Studies Toward Chelation Assisted *Ortho*-Selective C-H Bond Functionalization of Arenes

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

Pradeep Sadhu
Roll No. 11612209

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati- 781039
August 2016

Dedicated

To

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati — Pradeep Sadhu

August 2016

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Pradeep Sadhu has been working under my supervision since July 2011. I am forwarding his thesis entitled *"Studies Toward Chelation Assisted Ortho-Selective C-H Bond Functionalization of Arenes"* being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati

August 2016

Prof. Tharmalingam Punniyamurthy

Supervisor

Acknowledgement

I would like to express sincere gratitude to the kind people around me, who helped me directly and indirectly to transcend these significant milestones and motivated me on the path of success

First and foremost, my wholehearted thanks to my thesis supervisor Prof. Tharmalingam Punniyamurthy for his continuous support, motivation, invaluable guidance and suggestions throughout my Ph.D. helped me immensely to grow as a chemist. I am also thankful to him for giving me the freedom to explore organic chemistry and nurturing my love for the subject. My everlasting gratitude goes towards him.

I express my sincere thanks to doctoral committee members Prof. G. Krishnamoorthy, Dr. Subhendhu Sekhar Bag, and Prof. Arun Goyal for their evaluation and valuable suggestions during the entire period of my doctoral studies. My honest regards to all the faculty of the Department of Chemistry for their motivation and encouragement.

I am very grateful to the University Grants Commision (UGC), India for financial support and IIT Guwahati for all the facilities that were made available to me. I also thank Central Instrument Facility (CIF), IIT Guwahati for providing the instrument facility and DST for providing the X-ray facility.

My special thanks goes to all my past and present group members, Dr. Prasenjit Saha, Dr. S. Sakthivel, Dr. Tamminana Ramana, Dr. Rajesh Paul, Dr. Md Ashif Ali, Dr. Rapolu Kiran Kumar, Dr. Murali Mohan Guru, Dr. G. Sathish Kannan, Dr. Santhosh Kumar Alla, M. Kannan, M. Sengoden, G. Murgavel, G. Bharathiraja, Dinabandhu Sar, D. Mahesh, M. Vijay, V. Satheesh, Raghunath Bag, Pinaki, Sourav, Ritesh, Abhisikta and Rinki for the stimulating discussions, pleasant and helpful company and for all the fun we have had in the last five years.

I thank to other friends in IITG, especially Dr. Somasekhar, Dr. Murali, Dr. Chaitanya, Dr. Kiran, Dr. Kishore, Dr. Narasimha, Dr. Laxman, Dr. Ganesh, Srinu, Sunil, Satti, Suresh, Bheem, Nagendra, Unnava, Radha Krishna, Gopi, Dharm Dev, Ranganath, Ajay and Abhishek for their everyday help and support in all aspects.

I also take this opportunity to thank all of my Ph.D. batchmates (July, 11), the other research scholars in the chemistry department and all my IITG friends, who have shared their thoughts and views with me.

My heartful thanks also go to my dearest friends from outside IITG, Usha, Ayan, Darpan, Milan, Bheem, Gourav, Sathish, Madhu, Ramachandra, Phani, Ramesh, Nageswararao, Gopi, Ganesh, Suresh, Ramarao for their constant support and encouragement.

Finally, my deepest gratitude goes to my parents (Pulla Rao and Vara Lakshmi), brother (Devendra Kumar) for their unflagging love and support throughout my life. I feel deeply indebted to them for whatever I have achieved so far and I dedicate this work to them.

Pradeep Sadhu

List of Abbreviations

ac	acetyl	ee	enantiomeric excess
acac	acetylacetone	FG	functional group
Ad	adamantane	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
AIBN	azobisisobutyronitrile	IR	infrared
BTF	benzotrifluoride	*m*CPBA	*meta*-chloroperbenzoic acid
Bu	butyl	mp	melting point
BQ	1,4-benzoquinone	Ms	methanesulfonyl
CDC	cross-dehydrogenative coupling	MS	molecular sieves
Cy	Cyclohexyl	m/z	mass to charge ratio
DABCO	1,4-diazabicyclo[2.2.2]octane	NMP	*N*-methyl-2-pyrrolidone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	NMR	nuclear magnetic resonance
DCE	1,2-dichloroethane	NXS	*N*-halosuccinimide
DCM	dichloromethane	ORTEP	oak ridge thermal ellipsoid plot
DG	directing group	Pr	propyl
DME	1,2-dimethoxyethane	*p*TSA	*p*-toluenesulfonic acid
DMF	*N*,*N*-dimethylformamide	rt	room temperature
DMEDA	*N*,*N'*-dimethylethylenediamine	TBAB	*tetra*-*n*-butylammonium bromide
DMSO	dimethylsulfoxide	TBHP	*tert*-butyl hydroperoxide
DPPF	1,1′-bis(diphenylphosphino)ferrocene	Tf	trifluoromethanesulfonyl
dr	diastereomeric ratio	TFA	trifluoroacetic acid
EAS	electrophilic aromatic substitution	TFE	2,2,2-trifluoroethanol
EDG	electron donating group	TCP	trichloropropane
EWG	electron wthdrawing group	THF	tetrahydrofuran
TLC	thin layer chromatography	TMS	trimethylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylenediamine	TMTU	tetramethylthiourea
TBN	*tert*-butyl nitrite	Ts	*p*-toluenesulfonyl
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl	TM	transition metal

Abbreviations For Intensities of ^{1}H-NMR Signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	Hz	hertz
dt	doublet of triplet		
MHz	megahertz		

Abstract

The contents of this thesis are divided into four chapters. The introductory chapter focuses on the recent developments in chelation assisted C-H functionalization reactions. The second chapter presents Pd-catalyzed *N*-(2-halophenyl)-1*H*-tetrazol-5-amine directed chemo- and regioselective *ortho*-functionalization of arenes. The third chapter illustrates Cu(II)-catalyzed nitration of *N*-aryl ring of *N*,1-diaryl-1*H*-tetrazol-5-amine and *N*-aryl ring of *N*,4-diaryl-3-amino-1,2,4-triazole *via* chelation assisted C-H functionalization. The fourth chapter describes the Cu-mediated 8-aminoquinoline amide directed regioselective *N*-arylation of pyrroles, indoles, pyrazoles and carbazole *via* cross-dehydrogenative coupling (CDC).

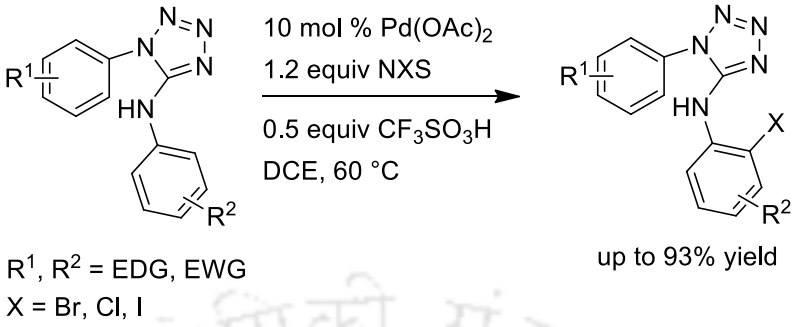
Chapter 1. Recent Developments in Chelation Assisted C-H Functionalization

Transition-metal-catalyzed reactions provide an effective method for the construction of complex organic frameworks. Most of these studies rely on the use of prefunctionalized starting materials, so called cross-coupling reactions. In this regard, C-H functionalization reactions emerged as a powerful synthetic tool for the conversion of carbon-carbon and carbon-hetero atom bond formation using simple starting materials. To accomplish a C–H functionalization reaction in a practically useful manner, issues regarding site-selectivity need to be addressed. The most effective and well-practiced approaches to attain site-selectivity is the use of a heteroatom directing group. In this context, over the past few years, diverse directing groups have been developed for the development of versatile C-H functionalization reactions such as halogenation, amination, nitration, cyanation, acetoxylation, hydroxylation, arylation, olefination, etc. Some of these results are presented.

Chapter 2. Pd-Catalyzed Aminotetrazole-Directed *Ortho*-Halogenation of Arenes

N-(2-halophenyl)-1*H*-tetrazol-5-amine substrates are known to exhibit herbicidal and anti-allergic properties. This chapter presents the synthesis of substituted *N*-(2-halophenyl)-1*H*-tetrazol-5-amine *via* chelation assisted C-H functionalization. The transformation is

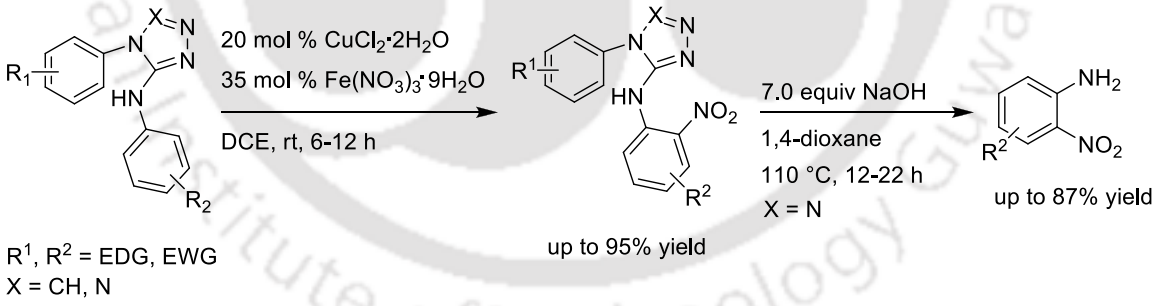
promoted by catalytic amount of $Pd(OAc)_2$ under acidic conditions in presence of *N*-halosuccinimide at moderate temperature (Scheme 1).



Scheme 1. *Ortho*-halogenation of *N*,1-diphenyl-1*H*-tetrazol-5-amines

Chapter 3. Room-Temperature Cu-Catalyzed *Ortho*-Nitration of Arenes *via* C−H Functionalization

The nitro group can be transformed into diverse functional groups and found applications in various fields such as pharmaceuticals, dyes and materials. This chapter focuses on the *ortho*-nitration of arenes using $CuCl_2{\cdot}2H_2O$ as catalyst and $Fe(NO_3)_3{\cdot}9H_2O$ as a nitro source. The protocol is extended for the nitration of *N*,4-diaryl-3-amino-1,2,4-triazoles. In addition, the directing group can be cleaved to furnish the aniline derivatives (Scheme 2).

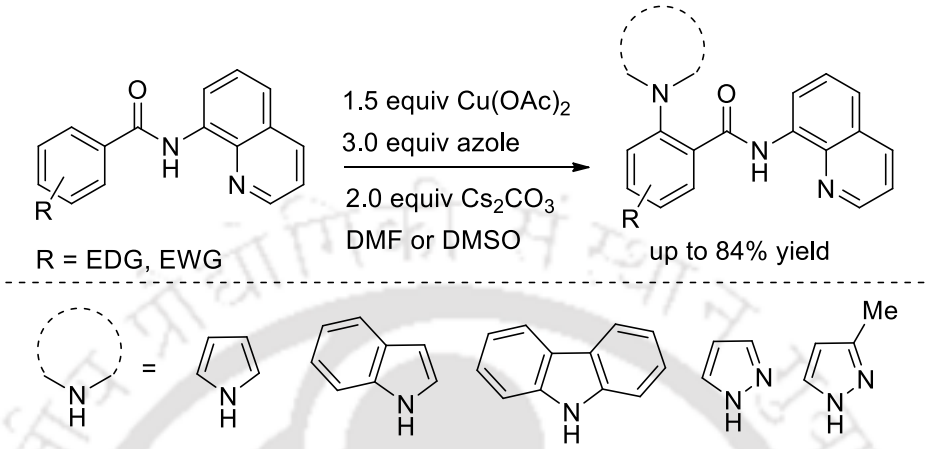


Scheme 2. Nitration of Arenes *via* Chelation assisted C-H functionalization

Chapter 4. Cu-Mediated *N*-Arylation of Pyrroles, Indoles, Pyrazoles, and Carbazole *via* Cross-Dehydrogenative Coupling (CDC)

N-Arylated azole structural motifs are present in numerous compounds with broad applications in biological and pharmaceutical sciences. In addition, 2-(1*H*-pyrrol-1-yl) benzoic acid derivatives are key synthons in the formation of heterocyclic compounds.

This chapter presents Cu(II)-promoted *N*-arylation of pyrroles, indoles, pyrazoles and carbazole using a removable amide directing group. The strategy represents an ideal and environmentally attractive because of their cleaner, shorter and regioselective approaches (Scheme 3).



Scheme 3. Regioselective *N*-Arylation of Azoles *via* Cross-Dehydrogenative Coupling

Contents

Chapter 2. Pd-Catalyzed Aminotetrazole Directed *Ortho*-Halogenation of Arenes

Chapter 3. Room-Temperature Cu-Catalyzed *Ortho*-Nitration of Arenes *via* C−H Functionalization

Chapter I

Recent Developments in Chelation Assisted C-H Functionalization

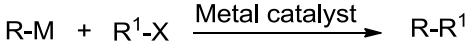
The development of effective methods for the synthesis of wide spectrum of substances with minimal environmental impact turned out to be very challenging for many organic chemists. In recent years, transition-metal-catalyzed reactions led to the development of elegant approaches towards the construction of complex organic frameworks.[1-15] While the extensively studied cross-coupling methods rely on the use of prefunctionalized starting materials, such as halide, triflate, boron or tin reagents,[4] C-H bond functionalization reactions by furnishing the target products in fewer steps and offering fundamentally ample library of simple starting materials and new perspectives in retro synthesis has emerged as a reliable synthetic tool for the conversion of ubiquitous carbon-hydrogen bonds into carbon-carbon or carbon-heteroatom bonds. Indeed, in these strategies, the issue of site-selectivity is not addressed. The most effective and well-practiced approaches to attain site-selectivity is the use of a heteroatom directing group for the functionalization of specific C-H bond.

1.1 The Cross-Coupling Reactions

Transition-metal-catalyzed cross-coupling reactions got broad range of applications in biological and material sciences.[2] This importance is attributed to its effective use in carbon-carbon and carbon-heteroatom bond formations. As a result, many cross-coupling synthetic methodologies have emerged over the years. Traditionally, Ullmann and Goldberg methods were employed for this purpose but these reactions were limited due to the use of stoichiometric amount of copper, limited substrate scope and high temperatures.[3] A major breakthrough in the field of cross-couplings is achieved by using catalytic amount of metal complexes in achieving the products under relatively milder conditions with broad scope. In general, the cross-coupling reactions essentially require halides or pseudo halides and organometallic nucleophilic reagents, some of them were shown in (Table 1).[4] Due to the strong impact of these strategies in organic synthesis Heck, Negishi and Suzuki received Nobel Prize in 2010 for their pioneer discoveries on cross-coupling reactions. In these catalytic processes, the transformation was achieved by oxidative addition of metal complex

with organic halide with subsequent transmetalation followed by reductive elimination producing the target product.

Table 1. Examples of Common Cross-Coupling Reactions



S. No	Reaction	Reactant A	Reactant B	Catalyst
1	Kumada	R-MgBr (sp^2, sp^3)	Ar-X	Pd, Ni, Fe
2	Heck	R (sp²)	Ar-X	Pd, Ni
3	Sonogashira	R—≡—H (sp)	R-X (sp^3, sp^2)	Pd and Cu
4	Negishi	R-ZnX (sp^3, sp^2, sp)	R-X (sp^3, sp^2)	Pd, Ni
5	Stille	R-SnR_3 (sp^3, sp^2, sp)	R-X (sp^3, sp^2)	Pd
6	Suzuki	R-$B(OR)_2$ (sp^2)	R-X (sp^3, sp^2)	Pd, Ni
7	Hiyama	R-SiR_3 (sp^2)	R-X (sp^3, sp^2)	Pd
8	Buchwald-Hartwig	R_2-NH	Ar-X	Pd
9	Fukuyama	R-Zn-I (sp^3)	RCO(SEt) (sp^2)	Pd, Ni

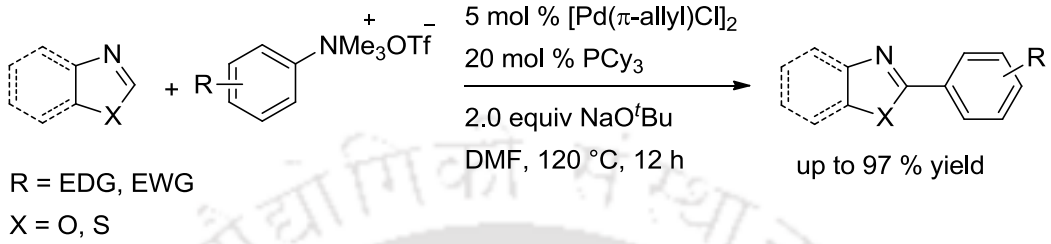
1.2 The C-H Bond Activation

C-H bonds are ubiquitous in organic molecules with high bond dissociation energy (113 kcal/mol) and hence relatively thermodynamically stable and less reactive. As a result, the reactions involving the functionalizations of C-H bonds were less exploited till date.[1] A few methods were available, but these were unselective and yielded a complicated mixture of products. The selectivity of this C-H bond functionalization can be achieved by 3 ways (i) Intrinsic[5] (ii) Intramolecular[6] and (iii) Directing group[7]

1.2.1 Intrinsic C-H Bond Functionalization

Intrinsic C-H bond functionalization involves the use of inherent substrate reactivity in exploiting functionalization of C-H bonds. For example, in case of electron rich heteroarenes, the differences in the reactivity of C-H bonds can be utilized to achieve the selectivity. For

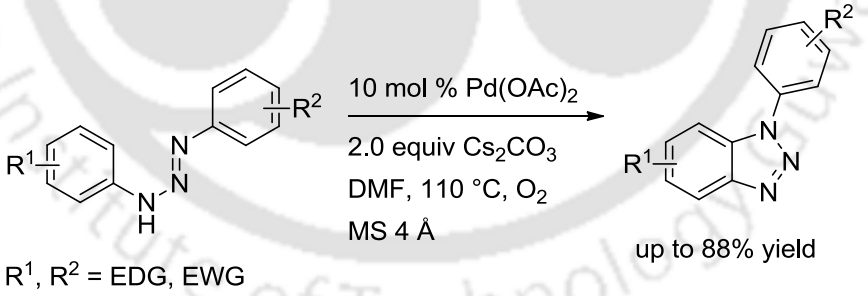
example, Wang and co-workers achieved the regioselective C-C bond formation using electron rich heteroarenes(Scheme 1).[5] The transformation was promoted using catalytic amount of palladium source and PCy_3 as a ligand in the presence of base at 120 °C to give the target cross-coupled products in good yields.



Scheme 1. C-H functionalization of Electron Rich Heteroarenes

1.2.2 Intramolecular C-H Functionalization

This method is used for the construction of cyclic molecules, where the C-H bond can be held in close proximity to the metal by structural restriction. For example, our group developed a new strategy for the construction of 1-aryl-1*H*-benzotriazoles through an intramolecular C-H functionalization fashion (Scheme 2).[6] $Pd(OAc)_2$ effectively involved in the C-H activation followed by C-N bond formation to furnish the cyclized products at moderate temperature in good yields.

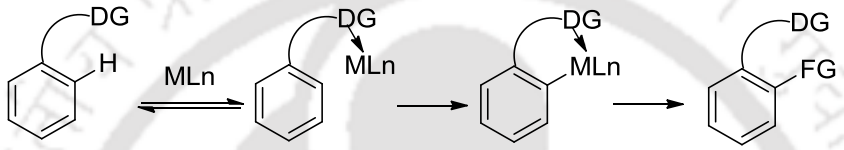


Scheme 2. Intramolecular C-H Amination *via* C-H Activation

1.2.3 Directing Group Assisted C-H Functionalization

Transition metal catalyzed selective activation of C-H bonds has shown great potential for the construction of value-added molecules through carbon-carbon or carbon-hetero atom bond formation.[1] In general, regioselectivity can be achieved through the introduction of a directing group, such director groups are usually (N- or O-) containing functional groups

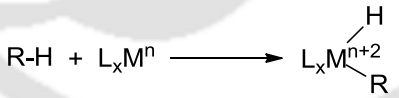
(Table 2).[7] In the past years, diverse directing groups have been developed to assist this selective C-H bond activation. These directing groups coordinate to the metal catalyst making the metal viable for attack and cleavage of proximal C-H bond, resulting in metalacycle intermediate and enabling the functionalization of specific C-H bond. Since most of these reactions are believed to proceed through cyclometalated chelate complexes as intermediates, the reactions were referred to as chelation assisted C-H functionalization reactions. The *ortho*-C(sp^2 or sp^3)-H bond cleavage (*ortho*-metelation) can be facilitated in the presence of transition metal (e.g., Pd, Rh, Ru, Cu etc.), leading to a versatile C-H bond functionalization reactions under basic or oxidative conditions.[8-15]



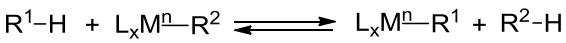
1.3 Mechanism of C-H Functionalization

The C-H functionalization reactions proceed *via* three kinds of mechanism depending on the nature of metal center: (i) oxidative addition, (ii) sigma-bond metathesis and (iii) electrophilic activation.[1j]

Oxidative Addition: Electron rich low valent transition metal complexes (Re, Fe, Ru, Rh, Ir, Pt) were involved in these reactions. These intermediates are unstable and generated in situ by thermal or photo chemical decomposition.



Sigma-Bond Metathesis: The alkyl or hydride complexes of transition metals with d^0 electronic configurations can undergo reversible sigma-bond metathesis reaction. The metals employed for these reactions are mainly from Group III of periodic table.



Electrophilic Activation: The post transition metals (Pd(II), Pt(II), Pt(IV), Hg(II)) generally involved in these reactions due to their Lewis-acidic character. In these reactions the substitution of proton occurs by a metal, hence called electrophilic activation.

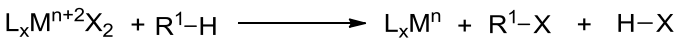
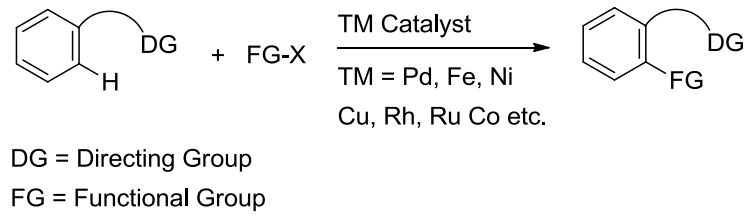
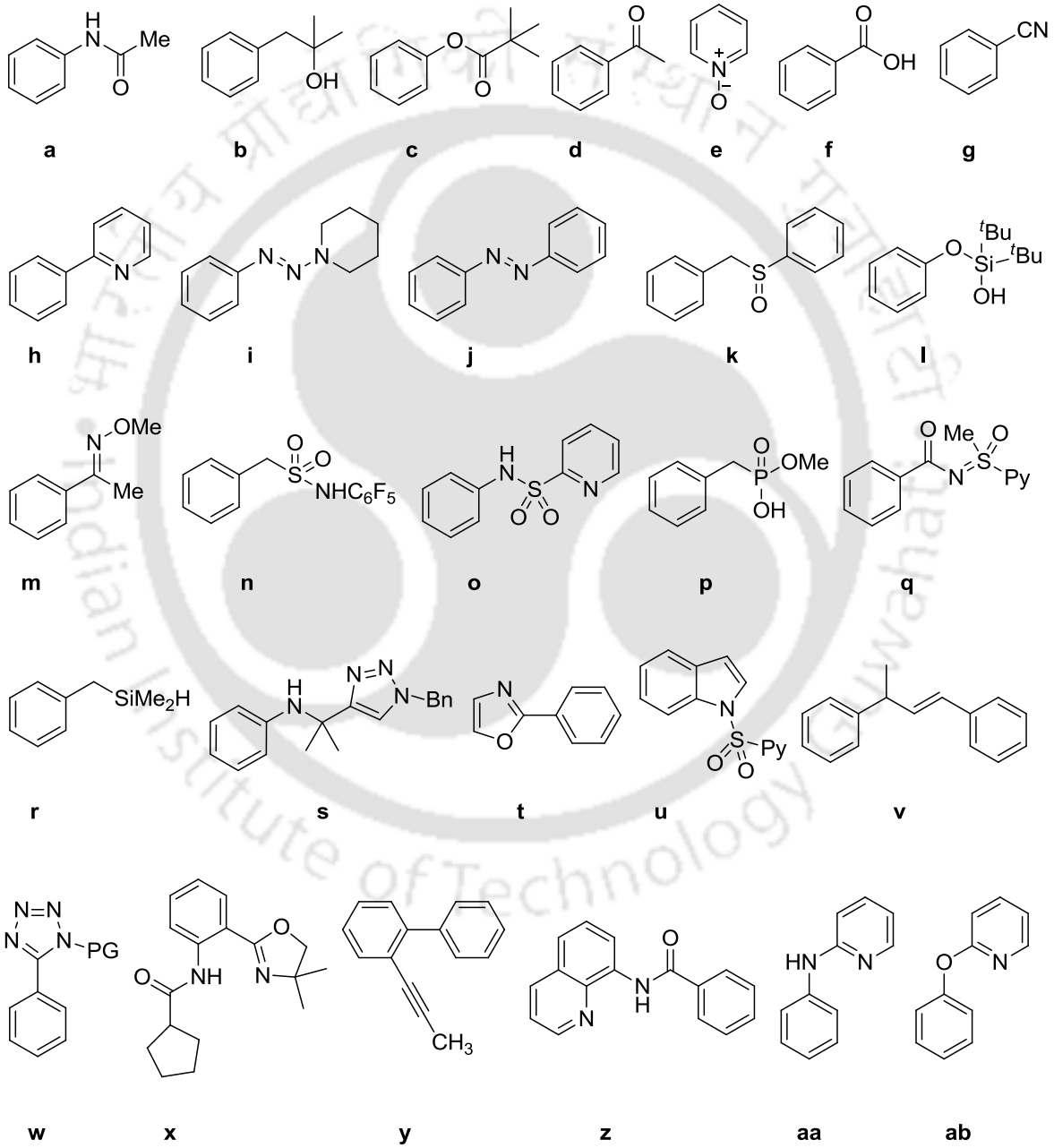


Table 2. Examples of Common Directing Groups



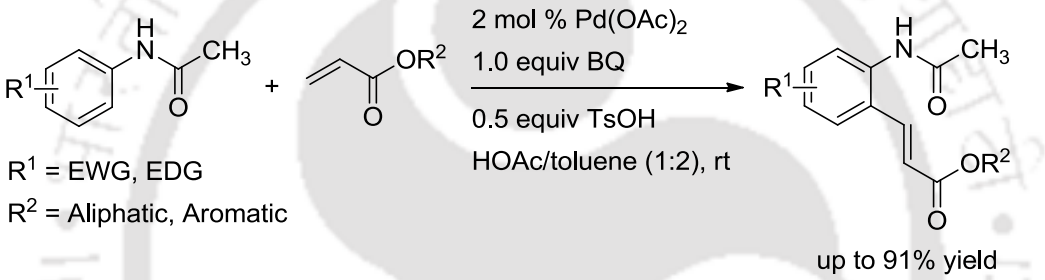


1.4 Carbon-Carbon and Carbon-Heteroatom Bonds Formation

Direct functionalization of non-activated C-H bonds using transition metals has emerged as a powerful synthetic tool for the construction of valuable structural motifs. These strategies feature atom- and step-economy, and simplified chemical synthesis.[7a, 8]

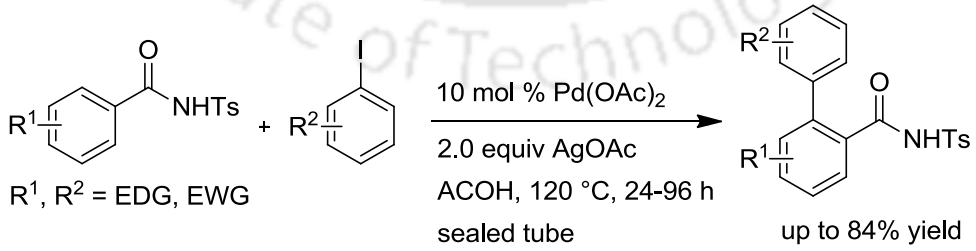
1.4.1. Carbon-Carbon Bond Formation

In 2002, Leeuwen and co-workers demonstrated a Pd-catalyzed protocol for *ortho*-olefination of anilides in presence of benzoquinone and TsOH at room temperature (Scheme 3).[7a] The protocol features formation of C-C bond *via* chelation assisted C-H functionalization, which can serve as an alternative to Heck type coupling reaction.



Scheme 3. Anilide Directed *Ortho*-Olefination of Arenes

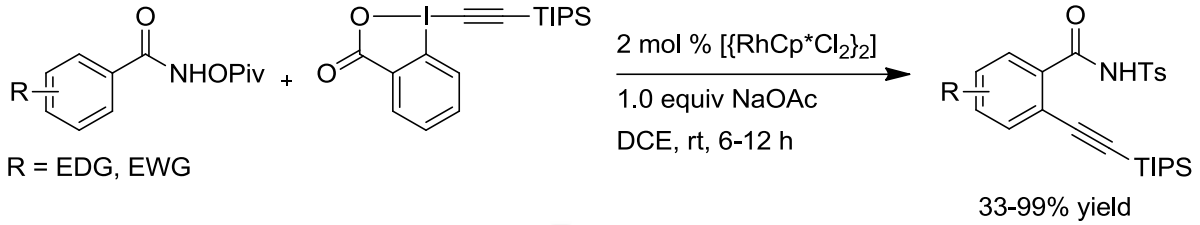
The regioselective construction of biaryl moieties *via* C-H functionalization was developed by Fabis group using *N*-tosylcarboxamide as a directing group and aryl iodide as a coupling partner in the presence of $Pd(OAc)_2$ (Scheme 4).[8h] The flexibility of *N*-tosylcarboxamide to convert it into valuable products allows one to derive wide variety of *ortho*-functionalized biaryl compounds.



Scheme 4. Pd-Catalyzed C-H *Ortho*-Arylation

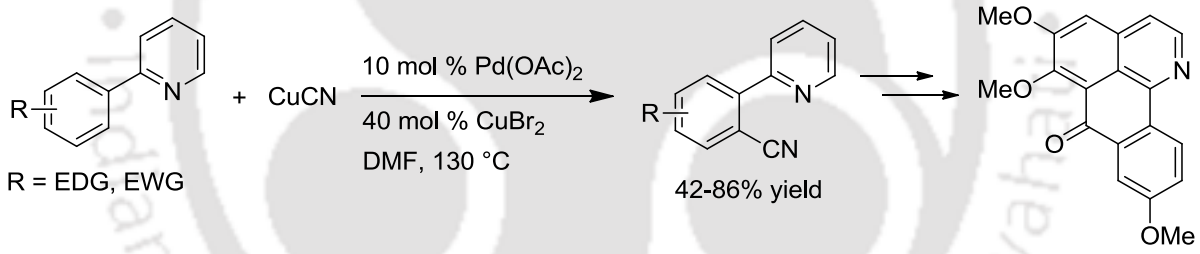
Rh-catalyzed *ortho*-C-H alkynylation of arenes using amide as a directing group and recyclable hypervalent iodine reagent as the alkyne source was devised by Loh and co-

workers under mild reaction conditions to produce monoalkynylated products in good yields (Scheme 5).[8i]



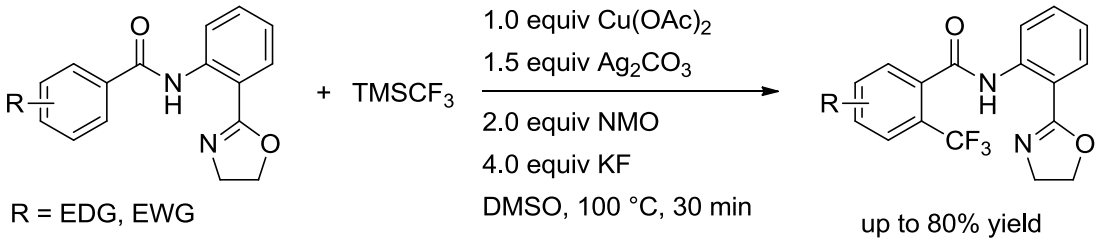
Scheme 5. Rh-Catalyzed C-H Alkynylation of Amides

Regioselective cyanation of C-H bond can be achieved using Pd-catalyzed directed C-H functionalization. For example, the cyanation of 2-aryl pyridines has been demonstrated by Cheng and co-workers using copper cyanide in the presence of $Pd(OAc)_2$ and $CuBr_2$ (Scheme 6).[8l] This approach provides an alternative route for the traditional Sandmeyer reaction and provides practical route for the synthesis of aromatic nitriles. Using this protocol, key intermediate of natural product Menispermum dauricum DC has been prepared.



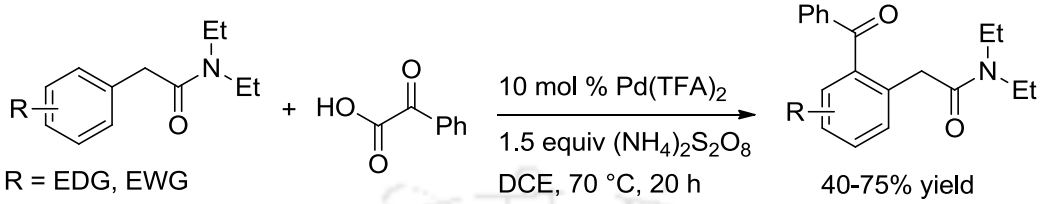
Scheme 6. *Ortho*-Cyanation of Arenes

Yu and co-workers accomplished *ortho*-trifluoromethylation of arenes with $TMSCF_3$ by a Cu-promoted C-H activation within 30 min using Ag_2CO_3 and NMO in presence of base KF (Scheme 7).[8r] The kinetic isotope experiments suggest that Cu-mediated C-H cleavage step is involved rather than electrophilic aromatic substitution.



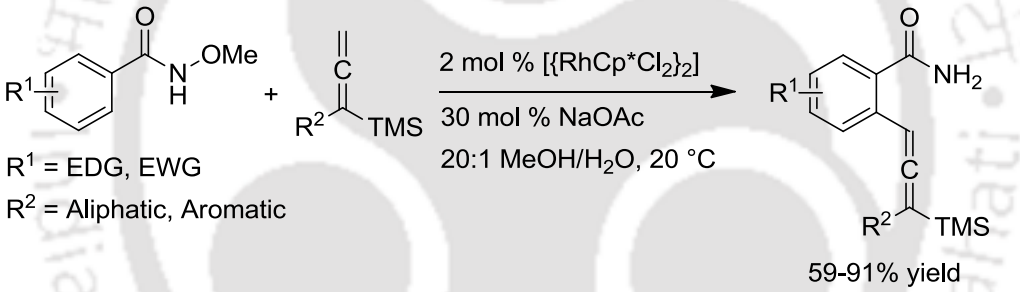
Scheme 7. Regioselective Cu-Mediated *Ortho*-Trifluoromethylation of Arenes

The oxidative decarboxylative benzoylation of phenylacetamides was demonstrated by Kim and co-workers using α-oxocarboxylic acids (Scheme 8).[8s] This coupling reaction is accomplished using $Pd(TFA)_2$ and $(NH_4)_2S_2O_8$ in DCE solvent at moderate temperature.



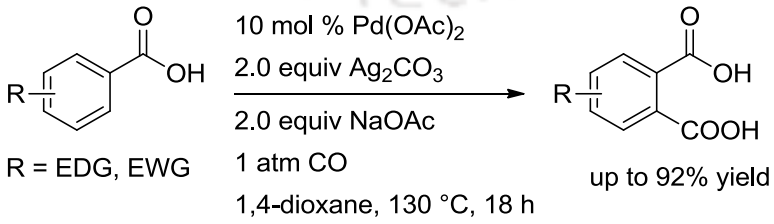
Scheme 8. Pd-Catalyzed Decarboxylative Acylation of Arenes

Ma group studied the synthesis of trisubstituted allenylsilanes derivatives by Rh-catalyzed *N*-methoxybenzamides directed *ortho*-allenylation of allenes(Scheme 9).[8t] The reaction proceeds *via* C-H bond cleavage, allene insertion, and β-H elimination to furnish 2-(3-silylallenyl)benzamides under ambient conditions.



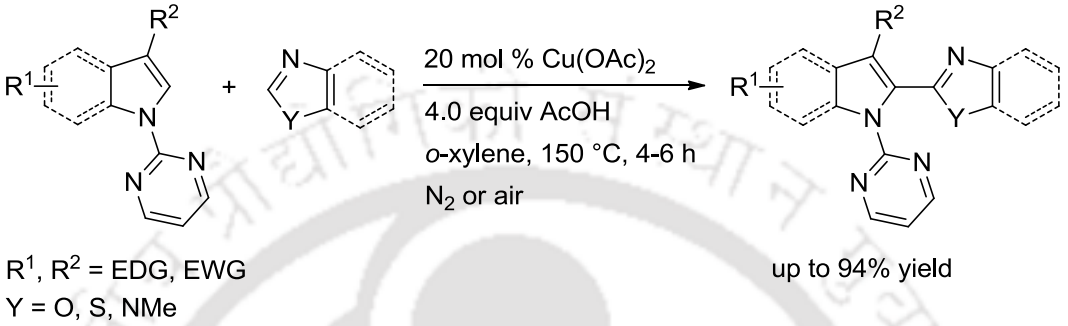
Scheme 9. Synthesis of Trisubstituted Allenylsilanes *via* C-H Functionalization

An example involving Pd-catalyzed C-H carboxylation of benzoic acid derivatives *via* C-H activation/CO insertion sequence using Ag_2CO_3 and NaOAc in 1,4-dioxane was demonstrated by Yu and co-workers (Scheme 10).[8u] In this reaction, strong electron withdrawing groups such as NO_2 and CO_2Me significantly reduces the yield.



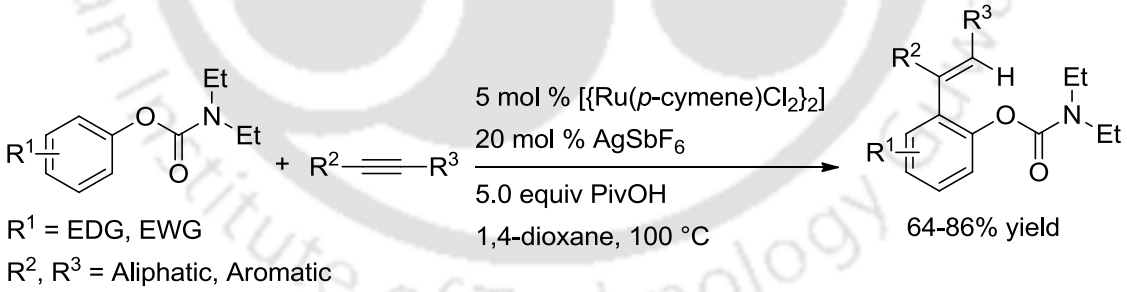
Scheme 10. Pd-Catalyzed Carboxylation *via* C-H activation

Cu-mediated intermolecular cross-dehydrogenative coupling of indoles and 1,3-azoles was developed by Miura and co-workers (Scheme 11).[8v] The regioselectivity of the reaction was achieved using 2-pyrimidyl group, which allows coupling at 2nd position of indoles by chelation. The transformation shows broad substrate scope with wide variety of indoles and azoles.



Scheme 11. Cross-Dehydrogenative Coupling of Indoles and Azoles

Jeganmohan and co-workers have described the *ortho*-alkenylation of phenol carbamates using Ru-complex, pivalic acid in 1,4-dioxane to furnish substituted alkene derivatives in a highly regio- and stereoselective manner (Scheme 12). [8w] The regioselectivity of the coupling product was determined by the substituents on the alkyne part. For example, Ph or ester groups on the alkyne are always positioned *trans* to the aromatic carbamate.



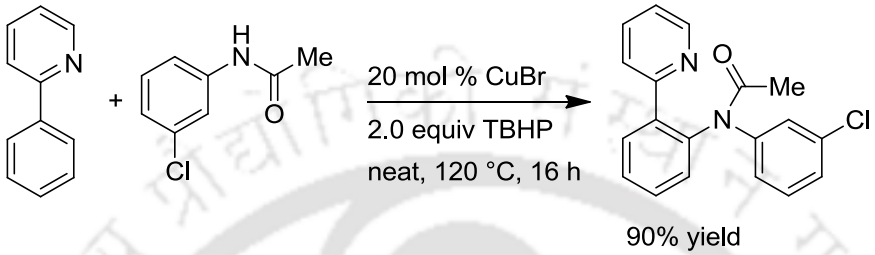
Scheme 12. Ru-Catalyzed Alkenylation of Aryl Carbamates with Alkynes

1.4.2. Carbon-Nitrogen Bond Formation

Nitrogen containing heterocyclic compounds found to have immense importance in organic synthesis because of their occurrence in natural products, pharmaceuticals and material sciences. Of all the C-N bond formation reactions, transition-metal-catalyzed, chelation

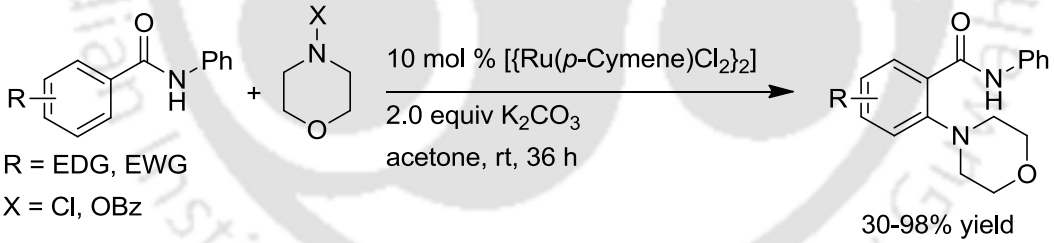
assisted C-H functionalization is particularly attractive because of its atom-economical and robust approach.[9]

Direct *ortho*-amidation of common 2-arylpyridine derivatives was achieved using CuBr in the presence of TBHP at 120 °C *via* cross-dehydrogenative coupling strategy (Scheme 13).[9a] This method is operationally simple and does not require specialized ligand or base.

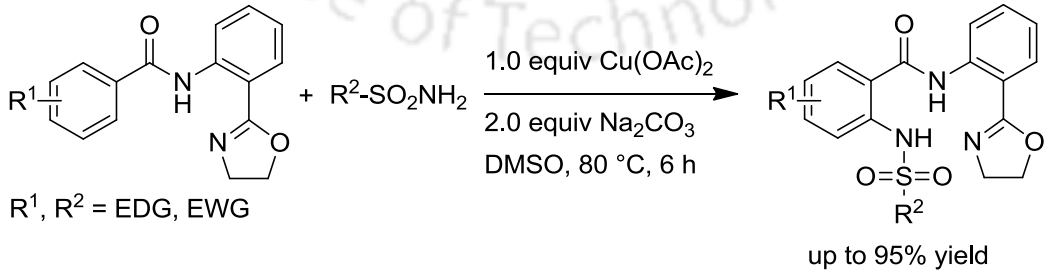


Scheme 13. Regioselective Amidation of 2-Arylpyridines

Yu and co-workers obtained heteroarylamine derivatives by intermolecular C-H amination directed by a weakly coordinating amide auxiliary. They used Ru-catalyst together with K_2CO_3 as a base in acetone at room temperature (Scheme 14).[9b] The reaction protocol is well-suited with heterocycles including pyrazole, thiophene, benzothiophene, furan, benzofuran and indole.



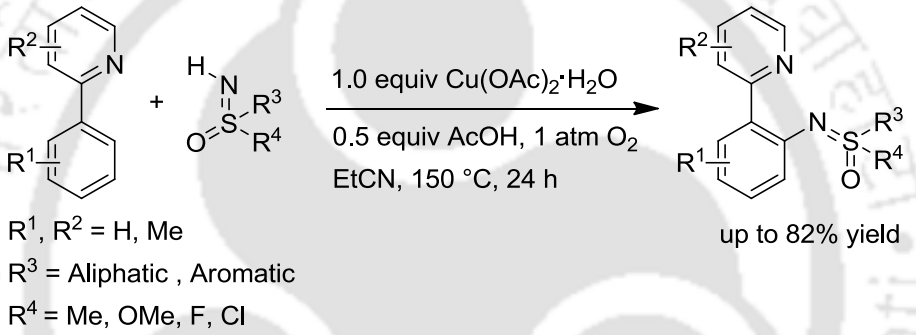
Scheme 14. Ru(II)-Catalyzed *Ortho*-C-H Amination of Arenes



Scheme 15. Regioselective C-N Bond Formation of Arenes *via* C-H Activation

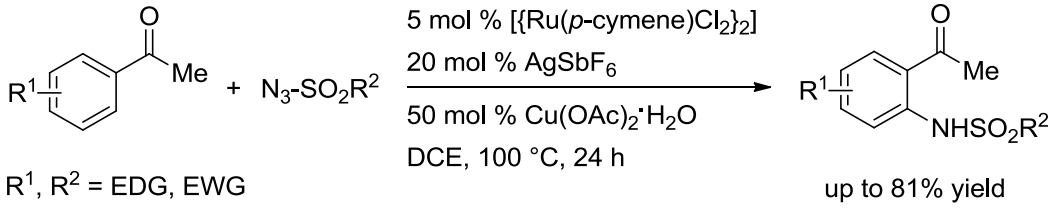
Direct C-H functionalization and C-N bond formation of arenes with sulfonamides results in the corresponding *ortho*-amination products (Scheme 15).[9c] Yu group developed an amide-tethered oxazoline as a directing group for the regioselective amination of arenes. This Cu-mediated protocol with Na_2CO_3 shows unprecedented level of compatibility with heterocyclic arenes and amine donors.

Cu-catalyzed regioselective C-N bond formation strategy has been employed for the synthesis of *N*-arylated sulfoximines by Bolm and co-workers (Scheme 16).[9d] Here, *N*-arylations of sulfoximines by dual C-H/N-H activation was demonstrated using pyridine nitrogen as a directing group to activate the remote positions in presence of $Cu(OAc)_2$ as an activator and oxygen as an oxidant.



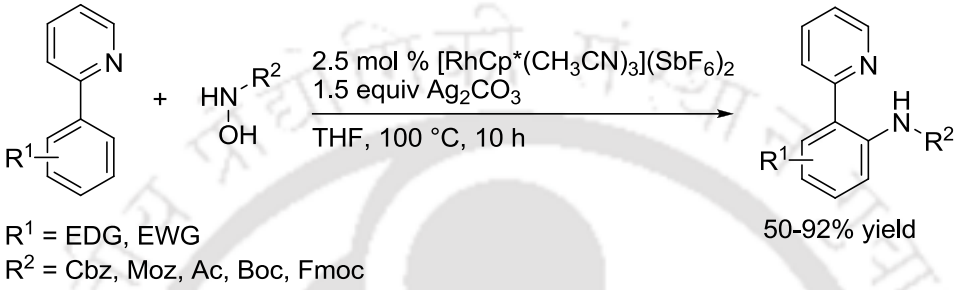
Scheme 16. Cu-Catalyzed Synthesis of *N*-Arylated Sulfoximines

$Ru/AgSbF_6$ catalyzed strategy was presented by Sahoo and co-workers in 2013 for *ortho*-C–H amidation using readily available, weakly co-ordinating aromatic ketones as a directing group and sulfonyl azides as coupling partners (Scheme 17).[9e] The reaction tolerates halo (F, Cl, Br and I), protecting (OTBS) and ester groups. Intermolecular competitive amidation between electron rich 4-OMe substituted substrate and electron deficient 4-COOMe substituted substrate found to give products in a ratio of 2.5:1 indicates that the electron rich substrates shows better reactivity compared to electron deficient substrates.



Scheme 17. Intermolecular *Ortho*-C-H Amidation of Aromatic Ketones

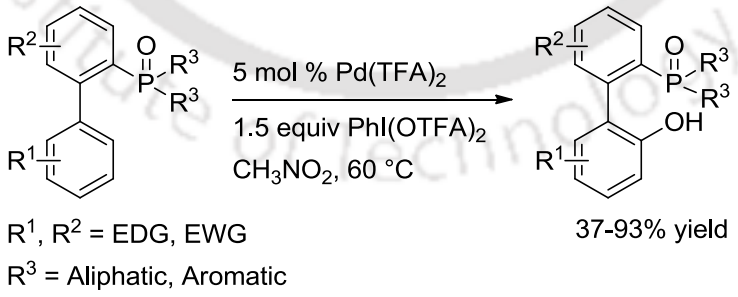
Zhao and co-workers, with the aid of a directing group, demonstrated Rh-catalyzed reactions between 2-aryl pyridines and *N*-hydroxycarbamates (Scheme 18).[9f] The transformation enabled the installation of variety of readily available *N*-carbamate protecting groups such as Cbz, Moz, Ac, Boc and even Fmoc. The intermolecular kinetic isotope study K_H/K_D = 1.5 indicates that the C-H bond cleavage might not be involved in rate determining step and further shows that the reaction goes *via* the formation of Rh(III)-Rh(I).



Scheme 18. Rh-Catalyzed C-H Amidation with *N*−Hydroxycarbamates

1.4.3. Carbon-Oxygen Bond Formation

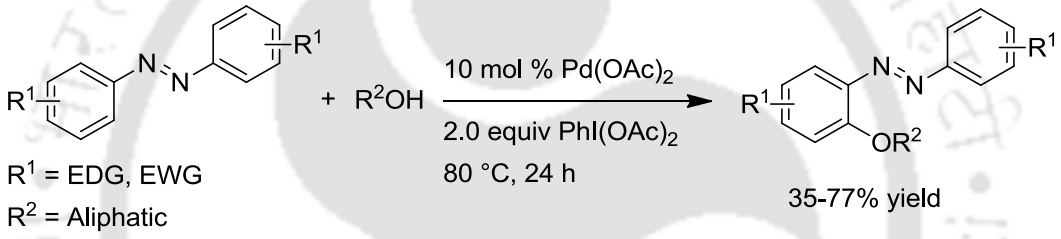
Oxygen containing heterocyclic structural motifs found in many diverse ranges of natural products and synthetic drug molecules. Traditionally, C-O bonds were constructed using Williamson ether synthesis, nucleophilic substitution and Ullman type couplings of alkyl halides with alkoxides. Each of these reactions requires either an excess of the alkoxide or use of harsh conditions. In this regard, recently transition-metal-catalyzed C-O bond formation reactions has occupied prominent position.[10]



Scheme 19. Diphenylphosphine Oxide Directed Hydroxylation of Arenes

The directed *ortho*-hydroxylation of diphenylphosphine oxides was devised by Yang and co-workers. The reactions were carried out using $Pd(TFA)_2$ as a catalyst along with hypervalent iodine as an efficient oxidant at moderate reaction conditions (Scheme 19).[10d] The phosphates such as triphenylphosphine oxide and α-diphenyl naphthalenyl phosphonate did not afford the target product, which shows that the seven-membered cyclopalladium pretransition state may play a crucial role in attaining the products.

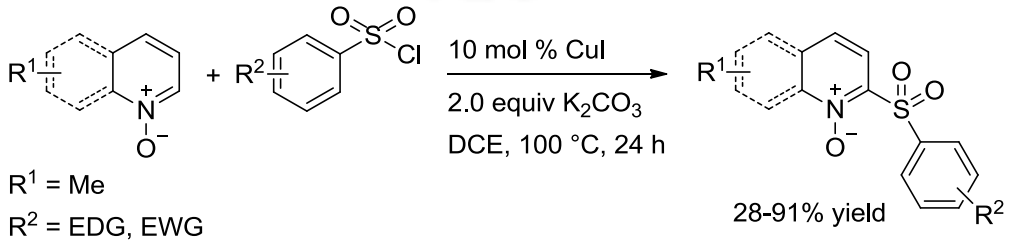
Sun's group disclosed a Pd-catalyzed alkoxylation of azobenzene substrates directed by the azo group using alcohols as alkoxylation reagents and diacetoxyiodobenzene as the oxidant (Scheme 20).[10i] Excess alcohol acts as a solvent as well as alkoxylation reagent. The substrates having electron withdrawing groups exhibited lesser reactivity compared to electron donating groups.



Scheme 20. Palladium Catalyzed Alkoxylation of Azobenzenes

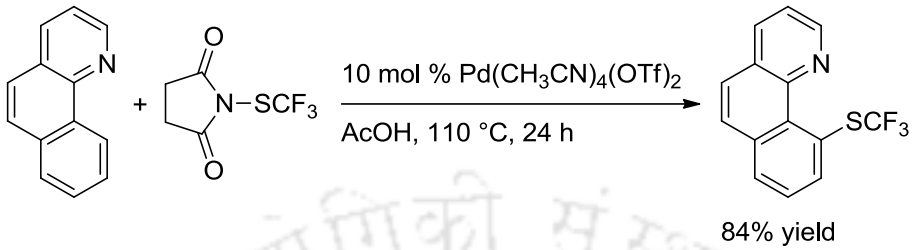
1.4.4. Carbon-Sulfur Bond Formation

Carbon-sulfur bond formation hold a preeminent position in the synthesis of valuable chemical entities such as amino acids and peptides and present in many drug candidates.[11] Wu *et al*. reported a Cu-catalyzed activation method for the sulfonylation directed by polar N^+-O^- bonds such as quinolone *N*-oxides (Scheme 21).[11a] The reaction shows complete selectivity at the 2-position with a wide range of substituted aryl sulfonyl chlorides.



Scheme 21. Sulfonylation of Quinolone *N*-Oxides Using Cu-Catalyst

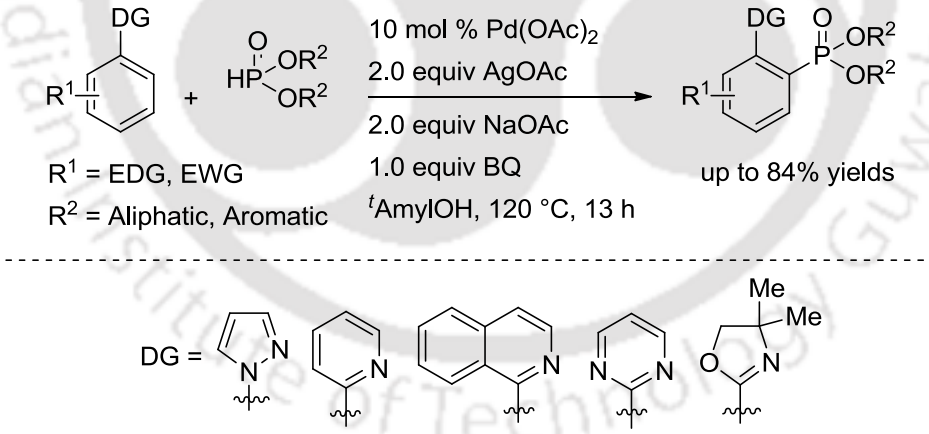
Shen and co-workers reported intermolecular monotrifluoromethylthiolation of arenes *via* Pd-catalyzed directed C-H bond activation in AcOH at 110 °C (Scheme 22).[11b] The deuterium labelling studies suggest that the C-H activation step is not the rate limiting step.



Scheme 22. Pd-Catalyzed Trifluoromethylthiolation of Arenes

1.4.5. Carbon-Phosphorous Bond Formation

Phosphorous compounds found wide range of applications in medicinal chemistry, material science and catalysis.[12] The Pd-catalyzed C(sp^2)-H phosphorylation directed by 2-aryl pyridines using H-phosphonates as phosphorylation reagents was reported by Yu group (Scheme 23).[12] The methodology was successfully applied for various nitrogen containing heterocycles and obtained products in good yields.

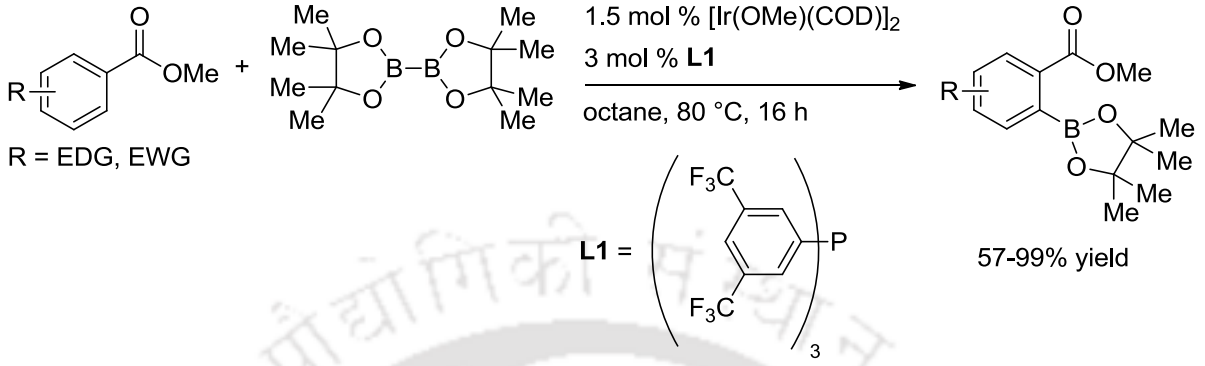


Scheme 23. Phosphorylation of Arenes *via* Directed C-H Activation

1.4.6. Carbon-Boron Bond Formation

Organoboron compounds are quite useful reagents in organic synthesis.[13] Ir-catalyzed regioselective C-H borylation of benzoate esters was shown by Miyaura and co-workers

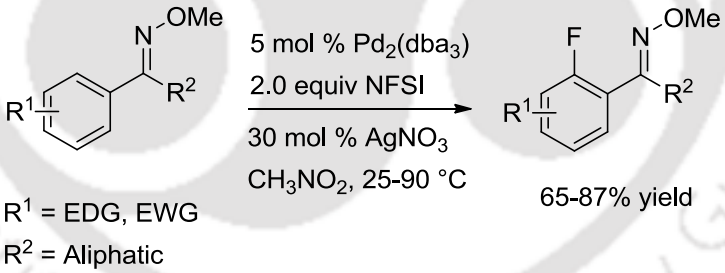
(Scheme 24).[13] Treatment of benzoate esters with bis(pinacolato)diboron produced *ortho*-borylated products in good yields by using non-polar solvents.



Scheme 24. Ir-Catalyzed *Ortho*-Borylation of Benzoate Esters

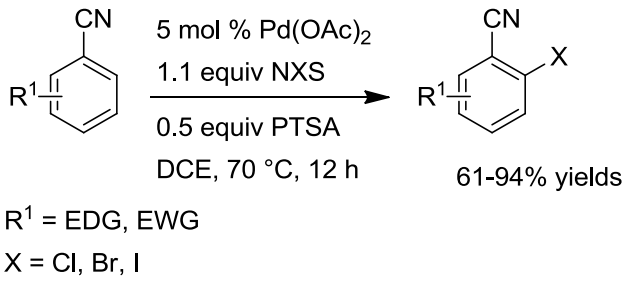
1.4.7. Carbon-Halogen Bond Formation

Fluorinated scaffolds are of great interest because the fluorine atom enhances the lipophilicity, bioavailability and metabolic stability of compounds.[14] The construction of C-F bond *via* Pd-catalyzed C-H functionalization with NFSI was presented by Xu and co-workers (Scheme 25).[14a] It is notable that the reaction does not proceed in the absence of $AgNO_3$.



Scheme 25. Directed *Ortho*-Fluorination of Arenes

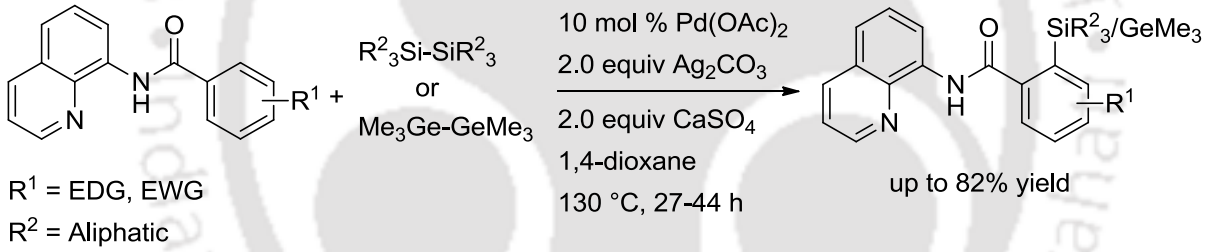
Aromatic halogen containing compounds are used as starting materials in various transformations such as cross-coupling reactions and were used in the preparation organolithium and Grignard reagents. Sun and co-workers reported Pd-catalyzed *ortho*-halogenation of arene substrates using cyano as a directing group (Scheme 26).[14c] The transformation provides broad substrate scope with high yields.



Scheme 26. *Ortho*-Halogenation of Arylnitriles *via* C-H Functionalization

1.4.8. Carbon-Silicon and Carbon-Germanium Bonds Formations

Silicon containing compounds find wide applications in synthetic and material sciences.[15] Kuninobo and Kanai groups reported Pd-catalyzed regioselective silylation and germanylation of benzamides using disilanes and hexamethyldigermane in the presence of Ag_2CO_3 as an oxidant and $CaSO_4$ as an additive in 1,4-dioxane at high temperature (Scheme 27).[15]



Scheme 27. Regioselective Silylation and Germanylation of Arenes

In conclusion, chelation assisted C-H functionalization reactions are powerful synthetic tool for the construction of carbon-carbon and carbon-hetero atom bonds. These reactions are site-selective, avoid prefunctionalization and occur under relatively milder reaction conditions. Furthermore, these strategies provide a viable route for the synthesis of various key intermediates in the synthesis of natural and unnatural biologically active molecules.

1.5. References

1. For recent reviews on C-H activation, see: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (c) Li, C.-J. Acc. *Chem. Res*. **2009**, *42*, 335. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Alberico, D.; Scott, M. E.;

Lautens, M. *Chem. Rev*. **2007**, *107*, 174. (f) Hickman, A. J.; Sanford, M. S. *Nature. Rev.* **2012**, *484*, 178. (g) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (i) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (j) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

2. (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054-3131. (b) *C-H and C-X Bond Functionalization: Transition Metal Mediation*; Ribas, X., Ed.; RSC Catalysis Series 11; RSC Publishing: Cambridge, 2013.
3. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. (b) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211. (c) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 4541. (d) Ullmann, F.; Illgen, E. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 380.
4. (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.
5. For example on intrinsic see: Zhu, F.; Tao, J.-L.; Wang, Z.-X. *Org. Lett*. **2015**, *17*, 4926.
6. For example on intramolecular see: (a) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem.–Eur. J*. **2009**, *15*, 7292. (b) Kumar, R. K.; Ali, M. A.; Punniyamurthy, T. *Org. Lett*. **2011**, *13*, 2102.
7. For examples of diverse directing groups, see: (a) Boele, M. D. K.; Strijdonck, G. P. F. V.; Vries, J. G. D.; Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (c) Li, J.; Kornhaaβ, C.; Ackermann, L. *Chem. Commun.* **2012**, *48*, 11343. (d) Padala, K.; Jeganmohan, M. *Org. Lett*. **2011**, *13*, 6144. (e) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc*. **2005**, *127*, 18020. (f) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem*. **1998**, *63*, 5211. (g) Li, W.; Xu, Z.; Sun, P.; Jiang, X.; Fan, M. *Org. Lett*. **2011**, *13*, 1286. (h) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc*. **2005**, *127*, 7330. (i) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y. Lee, Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927. (j) Lian, Y.; Bergman, R. G.; Lavis, L. D. Ellman, J. A. *J. Am. Chem. Soc*. **2013**, *135*, 7122. (k) Samanta, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5217. (l) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc*. **2011**, *133*, 12406. (m) Thirunavukkarasu, V. S.; Parthasarathy, K.;

Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9426. (n) Dia, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, D. H. X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y. H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (o) Rubia, A. -G.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927. (p) Meng, X.; Kim, S. *Org. Lett*. **2013**, *15*, 1910. (q) Yadav, M. R.; Shankar, M.; Ramesh, E.; Ghosh, K.; Sahoo, A. K. *Org. Lett*. **2015**, *17*, 1886. (r) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 7534. (s) Mamari, H. H. A.; Diers, E.; Ackermann, L. *Chem. Eur. J*. **2014**, *20*, 9739. (t) Shen, Y.; Liu, G.; Zhou, Z.; Lu, X.; *Org. Lett*. **2013**, *15*, 3366. (u) Lu, M.-Z.; Lu, P.; Xu, Y.-H.; Loh, T.-P. *Org. Lett*. **2014**, *16*, 2614. (v) Gandeepan, P.; Cheng, C.-H. *Org. Lett*. **2013**, *15*, 2084. (w) Seki, M. *ACS Catal*. **2011**, *1*, 607. (x) Giri, R.; Maugel, N. L.; Foxman, B. M.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667. (y) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc*. **2008**, *130*, 5636. (z) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. (aa) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett*. **2010**, *12*, 5426. (ab) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1470.

8. For examples of C-C bond formation, see: (a) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 4156. (b) Fu, G. C. Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (c) Huang, C.; Chottopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12405. (d) Wasa, M.; Worrel, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (e) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (f) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (g) Bedford, R. B.; Mitchell, C. J.; Webster, R. L. *Chem. Commun.* **2010**, *46*, 3095. (h) Péron, F.; Fossey, C.; Cailly, T.; Fabis, F. *Org. Lett*. **2012**, *14*, 1827. (i) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722. (j) Hafner, A.; Brase, S. *Angew. Chem., Int. Ed*. **2012**, *51*, 3713. (k) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (l) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett*. **2009**, *11*, 4716. (m) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (n) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett*. **2011**, *13*, 5464. (o) Hafner, A.; Brase, S. *Angew. Chem., Int. Ed*. **2012**, *51*, 3713. (p) Wang, X.; Truesdale, L.; Yu, J. Q. *J. Am. Chem. Soc*. **2010**, *132*, 3648. (q) Zhang, L. S.; Chen, K.; Chen, G.; Luo, S.; Guo, Q. Y.; Wei, J. B.; Shi, Z. J. *Org. Lett*. **2013**, *15*, 10. (r) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B.N.; Dai,

H.-X.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2014**, *53*, 10439. (s) Park, J.; Kim, M.; Sharm, S.; Park, E.; Kim, A.; Lee, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun*. **2013**, *49*, 1654. (t) Zeng, R.; Wu, S.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2013**, *135*, 18284. (u) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 14082. (v) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 6993. (w) Reddy, M. C.; Jeganmohan, M. *Chem. Commun*. **2013**, *49*, 481.

9. For C-N bond formation reactions see: (a) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, S.; Li, C.-J. *Adv. Synth. Catal*. **2010**, *352*, 632. (b) Shang, M.; Zeng, S.-H.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett*. **2013**, *15*, 5286. (c) Shang, M.; Zeng, S.-H.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (d) Wang, L.; Priebbenow, D. L.; Dong, W.; Bolm, C. *Org. Lett.* **2014**, *16*, 2661. (e) Bhanuchandra, M.; Yadav, M. R.; Rit, R. K.; Kuram, M. R.; Sahoo, A. K. *Chem. Commun*. **2013**, *49*, 5225. (f) Zhou, B.; Du, J.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett.* **2014**, *16*, 592.
10. For C-O bond formation reactions see: (a) Bracegirdle, S.; Anderson, E. A. *Chem. Commun*. **2010**, *46*, 3454. (b) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (c) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4210. (d) Zhang, H.-Y.; Yi, H.-M.; Wang, G.-W.; Yang, B.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 6186. (e) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (f) Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 5528. (g) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (h) Zhou, W.; Li, H.; Wang, L. *Org. Lett*. **2012**, *14*, 4594. (i) Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem*. **2013**, *78*, 10002.
11. For C-S bond formation reactions see: (a) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. *Org. Lett*. **2013**, *15*, 1270. (b) Xu, C.; Shen, Q. *Org. Lett*. **2014**, *16*, 2046.
12. For C-P bond formation reaction see: Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc*. **2013**, *135*, 9322.
13. For C-B bond formation reaction see: Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun*. **2010**, *46*, 159.
14. For C-X bond formation reactions see: (a) Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 10330. (b) Lin, A.; Huehls, B.; Yang, J. *Org. Chem. Front*. **2014**, *1*, 434. (c) Du, B.; Jiang, X.; Sun, P. *J. Org. Chem*. **2013**, *78*, 2786.

15. For C-Si and C-Ge bond formation reaction see: Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett*. **2014**, *16*, 1968.

Chapter II

Pd-Catalyzed Aminotetrazole Directed *Ortho*-Halogenation of Arenes

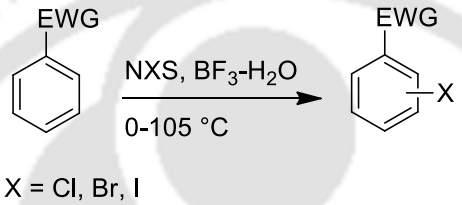
N-Aryl-5-aminotetrazole is an essential structural framework present in many compounds, which have shown potential applications in biological and medicinal sciences.[1] For example, the compounds having *N*-aryl-5-aminotetrazole core structure exhibit anti-inflammatory, anti-asthmatic, anti-viral, anti-neoplastic, cognition disorder and antibiotic properties. In particular, *N*-(2-halophenyl)-1*H*-tetrazol-5-amines are known to exhibit herbicidal and anti-allergic properties.[2]

Aryl halides are extremely valuable starting materials for the synthetic elaboration. For example, these functional groups have been used as precursors to organolithium and Grignard reagents as well as in nucleophilic aromatic substitution. Recently, aryl halides have also found wide spread synthetic utility as substrates for Pd- and Cu-catalyzed cross-coupling reactions to achieve diverse C-C, C-N, C-O and C-S bond formations.[3] In addition, aryl chlorides, bromides, and iodides serve as important components of a wide array of biologically active molecules.[4] The most common synthetic approach to prepare halogenated arenes is electrophilic aromatic substitution (EAS) reactions, using reagents such as *N*-halosuccinimides, peroxides or hypervalent iodine species. Despite of wide use of these transformations, they suffer from several notable disadvantages, such as (i) the substrate scope is often limited to activated arenes, (ii) occurrence of side reactions including benzylic halogenation and over halogenation of the arenes and (iii) the formation of multiple regioisomeric products, which results in decreased yields and the requirement for tedious separation processes.[5] Thus, considerable efforts have been recently made for the development of new methods for the regioselective C-H halogenation of arenes *via* cross coupling methods[6] and employing directing groups[7-10] using transition metal catalysis. Herein, we report a Pd-catalyzed 5-aminotetrazole directed chemo- and *ortho*-selective halogenation of arenes utilizing *N*-halosuccinimide as a halogen source.

2.1. Strategies for Halogenation of Arenes

2.1.1. Conventional Method

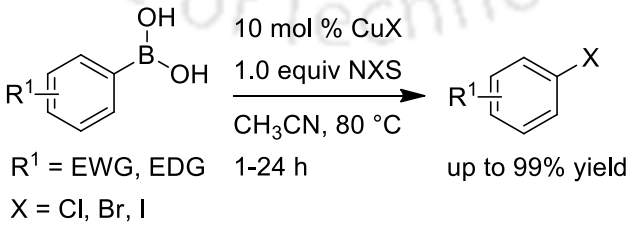
The classical method for halogenation of arenes, including that of deactivated aromatics involves the addition of excess of BF_3-H_2O to stoichiometric amounts of the substrate and *N*-halosuccinimide (NXS) (Scheme 1).[5d] However, the application of this method is not straight forward and it is associated with several issues such as the use of strong acids, elevated temperatures and a mixture of *ortho* and *para* isomers along with minute amounts of dihalogenated products. These make this process limited in its use.



Scheme 1. Lewis Acid Mediated Monohalogenation of Arenes

2.1.2. Cross-Coupling Reactions

Transition-metal catalyzed cross-coupling reactions provide a powerful synthetic tool for the construction of carbon-carbon and carbon-heteroatom bonds. This concept has enabled to overcome the aforementioned drawbacks associated with classical methods, developing milder and regioselective protocols. For example, Hynes and co-workers have carried out Cu-catalyzed halogenation of arenes of aryl boronic acids using *N*-halosuccinimides (Scheme 2).[6] This protocol is effective in accessing a library of halo benzenes with high functional group tolerance.



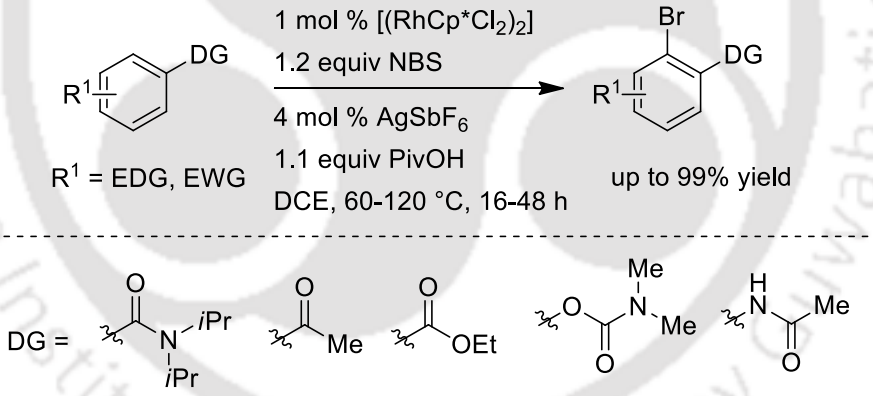
Scheme 2. Cu-Catalyzed *ipso*-Halogenation of Arylboronic Acids

2.1.3. Chelation Assisted C-H Bond Halogenation Reactions

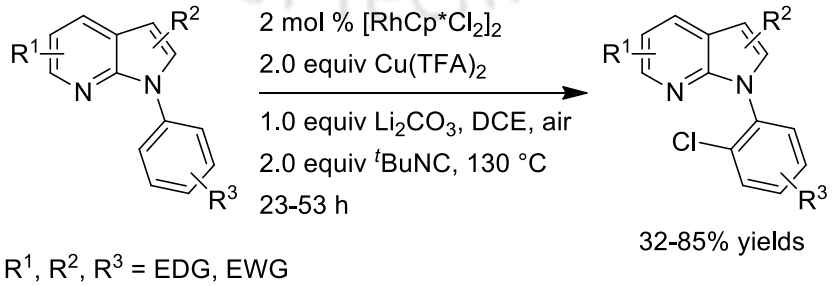
Transition-metal-catalyzed direct C-H bond functionalization of arenes occupied a preeminent position in synthetic organic chemistry to provide efficient and environmental friendly routes for the construction of carbon-carbon and carbon-hetero atom bonds. In this context, remarkable advances in the halogenation reactions have been achieved using various directing groups.

2.1.3.1. Rh-Catalyzed *Ortho*-Halogenation of Arenes

Rh has been identified as a highly useful catalyst for C-H bond activation. For example, Glorius and co-workers reported the use of [{RhCp*Cl_2}$_2$] with $AgSbF_6$ for *ortho* bromination and iodination of arenes (Scheme 3).[7a] This protocol shows compatibility with various directing groups such as tertiary benzamide, secondary benzamides, acetamides and phenylpyridines as a chelation sources, and catalytic transformation could tolerate a broad range of functional groups.



Scheme 3. Rh-Catalyzed Regioselective Halogenation of Arenes

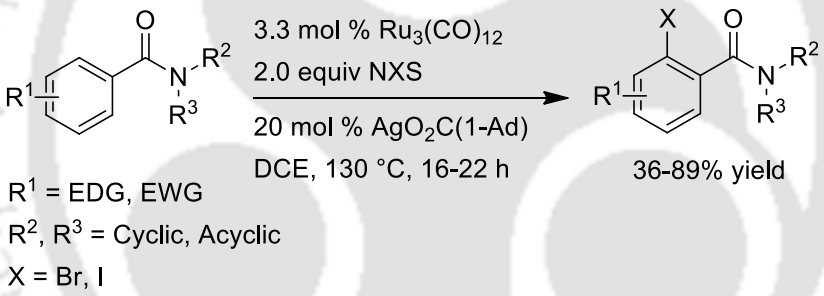


Scheme 4. Regioselective Chlorination of 7-Azaindoles

Xu and co-workers demonstrated Rh-catalyzed regioselective C-H chlorination of arenes using 7-azaindole as the directing group using $Cu(TFA)_2$ in the presence of Li_2CO_3 and ^{t}BuNC in DCE (Scheme 4).[7b] In this reaction, DCE acts as a readily available and practical chlorination source. This transformation provides access for the chlorination of substituted 7-azaindoles with good functional group tolerance.

2.1.3.2. Ru-Catalyzed *Ortho*-Halogenation of Arenes

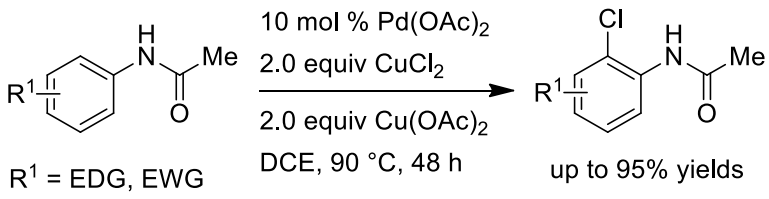
Ru catalysts contributed to a great extent towards their use as less expensive and efficient catalytic systems for the oxidative transformation of inert C-H bonds into various functional groups. Ackermann and co-workers described benzamide directed *ortho*-selective C-H bromination and iodination of arenes using $[Ru_3(CO)_{12}]$ and $AgO_2C(1\text{-Ad})$ in the presence of *N*-halosuccinimides (Scheme 5).[8] The isotopically labelled additive highlighted the reversible C-H ruthenation protocol.



Scheme 5. Ru-Catalyzed *Ortho*-Halogenation of Benzamides

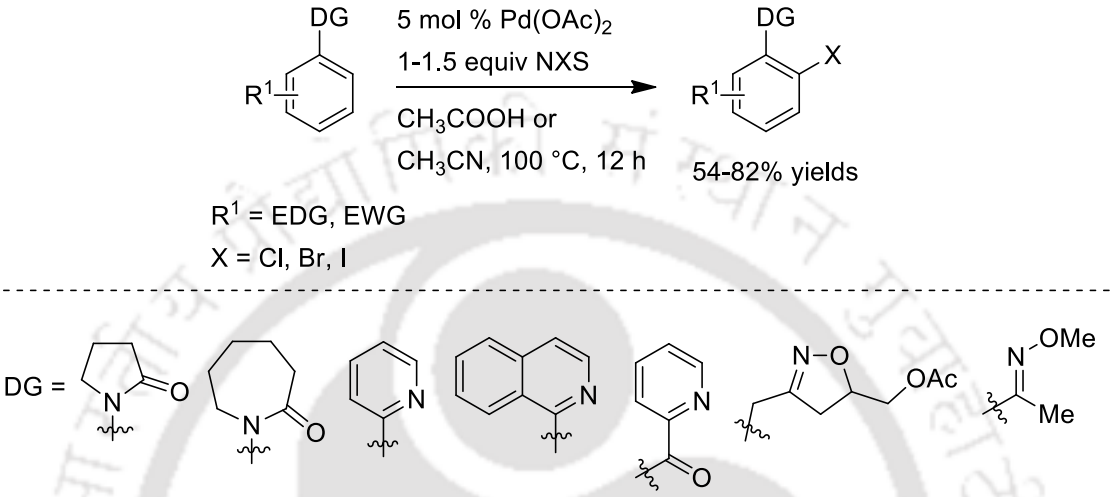
2.1.3.3. Pd-Catalyzed *Ortho*-Halogenation of Arenes

Pd is the most used catalyst for the construction of carbon-halogen bonds *via* C-H activation. The first report for Pd-catalyzed *ortho*-chlorination was reported for anilides by Shi and co-workers using $CuCl_2$ as a chlorine source and $Cu(OAc)_2$ as oxidant (Scheme 6).[9a]



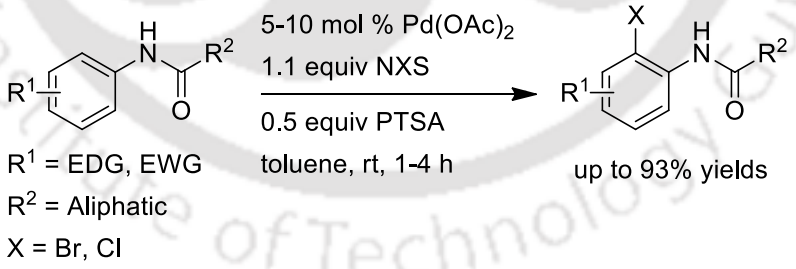
Scheme 6. Pd-Catalyzed Chlorination of Anilides

Sanford and co-workers accomplished Pd-catalyzed regioselective halogenation of arene substrates using *N*-halosuccinimides as halogen source in acetic acid or acetonitrile (Scheme 7).[9b] This transformation requires nitrogen containing heterocycles such as pyridines, oxime ethers, isoquinoline, aromatic aldehydes and benzylic methylene groups as chelation sources.



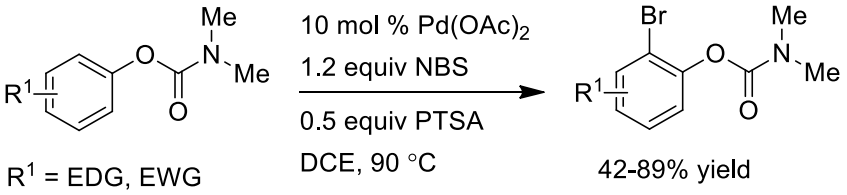
Scheme 7. Pd-Catalyzed *Ortho*-Halogenation of Arenes *via* Nitrogen Heterocycles

Pd-catalyzed *ortho*-halogenation of anilides has been achieved using unusual Pd^{I}–Pd^{II} tetrameric complex under aerobic conditions (Scheme 8).[9c] In this reaction, PTSA is used as an additive to furnish the halogenated arenes.



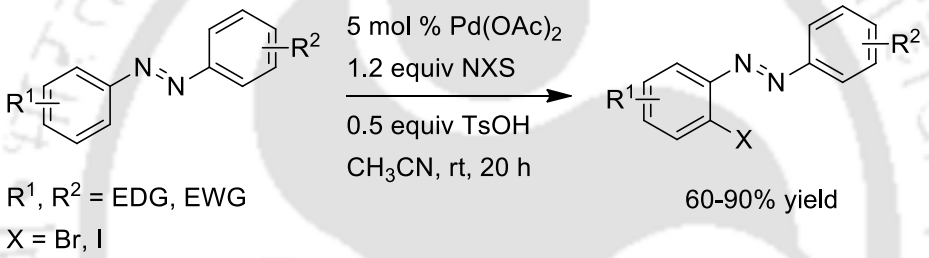
Scheme 8. *Ortho*-Halogenation of Anilides

$Pd(OAc)_2$ with PTSA has been employed by Nicholas and co-workers for the *ortho* C-H bromination of arenes using aryl-*O*-carbamates as a chelation source (Scheme 9).[9d]

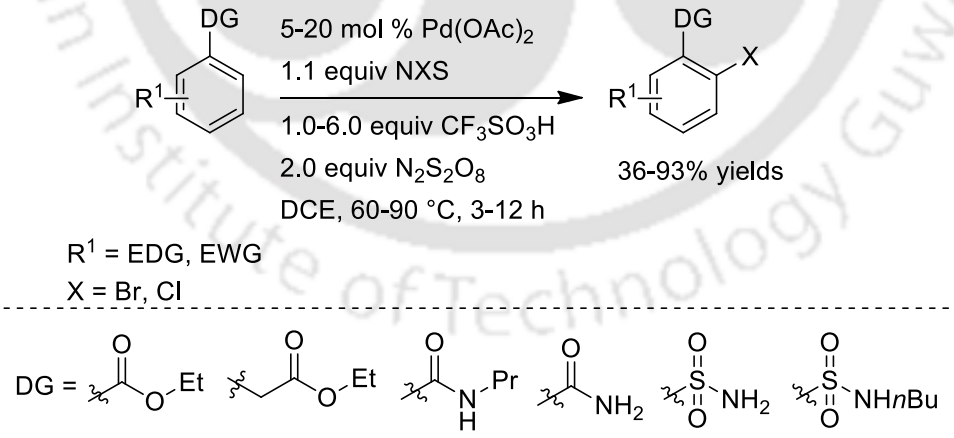


Scheme 9. Regioselective Bromination of Carbamates

Tian and co-workers adapted the same reaction condition for *ortho*-halogenation of azo compounds. This strategy has been successful in bringing out direct halogenation of the azo compounds selectively at *ortho* position (Scheme 10).[9e] The reaction was tested for unsymmetrical azo compounds and found electron-rich aryl groups prefer to be brominated selectively.



Scheme 10. Selective Halogenation of Azo Compounds

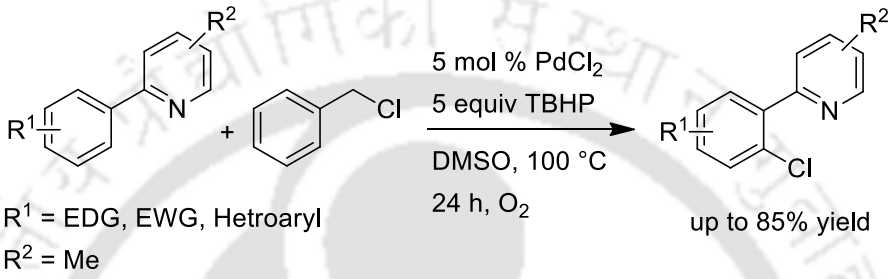


Scheme 11. Chemo- and Regioselective Halogenation of Electron-Deficient Arenes

Rao's group reported Pd-catalyzed *ortho*-chlorination/bromination of arenes in presence of CF_3SO_3H in DCE at moderate reaction conditions. The use of suitable oxidant ($Na_2S_2O_8$) is important in attaining the regioselectivity (Scheme 11).[9f] This method was fairly general

for wide variety of substrates such as benzoates, benzamides, sulfonamides, aromatic ketones and 2-phenylacetates and further, relative DG abilities have been demonstrated as NHAc > CONHPr > C=O > SO_2NHEt > CO_2Et, CONMePr > SO_2NEt_2.

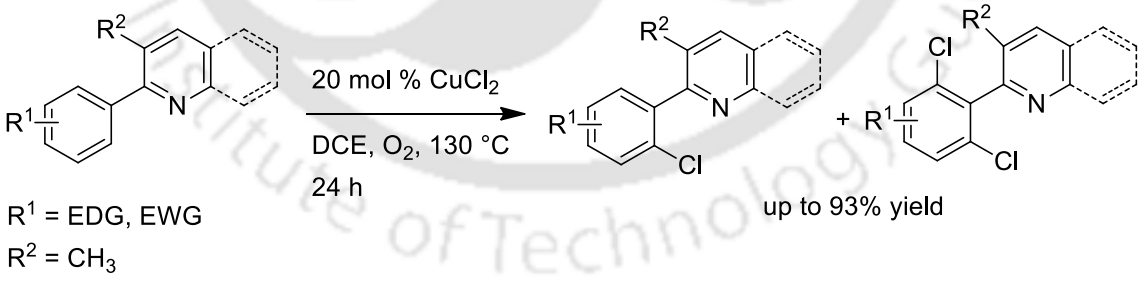
Pd-catalyzed strategy was devised by Zhang et al. for the chlorination of *ortho* C-H bond of 2-phenylpyridines using arylmethyl chlorides as chlorinating agent and TBHP as oxidant in DMSO in the presence of oxygen (Scheme 12).[9g]



Scheme 12. *Ortho*-Chlorination of Arenes Using Arylmethyl Chlorides

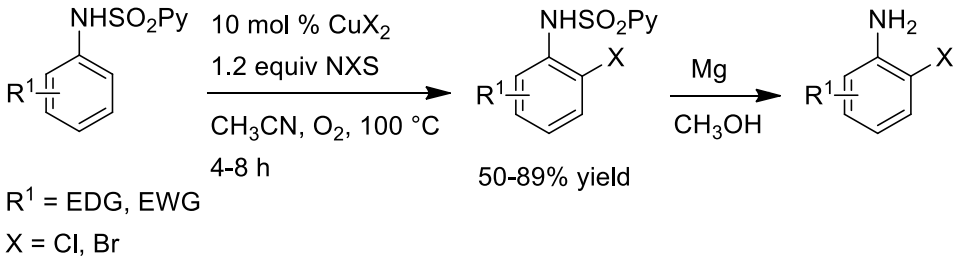
2.1.3.4. Cu-Catalyzed *Ortho*-Halogenation of Arenes

Cu catalysts are beneficial in C-H functionalization reactions with respect to cost and toxicity. Yu and co-workers demonstrated first Cu-catalyzed chlorination of arenes using DCE as a solvent as well as chlorination source in presence of O_2 (Scheme 13).[10a] The kinetic isotope experiment suggests that the reaction proceeds *via* SET mechanism.



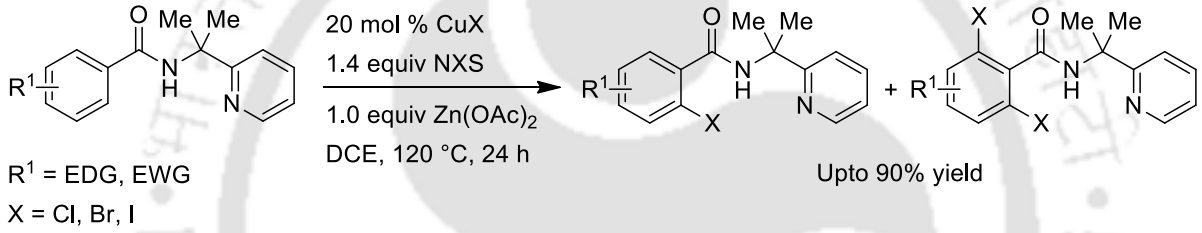
Scheme 13. Cu-Catalyzed *Ortho*-Chlorination of 2-Aryl Pyridine

Carretero and co-workers employed CuX_2-NXS for the regioselective halogenation of arenes using 2-pyridylsulfonyl and 2-pyrimidylsulfonyl as chelation sources (Scheme 14).[10b] The protected anilines could be cleaved in the presence of Mg/CH_3OH to afford free anilines.



Scheme 14. Removable 2-pyridylsulfonyl directed *Ortho*-Halogenation of Arenes

Shi group presented Cu-catalyzed *ortho*-halogenation of benzamides, directed by PIP (4-aminopyridine) directing group (Scheme 15).[10c] In this transformation $Zn(OAc)_2$ acts as a lewis acid to activate NXS reagent. The catalytic transformation is scalable and tolerates a broad range of functional groups at high temperatures.

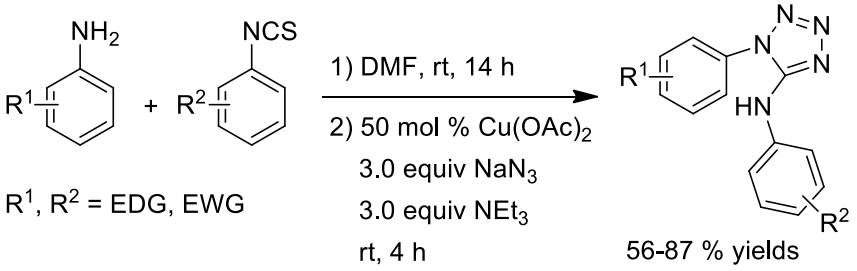


Scheme 15. PIP directed *Ortho*-Halogenation of Benzamides

2.2. Present Study

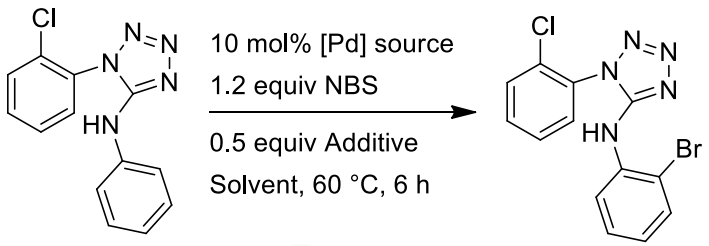
Taking cues from the existing literature, we envisioned that aminotetrazole could also acts as a directing group for the *ortho*-halogenation under Pd-catalysis.

Synthesis of Substituted *N*,1-Diphenyl-1*H*-tetrazol-5-amines (1a-n). The starting materials **1a-n** were prepared from isothiocyanates, anilines and NaN_3 in the presence of $Cu(OAc)_2$ *via* tandem addition, substitution and electrocyclization processes (Scheme 16).[11]



Scheme 16. Synthesis of *N*,1-diphenyl-1*H*-tetrazol-5-amine (**1a-n**)

Table 1. Optimization of the Reaction Conditions[a]

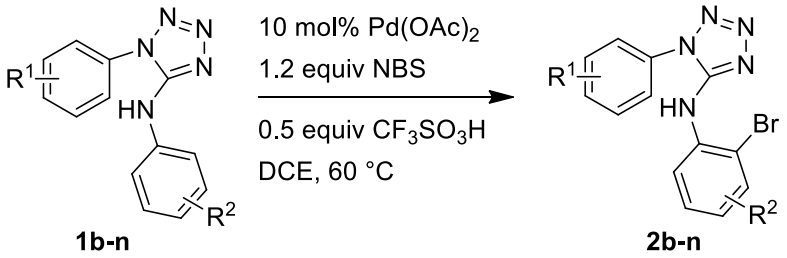


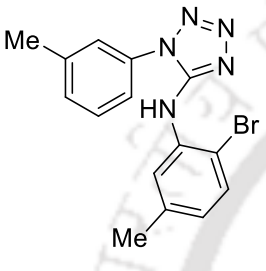
1a **2a**

Entry	Catalyst	Additive	Solvent	Yield (**2a**) (%)[b]
1	$Pd(OAc)_2$	TFA	DCE	60
2	$Pd(OAc)_2$	PTSA	DCE	50
3	**$Pd(OAc)_2$**	**CF_3SO_3H**	**DCE**	**92**
4	$Pd(OAc)_2$	CF_3SO_3H	CH_3CN	0
5	$Pd(OAc)_2$	CF_3SO_3H	toluene	0
6	$Pd(OAc)_2$	CF_3SO_3H	DME	40
7	$Pd(OAc)_2$	CF_3SO_3H	CH_3CO_2H	60
8	$PdCl_2$	CF_3SO_3H	DCE	47
9	$Pd(PPh_3)_2Cl_2$	CF_3SO_3H	DCE	55
10[c]	$Pd(OAc)_2$	CF_3SO_3H	DCE	72
11[d]	$Pd(OAc)_2$	CF_3SO_3H	DCE	43
12	-	CF_3SO_3H	DCE	10

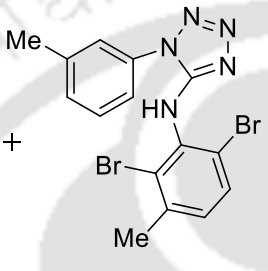
[a] Reaction conditions: substrate **1a** (1 mmol), Pd-source (10 mol %), NBS (1.2 mmol), additive (0.5 mmol), solvent (2 mL), 60 °C, 6 h. [b] Determined by 400 MHz ^{1}H NMR. [c] Temperature (40 °C) was used. [d] Pd-source (5 mol %) was used.

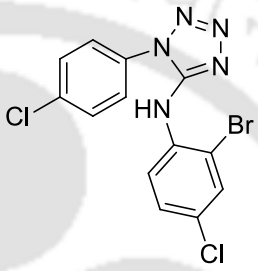
Table 2. *Ortho*-Bromination of *N*-Aryl Ring of *N*,1-Diaryl-1*H*-tetrazol-5-amine[a]



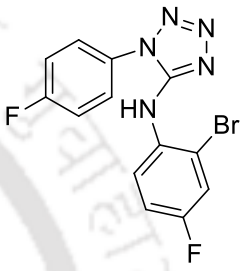


2b 6 h, 78%, 3.2:1 **2b'**

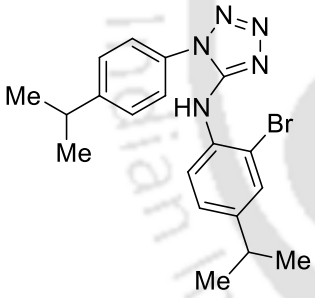




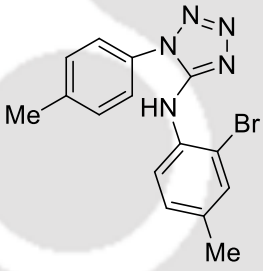
2c, 6 h, 84%



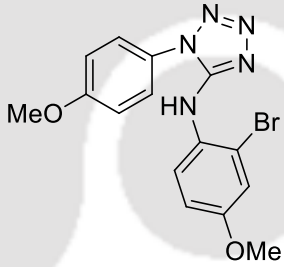
2d, 10 h, 82%



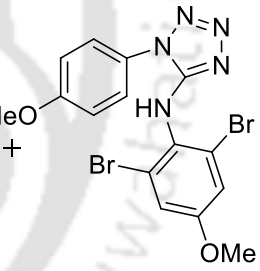
2e, 10 h, 88%

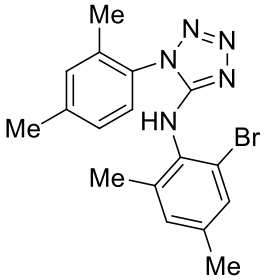


2f, 10 h, 91%

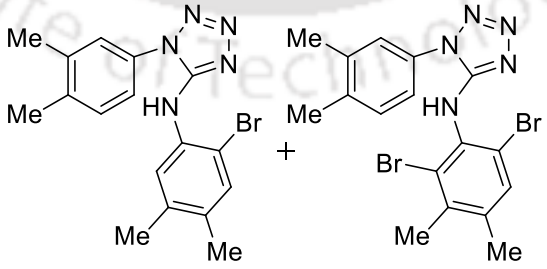


2g 6 h, 88%, 1:1 **2g'**

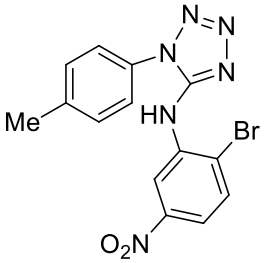




2h, 8 h, 63%

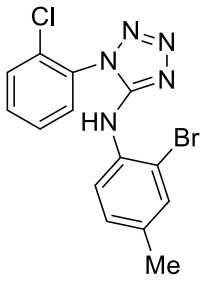


2i 6 h, 90%, 2.5:1 **2i'**

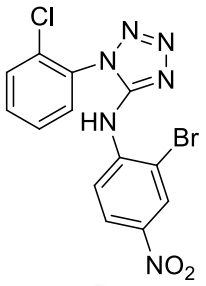


2j, 8 h, 79%

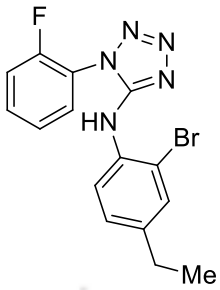
Table 2 Continues...



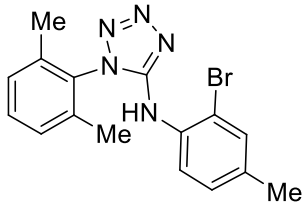
2k, 6 h, 92%



2l, 8 h, 74%



2m, 8 h, 79%



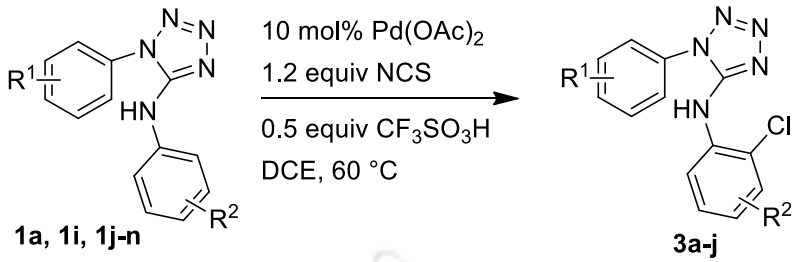
2n, 8 h, 89%

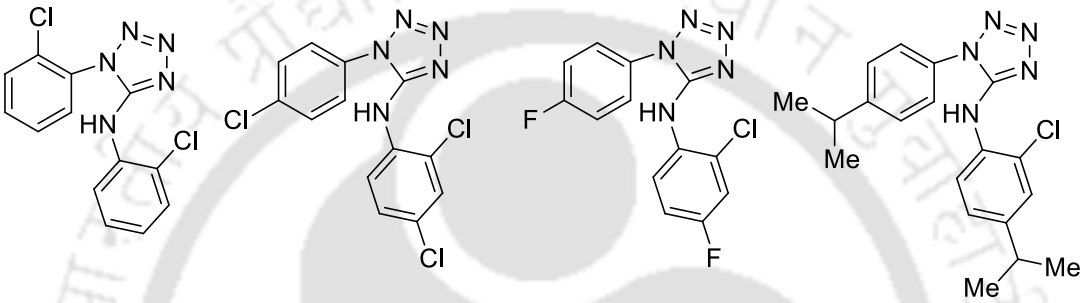
[a] Substrate (1 mmol), $Pd(OAc)_2$ (10 mol %), NBS (1.2 mmol), CF_3SO_3H (0.5 mmol), DCE (2 mL), 60 °C, 6-10 h.

We then commmenced the optimization studies for bromination using 1-(2-chlorophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine **1a** as a model substrate with *N*-bromosuccinimide (NBS) as a bromine source using different Pd-sources, solvents and additives at varied temperatures (Table 1). Gratifyingly, the reaction proceeded selectively to brominate the *ortho*-position of the *N*-aryl ring in high yield. In case of additives, CF_3SO_3H gave the desired product **2a** in 92% yield (entry 3), while CF_3CO_2H (TFA) and *p*-TsOH (PTSA) were found to be less effective in affording the target product in 50-60% yield. Amoung the solvents examined, 1,2-dichloroethane (DCE) gave the best results, whereas 1,2-dimethoxyethane (DME) and CH_3CO_2H gave inferior results, while CH_3CN and toluene were failed to produce the desired product. The catalytic activity of different Pd-sources was evaluated, and $Pd(OAc)_2$ exhibited greater reactivity to $PdCl_2$ and $Pd(PPh_3)_2Cl_2$. Lowering the quantity of the Pd-source and the temperature led to afford the target product **2a** in <72% yield. Control experiments without the Pd-source gave **2a** in 10% yield along with unreacted starting material **1a**.

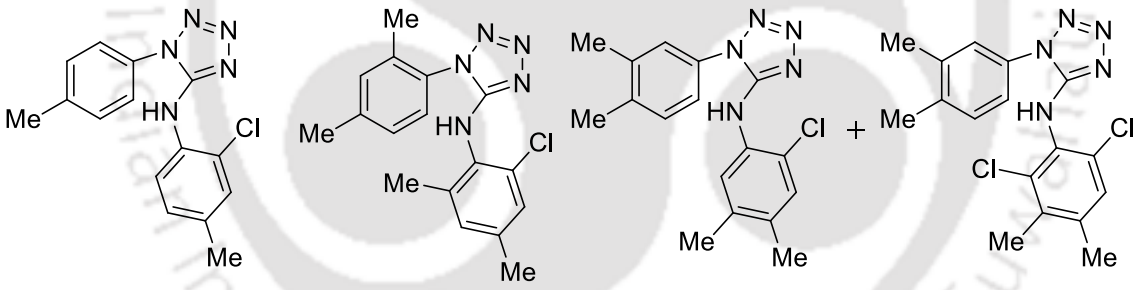
With the optimized conditions, the scope of the protocol was studied for the bromination of a wide range of substitured *N*,1-diaryl-1*H*-tetrazol-5-amines (Table 2). The substrates **1c-f** having 4-Cl, 4-F, 4-^{i}Pr and 4-Me substituents on both the aryl rings readily proceeded reaction to give the corresponding brominated products **2c-f** in 84%, 82%, 88% and 91% yields, respectively. Similarly, substrate bearing 2,4-diMe substituents **1h** required slightly longer reaction time to give the target product **2h** in 63% yield.

Table 3. *Ortho*-Chlorination of *N*-Aryl Ring of *N*,1-Diaryl-1*H*-tetrazol-5-amine[a]

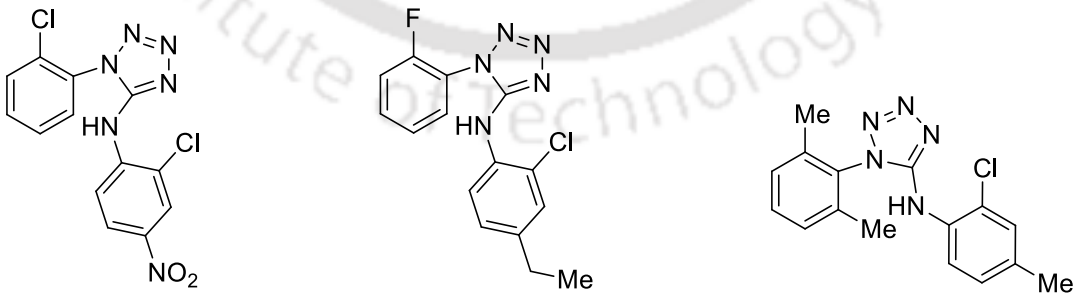




3a, 6 h, 86% **3b**, 6 h, 83% **3c**, 6 h, 88% **3d**, 10 h, 82%



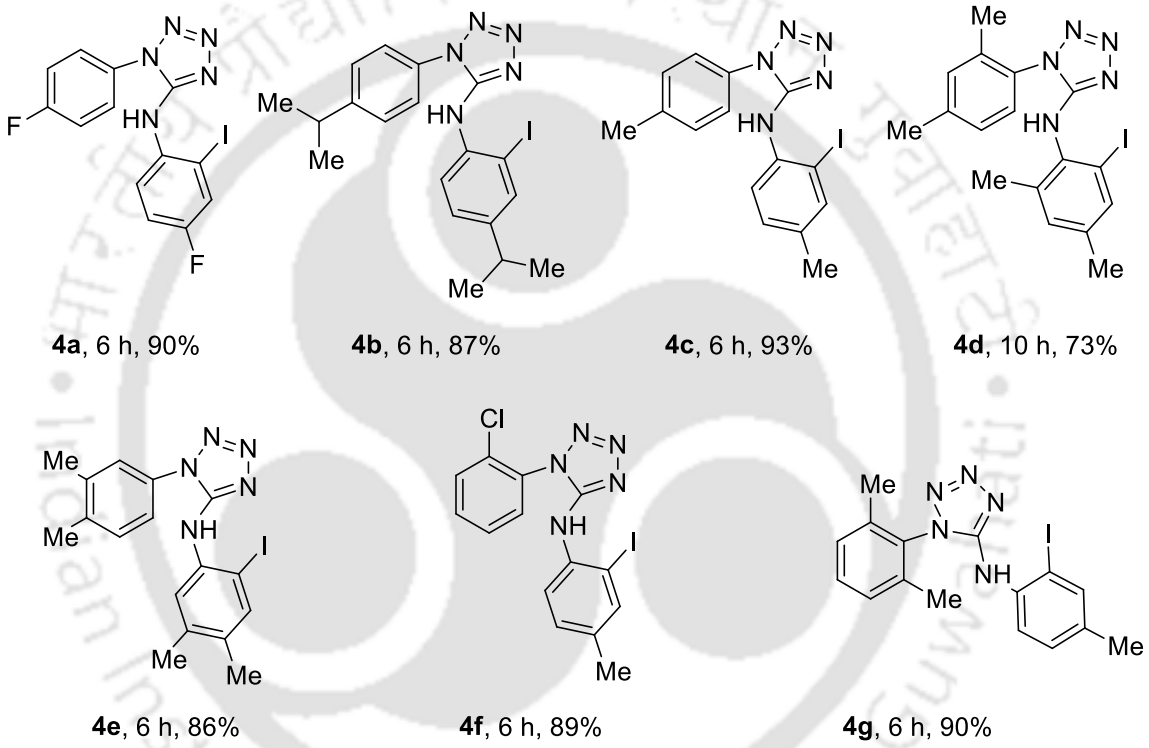
3e, 6 h, 83% **3f**, 10 h, 68% **3g** 6 h, 90%, 2.4:1 **3g'**



3h, 8 h, 79% **3i**, 6 h,82 % **3j**, 6 h, 90%

[a] Substrate (1 mmol), $Pd(OAc)_2$ (10 mol %), *N*-chlorosuccinimide (NCS) (1.2 mmol), CF_3SO_3H (0.5 mmol), DCE (2 mL), 60 °C, 6-10 h.

Table 4. *Ortho*-Iodination of *N*-Aryl Ring of *N*,1-Diaryl-1*H*-tetrazol-5-amine[a]



[a] Substrate (1 mmol), $Pd(OAc)_2$ (10 mol %), *N*-iodosuccinimide (NIS) (1.2 mmol), CF_3SO_3H (0.5 mmol), DCE (2 mL), 60 °C, 6-10 h.

Likewise, unsymmetrical substrates **1j-n** bearing electron donating and -withdrawing groups underwent reaction to afford the target *ortho*-brominated products **2j-n** in 74-92% yields. In case of the substrates having 3-Me and 3,4-diMe groups on the aryl rings, produced a mixture of 2-bromo and 2,6-dibromo compounds **2b** and **2b'**, and **2i** and **2i'** in 78% and 90% yields, respectively. In similar fashion, the substrate having 4-OMe group on the aryl rings **1g** produced a mixture of *ortho*-brominated products **2g** and **2g'** in 88% yield.

The protocol was extended to chlorination of the substituted *N*-aryl-1-aryl-1*H*-tetrazol-5-amine derivatives employing *N*-chlorosuccinimide (NCS) as a halogen source (Table 3). The symmetrically substituted substrates with 4-Cl, 4-F, 4-^{i}Pr, 4-Me and 2,4-diMe groups on the aryl rings proceeded smoothly to give the target *ortho*-chlorinated products **3b-f** in 68-88% yields. In addition, the unsymmetrical substrates **1a** and **1l-n** readily underwent reaction to afford the target products **3a** and **3h-j** in 86% and 79-90% yields, respectively, In case of substrate **1i** produced a mixture of 2-chloro- and 2,6-dichlorinated products **3g** and **3g'** in 90% yield.

Furthurmore, the protocol can be utilized for iodination of *N*-aryl-1-aryl-1*H*-tetrazol-5-amines in the presence of *N*-iodosuccinimide (NIS) as a halogen source (Table 4). The substrates having symmetrical substituents such as 4-F, 4-^{i}Pr, 4-Me, 2,4-diMe and 3,4-diMe groups both on the aryl rings were studied. In similar fashion, the reactions occurred to give the corresponding *ortho*-iodinated products **4a-e** in 73-93% yields, In addition, the substrate **1k** and **1n** with unsymmetrical substituents afforded the target products **4f** and **4g** in 89% and 90% yields, respectively. In these iodination reaction we have observed mono iodination as a sole products. Recrystallization of **4c** gave single crystal whose structre was confirmed by single crystal X-ray analysis (Figure 2).

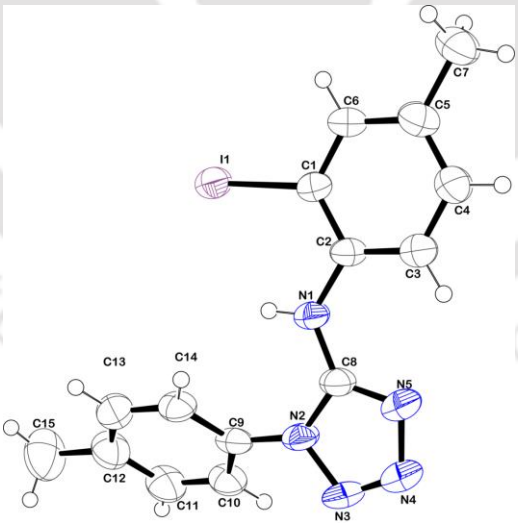
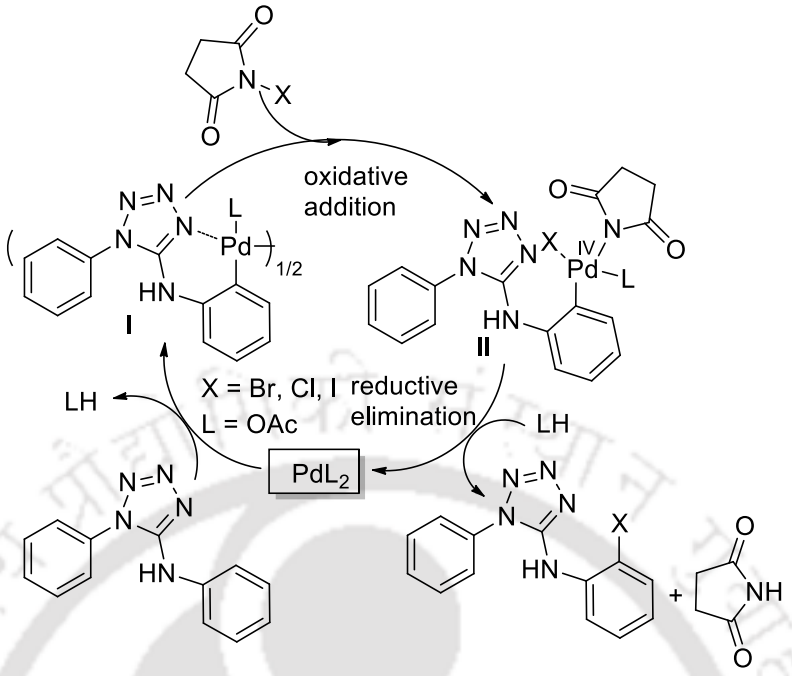


Figure 2. ORTEP diagram of *N*-(2-Iodo-4-methylphenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine **4c** with 50% ellipsoid.



Scheme 17. Plausible Catalytic Cycle

The proposed catalytic cycle is shown in Scheme 17. The reaction of *N*,1-diaryl-1*H*-tetrazol-5-amines with $Pd(OAc)_2$ may give a six membered cyclopalladated intermediate **I** *via* amino-tetrazole chelation assisted C-H bond activation.[12,9a] The intermediate **I** may then undergo oxidative addition with NXS to yield Pd(IV)[12c,d] complex **II**, which may complete the catalytic cycle *via* reductive elimination[12,9a] of the halogenated products and regeneration of the Pd(II) species. The function of the CF_3SO_3H may be presumably to protonate the carbonyl of the NXS that could lead to more effective X^- source.[9c] In addition, CF_3SO_3H may tune the electrophilicity of Pd(II) that could improve the C-H activation process.[12c]

In summary, Pd(II)-catalyzed 5-aminotetrazole assisted *ortho*-selective halogenation of *N*-aryl ring of *N*,1-diaryl-1*H*-tetrazol-5-amine derivatives has been described utilizing *N*-halosuccinimide as a halogenating agent *via* C-H bond activation at moderate temperature. The reaction is chemo- and regioselective and the halogenated products can be obtained in moderate to good yield.

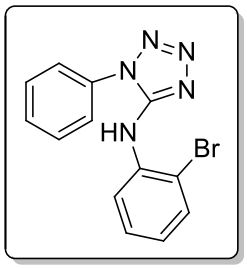
2.3. Experimental Section

2.3.1. General Information: $Pd(OAc)_2$ (99%), $PdCl_2$ (99%), $Pd(PPh_3)_2Cl_2$ (98%), *N*-bromosuccinimide (98%), *N*-chlorosuccinimide (98%) and *N*-iodosuccinimide (98%) were

purchased from Aldrich and were used as received. Trifluoromethanesulfonic acid (98%) was purchased from Spectrochem. The solvents were purchased and dried according to standard procedure prior to use. Purification of the reaction products was carried out by column chromatography using Rankem silica gel (60-120 mesh). Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 Varian spectrometer and Bruker Ultrashield^{TM} 300 using $CDCl_3$ as solvent and Me_4Si as internal standard and DMSO-d_6 was used as solvent. Chemical shifts (δ) were reported in ppm and spin-spin coupling constants (*J*) were given in Hz. Melting points were recorded in open capillary tubes using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS Instrument (model HAB 273). X-Ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany).

2.3.2. General Procedure for Halogenation of Aminotetrazoles. CF_3SO_3H (0.5 mmol) was added to a stirred solution of aminotetrazole **1** (1 mmol), $Pd(OAc)_2$ (10 mol %) and NXS (1.2 mmol) in DCE (2 mL) under air. The mixture was stirred at 60 °C for the appropriate time and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled to room temperature and treated with saturated $NaHCO_3$ (5 mL). The resulting solution was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford analytically pure *N*-(2-haloaryl)aminotetrazoles.

2.4. Characterization Data of *N*-(Haloaryl) Aminotetrazoles 2a-n, 3a-j, 4a-g



***N*-(2-Bromophenyl)-1-(2-chlorophenyl)-1*H*-tetrazol-5-amine 2a.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.71; 294 mg, 84% yield; white solid.

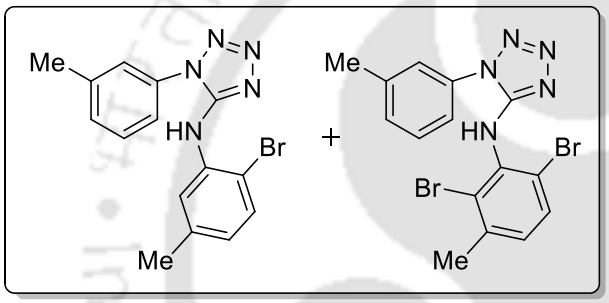
Mp 96-97 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 6.8 Hz, 2H), 7.50-7.47 (m, 2H), 7.37-7.33 (m, 2H), 7.13 (s, 1H), 7.04-7.00 (m, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.9, 134.6, 134.1, 131.7, 129.2, 128.4, 125.9, 124.9, 124.4, 124.1, 121.7, 120.2, 119.2.

FT-IR (KBr) 3445, 3387, 2956, 2926, 1714, 1603, 1567, 1517, 1487, 1380, 1111, 1072, 827, 751 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9ClBrN_5H$ 351.9781, found 351.9789.



***N*-(2-Bromo-5-methylphenyl)-1-*m*-tolyl-1*H*-tetrazol-5-amine 2b and**

***N*-(2,6-dibromo-3-methylphenyl)-1-*m*-tolyl-1*H*-tetrazol-5-amine 2b'.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.68; white solid; 283 mg, 78% yield; both isomers are reported together (ratio: 3.2:1 as determined by NMR).

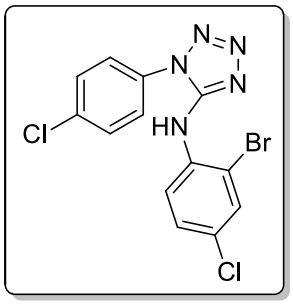
Mp 101-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H, major isomer), 8.30 (d, *J* = 9.2 Hz, 1H, minor isomer), 7.64 (s, 1H, major isomer), 7.57-7.50 (m, 4H, 2H major + 2H minor isomers), 7.41-7.36 (m, 6H, 3H major + 3H minor isomers), 7.16 (br s, 1H), 2.56 (s, 3H, minor isomer), 2.47 (s, 6H, 3H major + 3H minor isomers), 2.40 (s, 3H, major isomer).[1]

^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 150.8, 150.7, 141.3, 139.2, 137.7, 135.4, 134.8, 134.7, 132.3, 132.2, 131.5, 130.5, 125.0, 124.9, 121.2, 121.1, 120.3, 118.0, 117.2, 114.9, 108.9, 24.6, 23.0, 21.4.

FT-IR (KBr) 3365, 3086, 2918, 2857, 1958, 1598, 1559, 1522, 1493, 1449, 1385, 1313, 1124, 1089, 1046, 875, 795, 692 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}BrN_5H$ 344.0505, found 344.0504; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}Br_2N_5H$ 423.9689, found 423.9685.



***N*-(2-Bromo-4-chlorophenyl)-1-(4-chlorophenyl)-1*H*-tetrazol-5-amine 2c.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white solid; 320 mg, 84% yield.

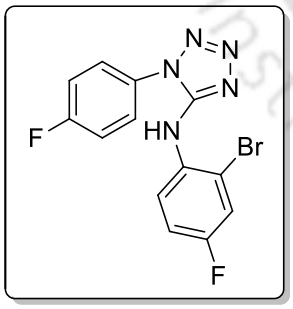
Mp 175-176 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.57-7.53 (m, 3H), 7.39 (dd, *J* = 8.8, 2.4 Hz. 1H), 7.13 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.8, 137.3, 133.4, 131.3, 131.0, 129.5, 129.2, 129.0, 128.7, 125.8, 122.2, 120.0.

FT-IR (KBr) 3434, 3364, 2923, 2846, 1733, 1602, 1561, 1399, 1259, 1086, 1034, 814, 735 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8BrCl_2N_5H$ 383.9413, found 383.9427.



***N*-(2-Bromo-4-fluorophenyl)-1-(4-fluorophenyl)-1*H*-tetrazol-5-amine 2d.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.62; white solid; 287 mg, 82% yield.

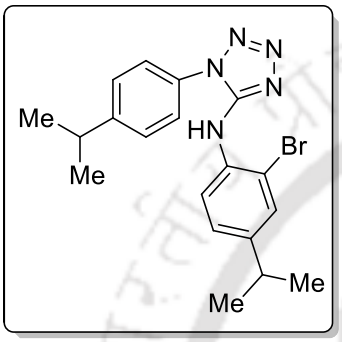
Mp 171-172 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47-8.44 (m, 1H), 7.61-7.57 (m, 2H), 7.39-7.33 (m, 2H), 7.30-7.27 (m, 1H), 7.16-7.11 (m, 1H), 6.97 (br s, 1H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 164.1, 161.6, 159.4, 156.9, 153.1, 151.7, 132.6, 128.5, 126.6, 126.5, 122.4, 122.3, 119.5, 119.2, 117.2, 117.0, 115.3, 115.1, 114.6, 114.5.

FT-IR (KBr) 3423, 3385, 2961, 2926, 2254, 1618, 1578, 1508, 1260, 1237, 1157, 1024, 809, 760 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8F_2BrN_5H$ 352.0004, found 352.0000.



_N_-(2-Bromo-4-isopropylphenyl)-1-(4-isopropylphenyl)-1_H_-tetrazol-5-amine 2e.

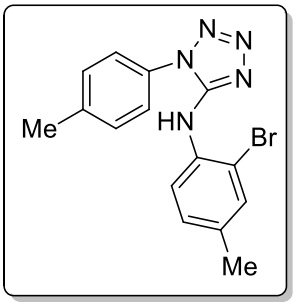
Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.64; thick colorless liquid; 352 mg, 88% yield.

^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.4 Hz, 1H), 7.50-7.45 (m, 4H), 7.35-7.34 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.10 (br s, 1H), 3.03-2.99 (m, 1H), 2.85-2.82 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 151.5, 151.0, 145.1, 133.5, 130.2, 130.0, 128.5, 126.8, 124.1, 119.2, 112.1, 33.9, 33.2, 23.8, 23.7.

FT-IR (KBr) 3372, 2961, 2928, 2870, 1598, 1556, 1523, 1460, 1388, 1364, 1316, 1238, 1117, 1084, 1058, 1013, 838, 710 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{22}BrN_5H$ 402.1113, found 402.1119.



***N*-(2-Bromo-4-methylphenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine 2f.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.72; white solid; 313 mg, 91% yield.

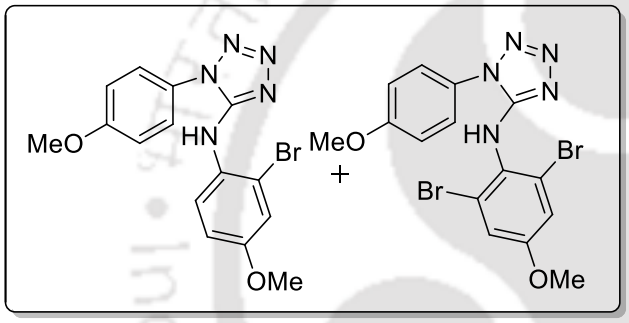
Mp 152-153 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.4 Hz, 1H), 7.47-7.42 (m, 4H), 7.32 (s, 1H), 7.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.09 (br s, 1H), 2.47 (s, 3H), 2.29 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.2, 141.1, 134.2, 133.4, 132.6, 131.3, 130.1, 129.6, 124.3, 119.0, 112.0, 21.4, 20.5.

FT-IR (KBr) 3381, 3085, 2917, 1599, 1566, 1525, 1318, 1235, 1179, 1083, 1038, 816, 720 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}BrN_5H$ 344.0505, found 344.0504.



***N*-(2-Bromo-4-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 2g and *N*-(2,6-dibromo-4-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 2g'.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; white solid; 366 mg, 88% yield; both isomers are reported together (ratio: 1:1 as determined by NMR).

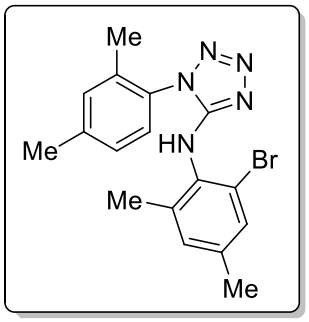
Mp 147-148 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.32 (d, *J* = 9.2 Hz, 1H), 7.49-7.46 (m, 5H), 7.13-7.06 (m, 4H), 7.02 (s, 1H), 6.95 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.80 (br s, 1H), 3.89 (s, 6H), 3.84 (s, 3H), 3.77 (s, 3H).

^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 161.2, 161.1, 155.6, 151.6, 151.1, 151.0, 128.5, 128.2, 126.2, 124.9, 124.7, 122.6, 120.9, 120.4, 120.2, 115.7, 115.6, 114.8, 113.6, 112.7, 56.7, 55.8.

FT-IR (KBr) 3434, 3393, 2925, 2851, 1603, 1523, 1486, 1263, 1209, 1086, 1021, 824, 801, 746 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd $C_{15}H_{14}BrN_5O_2H$ 376.0404, found 376.0404; $[M+H]^+$ calcd for $C_{15}H_{13}Br_2N_5O_2H$ 455.9416, found 455.9420.



***N*-(2-Bromo-4,6-dimethylphenyl)-1-(2,4-dimethylphenyl)-1*H*-tetrazol-5-amine 2h.**

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 234 mg, 63% yield.

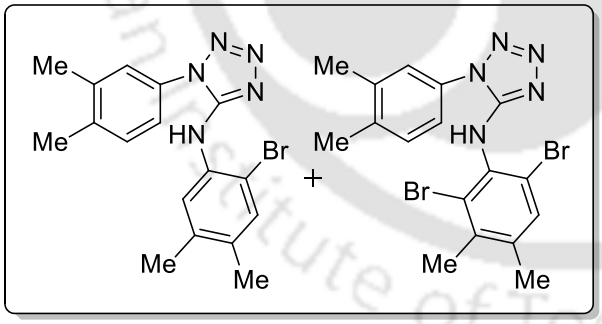
Mp 98-99 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (m, 4H), 7.02 (s, 1H), 5.73 (br s, 1H), 2.43 (s, 3H), 2.29 (s, 6H), 2.20 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 153.8, 141.6, 138.8, 137.6, 135.9, 132.5, 132.0, 131.2, 130.7, 128.6, 128.2, 126.9, 122.0, 21.2, 20.6, 18.9, 17.3.

FT-IR (KBr) 3370, 3247, 2959, 2923, 1714, 1587, 1515, 1476, 1381, 1293, 1227, 1102, 1087, 1027, 818, 734 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}BrN_5H$ 372.0818, found 372.0820.



***N*-(2-Bromo-4,5-dimethylphenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine 2i and**

***N*-(2,6-dibromo-3,4-dimethylphenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine 2i'.**

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.71; white solid; 354 mg, 90% yield; both isomers are reported together (ratio: 2.5:1 as determined by NMR).

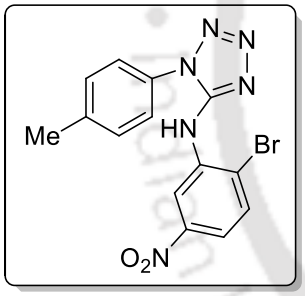
Mp 116-117 °C

^{1}H NMR (400 MHz, $CDCl_3$)δ 8.26 (s, 1H, major isomer), 8.24 (s, 1H, minor isomer), 7.40 (s, 1H, minor isomer), 7.38-7.37 (m, 2H, major isomer), 7.34-7.30 (m, 2H, 1H major + 1H minor isomers), 7.27 (s, 1H, major isomer), 7.19 (d, *J* = 8.4 Hz, 1H, minor isomer), 7.09 (br s, 1H), 2.38 (s, 15H, 6H major + 9H minor isomers), 2.32 (s, 3H minor isomer), 2.29 (s, 3H major isomer), 2.21 (s, 3H, major isomer).

^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 151.2, 151.0, 139.5, 137.7, 136.6, 133.8, 133.3, 132.8, 132.6, 132.4, 131.5, 130.2, 130.1, 129.4, 125.1, 121.3, 120.0, 116.0, 115.6, 108.6, 20.8, 20.3, 19.9, 19.87, 19.7, 19.0.

FT-IR (KBr) 3376, 2971, 2920, 1594, 1558, 1518, 1451, 1396, 1245, 1114, 1087, 1026, 874, 832, 723cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}BrN_5H$ 372.0818, found 372.0807; $[M+H]^+$ calcd for $C_{17}H_{17}Br_2N_5H$ 453.9866, found 453.9862.



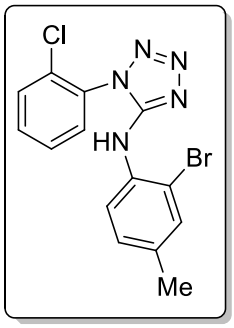
***N*-(2-Bromo-5-nitrophenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine 2j.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; 295 mg, 79% yield; thick yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.4 Hz, 1H), 7.56-7.47 (m, 6H), 2.50 (s, 3H).

^{13}C{H} NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 150.8, 150.6, 141.5, 137.9, 131.3, 129.5, 129.2, 124.2, 121.9, 119.0, 103.9, 21.4.

FT-IR (KBr) 3427, 2912, 2247, 1635, 1605, 1525, 1344, 1116, 1024, 998, 823, 764 cm^{-1}.

HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{11}BrN_6O_2Na$ 397.0030, found 397.0025.



***N*-(2-Bromo-4-methylphenyl)-1-(2-chlorophenyl)-1*H*-tetrazol-5-amine 2k.** Analytical TLC on silica gel, 1:4 ethyl acetate/ hexane R_f = 0.70; white solid; 337 mg, 92% yield.

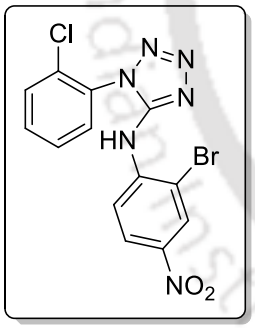
Mp 158-159 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.42 (s, 1H), 7.30-7.22 (m, 3H), 7.12 (br s, 1H), 6.97-6.93 (m, 1H), 2.44 (s, 3H).

^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 150.8, 141.3, 134.6, 131.5, 129.1, 128.4, 127.1, 126.3, 123.8, 122.6, 121.5, 119.0, 23.6.

FT-IR (KBr) 3381, 3104, 2921, 1898, 1605, 1567, 1515, 1314, 1093, 1034, 823, 736 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}BrClN_5H$ 363.9959, found 363.9957.



***N*-(2-Bromo-4-nitrophenyl)-1-(2-chlorophenyl)-1*H*-tetrazol-5-amine 2l.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; white solid; 293 mg, 74% yield.

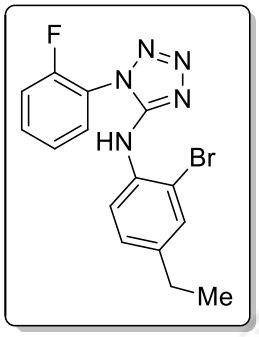
Mp 116-117 °C.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 8.36 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 9.2 Hz, 1H), 8.19-8.16 (m, 2H), 7.67- 7.61 (m, 3H), 7.56 (dd, *J* = 7.6, 1.6 Hz, 1H).

^{13}C{H} NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 150.6, 141.8, 141.2, 132.4, 130.5, 130.4, 128.8, 128.7, 128.1, 127.5, 123.7, 117.8, 111.1.

FT-IR (KBr) 3445, 3109, 2928, 2258, 1605, 1520, 1412, 1339, 1283, 1115, 1025, 1001, 827, 742 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8BrClN_6O_2H$ 394.9653, found 394.9658.



***N*-(2-Bromo-4-ethylphenyl)-1-(2-fluorophenyl)-1*H*-tetrazol-5-amine 2m.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 285 mg, 79% yield.

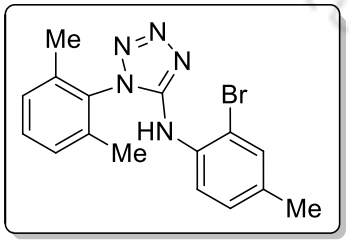
Mp 106-107 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.64-7.56 (m, 2H), 7.43-7.35 (m, 2H), 7.32 (s, 1H), 6.93 (br s, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 157.4, 154.8, 152.0, 141.0, 133.8, 133.4, 133.23, 133.2, 131.6, 129.4, 129.0, 128.4, 128.3, 126.09, 126.1, 125.0, 122.9, 120.3, 120.2, 120.0, 119.4, 117.8, 117.6, 112.4, 28.6, 15.5.

FT-IR (KBr) 3383, 3074, 2966, 2931, 2863, 1599, 1563, 1522, 1461, 1390, 1316, 1258, 1228, 1085, 1041, 979, 877, 824, 757, 663 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}BrFN_5H$ 362.0411, found 362.0413.



***N*-(2-Bromo-4-methylphenyl)-1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-amine 2n.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.55; white solid; 318 mg, 89% yield.

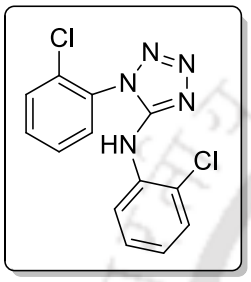
Mp 134-135 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.32-7.28 (m, 1H), 7.18-7.16 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.47 (br s, 1H), 2.16 (s, 3H), 1.95 (s, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.9, 136.6, 134.3, 133.1, 132.4, 131.5, 129.4, 129.3, 119.2, 112.1, 20.3, 17.4.

FT-IR (KBr) 3483, 3367, 3137, 3953, 2921, 2863, 2754, 2360, 1590, 1566, 1493, 1404, 1310, 1243, 1170, 1119, 1144, 1043, 891, 814, 775, 596 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}BrN_5H$ 360.0643, found 360.0644.



***N*,1-Bis(2-chlorophenyl)-1*H*-tetrazol-5-amine 3a.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.66; white solid; 264 mg, 86% yield.

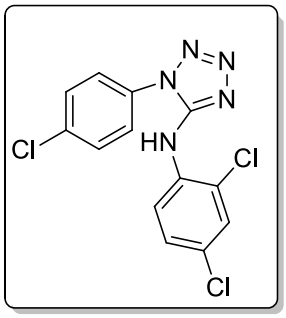
Mp 81-82 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.63-7.59 (m, 1H), 7.57-7.53 (m, 2H), 7.35-7.31(m, 2H), 7.01-6.97 (m, 1H), 6.82 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.8, 134.6, 133.0, 131.4, 131.3, 129.6, 129.4, 129.1, 128.9, 128.2, 124.0, 121.8, 119.2.

FT-IR (KBr) 3433, 2925, 2857, 2318, 1742, 1603, 1568, 1465, 1448, 1265, 1089, 1028, 795, 744 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9Cl_2N_5H$ 306.0308, found 306.0307.



1-(4-Chlorophenyl)-*N*-(2,4-dichlorophenyl)-1*H*-tetrazol-5-amine 3b. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 212 mg, 63% yield.

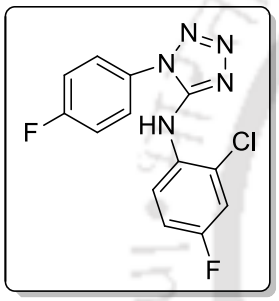
Mp 180-181 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.68-7.66 (m, 2H), 7.59-7.55 (m, 2H), 7.47-7.40 (m, 1H), 7.35-7.27 (m, 1H), 7.10 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 151.1, 135.9, 133.8, 131.0, 130.5, 130.2, 128.7, 128.5, 127.7, 125.4, 121.3.

FT-IR (KBr) 3459, 3375, 3096, 2915, 1652, 1652, 1599, 1559, 1511, 1491, 1467, 1275, 1260, 1093, 1048, 859, 831, 764, 749 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8Cl_3N_5H$ 339.9918, found 339.9907.



***N*-(2-Chloro-4-fluorophenyl)-1-(4-fluorophenyl)-1*H*-tetrazol-5-amine 3c.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.61; white solid; 270 mg, 88% yield.

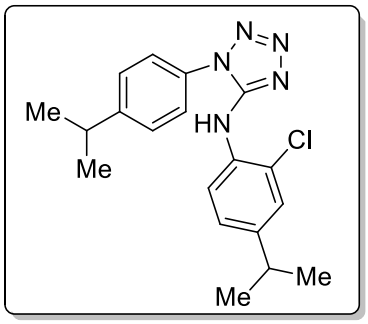
Mp 101-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.41 (m, 1H), 7.60-7.56 (m, 2H), 7.38-7.33 (m, 2H), 7.15-7.06 (m, 2H), 6.92 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 164.0, 161.4, 159.3, 156.8, 153.0, 151.7, 131.4, 128.5, 126.5, 126.4, 125.0, 124.8, 122.62, 122.6, 117.0, 116.8, 116.4, 116.2, 114.8, 114.5, 114.3.

FT-IR (KBr) 3398, 3325, 2981, 2394, 1685, 1612, 1578, 1502, 1365, 1260, 1242, 1162, 1023, 826, 793 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8F_2ClN_5H$ 308.0509, found 308.0509.



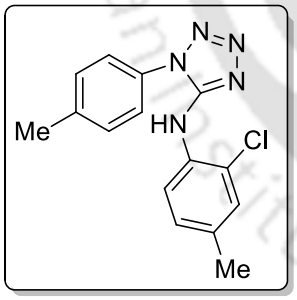
***N*-(2-Chloro-4-isopropylphenyl)-1-(4-isopropylphenyl)-1*H*-tetrazol-5-amine 3d.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.60; thick colorless liquid; 291 mg, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.0 Hz, 1H), 7.50-7.45 (m, 4H), 7.19-7.16 (m, 2H), 7.06 (br s, 1H), 3.05-2.98 (m, 1H), 2.87-2.80 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 6H), 1.21 (d, *J* = 6.8 Hz, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.7, 151.1, 144.8, 132.4, 130.2, 128.6, 126.8, 126.2, 124.1, 119.1, 33.9, 33.3, 23.8, 23.7.

FT-IR (KBr) 3388, 3043, 2961, 2928, 2870, 1908, 1599, 1556, 1523, 1461, 1416, 1390, 1317, 1240, 1117, 1143, 1085, 1051, 1013, 980, 909, 837, 780, 723, 676 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{22}ClN_5H$ 356.1636, found 356.1637.



***N*-(2-Chloro-4-methylphenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine 3e.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white solid; 249 mg, 83% yield.

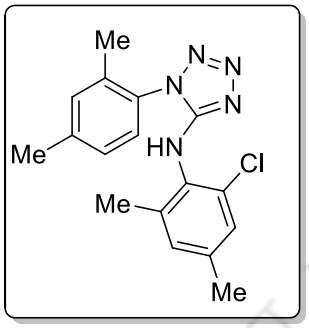
Mp 137-138 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 7.46-7.41 (m, 4H), 7.16-7.13 (m, 2H), 7.04 (br s, 1H), 2.47 (s, 3H), 2.29 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.2, 141.2, 133.8, 132.3, 131.3, 130.1, 129.5, 129.0, 124.3, 121.4, 119.0, 21.5, 20.7.

FT-IR (KBr) 3397, 3085, 2922, 2851, 1619, 1604, 1561, 1525, 1380, 1316, 1234, 1087, 1046, 817 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}ClN_5H$ 300.1010; found 300.1007.



***N*-(2-Chloro-4,6-dimethylphenyl)-1-(2,4-dimethylphenyl)-1*H*-tetrazol-5-amine 3f.**

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; white solid; 222 mg, 68% yield.

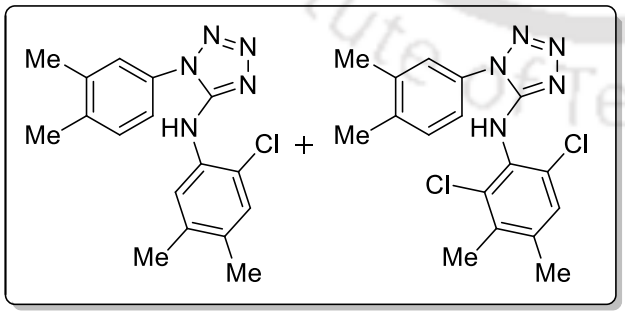
Mp 102-103 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 7.22 (s, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 5.72 (br s, 1H), 2.43 (s, 3H), 2.28 (s, 6H), 2.19 (s, 3H).

$^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 153.9, 141.7, 138.4, 137.5, 136.0, 132.6, 130.9, 130.6, 128.6, 128.3, 127.7, 126.9, 21.3, 20.9, 18.7, 17.4.

FT-IR (KBr) 3158, 3065, 2968, 2923, 1587, 1512, 1478, 1312, 1285, 1227, 1114, 1085, 1027, 850, 816 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}ClN_5H$ 328.1323, found 328.1323.



***N*-(2-Chloro-4,5-dimethylphenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine 3g and**

***N*-(2,6-dichloro-3,4-dimethylphenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine 3g'.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white solid; 304 mg, 90% yield; both isomers are reported together (ratio: 2.4:1 as determined by NMR).

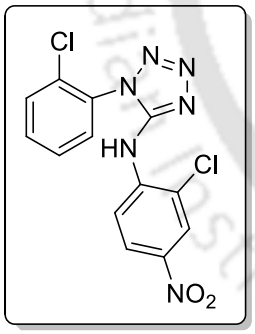
Mp 130-131 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, major isomer), 8.21 (s, 1H, minor isomer), 7.38 (s, 1H, minor isomer), 7.36 (d, *J* = 11.6 Hz, 1H, major isomer), 7.29 (dd, *J* = 8.0, 2.4 Hz, 2H, major isomer), 7.20 (s, 1H, minor isomer), 7.14 (d, *J* = 8.4 Hz, 1H, minor isomer), 7.10 (s, 1H, major isomer), 7.02 (br s, 1H), 2.36 (s, 12H, 6H major + 6H minor isomers), 2.30 (3H, minor isomer), 2.28 (3H, major isomer), 2.27 (3H, minor isomer), 2.19 (3H, major isomer).

^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 151.1, 151.0, 139.6, 137.0, 134.8, 132.6, 132.3, 132.2, 132.1, 131.5, 130.2, 130.15, 129.5, 128.7, 125.2, 122.1, 121.2, 120.0, 118.3, 115.8, 20.4, 19.9, 19.8, 19.7, 19.0, 16.9.

FT-IR (KBr) 3158, 3065, 2968, 2923, 1587, 1512, 1478, 1312, 1285, 1227, 1114, 1085, 1027, 850, 816, 732 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}ClN_5H$ 328.1323; found 328.1318; $[M+H]^+$ calcd for $C_{17}H_{17}Cl_2N_5H$ 362.0934; found 362.0927.



***N*-(2-Chloro-4-nitrophenyl)-1-(2-chlorophenyl)-1*H*-tetrazol-5-amine 3h.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.20; white solid; 276 mg, 79% yield.

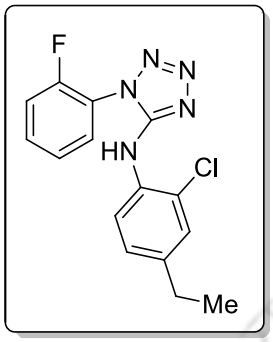
Mp 135-136 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 9.2 Hz, 1H), 8.29-8.24 (m, 2H), 7.75-7.56 (m, 4H), 7.19 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 151.0, 142.3, 140.4, 133.0, 131.2, 130.9, 129.3, 128.8, 124.8, 124.0, 121.5, 118.0.

FT-IR (KBr) 3439, 3112, 2932, 2249, 1624, 1524, 1409, 1337, 1279, 1125, 1045, 1003, 810, 725, 649 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8Cl_2N_6O_2H$ 351.0159, found 351.0157.



***N*-(2-chloro-4-ethylphenyl)-1-(2-fluorophenyl)-1*H*-tetrazol-5-amine 3i.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 259 mg, 82% yield.

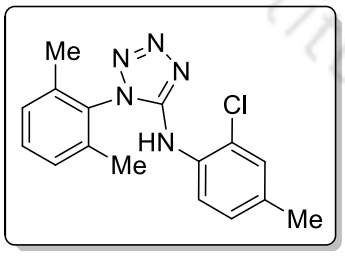
Mp 113-114 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 1H), 7.61-7.55 (m, 2H), 7.46-7.36 (m, 2H), 7.15-7.12 (m, 2H), 6.91 (br s, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 157.3, 154.8, 152.0, 140.6, 133.2, 133.1, 132.3, 128.4, 128.3, 127.7, 126.13, 126.1, 121.9, 120.4, 120.3, 119.4, 117.8, 117.6, 28.1, 15.5.

FT-IR (KBr) 3444, 3066, 2970, 2871, 1602, 1522, 1503, 1464, 1390, 1318, 1257, 1230, 1131, 1021, 874, 755, 708 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}ClFN_5H$ 318.0916, found 318.0912.



***N*-(2-Chloro-4-methylphenyl)-1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-amine 3j.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 281 mg, 90% yield.

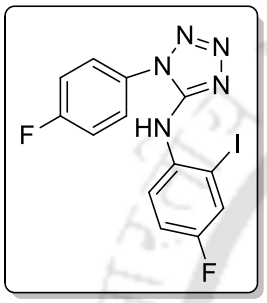
Mp 130-131 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 1H), 7.31-7.28 (m, 2H), 7.18-7.16 (m, 2H), 6.49 (br s, 1H), 2.30 (s, 3H), 2.08 (s, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.9, 136.8, 134.0, 132.1, 131.6, 129.5, 129.4, 128.8, 121.6, 119.4, 20.5, 17.4.

FT-IR (KBr) 3141, 3056, 2924, 2886, 1701, 1657, 1611, 1556, 1501, 1478, 1445, 1379, 1305, 1263, 1242, 1208, 1161, 785 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}ClN_5H$ 314.1167, found 314.1168.



***N*-(4-Fluoro-2-iodophenyl)-1-(4-fluorophenyl)-1*H*-tetrazol-5-amine 4a.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.66; white solid; 360 mg, 90% yield.

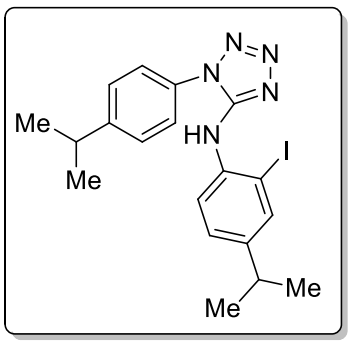
Mp 173-174 °C.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) δ 8.35-8.31 (m, 1H), 7.63-7.59 (m, 2H), 7.48 (dd, *J* = 8.0, 3.2 Hz, 1H), 7.37-7.33 (m, 2H), 7.17-7.12 (m, 1H), 6.83 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 163.3, 160.8, 159.4, 156.9, 152.1, 135.7, 128.3, 126.3, 126.2, 125.0, 124.8, 123.8, 116.3, 116.1, 115.3, 115.1, 93.0.

FT-IR (KBr) 3427, 2255, 2128, 1645, 1578, 1522, 1509, 1234, 1048, 1025, 103, 825, 764, 632 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8F_2IN_5H$ 399.9865, found 399.9856.



***N*-(2-Iodo-4-isopropylphenyl)-1-(4-isopropylphenyl)-1*H*-tetrazol-5-amine 4b.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 388 mg, 87% yield.

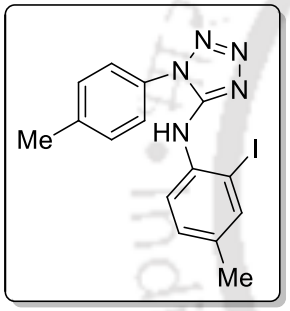
Mp 109-110 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H),7.47-7.37 (m, 4H), 7.17 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.87 (br s, 1H), 2.95-2.90 (m, 1H), 2.74-2.69 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.8, 151.6, 145.9, 136.7, 136.3, 130.2, 128.6, 127.9, 124.6, 119.1, 88.6, 34.0, 33.2, 23.92, 23.9.

FT-IR (KBr) 3492, 337, 2960, 2868, 1593, 1557, 1523, 1483, 1460, 1410, 1388, 1314, 1261, 1084, 1058, 1031, 1013, 837, 749 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{22}IN_5H$ 448.0993, found 448.0997.



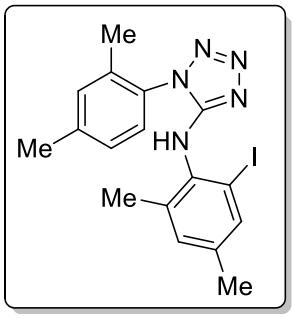
***N*-(2-Iodo-4-methylphenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine 4c.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.73; white solid; 364 mg, 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.4 Hz, 1H), 7.55 (s, 1H), 7.49-7.42 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.92 (br s, 1H), 2.47 (s, 3H), 2.26 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$)δ 151.5, 141.1, 139.1, 136.0, 134.8, 131.2, 130.5, 130.0, 124.5, 118.7, 88.3, 21.4, 20.3.

FT-IR (KBr) 3456, 3352, 2922, 2846, 1722, 1594, 1559, 1523, 1478, 1380, 1305, 1085, 1035, 818, 740 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}IN_5H$ 392.0367, found 392.0368.



***N*-(2-Iodo-4,6-dimethylphenyl)-1-(2,4-dimethylphenyl)-1*H*-tetrazol-5-amine** **4d**.

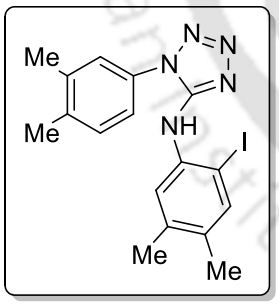
Analytical TLC on silica gel,1:4 ethyl acetate/hexane R_f = 0.53; brown liquid; 307 mg, 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.21 (d, *J* = 6.4 Hz, 1H), 7.04 (s, 1H), 5.55 (br s, 1H), 2.42 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H).

^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 153.6, 141.8, 139.5, 137.3, 136.9, 136.1, 134.8, 132.7, 132.4, 128.5, 128.3, 127.0, 99.7, 21.4, 20.5, 19.5, 17.7.

FT-IR (KBr) 3389, 3054, 2922, 2851, 1599, 1565, 1520, 1453, 1386, 1245, 1113, 1087, 1022, 877, 819, 639 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}IN_5H$ 420.0680, found 420.0682.



***N*-(2-Iodo-4,5-dimethylphenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine** **4e.**

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.71; white solid; 362 mg, 86% yield.

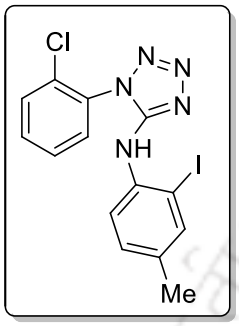
Mp 153-154 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.47 (s, 1H), 7.37-7.33 (m, 3H), 6.91 (br s, 1H), 2.36 (s, 6H), 2.27 (s, 3H), 2.16 (s, 3H).

$^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 151.3, 139.6, 139.0, 138.8, 136.1, 133.7, 131.5, 130.1, 125.3, 121.8, 120.0, 84.1, 20.0, 19.9, 19.8, 18.8.

FT-IR (KBr) 3359, 3054, 2950, 2919, 2851, 1589, 1557, 1518, 1450, 1393, 1245, 1084, 873, 831 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}IN_5H$ 420.0680, found 420.0685.



1-(2-Chlorophenyl)-*N*-(2-iodo-4-methylphenyl)-1*H*-tetrazol-5-amine 4f. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.72; white solid; 364 mg, 89% yield.

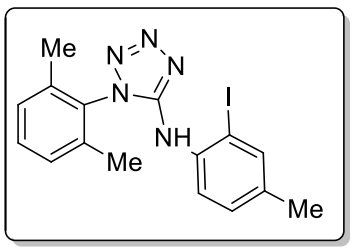
Mp 108-109 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.44-8.42 (m, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.35-7.30 (m, 2H), 7.18 (br s, 1H), 7.12 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.02 (td, *J* = 8.0, 1.6 Hz, 1H), 2.52 (s, 3H).

$^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 150.6, 144.9, 141.0, 134.5, 132.5, 129.1, 128.3, 125.0, 123.9, 122.5, 121.5, 119.0, 103.2, 28.4.

FT-IR (KBr) 3467, 3387, 2922, 2840, 1603, 1566, 1520, 1470, 1374, 1317, 1088, 1017, 576 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}ClIN_5H$ 411.9820, found 411.9831.



1-(2,6-Dimethylphenyl)-*N*-(2-iodo-4-methylphenyl)-1*H*-tetrazol-5-amine 4g: Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; 364 mg, 90% yield.

Mp 156-157 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 1.2 Hz, 1H), 7.34-7.30 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.12 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.36 (br s, 1H), 2.16 (s, 3H), 1.98 (s, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 152.1, 138.9, 136.8, 135.7, 134.8, 131.6, 130.4, 129.5, 129.4, 118.7, 88.3, 20.2, 17.5.

FT-IR (KBr) 3343, 3201, 2920, 2858, 1596, 1588, 1561, 1525, 1486, 1473, 1445, 1376, 1308, 1236, 1169, 1087, 984, 868, 811, 777, 730 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}IN_5H$ 406.0523, found 406.0524.

2.5. References

1. (a) Girijavallabhan, V. M.; Pinto, P. A.; Genguly, A. K.; Versace, R. W. Eur. Patent EP274867, **1988**; *Chem. Abstr*. **1989**, *110*, 23890. (b) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538. (c) Habich, D. *Synthesis* **1992**, 358. (d) Akimoto, H.; Ootsuand, K.; Itoh, F. Eur. Patent EP530537, 1993; *Chem. Abstr*. **1993**, *119*, 226417. (e) Mitch, C. H.; Quimby, S. J. Int. Patent WO 9851321, 1998; *Chem. Abstr*. **1998**, *130*, 13997.
2. Fritz, M.; Kaori, K.; Yashio, K.; Haruko, S.; keiko, T.; Yuichi, O.; Yumi, H.; Katsuhiko, S.; Takahisa, A.; Toshio, G.; Seishi, I. Patent EP 0855394 A1, **1998**.
3. For some studies on cross coupling reactions, see: (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 1385. (b) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 3657. (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (d) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587.
4. Halogen containing biological active molecules: (a) Butler, A.; Walker, J. V. *Chem. Re*v. **1993**, *93*, 1937.
5. Electrophilic aromatic Substitution: (a) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley: New York, 1990. (b) De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976, Chapter 5. (c) Merkushev, E. B.

Synthesis **1988**, 923. (d) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.

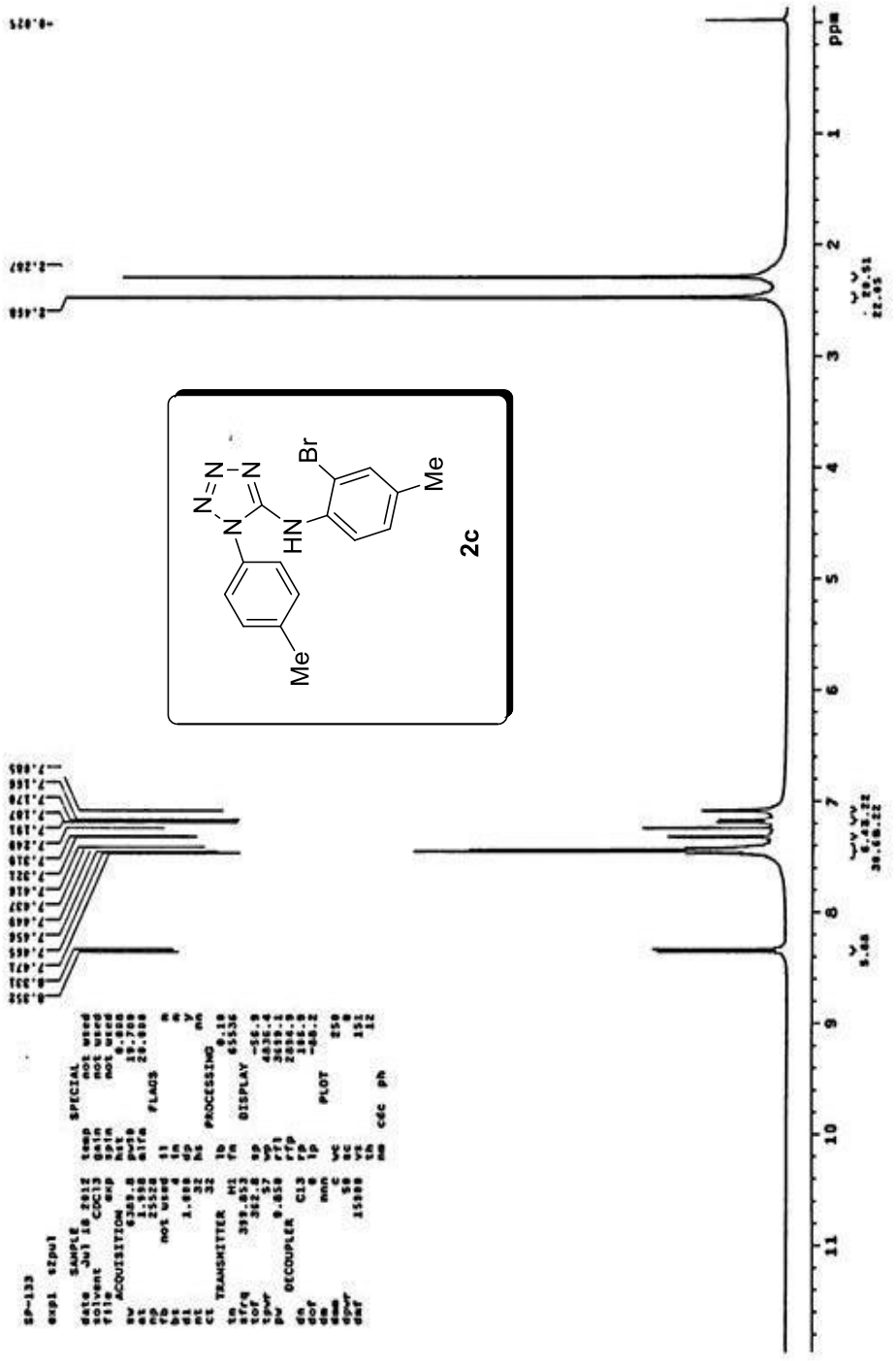
6. For cross-coupling reactions see: Wu, H.; Hynes, J. *Org. Lett*. **2010**, *12*, 1192.
7. For Rh-catalyzed Halogenation reactions see: (a) Schroder, N.; Delord, J. W.; Glorius, F. *J. Am. Chem. Soc.* **2012,** *134*, 8298. (b) Qian, G.; Hong, X.; Liu, B.; Mao, H.; Xu, B. *Org. Lett.* **2014**, *16*, 5294.
8. For Ru-catalyzed Halogenation reactions see: Wang, L.; Ackermann, L. *Chem. Commun*. **2014**, *50*, 1083.
9. For Pd-catalyzed Halogenation reactions see: (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006,** *128*, 7416. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006,** *8*, 2523. (c) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed*. **2011**, *50*, 5524. (d) John, A.; Nicholas, K. M. *J. Org. Chem*. **2012**, *77*, 5600. (e) Ma, X.-T.; Tian, S.-K. *Adv. Synth. Catal*. **2013**, *355*, 337. (f) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed*. **2013**, *52*, 4440. (g) Zhang, G.; Sun, S.; Yang, F.; Zhang, Q.; Kang, J.; Wu, Y.; Wu, Y. *Adv. Synth. Catal*. **2015**, *357*, 443.
10. For Cu-catalyzed Halogenation reactions see: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Urones, B.; Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun*. **2013**, *49*, 11044. (c) Li, B.; Liu, B.; Shi, B.-F. *Chem. Commun*. **2015**, *51*, 5093.
11. For preparation tetrazole, see: (a) Batey, R. A.; Powell, D. A. *Org. Lett.* **2000**, *2*, 3237. (b) Yu, Y.; Ostrech, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2004**, *45*, 7787. (c) Ramana, T.; Punniyamurthy, T. *Chem. Eur. J.* **2012**, *18*, 13279. (d) SathishKumar, M.; Shanmugavelan, P.; Nagarajan, S.; Dinesh, M.; Ponnuswamy, A. *New J. Chem*. **2013**, *37*, 488. (e) Jadhav, N. C.; jagadhane, P. B.; Patel, K. N.; Telvekar, V. N. *Tetrahedron Lett.* **2013**, *54*, 101. (f) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem.* **2012**, *77*, 3716. (g) Yella, R.; Khatun, N.; Rout, S. K.; Patel, B. K. *Org. Biomol. Chem.* **2011**, *9*, 3235.
12. (a) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007,** *129*, 15142. (b) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Canty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012,** *134*, 12002. (c) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.;

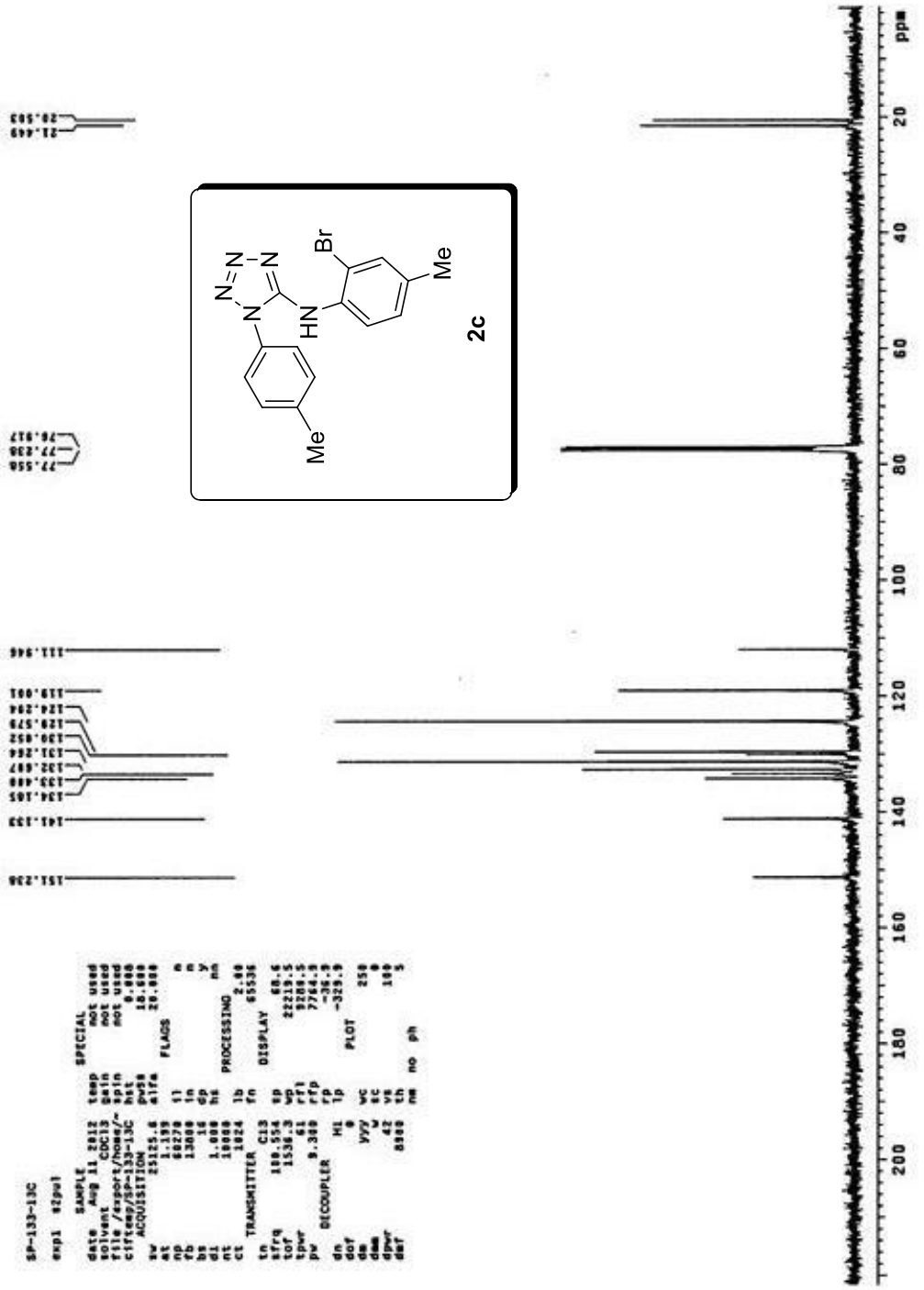
Liu, L. *J. Am. Chem. Soc.* **2010,** *132,* 468. (d) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009,** *11,* 3250. (e) Zhang, L.-S.; Chen, K.; Chen, G.; Li, B.-J.; Luo, S.; Guo, Q.-Y.; Wei, J.-B.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 10.

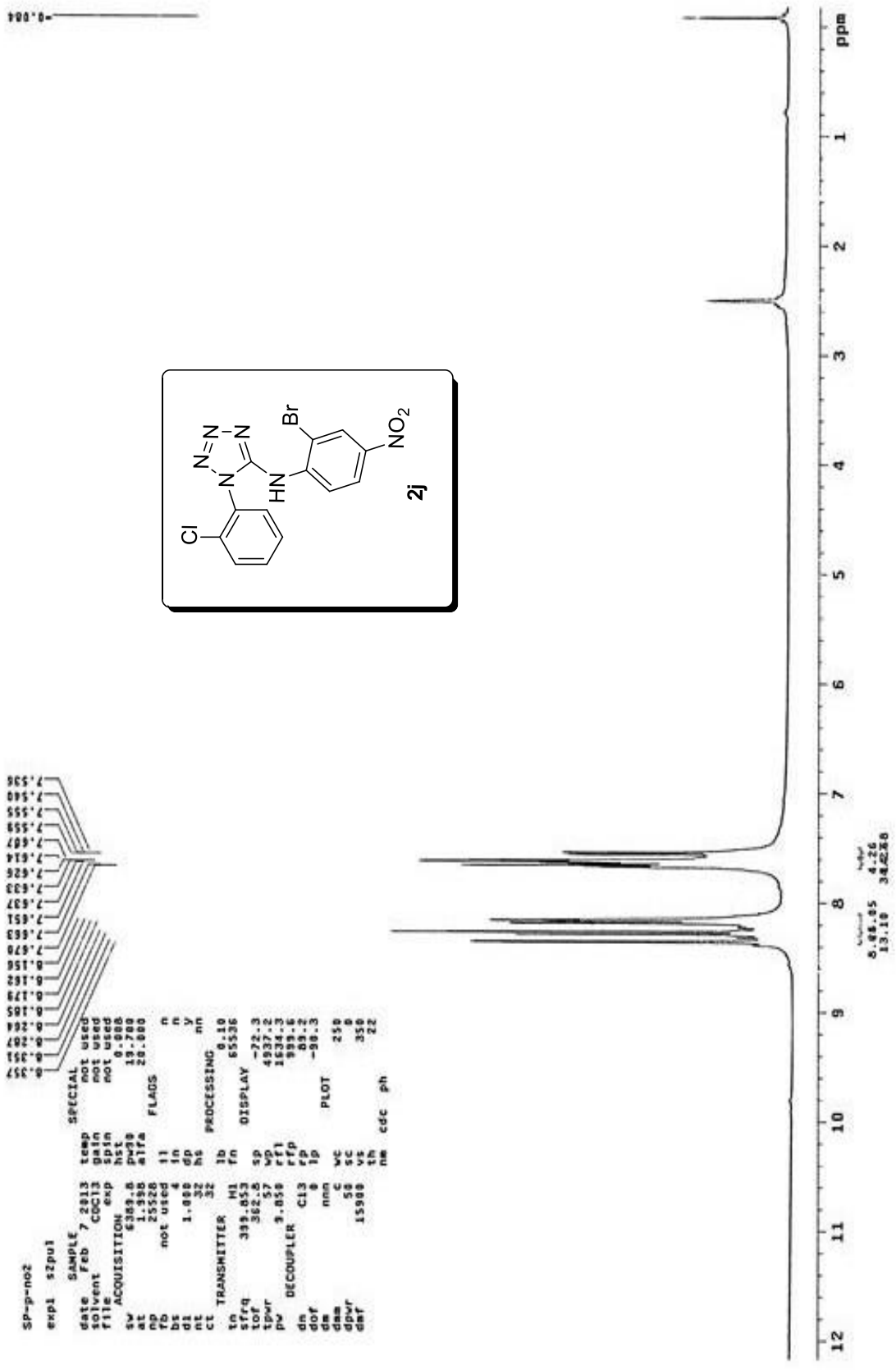
Crystal Data and Structure Refinement for 4b at 296(2) K

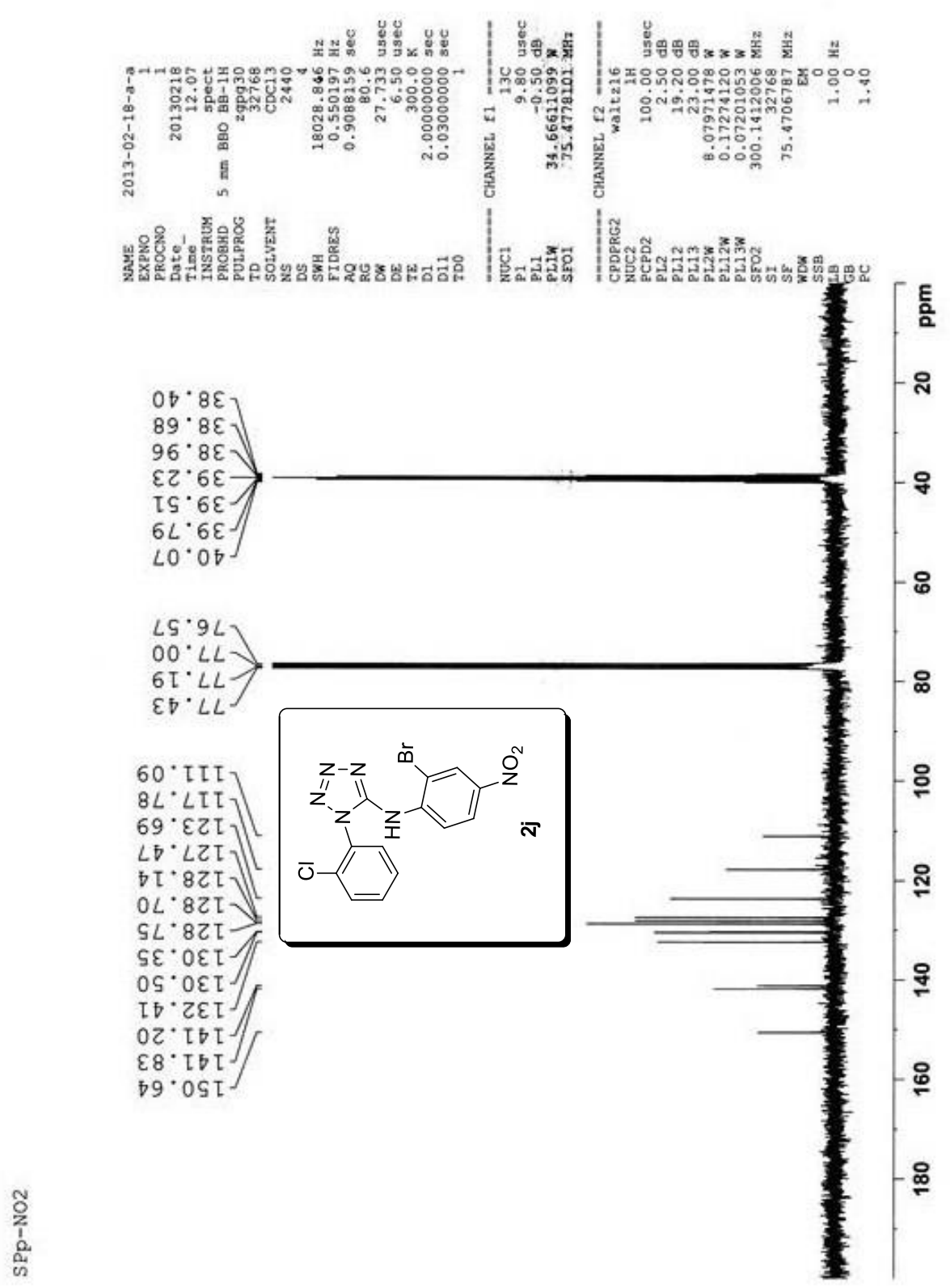
Identification code	**4b**
Empirical formula	C_{15} H_{14} I N_5
Formula weight	391.21
Temperature	296(2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
	Loop xyz
	'x, y, z'
	'-x+1/2, y+1/2, -z+1/2'
	'-x, -y, -z'
	'x-1/2, -y-1/2, z-1/2'
Unit cell dimensions	*a* = 7.6397(2) Å α(°) = 90.00
	b = 9.8963(2) Å β(°) = 90.1540(10)
	c = 20.2534(4) Å γ(°) = 90.00
Volume	1531.25(6) $Å^3$
Z	4
Density (calculated)	1.697 Mg/m^3
Absorption coefficient	2.092 mm^{-1}
F(000)	768.0
Crystal size	0.32 x 0.26 x 0.14 mm
Theta range for data collection	2.01 to 27.66 °
Index ranges	-9<=h<=9, -12<=k<=12, -24<=l<=25
Reflections collected	3254
Independent reflections	2903 [R (int) = 0.0339]
Completeness to theta = 27.66°	91.3 %
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3254/ 0 /192
Goodness-of-fit on F^2	1.156
Final R indices [I>2sigma (I)]	*R1* = 0.0357, *wR2* = 0.0920
R indices (all data)	*R1* = 0.0396, *wR2* = 0.0934

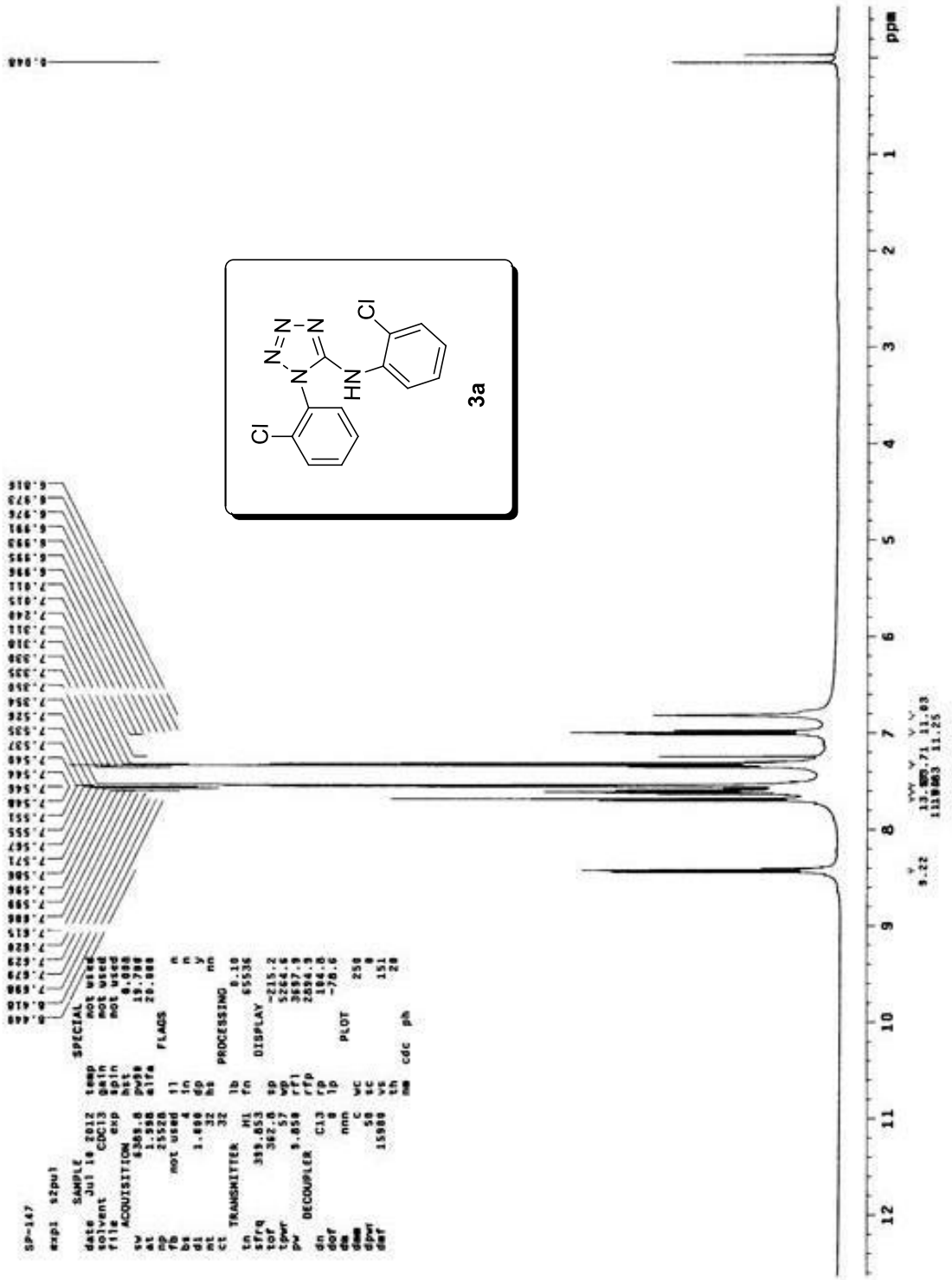
2.6. Selected Spectra

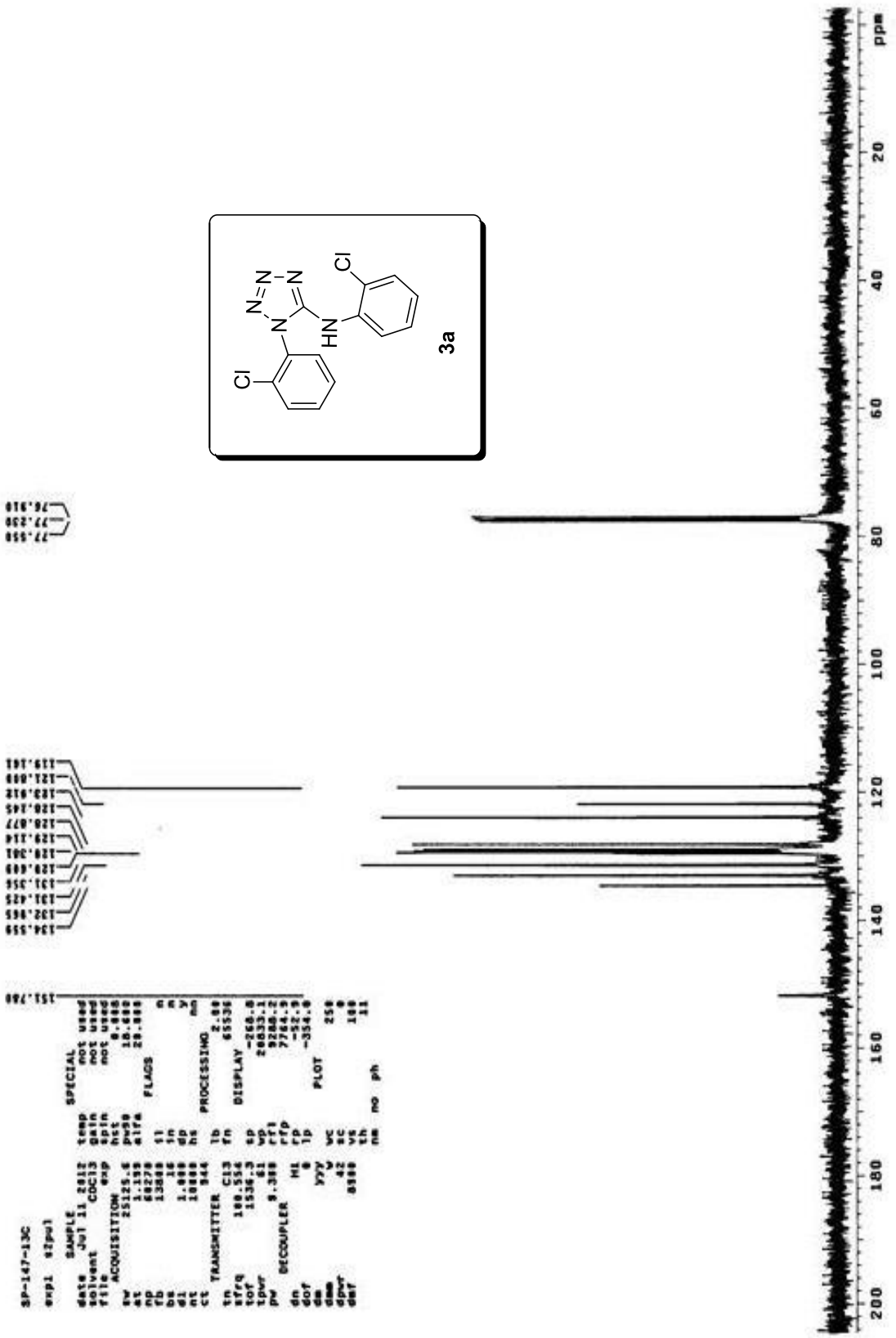


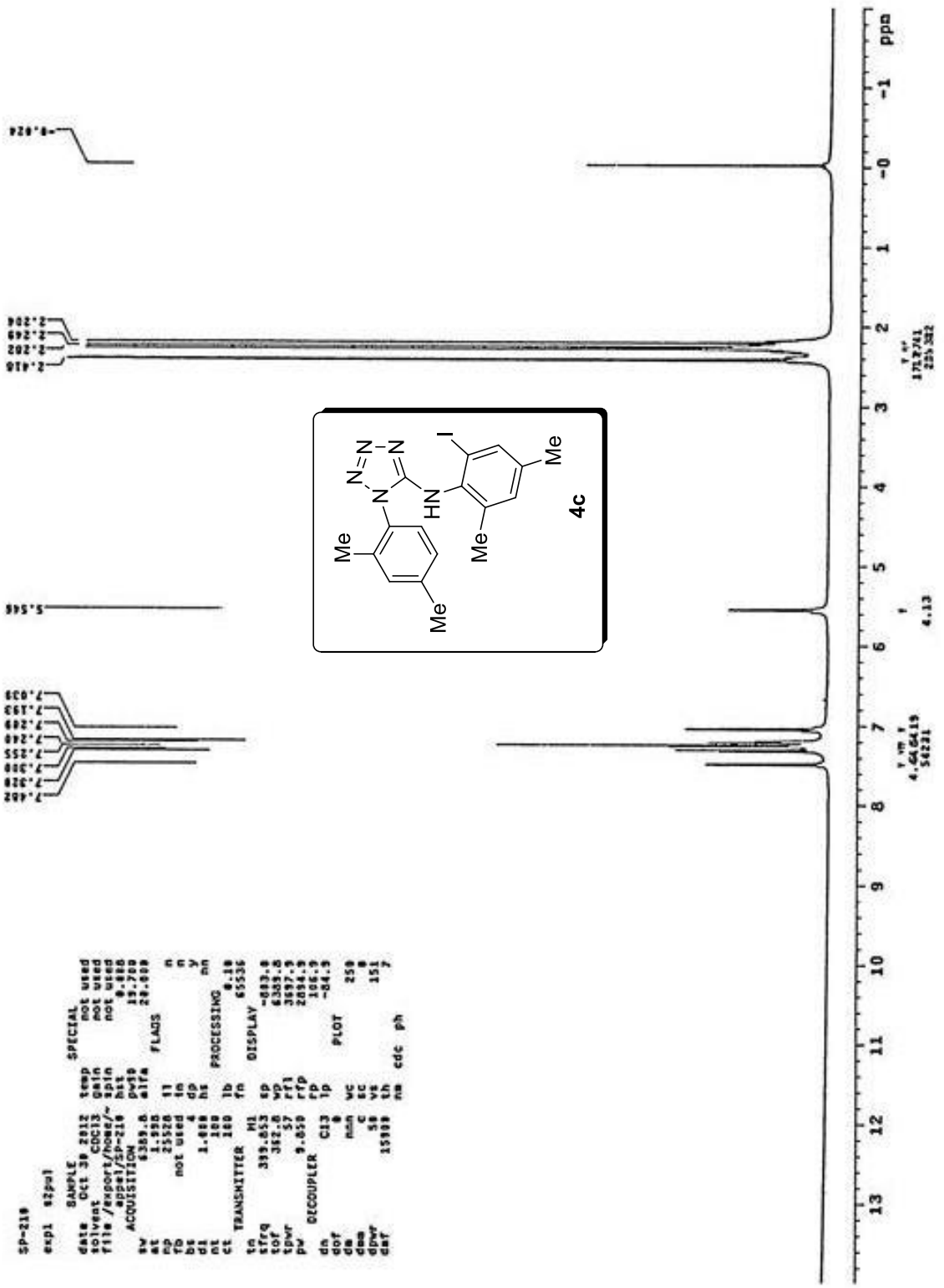

Br
Me
HN
N
N
N
Me
2c
ppm

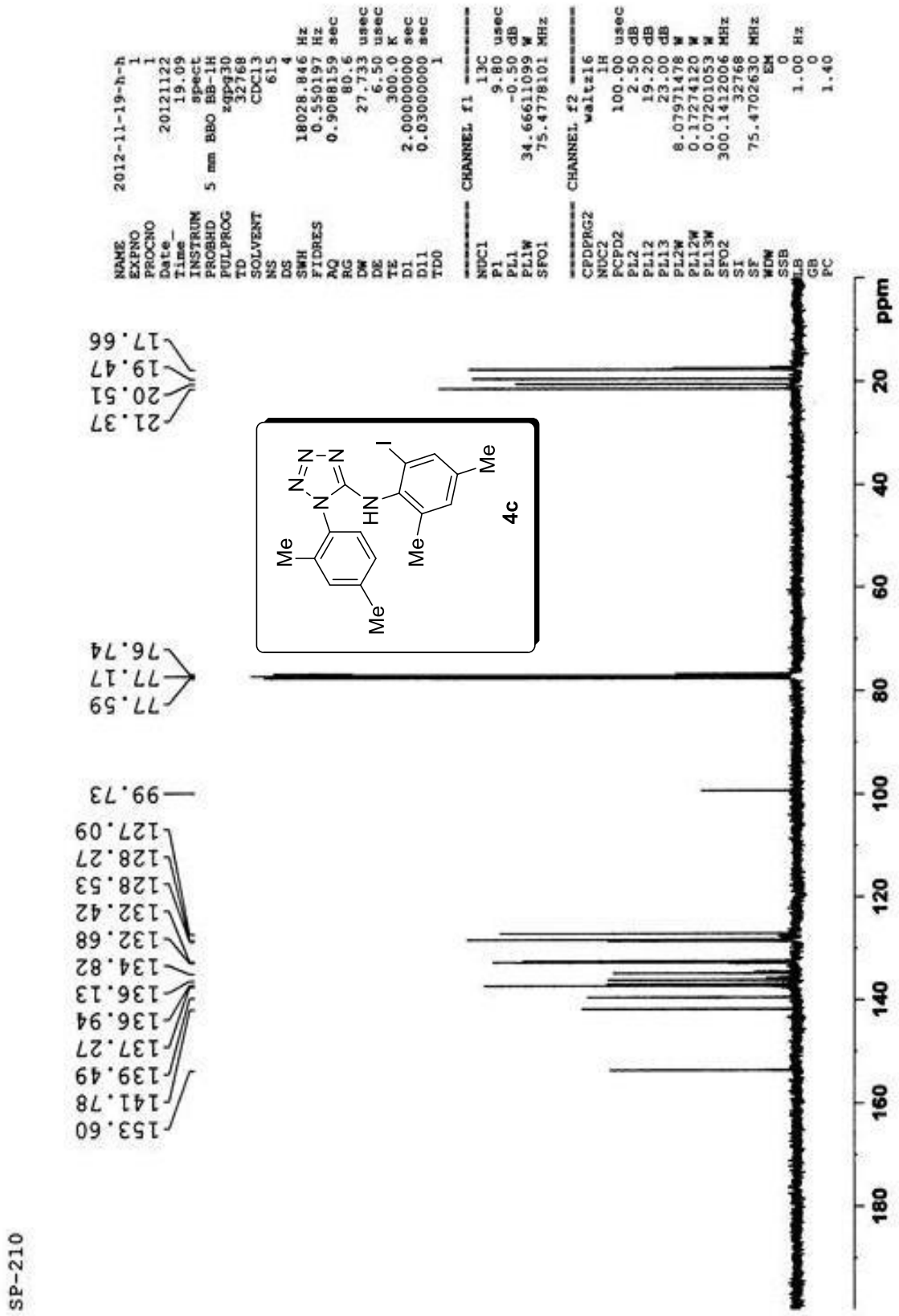

Br
NO2
HN
N
N
N
Cl
2j
ppm


SPp-NO2
NAME 2013-02-18-a-a
EXPNO 1
PROCNO 1
Date_ 20130218
Time 12.07
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 2440
DS 4
SWH 18028.846 Hz
FIDRES 0.550197 Hz
AQ 0.9088159 sec
RG 80.6
DW 27.733 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 9.80 usec
PL1 -0.50 dB
PL1W 34.66611099 W
SFO1 75.4778101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 2.50 dB
PL12 19.20 dB
PL13 23.00 dB
PL2W 8.07971478 W
PL12W 0.17274120 W
PL13W 0.07201053 W
SFO2 300.1412006 MHz
SI 32768
SF 75.4706787 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
38.40
38.68
38.96
39.23
39.51
39.79
40.07
76.57
77.00
77.19
77.43
111.09
117.78
123.69
127.47
128.14
128.70
128.75
130.35
130.50
132.41
141.20
141.83
150.64
Br
NO2
HN
Cl
2j
ppm
180
160
140
120
100
80
60
40
20


3a
Cl
HN
N
N
N
Cl
ppm


3a
Cl
HN
N
Cl
ppm
20
40
60
80
100
120
140
160
180
200


4c
Me
Me
Me
I
HN
N
N
N
ppm


SP-210
153.60
141.78
139.49
137.27
136.94
136.13
134.82
132.68
132.42
128.53
128.27
127.09
99.73
77.59
77.17
76.74
21.37
20.51
19.47
17.66
4c
Me
Me
Me
Me
I
HN
N
N
N
ppm
180
160
140
120
100
80
60
40
20

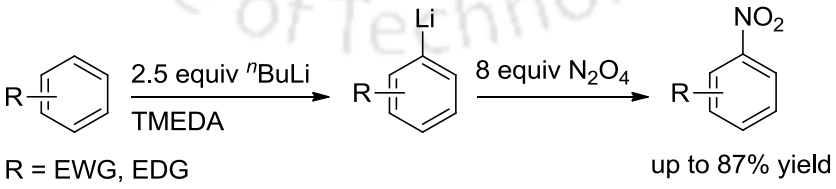
Chapter III

Room-Temperature Cu-Catalyzed *Ortho*-Nitration of Arenes *via* C−H Functionalization

Aromatic nitro compounds are versatile building blocks present in numerous compounds which got potential applications in various fields such as, pharmaceuticals and material chemistry.[1] They have also been widely utilized over the years as explosives and precursors for azo dyes. Moreover, the nitro group possesses an indispensable significance in organic synthesis due to its easy availability and transformation into other diverse functional groups. The electrophilic nitration of arenes has long been the classical synthetic approach for the preparation of the aromatic nitro compounds. However, these traditional processes often suffer from poor selectivity and imperfect functional group tolerance under harsh conditions.[2] To overcome these drawbacks, several approaches have been explored including the *ipso*-nitration,[3] the *ipso*-oxidation,[4] and the cross-coupling protocols of aryl halides, triflates and nonaflates with nitrite under transition-metal catalysis.[5,6] However, the use of prefunctionalized starting materials causes toxic-waste. In this context, the use of directed C-H functionalization is advantageous in attaining the regioselective products *via* C-H activation.[7-9] In chapter 2, we successfully demonstrated the use of aminotetrazole as a directing group for selective halogenation. In this chapter, we report a Cu-catalyzed aminotetrazole directed *ortho*-nitration of arene C-H bond.

3.1. Strategies for Nitration of Arenes

3.1.1. *ipso*-Nitration of Arenes

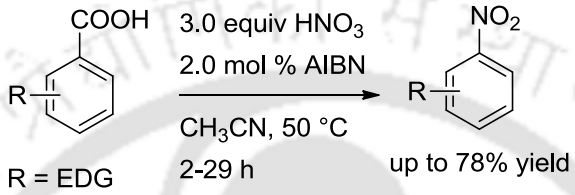


Scheme 1. Nitration of Phenyllithium using Dinitrogen tetroxide

In 1997, Eaton and co-workers developed a regioselective approach for the synthesis of nitroarenes using phenyllithiums in the presence of dinitrogen tetroxide (N_2O_4) at low

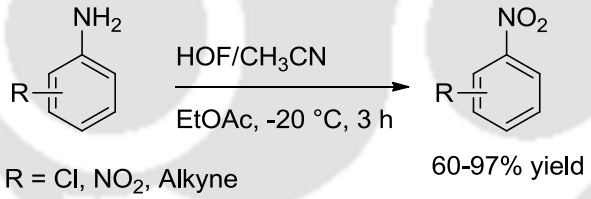
temperature of -70 °C (Scheme 1).[3a] The reaction is compatible with substrates bearing electron donating and electron withdrawing groups to afford the corresponding nitroarenes in high yields.

The AIBN catalyzed nitrodecarboxylation of benzoic acids using HNO_3 was reported by Roy and co-workers (Scheme 2).[4b] The reaction involves radical pathways rather than ionic which is reminiscent to Hunsdiecker-type halodecarboxylation reaction.

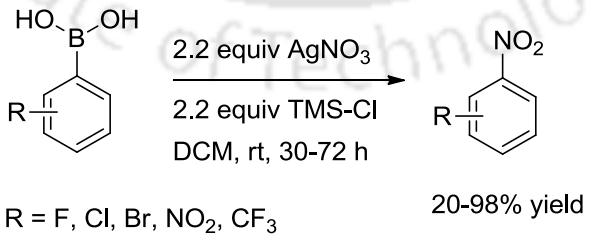


Scheme 2. Nitrodecarboxylation of Benzoic Acids

Tour and co-workers presented HOF as an oxidizer for electron-deficient anilines (Scheme 3).[4c] HOF was generated in situ by bubbling a 20% F_2 in helium mixture through 3% water in acetonitrile at -20 °C. The high yields of oxidized products make HOF a useful reagent for this reaction.



Scheme 3. Synthesis of Nitroarenes *via* Oxidation of Anilines

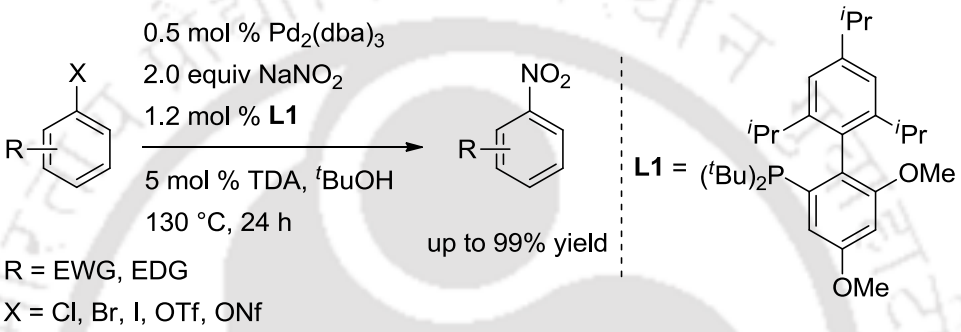


Scheme 4. *ipso*-Nitration of Arylboronic Acids

Olah and co-workers disclosed the synthesis of nitroarenes from aryl boronic acids *via ipso*-nitration (Scheme 4).[3b] The reaction was materialized using $AgNO_3$ and TMSCl system

in DCM at room temperature in moderate to good yields This method is operationally simple and selective under milder reaction conditions.

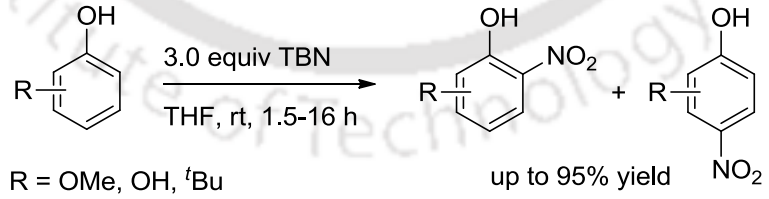
Buchwald and co-workers demonstrated Pd-catalyzed conversion of aryl chlorides, triflates and nonaflates to aryl nitro compounds in the presence of phase transfer catalyst (TDA) using $NaNO_2$ as a nitration source in ^tBuOH at 130 °C (Scheme 5).[5a] This reaction shows rate of transmetalation in the order of Cl > Br > I. A wide range of functional groups are tolerated under these conditions, providing the desired nitroarenes in high yields.



Scheme 5. Pd-Catalyzed *ipso*-Nitration of Arenes

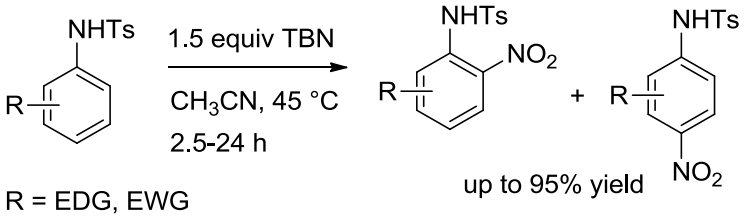
3.1.2. Nitration of Arenes

Savinov and co-workers developed the nitration of arenes using operationally simple *tert*-butyl nitrite (TBN) as a nitration source for broad range of phenolic substrates in THF at room temperature (Scheme 6).[6c] The protocol provides a mixture of *ortho* and *para* nitro derivatives.



Scheme 6. Nitration of Phenolic Substrates

Arns group presented nitration of aryl sulfonamides using TBN at mild reaction conditions (Scheme 7).[6b] This reaction was also exhibited a high degree of selectivity at *ortho* and *para* positions for sulfonamide functionalized aryl derivatives.



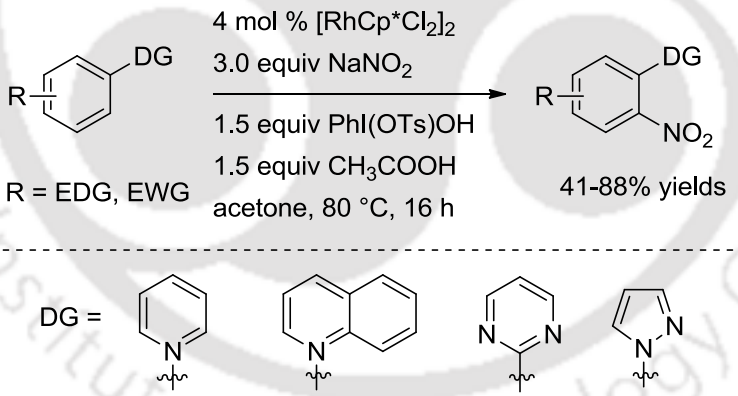
Scheme 7. Nitration of Aromatic Sulfonamides

3.1.3. Chelation Assisted *Ortho*-Nitration of Arenes

The directed C-H nitration of arenes using transition metals has recently ermerged as an alternative tool for the standard cross-coupling strategies.

3.1.3.1. Rh-Catalyzed *Ortho*-Nitration of Arenes

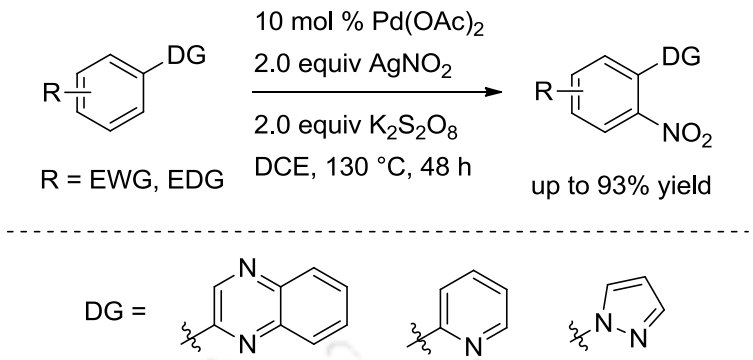
Li and co-workers reported the Rh-catalyzed regioselective C-H nitration of arenes directed by various nitrogen containing heterocycles such as pyridine, pyrazole and pyrimidine rings using $NaNO_2$ as a nitration source (Scheme 8).[7] In this transformation, hypervalent iodine acts as an oxidizing agent for the single-electron oxidation of Rh^{III} to Rh^{IV}.



Scheme 8. Rh-Catalyzed *Ortho*-Nitration of Arenes

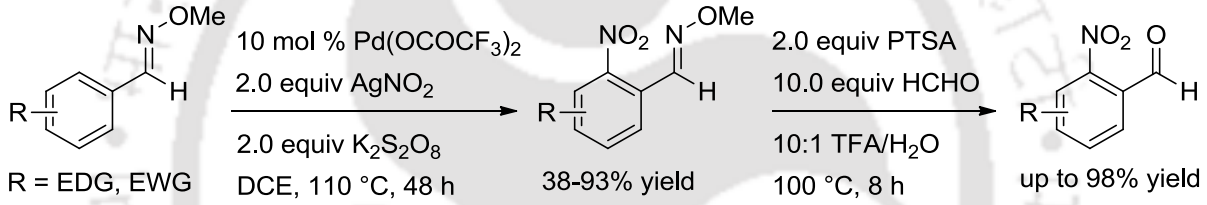
3.1.3.2. Pd-Catalyzed *Ortho*-Nitration of Arenes

Pd-catalyzed direct *ortho*-nitration of aryl C-H bond using nitrogen containing heterocycles was demonstrated by Xu group (Scheme 9) .[8a] This reaction uses $AgNO_2$ as nitration source and $K_2S_2O_8$ as oxidizing agent with various directing groups such as isoquinoline, pyridine, and pyrazole.



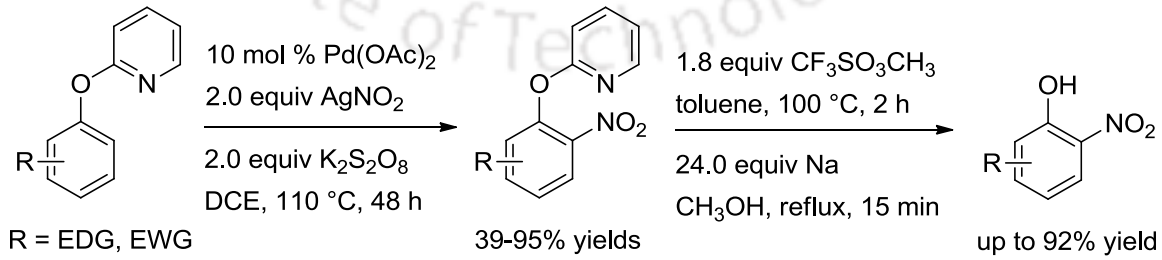
Scheme 9. Regioselective Nitration of Arenes

Liu and co-workers employed Pd-$K_2S_2O_8$ with $AgNO_2$ for *ortho*-nitration of arenes (Scheme 10).[8b] The reaction involves *ortho*-methyl aldoxime group as a directing group, which can be cleaved to furnish *ortho*-nitrobenzaldehydes.



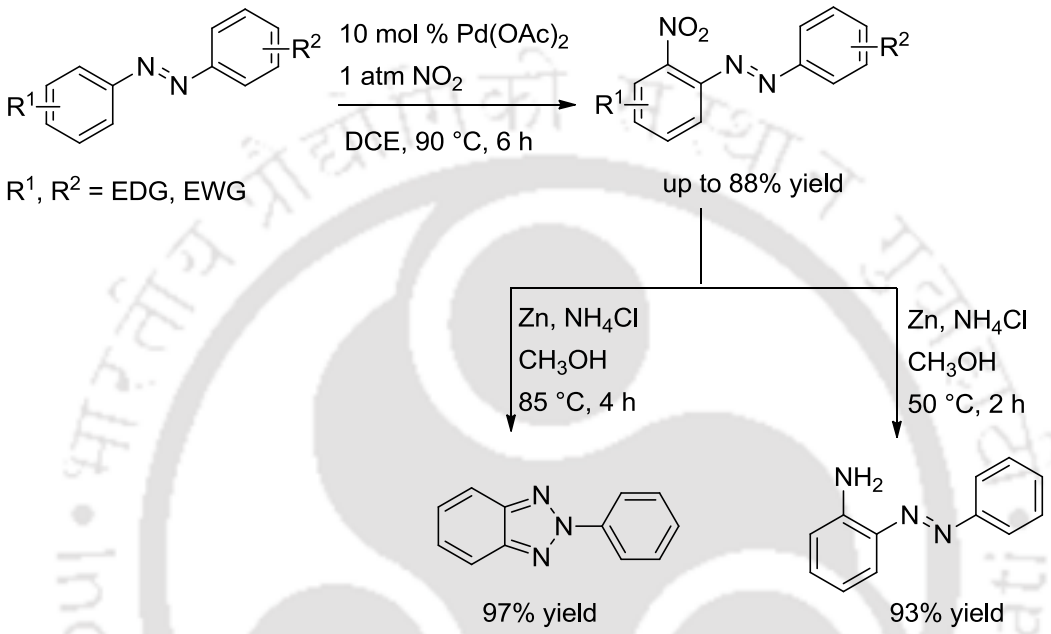
Scheme 10. Pd-Catalyzed *Ortho*-Nitration of Oximes

The same group developed a three-step processes for the *ortho*-nitration of phenols using 2-pyridinyloxy directing group (Scheme 11).[8c] The substrates bearing various substituents such as halo, alkyl, aryl, methoxy, trifluoromethoxy, acetyl and cyano are tolerated to give the target products in good yields.



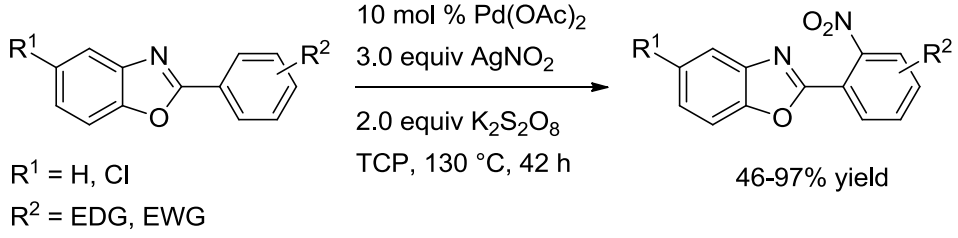
Scheme 11. Synthesis of *Ortho*-Nitrophenol Derivatives

Pd-catalyzed azo group directed *ortho*-nitration of arenes was demonstrated by Sun and co-workers using nitrogen dioxide (NO_2) as a nitro source (Scheme 12).[8d] The synthetic utility of the resulting nitrated azobenzenes was demonstrated by reducing them with Zn/NH_4Cl to give the corresponding amines, which can be cyclized subsequently to provide the respective benzotriazoles.



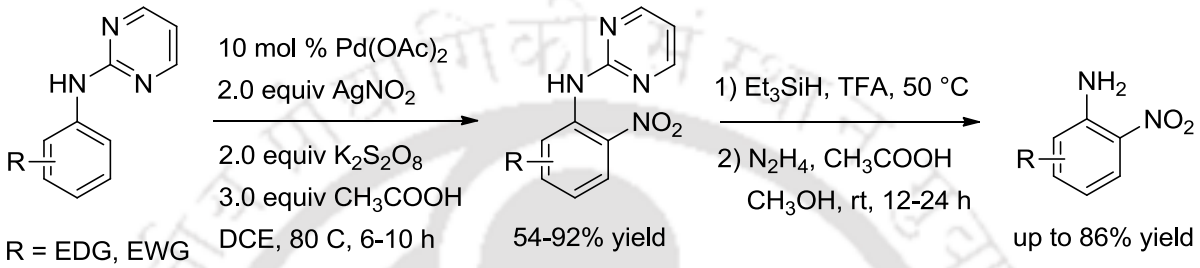
Scheme 12. Pd-Catalyzed *Ortho*-Nitration of Azo Compounds

Pd-catalyzed *ortho*-nitration of 2-arylbenzoxazoles has been described using $AgNO_2$ in the presence of oxidizing agent $K_2S_2O_8$ in TCP (trichloropropane) at high temperature (Scheme 13).[8e] The transformation featured a good functional group compatibility for both electron donating and -withdrawing substituents on phenyl ring and proceeds smoothly to give the corresponding nitration products.



Scheme 13. *Ortho*-Nitration of 2-Arylbenzoxazoles

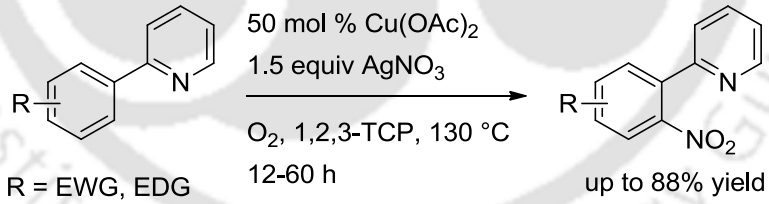
Kapur and co-workers disclosed a Pd-catalyzed regioselective nitration of arenes using aminopyrimidine as a directing group in the presence of $AgNO_2$, $K_2S_2O_8$ and AcOH in DCE (Scheme 14).[8f] The important outcome of this reaction is the production of nitrated anilines by the cleavage of the directing group, accomplished by reducing the pyrimidine ring using triethylsilane in TFA, followed by the treatment of N_2H_4/CH_3COOH in CH_3OH at room temperature.



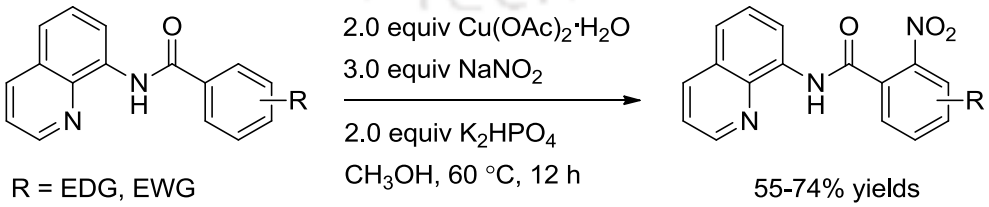
Scheme 14. Pyrimidine Directed Regioselective Nitration of Arenes

3.1.3.3. Cu-Catalyzed *Ortho*-Nitration of Arenes

Liu and co-workers reported the Cu-mediated *ortho*-nitration of arenes using 2-arylpyridine as a chelation source in 1,2,3-trichloropropane (1,2,3-TCP) under molecular oxygen, leading to the synthesis of nitroarenes with high regioselectivity (Scheme 15).[9a]



Scheme 15. Cu-Catalyzed *Ortho*-Nitration of Arenes



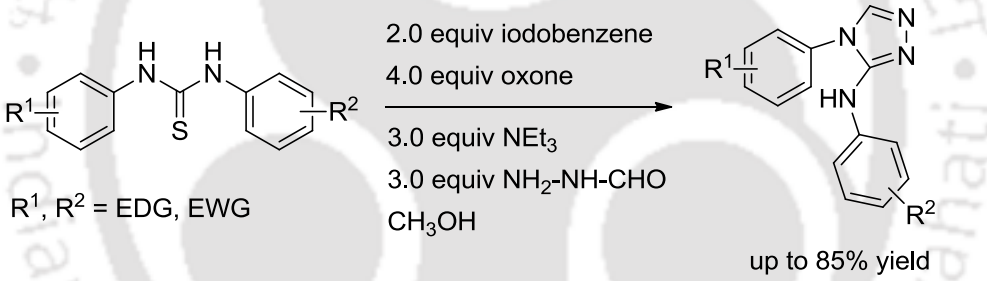
Scheme 16. Chelation-Assisted *Ortho*-C-H Nitration

Tan and co-workers reported a Cu-catalyzed *ortho*-nitration of 8-aminoquinolline amide with $NaNO_2$ (Scheme 16).[9b] In this reaction, dinitration could be achieved by altering the reaction conditions to AgOAc instead of K_2HPO_4 in DMF. The directing group can be removed under basic conditions to afford valuable benzoic acid derivatives.

3.2. Present Study

We have studied the Cu-catalyzed *ortho*-nitration of *N*,1-diphenyl-1*H*-tetrazol-5-amine and *N*,4-diaryl-3-amino-1,2,4-triazoles *via* chelation assisted C-H functionalization strategy. Further, we have developed a protocol for the removal of directing group in presence of base.

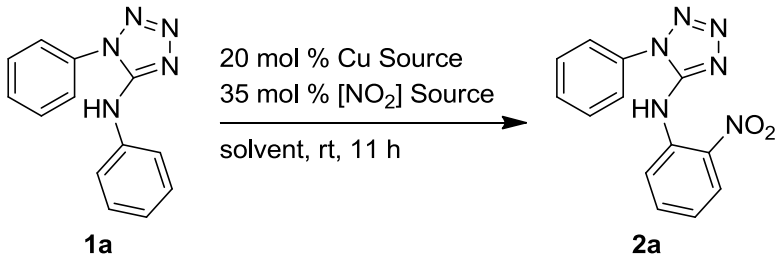
Synthesis of *N*,1-diphenyl-1*H*-tetrazol-5-amines (1a-n). The starting precursors, *N*,4-diaryl-3-amino-1,2,4-triazoles were prepared from 1,3-disubstituted thioureas in presence of hypervalent iodine (III) reagent, base and formyl hydrazide in methanol *via* electrocyclization processes (Scheme 17).[10]



Scheme 17. Synthesis of *N*,4-diaryl-3-amino-1,2,4-triazoles

First, the optimization of reaction conditions for nitration was carried out using *N*-aryl-1-aryl-1*H*-tetrazol-5-amine **1a** as a standard substrate using a series of copper salts as catalyst with different nitro sources and solvents (Table 1). To our delight, the reaction occurred selectively at the *ortho*-position of the *N*-aryl ring without affecting the 1-aryl ring to afford **2a** in 95% yield when the substrate **1a** was stirred with $CuCl_2 \cdot 2H_2O$ (20 mol %) and $Fe(NO_3)_3 \cdot 9H_2O$ (35 mol %) in 1,2-dichloroethane (DCE) for 11 h at room temperature. Among the copper sources screened, $CuCl_2 \cdot 2H_2O$ exhibited superior results compared to $Cu(OAc)_2 \cdot H_2O$, $Cu(OTf)_2$, $CuSO_4 \cdot 5H_2O$, $Cu(NO_3)_2 \cdot 3H_2O$, CuI, $CuBr_2$, CuBr, and CuCl (entries 1−9).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	Cu source	[NO_2] source	solvent	yield (%)
1	$Cu(OAc)_2 \cdot H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	52
2	$Cu(OTf)_2$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	48
3	$CuSO_4 \cdot 5H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	trace
4	CuI	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	44
5	CuCl	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	84
6	$CuBr_2$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	86
7	$Cu(NO_3)_2 \cdot 3H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	10
8	CuBr	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	74
9	**$CuCl_2 \cdot 2H_2O$**	**$Fe(NO_3)_3 \cdot 9H_2O$**	**DCE**	**95**
10[b]	$CuCl_2 \cdot 2H_2O$	$Ca(NO_3)_2 \cdot 4H_2O$	DCE	trace
11	$CuCl_2 \cdot 2H_2O$	$Bi(NO_3)_3 \cdot 5H_2O$	DCE	21
12[c]	$CuCl_2 \cdot 2H_2O$	$AgNO_3$	DCE	26
13[d]	$CuCl_2 \cdot 2H_2O$	$NaNO_2$	DCE	24
14	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCM	89
15	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	THF	trace
16	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	toluene	74
17	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DMF	n.d.
18	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	CH_3CN	62
19[e]	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	61

20	-	$Fe(NO_3)_3·9H_2O$	DCE	trace
21[f]	$Cu(NO_3)_2·3H_2O$	-	DCE	50

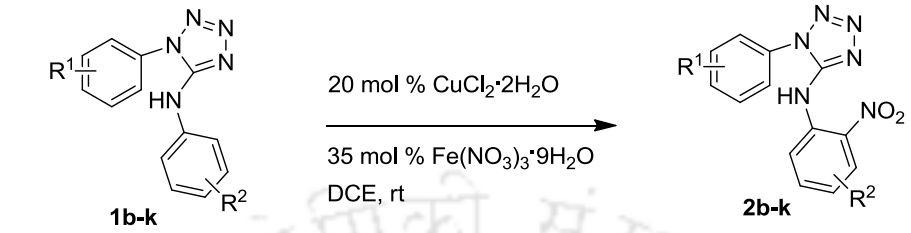
[a] Reaction conditions: *N*,1-diphenyl-1*H*-tetrazol-5-amine **1a** (1 mmol), Cu source (20 mol %), $Fe(NO_3)_3.9H_2O$ (35 mol %), solvent (3 mL), rt, 11 h. [b] $Ca(NO_3)_3·4H_2O$ (50 mol %) was used. [c] $AgNO_3$ (1.1 equiv) was used. [d] $NaNO_2$ (1.1 equiv) was used. [e] $CuCl_2·2H_2O$ (10 mol %) was used. [f] $Cu(NO_3)_2·3H_2O$ (100 mol %) was used.

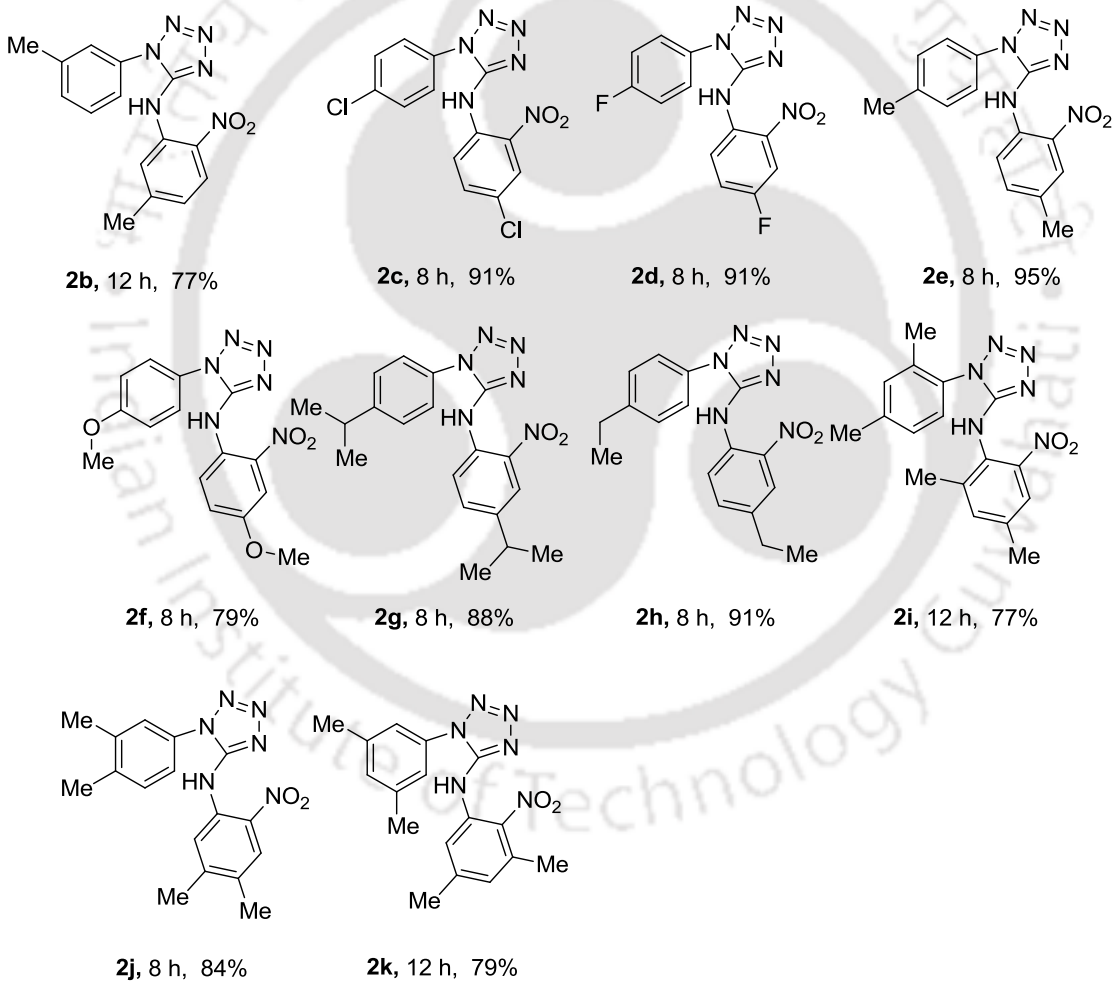
In a set of additives examined, $Fe(NO_3)_3·9H_2O$ gave the best results, whereas $Ca(NO_3)_2·4H_2O$, $AgNO_3$, $Bi(NO_3)_3·5H_2O$, and $NaNO_2$ afforded the target product in <26% yield (entries 10−13). In case of solvents, DCE was found to be the solvent of choice giving the highest yield, whereas dichloromethane (DCM), toluene and CH_3CN afforded **2a** in 62 −89% yields. While, THF and DMF produced inferior results (entries 14 −18). Decreasing the amount of the Cu source (10 mol %) led to the formation of **2a** in 61% yield (entry 19). Control experiments confirmed that the absence of Cu source could not give the desired product **2a** was not observed and the starting material **1a** was recovered intact (entry 20). Whereas, the use of a stoichiometric amounts of $Cu(NO_3)_2·3H_2O$ without $Fe(NO_3)_3·9H_2O$ furnished **2a** in 50% yield (entry 21).

With the optimized conditions in hand, we sought to further explore the reaction scope of substrates having symmetrical and unsymmetrical substituents on the aryl rings (Table 2-3). First, the symmetrical substituents on the aryl rings **1b-h** having 3-methyl, 4-chloro, 4-fluoro, 4- methyl, 4-methoxy, 4- isopropyl, and 4-ethyl substituents on the aryl rings readily afforded to give the target nitration products **2b-h** in 77-95% yields. Similarly, the substrates **1i-k** containing 2,4-, 3,4-, and 3,5-dimethyl substituents proceeded smoothly to give the corresponding nitration products **2i-k** in 77-84% yields. Likewise, the substrates having the unsymmetrical substituents on the aryl rings were treated with the optimized reaction conditions (Table 3). While, the substrates **1l-p** with 2-chloro, 4-fluoro, 4-isopropyl, naphthyl, and 4-nitro substituents readily underwent reaction to produce the target nitration products **2l-p** in 75-94% yields. The substrates **1q** having 2-fluoro and 4-ethyl substituents underwent reaction to furnish **2q** in 86% yield. In addition, the substrates **1r-v** having 2,6-dimethyl, 4- methyl, 4-nitro, 4-acetanilide, and 4-cyano substituents furnish **2r-v** in 77-93% yields. Next, the scope of the reaction was extended for the nitration of *N*,4-diaryl-3-amino-1,2,4-triazoles (Table 4). Under the optimized reaction conditions, the substrate **3a**.

proceeded smoothly with greater reactivity compared to the corresponding 5-aminotetrazole derivative to yield the nitration product **4a** in 6 h with 84% yield.

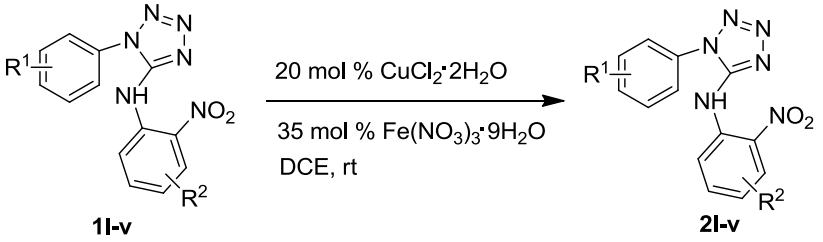
Table 2. Reaction of Symmetrical *N*,1-Diaryl-5-aminotetrazoles[a, b]

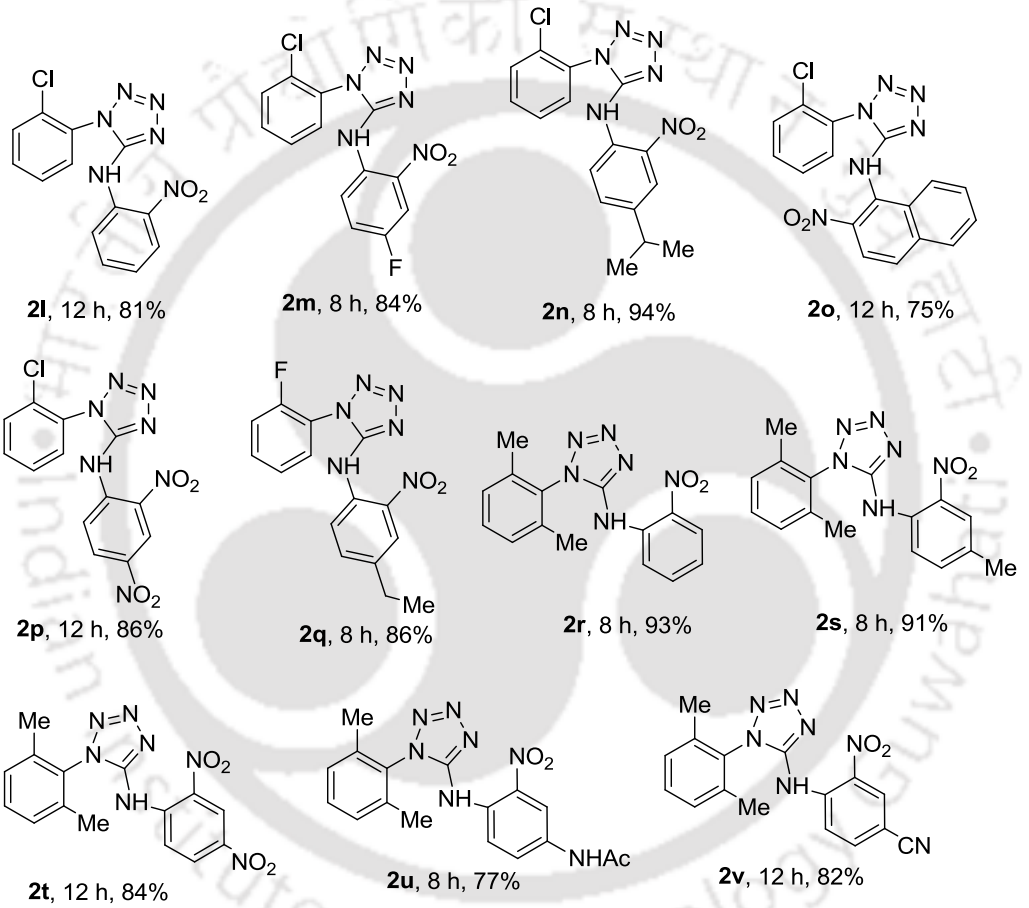




[a] Reaction conditions: *N*-phenyl-1*H*-tetrazol-5-amine **1b-k** (1 mmol), $CuCl_2·2H_2O$ (20 mol %), $Fe(NO_3)_3·9H_2O$ (35 mol %), DCE (3 mL), rt. [b] Isolated yield.

Table 3. Reaction of Unsymmetrical*N*,1-Diaryl-5-aminotetrazoles[a, b]

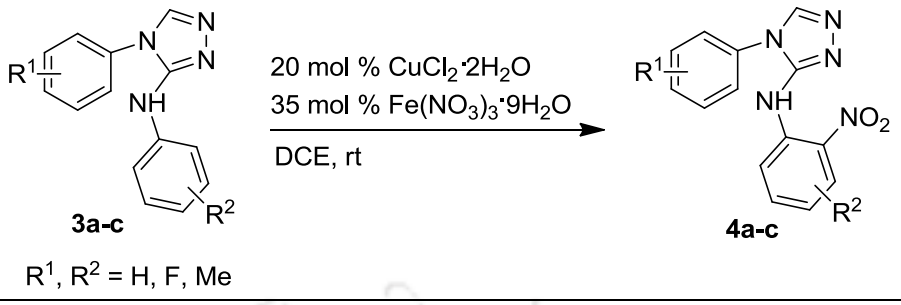


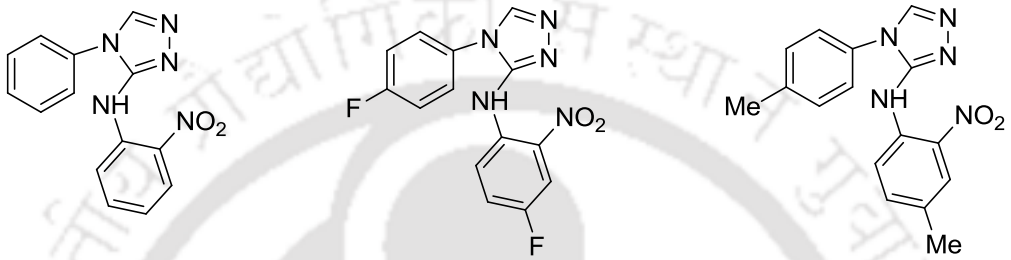


[a] Reaction conditions: *N*-phenyl-1*H*-tetrazol-5-amine **1l-w** (1 mmol), $CuCl_2 \cdot 2H_2O$ (20 mol %), $Fe(NO_3)_3 \cdot 9H_2O$ (35 mol %), DCE (3 mL), rt. [b] Isolated yield.

Likewise, the substrates having symmetrical substituents on the aryl rings such as, 4-fluoro and 4-methyl **3b** and **3c** groups readily underwent the reaction to afford **4b** and **4c** in 6 h with 82% and 87% yields, respectively.

Table 4. Reaction of *N*,4-Diaryl-3-amino-1,2,4-triazoles[a, b]



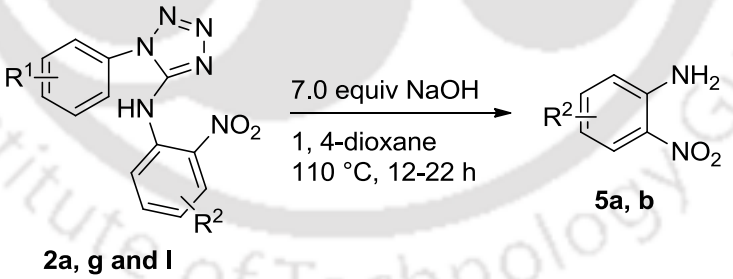


4a, 6 h, 84% **4b**, 6 h, 82% **4c**, 6 h, 87%

[a] Reaction conditions: *N*,4-diphenyl-4*H*-1,2,4-triazol-3-amine **3a-c** (1 mmol), $CuCl_2 \cdot 2H_2O$ (20 mol %), $Fe(NO_3)_3 \cdot 9H_2O$ (35 mol %), DCE (3 mL), rt. [b] Isolated yield.

Finally, we attempted a removal of the tetrazole directing group using for the products **2a**, **2g**, and **2l** (Table 5). The reaction readily occurred with NaOH in 1,4-dioxane at 110 °C to

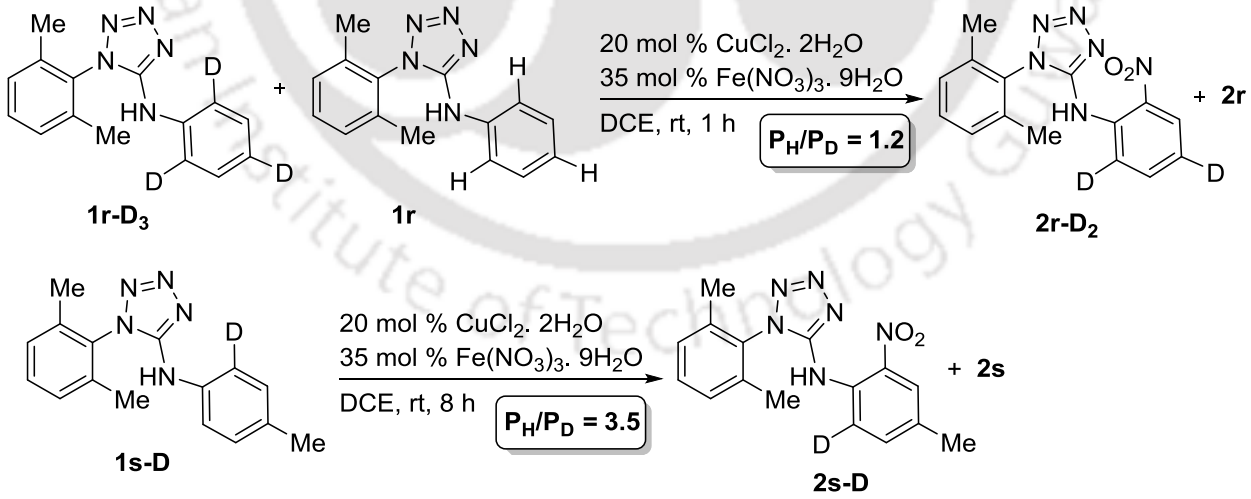
Table 5. Removal of Directing Group[a, b]



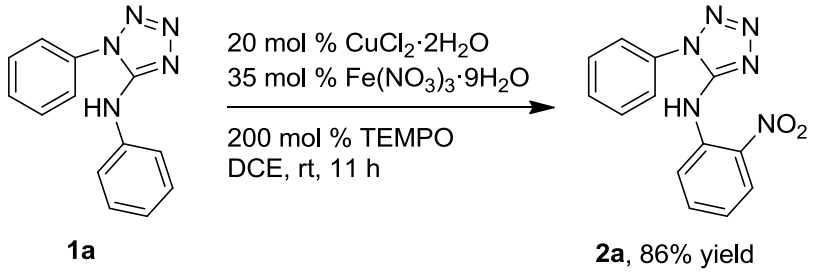
entry	substrate	product	time (h)	yield (%)
1	R^1, R^2 = H (**2a**)	R^2 = H (**5a**)	22	78
2	R^1, R^2 = ^{i}Pr (**2g**)	R^2 = ^{i}Pr (**5b**)	12	87
3	R^1 = 2-Cl, R^2 = H (**2l**)	R^2 = H (**5a**)	22	84

[a]Reaction conditions: *N*-(2-Nitrophenyl)-1-phenyl-1*H*-tetrazol-5-amine **2a,g** and **l** (1 mmol), NaOH (5 equiv), 1,4-dioxane (3 mL), 110 °C. [b] Isolated yield.

furnish the corresponding 2-nitroaniline derivatives in good yields.[11] The proposed mechanism is shown in Scheme 20. The intermolecular kinetic isotope studies of the substrates **1r** and **1r-D$_3$** gave P_H/P_D = 1.2 (21% conversion), whereas, intramolecular kinetic isotope experiments of the substrate **1s-D** afforded P_H/P_D = 3.5 (Scheme 18).[12] These results suggest that the substrate binding step is the product determining step.[13] Then, the application of a radical scavenger studied. However, TEMPO does not inhibit the rate of the reaction, which suggests that the reaction may not involve a radical intermediate (Scheme 19).[14] Moreover, the ESI-MS studies of the crude reaction mixture of **1a** before work up revealed the presence of four major species: [**2a** + H]$^+$ and three copper complexes {[**2a**·Cu]$^+$, [(**2a**)$_2$·Cu]$^+$ and [(**2a**)$_2$·CuCl]$^+$} (Figure 1).[15] While, attempts to isolate the species as single crystals remained unsuccessful. Inaddition, $CuCl_2·2H_2O$ and $Fe(NO_3)_3·9H_2O$ are were insoluble in 1,2-dichloroethane, however, with substrate **1a** they readily dissolve to give a yellow solution, which suggest that the substrate **1a** may first bind with the hydrated $CuCl_2$ to give a soluble intermediate ***a*** that may undergo reaction with $Fe(NO_3)_3·9H_2O$ to furnish the intermediate ***b*** (Scheme 20).[16] The subsequent intramolecular *ortho*-nitration via an aromatic electrophilic substitution can afford the intermediate ***c***, which can give the target product **2**, and the hydrated CuX_2 to complete the catalytic cycle.



Scheme 18. Kinetic Isotope Experiments



Scheme 19. Radical Scavenger Experiment

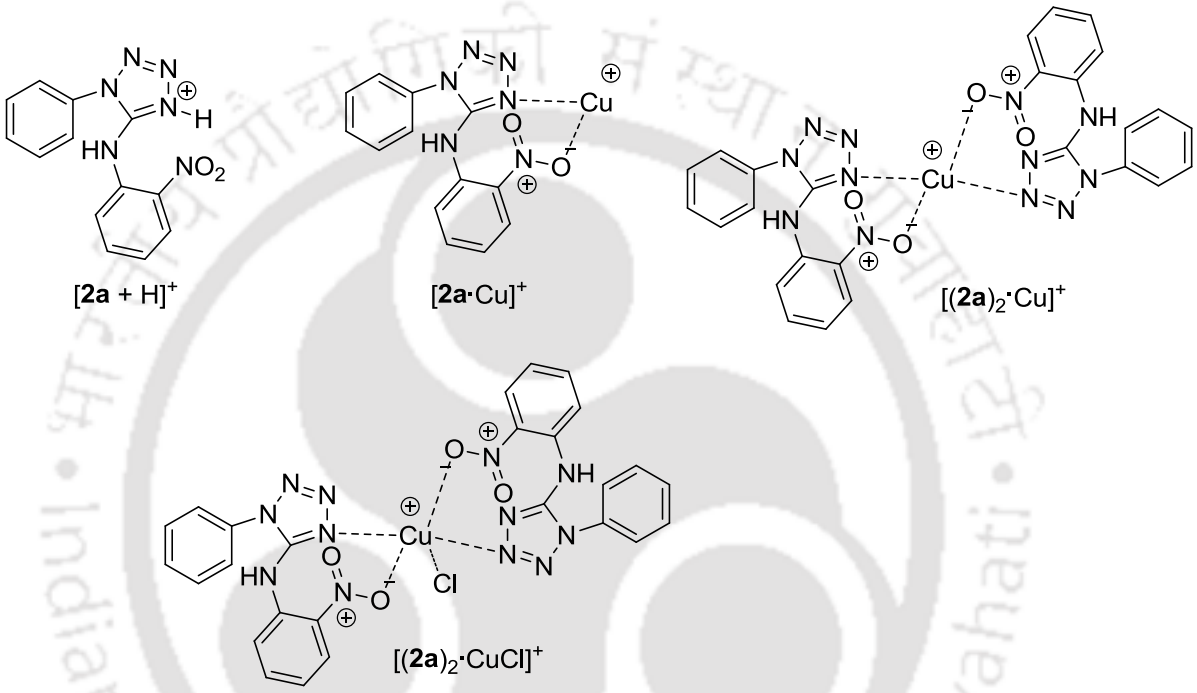
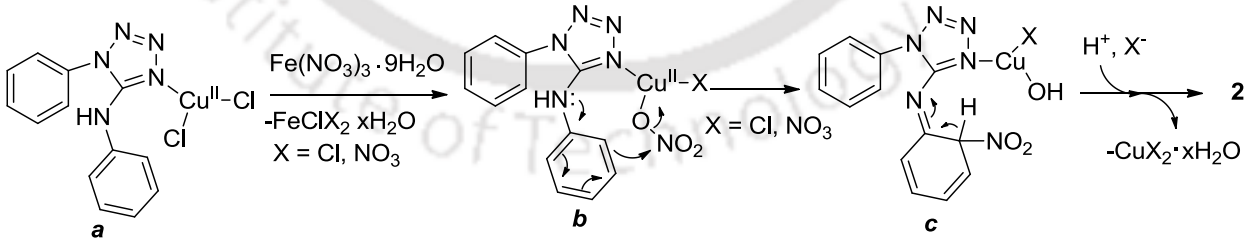


Figure 1. Major Species Identified During ESI-MS Analysis of the Reaction Mixture of **1a**



Scheme 20. Proposed Catalytic Cycle

In summary, Cu-catalyzed chemo- and regioselective nitration of arenes using iron(III) nitrate as nitration source was demonstrated. The reaction shows good functional group tolerance in attaining the product with excellent selectivity. we have further extended protocol to 3-amino-1,2,4-triazoles. Finally, synthetic utility of the protocol has been

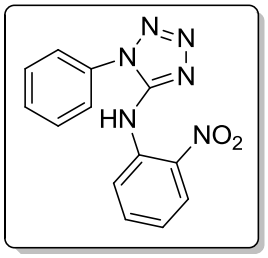
demonstrated by the removal of 5-aminotetrazoles to afford substituted 2-nitroanilines in good yields.

3.3. Experimental Section

3.3.1. General Information. $Cu(OTf)_2$ (98%), CuI (98%) and CuCl (90%) purchased from Aldrich, $Cu(OAc)_2{\cdot}H_2O$ (98%), $CuBr_2$ (98%), $Cu(NO_3)_2{\cdot}3H_2O$ (99%), $CuCl_2{\cdot}2H_2O$ (99%) and $Fe(NO_3)_3{\cdot}9H_2O$ (98%) purchased from Merck and $CuSO_4{\cdot}5H_2O$ (99%) obtained from Rankem were used as received. The solvents were purchased from Rankem and dried according to standard procedure prior to use. 5-Aminotetrazoles and 3-amino-1,2,4-triazoles were prepared according to reported procedure.[10] Purification of the reaction products was carried out by column chromatography using Rankem silica gel (60-120 mesh). Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on Bruker Avance III 600, DRX-400 Varian spectrometer and Bruker Ultrashield^{TM} 300 using $CDCl_3$ and DMSO-d_6 as solvent and Me_4Si as internal standard. Chemical shifts (δ) were reported in ppm and spin-spin coupling constants (J) were given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Thermo Fisher Scientific spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS Instrument (model HAB 273). Single crystal was measured on a Super Nova, single source at offset, Eos diffractometer. Using Olex2, structure was solved with the superflip structure solution program using charge flipping and refined with the Olex2 refine refinement package using Gauss−Newton minimisation.

3.3.2. General Procedure for *Ortho*-Nitration of Arenes. To a stirred solution of 1,*N*-diaryl-5-aminotetrazole or *N*,1,-diaryl-3-amino-1,2,4-triazoles 3a-c (1 mmol) in DCE (3 mL), $CuCl_2{\cdot}2H_2O$ (20 mol %) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol %) were added at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture, and the resultant solution was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent to afford analytically pure products.

3.4. Characterization Data of 2a-v, 4a-c



***N*-(2-Nitrophenyl)-1-phenyl-1*H*-tetrazol-5-amine 2a.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.61; yellow solid; 268 mg, yield 95%.

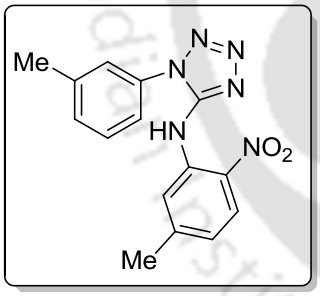
Mp 186-187 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (br s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 8.26 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.77-7.59 (m, 6H), 7.16-7.12 (m, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 150.8, 137.1, 135.9, 135.0, 132.4, 131.2, 130.9, 126.4, 124.8, 122.4, 120.2.

FT-IR (KBr) 3228, 2854, 1598, 1564, 1538, 1525, 1381, 1336, 1280, 1121, 1092, 1019 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{10}N_6O_2$ 283.0938, found 283.0948.



***N*-(5-Methyl-2-nitrophenyl)-1-(*m*-tolyl)-1*H*-tetrazol-5-amine 2b.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.66; yellow solid; 239 mg, yield 77%.

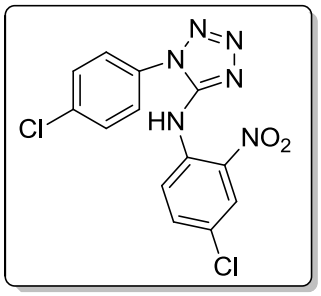
Mp 188-189 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 8.72 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.43-7.37 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 1H), 2.49 (s, 3H), 2.48 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 150.8, 149.4, 135.9, 133.0, 1321.3, 131.9, 130.6, 126.4, 125.2, 123.5, 121.7, 120.0, 22.5, 21.6.

FT-IR (KBr) 3095, 2923, 1592, 1534, 1489, 1324, 1281, 1161, 1091, 870, 846 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1251, found 311.1251.



***N*-(4-Chloro-2-nitrophenyl)-1-(4-chlorophenyl)-1*H*-tetrazol-5-amine 2c.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.69; yellow solid; 318 mg, yield 91%.

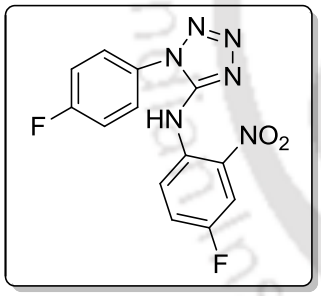
Mp 187-188 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (br s, 1H), 8.96 (d, *J* = 9.2 Hz, 1H), 8.27 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.5, 137.6, 137.2, 135.1, 134.4, 131.3, 130.7, 127.8, 126.0, 125.9, 121.7.

FT-IR (KBr) 3259, 2921, 1639, 1538, 1499, 1341, 1275, 1245, 1154, 1091, 903, 838 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8Cl_2N_6O_2$ 351.0167, found 351.0163.



***N*-(4-Fluoro-2-nitrophenyl)-1-(4-fluorophenyl)-1*H*-tetrazol-5-amine 2d.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.62; yellow solid; 289 mg, yield 91%.

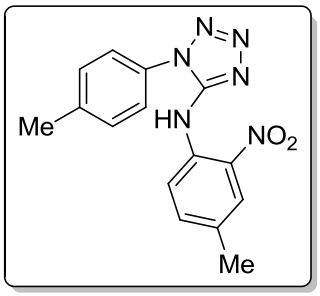
Mp 170-171 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.59 (br s, 1H), 9.00-8.98 (m, 1H), 7.99 (dd, *J* = 8.4, 3.0 Hz. 1H), 7.62-7.59 (m, 2H), 7.55-7.52 (m, 1H), 7.41-7.38 (m, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.7, (d, *J* = 252.0 Hz), 157.4 (d, *J* = 245.3 Hz), 150.8, 134.8, 132.4, 128.2, 127.2 (d, *J* = 9.0 Hz), 125.0 (d, *J* = 22.5 Hz), 122.0 (d, *J* = 7.5 Hz), 118.3 (d, *J* = 22.5 Hz), 112.8 (d, *J* = 27.0 Hz).

FT-IR (KBr) 3260, 3091, 2923, 1598, 1576, 1537, 1513, 1468, 1384, 1336, 1284, 116, 1137, 1090, 949, 843 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8F_2N_6O_2$ 319.0750, found 319.0748.



***N*-(4-Methyl-2-nitrophenyl)-1-(*p*-tolyl)-1*H*-tetrazol-5-amine 2e.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.73; yellow solid; 295 mg, yield 95%.

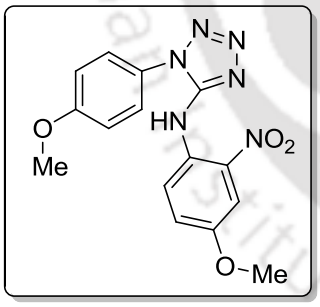
Mp 192-193 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.63 (br s, 1H), 8.83 (d, *J* = 8.8 Hz, 1H), 8.05 (s, 1H), 7.56 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45 (s, 4H), 2.48 (s, 3H), 2.38 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.9, 141.6, 138.1, 134.7, 133.7, 132.5, 131.4, 129.8, 126.0, 124.6, 120.1, 21.6, 20.6.

FT-IR (KBr) 3083, 2922, 2852, 1594, 1524, 1463, 1333, 1303, 1247, 1116, 927, 811 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1251, found 311.1251.

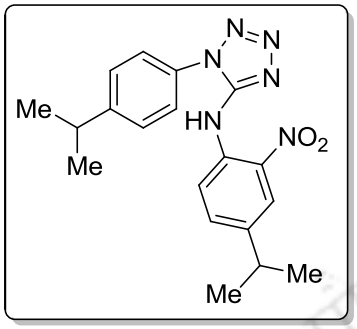


***N*-(4-Methoxy-2-nitrophenyl)-1-(4-methoxyphenyl)-1*H*-tetrazol-5-amine 2f.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.36; brown solid; 270 mg, yield 79%.

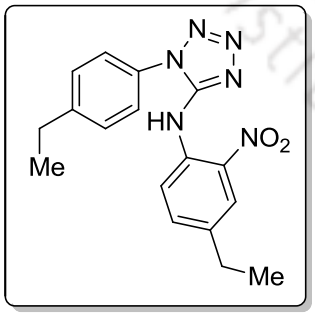
Mp 166-167 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 8.87 (d, *J* = 9.6, 2.8 Hz, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.48-7.45 (m, 2H), 7.36 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.15-7.11 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 161.6, 154.3, 151.2, 135.2, 130.1, 126.5, 125.3, 124.8, 121.6, 115.9, 108.6, 56.2, 55.9.

FT-IR (KBr) 3259, 2924, 2852, 1599, 1562, 1534, 1384, 1268, 1245, 1024, 998, 830 cm^{-1}
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_6O_4$ 343.1149, found 343.1153.



***N*-(4-Isopropyl-2-nitrophenyl)-1-(4-isopropylphenyl)-1*H*-tetrazol-5-amine 2g.** Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.57; yellow solid; 322 mg, yield 88%.
Mp 116-117 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (br s, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 4H), 3.06-2.99 (m, 1H), 2.97-2.92 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 6H).
^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 152.3, 150.9, 143.4, 135.7, 134.8, 133.9, 130.0, 128.8, 124.5, 123.5, 120.2, 34.2, 33.4, 23.9, 23.8.
FT-IR (KBr) 2963, 1627, 1596, 1535, 1518, 1425, 1338, 1283, 1252, 1087, 1013, 841 cm^{-1}.
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{22}N_6O_2$ 367.1877, found 367.1884.



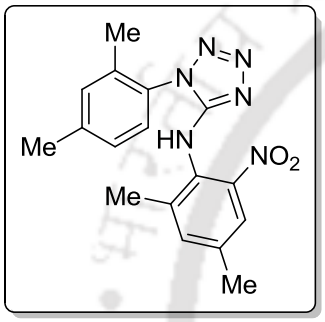
***N*-(4-Ethyl-2-nitrophenyl)-1-(4-ethylphenyl)-1*H*-tetrazol-5-amine 2h.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.69; yellow solid; 308 mg, yield 91%.
Mp 114-115 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (br s, 1H), 8.80 (d, *J* = 8.8, 0.8 Hz, 1H), 8.03 (s, 1H), 7.56 (d, *J* = 8.4 Hz. 1H), 7.47 (s, 4H), 2.77 (q, *J* = 8.0 Hz, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.8, 147.6, 138.7, 136.7, 134.7, 133.8, 130.1, 129.9, 124.8, 124.6, 120.1, 28.8, 27.9, 15.4, 15.2.

FT-IR (KBr) 3245, 2960, 2926, 1596, 1559, 1531,m 1516, 1384, 1335, 1251, 1183, 1086, 915, 843 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1564.



***N*-(2,4-Dimethyl-6-nitrophenyl)-1-(2,4-dimethylphenyl)-1*H*-tetrazol-5-amine 2i.**

Analytical TLC on silica gel, 1:4 ethyl acetate/ hexane R_f = 0.51; yellow solid; 260 mg, yield 77%.

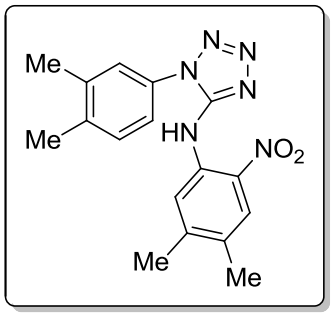
Mp 188-189 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.363 (br s, 1H), 8.34 (s, 1H), 7.20 (s, 1H), 7.14 (s, 2H), 6.79 (s, 1H), 2.45 (s, 3H), 2.42 (s, 6H), 2.40 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.9, 145.3, 141.1, 136.7, 135.3, 133.9, 132.5, 132.3, 127.4, 121.9, 118.4, 22.1, 21.4, 21.2.

FT-IR (KBr) 2922, 1615, 1544, 1493, 1377, 1344, 1294, 1249, 1091, 851, cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1565.



***N*-(4,5-Dimethyl-2-nitrophenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine 2j.**

Analytical TLC on silica gel, 1:4 ethyl acetate/ hexane R_f = 0.52; yellow solid; 284 mg, yield 84%.

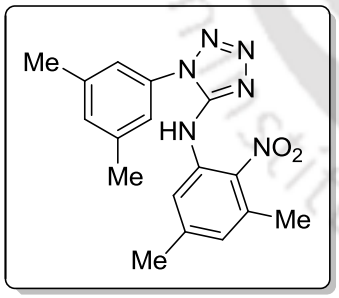
Mp 158-159 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (br s, 1H), 8.63 (s, 1H), 7.93 (s, 1H), 7.38-7.26 (m, 3H), 2.36 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.7, 148.3, 140.0, 139.7, 133.8, 132.6, 131.6, 131.3, 129.9, 126.3, 125.5, 121.7, 120.3, 20.8, 19.9, 19.8, 19.1.

FT-IR (KBr) 3266, 2921, 2852, 1593, 1529, 1504, 1406, 1323, 1298, 1259, 1135, 1092, 905, 892 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1563.



***N*-(3,5-Dimethyl-2-nitrophenyl)-1-(3,5-dimethylphenyl)-1*H*-tetrazol-5-amine 2k.**

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.60; yellow solid; 267 mg, yield 79%.

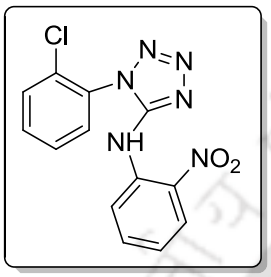
Mp 180-181 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 8.30 (s, 1H), 7.18 (s, 1H), 7.12 (s, 2H), 6.76 (s, 1H), 2.40 (s, 9H), 2.37 (s, 3H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.8, 145.2, 140.9, 136.5, 135.2, 133.8, 132.3, 132.2, 127.2, 121.7, 118.2, 22.0, 21.3, 21.1.

FT-IR (KBr) 3094, 2922, 2844, 1606, 1539, 1491, 1339, 1293, 1249, 1093, 1033, 871, 850 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1566.



1-(2-Chlorophenyl)-*N*-(2-nitrophenyl)-1*H*-tetrazol-5-amine 2l. Analytical TLC on silica gel, 1:4 ethyl acetate/ hexane R_f = 0.71; yellow solid; 256 mg, yield 81%.

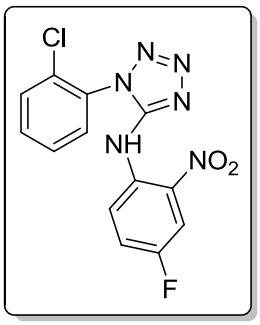
Mp 135-136 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 10.38 (br s, 1H), 8.82 (d, *J* = 8.8 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.65-7.58 (m, 1H), 7.56 (d, *J* = 3.6 Hz, 2H), 7.09 (t, *J* = 8.8 Hz, 1H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 136.9, 135.6, 134.7, 133.3, 131.8, 131.5, 129.4, 129.3, 128.9, 126.2, 122.3, 119.8.

FT-IR (KBr) 3290, 3090, 2923, 1600, 1570, 1537, 1503,m 1394, 1342, 1321, 1265, 1087, 887, 767, 739 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9ClN_6O_2$ 317.0548, found 317.0547.



1-(2-Chlorophenyl)-*N*-(4-fluoro-2-nitrophenyl)-1*H*-tetrazol-5-amine 2m. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.670; yellow solid; 281 mg, yield 84%.

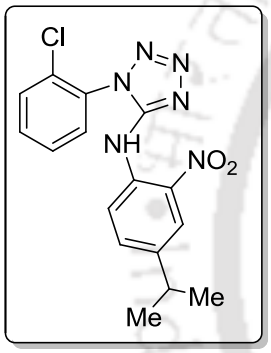
Mp 142-143 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 8.96-8.92 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.59-7.49 (m, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.1 (d, *J* = 245.5 Hz), 151.5, 133.5, 132.4, 131.9, 131.7, 129.5, 129.4, 129.0, 124.9 (d, *J* = 22.1 Hz), 121.9 (d, *J* = 7.6 Hz), 112.8 (d, *J* = 27.5 Hz).

FT-IR (KBr) 2923, 2857, 1631, 1541, 1521, 1338, 1247, 1067, 947, 759 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8ClFN_6O_2$ 335.0454, found 335.0462.



1-(2-Chlorophenyl)-*N*-(4-isopropyl-2-nitrophenyl)-1*H*-tetrazol-5-amine 2n. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.69; yellow solid; 337 mg, yield 94%.

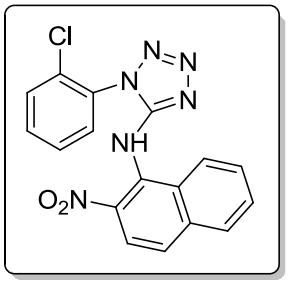
Mp 156-157 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (br s, 1H), 8.81 (d, *J* = 9.0 Hz, 1H), 8.08 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.67-7.63 (m, 2H), 2.99-2.94 (m, 1H), 1.28 (m, 6H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 151.8, 143.7, 135.8, 134.9, 133.7, 133.4, 132.1, 131.7, 129.64, 129.60, 129.0, 123.6, 120.2, 33.5, 23.8.

FT-IR (KBr) 2963, 2926, 1627, 1601, 1562, 1536, 1519, 1461, 1336, 1265, 1208, 1160, 1037, 928, 839 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}ClN_6O_2$ 359.1018, found 359.1021.



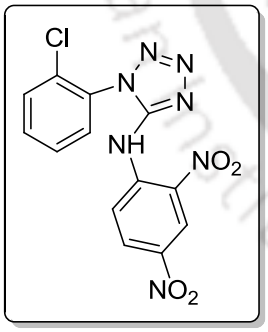
1-(2-Chlorophenyl)-*N*-(2-nitronaphthalen-1-yl)-1*H*-tetrazol-5-amine 2o. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; reddish yellow gummy liquid; 275 mg, yield 75%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.8 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.72-7.59 (m, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.84 (br s, 1H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 152.4, 134.8, 134.7, 132.2, 129.2, 128.94, 128.90, 128.8, 128.1, 127.9, 125.6, 125.3, 123.8, 121.9, 121.5, 119.1.

FT-IR (neat) 3113, 2925, 16.03, 1567, 1520, 1452, 1312, 1232, 1087, 1053, 1034, 802, 772, 750 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{11}ClN_6O_2$ 367.0710, found 367.0710.



1-(2-Chlorophenyl)-*N*-(2,4-dinitrophenyl)-1*H*-tetrazol-5-amine 2p. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; orange solid; 311 mg, yield 86%.

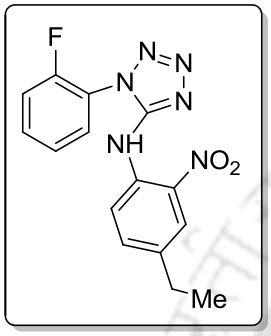
Mp 189-190 °C.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 10.37 (br s, 1H), 8.86-8.85 (m, 1H), 8.81-8.78 (m, 1H), 8.34-8.31 (m, 1H), 7.54-746 (m, 2H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 150.4, 140.6, 139.7, 133.4, 133.2, 131.1, 130.9, 130.4, 129.1, 128.7, 128.5, 122.1, 120.1.

FT-IR (KBr) 3260, 3105, 2855, 1604, 1588, 1543, 1510, 1424, 1342. 1312, 1251, 1142, 1039, 912, 846, 772 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8ClN_7O_4$ 362.0399, found 362.0398.



***N*-(4-Ethyl-2-nitrophenyl)-1-(2-fluorophenyl)-1*H*-tetrazol-5-amine 2q.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.72; yellow solid; 282 mg, yield 86%.

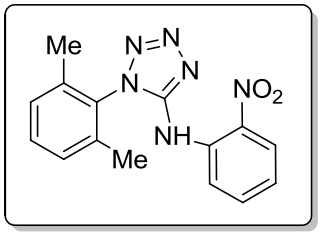
Mp 139-140 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 10.43 (br s, 1H), 8.71 (d, *J* = 8.8 Hz, 1H), 7.99 (s, 1H), 7.67-7.51 (m, 3H), 7.44-7.39 (m, 2H), 2.64 (q, *J* = 8.0 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5 (d, *J* = 253.2 Hz), 151.4, 138.8, 136.9, 134.7, 133.63, 133.60, 133.5, 128.4, 126.1 (d, *J* = 3.8 Hz), 124.7, 119.9 (d, *J* = 11.4 Hz), 117.9 (d, *J* = 19.0 Hz), 27.8, 15.1.

FT-IR (KBr) 3276, 2964, 2926, 1597, 1536, 1505, 1416, 1343, 1300, 1110, 1088, 889, 760 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}FN_6O_2$ 329.1157, found 329.1155.



1-(2,6-Dimethylphenyl)-*N*-(2-nitrophenyl)-1*H*-tetrazol-5-amine 2r. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow solid; 288 mg, yield 93%.

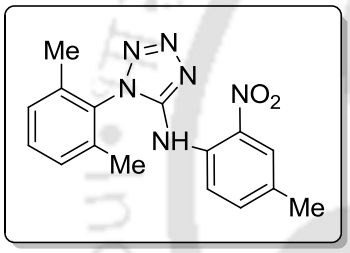
Mp 196-197 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (br s, 1H), 8.94 (d, *J* = 8.8 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 2.03 (s, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.5, 137.1, 136.7, 135.8, 134.7, 132.0, 129.7, 129.4, 126.3, 122.2, 120.0, 17.60, 17.56.

FT-IR (KBr) 3089, 2928, 2855, 1598, 1568, 1538, 1503, 1380, 1340, 1321, 1282, 1240, 1146, 1034, 910, 842, 740 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1256, found 311.1264.



1-(2,6-Dimethylphenyl)-*N*-(4-methyl-2-nitrophenyl)-1*H*-tetrazol-5-amine 2s. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.72; yellow solid; 295 mg, yield 91%.

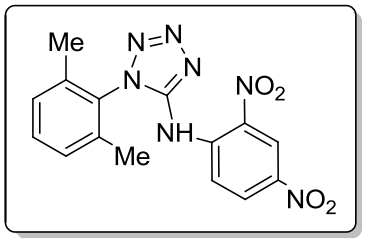
Mp 192-193 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H), 8.78 (d, *J* = 8.8 Hz, 1H), 7.96 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H), 2.00 (s, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.5, 138.0, 136.6, 134.4, 133.4, 132.3, 131.8, 129.5, 129.3, 125.8, 119.7, 20.4. 17.5.

FT-IR (KBr) 3230, 3062, 2960, 2923, 1600, 1563, 1522, 1408, 1375, 1334, 1264, 1113, 1092, 1027, 924, 830 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_6O_2$ 325.1408, found 325.1416.



1-(2,6-Dimethylphenyl)-*N*-(2,4-dinitrophenyl)-1*H*-tetrazol-5-amine 2t. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; yellow solid; 298 mg, yield 84%.

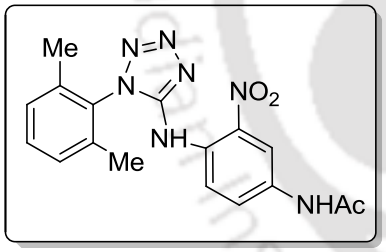
Mp 188-189 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (br s, 1H), 9.21 (d, *J* = 9.6 Hz, 1H), 9.11 (s, 1H), 8.56 (d, *J* = 9.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.03 (s, 6H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 150.7, 141.1, 140.0, 136.5, 133.5, 132.4, 131.1, 129.9, 128.9, 122.7, 120.7, 17.6.

FT-IR (KBr) 3251, 3113, 2924, 2854, 1606, 1586, 1548, 1511, 1424, 1345, 1310, 1264, 1144, 1116, 1019, 909, 842 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}N_7O_4$ 356.1107, found 356.1097.



***N*-(4-((1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)amino)-3-nitrophenyl)acetamide 2u.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; yellow solid; 283 mg, yield 77%.

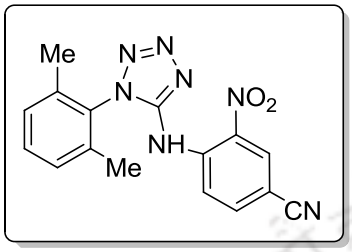
Mp 262-263 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (br s, 1H), 8.90 (d, *J* = 9.2 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H), 7.98 (br s, 1H), 7.93 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.24 (s, 3H), 2.06 (s, 6H).

^{13}C{H} NMR (150 MHz, $CDCl_3$ + DMSO-d_6 + CD_3OD) δ 168.3, 150.6, 135.4, 134.4, 133.3, 130.8, 129.4, 128.45, 128.4, 126.7, 119.6, 114.7, 22.8, 16.2.

FT-IR (KBr) 3334, 3238, 1674, 1611, 1546, 1360, 1296, 1273, 1260, 1091, 1016, 886, 773 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}N_7O_3$ 368.1471, found 368.1480.



4-((1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)amino)-3-nitrobenzonitrile 2v. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.30; yellow solid; 275 mg, yield 82%.

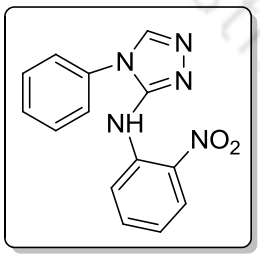
Mp 205-206 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (br s, 1H), 9.15 (d, *J* = 8.8 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 2.01 (s, 6H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.8, 139.2, 138.8, 136.5, 134.1, 132.3, 130.8, 129.8, 129.0, 121.1, 116.7, 105.8, 17.5.

FT-IR (KBr) 3504, 2922, 2852, 2237, 1629, 1557, 1519, 1383, 1283, 1194, 1092, 852, 775, 674 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}N_7O_2$ 336.1209, found 336.1206.



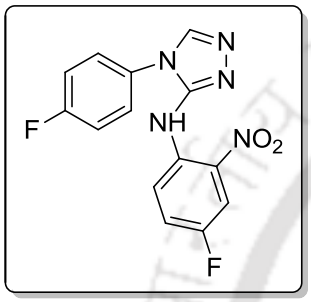
***N*-(2-Nitrophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-amine 4a.** Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.40; yellow solid; 236 mg, yield 84%.

Mp 176-177 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (br s, 1H), 8.97 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.11 (s, 1H), 7.67-7.58 (m, 4H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 8.0 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 149.2, 140.6, 137.2, 136.9, 134.1, 132.1, 131.0, 130.6, 126.2, 125.8, 121.0, 119.9.

FT-IR (KBr) 3451, 3053, 2923, 2852, 1617, 1564, 1553, 1507, 1444, 1384, 1272, 1193, 1145, 1023, 841, 736, 609 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}N_5O_2$ 282.0991, found 282.0991.



***N*-(4-Fluoro-2-nitrophenyl)-4-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-amine 4b.** Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.42; reddish yellow solid; 260 mg, yield 82%.

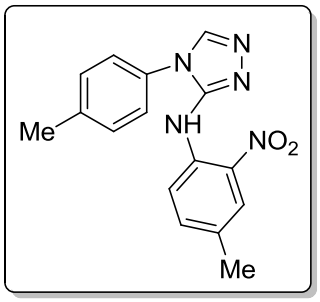
Mp 189-190 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 9.08-9.04 (m, 1H), 8.12 (s, 1H), 7.93 (dd, J = 8.4, 2.8 Hz, 1H), 7.50-7.43 (m, 3H), 7.39 (t, *J* = 8.0 Hz, 2H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 164.8 (d, *J* = 251.7 Hz), 156.9 (d, *J* = 244.0 Hz), 149.3, 140.7, 133.84 (d, *J* = 4.6 Hz), 133.8, 128.2 (d, *J* = 8.4 Hz), 127.9 (d, *J* = 3.0 Hz), 125.0 (d, *J* = 22.9 Hz), 121.7 (d, *J* = 7.6 Hz), 118.3 (d, *J* = 22.9 Hz), 112.3 (d, *J* = 26.7 Hz).

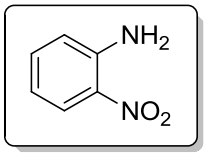
FT-IR (KBr) 1629, 1599, 1557, 1514, 1384, 1337, 1236, 1162, 1131, 1001, 944, 878, 837, 760, 704 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_9F_2N_5O_2$ 318.0803, found 318.0802.



***N*-(4-Methyl-2-nitrophenyl)-4-(*p*-tolyl)-4*H*-1,2,4-triazol-3-amine 4c.** Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.45; reddish yellow solid; 269 mg, yield 87%.
Mp 176-177 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (br s, 1H), 8.90 (d, *J* = 8.8 Hz, 1H), 8.08 (s, 1H), 8.0 (s, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H).
^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 149.5, 141.0, 140.7, 138.1, 135.1, 133.9, 131.5, 131.0, 129.5, 125.8, 125.6, 120.0, 21.5, 20.5.
FT-IR (KBr) 3471, 1731, 1632, 1598, 1514, 1449, 1386, 1238, 1163, 946, 837, 782 cm^{-1}.
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}N_5O_2$ 310.1306, found 310.1306.

3.5. General Procedure for the Removal of Directing Group. To a stirred solution of **2a**, **2g** and **2l** (1 mmol) in 1,4-dioxane (3 mL), NaOH (7.0 mmol, 280 mg) was added at room temperature, and the mixture was stirred at 110 °C for 12-22 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the resultant mixture was extracted with ethyl acetate (3 x 10 mL) and washed with brine (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent.

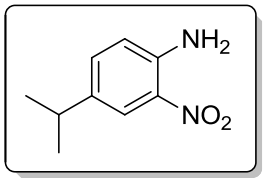


2-Nitroaniline 5a.[17] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.40; yellow solid.
Mp 71-72 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.36 (td, *J* = 6.6, 1.2 Hz, 1H), 6.81 (dd, *J* = 9.0, 1.2 Hz, 1H), 6.71 (td, *J* = 7.8 Hz, 1.2, 1H), 6.07 (br s, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 144.9, 135.8, 132.5, 126.4, 118.9, 117.1.

FT-IR (KBr) 3479, 3352, 1630, 1593, 1507, 1433, 1347, 1253, 1093, 995, 745 cm^{-1}.



4-Isopropyl-2-nitroaniline 5b. Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.40; thick yellow liquid; 157 mg, yield 87%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 1.6 Hz, 1H), 7.28 (m, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.96 (br s, 2H).

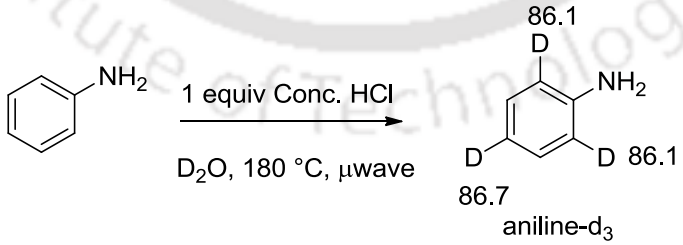
^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 143.1, 138.1, 135.0, 127.3, 123.1, 119.0, 33.1, 23.9.

FT-IR (neat) 3483, 3364, 2954, 2917, 1638, 1561, 1520, 1466, 1409, 1335, 1249, 1167, 1085, 952, 818 cm^{-1}.

3.6. Kinetic Study

Preparation of Aniline-d_3 (Scheme 21). The titled compound was prepared according to the reported procedure[12a] and the deuterium incorporation was determined by ^{1}H NMR analysis of the mixture. Characterization data for the deuterated product only. 1;4 ethyl acetate/ hexane, R_f = 0.32; pale brown solid; yield 85%.

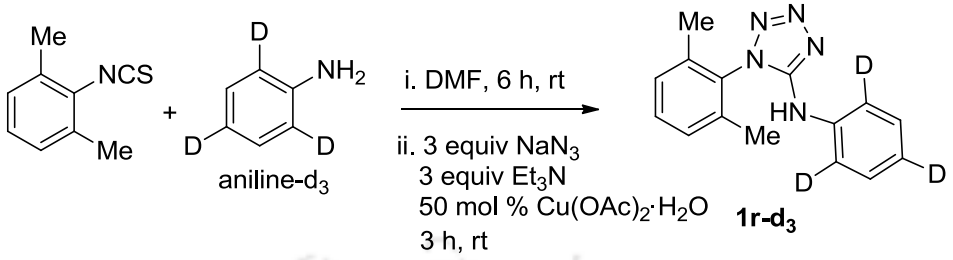
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2H), 3.62 (bs, 2H).



Scheme 21

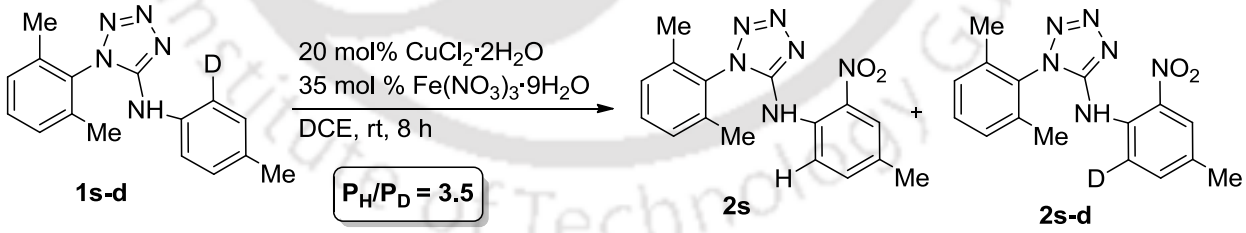
Preparation of 1-(2,6-Dimethylphenyl)-*N*-(2-nitrophenyl)-1*H*-tetrazol-5-amine-d_3 1r-d_3 (Scheme 22). The titled compound was prepared according to the reported procedure. 3:7

ethyl acetate/ hexane; R_f = 0.25; white solid; yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.35 (s, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 6.10 (bs, 1H), 2.06 (s, 6H).



Scheme 22

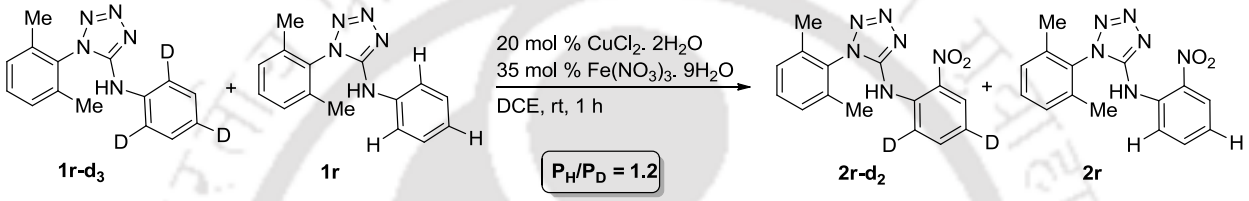
Intramolecular Kinetic Isotope Effect Study (Scheme 23). To a stirred solution of *N*-(2-deuterio-4-methylphenyl)-1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-amine **1s-d** (0.5 mmol, 140 mg) in DCE (2 mL), $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.1 mmol, 17 mg) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol %, 0.175 mmol, 71 mg) were added at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After 8 h, saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture and the resultant mixture was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford a 22:78 mixture of **2s** and **2s-d** as a yellow solid in 83% (138 mg) yield. The ratio of deuterium to hydrogen was determined from the ^{1}H NMR relative integration values of H_a (8.84 ppm) based on H_b (7.58 ppm).



Scheme 23

Intermolecular Kinetic Isotope Effect Study (Scheme 24). To a stirred solution of 1-(2,6-dimethylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (**1r**) (0.58 mmol, 156 mg) and 1-(2,6-dimethylphenyl)-*N*-(2,4,6-trideuteriophenyl)-1*H*-tetrazol-5-amine(**1r-d$_3$)** (0.42 mmol, 111 mg) in DCE (2 mL), $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.2 mmol, 34 mg) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol

%, 0.35 mmol, 141 mg) were added at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After 1.5 h, saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture and the resultant mixture was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford a mixture of **2r-d$_2$** and **2r** as a yellow solid in 18% (56 mg) yield. The ratio of deuterium to hydrogen was determined by the ^{1}H NMR relative integration values of H_a (8.96 ppm) based on H_b (8.24 ppm).



Scheme 24

3.7. References

(1) Ono, N. *The Nitro Group in organic synthesis*, Wiley-VCH, New York, 2001. (b) Zollinger, H. *Color Chemistry*, Wiley-VCH, New York, 1987, 161.

(2) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: Weinheim, 1989. (b) Olah, G. A.; Kuhn, S. J. *J. Am. Chem. Soc.* **1962**, *84*, 3684. (c) Olah, G. A.; Prakash, G. K. S.; Wang, Q.; Li, X. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A.; Wiley: Chichester, 1995; Vol. 6.

(3) For *ipso*-nitration reactions, see: (a) Tani, K.; Lukin, K.; Eaton, P. E. *J. Am. Chem. Soc.* **1997**, *119*, 1476. (b) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett*. **2004**, *6*, 2205.

(4) For *ipso*-oxidation reactions, see: (a) Firouzabadi, H.; Amani, N. I. K. *Green Chem.* **2001**, *3*, 131. (b) Das, J. P.; Sinha, P.; Roy, S. *Org. Lett*. **2002**, *4*, 3055. (c) Dirk, S. M.; Mickelson, E. T.; Henderson, J. C.; Tour, J. M. *Org. Lett*. **2002**, *2*, 3405.

(5) For examples, see: (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 12898. (b) Prakash, G. K. S.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1726.

(6) For examples, see: (a) Yan, G.; Yang, M. *Org*. *Biomol*. *Chem*. **2013**, *11*, 2554. (b) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun.* **2013**, *49*, 514. (c) Koley, D.; Colòn, O. C.; Savinov, S. N. *Org. Lett*. **2009**, *11*, 4172.

(7) For Rh catalyzed example see: Xie, F.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed*. **2013**, *52*, 11862.

(8) For Pd catalyzed example see: (a) Liu, Y.-K.; Lou, S.-J.; Xu, D.-Q, Xu, Z.-Y. *Chem. Eur. J*. **2010**, *16*, 13590. (b) Zhang, W.; Wu, D.; Zhang, J.; Liu, Y. *Eur. J. Org. Chem*. **2014**, 5827. (c) Zhang, W.; Zhang, J.; Ren, S.; Liu, Y. *J. Org. Chem*. **2014**, *79*, 11508. (d) Dong, J.; Jin, B.; Sun, P. *Org. Lett*. **2014**, *16*, 4540. (e) Qiao, H.-J, Yang, F.; Wang, S.-W.; Leng, Y.-T.; Wu, Y.-J. *Tetrahedron* **2015**, *71*, 9258. (f) Pawar, G. G.; Brahmanandan, A.; Kapur, M. *Org. Lett.* **2016**, *18*, 448.

(9) For Cu catalyzed example see: (a) Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay, T. A.; Bi, X.; Liu, Q. *Org. Lett*. **2011**, *13*, 6536. (b) Liu, J.; Zhuang, S.; Gui, Q.; Chen, X.; Yang, Z.; Tan, Z. *Adv. Synth. Catal*. **2015**, *357*, 732.

(10) (a) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem*. **2012**, *77*, 3716. (b) Jadhav, N. C.; Jagadhane, P. B.; Patel, K. N.; Telvekar, V. N. *Tetrahedron Lett*. **2013**, *54*, 101.

(11) (a) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (b) Opatz, T.; Lahm, G. *Org. Lett*. **2014**, *16*, 4201. (c) Martínez, A. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun*. **2014**, *50*, 2801.

(12) For isotope studies, see: (a) Martins, A.; Lautens, M. *Org. Lett*. **2008**, *10*, 4351. (b) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (c) Gòmez-Gallego, M.; Sierra, M. A. *Chem. Rev*. **2011**, *111*, 4857.

(13) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(14) (a) Bolm, C.; Magnus, A. S.; Hildebrand, J. P. *Org. Lett.* **2000**, *2*, 1173. (b) Ansari, I. A.; Gree, R. *Org. Lett.* **2001**, *3*, 1507. (c) Angelin, M.; Hermansson, M.; Dong, H.; Ramström, O. *Eur. J. Org. Chem.* **2006**, 4323. (d) Voica, A. F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nature Chem.* **2012**, *4*, 629.

(15) Tsybizova, A.; Ryland, B. L.; Tsierkezos, N.; Stahl, S. S.; Roithova, J.; Schröder, D. *Eur. J. Inorg. Chem.* **2014**, 1407.

(16) (a) Padhi, S. K.; Manivannan, V. *Inorg. Chem.* **2006**, *45*, 7994. (b) Ruttink, P. J.; Terlouw, J. K., Luider, T. M.; Burgers, P. C. *J. Mass Spectrom.* **2011**, *46*, 223.

(17) Zolfigol, M. A.; Khazaei, A.; Moosavi-Zare, A. R.; Zare, A.; Kruger§, H. G.; Khakyzadeh, V.; Kazem-Rostami, M. *J. Org. Chem.* **2012**, *77*, 3640.

3.8. Mass Spectra of Reaction Mixture

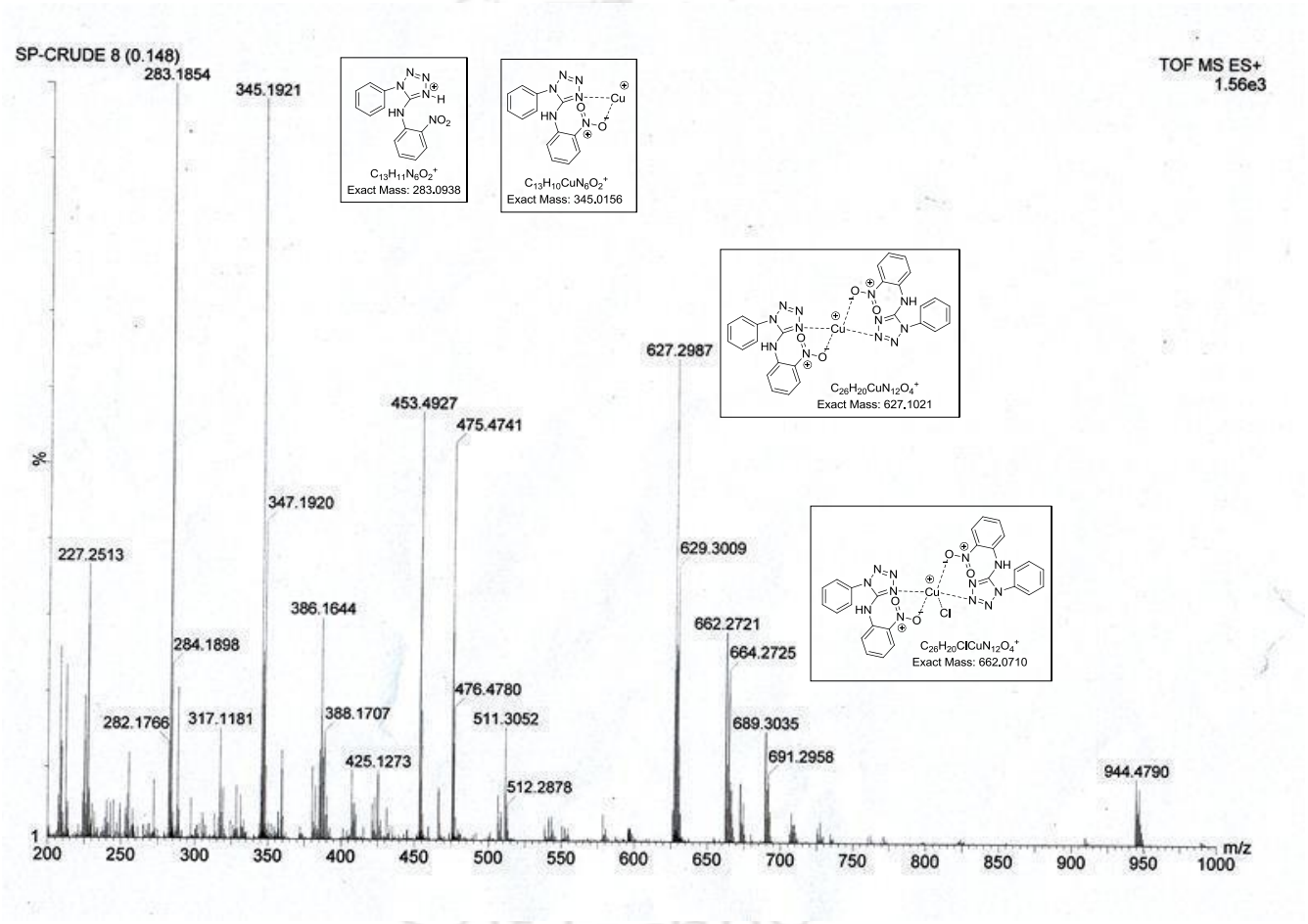
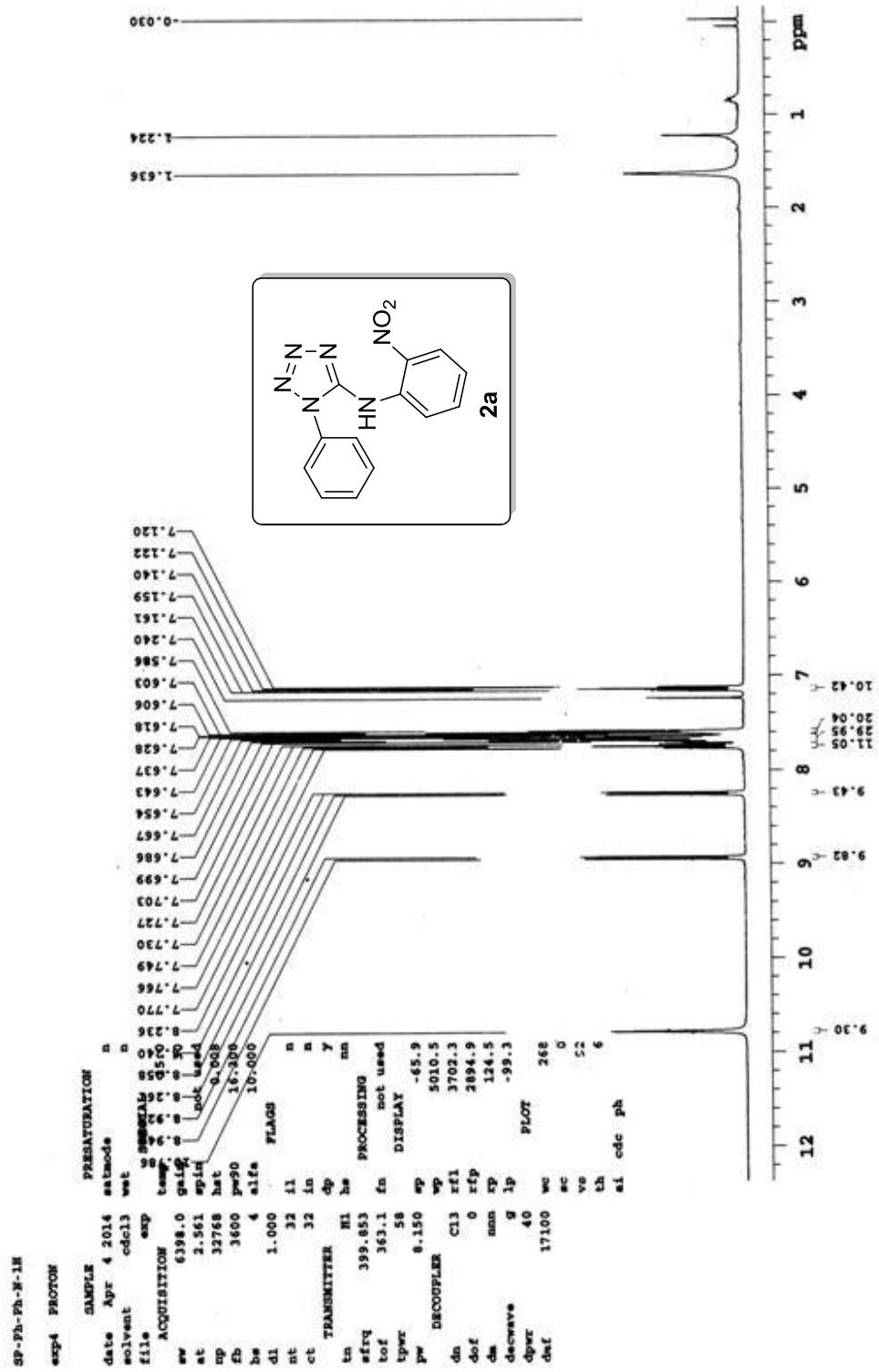
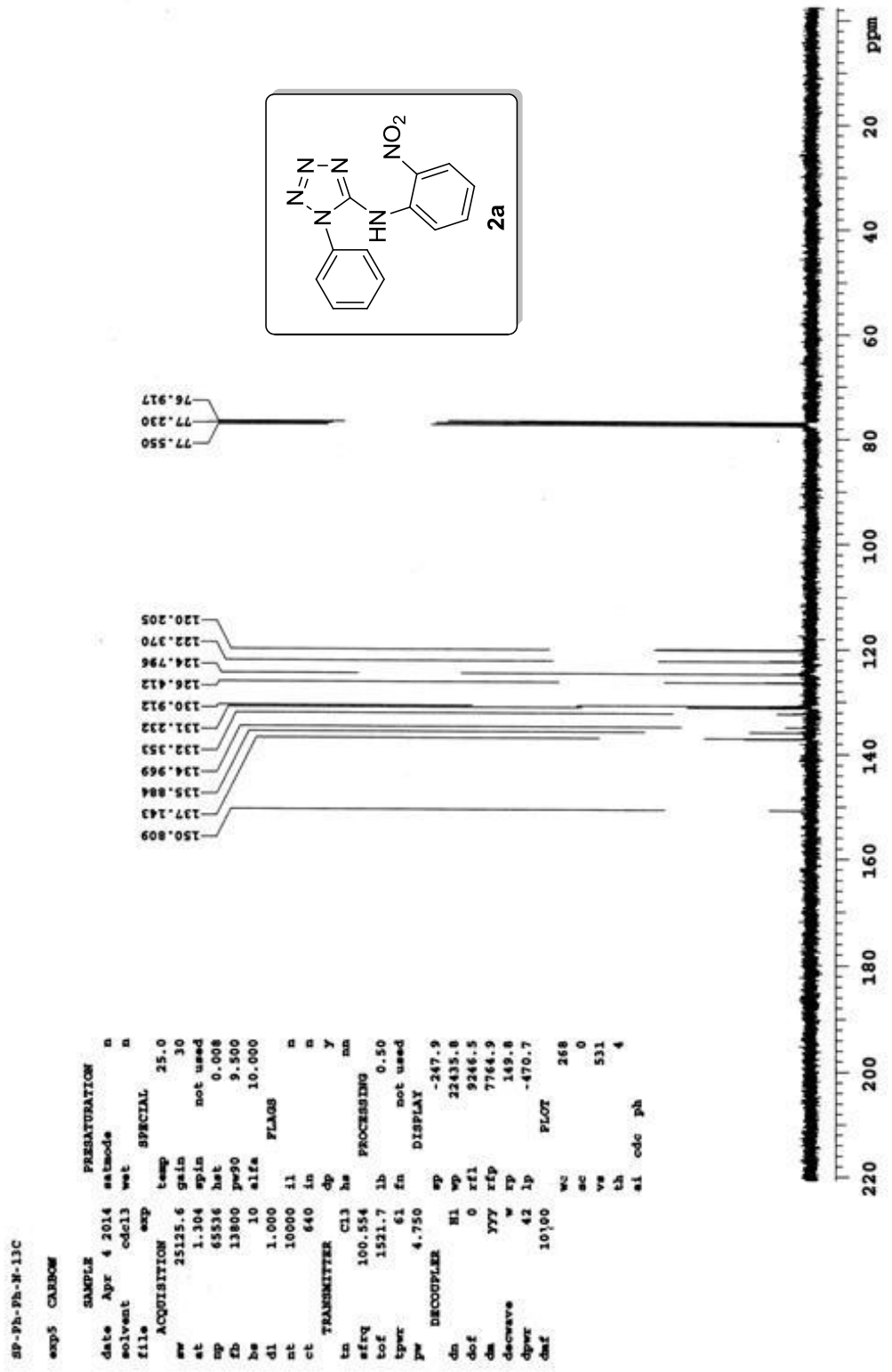
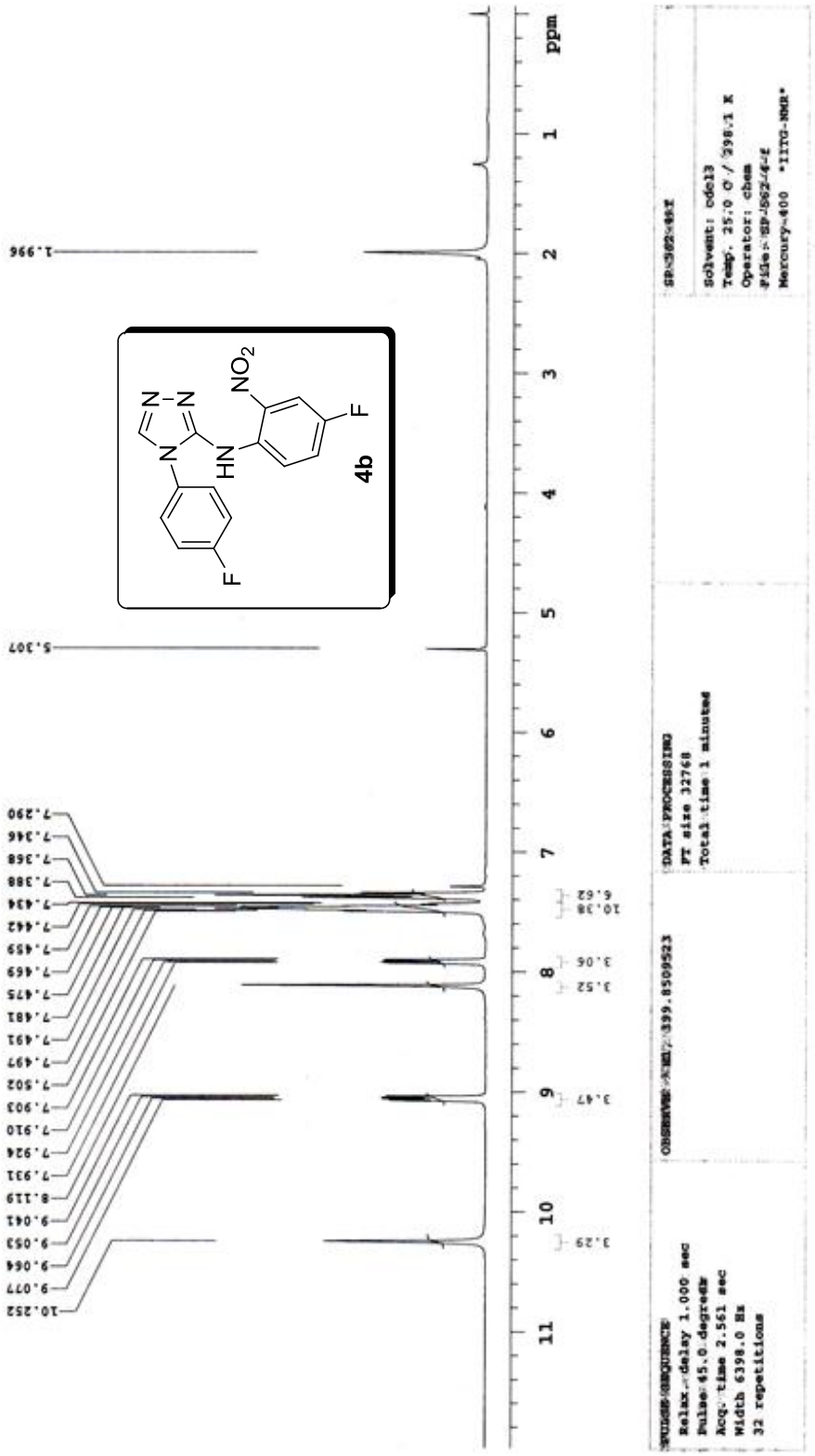


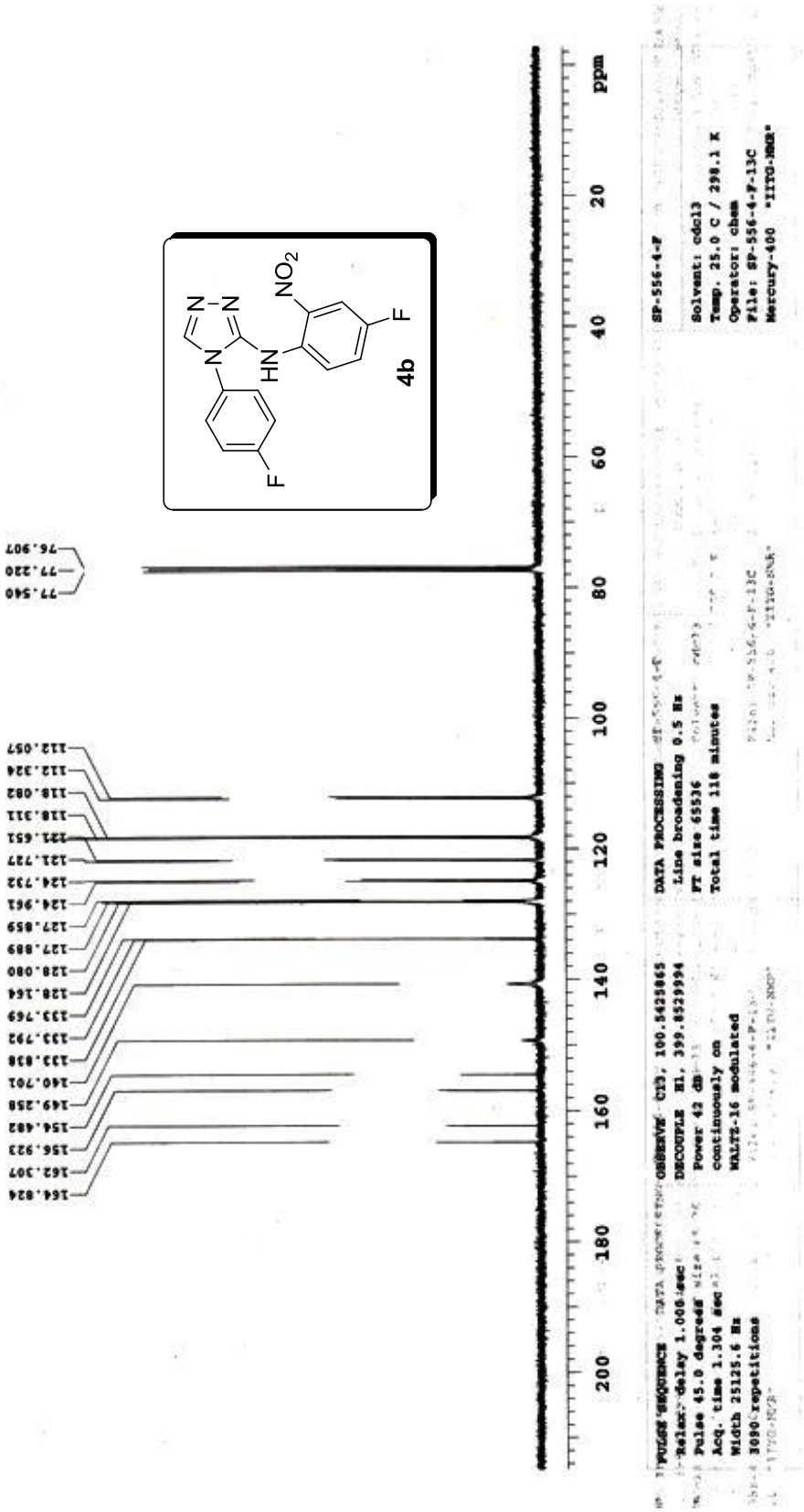
Figure 2. Mass spectra of reaction mixture **1a** prior to work up

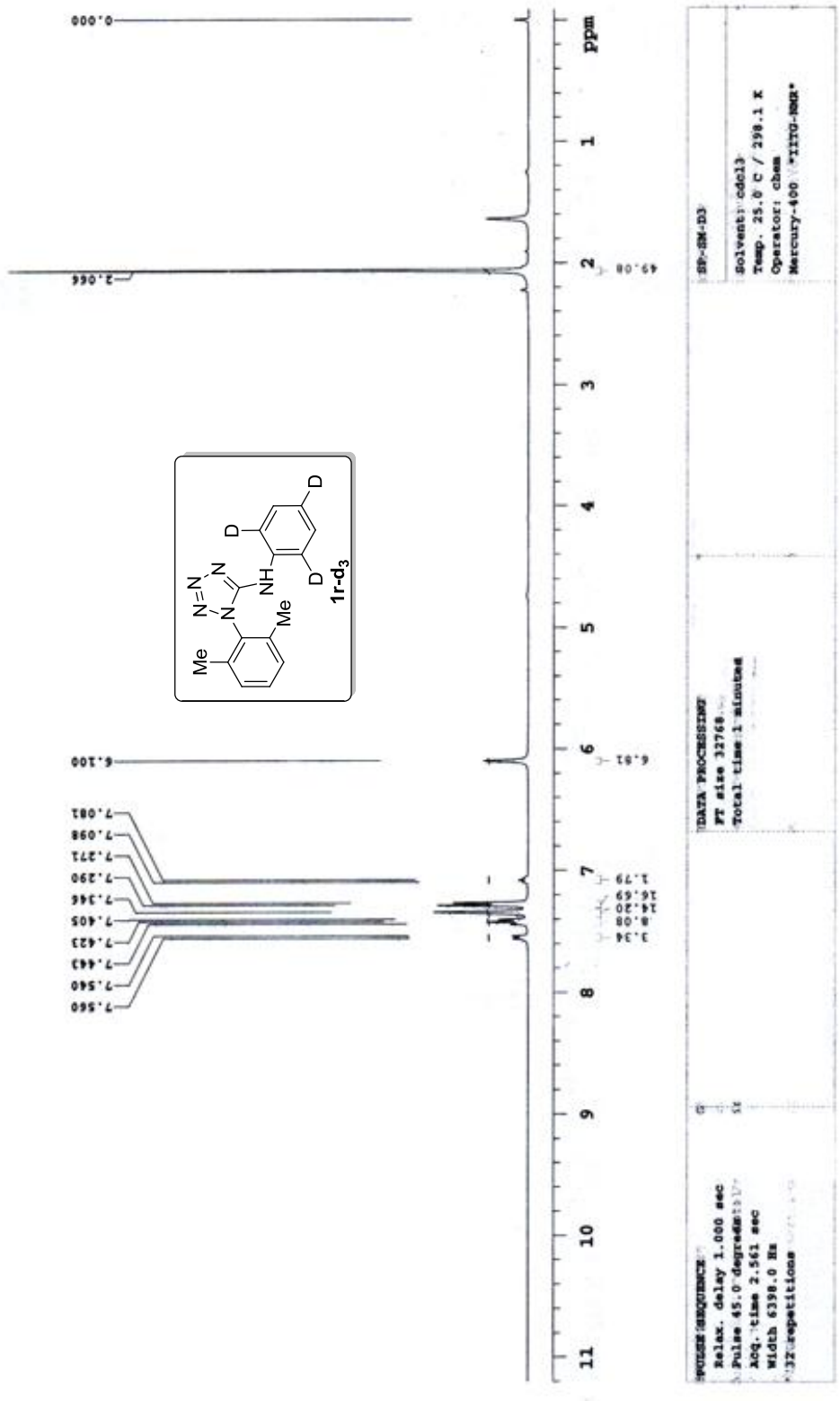
3.9. Selected Spectra

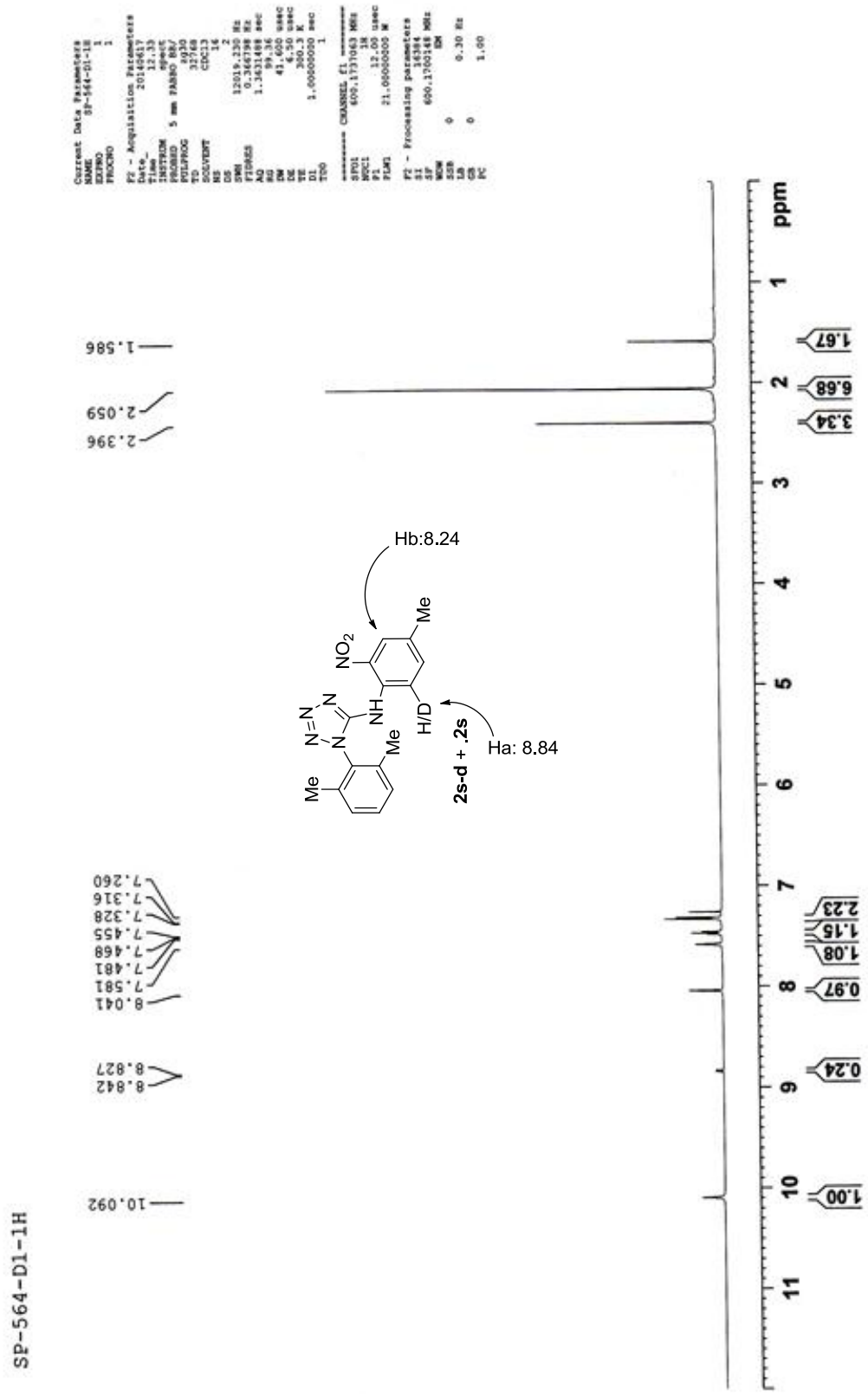


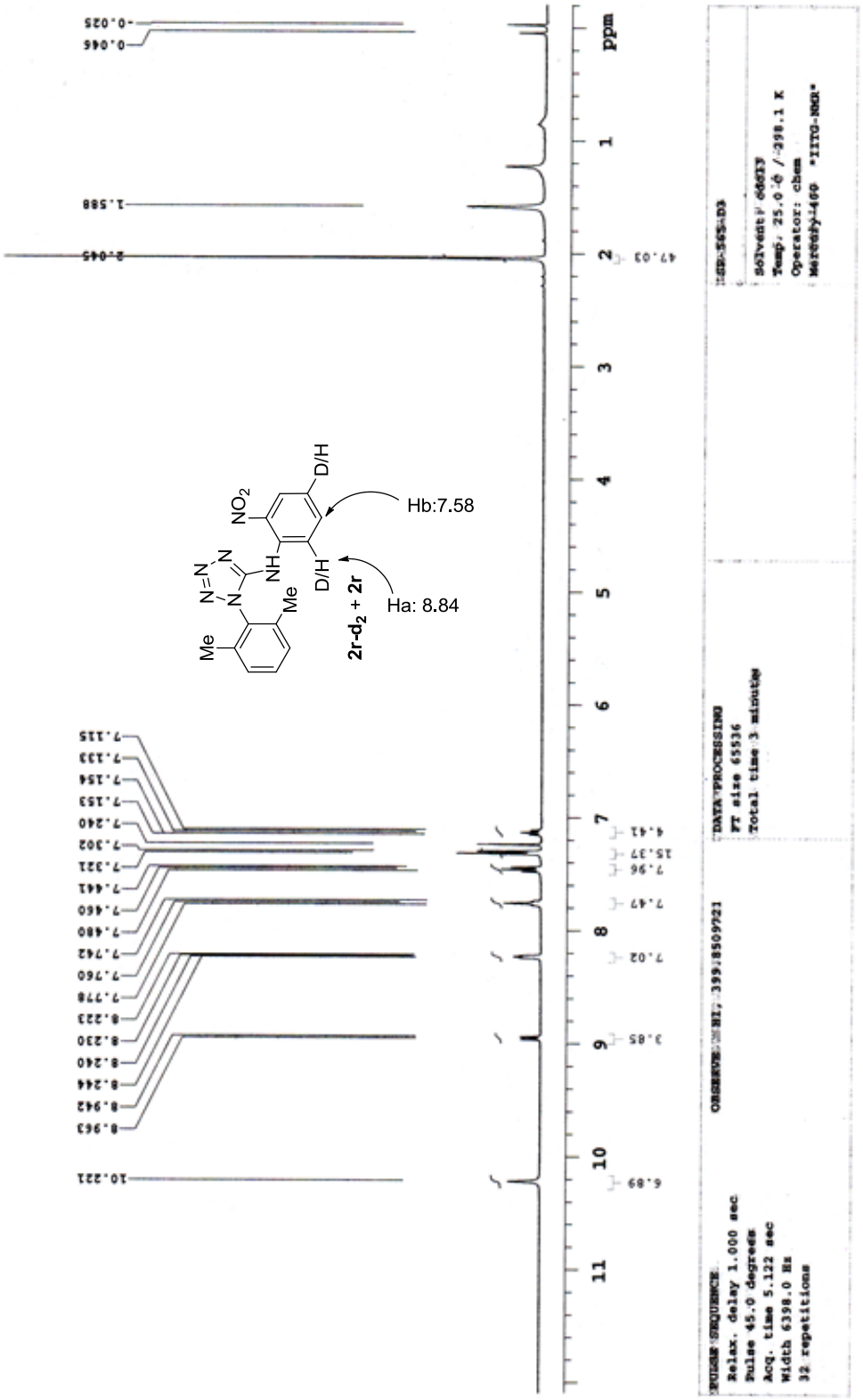

SP-Ph-Ph-N-13C
exp5 CARBON
SAMPLE
date Apr 4 2014
solvent cdcl3
file
ACQUISITION
sw 25125.6
at 1.304
np 65536
fb 13800
bs 10
d1 1.000
nt 10000
ct 640
TRANSMITTER
tn C13
sfrq 100.554
tof 1521.7
tpwr 61
pw 4.750
DECOUPLER
dn H1
dof 0
dm yyy
dmvave w
dpwr 42
dmf 10100
PRESATURATION n
satmode
wet n
SPECIAL
temp 25.0
gain 30
spin not used
hst 0.008
pw90 9.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -247.9
wp 22435.8
rf1 9246.5
rfp 7764.9
rp 149.8
lp -470.7
PLOT
wc 268
sc 0
vs 531
th 4
al cdc ph
2a
NO2
HN
N
N
N
150.809
137.143
135.884
134.969
133.353
132.232
130.913
126.412
124.796
122.370
120.305
77.550
77.230
76.917
220
200
180
160
140
120
100
80
60
40
20
ppm


4b
NO2
F
HN
N
F
ppm
1.996
5.307
7.290
7.346
7.368
7.388
7.434
7.442
7.459
7.469
7.475
7.481
7.491
7.497
7.502
7.903
7.910
7.924
7.931
8.119
9.041
9.053
9.064
9.077
10.252
6.62
10.38
3.06
3.52
3.47
3.29
DATA PROCESSING
FT size 32768
Total time 1 minutes
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "ITTG-NMR"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions


NO2
F
HN
N
N
F
4b
77.540
77.220
76.907
112.057
112.324
118.082
118.311
121.651
121.727
124.732
124.961
127.859
127.889
128.080
128.164
133.769
133.792
133.838
140.701
149.258
154.482
156.923
162.307
164.824
200
180
160
140
120
100
80
60
40
20
ppm


0.000
2.056
6.100
7.081
7.098
7.271
7.290
7.346
7.405
7.423
7.443
7.540
7.560
ppm
Me
Me
N=N
N
NH
D
D
D
1r-d3


SP-564-D1-1H
ppm
1.586
2.059
2.396
7.260
7.316
7.328
7.455
7.468
7.481
7.581
8.041
8.827
8.842
10.092
1.67
6.68
3.34
1.00
0.24
0.97
1.08
1.15
2.23
Hb:8.24
Ha: 8.84
2s-d + .2s
H/D
NO2
NH
Me
Me
Me


Hb:7.58
Ha: 8.84
2r-d2 + 2r
ppm

Chapter IV

Cu-Mediated *N*-Arylation of Pyrroles, Indoles, Pyrazoles, and Carbazole *via* Cross-Dehydrogenative Coupling (CDC)

The compounds containing *N*-arylated azole structural motif are of great interest because of their potential applications in biological and pharmaceutical sciences (Figure 1).[1] In addition, 2-(1*H*-pyrrol-1-yl)benzoic acid derivatives constitute key synthons in the construction of heterocyclic compounds as well as drug candidates.[2]

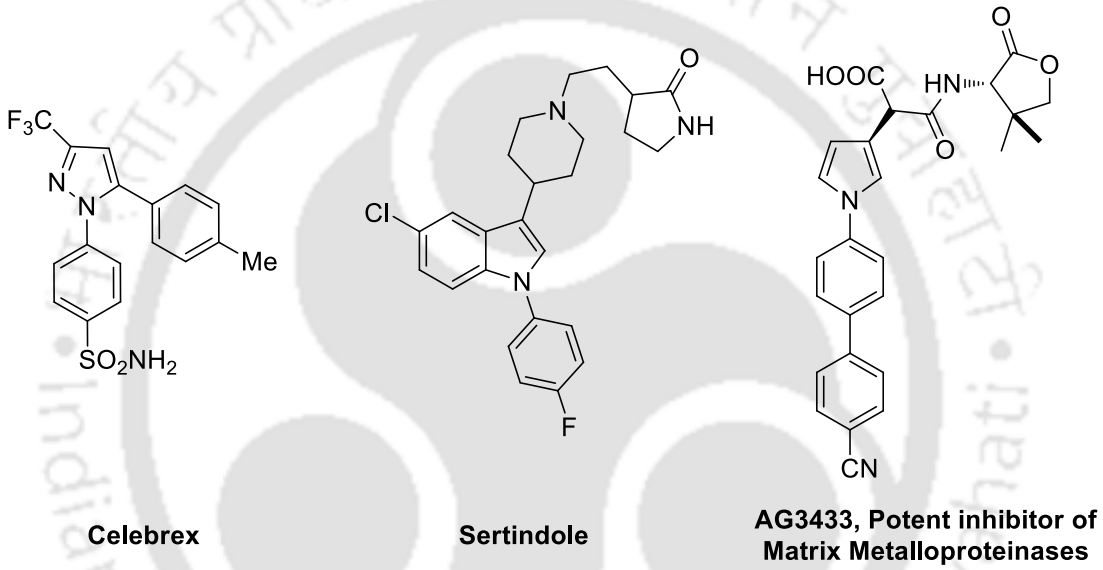


Figure 1. Examples of Some Biologically Active Compounds

Traditionally, *N*-arylation of azoles was performed using Ullmann-type coupling with aryl halides.[3,4] Recently, the scope of the reaction has been significantly expanded by Buchwald-Hartwig and Chan-Lam type cross-coupling reactions using aryl halides,[5] aryl boronic acids,[6] aryl bismuth[7] and aryl lead[8] reagents as coupling partners. Although, these methods are proven to be effective routes for the synthesis of requisite *N*-arylated azoles with wide substrate scope, the use of prefunctionalized substrate precursors and elevated temperatures limits their practical use. In this context, the directed C-H functionalization[9-16] and C-N bond formation[10] *via* cross-dehydrogenative coupling represents an ideal strategy because of their cleaner, shorter and regioselective approaches. *N*-(Quinolin-8-yl)benzamide based directing groups displays wide applications in selective C-H functionalization reactions. This reagent

owing to its significant chelation property toward metals have now been well accepted and utilized in the construction of carbon-carbon and carbon-heteroatom bonds. As part of our research work carried out in our laboratory on chelation assisted C-H functionalization, here, we report a Cu-promoted direct *N*-arylation of pyrroles, indoles, pyrazoles and carbazoles using *N*-(quinolin-8-yl)benzamide as a directing group.

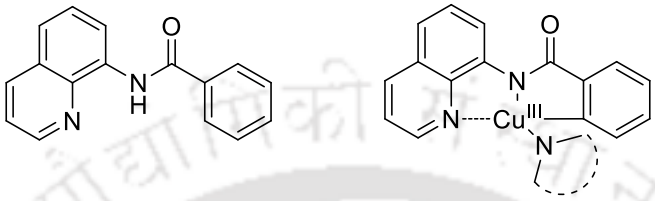
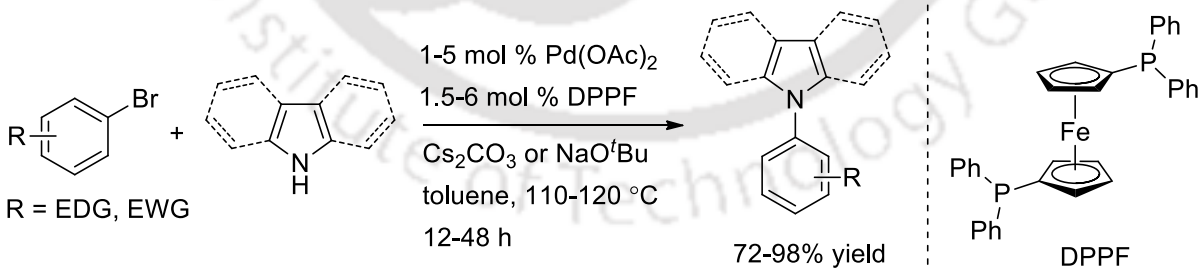


Figure 2. Structures of Directing Group and Metal Complex

4.1. Cross-Coupling Reactions

4.1.1. Pd-Catalyzed *N*-Arylation of Azoles

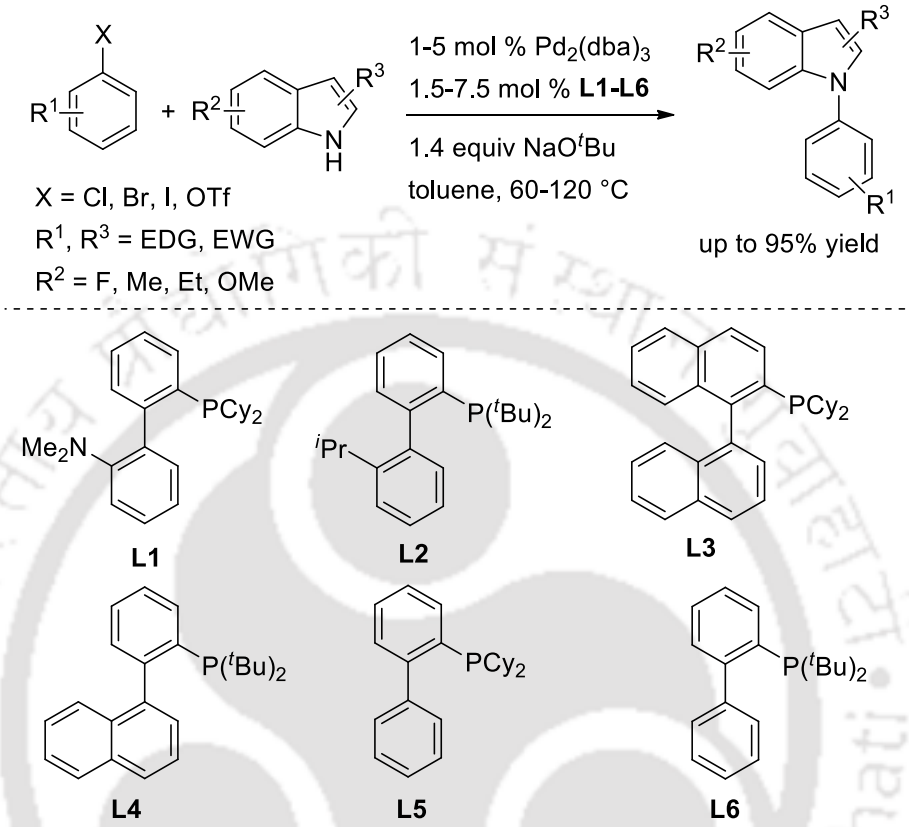
Pd-catalyzed cross-coupling for *N*-arylation of azoles has attracted considerable interest due to their broad substrate scope, which in turn led to the synthesis of fascinating number of biological and medicinally important molecules. In 1998, Hartwig and co-workers devised a $Pd(OAc)_2$-catalyzed cross-coupling of aryl bromides with azoles in the presence of Cs_2CO_3 or NaO^tBu (Scheme 1).[5a] This catalytic transformation encompassed the arylations of *N*-heterocyclic amines such as pyrroles, indoles and carbazoles in high yields.



Scheme 1. Pd-catalyzed *N*-Arylation of Heterocyclic amines

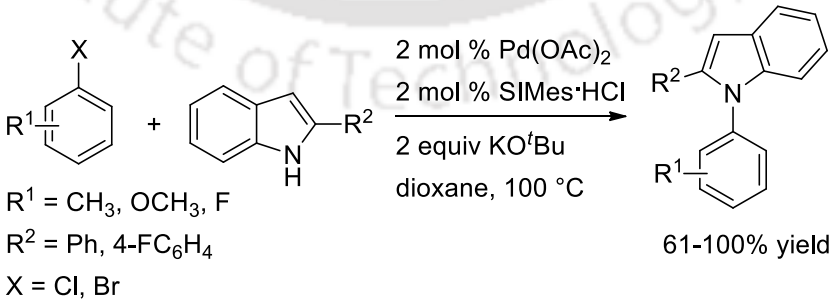
Buchwald group demonstrated *N*-arylation of a variety of substituted indoles using bulky, electron-rich phosphines as ligands in combination with $Pd_2(dba)_3$ (Scheme 2).[5b] Using this

catalyst system, the coupling of indoles with aryl iodides, bromides, chlorides, and triflates has been achieved.



Scheme 2. Cross-Coupling of Substituted Indoles with Aryl Halides and Triflates

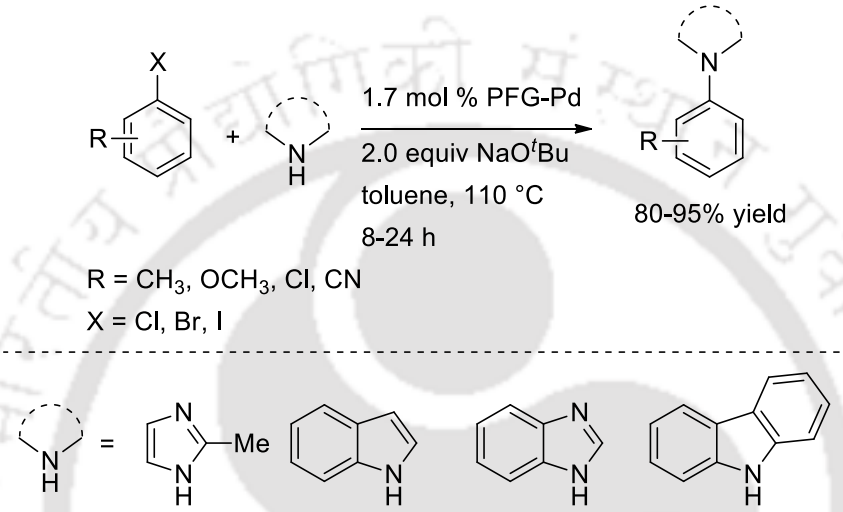
Nolan and co-workers developed a Pd/imidazolium salt system for *N*-arylation of azoles using aryl chlorides and aryl bromides (Scheme 3). The use of *N*-heterocyclic carbene ligands shows several advantages such as (i) stabilization of metal complex, (ii) improved thermal



Scheme 3. *N*-Heterocyclic Carbenes for *N*-Arylation of Azoles

stability, (iii) metal complex resistance to ligand dissociation, which makes these nucleophilic carbenes as catalyst modifiers to give the products in high yields.

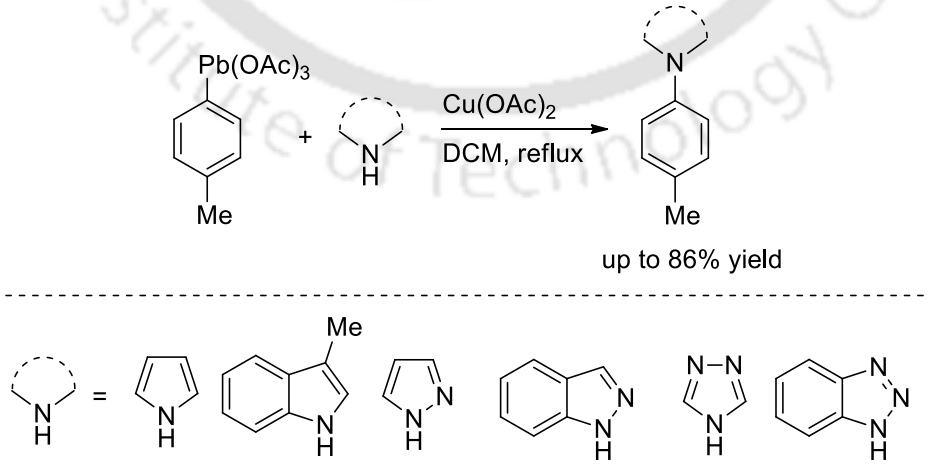
Alamdari and co-workers described the reaction of aryl halides with azoles using 1.7 mol % of PFG-Pd along with NaO^{t}Bu to give the target *N*-arylated azole products in high yields (Scheme 4).[5f] The reported heterogeneous PFG-Pd catalyst exhibits high activity and also can be recyclable without loss of activity.



Scheme 4. Heterogeneous Pd-catalyzed *N*-Arylation Reactions

4.1.2. Cu-Catalyzed *N*-Arylation of Azoles

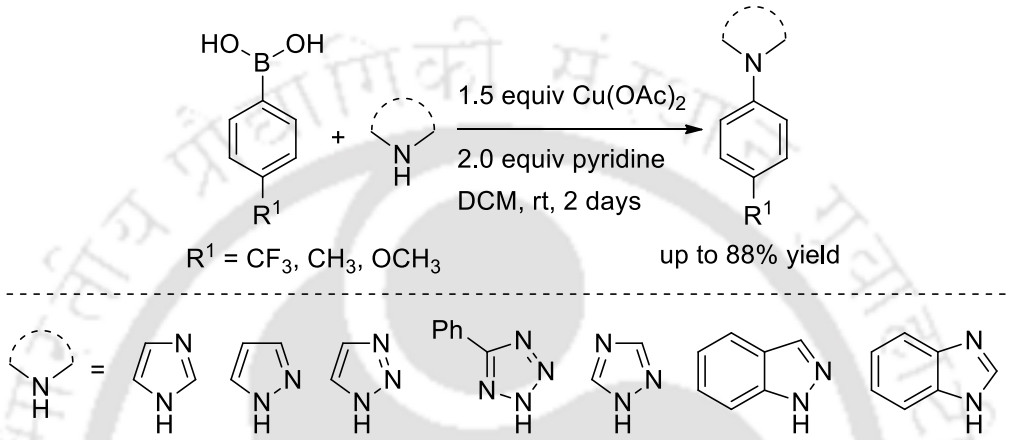
Cu-catalyzed *N*-arylation of azoles has received a great attention in recent years due to their high abundance, less toxic nature and cost effectiveness. In 1995, Avandano and co-workers



Scheme 5. *N*-Arylation of Azoles Using Aryllead Triacetates

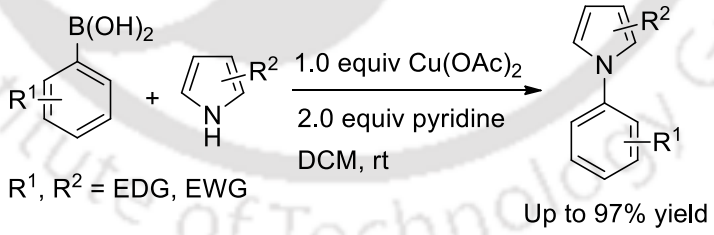
presented a method for the *N*-arylation of heterocycles employing *p*-tolyllead triacetate as an arylation source using catalytic amount of $Cu(OAc)_2$ at reflux conditions in DCM. The protocol shows broad substrate scope with various azoles (Scheme 5).[8]

Chan-Lam and co-workers reported *N*-arylation of nitrogen heterocycles using arylboronic acids as a coupling partners under mild reaction conditions in presence of pyridine (Scheme 6).[6a]



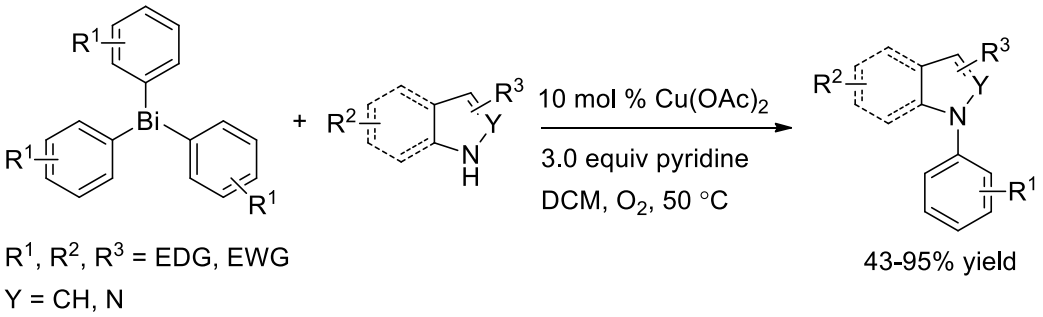
Scheme 6. Cu-Mediated Cross-Coupling of Arylboronic Acids and *N*-Heterocycles

Srirangam and co-workers achieved *N*-arylation of pyrroles by cross-coupling with arylboronic acids at room temperature in the presence of stoichiometric amount of $Cu(OAc)_2$ (Scheme 7).[6b] The generality of this reaction has been established with variously substituted pyrroles as well as boronic acids.



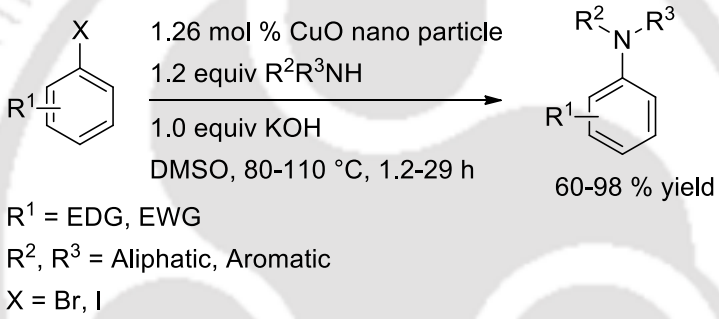
Scheme 7. *N*-Arylation of Substituted Pyrroles

N-Arylation of indoles, indazoles, pyrroles and pyrazoles has been reported using highly functionalized trivalent organobismuth reagents. The transformation is promoted by catalytic amounts of $Cu(OAc)_2$ and tolerates various functional groups (Scheme 8).[7]

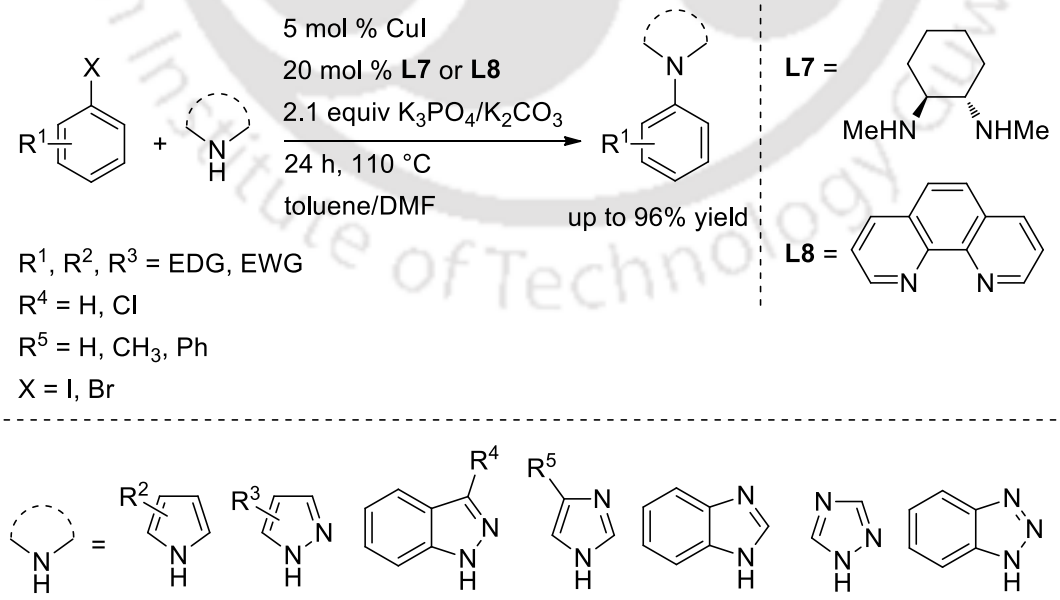


Scheme 8. Trivalent Organobismuth Reagent as Arene Source

Our group reported CuO nanoparticles catalyzed C-N cross-coupling of amines with aryl halides (Scheme 9).[5d] The reaction is simple and efficient and operates under air. The catalyst is reusable without significant loss in catalytic activity.



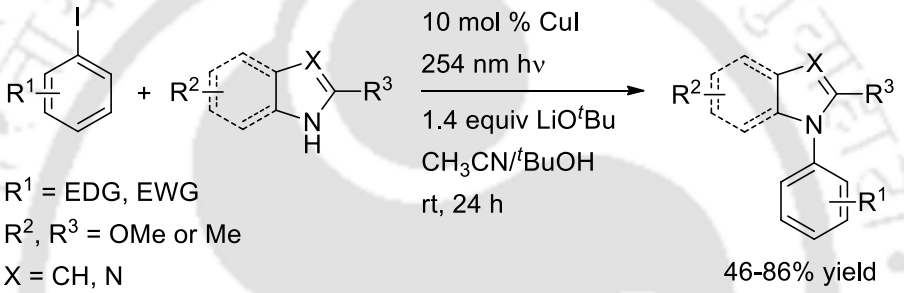
Scheme 9. CuO Nanoparticle Catalyzed N-Arylation of Heretocycles



Scheme 10. CuI-Catalyzed *N*-Arylation of π-Excessive Nitrogen Heterocycles

Buchwald and co-workers presented a CuI-catalyzed *N*-arylation of π-excessive nitrogen heterocycles such as pyrroles, pyrazoles, indazoles, imidazoles, and triazoles by coupling with aryl iodides or aryl bromides in the presence of diamine ligands (Scheme 10).[5c] The catalytic system is general for various nitrogen containing heterocycles and could tolerate hindered substrates and various functional groups such as aldehydes, ketones, alcohols, primary amines and nitriles on the aryl halide or heterocycle.

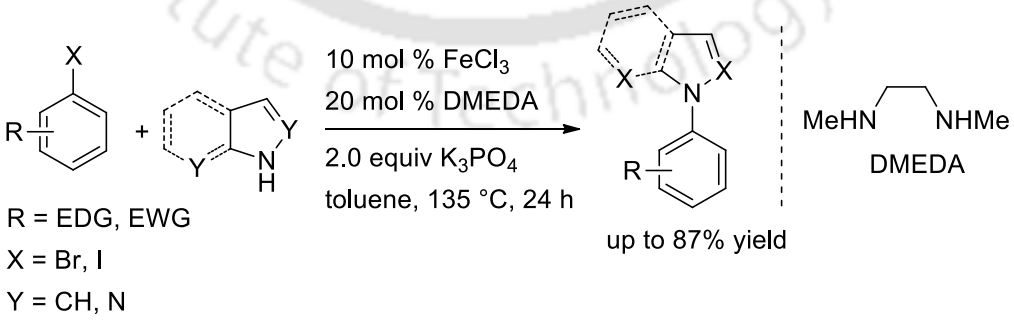
Fu and co-workers devised photoinduced CuI catalyzed C−N coupling of pharmacophores such as indoles, benzimidazoles, and imidazoles with hindered/deactivated/heterocyclic aryl iodides (Scheme 11).[5e] This protocol features the use of simple and inexpensive Cu catalyst without ligand under mild conditions.



Scheme 11. Photoinduced Cu-Catalyzed *N*-Arylation of Heterocycles

4.1.4. Fe-Catalyzed *N*-Arylation of Azoles

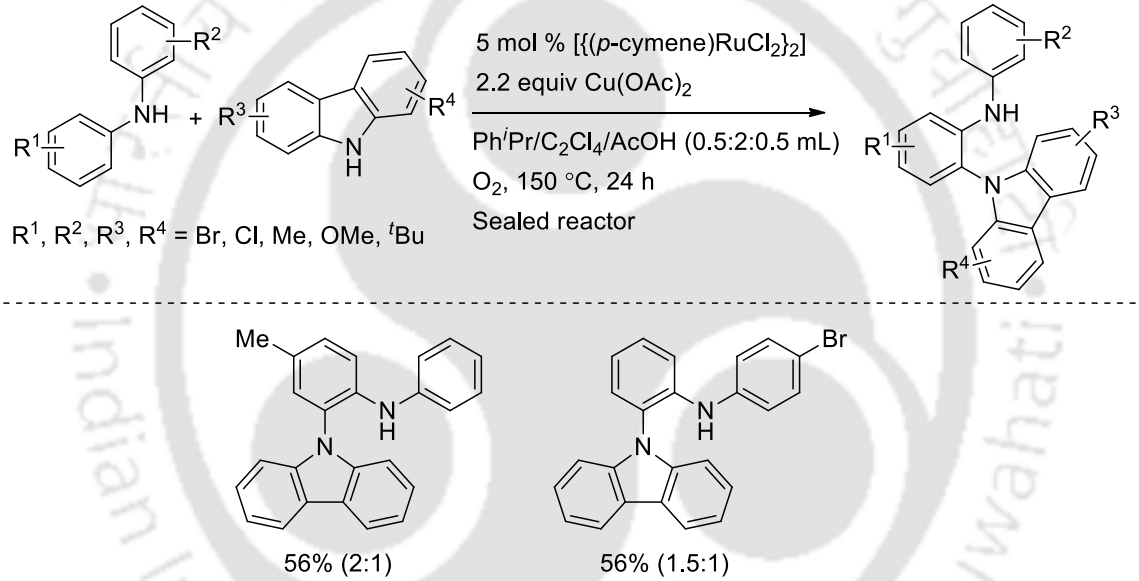
Bolm and co-workers developed Fe-catalyzed *N*-arylation of azoles using DMEDA as a ligand in presence of K_3PO_4 at elevated temperatures. The protocol exhibits broad scope in terms of azoles as well as aryl halides (Scheme 12).



Scheme 12. Fe-catalyzed *N*-arylation of azoles

4.1.5. *N*-Arylation of Azoles *via* Cross-Dehydrogenative Coupling

Transition-metal-catalyzed cross-dehydrogenative coupling (CDC) reactions are particularly attractive because they obviates the use of preactivation and/or preoxidation of either coupling partners and they are also atom economical. For example, Patureau and co-workers carried out the regioselective *N*-arylation of carbazoles *via* CDC using $[Ru(p\text{-cymene})Cl_2]_2$ catalyst and $Cu(OAc)_2$ as a sole oxidant in the presence of O_2 as a terminal oxidant at high temperature (Scheme 13).[14] In case of unsymmetrical amine substrates having electron donating and electron withdrawing substituents on phenyl rings; amination occurs at the *ortho* position of most electron rich phenyl ring.

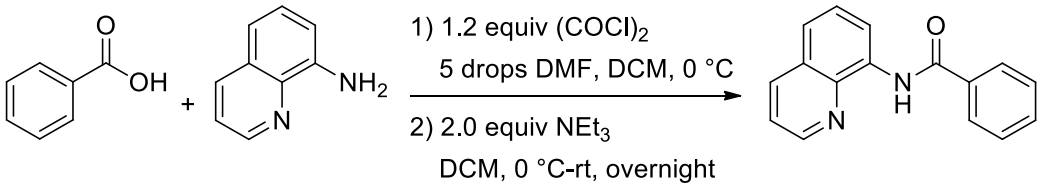


Scheme 13. Ru-Catalyzed *N*-arylation of azoles *via* CDC

4.2. Present Study

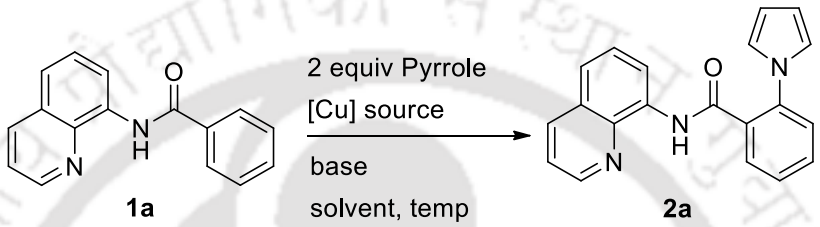
The synthesis of *N*-arylation of azoles such as pyridines, indoles, pyrazoles and carbazole using *N*-(quinolin-8-yl)benzamide as a directing group *via* Cu-mediated cross dehydrogenative coupling strategy.

Synthesis of *N*-(Quinolin-8-yl)benzamide (1a-r). The starting precursors, *N*-(quinolin-8-yl)benzamide, were prepared from coupling of acid chloride and amine in the presence of base.[17]



Scheme 14. Synthesis of *N*-(quinolin-8-yl)benzamide

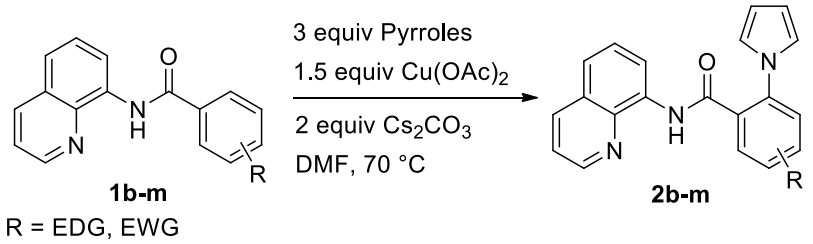
Table 1. Optimization of Reaction Conditions[a]

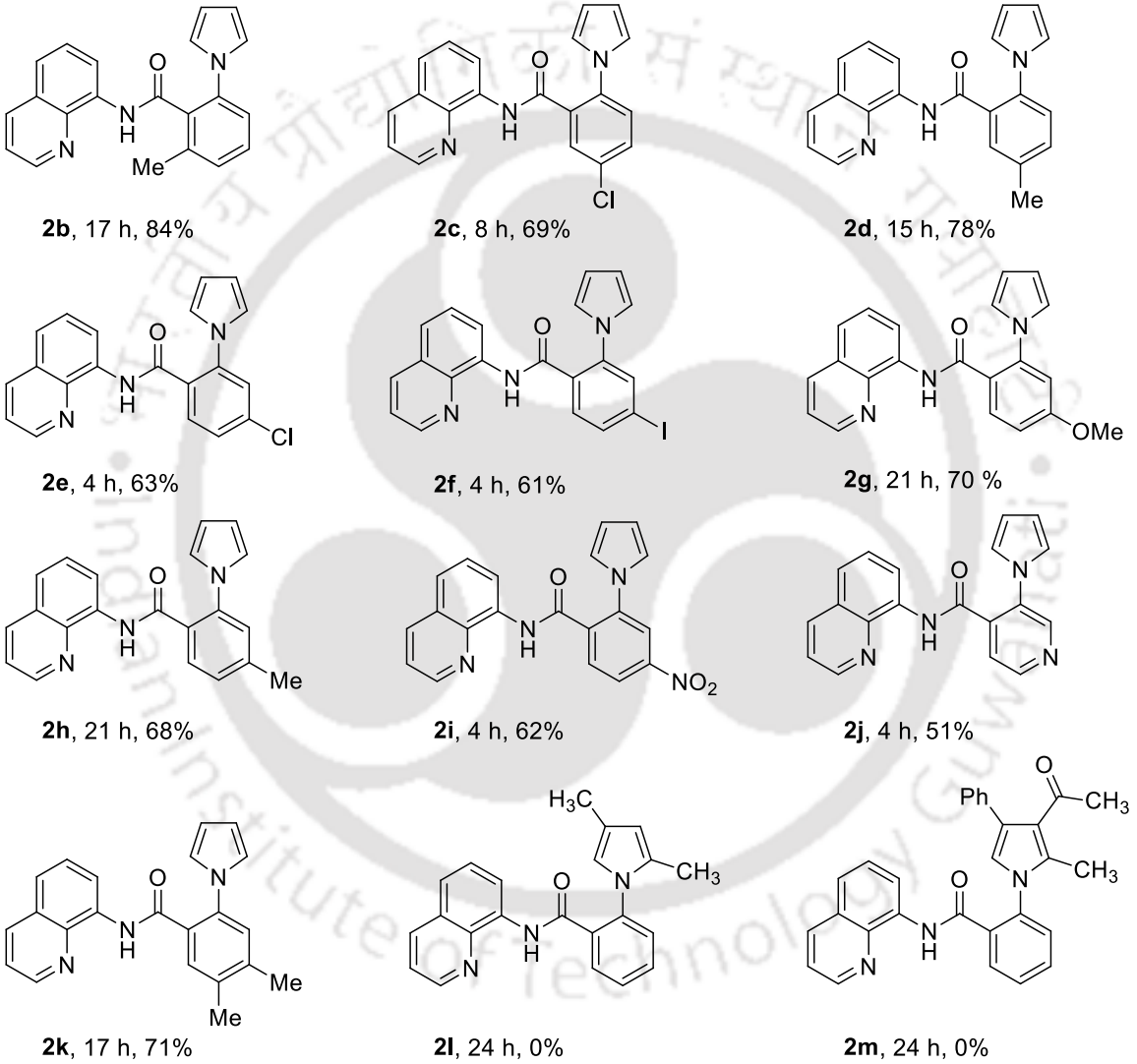


Entry	[Cu] (equiv)	Base	Solvent	Yield (%)[a,b]
1	$Cu(OAc)_2$ (1)	K_2CO_3	DMSO	34
2	$Cu(OAc)_2$ (1)	Na_2CO_3	DMSO	trace
3	$Cu(OAc)_2$ (1)	Cs_2CO_3	DMSO	44
4	$Cu(OAc)_2$ (1)	Cs_2CO_3	NMP	10
5	$Cu(OAc)_2$ (1)	Cs_2CO_3	*i*PrOH	trace
6	$Cu(OAc)_2$ (1)	Cs_2CO_3	1,4-dioxane	0
7	$Cu(OAc)_2$ (1)	Cs_2CO_3	DMF	51
8	$Cu(OAc)_2$ (1.5)	Cs_2CO_3	DMF	71
9	$Cu(OAc)_2$ (2.0)	Cs_2CO_3	DMF	70
10[c]	$Cu(OAc)_2$ (1.5)	Cs_2CO_3	DMF	64
11[d]	**$Cu(OAc)_2$ (1.5)**	**Cs_2CO_3**	**DMF**	**79**
12[e]	$Cu(OAc)_2$ (1.0)	Cs_2CO_3	DMF	50
13[e]	$Cu(OAc)_2$ (0.2)	Cs_2CO_3	DMF	18
14	-	Cs_2CO_3	DMF	0

[a] Reaction conditions: *N*-(quinolin-8-yl)benzamide **1a** (0.2 mmol), $Cu(OAc)_2$, pyrrole (0.4 mmol), base (0.4 mmol), solvent (1 mL), 70 °C, 21 h. [b] Isolated yield. [c] Pyrrole (0.3 mmol) was used. [d] Pyrrole (0.6 mmol) was used. [e] Using O_2 ballon.

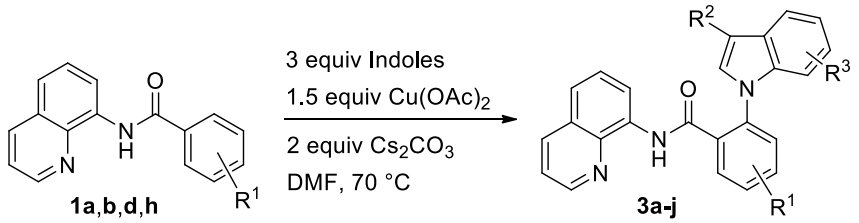
Table 2. Reaction of *N*-(Quinolin-8-yl)benzamide **1a** with Different Pyrroles[a-b]

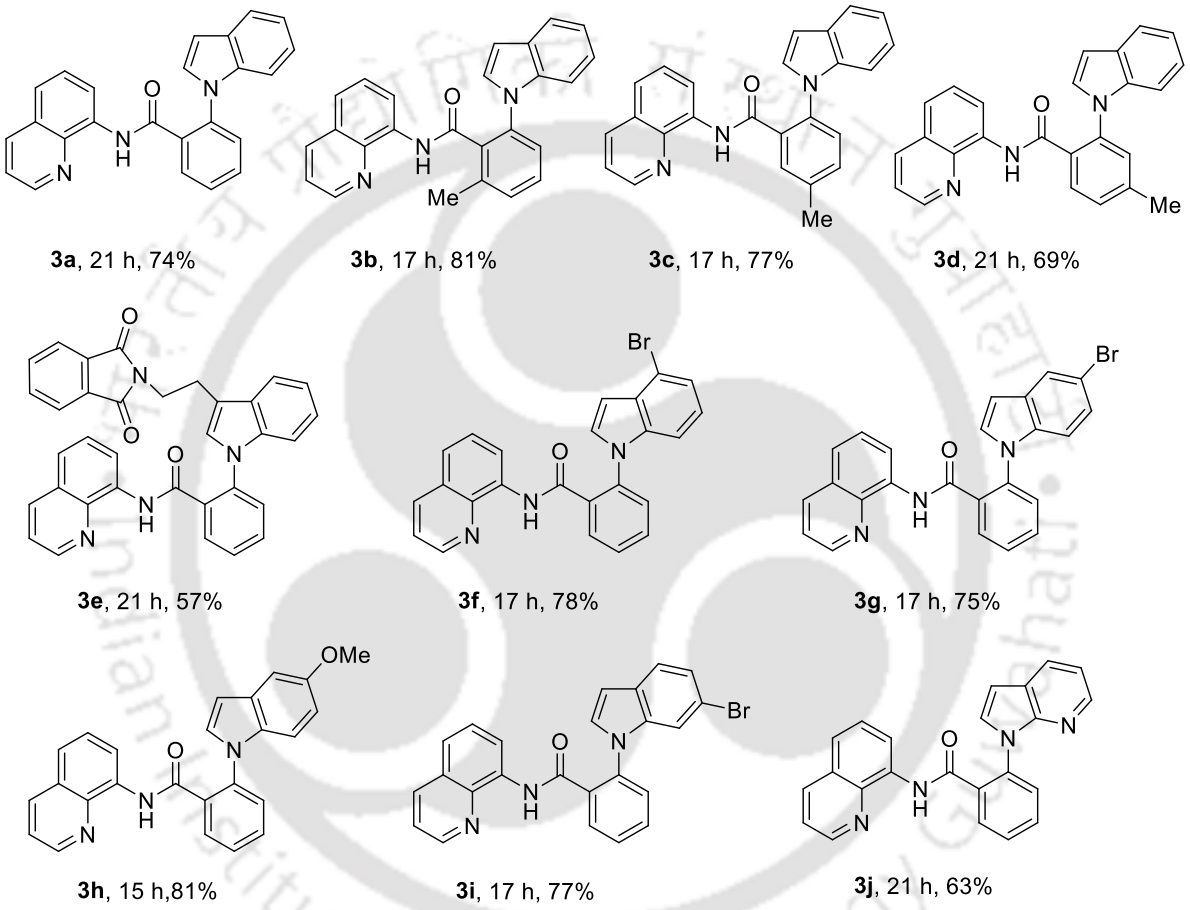




[a] Reaction conditions: *N*-(quinolin-8-yl)benzamide **1a** (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol), pyrrole (0.6 mmol), Cs_2CO_3 (0.4 mmol), DMF (1 mL), 70 °C. [b] Isolated yield.

Table 3. Reaction of *N*-(Quinolin-8-yl)benzamide **1a** with Different Indoles[a,b]





[a] Reaction conditions: *N*-(quinolin-8-yl)benzamide **1a** (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol), indole (0.6 mmol), Cs_2CO_3 (0.4 mmol), DMF (1 mL), 70 °C. [b] Isolated yield.

Optimization reaction conditions for amination was carried out using *N*-(quinolin-8-yl)benzamide **1a** and pyrrole as the model substrates with different bases, solvents and varied amounts of $Cu(OAc)_2$ (Table 1). To our delight, the amination selectively occurred at the *ortho*-position to furnish the target product **2a** in 34% yield when the substrates were stirred with 1 equiv $Cu(OAc)_2$ at 70 °C in the presence of K_2CO_3 in DMSO (entry 1). The use of

Cs_2CO_3 as the base led to an increase in the product formation to 44% (entry 3), while Na_2CO_3 afforded inferior results (entry 2). Solvent screening experiments showed that the choice of the solvent DMF led to an increase in the yield to 51%, whereas NMP, *i*PrOH and 1,4-dioxane were not effective (entries 4-7). Increasing the amount of $Cu(OAc)_2$ (1.5 equiv) and pyrrole (3 equiv) led to the further improvement in the yield to 79% (entries 8-11). Recrystallization of **2a** in CH_3CN gave single crystal whose structure was determined by X-ray analysis (Figure 3). A control experiment confirmed that in the absence of $Cu(OAc)_2$ the formation of **2a** was not observed and the starting material was recovered intact.

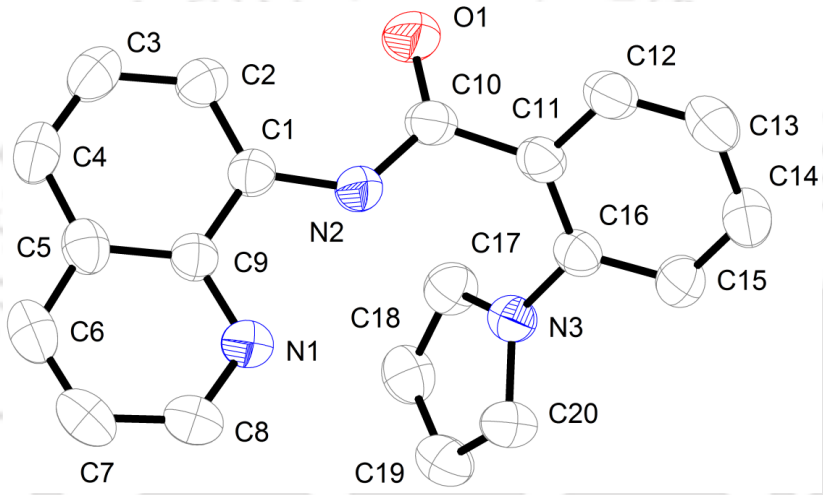
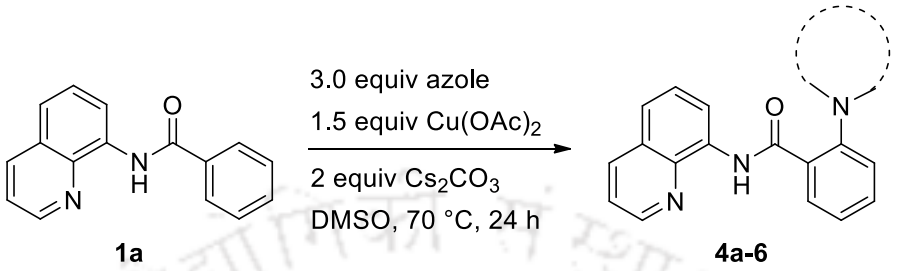


Figure 3. ORTEP diagram of 2-(1*H*-Pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide **2a** with 50% ellipsoid [CCDC 1427013].

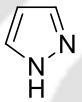
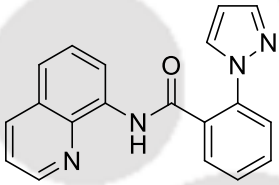
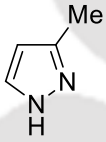
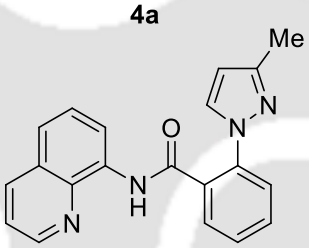
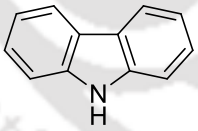
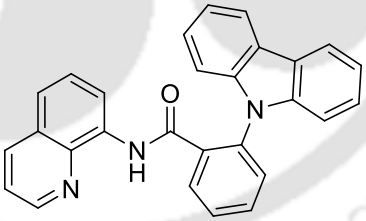
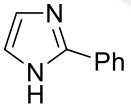
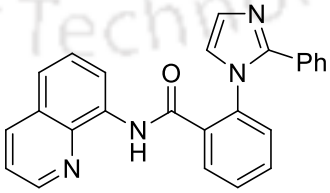
Having the optimal conditions in hand, we investigate the scope of the protocol for the reaction of pyrrole with a series of substitted 8-aminoquinoline amide derivatives (Table 2). The substrates **1b** having 2-Me substituent underwent reaction to give the desired product **2b** in 84% yield. The substrates **1c-d** bearing 3-Cl and 3-Me functionalities readily reacted to furnish the target products **2c** and **2d** in 69 and 78% yields, respectively, while **1e-i** bearing electron donating and electron withdrawing groups in the *para* position proceeded reaction smoothly to afford the corresponding *ortho*-aminated products **2e-i** in 61-70% yields. Heterocyclic derivative, isonicotinamide **1j** underwent reaction to give the aminated product **2j** in 51% yield, whereas disubstituted derivative 3,4-diMe **1k** underwent of reaction to yield the target product **2k** in 71% yield. In case of reaction highly substituted pyrrole such as 1-(2-

methyl-4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one using 8-aminoquinoline amide, no product was observed and the starting material was recovered intact.

Table 4. Substrate Scope of *N*-(Quinolin-8-yl)benzamide **1a** with Different Azoles[a-c]



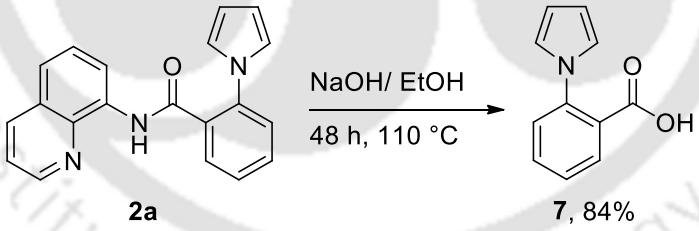
1a **4a-6**

entry	azole (3 equiv)	product	yield (%)[a,b]
1		 **4a**	54 (12)[c]
2		 **4b**	58 (14)[c]
3		 **5**	41 (7)[c]
4		 **6**	0

[a] Reaction conditions: *N*-(quinolin-8-yl)benzamide **1a** (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol), azole (0.6 mmol), Cs_2CO_3 (0.4 mmol), DMSO (1 mL), 70 °C, 24 h. [b] Isolated yield. [c] Using DMF.

These results suggest that the protocol is compatible with the substrates bearing substitution at *ortho*, *meta* as well as *para* positions. As well as the substrates bearing electron withdrawing group proceeded smoothly to furnish the target products. In case of substrates bearing electron withdrawing groups **2i** exhibit greater reactivity compared to that having electron donating group **2g**. In addition, the substrates containing halides such as chlorine **2c**, **2e** and iodine **2i** are tolerated to produce to give the target products under these reaction conditions. Furthermore, we explored the scope of the procedure for the reactions of different azoles with *N*-(quinolin-8-yl)benzamide **1a** as the representative example **(**Table 4). These reactions exhibited superior results employing DMSO as the solvent compared to that of DMF. For examples, pyrazole underwent reaction to produce the target product **4a** in 54% yield.

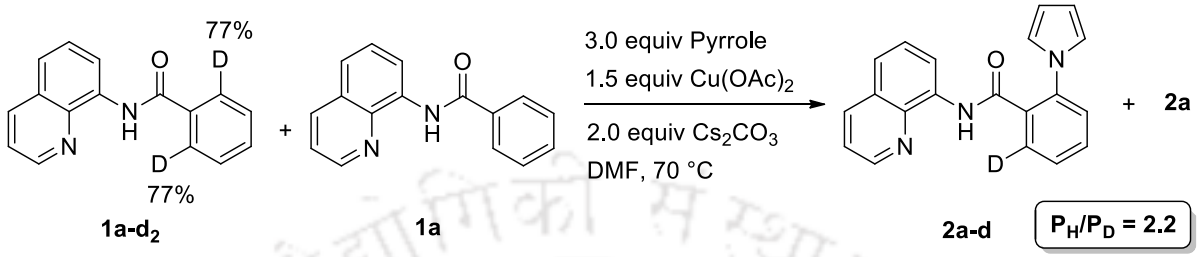
Similarly, with 3-methylpyrazole proceeded to afford the formation of **4b** in 58% yield. In addition, the reaction of carbazole produced the desired cross-coupled product **5** in 41% yield. 2-phenylimidazole failed react to yield **6** and starting materials were recovered. Finally, the removal of the directing group was revealed using compound **2a** as the representative example (Scheme 15).[13e] The compound **2a** underwent readily hydrolysis in presence of NaOH in ethanol at 110 °C to afford 2-(1*H*-pyrrol-1-yl) benzoic acid **7** in 84% yield.



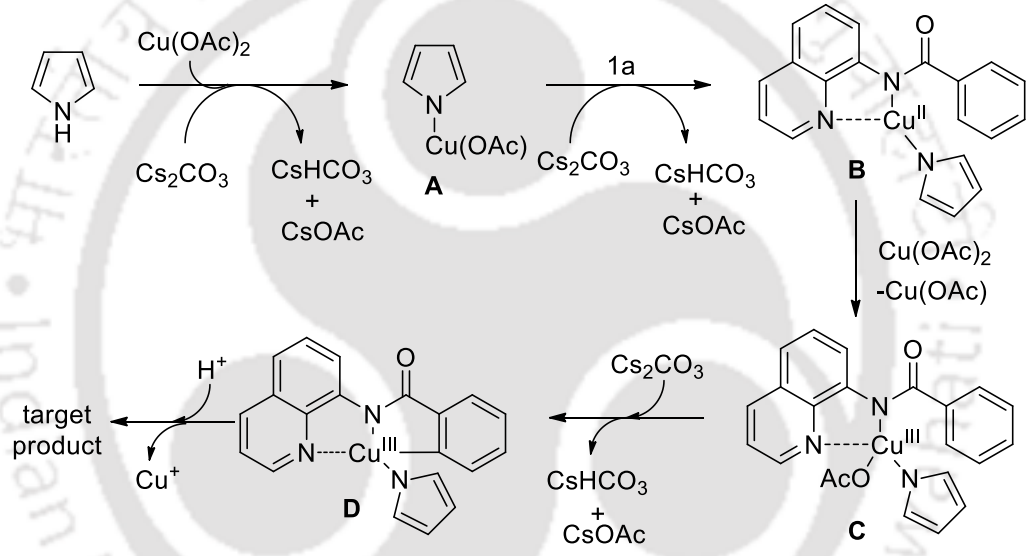
Scheme 15. Removal of Directing Group

The proposed reaction pathway is shown in Scheme 17. The Kinetic isotope suggest that the C-H bond cleavage taking place in the rate determining step. First, In the presence of base, azole may undergo reaction with $Cu(OAc)_2$ to give copper(II) species **A**,[14] which may react with the substrate **1a** *via* ligand exchange to produce copper(II) intermediate **B**. $Cu(OAc)_2$-mediated oxidation of **B** may lead to the formation of copper(III) species **C**. Intramolecular C-H cupration of the aryl ring may give the intermediate **D**, which can

provide the target product by reductive elimination followed by protonation. This proposed reaction pathway also explains the necessity of excess $Cu(OAc)_2$ and base to furnish the desired products in good yields.



Scheme 16. Kinetic Isotope Study



Scheme 17. Proposed Catalytic Cycle

In summary, Cu-mediated 8-aminoquinoline amide directed *N*-arylation of pyrroles, indoles, pyrazoles and carbazole is developed via intermolecular cross-dehydrogenative coupling reaction. This protocol exhibits broad substrate scope and high functional group tolerance, which may open a new avenue for further development of dehydrogenative coupling protocols for the coupling azoles with hydrocarbons.

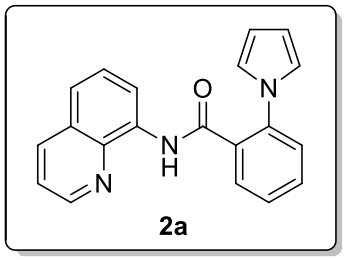
4.3. Experimental Section

4.3.1. General Information: $Cu(OAc)_2$ (98%), Cs_2CO_3, 8-aminoquinoline (98%), pyrazole (98%), 3-methylpyrazole (97%) and 2-phenyl imidazole (98%) were purchased

from Aldrich and used as received. Pyrrole (99%) was purchased from Otto and distilled under nitrogen according to the standard procedure.[1] Indole (99%) was purchased from Otto and used as received. Substituted indoles and pyrroles were purchased from Avra synthesis. The solvents were purchased and dried according to standard procedure prior to use.[2] Substituted 8-aminoquinoline amides were prepared according to reported procedure.[3] 1-(2-methyl-4-phenyl-1H-pyrrol-3-yl)ethan-1-one[4] and 2-(2-(1H-indol-3-yl)ethyl)isoindoline-1,3-dione[5] were prepared according to the literature procedure. Purification of the reaction products was carried out by column chromatography using Merck aluminium oxide active, neutral Activity I-II . Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on Bruker Avance III 600 using $CDCl_3$ as solvent and Me_4Si as internal standard. Chemical shifts (δ) were reported in ppm and spin-spin coupling constants (J) were given in Hz. Melting points were determined using Büchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Thermo Fisher Scientific spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS Instrument (model HAB 273). X-Ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation. The structure was solved by direct method using *SHELXL-97* (Göttingen, Germany).

4.3.2. General Procedure for *N*-Arylation of Azoles. Azoles (0.6 mmol, 3 equiv) were added to a stirred solution of the substrates **1** (0.2 mmol, 1 equiv), $Cu(OAc)_2$ (0.3 mmol, 1.5 equiv, 54.5 mg), Cs_2CO_3 (0.4 mmol, 2 equiv, 130 mg) and solvent (1 mL) at 70 °C under air. The mixture was stirred and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After the appropriate time, the resulting solution was diluted with ethyl acetate (3 x 15 mL) and then washed with $NH_3{\cdot}H_2O$ (1 x 5 mL) and brine (2 x 5 mL). Drying over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on neutral alumina column chromatography using n-hexane and ethyl acetate as eluent to afford analytically pure substituted *N*-arylated azoles.

4.4. Characterization Data of Substituted *N*-Arylated of Azoles 2a-w



2a

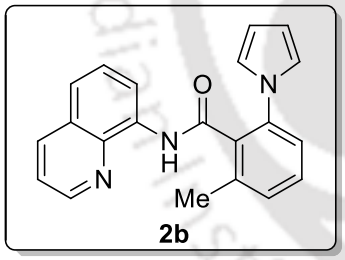
2-(1*H*-Pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; white solid; 49 mg, yield 79%; mp 141-142 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.84 (d, *J* = 7.8 Hz, 1H), 8.66-8.65 (m, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.59-7.44 (m, 5H), 7.41-7.39 (m, 1H), 6.99 (s, 2H), 6.18 (s, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 165.8, 148.1, 138.9, 138.6, 136.3, 134.7, 132.6, 131.6, 130.1, 128.0, 127.5, 126.5, 122.13, 122.1, 121.8, 121.5, 116.8, 110.6.

FT-IR (KBr) 1670, 1601, 1522, 1498, 1385, 1329, 1262, 1070, 1014, 924, 898 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{15}N_3O$ 314.1293, found 314.1286.



2b

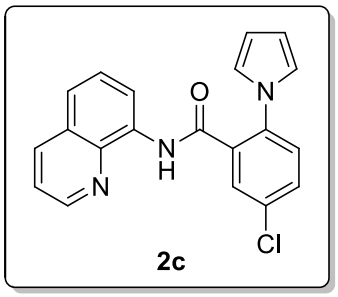
2-Methyl-6-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; white solid; 55 mg, yield 84%; mp 146-147 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.72 (br s, 1H), 8.82 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 8.68 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.13 (dd, *J* = 9.0 Hz, 1.8 Hz, 1H), 7.55-7.50 (m, 2H), 7.43-7.39 (m, 2H), 7.29-7.27 (m, 2H), 7.00-6.99 (m, 2H), 6.10-6.09 (m, 2H), 2.52 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 166.4, 148.3, 138.63, 138.6, 137.4, 136.4, 134.4, 133.6, 130.1, 129.3, 128.1, 127.5, 123.4, 122.2, 121.8, 116.9, 110.0, 19.9.

FT-IR (KBr) 3471, 1676, 1510, 1483, 1326, 1265, 1123, 1088, 951, 897 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}N_3O$ 328.1450, found 328.1448.



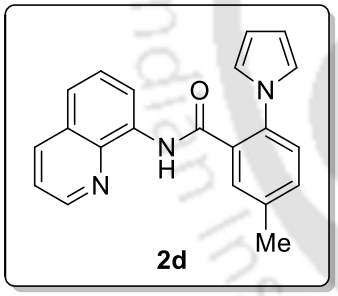
5-Chloro-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; white solid; 48 mg, yield 69%; mp 173-174 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.80 (d, *J* = 7.2 Hz, 1H), 8.65 (d, *J* = 3.6 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.55-7.51 (m, 3H), 7.42-7.40 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 2H), 6.19 (s, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.2, 148.2, 138.5, 137.3, 136.3, 134.3, 133.7, 133.3, 131.6, 130.1, 128.0, 127.8, 127.4, 122.4, 122.1, 121.9, 116.9, 111.0.

FT-IR (KBr) 3330, 1670, 1523, 1494, 1327, 1260, 1108, 1073, 925, 825 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{14}ClN_3O$ 348.0904, found 348.0901.



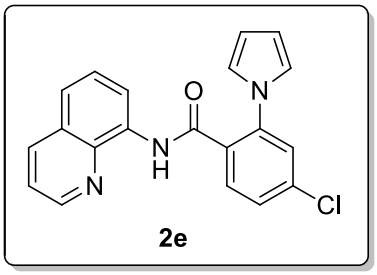
5-Methyl-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; white solid; 51 mg, yield 78%; mp 145-146 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.87 (br s, 1H), 8.83 (d, *J* = 7.2 Hz, 1H), 8.65 (d, *J* = 3.6 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.69 (s, 1H), 7.55-7.49 (m, 2H), 7.41-7.36 (m, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 2H), 6.16 (s, 2H), 2.46 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 166.0, 148.1, 138.6, 137.6, 136.4, 136.3, 134.7, 132.4, 132.2, 130.5, 128.0, 127.5, 126.4, 122.2, 122.0, 121.8, 116.8, 110.4, 21.2.

FT-IR (KBr) 1665, 1648, 1524, 1485, 1384, 1327, 1262, 1070, 1015, 824 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}N_3O$ 328.1450, found 328.1458.



2e

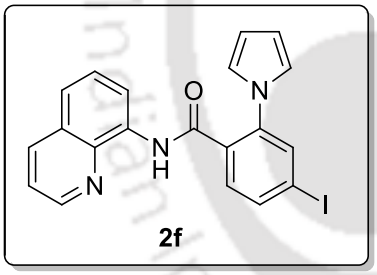
4-Chloro-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; thick liquid; 44 mg, yield 63%.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.81 (d, *J* = 7.2 Hz, 1H), 8.64 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.55-7.50 (m, 2H), 7.45-7.44 (m, 2H), 7.41-7.39 (m, 1H), 6.97 (s, 2H), 6.19 (s, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.8, 148.1, 139.8, 138.5, 137.3, 136.3, 134.4, 131.5, 130.7, 128.0, 127.6, 127.4, 126.5, 122.3, 122.0, 121.9, 116.8, 111.2.

FT-IR (neat) 1673, 1595, 1527, 1482, 1385, 1326, 1263, 1108, 1021, 920, 825 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{14}ClN_3O$ 348.0904, found 348.0904.



2f

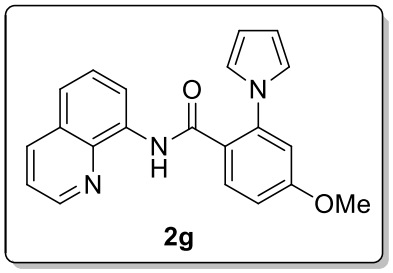
4-Iodo-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; white solid; 54 mg, yield 61%; mp 125-126 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.80 (d, *J* = 7.2 Hz, 1H), 8.64-8.63 (m, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.82-7.81 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.55-7.50 (m, 2H), 7.41-7.39 (m, 1H), 6.96 (s, 2H), 6.18 (s, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.9, 148.2, 139.6, 138.5, 136.5, 136.3, 135.3, 134.4, 131.8, 131.5, 128.0, 127.4, 122.3, 122.0, 121.9, 116.8, 111.2, 97.1.

FT-IR (KBr) 1669, 1583, 1523, 1488, 1384, 1263, 1067, 1017, 929, 896 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{14}IN_3O$ 440.0260, found 440.0266.



2g

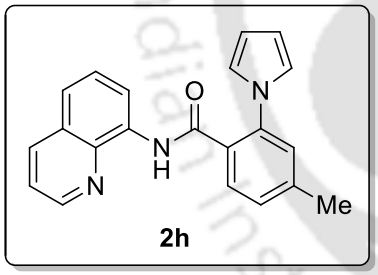
4-Methoxy-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.32; white solid; 48 mg, yield 70%; mp 127-128 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 8.83 (d, *J* = 7.2 Hz, 1H), 8.63 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 8.11 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.39-7.37 (m, 1H), 7.01-6.98 (m, 3H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.192-6.19 (m, 2H), 3.90 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 165.4, 162.1, 148.0, 140.5, 138.6, 136.2, 134.8, 132.0, 128.0, 127.5, 124.8, 122.1, 121.8, 121.7, 116.6, 113.2, 111.9, 110.7, 55.9.

FT-IR (KBr) 3439, 1664, 1609, 1522, 1325, 1246, 1232, 1048, 898 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}N_3O_2$ 344.1399, found 344.1402.



2h

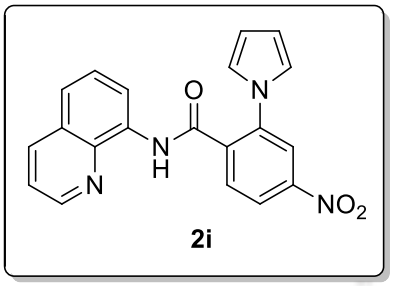
4-Methyl-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; white solid; 44 mg, yield 68%; mp 140-141 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.89 (br s, 1H), 8.84 (d, *J* = 7.2 Hz, 1H), 8.64-8.63 (m, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.39-7.37 (m, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 6.98 (s, 2H), 6.18 (s, 2H), 2.46 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 165.8, 148.0, 142.3, 138.8, 138.6, 136.2, 134.7, 130.2, 129.7, 128.2, 128.0, 127.5, 127.1, 122.1, 121.9, 121.7, 116.7, 110.5, 21.5.

FT-IR (KBr) 1668, 1614, 1524, 1487, 1385, 1326, 1262, 1099, 1072, 897 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}N_3O$ 328.1450, found 328.1451.



2i

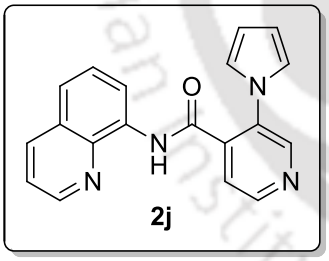
4-Nitro-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.10; thick yellow liquid; 44 mg, yield 62%.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.99 (br s, 1H), 8.80 (d, *J* = 3.6 Hz, 1H), 8.65 (d, *J* = 3.6 Hz, 1H), 8.32-8.29 (m, 2H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 3.6 Hz, 2H), 7.44-7.42 (m, 1H), 7.03 (s, 2H), 6.24 (s, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 163.8, 149.4, 148.3, 139.7, 138.5, 137.4, 136.4, 134.0, 131.5, 128.0, 127.4, 122.8, 122.0, 121.9, 121.8, 121.3, 117.1, 111.9.

FT-IR (neat) 1678, 1525, 1486, 1348, 1262, 1074, 1023, 946, 898 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{14}N_4O_3$ 359.1144, found 359.1147.



2j

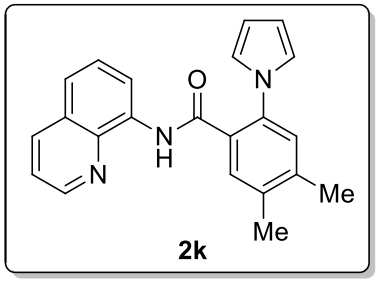
3-(1*H*-Pyrrol-1-yl)-*N*-(quinolin-8-yl)isonicotinamide 2j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.20; white solid; 32 mg, yield 51%; mp 179-180 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.03 (br s, 1H), 8.81 (t, *J* = 4.2 Hz, 1H), 8.78 (s, 1H), 8.75 (d, *J* = 4.8 Hz, 1H), 8.66-8.65 (m, 1H), 8.15-8.14 (m, 1H), 7.79 (d, *J* = 4.8 Hz, 1H), 7.56 (d, *J* = 4.2 Hz, 2H), 7.44-7.42 (m, 1H), 7.015-7.01 (m, 2H), 6.273-6.27 (m, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 163.3, 148.9, 148.3, 147.9, 138.7, 138.5, 136.4, 134.2, 134.0, 128.0, 127.4, 123.2, 122.8, 122.2, 122.0, 117.2, 111.6.

FT-IR (KBr) 1677, 1527, 1486, 1425, 1326, 1265, 1114, 1076, 1013, 922, 826 cm^{-1}.

HRMS (APCI) m/z: $[M+H]^+$ calcd for $C_{19}H_{14}N_4O$ 315.1246, found 315.1243.



2k

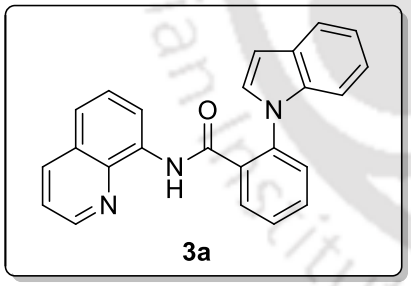
4,5-Dimethyl-2-(1*H*-pyrrol-1-yl)-*N*-(quinolin-8-yl)benzamide 2k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; white solid; 48 mg, yield 71%; mp 195-196 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.87 (br s, 1H), 8.83 (d, *J* = 7.8 Hz, 1H), 8.63 (d, *J* = 3.0 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.39-7.37 (m, 1H), 7.20 (s, 1H), 6.95 (s, 2H), 6.16 (s, 2H), 2.37 (s, 3H), 2.36 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 165.9, 148.0, 140.8, 138.6, 136.6, 136.3, 136.2, 134.8, 131.1, 129.8, 128.0, 127.7, 127.5, 122.2, 121.9, 121.7, 116.7, 110.3, 19.9, 19.5.

FT-IR (KBr) 1662, 1529, 1488, 1385, 1329, 1263, 1090, 1023, 862 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}N_3O$ 342.1606, found 342.1608.



3a

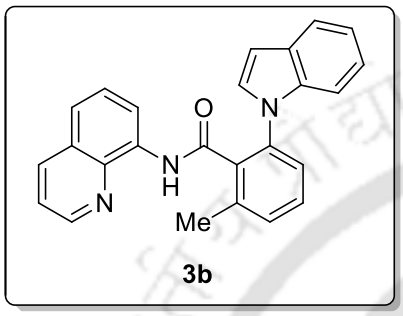
2-(1*H*-Indol-1-yl)-*N*-(quinolin-8-yl)benzamide 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; white solid; 54 mg, yield 74%; mp 133-134°C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.96 (br s, 1H), 8.72 (d, *J* = 7.2 Hz, 1H), 8.14-8.13 (m, 1H), 8.02 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.66 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.59-7.51 (m, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 3.0 Hz, 1H), 7.26-7.24 (m, 1H), 7.23-7.20 (m, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H).

$^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 164.9, 147.8, 138.2, 137.5, 137.1, 135.9, 134.4, 133.6, 132.0, 131.3, 129.6, 129.1, 128.3, 128.2, 127.7, 127.3, 122.8, 121.9, 121.5, 121.2, 120.6, 116.5, 110.7, 104.8.

FT-IR (KBr) 1672, 1596, 1482, 1385, 1326, 1264, 1212,1143, 1012, 897 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{17}N_3O$ 364.1450, found 364.1451.



3b

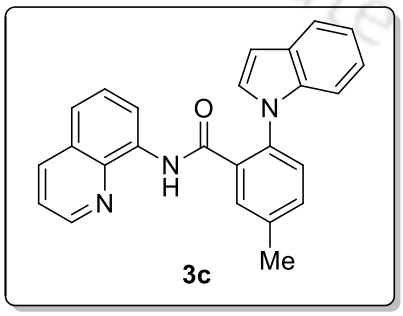
2-(1*H*-Indol-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide 3b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; white solid; 61 mg, yield 81%; mp 175-176 °C.

^1H NMR (600 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 8.64 (d, *J* = 7.2 Hz, 1H), 8.29 (d, *J* = 3.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.50-7.39 (m, 5H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.32 (s, 1H), 7.25-7.23 (m, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.36 (s, 1H), 2.57 (s, 3H).

$^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 165.9, 147.9, 138.2, 138.1, 137.5, 136.7, 136.1, 135.5, 134.1, 130.2, 130.1, 129.1, 128.9, 127.7, 127.2, 125.4, 122.3, 122.1, 121.5, 120.9, 120.3, 116.6, 110.8, 103.7, 20.0.

FT-IR (KBr) 1675, 1596, 1524, 1482, 1385, 1326, 1264, 1212, 1116, 1012, 897 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{19}N_3O$ 378.1606, found 378.1598.



3c

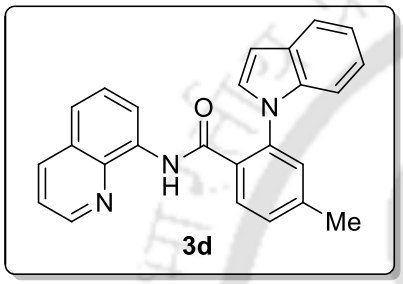
2-(1*H*-Indol-1-yl)-5-methyl-*N*-(quinolin-8-yl)benzamide 3c . Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; white solid; 58 mg, yield 77%; mp 147-148 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.94 (br s, 1H), 8.72 (d, *J* = 7.2 Hz, 1H), 8.00-7.97 (m, 2H), 7.94 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.47-7.39 (m, 6H), 7.25-7.20 (m, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 3.0 Hz, 1H), 2.53 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 165.1, 147.7, 138.4, 138.3, 137.7, 135.9, 134.5, 133.3, 132.7, 131.6, 129.5, 129.2, 128.3, 127.7, 127.3, 122.7, 121.8, 121.5, 121.1, 120.5, 116.5, 110.7, 104.6, 21.3.

FT-IR (KBr) 1729, 1667, 1524, 1485, 1384, 1327,1260, 1133, 928, 825 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{19}N_3O$ 378.1606, found 378.1604.



3d

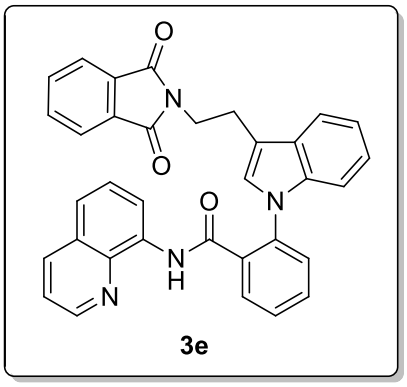
2-(1*H*-Indol-1-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide 3d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colourless thick liquid; 52 mg, yield 69%.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (br s, 1H), 8.72 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.98-7.96 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.33 (s, 1H), 7.27-7.23 (m, 2H), 7.22-7.19 (m, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 2.48 (s, 3H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.9, 147.7, 142.8, 138.2, 137.6, 137.0, 135.9, 134.5, 131.3, 130.5, 129.6, 129.2, 129.1, 128.8, 127.7, 127.3, 122.7, 121.7, 121.5, 121.2, 120.6, 116.4, 110.7, 104.8, 21.5.

FT-IR (neat) 1666, 1527, 1461, 1327, 1276, 1212, 1135, 1012, 900 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{19}N_3O$ 378.1606, found 378.1597.



3e

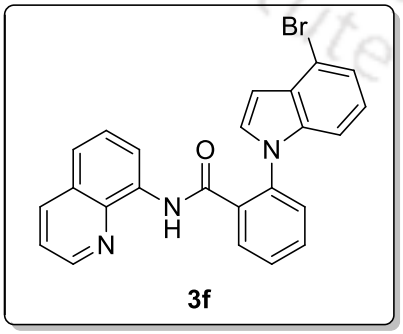
2-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-*N*-(quinolin-8-yl)benzamide 3e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.24; white solid; 61 mg, yield 57%; mp 179-180 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.71 (d, *J* = 7.2 Hz, 1H), 8.18 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.99 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 7.95 (dd, *J* = 9.2 Hz, 1.2 Hz, 1H), 7.80-7.94 (m, 2H), 7.69-7.63 (m, 2H), 7.59-7.57 (m, 2H), 7.56-7.52 (m, 2H), 7.47-7.42 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.27-7.25 (m, 1H), 7.23-7.21 (m, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 3.42-3.39 (m, 2H), 2.90-2.87 (m, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 168.3, 165.0, 147.8, 138.1, 137.9, 137.0, 135.9, 134.4, 134.1, 133.4, 132.3, 132.0, 131.4,129.1, 128.1, 127.6, 127.3, 126.8, 123.3, 123.1, 121.8, 121.5, 120.5, 120.5, 119.3, 116.4, 114.7, 110.7, 37.9, 24.5.

FT-IR (KBr) 2921, 1770, 1711, 1668, 1527, 1486, 1397, 1328, 1258, 1224,1128, 1052, 825 cm^{-1}.

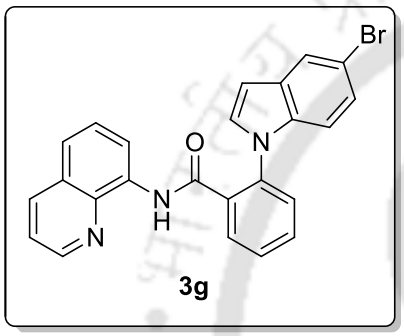
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{34}H_{24}N_4O_3$ 537.1927, found 537.1294.



3f

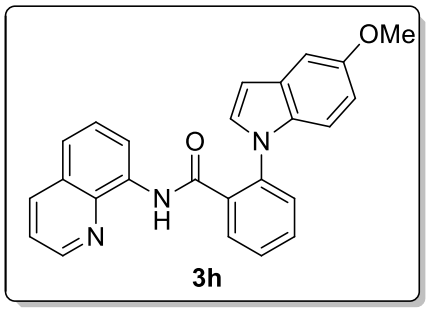
2-(4-Bromo-1*H*-indol-1-yl)-*N*-(quinolin-8-yl) 3f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; white solid; 69 mg, yield 78%; mp 148-149 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (br s, 1H), 8.63 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 4.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.60-7.51 (m, 2H), 7.43-7.30 (m, 4H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.22-7.17 (m, 2H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 3.2 Hz, 1H).
^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 164.6, 147.9, 138.2, 137.8, 136.6, 136.1, 134.2, 133.5, 132.1, 131.4, 130.3, 129.7, 128.7, 128.4, 127.7, 127.2, 123.7, 123.6, 122.1, 121.7, 116.6, 115.1, 109.9, 105.1.
FT-IR (KBr) 1668, 1596, 1486, 1385, 1359, 1297, 1203, 1179, 1086, 888 cm^{-1}.
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{16}BrN_3O$ 444.0535, found 444.0532.



3g

2-(5-Bromo-1*H*-indol-1-yl)-*N*-(quinolin-8-yl)benzamide 3g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; white solid; 66 mg, yield 75%; mp 141-142 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 8.71 (dd, *J* = 7.6 Hz, 2.0 Hz, 1H), 8.11-8.09 (m, 2H), 8.02 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.67-7.65 (m, 1H), 7.62-7.58 (m, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.48-7.41 (m, 2H), 7.34 (d, *J* = 2.4 Hz, 2H), 7.30-7.25 (m, 2H), 6.43 (d, J = 3.2 Hz, 1H).
^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.8, 147.8, 138.1, 136.5, 136.2, 136.1, 134.2, 133.9, 132.1, 131.2, 131.1, 130.3,128.7, 128.2, 127.7, 127.3, 125.6, 123.7, 122.1, 121.7, 116.4, 113.9, 112.2, 104.1.
FT-IR (KBr) 1669, 1596, 1486, 1386, 1327, 1289, 1227,1198, 1053, 896 cm^{-1}.
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{16}BrN_3O$ 442.0555, found 442.0554.



3h

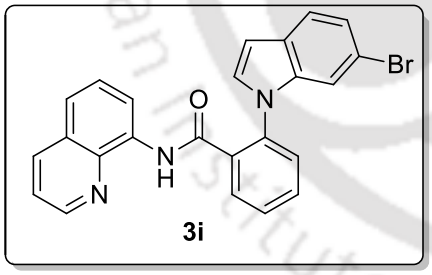
2-(5-Methoxy-1*H*-indol-1-yl)-*N*-(quinolin-8-yl)benzamide 3h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.32; white solid; 64 mg, yield 81%; mp 150-151 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (br s,1H), 8.73 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 8.13-8.09 (m, 2H), 7.99 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.66 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.58-7.52 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.41-7.36 (m, 2H), 7.27-7.22 (m, 2H), 6.97 (d, J = 2.4 Hz, 1H), 6.91-6.88 (m, 1H), 6.44 (d, J = 3.2 Hz, 1H), 3.81 (s, 3H).

^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 165.0, 154.8, 147.7, 138.2, 137.1, 136.0, 134.4, 133.5, 132.8, 131.9, 131.1, 130.1, 129.7, 128.1, 127.7, 127.2, 121.9, 121.5, 116.4, 112.8,111.4, 104.5, 102.9, 56.0.

FT-IR (KBr) 1668, 1598, 1487, 1386, 1327, 1256, 1218, 1193, 1032, 899 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{19}N_3O_2$ 394.1556, found 394.1556.



3i

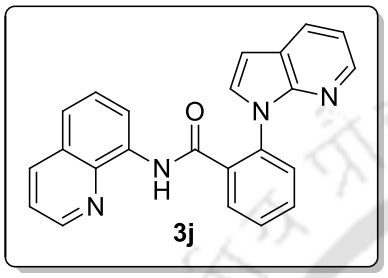
2-(6-Bromo-1*H*-indol-1-yl)-*N*-(quinolin-8-yl)benzamide 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; white solid; 68 mg, yield 77%; mp 110-111 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (br s, 1H), 8.63 (dd, J = 7.6 Hz, 1.6 Hz,1H), 8.03-7.99 (m, 2H), 7.91 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.60-7.57 (m, 2H), 7.54-7.50 (m, 1H), 7.46-7.37 (m, 1H), 7.35-7.31 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.17-7.14 (m, 3H), 6.36 (d, J = 3.2 Hz, 1H).

$^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 164.8, 147.9, 138.2, 138.1, 136.3, 136.0, 134.2, 134.1, 132.0, 131.1, 129.8, 128.7, 128.24, 128.2, 127.7, 127.2, 123.9, 122.4, 122.0, 121.6, 116.4, 116.3, 113.7, 104.7.

FT-IR (KBr) 1671, 1597, 1485, 1385, 1327, 1267, 1230, 1137, 1052, 891 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{16}BrN_3O$ 442.0555, found 442.0553.



3j

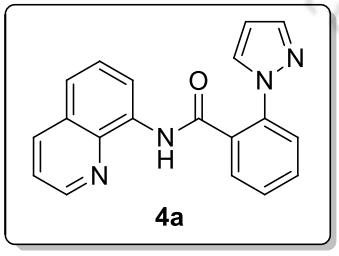
2-(1*H*-Pyrrolo[2,3-b]pyridin-1-yl)-*N*-(quinolin-8-yl)benzamide 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.28; colourless thick liquid; 46 mg, yield 63%.

^1H NMR (600 MHz, $CDCl_3$) δ 9.91 (br s, 1H), 8.60 (d, *J* = 7.2 Hz, 1H), 8.24 (d, *J* = 4.8 Hz, 1H), 8.12-8.11 (m, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.60-7.56 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.38-7.32 (m, 3H), 7.19-7.17 (m, 1H), 6.97-6.95 (m, 1H), 6.40 (d, *J* = 3.6 Hz, 1H).

$^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 165.5, 148.7, 147.9, 143.9, 138.3, 136.0, 135.6, 134.5, 134.2, 131.8, 130.4, 129.5, 129.2, 128.7, 128.4, 127.8, 127.3,121.8, 121.51, 121.5, 116.8, 116.5, 102.4.

FT-IR (KBr) 1670, 1586, 1485, 1384, 1326, 1281, 1202, 1130, 1052, 896 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{16}N_4O$ 365.1402, found 365.1408.



4a

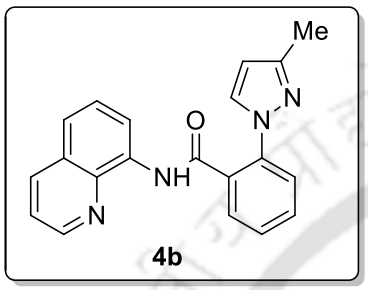
2-(1*H*-Pyrazol-1-yl)-*N*-(quinolin-8-yl)benzamide 4a. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.48; white solid; 34 mg, yield 54%; mp 122-123 °C.

^1H NMR (600 MHz, $CDCl_3$) δ 9.99 (br s, 1H), 8.83 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 8.70 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.13 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J*

= 2.4 Hz, 1H), 7.63-7.60 (m, 3H), 7.55-7.50 (m, 3H), 7.42-7.40 (m, 1H), 6.30-6.29 (m, 1H). $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 165.8, 148.3, 141.6, 138.6, 138.2, 136.3, 134.7, 132.5, 131.4, 130.7, 129.7, 128.4, 128.0, 127.5, 125.8, 122.1, 121.8, 116.9, 107.7.

FT-IR (KBr) 1671, 1603, 1520, 1485, 1385, 1326, 1265, 1099, 1043, 937, 826 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{14}N_4O$ 315.1246, found 315.1247.



4b

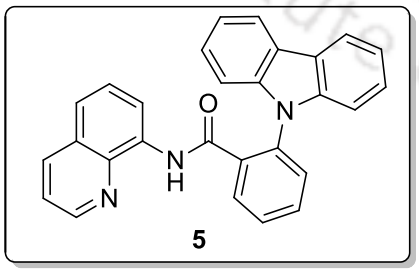
2-(3-Methyl-1*H*-pyrazol-1-yl)-*N*-(quinolin-8-yl)benzamide 4b. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.51; colourless thick liquid; 38 mg, yield 58%.

^1H NMR (600 MHz, $CDCl_3$) δ 10.01 (br s, 1H), 8.83 (d, *J* = 7.8 Hz, 1H), 8.70 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.13 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.85-7.84 (m, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.62-7.57 (m, 2H), 7.55-7.47 (m, 3H), 7.41-7.39 (m, 1H), 6.042-6.04 (m, 1H), 2.18 (s, 3H).

$^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 166.0, 150.9, 148.3, 138.7, 138.2, 136.3, 134.8, 132.2, 131.6, 131.5, 129.8, 128.1, 128.0, 127.4, 125.9, 122.1, 121.8, 116.9, 107.7, 13.8.

FT-IR (neat) 1676, 1524, 1485, 1326, 1265, 1129, 948, 826 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{16}N_4O$ 329.1402, found 329.1403.



5

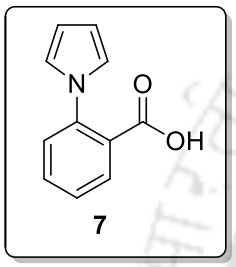
2-(9*H*-Carbazol-9-yl)-*N*-(quinolin-8-yl)benzamide 5. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; white solid; 34 mg, yield 41%; mp 184-185 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.46 (br s, 1H), 8.62-8.61 (m, 1H), 8.41 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.87 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.71-7.68 (m, 3H), 7.49 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.40-7.33 (m, 5H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.24 (td, *J* = 7.8 Hz, 1.2 Hz, 2H), 7.11-7.09 (m, 1H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 164.2, 147.5, 142.1, 138.2, 135.7, 135.6, 134.4, 132.9, 132.1, 129.7, 129.0, 127.5, 127.1, 126.5, 124.7, 121.6, 121.3, 120.6, 120.3, 116.4, 110.5.

FT-IR (KBr) 3320, 1669, 1527, 1451, 1259, 920, 822 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{19}N_3O$ 414.1606, found 414.1614.



7

2-(1*H*-Pyrrol-1-yl)benzoic acid 7. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.25; pale brown solid; 31 mg, yield 84%; mp 96-97 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95-7.94 (m, 1H), 7.16 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 6.85-6.84 (m, 2H), 6.33-6.32 (m, 2H).

^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 170.1, 141.1, 133.3, 131.6, 127.4, 127.3, 126.5, 122.3, 110.1.

FT-IR (KBr) 1670, 1600, 1499, 1407, 1303, 1263, 1078, 942 cm^{-1}.

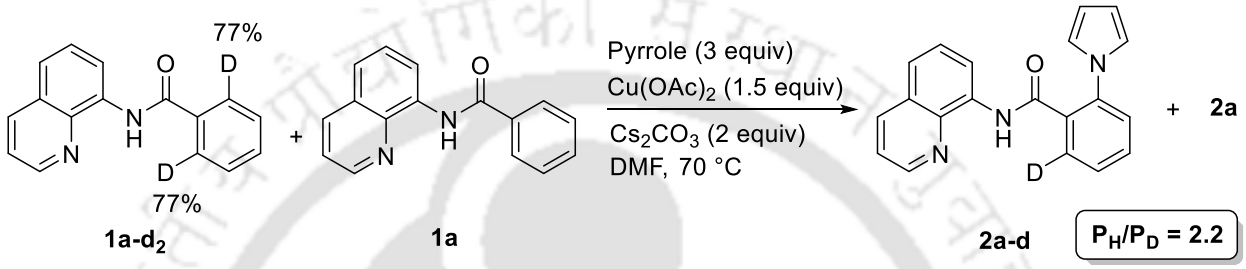
HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{10}NO_2$ 188.0712, found 188.0712.

4.5. Kinetic Study

Preperation of *N*-(Quinolin-8-yl)benzamide-2,6-d_2 (1a-d_2)[18] The titled compound was prepared according to the reported procedure. 1:9 ethyl acetate/hexane; R_f = 0.40; white solid; yield 82%.

Intermolecular Kinetic Isotope Effect Study (Scheme 18). Pyrrole (0.6 mmol, 3 equiv, 40.2 mg) were added to a stirred solution of *N*-(quinolin-8-yl)benzamide **1a** (0.13 mmol, 32.4 mg), *N*-(quinolin-8-yl)benzamide-2,6-d_2 **1a-d_2** (0.07 mmol, 17.4 mg), $Cu(OAc)_2$ (0.3 mmol,

1.5 equiv), Cs_2CO_3 (0.4 mmol, 2 equiv), solvent (1 mL) at 70 °C under air. The mixture was stirred for 3 h and the resulting solution was diluted with ethyl acetate (3 x 10 mL) and then washed with $NH_3 \cdot H_2O$ (1 x 5 mL) and brine (2 x 5 mL). Drying over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on neutral alumina column chromatography using n-hexane and ethyl acetate as eluent to afford a mixture of **2a** and **2a-d$_2$** as a white solid in 19% (12 mg) yield. The ratio of deuterium to hydrogen was determined by the ^{1}H NMR relative integration values of H_a (7.90) based on H_b (8.84).[19]



Scheme 18

4.6. References

1. For some examples see: (a) Greco, G.; Novellino, E.; Fiorini, I.; Nacci, V.; Campiani, G.; Ciani, S. M.; Garofalo, A.; Bernasconi, P.; Mennini, T. *J. Med. Chem.* **1994**, *37*, 4100. (b) Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59. (c) Balle, T.; Perregaard, J.; Ramirez, M. T.; Larsen, A. K.; Søby, K. K.; Liljefors, T.; Andersen, K. *J. Med. Chem.* **2003**, *46*, 265. (d) Wu, Y.; Li, Y.; Gardner, S.; Ong, B. S. *J. Am. Chem. Soc.* **2005**, *127*, 614. (e) Gee, M. M. M.; Gemma, S.; Butini, S.; Ramunno, A.; Zisterer, D. M.; Fattorusso, C.; Catalanotti, B.; Kukreja, G.; Fiorini, I.; Pisano, C.; Cucco, C.; Novellino, E.; Nacci, V.; Williams, D. C.; Campiani, G. *J. Med. Chem.* **2005**, *48*, 4367. (f) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z. *J. Am. Chem. Soc.* **2006**, *128*, 5592.
2. For some examples see: (a) Rault, S.; Sévricourt, M. C. D. Godard, A. M.; Robba, M. *Tetrahedron Lett*. **1985**, *26*, 2305. (b) Strobel, H.; Wohlfart, P.; Safarova, A.; Walser, A.; Suzuki, T.; Dharanipragada, R. M. PCT. Int. Appl. WO 2002064545, 2002. (c) Burri, K.; Hoffner, J.; Islam, K.; Mukhija, S. PCT. Int. Appl. WO 2002070464, 2002. (d) Yang, G.; Alan, H.; John, P.; Wallace, P.; Andrew, T.; Taeyoung, Y.; He, Z. PCT. Int. Appl. WO 2003082826, 2003. (e) Druzhinin, S. I.; Kovalenko, S. A.; Senyushkina, T. A.; Demeter, A.; Januskevicius, R.; Mayer, P.; Stalke, D.; Machinek, R.; Zachariasse, K. A. *J. Phys.*

Chem. A **2009**, *113*, 9304. (f) Aiello, F.; Garofalo, A.; Grande, F. *Tetrahedron Lett.* **2010**, *51*, 6635. (g) De, W. K.; Maes, L. J. R. M.; Meerpoel, L. PCT. Int. Appl. WO 2012084804, 2012. (h) Grande, F.; Brizzi, A.; Garofalo, A.; Aiello, F. *Tetrahedron* **2013**, *69*, 9951.

3. For selected review see: Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 6954.
4. For some examples see: (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, C.; Lemaire, M. *Chem. Rev*. **2002**, *102*, 1359. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed*. **2003**, *42*, 5400.
5. For some examples using aryl iodide see: (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett*. **2000**, *2*, 1403. (c) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem*. **2004**, *69*, 5578. (d) Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett*. **2007**, *9*, 3397. (e) Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 13107. (f) Fareghi-Alamdari, R.; Haqiqi, M. G.; Zekri, N. *New J. Chem*. **2016**, *40*, 1287.
6. For some examples using aryl boronic acid see: (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941. (b) Yu, S.; Saenz, J.; Srirangam, K. *J. Org. Chem*. **2002**, *67*, 1699.
7. For some example using organobismuth reagents see: Petiot, P.; Dansereau, J.; Ganon, A. *RSC Adv*. **2014**, *4*, 22255.
8. For some example using aryl lead see: López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem*. **1995**, *60*, 5678.
9. For some recent reviews on C-H Funtionalization see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed*. **2011**, *50*, 11062. (d) Ackermann, L.; *Chem. Rev*. **2011**, *111*, 1315. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev*. **2012**, *112*, 5879. (g) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed*. **2013**, *52*, 11726. (h) Zhang, F.; Spring, D. R. *Chem. Soc. Rev*. **2014**, *43*, 6906. (i) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev*. **2014**, *43*, 901. (j)

Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (k) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front*. **2015**, *2*, 1107.

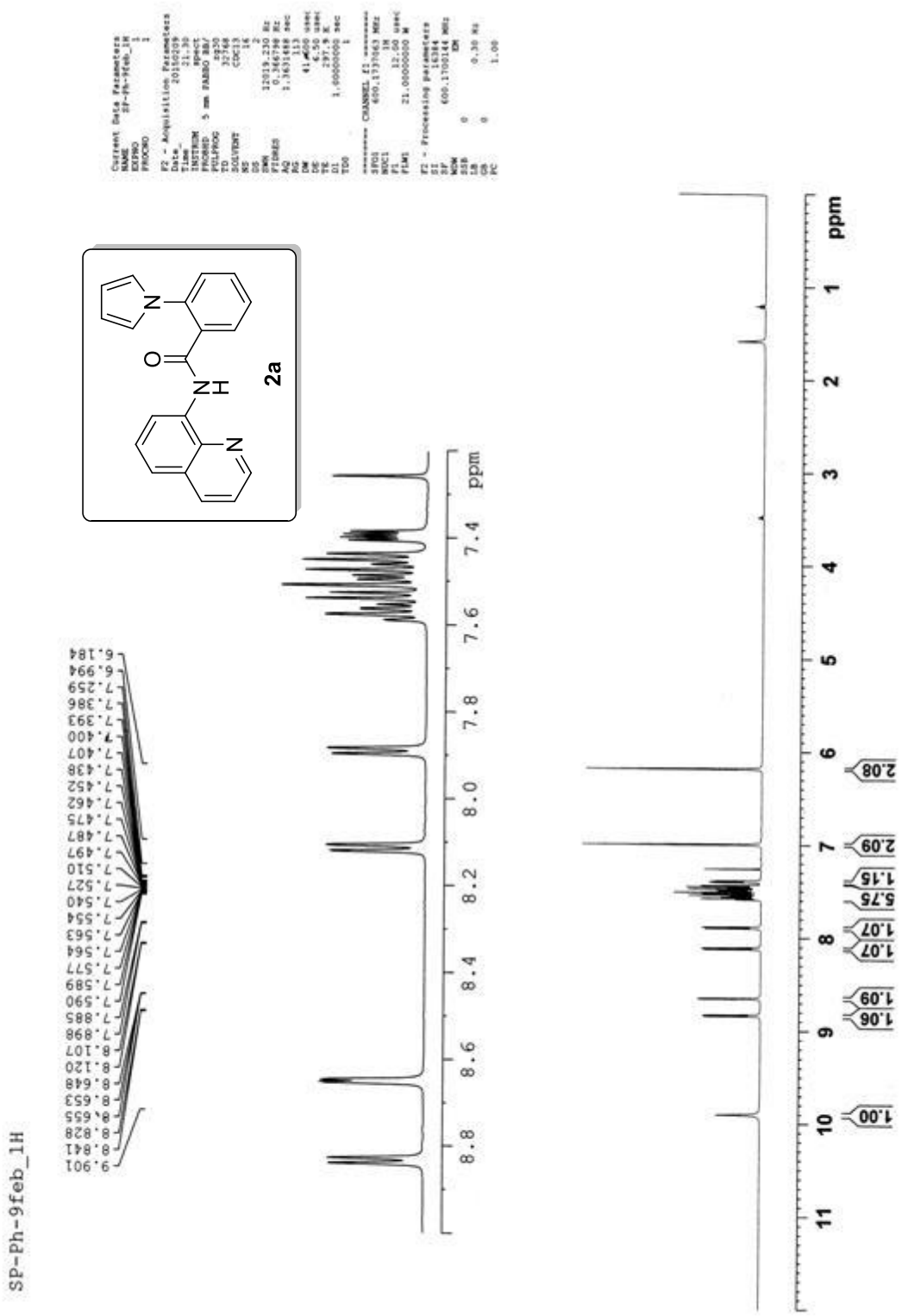
10. For some examples on directed C-N bond formations see: (a) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (b) John, A.; Nicholas, K. M. *J. Org. Chem*. **2011**, *76*, 4158. (c) Shang, M.; Zeng, S.-H.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett*. **2013**, *15*, 5286. (d) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem. Int. Ed*. **2013**, *52*, 6043. (e) Wang, L.; Priebbenow, D. L.; Dong, W.; Bolm, C. *Org. Lett*. **2014**, *16*, 2661. (f) Martinez, Á. M.; Rodriguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun*. **2014**, *50*, 2801. (g) Li, Q.; Zhang, S.-Y, He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett*. **2014**, *16*, 1764. (h) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646. (i) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (j) Mahesh, D.; Sadhu, P.; Punniyamurthy, T. *J. Org. Chem*. **2015**, *80*, 1644. (k) Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett*. **2015**, *17*, 2482.
11. For some examples on Ru-catalyzed C-H Funtionalization see: (a) Corbet, M.; Campo, F. D. *Angew. Chem., Int. Ed*. **2013**, *52*, 9896. (b) Rouquet, G.; Chatani, N. *Chem. Sci*. **2013**, *4*, 2201. (c) Fernández-Salas, J.; Manzini, S.; Piola, L.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun*. **2014**, *50*, 6782. (d) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun*. **2014**, *50*, 29. (e) Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C. *Angew. Chem., Int. Ed*. **2014**, *53*, 269.
12. For some examples on Rh-catalyzed C-H Funtionalization see: (a) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (b) Parthasarathy, K.; Bolm, C. *Chem. - Eur. J*. **2014**, *20*, 4896. (c) Shibata, K.; Chatani, N. *Org. Lett*. **2014**, *16*, 5148. (d) Qin, X.; Li, X.; Huang, Q.; Liu, H.; Wu, D.; Guo, Q.; Lan, J.; Wang, R.; You, J.; *Angew. Chem., Int. Ed*. **2015**, *54*, 7167.
13. For some examples on Pd-catalyzed C-H Funtionalization see: (a) Lennartz, P.; Raabe, G.; Bolm, C. *Adv. Synth. Catal.* **2012**, *354*, 3237. (b) Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 9322. (c) Sadhu, P.; Alla, S. K.; Punniyamurthy, T. *J. Org. Chem*. **2013**, *78*, 6104. (d) Dastbaravardeh, N.; Toba, T.; Farmer, M. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 9877.

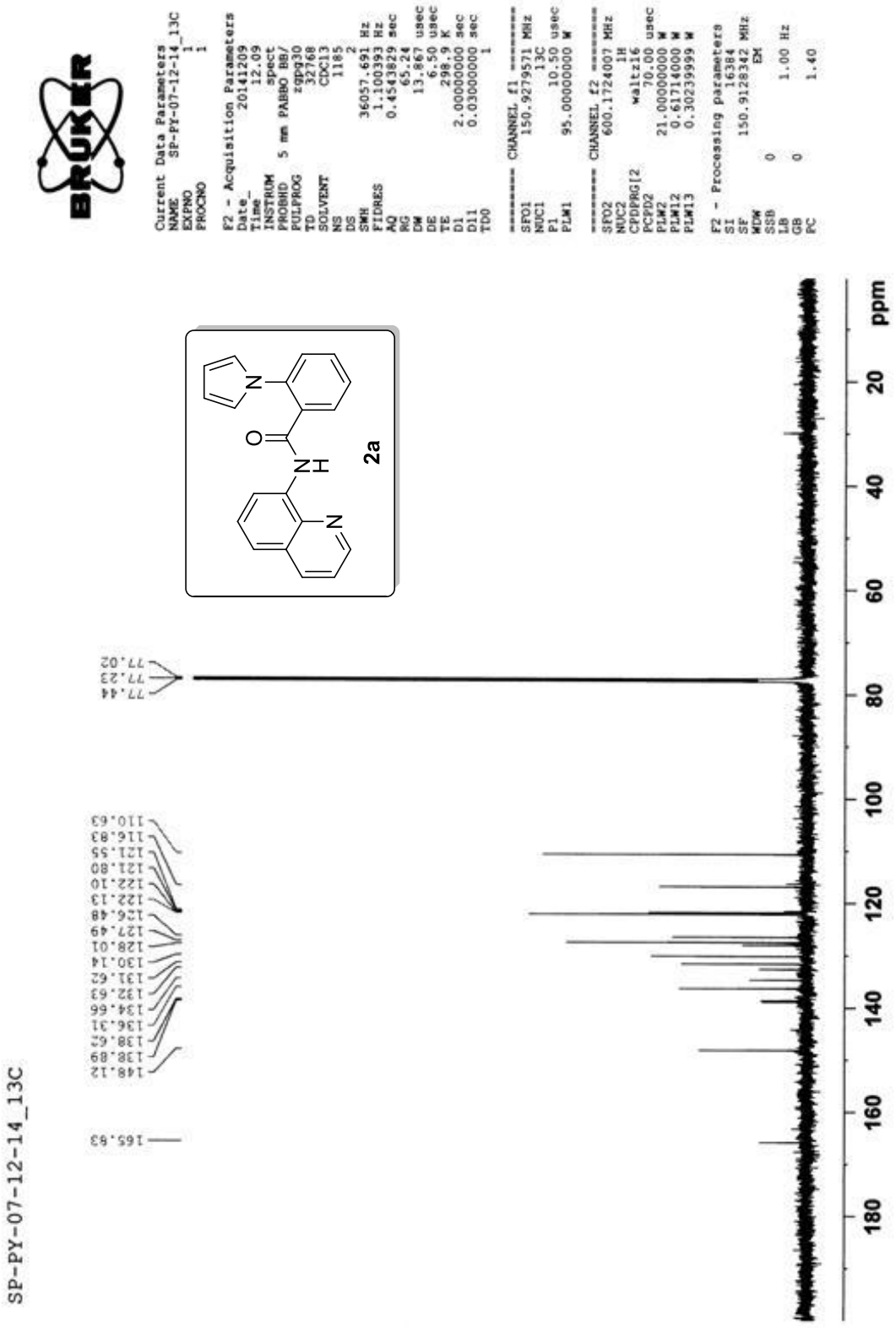
14. For *N*-arylation of azole see: Louillat, M.-L.; Biafora, A.; Legros, F.; Patureau, F. W. *Angew. Chem., Int. Ed*. **2014**, *53*, 3505.
15. For some examples of first row transition metal catalyzed reactions see: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (c) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. (d) Corbet, M.; Campo, F. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896. (e) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc*. **2013**, *135*, 9342. (f) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590. (g) Wang, S.; Guo, R.; Wang, G.; Chen, S.-Y.; Yu, X.-Q. *Chem. Commun*. **2014**, *50*, 12718. (h) Liu, J.; Yu, L.; Zhuang, S.; Gui, Q.; Chen, X.; Wang, W.; Tan, Z. *Chem. Commun*. **2015**, *51*, 6418. (i) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130. (j) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed*. **2015**, *54*, 8551.
16. For some examples see: (a) Zhu, W.; Zhang, D.; Yang, N.; Liu, H. *Chem. Commun.* **2014**, *50*, 10634. (b) Larsson, P.-F, Wallentin, C.-J.; Norrby, P.-O. *ChemCatChem* **2014**, *6*, 1277.
17. (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (b) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354.
18. Liang, H.-W.; Ding, W.; Jiang, K.; Shuai, L.; Yuan, Y.; Wei, Y.; Chen, Y.-C. *Org. Lett*. **2015**, *17*, 2764.
19. Li, Q.; Zhang, S.-Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett*. **2014**, *16*, 1764.

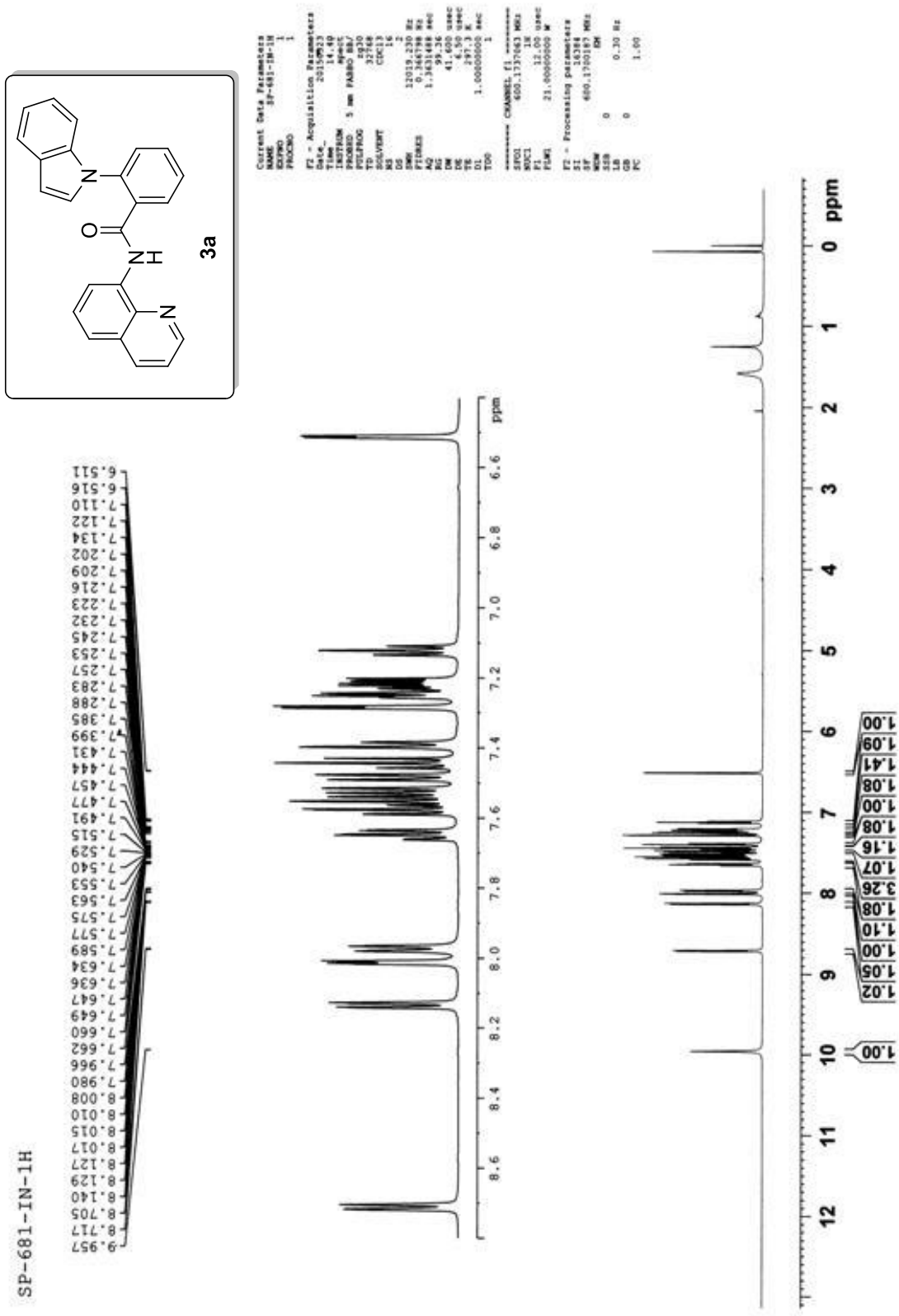
Crystal Data and Structure Refinement for 2a at 296(2) K

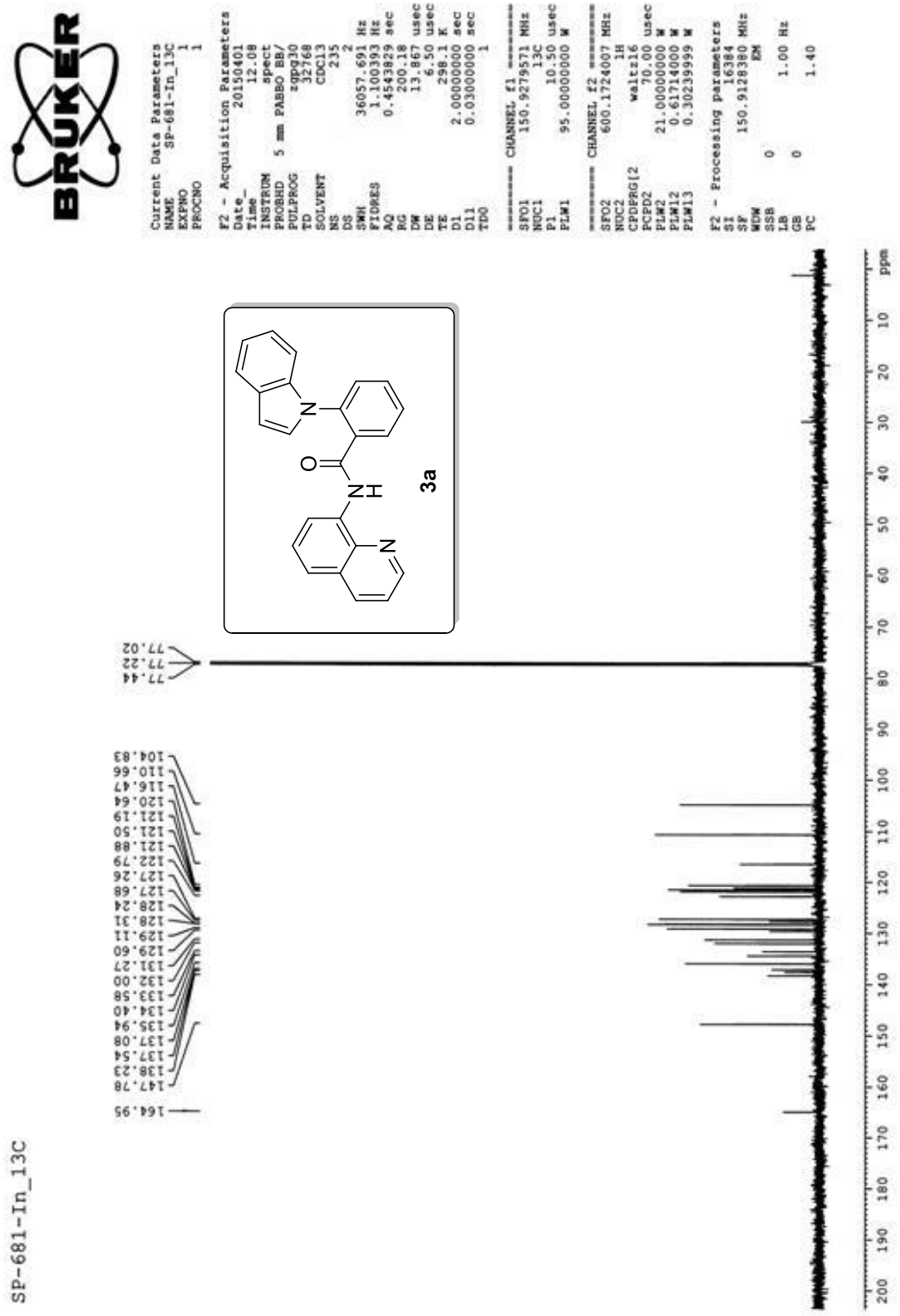
Identification code	**2a**
Empirical formula	C_{20} H_{15} N_3 O
Formula weight	313.35
Temperature	296(2)
Wavelength	0.71073
Crystal system	monoclinic
Space group	'$P2_1/n$'
Unit cell dimensions	a = 9.7059(3) Å
	b = 15.7541(4) Å
	c = 10.5250(3) Å
	$\alpha = \gamma = 90°$
	β = 95.513(2)°
Volume	1601.91(8) $Å^3$
Z	4
Density (calculated)	1.299 Mg/m3
Absorption coefficient	0.083
F(000)	656
Crystal size	0.44 x 0.36 x 0.28
Theta range for data collection	2.33° to 24.99°
Index ranges	-10<=h<=10, -18<=k<=18, -12<=l<=12
Reflections collected	21958
Independent reflections	2701
Completeness to theta = 24.99°	95.60 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2701 / 0 / 217
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma (I)]	*R1* = 0.0405, *wR2* = 0.0961
R indices (all data)	*R1* = 0.0466, *wR2* = 0.1011

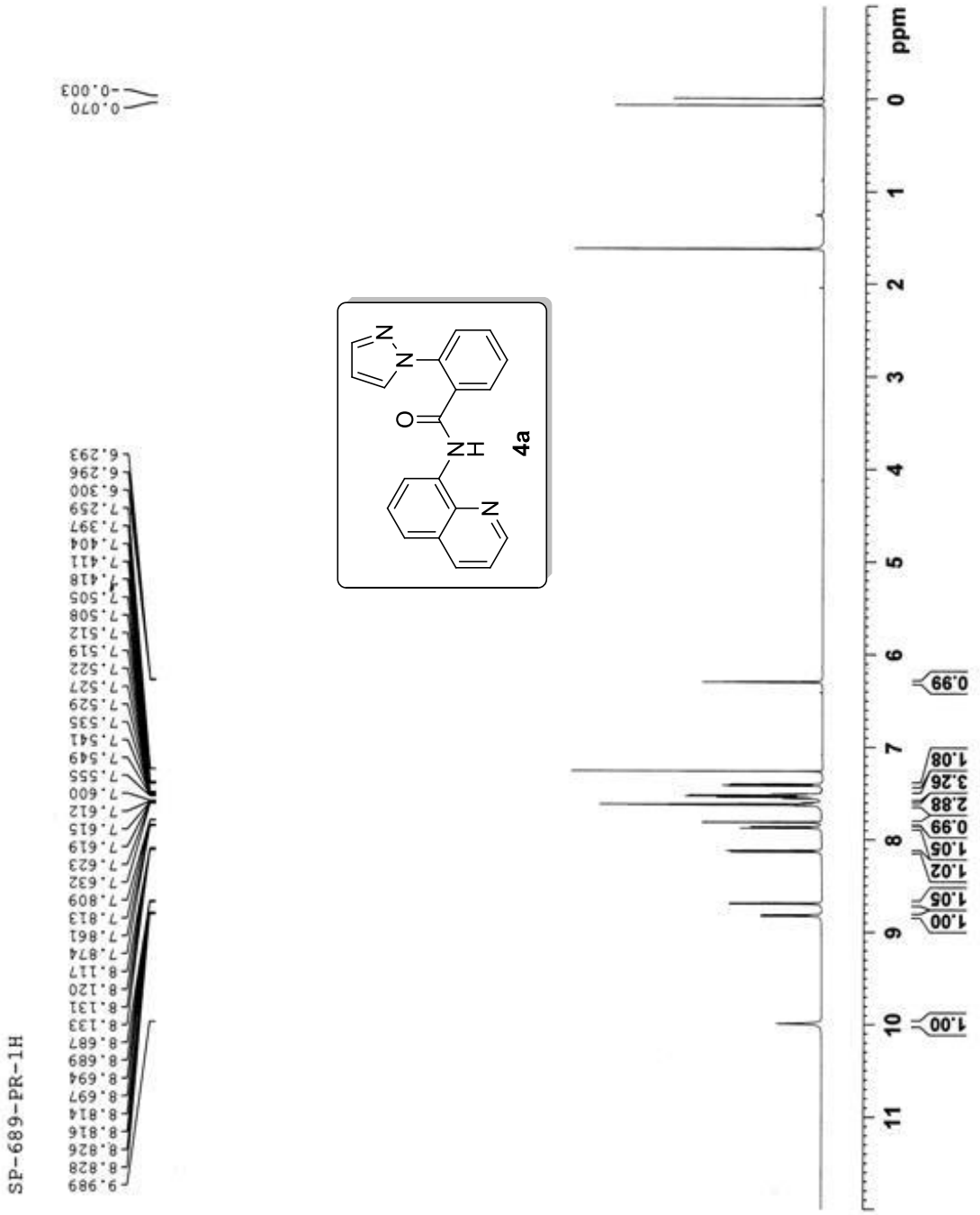
4.7. Selected Spectra

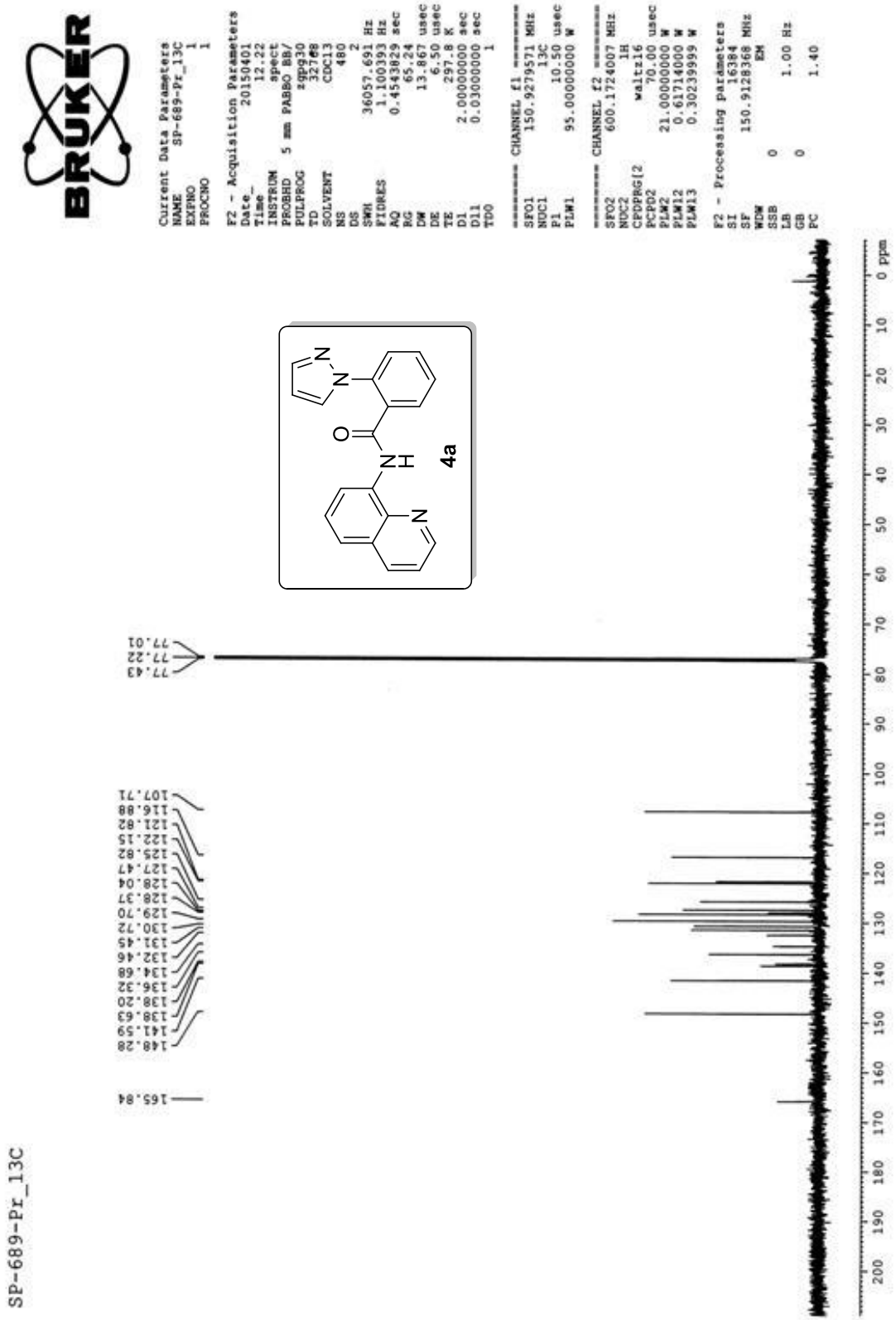


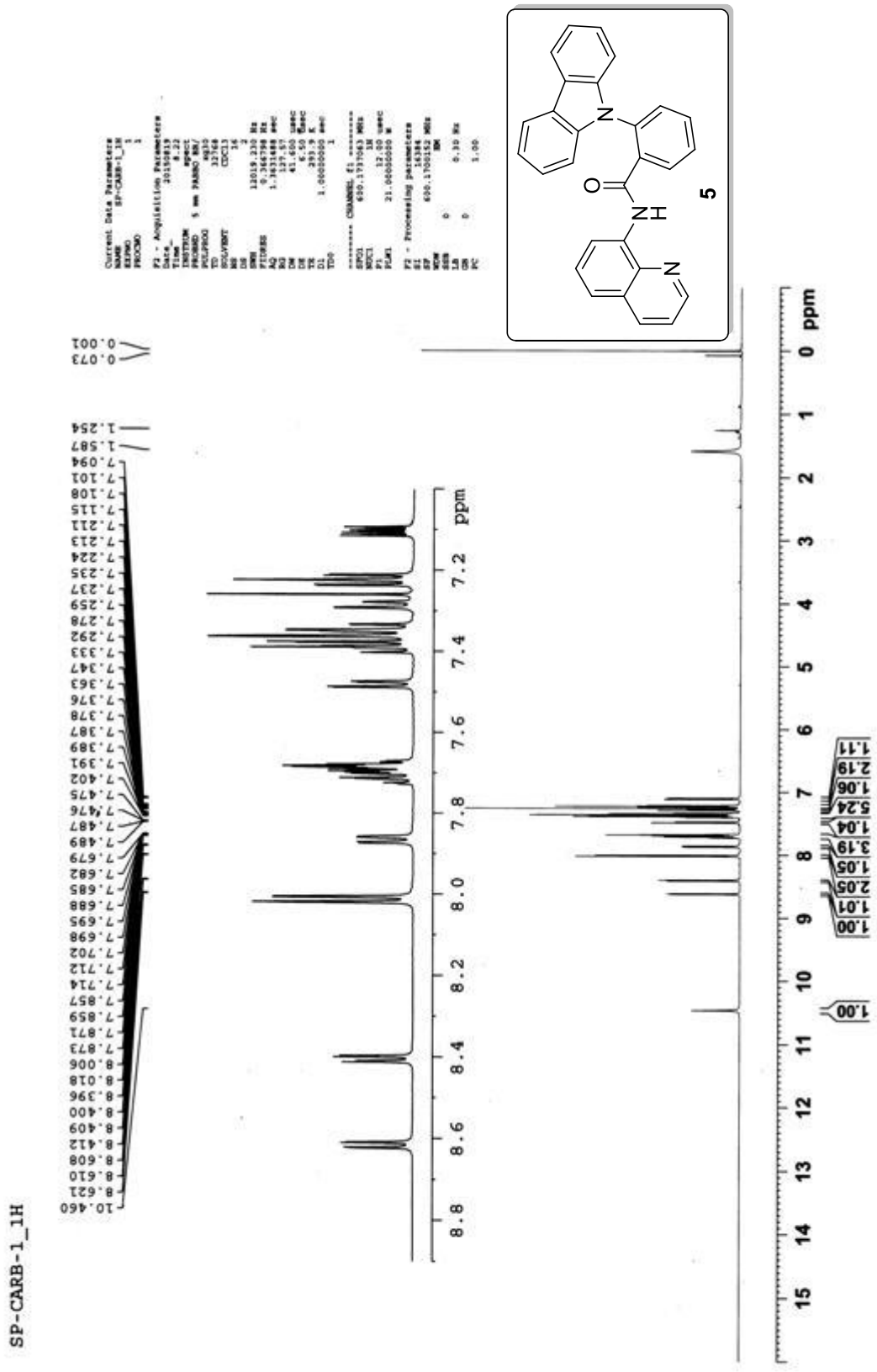

SP-PY-07-12-14_13C
Current Data Parameters
NAME SP-PY-07-12-14_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141209
Time_ 12.09
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1185
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543829 sec
RG 65.24
DW 13.867 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W
======== CHANNEL f2 ========
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W
F2 - Processing parameters
SI 16384
SF 150.9128342 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
2a
77.02
77.23
77.44
110.63
116.83
121.55
121.80
122.10
122.13
126.48
127.49
128.01
130.14
131.62
132.63
134.66
136.31
138.62
138.89
148.12
165.63
ppm

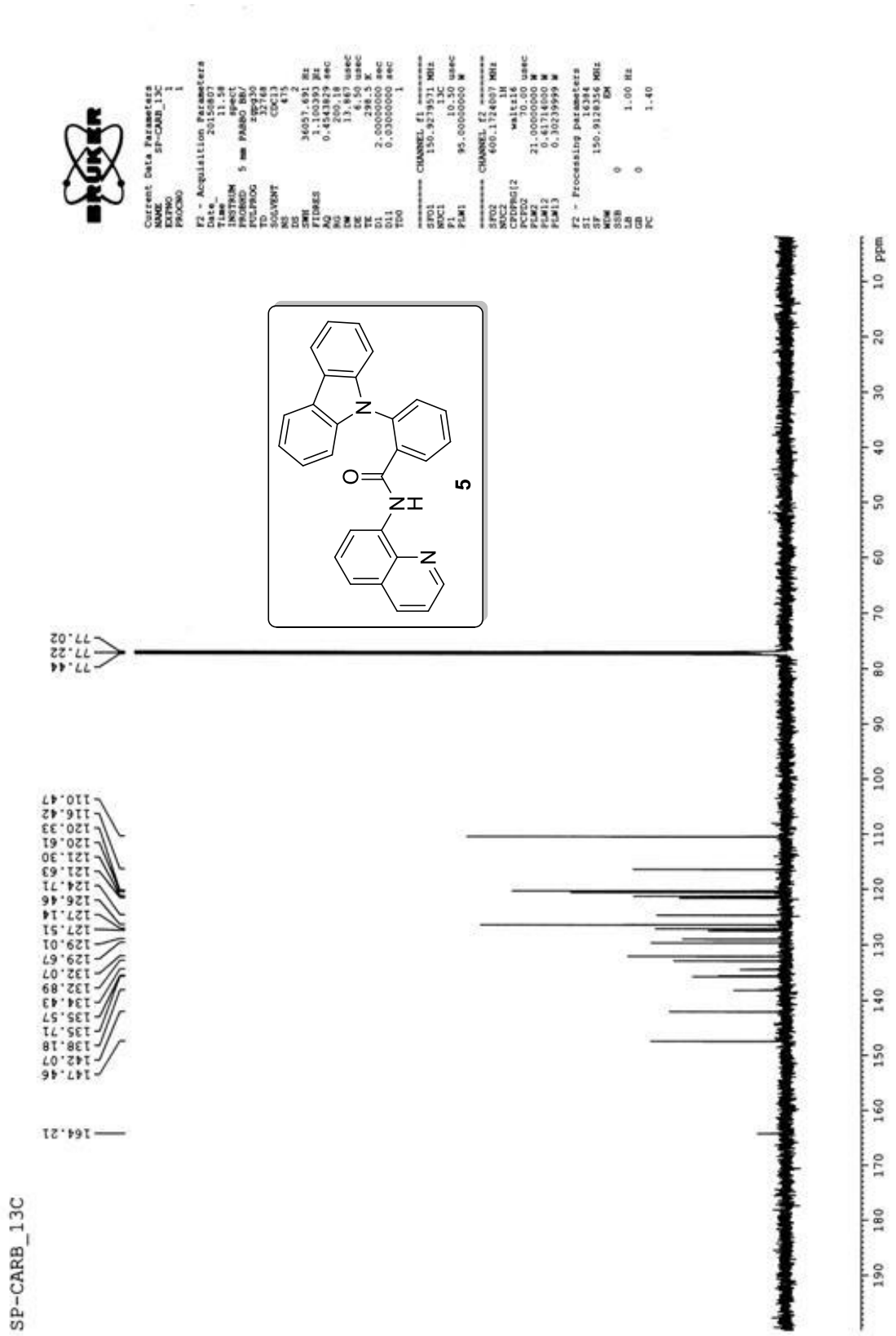

3a
SP-681-IN-1H
ppm


BRUKER
Current Data Parameters
NAME SP-681-In_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150401
Time_ 12.08
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 235
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543829 sec
RG 200.18
DW 13.867 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W
======== CHANNEL f2 ========
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W
F2 - Processing parameters
SI 16384
SF 150.9128380 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
3a
77.02
77.22
77.44
104.83
110.66
116.47
120.64
121.19
121.50
121.88
122.79
127.26
127.68
128.24
128.31
129.11
129.60
131.27
132.00
133.58
134.40
135.94
137.08
137.54
138.23
147.78
164.95
SP-681-In_13C
ppm

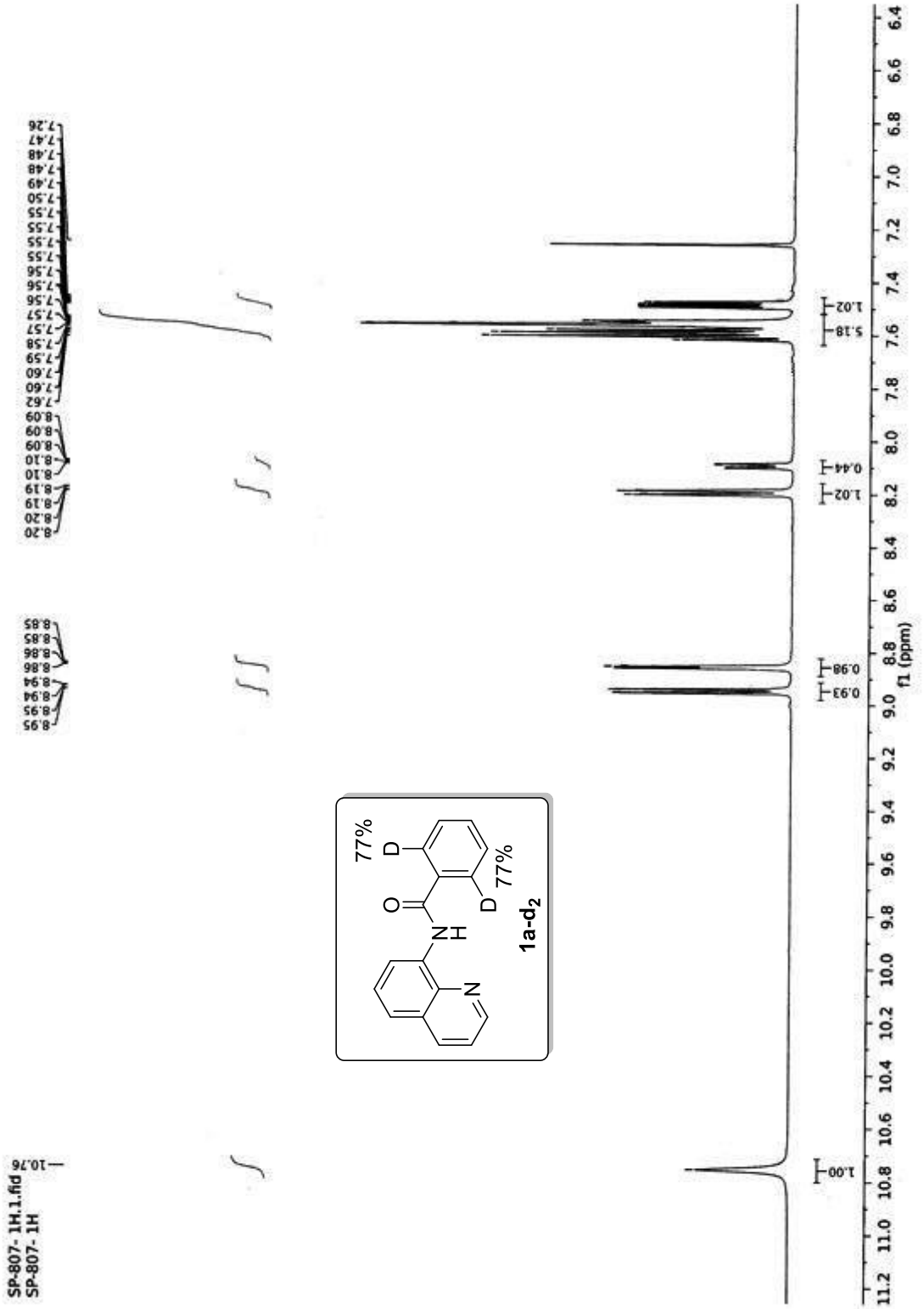

SP-689-PR-1H
4a
ppm

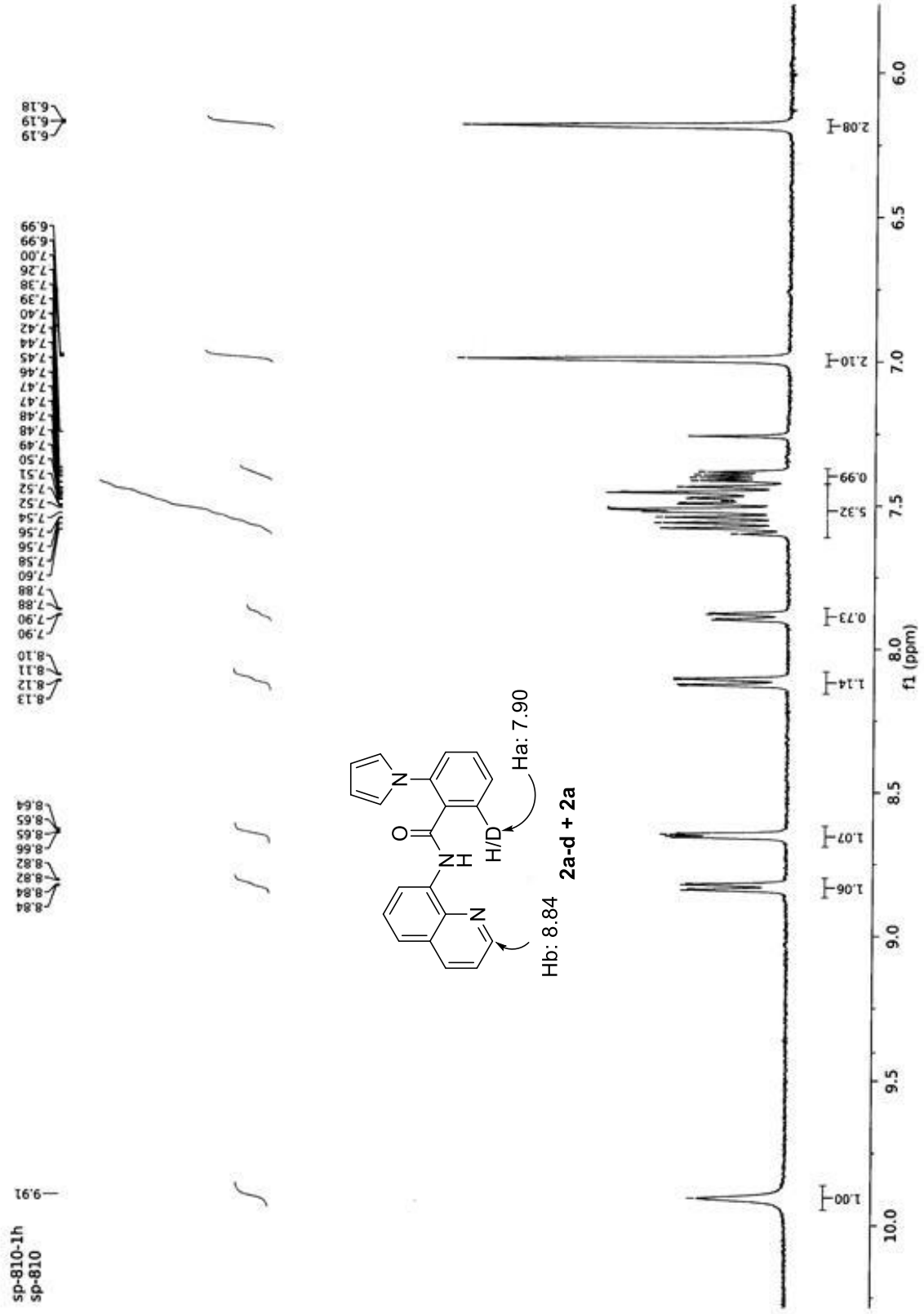

Current Data Parameters
NAME SP-689-Pr_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150401
Time 12.22
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 480
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543029 sec
RG 65.24
DW 13.867 usec
DE 6.50 usec
TE 297.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W
CHANNEL f2
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W
F2 - Processing parameters
SI 16384
SF 150.9128368 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
4a
77.43
77.22
77.01
165.84
148.28
141.59
138.63
138.20
136.32
134.68
132.46
131.45
130.72
129.70
128.37
128.04
127.47
125.82
122.15
121.82
116.88
107.71
0 ppm
SP-689-Pr_13C


SP-CARB-1_1H
5
ppm


SP-CARB_13C
5
77.44
77.22
77.02
164.21
147.46
142.07
138.18
135.71
135.57
134.43
132.89
132.07
129.67
129.01
127.51
127.14
126.46
124.71
121.63
121.30
120.61
120.33
116.42
110.47
10 ppm

1.


SP-807- 1H.1.fid
SP-807- 1H
f1 (ppm)
1.00
0.93
0.98
1.02
0.44
1.02
5.18
1.02
77%
D
77%
D
O
NH
N
1a-d2


sp-810-1h
sp-810
f1 (ppm)
Ha: 7.90
Hb: 8.84
H/D
2a-d + 2a

Conclusions

The chapter 1 covers the literature survey of the transition-metal-catalyzed cross-coupling, C-H activation, chelation-assisted C-H functionalization and their mechanisms.

Chapter 2 presents Pd-catalyzed *ortho*-halogenation of *N*-aryl ring of *N*,1-diphenyl-1*H*-tetrazol-5-amines using chelation assisted C-H functionalization utilizing *N*-halo succinimide (NXS) as halogen source and CF_3SO_3H as an additive at moderate temperature. The protocol is general affording effective routes for the halogenation with high yields.

Chapter 3, demonstrates a room temperature Cu-catalyzed chemo- and regioselective nitration of arenes using $Fe(NO_3)_3{\cdot}9H_2O$ as a nitro source in the absence of additives. In these reactions, 5-aminotetrazole and 3-amino-1,2,4-triazoles serve as the chelating groups. The mechanistic as[ects have been illustrated based on kinetic isotope studies, ESI-MS and radical scavenger experiments. The directing group can be cleaved to produce 2-nitroanilines in good yields.

Chapter 4, focuses on Cu-mediated regio-selective cross-dehydrogenative coupling (CDC) approach for the *N*-arylation of azoles under basic conditions. The reaction of pyrroles, indoles, pyrazoles and carbazole has been demonstrated. The kinetic studies show that the C-H bond cleavage takes place in the rate determining step.

List of Publications

Thesis Work

1. "Pd(II)-Catalyzed Aminotetrazole-Directed *Ortho*-Selective Halogenation of Arenes" **Pradeep Sadhu**, Santhosh Kumar Alla and Tharmalingam Punniyamurthy. *J. Org. Chem.* **2013**, *78*, 6104.

2. "Room-Temperature Cu(II)-Catalyzed Chemo- and Regioselective *Ortho*-Nitration of arenes *via* C-H Functionalization" **Pradeep Sadhu**, Santhosh Kumar Alla and Tharmalingam Punniyamurthy. *J. Org. Chem.* **2015**, *80*, 8245.

3. "Copper(II)-Mediated Regioselective *N*-Arylation of Pyrroles, Indoles, Pyrazoles and Carbazole *via* Dehydrogenative Coupling" **Pradeep Sadhu** and Tharmalingam Punniyamurthy. *Chem. Commun*. **2016**, *52*, 2803.

Excluding Thesis Work

1. "Iodobenzene Catalyzed C-H Amination of *N*-Substituted Amidines using *m*-Chloro-perbenzoic Acid" Santhosh Kumar Alla, Rapolu Kiran Kumar, **Pradeep Sadhu** and Tharmalingam Punniyamurthy. *Org. Lett.* **2013**, *15*, 1334.

2. "Organocatalytic Syntheses of Benzoxazoles and Benzothiazoles Using Aryl Iodide and Oxone *via* C-H Functionalization and *C-O*/*S* Bonds Formation" Santhosh Kumar Alla, **Pradeep Sadhu** and Tharmalingam Punniyamurthy. *J. Org. Chem.* **2014**, *79*, 7502.

3. "Copper(I)-Catalyzed Regioselective Amination of *N*-Aryl Imines Using $TMSN_3$ and TBHP: A Route to Substituted Benzimidazoles" Devulapally Mahesh, **Pradeep Sadhu** and Tharmalingam Punniyamurthy. *J. Org. Chem.* **2015**, *80*, 1644.

4. "Copper(II)-Catalyzed Oxidative Cross-Coupling of Anilines, Primary Alkyl Amines, and Sodium Azide Using TBHP: A Route to 2-Substituted Benzimidazoles" Devulapally Mahesh, **Pradeep Sadhu** and Tharmalingam Punniyamurthy. *J. Org. Chem.* **2016**, *81*, 3227.

5. "Copper(II)-Catalyzed Nitroaldol (Henry) Reaction: Recent Developments" Govindarasu Murugavel, **Pradeep Sadhu** and Tharmalingam Punniyamurthy. *Chem. Rec*. **2016**, DOI: 10.1002/tcr.201500268.

Conferences

1. "Pd(II)-Catalyzed Aminotetrazole-Directed *Ortho*-Selective Halogenation of Arenes" **Pradeep Sadhu**, Santhosh Kumar Alla and Tharmalingam Punniyamurthy. 9th J-NOST Conference organized by IISER, Bhopal December 04-06, 2013.
2. "Pd(II)-Catalyzed Aminotetrazole Directed Chemo- and Regioselective *Ortho*-Halogenation of Arenes" **Pradeep Sadhu**, Santhosh Kumar Alla and Tharmalingam Punniyamurthy. International Symposium on Nature Inspired Initiatives in Chemical Trends, IICT Hyderabad, March 02-05, 2014.
3. "Copper(II)-Mediated 8-Aminoquinoline Amide Directed Regioselective *N*-arylation of Azoles *via* Cross-Dehydrogenative Coupling" **Pradeep Sadhu** and Tharmalingam Punniyamurthy. 19th CRSI National Symposium in Chemistry, North Bengal University, July 13-16, 2016.