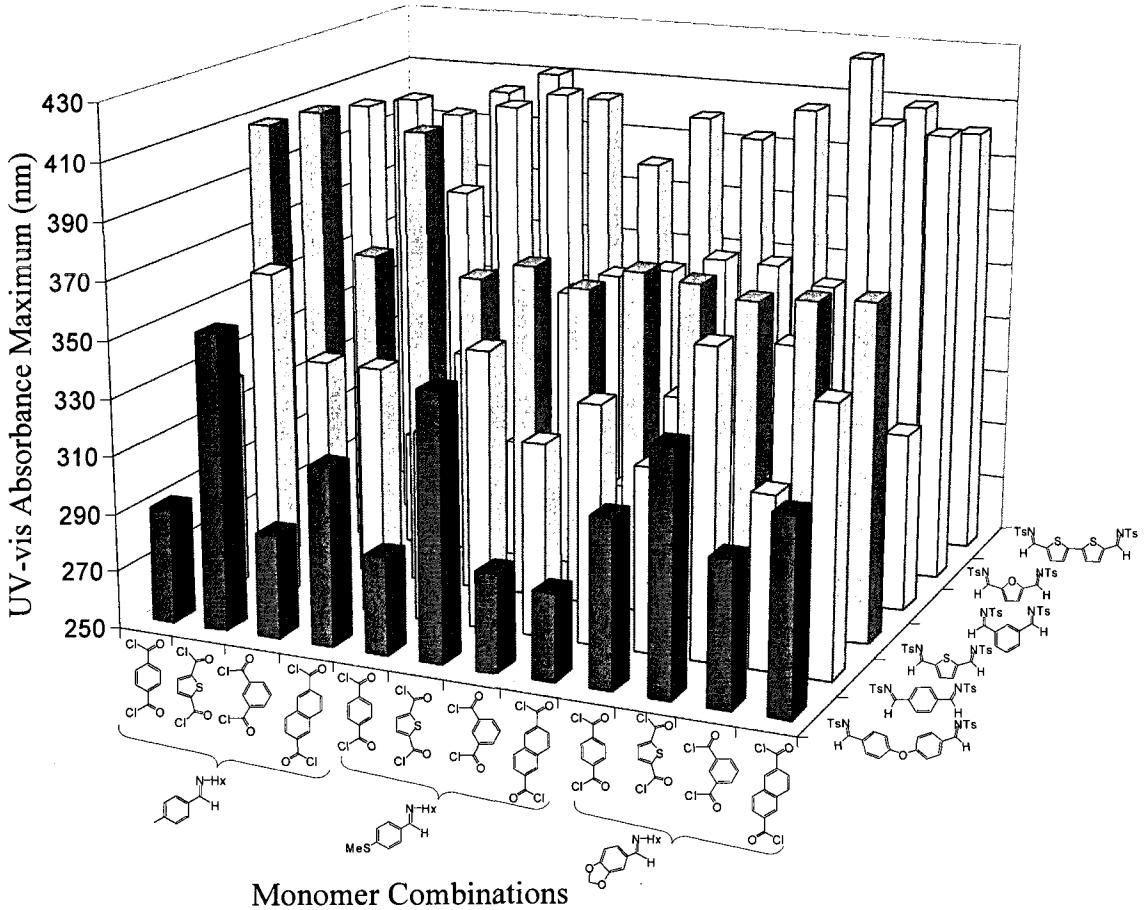
a. UV-vis maximum absorbance b. Fluorescence excitation/emission maximum c. R = piperonyl 

Polymers[c]	λ_{max}[a] (nm)	Fluorescence (nm)[b]		Polymers[c]	λ_{max}[a] (nm)	Fluorescence (nm)[b]	
		Exc.	Emis			Exc.	Emis
	314	363	477		310	357	476
	367	381	475		365	381	475
	306	343	445		302	323	415
	357	361	457		410	412	515
	308	342	450		300	329	415
	406	420	526		410	421	527
	357	368	474		343	362	478
	363	381	479		367	381	479
	339	374	466		312	354	461
	351	376	469		408	412	519
	334	367	463		317	356	461
	426	420	523		402	420	529

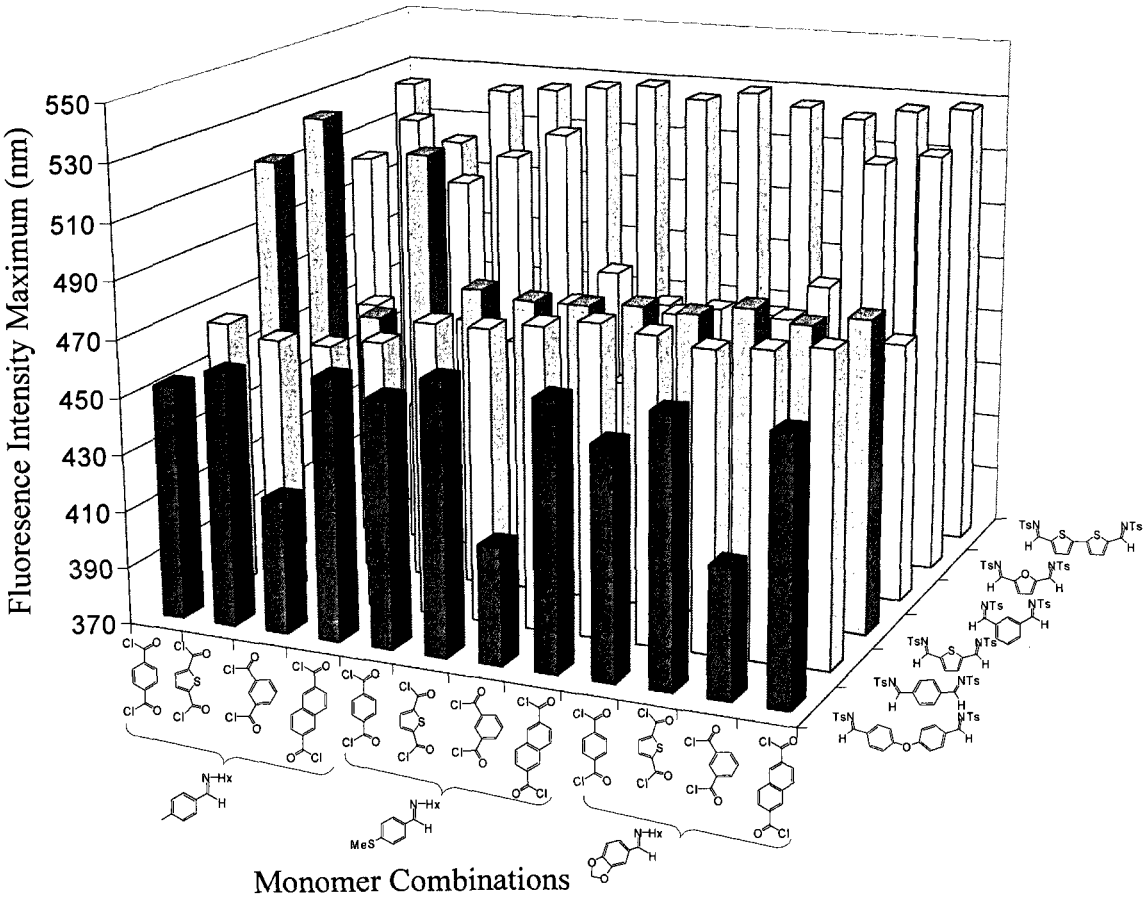
a. UV-vis maximum absorbance b. Fluorescence excitation/emission maximum c. R = 4-C_6H_4SMe

Figure 4.3: Library of Conjugated Polymers. a) Plot of UV/vis absorbance maximum (nm) vs. structure. b) Fluorescence maximum (nm) vs. structure.

a)



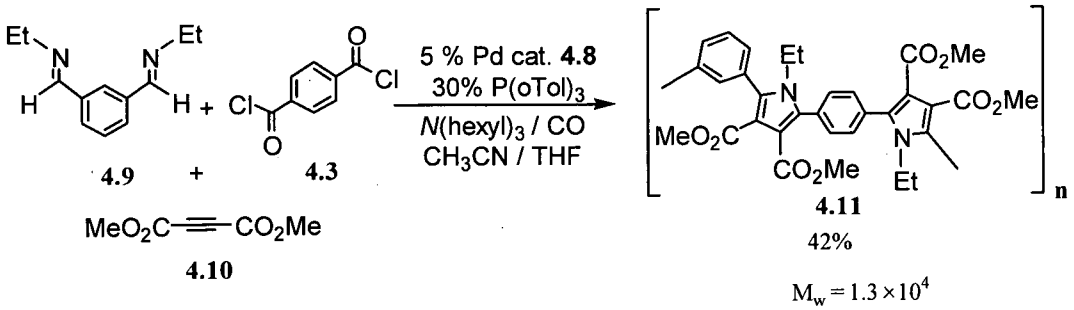
b)


Fluoresence Intensity Maximum (nm)
550
530
510
490
470
450
430
410
390
370
Monomer Combinations

4.2 Conclusions

In conclusion, we have described to our knowledge a novel approach to synthesize new conjugated materials in a modular fashion: by the metal catalyzed coupling of multiple basic building blocks. In light of the often involved multistep syntheses of the substituted conjugated polymers by classical methods, and the importance of these compounds in materials science, this provides a useful method to efficiently design new variants of these polymers. From a building block perspective, this approach can employ monomers of similar complexity to those used in bulk, commodity polymer production (*e.g.* diimines instead of diamines, diacid chlorides instead of diacids). By coupling these with other simple substrates (*e.g.* aldehydes, amines), this can provide a potentially powerful platform to generate new materials, and do so in a fashion similar to metal catalyzed polymerizations demonstrated to be of high current utility. Considering the diversity of metal based reactions and processes available, this metal catalyzed, basic building block approach can in principle be applied to a range of other polymers derived from monomers such as those in Figure 4.1. An illustration of this is in Scheme 4.2, where in this case conjugated pyrrole polymers **4.11** can be assembled, directly from simple alkynes **4.10**, diimines **4.9**, and acid chlorides **4.3**, with HCl and CO_2 as the only byproducts. In principle, this multicomponent coupling of basic monomer units holds the potential to be equally applicable to coupling alternative combinations of monomers into new classes of polymers. Studies directed towards this goal, as well as exploiting this approach to incorporate further levels of complexity and function into the present conjugated polymers, are currently underway.

Scheme 4.2: One-Pot, Multicomponent Synthesis of Conjugated Pyrrole-Based Polymers.



4.9 + **4.3**

$MeO_2C{\equiv}CO_2Me$

4.10

4.11

42%

$M_w = 1.3 \times 10^4$

4.3 Experimental Section

General Procedures

Unless otherwise noted, all reactions were carried out under an inert atmosphere in a dry box or using standard Schlenk or vacuum line techniques. Palladium catalyst **4.8** was prepared according to previously reported procedure, by pretreating $Pd_2dba_3 \cdot CHCl_3$ with imine and acid chloride.[17] $Pd_2dba_3 \cdot CHCl_3$ was prepared according to literature procedures.[27] Imine[26] **4.5a-h** were prepared according to the literature procedures. Di-*N*-tosylimines **4.4a-g** were prepared in analogy to literature procedures, as described below.[22] Carbon monoxide (99.99%) was purchased from Matheson and used as received. All other reagents were used as received from commercial suppliers.

Acetonitrile was freshly purified by distillation over CaH_2 under nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Deuterated solvents were dried as their protio analogous, and transferred under vacuum and stored over 3 and 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on Mercury 400 MHz and Unity 500 MHz Varian NMR spectrometers. The degree of polymerization and polydispersity were measured by Gel Permeation Chromatography (GPC) in THF using a Water 510 liquid chromatography pump, equipped with two (HR1 and HR2) Styragel columns and a refractive index detector (Varian RI-4). Polystyrene standards (Scientific Polymer Products, Inc., NY) with a narrow molecular weight distribution were used for calibration. UV-vis spectra were recorded on a Varian Cary 50 spectrophotometer, between 190-850 nm wavelength in CH_2Cl_2. Fluorescence excitation/emission

spectra were acquired using a Jobin Yvon-Spex FluoroMax 2 Spectrofluorometer with a 150 W continuous ozone-free lamp in CH_2Cl_2. MALDI-TOF-MS analysis was performed on a Kratos Kompact MALDI-III-TOF bench top model instrument which generates a maximum laser beam at a wavelength of 337 nm (N2 laser light, 3 ns pulse width. The average of 100 laser shots was represented in the mass spectra. The polymer sample (5 mg/mL) was dissolved in chloroform and dithranol-LiBr in THF solution was added as matrix in a 1:2 volume ratio. A spot of the sample was placed on the sample slide and the solvent was allowed to evaporate slowly before being put into the vacuum chamber of the mass spectrometer. High Resolution Mass Spectral analyses were obtained from the McGill University Mass Spectral Facility.

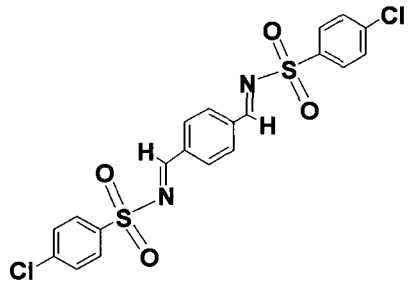
Synthesis of Starting Materials

Procedures for the Synthesis of 1,4-*N*-Benzylidene-bis(4-chloro-benzenesulfonamide) (4.4a):

Terephthalaldehyde (2.00 g, 14.9 mmol) was added to 120 mL of toluene in 250 mL round-bottom flask. To this solution was added 4-chlorobenzenesulfonamide (5.71 g, 29.8 mmol), *p*-toluenesulfonic acid (2.85 g, 14.9 mmol) and 3 Å of molecular sieves. A Dean-Stark trap was placed on the top of the condenser and the mixture was refluxed for 24 h. The reaction mixture was filtered while hot and the white solid collected was washed with Et_2O (100 mL) and MeOH (100 mL). This material was dried under vacuum, yielded 87% of a pale grey solid (6.2 g). The product can be further dried by dissolving the solid in THF (20 mL) and stirring over of 4 Å molecular sieves under an inert atmosphere.

^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 9.09 (s, 2H), 8.04 (s, 4H), 7.96-7.94 (d, 4H), 7.56-7.54 (d, 4H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 169, 140.9, 137.6, 136.6, 131.6, 129.8, 129.7.

HRMS. Calculated for $C_{20}H_{15}Cl_2N_2O_4S_2^+$: 480.9846 found: 480.9844

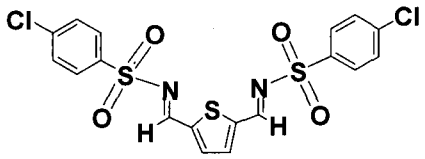


Procedures for the Synthesis of Other Di-Tosylimines:

The corresponding di-aldehyde (14.9 mmol) was added to 120 mL of toluene in a round-bottom flask. To this was added 4-chlorobenzenesulfonamide (5.71 g, 29.8 mmol), 10% by weight of Amberlyst 15 (ion-exchange resin strongly acidic), and 4Å of molecular sieves powder. A Dean-Stark trap was placed on the top of the condenser and the mixture was refluxed for 48 h. The reaction mixture was filtered while hot and white solid collected was washed with Et_2O (4 × 50 mL). The material was dried under vacuum to afford the final product. The product can be further dried by dissolving the solid in THF (20 mL) and stirring of 4 Å molecular sieves under an inert atmosphere.

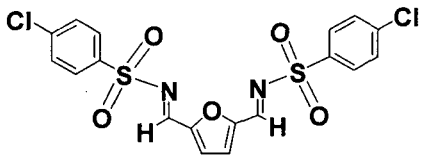
2,5-*N*-thiophen-2-ylmethylene-bis(4-chloro-benzenesulfonamide) (4.4d): Yield: 67%, a pale brown solid. ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 9.08 (s, 2H), 7.88-7.85 (d, 4H), 7.75 (s, 2H), 7.36-7.34 (d, 4H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 161.3, 145.9, 145.3, 137.5, 135.3, 138.1, 129.9.

HRMS. Calculated for $C_{18}H_{13}Cl_2N_2O_4S_3^+$: 486.9306 found: 486.9301



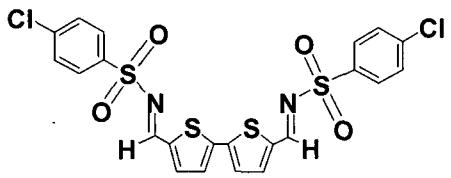
2,5-*N*-furan-2-ylmethylene-bis(4-chloro-benzenesulfonamide) (4.4e): Yield: 55%, Yellowish solid. ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 8.86 (s, 2H), 7.88-7.86 (d, 4H), 7.41-7.36 (d, 4H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 158.4, 153.5, 145.7, 135.2, 130.8, 128.6, 127.5.

HRMS. Calculated for $C_{18}H_{13}Cl_2N_2O_5S_2^+$: 470.9630 found: 470.9629



Bis(4-chloro-*N*-thiophen-2-ylmethylene-benzenesulfonamide) (4.4f): Yield: 55%, brownish solid. ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 9.05 (s, 2H), 7.86 (d, 4H), 7.65 (d, 2H), 7.39 (d, 4H), 7.38 (d, 2H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 161.7, 145.8, 144.9, 139.9, 138.9, 135.6, 130.1, 128.4, 127.5.

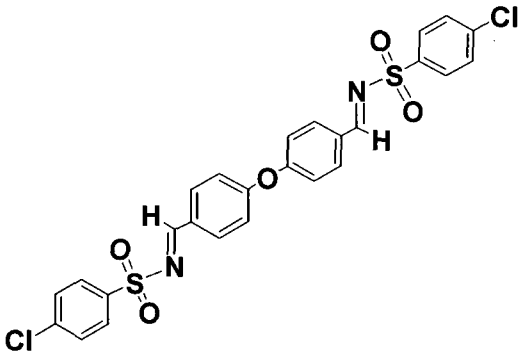
HRMS. Calculated for $C_{22}H_{14}Cl_2N_2O_4S_4Na^+$: 590.9299 found: 590.9296



***N*-(4-phenoxy-benzylidene)-bis(4-chloro-benzenesulfonamide) (4.4g):**

^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 8.9 (s, 2H), 7.97-7.96 (d, 4H), 7.89-7.87 (d, 4H), 7.36-7.35 (d, 4H), 7.12-7.10 (d, 4H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 168.4, 161.9, 142.6, 135.8, 134.2, 130.2, 128.4, 128.2, 119.8.

HRMS. Calculated for $C_{26}H_{19}Cl_2N_2O_5S_2^+$: 573.0345 found: 573.0348



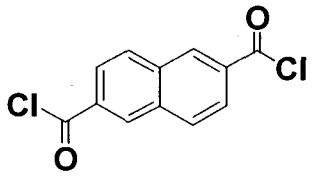
General Procedure for the Synthesis of Di-Acid Chlorides (4.3):

Dicarbonyl dichlorides **4.3** were prepared from the corresponding dicarboxylic acids. To a solution of dicarboxylic acid (9 mmol) in CH_3CN (100 mL) was added thionyl chloride (3.2 g, 27 mmol) and the mixture was refluxed for 3 h. The solvent

was then removed *in vacuo* and solid product repeatedly washed with Et_2O to afford the final product.

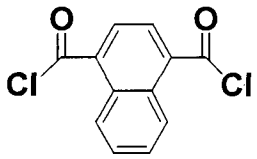
Naphthalene-2,6-dicarbonyl dichloride (4.3c): Yield: 78% ^1H NMR (400MHz, $CDCl_3$): δ 8.79 (s, 2H), 8.19-8.18 (d, 2H), 8.17-8.13 (d, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 168.2, 135.4, 133.9, 133.8, 131.0, 126.9.

HRMS. Calculated for $C_{12}H_6Cl_2O_2$: 251.9714 found: 251.9724



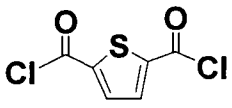
Naphthalene-1,4-dicarbonyl dichloride (4.3h): Yield: 65% ^1H NMR (400MHz, $CDCl_3$): δ 8.64 (s, 2H), 8.45 (s, 2H), 7.78 (s, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 167.5, 136.3, 130.8, 130.3, 130.05, 125.6.

HRMS. Calculated for $C_{12}H_6Cl_2O_2$: 251.9719 found: 251.9725



Thiophene-2,5-dicarbonyl dichloride (4.3d): Yield: 67% ^1H NMR (400MHz, $CDCl_3$): δ 7.9 (s, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 160.04, 145.7, 136.6.

HRMS. Calculated for $C_6H_2Cl_2O_2S$: 207.9232 found: 207.9238

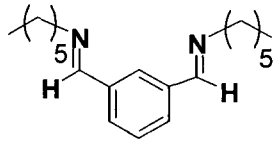


Representative Procedure for the Synthesis of Di-Imines (4.5i, j)

Di-imines **4.5i, j** were prepared from the corresponding di-aldehyde in analogy to literature procedure.[23] To a solution of isophatalaldehyde (1.00 g, 7.5 mmol) in 100 mL of Et_2O was added *N*-hexylamine (1.5 g, 15 mmol) and anhydrous $MgSO_4$ (21.6 g, 180 mmol). After stirring this mixture for 24 h at ambient temperature, it was filtered and the solvent was evaporated to give a yellow oil. The product was purified by vacuum distillation to afford 2.00 g of the final product as a pale yellow oil.

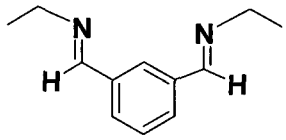
Hexyl-(3-hexyliminomethyl-benzylidene)-amine (4.5i):

Yield: 90% ^{1}H NMR (400MHz, $CDCl_3$): δ 8.29 (s, 2H), 8.04 (s, 1H), 7.8 (d, 2H), 7.41 (t, 1H), 3.6 (q, 4H), 1.65 (m, 4H), 1.38 (s, br, 12H), 0.92 (s, 6H). ^{13}C NMR (125MHz, $CDCl_3$): δ 160.04, 137.2, 130, 129.2, 128, 62.01, 31.01, 31.8, 27.5, 22.3, 16.1. HRMS. Calculated for $C_{20}H_{32}N_2$: 300.2662 found: 300.2664



Ethyl-(3-ethyliminomethyl-benzylidene)-amine (4.5j):

Yield: 87% ^{1}H NMR (400MHz, $CDCl_3$): δ 8.27 (s, 2H), 8.02 (s, 1H), 7.78 (d, 2H), 7.4 (t, 1H), 3.61 (q, 4H), 1.25 (t, 6H). ^{13}C NMR (125MHz, $CDCl_3$): δ 160, 137.1, 130, 129.2, 128, 56.1, 16.2. HRMS. Calculated for $C_{12}H_{16}N_2$: 188.1325 found: 188.1332



Typical Procedure for the Synthesis of π-Conjugated Imidazole-Containing Polymers:

Di-acidchloride **4.3** (0.246 mmol) and imine **4.5** (0.493 mmol) were dissolved in 12 mL of CH_3CN:THF (1:1) solution and stirred for 15 min in a 50 mL reaction bomb. To this was added palladium catalyst **4.8** (9.6 mg, 0.0123 mmol), P(*o*-tol)$_3$ (22.6 mg, 0.074 mmol) in 5 mL of THF, and *N*(hexyl)$_3$ (199 mg, 0.74 mmol) in 3 mL of THF. Benzylbenzoate was also added to this mixture as an internal standard. The entire mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) added. After heating to 45 °C for 16 h, the mixture was degassed, an aliquot of the crude deep red solution was analyzed by ^{1}H NMR, and the yield of **4.2** was determined by comparison to the internal standard. Based upon the yield of **4.2,** 0.8 equivalents of di-tosylimine **4.4** and *N*(hexyl)$_3$ (95 mg, 0.354 mmol) were added to the reaction bomb and the mixture was heated at 45 °C for 20 h under nitrogen. The dark yellow solution was then filtered over celite and solvent was removed *in vacuo*. The product was purified by adding CH_3CN (20 mL) and cooling the solution to -20 °C to form a yellow-red precipitate. The CH_3CN solution was then decanted and the precipitate was further washed with CH_3CN followed by cooling to -20 °C. This procedure was repeated several times until all impurities are removed and the final product was obtained as yellow to dark orange oil.

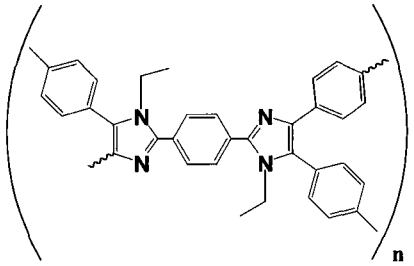
Characterization of Polyimidazoles (^{1}H, ^{13}C, UV-vis, Fluoresence, and GPC Data

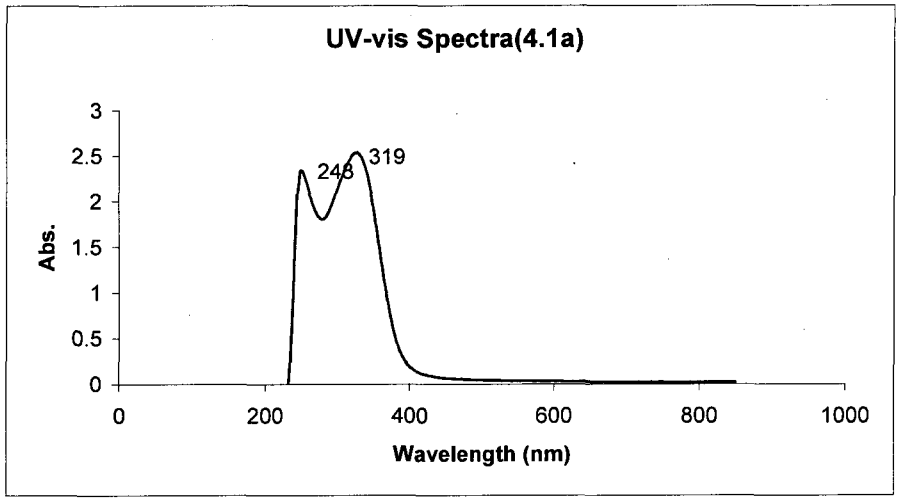
Poly[1-Ethyl-2,4-diphenyl-5-tolyl-1*H*-imidazole] (4.1a): Yellow solid, Isolated yield: 72% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 7.87-7.71 (d, 3H), 7.54-7.31 (m, 7H), 4.0 (s, br, 2H), 2.45 (s, 3H), 1.06 (s, br, 3H). ^{13}C NMR (125MHz, CD_2Cl_2, 60

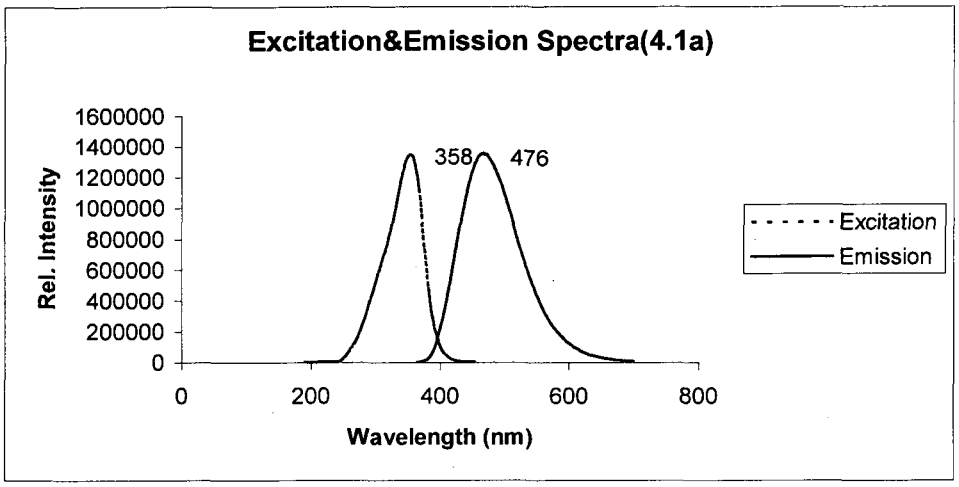
°C): δ 182, 146.2, 139.1, 137.8, 134.2, 133.1, 132.9, 131.1, 130.9, 130.2, 129.9, 129.7, 129.2, 126.7, 126.4, 39.9, 21.3, 16.2.

GPC Analysis:

M_n (Daltons): 2.68×10^3 M_w (Daltons): 3.11×10^3 Polydispersity: 1.16



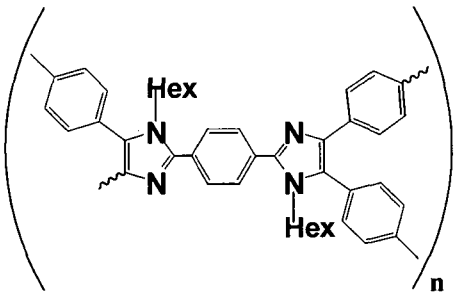




Poly[1-Hexyl-2,4-diphenyl-5-*p*-tolyl-1*H*-imidazole](4.1b): Yellow oil, Isolated yield: 70% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 7.93-7.85 (m, 2H), 7.80-7.74 (m, 2H), 7.41-7.34 (m, 6H), 3.96 (s, br, 2H), 2.47 (s, br, 3H), 1.41 (s, br, 2H), 1.16 (s, br, 4H), 0.77 (s, br, 5H). ^{13}C NMR (125MHz, CD_2Cl_2, 60 °C): δ 170.6, 140.1, 139.7, 137.9, 133.2, 131.6, 131.1, 130.8, 130.2, 129.9, 129.9, 129.5, 129.2, 126.6, 126.3, 45.09, 31.07, 30.5, 26.1, 22.7, 21.8, 13.8.

GPC Analysis:

M_n (Daltons): 4.37×10^3 M_w (Daltons): 5.41×10^3 Polydispersity: 1.24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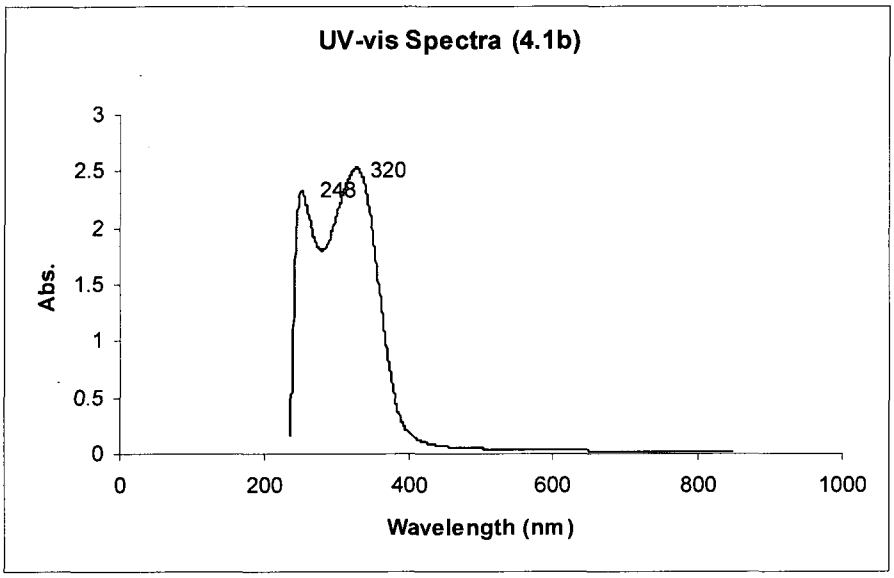
N
N
N
Hex
n


UV-vis Spectra (4.1b)
Abs.
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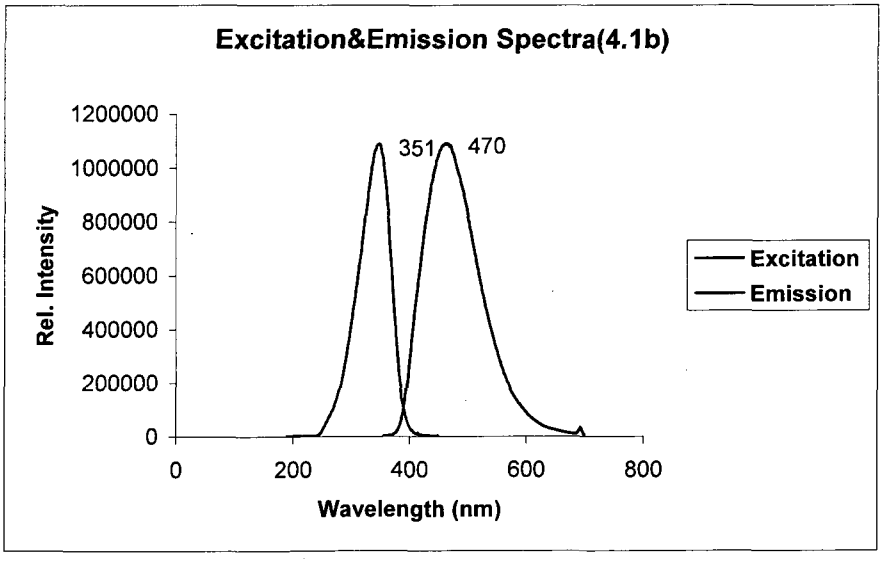
2
1.5
1
0.5
0
248
320
0
200
400
600
800
1000
Wavelength (nm)


Excitation&Emission Spectra(4.1b)
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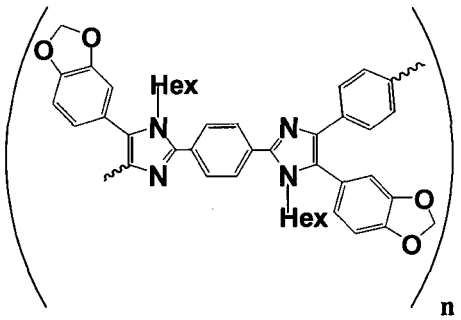
800000
600000
400000
200000
0
351
470
0
200
400
600
800
Wavelength (nm)
Excitation
Emission

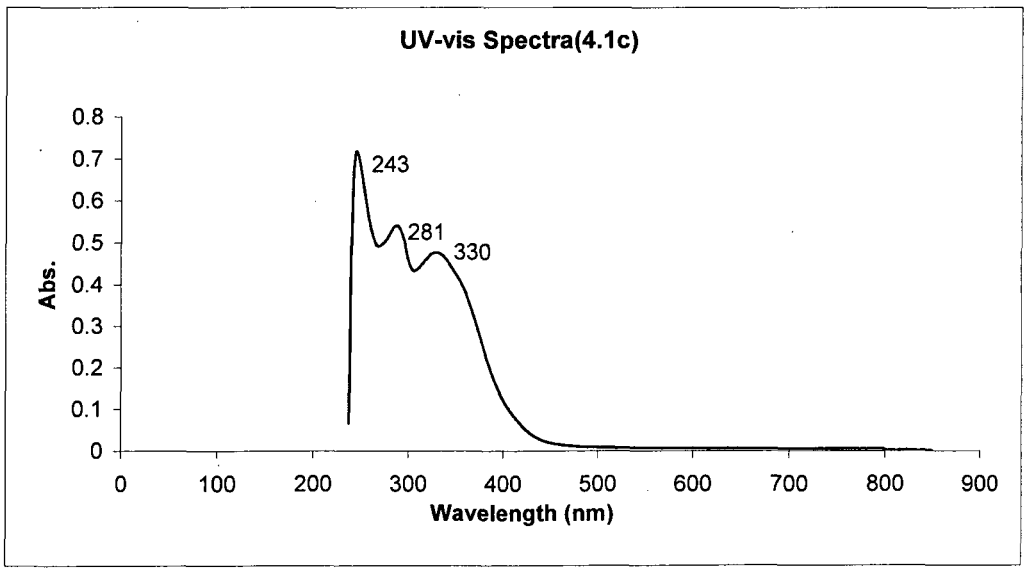
Poly[5-Benzo[1,3]dioxol-5-yl-1-hexyl-2,4-diphenyl-1*H*-imidazole](4.1c): Orange oil, Isolated yield: 68% ^{1}H NMR (400MHz, CD_2Cl_2): δ 8.21-7.71 (m, 4H), 7.51-7.42 (d, 1H), 7.04-6.82 (m, 2H), 6.19-6.04 (s, broad, 2H), 4.02 (s, br, 2H), 1.59 (s, br, 4H), 1.12 (s, br, 4H), 0.72 (s, br, 5H). ^{13}C NMR (125MHz, CD_2Cl_2): δ 192.1, 148.8, 148.5, 129.8, 129.6, 129.5, 129.2, 129.0, 128.9, 128.1, 127.9, 126.8, 126.7, 126.5, 111.4, 109.3, 102.06, 31.6, 31.06, 26.9, 26.1, 22.4, 13.8.

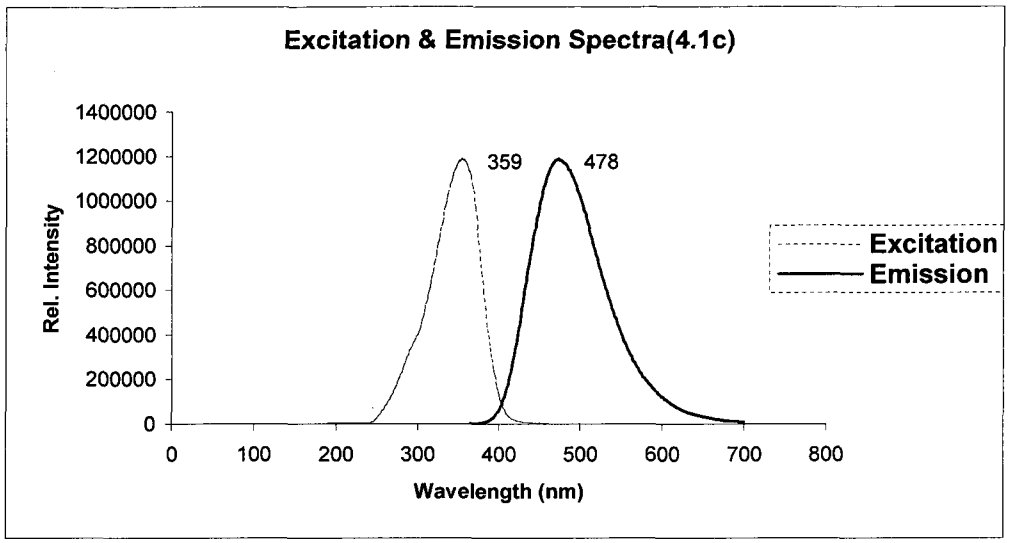
GPC Analysis:

M_n (Daltons): 4.43×10^3 M_w (Daltons): 5.15×10^3 Polydispersity Index: 1.16



UV-vis/Fluoresence Spectra:



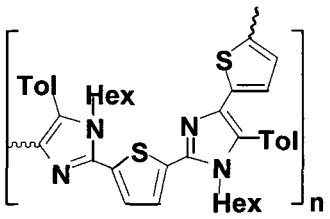


Poly[1-Hexyl-2,4-di-thiophen-2-yl-5-*p*-tolyl-1*H*-imidazole](4.1d)

Dark orange oil, Isolated yield: 54% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 7.33-7.26 (s, br, 8H), 3.95-3.2 (s, br, 2H), 2.49-2.35 (s, br, 3H), 1.6 (s, br, 2H), 1.24 (s, br, 4H), 0.86 (s, br, 5H). ^{13}C NMR (125MHz, CD_2Cl_2, 60 °C): δ 162.3, 144.3, 136.2, 135.4, 132.2, 131.2, 130.9, 130.4, 130.2, 130.1, 129.9, 128.8, 128.5, 126.8, 126.3, 124.2, 45.4, 31.9, 31.1, 27.3, 22.8, 22.6, 14.05.

GPC Analysis:

M_n (Daltons): 4.63×10^3 M_w (Daltons): 5.47×10^3 Polydispersity: 1.18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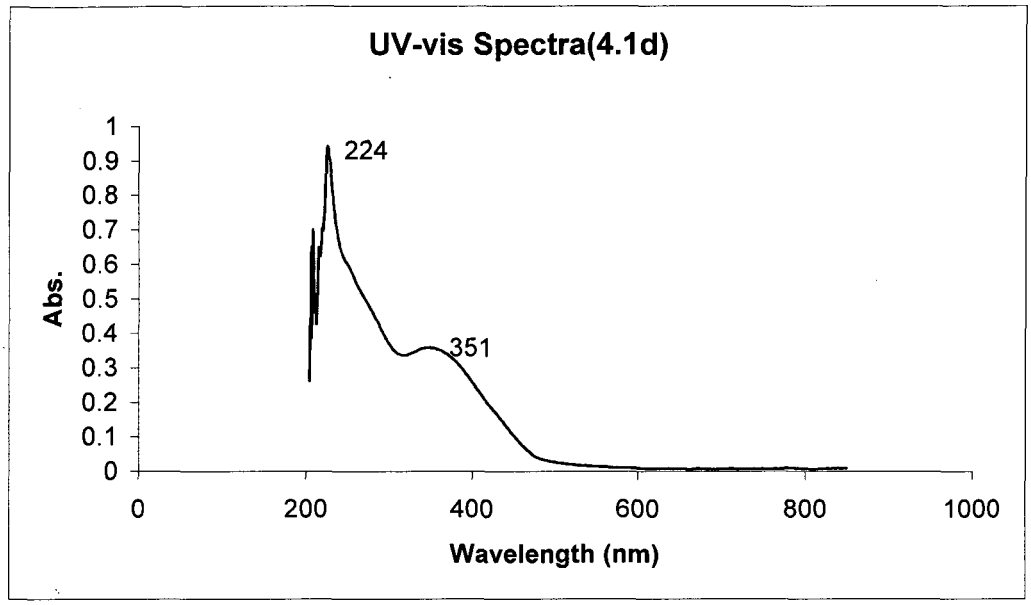
N
S
N
N
S
Tol
Hex
n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0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
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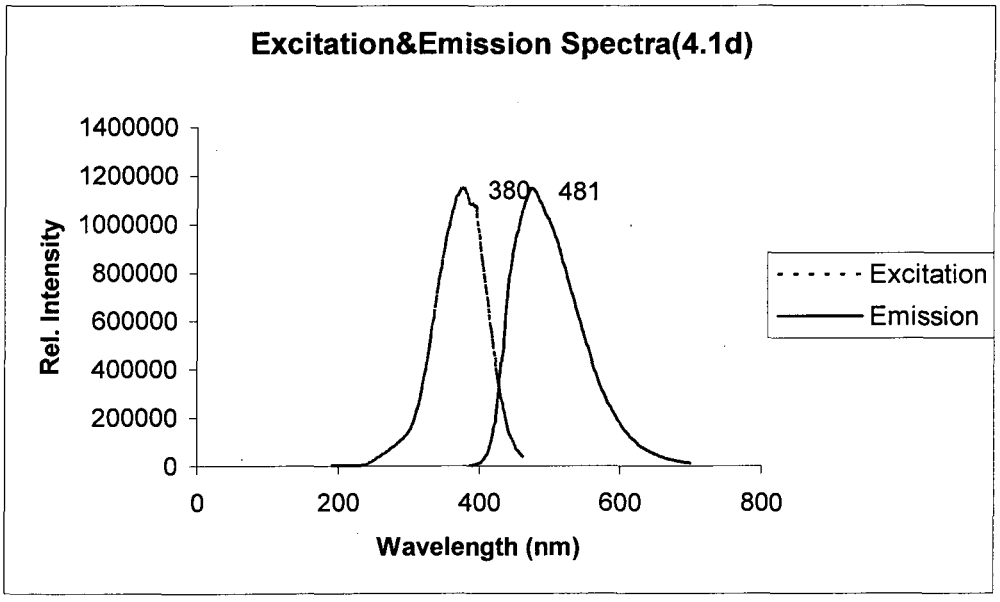
351
0
200
400
600
800
1000
Wavelength (nm)


Excitation&Emission Spectra(4.1d)
Rel. Intensity
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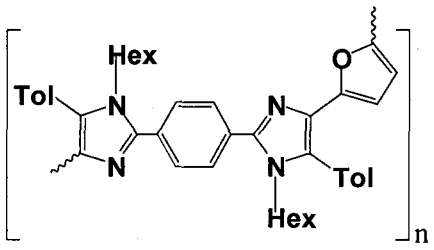
1000000
800000
600000
400000
200000
0
380
481
0
200
400
600
800
Wavelength (nm)
Excitation
Emission

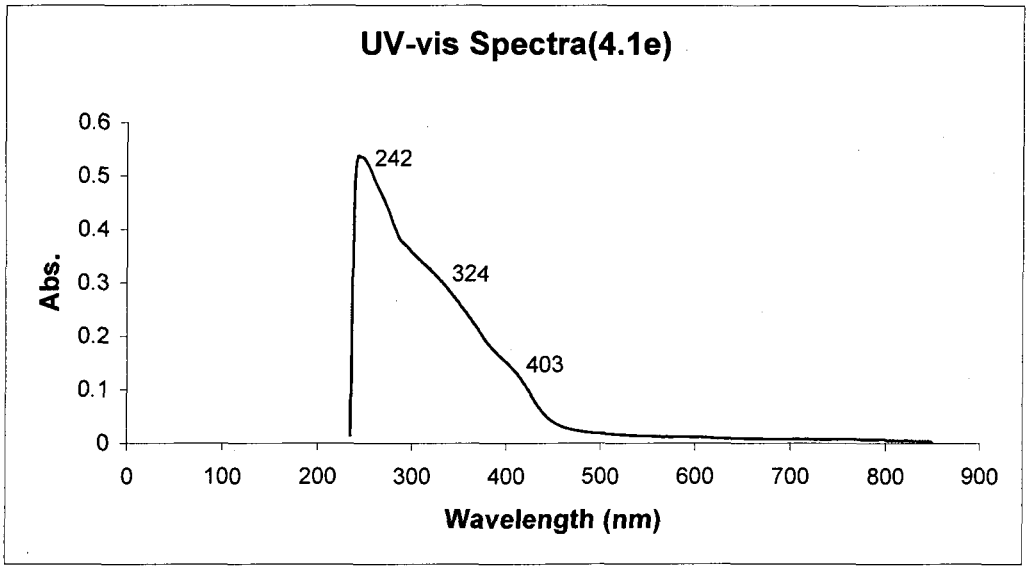
Poly[4-Furan-2-yl-1-hexyl-2-phenyl-5-*p*-tolyl-1*H*-imidazole](4.1e)

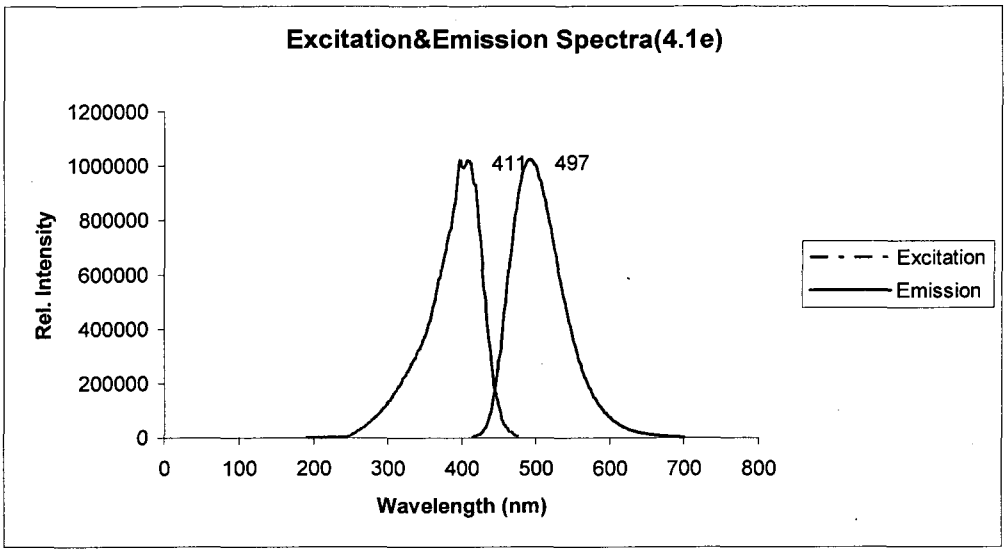
red oil, Isolated yield: 61% ^{1}H NMR (400MHz, CD_2Cl_2): δ 7.88-7.81 (m, 5H), 7.35-7.13 (m, 7H), 4.01 (s, br, 2H), 2.34 (s, br, 3H), 1.34 (s, br, 2H), 0.92 (m, br, 4H), 0.75 (m, br, 5H). ^{13}C NMR (125MHz, CD_2Cl_2): δ 164.3, 148.2, 140.02, 137.4, 133.5, 132.1, 130.9, 130.7, 130.5, 129.9, 129.7, 129.5, 128.6, 128.2, 127.5, 126.4, 106.5, 108.1, 45.8, 31.7, 31.4, 26.2, 23.8, 21.6, 14.2.

GPC Analysis:

M_n (Daltons): 3.93×10^3 M_w (Daltons): 4.45×10^3 Polydispersity: 1.13





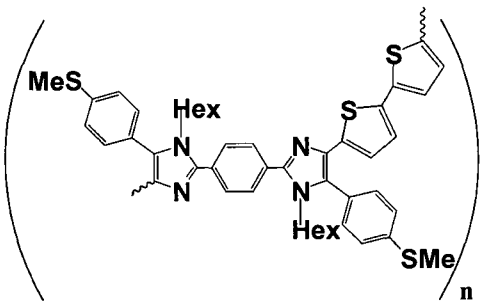


Poly[4-[2,2']Bithiophenyl-5-yl-1-hexyl-5-(4-methylsulfanyl-phenyl)-2-phenyl-1*H*-imidazole](4.1f)

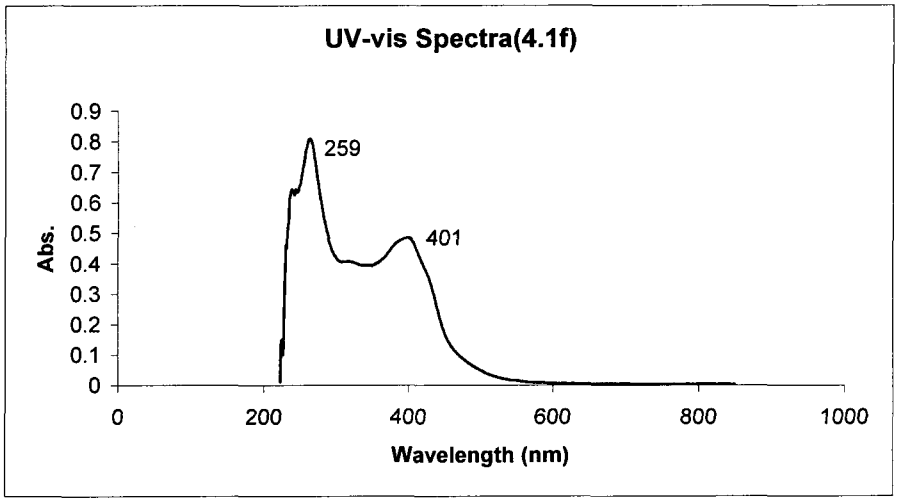
Dark orange oil, Isolated yield: 74% ^{1}H NMR (400MHz, CD_2Cl_2): δ 7.82-7.2 (m, br, 7H), 6.85-6.68 (d, 1H), 3.98 (s, br, 2H), 2.58 (s, 3H), 1.35 (s, br, 3H), 1.05 (s, br, 6H), 0.79 (s, br, 4H). ^{13}C NMR (125MHz, CD_2Cl_2): δ 162, 147.7, 141.6, 137.8, 135.8, 133.8, 131.6, 130.0, 129.7, 129.4, 129.2, 127.8, 127.2, 126.4, 126.2, 125.8, 124.5, 123.7, 123.2, 45.8, 31.09, 30.5, 26.1, 22.4, 13.9, 13.8.

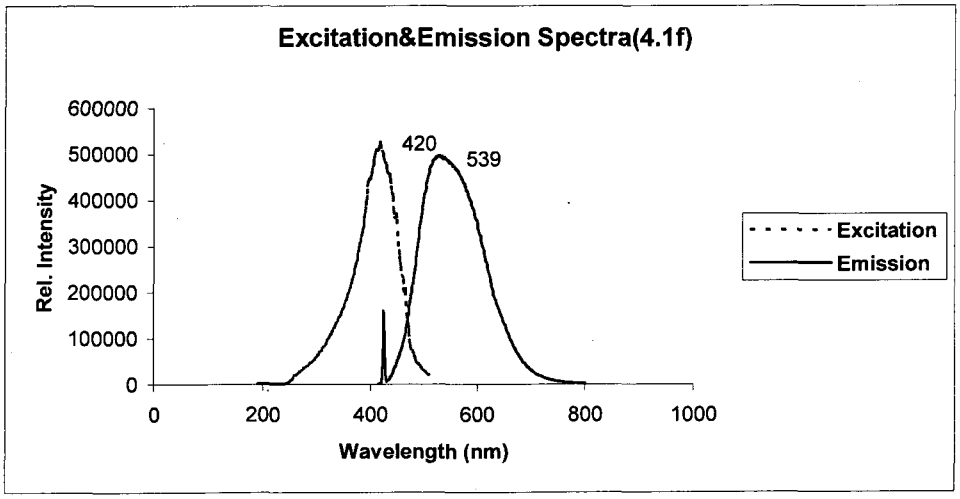
GPC Analysis:

M_n (Daltons): 3.79×10^3 M_w (Daltons): 4.35×10^3 Polydispersity: 1.15



UV-vis/Fluoresence Spectra:



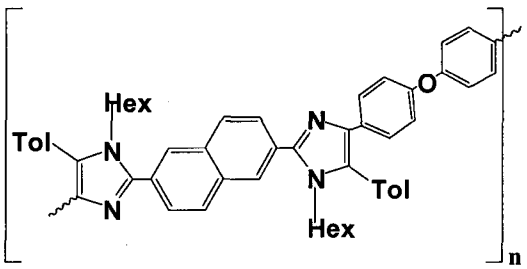


Poly[1-Hexyl-2-naphthalen-2-yl-4-(4-phenoxy-phenyl)-5-*p*-tolyl-1*H*-imidazole](4.1g)

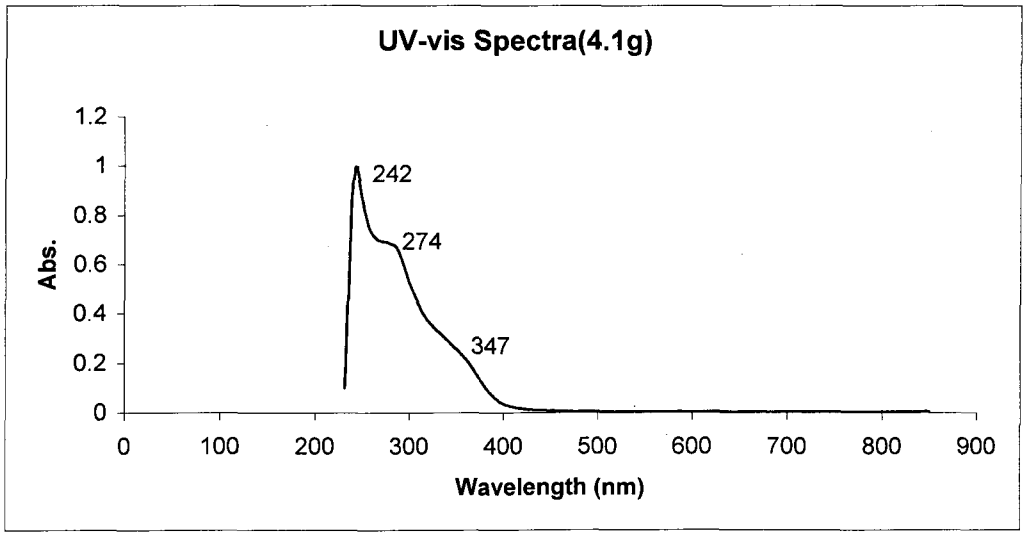
Yellow oil, Isolated yield: 65% ^{1}H NMR (400MHz, CD_2Cl_2): δ 8.3-7.9 (m, 2H), 7.54 (s, 2H), 7.35-7.33 (m, 4H), 6.87 (s, 2H), 4.01(s, br, 2H), 2.46 (s, br, 3H), 1.43 (s, br, 2H), 1.03 (s, br, 5H), 0.711 (s, br, 4H). ^{13}C NMR (125MHz, CD_2Cl_2): δ 192.4, 156, 146.8, 139.9, 136.8, 134.04, 132.3, 132.1, 131.9, 131.7, 131.4, 131.1, 130.8, 130.2, 130.0, 129.3, 129.1, 129.0, 128.8, 128.6, 128.4, 128.3, 127.4, 120.1, 118.6, 117.7, 45.2, 30.9, 30.8, 26.03, 22.3, 21.3, 13.7.

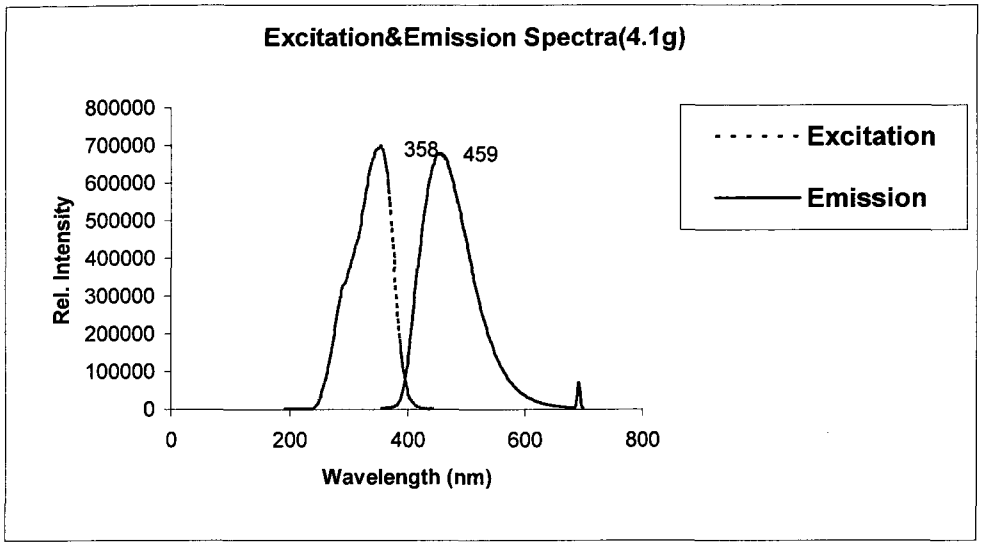
GPC analysis:

M_n (Daltons): 4.15×10^3, M_w (Daltons): 4.83×10^3, Polydispersity index:1.16



UV-vis/Fluoresence Spectra:



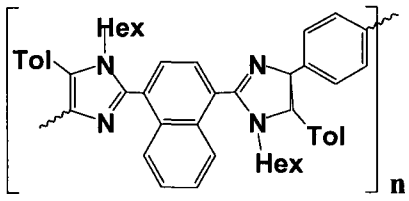


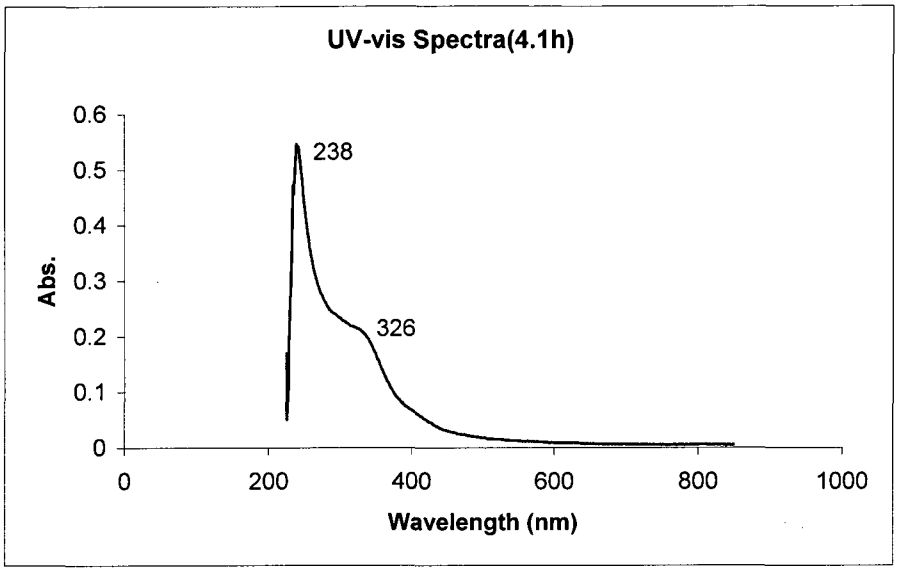
Poly[1-Hexyl-4-(4-methyl-benzyl)-2-naphthalen-1-yl-4-phenyl-4,5-dihydro-1*H*-imidazole](4.1h):

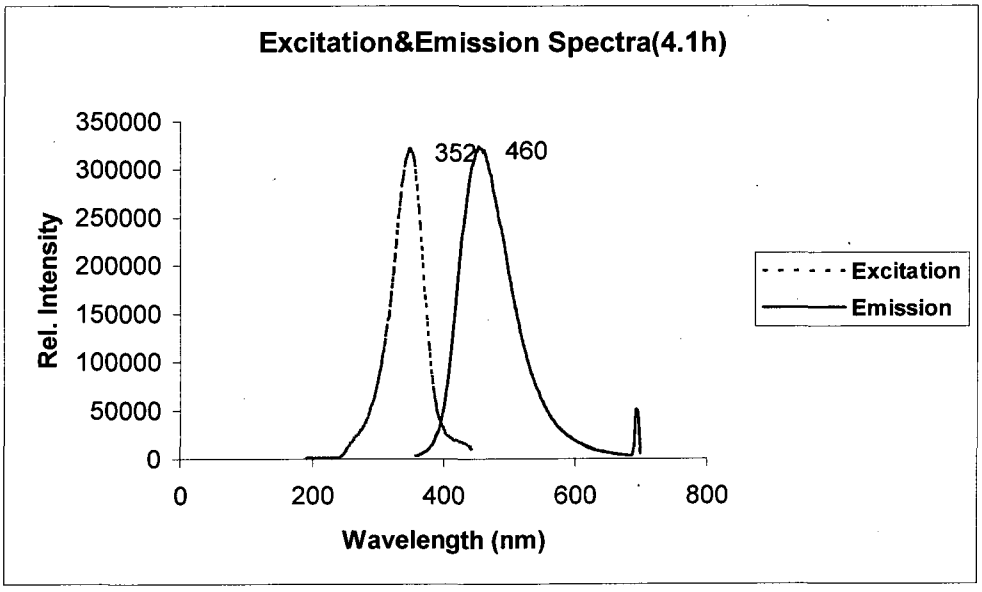
Yellow oil, Isolated yield: 46% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 8.18-6.65 (m, br, 10 H), 4.12-3.88 (m, br, 2H), 2.33 (s, br, 3H), 1.6-0.65 (m, br, 11H). ^{13}C NMR (125MHz, CD_2Cl_2, 60 °C): δ 170, 144.8, 139.9, 138.5, 138.1, 134.8, 132.8, 132.1, 131.0, 129.9, 129.7, 129.5, 129.2, 129.02, 128.7, 128.3, 128.0, 126.9, 126.8, 126.5, 126.3, 122.7, 44.6, 31.6, 29.8, 26.9, 22.7, 22.1, 13.9.

GPC analysis:

M_n (Daltons): 3.95×10^3, M_w (Daltons): 4.67×10^3, Polydispersity index:1.18


Hex
Tol
N
N
N
N
Tol
Hex
n


UV-vis Spectra(4.1h)
Abs.
0.6
0.5
0.4
0.3
0.2
0.1
0
238
326
0
200
400
600
800
1000
Wavelength (nm)

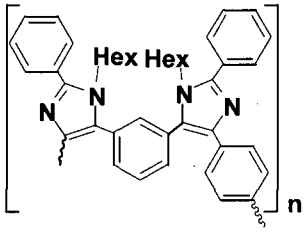

Excitation&Emission Spectra(4.1h)
Rel. Intensity
350000
300000
250000
200000
150000
100000
50000
0
352
460
0
200
400
600
800
Wavelength (nm)
Excitation
Emission

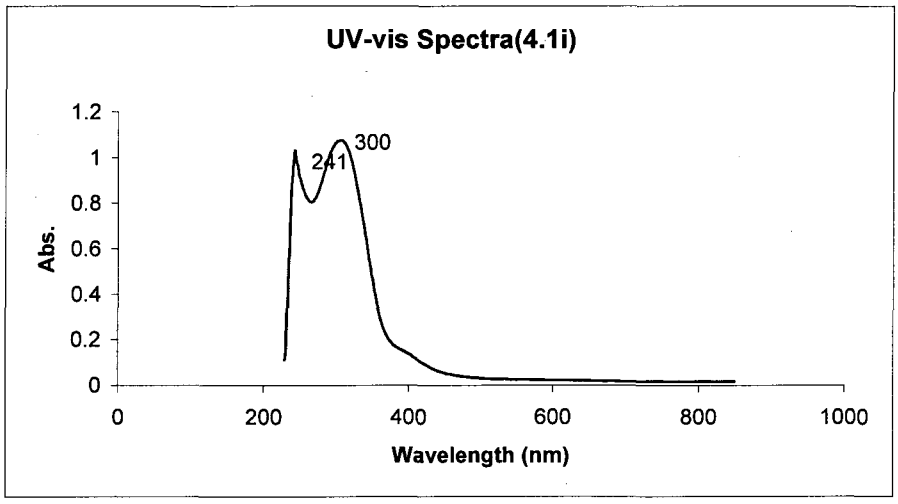
Poly[1-Hexyl-2,4,5-triphenyl-1*H*-imidazole](4.1i):

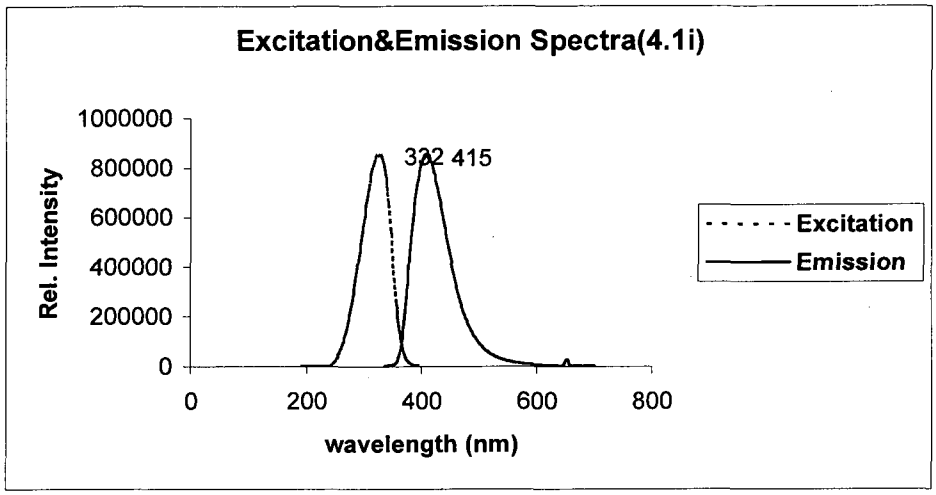
Yellow oil, Isolated yield: 72% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 7.78-7.61 (s, br, 2H), 7.59-7.2 (m, br, 6H), 3.98 (s, br, 2H), 1.58 (s, br, 2H), 1.05 (m, 4H), 0.78 (s, br, 5H). ^{13}C NMR (125MHz, CD_2Cl_2, 60 °C): δ 170.2, 147.8, 142.3, 140.01, 137.9, 133.2, 132.7, 131.9, 131.6, 129.5, 129.4, 129.27, 129.24, 128.8, 126.6, 126.5, 44.8, 31.8, 31.1, 26.1, 22.8, 22.5, 13.7.

GPC analysis:

M_n (Daltons): 4.12×10^3, M_w (Daltons): 4.84×10^3, Polydispersity index:1.17





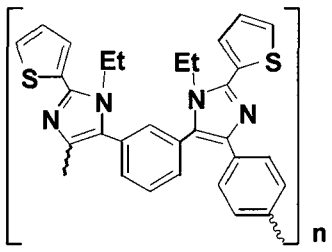


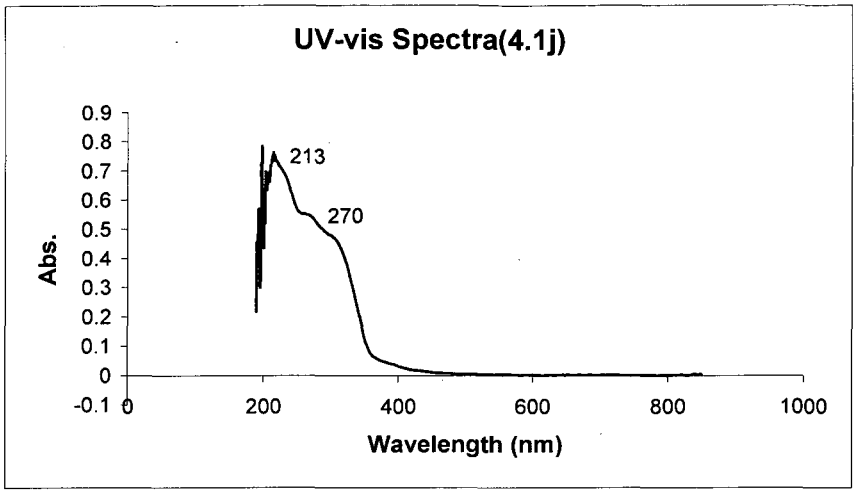
Poly[1-Ethyl-4,5-diphenyl-2-thiophen-2-yl-1*H*-imidazole](4.1j):

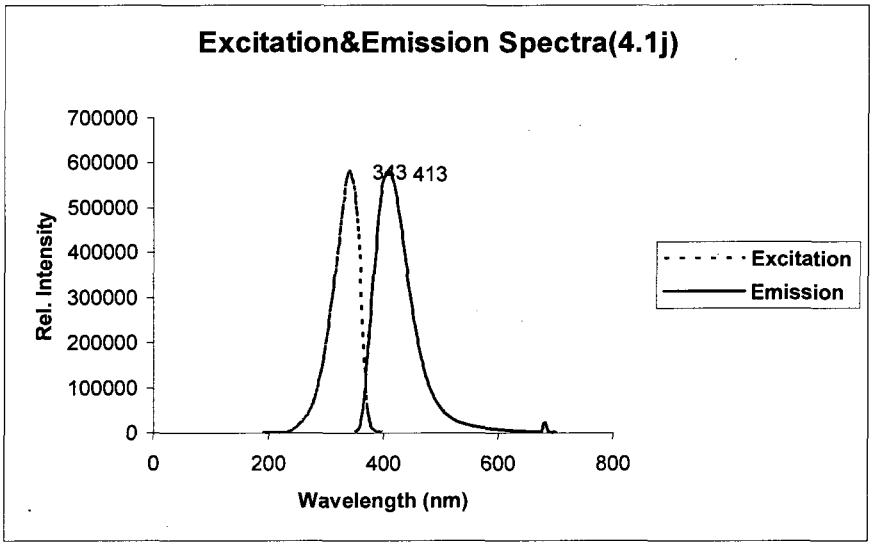
Yellow oil, Isolated yield: 64% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 7.41-7.15 (m, br, 10 H), 3.97 (s, br, 2H), 1.10 (s, br, 3H). ^{13}C NMR (125MHz, CD_2Cl_2, 60 °C): δ 165.4, 143.9, 136.3, 134.5, 134.2, 129.9,128.3, 127.8, 126.2, 124.7, 124.5, 124.3, 124.1, 123.9, 121.8, 121.1, 40.01, 16.03.

GPC analysis:

M_n (Daltons): 3.84×10^3, M_w (Daltons): 4.45×10^3, Polydispersity index:1.16







Procedure for the Synthesis of Pyrrole-Based Polymer (4.11)

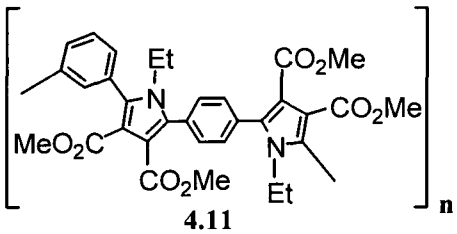
Ethyl-(3-ethyliminomethyl-benzylidene)-amine **4.9** (100 mg, 0.53 mmol) and isophthaloyl dichloride **4.3** (107.6 mg, 0.53 mmol) were dissolved in 10 mL of CH_3CN:THF (1:1) solution and stirred for 15 min in a 50 mL reaction bomb. To this was added palladium catalyst **4.8** (20.9 mg, 0.0265 mmol), P(*o*-tol)$_3$ (48.7 mg, 0.159 mmol) in 5 mL of THF, and *N*(hexyl)$_3$ (285 mg, 1.06 mmol) in 3 mL of THF.

Benzylbenzoate was also added to this mixture as an internal standard. The entire mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) added. After heating to 45 °C for 16 h, the mixture was degassed and an aliquot of the crude deep red solution was analyzed by ^{1}H NMR and the yield of the poly(Münchnone) was determined by comparison to the internal standard. Based upon the NMR yield, dimethylacetylenedicarboxylate **4.10** (30 mg, 0.212 mmol) was added to the reaction bomb and the mixture was further heated at 45 °C for 16 h. The dark red solution was then filtered over celite and solvent was removed *in vacuo*. The resulting deep red oil was dissolved in CH_3CN and filtered over celite to remove some solid impurities. The filtrate was kept at -20 °C to form red precipitate. The CH_3CN solution was then decanted and the precipitate was further washed with CH_3CN followed by cooling to -20 °C. This procedure was repeated several times until all impurities are removed and the final product was obtained as red oil.

Poly [1-Ethyl-2,5-diphenyl-1*H*-pyrrole-3,4-dicarboxylic acid dimethyl ester] (4.11) Red oil, Yield: 42% ^{1}H NMR (400MHz, CD_2Cl_2, 60 °C): δ 8.18-7.80 (m, br, 2H), 7.89-7.19 (m, br, 9H), 3.84-3.64 (s, br, 2H), 3.62-3.45 (s, 6H), 1.08-0.82 (s, br, 3H). ^{13}C NMR (125MHz, CD_2Cl_2, 60 °C): δ 165.9, 165.4, 136.9, 133.2, 131.6, 130.8, 129.3, 128.7, 128.2, 127.1, 126.5, 115.6, 114.5, 52.04, 51.7, 40.2, 16.2.

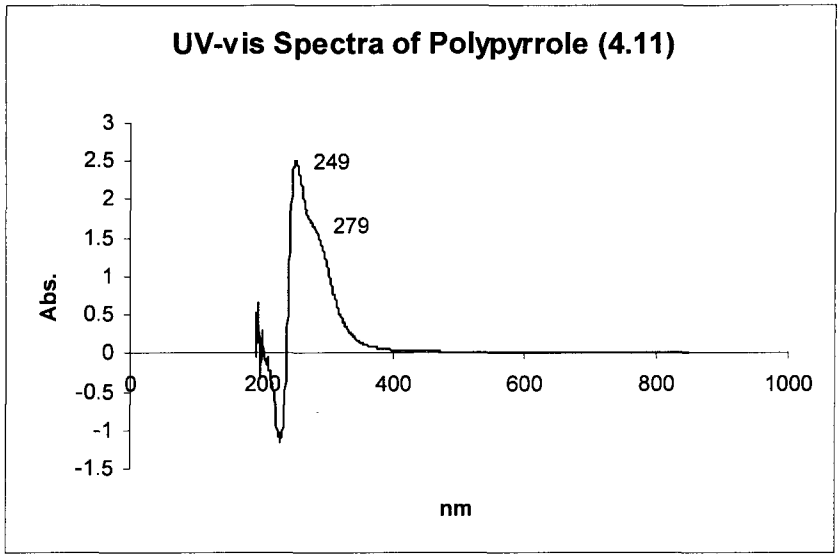
GPC Analysis:

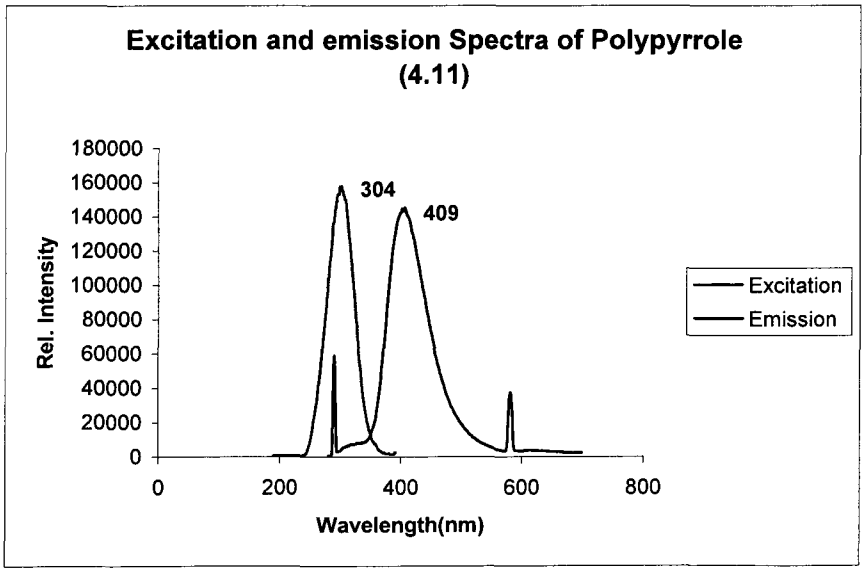
M_n (Daltons): 7.20×10^3 M_w (Daltons): 1.30×10^4 Polydispersity: 1.80



4.11

UV-vis and Fluoresence Data:

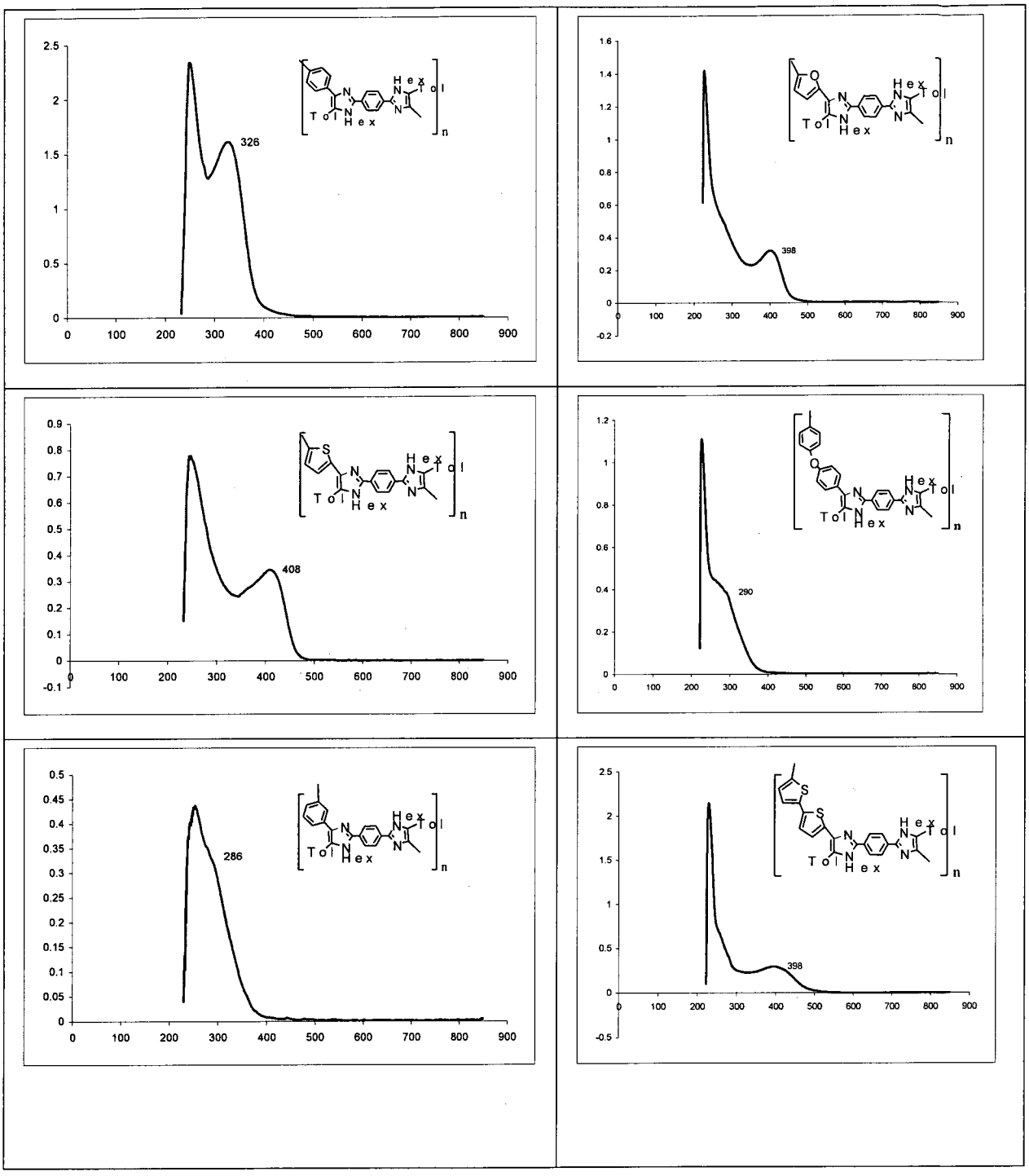


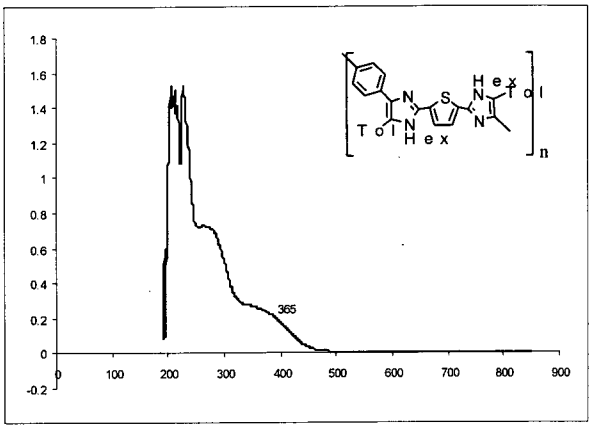


Procedure for the Library Synthesis

Following the procedure in section IV, di-carbonyldichloride **4.3** (0.492 mmol) and imine **4.5** (0.984 mmol) were dissolved in 12 mL of CH_3CN:THF (1:1) solution and stirred for 15 min in a 50 mL reaction bomb (Scheme 4.3). To this was added palladium catalyst **4.8** (19.4 mg, 0.0246 mmol), P(*o*-tol)$_3$ (45.2 mg, 0.147 mmol) in 5 mL of THF, and *N*(hexyl)$_3$ (397 mg, 1.48 mmol) in 3 mL of THF. Benzylbenzoate was also added to this mixture as an internal standard. The entire mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) added. After heating to 45 °C for 16 h, the mixture was degassed and an aliquot of the crude deep red solution was analyzed by ^{1}H NMR and the yield of the bisMünchnone **4.2** was determined by comparison to the internal standard. This mixture was further divided into six portions and 0.8 equivalents of di-tosylimine **4.4** and *N*(hexyl)$_3$ (95 mg, 0.354 mmol) were added to each portion and heated at 45 °C for 20 h. The resulting solution was filtered over celite and solvent was removed in *vacuo*. A dilute solution of each sample in CH_2Cl_2 was prepared and UV-vis and Fluorescence excitation/emission spectra obtained.

UV-vis Spectra of the Library Compounds

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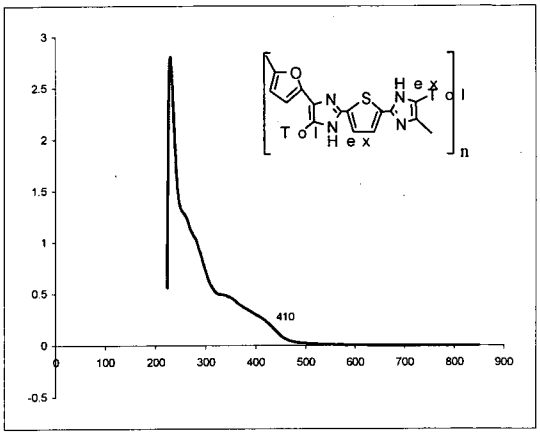
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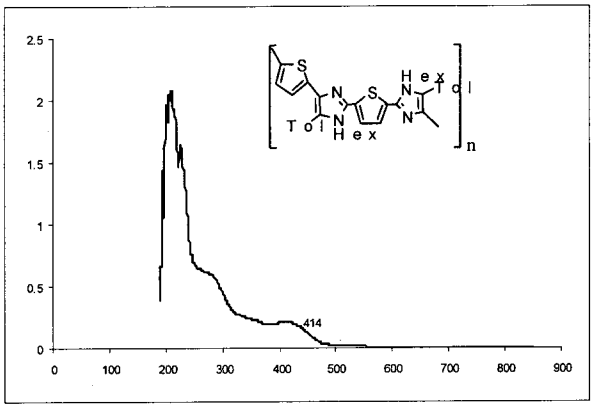
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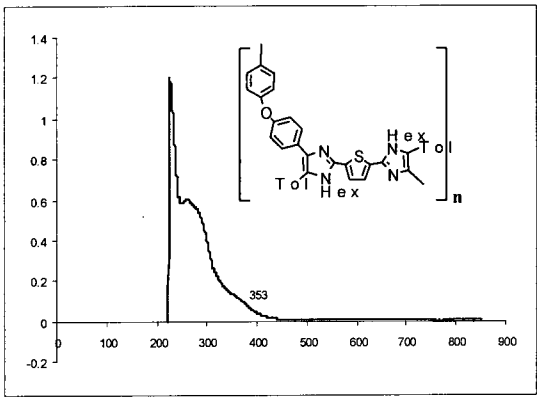
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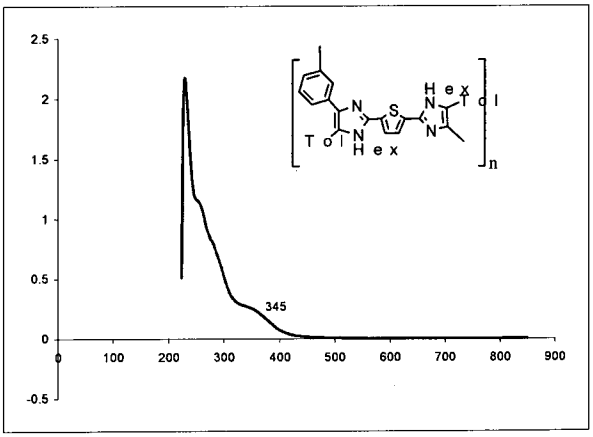
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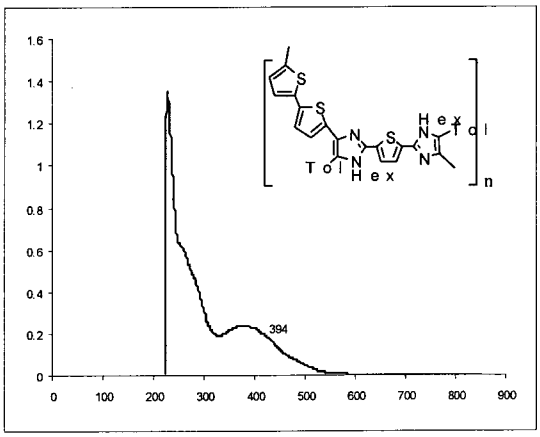
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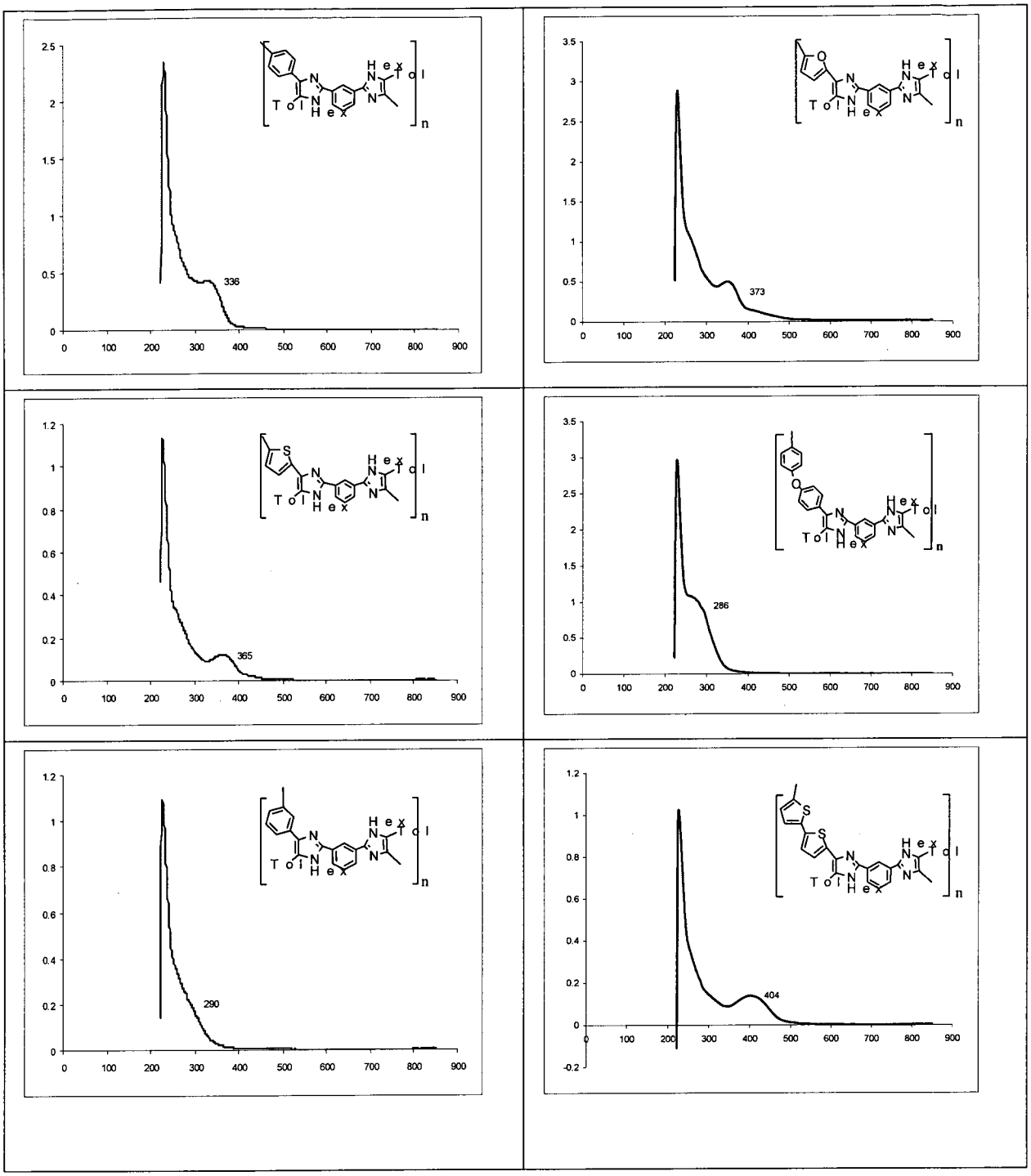
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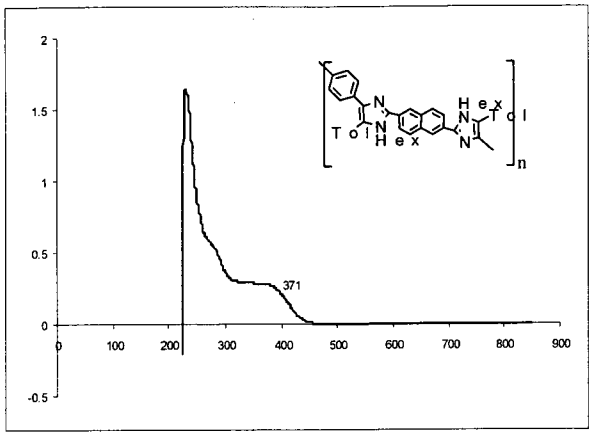
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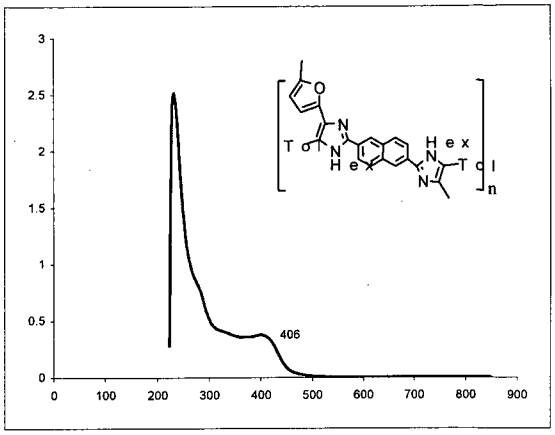
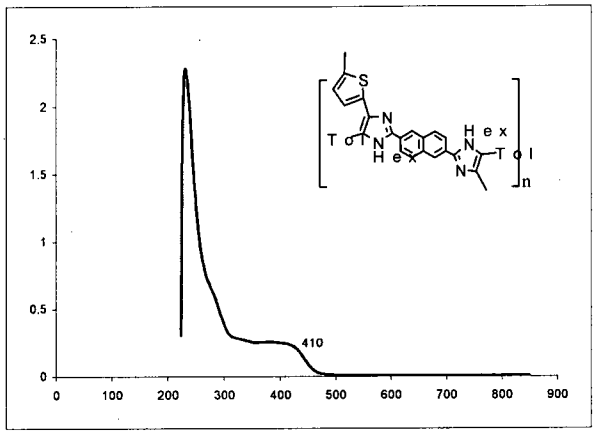

406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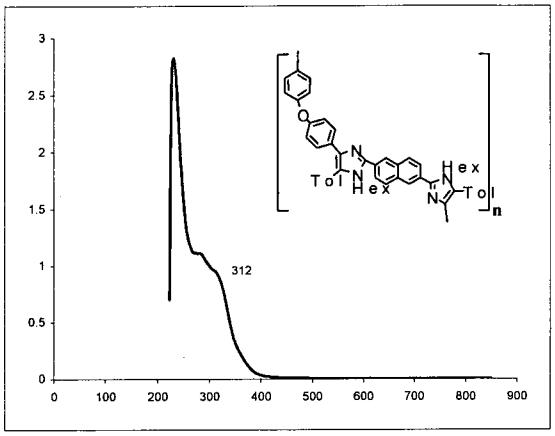
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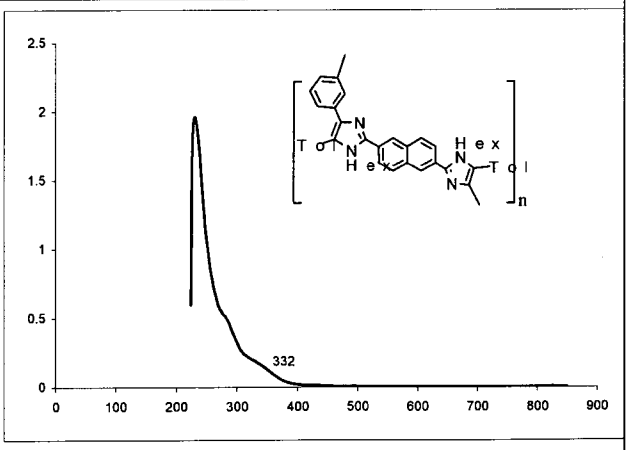
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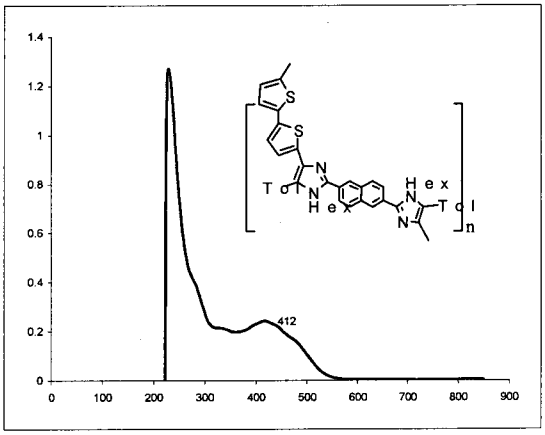
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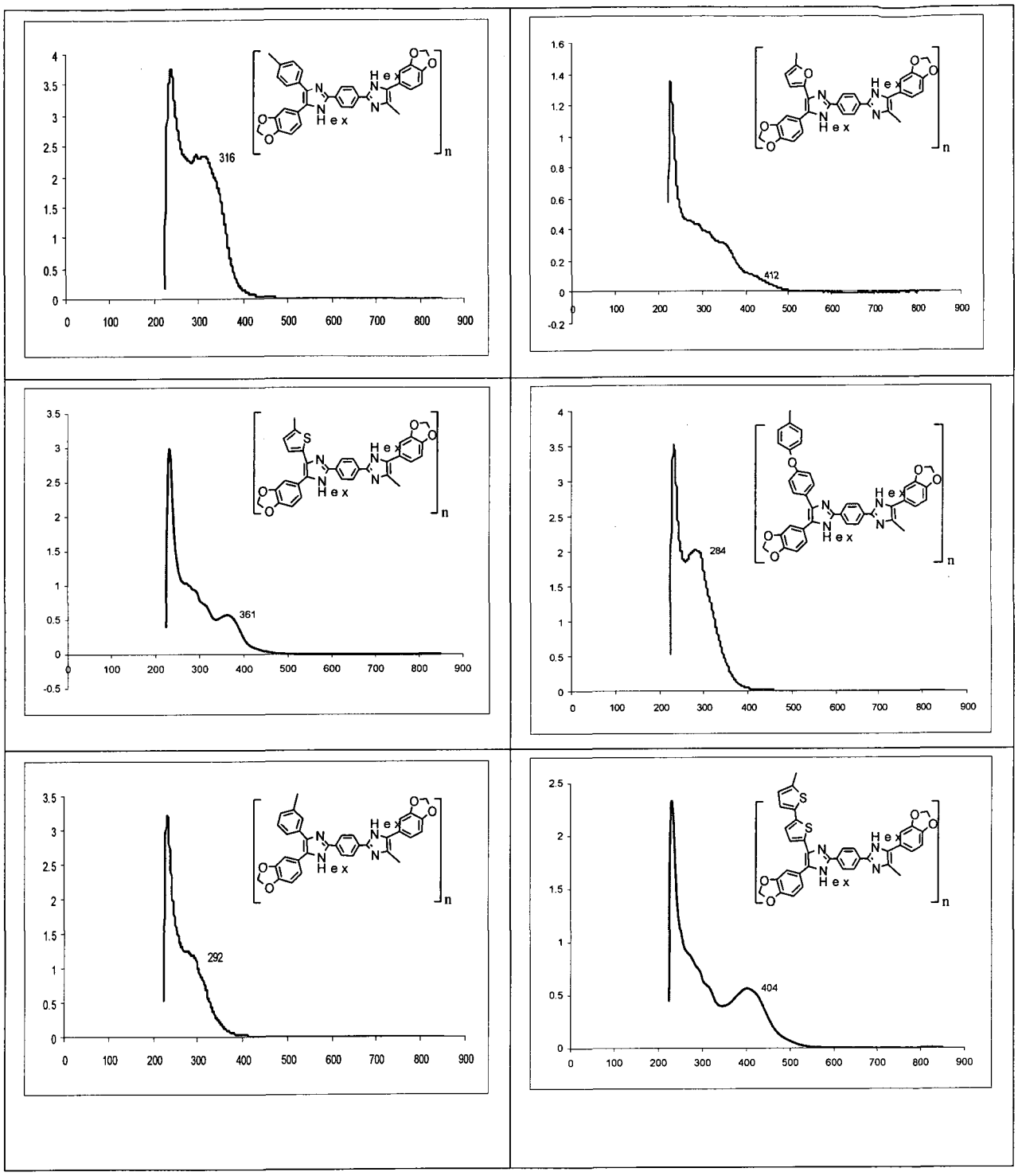
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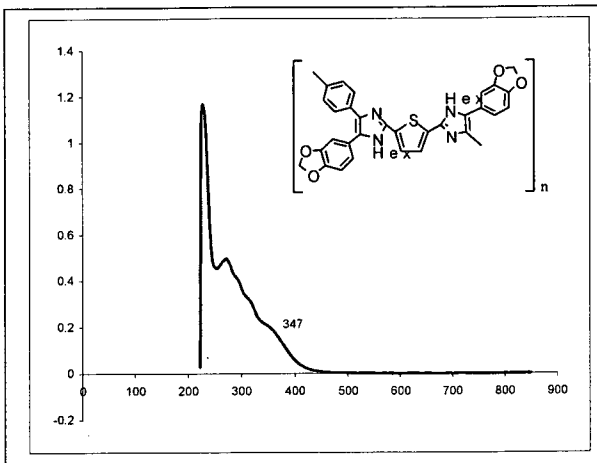
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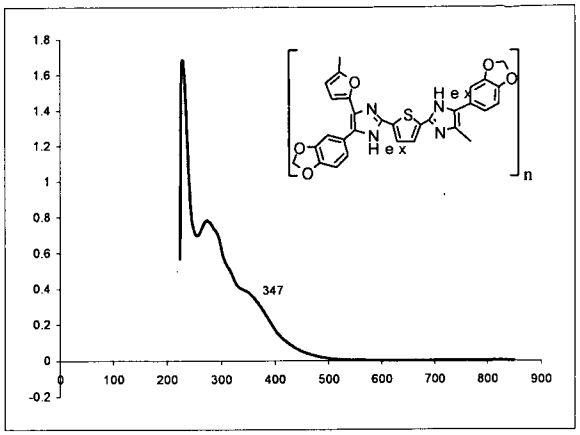
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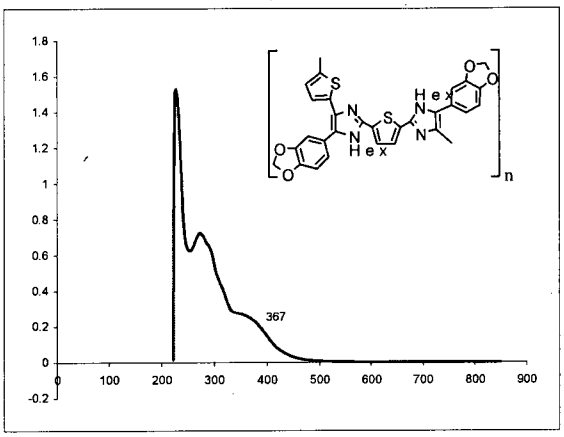
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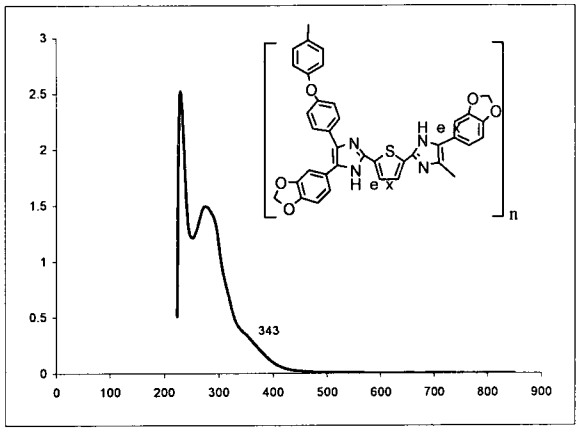
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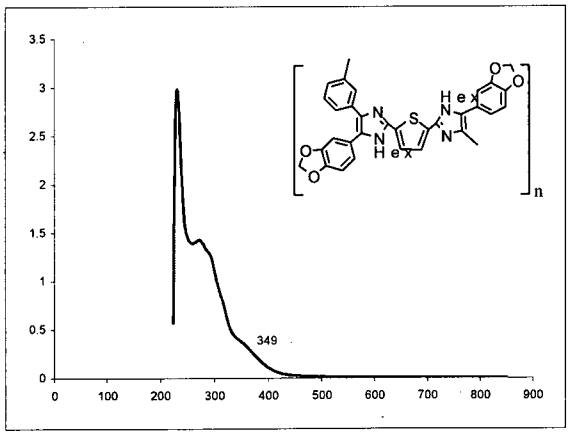
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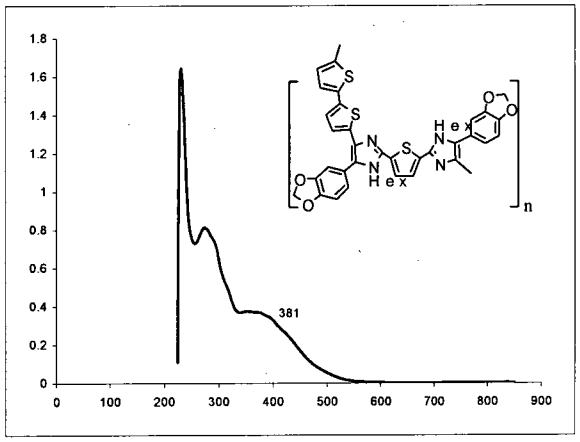
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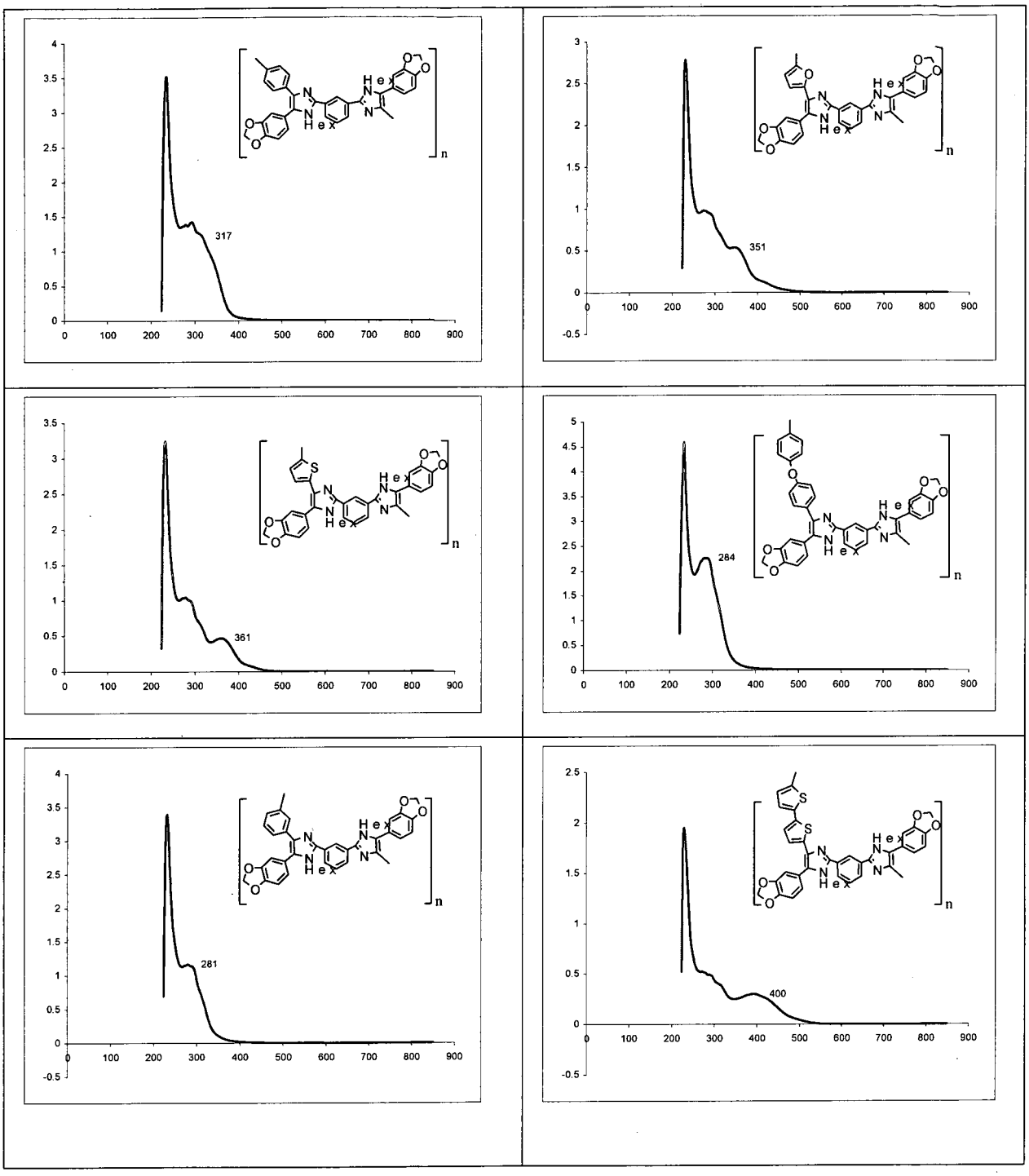
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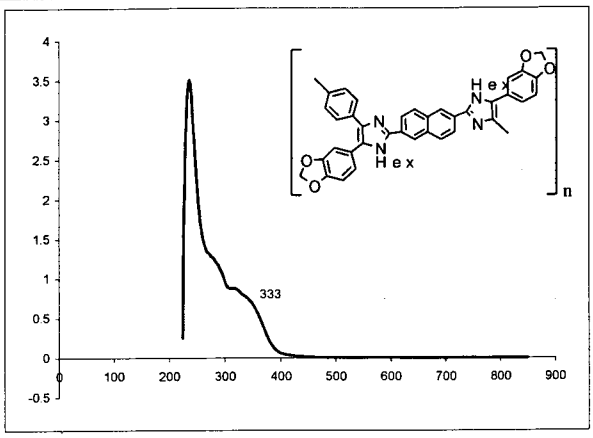
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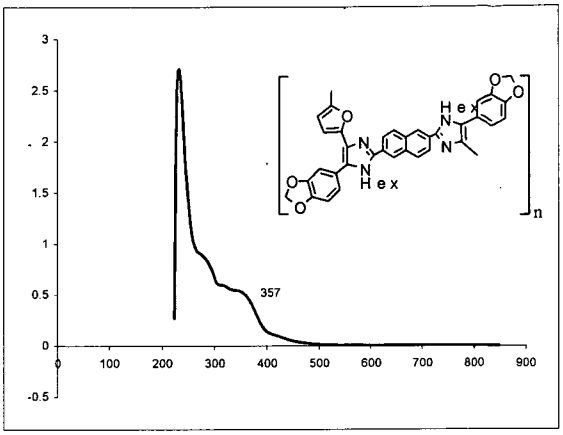
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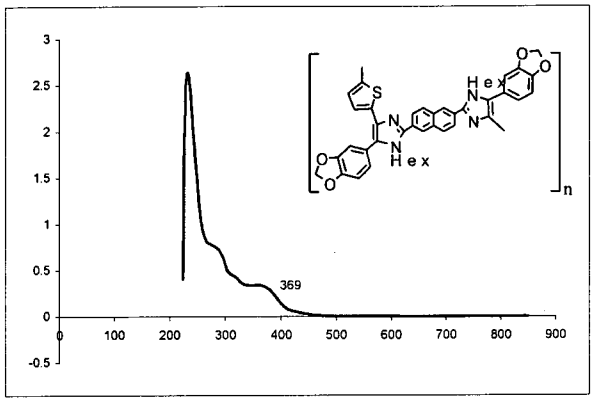
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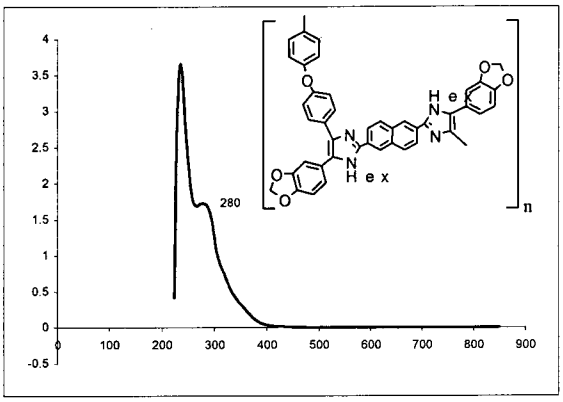
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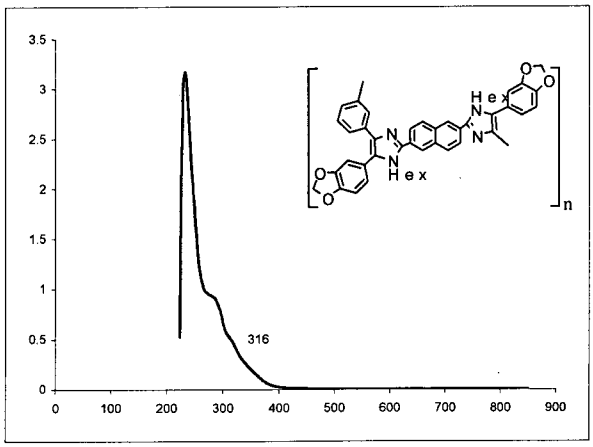
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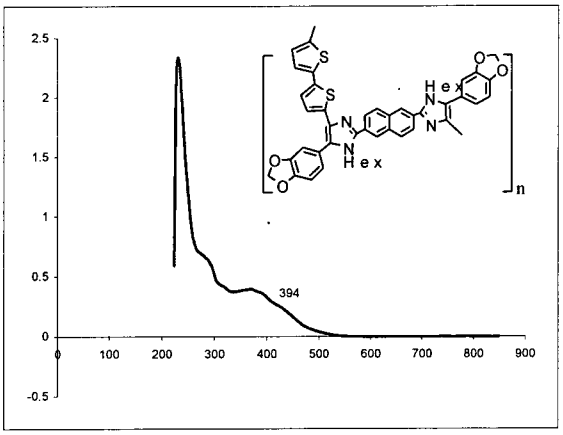
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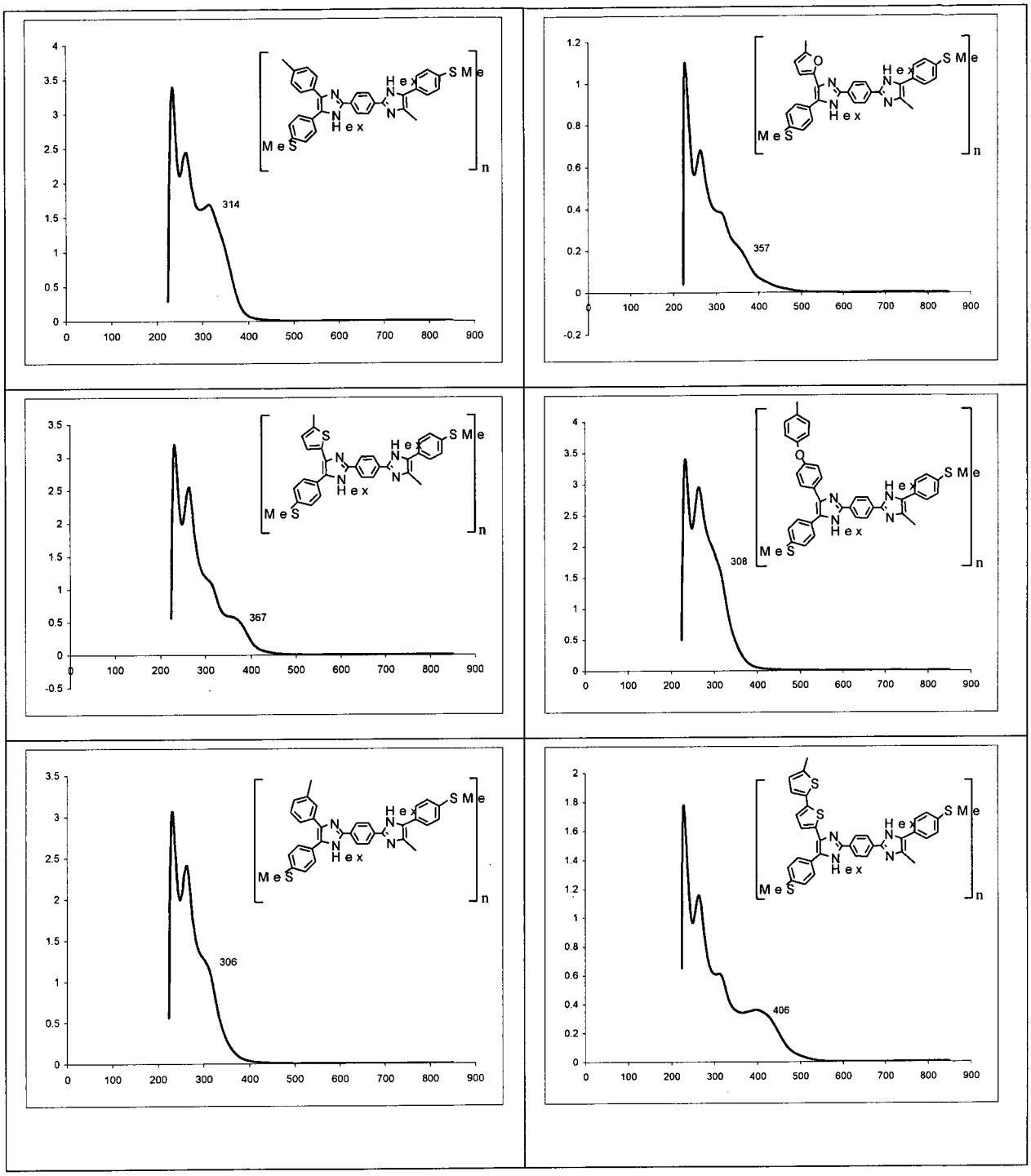
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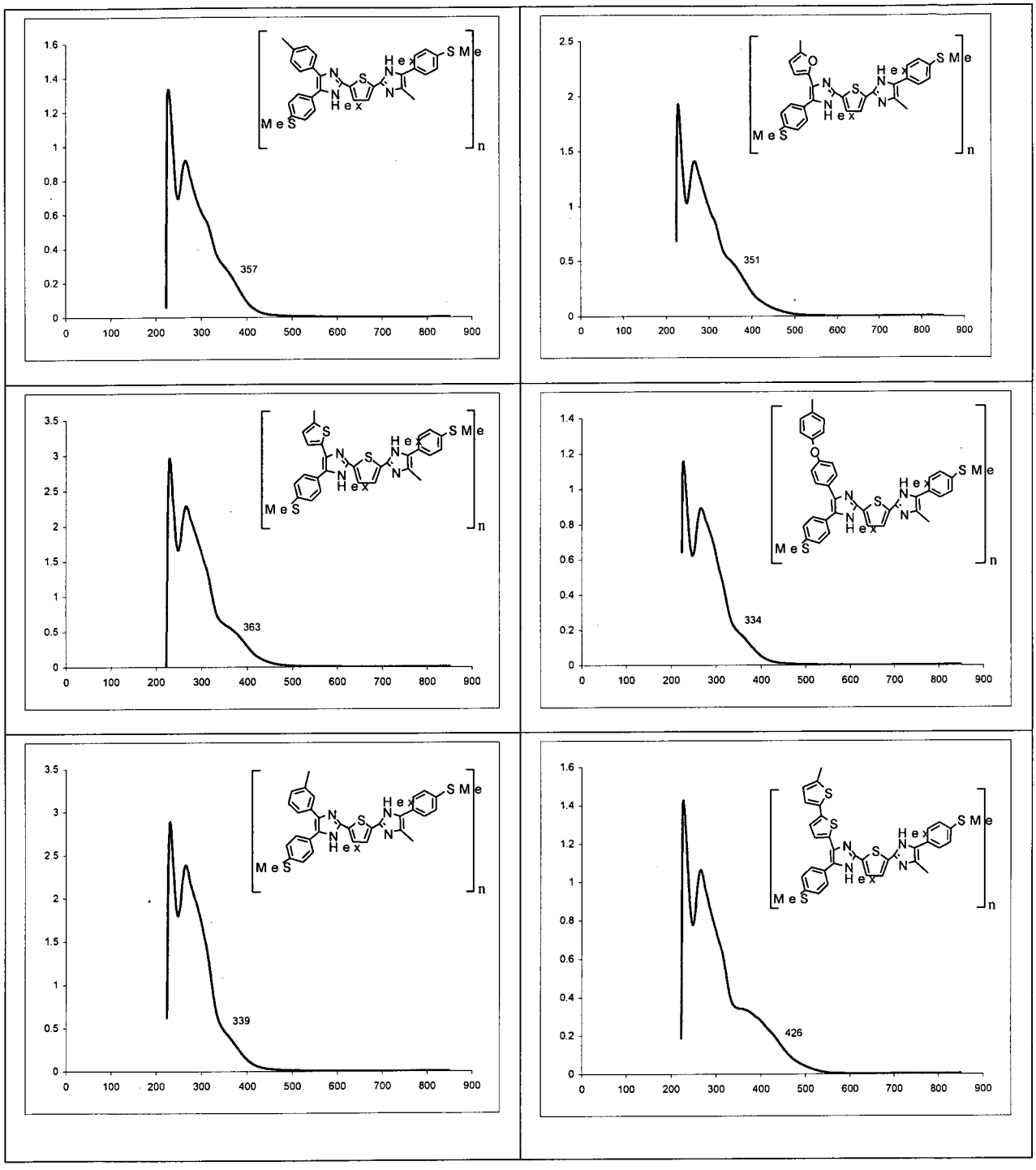
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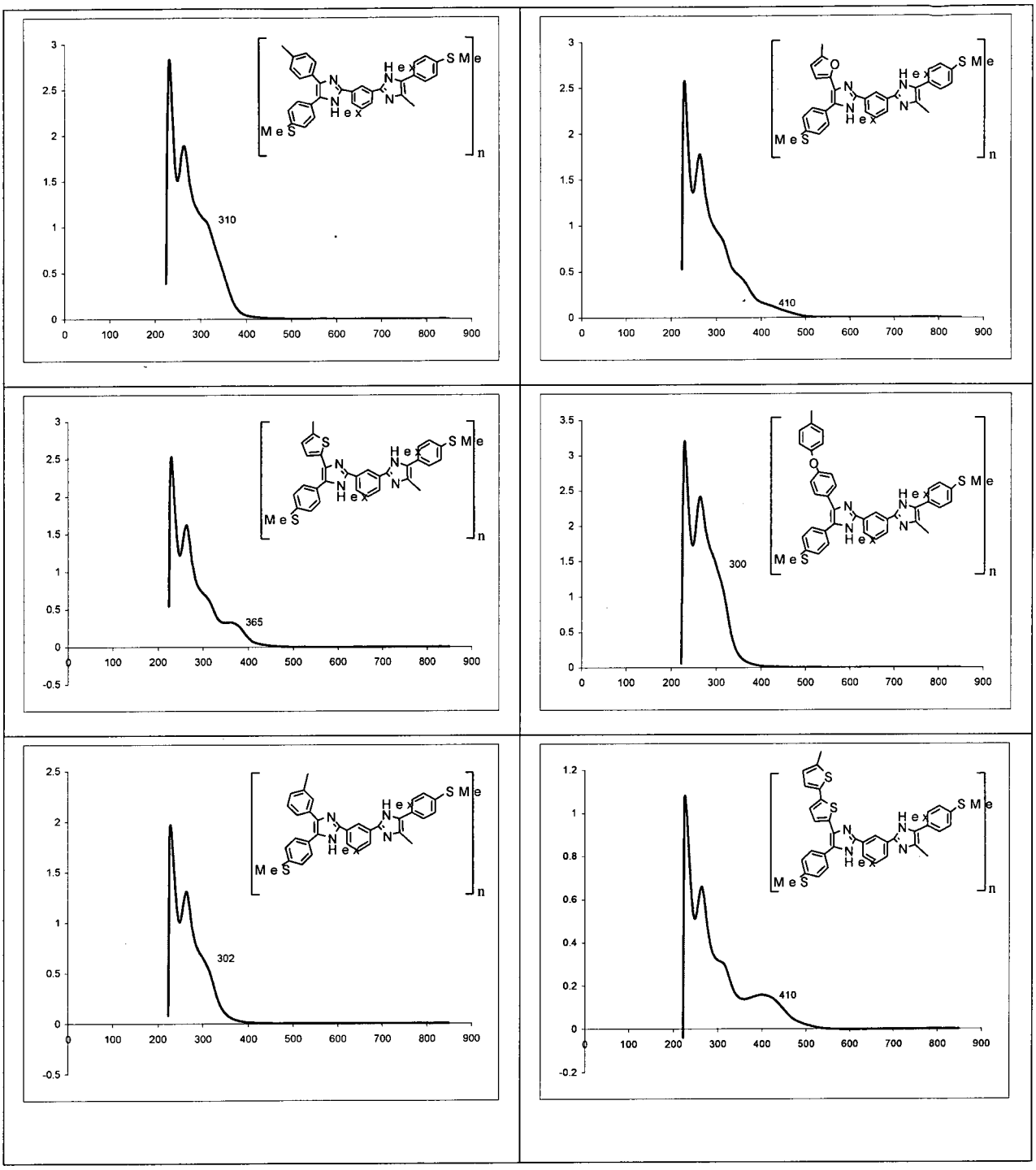
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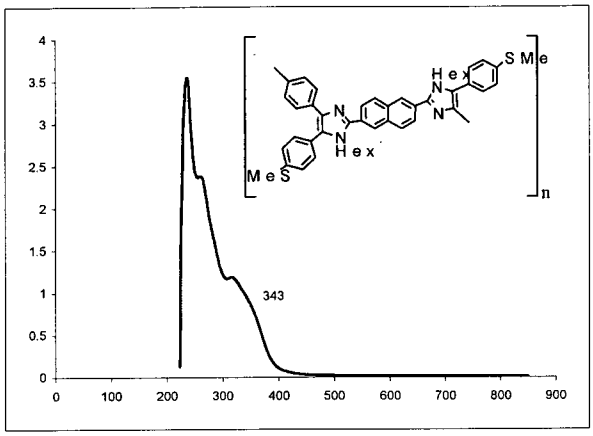
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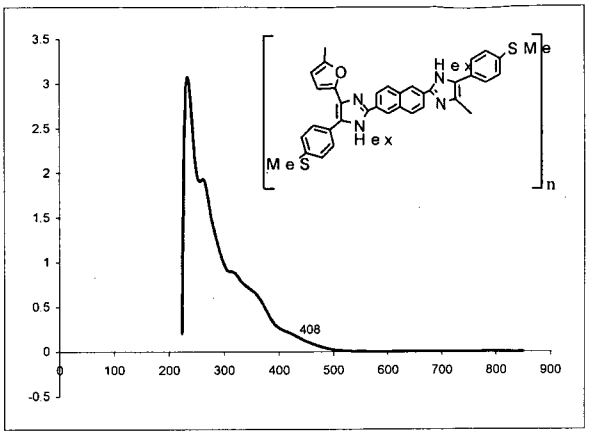
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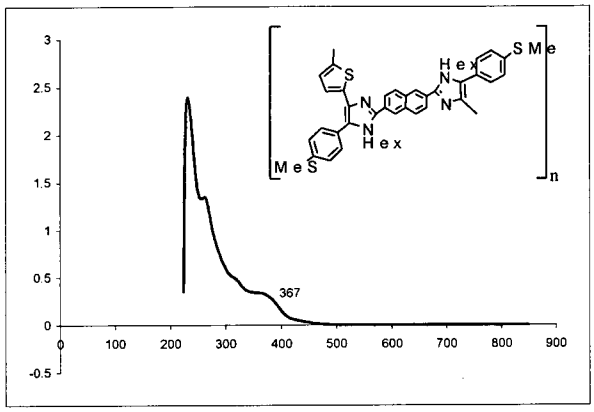
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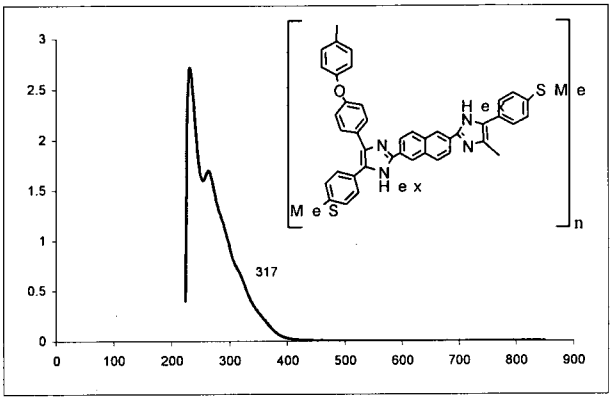
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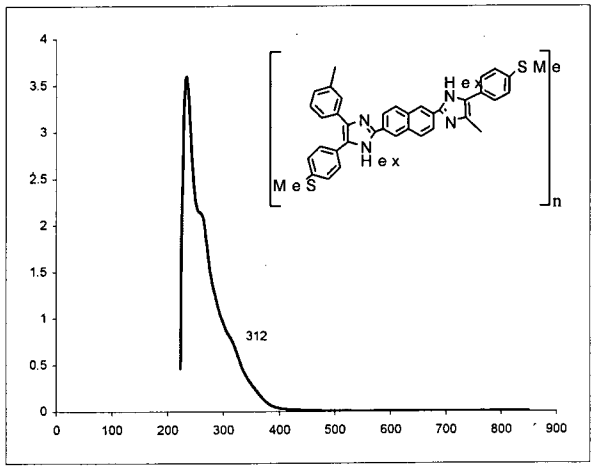
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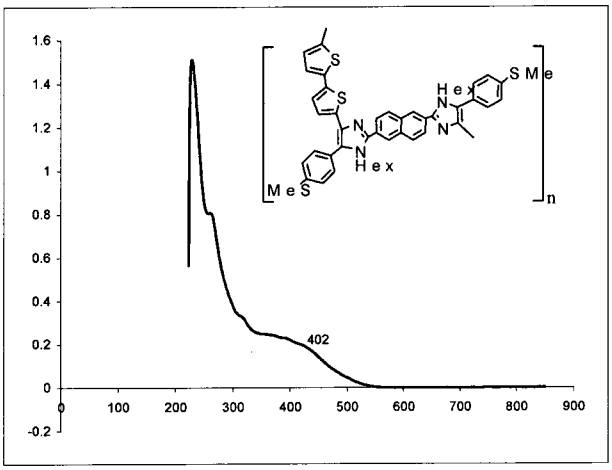
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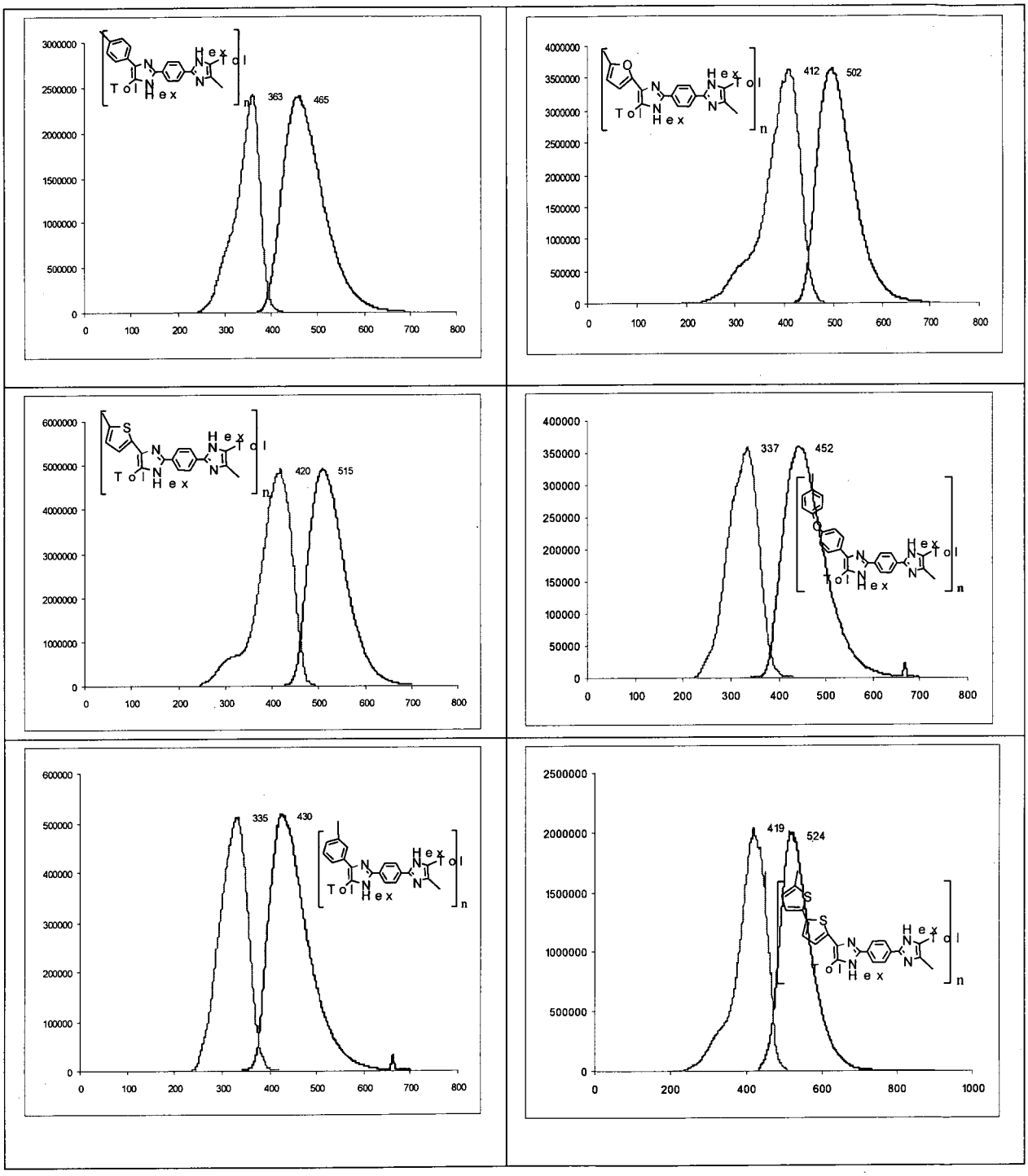
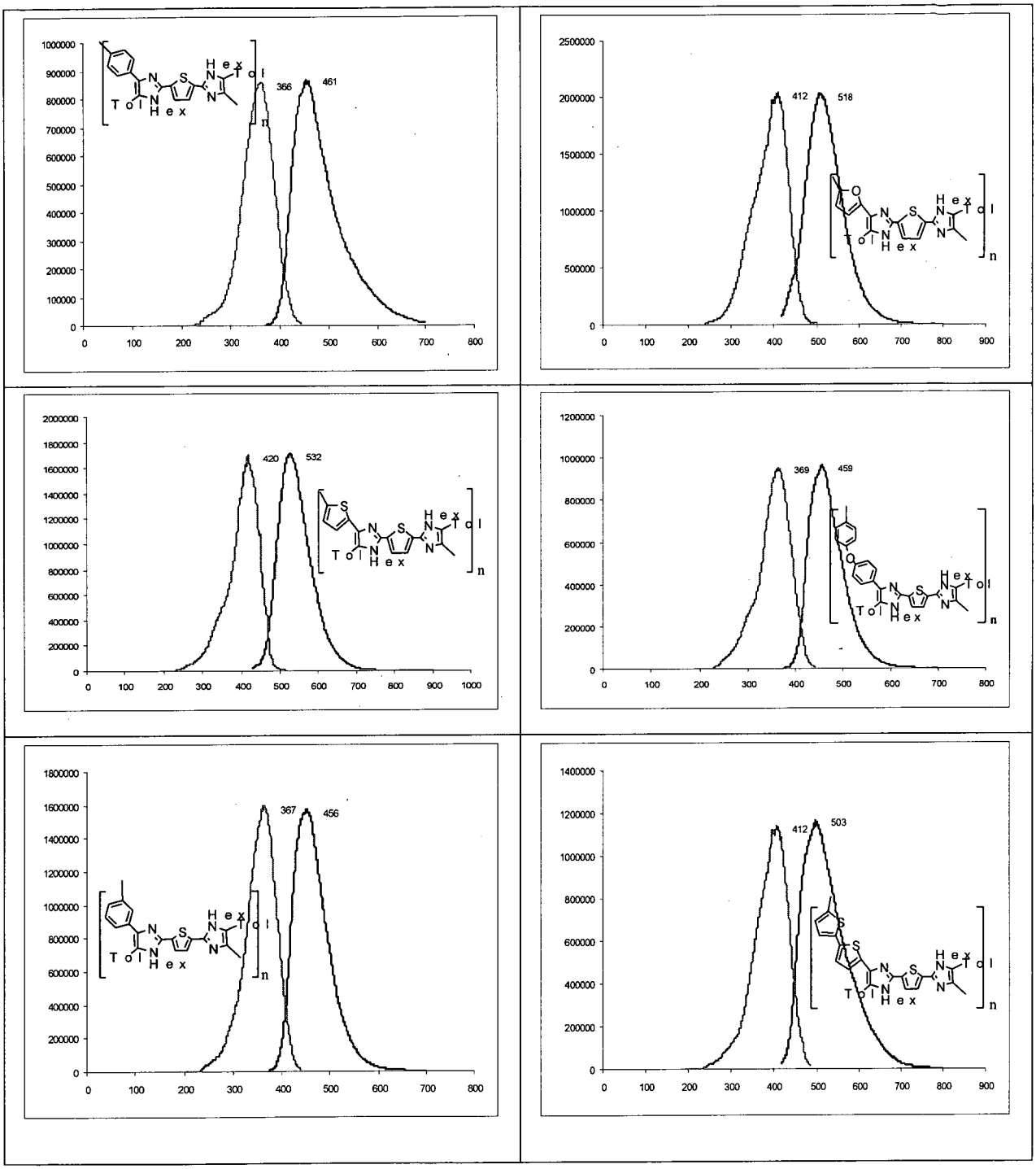
Fluorescence Excitation/Emission Spectra of the Library Compounds

Excitation: ———

Emission: ———

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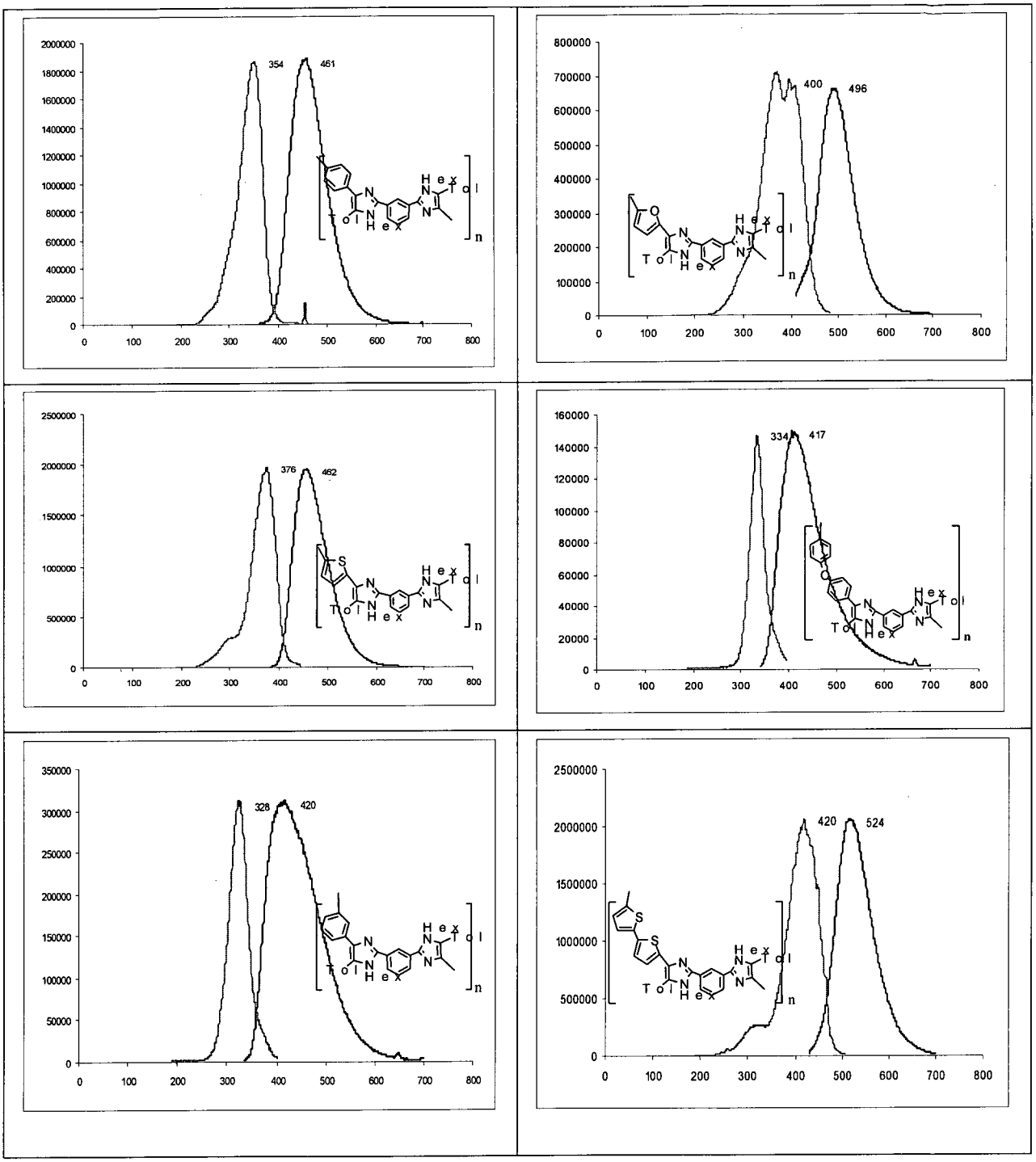
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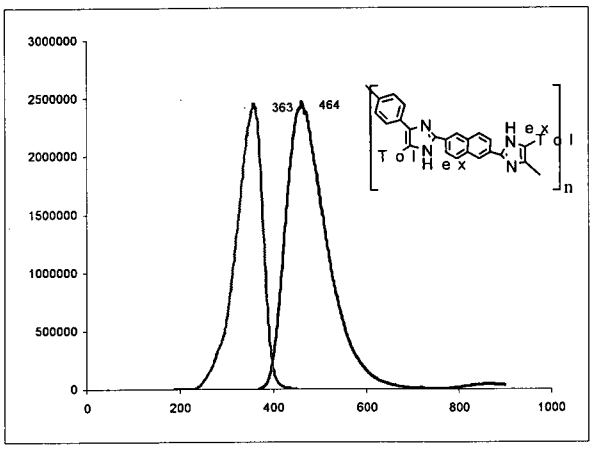
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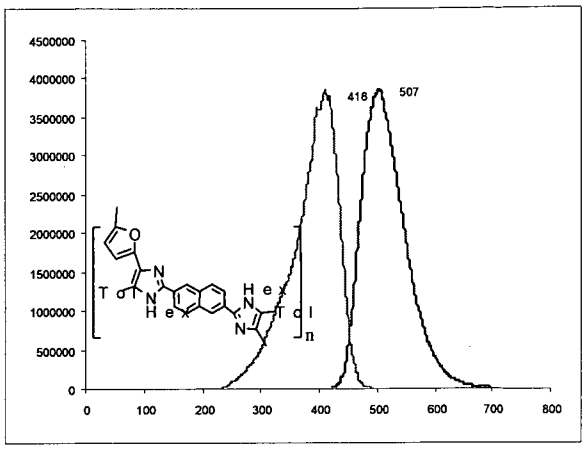
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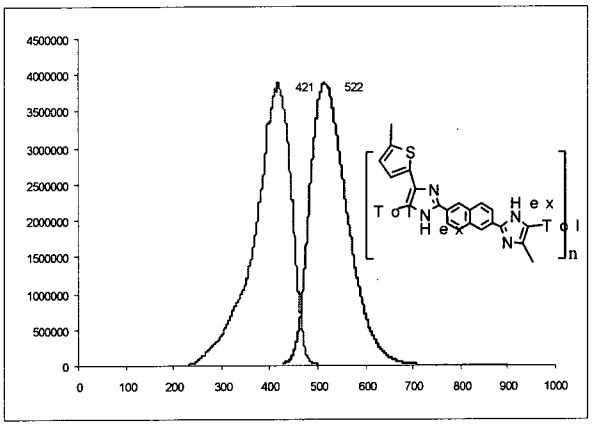
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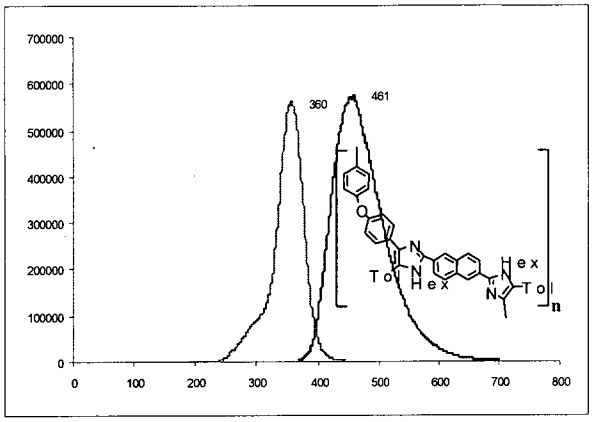
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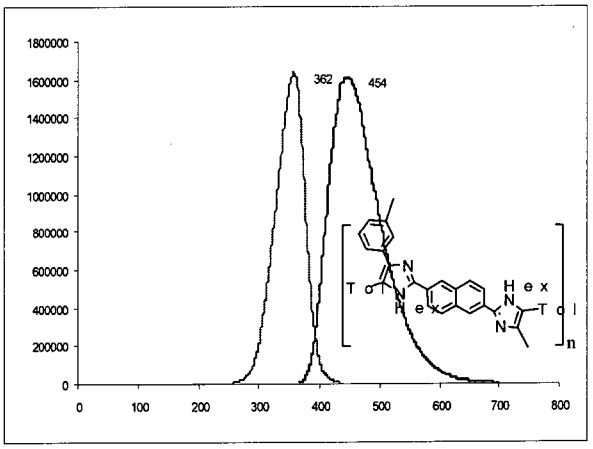
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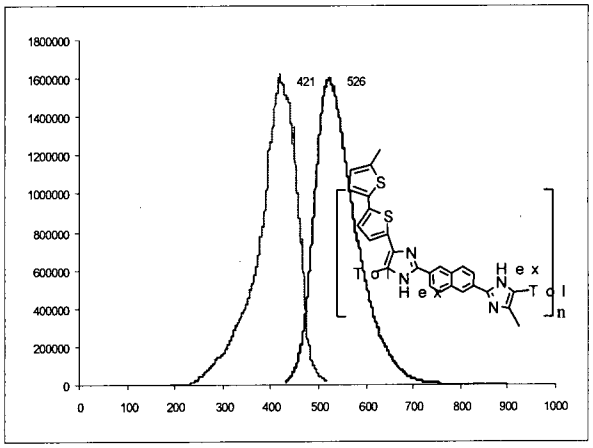
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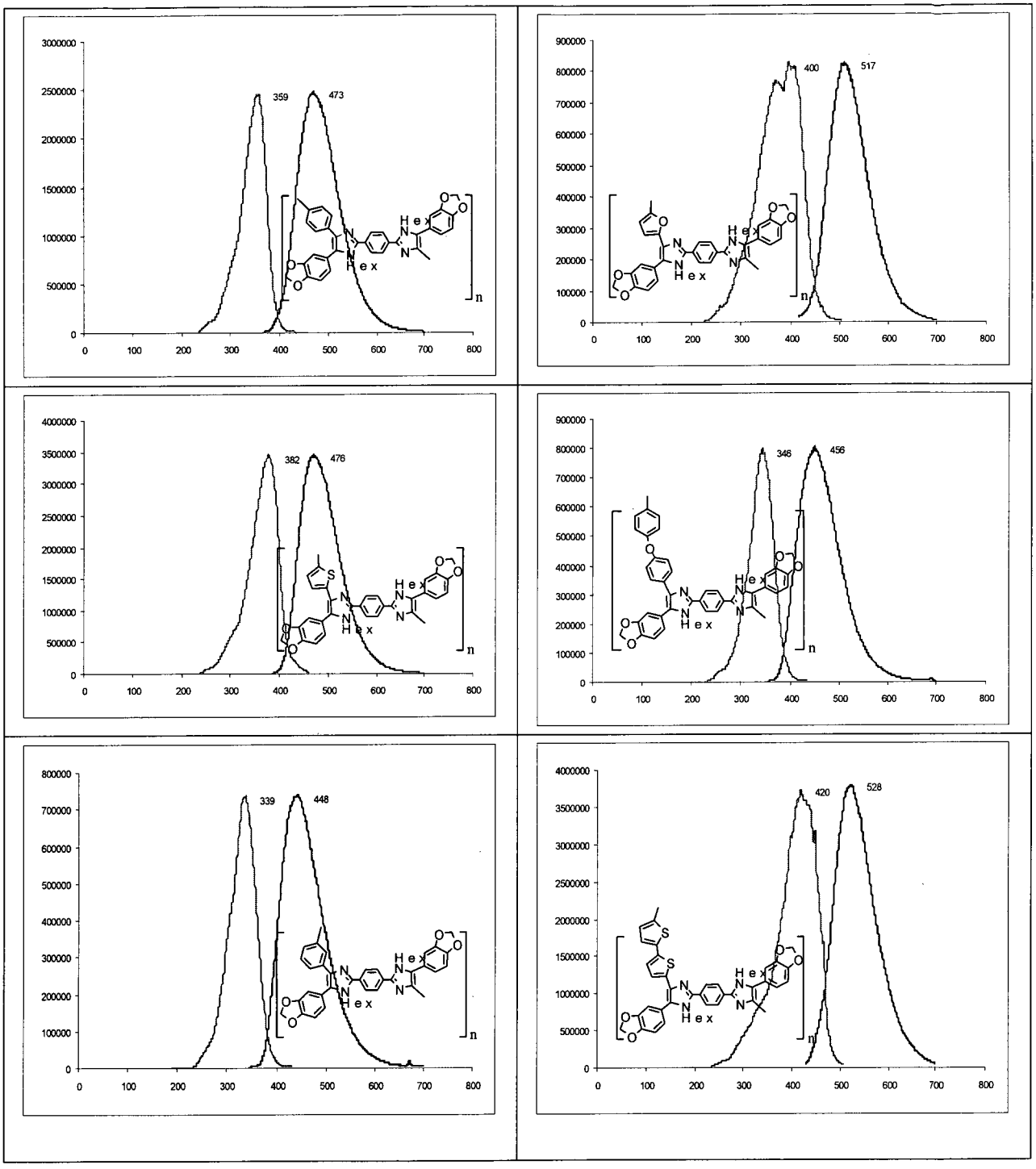
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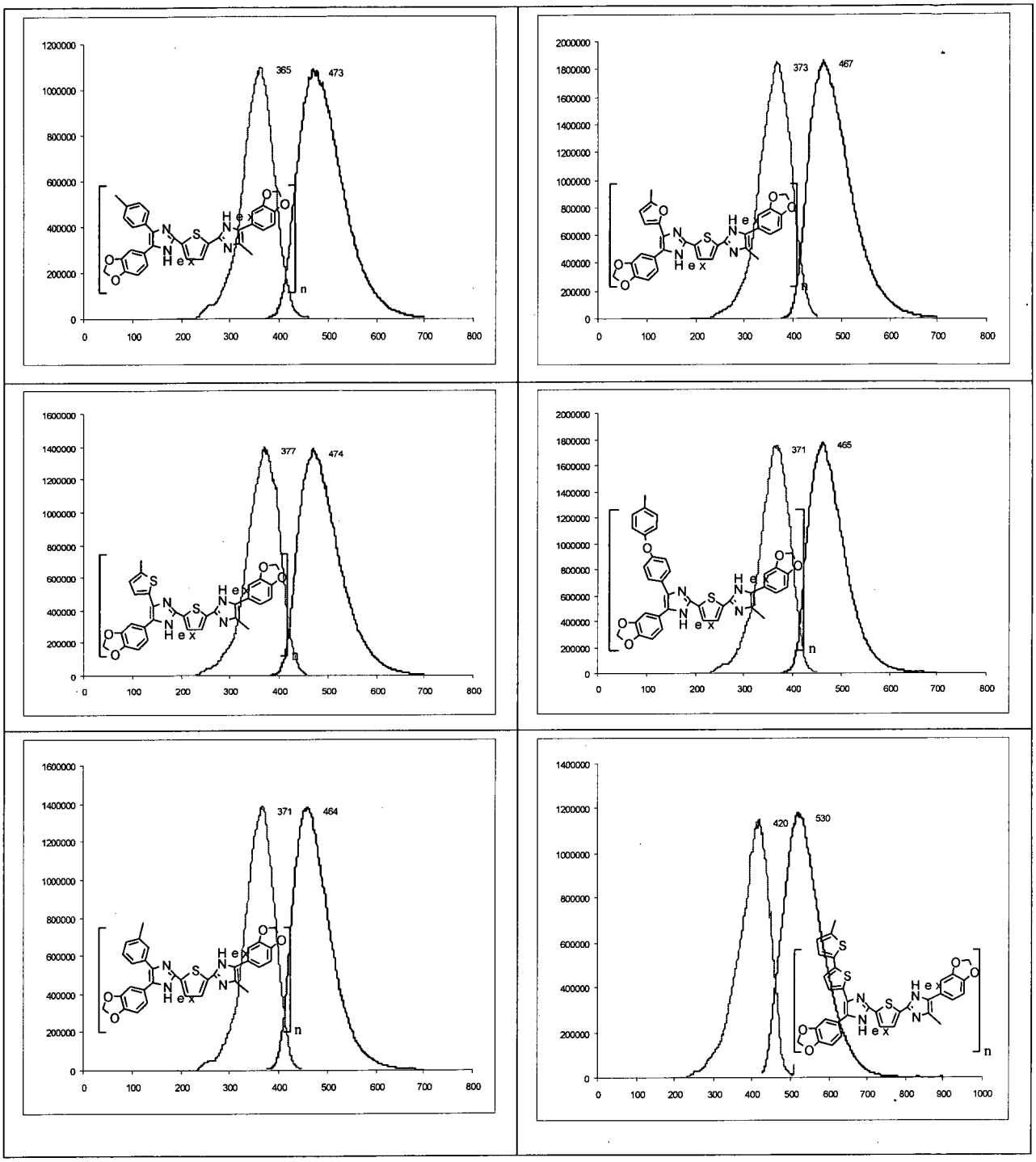
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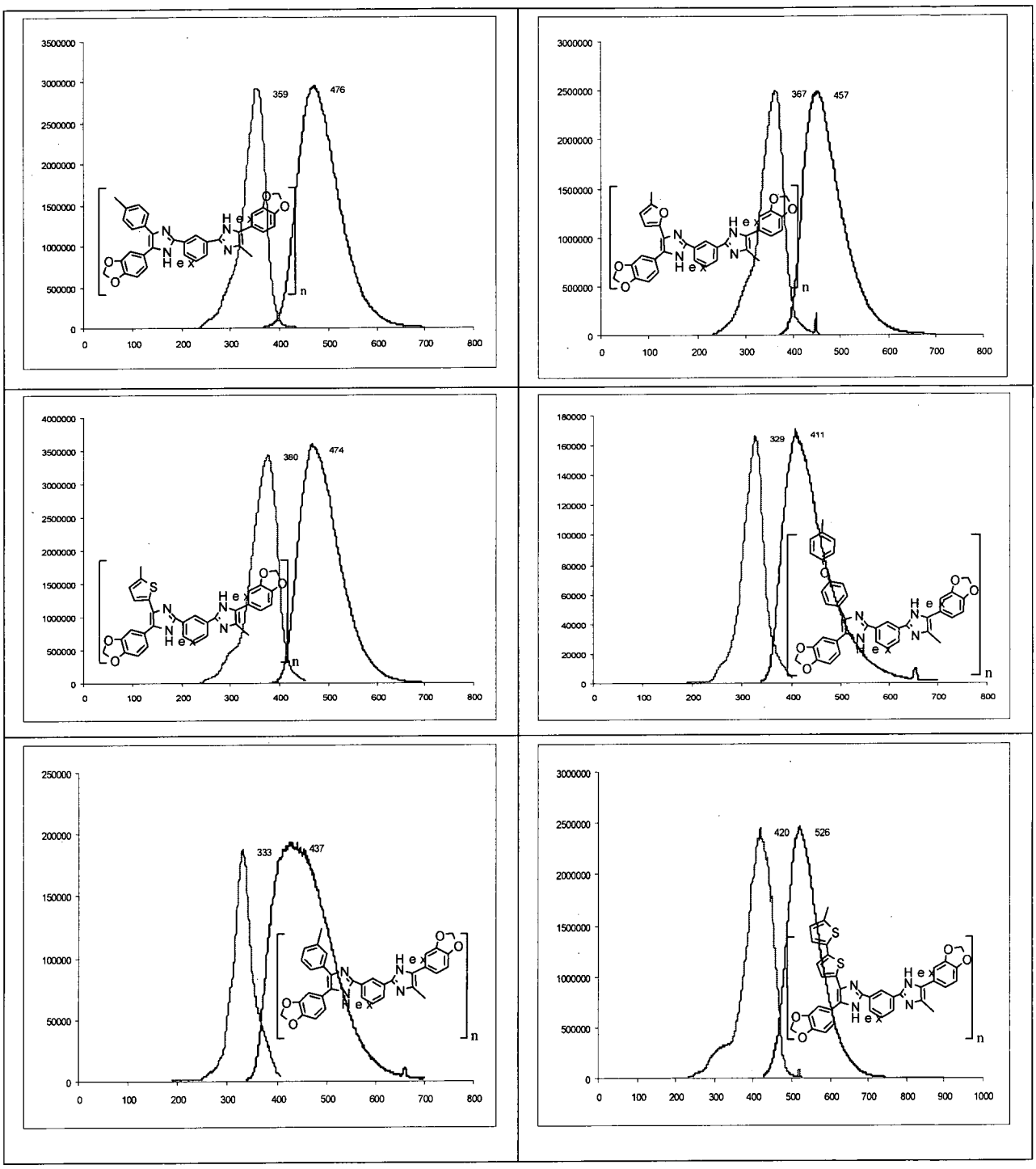
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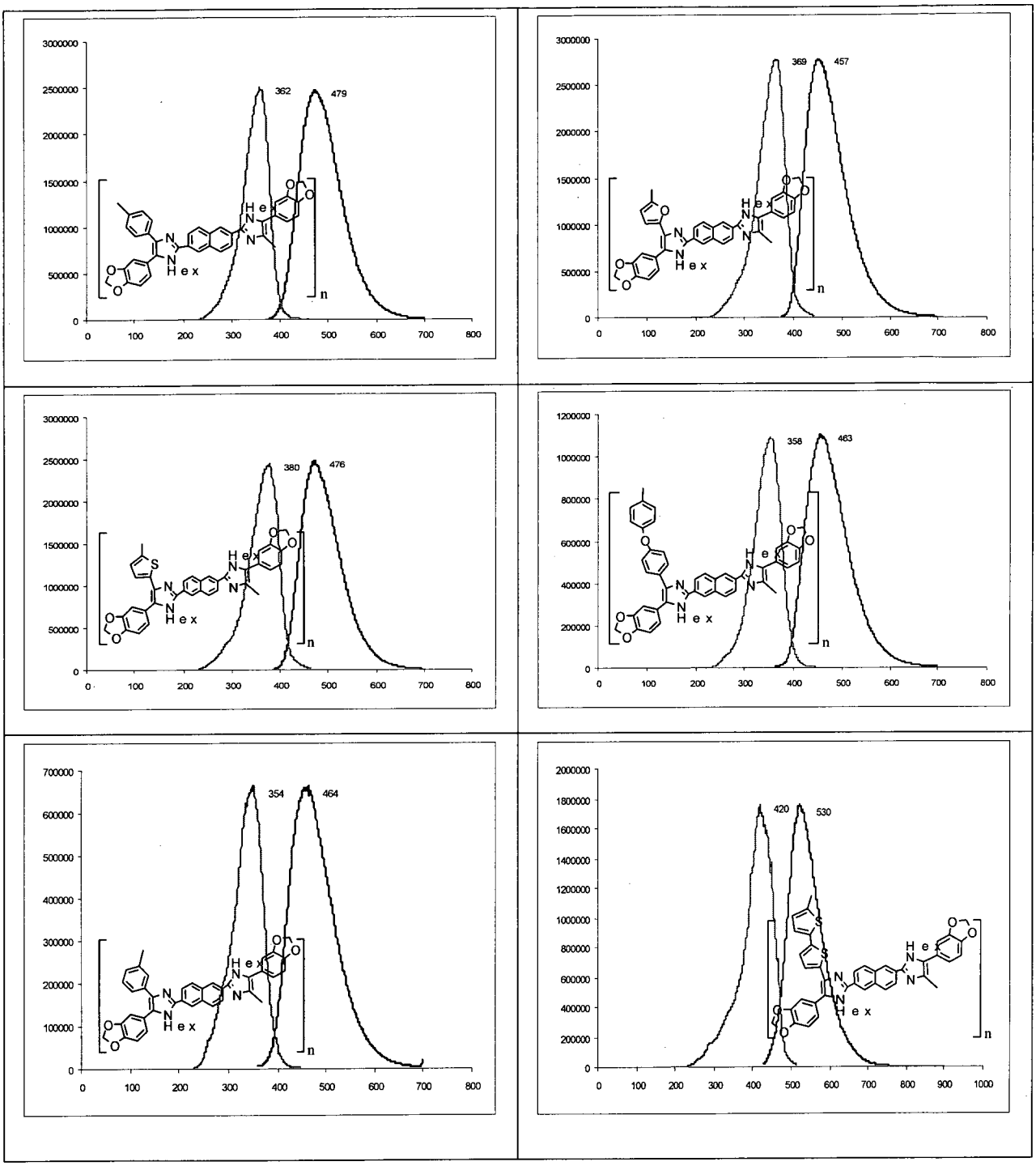
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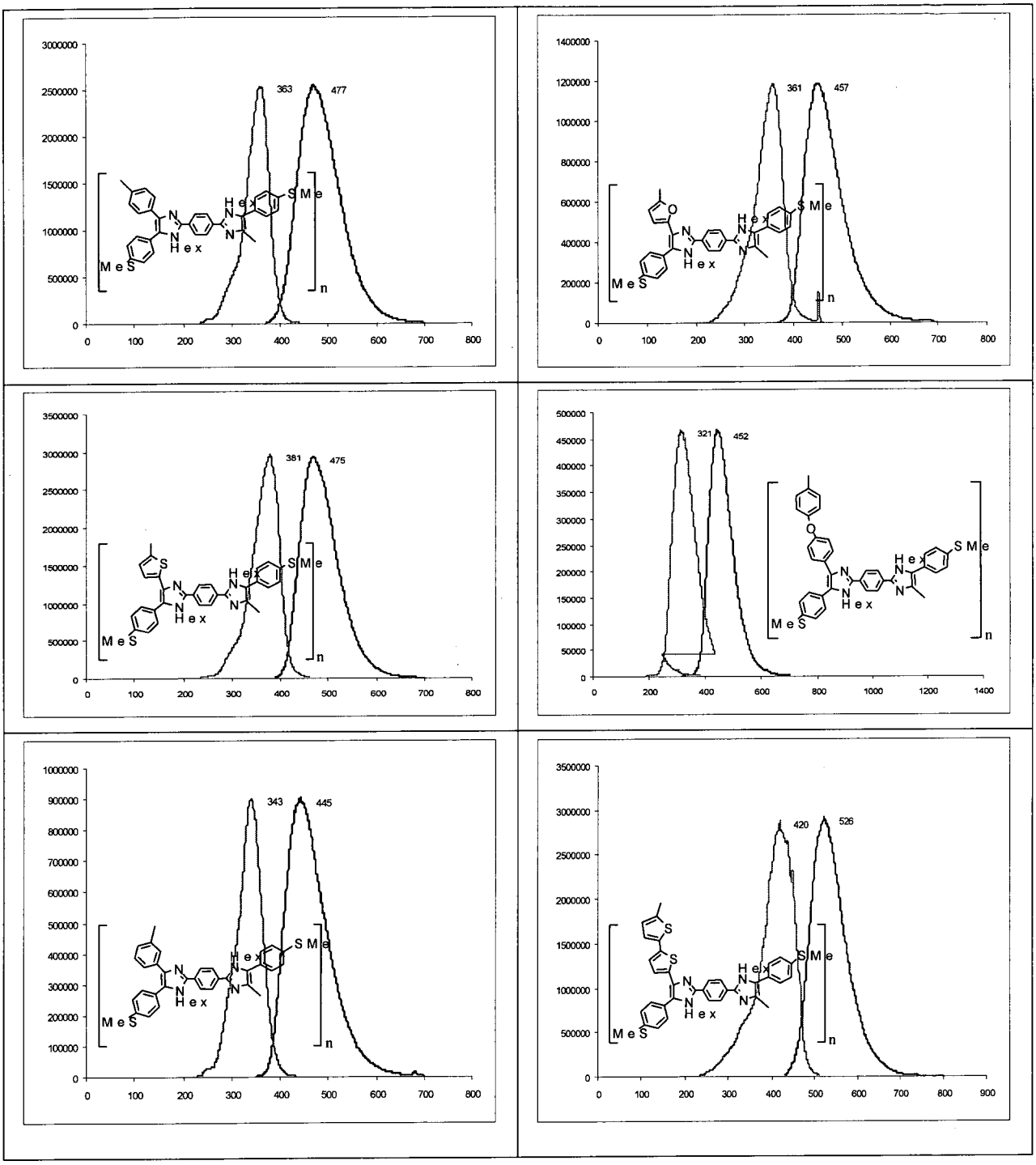
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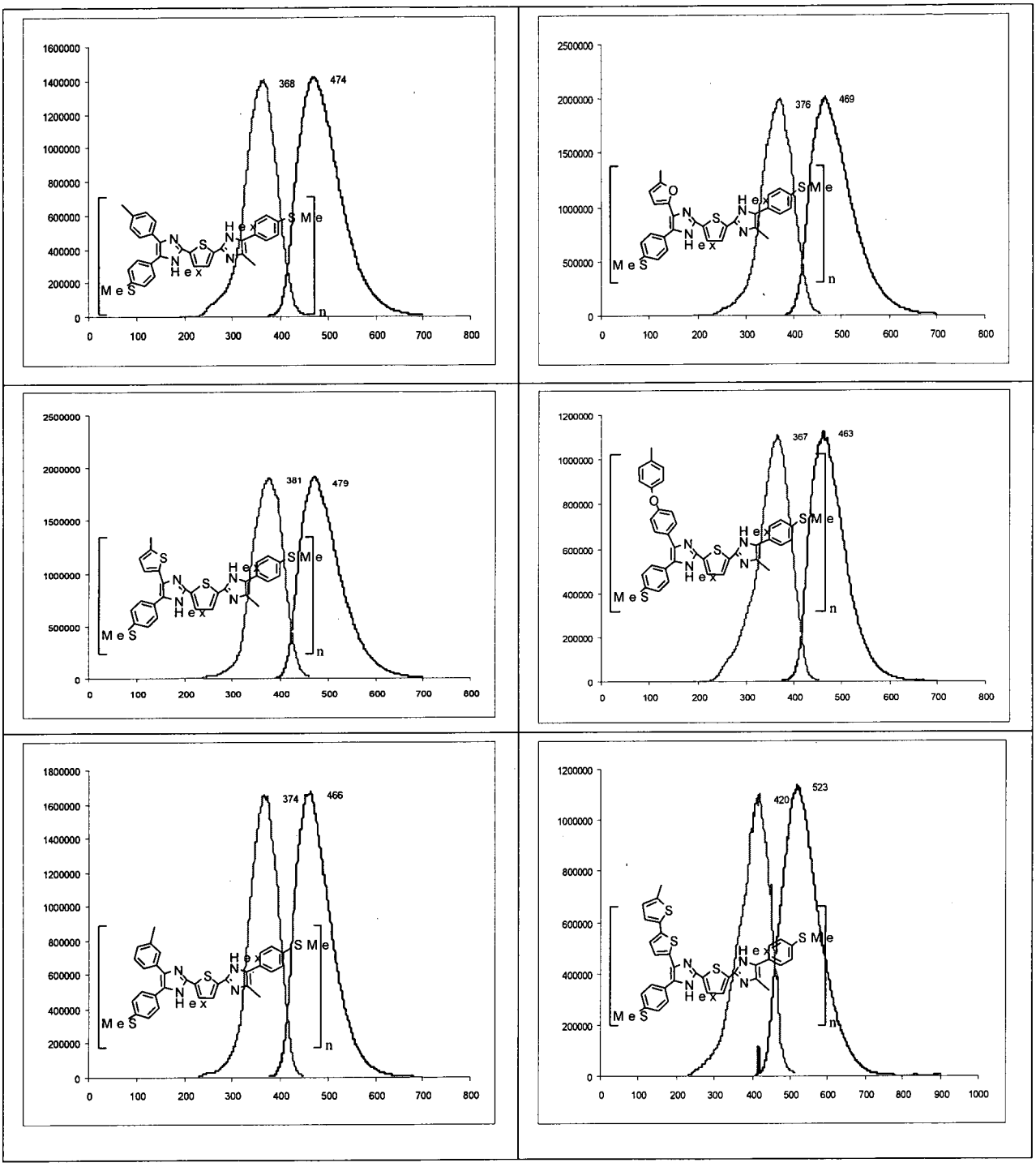
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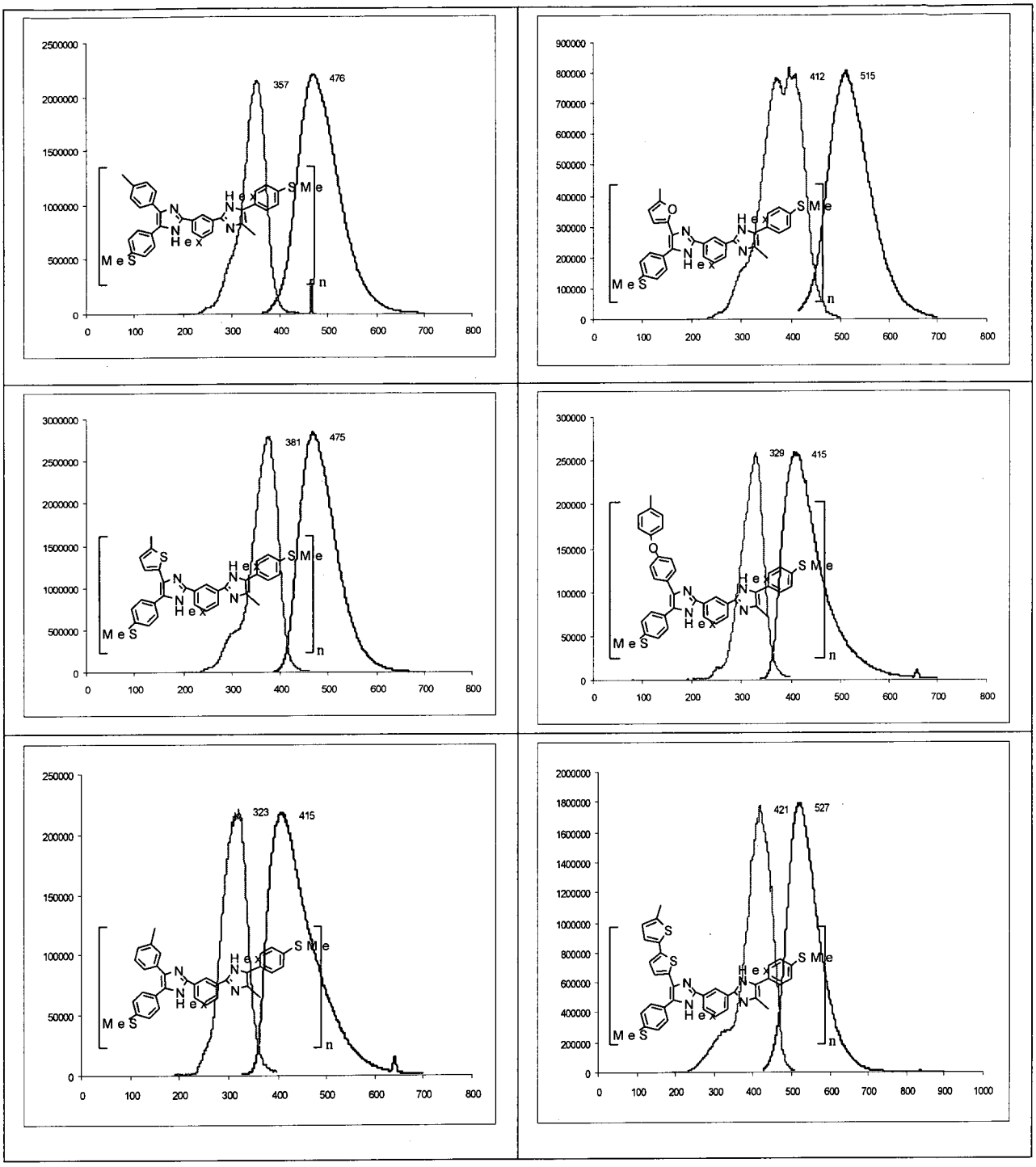
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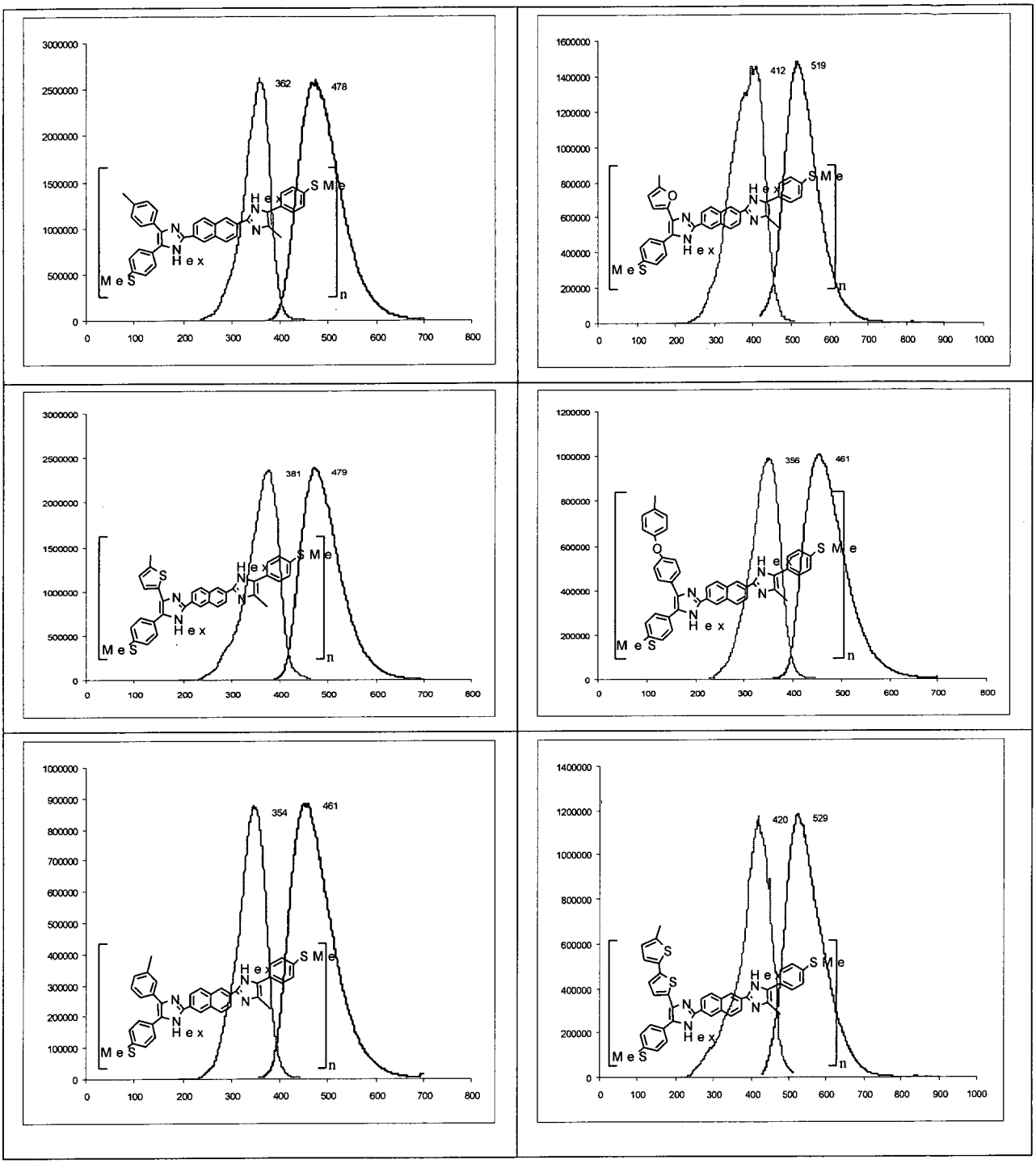
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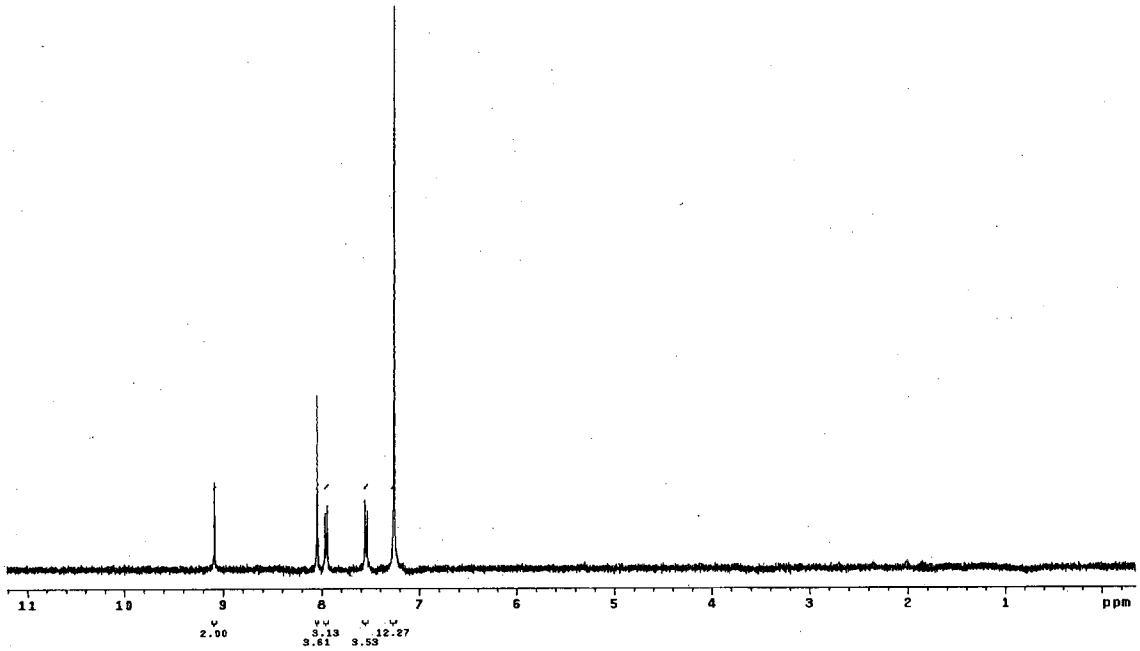
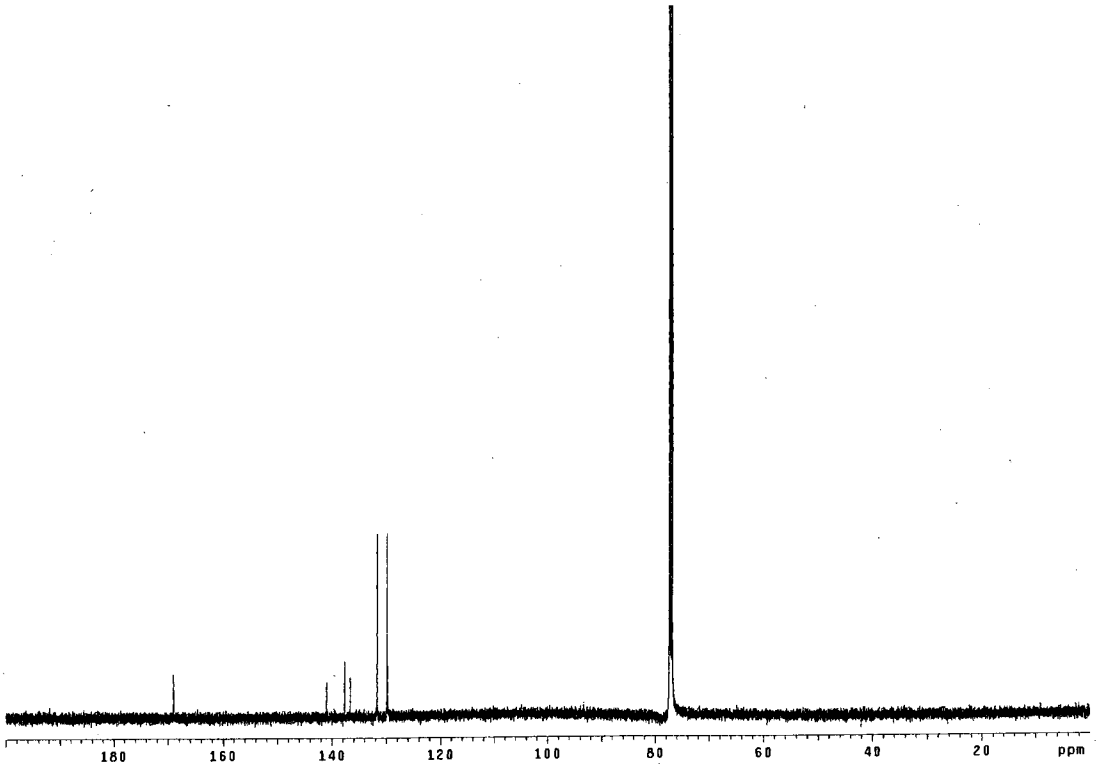
NMR Data

NMR Spectra of Starting Materials:

^{1}H NMR Spectra of 1, 4-*N*--Benzylidene-bis(4-chloro-benzenesulfonamide) (4.4a):

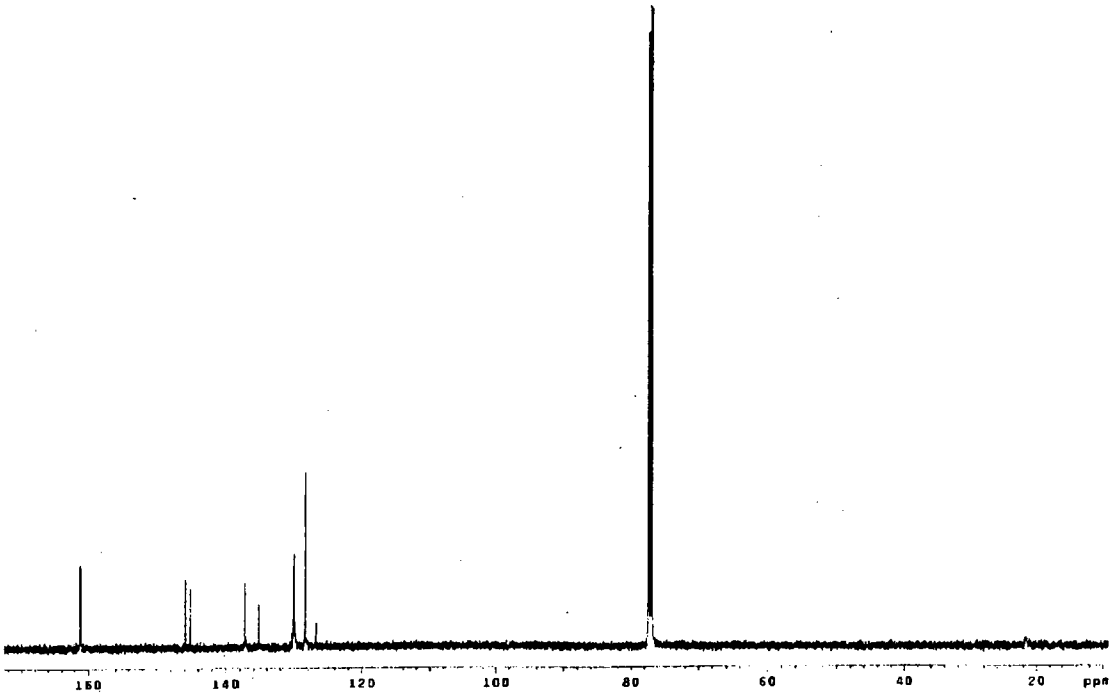


^{13}C NMR:

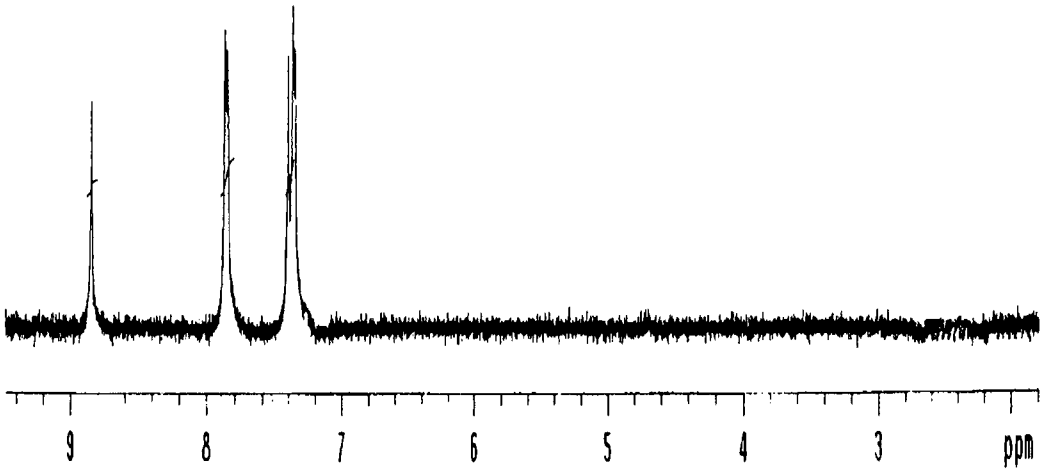


2, 5-*N*-thiophen-2-ylmethylene-bis(4-chloro-benzenesulfonamide) (4.4d):

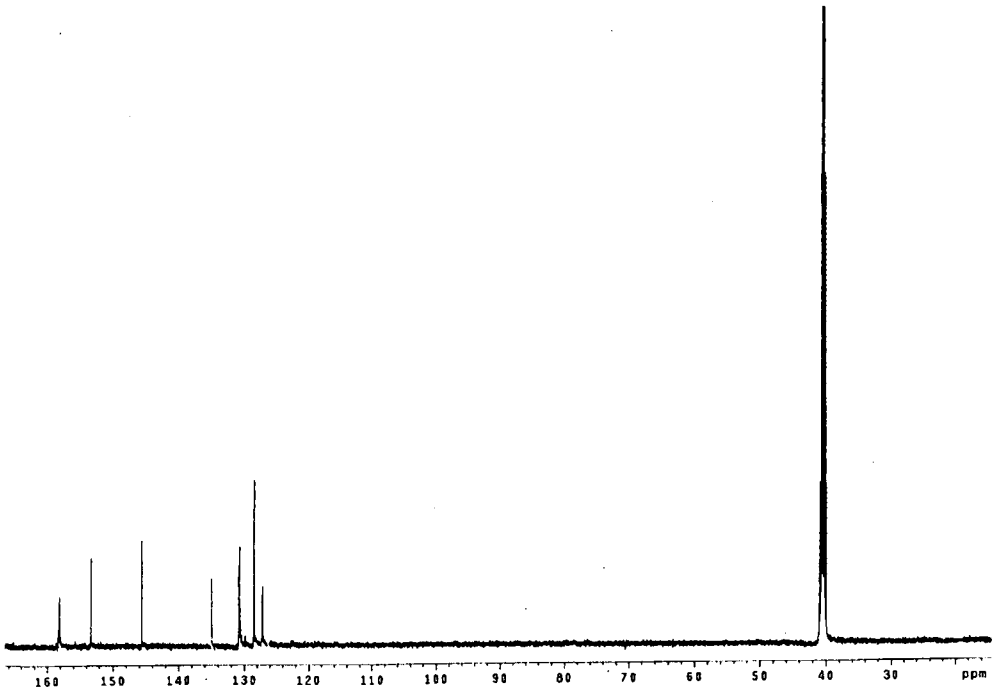
^{13}C NMR:



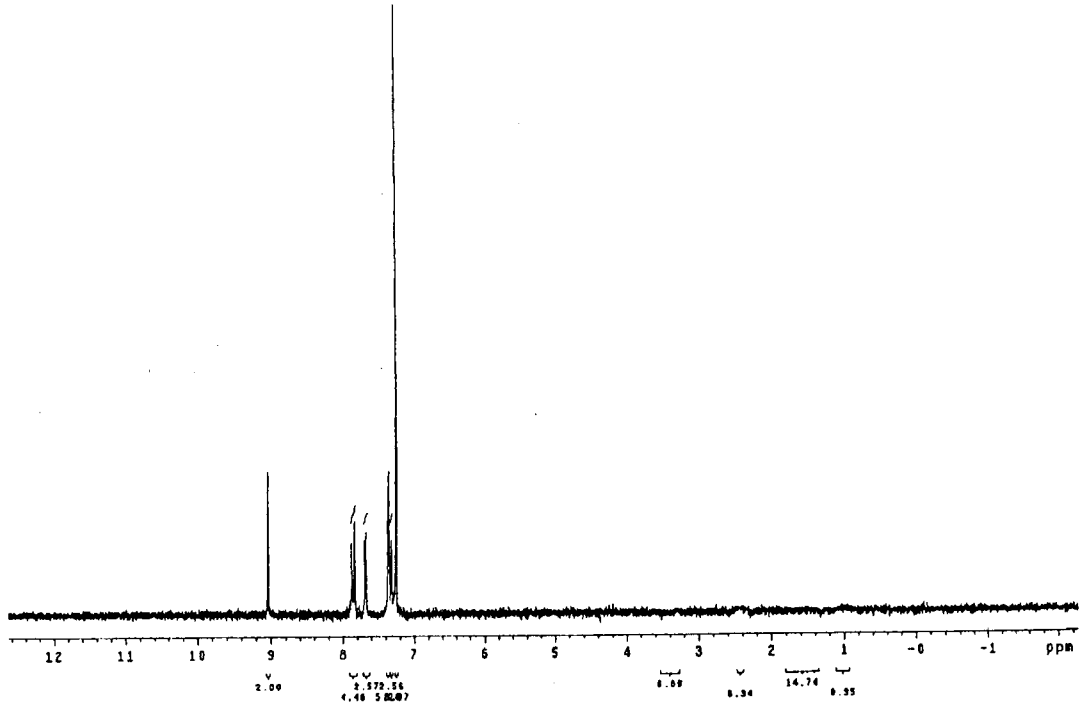
2, 5-*N*-furan-2-ylmethylene-bis(4-chloro-benzenesulfonamide) (4.4e):



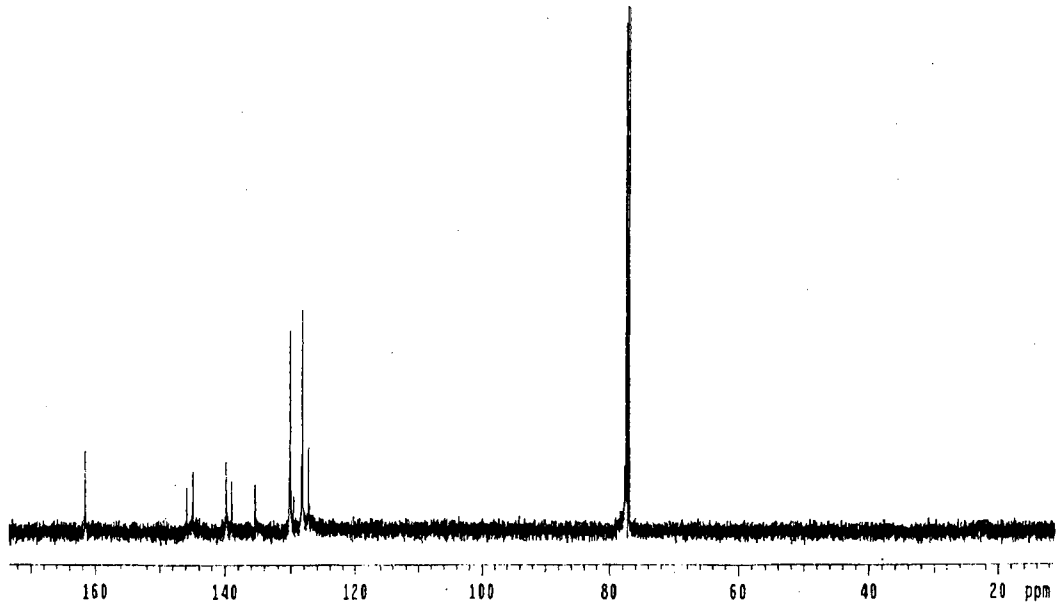
^{13}C NMR:



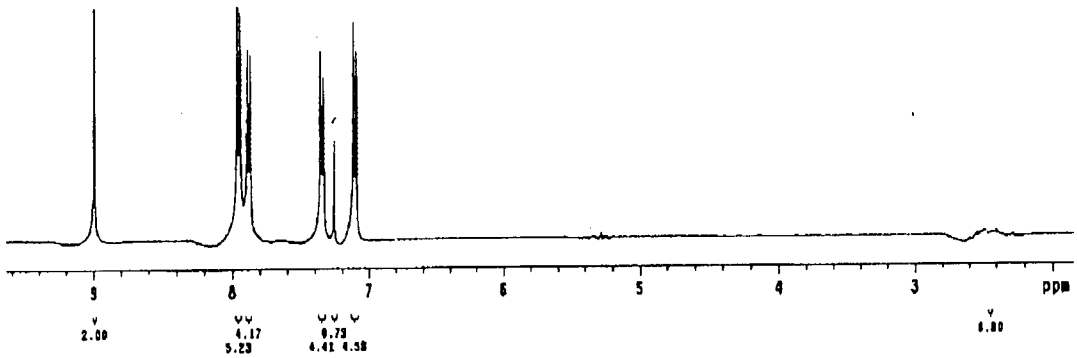
Bis(4-chloro-*N*-thiophen-2-ylmethylene-benzenesulfonamide) (4.4f):



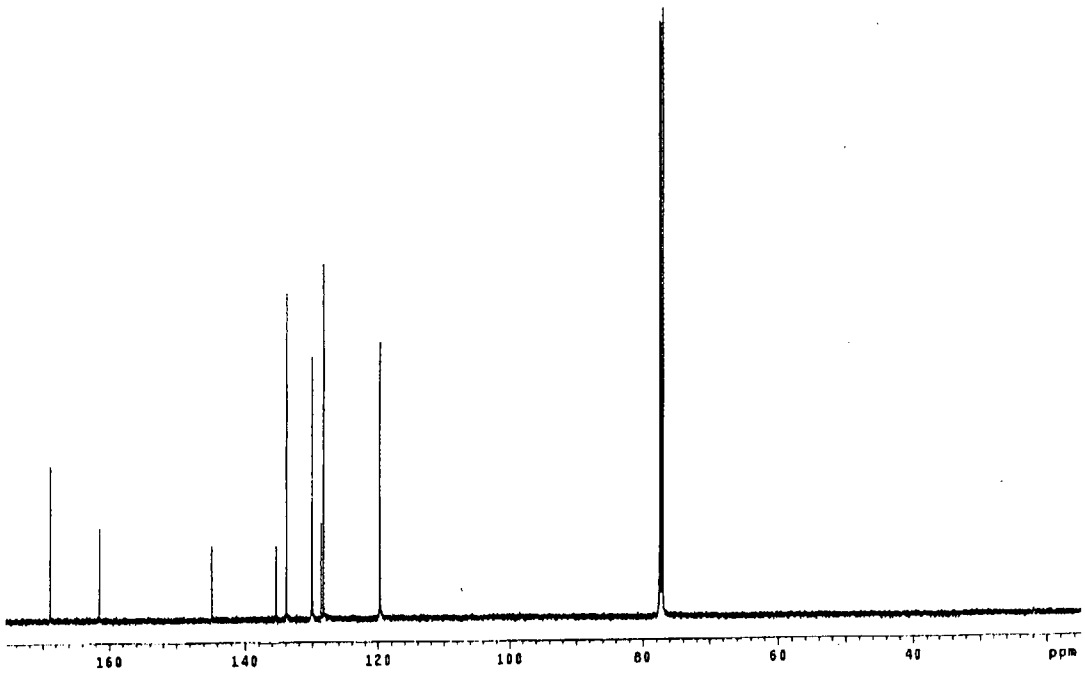
^{13}C NMR:



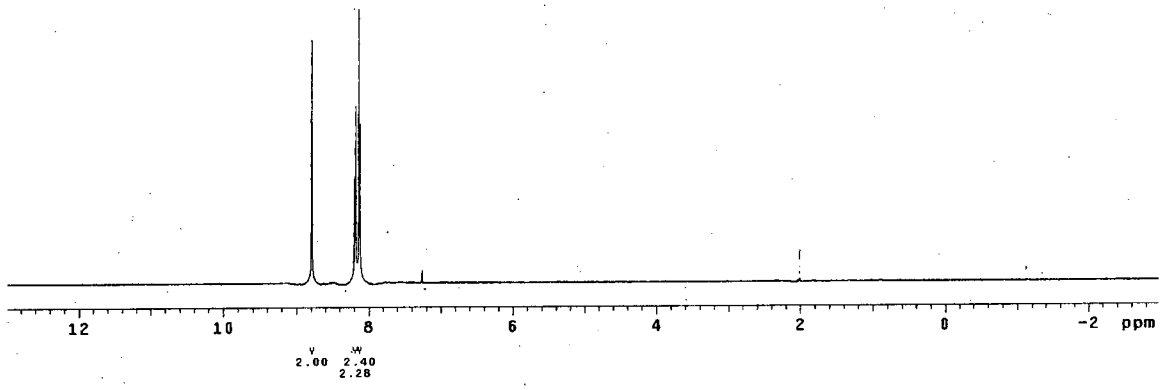
***N*-(4-phenoxy-benzylidene)-bis(4-chloro-benzenesulfonamide) (4.4g):**



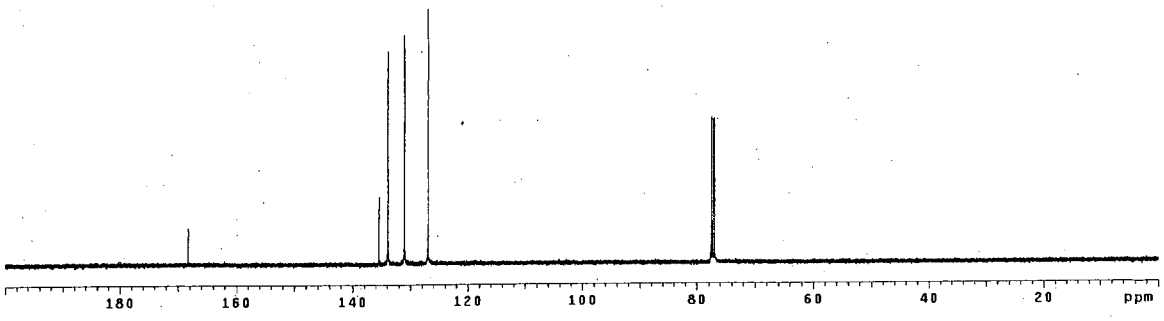
^{13}C NMR:



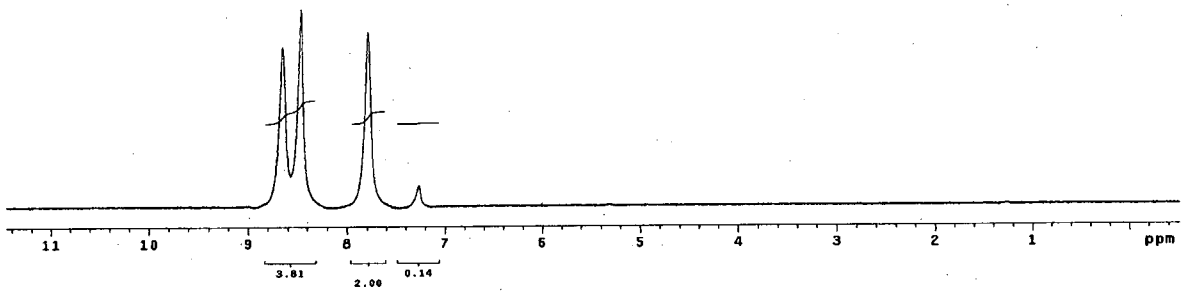
^{1}H NMR of Naphthalene-2, 6-dicarbonyl dichloride (4.3c):



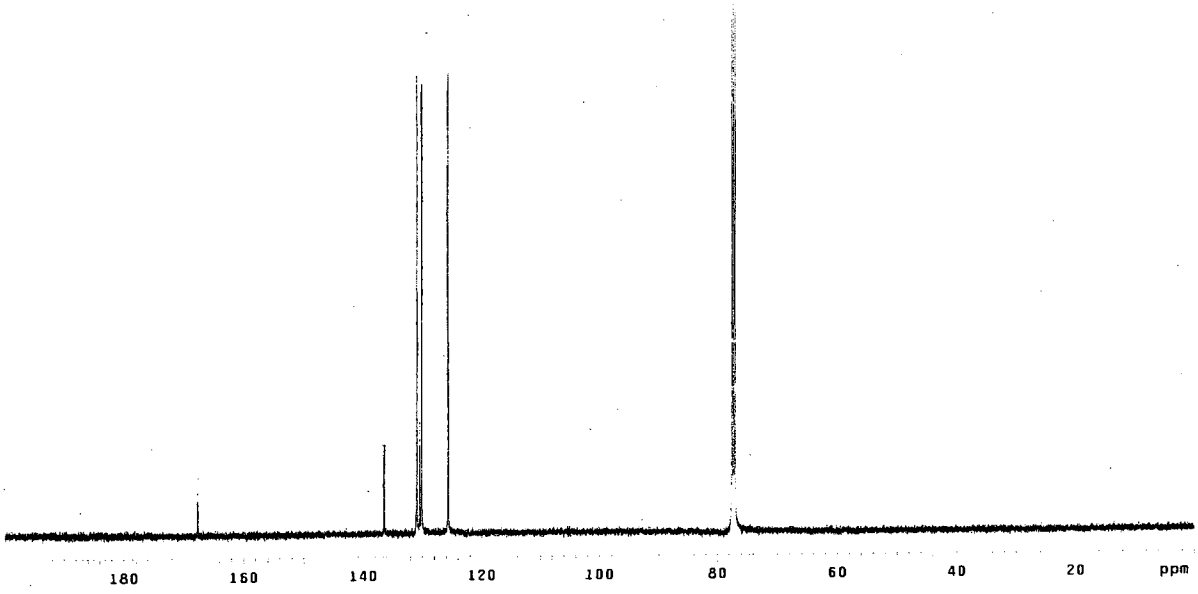
^{13}C NMR:



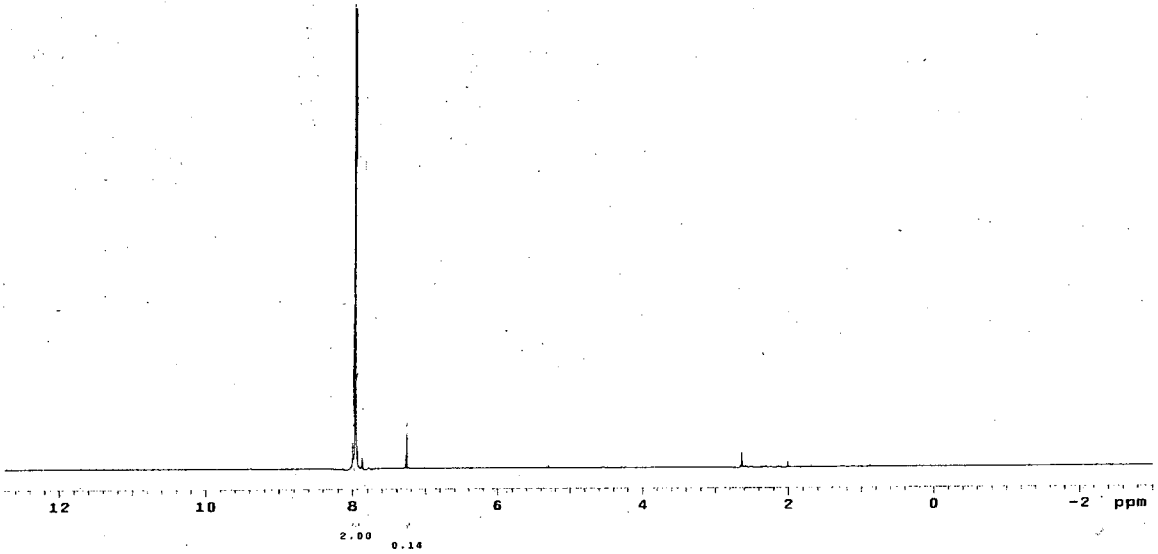
^{1}H NMR of Naphthalene-1, 4-dicarbonyl dichloride (4.3h):



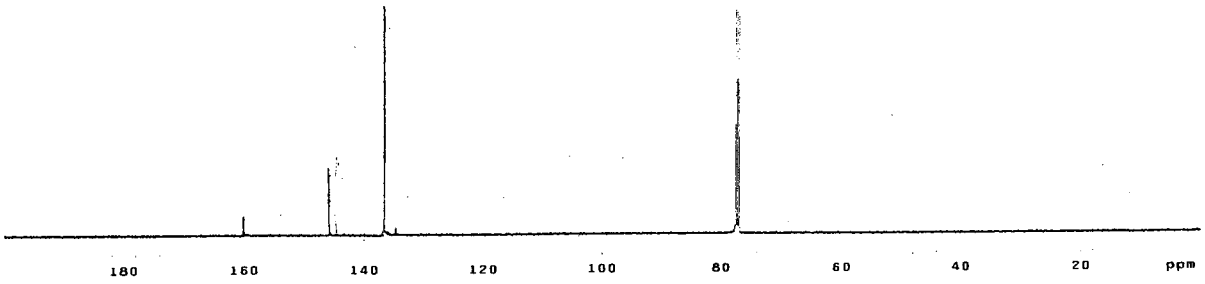
^{13}C NMR:



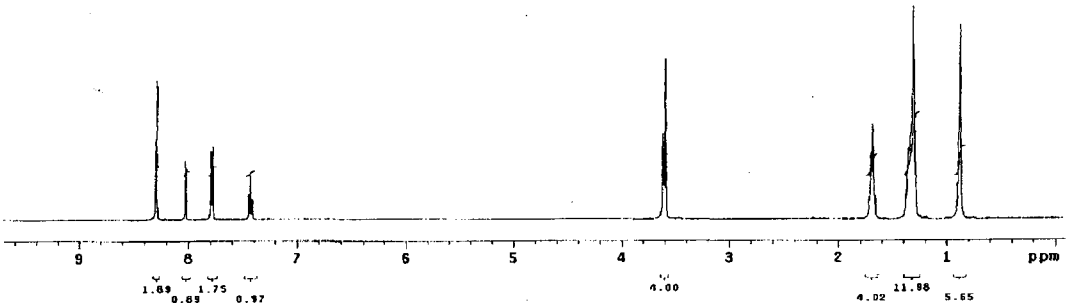
^{1}H NMR of Thiophene-2, 5-dicarbonyl dichloride (4.3d):



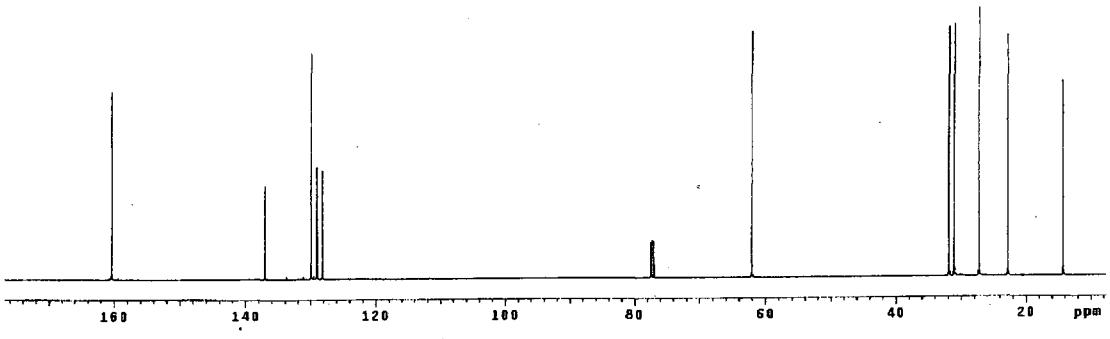
^{13}C NMR:



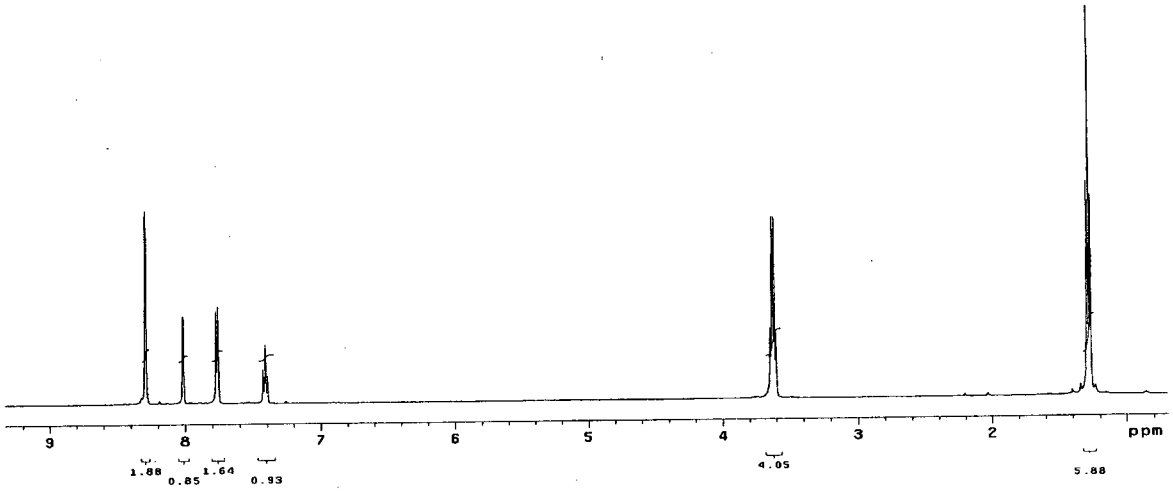
^{1}H NMR of Hexyl-(3-hexyliminomethyl-benzylidene)-amine (4.5i):



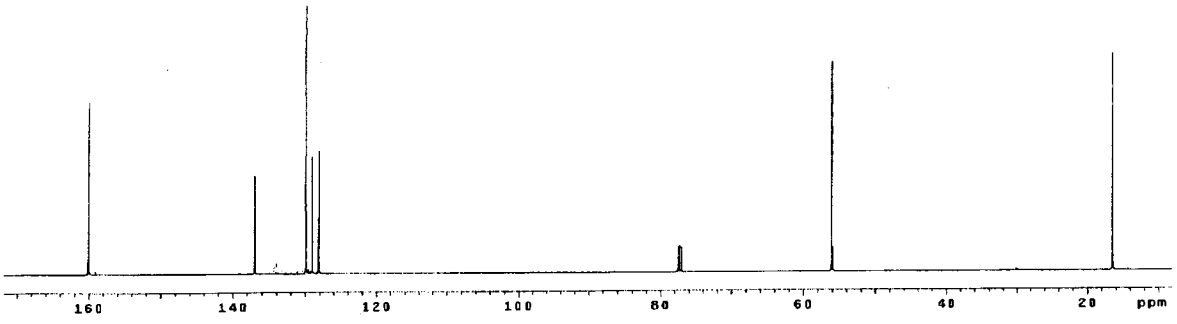
^{13}C NMR:



^{1}H NMR of Ethyl-(3-ethyliminomethyl-benzylidene)-amine (4.5j):

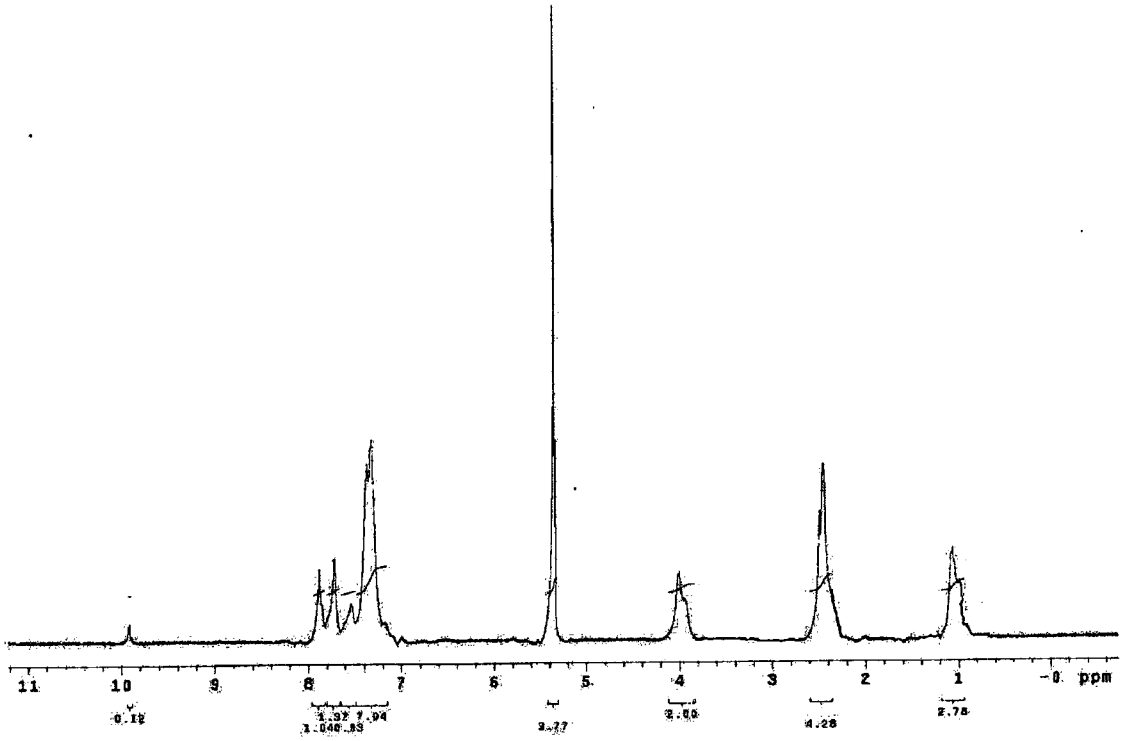


^{13}C NMR:

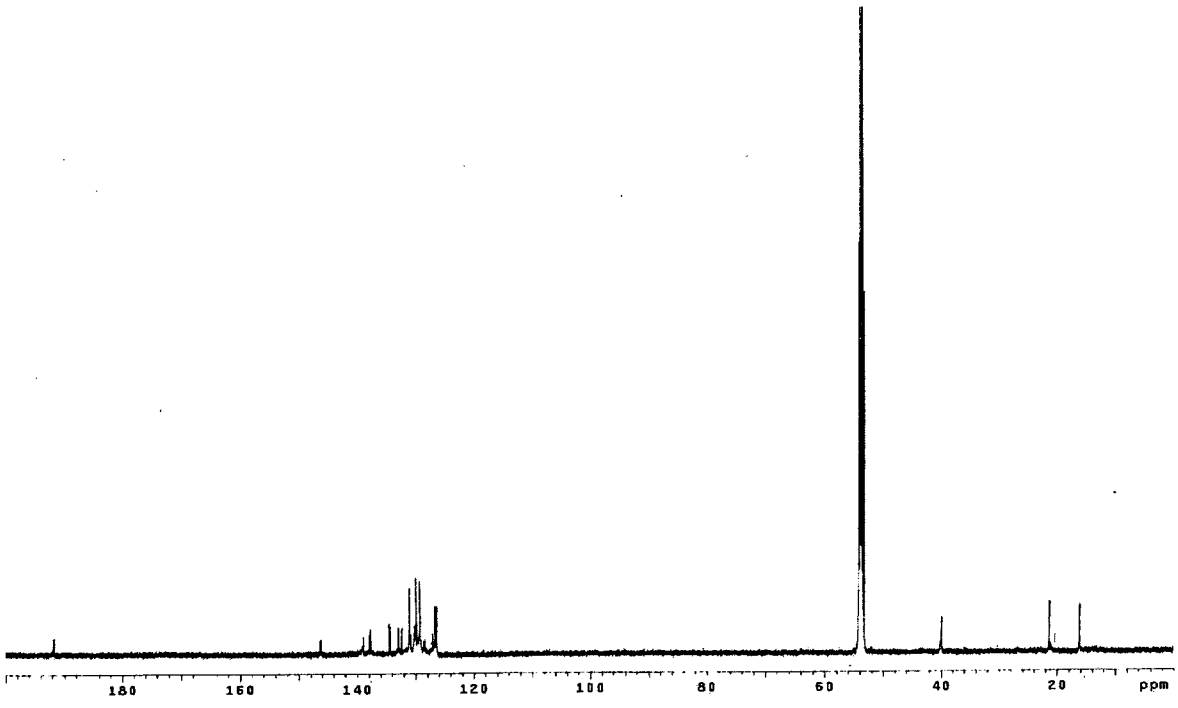


NMR Spectra of Imidazole Containing Polymers:

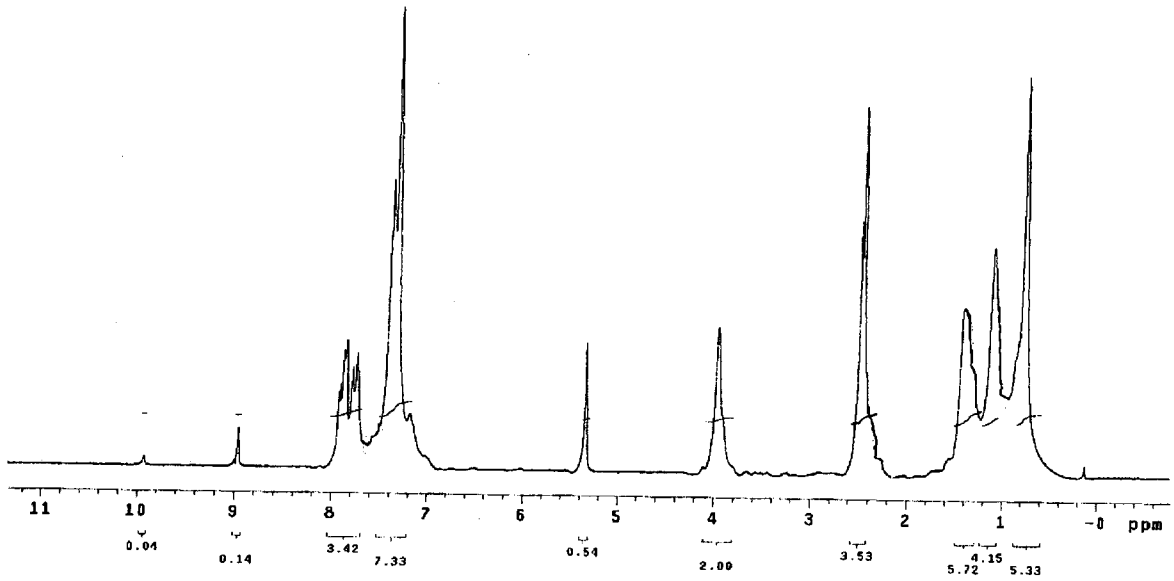
^{1}H NMR(4.1a)



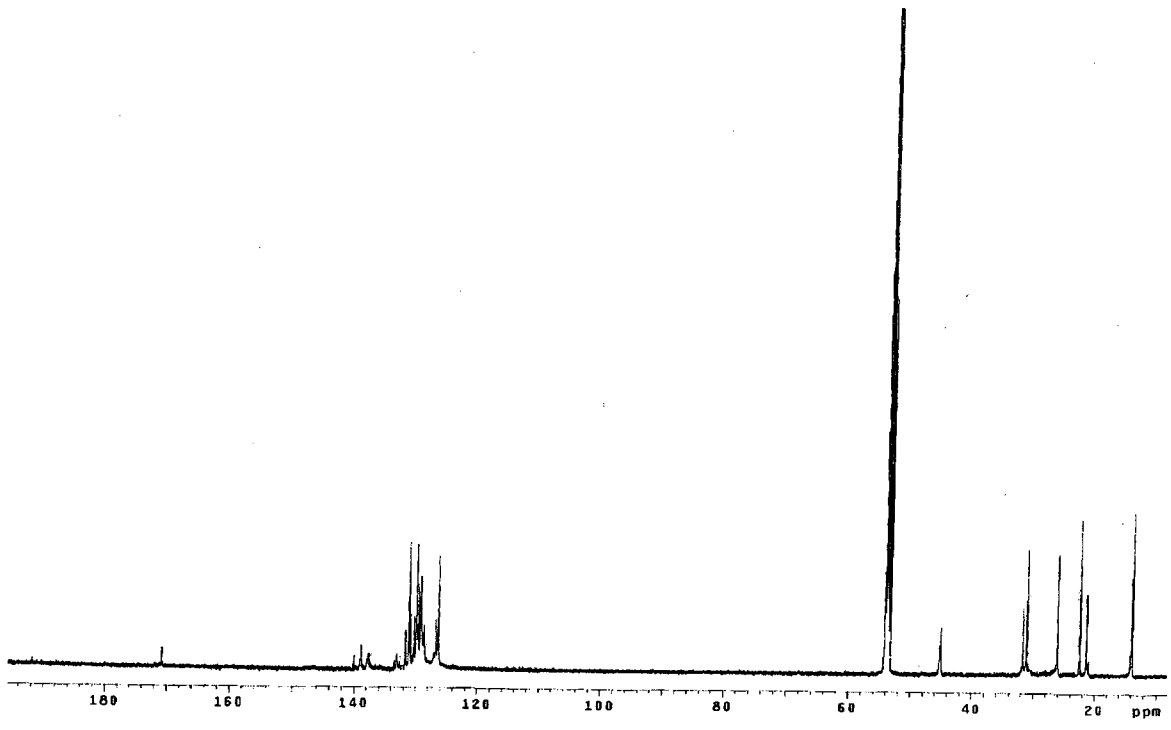
^{13}C NMR(4.1a)



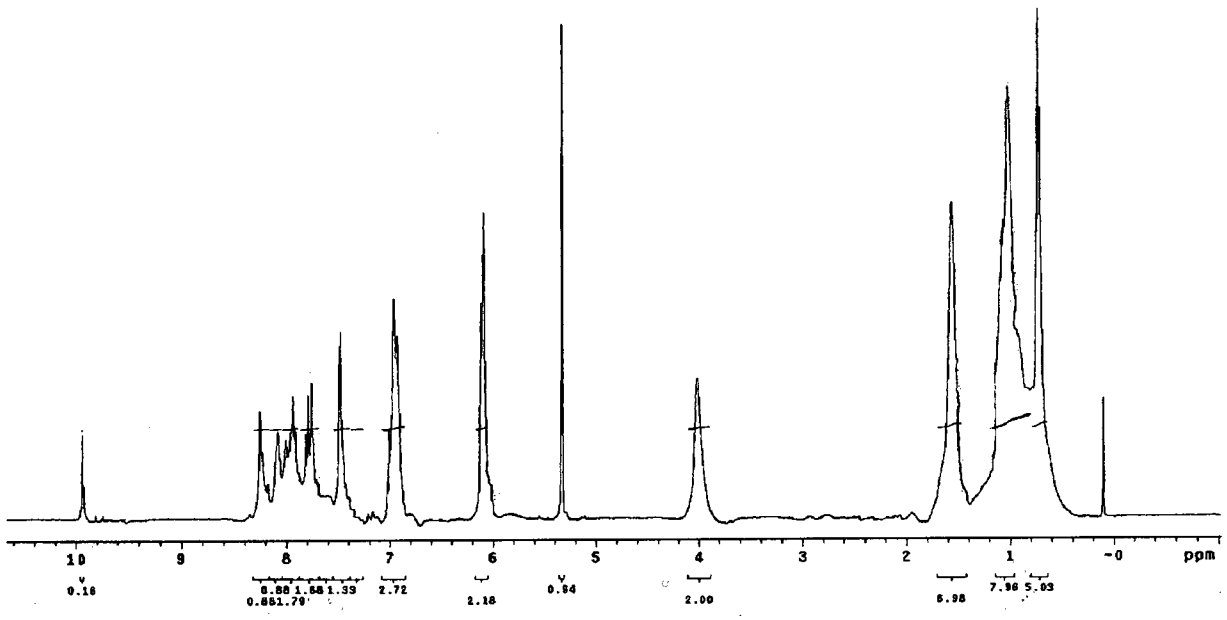
^{1}H NMR(4.1b)



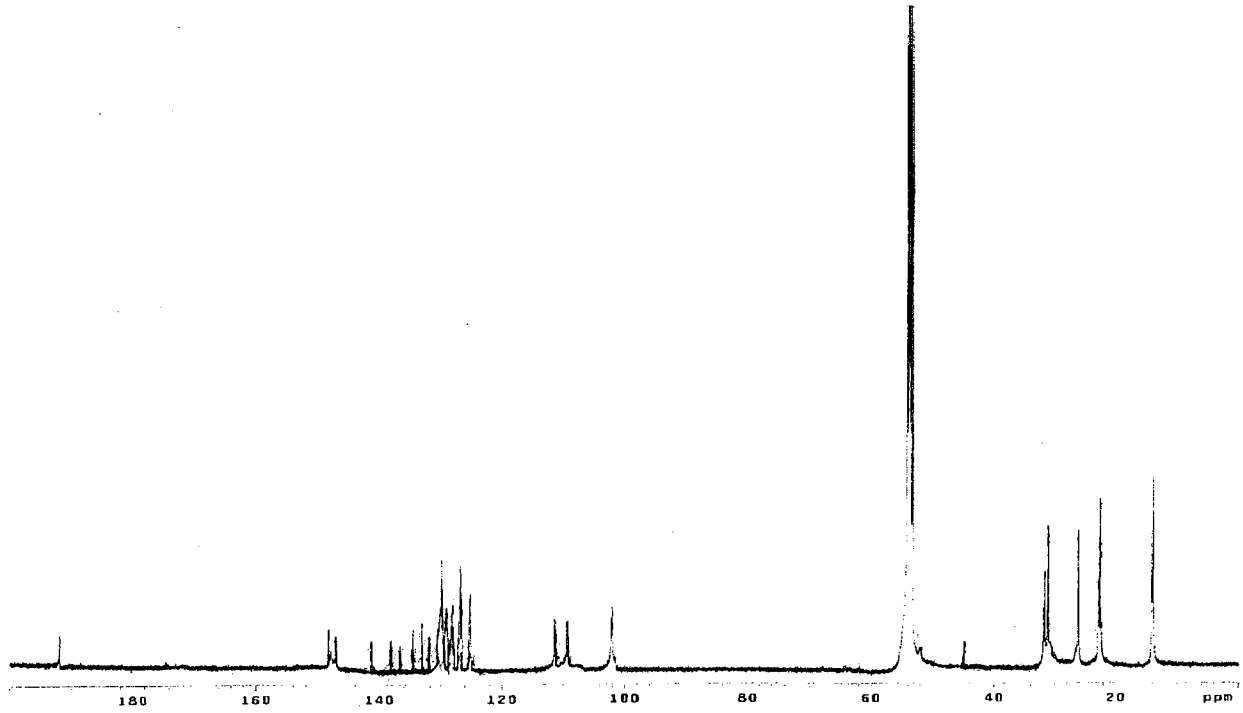
^{13}C NMR(4.1b)



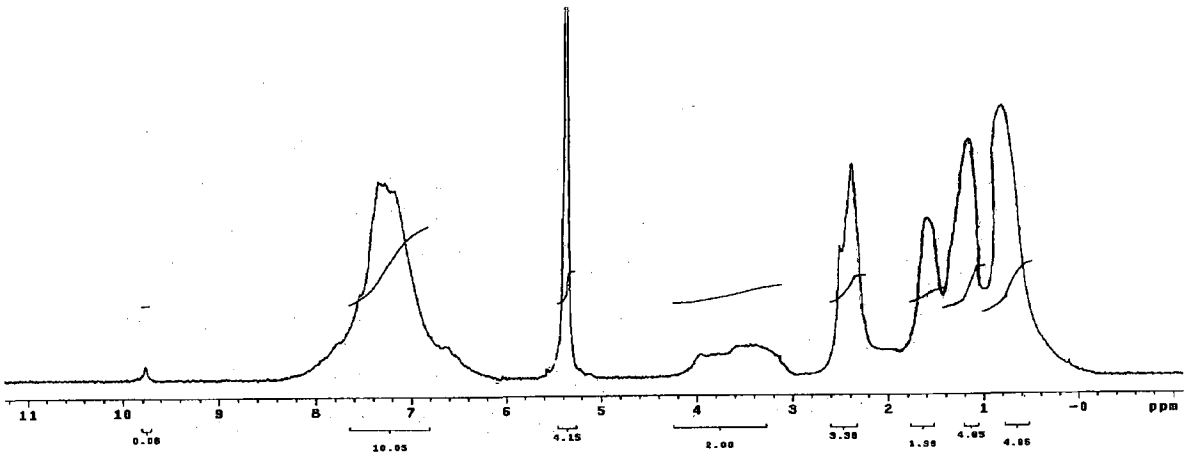
^{1}H NMR(4.1c)



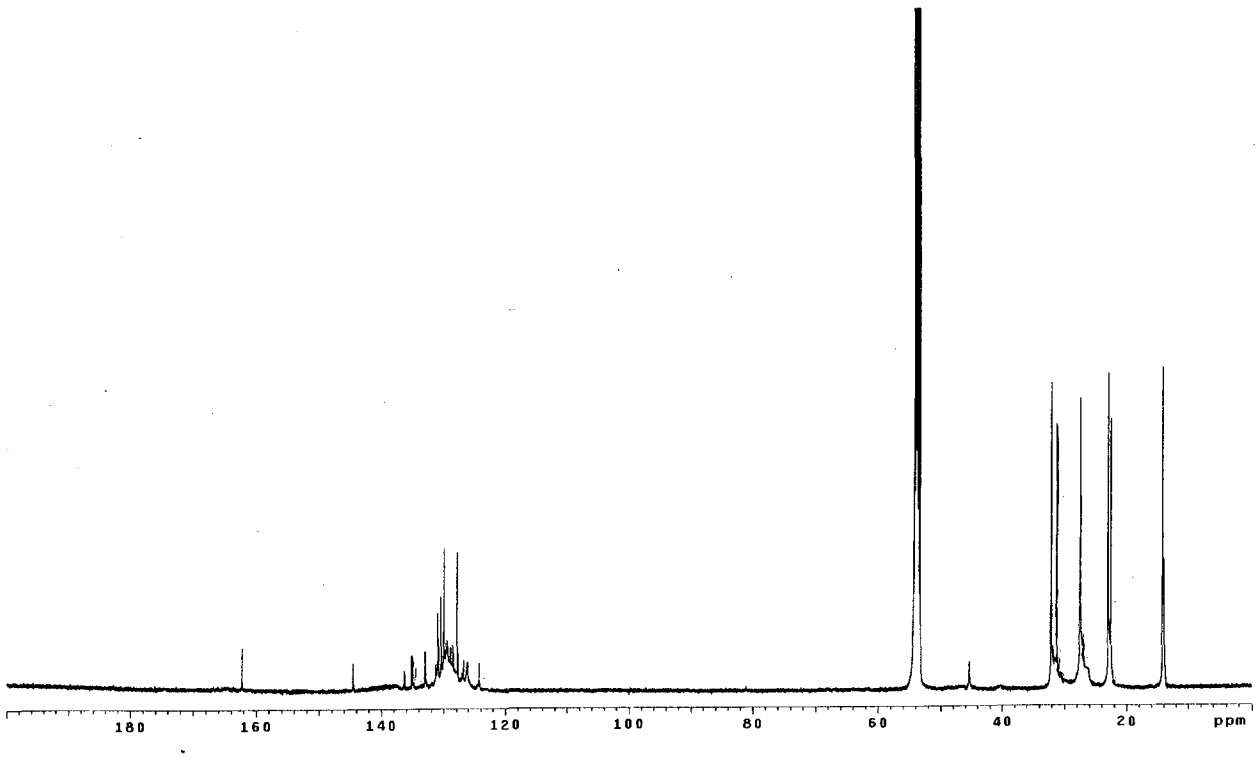
^{13}C NMR(4.1c)



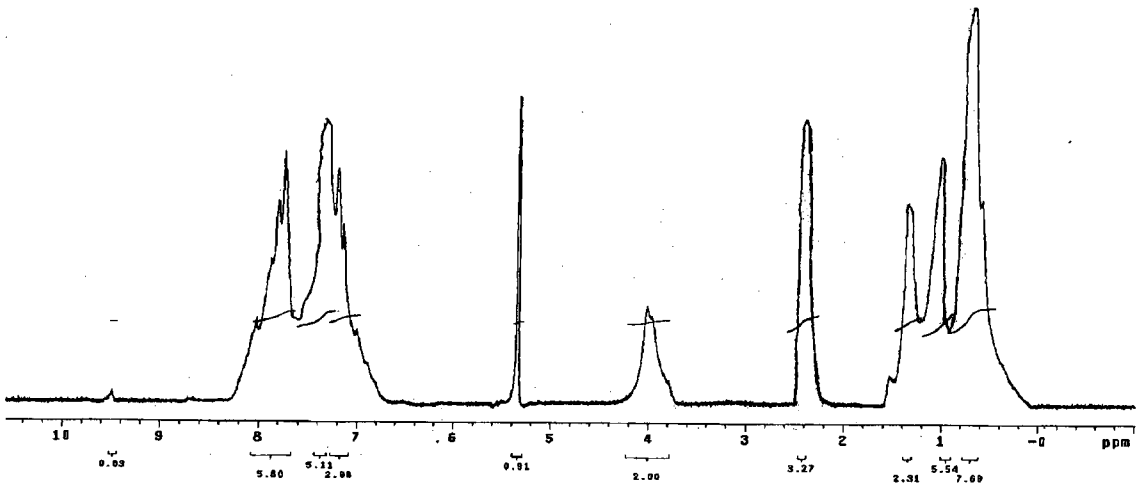
^{1}H NMR(4.1d)



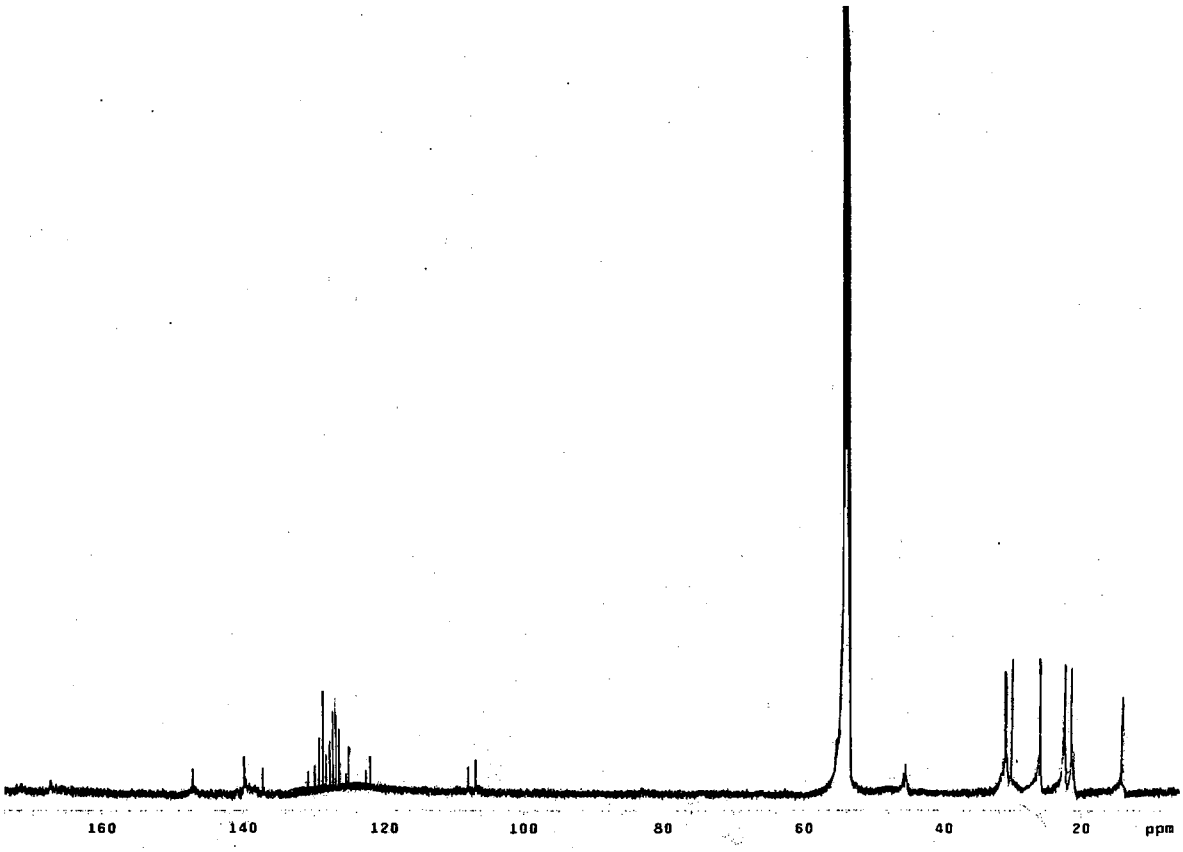
^{13}C NMR(4.1d)



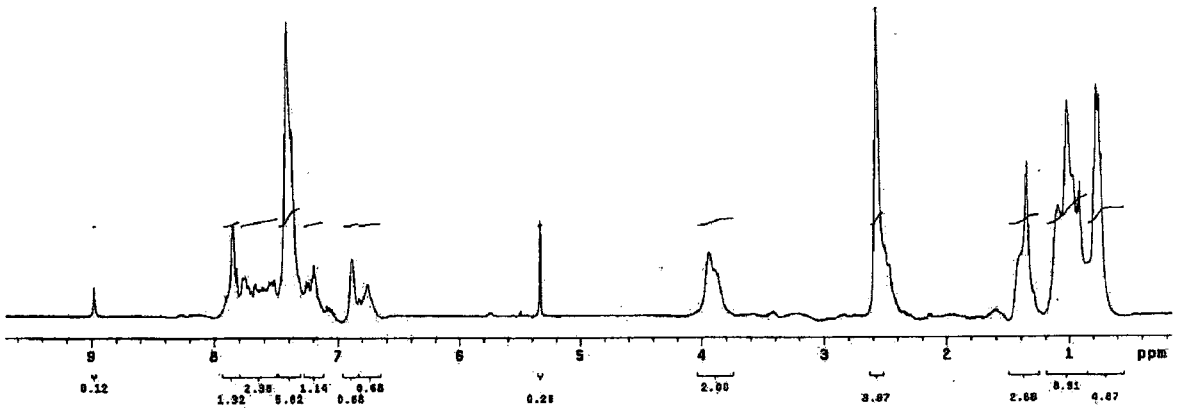
^{1}H NMR(4.1e)



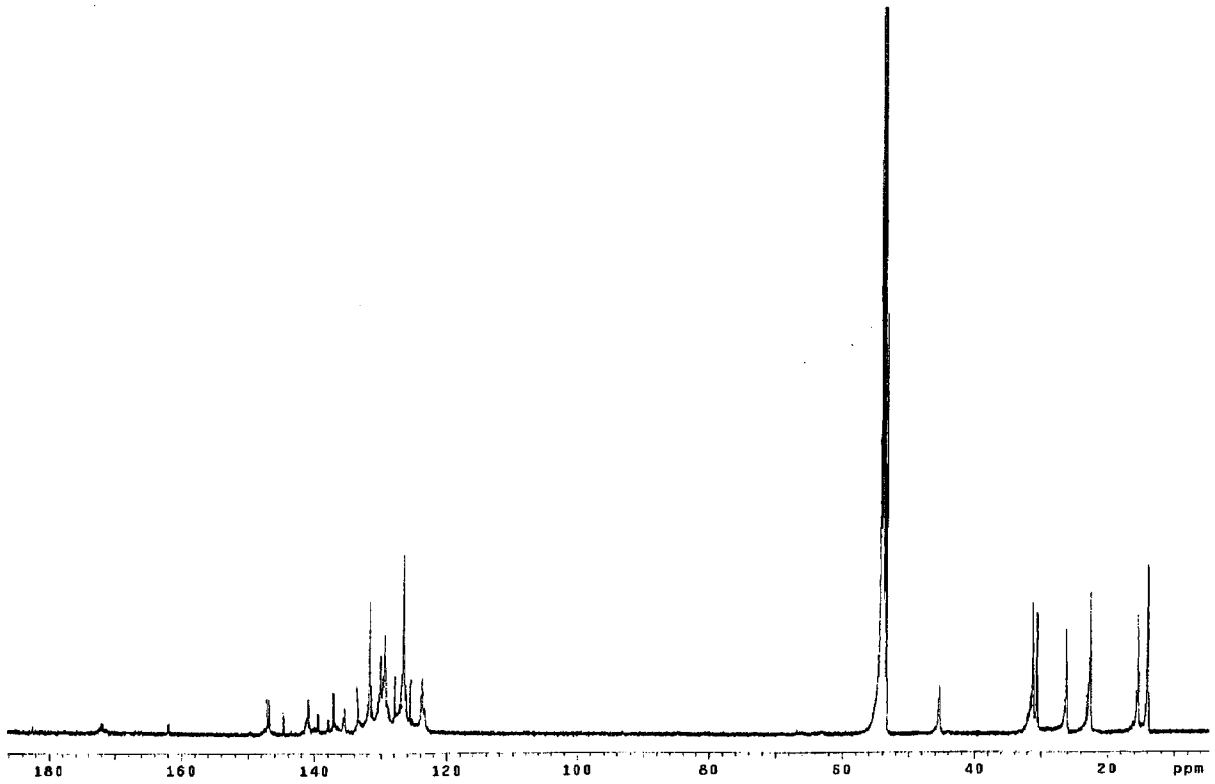
^{13}C NMR(4.1e)



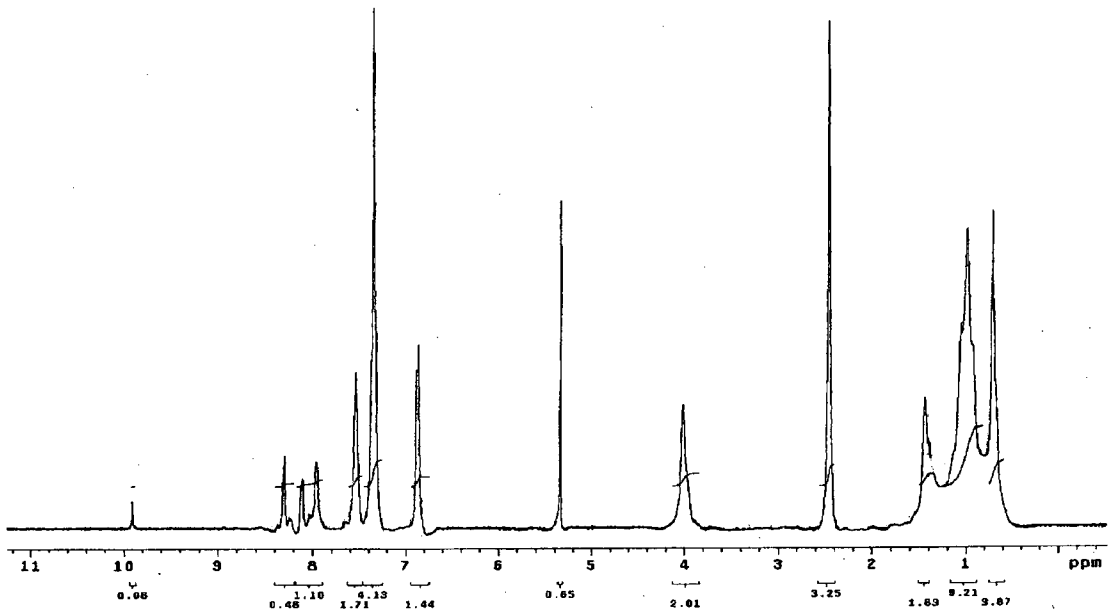
^{1}H NMR(4.1f)



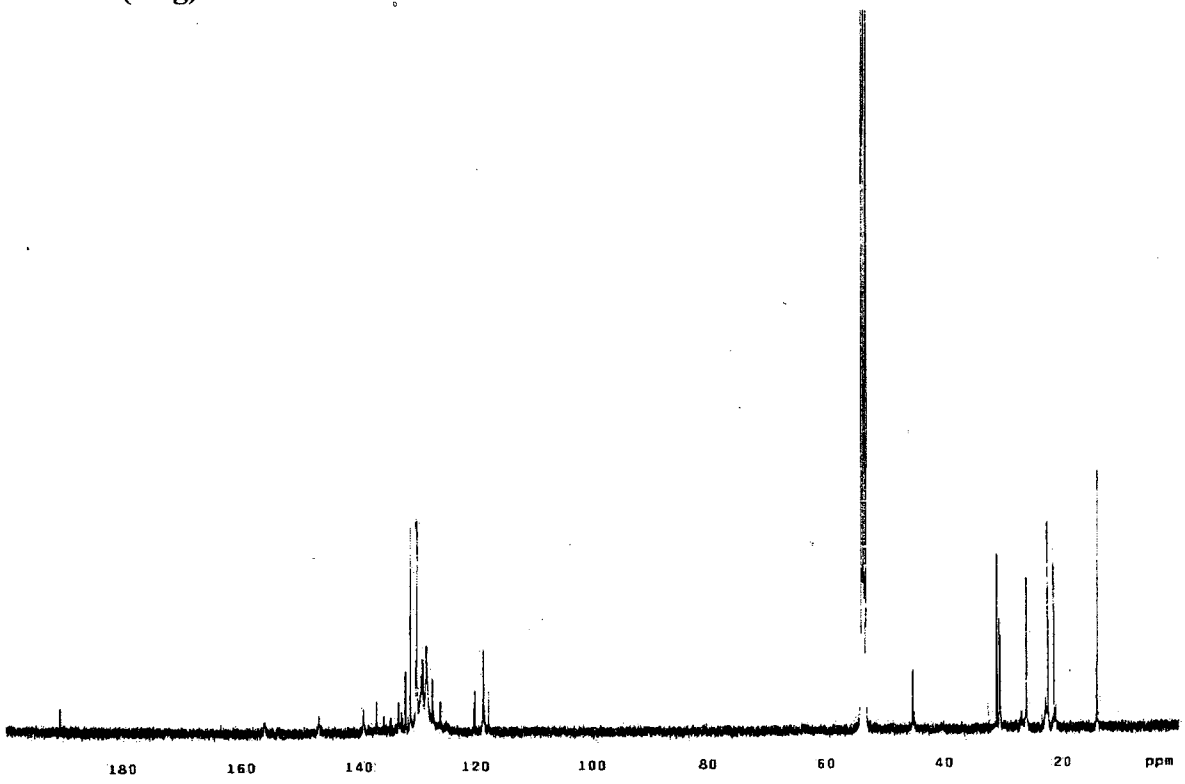
^{13}C NMR(4.1f)



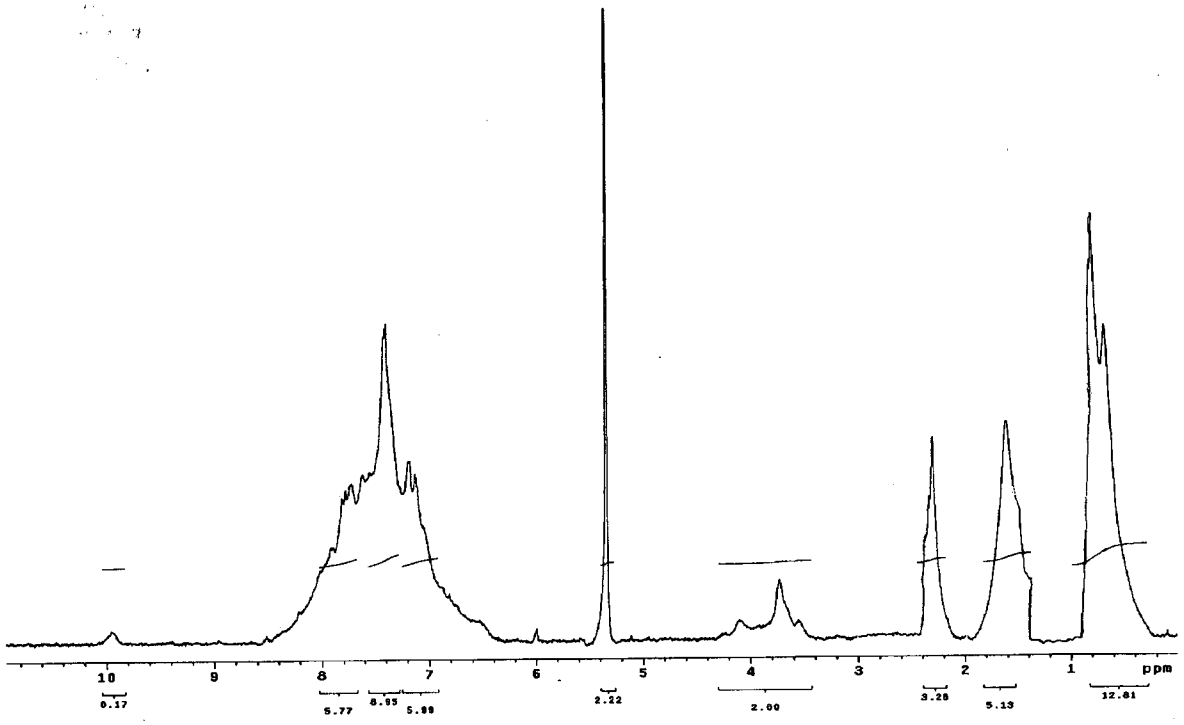
^{1}H NMR(4.1g)



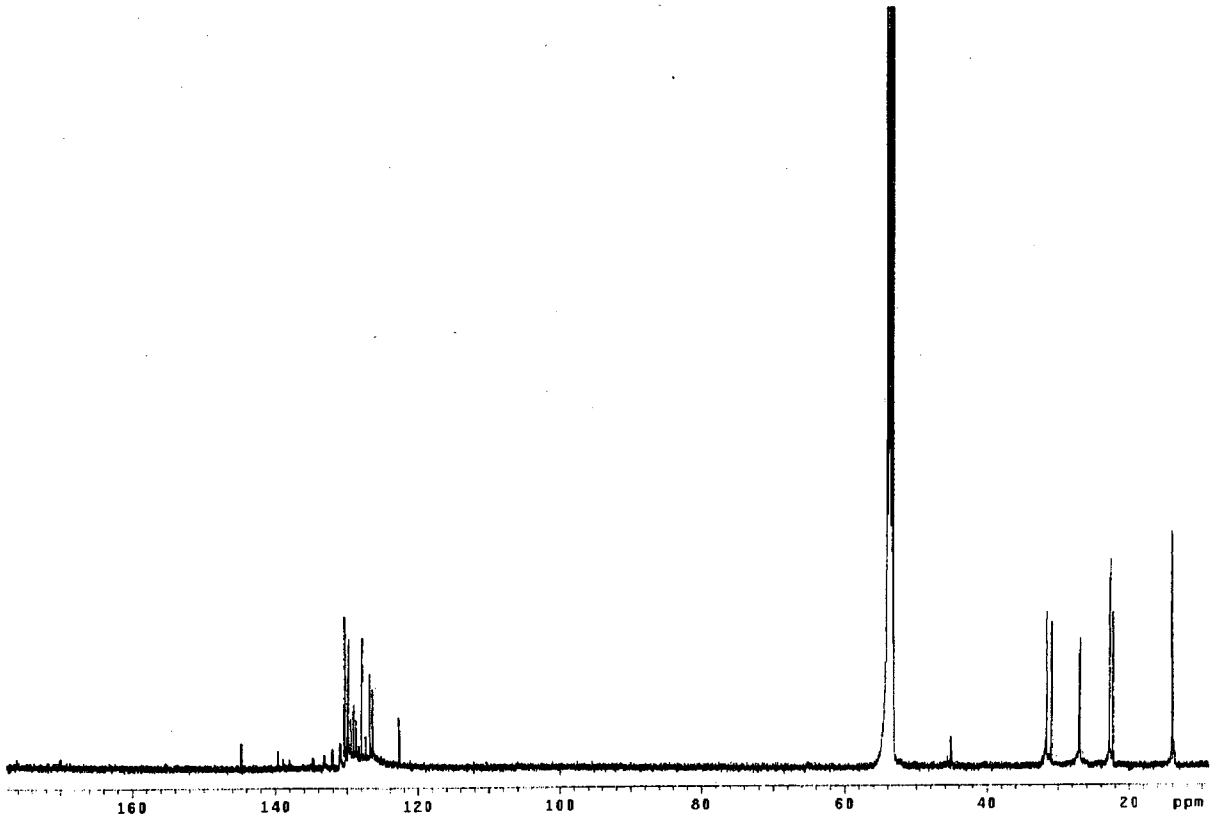
^{13}C NMR(4.1g)



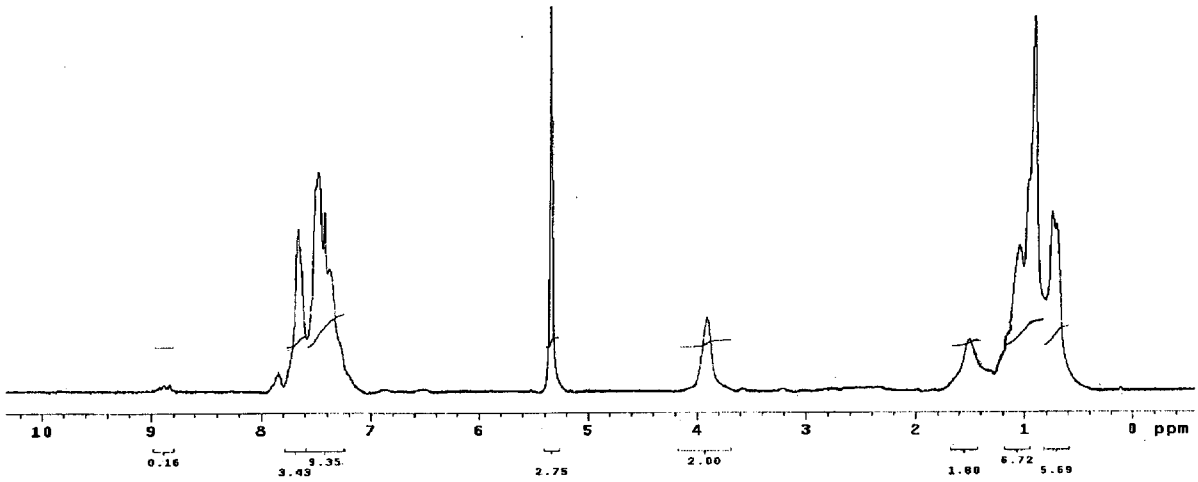
^{1}H NMR(4.1h)



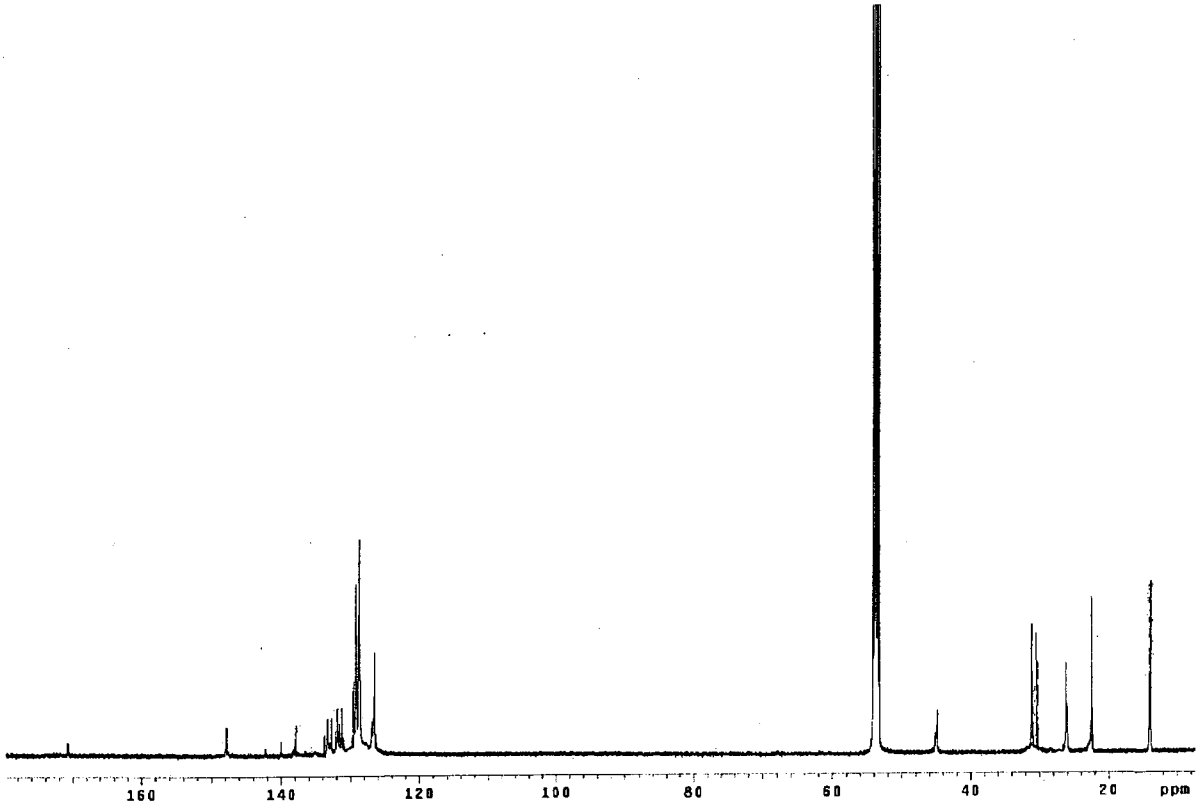
^{13}C NMR(4.1h)



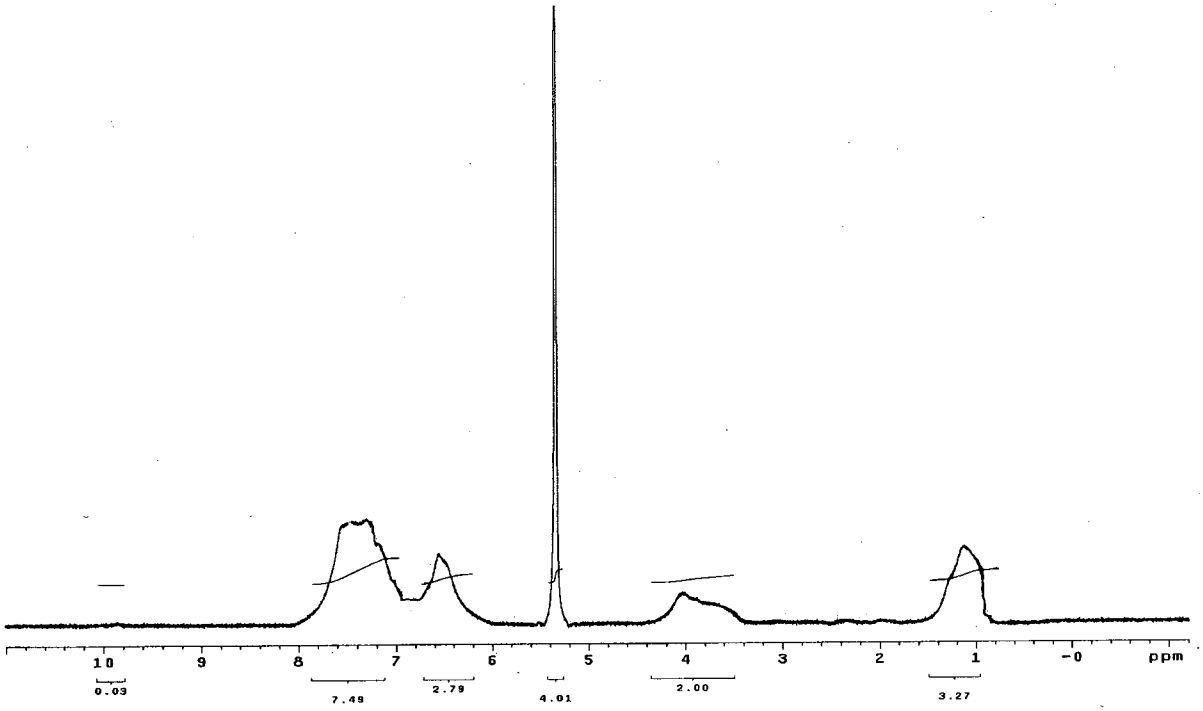
^{1}H NMR(4.1i)



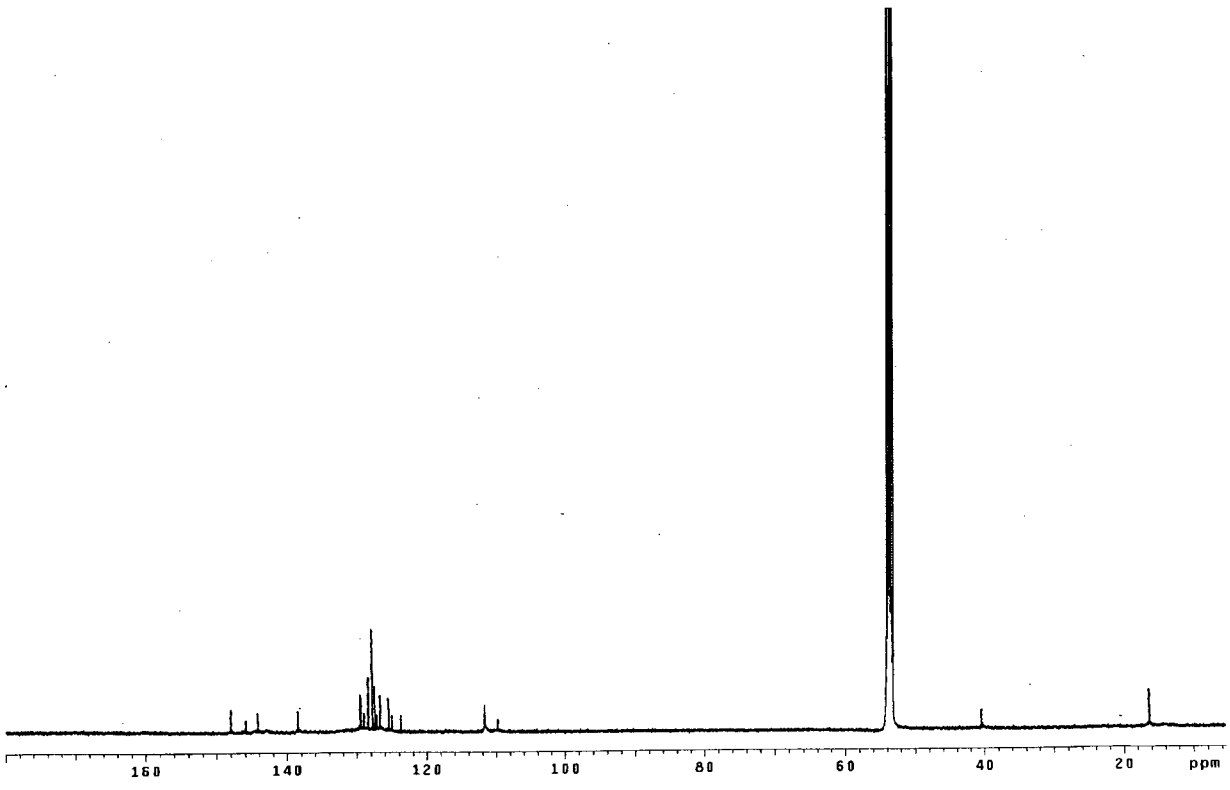
^{13}C NMR(4.1i)



^{1}H NMR(4.1j)

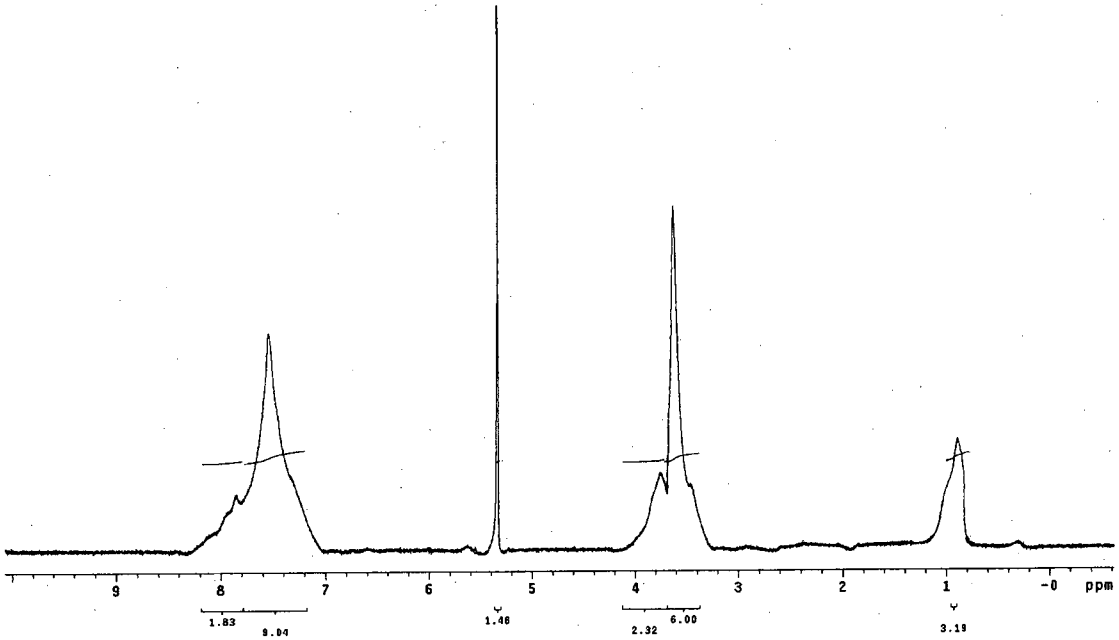


^{13}C NMR(4.1j)

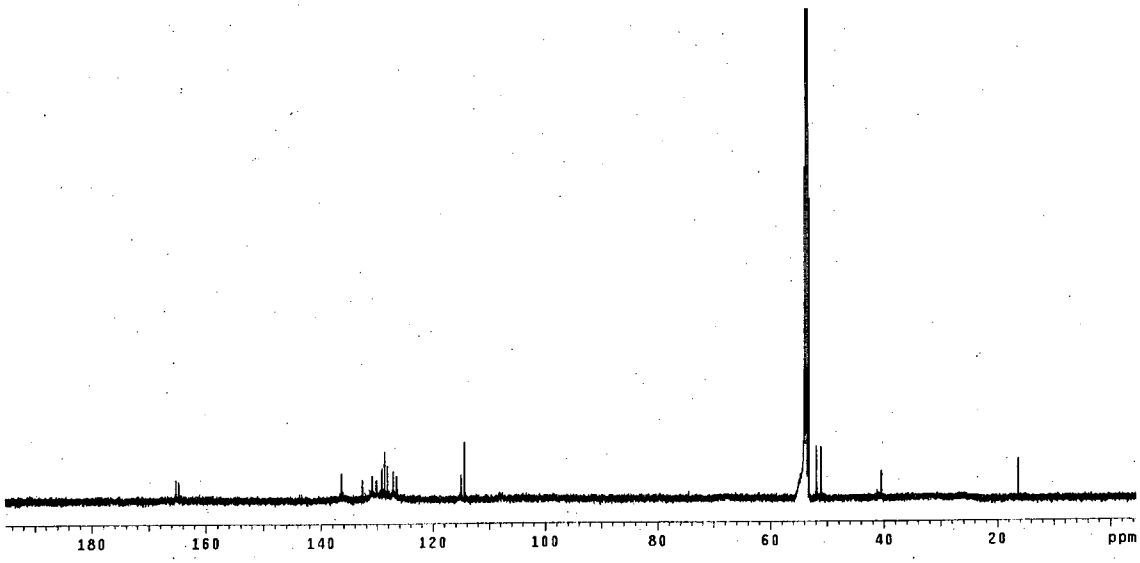


NMR Spectra of Conjugated Pyrrole-Based Polymer (4.11)

^{1}H NMR



^{13}C NMR



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CHAPTER FIVE

Mechanistic Studies on Palladium Catalyzed Multicomponent Synthesis of Imidazole-Containing Conjugated Materials

Preface

In Chapter 4, we described the design of a palladium catalyzed multicomponent route to generate imidazole-containing conjugated materials. In this chapter, we will discuss in more detail the progress of this reaction, identification of the end groups on the polymer backbone, and the potential mechanism by which this polymerization is terminated.

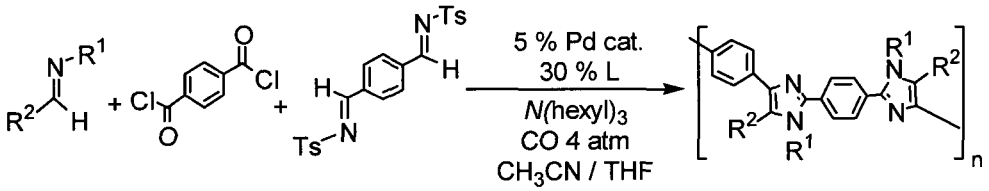
5.0 Introduction

The synthesis of complex molecular scaffolds directly from readily available building blocks provides a useful alternative to multistep synthesis. In addition to minimizing the numbers of steps required to synthesize structures, if the substrates employed are easily diversified, these reactions are directly amenable to forming families of products. Transition metal catalysis can be a powerful tool in developing such transformations, by activating what are often unreactive substrates towards coupling via metal-based reactions.[1] We have recently shown that this approach can

be utilized to construct a range of products, including α-amino acid derivatives,[2] ß-lactams,[3] pyrroles,[4] and imidazoles,[5] all in one-step and from basic precursors.

As described in Chapter 4, this metal catalyzed approach can also be used to generate π-conjugated imidazole-containing polymers and/or oligomers (Scheme 5.1). This transformation employs bifunctional substrates capable of undergoing simultaneous cyclization and polymerization, such as di-imines, di-acid chlorides, and di-*N*-tosylimines, each of which are commercially available or can be easily prepared. In order to understand the scope and limitation of this polymerization, we have undertaken mechanistic studies on this reaction. We describe below the results of this work, which includes the identification of the polymer end groups by NMR spectroscopy and MALDI-TOF-MS analysis. In addition, possible side reactions that can diminish the efficiency of the polymerization have been explored.

Scheme 5.1: One-Pot Synthesis of π-Conjugated Imidazole-Containing Polymers

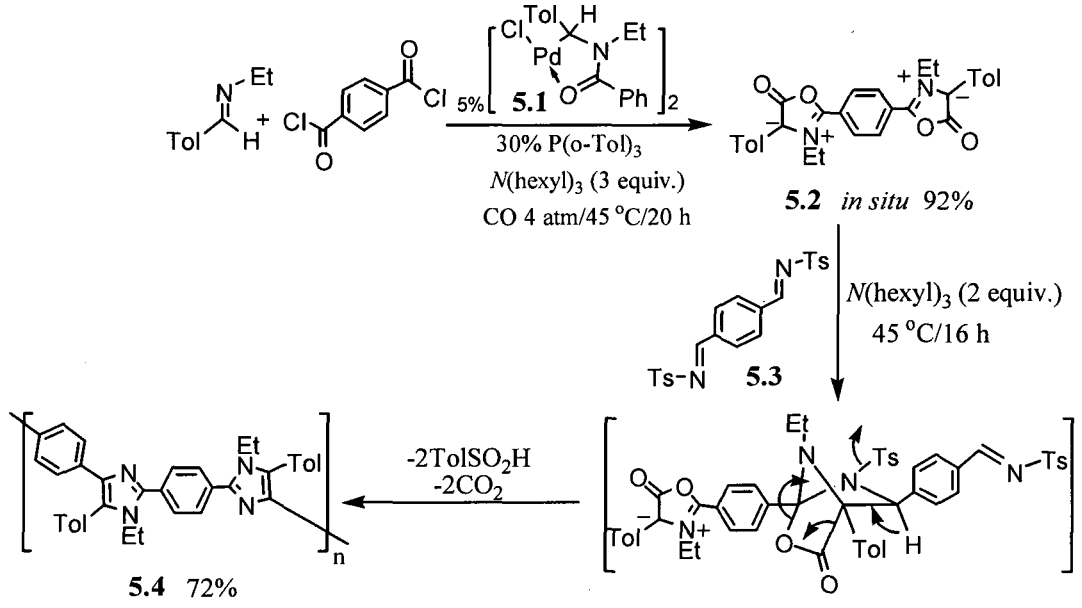


5.1 Results and Discussion

5.1.1 Influence of Monomer Ratio on Molecular Weight

As we showed in Chapter 4, the palladium catalyzed reaction of terephthaloyl dichloride, the imine EtN=CH(Tol) (Et= CH_2CH_3, Tol= 4-$C_6H_4CH_3$), and carbon monoxide generates the coupling product **5.2**, which contains two mesoionic 1,3 oxazolium-5-oxides (commonly known as Münchnones) tethered by a phenyl ring. The subsequent addition of the diimine **5.3** to this product results in its dipolar cycloaddition to the Münchnone, which upon the loss of CO_2 and sulfinic acid generates the imidazole containing polymer **5.4** in 72 % isolated yield (Scheme 5.2).

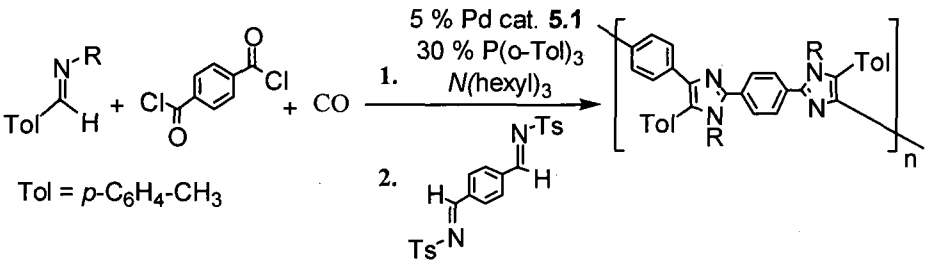
Scheme 5.2: Catalytic Formation of Imidazole-Containing Polymer **5.4**



Interestingly, GPC analysis of the isolated polymer reveals that it is mostly short oligomers, with an average molecular weight (M_n) of 1.1×10^3. This correlates approximately with two repeating units in **5.4** (n=2). This is despite the fact that a 1:1 ratio of **5.2**:**5.3** was employed in the reaction, as determined by calculating their in

situ concentrations by ^{1}H NMR analysis. This ratio is expected to generate high molecular weight polymers in this condensation polymerization. As shown in Table 5.1, the molecular weight of the polymers can be modulated by varying the amount of the di-*N*-tosylimine **5.3** added to **5.2**. Surprisingly, lowering the concentration of **5.3** to a sub-stoichiometric amount of 1:0.8 of **5.2:5.3** leads to the formation of higher molecular weight polymers of $M_n = 2.2 \times 10^3$ in similar yield (entry 3). Further dropping the concentration of **5.3** leads to lower molecular weight polymers, along with an incomplete conversion of **5.2** into the product (e.g. 1:0.6 ratio, entry 4).

Table 5.1: Effect of Stoichiometric Ratio on Polymerization[c]



Entry	R	Ratio[a] 5.2:5.3	Yield % (5.4)	M_w ($\times 10^3$)	M_n ($\times 10^3$)	Polydispersity index
1	Et	1:1.2	70	1.6	1.2	1.33
1	Et	1:1	70	1.7	1.1	1.54
3	Et	1:0.8	72	2.7	2.2	1.23
4[b]	Et	1:0.6	40	1.7	1.3	1.31
5	Hexyl	1:1	71	3.3	2.7	1.22
6	Hexyl	1:0.8	70	5.4	4.5	1.20

a. The ratio of **5.2:5.3** is calculated based upon the in situ yield of **5.2**, determined by means of ^{1}H NMR analysis using an internal standard b. Incomplete conversion, 40 % product was formed along with unreacted di-Münchnone **5.2**.

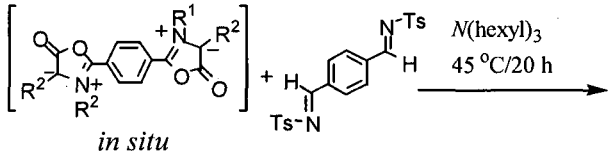
Employing longer alkyl chain substituted imines such as hexylN=CH(Tol), increases the solubility of this product, and also leads to the formation of higher

molecular weight polymers (M_n = 4.5 × 10^3). However, once again the highest molecular weights are observed with a sub-stoichiometric amount of **5.3** (entry 6).

5.1.2 End Group Analysis

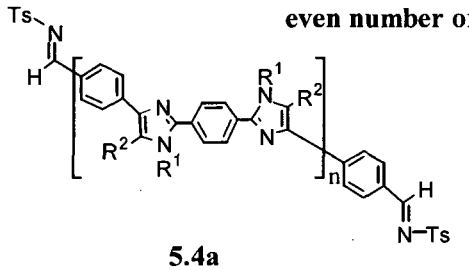
Considering that condensation polymerizations such as these should provide optimum chain length with a 1:1 ratio of the reagents, the data in Table 5.1 indicates that the polymerization is being influenced by some other phenomenon, whereby the formation of higher molecular weight products is inhibited. In order to further probe this molecular weight effect, the polymer was analyzed more closely by NMR

Scheme 5.3: Three Possible Structures for Polymer **5.4**

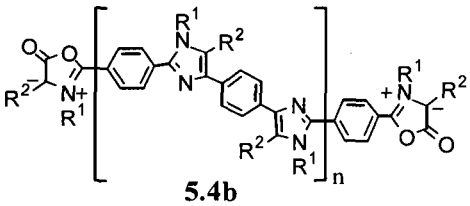


5.2 **5.3**

even number of imidazole rings

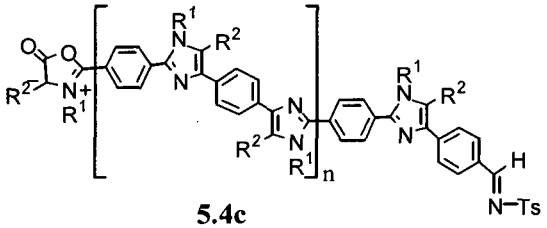


5.4a
Two tosylimine end groups



5.4b
Two Münchnone end groups

odd number of imidazole rings

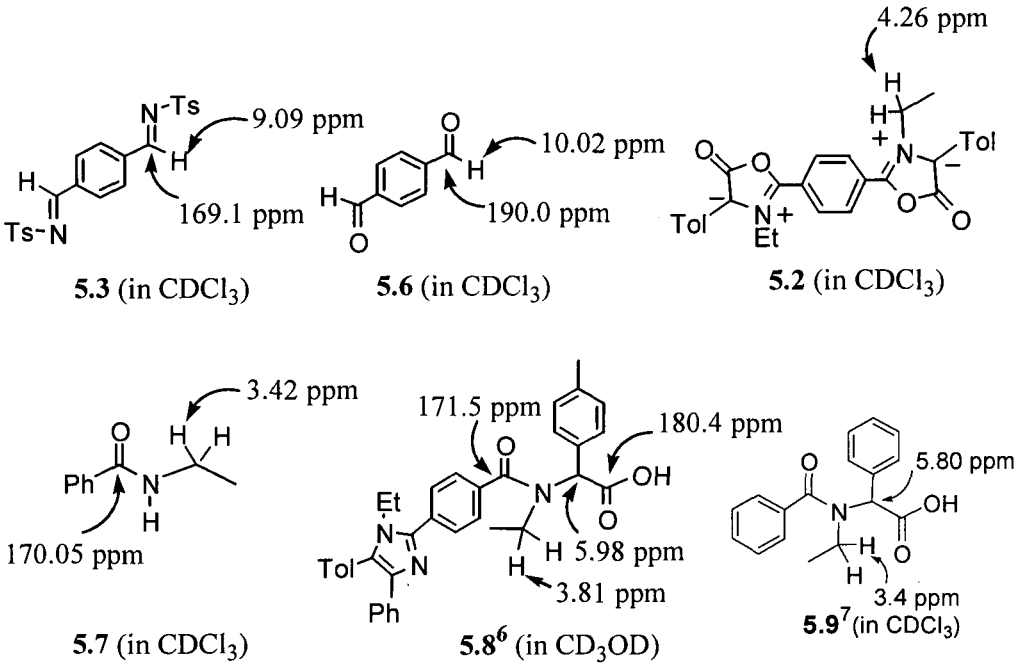


5.4c
Tosylimine and Münchnone end groups

spectroscopy. As shown in Scheme 5.3, the polymer structures from this reaction are expected to contain either imine or Münchnone end groups. This can result in three possible polymer structures, depending upon whether the number of imidazole units is even or odd. Polymers with even numbers of imidazole units are expected to have two *N*-tosylimines or two Münchnone end groups (**5.4a** or **5.4b**). Alternatively, polymers with odd numbers of imidazoles should have a *N*-tosylimine on one side and a Münchnone as the other end group (**5.4c**).

In order to probe for the presence of these end groups in the polymer, the ^{1}H and ^{13}C NMR spectra of polymer **5.4** was compared to several model compounds. As shown in Figure 5.1, the *N*-tosylimine **5.3** has a strongly dishielded imine proton in the ^{1}H NMR spectra (C**H**=N(Ts) at 9.09 ppm), and a strongly dishielded imine carbon in the ^{13}C NMR spectra (**C**H=N(Ts) at 169.1 ppm). Alternatively, the

Figure 5.1: ^{1}H and ^{13}C NMR Chemical Shifts of Model Compounds



5.3 (in $CDCl_3$) **5.6** (in $CDCl_3$) **5.2** (in $CDCl_3$)

5.7 (in $CDCl_3$) **5.8**[6] (in CD_3OD) **5.9**[7] (in $CDCl_3$)

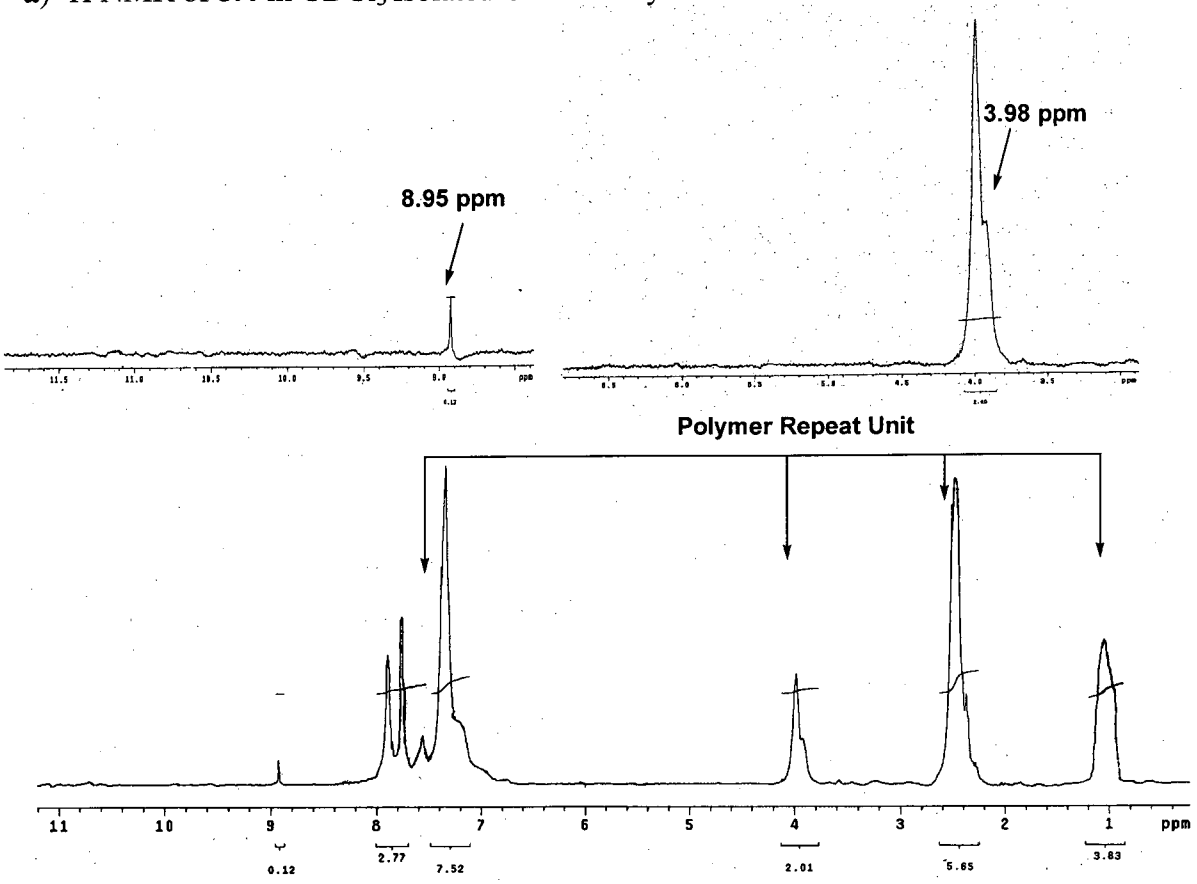
Münchnone in **5.2** has an *N*- ethyl ($C\mathbf{H}_2CH_3$) signal at 4.26 ppm. Since each of these resonances is distinct from those in the polymer backbone, they should be observed in the NMR spectra of the isolated polymers.

The ^1H and ^{13}C NMR spectra of the purified sample of **5.4** are shown in Figure 5.2. As can be seen in Figure 5.2a, in addition to the resonance for the imidazole-containing polymer repeat unit, a signal at 8.95 ppm is observed in the ^1H NMR spectra, which correlates with the presence of *N*-tosylimine units. Furthermore, ^{13}C NMR analysis shows a signal at 170 ppm, corresponding to this end group (Figure 5.2b). Similarly, isolation of the polymer under hydrolytic workup conditions reveals the presence of an aldehyde end group in the ^1H (9.92 ppm) and ^{13}C (192 ppm) NMR spectra (Figure 5.2c, d). The latter arises from the hydrolysis of the *N*-tosylimine end group (the corresponding dialdehyde **5.6** signals appear at 10.02 ppm and 190.0 ppm in ^1H and ^{13}C NMR spectra, respectively, Figure 5.1).

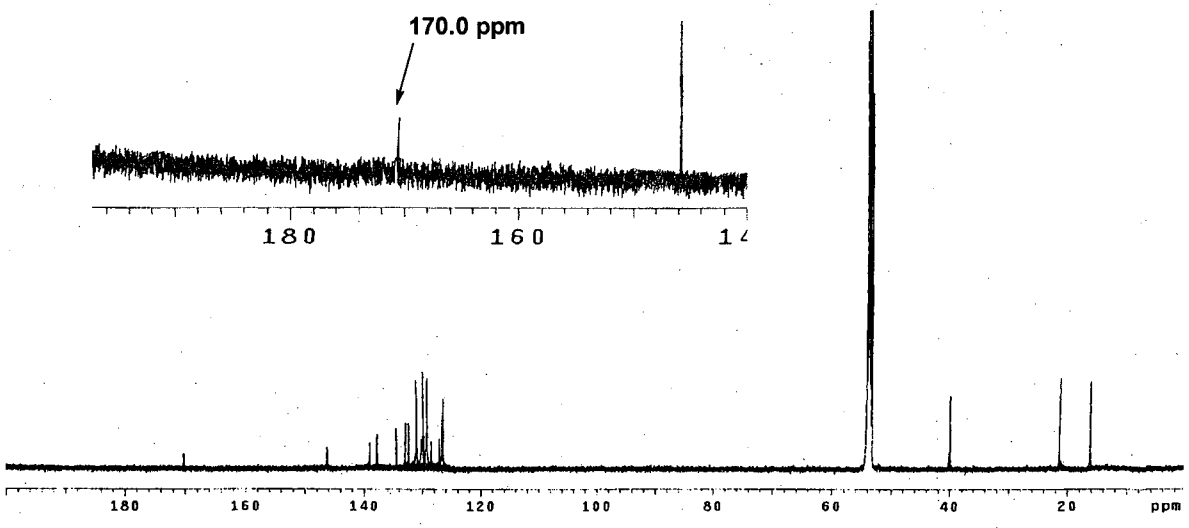
No evidence for the presence of a Münchnone end group was observed in any of these spectra (Figure 5.2 a-d). Since Münchnones can be hydrolyzed to α-amido acids[2] or decompose to amides,[5] ^1H and ^{13}C NMR spectra of the model compounds **5.7, 5.8,** and **5.9** were taken (Figure 5.1). Careful analysis of the NMR spectra of polymer **5.4** (Figure 5.2) isolated upon hydrolytic workup reveals the presence of signals that are consistent with an α-amido acid end group. The signals at 5.80 ppm and 3.40 ppm of the isolated polymer in $CDCl_3$ (Figure 5.2c) correlate with the corresponding signals in model compound **5.9,** and can be assigned to (C**H**(Tol)) and *N*-ethyl ($C\mathbf{H}_2CH_3$) in the amido acid unit, respectively. Similarly, the signal at 5.98 ppm in the polymer sample in CD_3OD (Figure 5.2e) also correlates with the corresponding signal in **5.8**. It is notable; however, that these α-amido acid end group

Figure 5.2: ^{1}H, and ^{13}C NMR of **5.4**

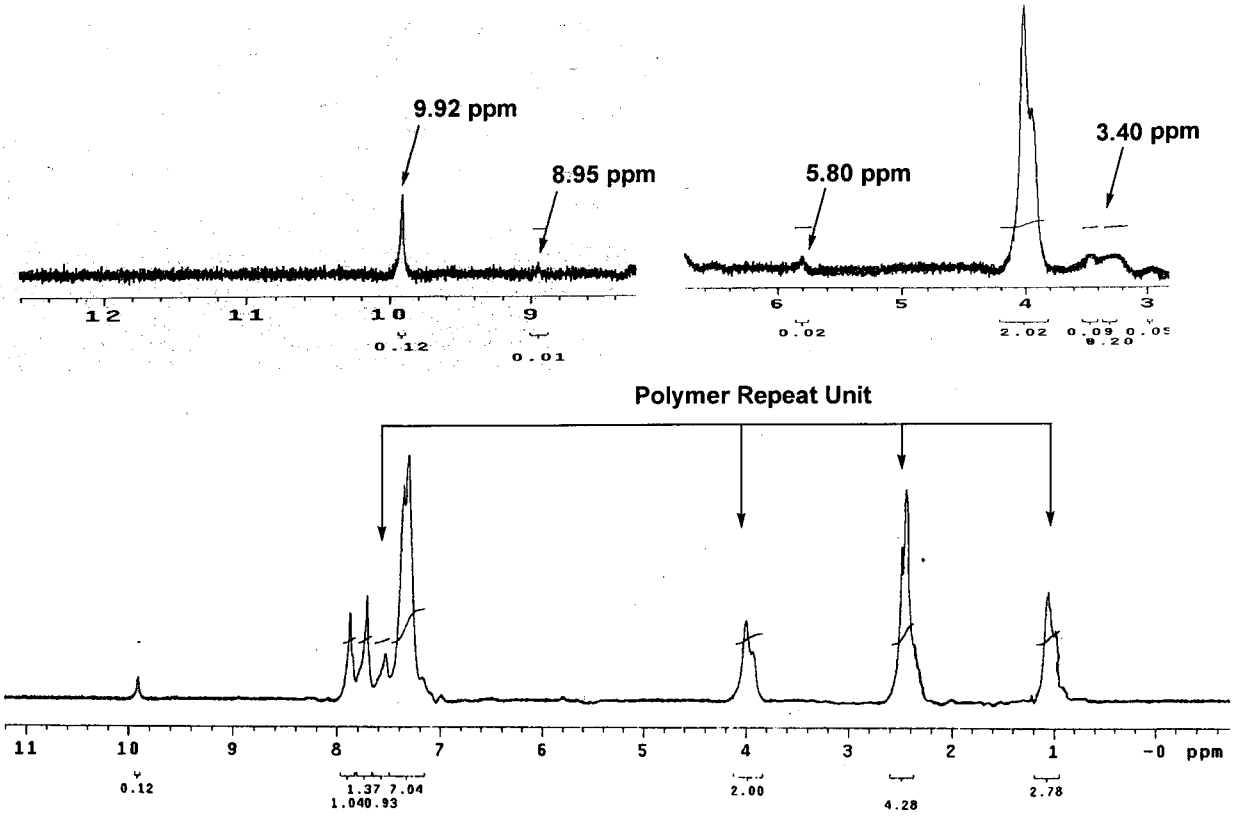
a) ^{1}H NMR of **5.4** in $CDCl_3$ Isolated Under Anhydrous Conditions



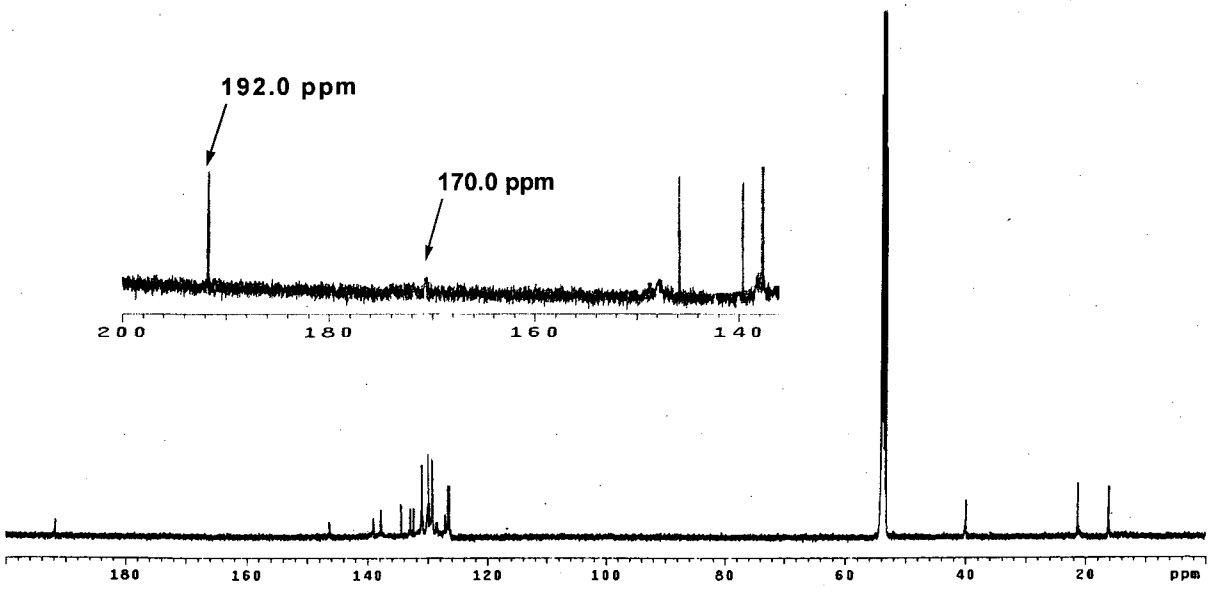
b) ^{13}C NMR of **5.4** in $CDCl_3$ Isolated Under Anhydrous Conditions



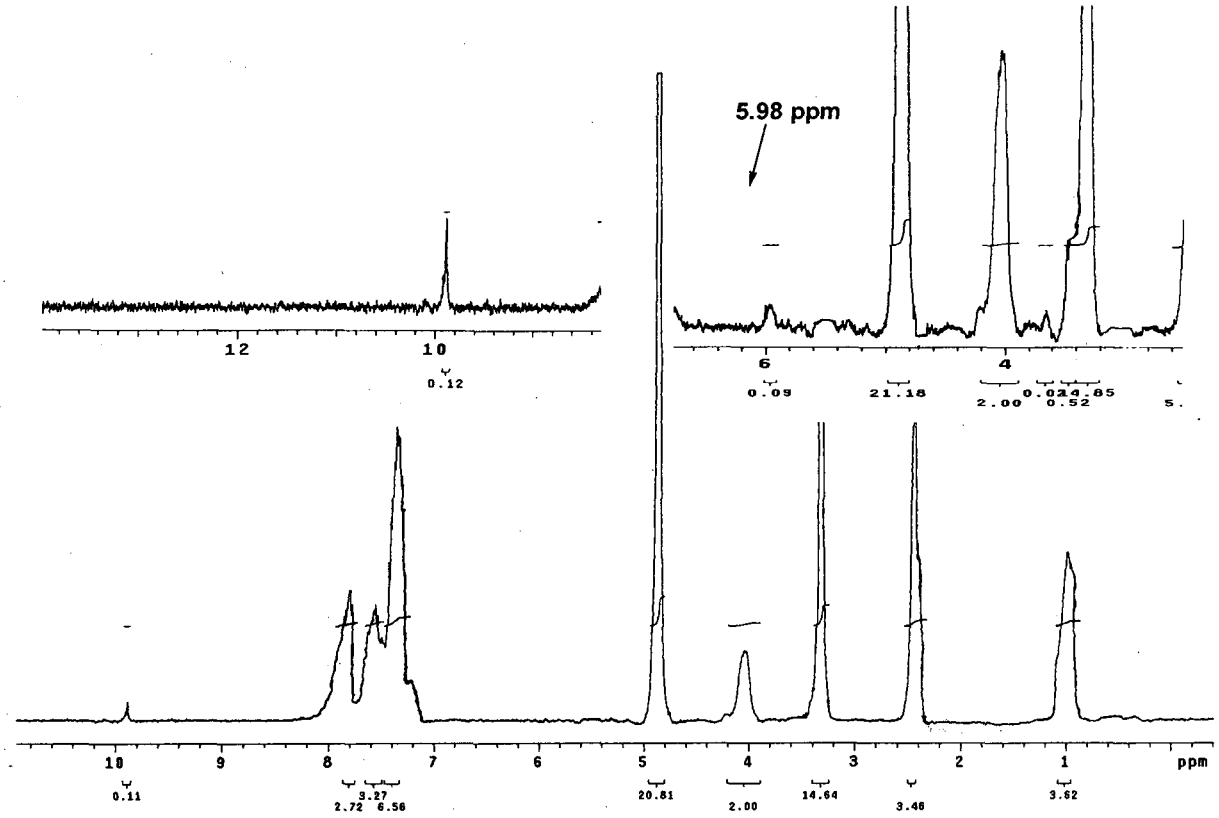
c) ^{1}H NMR of **5.4** in $CDCl_3$ Isolated Under Hydrolytic Conditions



d) ^{13}C NMR of **5.4** in $CDCl_3$ Isolated Under Hydrolytic Conditions



e) ^{1}H NMR of **5.4** in CD_3OD Isolated Under Hydrolytic Conditions



signals are not observed in the ^{1}H NMR spectra of the polymer isolated under non-hydrolytic conditions.

MALDI-TOF MS analysis of **5.4** provides further insight into the structure of the polymer. The mass spectrum shows a series of peaks with the same interval of the imidazole repeating units (520 amu). As illustrated in Figure 5.3, mass peaks for polymers with an even number of imidazole and two terminal aldehyde units are clearly observed (1175 m/z, 1696 m/z). These correlate with the structure of **5.4a** in Scheme 5.3, in which the imine unit has been hydrolyzed upon purification. While no polymers with Münchnone end groups are detected (e.g. **5.2b**), ions correlating

Figure 5.3: MALDI-TOF MS of **5.4**

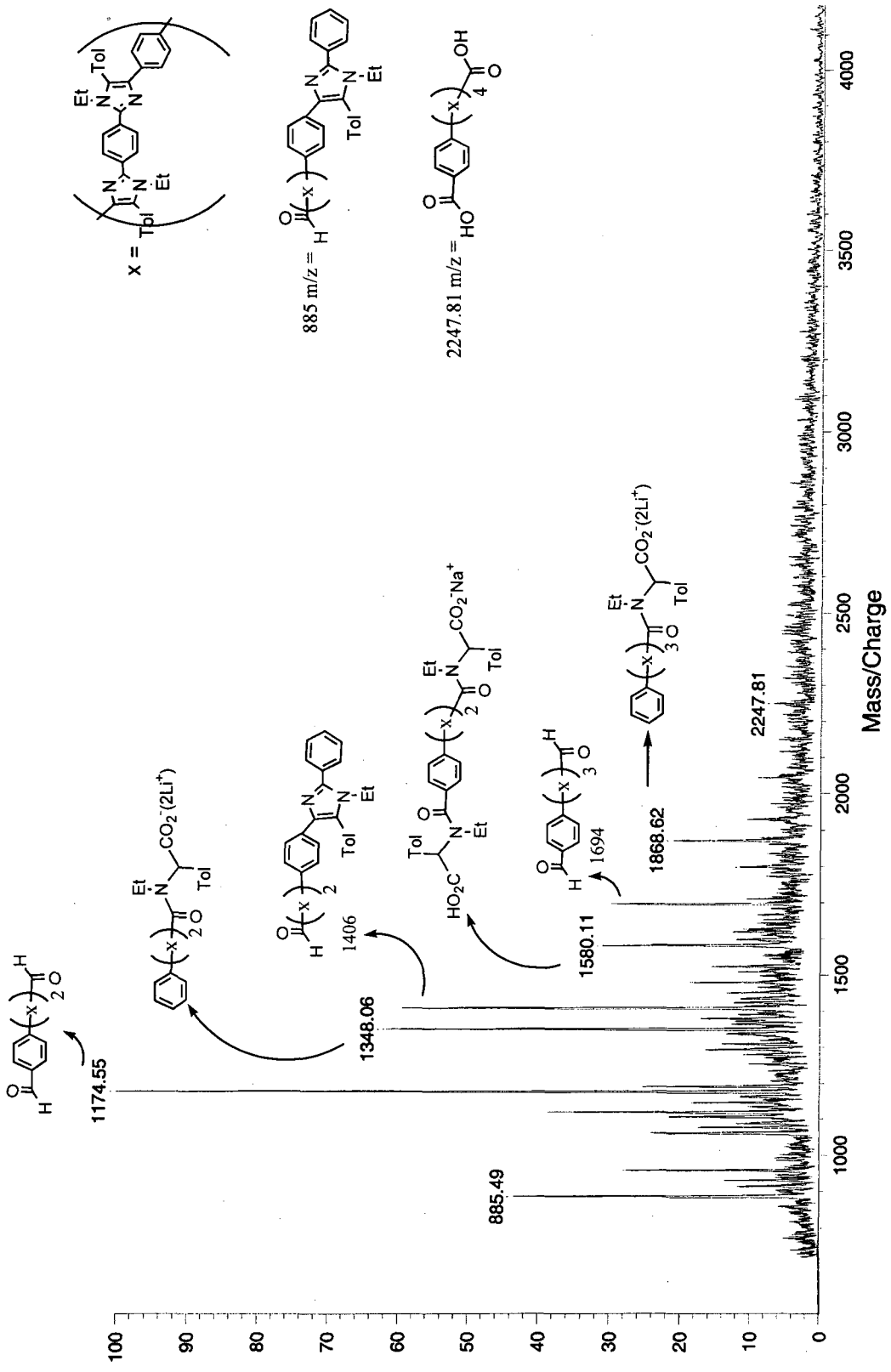
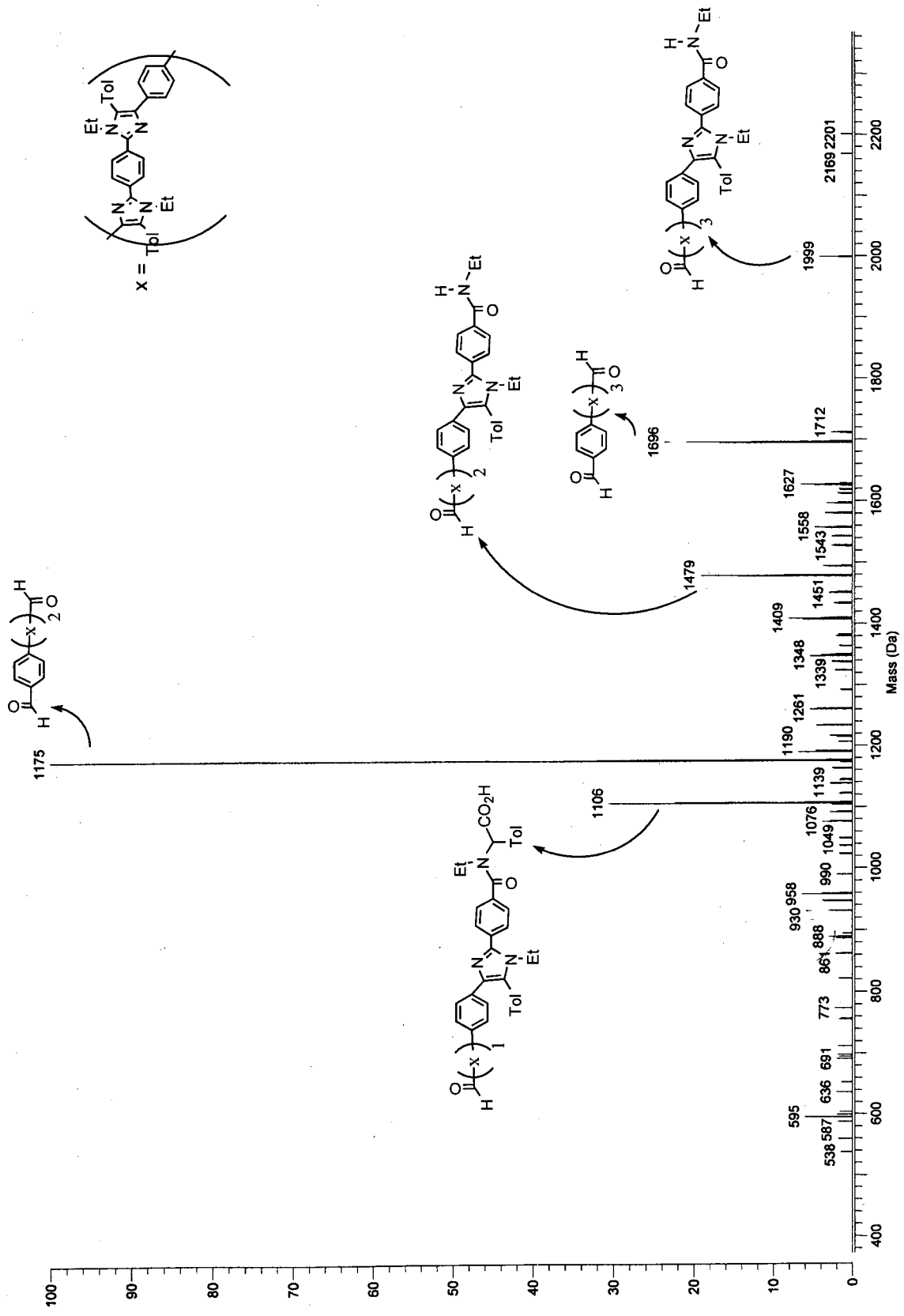


Figure 5.4: High Resolution ESI-MS of **5.4**



with α-amido acid end groups are observed (1348 m/z, 1580 m/z, 1868 m/z, 2247 m/z). The latter would arise from the hydrolysis of the Münchnone units.

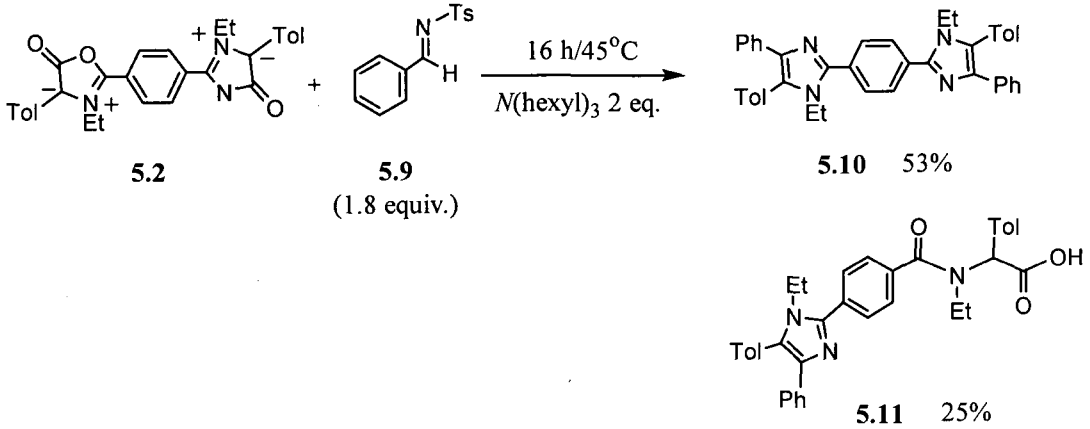
As shown in Figure 5.4, similar results were obtained in the ESI-MS of the polymers. The latter shows intense peaks for di-aldehyde teminated polymers with even number of imidazole units (e.g. 1175 m/z, 1696 m/z), and aldehyde plus amide or α-amido acid end groups for the polymers with odd number of imidazole units (1106 m/z, 1479 m/z, 1999 m/z). Together, this MS data and $^{1}H/^{13}C$ NMR end group analysis suggest that the Münchnone units in the polymer are prone to decomposition during the polymerization, and at least upon hydrolytic workup are observable as α-amido acid end groups. This decomposition of Münchnone likely results in the formation of lower molecular weight products.

5.1.3 Control Experiments

The lack of any observed Münchnone end groups in polymer **5.4**, either by Mass spectral or NMR analysis suggests that the Münchnone units on the growing polymer may undergo chain termination reactions, which prevents the formation of higher molecular weight products. This rapid termination may occur due to other possible competing reactions. In order to further probe this termination step, the reaction of **5.2** with sub-stoichiometric amount of **5.9** (Scheme 5.4) was examined. It was envisaged that if the amount of **5.9** is insufficient, a small quantity of Münchnone

would be present after the reaction, which could undergo decomposition similar to that terminating the polymerization.

Scheme 5.4: Sub-Stoichiometric Reaction of **5.2** with **5.9**



5.2 **5.9** (1.8 equiv.) **5.10** 53%

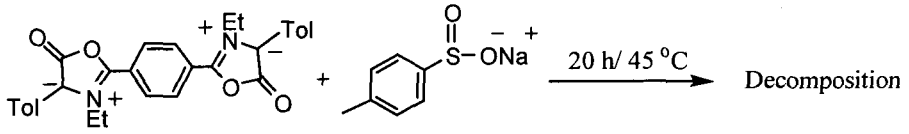
5.11 25%

As anticipated from the stoichiometry of the reaction, the di-imidazole **5.10** is generated in 53% of the isolated yield. In addition, a second more polar product was isolated by column chromatography on silica with ethyl acetate:methanol (8:2) as eluent in 25% yield. NMR (^{1}H and ^{13}C) and HRMS analysis demonstrate this product is the imidazole-α-amido acid **5.11,** analogous to that observed as a polymer end group. Notably, the presence of **5.11** was not observed in the crude ^{1}H NMR spectra of this reaction. This could be due to the generation of an intermediate during the reaction that hydrolyzes to **5.11** upon workup or potentially a broadening of the ^{1}H NMR signals of **5.11** in the reaction mixture. At present, we can not distinguish between these possibilities.

Our previous studies on imidazole synthesis revealed that the sulfonyl anion released by cycloaddition can undergo competing reaction with electrophilic substrates in the reaction mixture.[5] In order to investigate the possible interaction of this anion with the Münchnone, the reaction of an independently synthesized **5.2** with

sodium-*p*-toluene sulfinate **5.12** was examined (Scheme 5.5). Monitoring the reaction by ^{1}H NMR analysis reveals the disappearance of **5.2** over the course of 20 h at 45 °C, and the growth of a series of peaks at the chemical shift of 3-4 ppm. Unfortunately, no product could be isolated from this reaction. Nevertheless, since similar conditions are used for the reaction of **5.2** with **5.3**, it is conceivable that analogous decomposition might occur during the polymerization.

Scheme 5.5: Reaction of Sulfonyl Anion with **5.2**

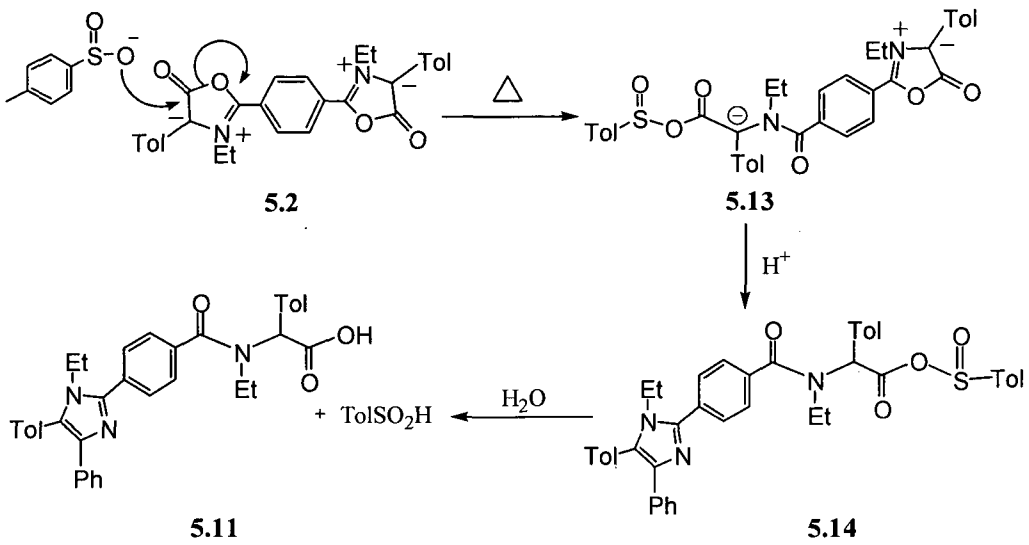


5.2 **5.12**

It is plausible that the sulfonyl anion reacts with **5.2** through the addition to the electrophilic carbonyl group, resulting in the formation of the anionic species **5.13** (Scheme 5.6). The adduct **5.13** may abstract proton from another reagent in the reaction or simply decompose. Notably, the analysis of the MALDI-TOF MS of the polymer **5.4** displays no evidence for the presence of a sulfinate end group. However, the reaction of **5.2** with sulfonyl anion implies that a similar process may occur during the polymerization leading to decomposition of the terminal Münchnone group.

Overall, these two control experiments suggest that the sulfonyl anion, or potentially undetected water impurities, may be non-innocent in the polymerization. This could lead to adduct **5.13**, or something similar, which converts to an α-amido acid upon hydrolytic workup.

Scheme 5.6: A Postulated Nucleophilic Attack on **5.2**



5.2 Conclusions

These data show that the molecular weight of the materials generated from this palladium catalyzed multicomponent polymerization are unusually influenced by reagent ratios, with the maximum chain length obtained when a sub-stoichiometric amount of di-*N*-tosylimine is employed. ^{1}H and ^{13}C NMR, and MALDI-TOF MS analysis clearly shows the presence of an imine end group in the polymer, which converts to an aldehyde upon hydrolytic workup. In addition, no evidence for Münchnone end groups is detected, and instead units arising from their hydrolysis (α-amido acids) are observed. These results suggest that the Münchnone units may be decomposes during polymerization, potentially due to the presence of sulfonyl anion, and therefore influencing polymer molecular weights.

5.3 Experimental Section

General Procedures

Unless otherwise noted, all reactions were carried out under an inert atmosphere in a dry box or using standard Schlenk or vacuum line techniques. Palladium catalyst (**5.1**) was prepared according to previously reported procedure, by pretreating $Pd_2dba_3 \cdot CHCl_3$ with imine and acid chloride.[2, 5] $Pd_2dba_3 \cdot CHCl_3$ was prepared according to literature procedures.[8] Imines[9] was prepared according to the literature procedures. Carbon monoxide (99.99%) was purchased from Matheson and used as received. All other reagents were used as received from commercial suppliers.

Acetonitrile was freshly purified by distillation over CaH_2 under nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Deuterated solvents were dried as their protio analogous, and transferred under vacuum and stored over 3 and 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on Mercury 400 MHz and Unity 500 MHz Varian NMR spectrometers. The degree of polymerization and polydispersity were measured by Gel Permeation Chromatography (GPC) in THF. A Waters 510 liquid chromatography pump, equipped with two (HR1 and HR2) Styragel columns connected in series, and a refractive index detector (Varian RI-4) were used at room temperature. Polystyrene standards (Scientific Polymer Products, Inc., NY) with a narrow molecular weight distribution were used for calibration. MALDI-TOF-MS analysis was performed on a Kratos Kompact MALDI-III-TOF bench top model instrument which generates a maximum laser out of 6 mw at a wavelength of 337 nm (N_2 laser light, 3 ns pulse width). The average of 100 laser shots was represented in

the mass spectra. The polymer sample (5 mg/mL) was dissolved in chloroform and dithranol-LiBr in THF solution was added as matrix in a 1:2 volume ratio. A spot of the sample was placed on the sample slide, and the solvent was allowed to evaporate slowly before being put into the vacuum chamber of the mass spectrometer.

Synthesis of 5.3

Terephthalaldehyde (2.00 g, 14.9 mmol) was added to 120 mL of toluene in 250 mL round bottom flask. To this solution was added *p*-toluenesulfonamide (5.09 g, 29.8 mmol), *p*-toluenesulfonic acid (2.85 g, 14.9 mmol) and 3 Å of molecular sieves. A Dean-Stark trap was also set up on the top of the condenser and the entire mixture was refluxed for 24 h. Upon the completion of this period, the reaction mixture was hot filtered through the Buchner funnel and the white solid on the filter funnel was repeatedly washed with Et_2O (100 mL) and MeOH (100 mL). The resulting solid was then filtered to give 6.2 g of a pale grey solid. Yield: 87% The product can be further dried by dissolving the solid in THF (20 mL) and stirring over of 4 Å molecular sieves under an inert atmosphere.

^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 9.09 (s, 2H), 8.04 (s, 4H), 7.96-7.94 (d, 4H), 7.56-7.54 (d, 4H), 2.44 (s, 6H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 169, 140.9, 137.6, 136.6, 131.6, 129.8, 129.7, 21.8.

HRMS. $C_{22}H_{21}N_2O_4S_2^+$: 441.0946 found: 441.0944

Synthesis of Polymer 5.4:

Terephthaloyl dichloride (50 mg, 0.246 mmol) and EtN=CH(Tol) (72.5 mg, 0.493 mmol) were dissolved in 12 mL of CH_3CN:THF (1:1) solution and stirred for 15 min in a 50 mL reaction bomb. To this was added the palladium catalyst **5.1** (9.7 mg, 0.0123 mmol), P(*o*-Tol)$_3$ (22.6 mg, 0.074 mmol) in 5 mL of THF, and *N*(hexyl)$_3$ (199 mg, 0.74 mmol) in 3 mL of THF. Benzylbenzoate was also added to this mixture as an internal standard. The mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) added. After heating to 45 °C for 16 h, the mixture was degassed, and an aliquot of the crude deep red solution analyzed by ^{1}H NMR, and the yield of the di-Münchnone **5.2** was determined by comparison to the internal standard. Based upon the ^{1}H NMR yield, imine **5.3** (85 mg, 0.177 mmol) and *N*(hexyl)$_3$ (95 mg, 0.354 mmol) were added to the reaction, and the mixture heated at 45 °C for 20 h. The dark yellow solution was then filtered through celite, and solvent was removed *in vacuo* to give an oil. The product was purified by adding CH_3CN (20 mL) and cooling the solution to -20 °C, resulting in the precipitation of **5.4** as a yellow-red solid. The CH_3CN solution was then decanted, and the precipitate was further washed with CH_3CN (20 mL), followed by cooling to -20 °C. This procedure was repeated several times until all impurities were removed and the final product obtained as yellow-dark orange oil. For reactions that produced low molecular weight polymers, the product was isolated by washing with Et_2O rather than CH_3CN. Yellow oil, Isolated yield: 72% ^{1}H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.87-7.71 (d, 3H), 7.54-7.31 (m, 7H), 4.0 (s, br, 2H), 2.45 (s, 3H), 1.06 (s, br, 3H). ^{13}C NMR

(125MHz, $CDCl_3$, 60 °C): δ 182, 146.2, 139.1, 137.8, 134.2, 133.1, 132.9, 131.1, 130.9, 130.2, 129.9, 129.7, 129.2, 126.7, 126.4, 39.9, 21.3, 16.2.

Reaction of 5.2 with Sodium-*p*-Toluene Sulfinate

Terephthaloyl dichloride (50 mg, 0.246 mmol) and EtN=CH(*p*-tolyl) (72.5 mg, 0.493 mmol) were dissolved in 12 mL of CH_3CN:THF (1:1) solution and stirred for 15 min in a 50 mL reaction bomb. To this was added the palladium catalyst **5.1** (9.7 mg, 0.0123 mmol), P(*o*-Tol)$_3$ (199 mg, 0.74 mmol) in 5 mL of THF, and *N*(hexyl)$_3$ (199 mg, 0.74 mmol) in 3 mL of THF. Benzylbenzoate was also added to this mixture as an internal standard. The mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) added. After heating to 45°C for 16 h, the mixture was degassed, and an aliquot of the crude deep red solution was analyzed by ^{1}H NMR and the yield of **5.2** was determined. Based upon this ^{1}H NMR yield, 2 equivalents of sodium-*p*-toluene sulfinate **5.12** (39.4 mg, 0.22 mmol) was added and the mixture heated at 45 °C for 20 h. The deep red reaction color slowly disappeared during the course of the reaction and ^{1}H NMR analysis of the resulting yellow crude mixture demonstrates the disappearance of **5.2**, and growth of a series of peaks at the chemical shift of 3-4 ppm. Attempts to isolate any products from this reaction were not successful.

Reaction of 5.2 with *N*-Benzylidene-4-Methyl-Benzenesulfonamide (5.9)

Terephthaloyl dichloride (50 mg, 0.246 mmol) and EtN=CH(*p*-tolyl) (72.5 mg, 0.493 mmol) were dissolved in 12 mL of CH_3CN:THF (1:1) solution and stirred for 15 min in a 50 mL reaction bomb. To this was added the palladium catalyst **5.1** (9.7 mg, 0.0123 mmol), P(*o*-Tol)$_3$ (199 mg, 0.74 mmol) in 5 mL of THF, and *N*(hexyl)$_3$ (199 mg, 0.74 mmol) in 3 mL of THF. Benzylbenzoate was also added to this mixture as an internal standard. The mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) added. After heating to 45 °C for 16 h, the mixture was degassed, and an aliquot of the crude deep red solution was analyzed by ^{1}H NMR and the yield of **5.2** was determined. Based upon this ^{1}H NMR yield, 1.8 equivalents of *N*-benzylidene-4-methyl-benzenesulfonamide **5.9** (112 mg, 0.4 mmol) and *N*(hexyl)$_3$ (269 mg, 1.0 mmol) were added, and the mixture was heated at 45 °C for 16h. After the completion of the reaction period, the yellow crude mixture was filtered over celite and solvent was removed under reduced pressure to give yellowish oil. TLC analysis of this oil displays two distinct blue spots under UV irradiation in hexane: ethyl acetate (8:2). One spot with a Rf=0.25 corresponds to diimidazole **5.10** and the second spot on the baseline related to the carboxylic acid adduct **5.11**. These two compounds were isolated by column chromatography on silica using hexane:ethyl acetate (8:2), and ethyl acetate:methanol (8:2) eluents, respectively.

2, 2'-Phenyl-Bis[1-Ethyl-4-phenyl-5-*p*-tolyl-1*H*-imidazole] (5.10)

White solid, Isolated yield: 53% ^{1}H NMR (400MHz, $CDCl_3$): δ 7.84 (s, 4H), 7.56 (d, 4H), 7.34-7.32 (q, 8H), 7.22-7.20 (t, 4H), 7.15-7.13 (t, 2H), 4.0 (q, 4H), 2.46 (s, 6H),

1.05 (t, 6H). ^{13}C NMR (125MHz, $CDCl_3$): δ 146.8, 138.8, 138.07, 134.8, 132.09, 131.1, 130.08, 130.06, 129.63, 129.61, 128.5, 128.2, 126.9, 126.4, 39.9, 21.6, 16.5.

HRMS Calculated for $C_{42}H_{39}N_4^+$: 599.3146 Found: 599.3142

{Ethyl-[4-(1-ethyl-4-phenyl-5-*p*-tolyl-1*H*-imidazol-2-yl)-benzoyl]-amino}-*p*-tolyl-acetic acid (5.11)

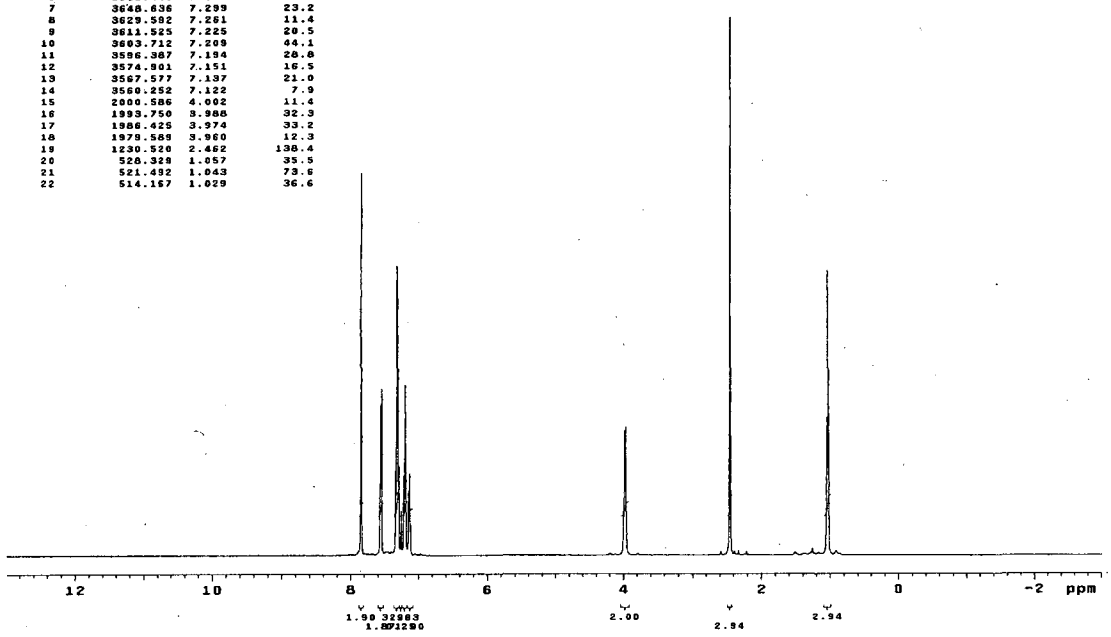
Yellow oil, Isolated yield: 25% ^1H NMR (400MHz, CD_3OD, 60 °C): δ 7.78-7.76 (d, 2H), 7.67-7.65 (d, 2H), 7.41-7.39 (d, 2H), 7.32-7.26 (q, 5H), 7.17-7.13 (m, 6H), 5.98 (s, br, 1H), 3.98-3.81 (q, 4H), 2.41 (s, 3H), 2.34 (s, 3H), 0.98 (t, 3H), 0.85 (s, br, 3H). ^{13}C NMR (125MHz, CD_3OD, 60 °C): δ 180.4, 171.5, 146.2, 140.4, 138.3, 138.04, 134.2, 132.1, 132.02, 130.09, 130.03, 129.8, 129.4, 129.1, 128.8, 128.2, 126.9, 126.5, 126.2, 125.5, 124.9, 58.1, 39.8, 39.4, 21.6, 21.3, 16.5, 16.1.

HRMS Calculated for $C_{36}H_{36}N_3O_3^+$: 558.2758 Found: 558.2751

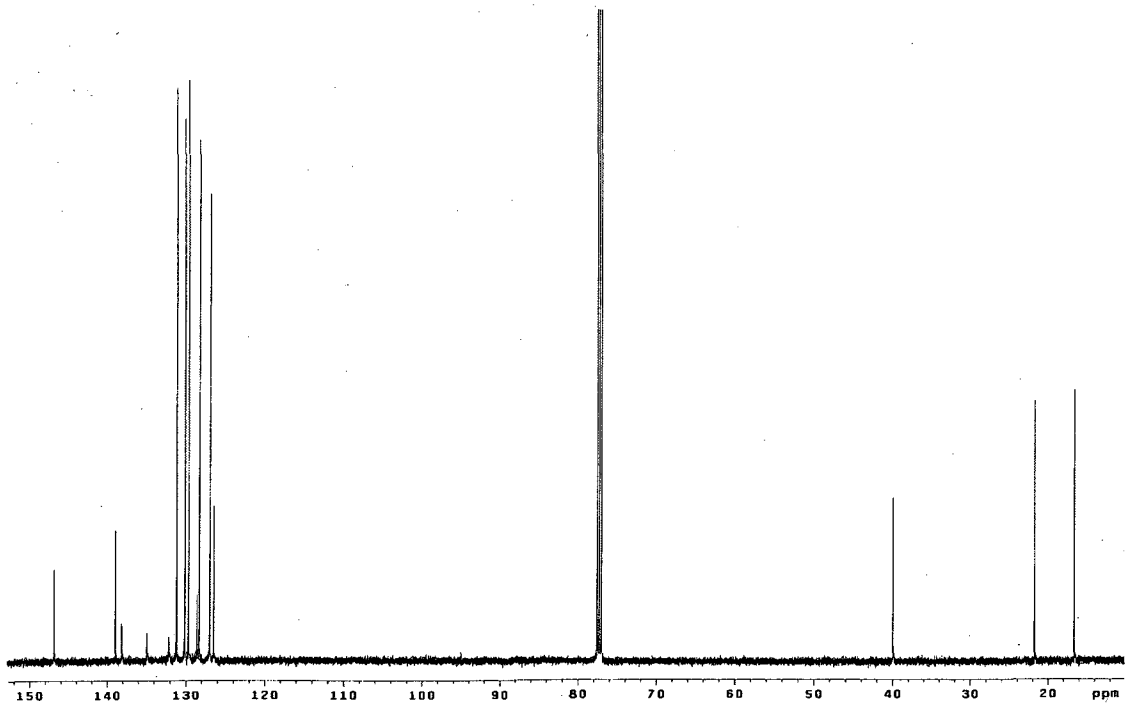
NMR Spectra of 2, 2'-Phenyl-bis[1-Ethyl-4-phenyl-5-*p*-tolyl-1*H*-imidazole] (5.10)

^{1}H NMR:

INDEX	FREQUENCY	PPM	HEIGHT
1	3923.555	7.849	98.6
2	3783.410	7.568	38.7
3	3776.085	7.554	43.1
4	3670.122	7.342	22.1
5	3662.309	7.326	74.7
6	3656.448	7.314	71.5
7	3648.636	7.299	23.2
8	3629.582	7.261	11.4
9	3611.525	7.225	20.5
10	3603.712	7.209	44.1
11	3596.387	7.194	28.8
12	3574.901	7.151	16.5
13	3567.577	7.137	21.0
14	3560.252	7.122	7.9
15	2000.586	4.002	11.4
16	1993.750	3.988	32.3
17	1986.425	3.974	33.2
18	1979.588	3.960	12.3
19	1230.520	2.462	138.4
20	528.328	1.057	35.5
21	521.492	1.043	73.6
22	514.167	1.029	36.6

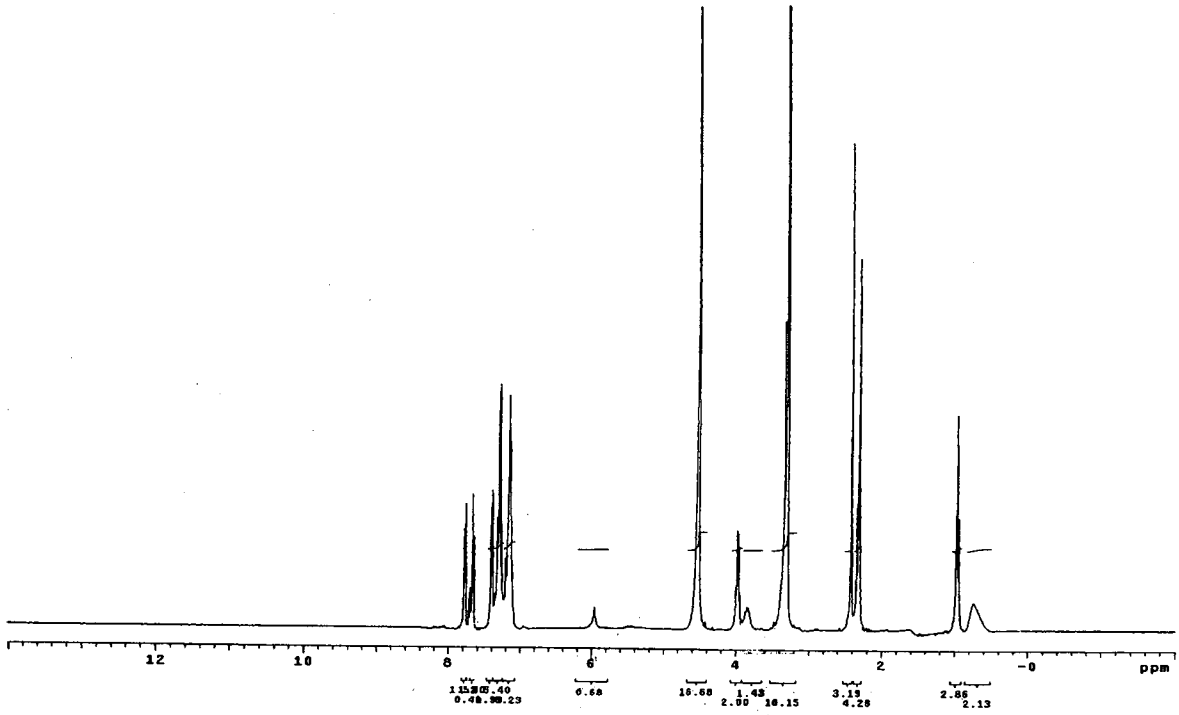


^{13}C NMR:

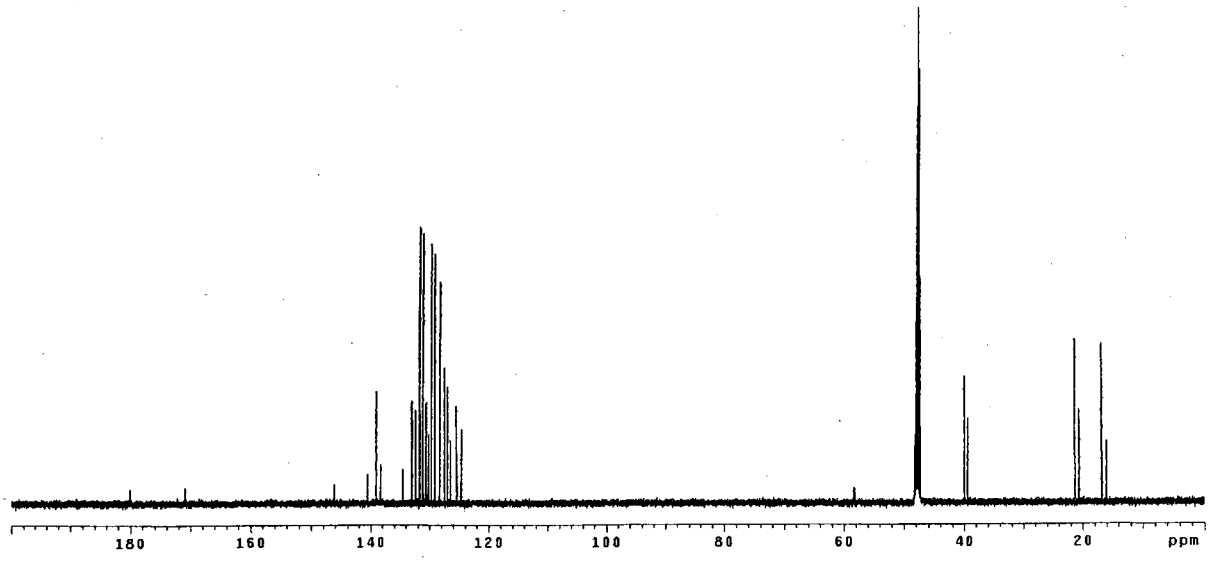


NMR Spectra {Ethyl-[4-(1-ethyl-4-phenyl-5-*p*-tolyl-1*H*-imidazol-2-yl)-benzoyl]-amino}-p-tolyl-acetic acid (5.11)

^{1}H NMR:



^{13}C NMR:



5.4 References

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CHAPTER SIX

Conclusions, Contributions to Original Knowledge, and Suggestions for Future Work

This chapter gives a brief summary of the results and conclusions presented in this thesis, as well as the contributions to the original knowledge. Based upon the results presented in this thesis, suggestions for future work are also provided.

6.0 Conclusions and Contributions to Original Knowledge

The results presented in this thesis demonstrate that a range of imidazole-based products can be assembled from basic and readily diversified building blocks brought together at once by metal catalysis. For instance, it was shown in Chapter 2 that substituted imidazoles can be prepared in a one step reaction via the palladium catalyzed coupling of two imines and an acid chloride. Mechanistic studies show that this reaction proceeds via the initial palladium catalyzed formation of 1,3-oxazolium-5-olates (Münchnones), followed by its in situ trapping with *N*-tosyl substituted imines to generate the final product. By gaining insight into this mechanism, as well as its potential side reactions (e.g., iminium salt decomposition), a catalytic reaction was developed that could selectively couple these three units together to generate imidazoles in high yield. Overall, this reaction provides not

only a straightforward synthesis of imidazoles, but also one that is readily diversified by modulating the imine or acid chloride building blocks. The utility of this approach was illustrated by the one-pot, regioselective assembly of SB 202190, a potent p38 MAP kinase and anti-inflammatory agent, from available imine and acid chloride substrates.

The imidazolone nucleus is also an important pharmaceutically relevant core and found in a range of biologically relevant products, including anti-inflammatory, anticancer agents and angiotensin II receptor antagonists. Thus, development of a direct and efficient route to assemble these heterocycles is of interest. As described in Chapter 3, the palladium catalyzed four component coupling of imines, chloroformates, organotin reagents, and carbon monoxide can be utilized to generate ketocarbamates; which can undergo cyclization in the presence of ammonium acetate to generate imidazolones. This provides a one-pot, five component coupling route to a range of di- and tri- substituted imidazolones, wherein each of the three substituents about the ring can be independently controlled and varied. These products can be further functionalized via cross coupling reactions, providing a new route to generate polysubstituted imidazoles.

In addition to small molecules, we have shown that this palladium catalyzed multicomponent coupling approach can be further extended to generate π-conjugated polymers. This can be achieved by employing appropriate bifunctional monomers, such as di-imines, di-acid chlorides, and di-*N*-tosylimines. In an analogous fashion to that in Chapter 2, these units can be brought together via a palladium catalyzed reaction to generate imidazole containing oligomers (Chapter

4). Overall, this provides a new and one step route to access diverse arrays of conjugated materials. The diversity of products available via this approach was illustrated by developing a library of 72 different conjugated imidazole-containing materials from basic pool of three imines, four di-acids, and six di-*N*-tosylimines. The UV-vis absorbance and fluorescence excitation/emission spectra of these compounds demonstrate that their optical properties can be varied by over 150 nm by modulating the monomer units on the polymer backbone. This feature can provide a new avenue in the design of conjugated polymers where fine tuning of the polymer band gap is required.

Mechanistic studies on this palladium catalyzed polymerization (Chapter 5) reveal that this process is influenced by the reagent ratios, with optimal molecular weight polymers is obtained under sub-stoichiometric ratio of di-*N*-tosylimine. ^{1}H and ^{13}C NMR, along with MALDI-TOF-MS analysis, clearly demonstrate the presence of imine end groups in the polymer, along with Münchnone decomposition end groups. The latter suggests that these units may decompose during the polymerization, perhaps in the presence of sulfonyl anion released by cycloaddition, thereby influencing polymer molecular weights.

6.1 Suggestions for Future Work

Experimental evidence reveals that the palladium catalyzed multicomponent coupling polymerization is affected by other mechanisms by which the formation of higher molecular weight products is inhibited. Further studies towards a better

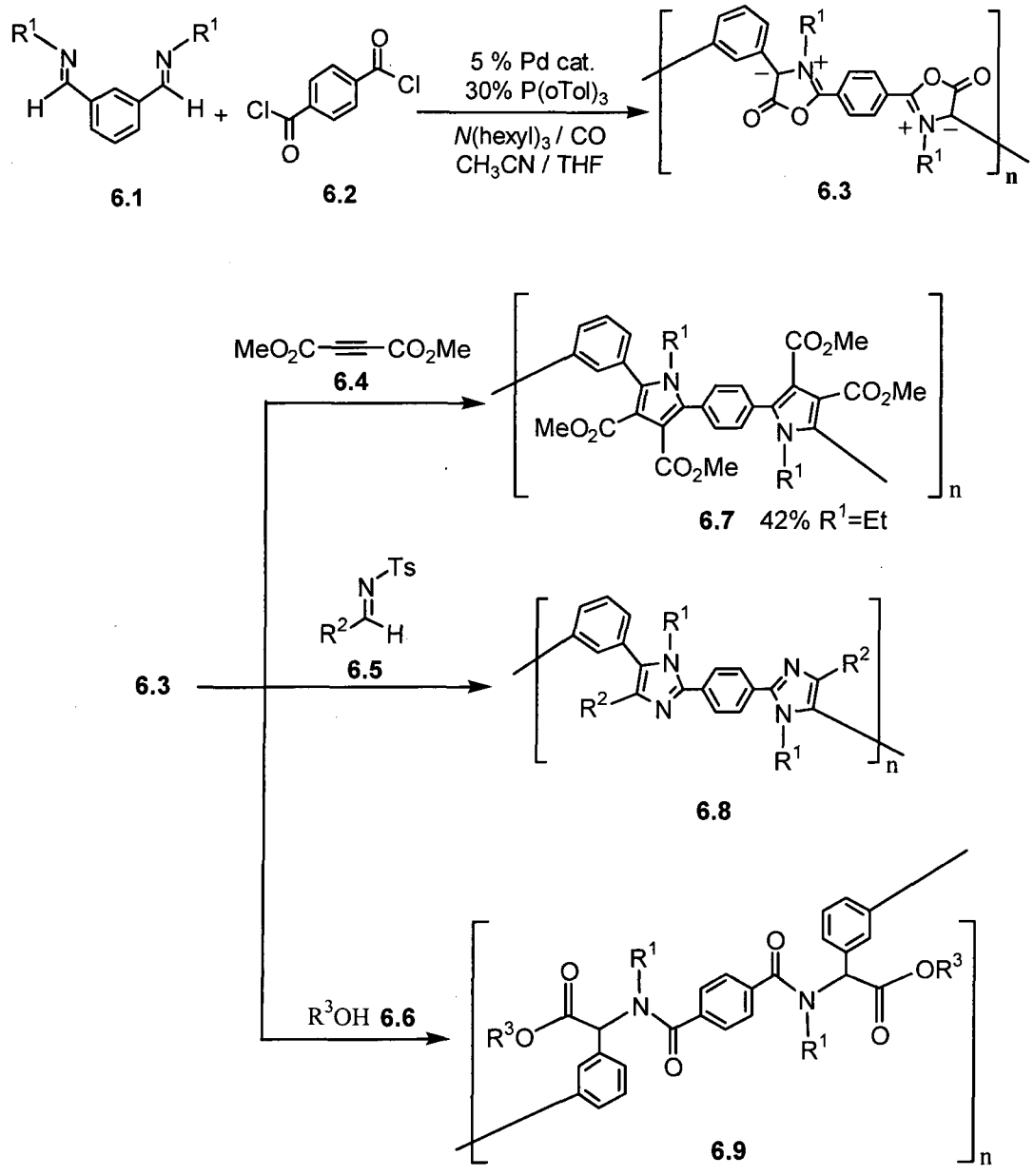
understanding of these phenomena are necessary in order to improve the efficiency of this reaction. For example, since Münchnones are prone to decomposition in the presence of sulfonyl anions, generated during the cycloaddition step, any efforts to inhibit such side reactions might favor the generation of higher molecular weight polymers. In particular, the effect of appropriate electrophilic substrates as sulfonyl anion scavengers should be examined.

Based on the results provided in Chapter 4, a range of π-conjugated imidazole-containing polymers can be assembled from readily available precursors. Since it is shown that subtle structural modifications of the substituents on the polymer backbone can have a significant impact on their optical properties, studies involve expanding the scope of this reaction to incorporate other substrates into the conjugated polymers are of prime importance. For instance, non-enolizable C-alkyl substituted imines, or other aryl-, heteroaryl- or fused-aromatic systems, can be examined as potential coupling partners. In addition, it is of great interest to evaluate other physical properties of these polymers, including their conductivity, thermal stability and others.

As briefly mentioned in Chapter 4, the coupling of di-imine **6.1**, di-acid chloride **6.2** and alkyne **6.4,** lead to the formation of conjugated pyrrole polymers **6.7**. This reaction presumably proceeds via in situ formation of Münchnone-containing polymer **6.3** which can undergo cyclization with alkyne to form **6.7** (Scheme 6.1). Future work should focus on further improvement of the efficiency of this reaction and yield of **6.3**, perhaps by utilizing other bulky phosphine ligands in catalysis, or increasing carbon monoxide pressure. Considering the vast number of reactions that

utilize Münchnones as intermediates, this protocol could be useful in developing new routes to a range of interesting polymers. For instance, by coupling of **6.3** with simple *N*-tosylimine **6.5** or alcohol **6.6**, novel polymeric structures such as **6.8** and **6.9** can be assembled, respectively.

Scheme 6.1: A Potential Route to Other Polymers



APPENDIX A

The Palladium Catalyzed Multicomponent Synthesis of Imidazole-Containing Macrocycles

A.0 Introduction

In Chapter 4 we described the development of a palladium catalyzed multicomponent synthesis of imidazole-containing conjugated polymers directly from imines and acid chlorides In addition to providing facile access to these materials, this reaction can be used to synthesize variously substituted conjugated polymers by modulation of the building blocks employed. While a range of mono- and di-imines and/or acid chlorides were employed in this study, one exception was in the use of simple para-arylene spaced di-imines. Herein, we report the results of our work to employ these substrates in our palladium catalyzed multicomponent polymerization process. This has ultimately led to the catalytic synthesis of a novel imidazole-containing conjugated macrocycle.

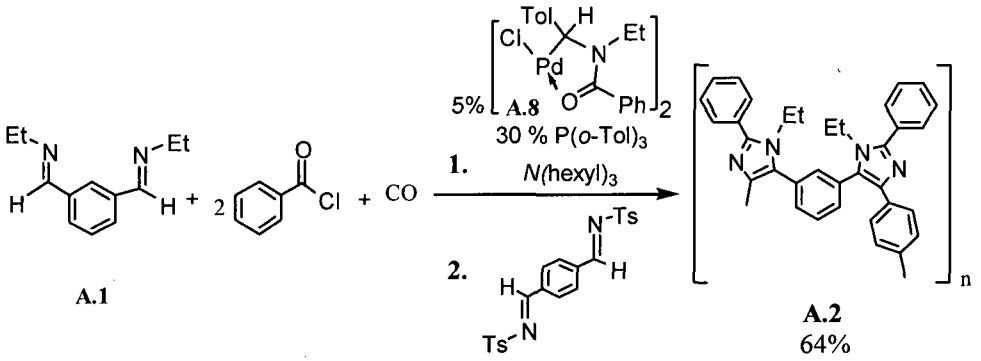
A.1 Results and Discussion

A.1.1 Use of Para-Arylene Spaced Di-Imine (A.3)

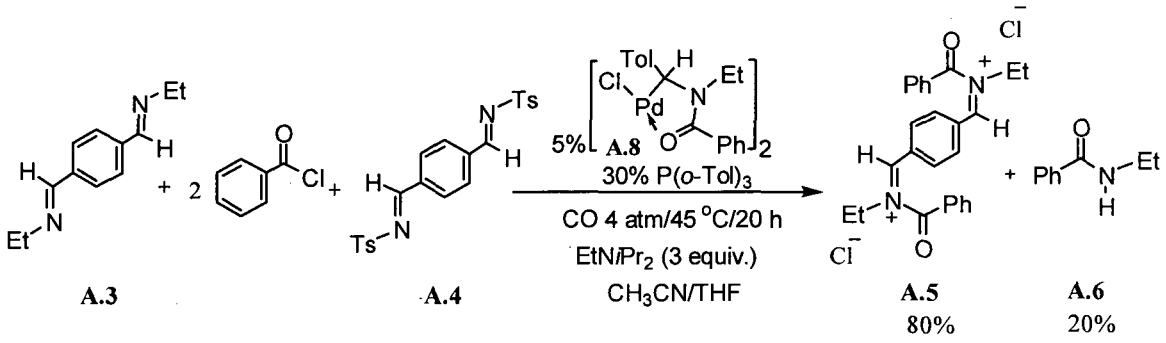
As described in Chapter 4, the meta-substituted arylene di-imine **A.1** can be readily incorporated into the palladium catalyzed synthesis of imidazole-containing polymers, as illustrated in Scheme A.1. In contrast, the analogous reaction of the para-substituted di-imine **A.3**, benzoyl chloride and di-*N*-tosylimine **A.4** does not

lead to the formation of any polymeric product (Scheme A.2). Instead, careful examination of the crude mixture reveals the formation of di-iminium salts **A.5** as the major product of this reaction. Employing more pressing conditions, such as increasing the CO pressure or temperature, did not influence the progress of the reaction.

Scheme A.1: Synthesis of Imidazole-Containing Polymer **A.2** Using Meta-Arylene Spaced Di-Imine **A.1**



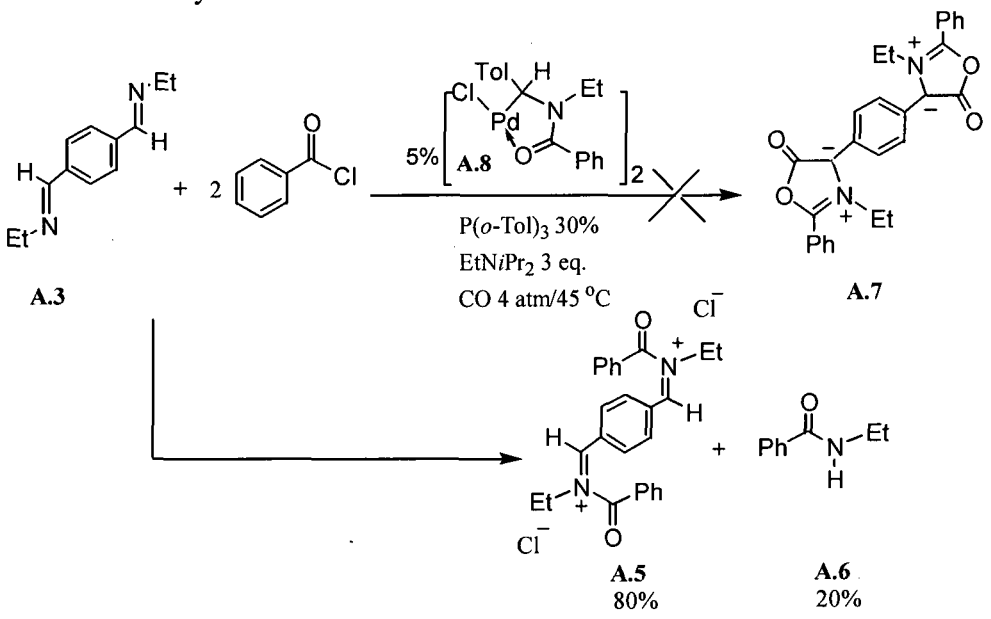
Scheme A.2: Use of Para-Arylene Spaced Di-Imine **A.3**



In order to probe why **A.3** did not participate in the polymerization reaction, the di-*N*-tosylimine **A.4** was excluded from the reaction mixture, in an attempt to generate the di-Münchnone product **A.7** (Scheme A.3). Consistent with our

previous results, only di-iminium salts **A.5** (80%) along with small quantity of amide **A.6** (20%) were found as the major products in this reaction. The latter was presumably formed by decomposition of **A.3** under thermal conditions.[1] Monitoring this reaction by ^{1}H NMR spectroscopy reveals that treating the benzoyl chloride with **A.3** in the presence of palladium catalyst **A.8**, P(*o*-Tol)$_3$ 30%, EtN*i*Pr$_2$ (2 eq.) lead to the quantitative formation of di-iminium salt **A.5** at ambient temperature in 15 min as a pale yellow solution. The subsequent addition of the CO (4 atm) followed by heating at 45 °C resulted in the rapid generation of a dark green

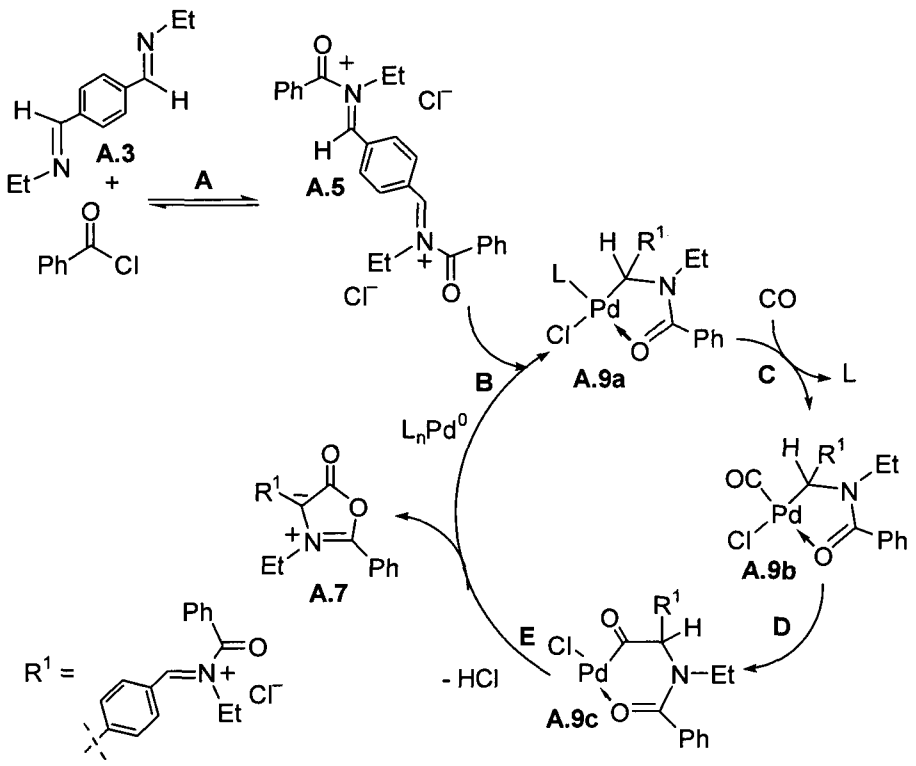
Scheme A.3: Catalytic Formation of **A.7**



solution, and precipitation of the palladium catalyst as a black sediment within 10 min. Similar results were obtained when the reaction was carried out at higher CO pressure (25 atm). Increasing the reaction temperature to 65 °C or higher resulted in faster formation of palladium sediment. These data suggest that the formation of di-

iminium salt **A.5** is not inhibiting the polymerization reaction with **A.3**, and the problem is instead later in the catalytic cycle (Scheme A.4).

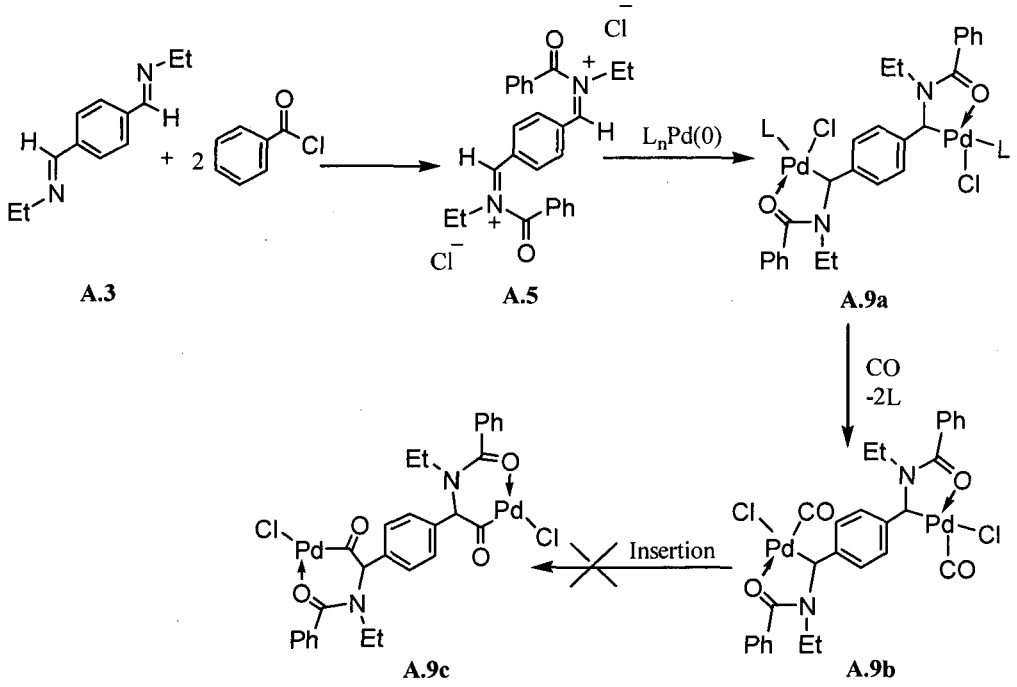
Scheme A.4: Catalytic Cycle for the Formation of Di-Münchnone **A.7**



As shown in Scheme A.4, the next step in the catalytic cycle after iminium salt generation is the oxidative addition of this intermediate to palladium(0) (step B). This step was evaluated by the stoichiometric reaction of **A.5** and $Pd_2dba_3 \cdot CHCl_3$ (Scheme A.5.). Monitoring this reaction by ^1H NMR spectroscopy reveals the conversion of **A.5** into a new product over the course of 30 min. This product has ^1H NMR data consistent with the palladacycle **A.9a**. This includes a shift in the hydrogen on the former imine carbon upfield (δ 5.68 ppm, s), suggesting a reduction

in the C=N π-bond, while the ethyl group CH_2 unit becomes diastereotopic (δ 3.43-3.48 ppm, dd, CH_2CH_3), suggesting the formation of a chiral product. These signals are analogous to those observed in previously synthesized palladium-chelated amides of this form.[2]

Scheme A.5: Formation of Palladacycle **A.9a**



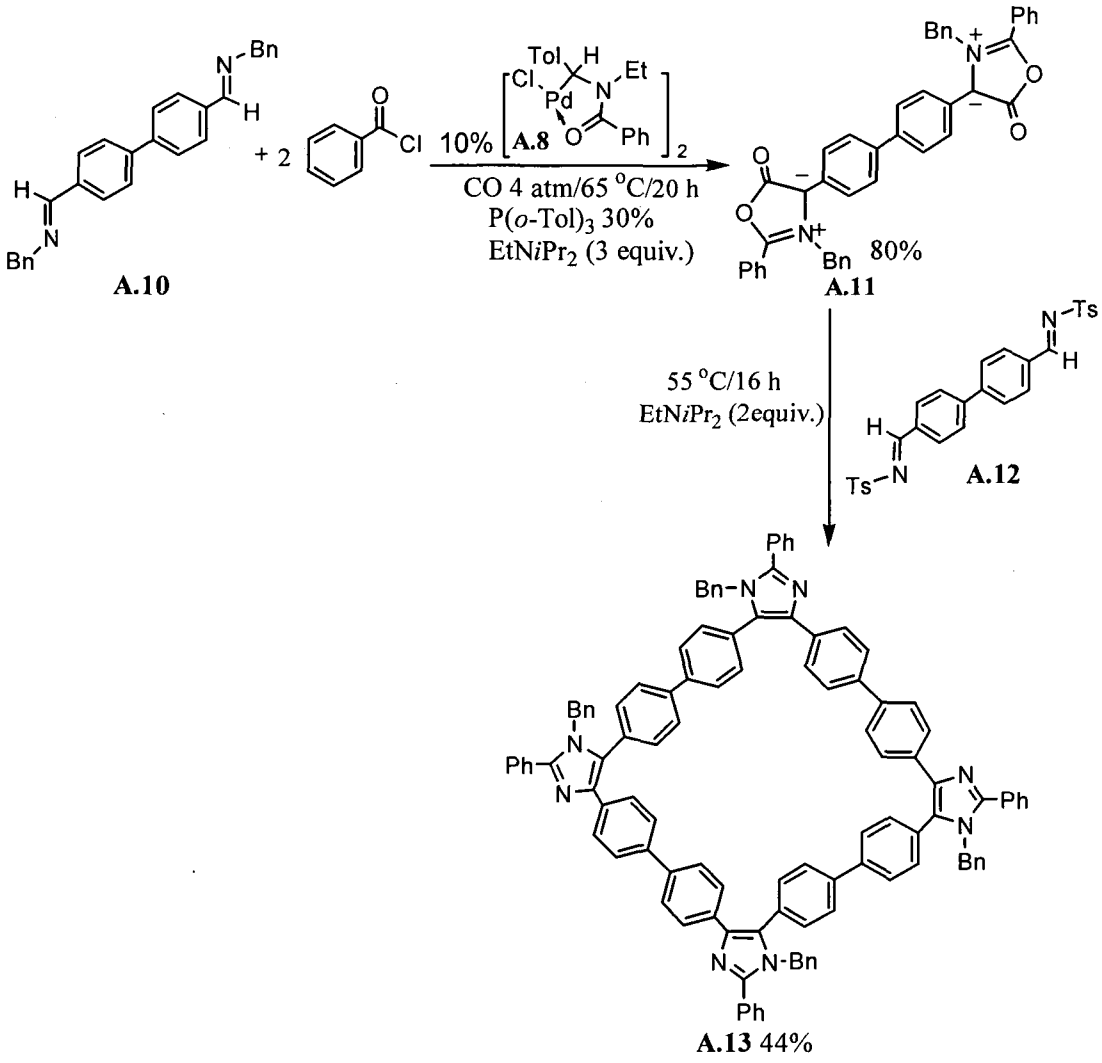
While the formation of **A.9a** is rapid, the addition of 1 atm CO to a solution of this product results in its immediate decomposition to form palladium sediments. Considering these results, and that the meta-substituted di-imine **A.1** undergoes facile CO insertion from this same palladacycle to generate Münchnones, it seems likely that the position of the para-subsituted imine in **A.9a** is leading to a decomposition of the latter in the presence of CO. A plausible rationale for this behavior with **A.3** is that the para-electron withdrawing group is inhibiting CO

insertion. This could arise from an inductive effect decreasing the nucleophilicity of the carbon on palladium, thereby slowing CO insertion, and/or this same effect destabilizing the electron poor CO coordinated **A.9b**. Notably, similar results have been observed when electron difficient imines are employed in the palladium catalyzed Münchnone synthesis.[2]

A.1.2. Use of Para-Biphenylene Spaced Di-imines

To address the inability of **A.3** to participate in carbonylation, we set out to diminish the electron withdrawing effect of the di-imine substrate by introducing one more phenyl spacer between two imines. The di-imine **A.10** can be prepared from its corresponding dialdehyde.[3] This imine was reacted with benzoyl chloride in the presence of 10% of palladium complex **A.8**, P(*o*-Tol)$_3$ 30%, Et*N*i*P*r$_2$ (3eq.), 4 atm of CO at 65 °C for 16 h (Scheme A.6). In situ ^{1}H NMR analysis of the product mixture reveals the disappearance of **A.3**, and formation of a new product (**A.11**) that contains a benzylic CH_2 signal (δ 5.45, s) analogous to that observed in other Münchnone products.[4] The subsequent addition of the di-*N*-tosylimine **A.12** and heating to 55 °C for 16 h resulted in the reaction solution turning from deep orange to light yellow. Filtration of the reaction solution through celite, and precipitation of the product by the addition of diethyl ether results in the isolation of the cyclic product **A.13**, rather than a polymeric product, in 44% yield. In addition, lower molecular weight linear oligomers can be observed in the diethylether solution.

Scheme A.6: An Efficient Synthesis of **A.13**



The product **A.13** was characterized by ^{1}H and ^{13}C NMR spectroscopy, which reveal the observed aryl, benzyl and imidazole unit, and most conclusively by MALDI-TOF mass spectroscopy. The latter shows a single mass for the product correlating to that of the cyclic **A.13**. Notably, neither ^{1}H NMR spectroscopy, nor mass spectra, show any evidence of an end group on the isolated product. These, together with the exact mass for the cyclic product, are consistent with a cyclic structure of **A.13**.

The ability to carbonylative **A.10** suggests that the additional phenyl spacer between two imines does decrease the inductive effect of the second imine. The coupling of the di-Münchnone **A.11** with a di-*N*-tosylimine **A.12** generates a 4,5-substituted imidazoles, which has approximately 72° between the two biphenyl units. This is presumably sufficiently close to 90° to generate macrocyclic square **A.13**, rather than linear polymers. Preliminary UV-vis and fluorescence data of **A.13** show that this compound exhibits an intense blue photoluminescence with the emission maximum at 442 nm.

A.2 Conclusions

Our experimental results show that the *p*-substituted di-imine such as **A.3** does not undergo the palladium catalyzed multicomponent polymerization process. Control experiments indicate that the formation of **A.7** is inhibited due to the electron withdrawing effect of the imine subtituent on para position, which ultimately diminishes the ability of CO to insert into the palladium-carbon bond of the oxidative-addition complex **A.9a.** This electron withdrawing effect can be reduced by employing one more phenyl spacer between two imines functionality. Interestingly, however, this results in the generation of the macrocyclic **A.13**, rather than a conjugated polymer.

A.3 Experimental Section

General Procedures

Unless otherwise noted all reactions were carried out under an inert atmosphere in a dry box or using standard Schlenk or vacuum line techniques. Palladium catalyst **A.8** was prepared according to previously reported procedure, by pretreating $Pd_2dba_3 \cdot CHCl_3$ with imine and acid chloride.[1, 2] Di-imine **A.1**, **A.3**, and **A.10**, and di-*N*-tosylimine **A.4** and **A.12** were prepared in analogy to literature procedures.[5, 6] Carbon monoxide (99.99%) was purchased from Matheson and used as received. All other reagents were used as received from commercial suppliers.

Acetonitrile was freshly purified by distillation over CaH_2 under nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Deuterated solvents were dried over drying agents, transferred under vacuum and stored over 3 and 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on Mercury 400 MHz and Unity 500 MHz Varian NMR spectrometers. MALDI-TOF-MS analysis was performed on a Kratos Kompact MALDI-III-TOF bench top model instrument which generates a maximum laser beam at a wavelength of 337 nm (N2 laser light, 3 ns pulse width). The average of 100 laser shots was represented in the mass spectra. The polymer sample (5 mg/mL) was dissolved in chloroform and dithranol-LiBr in THF solution was added as matrix in a 1:2 volume ratio. A spot of the sample was placed on the sample slide and the solvent was allowed to evaporate slowly before being put into the vacuum chamber of the mass spectrometer. UV-vis spectra were recorded on a Varian Cary 50 spectrophotometer, between 190-850 nm wavelengths. Fluorescence

excitation/emission spectra were acquired using a Jobin Yvon-Spex FluoroMax 2 Spectrofluorometer with a 150 W continuous ozone-free lamp in CH_2Cl_2.

Attempted Polymerization with Di-Imine A.3 (Scheme A.2)

Ethyl-[4-(Ethyliminomethyl)-benzylidene]-amine (50 mg, 0.265 mmol) and benzoyl chloride (74 mg, 0.53 mmol) were dissolved in 6 mL of CH_3CN:THF solution (1:1) and stirred in the reaction bomb for 15 min. To this was added palladium catalyst **A.8** (10.4 mg, 0.013 mmol), P(*o*-tol)$_3$ (24.4 mg, 0.079 mmol) in 3 mL of THF, and Et*i*Pr$_2$ (103 mg, 0.795 mmol) in 3 mL of CH_3CN. 1, 4-*N*-Benzylidene-bis(4-methyl-benzenesulfonamide) **A.4** (116 mg, 0.265 mmol) was then added to this reaction. Benzyl benzoate was also added to this mixture as an internal standard. The entire mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) was introduced. After heating the mixture at 45°C for 2 h, the pale yellow reaction solution slowly turned to dark green and palladium black precipitated out of the solution. ^{1}H NMR analysis of the crude mixture revealed the presence of the di-iminium salt **A.5** (^{1}H NMR: δ 3.42 (q, 2H) and 1.23 (t, 3H) corresponds to *N*-ethyl group $\mathbf{CH_2CH_3}$) as the major product (80%).

Attempted Synthesis of Münchnone A.7 (Scheme A.3):

Ethyl-[4-(Ethyliminomethyl)-benzylidene]-amine (50 mg, 0.265 mmol) and benzoyl chloride (74 mg, 0.53 mmol) were dissolved in 6 mL of CH_3CN:THF solution (1:1) and stirred in the reaction bomb for 15 min. To this was added palladium catalyst **A.8** (10.4 mg, 0.013 mmol), P(*o*-tol)$_3$ (24.4 mg, 0.079 mmol) in 3 mL of THF, and Et*i*Pr$_2$N (103 mg, 0.795 mmol) in 3 mL of CH_3CN. Benzyl benzoate was also added to this mixture as an internal standard. The entire mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) was introduced. After heating the mixture at 45 °C for 2 h, the pale yellow reaction solution slowly turned to dark green and palladium black precipitated out of the solution. ^{1}H NMR analysis of this crude mixture revealed the presence of the diiminium salt **A.5** (^{1}H NMR: δ 3.42 (q, 2H) and 1.23 (t, 3H) corresponds to *N*-ethyl group $\mathbf{CH_2CH_3}$) as the major product. Similar results were obtained when this reaction was carried out at higher CO pressure (e.g. 20 atm).

Monitoring the Attempted Formation of Münchnone A.7 by ^{1}H NMR

Ethyl-[4-(Ethyliminomethyl)-benzylidene]-amine (20 mg, 0.11 mmol) and benzoyl chloride (31mg, 0.22mmol) were dissolved in CD_3CN and placed in an NMR tube. To this was added palladium catalyst **A.8** (4.4 mg, 5.5 mmol), P(*o*-tol)$_3$ (10 mg, 0.033 mmol) and Et*i*Pr$_2$N (42.6 mg, 0.33 mmol). The quantitative formation of diiminium salt **A.5** was confirmed by NMR analysis (^{1}H NMR: δ 3.42 (q, 2H) and 1.23 (t, 3H) corresponds to *N*-ethyl group $\mathbf{CH_2CH_3}$). The mixture was

further frozen in liquid nitrogen, evacuated, and carbon monoxide (20 psi) was added into the NMR tube. Upon the addition of carbon monoxide into the solution, the reaction mixture slowly turned to dark green color followed by the formation of the palladium precipitate within 2 h at ambient temperature.

Stoichiometric Reaction of A.5 with Pd_2dba_3•$CHCl_3$

Ethyl-[4-(Ethyliminomethyl)-benzylidene]-amine (25 mg, 0.137 mmol) and benzoyl chloride (38 mg, 0.27 mmol) were dissolved in 6 mL of CH_3CN:THF solution (1:1) and stirred in the reaction bomb for 15 min. The quantitative formation of di-iminium salt **A.5** was confirmed by NMR analysis (^{1}H NMR: δ 3.42 (q, 2H) and 1.23 (t, 3H) corresponds to *N*-ethyl group $C\mathbf{H_2}C\mathbf{H_3}$). To this solution was added Pd_2dba_3•$CHCl_3$ (142 mg, 0.137 mmol) and the mixture stirred at ambient temperature for 2 h under nitrogen until all the Pd_2dba_3•$CHCl_3$ was dissolved, leading to a clear yellow mixture. The solvent was then removed under reduced pressure to give a yellow solid. This product was purified by adding Et_2O (20 mL) and cooling the solution to -20 °C to form a yellow precipitate. The Et_2O solution was then decanted and the precipitate was further washed with Et_2O followed by cooling to -20 °C. This procedure was repeated several times. ^{1}H NMR spectroscopy of this product reveals the formation of palladium-chelated amide **A.9a** which was partially purified. These data include a shift in the hydrogen on the former imine carbon upfield (5.68 ppm, s, 1H)), and the ethyl group CH_2 unit becomes diastereotopic (3.43-3.48 ppm, dd, $C\mathbf{H_2}CH_3$), respectively.

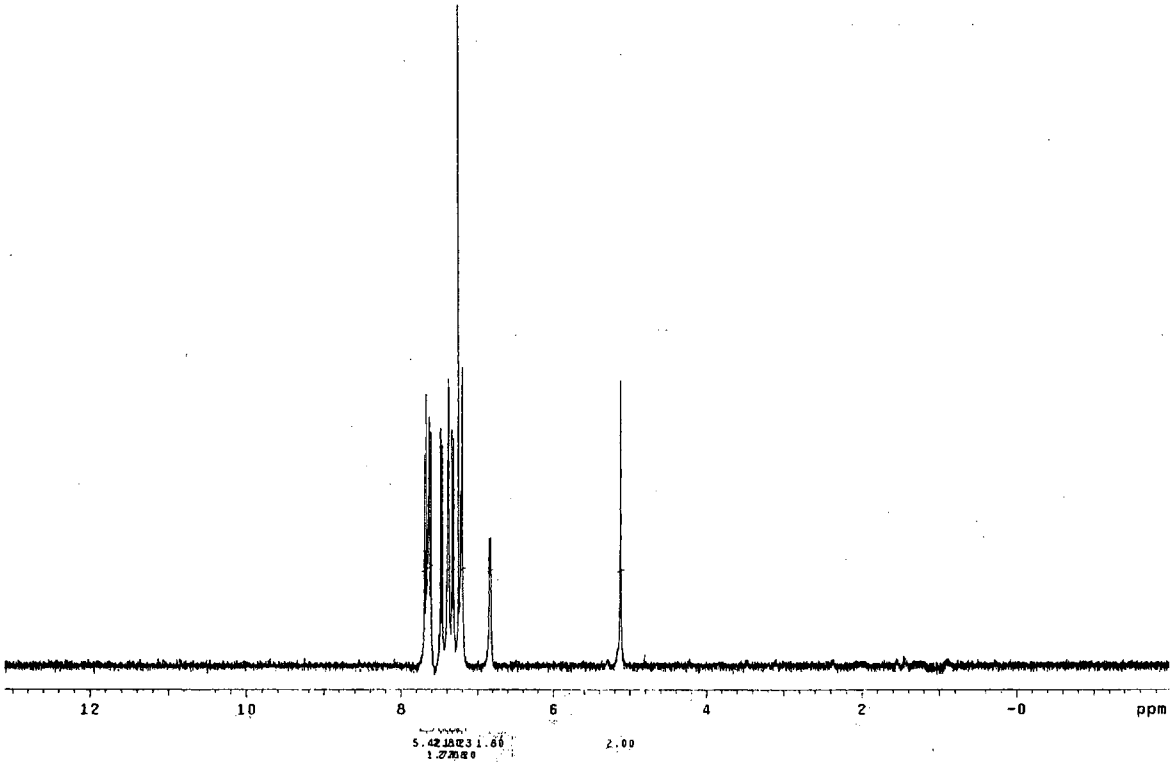
Synthesis of Imidazole-Containing Macrocycle A.13:

Benzyl-[4'-(benzylimino-methyl)-biphenyl-4-ylmethylene]-amine (100 mg, 0.26 mmol) and benzoyl chloride (72 mg, 0.52 mmol) was dissolved in $CHCl_3$ (3 mL) and stirred for 6 h at ambient temperature under nitrogen. After confirming the formation of the corresponding di-iminium salt by ^1H NMR, the solvent was removed under reduced pressure and the pale yellow oil was redissolved in CH_3CN:THF 1:1 (10 mL). To this was added palladium catalyst **A.8** (10 mol%), P(*o*-tol)$_3$ (30 mol%) in 3 mL of THF, and Et*i*Pr$_2$ (3eq.) in 3 mL of CH_3CN. Benzyl benzoate was also added to this mixture as an internal standard. The entire mixture was frozen in liquid nitrogen, evacuated, and carbon monoxide (60 psi) was added. After heating to 65 °C for 16 h, the mixture was degassed, and an aliquot of the crude deep red solution was analyzed by ^1H NMR and the yield of **A.11** was determined by comparison to the internal standard. Based upon the NMR yield, bis(*N*-benzylidene-4-methyl-benzenesulfonamide) **A.12** (108 mg, 0.21 mmol) was added to the solution and heated at 65 °C for additional 16 h under nitrogen. The resulting yellow crude mixture was then filtered over celite and solvent was removed in *vacuo*. The yellow oil was repeatedly washed with Et_2O (150 mL) and the Et_2O layers were decanted. The resulting solid was fractionally precipitated from CH_2Cl_2: EtOAc to afford **A.13** as a pale yellow solid. Yield: 44% ^1H NMR (400MHz, $CDCl_3$, 60 °C): δ 7.7-7.68 (d, 3H), 7.66-7.61 (m, 3H), 7.49-7.47 (d, 2H), 7.39-7.38 (m, 3H), 7.34-7.32 (d, 2H), 7.25- 7.20 (m, 3H), 6.85-6.83 (m, 2H), 5.13 (s, 2H). ^{13}C NMR (125MHz, $CDCl_3$, 60 °C): δ 147.8, 138.7, 138.3, 137.6, 135.2, 131.6, 131.2,

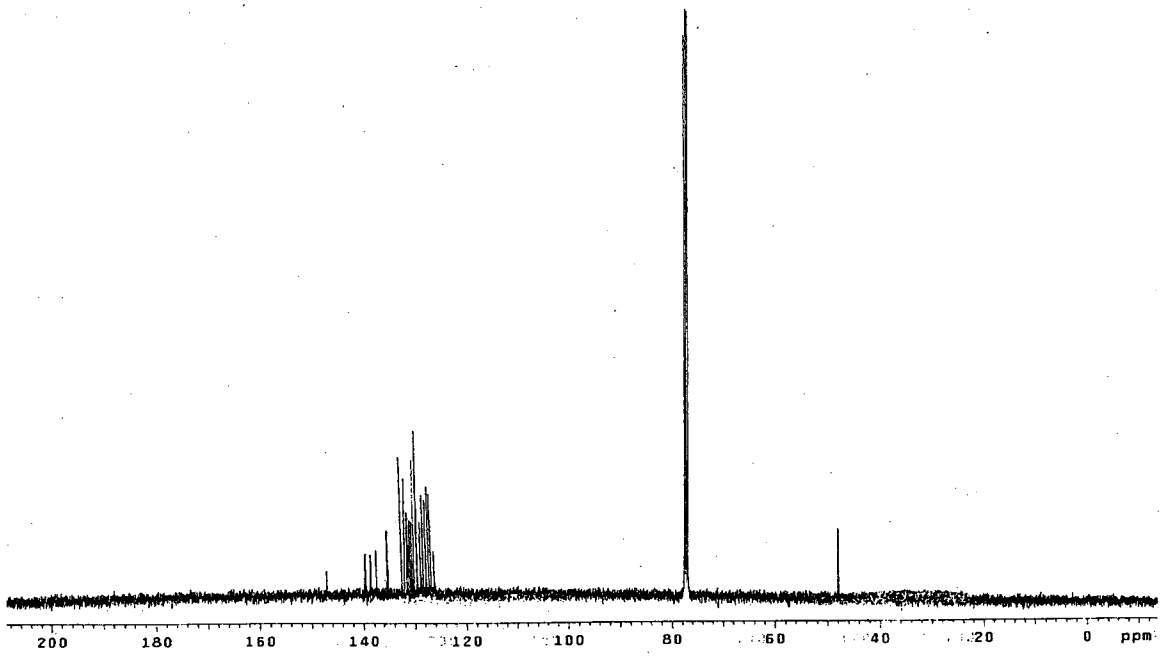
130.5, 129.4, 129.2, 129.02, 128.6, 128.4, 128.2, 127.6, 127.1, 126.8, 126.4, 126.3, 48.1. MALDI-TOF-MS: 1536 m/z

NMR Spectra of Imidazole-Containing Macrocycle A.13

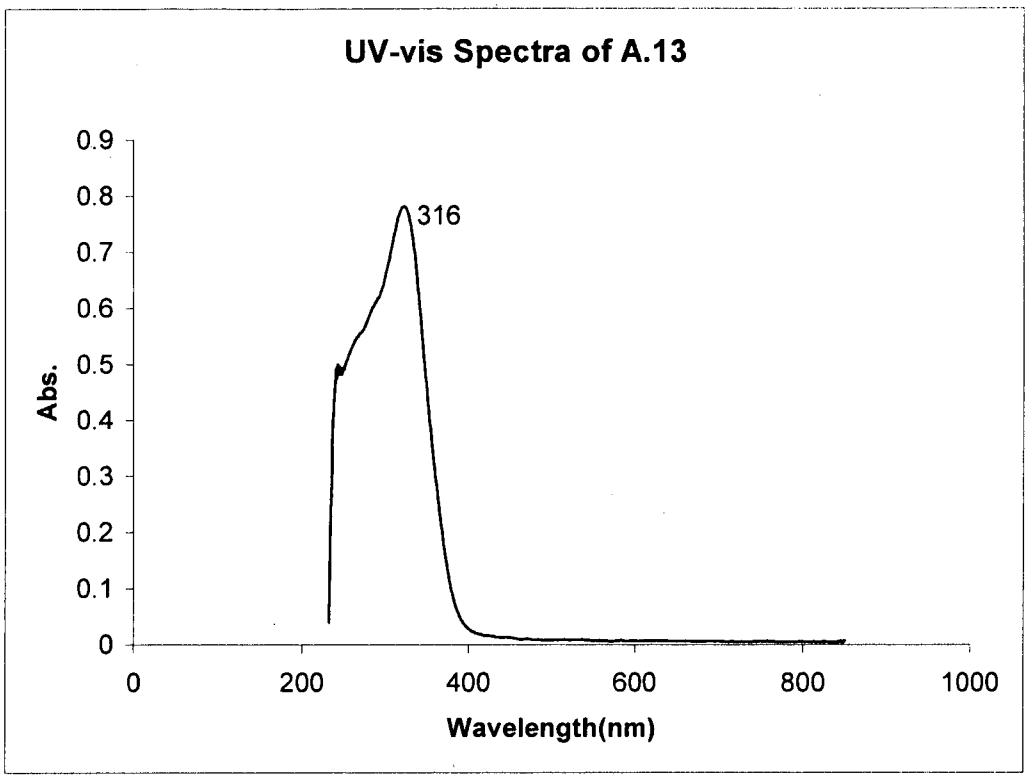
^{1}H NMR:

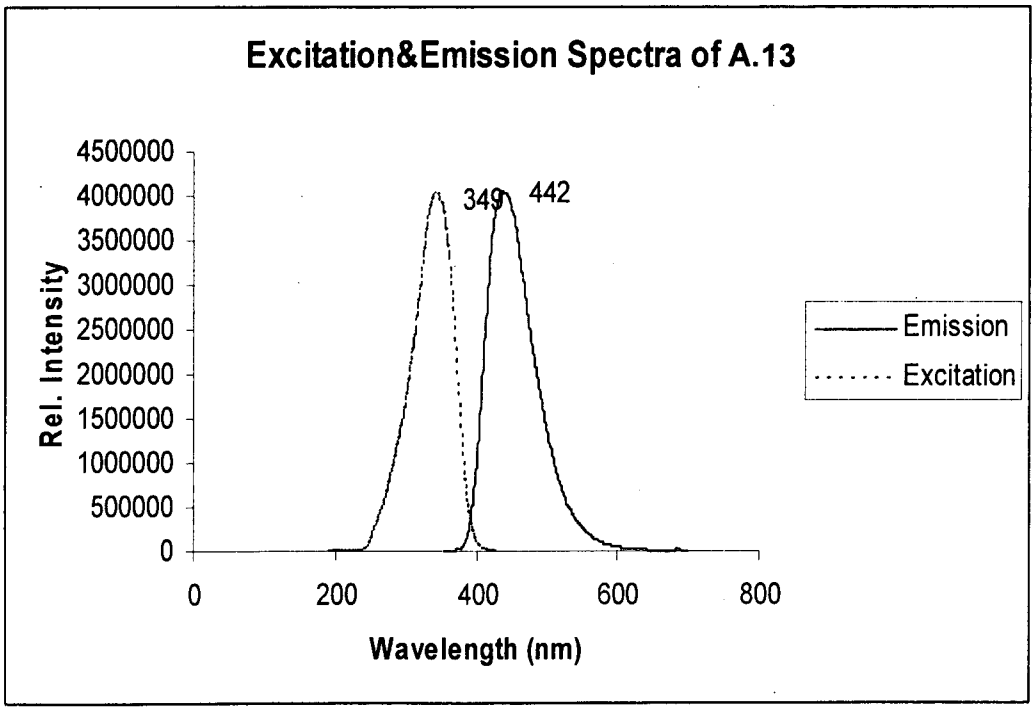


^{13}C NMR:



UV-vis & Fluorescence Spectra of A.13





A.4 References

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