Metal Catalyzed Sequential Carbon-Carbon and/or Carbon-Nitrogen bond formation

Thesis Submitted to the AcSIR for the Award of

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In Chemical Sciences

By

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UNDER THE GUIDANCE OF

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November 2014

DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune – 411008
November–2014 **(Yogeshkumar M. Goriya)**

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled ***Metal Catalyzed Sequential Carbon-Carbon and/or Carbon-Nitrogen bond formation*** submitted by Mr. ***Yogeshkumar M. Goriya*** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor Of Philosophy***, embodies original research work under my supervision. We further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Yogeshkumar M. Goriya (Student)

Dr. C. V. Ramana (Supervisor)

Dedicated To...

My Beloved Parents

&

Rev. Dadaji

(Pandurangshashtri Athavale,

Founder,- Swadhyay Parivar)

Acknowledgements

A research thesis is an inspiring experience, of knowledge enhancement, more importantly of realising that individual effort is actually an outcome of the support of many. That is probably why thesis writers feel the urge to write acknowledgements!

I must first express my sincere and heartfelt gratitude to my research supervisor and teacher ***Dr C. V. Ramana*** *for giving me the opportunity of doing my Ph.D. in his group, for his enormous support and for his guidance in the course of my scientific research. His humanity and scientific curiosity were a constant source of inspiration for me. Working with him was a great pleasure and learning experience.*

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Finally, I am immensely thankful to Rev. Dadaji (Founder, Swadhyaya Parivar) – he has been my pillar of inspiration in my life and while I write these heartfelt acknowledgements, I feel all the more grateful to God for all that He has given me and I have used directly and indirectly for this research.

Yogesh Goriya

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Ad-CO_2H	–	1-Adamantane carboxylic acid
Aq.	–	Aqueous
Bu	–	Butyl
Cat.	–	Catalytic/catalyst
Cy	–	Cyclohexyl
DCM	–	Dichloromethane
Conc.	–	Concentrated
DMA	–	Dimethylacetamide
DMF	–	*N,N*-Dimethylformamide
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
EtOAc	–	Ethyl acetate
HRMS	–	High Resolution Mass Spectroscopy
IBX	–	2-iodoxybenzoic acid
Liq.	–	Liquid
LDA	–	Lithium diisopropylamide
L-Pro	–	L-proline
Me	–	Methyl
NMP	–	N-Methyl-2-pyrrolidone
NMR	–	Nuclear Magnetic Resonance
Py	–	Pyridine
Ph	–	Phenyl
rt	–	Room temperature
Sat.	–	Saturated
THF	–	Tetrahydrofuran
Triton B	–	Trimethylbenzylammonium hydroxide
TBAOH	–	Tetrabutylammonium hydroxide
λ_{max}	–	Absorption
Λ_{em}	–	Emission

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

GENERAL REMARKS

- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.
- The melting points are uncorrected and the temperatures are in the degree centigrade scale.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

CONTENTS

Name of the Candidate	YogeshKumar M. Goriya
Degree, Enrolment No. and Date	Ph. D in Chemical Sciences (10CC11J26102); January 2011
Title of the Thesis	Metal Catalyzed Sequential Carbon-Carbon and/or Carbon-Nitrogen bond formation
Research Supervisor	Dr. C. V. Ramana (AcSIR, CSIR-NCL, Pune)

ABSTRACT

The thesis entitled "***Metal Catalyzed Sequential Carbon-Carbon and/or Carbon-Nitrogen Bond Formation***" is divided into two chapters. Each chapter was further subdivided into Introduction, Results and Discussion, Experimental and References. The first chapter details three new methodologies featuring the operation of Cu-catalyzed "S_NAr of electron deficient aryl halides with azide and subsequent transformation of the intermediate azide" in sequence to arrive at the synthesis of primary aryl amines, pseudo-indoxyl derivatives and the 2-aroyl indole derivative. The second chapter describes a new concept comprising of a one-pot ruthenium-catalyzed functionalization of both aryl and heteroaryl units of 2-phenyl pyridine derivatives *via* sequential direct and directed C–H activations.

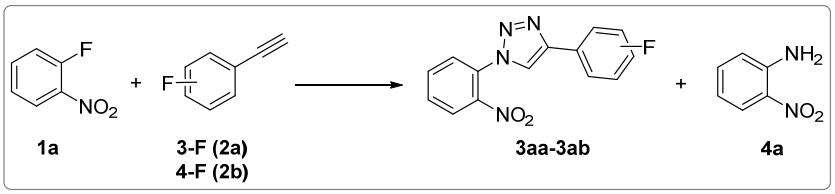
Chapter I: Copper catalyzed sequential C–N bond formations with NaN_3: One pot synthesis of primary arylamines, 2,2-disubstituted-3-indolinones and 2-aroyl indoles

The development of mild, efficient, atom economical and environment friendly approaches for the formation of carbon–carbon (C–C) and carbon–hetero (C–X) atom bonds occupies the central role in organic synthesis. Since the first reaction reported by Ullmann for C–N coupling in 1901, till today great effort has been made in this field by various research groups during the last two decades with the introduction of a wide variety of copper sources and ligands. A wide range of aryl/heteroaryl halides (X = Cl, Br, I) are compatible for *N*-arylations with myriad nitrogen centered nucleophiles. Quite surprisingly, out of these entire groups of nitrogen nucleophiles, azides (e.g. NaN_3) have not been significantly explored until recently.

Cu-catalyzed direct amination of aryl halide using NaN_3 as ammonia surrogate:

Recently, we reported a one-pot approach for the synthesis of 1,4-diaryltriazoles under the classical Cu(II)-ascorbate redox system involving the S_NAr of fluronitrobenzenes with azide and the subsequent click reaction. This has been developed to synthesize a

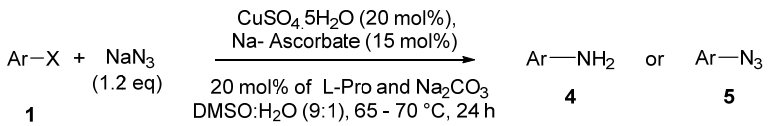
collection of isomeric compounds with the modular positioning of X (Cl, Br, I) and NO_2 on a flexible tricyclic template and to learn how the halo–nitro interaction will vary in these positional isomers. In continuation, we intended to explore the same with isomeric fluoro-nitro derivatives of diphenyl-1,2,3-triazoles. In this regard, when examined the one-pot S_NAr–click reaction of *o*-nitro fluorobenzenes (**1a**) with *m*/*p*-fluorophenyacetylene (**2a–2b**) under the standardized conditions, the 2-aminonitrobenzene (**4a**) was obtained as the major product along with the 1,4-diaryl triazoles (**3aa** or **3ab**) (Scheme 1).

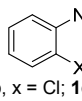
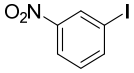
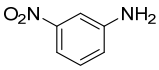


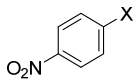
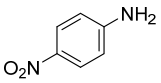
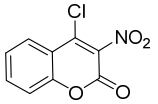
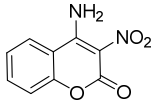
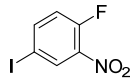
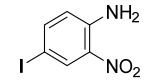
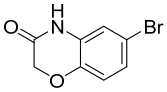
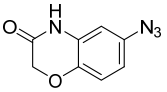
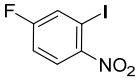
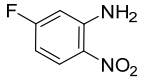
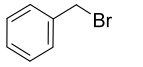
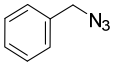
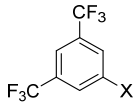
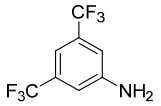
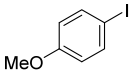
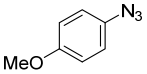
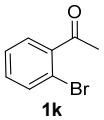
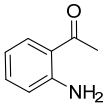
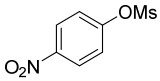
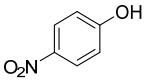
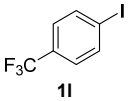
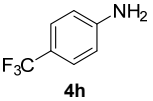
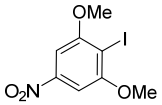
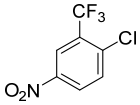
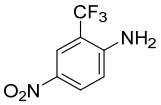
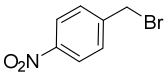
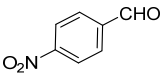
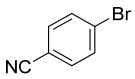
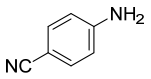
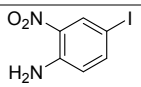
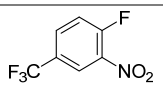
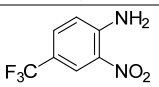
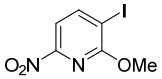
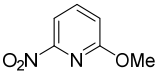
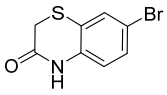
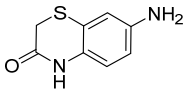
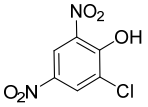
Scheme 1: *Reagents and conditions: 1.2 eq. NaN_3, $CuSO_4$ (20 mol%), Na-ascorbate (15 mol%), L-proline (20 mol%), Na_2CO_3 (20 mol%), DMSO:H_2O (9 : 1), 65-70 °C, 24 h.*

Since both the azidation and the azide reduction are facile under the same conditions, a systematic investigation for the azide reduction has been carried out by varying the reaction parameters. Control experiments revealed that the presence of ascorbate is essential and that the rate of the reaction is enhanced by the presence of the Cu(II)–salt and proline and that proline plays an important role in the stabilization of Cu(I). With this information, this one pot azidation-reduction reaction has been generalized as a new tool for the synthesis of primary aryl amines. As shown in Table 1, a wide range of aryl halides have been employed in this context. In general, the reactions are very facile when the electron withdrawing groups (nitro or -CF_3) are placed either at *ortho*- or *para*- to the leaving halo group.The pseudo halides like –OMs were also found to be compatible under the present reaction conditions. However, the yields were found to be low. The 'S_NAr–azide reduction' is also facile with hetero-aromatic halides, and afforded the corresponding amine or azide in good yields.

Table 1: *The scope of one-pot amination reaction of aryl halide with NaN_3 under Cu(II)-ascorbate redox system*



Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	 **1b**, x = Cl; **1c**, x = I	 **4a**	71% (Cl), 76% (I)	13	 **1q**	 **4m**	28%
2	 **1d**	 **4b**	77%	14	 **1r**	 **4n**	42%

3	 **1e**, x = Br; **1f**, x = I	 **4c**	76% (Br), 87% (I)	15	 **1s**	 **4o**	76%
4	 **1g**	 **4d**	69%	16	 **1t**	 **5a**	68%
5	 **1h**	 **4e**	67%	17	 **1u**	 **5b**	49%
6	 **1i**, x = OMs;**1j**, x = I	 **4f**	24% (OMs) 57% (I)	18	 **1v**	 **5c**	53%
7	 **1k**	 **4g**	77%	19	 **1w**		71%
8	 **1l**	 **4h**	68%	20	 **1x**	No Reaction	---
9	 **1m**	 **4i**	72%	21	 **1y**		28%
10	 **1n**	 **4j**	54%	22	 **1z**	No Reaction	---
11	 **1o**	 **4k**	78%	23	 **1aa**		32%
12	 **1p**	 **4l**	73%	24	 **1aa**	No Reaction	---

The isolation of the intact aryl azides from iodobenzene and from *p*-alkoxy substituted derivatives indicate that the Cu(I)-mediated decomposition of the azide group depends upon the relative electrophilicity of the azide group which is controlled by the nature of the aryl substituent. These observations have revealed that preferential azide decomposition occurs *via* form I, where the double bond character of the fissile N—N_2 bond is decreased and the entropy of activation for the rupture of this bond is lowered with the electron withdrawing substituents (Figure 1).

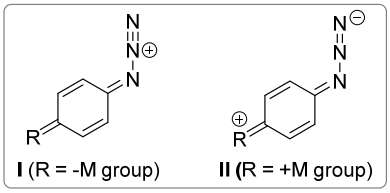
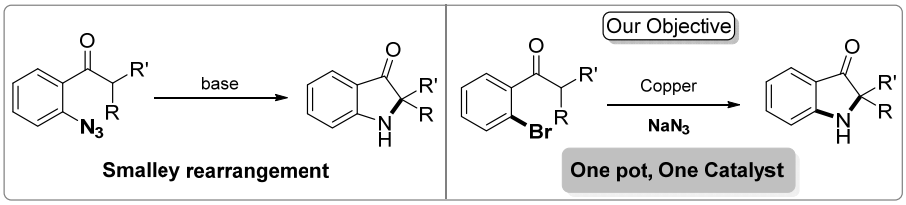


Figure 1: *Two canonical forms of the arylazides*

Copper catalyzed synthesis of pseudo indoxyl derivatives:

As mentioned above, a nominal deactivation of aryl ring is sufficient for displacement of N_2 from the electrophilic azide. This is quite interesting, since if an internal nucleophile is employed for such a displacement, it results in ring annulation. Indeed, in 1979, Smalley reported the base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to the 2,2-disubstituted indolin-3-one core which is one of the important structural units present in many natural products. Given our current interest in the synthesis of natural products having the indolin-3-one core, we started a program on examining the possibility of a one-pot [Cu]-catalysed S_NAr and the Smalley rearrangement of α-halophenyl *sec*-alkyl ketones (Scheme 2).



Scheme 2: *Smalley cyclization and our concept for indol-3-one ring system*

The work in this direction began with the screening of the four α-halophenyl isopropyl ketones under the previously optimized conditions. As shown in Table 2, these experiments revealed that the bromo-derivative **6a** is the better substrate. Subsequently control experiments revealed that the presence of the copper salt is essential and the $CuSO_4$ was found to be best among the various Cu-sources screened (Table 2).

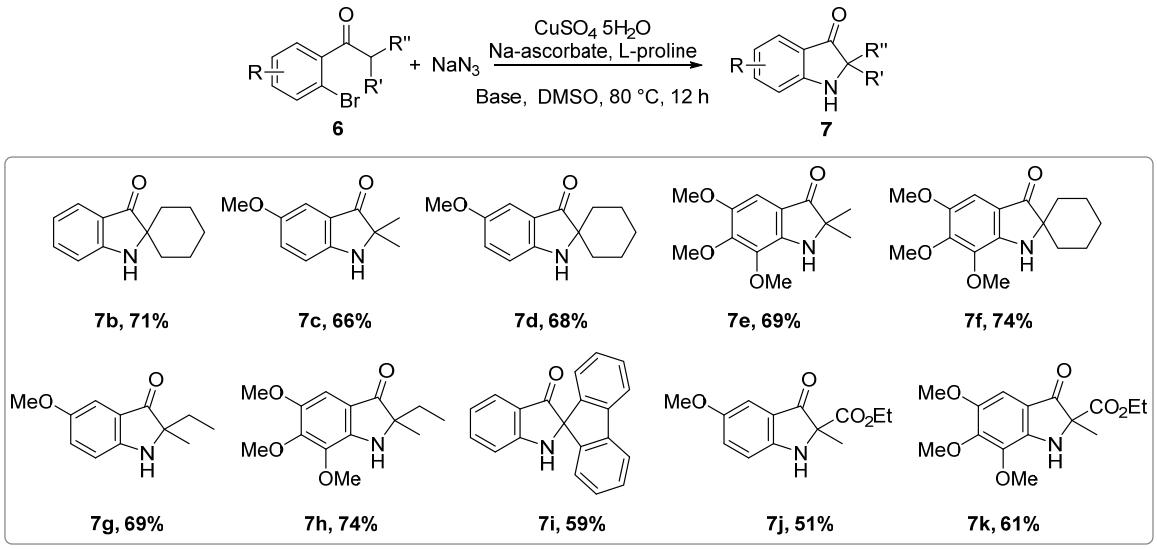
Table 2: *Optimization of Reaction Condition with various Cu–catalysts*

6a **7a**

Entry[a]	Cu-catalyst	Base	Yield[c]	Entry[a]	Cu-catalyst	Base	Yield[c]
1	$CuSO_4\ 5H_2O$	K_2CO_3	65%	**8**	CuI	K_2CO_3	36%
2	$CuSO_4\ 5H_2O$	KOH	23%	**9**	CuI	KOH	61%
3	$CuSO_4\ 5H_2O$	Cs_2CO_3	57%	**10**	CuI	-------	46%[b]
4	$CuSO_4\ 5H_2O$	Triton B	59%	**11**	CuI	-------	36%
5	$CuSO_4\ 5H_2O$	TBAOH	51%	**12**	CuI	-------	53%[b, d]
6	$CuSO_4\ 5H_2O$	Et_3N	41%	**13**	Cu_2O	K_2CO_3	36%[b]
7	$CuSO_4\ 5H_2O$	------	33%	**14**	$Cu(OAc)_2$	K_2CO_3	43%

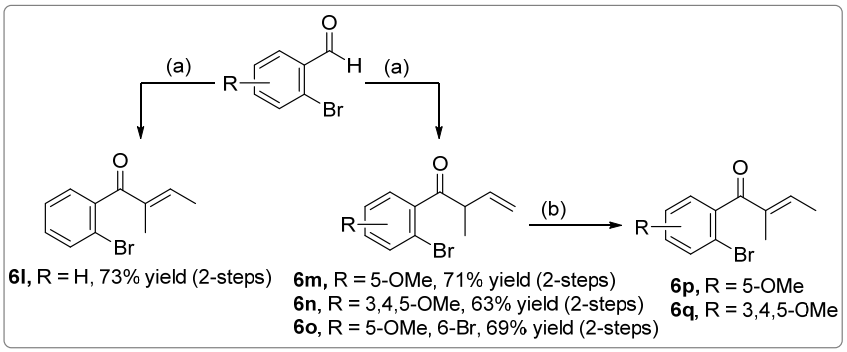
[a] all reactions performed with 1.2 eq NaN_3; 20 mol% L-proline, Na-ascorbate, Cu-cat in DMSO; [b] reaction without Na-ascorbate; [c] isolated yields [d] PEG as a solvent

Next, the scope of this reaction has been examined by employing variously substituted α-bromophenyl *sec*-alkylketones. As shown in Scheme 3, the yields with the electron-rich aryl derivatives are comparatively better than with the simple unsubstituted benzene derivatives. The reaction was also compatible with the α-keto esters (**7j–7k**) and afforded the corresponding 3-oxoindoline-2-carboxylate in moderated yields.



Scheme 3: *Scope of the [Cu]-catalyzed one-pot S_NAr – Smalley Cyclization*

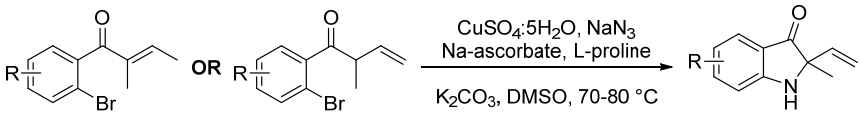
Next, the feasibility of this S_NAr–Smalley rearrangement reaction was examined with the corresponding α-bromophenyl *sec*-alkenyl ketones. The synthesis of model substrates **6l–6q** involves the crotylation of a 2-bromobenzladehyde derivative under Barbier conditions and subsequent oxidation of the resulting homoallylic alcohols afforded either α,β-usaturated ketone **6l** or the β,γ-usaturated ketones (**6m, 6n** and **6o**). The β,γ-usaturated ketones **6n** and **6o** were isomerised with DBU in CH_2Cl_2 to get the corresponding α,β-unsaturated ketones (**6p** and **6q**) (Scheme 4).



Scheme 4: *Reagents and conditions: (a) i. crotyl bromide, Zn, THF, 0 °C to rt; ii. IBX, EtOAc, reflux, 3-4 h; (b) DBU, CH_2Cl_2, 5m*

Next, the one pot S_NAr–Smalley cyclization of α,β-unsaturated ketones (**6l**, **6p**, and **6q**) and β,γ-unsaturated ketones **6m–6o** gave exclusively the 2-vinylindolin-3-one derivatives (**7l–7o**) in very good yields (Table 3).

Table 3: *Synthesis of 2-vinylindolin-3-one derivatives*



Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	**6l**	**7l**	**67%**	4	**6o**	**70**	**72%**
2	**6m**	**7m**	**71%**	5	**6p**	**7m**	**72%**
3	**6n**	**7n**	**74%**	6	**6q**	**7n**	**69%**

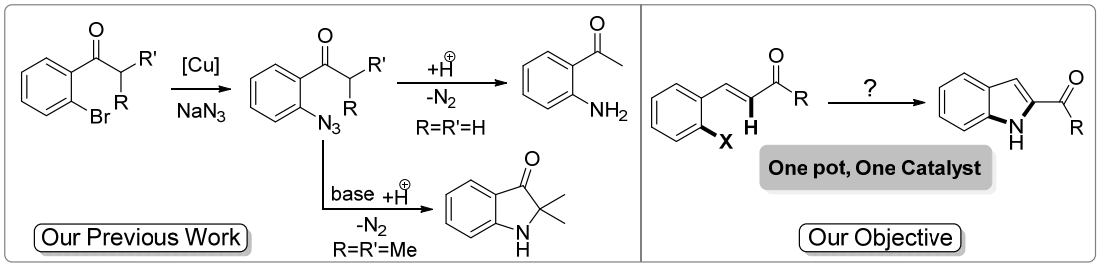
After having a set of indol-3-ones derivatives which are fluorescent in nature, their photophysical properties were studied. The indol-3-ones (**7a–7o**) display the Stokes shift ranging from 70 to 130 nm (Table 4). The indol-3-one **7j** having a single methoxy substituent on the aryl ring and a carboxylate group at C2 displayed a large Stokes shift (121 nm).

Table 4: *Optical properties of compounds **7a–7o***

Compound	λ_{max} (nm)[a]	λ_{em} (nm)[a]	Stokes shift (nm)[b]	Compound	λ_{max} (nm)[a]	λ_{em} (nm)[a]	Stokes shift (nm)[b]
7a	395	473	78	**7i**	415	536	121
7b	421	523	98	**7j**	402	509	107
7c	395	467	72	**7k**	401	492	91
7d	370	430	60	**7l**	396	477	81
7e	405	499	94	**7m**	421	527	106
7f	400	493	93	**7n**	406	504	98
7g	425	528	103	**7o**	425	503	78
7h	406	499	93				

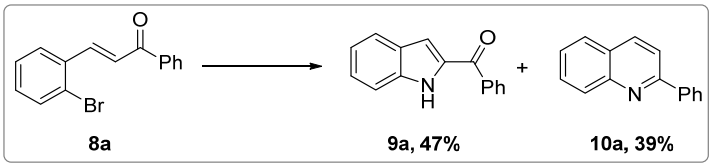
Copper catalyzed synthesis of 2-aroyl indole derivatives:

Having successfully demonstrated the one-pot S_NAr–Smalley cyclization for indolinones, as a logical extension, we next asked a simple question – is the synthesis of 2-aroylindoles possible *via* sequential S_NAr – nitrene insertion from the 2-bromochalcones?



Scheme 5: *Our previous approach for C–N bond* formation *and intended hypothesis for 2-aroyl indole*

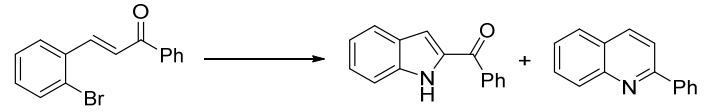
Our journey started with the examining of the reaction of α-bromochalcone **8a** under the previously established conditions [20 mol% of each of $CuSO_4 \cdot 5H_2O$, sodium ascorbate and L-proline, 1.5 equivalents of K_2CO_3 and NaN_3 in DMSO at 80 ºC for 15h] which resulted in a mixture of the required 2-benzoylindole (**9a**, 47%), along with the 2-phenylquinoline (**10a**, 39%) (Scheme 6).



Scheme 6: *Reagent and condition: $CuSO_4 \cdot 5H_2O$ (20 mol%), NaN_3 (1.5 equiv.), Na-ascorbate (20 mol%), L-proline (20 mol%), K_2CO_3 (1.5 equiv.) in DMSO at 80 ºC for 15 h*

Encouraged with these promising early results, the optimization of this reaction was carried out by employ various copper sources. As shown in Table 5, CuI was found to be the best catalyst for the present transformation and the presence of base, like K_2CO_3 (4.0 equivalents) is essential.

Table 5: *Optimization of Reaction Conditions*

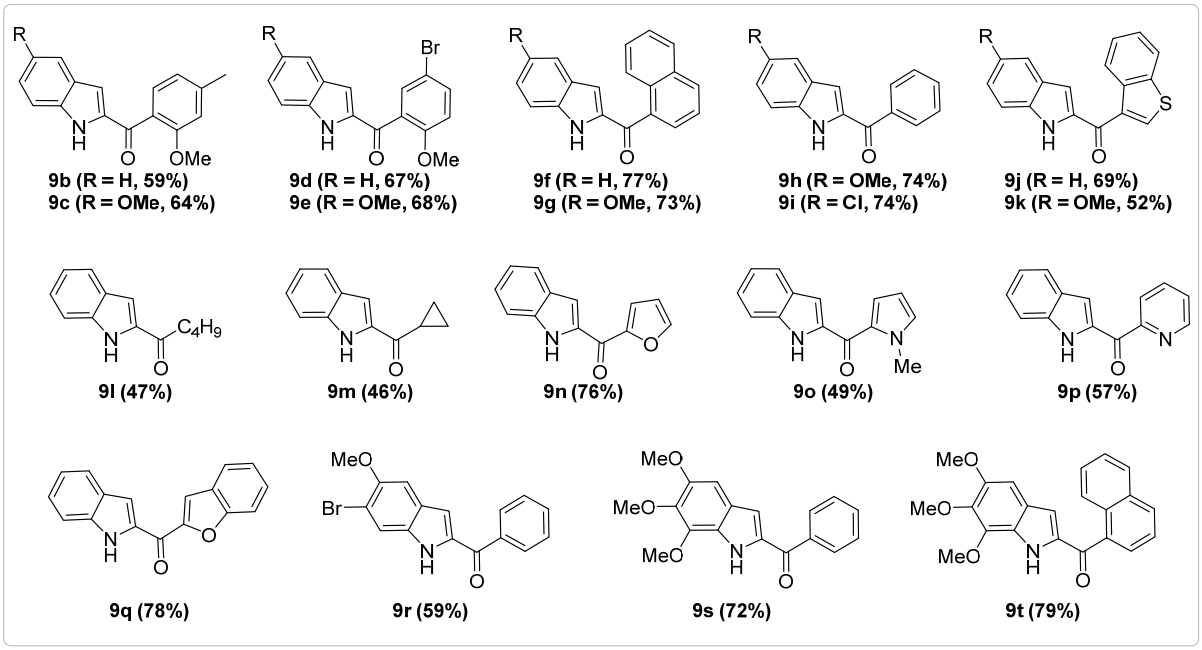


Sr. No	Catalyst	Solvent	Base	Yield (**9a**)[b, c, d]	Yield (**10a**)[b, c, d]
1	CuI	DMSO	1.5	56%	41%
2	CuI	DMA	1.5	62%	38%
3	CuI	NMP	1.5	69%	26%
4	CuI	NMP	----	47%	13% (39%)
5	CuI	NMP	2.0	80%	20%
6	CuI	NMP	3.0	81%	5% (4%)
7	CuI	NMP	4.0	86%	3%
8	CuI	NMP	1.5[e]	49%[f]	51%
9	CuI	NMP	3.0[f]	72%[g]	27%
10	$CuSO_4$	NMP	1.5	52%[e]	5% (27%)[e]
11	**CuI**	**NMP**	**4.0**	**87%**	**1%**
12	CuI	NMP	3.0	75%	7% (17%)
13	CuCl	NMP	4.0	84%	---(4%)
14	Cu_2O	NMP	3.0	54%	24%(21%)
15	-----	NMP	4.0	ND	ND

[a]Reaction condition: *o*-bromochalcone (**1a**, 1eq.), NaN_3 (1.5 eq.), CuI (20 mol %), L-proline (0.2 eq.), K_2CO_3 (4.0 eq.) in NMP at 100 ºC for 15h;[b] L-proline (1.0 eq.) was used for entries 2–11; [c]Yield based on GC; [d]Isolated yield; [e](20 mol%)Na-ascorbate was used; [f] Cs_2CO_3 used as a base; [g]K_2CO_3 use as base; [i] parenthesis indicate (%) starting intact.

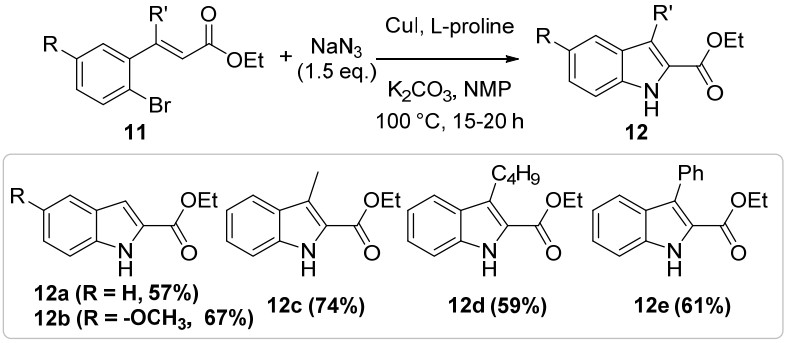
After optimizing the reaction conditions, the generality of the current reaction has been examined with several substrates as shown in Scheme 7. Myriad substrates having

substituents next to the carbonyl have been varied (from aromatic/alkyl/heteroaromatic) and gave the desired products in moderate to good yields.



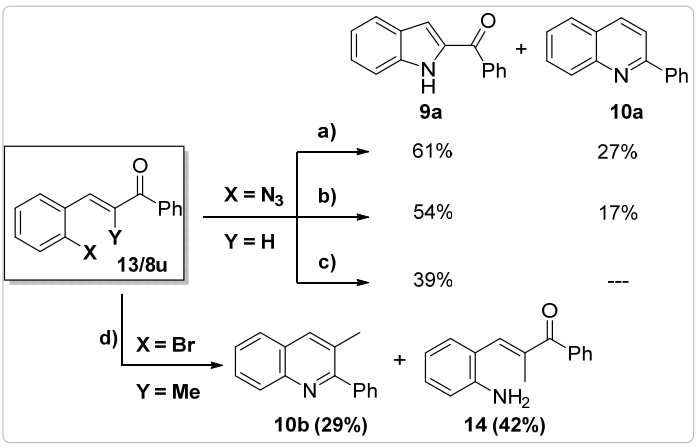
Scheme 7: *Scope of the [Cu]-catalyzed 2-aroyl indole synthesis*

Similarly, the computability of variously substituted *o*-bromocinnamate has been examined. As shown in Scheme 8, the one-pot S_NAr–Smalley cyclization with the bromocinnamates proceeded smoothly and provided the corresponding indoles **12a**–**12e** in good yields. These experiments revealed that the carboxylate group can be a suitable alternative for the aroyl group



Scheme 8: *Cu (I)-catalyzed synthesis of indole-2-carboxylates*

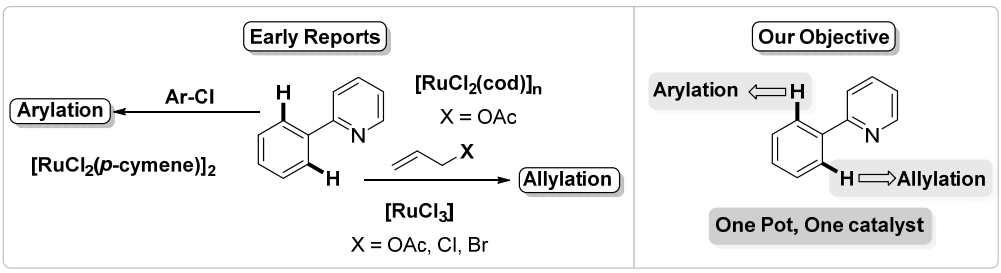
To understand the course of this one-pot reaction, control experiments have been conducted employing the 2-azidochalcone **13** and the bromochalcone **8u** (having a methyl group in place of the hydrogen atom to be abstracted) and Scheme 9 provides the detailed experimental conditions along with the outcome and tentative mechanistic proposal. Considering the results obtained from these experiments and the previous reports, a concerted process having Cu-participation in both the steps has been proposed.



Scheme 9: *Reagents and conditions: a) CuI (20 mol %), L-proline (20 mol %), K_2CO_3 (4.0 eq.) in NMP at 100 °C, for 15h; b) CuI (20 mol %), NMP at 100 °C for 15h ; c) NMP at 100 °C for 15h; d) same as condition (a) along with NaN_3 (1.5 eq.)*

Chapter II: Ru-Catalyzed Sequential C–H Activation: Directed and Direct C–H Activation of 2-Phenylpyridine Derivatives

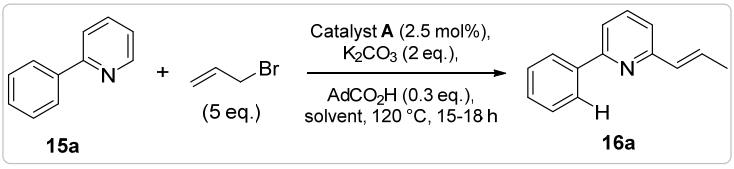
Transition-metal catalyzed functionalization of aryl/heteroaryl C–H bonds to form C–C bond has recently attracted attention because these reactions provide more desirable step- and atom economy than those reactions where the prefunctionalization of aryl/heteroaryl rings is required. Pyridine derivatives are interesting in this regard, because pyridine moiety is one of the conventional functional groups employed as a ligand. Moreover, it is also present in various biologically active molecules. Generally, the direct C–alkylation of pyridine can be achieved by using N-oxides, N-iminopyridinium ylides, or Lewis acids; which increase the acidity of the C–H bond at the C2 position. On the other hand, for directed alkylations, the pyridine moiety needs to be electron rich, because the catalytic cycle involves the coordination of the nitrogen atom with a metal complex. However, in general, both direct and directed C–H activation have been approached separately by using various transition-metal complexes.



Scheme 10: *Intended Ru-catalyzed sequential C–H activation*s

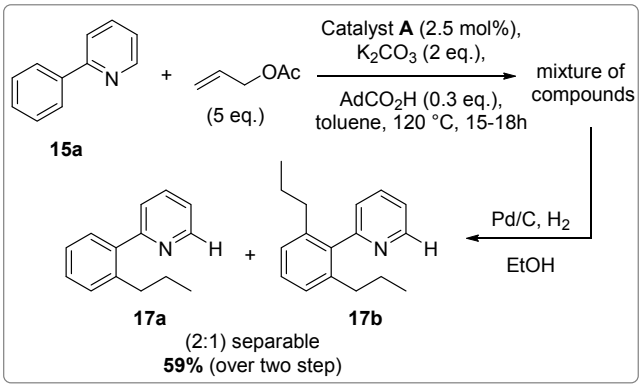
Our interest in this context was about the possibility of multiple C–H activations in one pot. Our initial speculation was about the one-pot Ru-catalyzed directed allylation and

arylation of 2-phenylpyridine derivatives using one catalyst. The directed allylation or arylation of 2-phenyl pyridine derivatives has been well documented and the ruthenium complexes employed are different (Scheme 10). Our journey in this context started with the examination of the possibility of a directed allylation of the 2-phenyl pyridine (**15a**) reaction under the arylation conditions reported by Ackermann's group (Scheme 11).



Scheme 11: *Initial attempt for allylation of 2-phenyl pyridine*

The allylation reaction of **15a** was carried out using allyl bromide, K_2CO_3 (2.0 equiv), adamantane-1-carboxylic acid ($AdCO_2H$, 0.3 equiv), and [{Ru(*p*-cymene)Cl_2}$_2$] (**A**; 2.5 mol%) in either toluene or NMP (N-methyl-2-pyrrolidone) at 120 °C, gave a single product **16a** in 67% and 63% yield respectively. Interestingly, the spectral data analysis of **16a** revealed that the reaction proceeded with an unexpected direct C–H activation of the pyridine ring and provided **16a** having an *E*-configured 2-propenyl group on the carbon next to the nitrogen atom of the pyridine moiety. This was quite surprising as the direct C–H activation of pyridine ring needs a different set of catalysts/reactions conditions. Next, the compatibility of other ruthenium complexes for the present transformation has been examined. With a majority of the complexes, the direct allylation was the exclusive event, but the yields are poor.



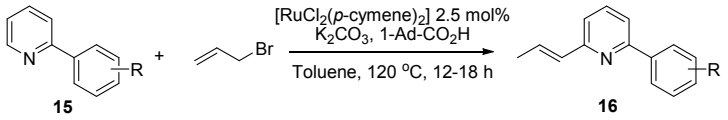
Scheme 12: The *reaction with allyl acetate*

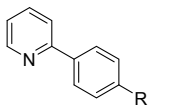
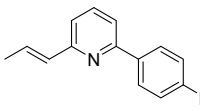
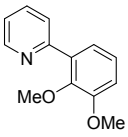
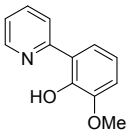
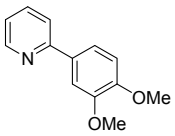
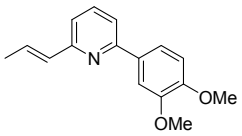
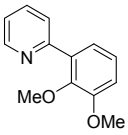
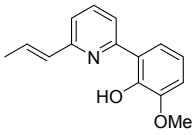
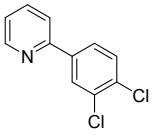
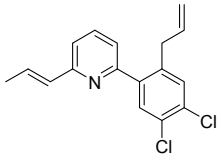
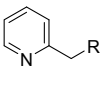
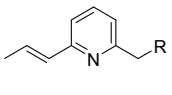
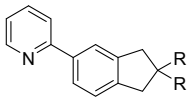
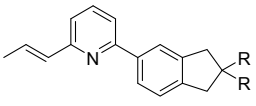
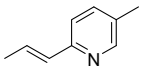
Coming to the reactions with other allyl halides, allyl bromide was best amongst the corresponding chloride or iodide and there was no reaction when crotyl bromide was employed. Interestingly, the reaction of **16a** with allyl acetate, under similar conditions, gave a mixture of products, which upon olefin hydrogenation afforded the separable mono- and dialkylation products, **17a** and **17b**, respectively in 59% yield over two steps (Scheme 12).

The different reactivity of allyl bromide and allyl acetate and the results obtained from a control experiment using the allyl bromide salt of **15a** suggests that the reaction might be proceeding through the N-allylation of pyridine in the case of allyl bromide, a transformation that would increase the acidity of the C–H bond at the C2 position.

The scope of this direct allylation of pyridine rings has been examined employing diverse 2-arylpyridine derivatives. With a majority of the substrates the direct allylation reaction was facile.The double $C_{SP}{}^2$–H activation product (**15e**) was observed with 2-(3,4-dichlorophenyl)pyridine and the *ortho*-O-desmethyl were observed together with the C6-propenylation of 2-(2,3-dimethoxyphenyl)pyridine (**15g**) under the present reaction in 61% and 63% yields respectively. The simple alkyl pyridines **15h–15k** have also been found to be compatible for the present reaction and provided exclusively the sp^2 C–H alkenylation products **16h–16k** in moderate to poor yields (Table 6).

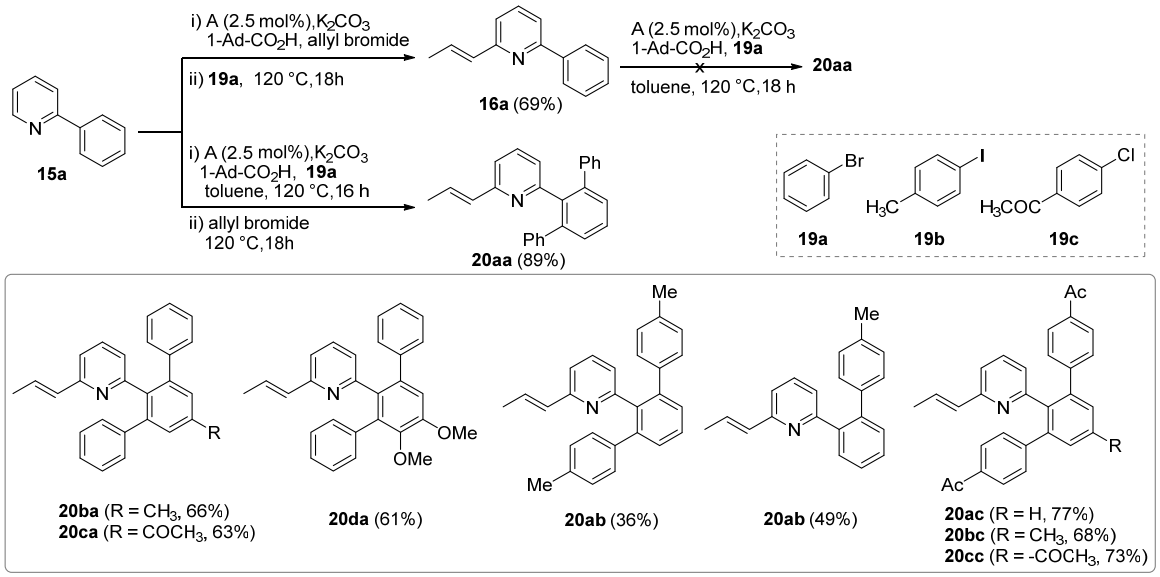
Table 6: *The scope of the Ru-catalyzed propenylation reaction of substituted phenyl derivatives*



Entry	Substrate	Product (Yield)	Entry	Substrate	Product (Yield)
1 2 3	 **15a, R = H** **15b, R = Me** **15c, R = -COCH$_3$**	 **16a, R = H, 67%** **16b, R = Me, 63%** **16c, R = -COCH$_3$, 66%**	5	 **15g**	 **18, 63%**
4	 **15d**	 **16d, 62%**	6	 **15g**	 **16g, 62%[b]**
5	 **15e**	 **16e, 61%**	8 9 10	 **15h, R = H** **15i, R = Me** **15j, R = -CH$_2$OBn**	 **15h, R = H, 67%** **15i, R = Me, 65%** **15j, R = -CH$_2$OBn, 22%**
6	 **15f, R = CO$_2$Et**	 **16f, R = CO$_2$Et, 48%**	11	 **15k**	 **16k, 54%**

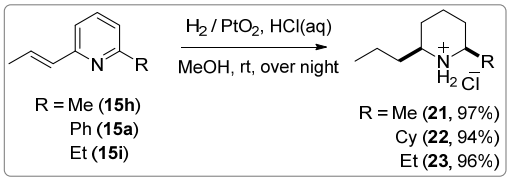
Having established an unprecedented direct allylation of pyridine derivatives, next we examined the compatibility of this reaction in combination with the directed arylation for one-pot sequential C–H activations employing 2-phenyl pyridine as the model substrate. Initial attempts comprising the alkenylation followed by arylation employing bromobenzene

(**19a**) gave exclusively the alkenylation product **16a** indicating that the arylation is not facile after allylation. However, when the reaction sequence was changed, i.e., arylation followed by alkenylation, **20aa** resulting from the direct and directed C–H activation/functionalization was obtained in 89% yield. The scope of these one-pot sequential C–H activations has been explored by employing various 2-phenyl pyridines with aryl halides (**20a–20c**) and the results are summarized in Scheme 13. The reaction of substrates **15a–15d** with various arylating agent **19a–19c** afforded the diarylated and alkenylated products in 60–70% yield.



Scheme 13: *A one pot sequential arylation and allyation of 2-phneylpyridine derivatives*

Subsequently, the exhaustive hydrogenolysis of compound **15h** has been carried out employing a catalytic amount of PtO_2 in aq.HCl/EtOH at 50 bars H_2 pressure to synthesize the natural product (±)-dihydropinidine hydrochloride (**21**). Similarly, the hydrogenation of the compounds **15a** and **15i** afforded the completely reduced products **22** and **23** respectively (Scheme 14).



Scheme 14: *The synthesis of (±)-dihydropinidine and related compounds*

CHAPTER I:

Copper catalyzed sequential C–N bond formations with NaN_3: One pot synthesis of primary arylamines, 2,2-disubstituted-3-indolinones and 2-aroyl indoles

INTRODUCTION

At the heart of Organic Synthesis, the formation of carbon–carbon (C–C) and carbon–hetero (C–X) atom bonds occupies the central role. From the early days of organic synthesis, the search for the new methods for forging C–C and C–X bonds has unveiled new inventions that influenced the direction of chemical research and aided the rapid development of civilization seen during the last two centuries.[1] Initially, it was the simple acids and bases that were employed for mediating organic transformations, especially those involving active methylene groups and carbonyl compounds. For example, the early named reactions such as Aldol, Claisen, Perkin, Stobbe condensations, to name a few, employed either simple acids or bases to mediate the C–C bond formations.[2] In the early 20th century, the organometallic reagents/reactions started appearing with due efforts from Barbier and Grignard that revolutionized the organic synthetic portfolio by allowing new avenues for the key C–C bond formations.[3] Subsequently, notable progress was made with the rearrangements, the sigmatropic and pericyclic reactions that have led to the synthetic chemists manipulating the existing C–C bonds and forging multiple bonds in a single operation.[4]

This organized development that has occurred from the beginning of the 19th century to the middle of the 20th century, especially in terms of the new synthetic tools aimed at the formation of C–C and C–X bonds, has witnessed an exponential growth after transition metal complexes entered the armoury of the synthetic chemists.[5] Starting with the simple small molecules activation,[6] then cross couplings[7] and now recently, the olefin metathesis[8] reactions catalyzed by Rh-, Pd- and Ru/W-complexes, now a wide range of metals and their complexes have entered in this domain and many synthetic transformations that would have been otherwise impossible employing traditional organic methods have been unveiled.

The formation of Ary–C and Aryl–heteroatom bonds needs a special mention. Nowadays, the cross-coupling reactions are the text book reactions - especially the Pd-catalyzed ones. The era of the cross coupling chemistry started with the seminal contributions of Heck and Mizoraki on the coupling of functionalized aryl compounds ArX (X = halogen, Sn, B, Si etc.) with olefins.[9] When it comes to the C-heteroatom bond formations, until recently it was either the nucleophilic aromatic substitution (S_NAr) or the Ullmann coupling reactions that have been widely employed for this purpose. The nucleophilic aromatic substitution is one of the classical methods for making such type of fundamental organic transformation.[10] However, this method has suffered due to the limited scope of substrates (limited to electron deficient aryl halides) and the requirement of harsh conditions, as well as the lower tolerance of other sensitive functionalities on the substrates. The reaction with unactivated (electron rich) aryl halides required high temperatures. The nucleophilic

additions to benzynes have been used as an alternative to the S_NAr reaction.[11] However, the problem is the poor regioselectivity and also the lack of substrate diversity. Another approach in this context was the unimolecular substitution reactions – the substitution of diazonium with nucleophile (the Sandmeyer reaction).[12] The fourth approach is the aromatic radical substitution reactions ($S_{RN}1$).[13] However, all these uncatalyzed methods have limited scope and also lower functional group tolerance.

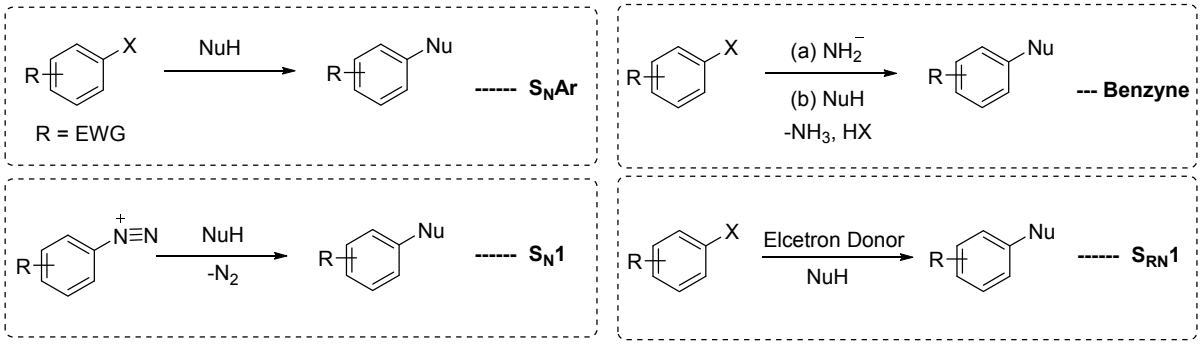


Figure S1.1: *Various classical approaches of Nucleophilic Aromatic substitutions*

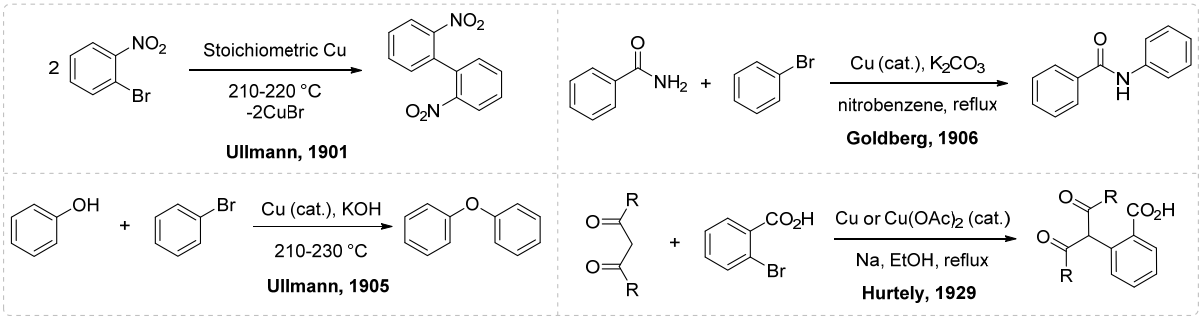
Keeping the major focus of the next chapter that deals with the Cu-catalyzed S_NAr with azide and subsequent reactions of the azide functional unit, the following description is divided into four parts limiting the attention mainly on the

1. Cu-catalyzed C–N couplings: Ullmann Reaction
2. Sequential C–N_3 coupling and azide transformations
3. Synthesis of 2,2-disubstituted indolin-3-ones using aryl azides
4. Synthesis of 2-aroylindoles using aryl azides

1. Copper Catalyzed C–N Coupling: Ullmann Reaction & Recent Developments

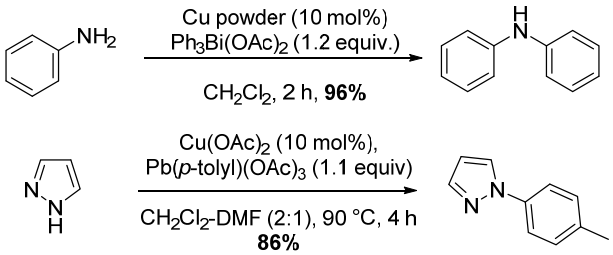
Quite interestingly, much earlier before recent innovations with the transition metal complexes, in the early days of the 20th century, Fritz Ullmann and his wife Irma Goldberg reported initially the dimerization of *o*-bromonitrobenzene leading to 2,2-dinitrobiphenyl employing Cu powder.[14] Later, the same Cu-mediated reaction for the C–N and C–O bond formations has been developed - which were ultimately identified as Ullmann reactions.[15] Despite the fact that the early reports on Ullmann reaction employed the electron deficient aryl halides however, unlike with the classical S_NAr reactions, Ullmann reactions do not require strong nucleophiles and are operative only when the copper-powder is present. After five years of initial disclosure on the stoichiometric version, the catalytic Ullmann reaction was reported in 1906 for aryl amination and aryl amidation by Irma Goldberg.[16] It was the first time where electron rich aryl halides were employed as coupling partners. About 30

years later, Hurtley reported carbon-carbon coupling using Cu bronze or Cu $(OAc)_2$ between the *o*-bromobenzoic acid and *β*-dicarbonyls (Scheme S1.1).[17]



Scheme S1.1: *Pioneering contributions to copper-mediated coupling reactions*

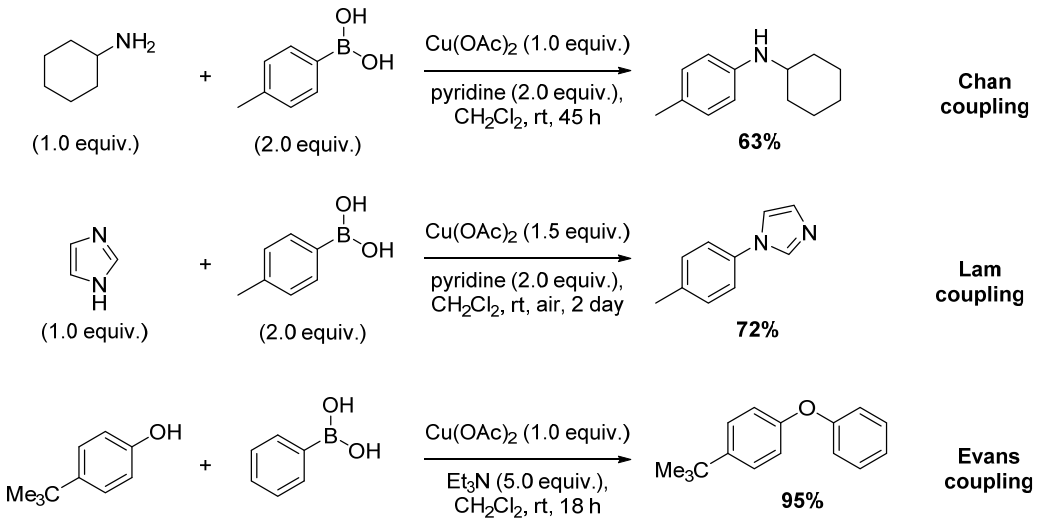
However the importance of these original Ullmann type couplings cannot be overstated because of harsh reaction conditions, limited substrate scope and moderate yields. Generally, these reactions were conducted using the stoichiometric copper reagent with a strong base in a high boiling solvent at reaction temperatures of about 200 °C and moreover taking long reaction time. Until the end of the 20th century, Ullmann coupling had remained relatively undeveloped, even though it has numerous applications in industry as well as in the synthesis of various heterocycles and biologically important natural products.[18] Barton[19] and Avendano[20] have attempted to carry out the Ullmann coupling employing mild conditions and explored the combinations of triphenylbismuthbistrifluoroacetate and *p*-tolyllead triacetate respectively as new arylating agents. Even though mild reaction conditions were used than in previous reports, the substrate scope was limited and also the success of the reaction was found to be sensitive to steric hindrance (Scheme S1.2).



Scheme S1.2: *Barton and Avendano C–N coupling using aryl bismuth and aryl lead reagent*

1.1. Chan-Lam coupling

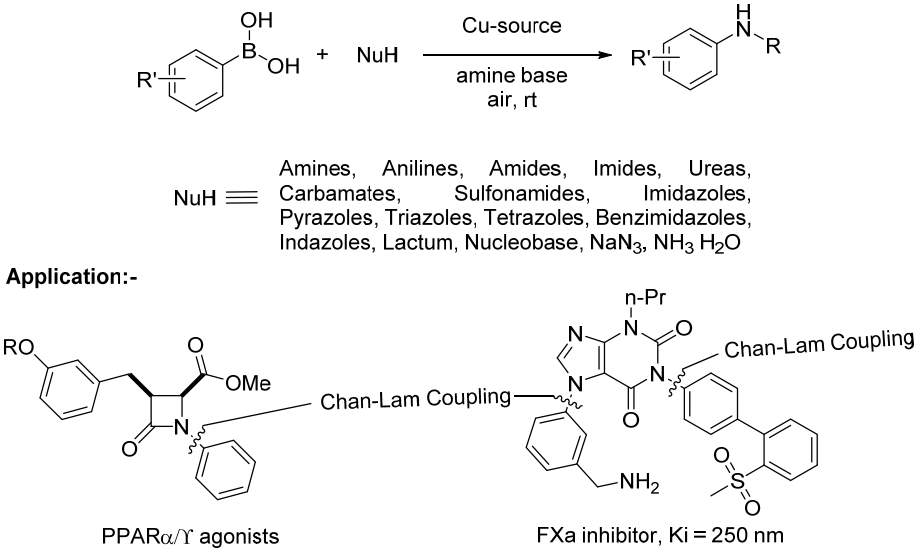
In 1998, the research groups of Chan[21], Lam[22] and Evans[23] have independently described the practically simple conditions for Ullmann coupling by switching the coupling partner from aryl halide to aryl boronic acid (Scheme S1.3).



Scheme S1.3: *C–N and C–O coupling with boronic acid reported by Chan-Lam-Evans*

The preliminary communication by the Chan group reported N- and O-arylation with phenylboronic acid in the presence of cupric acetate and tertiary amine at room temperature. A wide range of nucleophiles such as phenols, amines, anilines, amides, imides, ureas, carbamates, sulfonamides, and also aromatic heterocycles like imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles have been found to be suitable. [21]

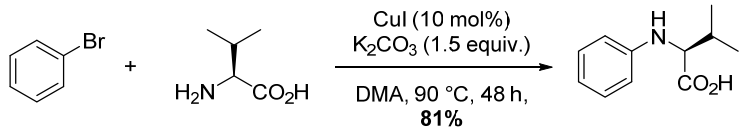
The potential of this reaction has been further extended by Chan, Lam and other research groups in the synthesis of medicinally important compounds and also for C–S, C–Se, C–Te, C–Cl, C–Br, C–I bond formations under mild reaction conditions (Scheme S1.4).[24]



Scheme S1.4: *Chan-Lam coupling with Various N-Nucleophile and its Application*

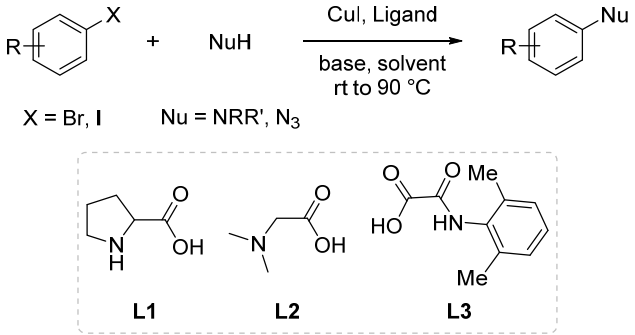
Following this, an outstanding contribution in this area has been documented by Ma's group. In 1998, Ma *et al* revealed that the addition of simple organic ligands enhanced the efficiency of the Ullmann coupling drastically. During their study in the synthesis of

Benzolactam-V8, the addition of α-amino acid had accelerated the copper-catalyzed coupling reaction between aryl bromide and α-amino acids (Scheme S1.5).[25] The reaction with cyclic amino acids was even more facile than that with the acyclic *N*-alkyl amino acid. It was also observed that the reaction proceeded with the retention of the configuration in most of the cases. The C–N coupling was facile with aryl iodides as well; however, aryl chloride is incompatible and also the success of this reaction suffers from steric factors associated with the substrates.



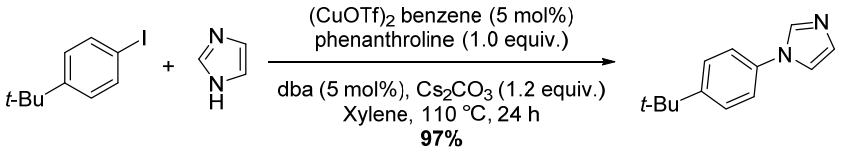
Scheme S1.5: *Copper-Catalyzed Couplings of Aryl Halides and α-Amino Acids*

Subsequently, the scope of this reaction has been expanded by employing various nitrogen nucleophiles and screening various ligands. It was revealed that the α-amino acids, in particular L-proline (**L1**) and *N*,*N*-dimethylglycine (**L2**) are the best ligands and that they form a bidentated complex with CuI. By employing these ligands, the Ullmann coupling of numerous aryl bromides with primary alkyl/aryl amines, cyclic secondary amines, and *N*-containing heterocycles have been examined at ambient temperatures (40–90 °C). Ma's group also revealed that *ortho*-amide group can also accelerate Ullmann-type reactions. Recently, the 2-(2,6-dimethylphenylamino)-2-oxoacetic acid (DMPAO) ligand (**L3**) has been introduced by this group as an effective ligand in this regard (Scheme S1.6).[26]



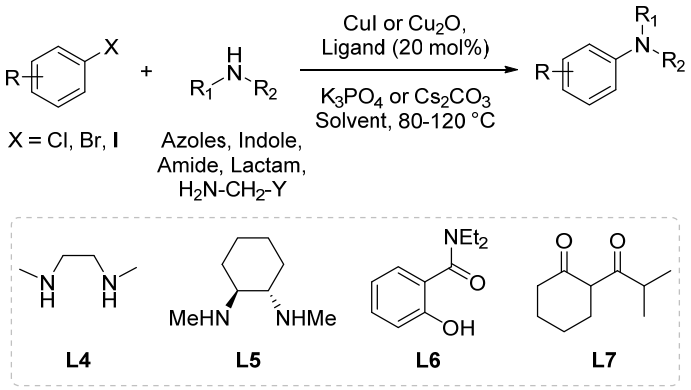
Scheme S1.6: *CuI/Amino acid catalyzed couplings of Ar–X with various nucleophiles by Ma et al*

A year later, in 1999, Buchwald and co-workers reported the *N*-arylation of imidazoles using $(CuOTf)_2$-benzene as catalyst and 1,10-phenanthroline, dibenzylideneacetone (dba) as additives and Cs_2CO_3 as a base in xylenes at relatively low temperature (Scheme S1.7).[27] The aryl iodides were found to be the better substrates than the aryl bromides and also the reaction was sensitive to steric hindrance in either aryl halide or imidazole.



Scheme S1.7: *Copper-Catalyzed N-arylation of imidazoles*

Since the first preliminary observation for *N*-arylation of imidazoles, Buchwald's group developed a variety of Cu-catalytic systems by introducing a wide range of ligands such as *N,N*'-dimethylethylenediamine (**L4**), *trans-N,N*'-dimethyl-1,2-cyclohexanediamine (**L5**) for the N-arylation of various nitrogen heterocycles including pyrroles, pyrazoles, indazoles, imidazoles, triazoles, indole, amide, lactam, and so on with myriad aryl/heteroaryl halides. Also, they showed that diethylsalicylamide (**L6**) is an efficient bidented ligand particularly for the *N*-arylation of primary alkylamines with aryl bromides. Furthermore, they have also documented room-temperature coupling of aryl iodides with amines as well as amino alcohols using CuI and cyclic *β*-diketone (**L7**) as a ligand (Scheme S1.8).[28]

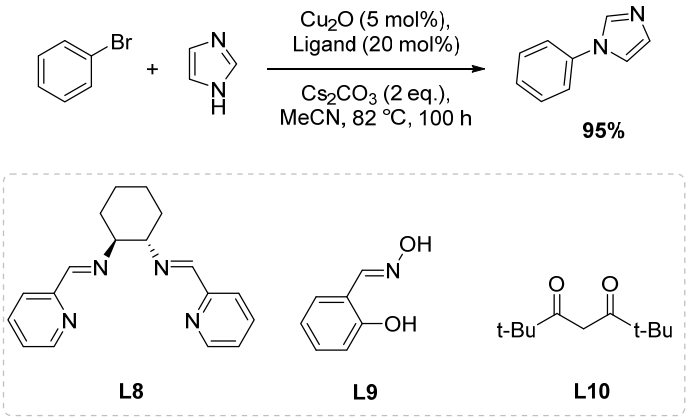


Scheme S1.8: *Cu-catalyzed C–N coupling using diamine and β-diketone as ligands by Buchwald et al*

Along with the Ma and Buchwald groups, Taillefer's group has also made some important contributions in the area of Cu-catalyzed C–N couplings. In 2001, in their initial report, the Taillefer group demonstrated the *N*-arylation of imidazole with aryl bromides or iodides employing an inexpensive, air-stable Cu_2O as a catalyst in combination with simple chelating ligand (Scheme S1.9).[29]

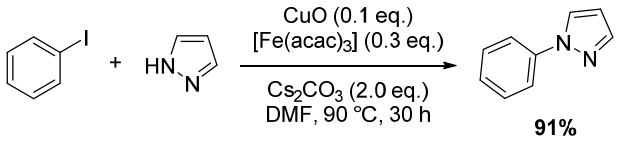
The reaction was compatible with a broad range of aryl halides, comprising of sterically hindered, electron-poor, and electron-rich aryl halides under particularly mild conditions (50–82 °C). In addition to that, they have also explored the scope of nucleophiles encompassing various azoles (with the exception of tetrazoles), amides, carbamates and the pyridazin-2-one derivative with aryl halides (X = Br, I) using polydentate ligands with a coordinating site including oxygen- and/or nitrogen like Schiff base and an oxime type (**L8**

and **L9**) in DMF or CH_3CN using a mild base at 50–80 °C. However, the coupling with sulfonamides and some selective amides are sluggish. Recently, they showed that *β*-diketones (**L10**) [2,2,6,6- tetramethyl-3,5-heptadione (TMHD)] also enable the N-arylation of aromatic and aliphatic secondary acyclic amides (Scheme S1.9).[30]



Scheme S1.9: *C–N coupling of Ar–X using various bidentate ligands by Taillefer et al*

Successively, the N-arylation of pyrazole with aryl iodides employing cooperative bimetallic catalysis with Fe and Cu such as (CuO-[$Fe(acac)_3$]) along with the base in DMF at 90 °C has been documented (Scheme S1.10).[31] The catalytic system also allows the N-arylation of various nitrogen nucleophiles (azoles and a cyclicamide) with differently substituted aryl halides, where the halides can be I, Br, or Cl.

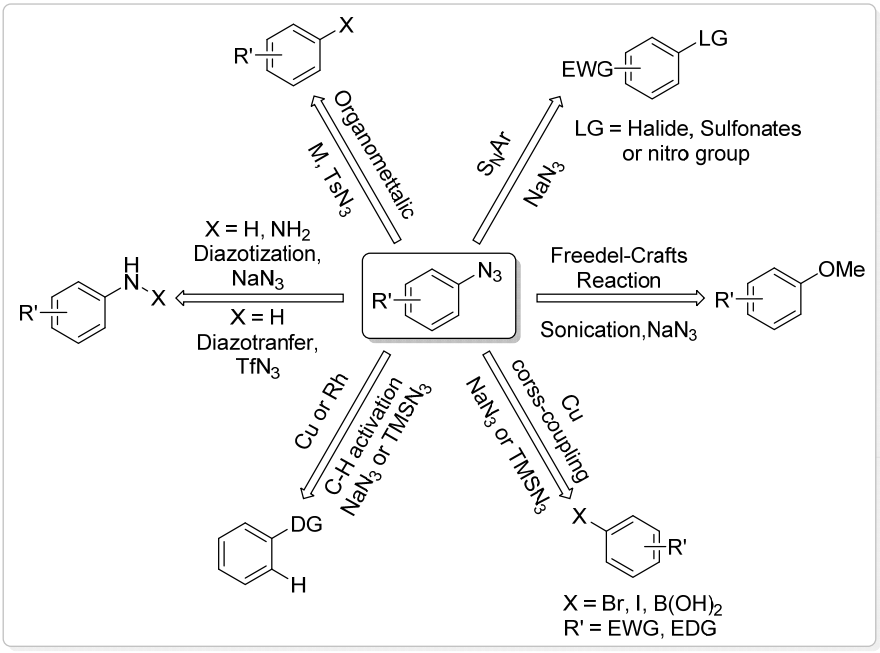


Scheme S1.10: *Iron-copper catalyzed N-arylation of pyrazole*

In summary, during the last two decades, outstanding contributions from various groups have made the Ullmann C–N coupling reaction a practical tool in the synthesis of complex targets with the introduction of a wide variety of copper sources and ligands. A wide range of aryl/heteroaryl halides (X = Cl, Br, I) are compatible for *N*-arylations with nitrogen centered nucleophilies ranging from ammonia (useful for the synthesis of aniline), aryl/heteroaryl amine, alkyl (cyclic or 1°/2° acyclic) amine and numerous N-heterocycles.[32] Quite surprisingly, out of these entire nitrogen nucleophiles, azides (e.g. NaN_3) have not been significantly explored until recently. Following are some of the recent reports on the synthesis of aryl azides by the Ullmann coupling as well as their application in the synthesis of various heterocycles (only cascade reaction using sodium azide).

2. Sequential C–N_3 coupling and azide transformations

Peter Grieß has synthesized the first organic azide (phenyl azide) over 180 years ago in 1834. Azide groups have various applications such as, as the active functional group in biologically active molecules (AZT or azido-thalidomide in which the azide group is essential for the anti-viral activity), as photoaffinity labelling agents, for photo cross-linking with polymer surfaces and for enzyme immobilization.[33] More fascinatingly, arylazides are well known for bioconjugation.[34] In addition to these, aryl azides have seen wide application in industry and academia because it is an important intermediate in the synthesis of various heterocycles.[35] The main drawback of azides is their explosive property (e.g. in explosives technology, it is used in detonators). However, because of the popularization of the azide-alkyne cycloaddition as a "click reaction" by Sharpless and Meldal during the last decade, the chemistry of azides has seen tremendous applications across the various branches of chemistry, biology and materials.[36]



Scheme S1.11: *Synthetic approaches for aryl azide*

Scheme S1.11 represent the general synthetic methods for the aryl azide preparation.[35, 37] The diazotization of an aryl amine followed by the treatment with NaN_3 as well as of aryl hydrazine using nitrosyl ions or their equivalent, and the nucleophilic substitution reaction of activated aryl halide with sodium azide are the classical way for the synthesis of aryl azide. The reaction of organometallic reagent (Grignard or Lithium reagent of aryl halide) with electrophilic azide (tosyl azide) was developed in this regard. Diazo transfer to primary amines by using an efficient diazo-transfer reagent (for example TfN_3,

Imidazole-1-sulfonyl azide hydrochloride, 2-azido-1,3-dimethylimidazolinium hexafluorophosphate) under suitable reaction conditions is an alternative method for the synthesis of aryl azides. The reaction of nitrosoarenes with HN_3, base-induced cleavage of triazenes and the direct azidation of arenes using $NaICl_2$ and NaN_3 are some of the alternative methods reported for the synthesis of aryl azides.

2.1. Reaction of aryl azides

The reactivity of aryl azide could be explained by looking at its mesomeric structure:

(a) Electrophilic reaction at Nα (**C**); for example intramolecular cyclization of arylnitrenium ions,

(b) Nucleophilic reaction at Nγ (**C**); for example the Staudinger reduction,

(c) [3+2] Cycloaddition with suitable dipolarophiles (**B** and **C**); for example the Huisgen reaction, and

(d) They undergo decomposition to nitrene *via* rapture of N–N_2 single bond (between Nα–Nβ) *via* N_2 elimination either thermochemically or photolytically and furthermore intermediate nitrene undergo cycloaddition or rearrangements or insertion reactions (Figure S1.2).

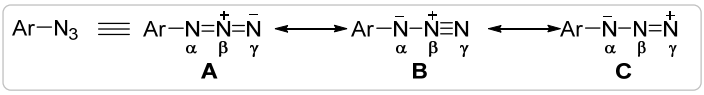
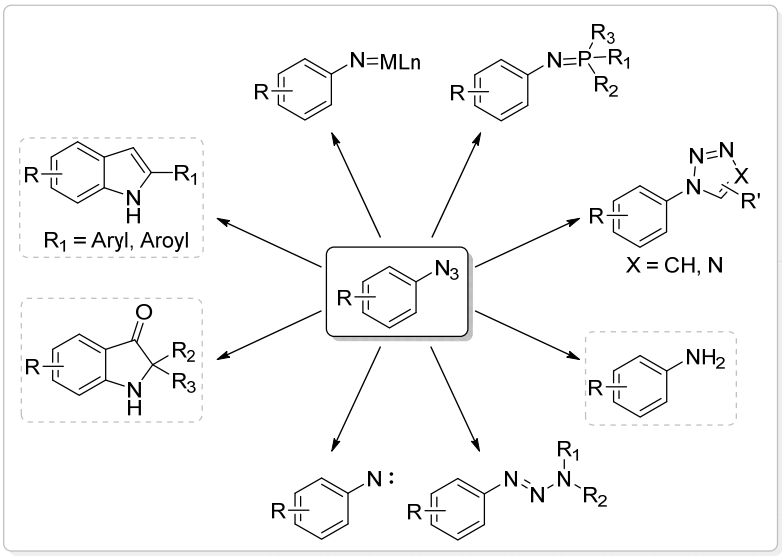


Figure S1.2: *Mesomeric structure of Aryl azide*



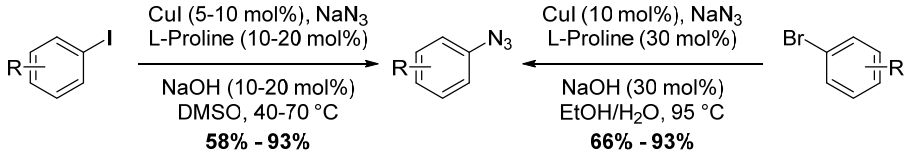
Scheme S1.12: *Reaction of Aryl Azide*

Scheme S1.12 presents some of the important transformations employing aryl azides.[35, 38] In recent years, the focus has mainly been on the cycloadditions with azides

giving either triazole or tetrazoles. Also, azides have been used as sources to generate highly reactive nitrene intermediate as well as employed as an amine surrogate (The Staudinger Reduction). The intermediate nitrenes could undergo cycloadditions; insertion into C–H bonds; rearrangements and also react with various electron rich heteroatoms (N, S, P) to form the corresponding ylides. Considering the focus of our research that we present in the next chapter, the further discussion on this topic will be restricted mainly to aryl azide reactions leading to anilines, (one pot azidation and reduction), and the synthesis of 2,2-disubstituted indol-3-one (Smalley Cyclization) and the synthesis of 2-aroyl indole (C–H insertion).

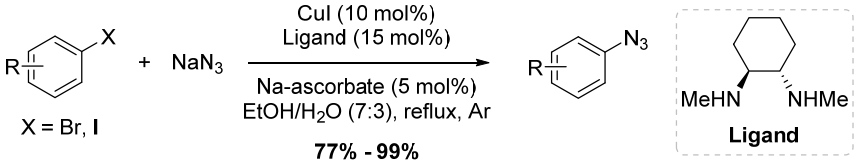
2.2. Cu-Catalyzed C–N_3 Coupling

In 2004, Ma *et al* described Cu-catalyzed aryl azide synthesis *via* an amino acid (L-proline) promoted coupling reaction between aryl halide and sodium azide. Both aryl iodides and bromides were suitable, but they required different conditions. In DMSO, the aryl iodides gave better results, whilst EtOH/water was the better combination for bromides. This method provided various aryl azides in good to excellent yields with good functional group tolerance such as alkoxy, amino, bromo, fluoro, hydroxy, and carboxylate and also sterically hindered aryl bromide worked well (Scheme S1.13).[39]



Scheme S1.13: *CuI/L-proline catalyzed synthesis aryl azide from aryl halide*

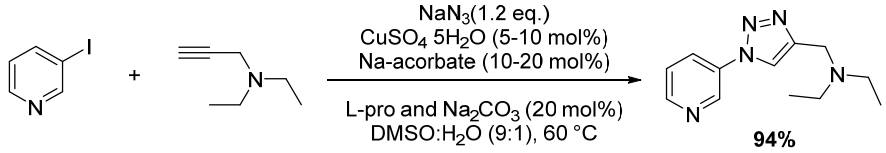
One year later, Liang and coworkers reported the CuI/diamine catalyzed synthesis of aryl azides from the corresponding aryl halides. Several aryl iodides/bromides converted into the corresponding aryl azides in excellent yields. The use of sodium ascorbate was found to have a positive effect on the stabilization of the catalyst system. Moreover, microwave heating instead of conventional heating was also employed (Scheme S1.14).[40]



Scheme S1.14: *CuI/diamine catalyzed synthesis aryl azide from aryl halide*

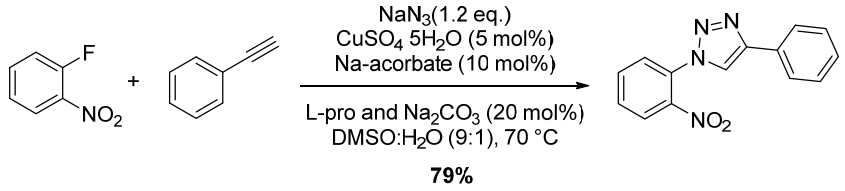
In 2004, Fokin and coworkers explored the first reliable one pot synthesis of 1,2,3-triazoles from aryl iodide, NaN_3 and alkynes. The 1,4-disubstituted 1,2,3-triazoles are

obtained in excellent yields using $CuSO_4$, L-proline, Na-ascorbate, Na_2CO_3 in DMSO and H_2O (9:1) as the solvent at 60 °C (Scheme S1.15).[41] This method is also convenient for aliphatic halides to provide the required triazoles without isolation of potentially unstable organic azide intermediates.



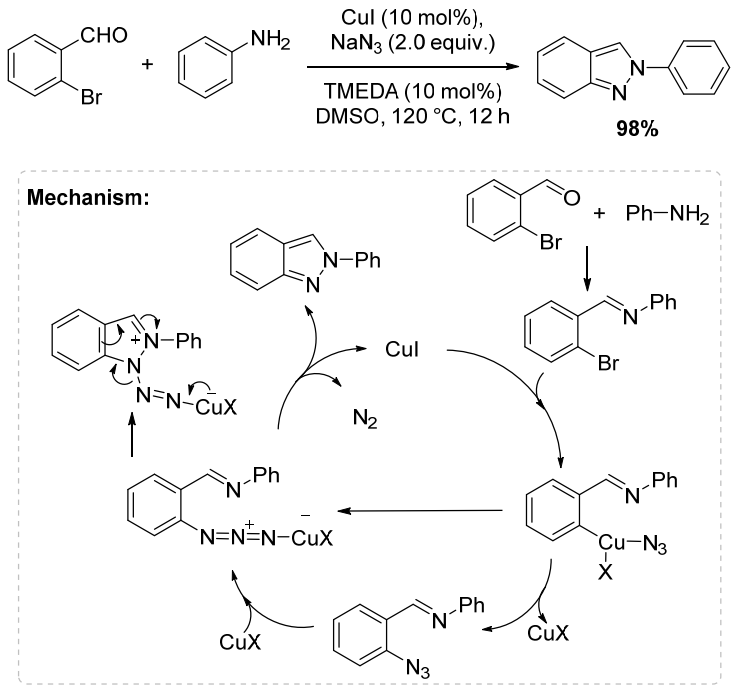
Scheme S1.15: *One pot synthesis of 1,2,3-triazoles from alkyl/aryl/vinyl iodides, NaN_3, and alkynes*

In 2009, we have also reported the one-pot two-step sequence involving a nucleophilic aromatic substitution (S_NAr) of activated fluoro-benzenes with the azide nucleophile and *in situ* Huisgen cycloaddition of the resulting aryl azides with alkynes for a rapid access to 1,4-disubstituted triazoles.[42] The course of the reaction is S_NAr with the azide nucleophile followed by the cycloaddition of the resulting nitro azidobenzene intermediate and both the reactions are catalyzed by Cu(I). Furthermore, the reactions are generally regioselective and various sugars alkynes as well as commonly employed protecting groups are found to be compatible with the conditions employed (Scheme S1.16).



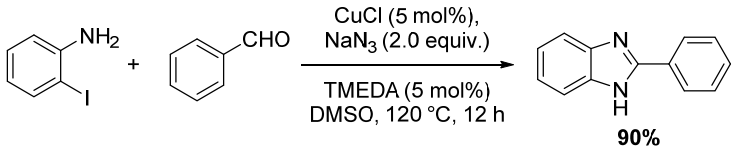
Scheme S1.16: *Cu(I)-promoted one-pot 'S_NAr–click reaction' of fluoronitrobenzenes*

In 2011, Sunwoo Lee and co workers described the copper catalyzed, one-pot, three-component reaction for the synthesis of 2H-Indazole through C−N and N−N bond formation.[43] The one-pot three-component reactions of 2-bromobenzaldehyde, primary amines and NaN_3 in the presence of CuI, TMEDA and DMSO at 120 °C provide the 2H-Indazole in 98% yield. This method was characterized with a broad substrate scope and high tolerance for a variety of functional groups. A proposed mechanism involves the initial formation of the azido compound from imine in the presence of copper and subsequently addition of the N-atom of benzylideneaniline to the azide complexes with copper followed by N_2 elimination (Scheme S1.17).



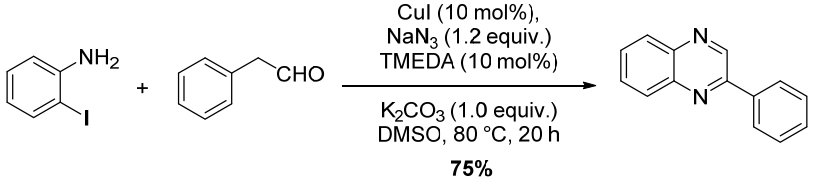
Scheme S1.17: *Copper catalyzed one-pot three-component synthesis of 2H-Indazole*

Subsequently, benzimidazoles have been synthesized by the copper-catalyzed, one-pot, three-component reaction of 2-iodoanilines, benzaldehyde and NaN_3.[44] The reaction was facile with 2-bromoaniline as well as with various aliphatic and heteroaromatic aldehydes. Additionally, this reaction showed tolerance for functional groups such as the ester, nitro, and chloro groups (Scheme S1.18).



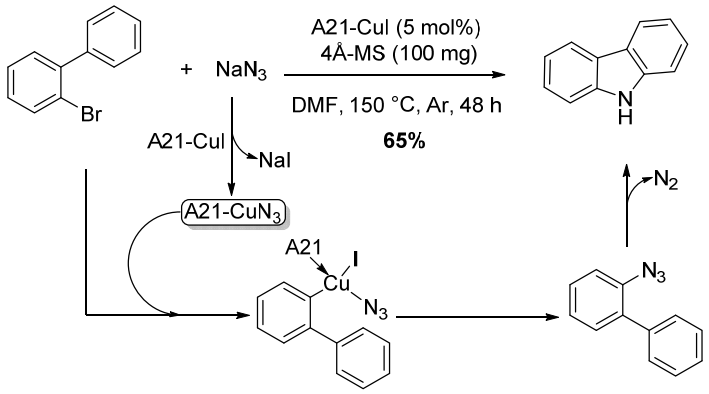
Scheme S1.18: *Copper catalyzed one-pot three-component synthesis of Benzimidazoles*

Another example of the copper catalyzed one-pot, three-component reaction for the preparation of quinoxalines employing 2-iodoanilines, aryl acetaldehydes and sodium azide was documented by Chen *et al* in 2013.[45] The reaction was unsuccessful with iodopyridine as well as with alkyl, heteroaryl and electron deficient aldehydes (Scheme S1.19).



Scheme S1.19: *Copper catalyzed one-pot three-component synthesis of quinoxalines*

Very recently Jiao *et al* reported a novel one-pot method for synthesis of carbazoles *via* Cu-catalyzed azidation of biphenyl halides with sodium azide and subsequent nitrene C–H insertion.[46] The reactions of electron rich substrates were more compatible than that of electron deficient substrates. The bromo or iodo biphenyls derivatives were seen to provide the desired carbazoles in moderate to good yields. On the other hand, the chloro derivatives were found be inactive under these reaction conditions. Moreover, the A21-Cu catalyst that has been employed for this purpose did not show significant leaching of copper even after the catalyst was recycled 4 times. A possible mechanism comprises the initial generation of the azide–Cu complex, which undergoes subsequent oxidative addition and reductive elimination and produces the key intermediate aryl azide with regeneration of the Cu-catalyst. Finally, a thermolytic cleavage of arylazide and cyclization afforded the desired product (Scheme S1.20).



Scheme S1.20: *Copper-catalyzed one pot synthesis of carbazoles and the proposed mechanism*

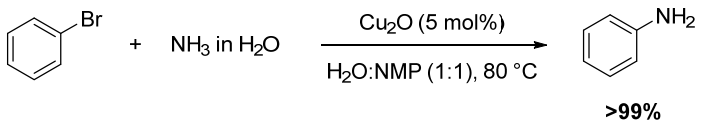
2.3. Synthesis of Anilines

The coupling of aryl halides with ammonia and the reduction of nitro group are the traditional methods for the synthesis of anilines. However, the harsh reaction conditions, such as high reaction temperatures and pressures make the direct coupling reaction using ammonia less practical. One of limitations in transition metal catalyzed coupling reactions with ammonia is catalyst poisoning due to the formation of stable metal-ammonia complexes. Due to the higher reactivity of the primary aryl amine over ammonia towards arylation, over reaction leading to di- and triaryl amines is another problem.[47] As a consequence of these issues, employing protected ammonia surrogates for coupling followed by the removal of the protecting group to obtain the free aniline moiety has been investigated.[48] However, these methods required additional steps to remove the protecting group, which is not atom economic and environmentally benign because it creates a lot of waste from deprotection. As a result, efforts have been undertaken to use sodium azide as the ammonia surrogate in the

synthesis of anilines.[49] A brief account on the preparation of various substituted anilines using either the ammonia surrogate, ammonia or sodium azide is presented below.

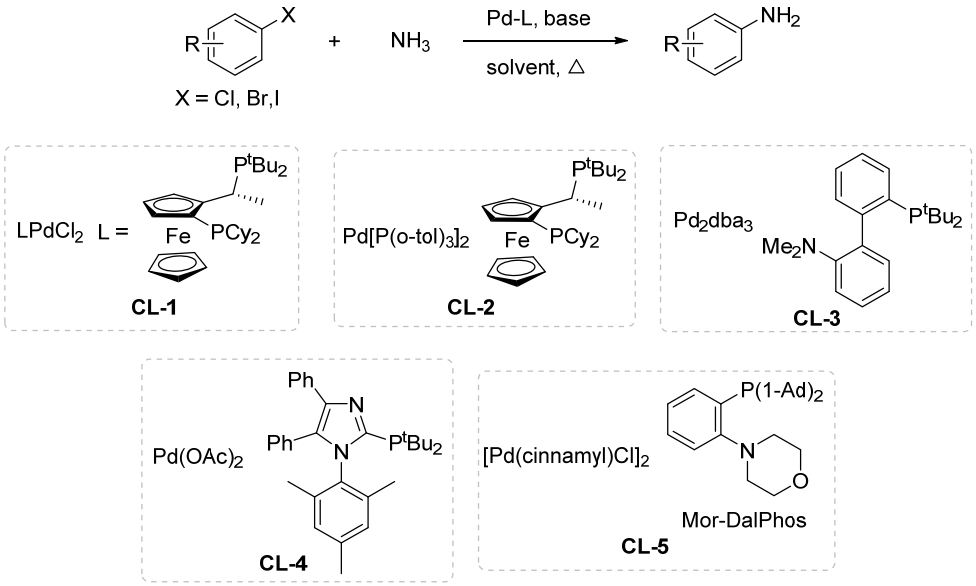
2.3.1. C–N cross coupling with ammonia

Copper catalyzed amination of aryl halide using ammonia has been known for a long time, but harsh reaction conditions and high catalyst loading hamper its application. In 1999 Vedejs and co-workers reported a single isolated example of a ligand-free copper mediated amination of an aryl bromide in aq. ammonia.[50] Although the yield was good and the reaction performed at 70 °C, it required high pressure as well as long reaction time that limited its application. In 2009, Wolf *et al* reported the copper catalyzed general method for the synthesis of aniline from several activated and non-activated aryl halides using ammonia in aqueous solution in water and NMP (1:1) at 80 °C.[51] The base has a substantial effect on the outcome of the reaction. Also, the reaction of aryl chloride under convectional heating required the *o*-carboxylic acid group for obtaining good yields (Scheme S1.21).



Scheme S1.21: *Copper-catalyzed amination of aryl bromide*

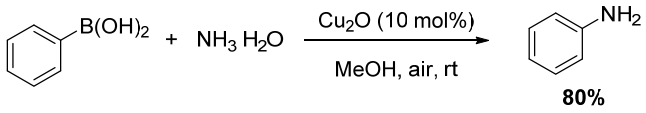
In 2006, Hartwig *et al* reported the first palladium catalyzed synthesis of substituted anilines with ammonia employing a modified palladium complex by the JosiPhos-type a phosphine ligand (Scheme S1.22).[52]



Scheme S1.22: *Various approaches for the palladium catalyzed synthesis of primary aryl amine*

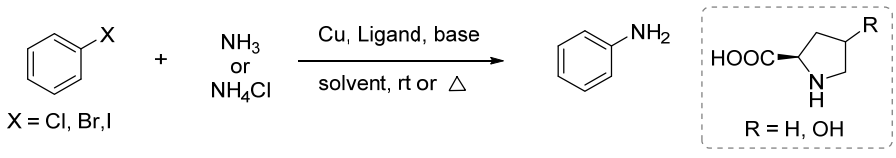
The best results were obtained with the catalyst-(CyPF-t-Bu)$PdCl_2$ (**CL-1**), a strong base like sodium tert-butoxide, and 2-dimethoxyethane (DME) as solvent at 90 °C. The reaction conditions are compatible with the electron rich aryl/heteroaryl halides and some sterically hindered halides also converted to the corresponding amines with high yields (68% – 94%) and selectivity. Subsequently, this group and others have developed various other catalytic systems by screening a wide range of ligands to improve the yields and selectivity (Scheme S1.22).[53]

Room temperature copper catalyzed amination of aryl boronic acids has been developed by Hua Fu *et al*.[54] This reaction was ligand as well as base free. The high yields for the amination were obtained when Cu_2O (10 mol%) was used as a catalyst in methanol under air atmosphere at room temperature. However, it was observed that the amination reaction was completely stopped either in the presence of base or in the absence of air. In general, the electron rich substrates gave better yields when compared with the electron deficient arylboronic acids (Scheme S1.23).



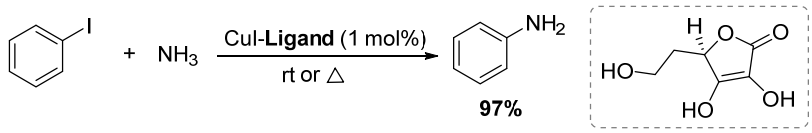
Scheme S1.23: *Cu-catalyzed synthesis of primary arylamines by coupling aromatic boronicacids*

In 2008, Chang and coworkers reported the Cu-catalyzed room temperature amination of aryl halides with less expensive ammonium salts such as NH_4Cl and aqueous NH_3 solution, using L-proline as the ligand.[55] The reaction condition seems to be compatible for various functional groups such as hydroxyl, nitrile, nitro, halogen, and ketone. The lack of reactivity with sterically hindered or electron rich aryl iodides are some of the major limitations. In 2009, Ma *et al* reported that replacing the L-proline with 4-hydroxy-L-proline, the amination of sterically hindered aryl bromides could be successfully achieved (Scheme S1.24).[56]



Scheme S1.24: *Cu/Ligand catalyzed approaches for preparation of aniline derivatives*

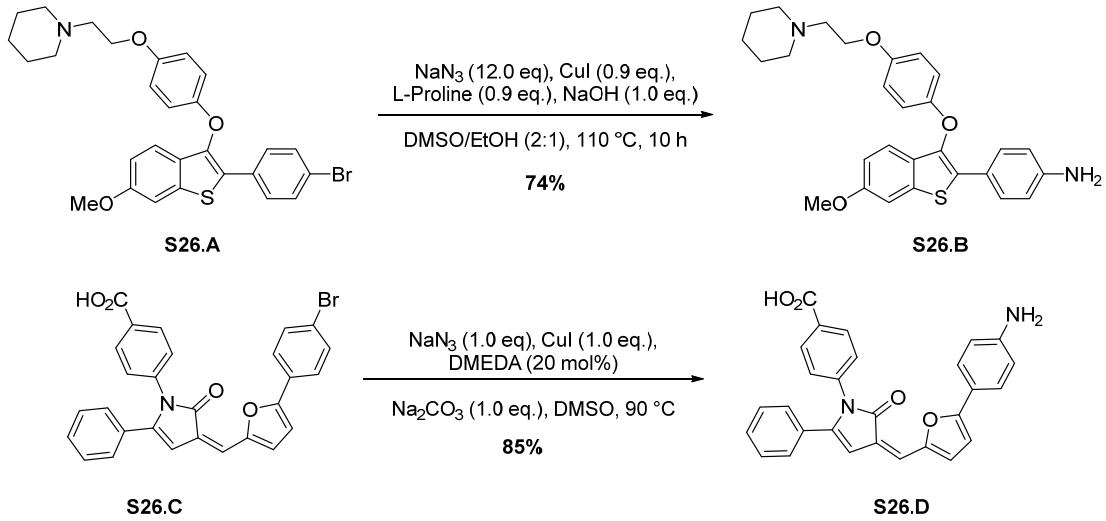
In 2012, Page *et al* reported that the copper(I) salt/ascorbate (ascorbic acid) system effectively catalyzed the amination of aryl halides in liquid ammonia. Reactions performed with various aryl halides irrespective of *o*-, *m*-, and *p*-substitution, afforded the anilines in good to excellent yields (Scheme S1.25).[57]



Scheme S1.25: *Copper(I)-catalyzed amination of aryl iodides*

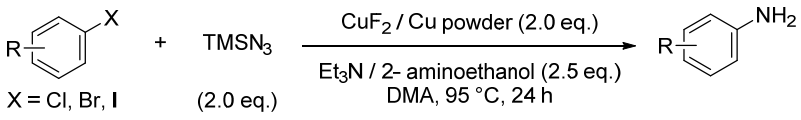
2.3.2. Azide anion as the ammonia surrogate

The first example of the copper catalyzed amination of aryl halides using sodium azide was reported by Thatcher and co-workers during their study on the synthesis of the selective Estrogen Receptor Modulator.[58] The attempted amination of the bromo compound (**S26.A**) with sodium azide (12.0 eq.) in the presence of equimolar amounts of CuI and NaOH in DMSO/ethanol at 110 °C gave amino compound (**S26.B**) directly. In a similar manner Helquist *et al* also described the conversion of aryl bromide (**S26.C**) to the corresponding amine (**S26.D**) employing CuI, NaN_3 and DMEDA in place of L-proline.[59] The full conversion to amine was achieved by using a stoichiometric cuprous iodide (Scheme S1.26).

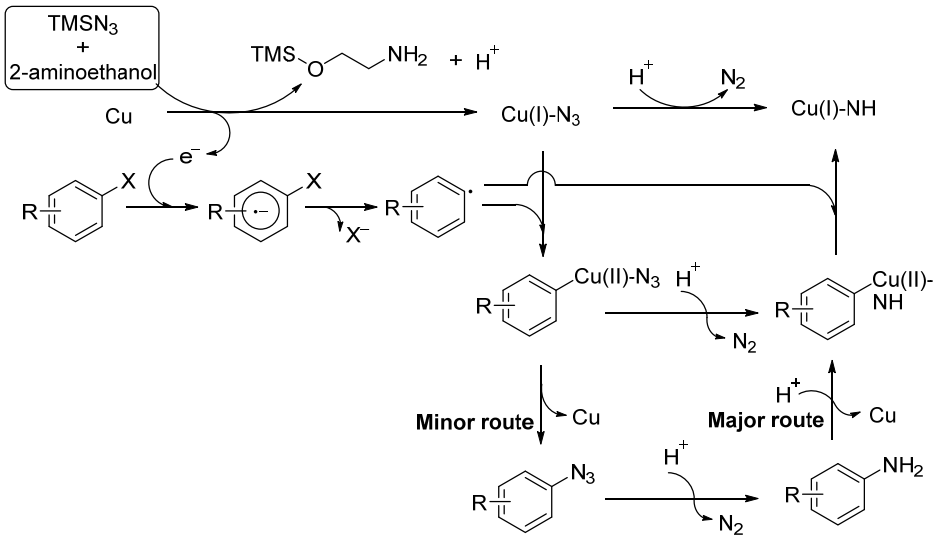


Scheme S1.26: *Direct amination approach reported by Thatcher et al and Helquist et al*

In 2010, Sajiki and co-workers reported the first systematic investigation for the direct amination of aryl bromides employing trimethylsilyl azide ($TMSN_3$) as the ammonia source in the presence of stoichiometric CuF_2 and Et_3N or 2-aminoethanol.[60] The reaction of the electron deficient aryl halides under optimised reaction conditions work smoothly to give corresponding anilines in excellent yields. With electron rich aryl halides, the copper powder was found to be significantly more effective than CuF_2 (Scheme S1.27).

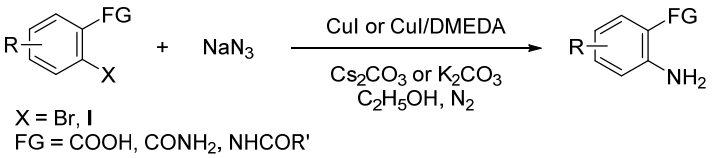


Scheme S1.27: *Cu-catalyzed reductive amination of aryl halides according to Sajiki et al*



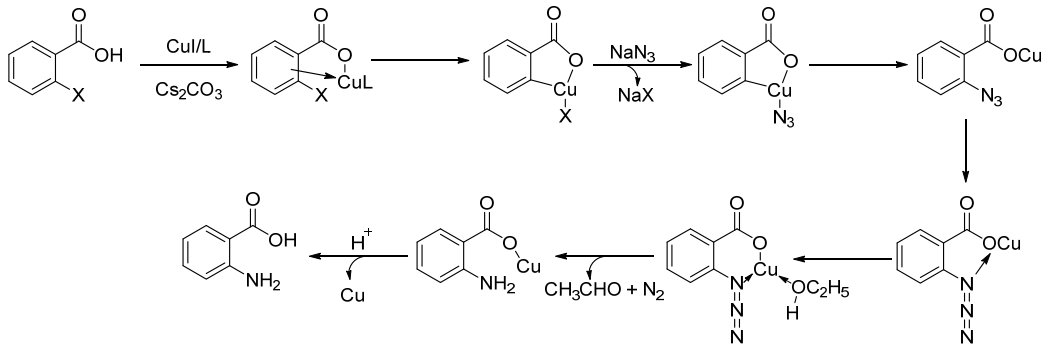
Scheme S1.28: *Proposed mechanism for one pot azide reduction*

The detailed mechanism of this reaction has been reported recently. Two pathways have been proposed which differ at the intermediate copper complex that undergoes the oxidative addition with the aryl halide. The major path seems to be *via* the copper(I) amide whereas in the minor path the intermediate is the copper(I) azide complex (Scheme S1.28).[61]



Scheme S1.29: *Cu-catalyzed direct amination of o-functionalized haloarenes according to Qiao et al*

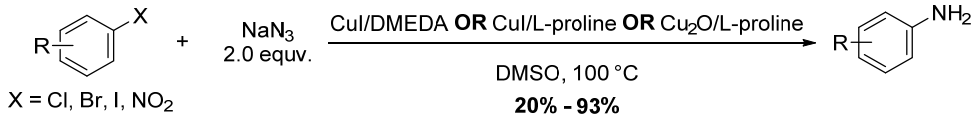
The copper catalyzed direct amination of *o*-substituted aryl halides with NaN_3 as the ammonia source in ethanol was explored by Qiao and Fu. Several *o*-functionalized aryl halides [such as 2-halobenzoic acid, 2-halobenzamide, and N-(2-bromophenyl)acetamide] were explored under present condition. The reaction of 2-bromo derivative worked smoothly, whereas in the case of 2-chloro derivatives, an additional 20 mol% of DMEDA ligand was required for good yields (Scheme S1.29).[62]



Scheme S1.30: *Proposed mechanism for the Cu catalyzed direct amination of o-substituted haloarenes*

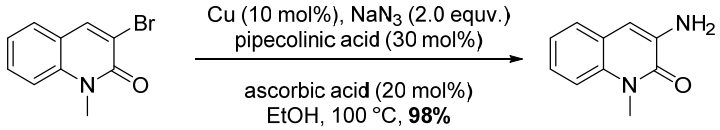
The proposed reaction mechanism for 2-halobenzoic acid is that first copper makes a coordination complex with the *ortho*-carboxyl group and subsequent intramolecular oxidative addition and exchange of X^- with N_3^- gives the intermediate. This upon reductive elimination leads to the azide intermediate. Next, the intermediate coordinate with ethanol followed by the oxidation-reduction sequence leads to aniline (Scheme S1.30).

Helquist *et al* also reported the synthesis of primary aryl amines through a Cu-assisted aromatic substitution reaction with NaN_3.[63] The best yields were obtained using 1 equiv of Cu_2O/proline in DMSO at 100 °C and the reaction was compatible with various electron rich and deficient aryl halides. On the other hand, with sterically hindered substrates, longer reaction times are required and the yields are moderate to poor (Scheme S1.31).



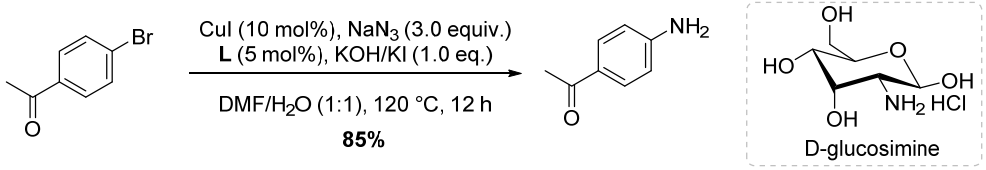
Scheme S1.31: *Copper-mediated reductive amination of aryl halides according to Helquist et al*

An efficient amination of various heterocycles has been reported by Alami *et al*. using Cu-powder/pipecolinic acid as the catalytic system, ascorbic acid as additive and NaN_3 as the amino source in EtOH as the solvent at 100 °C. Several aryl/heteroaryl halides, sterically hindered and base sensitive substrates were compatible under these conditions (Scheme S1.32).[64]



Scheme S1.32: *Copper-catalyzed direct amination of heterocyclic halides according to Alami et al*

In 2011, Sekar and co-workers showed that D-Glucosamine is an efficient ligand for the copper-catalyzed selective synthesis of anilines from aryl halides employing NaN_3. The reaction is highly selective towards aniline formation in the presence of many competitive nucleophiles. The reaction proceeds in a domino fashion by the *in situ* reduction of aryl azides to the aniline in the presence of KI (Scheme S1.33).[65]



Scheme S1.33: *Cu-catalyzed direct amination of Ar-X using D-glucosimine as ligand by Sekar*

3. Synthesis of 2,2-disubstituted indolin-3-ones using aryl azides

2,2-Disubstituted 1,2-dihydro-3H-indol-3-one (trivially known as pseudo-indoxyl) is one of the important structural units present in many natural products and biologically active small molecules (Figure S1.3).[66] Apart from their use as intermediates in the synthesis of natural products[67], in recent years, the indol-3-one derivatives have also found important applications in the areas of fluorescence dyeing and in solar cell applications.[68]

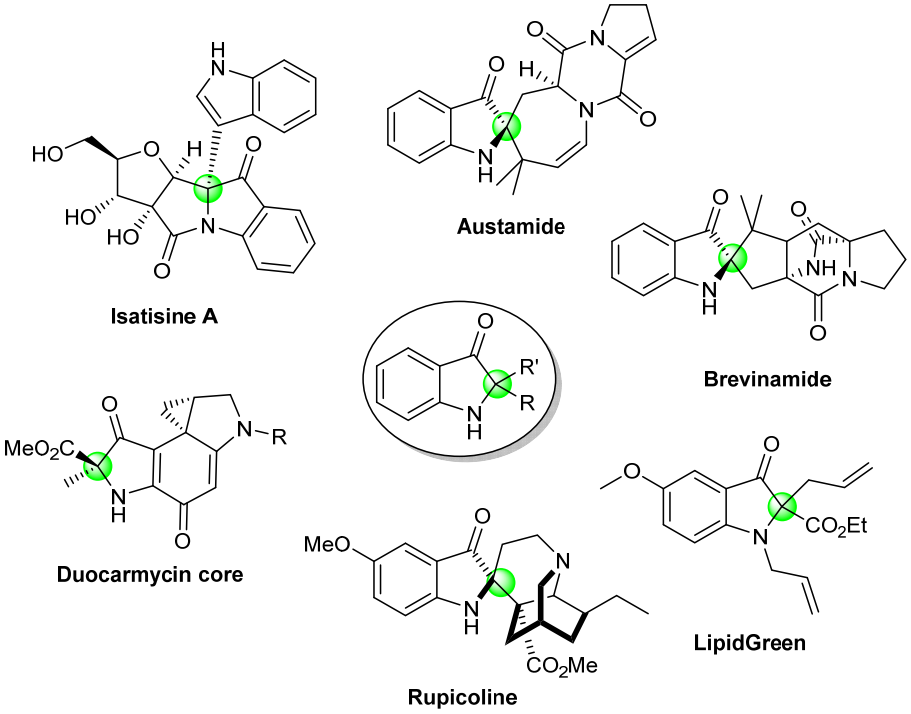
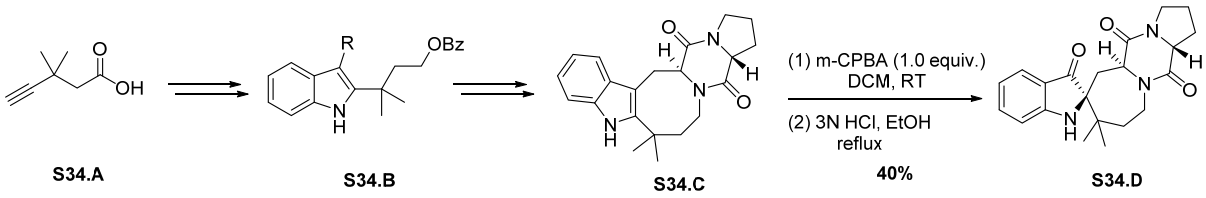


Figure S1.3: *Natural product and biological important molecule with pseudo-indoxyl core*

The oxidative rearrangement of the 2,3-disubstituted indoles,[69] addition of Grignard reagents to 2-arylindolone followed by the acid-catalyzed pinacol rearrangement[70] and carbon centered nucleophiles to a spiro[furan/pyran-2,2'-indolin]-3'-ones[71] are some of the important methods that have been developed for constructing the indolinone unit. Base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to 2,2-disubstituted indolin-3-ones – trivially known as the Smalley cyclization is one of important methods in this regards.[72] Recently, the metal catalyzed intramolecular amination,[73] cycloisomerization of 2-alkynyl aryl azides[74] as well as interrupted Ugi reaction,[75] Mannich–Henry reaction of 2-aryl-3H-indol-3-ones[76] and the reaction of amino acids with arynes[77] have been developed in the context of the synthesis of 2,2-disubstituted indolin-3-ones. The concise discussion of some selected methods for the synthesis of the spiroindolin-3-one derivatives is given below in chronological order.

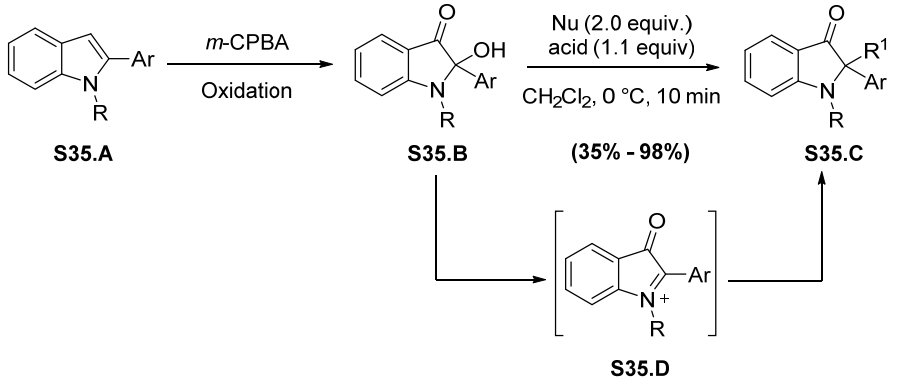
The Oxidative Rearrangement of 2,3-disubstituted indoles

Kishi *et al* showed the synthesis of 2,2-disubstituted indol-3-one from the 2,3-disubstituted indole using *m*-CPBA oxidation, followed by acid-catalyzed pinacol rearrangement during the study of the total synthesis of tetrahydroaustamide (S34.D).[78] They also reported that the reactions proceed with stereospecificity and the stereochemistry of the oxidation step governed the overall stereochemistry (Scheme S1.34).



Scheme S1.34: *Oxidative rearrangement approach for 2,2-disubstituted indol-3-one by Kishi et al*

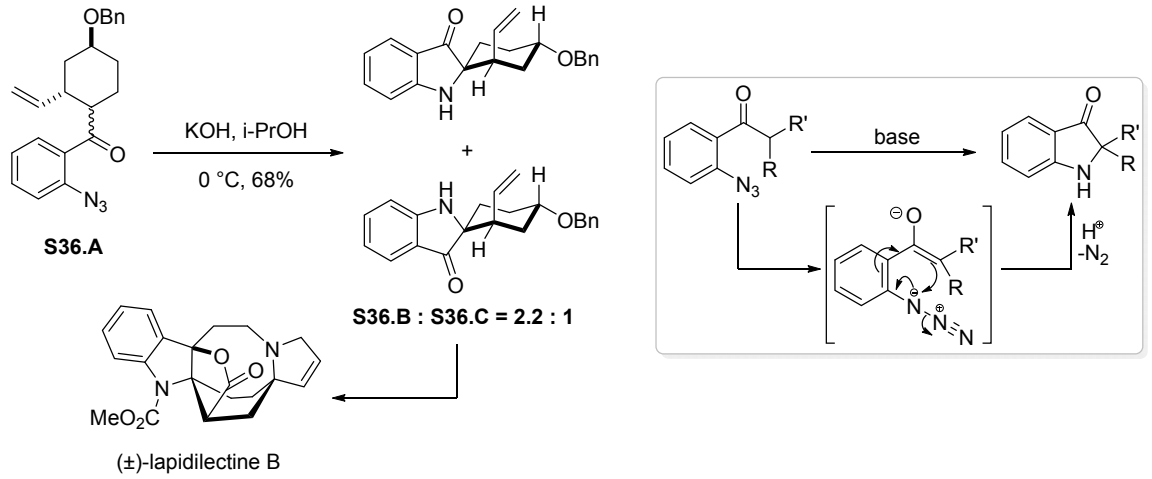
Kawasaki and coworkers reported the preparation of pseudoindoxyl derivatives from the N-protected 2-aryl indole (**S35.A**) during their study towards the total synthesis of (±)-Hinckdentine A. The reaction sequences include the oxidation of 2-aryl indole with *m*-CPBA, followed by the acid-mediated Mannich-type addition with a carbon nucleophile (Scheme S1.35).[67d, 69e]



Scheme S1.35: *Synthesis of pseudoindoxyl derivatives according to Kawasaki et al*

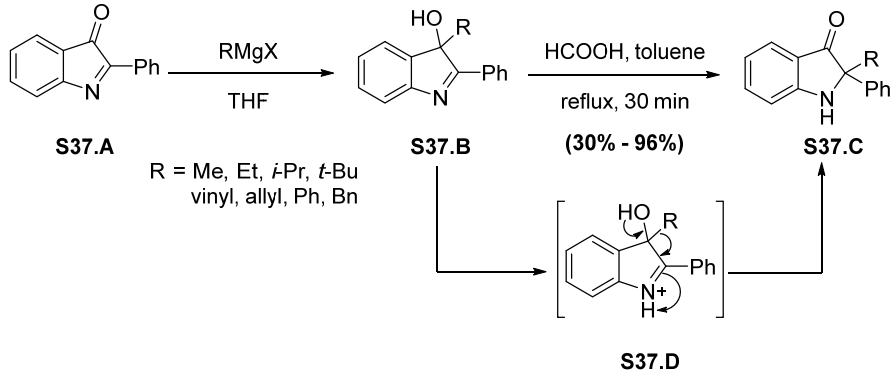
The Smalley Cyclization

In 1979, Ardakani and Smalley reported the base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to 2,2-disubstituted indolin-3-ones – trivially known as the Smalley cyclization.[72a] However, the reaction with the ester substituent (R = R' = CO_2Et or R = CO_2Et, R' = Ph) required higher temperature, like in boiling xylene and *o*-chlorobenzene respectively to obtain the corresponding indoxylderivatives in moderate yields. Later, in 2004, Pearson's group employed the Smalley cyclization as a key step in the total synthesis of the (±)-Lapidilectine B alkaloid (Scheme S1.36).[79]



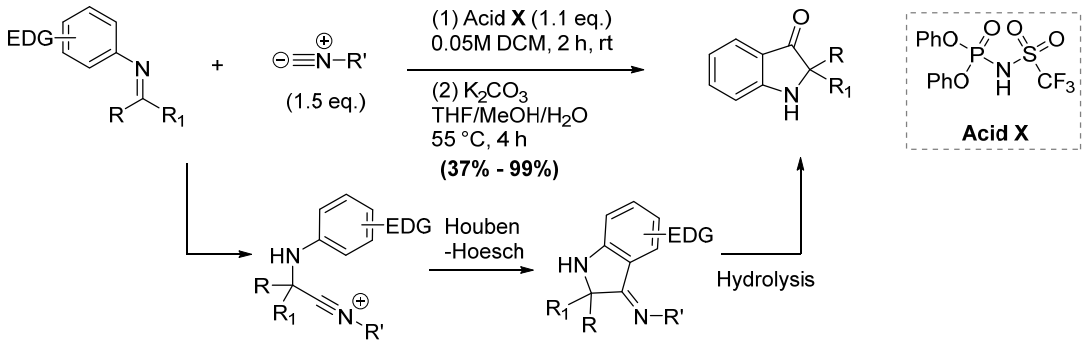
Scheme S1.36: *Smalley cyclization and representative synthesis of (±)-Lapidilectine B*

McWhorter *et al* have demonstrated a simple two step method for the preparation of 2,2-disubstituted indol-3-one from 2-aryl-3*H*-indol-3-ones employing the addition of Grignard reagent followed by acid catalyzed rearrangement. When R = *t*-Bu was employed, the rearrangement was more facile compared to the other substrates and proceeded at room temperature with formic acid in chloroform (Scheme S1.37).[70b]



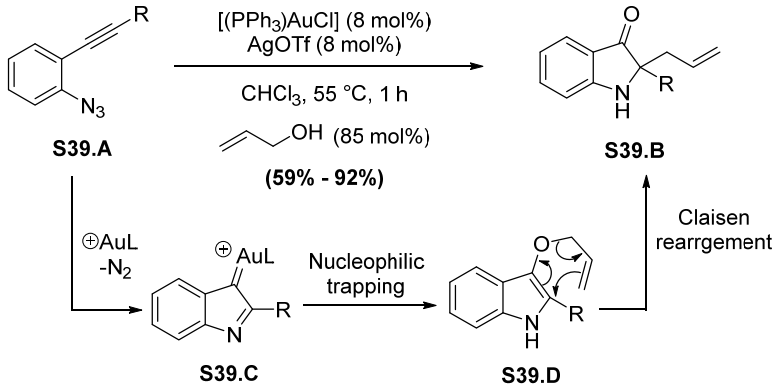
Scheme S1.37: *Synthesis of 2,2-disubstituted indol-3-one according to McWhorter et al*

Sorensen *et al* reported the interrupted Ugi reaction approach to prepare the substituted indoxyls and aminoindoles. The reaction proceeds through the attack of the nitrile nucleophile on imine followed by an internal attack of the electron-rich aromatic ring on an electrophilic nitrilium ion and then the hydrolysis of imines gave the indoxyl derivatives (Scheme S1.39).



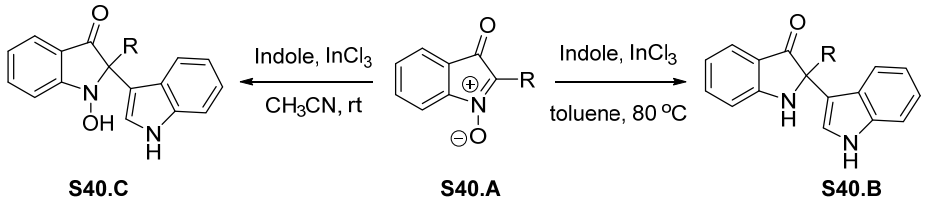
Scheme S1.38: *The interrupted Ugi approach to indoxyls derivatives*

Gold catalyzed cyclization of 2-alkynyl arylazides has been reported for the synthesis of 2,2-disubstituted indol-3-one.[74] Gagosz *et al* reported the one step synthesis of pseudoindoxyl (**S39.B**) *via* sequential gold catalyzed cyclization of 2-alkynyl arylazides, subsequently trapping the allylic nucleophile by the intermediate gold complex (**S39.C**) followed by the claisen rearrangement. The reaction has a wide substrate scope for the allylic nucleophiles, as well as good functional groups tolerance present either on the aromatic ring, on the alkyne substituent, or on the nucleophile. The reaction with nucleophiles other than the allylic nucleophile (would not be suitable for the rearrangement) gave only 2, 3-substitutes indoles (Scheme S1.39).



Scheme S1.39: *Preparation of pseudoindoxyl through amino-oxy-allylation principle Gagosz et al*

Recently from our group, we have studied the $InCl_3$ catalyzed Friedel-Crafts type alkylation of isatogens with indole (Scheme S1.40).[80] The treatment of isatogen with indole in acetonitrile solvent at room temperature led to the observation of the N–OH pseudoindoxyl (**S40.C**), whereas the same reaction taking toluene as a solvent at 80 °C results in the reduced addition product (**S40.B**).



Scheme S1.40: *Friedel-Crafts alkylation of isatogens with indole*

4. Synthesis of 2-aroylindoles using aryl azides

Indole is one of the most commonly encountered heterocyclic units in a wide range of bioactive molecules.[81] Indole derivatives having a carbonyl functional group at C2 are important building blocks for natural products/pharmacologically active compounds synthesis, in particular for C2–aroyl indole derivatives.[82] The C2–aroyl indole derivatives without any N- or C3 substituent have been identified as potent small molecular modulators for diverse biological targets such as cell surface receptors (receptor tyrosine kinase),[83] nuclear receptor proteins,[84] cyclooxygenase and histone deacetylases[85] and have also proven to be important in controlling the polymerization of tubulin.[86]

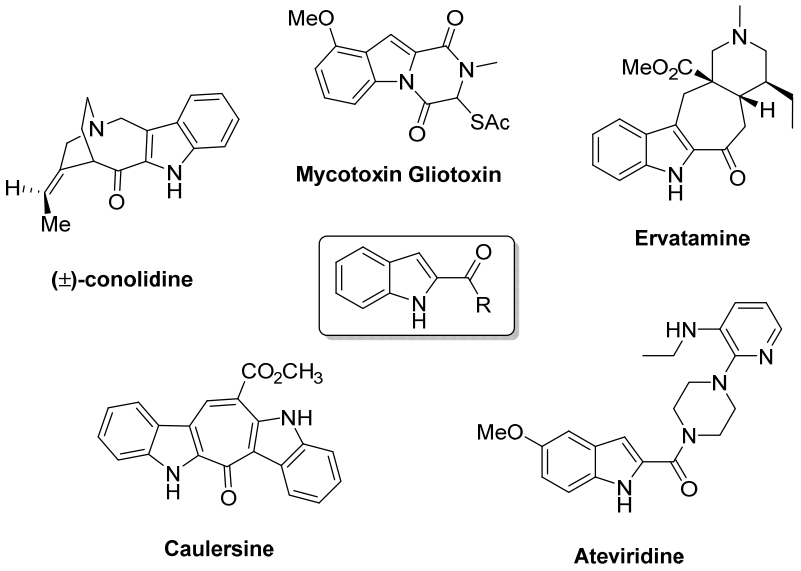
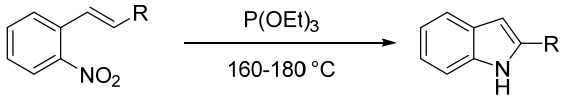


Figure S1.4: *Natural product and Biological active molecule with 2-Aroyl indole core*

Generally, the 2-aroyl indole derivatives are prepared by the "Cadogan–Sundberg indole synthesis",[87] as well as the addition of 2-lithioindole to various acyl electrophiles.[88] The hydrolytic ring-opening and base-catalysed cyclization of Isatins[89] as well as some cascade reactions between *o*-substituted aryl amide and α-substituted ketones/sulfurylides were explored in this direction.[90] Recently, transition metal catalyzed C–H activation,[91] as well as C–H amination[92] and iodine mediated intramolecular amination[93] were developed in

this regard. A brief account about the reported methods for the 2-aroyl indole synthesis is described below.

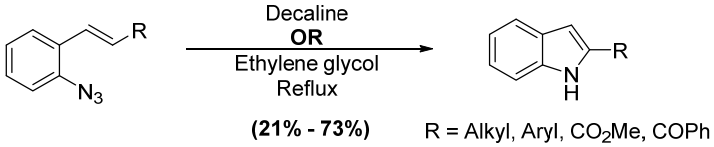
In 1965, Sundberg reported that the reduction of alkyl/aroyl-*o*-nitrostyrenes with triethyl phosphite resulted in indole.[87b] They suggested that the reduction of *o*-nitrostilbene might be proceeding *via* 1-hydroxy-2-phenylindole as an intermediate. The reactions with styrene having an alkyl substitution proceed smoothly with moderate to good yields. In case of 2-acyl or 2-aroyl substituents, the reaction was sluggish and the yields are poor (Scheme S1.41).



Scheme S1.41: *Cyclization of β–substituted o-nitrostyrene with triethyl phosphite*

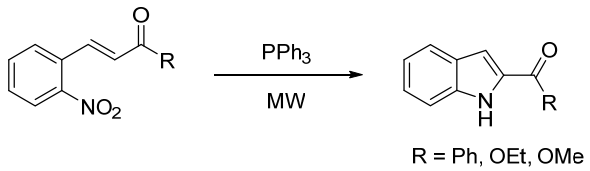
Via Pyrolysis or Photolysis of *ortho*-Azidostyrene

In 1972, Sundberg reported the synthesis of 2-aryl/aroyl indole *via* pyrolysis of o-azidostyrenes using decaline or ethylene glycol as a solvent under reflux conditions.[94] The reaction with *β*-alkyl- and *β*-aryl-*o*-azidostyrenes proceeds well, while in the case of *β*-acyl-*o*-azidostyrenes, the result was satisfactory (Scheme S1.42).



Scheme S1.42: *2-Aroyl indole via pyrolysis of o-azidostyrenes*

Recently, Creencia and co-workers reported the synthesis of 2-aroyl indole *via* the Sundberg-Cadogan reaction, using microwave radiation as the source of heat instead of conventional heating.[95] The reaction of 2-nitrochalcone or alkyl 2-nitrocinnamates and triphenylphosphine under microwaves irradiation at 80–200 W for 10-15 min gave the corresponding carbonyl indole in moderate to good yields (Scheme S1.43).

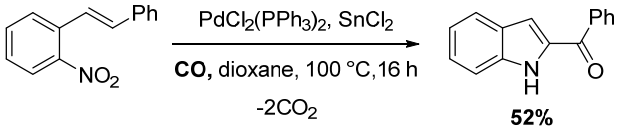


Scheme S1.43: *Microwave-assisted Cadogan reaction for the synthesis of 2-aroyl indole*

In the Sundberg-Cadogan indole synthesis, the involvement of a singlet nitrene and its insertion across the C–H bond of the olefin unit is a generally accepted mechanism during nitro-reduction processes .[96]

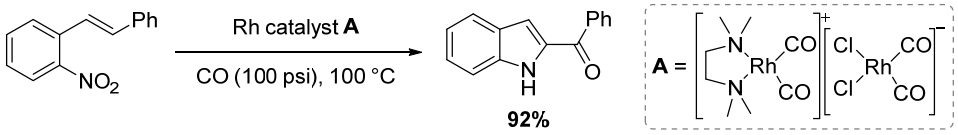
Using carbon monoxide (CO) as the reducing agent/deoxygenating agent

Watanabe *et al* developed an efficient synthesis of 2-aryl/aroyl indole through the reductive N-heterocyclization of various 2-nitrostyrene derivatives using a carbon monoxide (20 kg cm^{-2} initial pressure) and dichlorobis(tripheny1phosphine)palladium catalyst along with tin(II)chloride ($PdCl_2(PPh_3)$-$(SnC1_2)$ at 100 °C for 16 h. The deuterium labelling showed that reactions proceed *via* a nitrene intermediate and with CO acting as a deoxygenating agent (Scheme S1.44).[97]



Scheme S1.44: *Pd–Catalyzed reductive N-heterocyclization of 2-nitrostyrene*

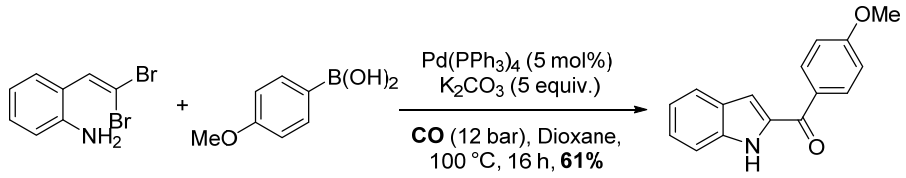
Recently, Alper *et al* have developed an efficient method for the synthesis of indole from *o*-vinylnitroarenes *via* a reductive N–cyclization using an ionic diamine rhodium complex (**A**) as a catalyst with carbon monoxide as a reducing agent. The catalytic system also allows direct access to indoles with ester and ketone groups at the 2- or 3-position, in good yields (Scheme S1.45).[98]



Scheme S1.45: *Diamine Rhodium catalyzed reductive N-heterocyclization of 2-nitrovinylarenes*

Miscellaneous Reaction

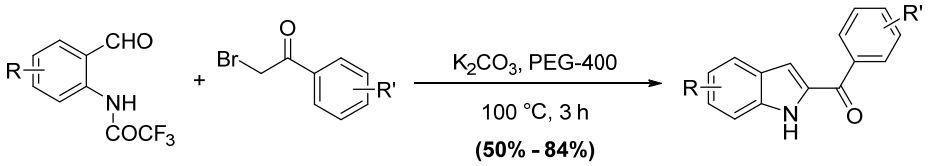
In 2009, Florent and Co-workers reported a palladium catalyzed synthesis of 2-aroyl indoles from the corresponding 2-*gem*-dibromovinylanilines, boronic acids and CO *via* a sequential C–N coupling/carbonylation/C-C coupling. The reaction has wide substrate scope, including various aryl/heteroaryl boronic acids and good functional group tolerance (Scheme S1.46).[99]



Scheme S1.46: *Pd-Catalyzed domino C–N Coupling/Carbonylation/Suzuki Coupling reaction*

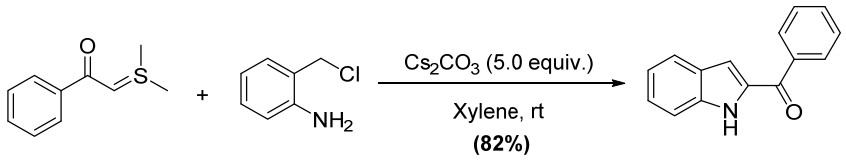
A one pot approach for the synthesis of 2-aroyl indoles through the reaction between N-protected *o*-amino benzaldehyde and α-bromo acetophenones in the presence of K_2CO_3

and PEG-400 as a reusable solvent was developed by Zhang and coworkers (Scheme S1.47).[90b]



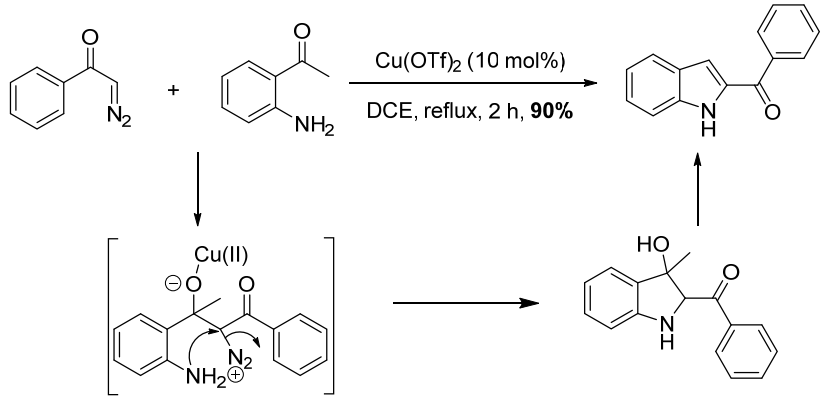
Scheme S1.47: *One pot synthesis of 2-aroyl indole by Zhang et al*

In 2012, Xiao *et al* developed a catalyst free cascade reaction sequence for the synthesis of 2-aroyl indole through the reaction between sulfurylides and N-(orthochloromethyl)aryl amides using caesium carbonate as base in xylenes at room temperature (Scheme S1.48).[90c]



Scheme S1.48: *One pot cascade approach for 2-aroyl indole by Xiao et al*

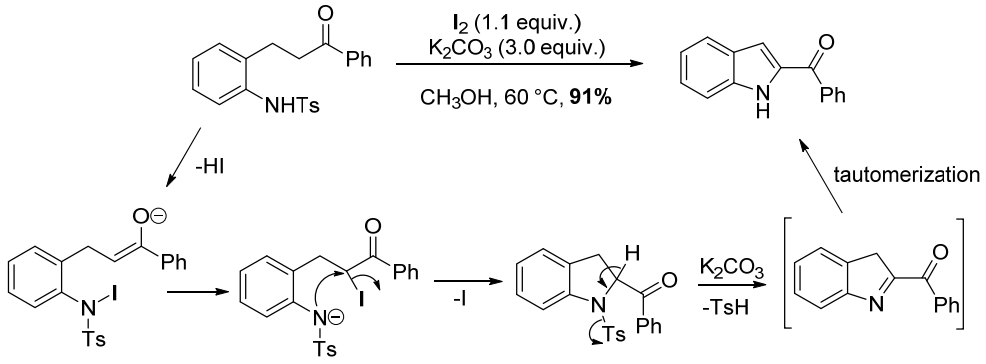
Sridhar *et al* explored the direct and efficient 2-aroyl indole synthesis *via* copper triflate catalyzed coupling between α-diazoketones and *o*-amino aryl/alkyl ketones in DCE. A wide range of 2,3-disubstituted indole derivatives were also prepared from α-diazoketones and 2-aminoaryl or alkyl ketones. The plausible mechanism for this reaction is, first $Cu(OTf)_2$ activates the carbonyl group of the aryl ketone to facilitate the nucleophilic attack of the diazo compound. The next step is the intramolecular displacement of N_2 by aryl amine followed by dehydration to afford the indole (Scheme S1.49).[100]



Scheme S1.49: *Synthesis of indoles from α-diazoketones with 2-aminoalkyl or arylketones*

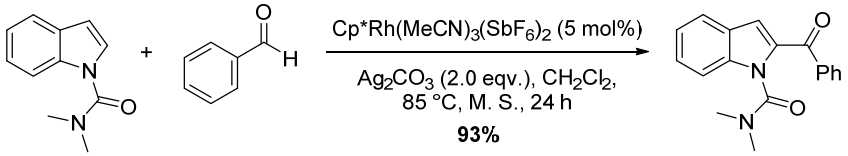
Recently, Zhang *et al* reported the N-protecting group dependent synthesis 2-acylindoles *via* iodine-mediated intramolecular C–N bond formation. The reaction was viable with various substrates in the aroyl part, including aryl, heteroaryl, alkyl as well as functional

group tolerance at the aniline side. The plausible mechanism for intramolecular amination is given below (Scheme S1.50).[93]



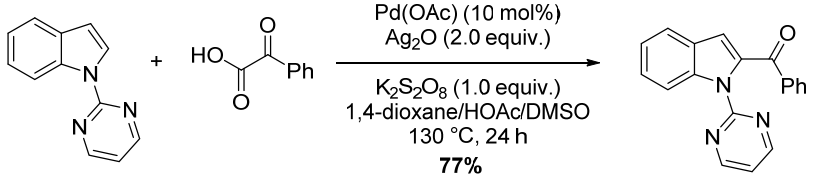
Scheme S1.50: *Iodine-mediated intramolecular amination of ketones*

Yuanchao Li and co-workers reported that the 2-aroylindoles can be directly prepared by rhodium catalyzed oxidative C2-acylation of N-protected indoles *via* C–H bond activation with aryl and alkyl aldehydes using N,N-dimethylcarbamoyl as a directing group. This reaction has wide scope with electron-poor and electron-rich aryl aldehydes, whereas the reactions with alkyl aldehydes are effective but require longer reaction time. The directing group was removed by simply treating the resulting product with ethanolic KOH for getting the NH free aroyl indole (Scheme S1.51).[91a]



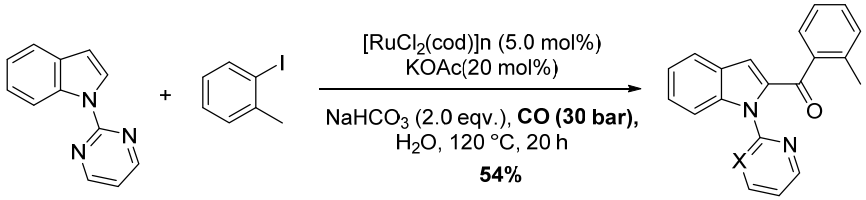
Scheme S1.51: *Rh-catalyzed oxidative C2–acylation of indoles*

In 2013, decarboxylative palladium-catalyzed directed C–H bond activation of indoles with α-oxocarboxylic acids was reported by Chengjian Zhu *et al* for the synthesis of the 2-aroyl indoles. The key feature is the requirement of 2-pyrimidyl directing group, which can later be removed by base treatment. Generally, α-oxocarboxylic acids possessing an electron-donating group gave the products in higher yields than those with electron-withdrawing analogues (Scheme S1.52).[91b]



Scheme 1.52: *Palladium-catalyzed decarboxylative C2-actlation of indoles*

Very recently in 2014, Matthias Beller and coworkers showed ruthenium catalyzed pyridine/2-pyrimidyl directed carbonylative C–H arylation with water as the solvent (Scheme 1.53) .[101]



Scheme 1.53: *Ruthenium-catalyzed ortho-directed carbonylative direct arylation*

RESULT AND DISCUSSION

Anilines are simple, yet most important substructural units in many biologically active compounds as well as valuable synthons in organic synthesis.[102] As it has been briefed earlier, the transition metal catalyzed amination of various aryl halides or pseudo halides employing ammonia or its surrogates is an ever expanding class of reactions developed in this regard.[48, 53, 103] One of the major limitations with these methodologies is the formation of appreciable amounts of polyarylated amines as a consequence of more reactivity of the primary aryl amine than ammonia towards arylation.[47] Amongst the recent methods for primary aryl amines preparation, the use of sodium azide as ammonia surrogate is one of latest developments during the last 5 years.[49] In the previous section, we described some of the investigations in this context that have appeared along with our disclosure and some have also appeared afterwards.

Our entry in this area was accidental. The amination of nitro-substituted arylhalides was observed while dealing with the one-pot S_NAr and azide-alkyne cycloaddition under copper(I) catalysis (CuAAC).[42, 104] The recent discovery of the Meldal[105] and Sharpless[36a] groups revealing the dramatic rate acceleration of the azide-alkyne cycloaddition[106] under copper(I) catalysis (CuAAC) has extended this reaction to many branches of chemistry ranging from bio- to materials and polymers and is often referred as 'the click reaction'.[36, 107] The inaugural protocol that employs the Cu(II) salts with ascorbate is the method of choice for the preparative synthesis of 1,2,3-triazoles, though there are several other mild alternatives that have been disclosed, especially dealing with the bio-conjugations.[108] From our group, earlier, we have reported a one-pot approach for the synthesis of 1,4-diaryltriazoles under the classical Cu(II)-ascorbate redox system, through the S_NAr of *o*- and *p*-fluoronitrobenzenes with NaN_3 and the subsequent Huisgen [3+2] cycloaddition of the intermediate aryl azides with various alkynes, both being the S_NAr and [3+2] cycloaddition are promoted by the Cu(II)-ascorbate redox system.[42] Next, we have described the potential of the S_NAr-click reaction in crystal engineering to synthesize a collection of isomeric compounds with the modular positioning of X (Cl, Br, I) and NO_2 on a flexible tricyclic template and examined the occurrence and nature of the halo-nitro synthon with respect to their relative disposition (Figure 1.1).[104]

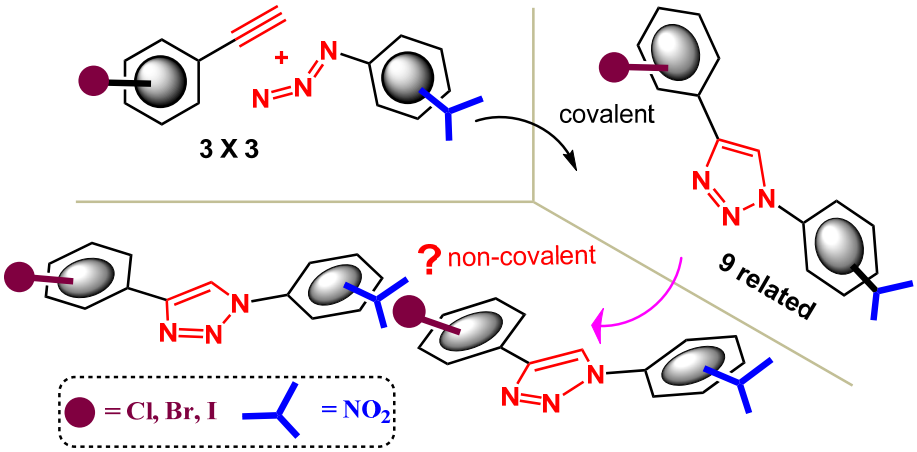
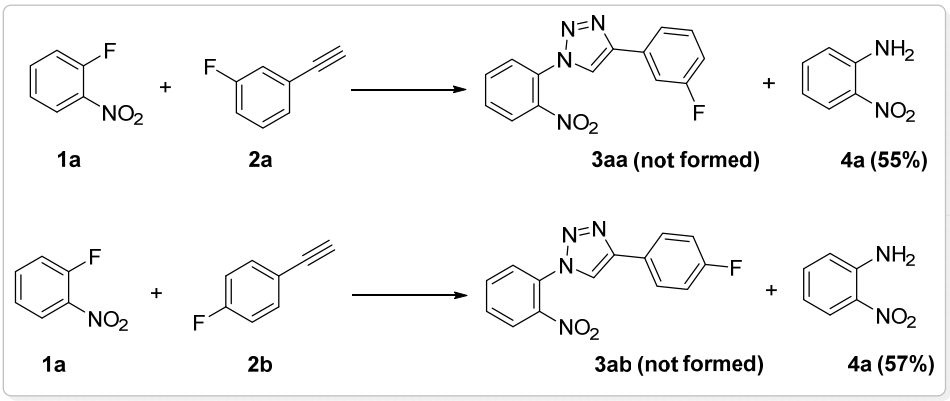


Figure 1.1: *Designed isomers and possible halo···NO_2-synthon geometries*

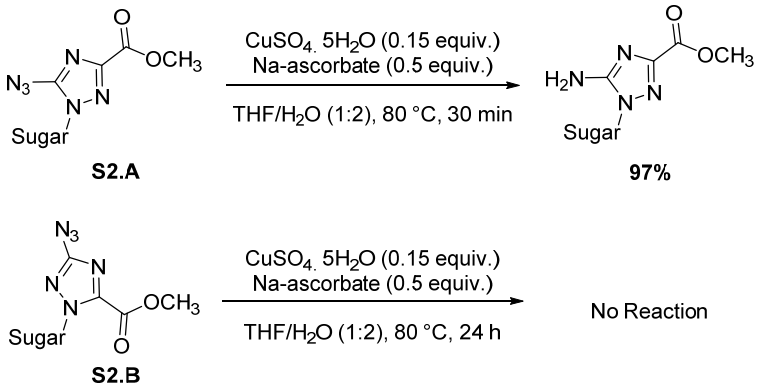
In continuation, we intended to explore the same with isomeric fluoro-nitro derivatives of diphenyl-1,2,3-triazoles. In this regard, the one-pot S_NAr-click reaction of *o*-nitro fluorobenzenes (**1a**) with *m*/*p*-fluorophenyacetylene (**2a–2b**) has been examined under the standardized conditions.[42] Interestingly, the 2-aminonitrobenzene (**4a**) was obtained as the major product instead of our required 1,4-diaryl triazole (**3aa** or **3ab**). This is quite interesting and might be resulting from the competitive reduction of the intermediate aryl azide[37, 109] (Scheme 1.1) before the cycloaddition.



Scheme 1.1: *Reagents and conditions: 1.2 eq. NaN_3, $CuSO_4$ (20 mol%), Na-ascorbate (15 mol%), L-proline (20 mol%), Na_2CO_3 (20 mol%), DMSO-H_2O (9 : 1), 65-70 °C, 24 h*

A literature survey has revealed that Peng and co-workers[110] have reported the conversion of azide to amine under the Cu(II)-ascorbate redox system (Scheme 1.2). They observed the reduction of a triazolyl azide during the CuAAC reaction (Copper-catalyzed Azide–Alkyne Cycloaddition) [Na-ascorbate (0.5 equiv) and copper sulfate (0.15 equiv) in THF/water, 70 °C (oil bath)]. The reduction in general was dictated by the azide positioning. For example, the reduction of 5-azidotriazole nucleoside **S2.A** was facile within 30 minutes. Interestingly, the 3-azidotriazole nucleoside **S2.B** was found to be extremely stable even at

reflux temperatures. It has been suggested that the electronic properties of azide contribute significantly to their ease of reduction to amines. Under similar conditions when examined, the reduction of the 4-nitro azido benzene was found incomplete even after longer reaction times and the corresponding aniline was obtained in poor yields. Despite having a useful method in hand, the potential of this reaction has been not explored by this group.

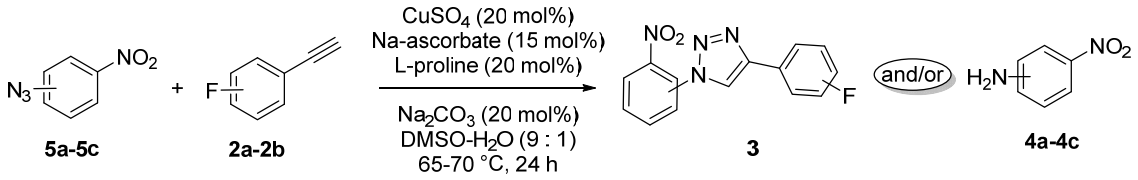


Scheme 1.2: *Reduction azido compounds under Cu-catalyzed Huisgen conditions*

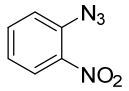
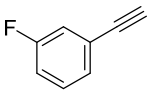
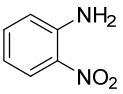
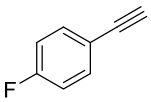
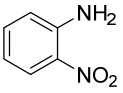
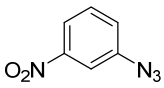
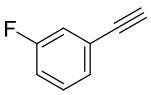
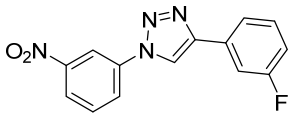
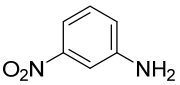
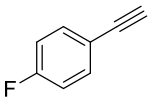
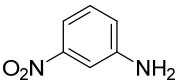
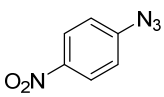
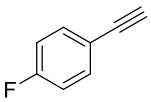
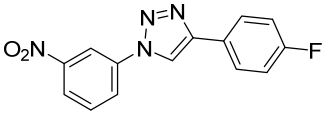
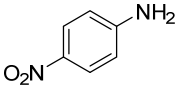
Given the fact that the S_NAr reaction with azides require the same Cu-catalytic system and intrigued by the lack of information on how the electronic nature of the substituents, and of the catalyst, ligand, etc. influence the ease of azide reductions, a systematic investigation on these aspects has been undertaken with a broad objective of developing a Cu-catalyzed synthesis of anilines from aryl halides by employing azide as a surrogate.

As a first step in this direction, all the three isomeric nitroarylazides (**5a**–**5c**) have been prepared from the corresponding nitro anilines following the established protocols. Subsequently, the [3+2]-cycloaddition reaction of these isomeric aryl azides was examined employing the fluoro alkynes **2a** and **2b**. The *o*-azido nitro benzene exclusively gave the corresponding aniline **4a** (Table 1.1, entries 1–2). On the other hand, in the reaction of *m*-azido nitrobenzene with alkyne **2a**, the aniline **4b** was obtained as the major product along with the triazole **3ba** in 23% yield, while with the alkyne **2b**, only the reduction was observed (Table 1.1, entries 3–4). The formation of triazole **3ba** was confirmed by ^{1}H NMR spectrum, where the characteristic the peak of triazole ring proton was seen to resonate at δ 8.35 ppm as a singlet and the $-NH_2$ protons corresponding to 2-nitro aniline were seen to resonate at δ 6.06 ppm as a broad singlet. Similarly, when *p*-azido nitrobenzene **5c** was treated with alkyne **2b,** triazole **3cb** was formed in 13% yield along with the corresponding aniline **4c** in 65% yield (Table 1.1, entry 5).

Table 1.1: *Cu-catalyzed [3+2]-cycloaddition reaction of aryl azides with alkyne **2a** and **2b***

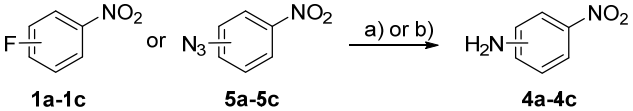


5a-5c 2a-2b 3 4a-4c

Entry	Substrates		Triazole **3** (% yield)	Aniline **4** (% yield)
1	 **5a**	 **2a**	---	 **4a, 57%**
2	**5a**	 **2b**	---	 **4a, 63%**
3	 **5b**	 **2a**	 **3ba, 23%**	 **4b, 52%**
4	**5b**	 **2b**	---	 **4b, 67%**
5	 **5c**	 **2b**	 **3cb, 13%**	 **4c, 65%**

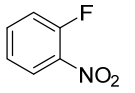
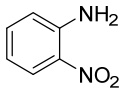
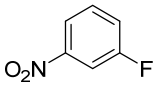
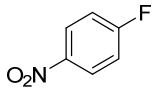
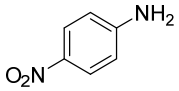
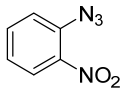
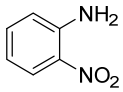
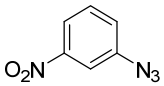
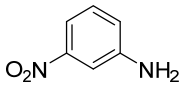
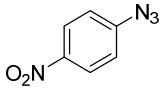
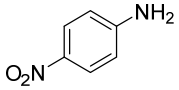
Intrigued by this, the three isomeric azidonitrobenzenes (**5a**–**5c**) have been subjected alone to these conditions. All the three isomers gave the corresponding nitroanilines in very good yields. Next examined was the one-pot S_NAr followed by azide reduction using the three isomeric fluronitrobenzenes (**1a**–**1c**). The one-pot S_NAr-azide reduction was found to be facile with both the 2- and 4-fluoronitrobenzenes (**1a** and **1c**) and the 3-fluoronitrobenzene (**1b**) was found to be intact under these conditions (Table 1.2). These results indicated that a nominal deactivation is required for the azide reduction when compared to that of S_NAr.

Table 1.2: *Cu-catalyzed one-pot S_NAr-azide reduction of isomeric azidonitrobenzenes and fluoronitrobenzenes*



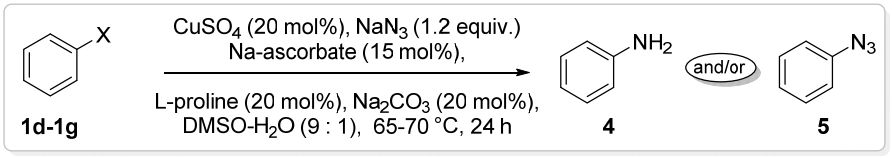
1a-1c 5a-5c 4a-4c

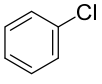
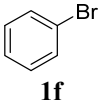
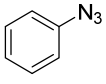
Reagents and conditions: (a) NaN_3 (1.2 equiv.), $CuSO_4$ (20 mol%), Na-ascorbate (15 mol%), L-proline (20 mol%), Na_2CO_3 (20 mol%), DMSO-H_2O (9 : 1), 65-70 °C, 24 h; (b) same as condition a without NaN_3.

Entry	Substrates	conditions	Aniline **4** (% yield)
1	 **1a**	*a*	 **4a, 71%**
2	 **1b**	*a*	--
3	 **1c**	*a*	 **4c, 73%**
4	 **5a**	*b*	 **4a, 67%**
5	 **5b**	*b*	 4b,61%
6	 **5c**	*b*	 **4c, 68%**

As a control, the simple aryl halides (Ar–X) were also subjected for the one pot 'S_NAr-azide reduction'. The F-/Cl-/Br-benzenes were intact under these conditions and the iodobenzene was smoothly converted to azidobenzene (71%).

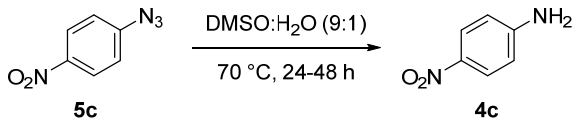
Table 1.3: *Reactivity of various aryl halides with azide*



Entry	Substrates	Aniline **4** (% yield)	Azide **5** (% yield)
1	 **1d**	---	---
2	 **1e**	---	---
3	 **1f**	---	---
4	 **1g**	---	 **5d,** 71%

Since both the azidation and the reduction were promoted under similar conditions, we speculated whether this reaction provides the general method to prepare aryl amines as a complement with the available reports for the preparation of aromatic primary amines. In this regard, we started our initial experiments on the reduction of 4-azidonitrobenzene performed employing all the components individually (Table 1.4). The reduction of azide in the presence of L-proline as well as in $CuSO_4$ were found to not be facile, whereas the presence of Na-ascorbate could facilitate the reduction but the reaction was incomplete even after 48h and the required aniline was obtained in 67% yield based on the starting material recovered. Next, we added $CuSO_4$ along with Na-ascorbate (each 20 mol%), but little improvement was observed in product formation and the starting material remaining intact even after 48h.

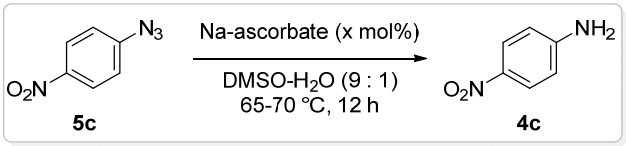
Table 1.4: *Reduction of azide in presence of various reagents*



5c **4c**

Reagent (20 mol%)	Time (h)	**4c** (% yield)
L-proline	24	No reaction
$CuSO_4$	24	No reaction
Na-ascorbate	48	67%
Na-ascorbate + $CuSO_4$	48	78%

After these initial experiments, we started a systematic investigation for the azide reduction by varying the reaction parameters. In the beginning, we conducted various reactions with different concentrations of reagent and the conversion of product was monitored by GC at regular interval. Our first experimentation in this started with the examination of the reaction against the influence of the concentration of Na-ascorbate (10 mol% to 100 mol%) and collected the reaction samples after 1, 2, 6, and 12 h. The result obtained from these experiments revealed that the ascorbate could facilitate the reduction alone albeit it was required in stoichiometric amounts. (1 equiv. ascorbate, 2 h, 99% conversion, 94% isolated yield, Figure 1.2). However, for cases where the concentration was less than 100 mol%, it was observed that reactions were stopped after some conversion.



5c **4c**

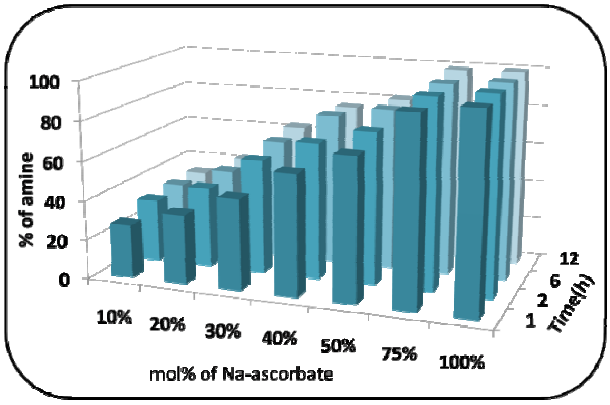
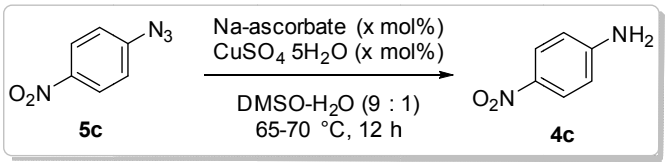


Figure 1.2: *The effect of Na-ascorbate (x mol%) on the outcome of the 4-azidonitrobenze reduction*

Next, we studied the azide reduction in the presence of Na-ascorbate and $CuSO_4$ by varying the concentration from 1 mol% to 20 mol % of each (Figure 1.3). The result showed that the reduction was sluggish and the reactions were incomplete even after 24 h heating. In the presence of 1 mol% concentration, 22% and 60% of aniline were formed after 1 h and 12 h respectively, whereas in the case of 20 mol%, the conversion was 38% and 69% respectively.



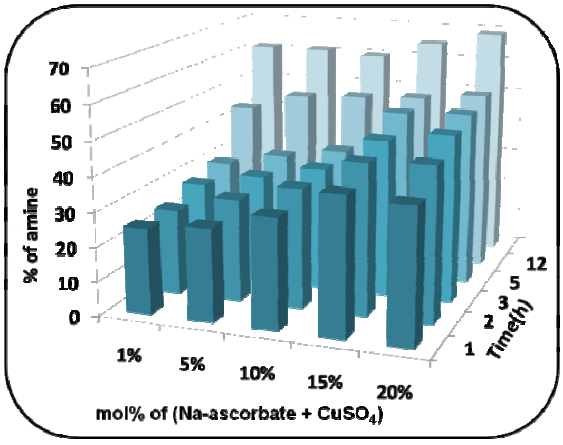


Figure 1.3: *The effect of [(Na-ascorbate+$CuSO_4$) (x mol%)] on the outcome of the 4-azidonitrobenze reduction*

Next, we have introduced a fixed amount of base (20 mol% Na_2CO_3) and concentrations of Cu(II)-ascorbate salt were varied from 1 mol% to 20 mol % of each (Figure 1.4). As can be seen from the Figure 1.4, there was an improvement in conversion, but it was not substantial and the reaction also not completed even after 24 h heating. In the presence of

1 mol% Cu(II)-ascorbate salt, the conversion was the same as observed in the previous case, but in the presence of 20 mol% Cu(II)-ascorbate, 90% aniline were formed after 24 h.

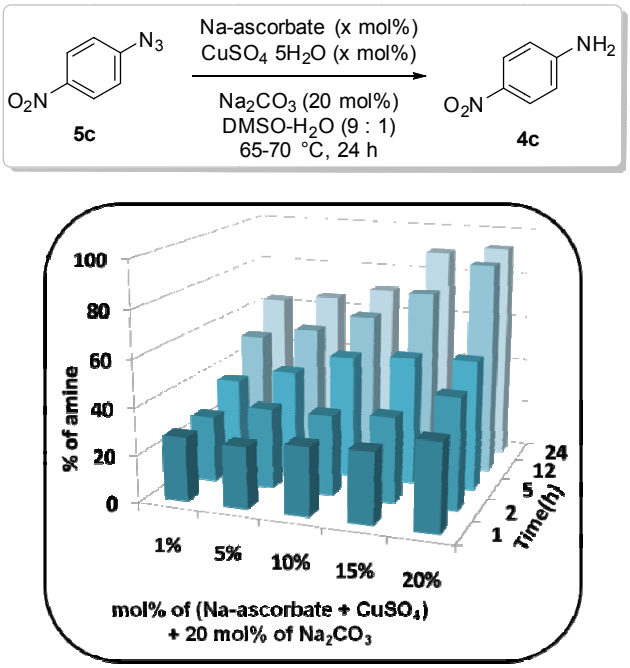


Figure 1.4: *The effect of [(Na-ascorbate +$CuSO_4$) (x mol%) and Na_2CO_3 (20 mol%)] on the outcome of the 4-azidonitrobenze reduction*

The role of L-proline has been examined subsequently. The reactions were carried out with varying concentrations of Cu(II) salt and Na-ascorbate from 1 mol% to 20 mol% of each (Figure 1.5) with fixed concentrations of base and proline (20 mol % each).

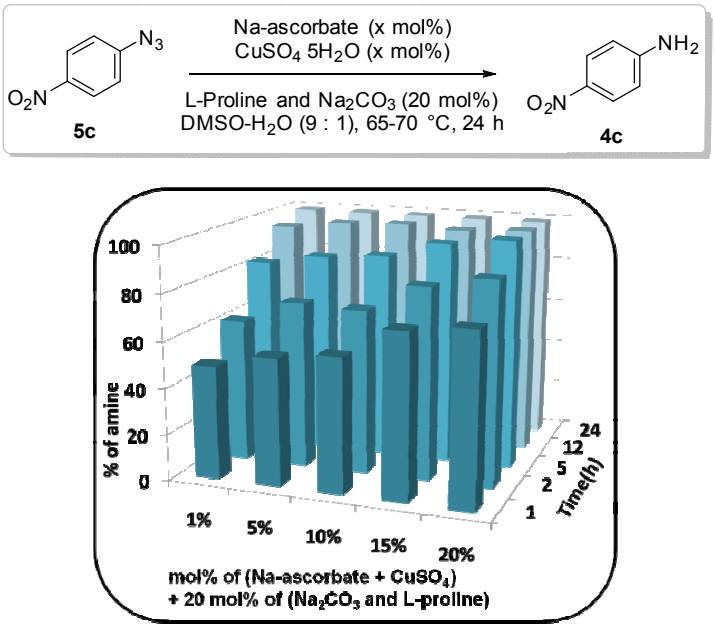
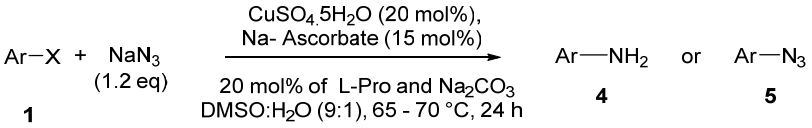


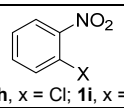
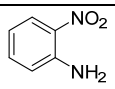
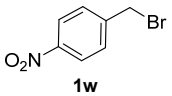
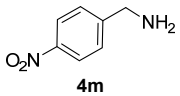
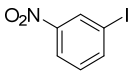
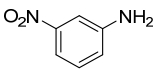
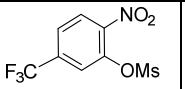
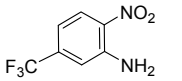
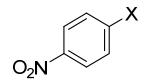
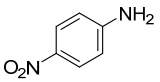
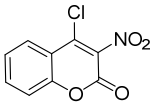
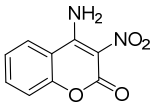
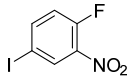
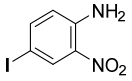
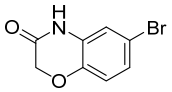
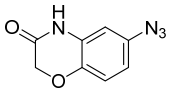
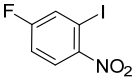
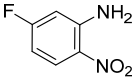
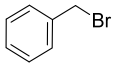
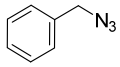
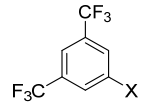
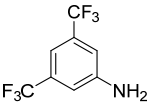
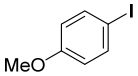
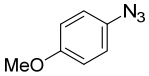
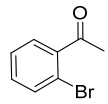
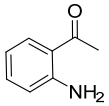
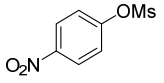
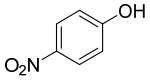
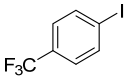
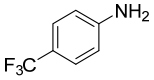
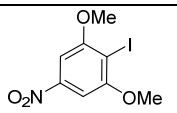
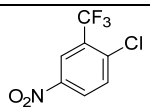
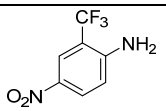
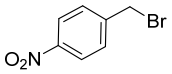
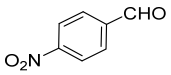
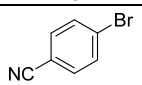
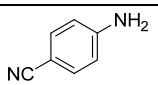
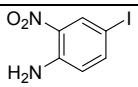
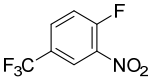
Figure 1.5: *The effect of [(Na-ascorbate +$CuSO_4$) (x mol%) and Na_2CO_3 + L-proline (20 mol%)] on the outcome of the 4-azidonitrobenze reduction*

The results were exciting even with 1 mol% of the Cu (II)–ascorbate redox system: the reactions were close to completion within 12 h (99% conversion 84% isolated yield). On the other hand, when reaction with 20 mol% of Cu (II)–ascorbate redox system was employed, 99% conversion of the azidobenzene was seen within 5 h only. These experiments revealed that the presence of ascorbate is essential and that the rate of the reaction is enhanced by the presence of the Cu (II)-salt and proline and that proline is playing an important role in the stabilization of the Cu(I)-species (*in situ* generated from the Cu (II)-salt by Na-ascorbate).[111]

After successfully optimizing the reaction condition for the reduction of the intermediate arylazide, next, the scope of the one pot azidation-reduction reaction was examined employing a wide range of deactivated aryl halides. Table 1.5 shows the generality of the present amination and also the limitations. Under optimized reaction conditions, the *o*-chloronitrobenzene, *p*-bromo nitrobenzene, and also the corresponding iodonitrobenzenes gave the corresponding nitroanilines in comparable yields (Table 1.5, entries 1 and 3). Gratifyingly, *m*-iodo nitrobenzene as well as 3,5-bis(trifluoromethyl) iodobenzene also afforded the corresponding anilines **4b** and **4f** in 77% and 57% yields respectively (Table 1.5, entries 2 and 6). In general, the reactions are very facile when the electron withdrawing groups (nitro or $-CF_3$) are placed either at the *ortho*- or *para*- to the leaving halo group. For example, the amination of 3-nitro-4-fluoroiodobenzene (**1m**) selectively occurred at *ortho*- to the nitro group *via* fluorine displacement (Table 1.5, entry 4), whereas in case of 2-nitro-4-fluoroiodobenzene (**1n**), the reaction gave mainly the 2-nitro-4-fluoroaniline (**4e**) with a net displacement of the iodo group (Table 1.5, entry 5). The compound **4e** was confirmed with the help of NMR and Mass spectrum. In ^{1}H NMR spectrum of compound **4e**, all the three aromatic protons resonated at δ 6.37–6.50 (m, 2H), 8.15 (dd, J = 5.9, 9.3 Hz, 1H) ppm and $-NH_2$ protons at δ 6.22 ppm as a broad singlet. In ^{13}C NMR spectrum of compound **4e**, all the carbons resonated as doublets with coupling constants ranging from 12–26 Hz due the presence of fluorine on the aryl ring. The three aromatic carbons (CH) resonated at δ 103.6 (d, J = 26.0 Hz), 105.7 (d, J = 24.7 Hz) and 129.3 (d, J = 12.1 Hz) ppm as doublets. Similarly, three quaternary carbons resonated at δ 146.7 (d, J = 13.3 Hz) as doublet and 164.3, 169.4 ppm as singlet. In the ESI mass spectrum, the strong peak presence at m/z 179.1590 [96% $(M+Na)^+$] confirmed the constitution of the compound **4e**. Furthermore, the compound **4e** was confirmed by comparing the NMR data with the reported data.

Table 1.5: *The scope of one-pot amination reaction of aryl halide with NaN_3 under Cu(II)-ascorbate redox system*



Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	 **1h**, x = Cl; **1i**, x = I	 **4a**	**71% (Cl), 76% (I)**	13	 **1w**	 **4m**	**28%**
2	 **1j**	 **4b**	**77%**	14	 **1x**	 **4n**	**42%**
3	 **1k**, x = Br; **1l**, x = I	 **4c**	**76% (Br), 87% (I)**	15	 **1y**	 **4o**	**76%**
4	 **1m**	 **4d**	**69%**	16	 **1z**	 **5e**	**68%**
5	 **1n**	 **4e**	**67%**	17	 **1aa**	 **5f**	**49%**
6	 **1o**, x = OMs; **1p**, x = I	 **4f**	**24% (OMs) 57% (I)**	18	 **1ab**	 **5g**	**53%**
7	 **1q**	 **4g**	**77%**	19	 **1ac**	 **xx**	**71%**
8	 **1r**	 **4h**	**68%**	20	 **1ad**	No Reaction	**---**
9	 **1s**	 **4i**	**72%**	21	 **1ae**	 **xx**	**28%**
10	 **1t**	 **4j**	**54%**	22	 **1af**	No Reaction	**---**
11	 **1u**	**4k**	**78%**	23	**1ag**	**xx**	**32%**
12	**1v**	**4l**	**73%**	24	**1ah**	No Reaction	**---**

The pseudo halides like –OMs were also found to be compatible under the present reaction conditions. However, the yields were found to be low. For example, the substrate **1o**

and **1x** having the $–CF_3$ or the $–NO_2$ group either at the *m*- or the *p*- position gave the required anilines **4f** and **4n** in 24% and 42% yields respectively (Table 1.5, entries 6 and 14). However, in case of 4-nitrophenyl methanesulfonate, only the hydrolysis was observed (Table 1.5, entry 19). The 'S_NAr-azide reduction' is also facile with hetero-aromatic halides, such as 7-bromo-2H-benzo[b][1,4]thiazin-3 (4H)-one (**1v**) and 4-chloro-3-nitro-coumarin (**1y**). They gave the corresponding amines **4l** and **4o** in 73% and 76% yields respectively (Table 1.5, entries 12 and 15). In the ^{1}H NMR spectrum of compound **4l**, $–NH_2$ and –NH protons appeared at δ 4.02 and 9.80 ppm as singlets respectively. On the other hand, in the ^{1}H NMR spectrum of **4o**, the $–NH_2$ protons were seen to resonate at somewhat more downfield region (at δ 9.50 ppm as a singlet). However, when 6-bromo-2H-benzo[b] [1,4]oxazin-3(4H)-one (**1z**) was subjected for one-pot amination, the corresponding azide **5e** was isolated exclusively in 68% yield (Table 1.5, entry 16). The compound was characterized with the help of NMR and the presence of azido group was further confirmed by IR spectra showing the strong N=N=N stretching frequency at 2111 cm^{-1}. Similarly, the reaction of benzyl bromide or 4-iodo anisole also gave exclusively the corresponding azides in moderate to good yields (Table 1.5, entries 17 and 18). Next, the substrates having an acetyl group instead of nitro or CF_3 have been examined under these conditions. The 2'-bromo acetophenone gave 2'-amino acetophenone (**4g**) in 77% yield (Table 1.5, entry 7). This revealed that a nominal deactivation is required for the reduction. The 4-nitrobenzyl bromide gave mainly the 4-nitrobenzaldehyde (28%) and an unidentified complex mixture, indicating the competitive halide hydrolysis and subsequent oxidation (Table 1.5, entry 21). When the 3-iodo-2-methoxy-6-nitropyridine was subjected for amination, dehalogenation was observed instead of amination (Table 1.5, entry 23). When there are +M groups present at *o*- or *p*-position along with the –M groups, the initial S_NAr seems to not be facile (Table 1.5, entries 20, 22 and 24).

The isolation of the intact aryl azides from iodobenzene as well as from *p*-alkoxy substituted derivatives indicated that the Cu(I)-mediated decomposition of the azide group depends upon the relative electrophilicity of the azide group, which is controlled by the nature of the aryl substituent.[38, 112] It has been proposed earlier that aryl azides exist in two octet resonance structure forms I and II (Figure 1.6), amongst which the former is predominant when the *p*-substituent is an electronic withdrawing group.[113]

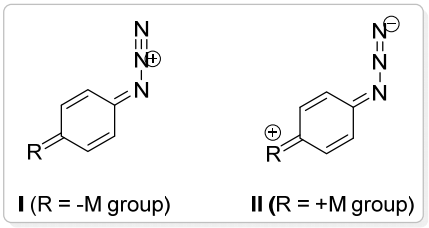


Figure 1.6: *Two canonical forms of the aryl azides*

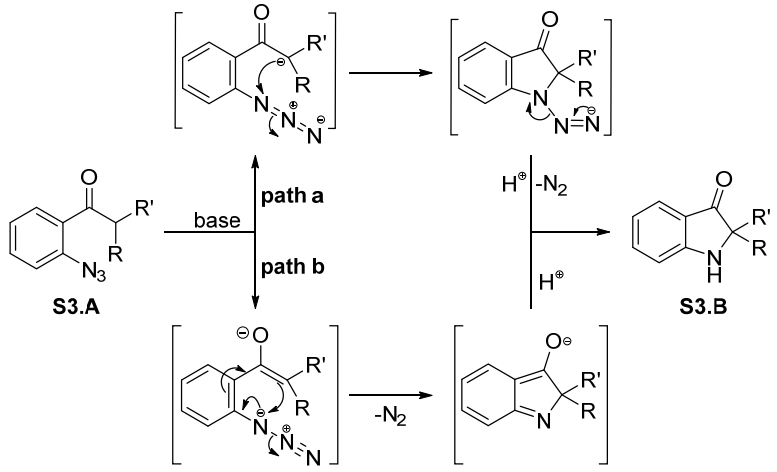
Therefore, with the available information, we propose that under the present conditions preferential azide decomposition occurs *via* form **I**, where the double bond character of the fissile N–N_2 bond is decreased and the entropy of activation for the rupture of this bond is lowered with the electron withdrawing substituents,[112] whereas in case of electron rich substituents, the rupture of the N–N_2 bond and –N_2 elimination was not facile due to increased bond order.

To conclude, we have developed a copper catalysed one pot synthesis of primary aryl amines from deactivated aryl halides employing sodium azide as a nitrogen surrogate. The Cu(II)-ascorbate redox system found to be the optimum system for the one-pot azidation and the reduction of intermediate azides to the corresponding anilines. Control experiments revealed the essential role of ascorbate and proline in the present reaction and the course of the reaction as S_NAr with azide proceeding with an *in situ* reduction of arylazide intermediates. Since the S_NAr reaction of deactivated aryl halides with azide are promoted under the same Cu(II)-ascorbate redox system, and the azide-alkyne cycloaddition and amine reduction are also feasible under these catalytic conditions, we believe that the integration of all these possibilities on designed substrates with complementary functional groups will provide a platform for developing multi-component reactions leading to simple means of molecular complexity generation and small molecules library synthesis.

Copper catalyzed synthesis of pseudo indoxyl derivatives

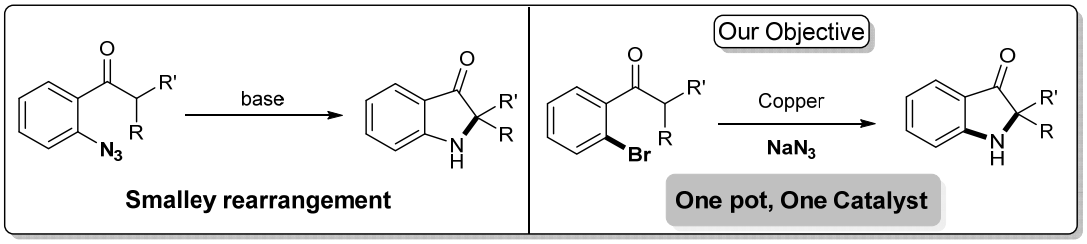
In our previous exercise, we noticed that the reduction of the aryl azides is facile when the aryl ring contains electronic withdrawing groups such as nitro, carbonyl, $-CF_3$ and others, and that this reduction occurs *via* the displacement of N_2 from the electrophilic azide. This is quite interesting, since if an internal nucleophile is employed for such a displacement, it results in the ring annulation. Indeed, in 1979, Smalley reported the base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to 2,2-disubstituted indolin-3-ones.[72a] We wondered whether our S_NAr azide can be combined with the Smalley cyclization to arrive at a one-pot synthesis of 2,2-disubstituted indolin-3-ones from simple 2-haloacetophenones. As mentioned previously, the 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-one (trivially known as pseudo indoxyl) is one of the important structural units present in some of the indole-class of natural products[66] and these derivatives have also found important applications in the areas of fluorescence dyeing and in solar cell applications.[68]

Coming to the Smalley cyclization, in 1979, Ardakani and Smalley reported the base-induced intramolecular cyclization of α-azidophenyl *sec*-alkyl ketones leading to 2,2-disubstituted indolin-3-ones (Scheme 1.3).[72a] The reaction comprises of an anchimerically assisted cyclization *via* a mesomeric anion in basic media to indoxyl derivative, but later they revealed that loss of nitrogen from the azido ketone anion (path a) is favoured rather than a path involving the enolate π-system (path b).[72b] Despite its simplicity and the importance of the resulting products, further advances on this cyclization are scarce. There is only a single report, wherein this reaction has been used as the key step in a total synthesis.[79] Partially, this was because the substrates of this Smalley Rearrangement require free fabricated α-azidophenyl *sec*-alkyl ketones which, in general, are prepared by multi-step procedures.



Scheme 1.3: *Synthesis of 2,2-disubstituted indolin-3-one via Smalley cyclization*

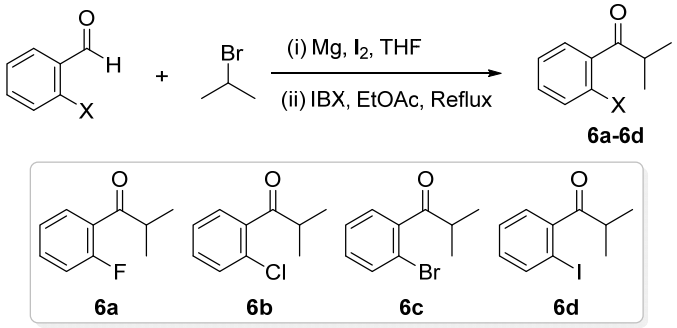
Inspired by our early studies on the S_NAr-cycloaddition and S_NAr-azide reduction, and given our current interest in the synthesis of natural products having the indolin-3-one core, we started a program on examining the possibility of a one-pot [Cu]-catalysed S_NAr and the Smalley rearrangement of α-halophenyl *sec*-alkyl ketones (Scheme 1.4).



Scheme 1.4: *Smalley cyclization and our concept for indol-3-one ring system*

Present Work:

The work in this direction began with the identification of the optimum leaving group for the S_NAr with azide. For that, we prepared four *o*-halophenyl isopropyl ketones derivative through the isopropyl bromide Grignard addition to the corresponding *o*-halobenzaldehyde, and subsequently, the crude alcohol was subjected for the IBX oxidation, which provided the required *o*-halophenyl isopropyl ketones (Scheme 1.5, yields were not optimized). The compounds were confirmed by comparing the NMR data with the data reported in the literature.



Scheme 1.5: *Synthesis of o-halophenyl isopropyl ketones (**6a–6d**)*

After having a set of *o*-halophenylisopropyl ketone substrates in hand, our next objective was to identify the optimum leaving group for the S_NAr with azide. For that the four α-halophenyl isopropyl ketones (**6a**–**6d**) were subjected under the previously optimized conditions for the S_NAr reactions with sodium azide. The conditions employed involve the use of 20 mol% of each of $CuSO_4 \cdot 5H_2O$, sodium ascorbate and L-proline, 1.5 equivalents of K_2CO_3, and DMSO as the solvent. As shown in Table 1.6, these initial experiments revealed that the bromo-derivative **6c** is the better substrate in comparison to the remaining three. The reactions with the fluro- and chloro substrates were found to be incomplete even after

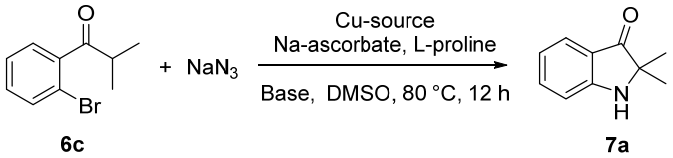
prolonged heating under the above mentioned conditions. Along with the requisite S_NAr – Smalley cyclization, the dehalogenaion of the starting halo-derivative and also the *in situ* reduction of the intermediate azide are the competing reactions. The S_NAr reaction with the iodo derivative (**6d**) was found to be facile. However, the corresponding dehalogenated derivative was isolated in substantial amounts (Table 1.6, entry 4). In case of the bromo-derivative **6c**, although the displacement reaction was slow, the required **7a** was obtained as the main product in 65% yield (Table 1.6, entry 3). The product **7a** was confirmed by NMR analysis as well as by comparing the spectral data with the reported compound. In the ^1H NMR spectrum of compound **7a**, the two methyl groups resonated together at δ 1.31 ppm as a singlet and the N–H proton appeared at δ 4.69 ppm as a singlet. In the ^{13}C NMR spectrum of compound **7a**, the characteristic peak of the newly generated quaternary carbon resonated at δ 63.9 ppm and the carbonyl carbon appeared at δ 205.2 ppm. The two methyl carbons resonated together at δ 24.4 ppm. Furthermore, the presence of a strong peak in the HRMS spectra at m/z 162.0913 confirmed the constitution of the compound **7a**.

Table 1.6: *Screening of leaving group for One-pot synthesis of indol-3-one*

Entry	X	7a	8	4p
1	**F**	29%	18%	31%
2	**Cl**	16%	21%	27%
3	**Br**	**65%**	**7%**	**9%**
4	**I**	41%	16%	39%

After identifying bromo as the optimum leaving group for the S_NAr with azide, next the optimization of reaction conditions has been explored. In this regards, the optimization experiments were carried out using substrate **6c** as the model substrate in the presence of 20 mol% of each of $CuSO_4 \cdot 5H_2O$, sodium ascorbate and L-proline, 1.5 equivalents of K_2CO_3, and with DMSO as the solvent. Control experiments revealed that the presence of the copper salt is essential and among the various Cu-sources investigated, $CuSO_4$ was found to be the best (Table 1.7, entries 7–14). Coming to the various bases screened, the best results were obtained with K_2CO_3 (Table 1.7, entries 1–7).

Table 1.7: *Optimization of Reaction Condition with various Cu–catalysts*

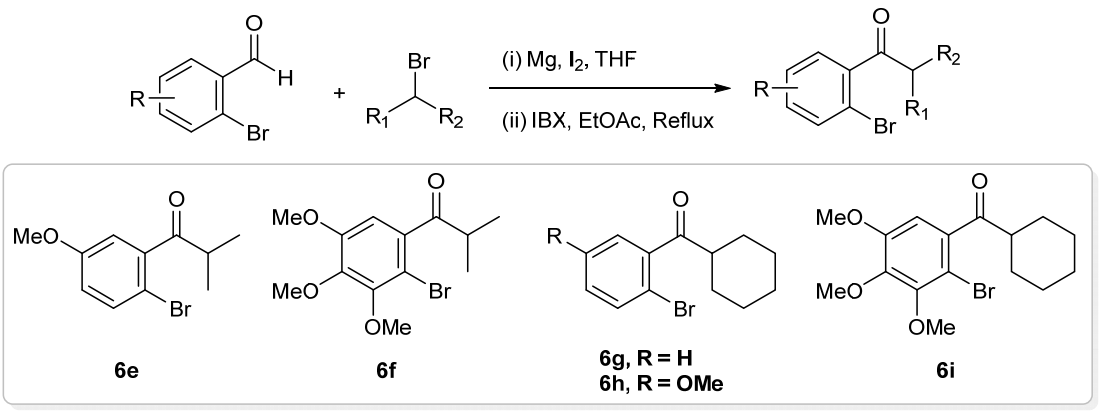


6c **7a**

Entry[a]	Cu-catalyst	Base	Yield[c]
1	$CuSO_4\ 5H_2O$	K_2CO_3	65%
2	$CuSO_4\ 5H_2O$	KOH	23%
3	$CuSO_4\ 5H_2O$	Cs_2CO_3	57%
4	$CuSO_4\ 5H_2O$	Triton B	59%
5	$CuSO_4\ 5H_2O$	TBAOH	51%
6	$CuSO_4\ 5H_2O$	Et_3N	41%
7	$CuSO_4\ 5H_2O$	------	33%
8	CuI	K_2CO_3	36%
9	CuI	KOH	61%
10	CuI	-------	46%[b]
11	CuI	-------	36%
12	CuI	-------	53%[b, d]
13	Cu_2O	K_2CO_3	36%[b]
14	$Cu(OAc)_2$	K_2CO_3	43%

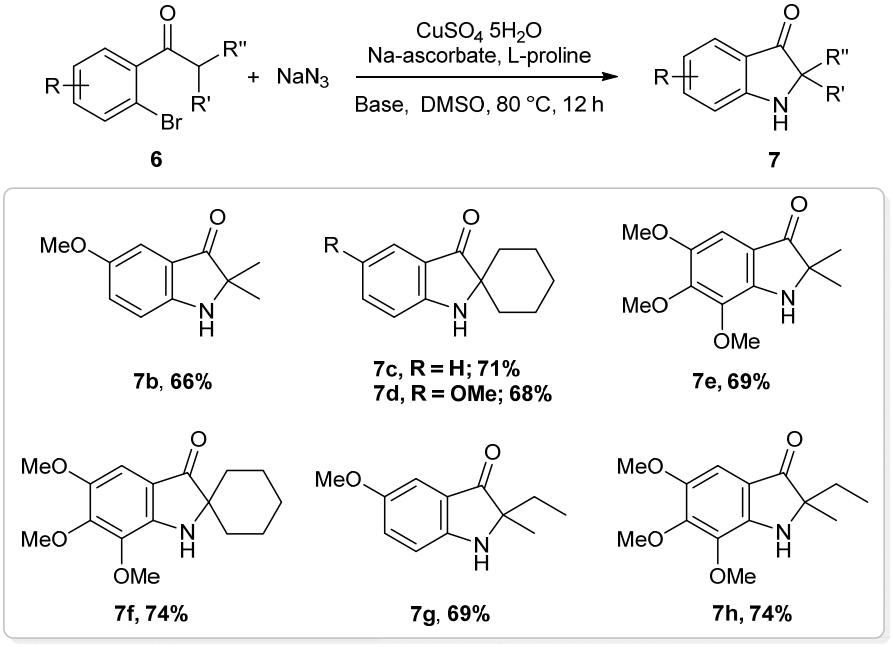
[a] all reactions performed with 1.2 eq NaN_3; 20 mol% L-proline, Na-ascorbate, Cu-cat in DMSO; [b] reaction without Na-ascorbate; [c] isolated yields [d] PEG as a solvent

After optimizing the reaction conditions, the next plan was to expand the scope of the current reaction to arrive at a diverse set of pseudoindoxyl compounds and examine their physical properties such as fluorescence etc. The first set of substrates has been synthesized following the established two step sequence - i.e. the addition of *in situ* prepared appropriate secondary alkyl Grignard reagent to a substituted *o*-bromobenzaldehyde and the oxidation of the resulting crude alcohol with IBX in ethyl acetate as a solvent under reflux conditions. Scheme 1.6 provides the details of the various *o*-bromophenyl *sec*-alkylketones (**6e–6i)** synthesized (yields were not optimized).



Scheme 1.6: *Synthesis of substrates **6e–6i***

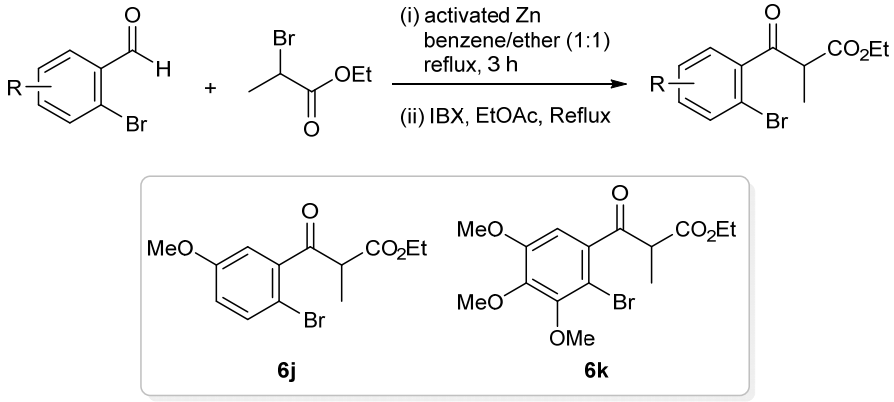
Having this set of substrates (**6e**–**6i)**, examined next their one-pot S_NAr – Smalley cyclization under optimized conditions was considered. As shown in Scheme 1.7, the reaction was facile with various *o*-bromophenyl *sec*-alkyl ketones and provided the indolin-3-one derivatives in moderate to good yields. The yields with the more electron rich aryl derivatives were slightly better than with relatively less electron rich derivatives. For examples, the yields of compounds **7e**,**7f**, and **7h** containing three methoxy groups each (69%, 74%, 74%) were little better than that of the compounds **7b**, **7c**, **7g** containing one methoxy group each (66%, 71%, 69%) respectively.



Scheme 1.7: *[Cu]-catalyzed one-pot S_NAr – Smalley Cyclization of o-bromophenyl sec-alkyl ketones*

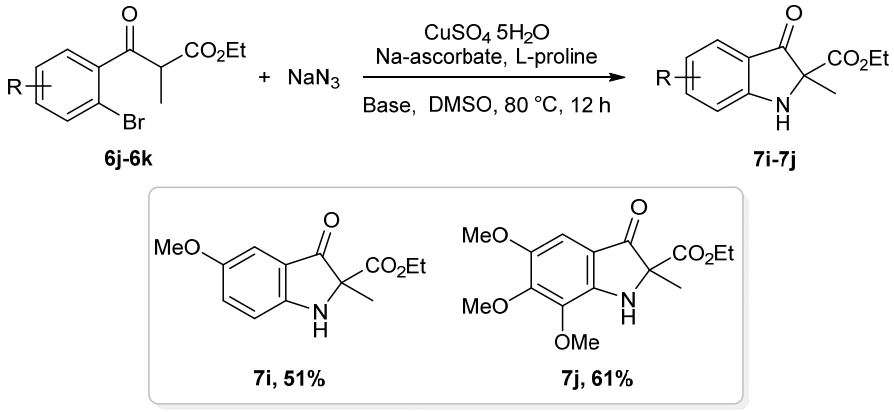
To further extend the scope of the reaction, the β-keto ester derivatives **6j** and **6k**, we have been synthesized following the literature procedures. Thus, the Reformatsky reaction of *o*-bromobenzaldehyde with ethyl 2-bromopropionate using activated Zn in

benzene/diethylether (1:1) as the solvent under reflux conditions gave the corresponding β-hydroxy ester which was treated directly without any purification with IBX in ethyl acetate under reflux to afford β-keto ester derivative **6j** (Scheme 1.8, yields were not optimized). Similarly, the other β-keto ester derivative **6k** was prepared following the same protocol.



Scheme 1.8: *Synthesis of β-keto ester substrate **6j** and **6k***

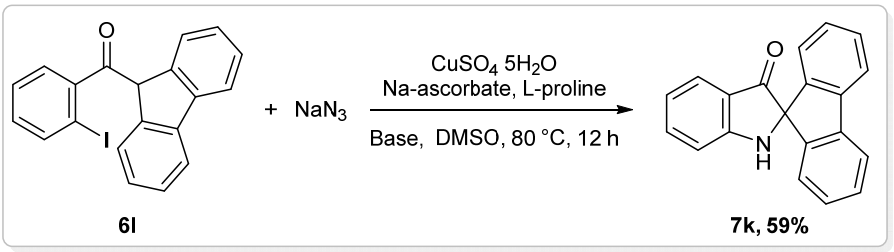
These two β-keto esters have been subjected for the one-pot S_NAr–Smalley cyclization under standard conditions. The one-pot S_NAr–Smalley cyclization of these substrates proceeded smoothly and provided the corresponding methyl 3-oxoindoline-2-carboxylate: the main core of the Lipid Green dye (**7i**) (Scheme 1.9).[68c]



Scheme 1.9: *[Cu]-catalyzed one-pot S_NAr – Smalley Cyclization of β-keto esters derivatives*

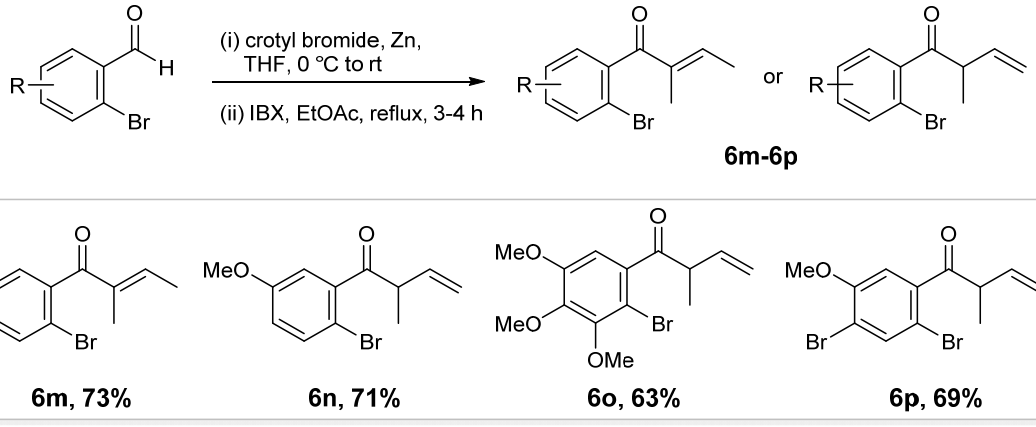
In addition, we also examined the compatibility of this reaction with sterically hindered substrate **6l**. The substrate **6l** was prepared through the reaction of *o*-iodobenzoyl chloride with fluorene in the presence of LDA using THF as a solvent. The structure of compound **6l** was confirmed with the help of ^1H and ^{13}C NMR spectral data analysis. Next, the compound **6l** was subjected for the S_NAr–Smalley cyclization under the established conditions to obtain 3-indolinone **7k** in 59% yield (Scheme 1.10). All the compounds (**7b**–**7k**) were confirmed by NMR and HRMS. In the ^1H NMR spectra, the disappearance of the characteristic C_α–H of carbonyl was observed and usually the 3-indolinone N–H protons

resonated at δ 4 to 5 ppm. Furthermore in the ^{13}C NMR spectra, the characteristic spiro-carbon resonated between 63 to 90 ppm and the quaternary carbon of carbonyl moiety was at δ 200 to 205 ppm range in all the compounds.



Scheme 1.10: *[Cu]-catalyzed one-pot S_NAr – Smalley cyclization of compound* ***6l***

Next, we moved to examine the feasibility of this one pot S_NAr–Smalley rearrangement with α-bromophenyl *sec*-alkenyl ketones. The synthesis of model substrates **6m–6p** involves the crotylation of a 2-bromobenzladehyde derivative under Barbier condition employing crotyl bromide with activated Zn in THF as solvent and subsequent IBX oxidation of the resulted homoallylic alcohols in ethyl acetate under reflux condition afforded α,β-usaturated ketone **6m** from 2-bromobenzladehyde, whereas β,γ-usaturated ketones (**6n, 6o** and **6p**) were obtained from 2-bromo-5-methoxybenzaldehyde, 2-bromo-3,4,5-trimethoxybenzaldehyde and 2,4-dibromo-5-methoxybenzaldehyde respectively (Scheme 1.11).

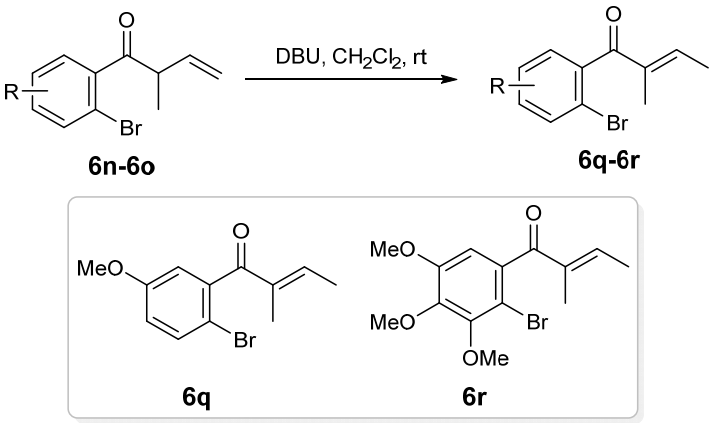


Scheme 1.11: *Synthesis of α-bromophenyl sec-alkenyl ketones* ***6m–6p***

The compounds **6m**–**6p** were fully characterized by spectral and analytical data. In the ^1H NMR spectrum of compound **6m**, the C_β–H appeared as multiplet at δ 6.29–6.34 ppm and the two methyl group protons appeared at δ 1.85 (td, J = 0.9, 6.9 Hz, 3H) and 1.94 (d, J = 0.9 Hz, 3H) ppm. In the ^{13}C NMR spectrum of compound **6m**, four quaternary carbons resonated as singlets at δ 119, 138, 141, 197 ppm. Likewise in the ^1H NMR spectrum of compound **6n**, the olefinic –CH_2 and –CH protons appeared at δ 5.08–5.17 and 5.77–5.95

ppm as multiplet respectively, and two methyl protons appeared at δ 1.32 ppm as doublet with a coupling constant J = 6.95 Hz and 3.78 ppm as singlet. In the ^{13}C NMR spectrum of compound **6n**, the characteristic olefinic $–CH_2$ carbons resonated at δ 117.4 ppm, whereas the C_α to the carbonyl group appeared at δ 50.1 ppm as a doublet.

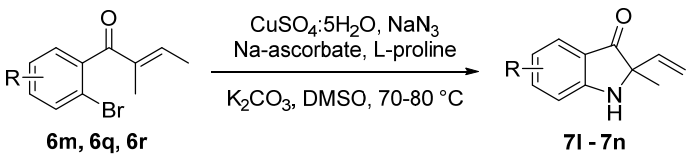
Later, **6n** and **6o** were isomerised with DBU in CH_2Cl_2 to get the corresponding α,β-usaturated ketones (**6q** and **6r**) (Scheme 1.12). The structure of compounds **6q–6r** was established with the help of spectral and analytical data. In the ^1H NMR of compound **6q**, the terminal olefinic $–CH_2$ protons were seen to disappear and the remaining one olefinic proton resonated at δ 6.36 (qq, J = 1.3, 7.0 Hz, 1H) ppm as well as three methyl group protons appeared at δ 1.85 (qd, J = 0.9, 7.0 Hz, 3H), 1.92–1.94 (m, 3H) and 3.77 (s, 3H) ppm. In the ^{13}C NMR spectrum of compound **6q**, the newly generated quaternary center appeared at δ 137.9 ppm as a singlet and three methyl carbons resonated at δ 10.6, 15.2, 55.5 ppm. This was further confirmed by the presence of a strong peak in ESI-MS at 291.18 (75%, $[M+Na]^+$).

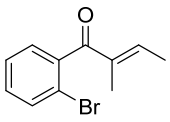
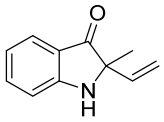
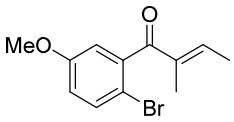
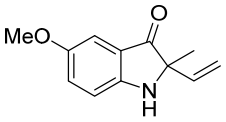
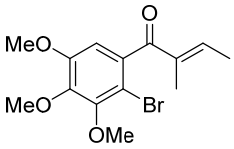
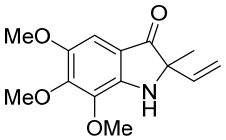


Scheme 1.12: *Synthesis of α-bromophenyl sec-alkenyl ketones **6q–6r***

After successful synthesis of the α-bromophenyl *sec*-alkenyl ketones (**6m–6r**), our next concern was the examination of these substrate under present reaction condition. The one pot S_NAr–Smalley cyclization of α,β-usaturated ketones (**6m**, **6q**, and **6r**) afforded the 2-vinylindolin-3-one derivatives **7l–7n** in moderate to good yields (Table 1.8).

Table 1.8: *Synthesis of 2-vinylindolin-3-one from α-bromophenyl sec-alkenyl ketones (α,β-usaturated ketones isomers)*

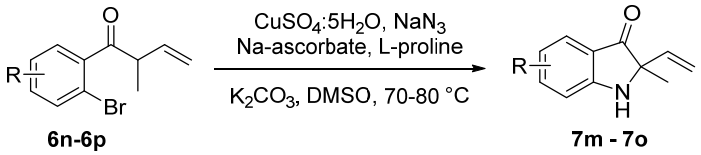


Entry	Substrate	Product	Yield
1	 **6m**	 **7l**	**67%**
2	 **6q**	 **7m**	**72%**
3	 **6r**	 **7n**	**69%**

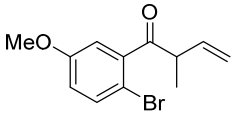
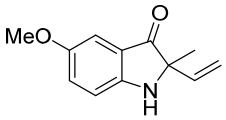
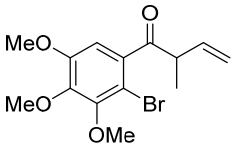
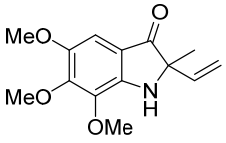
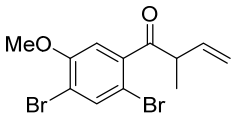
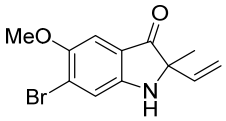
The structures of the compounds **7l–7n** were confirmed with the help of NMR and HRMS. For example, in the ^{1}H NMR spectrum of compound **7l**, the vinylic –CH_2 and –CH resonated at 5.14 (dd, J = 0.8, 10.3 Hz, 1H), 5.34 (dd, J = 0.8, 17.2 Hz, 1H), and 5.87 (dd, J = 10.4, 17.24 Hz, 1H) ppm respectively. Most importantly the disappearances of one methyl group from α,β-usaturated ketones was observed and the remaining methyl protons appeared at δ 1.44 ppm as a singlet and the N–H resonated as a broad singlet at δ 4.72 ppm. The aromatic protons resonated between 6.77–7.60 ppm. In the ^{13}C NMR spectrum of compound **7l**, the vinylic –CH_2 carbon appeared as a triplet at 114.5 ppm, and the methyl attached to the spiro carbon resonated at δ 22.8 ppm. The newly formed spiro quaternary carbon resonated at δ 69.3 ppm and carbonyl carbon resonated at δ 202.3 ppm as singlet respectively. The presence of a strong peak in HRMS at 204.1019 [M+H]$^{+}$] confirmed the constitution of the compound **7l**.

Subsequently, β,γ-usaturated ketones **6n**–**6p** also subjected for the Cu-catalyzed one pot S_NAr – Smalley cyclization under optimized reaction conditions. The reaction proceeded smoothly and provided the corresponding indolin-3-ones derivatives **7m-7o** in very good yields (Table 1.9). The reaction outcome of isomeric substrates revealed that, the position of olefin does not have that much influence on the outcome of the product. For example, the reaction with either the α,β-isomer of compound **6q** or the β,γ-isomer of compound **6n** afforded the 2-vinylindolin-3-one **7m** in 72% and 71% yields respectively (Table 1.8, entry 2 and Table 1.9 entry 1). From the above experiments, it seems reasonable that the Smalley cyclization of all the substrates **6m–6r** proceeds through the 2-methyl-1-phenylbuta-1,3-dien-1-olate intermediate in which α-carbon preferentially adds across the azide.

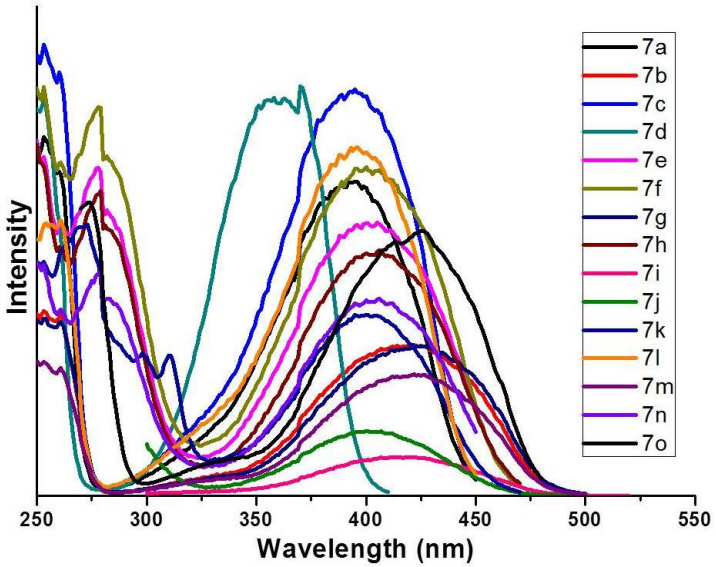
Table 1.9: *Synthesis of 2-vinylindolin-3-one from α-bromophenyl sec-alkenyl ketones (β,γ-usaturated ketones isomers)*



6n-6p 7m - 7o

Entry	Substrate	Product	Yield
1	 **6n**	 **7m**	**71%**
2	 **6o**	 **7n**	**74%**
3	 **6p**	 **7o**	**72%**

After establishing the validity of the methodology for the preparation of indol-3-one, their photo–physical properties were studied, as these compounds are fluorescent in nature (Figure 1.7).[68b, 114] Figure 1.7 represents the UV–absorption and emission spectra of the compounds 7**a**–**7n** measured in MeOH.



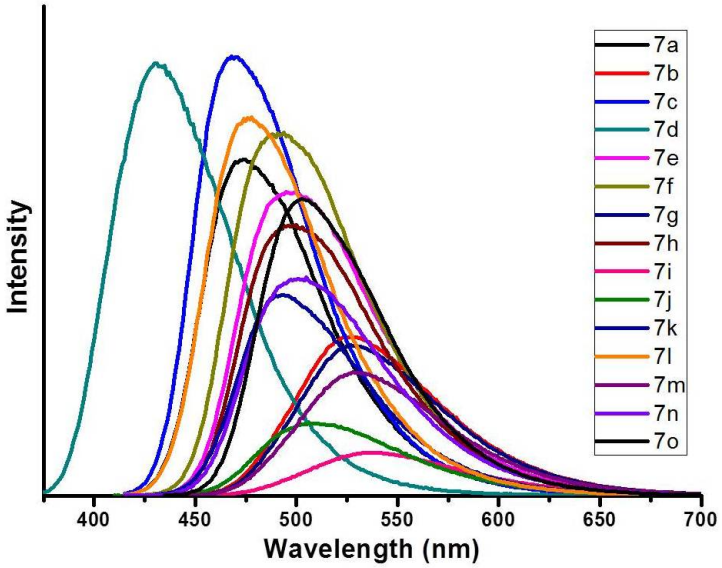
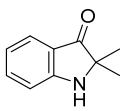
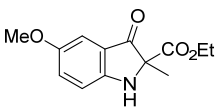
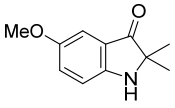
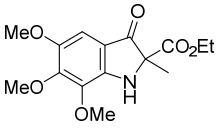
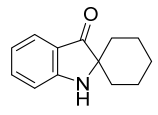
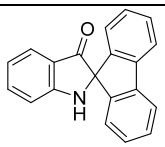
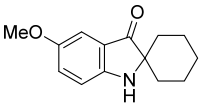
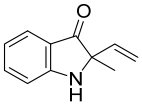
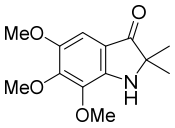
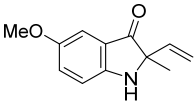
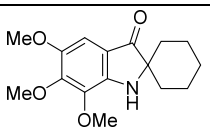
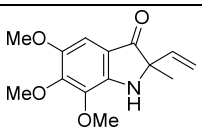
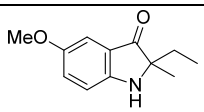
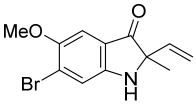
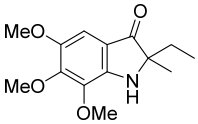


Figure 1.7: *Absorption spectra (A) and emission spectra (B) of compound **7a–7o***

It is speculated that the fluorescence in the 1,2-dihydroindol-3-one core structure is mainly because of the auxochrome, *viz* the amino group which acts as a donor and the carbonyl group as an acceptor which are connected *via* a benzene ring. The λ_{max} and λ_{em} of the substrates depends mainly on the nature of donor and acceptor parts of the substrate. The observed optical data revealed that the compounds with a methoxy group on the phenyl ring showed absorption and emission at longer wavelengths than those substrates having no substituent on the benzene ring or trimethoxy substituted benzene (Table 1.10). Thus, this indicates that the –OMe group placed *para* to the amino group enhanced the donor capacity of the amino group and thereby shifted the peak to a longer wavelength. The presence of three –OMe groups on the benzene ring seems to decrease the acceptor ability of the carbonyl group. A similar trend was also noticed in the Stokes shifts (ranging from 70 nm – 120 nm) displayed by these indol-3-ones. The indol-3-one **7i** having a single methoxy substituent on the aryl ring and a carboxylate group at C2 displayed a large Stoke shift (121 nm).

Table 1.10: *Optical properties of compounds **7a** – **7o***

Compound	λ_{max} (nm)[a]	λ_{em} (nm)[a]	Stokes shift (nm)[b]	Compound	λ_{max} (nm)[a]	λ_{em} (nm)[a]	Stokes shift (nm)[b]
 **7a**	395	473	78	 **7i**	415	536	121
 **7b**	421	523	98	 **7j**	402	509	107

 **7c**	395	467	72	 **7k**	401	492	91
 **7d**	370	430	60	 **7l**	396	477	81
 **7e**	405	499	94	 **7m**	421	527	106
 **7f**	400	493	93	 **7n**	406	504	98
 **7g**	425	528	103	 **7o**	425	503	78
 **7h**	406	499	93				

[a] Measured in MeOH; [b] Stokes shift = λ_{em} - λ_{max}

Conclusion

To conclude, we have developed a simple protocol for the synthesis of 2,2-disubstituted-3-indolinones using a catalytic Cu(I)-ascorbate redox system for the S_NAr with azide followed by Smalley cyclization from *α*-bromophenyl *sec*-alkyl/*sec*-alkenyl ketones. The reaction with *α*-bromophenyl *sec*-alkenyl ketones irrespective of double bond position, the vinylindolin-3-one derivatives are obtained in good yields. A comparison of optical properties of all the synthesized pseudo indoxyl derivatives revealed interesting results. The Stokes shifts were observed in the ranges from 70 nm – 120 nm and the compound **7i**, in which the main core of the Lipid Green dye has a single methoxy substituent on the aryl ring and a carboxylate group at C2, displayed a highest Stoke shift of 121 nm.

Cu(I)-catalyzed synthesis of 2-Aroyl indole

In our previous exercises, we have demonstrated that the reduction of the aryl azides is facile when the aryl ring contains electronic withdrawing groups such as nitro, carbonyl, and $–CF_3$ etc, and that this reduction occurs *via* the displacement of N_2 from the electrophilic azide. Subsequently, we also detailed that if an internal nucleophile is employed for such a displacement, it results in the ring annulation. As a logical extension, we next asked a simple question – is the synthesis of 2-aroylindoles possible *via* the S_NAr–Nitrene insertion from the 2-bromochalcones?

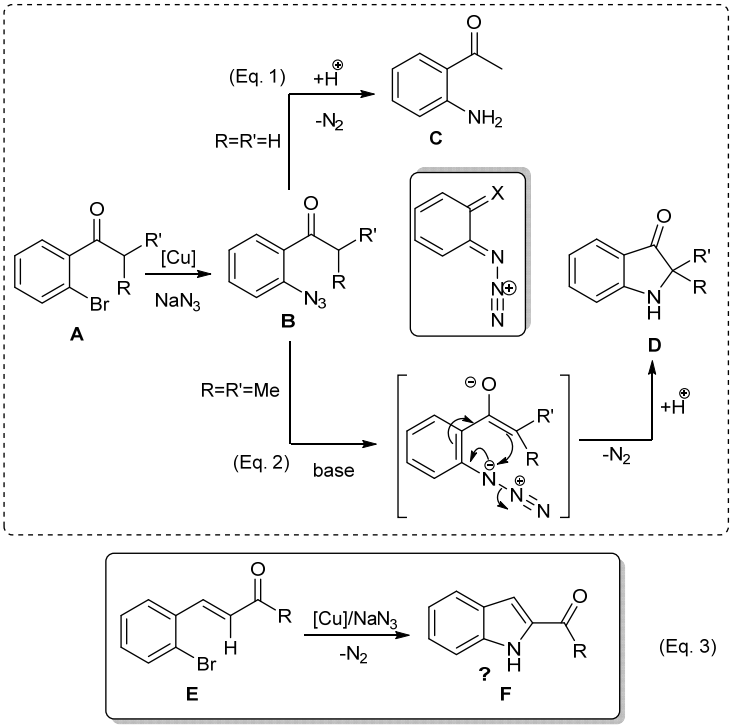
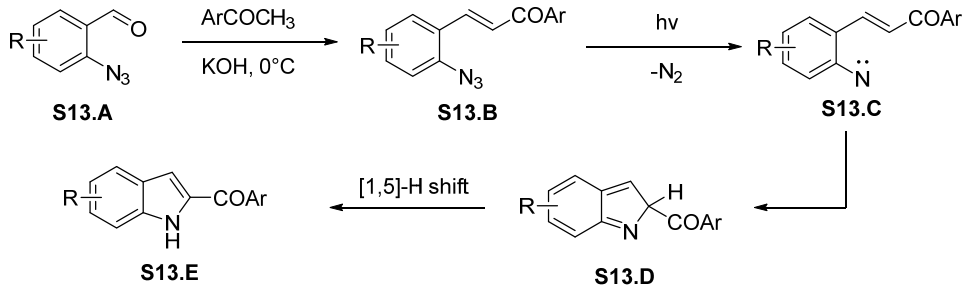


Figure 1.8: *Our previous approach for C–N bond formation and intended hypothesis for 2-aroyl indole*

Indole is one of the most important nitrogen containing heterocycles present in many bioactive molecules.[81] The early disclosures of its constitution/structure in dealing with the synthesis of indigo, "indole synthesis", has witnessed a constant progress during the last two centuries and has bagged several name reactions.[115] Indole derivative in particular, 2-aroyl indole as well as indole-2-carboxylate derivatives present in many natural products or in pharmacologically active compounds having an important biological activity like tubulin polymerization inhibitors, cPLA2 inhibition, histamine H4 receptor antagonist, PPAR agonists and so on.[83-86] The examination of these derivatives across a wide range of biological targets was, in particular, possible because of their ready availability and because

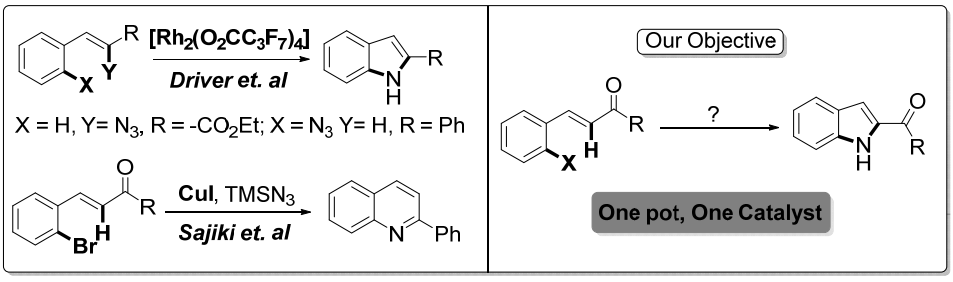
of the development of reliable protocols for their synthesis. Some of the general approaches towards the synthesis of the 2-aroyl indole derivatives have been described in the Introduction and it has been revealed that the methods involving the formation of N–C bond *via* nitrene intermediates proceeds either in a step-wise (aziridine formation) or in a concerted fashion (C–H insertion).[87-93] Coming to the involvement of aryl azides for generating such nitrene intermediates, a couple of examples need a mention.

In 1999, Lahiri and co-workers reported the photochemical intramolecular cyclization of *o*-azido chalcones to the 2-aroyl indole derivatives in methanol. A mechanism involving an electrocyclization of the intermediate nitrene and [1,5]–H shift leading to 2-aroyl indole has been proposed (Scheme 1.13).[116]



Scheme 1.13: *Synthesis of 2-aroyl indole via photolytic intramolecular cyclization*

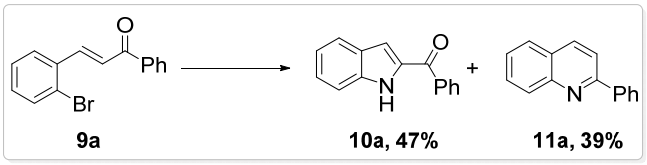
In 2008, Driver and co-workers reported intramolecular C–H amination from either side of α-azidoacrylates or aryl azides *via* a Rh-catalyzed decomposition of azide leading to indole derivatives. A stepwise mechanism, where C–N bond formation precedes N–H bond formation, has been proposed based on some control experiments. The major limitation of this approach is that the reactions are not compatible with substrates having the alkyl groups next to the carbonyl.[92] In 2012, as a part of amination of aryl halides using NaN_3, Sajiki and co-workers have documented an example wherein the 2-bromochalcone was converted directly into 2-phenylquinoline in 82% yield.[117] A mechanism involving the initial Cu(0) or Cu(I)-mediated C–N coupling with azide, subsequent azide reduction and finally the cyclization of the intermediate 2-aminochalcone as shown in Scheme 1.14.



Scheme 1.14: *Copper-mediated reductive amination of 2-bromochalcone with $TMSN_3$*

This report of Sajiki and co-workers is quite interesting and has also alarmed us of the possible risks in our proposal of developing a one-pot [Cu]-catalysed synthesis of 2–aroylindoles from *o*-bromochalcones through the initial formation of an aryl azide intermediate followed by subsequent C–H insertion. However, considering our previous experience, we reasoned that if the intermediate nitrene is sufficiently stabilized by varying the nature of the copper complex, there is a chance for the C–H insertion over the competing reduction of this nitrene.

Having set this objective, our journey started in the direction of discovering the right reaction conditions to convert the bromochalocone (**9**) into 2-benzoylindole (**10**). The model substrate **9a** was prepared by treatment of an *o*-bromobenzaldehyde with acetophenone in the presence of aqueous NaOH in ethanol (4 mL) at ambient temperature to access the requisite *o*-bromochalcone **9a**. The initial experiments with simple α-bromochalcone **9a** under the previously established conditions [20 mol% of each of $CuSO_4 \cdot 5H_2O$, sodium ascorbate and L-proline, 1.5 equivalents of K_2CO_3 and NaN_3 in DMSO at 80 ºC for 15h] gave a mixture of the required 2-benzoylindole (**10a**, 47%), along with the 2-phenylquinoline (**11a**, 39%) (Scheme 1.15). In the ^{1}H NMR spectrum of compound **10a**, the indole NH proton resonated at δ 9.27 ppm as broad singlet and, most importantly, the olefinic protons were seen to disappear. In the ^{13}C NMR spectrum of compound **10a**, the carbonyl carbon appeared at δ 187.2 (s) ppm and the newly generated quaternary centre resonated at δ 127.7 (s) ppm. The spectral data of compound **10a** was in good agreement with the reported data. Likewise, the physical data of quinolone **11a** was comparable with the data reported earlier.

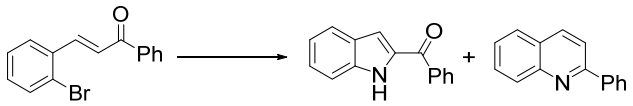


Scheme 1.15: *Reagent and condition: $CuSO_4 \cdot 5H_2O$ (20 mol%), NaN_3 (1.5 equiv.), Na-ascorbate (20 mol%), L-proline (20 mol%), K_2CO_3 (1.5 equiv.) in DMSO at 80 ºC for 15 h.*

Having a highly promising result, we next focussed on the optimization of the reaction conditions to increase the ratio for 2-aroyl indole formation. As shown in Table 1.11, among the various copper sources employed, CuI was found to be the best for the present transformation. The outcome of the required 2-aroylindole increased by switching the solvent from DMSO, DMA to NMP (Table 1.11, entries 2–4). Although the presence of Na-ascorbate is not essential, yet the presence of a base like K_2CO_3 (4.0 equivalents) is highly required (Table 1.11, entry 8). However, other bases such as Cs_2CO_3 and Na_2CO_3 did not show any

improvement in the yield (Table 1.11, entries 9–10). Reducing the concentration of the ligand L-proline from 100 mol% to 20 mol% did not show any effect on the reaction efficiency (Table 1.11, entry 12).

Table 1.11: Optimization of reaction condition[a]



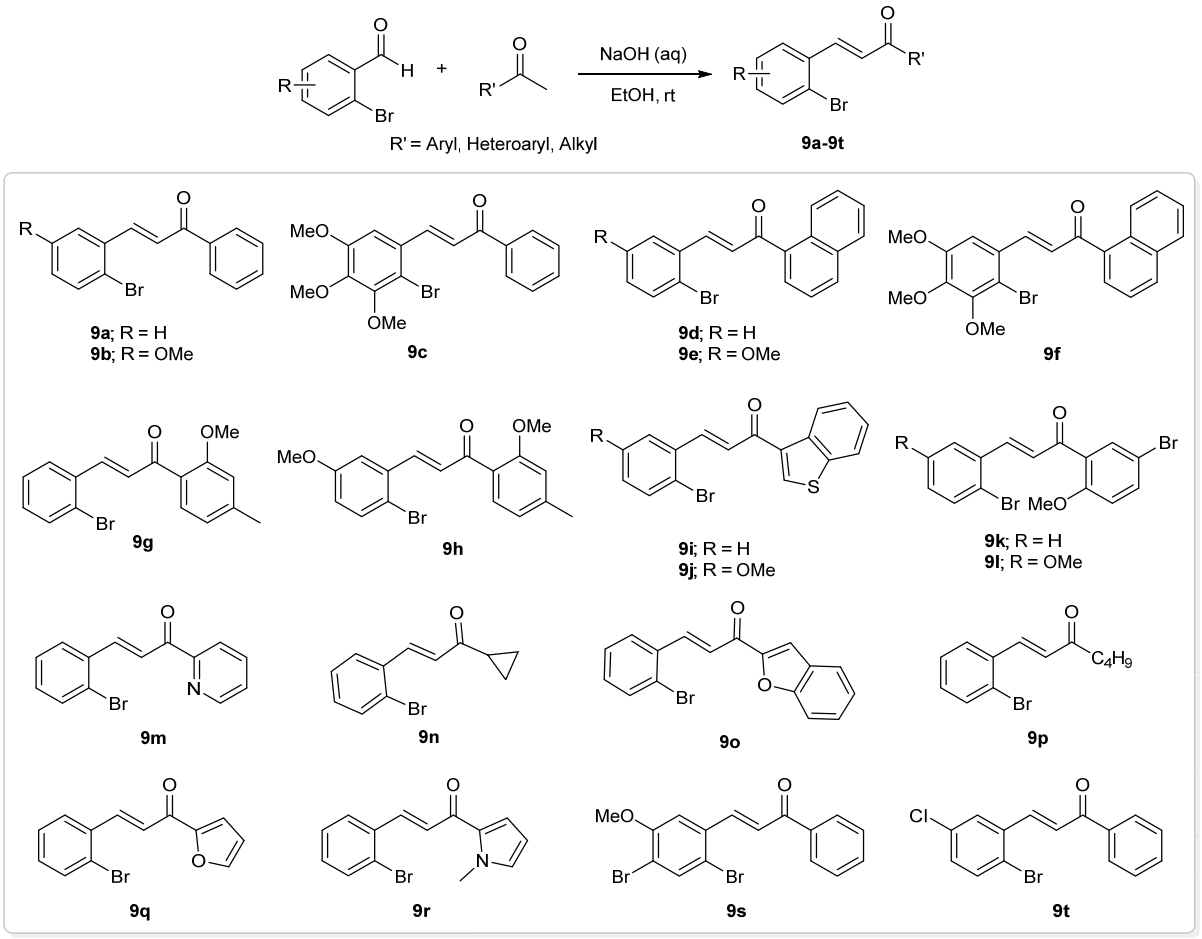
9a **10a** **11a**

Sr. No	Catalyst	Solvent	Base	Yield (**10a**)[b, c, d]	Yield (**11a**)[b, c, d]
1	CuI	DMSO	1.5	56%	41%
2	CuI	DMA	1.5	62%	38%
3	CuI	NMP	1.5	69%	26%
4	CuI	NMP	----	47%	13% (39%)
5	CuI	NMP	2.0	80%	20%
6	CuI	NMP	3.0	81%	5% (4%)
7	CuI	NMP	4.0	86%	3%
8	CuI	NMP	1.5[e]	49%[f]	51%
9	CuI	NMP	3.0[f]	72%[g]	27%
10	$CuSO_4$	NMP	1.5	52%[e]	5% (27%)[e]
11	**CuI**	**NMP**	**4.0**	**87%**	**1%**
12	CuI	NMP	3.0	75%	7% (17%)
13	CuCl	NMP	4.0	84%	---(4%)
14	Cu_2O	NMP	3.0	54%	24%(21%)
15	-----	NMP	4.0	ND	ND

[a]Reaction condition: *o*-bromochalcone (**1a**, 1eq.), NaN_3 (1.5 eq.), CuI (20 mol %), L-proline (0.2 eq.), K_2CO_3 (4.0 eq.) in NMP at 100 ºC for 15h;[b] L-proline (1.0 eq.) was used for entries 2–11; [c]Yield based on GC; [d]Isolatedyield; [e](20 mol%)Na-ascorbate was used; [f] Cs_2CO_3 used as a base;[g] K_2CO_3 use as base; [i] parenthesis indicate (%) starting intact.

After optimizing the reaction conditions, we have next prepared the various starting *o*-bromochalcones derivatives **9a**–**9t** following the literature procedures. As shown in scheme 1.16, the synthesis involved the treatment of a *o*-bromobenzaldehyde derivative with acetophenone in the presence of aqueous NaOH in ethanol (4 mL) at ambient temperature till TLC showed the disappearance of starting material. The entire compound were characterised by NMR and Mass spectrum. For examples, in the ^{1}H NMR spectrum of compound **9b**, the characteristic *trans* olefinic protons were seen to appear at δ 7.37 and 8.06 ppm as doublet with coupling constant J = 15.7 Hz. The methyl (–OMe) protons resonated at δ 3.84 ppm as a

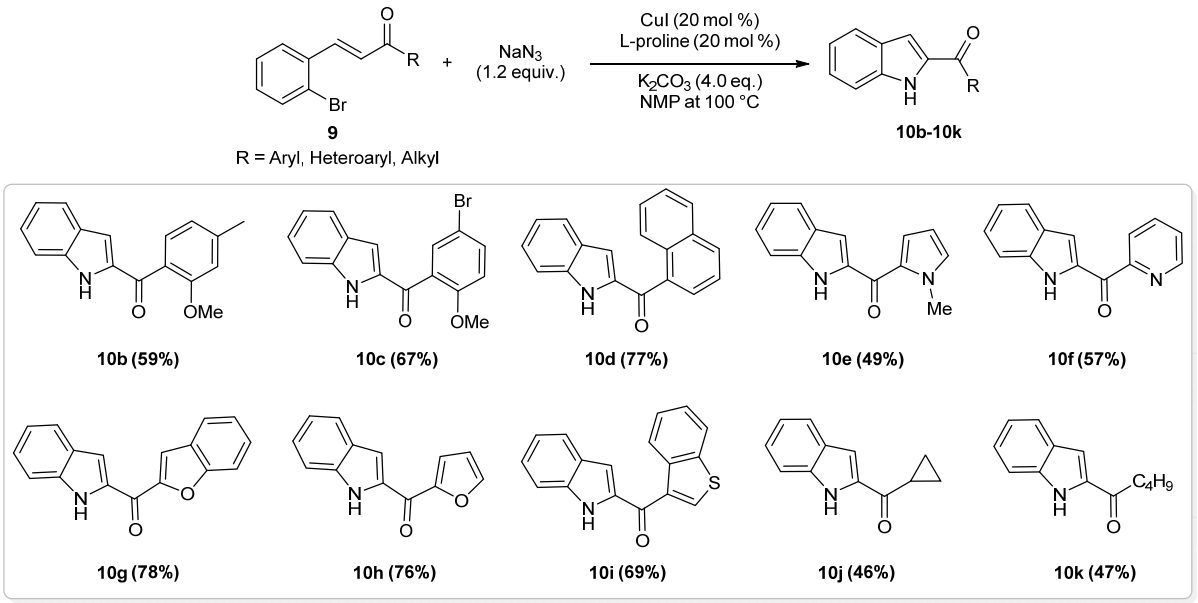
singlet and the remaining eight aromatic protons were seen to resonate between δ 6.83–8.02 ppm. In the ^{13}C NMR spectrum of compound **9b**, the methyl carbon resonated at δ 55.6 ppm as quartet, whereas the quaternary carbon like carbonyl, carbon attached to –OMe and carbon attached to Br were seen to resonate respectively at δ 190.5, 159.0 and 116.5 ppm as singlet. The carbons of the phenyl ring as well as olefin appeared at δ 113.0, 117.4, 125.2, 128.6 (4C), 132.9, 134.1, 143.2 ppm. Finally, the presence of a strong peak in the mass spectrum at m/z 316.81 confirmed the compound **9b**.



Scheme 1.16: *Synthesis of o-bromochalcones derivatives **9b–9t***

After having a diverse set of substrates in our hand, the generality of the current reaction has been examined first by selecting the substrates where the nature of substituent next to the carbonyl has been varied from aromatic to heteroaromatic, cycloalkyl and alkyl groups (Scheme 1.17). The reactions with other aromatic/heterocyclic rings like naphthyl, furyl, pyrrol, pyridine, benzofuran and benzothiophene gave the desired products in moderate to good yields. All the products were confirmed by analyzing the spectral data and mass spectra. For examples, in the ^{1}H NMR spectrum of compound **10b**, the olefinic protons were seen to disappear and the N-H of the indole unit was seen to resonate at δ 9.43 ppm as a

singlet. The two methyl group protons resonated at δ 2.43 and 3.82 ppm as singlet, whereas the remaining eight aromatic protons were seen to resonate between δ 6.84-7.64 ppm.

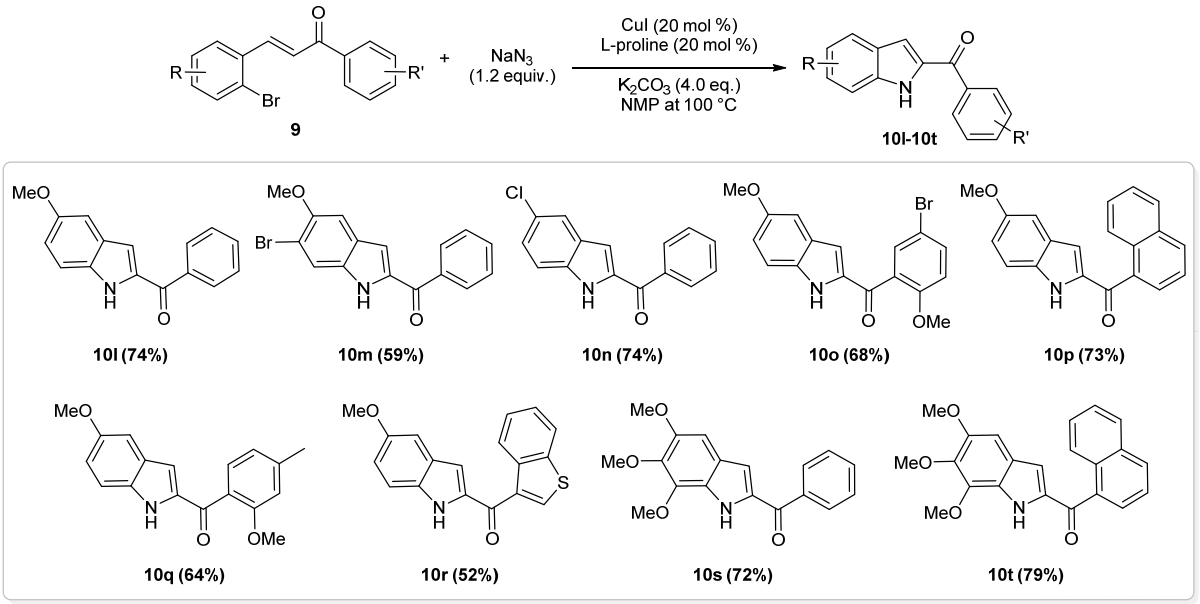


Scheme 1.17: *Scope of the [Cu]-catalyzed 2-aroyl indole synthesis*

However, when the aryl ring was replaced by an alkyl or cyclopropyl group, the yields were seen to decrease. The cyclopropyl ring was found intact under the present reaction conditions and it was confirmed by NMR analysis. In the ^{1}H NMR spectrum of compound **10j**, the N–H proton resonated at δ 9.24 as singlet, whereas the two –CH_2 and one –CH of cyclopropyl ring were seen to resonate at δ 1.02–1.11 (m, 2H), 1.25–1.32 (m, 2H), and 2.59–2.71 (m, 1H) ppm respectively. In the ^{13}C NMR spectrum of compound **10j**, the two –CH_2 appeared at δ 11.4 ppm as a triplet and one –CH at δ 17.5 ppm as a doublet, whereas the carbony carbon resonated at δ 192.9 ppm as a singlet. It was further confirmed by HRMS, where the strong peak was observed at m/z 186.0916.

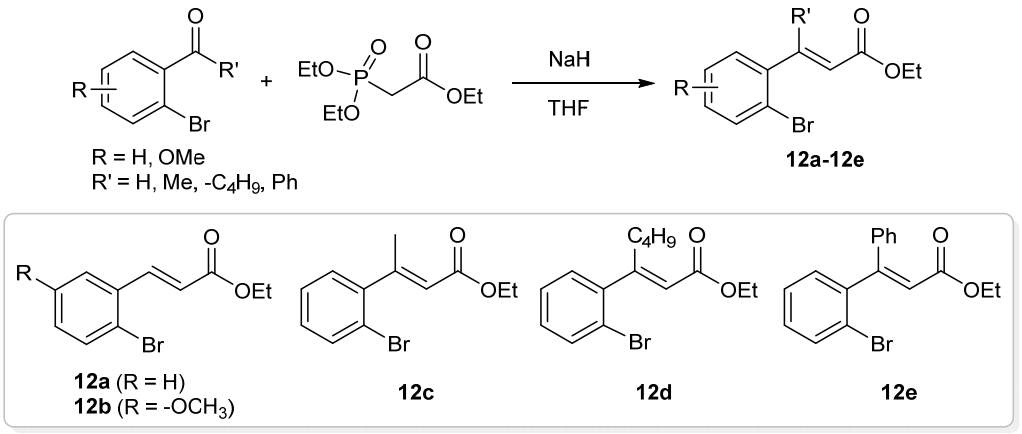
Next, the scope of the present reaction has been further extended by employing 2-bromochalcones having different substituents on both the phenyl rings (Scheme 1.18). The substituents on the bromoaryl ring did not have much influence on the reaction outcome. Bromo or chloro functional groups were found to be intact under the present reaction conditions and provided the corresponding bromo indole **10m** and chloro indole **10n** derivative in 59% and 74% yields respectively. The compound **10m** was confirmed with the help of NMR and HRMS. In the ^{1}HNMR spectrum of compound **10m**, the three indole ring protons were seen to resonate at δ 7.06, 7.11 and 7.71 as a singlet and the N–H proton resonated at δ 9.20 ppm as a singlet. In the ^{13}C NMR spectrum of compound **10m**, the –OMe carbon appeared at δ 56.6 ppm, whereas the carbon attached to bromo was seen to resonate at

δ 113.3 ppm as singlet and the carbonyl carbon appeared at δ 186.9 ppm. The presence of a strong peak in HRMS at m/z 330.0132 confirmed the compound **10m** and in addition to that the presence of another strong peak at m/z 332.0101 in a 1:1 ratio confirmed that the bromine was present in compound **10m**. On the other hand, with substrates having the electron donating group on the aryl ring next to the carbonyl, the reaction yields are moderate.



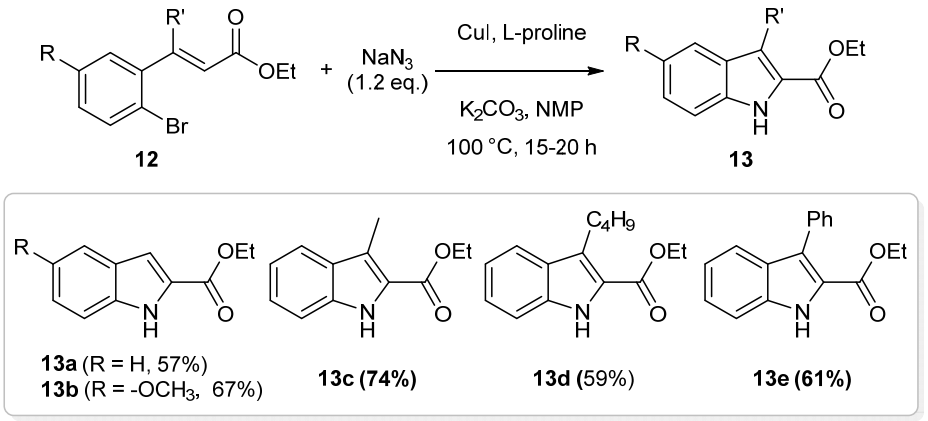
Scheme 1.18: *Copper catalyzed one pot synthesis of 2-aroyl indole derivatives*

Next, to look at the compatibility of an ester group, the required esters derivatives were prepared through a 2-carbon Wittig homologation of the corresponding *o*-bromobenzaldehyde provided the required *o*-bromocinnamate and the 2-bromo-5-methoxy cinnamate are in good yields. In addition to that, we have also synthesized the C3-substituted *o*-bromocinnamates following the same reaction sequence (two carbon Wittig homologation) from the corresponding ketone in order to examine the suitability of the C3-substituted *o*-bromocinnamates (Scheme 1.19). All these starting compound have been characterized with the help of NMR and Mass. For examples, in the ^{1}H NMR spectrum of compound **12c** (*cis:trans* = 1:4 ratio) olefinic proton appeared at δ 5.80 (m, 1H, major) and 5.99 (m, 0.24H, minor) ppm for trans and cis respectively. Similarly the methyl protons were seen to resonated at δ 2.15 (d, J = 1.4 Hz, 0.82H, minor), and 2.48 (br d, J = 1.4 Hz, 3H, major) ppm. In the ^{13}C NMR spectrum of compound **12c**, the ester carbonyl group appeared at δ 165.0 (s, minor) and 166.3 (s, major) ppm. Two $-CH_3$ and one $-CH_2$ carbons appeared at δ 13.8 (q, minor), 14.2 (q, major), 20.3 (q, major), 26.0 (q, minor) and 59.7 (t, minor), 59.9 (t, major) ppm respectively.



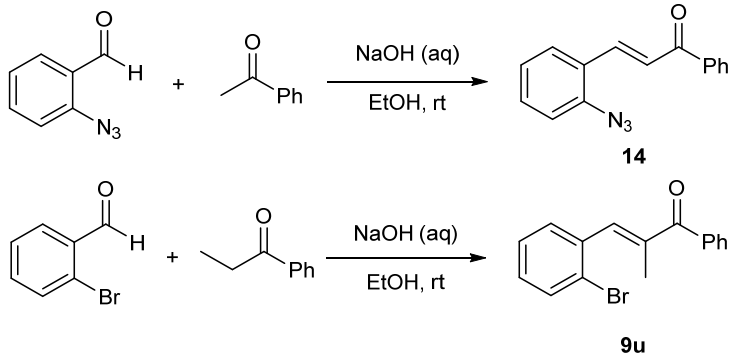
Scheme 1.19: *Synthesis of o-bromocinnamates derivatives*

After having a series of *o*-bromocinnamates derivatives and C3-substituted *o*-bromocinnamates derivatives in hand, first, the *o*-bromocinnamate and the 2-bromo-5-methoxy cinnamate were subjected for the current reaction conditions. To our delight, as expected, the corresponding indoles **13a** and **13b** were obtained respectively in good yields. The amide derivative of compound **13a,** is knows as non-imidazole histamine H 4 antagonists. In the ^{1}H NMR spectrum of compound **13a**, the characteristic olefinic proton peaks were seen to disappear and the indole N-H and C3–H were seen to resonate at δ 8.90 and 7.14 ppm as singlet respectively. In the ^{13}C NMR spectrum of compound **13a**, the new quaternary carbon at δ 127.9 ppm was observed. Similarly, the one-pot copper catalyzed S_NAr-cyclization reaction of the remaining C3-substituted *o*-bromocinnamates also proceeded smoothly to afford the corresponding indole-2-carboxylates **13c–13e** in moderate to good yields (Scheme 1.20). From these experiments, it was revealed that the carboxylate group can be a suitable alternative for the aroyl group. The structures of compounds **13c–13e** was confirmed with the help of spectral data. For example, like earlier results, the disappearance of the alkene peaks and the appearance of a broad singlet at δ 8.72 ppm belonging to the N–H proton confirmed the indole moiety in the ^{1}H NMR of compound **13c**. The C3 methyl protons were seen to resonated at δ 2.61 ppm as a singlet, whereas the remaining aromatic C–H appeared at δ7.14 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H) ppm. In the ^{13}C NMR spectrum of compound **13c**, the C3 methyl carbon appeared at δ 9.9 ppm and four quaternary carbons along with newly formed ones resonated at δ 120.2, 123.4, 128.5, 135.8, 162.7 ppm as a singlet. One –CH_3 carbon and –CH_2 carbon of ester group resonated at δ 14.5 and 60.7 ppm as a quartet and triplet respectively.



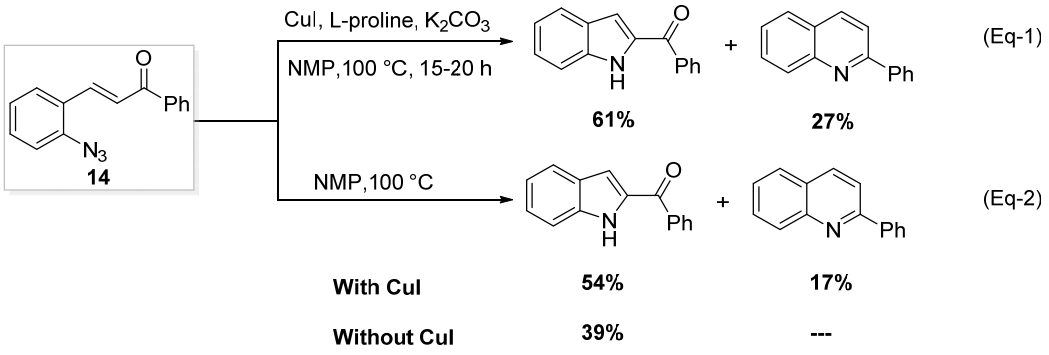
Scheme 1.20: *Cu (I)-catalyzed synthesis of indole-2-carboxylates*

To understand the course of the reaction, control experiments were conducted with the 2-azidochalcone **14** and with the bromochalcone **9u** having a methyl group in place of hydrogen atom to be abstracted. These were prepared through Aldol condensation from 2-azido benzaldehyde and acetophenone as well as from 2-bromo benzaldehyde and propiophenone respectively (Scheme 1.21). Both the compounds were confirmed by comparing the spectral data with the reported one in literature.



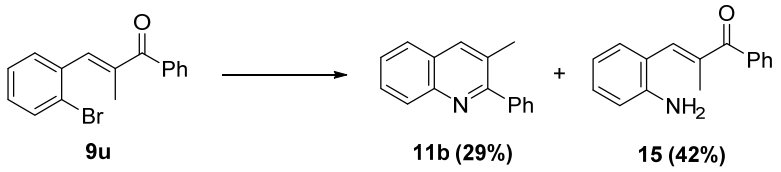
Scheme 1.21: *Synthesis of compound **14** and **9u***

Next, the *o*-azido chalcone was treated under three different conditions as shown below in Eq-1 and Eq-2. When the reaction of 2-azidochalcone **14** was performed with CuI under optimized conditions, this resulted in a mixture of indole **9a** and quinoline **11a** derivatives in 61% and 27% yields respectively (Scheme 1.22, Eq-1). A similar result was obtained when the reaction was conducted only with 20 mol% CuI and without any other additive (Scheme 1.22, Eq-2). On the other hand, when **14** was heated alone in NMP without any catalyst or additive, it gave exclusively indole in 39% yield (Scheme 1.22, Eq-2). The results revealed that the 2-aroyl indole formation proceeding through arylazide intermediate as well as Eq-2 also suggested that the CuI not only catalysed the first step of S_NAr with NaN_3 but it also had some role in C–H amination.



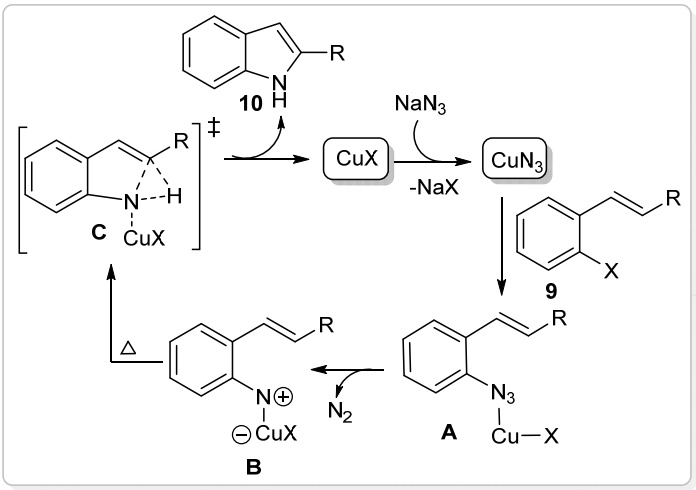
Scheme 1.22: *Reagents and conditions: CuI (20 mol %), L-proline (20 mol %), K_2CO_3 (4.0 eq.) in NMP at 100 °C, for 15 h; b) CuI (20 mol %), NMP at 100 °C for 15 h; c) NMP at 100 °C for 15 h.*

Afterwards, when we performed the reaction of *o*-bromochalcone **9u** with a C2–methyl substituent under standard conditions, this resulted in the formation of a mixture of quinoline **11b** and the aniline derivative **15** in 29% and 42% yields respectively. Both the compound has been characterised with the help of NMR spectral data analyses. In the ^{1}H NMR spectrum of the compound **11b**, the methyl group resonated at δ 2.46 ppm as singlet and the characteristic C4–H of quinoline ring resonated at δ 8.01 ppm as singlet, whilst the disappearance of the olefinic proton was observed. In the ^{13}C NMR spectrum of compound **11b**, the methyl carbon appeared at δ 20.6 ppm as quartet and most importantly the carbonyl peak disappeared and the five quaternary carbons including newly formed ones were seen to resonate at δ 127.6, 129.2, 140.8, 146.6, 160.5 ppm as singlets. In the ^{1}H NMR spectrum of compound **15**, the –NH_2 protons resonated at δ 3.62 ppm as a broad singlet and the methyl group appeared at δ 2.16 (d, J = 1.4 Hz, 3H) ppm. In the ^{13}C NMR spectrum of compound **15**, the methyl carbon resonated at δ 14.4 ppm as quartet; the carbonyl carbon resonated at δ 199.2 ppm as a singlet and, most importantly, the quaternary carbon attached to bromine carbon disappeared. These results clearly indicate that while the involvement of a nitrene-intermediate essentially leads to indole formation, however, when the copper salt is present, the yields are better, indicating the possible involvement of a copper-nitrenoid species. However, the reduction of the aryl azide seems to be a competing process at high azide concentrations.



Scheme 1.23: *Reagents and conditions: CuI (20 mol %), NaN_3 (1.5 eq.), L-proline (20 mol %), K_2CO_3 (4.0 eq.) in NMP at 100 °C, for 15 h.*

With the available information in hand and considering the previous reports,[43, 118] we propose the following tentative mechanism. Earlier, it has been shown that the [Cu] is required for the S_NAr with azide and that the decomposition of the azide takes place after the aryl azide formation.[39, 43, 46] There exist two possibilities for the subsequent C–N bond formation.[96, 119] A step-wise process involving an initial C–N bond formation and subsequent C–H bond cleavage,[92b, 96, 119] or a concerted process[46, 92b] with the simultaneous breaking of the C–H bond and the formation of the C–N bond. Considering the fact that the reacting olefin in the present case is electron deficient and that the chalcone **9u** having a 2-methyl substituent did not provide any indole derivative (the formation of which is expected due to the migration of the methyl group if it is a step-wise process),[92b] we propose a plausible mechanism which involves a concerted process operating in the present case, having Cu-participation in both the steps (Scheme 1.24). First, there is the generation of the Cu-N_3 complex; this subsequently undergoes oxidative addition with the *o*-bromo chalcone (**9a**) to give complex **A**. Next, the complex **A** provides the copper nitrenoid intermediate **B** through the elimination of N_2. This is later transformed to a highly transient copper species **C** through nitrene insertion into the C–H bond in a concerted way and finally complex **C** is converted to product **10a** with the regeneration of the catalyst. In the other mechanism, the complex **A** produces the intermediate *o*-azidochalcone by reductive elimination with the regeneration of the Cu-catalyst. Finally, arylazide undergoes cyclization to form the desired product **10a** *via* a thermolytic process.



Scheme 1.24: *Plausible catalytic cycle for Cu(I) catalyzed C–N bond formation*

Conclusion

To conclude, we have developed a simple procedure for the synthesis of 2-aroylindole derivatives comprising a one-pot CuI-catalyzed S_NAr reaction of *o*-bromochalcones with

sodium azide and subsequent intramolecular cyclization through nitrene C–H insertion. This protocol is also applicable with the 2'-bromocinnamates giving the indole-2-carboxylates. This Cu-catalyzed process involves a set of three reactions – I. S_NAr with azide and II. conversion of azide to nitrene; and III. intramolecular insertion of nitrene across the C–H bond – with a net formation of two new C–N bonds.

EXPERIMENTAL

A. General procedure for Cu-catalyzed one pot azidation-reductions to primary amine:

To a solution of halobenzene (1 equiv) in DMSO/H_2O (9:1, 10 mL for 1 mmol substrate) were added L-proline (0.2 equiv), Na_2CO_3 (0.2 equiv), NaN_3 (1.2 equiv), sodium ascorbate (0.15 equiv), and $CuSO_45H_2O$ (0.2 equiv). The mixture was stirred for 24 h at 70 °C (oil bath temperature) and then the mixture was poured into 30 mL of ice-cold water and the aqueous layer was extracted with ethyl acetate (3 X 30 mL). Combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by either crystallization or by silica gel column chromatography procured the primary aryl amine in moderate to good yields.

2-Nitroaniline (4a):

Yellow solid; R_f = 0.5 (30% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.06 (br s, 2H), 6.70 (dt, J = 1.3, 8.4 Hz, 1H), 6.80 (dd, J = 1.2, 8.4 Hz, 1H), 7.35 (dt, J = 1.5, 8.4 Hz, 1H), 8.1 (dd, J = 1.5, 8.6 Hz, 1H) ppm.

3-Nitroaniline (4b):

Yellow solid; R_f = 0.2 (20% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.98 (br s, 2H), 6.92 (ddd, J = 0.9, 2.3, 8.0 Hz, 1H), 7.25 (m, 1H), 7.46 (t, J = 2.2 Hz, 1H), 7.55 (ddd, J = 0.9, 2.2, 8.1 Hz, 1H) ppm.

4-Nitroaniline (4c):

Yellow solid; R_f = 0.2 (20% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.41(br s, 2H), 6.57–6.65(m, 2H), 8.01–8.09 (m, 2H) ppm.

4-Iodo-2-nitroaniline (4d):

Yellow solide; R_f = 0.4 (30% ethyl acetate/pet. ether); mp: 118–119 °C; IR (Nujol) ν: 3520, 3398, 3019, 1619, 1508, 1215, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.1 (s, 2H), 6.6 (d, J = 8.8 Hz, 1H), 7.6 (dd, J = 2.1, 8.8 Hz, 1H), 8.4 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 75.8 (s), 120.6 (d), 133.0 (s), 134.2 (d), 143.7 (d), 144.0 (s) ppm.

5-Fluoro-2-nitroaniline (4e):

Yellow solid; R_f = 0.4 (30% ethyl acetate/pet. ether); mp: 74–75 °C; IR (Nujol) ν: 3488, 3348, 1641, 1463, 1377, 1259, 845, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.22 (s, 2H), 6.37–6.50 (m, 2H), 8.15 (dd, J = 5.9, 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 103.6 (d, J = 26.0 Hz), 105.7 (d, J = 24.7 Hz), 129.3 (d, J = 12.1 Hz), 146.7 (s, J = 13.3 Hz), 164.3 (s),

169.4 (s) ppm; ESI–MS (*m/z*) 157.2353 [17% $(M+1)^+$], 179.1590 [96% $(M+Na)^+$], 197.2501 [10% $(M+K)^+$].

3,5-Bis(trifluoromethyl)aniline (4f):

Yellow solid; R_f = 0.2 (20% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.27 (s, 2H), 7.43 (s, 2H), 7.64 (m, 1H), ppm.

4-(Trifluoromethyl)aniline (4h):

Yellow solid; R_f = 0.2 (20% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.93 (br s, 2H), 6.66–6.70 (m, 2H), 7.36–7.40 (2H) ppm.

4-Nitro-2-(trifluoromethyl)aniline (4i):

Yellow solid; R_f = 0.3 (20% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.95 (s, 2H), 6.76 (d, J = 9.0 Hz, 1H), 8.17 (dd, J = 2.6, 9.0 Hz, 1H), 8.38 (d, J = 2.5 Hz, 1H) ppm.

4-Aminobenzonitrile (4j):

Yellow solid; R_f = 0.2 (30% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.21 (br s, 2H), 6.61–6.68 (m, 2H), 7.38–7.44 (m, 2H) ppm.

2-Nitro-4-(trifluoromethyl)aniline (4k):

Yellow solid; R_f = 0.3 (20% ethyl acetate/pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.38 (s, 2H), 6.91 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 2.1, 8.8 Hz, 1H), 8.44 (s, 1H) ppm.

7-Amino-2H-benzo[b][1,4]thiazin-3(4H)-one (4l):

R_f = 0.2 (40% ethyl acetate/pet. ether); mp: 156–157 °C; IR (Nujol) ν: 3403, 3196, 1673, 1608, 1462, 1377, 1245, 814 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.92 (s, 2H), 4.02 (s, 2H), 6.4 (dd, J = 2.5, 8.5 Hz, 1H), 6.5 (d, J = 2.4 Hz, 1H), 6.7 (d, J = 8.5 1H), 9.8 (s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 29.6 (t), 112.6 (d), 113.3 (d), 117.9 (d), 119.8 (s), 127.9 (s), 142.7 (s), 164.4 (s) ppm; ESI–MS (*m/z*) 181.1051 [100% $(M+1)^+$], 203.1070 [31% $(M+Na)^+$], 219.1430 [12% $(M+K)^+$].

4-Amino-3-nitro-2H-chromen-2-one (4o):

R_f = 0.2 (40% ethyl acetate/pet. ether); mp: 248–249 °C; IR (Nujol) ν: 3389, 3294, 1715, 1633, 1462, 1377, 1271, 1107, 769 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.2 (dd, J = 1.0, 8.3 Hz 1H), 7.3 (dd, J = 1.0, 8.2 Hz 1H), 7.6 (dt, J = 1.2, 7.2 Hz 1H), 8.3 (d, J = 8.2 Hz 1H), 9.5 (s, 2H); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 112.9 (s), 117.0 (d), 124.2 (d), 125.1 (d), 134.9

(d), 151.8 (s), 153.2 (s), 170.2 (s) ppm; ESI–MS (*m/z*) 207.1113 [6% $(M+1)^+$], 229.0860 [100% $(M+Na)^+$].

6-Azido-2H-benzo[b][1,4]oxazin-3(4H)-one (5e):

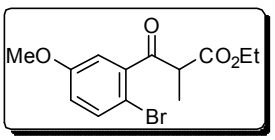
R_f = 0.5 (40% ethyl acetate/pet. ether); mp: 213–215 °C; IR (Nujol) ν: 2923, 2854, 2111, 1683, 1598, 1461, 1377, 1219, 802 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 4.6 (s, 2H),6.8 (d, J = 8.6 Hz, 1H), 6.9 (d, J = 2.2 Hz, 1H), 7.1 (dd, J = 2.2, 8.6 Hz, 1H), 8.6 (s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 67.1 (t), 114.6 (s), 118.3 (d), 118.8 (d), 126.9 (d), 142.8 (s), 165.6 (s) ppm.

B. General procedure for the preparation of compound 6j–6k:

To a magnetically stirred solution of *o*-bromo benzaldehyde (1.0 mmol) and activated Zn (3.0 mmol) and in the presence of catalytic amount of iodine in anhydrous diethylether and benzene (1:1) (5 mL), was slowly added a solution of ethyl 2-bromopropionate (1.5 mmol) in anhydrous diethylether and benzene (1:1) (5 mL) over a period of 15 min and further refluxed (80 °C) for 3 h in an argon atmosphere. The reaction mixture was cooled to 0 °C and quenched with 10% HCl (10 mL) and extracted with ethyl acetate (3-8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was used as such in the next reaction without further purification.

The crude β-hydroxy ester was dissolve in ethyl acetate and subsequently IBX (1.2 equiv.) was added slowly to a solution and then reaction mixture was reflux for 3-6 h. After complete consumption of starting material, the reaction mixture was cooled to room temperature and filtered through a celite pad. Solvent was evaporated under reduced pressure and the crude residue was purified over silica gel column (ethyl acetate and pet ether as eluent) to afford β-keto ester derivatives (**6j-6k**). Yields were not optimised.

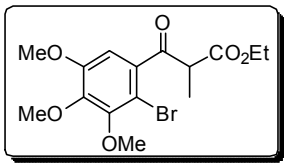
Ethyl 3-(2-bromo-5-methoxyphenyl)-2-methyl-3-oxopropanoate (6j):



Yellow liquid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, J = 7.1 Hz, 3H, major), 1.34 (t, J = 7.1 Hz, 1.6H, minor), 1.46 (d, J = 7.1 Hz, 3H, major), 1.57 (s, 1.5H, minor), 3.77 (s, 1.4H, minor), 3.78 (s, 3H, major), 4.12 (dq, J = 1.0, 7.2 Hz, 2H), 4.22–4.35 (m, 2H), 6.76–6.86 (m, 2H), 6.92 (d, J = 3.0 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.46 (dd, J = 1.0, 8.1 Hz, 0.4H, minor); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.0 (q, minor), 13.0 (q, major), 13.9 (q,

major), 14.2 (q, minor), 51.7 (d), 55.5 (q, minor), 55.6 (q, major), 60.8 (t, minor), 61.4 (t, major), 98.2 (s), 109.0 (s, major), 111.9 (s, minor), 114.5 (d, major), 114.9 (d, minor), 116.7 (d, minor), 117.8 (d, major), 133.6 (d, minor), 134.3 (d, major), 137.1 (s, minor), 141.4 (s, major), 158.7 (s, major), 158.8 (s, minor), 168.3 (s, minor), 169.9 (s, major), 173.4 (s), 199.4 (s) ppm; ESI-MS: 336.87 (100%, $[M+Na]^+$).

Ethyl 3-(2-bromo-3,4,5-trimethoxyphenyl)-2-methyl-3-oxopropanoate (6k):



Brown solid; R_f = 0.2 (10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.3 Hz, 3H, major), 1.34 (t, J = 7.3 Hz, 1.4H, minor), 1.47 (d, J = 6.9 Hz, 3H, major), 1.58 (s, 1.3H, minor), 3.83 (s, 1.5H, minor), 3.84 (s, 3H, major), 3.88 (s, 3H, major), 3.89 (s, 2.8H, minor), 3.90 (s, 3H, major), 4.06–4.16 (m, 2H, major), 4.28 (q, J = 7.1 Hz, 0.9H), 4.36 (q, J = 7.3 Hz, 1H), 6.64 (s, 0.4H, minor), 6.76 (s, 1H, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2 (q, minor), 13.2 (q, major), 14.0 (q, major), 14.2 (q, minor), 51.7 (d), 56.2 (q, minor), 56.2 (q, major), 60.9 (t, minor), 61.1 (q, 2C-major and 2C-minor), 61.3 (t, major), 98.3 (s), 106.1 (s, major), 108.1 (d, major), 108.2 (d, minor), 108.4 (s, minor), 131.7 (s, minor), 136.3 (s, major), 143.6 (s, minor), 145.0 (s, major), 151.0 (s, major), 151.2 (s, minor), 152.8 (s, major), 152.9 (s, minor), 168.2 (s, minor), 170.1 (s, major), 173.5 (s), 199.4 (s) ppm; ESI-MS: 396.71 (100%, $[M+Na]^+$).

C. General procedure for the preparation of compounds 6m–6r:

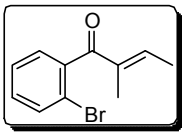
To a vigorously stirred suspension of Zn (5.0 eq.) and propargyl bromide (3.0 eq.) in THF (10 mL) was added a solution of aldehyde (1.0 eq.) in THF (10 mL) and the stirring was continued for another 30 min. The reaction mixture was cooled to 0 ºC, sat. NH_4Cl (10 mL) was added drop wise for 30 min and stirring was continued for additional 2 h. Reaction mixture was filtered through celite pad and the solvent was evaporated under vacuum. The crude mixtures diluted with water and extracted with ethyl acetate (3 X 25 mL), washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was used for next step without further purification.

Compounds 6m–6p: The crude alcohol was dissolved in ethyl acetate and subsequently treated with IBX (1.2 equiv.) slowly and then reaction mixture was refluxed for 3–6 h. After complete consumption of starting material, the reaction mixture was cooled to room temperature and filtered through a celite pad. Solvent was evaporated under reduced pressure

and the crude residue was purified over silica gel column (ethyl acetate and pet ether as eluent) to obtain the keto compounds **6m, 6n, 6o** and **6p** in 60–80% yields over two steps.

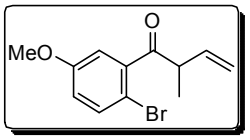
Compounds 6q–6r: Compound **6n** and **6o** have been stirred with DBU in CH_2Cl_2 for 5 min to afford the required α, β-usaturated ketones **6q** and **6r** respectively in quantitative yields.

(*E*)-1-(2-Bromophenyl)-2-methylbut-2-en-1-one (6m):



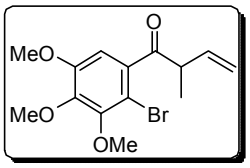
Yellow liquid; 73% yield; R_f = 0.4 (5% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (td, J = 0.9, 6.9 Hz, 3H), 1.94 (d, J = 0.9 Hz, 3H), 6.29–6.34 (m, 1H), 7.17 (dd, J = 1.4, 7.3 Hz, 1H), 7.22–7.26 (m, 1H), 7.30–7.34 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.6 (q), 15.1 (q), 119.4 (s), 126.8 (d), 128.5 (d), 130.3 (d), 132.8 (d), 138.2 (s), 141.6 (s), 145.1 (d), 197.6 (s) ppm; ESI-MS: 261.14 (75%, $[M+Na]^+$).

1-(2-Bromo-5-methoxyphenyl)-2-methylbut-3-en-1-one (6n):



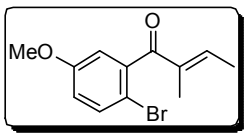
Yellow liquid; 71% yield; R_f = 0.5 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (d, J = 7.0 Hz, 3H), 3.78 (s, 3H), 3.87–4.01 (m, 1H), 5.07–5.17 (m, 2H), 5.86 (ddd, J = 7.7, 9.9, 17.6 Hz, 1H), 6.78–6.84 (m, 2H), 7.41–7.48 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.9 (q), 50.1 (d), 55.6 (q), 108.7 (s), 114.1 (d), 117.1 (d), 117.4 (t), 134.1 (d), 136.5 (d), 142.4 (s), 158.6 (s), 205.3 (s) ppm; ESI-MS: 290.95 (85%, $[M+Na]^+$).

1-(2-Bromo-3,4,5-trimethoxyphenyl)-2-methylbut-3-en-1-one (6o):



Yellow liquid; 63% yield; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (d, J = 7.0 Hz, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.94–4.12 (m, 1H), 5.08–5.17 (m, 2H), 5.86 (ddd, J = 7.8, 10.0, 17.6 Hz, 1H), 6.60 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1 (q), 50.2 (d), 56.2 (q), 61.1 (q, 2C), 105.5 (s), 107.6 (d), 117.2 (t), 136.7 (d), 137.3 (s), 144.5 (s), 151.0 (s), 152.8 (s), 205.2 (s) ppm; ESI-MS: 350.74 (90%, $[M+Na]^+$).

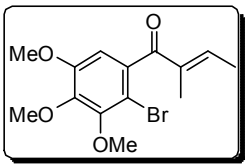
(*E*)-1-(2-Bromo-5-methoxyphenyl)-2-methylbut-2-en-1-one (6q):



Yellow liquid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (qd, J = 0.9, 7.0 Hz, 3H), 1.92–1.94 (m, 3H), 3.77 (s, 3H), 6.36 (qq, J = 1.3, 7.0 Hz, 1H), 6.71 (d, J = 3.0 Hz, 1H), 6.77–6.82 (m, 1H), 7.41 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (q), 15.2

(q), 55.5 (q), 109.6 (s), 113.8 (d), 116.4 (d), 133.5 (d), 137.9 (s), 142.2 (s), 145.4 (d), 158.4 (s), 197.6 (s) ppm; ESI-MS: 291.18 (75%, $[M+Na]^+$).

(*E*)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-2-methylbut-2-en-1-one (6r):

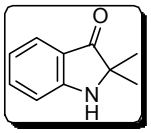


Yellow liquid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (br d, J = 6.8 Hz, 3H), 1.91 (d, J = 0.9 Hz, 3H), 3.81 (s, 3H), 3.88 (s, 6H), 6.33–6.38 (m, 1H), 6.52 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.6 (q), 15.1 (q), 56.2 (q), 61.1 (q, 2C), 106.1 (s), 107.3 (d), 137.0 (s), 137.9 (s), 143.6 (s), 144.9 (d), 150.8 (s), 152.8 (s), 197.4 (s) ppm; ESI-MS: 351.24 (100%, $[M+Na]^+$).

D. General procedure for synthesis of 2,2-disubstituted indolin-3-one:

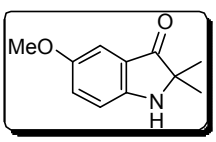
To a solution of α-bromophenyl sec-alkyl\alkenyl ketones (1.0 mmol) in DMSO, were added L-proline (0.2 mmol), K_2CO_3 (1.5 mmol), $CuSO_4$:$5H_2O$ (0.2 mmol), sodium ascorbate (0.2 mmol), and NaN_3 (1.2 mmol). The mixture was stirred for 12–18 h at 70 °C (oil bath temperature). The reaction mixture was diluted with 30 mL of water and extracted with ethyl acetate (3 X 30 mL). Combined organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified over silica gel (ethyl acetate and pet ether as eluent) to procure 2,2-disubstituted indolin-3-one.

2,2-Dimethylindolin-3-one (7a):



Brown solid; 65% yield; R_f = 0.4 (10% ethyl acetate/pet. ether); mp: 81–82 °C; IR (Nujol)v: 3363, 2924, 2855, 1681, 1619, 1464, 1375, 1142, 993, 760, 648 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 6H), 4.69 (s, 1H), 6.75–6.84 (m, 2H), 7.43 (ddd, J = 1.4, 7.1, 8.4 Hz, 1H), 7.60 (dt, J = 1.0, 7.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.4 (q, 2C), 63.9 (s), 112.5 (d), 118.7 (d), 119.5 (s), 125.0 (d), 137.2 (d), 159.6 (s), 205.2 (s) ppm; ESI-MS: 162.10 (65%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{10}H_{11}NOH^+$ 162.0913, found 162.0913.

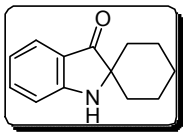
5-Methoxy-2,2-dimethylindolin-3-one (7b):



Brown solid; 66% yield; R_f = 0.2 (10% ethyl acetate/pet. ether); mp: 56–57 °C; IR (Nujol)v: 3324, 2924, 2854, 1679, 1494, 1462, 1376, 1234, 1139, 1029, 913, 793 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6H), 3.76 (s, 3H), 4.30 (s, 1H), 6.81 (dd, J = 0.5, 8.8 Hz, 1H), 7.04 (d, J = 2.6 Hz, 1H), 7.14 (dd, J = 2.7, 8.8 Hz, 1H); ^{13}C

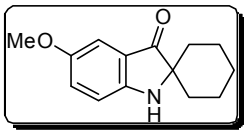
NMR (50 MHz, $CDCl_3$): δ 24.6 (q, 2C), 55.8 (q), 64.9 (s), 104.7 (d), 114.3 (d), 120.0 (s), 127.8 (d), 153.4 (s), 155.4 (s), 205.5 (s) ppm; ESI-MS (*m/z*): 190.07 (100%, $[M–H]^+$), 192.10 (25%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{11}H_{13}NO_2H^+$ 192.1019, found 192.1019**.**

Spiro[cyclohexane-1,2'-indolin]-3'-one (7c):



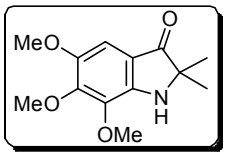
Yellow solid; 71% yield; R_f = 0.5 (10% ethyl acetate/pet. ether); mp: 133–134 °C; IR (Nujol)*v*: 3330, 2924, 2854, 1669, 1620, 1463, 1377, 1141, 971, 751, 664 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.34–1.54 (m, 5H), 1.68–1.91 (m, 5H), 5.04 (s, 1H), 6.79 (dt, *J* = 0.8, 7.8 Hz, 1H), 6.86 (br d, *J* = 8.3 Hz, 1H), 7.42 (ddd, *J* = 1.3, 7.1, 8.4 Hz, 1H), 7.60 (br d, *J* = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.5 (t, 2C), 24.8 (t), 32.8 (t, 2C), 66.9 (s), 112.6 (d), 118.8 (d), 120.4 (s), 125.0 (d), 137.0 (d), 159.9 (s), 204.9 (s) ppm; ESI-MS (*m/z*): 202.05 (100%, $[M+H]^+$), 224.01 (30%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{13}H_{15}NOH^+$ 202.1226, found 202.1226**.**

5'-Methoxyspiro[cyclohexane-1,2'-indolin]-3'-one (7d):



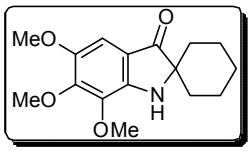
Yellow solid; 68% yield; R_f = 0.3 (15% ethyl acetate/pet. ether); mp: 63–64 °C; IR ($CHCl_3$)ν: 3404, 2925, 1714, 1601, 1489, 1460, 1377, 1269, 1217, 1118, 1029, 946, 811, 765, 721 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35–1.50 (m, 5H), 1.68–1.85 (m, 5H), 3.75 (s, 3H), 4.71 (s, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 2.6 Hz, 1H), 7.13 (dd, *J* = 2.7, 8.8, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7 (t, 2C), 24.6 (t), 31.7 (t, 2C), 55.9 (t), 90.4 (s), 104.3 (d), 114.6 (d), 120.0 (s), 128.1 (d), 154.6 (s), 166.6 (s), 204.5 (s) ppm; ESI-MS (*m/z*): 230.05 (100%, $[M–H]^+$), 232.09 (45%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{14}H_{17}NO_2H^+$ 232.1332, found 232.1331.

5,6,7-Trimethoxy-2,2-dimethylindolin-3-one (7e):



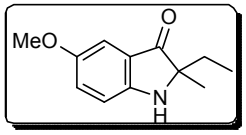
Yellow solid; 69% yield; R_f = 0.3 (20% ethyl acetate/pet. ether); mp: 74–75 °C; IR (Nujol)ν: 3360, 2854, 1704, 1617, 1459, 1376, 1297, 1133, 975, 722 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6H), 3.81 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.42 (s, 1H), 6.85 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9 (q, 2C), 56.3 (q), 60.5 (q), 61.1 (q), 64.6 (s), 100.2 (d), 114.1 (s), 139.0 (s), 148.0 (s), 149.9 (s), 150.4 (s), 204.3 (s) ppm; ESI-MS: 252.07 (75%, $[M+H]^+$), 273.96 (55%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{13}H_{17}NO_4H^+$ 252.1230, found 252.1227.

5',6',7'-Trimethoxyspiro[cyclohexane-1,2'-indolin]-3'-one (7f):



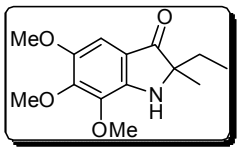
Brown solid; 74% yield; R_f = 0.4 (20% ethyl acetate/pet. ether); mp: 122–123 °C; IR (Nujol)ν: 3283, 2923, 1659, 1621, 1459, 1376, 1310, 1252, 1102, 1042, 964, 898, 783 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.37–1.50 (m, 5H), 1.72–1.89 (m, 5H), 3.80 (s, 3H), 3.96 (s, 6H), 4.76 (s, 1H), 6.84 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6 (t, 2C), 24.7 (t), 32.9 (t, 2C), 56.2 (q), 60.5 (q), 61.1 (q), 67.6 (s), 100.0 (d), 114.9 (s), 139.0 (s), 147.9 (s), 149.6 (s), 150.6 (s), 204.1 (s) ppm; ESI-MS: 292.17 (35%, $[M+H]^+$), 314.03 (65%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{16}H_{21}NO_4H^+$ 292.1543, found 292.1544.

2-Ethyl-5-methoxy-2-methylindolin-3-one (7g):



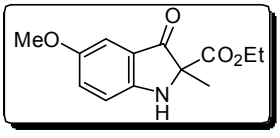
Yellow solid; 69% yield; R_f = 0.3 (15% ethyl acetate/pet. ether); mp: 76–77 °C; IR ($CHCl_3$)ν: 3341, 2967, 2927, 1670, 1496, 1455, 1262, 1228, 1140, 1029, 821, 788 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.79 (t, J = 7.5 Hz, 3H), 1.2 (s, 3H), 1.66 (dq, J = 7.3, 14.0 Hz, 1H), 1.73 (dq, J = 7.5, 14.9 Hz, 1H), 3.75 (s, 3H), 4.27 (s, 1H), 6.82 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 2.7, 8.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.1 (q), 23.1 (q), 31.0 (t), 55.7 (q), 68.3 (s), 104.4 (d), 114.1 (d), 120.9 (s), 127.8 (d), 153.2 (s), 156.2 (s), 205.6 (s) ppm; ESI-MS: 203.97 (100%, $[M–H]^+$), 205.97 (25%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{12}H_{15}NO_2H^+$ 206.1176, found 206.1174.

2-Ethyl-5,6,7-trimethoxy-2-methylindolin-3-one (7h):



Yellow liquid; 72% yield; R_f = 0.3 (20% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3344, 2967, 1676, 1618, 1501, 1469, 1370, 1301, 1134, 1091, 1002, 959, 792 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.78 (t, J = 7.4 Hz, 3H), 1.27 (s, 3H), 1.66 (dq, J = 7.3, 14.1 Hz, 1H), 1.73 (dq, J = 7.5, 14.9 Hz, 1H), 3.79 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H) 4.38 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.1 (q), 23.2 (q), 31.0 (t), 56.2 (q), 60.5 (q), 61.1 (q), 67.9 (s), 100.0 (d), 115.1 (s), 138.8 (s), 147.8 (s), 149.8 (s), 151.0 (s), 204.3 (s) ppm; ESI-MS: 266.01 (100%, $[M+H]^+$), 288.03 (35%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{14}H_{19}NO_4H^+$ 266.1387, found 266.1385.

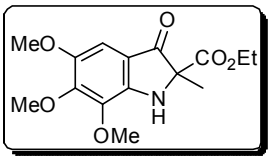
Ethyl 5-methoxy-2-methyl-3-oxoindoline-2-carboxylate (7i):



Yellow liquid; 51% yield; R_f = 0.3 (25% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3385,2700, 2400, 1703, 1495, 1219, 1108, 933, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3H), 1.63 (s, 3H), 3.76 (s, 3H), 4.14–4.28 (m, 2H), 4.95 (s, 1H), 6.93 (br d, J = 8.9 Hz, 1H), 7.03 (d, J = 2.7 Hz, 1H), 7.17 (dd, J = 2.8,

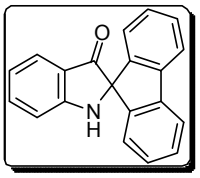
8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.1 (q), 55.8 (q), 62.6 (t), 71.5 (s), 104.9 (d), 115.1 (d), 120.2 (s), 128.1 (d), 154.4 (s), 156.9 (s), 169.4 (s), 196.8 (s) ppm; ESI-MS (*m/z*): 271.97 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{13}H_{15}NO_4H^+$ 250.1074, found 250.1073.

Ethyl 5,6,7-trimethoxy-2-methyl-3-oxoindoline-2-carboxylate (7j):



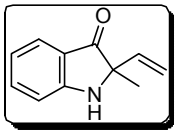
Yellow liquid; 61% yield; R_f = 0.2 (25% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3356, 2932, 1741, 1697, 1499, 1469, 1369, 1297, 1091, 931, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (br t, *J* = 7.1 Hz, 3H), 1.63 (s, 3H), 3.81 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 4.14–4.26 (m, 2H), 5.02 (s, 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 21.9 (q), 56.3 (q), 60.7 (q), 61.2 (q), 62.5 (t), 71.1 (s), 100.4 (d), 114.2 (s), 139.4 (s), 148.9 (s), 150.3 (s), 151.9 (s), 169.4 (s), 195.6 (s) ppm; ESI-MS: 332.03 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{15}H_{19}NO_6H^+$ 310.1285, found 310.1285.

Spiro[fluorene-9,2'-indolin]-3'-one (7k):



Yellow solid; 59% yield; R_f = 0.3 (20% ethyl acetate/pet. ether); mp: 211–212 °C; IR (Nujol)*v*: 3386, 2924, 1699, 1614, 1463, 1377, 1152, 1028, 748, 736, 649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (s, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 7.15–7.24 (m, 4H), 7.38 (dt, *J* = 1.2, 7.5 Hz, 2H), 7.54 (br t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 77.7 (s), 112.6 (d), 119.4 (d), 120.6 (d, 2C), 120.7 (s), 122.9 (d, 2C), 125.9 (d), 128.0 (d, 2C), 129.3 (d, 2C), 137.5 (d), 141.8 (s, 2C), 143.5 (s, 2C), 161.9 (s), 199.2 (s) ppm; ESI-MS (*m/z*): 283.97 (100%, $[M+H]^+$), 305.94 (90%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{20}H_{13}NOH^+$ 284.1070, found 284.1071.

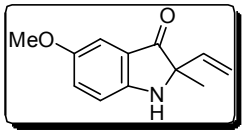
2-Methyl-2-vinylindolin-3-one (7l):



Yellow liquid; 67% yield; R_f = 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3346, 2973, 2926, 1682, 1620, 1470, 1324, 1133, 1099, 969, 752, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 3H), 4.72 (s, 1H), 5.14 (dd, *J* = 0.8, 10.4 Hz, 1H), 5.34 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.88 (dd, *J* = 10.4, 17.2 Hz, 1H), 6.77–6.89 (m, 2H), 7.45 (ddd, *J* = 1.3, 7.1, 8.4 Hz, 1H) 7.58 (br d, *J* = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8 (q), 68.3 (s), 112.4 (d), 114.5 (t), 119.0 (d), 119.3 (s), 125.3 (d), 137.3 (d), 137.5 (d),

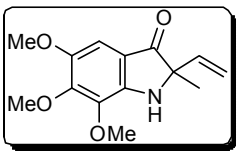
159.8 (s), 202.0 (s) ppm; ESI-MS: 174.01 (40%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{11}H_{11}NOH^+$ 174.0913, found 174.0913.

5-Methoxy-2-methyl-2-vinylindolin-3-one (7m):



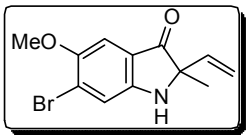
Yellow liquid; 71% yield; R_f = 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3346, 2927, 1681, 1495, 1440, 1270, 1227, 1125, 1028, 924, 821, 783 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 3H), 3.75 (s, 3H), 4.41 (s, 1H), 5.14 (dd, *J* = 0.8, 10.3 Hz, 1H), 5.34 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.87 (dd, *J* = 10.4, 17.24 Hz, 1H), 6.85 (dd, *J* = 0.4, 8.8 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 7.14 (dd, *J* = 2.7, 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8 (q), 55.8 (q), 69.3 (s), 105.0 (d), 114.2 (d), 114.5 (t), 119.7 (s), 127.9 (d), 137.7 (d), 153.6 (s), 155.6 (s), 202.3 (s) ppm; ESI-MS: 204.02 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{12}H_{13}NO_2H^+$ 204.1019, found 204.1019.

5,6,7-Trimethoxy-2-methyl-2-vinylindolin-3-one (7n):



Yellow liquid; 74% yield; R_f = 0.3 (25% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3344, 2932, 1684, 1618, 1500, 1469, 1304, 1123, 1090, 926, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.53 (s, 1H), 5.14 (br d, *J* = 10.5 Hz, 1H), 5.34 (br d, *J* = 17.2 Hz, 1H), 5.87 (dd, *J* = 10.5, 17.2 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8 (q), 56.3 (q), 60.6 (q), 61.2 (q), 68.9 (s), 100.5 (d), 113.8 (s), 114.3 (t), 137.8 (d), 138.9 (s), 148.1 (s), 150.0 (s), 150.6 (s), 201.1 (s) ppm; ESI-MS (*m/z*): 263.88 (100%, $[M+H]^+$), 285.99 (30%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{14}H_{17}NO_4H^+$ 264.1230, found 264.1230**.**

6-Bromo-5-methoxy-2-methyl-2-vinylindolin-3-one (7o):

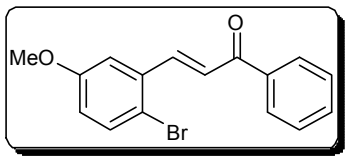


Yellow solid; 72% yield; R_f = 0.3 (15% ethyl acetate/pet. ether); mp: 154–155 °C; IR ($CHCl_3$)*v*: 3284, 2923, 1740, 1671, 1577, 1478, 1275, 1154, 1040, 848, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 3H), 3.84 (s, 3H), 4.43 (s, 1H), 5.15 (br d, *J* = 10.4 Hz, 1H), 5.34 (br d, *J* = 17.1 Hz, 1H), 5.85 (dd, *J* = 10.4, 17.1 Hz, 1H), 7.05 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.8 (q), 56.7 (q), 69.2 (s), 105.7 (d), 114.7 (t), 117.8 (d), 118.9 (s), 124.2 (s), 137.3 (d), 150.0 (s), 154.9 (s), 201.4 (s) ppm; HRMS (ESI+): calcd. for $C_{12}H_{12}BrNO_2H^+$ 282.0124, found 282.0129**.**

E. General procedure for the preparation of compound 9a–9t:

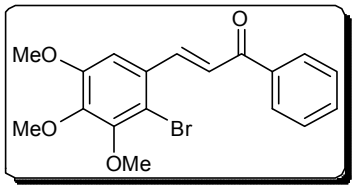
Compounds **9a–9t** were prepared according to literature procedure.[92b] Aqueous NaOH (2.5 N, 1 mL) was added drop-wise to a mixture of 2-bromobenzaldehyde (2.7 mmol), acetophenone (2.7 mmol) in ethanol (4 mL) at ambient temperature. After stirring overnight, the reaction mixture was poured into brine solution (20 mL) and extracted with CH_2Cl_2 (20 mL). The extract was washed with H_2O (2 × 30 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude was purified over silica gel (ethyl acetate and pet ether as eluent) afford the products **9a–9t**. Yields were not optimized.

(*E*)-3-(2-Bromo-5-methoxyphenyl)-1-phenylprop-2-en-1-one (9b):



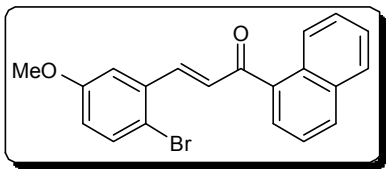
Yellow solid; R_f = 0.4 (5% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.83 (dd, J = 3.0, 8.8 Hz, 1H), 7.23 (d, J = 3.0 Hz, 1H), 7.37 (d, J = 15.7 Hz, 1H), 7.46–7.60 (m, 4H), 7.95–8.02 (m, 2H), 8.06 (d, J = 15.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.6 (q), 113.0 (d), 116.5 (s), 117.4 (d), 125.2 (d), 128.6 (d, 4C), 132.9 (d), 134.1 (d), 135.7 (s), 137.8 (s), 143.2 (d), 159.0 (s), 190.5 (s) ppm; ESI-MS: 316.81 (100%, $[M+H]^+$).

(*E*)-3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-phenylprop-2-en-1-one (9c):



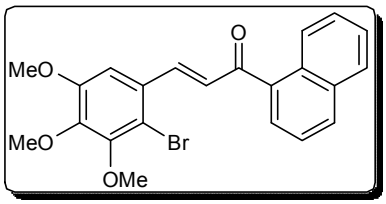
Yellow solid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 7.04 (s, 1H), 7.28 (d, J = 15.6 Hz, 1H), 7.48–7.52 (m, 2H), 7.56–7.61 (m, 1H), 7.97–8.00 (m, 2H), 8.09 (d, J = 15.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.3 (q), 61.0 (q), 61.2 (q), 106.3 (d), 113.5 (s), 124.5 (d), 128.6 (d, 4C), 130.4 (s), 132.8 (d), 138.0 (s), 143.6 (d), 145.1 (s), 151.2 (s), 152.9 (s), 190.8 (s) ppm; ESI-MS: 398.54 (100%, $[M+Na]^+$).

(*E*)-3-(2-Bromo-5-methoxyphenyl)-1-(naphthalen-1-yl)prop-2-en-1-one (9e):



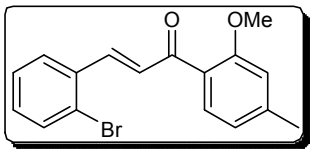
Brown solid; R_f = 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.82 (dd, J = 2.9, 8.7 Hz, 1H), 7.19 (d, J = 15.9 Hz, 1H), 7.21 (d, J = 2.9 Hz, 1H), 7.46–7.61 (m, 4H), 7.77–7.83 (m, 1H), 7.92 (d, J = 15.9 Hz, 1H), 7.90–8.03 (m ,2H), 8.34–8.39 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.6 (q), 112.7 (d), 116.5 (s), 117.8 (d), 124.4 (d), 125.6 (d), 126.5 (d), 127.5 (d), 127.6 (d), 128.4 (d), 129.6 (d), 130.5 (s), 131.9 (d), 133.8 (s), 134.0 (d), 135.3 (s), 136.4 (s), 144.2 (d), 159.0 (s), 195.2 (s) ppm; ESI-MS: 390.65 (Br-81) (65%, $[M+Na]^+$).

(*E*)-3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(naphthalen-1-yl)prop-2-en-1-one (9f):



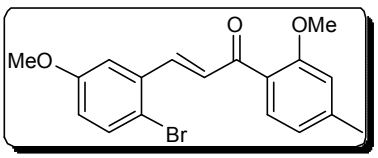
Yellow Thick liquid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 7.03 (s, 1H), 7.10 (d, *J* = 16.0 Hz, 1H), 7.52–7.57 (m, 3H), 7.79 (dd, *J* = 0.9, 6.9 Hz, 1H), 7.90–7.92 (m, 1H), 7.95 (d, *J* = 16.0 Hz, 1H), 8.0 (br d, *J* = 8.2 Hz, 1H), 8.31–8.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.2 (q), 61.0 (q), 61.2 (q), 106.2 (d), 113.6 (s), 124.4 (d), 125.6 (d), 126.5 (d), 127.5 (d, 2C), 128.4 (d), 129.0 (d), 130.0 (s, 2C), 130.5 (s), 131.8 (d), 133.9 (s), 136.6 (s), 144.7 (d), 145.2 (s), 152.9 (s, 2C), 195.6 (s) ppm; ESI-MS: 449.09 (100%, $[M+Na]^+$).

(*E*)-3-(2-Bromophenyl)-1-(2-methoxy-4-methylphenyl)prop-2-en-1-one (9g):



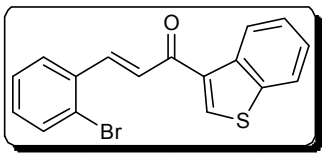
Off white solid; R_f = 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.88 (s, 3H), 6.79 (s, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 7.16–7.24 (m, 1H), 7.28–7.35 (m, 1H), 7.34 (d, *J* = 15.8 Hz, 1H), 7.57–7.69 (m, 3H), 7.97 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (q), 55.7 (q), 112.4 (d), 121.6 (d), 125.8 (s), 126.2 (s), 127.6 (d), 127.8 (d), 129.8 (d), 130.8 (d), 130.9 (d), 133.4 (d), 135.4 (s), 140.9 (d), 144.3 (s), 158.5 (s), 191.8 (s) ppm; ESI-MS: 353.02 (55%, $[M+Na]^+$).

(*E*)-3-(2-Bromo-5-methoxyphenyl)-1-(2-methoxy-4-methylphenyl)prop-2-en-1-one (9h):



Brown solid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 2.81 (s, 3H), 2.88 (s, 3H), 6.78–6.81 (m, 2H), 6.85 (d, *J* = 7.78 Hz, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 7.30 (d, *J* = 15.6 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (q), 55.5 (q), 55.7 (q), 112.4 (d), 113.0 (d), 116.4 (s), 117.1 (d), 121.6 (d), 126.2 (s), 130.0 (d), 130.8 (d), 133.9 (d), 136.1 (s), 141.1 (d), 144.3 (s), 158.4 (s), 158.9 (s), 192.0 (s) ppm; ESI-MS: 383.16 (65%, $[M+Na]^+$).

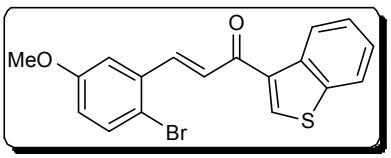
(*E*)-1-(Benzo[b]thiophen-3-yl)-3-(2-bromophenyl)prop-2-en-1-one (9i):



Yellow solid; R_f = 0.4 (5% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (dt, *J* = 1.8, 7.3 Hz, 1H), 7.36 (t, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.45 (dt, *J* = 1.4, 8.2 Hz, 1H), 7.52 (dt, *J* = 0.9, 8.2 Hz, 1H), 7.64 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.73 (dd, *J* = 1.4, 7.8 Hz,

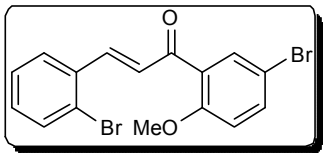
1H), 7.89 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 15.6 Hz, 1H), 8.37 (s, 1H), 8.79 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 116.5 (s), 122.3 (d), 125.7 (d, 2C), 125.8 (d), 126.6 (d), 127.7 (d), 127.8 (d), 131.2 (d), 133.5 (d), 135.0 (s), 135.9 (s), 136.7 (d), 137.0 (s), 139.9 (s), 142.1 (d), 184.9 (s) ppm; ESI-MS: 364.68 (100%, $[M+Na]^+$).

(*E*)-1-(Benzo[b]thiophen-3-yl)-3-(2-bromo-5-methoxyphenyl)prop-2-en-1-one (9j):



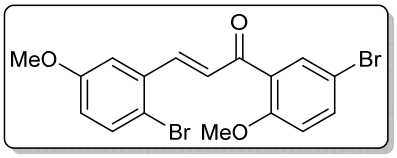
Yellow solid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.83 (dd, *J* = 2.8, 8.7 Hz, 1H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.34 (d, *J* = 15.6 Hz, 1H), 7.42–7.46 (m, 1H), 7.50–7.54 (m, 2H), 7.89 (dt, *J* = 0.9, 8.2 Hz, 1H), 8.08 (d, *J* = 15.6 Hz, 1H), 8.37 (s, 1H), 8.77 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.6 (q), 113.0 (d), 116.4 (s), 117.3 (d), 122.3 (d), 125.7 (d, 2C), 125.8 (d), 126.7 (d), 134.1 (d), 135.7 (s), 135.9 (s), 136.7 (d), 137.0 (s), 139.9 (s), 142.1 (d), 159.0 (s), 184.9 (s) ppm; ESI-MS: 395.21 (100%, $[M+Na]^+$).

(*E*)-1-(5-Bromo-2-methoxyphenyl)-3-(2-bromophenyl)prop-2-en-1-one (9k):



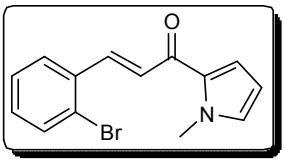
Yellow solid; R_f = 0.6 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.80 (d, *J* = 8.7 Hz, 1H), 7.17–7.37 (m, 2H), 7.21 (d, *J* = 15.7 Hz, 1H), 7.52–7.72 (m, 4H), 7.94 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.0 (q), 113.1 (s), 113.5 (d), 125.8 (s), 127.6 (d), 127.8 (d), 128.8 (d), 130.4 (s), 131.2 (d), 132.9 (d), 133.4 (d), 134.8 (s), 135.4 (d), 142.2 (d), 157.1 (s), 190.9 (s) ppm; ESI-MS: 418.77 (Br-81) (100%, $[M+Na]^+$).

(*E*)-1-(5-Bromo-2-methoxyphenyl)-3-(2-bromo-5-methoxyphenyl)prop-2-en-1-one (9l):



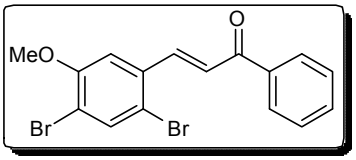
Off white solid; R_f = 0.5 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.87 (s, 3H), 6.82 (dd, *J* = 3.0, 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 2.9 Hz, 1H), 7.17 (d, *J* = 15.8 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.87 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.5 (q), 56.0 (q), 113.0 (d), 113.2 (s), 113.5 (d), 116.5 (s), 117.4 (d), 129.0 (d), 130.4 (s), 132.9 (d), 134.0 (d), 135.4 (d), 135.6 (s), 142.5 (d), 157.1 (s), 158.9 (s), 191.2 (s) ppm; ESI-MS: 447.19 (100%, $[M+Na]^+$).

(*E*)-3-(2-Bromophenyl)-1-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (9r):



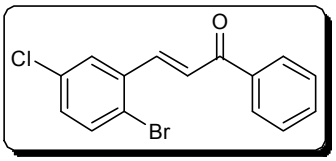
Yellow solid; R_f = 0.5 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.03 (s, 3H), 6.18 (dd, J = 2.4, 4.4 Hz, 1H), 6.89 (t, J = 1.9 Hz, 1H), 7.10 (dd, J = 1.6, 4.2 Hz, 1H), 7.20 (dt, J = 1.6, 7.6 Hz, 1H), 7.27–7.37 (m, 2H), 7.62 (dd, J = 1.3, 7.8 Hz, 1H), 7.69 (dd, J = 1.5, 7.7 Hz, 1H), 8.07 (d, J = 15.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.8 (q), 105.2 (s), 108.4 (d), 119.6 (d), 125.6 (s), 126.5 (d), 127.6 (d), 127.7 (d), 130.7 (d), 132.0 (d), 133.4 (d), 135.4 (s), 139.9 (d), 179.3 (s) ppm; ESI-MS: 311.94 (100%, $[M+Na]^+$).

(*E*)-3-(2,4-Dibromo-5-methoxyphenyl)-1-phenylprop-2-en-1-one (9s):



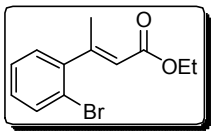
Yellow solid; R_f = 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.15 (s, 1H), 7.37 (d, J = 15.7 Hz, 1H), 7.46–7.64 (m, 3H), 7.78 (s, 1H), 7.94–8.02 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.5 (q), 110.0 (d), 114.8 (s), 116.6 (s), 125.4 (d), 128.6 (d, 4C), 133.0 (d), 134.9 (s), 137.0 (d), 137.7 (s), 142.6 (d), 155.5 (s), 190.4 (s) ppm; ESI-MS: 417.18 (100%, $[M+Na]^+$).

(*E*)-3-(2-Bromo-5-chlorophenyl)-1-phenylprop-2-en-1-one (9t):



Yellow solid; R_f = 0.6 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20 (dd, J = 2.4, 8.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.40–7.63 (m, 4H), 7.68 (d, J = 2.4 Hz, 1H), 7.94–8.07 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 123.5 (s), 125.8 (d), 127.6 (d), 128.6 (d, 2C), 128.7 (d, 2C), 131.0 (d), 133.1 (d), 133.8 (s), 134.5 (d), 136.5 (s), 137.5 (s), 141.6 (d), 189.7 (s) ppm; ESI-MS: 342.84 (100%, $[M+Na]^+$).

Ethyl (*E*)-3-(2-bromophenyl)but-2-enoate (12c):



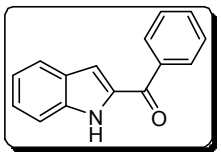
Yellow liquid; R_f = 0.5 (15% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (t, J = 7.2 Hz, 0.9H, minor), 1.31 (t, J = 7.2 Hz, 3H, major), 2.15 (d, J = 1.4 Hz, 0.82H, minor), 2.48 (br d, J = 1.4 Hz, 3H, major), 3.97 (q, J = 7.2 Hz, 0.6H, minor), 4.22 (q, J = 7.2 Hz, 2H, major), 5.80 (m, 1H, major), 5.99 (m, 0.24H, minor), 7.04–7.20 (m, 3H), 7.26–7.30 (m, 1H), 7.55–7.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8 (q, minor), 14.2 (q, major), 20.3 (q, major), 26.0 (q, minor), 59.7 (t, minor), 59.9 (t, major), 119.7 (d, minor), 120.5 (d, major), 120.6 (s), 127.1 (d, minor), 127.3 (d, major), 127.7 (d, minor), 128.49 (d, minor), 128.8 (d, major), 129.1 (d, major), 132.3 (d, minor), 133.0 (d, major), 142.4 (s, minor), 144.7 (s, major), 156.6 (s,

minor), 156.9 (s, major), 165.0 (s, minor), 166.3 (s, major) ppm; ESI-MS: 291.23 (100%, $[M+Na]^+$).

F. General procedure for Cu(I)-catalyzed synthesis of 2-aroyl indole:

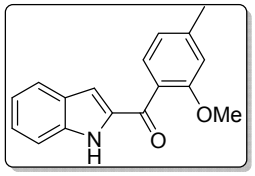
To a solution of *o*-bromochalcone (1.0 mmol) in NMP (1 mL), were added L-proline (0.2 mmol), K_2CO_3 (4.0 mmol), CuI (0.2 mmol), and NaN_3 (1.2 mmol). The mixture was stirred at 110 °C. After 15 h the reaction mixture was cooled and diluted with 30 mL of water and extracted with ethyl acetate (3 x 30 mL). Combined organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified over silica gel (ethyl acetate and pet ether as eluent) to obtain the 2-aroyl indole.

(1H-Indol-2-yl)(phenyl)methanone (10a):[93]



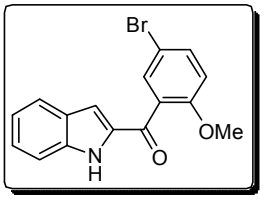
Light yellow solid; 76% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (s, 1H), 7.16 (dt, J = 1.0, 7.0 Hz, 1H), 7.37 (ddd, J = 1.0, 6.8, 8.4 Hz, 1H), 7.45–7.62 (m, 4H), 7.71 (d, J = 8.0 Hz, 1H), 7.96–8.01 (m, 2H), 9.27 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.2 (d), 112.9 (d), 121.0 (d), 123.2 (d), 126.5 (d), 127.7 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.4 (d), 134.3 (s), 137.5 (s), 138.0 (s), 187.2 (s) ppm.

(1H-Indol-2-yl)(2-methoxy-4-methylphenyl) methanone (10b):



Brown solid; 59% Yield; R_f 0.2 (10% ethyl acetate/pet. ether); mp: 112–113 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.82 (s, 3H), 6.84 (s, 1H), 6.86 (d, J = 6.8 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 7.12 (ddd, J = 0.9, 6.9, 7.9 Hz, 1H), 7.29–7.37 (m, 1H), 7.42–7.48 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (q), 55.7 (q), 112.2 (d), 112.5 (d), 112.8 (d), 120.7 (d), 120.8 (d), 123.1 (d), 125.4 (s), 126.3 (d), 127.6 (s), 130.0 (d), 135.9 (s), 137.7 (s), 142.8 (s), 157.6 (s), 187.1 (s) ppm; HRMS (ESI+): calcd. for $C_{17}H_{15}O_2NNa$ = 288.0995, found 288.0995**.**

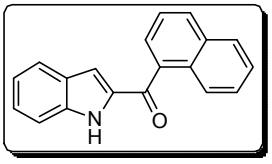
(5-Bromo-2-methoxyphenyl)(1H-indol-2-yl)methanone (10c):[120]



Brown solid; 67% Yield; R_f 0.5 (15% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 6.91 (m, 2H), 7.14 (ddd, J = 1.1, 6.8, 8.0 Hz, 1H), 7.36 (ddd, J = 1.0, 6.8, 7.9 Hz, 1H), 7.44–7.48 (m, 1H), 7.55–7.60 (m, 2H), 7.66 (br d, J = 8.2 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR (125 MHz,

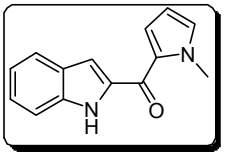
$CDCl_3$): δ 56.0 (q), 112.7 (2C, s and d), 113.4 (d), 113.6 (d), 121.1 (d), 123.3 (d), 126.8 (d), 127.5 (s), 129.8 (s), 132.0 (d), 134.5 (d), 135.2 (s), 137.9 (s), 156.5 (s), 185.4 (s) ppm.

(1H-Indol-2-yl)(naphthalen-1-yl)methanone (10d):



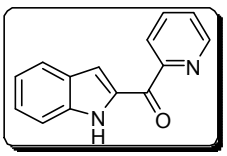
Yellow solid; 77% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); mp: 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, J = 1.0 Hz, 1H), 7.15 (t, J = 6.0 Hz, 1H), 7.38 (ddd, J = 0.8, 7.0, 8.0 Hz, 1H), 7.50–7.59 (m, 4H), 7.65 (d, J = 8.0 Hz, 1H), 7.88–7.95 (m, 2H), 8.04 (d, J = 8.3 Hz, 1H), 8.28–8.30 (m, 1H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.3 (d), 113.7 (d), 121.1 (d), 123.3 (d), 124.3 (d), 125.5 (d), 126.5 (d), 126.8 (d), 127.3 (d), 127.6 (s), 127.8 (d), 128.4 (d), 130.8 (s), 131.5 (d), 133.8 (s), 135.6 (s), 136.0 (s), 137.9 (s), 188.8 (s) ppm; HRMS (ESI+): calcd. for $C_{19}H_{13}ONNa$ = 294.0889, found 294.0890.

(1H-Indol-2-yl)(1-methyl-1H-pyrrol-2-yl) methanone (10e):



Brown solid; 46% Yield; R_f 0.2 (10% ethyl acetate/pet. ether); mp: 100–101 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.02 (s, 3H), 6.23 (dd, J = 2.7, 3.8 Hz, 1H), 6.94 (br s, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.20 (dd, J = 1.4, 3.9 Hz, 1H), 7.23 (s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.0 (q), 108.5 (d), 109.7 (d), 111.9 (d), 120.7 (d, 2C), 122.9 (d), 125.5 (d), 127.8 (s), 130.3 (s), 131.2 (d), 135.6 (s), 136.9 (s), 176.3 (s) ppm; HRMS (ESI+): calcd. for $C_{14}H_{12}ON_2H^+$ = 225.1022, found 225.1021**.**

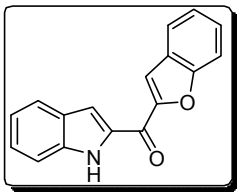
(1H-Indol-2-yl)(pyridin-2-yl)methanone (10f):



Yellow solid; 57% Yield; R_f 0.2 (10% ethyl acetate/pet. ether); mp: 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (t, J = 7.5 Hz, 1H), 7.36 (ddd, J = 0.5, 6.9, 7.9 Hz, 1H), 7.48–7.55 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.93 (dt, J = 1.5, 7.8 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.81 (d, J = 4.3 Hz, 1H), 10.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.4 (d), 113.3 (d), 120.8 (d), 123.3 (d), 124.2 (d), 126.3 (d), 126.7 (d), 127.4 (s), 135.0 (s), 137.4 (d), 137.7 (s), 148.5 (d), 155.0 (s), 181.2 (s) ppm; HRMS (ESI+): calcd. for $C_{14}H_{10}ON_2Na$ = 245.0685, found 245.0688**.**

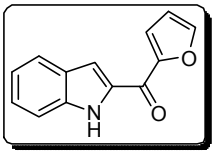
Benzofuran-2-yl(1H-indol-2-yl)methanone (10g):[121]

Yellow solid; 78% Yield; R_f 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.2



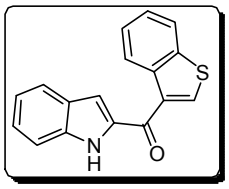
Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.88 (br s, 1H), 9.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 112.1 (d), 112.3 (d), 112.4 (d), 114.3 (d), 121.2 (d), 123.2 (d), 123.6 (d), 124.0 (d), 126.9 (d), 127.1 (s), 128.0 (s), 128.2 (d), 133.7 (s), 137.5 (s), 152.9 (s), 155.9 (s), 174.0 (s) ppm.

Furan-2-yl(1H-indol-2-yl)methanone (10h):[93]



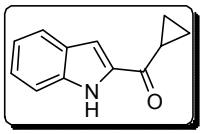
Brown solid; 76% Yield; R_f 0.5 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.63–6.64 (m, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.45–7.47 (m, 2H), 7.72 (br d, J = 8.6 Hz, 2H), 7.76 (d, J = 1.0 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.5 (d), 112.1 (d), 112.5 (d), 118.6 (d), 121.0 (d), 123.3 (d), 126.5 (d), 128.0 (s), 133.4 (s), 137.2 (s), 146.5 (d), 152.7 (s), 172.6 (s) ppm.

Benzo[b]thiophen-3-yl(1H-indol-2-yl)methanone (10i):



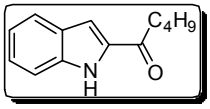
Light brown solid; 69% Yield; R_f 0.4 (10% ethyl acetate/pet. ether); mp: 187–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (t, J = 6.7 Hz, 1H), 7.25 (s, 1H), 7.38 (t, J = 6.6 Hz, 1H), 7.45–7.51 (m, 3H), 7.74 (d, J = 7.3, 1H), 7.93 (d, J = 7.3 Hz, 1H), 8.36 (s, 1H), 8.50 (d, J = 7.3 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.6 (d), 112.2 (d), 121.1 (d), 122.4 (d), 123.2 (d), 124.7 (d), 125.5 (d), 125.6 (d), 126.5 (d), 127.7 (s), 134.7 (s), 135.5 (2C, s and d), 137.2 (s), 137.6 (s), 140.0 (s), 181.2 (s) ppm; HRMS (ESI+): calcd. for $C_{17}H_{11}ONSH^+$ = 278.0634, found 278.0634.

Cyclopropyl (1H-indol-2-yl) methanone (10j):



Brown solid; 46% Yield; R_f 0.5 (10% ethyl acetate/pet. ether); mp: 143–145 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02–1.11 (m, 2H), 1.25–1.32 (m, 2H), 2.59–2.71 (m, 1H), 7.11–7.19 (m, 1H), 7.30–7.45 (m, 3H), 7.73 (dd, J = 0.5, 8.1 Hz, 1H), 9.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.4 (t, 2C), 17.5 (d), 109.1 (d), 112.2 (d), 120.8 (d), 122.9 (d), 126.1 (d), 127.6 (s), 135.8 (s), 137.3 (s), 192.9 (s) ppm; HRMS (ESI+): calcd. for $C_{12}H_{11}ONH^+$ = 186.0913, found 186.0916.

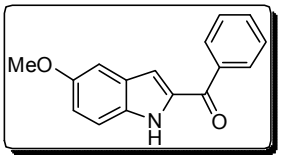
1-(1H-Indol-2-yl)pentan-1-one (10k):[122]



Brown solid; 47% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J = 7.4 Hz, 3H), 1.39–1.46 (m, 2H), 1.73–1.79 (m, 2H), 2.94 (t,

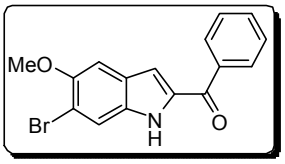
J = 7.6 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.20 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 9.09 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (q), 22.5 (t), 27.3 (t), 38.1 (t), 109.0 (d), 112.1 (d), 120.9 (d), 123.0 (d), 126.2 (d), 127.6 (s), 135.2 (s), 137.2 (s), 193.6 (s) ppm.

(5-Methoxy-1H-indol-2-yl)(phenyl)methanone (10l):[83]



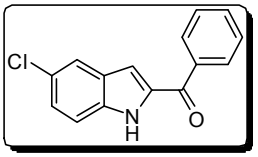
Yellow solid; 74% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.84 (s, 3H), 7.02–7.08 (m, 3H), 7.37–7.41 (m, 1H), 7.49–7.63 (m, 3H), 7.69–8.01 (m, 2H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6 (q), 102.6 (d), 112.5 (d), 113.3 (d), 118.4 (d), 127.9 (s), 128.4 (d, 2C), 129.2 (d, 2C), 132.2 (d), 133.3 (s), 134.7 (s), 138.1 (s), 154.7 (s), 187.1 (s) ppm.

(6-Bromo-5-methoxy-1H-indol-2-yl)(phenyl)methanone (10m):



Yellow solid; 59% Yield; R_f 0.2 (10% ethyl acetate/pet. ether); mp: 177–178 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.06 (s, 1H), 7.11 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.71 (s, 1H), 7.96 (s, 1H), 7.98 (s, 1H), 9.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.6 (q), 103.3 (d), 112.1 (d), 113.3 (s), 116.8 (d), 127.3 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.5 (d), 133.0 (s), 135.1 (s), 137.8 (s), 151.0 (s), 186.9 (s) ppm; HRMS (ESI+): calcd. for $C_{16}H_{12}O_2NBrH^+$ = 330.0124, found 330.0132.

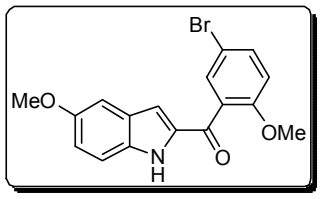
(5-Chloro-1H-indol-2-yl)(phenyl)methanone (10n):



Light yellow solid; 74% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); mp: 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08–7.09 (m, 1H), 7.32 (dd, *J* = 1.9, 8.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.52–7.56 (m, 2H), 7.61–7.65 (m, 1H), 7.68 (br s, 1H), 7.97–7.99 (m, 2H), 9.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.7 (d), 113.3 (d), 122.3 (d), 126.6 (s), 127.0 (d), 128.6 (d, 2C and s, 1C), 129.2 (d, 2C), 132.6 (d), 135.3 (s), 135.7 (s), 137.6 (s), 187.0 (s) ppm; HRMS (ESI+): calcd. for $C_{15}H_{10}ONClH^+$ = 256.0524, found 256.0522.

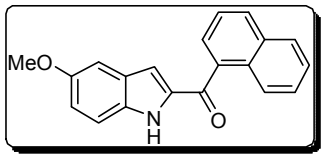
(5-Bromo-2-methoxyphenyl)(5-methoxy-1H-indol-2-yl)methanone (10o):

Yellow solid; 68% Yield; R_f 0.4 (15% ethyl acetate/pet. ether); mp: 168–170 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.82 (s, 3H), 6.84 (s, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.03–



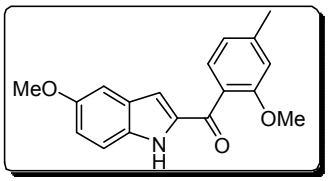
7.05 (m, 2H), 7.35 (d, J = 8.8 Hz, 1H), 7.56–7.59 (m, 2H), 9.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.6 (q), 56.1 (q), 102.8 (d), 112.3 (s), 113.0 (d), 113.2 (d), 113.4 (d), 118.9 (d), 127.9 (s), 129.9 (s), 132.1 (d), 133.4 (s), 134.4 (d), 135.6 (s), 154.8 (s), 156.5 (s), 185.0 (s) ppm; HRMS (ESI+): calcd. for $C_{17}H_{14}O_3NBrH^+$ = 360.0230, found 360.0234.

(5-Methoxy-1H-indol-2-yl)(naphthalen-1-yl)methanone (10p):[83]



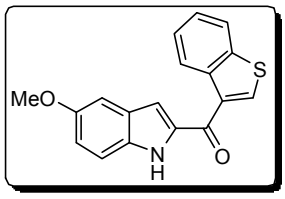
Brown solid; 73% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.87 (s, 1H), 7.01 (s, 1H), 7.06 (dd, J = 1.9, 8.9 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.52–7.57 (m, 3H), 7.87 (d, J = 7.1 Hz, 1H), 7.92–7.94 (m, 1H), 8.04 (d, J = 8.3 Hz, 1H), 8.27–8.28 (m, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6 (q), 102.8 (d), 113.2 (d), 113.3 (d), 118.7 (d), 124.3 (d), 125.5 (d), 126.5 (d), 127.3 (d), 127.7 (d), 127.9 (s), 128.4 (d), 130.8 (s), 131.5 (d), 133.5 (s), 133.8 (s), 135.7 (s), 136.4 (s), 154.8 (s), 188.5 (s) ppm.

(5-Methoxy-1H-indol-2-yl)(2-methoxy-4-methylphenyl)methanone (10q):



Grey solid; 64% Yield; R_f 0.3 (15% ethyl acetate/pet. ether); mp: 94–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.82 (s, 6H), 6.83–6.85 (m, 3H), 7.01–7.03 (m, 2H), 7.34 (d, J = 9.7 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9 (q), 55.7 (q), 55.8 (q), 102.8 (d), 112.2 (d), 112.5 (d), 113.1 (d), 118.1 (d), 120.6 (d), 125.4 (s), 128.0 (s), 130.0 (d), 133.1 (s), 136.4 (s), 142.8 (s), 154.7 (s), 157.6 (s), 186.8 (s) ppm; HRMS (ESI+): calcd. for $C_{18}H_{17}O_3NNa$ = 318.1101, found 318.1101.

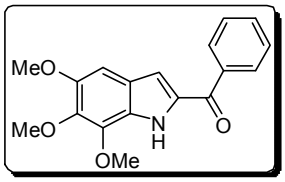
Benzo[b]thiophen-3-yl(5-methoxy-1H-indol-2-yl)methanone (10r):



Light yellow solid; 52% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); mp: 198–199 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (s, 3H), 7.06 (dd, J = 2.4, 8.9 Hz, 1H), 7.10 (br d, J = 1.8 Hz, 1H), 7.15 (br d, J = 1.3 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.46 (br t, J = 7.5 Hz, 1H), 7.51(br t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 8.33 (s, 1H), 8.47 (d, J = 8.1 Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.7 (q), 102.8 (d), 111.1 (d), 113.1 (d), 118.3 (d), 122.4 (d), 124.7 (d), 125.5 (d), 125.6 (d), 128.0 (s), 133.0 (s), 134.7 (s), 135.2 (d), 135.9

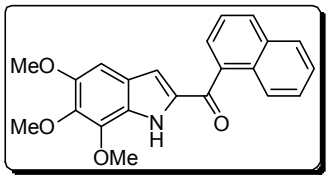
(s), 137.3 (s), 140.0 (s), 154.9 (s), 180.0 (s) ppm; HRMS (ESI+): calcd. for $C_{18}H_{13}O_2NSH^+$ = 308.0740, found 308.0741.

Phenyl(5,6,7-trimethoxy-1H-indol-2-yl)methanone (10s):[123]



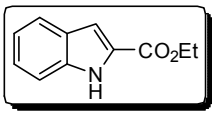
Light yellow solid; 72% Yield; R_f 0.3 (15% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.94 (s, 3H), 4.08 (s, 3H), 6.82 (s, 1H), 7.03 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.58–7.61 (m, 1H), 7.94 (d, J = 7.4 Hz, 2H), 9.29 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.2 (q), 61.1 (q), 61.5 (q), 98.0 (d), 112.8 (d), 123.4 (s), 127.6 (s), 128.4 (d, 2C), 129.1 (d, 2C), 132.1 (d), 134.2 (s), 138.2 (s), 138.9 (s), 141.6 (s), 150.4 (s), 186.4 (s) ppm.

Naphthalen-1-yl(5,6,7-trimethoxy-1H-indol-2-yl)methanone (10t):



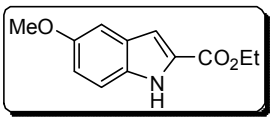
Yellow solid; 79% Yield; R_f 0.4 (20% ethyl acetate/pet. ether); mp: 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.95 (s, 3H), 4.10 (s, 3H), 6.75 (s, 1H), 6.82 (d, J = 2.2 Hz, 1H), 7.52–7.56 (m, 3H), 7.83 (br d, J = 7.1 Hz, 1H), 7.91–7.93 (m, 1H), 8.02 (d, J = 8.2 Hz, 1H), 8.23–8.26 (m, 1H), 9.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.2 (q), 61.2 (q), 61.5 (q), 98.0 (d), 113.7 (d), 123.2 (s), 124.3 (d), 125.5 (d), 126.5 (d), 127.2 (d), 127.5 (d), 128.0 (s), 128.3 (d), 130.8 (s), 131.3 (d), 133.7 (s), 135.8 (s, 2C), 138.9 (s), 141.7 (s), 150.4 (s), 187.9 (s) ppm; HRMS (ESI+): calcd. for $C_{22}H_{19}O_4NH^+$ = 362.1387, found 362.1390.

Ethyl 1H-indole-2-carboxylate (13a):[124]



Brown solid; 57% Yield, R_f 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.0 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.23 (s, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 9.0 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (q), 61.0 (t), 108.6 (d), 111.8 (d), 120.8 (d), 122.6 (d), 125.3 (d), 127.5 (s, 2C), 136.8 (s), 162.0 (s) ppm.

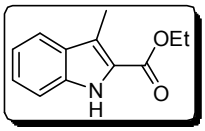
Ethyl 5-methoxy-1H-indole-2-carboxylate (13b):



Brown solid; 67% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3H), 3.84 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.99 (dd, J = 2.3, 9.0 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 7.14 (s, 1H),

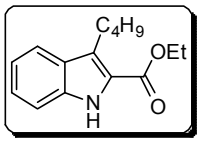
7.31 (d, J = 9.0 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (q), 55.7 (q), 61.0 (t), 102.5 (d), 108.2 (d), 112.7 (d), 116.9 (d), 127.8 (s), 127.9 (s), 132.1 (s), 154.7 (s), 161.9 (s) ppm; HRMS (ESI+): calcd. for $C_{12}H_{13}O_3NNa$ = 242.0788, found 242.0788.

Ethyl 3-methyl-1H-indole-2-carboxylate (13c):[124]



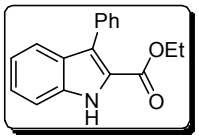
Light yellow solid; 74% Yield; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (t, J = 7.1 Hz, 3H), 2.61 (s, 3H), 4.42 (q, J = 7.1 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.9 (q), 14.5 (q), 60.7 (t), 111.6 (d), 119.9 (d), 120.2 (s), 120.8 (d), 123.4 (s), 125.5 (d), 128.5 (s), 135.8 (s), 162.7 (s) ppm.

Ethyl 3-butyl-1H-indole-2-carboxylate (13d):



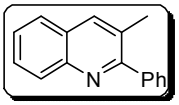
Off white solid; 59% Yield; R_f 0.4 (15% ethyl acetate/pet. ether); mp: 71–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.3 Hz, 3H), 1.39–1.44 (m, 5H), 1.63–1.69 (m, 2H), 3.10 (t, J = 7.7 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 8.24 Hz, 1H), 7.68 (d, J = 8.24 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0 (q), 14.4 (q), 22.8 (t), 24.5 (t), 33.2 (t), 60.6 (t), 111.7 (d), 119.8 (d), 120.9 (d), 123.0 (s), 125.4 (d and s), 128.1 (s), 135.9 (s), 162.5 (s) ppm; HRMS (ESI+): calcd. for $C_{15}H_{19}O_2NH^+$ = 246.1489, found 246.1491.

Ethyl 3-phenyl-1H-indole-2-carboxylate (13e):



Yellow solid; 61% Yield; R_f 0.4 (15% ethyl acetate/pet. ether); mp: 137–139 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (t, J = 7.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 7.11–7.18 (m, 1H), 7.32–7.49 (m, 5H), 7.52–7.58 (m, 2H), 7.63 (d, J = 8.3 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 60.9 (t), 111.7 (d), 120.9 (d), 121.8 (d), 122.8 (s), 124.3 (s), 125.8 (d), 127.2 (d), 127.7 (d, 2C), 127.9 (s), 130.6 (d, 2C), 133.5 (s), 135.7 (s), 162.0 (s) ppm; HRMS (ESI+): calcd. for $C_{17}H_{15}O_2NNa$ = 288.0995, found 288.0997.

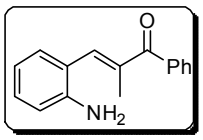
3-Methyl-2-phenylquinoline (11b):[125]



Colorless oil; 29% Yield; R_f 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.41–7.53 (m, 4H), 7.58–7.60 (m, 2H), 7.63–7.68 (m, 1H), 7.77 (d, J = 8.2 Hz, 1H), 8.01 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ

20.6 (q), 126.4 (d), 126.7 (d), 127.6 (s), 128.2 (d), 128.3 (d, 2C), 128.7 (d), 128.8 (d, 2C), 129.2 (s), 129.3 (d), 136.7 (d), 140.8 (s), 146.6 (s), 160.5 (s) ppm.

(*E*)-3-(2-Aminophenyl)-2-methyl-1-phenylprop-2-en-1-one (15):



Yellow Liquid; 42% Yield; R_f 0.2 (15% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.16 (d, J = 1.4 Hz, 3H), 3.63 (s, 2H), 6.71 (dd, J = 0.9, 8.1 Hz, 1H), 6.81 (dt, J = 0.9, 7.6 Hz, 1H), 7.09–7.25 (m, 3H), 7.40–7.54 (m, 3H), 7.73–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (q), 115.7 (d), 118.3 (d), 121.2 (s), 128.2 (d, 2C), 129.4 (d, 2C), 129.6 (d), 129.7 (d), 131.8 (d), 138.1 (s), 138.2 (d), 138.5 (s), 144.3 (s), 199.2 (s) ppm.

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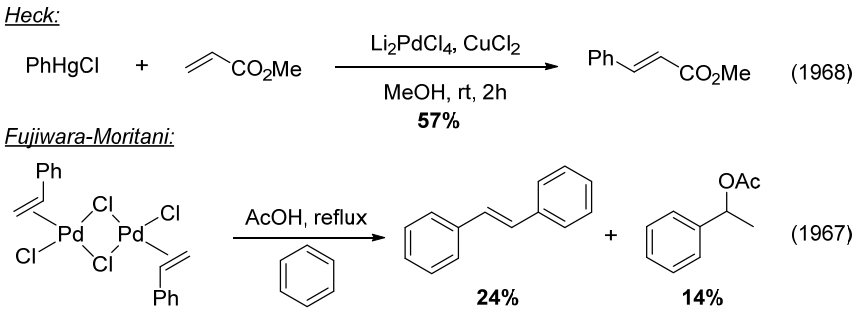
CHAPTER II:

Ru-Catalyzed Sequential C–H Activation: Directed and Direct C–H Activation of 2-Phenylpyridine Derivatives

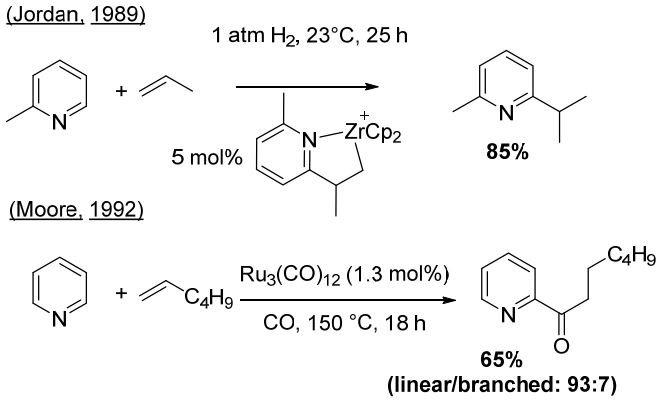
INTRODUCTION

During the past four decades, there has been a great deal of attention on the formation of Ary–C bonds using transition metal catalyzed cross-coupling reactions.[1] The era of the cross coupling chemistry started with the seminal contributions of Heck and Mizoraki on the coupling of functionalized aryl compounds ArX (X = halogen, Sn, B, Si etc.) with olefins.[2] Nowadays, the cross-coupling reactions are the text book reactions – especially the Pd-catalyzed ones. In 1968, Heck reported the first examples of oxidative coupling employing a stoichiometric amount of a palladium(II) species for C–C bond formation between phenylmercuric chloride (PhHgCl) with methyl acrylate.[3] Later, the catalytic version was described by Mizoroki and Heck in 1972, representing the coupling between iodobenzene and styrene using catalytic palladium.[4] Quite surprisingly, a year before Heck's original report in 1968, Fujiwara and Moritani in 1967 reported the direct coupling of benzene with the styrene-palladium chloride dimer (Scheme S2.1).[5]



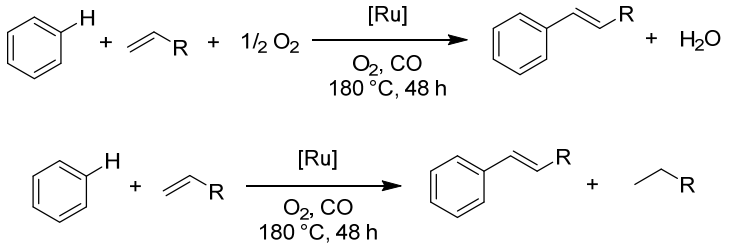
Scheme S2.1: *Palladium catalyzed C–C bond formation with acrylates and styrene*

Despite the fact that the Fujiwara-Moritani reaction does not need the pre-functionalized aryl halide or aryl mercury salts, it still almost required another two decades to have a breakthrough in this area. In the early 90's, the groups of Jordan and Moore have independently reported the regioselective alkylation and acylation of pyridine using zirconium and ruthenium metal catalysts respectively (Scheme S2.2).[6]



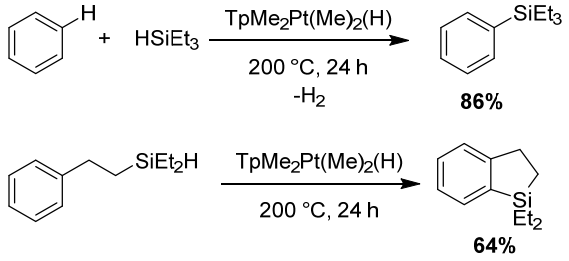
Scheme S2.2: *Metal catalyzed C–H alkylation and acylation of pyridine by Jordan and Moore*

The next effective contribution for direct C–H activation was Milstein's Heck-type oxidative coupling of benzene with olefins promoted by molecular oxygen, and is one of the most remarkable examples of ruthenium catalyzed arene C–H bond insertion reactions (Scheme S2.3).[7] The reaction is catalyzed by a readily available ruthenium complex such as $RuCl_3.3H_2O$ under a CO atmosphere condition.



Scheme S2.3: *Ru-catalyzed direct C–H bond activation of arene with alkenes*

In 2005, Hartwig reported a highly selective, inter- and intramolecular dehydrogenative coupling of silanes with arene C−H bonds in the presence of $TpMe_2PtMe_2H$ ($TpMe_2$=hydridotris(3,5-dimethylpyrazolyl)borate) and related platinum(IV) complexes (Scheme S2.4).[8] The reaction of the arenes occurred selectively at the least sterically hindered C–H bonds and preferentially with more electron-poor arenes. Intramolecular dehydrogenative coupling of silanes was also conducted for the first time in high yield to form both five- and six-membered organosilicon products.



Scheme S2.4: *Platinum catalyzed direct C–H activation with silanes*

Over the years, a broad range of new catalysts have been developed to directly transform C–H bonds into C–C or C–heteroatom bonds *via* C–H activation.[9] One of the important tasks in the direct C–H activations is how to achieve the metal insertion in a regioselective manner.[10] Generally, the electronics of the aromatic system affect the regioselectivity of direct C–H activations. For example, the inherent electronic bias of electron-rich heteroarenes has been in general amply used for the regioselective C–H functionalization. The other factors such as the steric nature of the substrate, solvent, additives and the electronic and steric nature of the catalyst can sometimes alter the

regiochemical outcome. In contrast, the regioselectivity of simple aromatic and electron-poor heteroaromatic systems is generally controlled through the use of a directing group.[11]

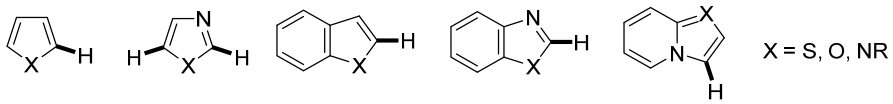
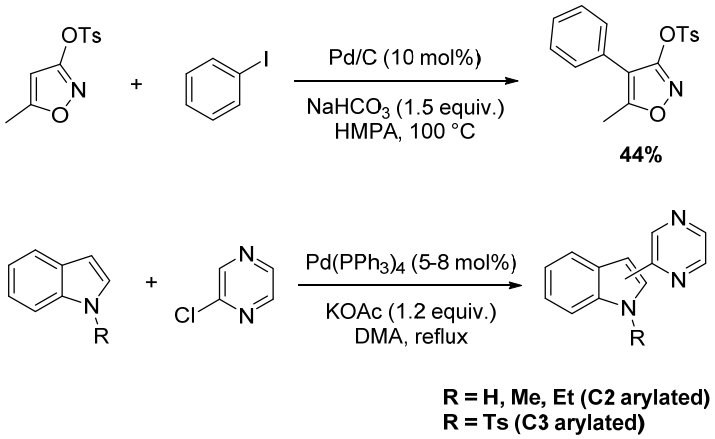


Figure S2.1: *Heterocycles with activated C–H bonds*

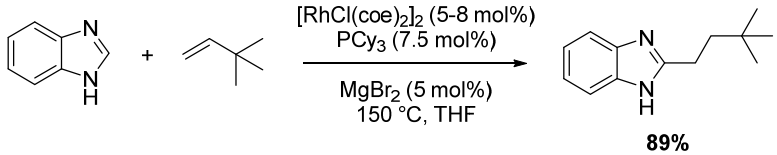
Thus, in general, these C–H activation protocols are broadly classified as direct and directed C–H activations. The following is a brief discussion on these two aspects covering some of the important findings in this context in chronological order.

Pioneering work in the area of direct C–H activation with electron-rich heteroarenes has been reported by Tajima[12] as well as Ohta[13] in the late 1980s (Scheme S2.5). The Pd-catalyzed direct arylation of isoxazole with iodobenzene and the arylation of indoles with chloropyrazines were documented. Subsequently, the applicability of this Pd-catalysed direct arylation has been extended to other 5- and 6-membered, as well as fused heteroaromatic systems by Miura, Greaney and other groups.[14]



Scheme S2.5: *Palladium catalyzed direct C–H activation of electron rich heterocycles*

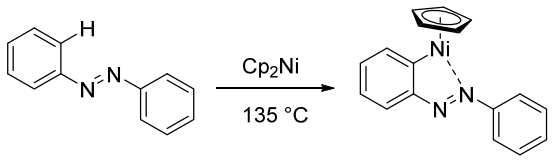
Bergman and Ellman groups have reported the intermolecular coupling of unactivated alkenes to heterocycles by using the Rh(I) catalyst (Scheme S2.6).[15] A wide range of heterocycles were employed in this reaction, and a variety of functional groups could be incorporated, including esters, nitriles, and acetals. The intermolecular coupling was found to be promoted by weak Lewis acids such as $MgBr_2$, which dramatically increased the reaction rate.



Scheme S2.6: *Rh(I)catalyzed C–H activation of electron rich heterocycles with alkene*

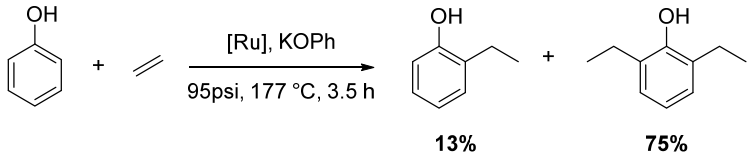
Directed C–H bond Activation Reactions of Arene:

The directed or chelation assisted C–H activation is a reaction made facile through metal chelation with a heteroatom, which thereby brings it into the proximity of the C–H bond, and consequently allows its activation/cleavage. The directing group assisted C–H activation was first observed in 1963, when Kleiman and Dubeck reported the preparation of the nickel complex through the *ortho*-selective functionalization of 1,2-diphenyldiazene with dicyclopentadienyl nickel (Scheme S2.7).[16] After this pioneering result, a large number of studies appeared demonstrating C–H bond cleavage using a stoichiometric amount of various transition-metals such as ruthenium, iridium, rhodium and palladium.[17]



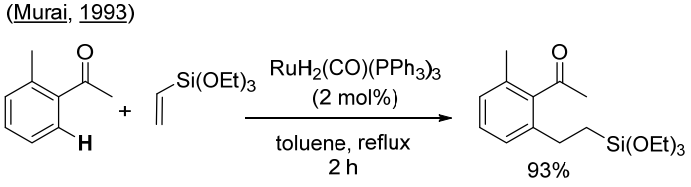
Scheme S2.7: *First example of C–H activation using a directing group*

However, in contrast with a variety of stoichiometric reactions involving C–H bond cleavage, the catalytic reactions using this process were developed much later. In 1986 Lewis reported directed C–H bond functionalization employing phenol as a directing group (Scheme S2.8).[18]



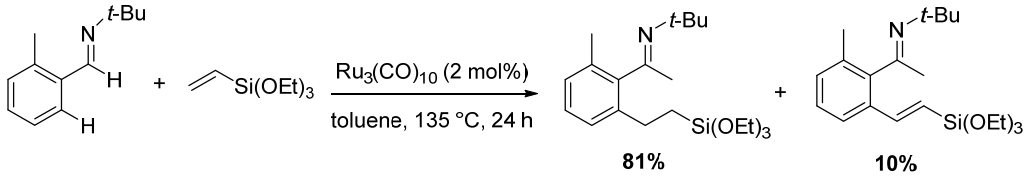
Scheme S2.8: *Chelation-assisted ortho-alkylation of phenol through C–H bond activation*

In 1993, Murai documented the first examples on the chelation-assisted, regioselective, catalytic C–H bond activation of arenes and the olefin coupling reaction.[19] As shown in Scheme S2.9, acetophenone is added to vinyl silane with a complete *ortho*-selective linear alkylation. The ruthenium complex $RuH_2(CO)(PPh_3)_3$ was found to be the best catalyst for this coupling reaction. The reaction is general and in many cases gave nearly quantitative yields.



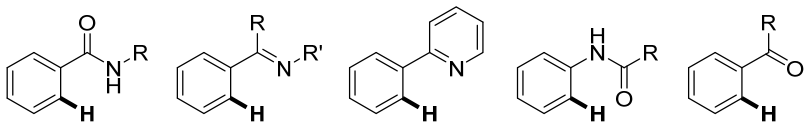
Scheme S2.9: *Ru-catalyzed C–H functionalization with vinylsilanes*

Afterwards, in 1996, Murai showed that nitrogen-containing chelating groups were also suitable directing groups for the C–H bond activation processes.[20] Aromatic imines, for examples aldimine, were employed for ruthenium catalyzed *ortho* C–H activation to create a new C–C bond. The required aldimine was obtained together with the byproduct arising from dehydrogenative coupling (Scheme S2.10).



Scheme S2.10: *First example of ruthenium catalyzed C–H activation with imine as directing group*

Thereafter, considerable progress was achieved by employing various catalysts for directed C–H bond transformations with myriad coupling partners. Common directing groups bear a lone pair of electrons that can coordinate to the transition metal and direct it into the selective C–H position. These include nitrogen and oxygen containing functional groups such as amides, imines, N-containing heterocycles, anilides and carbonyl functionalities.[21]



Scheme S2.11: *Directing group assisted C–H activation*

A number of synthetically useful protocols for directed C–H functionalization were developed during the last two decades employing various second-row transition metals in low oxidation states, predominantly palladium followed by ruthenium, rhodium and so on.[22] A vast number of C–H activation reactions have been reported over the past few years, and some of the selected examples of C–C bond forming reactions are discussed in the next section.

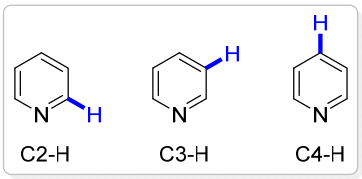
The major focus of the next chapter is the transition-metal-catalyzed C–H activation reaction comprising mainly of the:

I. direct C–H functionalization of pyridine involving C–C bond formation, and
II. pyridine directed C–H activation involving C–C bond formation.

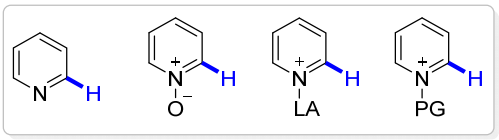
Direct C–H bond functionalization of pyridine:

The pyridine core is one of the privileged sub-units of biologically active small molecules and functional organic materials[23] and the synthesis of derivatives *via* C–H

activation is a promising approach in these areas. The pyridine core has three possible sites: C2, C3 and C4 for C–H bond functionalization. The selective functionalization of any of these three centers could be achieved either *via* chelation assistance (particularly for C3 and C4 C–H functionalization) or by manipulating the ring nitrogen (C2 functionalization).

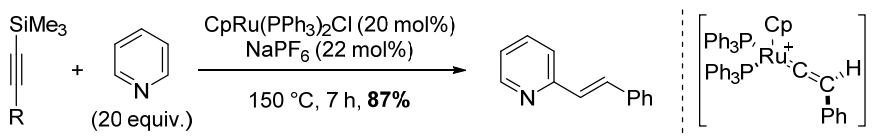


Generally, C2–H activation has been studied more in comparison to the C3–H and C4–H functionalization. In general, the C2–H functionalization of pyridine ring could be achieved *via* the activation of the ring nitrogen through their N-oxides or with some Lewis acid or N-iminopyridinium ylides, which apparently lead to an electron-deficient nitrogen that increases the acidity of the C2–H bond, whereas C3–H and C4–H activation usually depends on the selection of catalyst and ligands systems.[24]



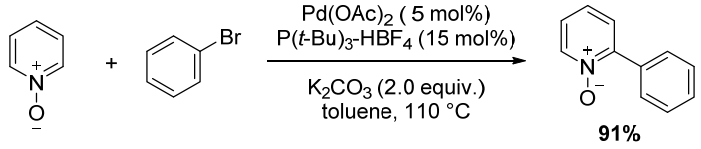
C2 Selective C–H functionalization of pyridine:

After initial reports by Jordan and Moore, the next one on C2 functionalization of pyridine was documented in 2003 by Murakami employing cationic ruthenium complexes.[25] The trimethylsilylacetylenes have been employed as electrophiles for the direct C2 alkenylation of pyridine. It has been proposed that the reaction proceeds through the formation of an allenyledene-ruthenium intermediate. Initially, pyridine coordinates to the ruthenium center by displacement of one of the phosphine ligands. Then [2+2] hetero-cycloaddition occurs to form a 4-membered ruthenacycle. Deprotonation of the *β*-hydrogen affords a neutral π-azaallyl complex and subsequent protonolysis produces the product. When bulky groups are present either on pyridine or on alkyne, the reactions failed under these conditions (Scheme S2.12).



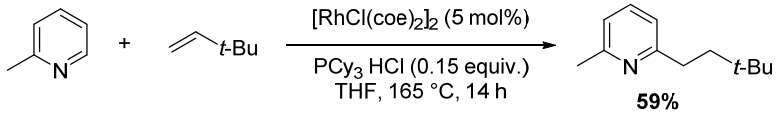
Scheme S2.12: *Ruthenium catalyzed C2 alkenylation of pyridine with (alkyn-1-yl)silanes*

Fagnou *et al* reported the palladium-catalyzed regioselective direct arylation of pyridine *N*-oxides using cationic Pd-complexes (Scheme S2.13).[26] The reaction of various aryl bromides with pyridine N-oxide afforded the corresponding 2-arylpyridine *N*-oxide in 45–91% yield. No diarylation was observed. Additionally 2-arylpyridine *N*-oxide products can easily be converted to the corresponding 2-aryl pyridines under mild conditions and in high yield *via* palladium-catalyzed hydrogenolysis.



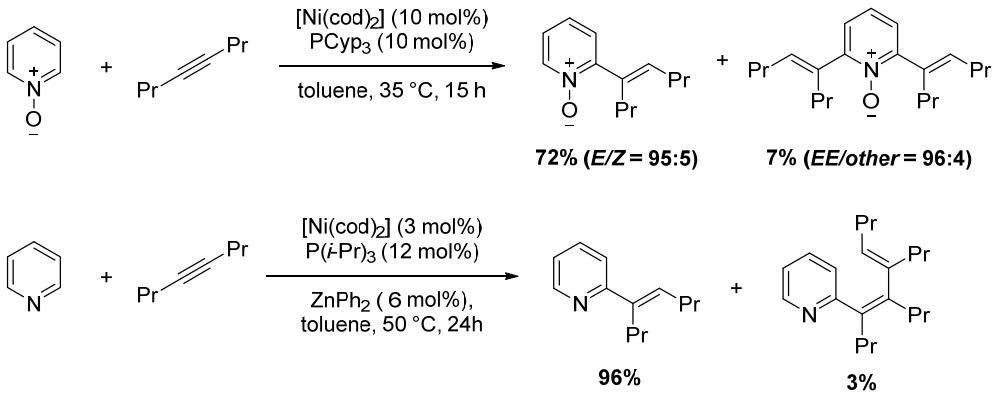
Scheme S2.13: *Pd-catalyzed C2 arylation of pyridine N-oxide with Ar–X*

In 2007, Bergman described the Rh(I)-catalyzed direct alkylation of pyridines. Increasing the bulk of the group located *ortho* to the pyridine ring nitrogen from methyl to isopropyl led to an increase in both the alkylation rate and product formation.[27]



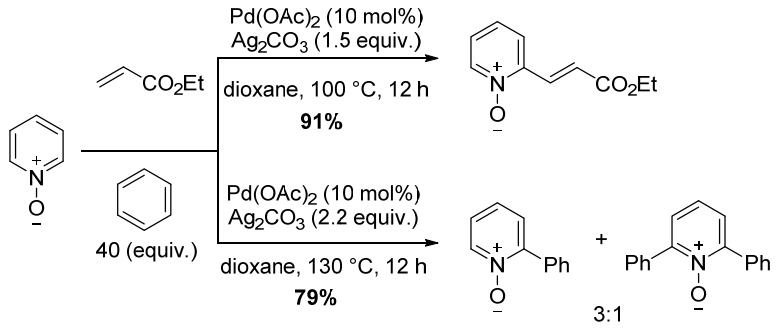
Scheme S2.14: *Rh-catalyzed C2 alkylation of pyridine with alkene*

Next, Nakao documented the nickel catalyzed C2 alkenylation of pyridine-N-oxides with alkynes to afford (*E*)-2-alkenylpyridine-N-oxides with complete regio and stereoselectivity. The resulting alkenylated pyridine-N-oxides were readily deoxygenated with PCl_3 to provide the free 2-alkenylpyridines in excellent yields. Next, the same group reported the direct C2 selective alkenylation of pyridines employing nickel/Lewis acid as a cooperative catalyst. A variety of pyridines have been alkenylated under mild conditions in a chemo-, regio-, and stereoselective manner (Scheme S2.15).[28]



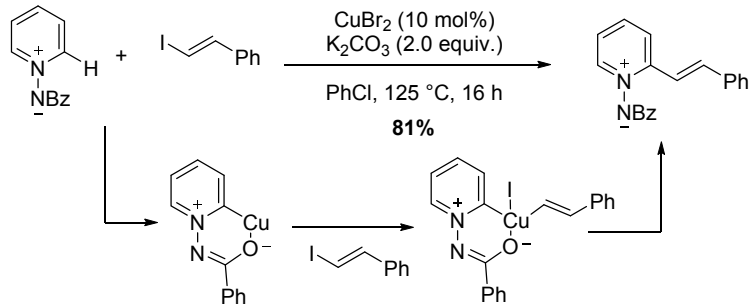
Scheme S2.15: *Nickel catalyzed C2 alkenylation of pyridine and pyridine-N-oxides*

Chang and co-workers have described the Pd-catalyzed direct alkenylation and cross coupling of pyridine *N*-oxides with acrylates and with unactivated arenes (Scheme S2.16).[29] The alkenylation reaction proceeded with high efficiency when the reaction of pyridine *N*-oxides and ethyl acrylate were performed in the presence of $Pd(OAc)_2$ in combination with Ag_2CO_3 (1.5 equiv.) and pyridine (1.0 equiv.) in 1,4-dioxane at 100°C. On the other hand, for oxidative arylation, only symmetrical arenes were employed.



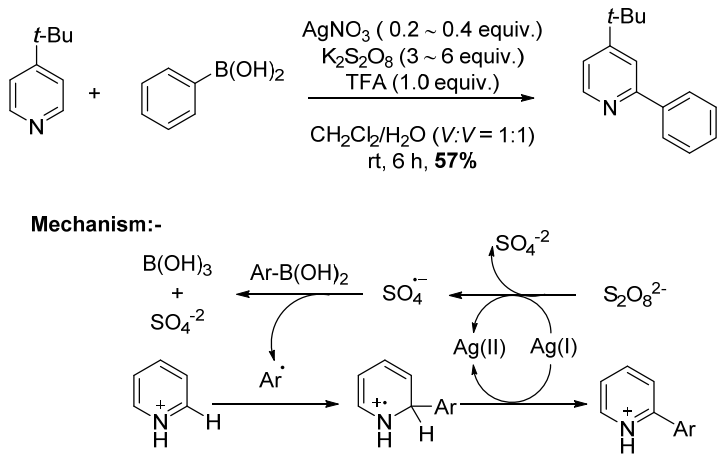
Scheme S2.16: *Pd-catalyzed direct C2 alkenylation and arylation of pyridine N-oxides*

Charette and co-workers reported a ligand-free Cu catalyzed direct C2–alkenylation of N-iminopyridinium ylides. The reaction is believed to pass through a Cu^{I}/Cu^{III} catalytic cycle and various electron-deficient heteroarenes converted in the corresponding alkenylated product in the presence of $CuBr_2$ and K_2CO_3 in toluene at 125 °C. The reactions were also facile with *Z*-alkenes, affording the *trans*-configuration due to *in situ* thermal isomerization (Scheme S2.17).[30]



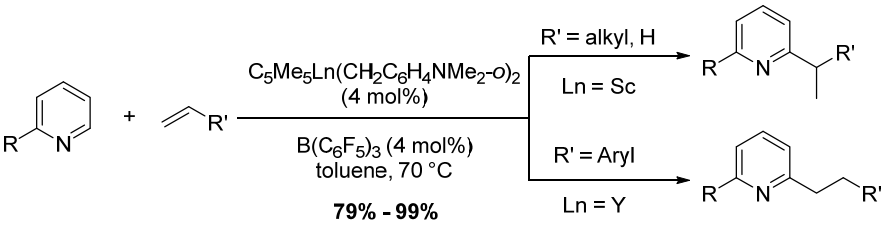
Scheme S2.17: *Cu-catalyzed direct C2 alkenylation of N-iminopyridinium ylides with alkenyl iodide*

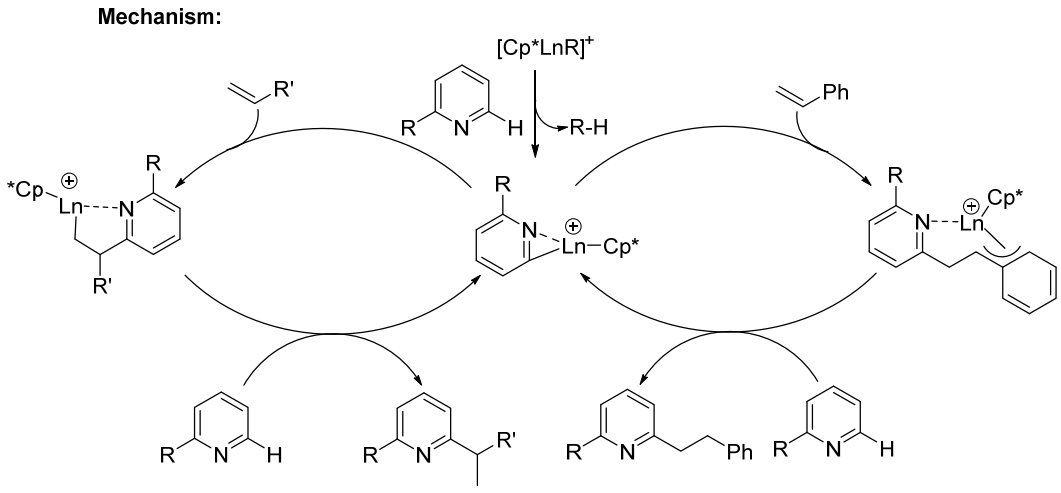
Room temperature direct arylation of pyridines with arylboronic acids using an inexpensive silver catalyst ($AgNO_3$) and co-oxidant ($K_2S_2O_8$) has been reported by Baran and co-workers. The reaction displays a broad scope with respect to both the heterocycle and boronic acid and proceeds under ambient conditions (Scheme S2.18).[31]



Scheme S2.18: *Direct C2 arylation of pyridines with arylboronic acids*

In 2011, Hou and co-workers reported a general method for the *ortho*-alkylation of pyridines with a wide range of olefins employing cationic half-sandwich rare-earth dialkyl complexes such as $(C_5Me_5)Ln(CH_2C_6H_4NMe_2\text{-}o)_2$ (Ln = Sc, Y) in combination with an activator such as $B(C_6F_5)_3$. The dialkylation product was observed after a long reaction time and they proposed that C–H bond activation (deprotonation) could be the rate-determining step (Scheme S2.19).[32]

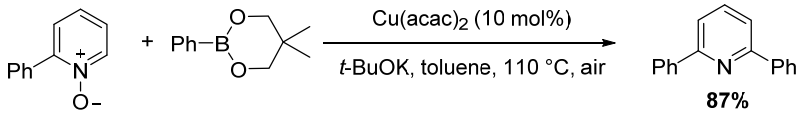




Scheme S2.19: *Rare-earth-catalyzed C–H addition of pyridines to olefins*

Recently, Wu and Chen described the copper-catalyzed direct C–H arylation of pyridine N-oxides with arylboronic esters leading to a wide range of 2-arylpyridines. The one pot reaction comprises of the arylation of pyridine N-oxides with arylboronic esters and

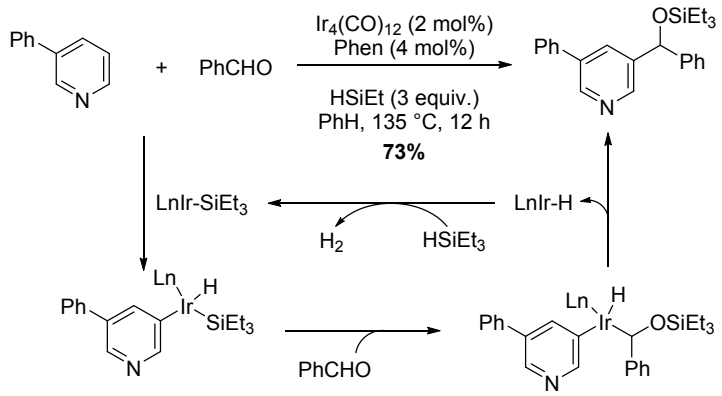
subsequent deoxygenation by an organoboron reagent as a reductant, producing the corresponding 2-aryl pyridines as the products. However, details of the mechanism of the formation of the 2-arylpyridines are still unclear (Scheme S2.20).[33]



Scheme S2.20: *Cu-catalyzed arylation of pyridine N-oxides with arylboronic esters*

C3 Selective C–H functionalization of pyridine:

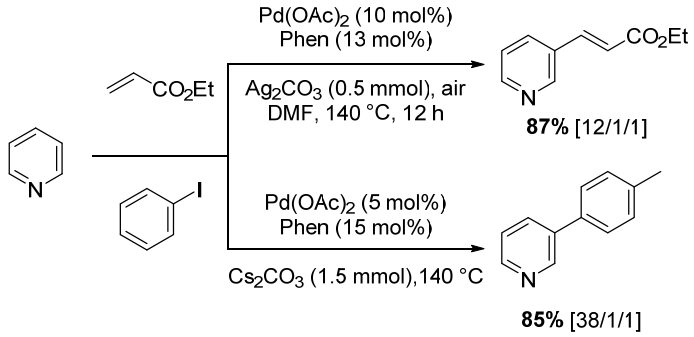
The direct C–H activation and functionalization at C3 of pyridine was less studied when compared to the C2–H activation. Some selected examples have been discussed below. In 2011, Shi and Li developed an iridium-catalyzed selective C3–H activation of pyridine and its addition to benzaldehyde in the presence of triethylsilane (Scheme S2.21). The reaction proceeds through meta-selective C–H activation of pyridine to give a (3-pyridyl)(silyl)iridium hydride species to which the carbonyl moiety of the aldehydes substrate is inserted. Subsequent reductive elimination results in the products and regenerates a catalytically active species upon reaction with triethylsilane.[34]



Scheme S2.21: *Ir-catalyzed meta-selective C3–H functionalization of pyridine*

In the same year, Yu and workers also reported the ligand promoted Pd catalyzed C-3 selective olefination as well as arylation of pyridines using 1,10-phenanthroline as the ligand (Scheme S2.22).[35] Various functional groups on the olefin were compatible under the given reaction conditions. However, the mechanism of the C3-selectivity remains elusive, through the kinetic isotope effect suggested C–H bond cleavage by a palladium catalyst rather than a Friedel–Crafts type mechanism. The arylation reaction was also compatible with various electron rich and deficient aryl iodides and some hetero aryl halides. The electron deficient

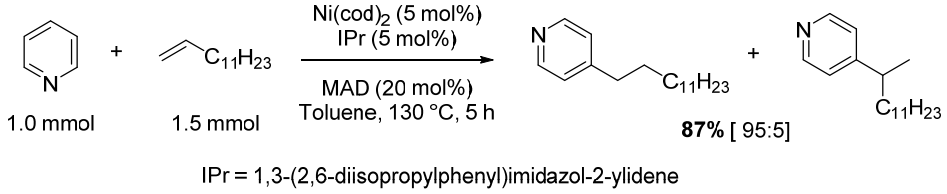
pyridines are less compatible and also aryl chlorides were found to be inactive under these conditions.



Scheme S2.22: *Pd-catalyzed C3 selective olefination and arylation of pyridines*

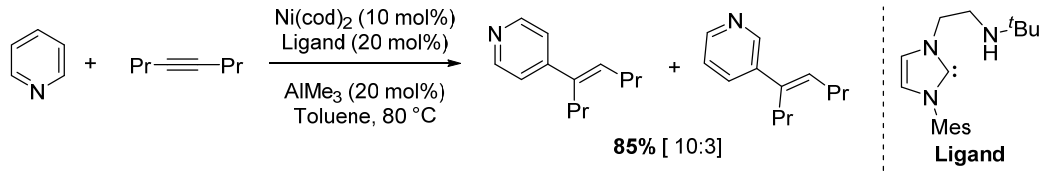
C4 Selective C–H functionalization of pyridine:

The first examples on the direct C4–H activation of pyridine were provided by Nakao and co-workers in 2010.[36] The addition of pyridine across alkenes and alkynes was catalyzed by nickel and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD). MAD is a very bulky aluminium based Lewis acid that was developed originally by Yamamoto and co-workers. The excellent C4-selectivity observed for the alkylation was due to the bulkiness of both the N-heterocyclic carbene ligand and MAD, which directs the metalation step to proceed exclusively at the C4–position (Scheme S2.23). A variety of substituents on both alkenes and pyridine are tolerated to give linear 4-alkylpyridines in modest to good yields.



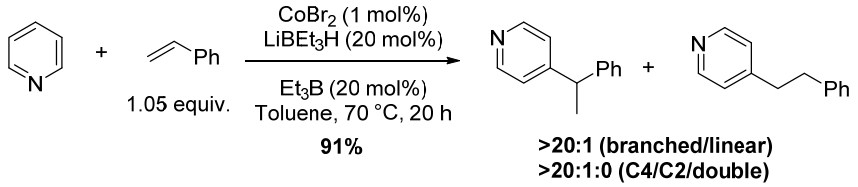
Scheme S2.23: *Ni-catalyzed direct C4 alkylation of pyridine with alkene*

The next effective contribution for direct C4 selective alkenylation of pyridine has been developed by Ong *et al* in 2010 employing the bimetallic nickel aluminun as catalyst (Scheme S2.24).[37] Additionally, they isolated for the first time the intermediate structure of a bimetallic η^2,η^1-pyridine nickel aluminum complex prior to its C–H activation, which serves as key evidence for bimetallic catalysis. Importantly, the C–H activation of 2-phenyl pyridine derivatives proceeded exclusively on the pyridyl ring.



Scheme S2.24: *Nickel-$AlMe_3$ catalyzed C4/C3 alkenylation of pyridine with alkyne*

In 2013, Matsunaga and co-workers described the cobalt catalyzed C4-selective direct alkylation of pyridines.[38] A catalytic amount of $CoBr_2$ in combination with $LiBEt_3H$ as the hydride source and Et_3B as the additive in toluene at 70 °C gave selectively branched adducts from styrene derivatives and linear adducts from aliphatic alkenes. The high catalyst turnover numbers (up to 3440; s/c=4000) observed in the reaction with styrene as well as the catalytic Et_3B has some key role for getting C4-selectivity (Scheme S2.25).



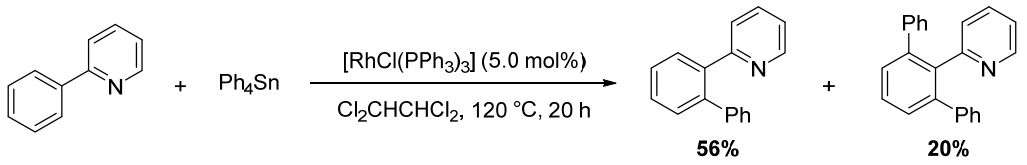
Scheme S2.25: *Cobalt-catalyzed direct C4 selective alkylation of pyridines with alkenes*

Pyridine directed C–H activation:

The Kleiman[16] and Cope[39] groups have reported the early examples on the directed C–H cleavage of azobenzene by employing Cp_2Ni as well as palladium and platinum complexes respectively in the middle of the 60s. The breakthrough discovery was made by Lewis[18] and Murai[19] during the late 20th century employing the catalytic ruthenium complexes for the directed C–H activation. Since then, considerable progress has been achieved by various catalysts for directed C–H bond transformations.[21] Pyridine is one of the well-studied ligands in the directed C–H activations. Indeed, there are more than a hundred papers exclusively dealing with the C–H activation of 2-phenylpyridine and employing a wide range of catalysts and electrophiles. The general scenario of the pyridine directed C–H activation with various electrophiles has been given in the tables at the end of this section (Page No. 146–149) and some of the selected reports using the ruthenium catalysts for this pyridine directed C–H activation will be discussed below.

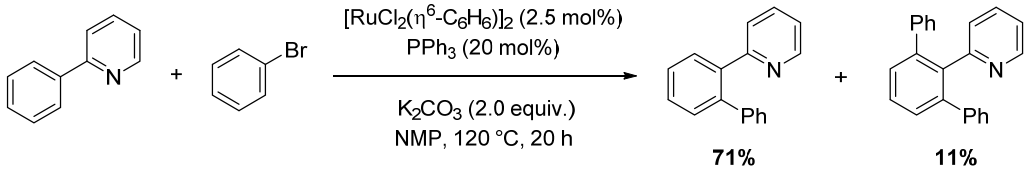
In 1998, Oi and co-workers reported the first examples of rhodium catalyzed pyridine directed arylation of 2-aryl-substituted pyridines employing the Wilkinson catalyst and aryl stannanes as the arylating reagents in DCE as solvent at 140 °C (Scheme S2.26).[40] Although

details of the mechanism of the catalytic system were not disclosed, the solvent likely served as the oxidizing agent in these transformations.



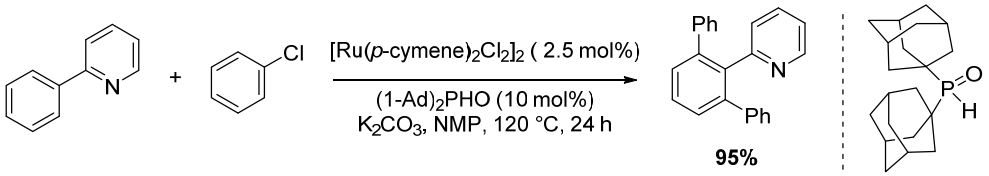
Scheme S2.26: *Rh-catalyzed arylation of 2-phneyl pyridine with aryl stannanes*

One of the early examples on the Ru-catalyzed directed arylation of 2-PhPy was reported by Oi and Inoue (Scheme S2.27).[41] $[\{RuCl_2(\eta^6\text{-}C_6H_6)\}_2]$ in the presence of PPh_3 employed as the catalyst. Other Ru(II) catalysts such as $RuCl_2(PPh_3)_3$ and $[RuCl_2(COD)]_n$/4 PPh_3 also showed similar activity. The order of reactivity of various arylhalide electrophiles is PhBr > PhI > PhOTf ≫ PhCl. The same catalytic systems were shown to enable the directed arylation of substituted ketimines, imidazolines, and oxazolines as pronucleophilic starting materials.[42] Steric hindrance (mainly at the *ortho* or the *meta* of the phenyl ring) played a crucial role on the outcome of mono *vs* diarylation products. This catalytic system was compatible with the aryl iodides and bromides.



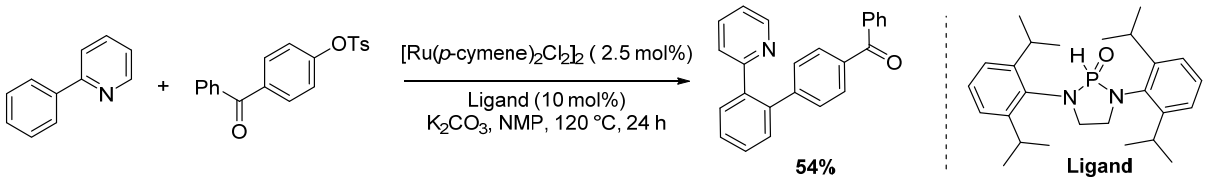
Scheme S2.27: *Ruthenium catalyzed arylation of 2-phneyl pyridine with aryl bromide*

In 2005, Ackermann and co workers extended the scope of this reaction by employing inexpensive and more available aryl chlorides as coupling partners (Scheme S2.28).[43] These advances were achieved using a catalytic system generated from $[RuCl_2(p\text{-cymene})]_2$ and secondary phosphine oxides (SPO) as preligands. Sterically hindered adamantly substituted phosphine oxide was found to be a highly efficient ligand and in general, the reactions afforded exclusively diarylation products. Furthermore, the reaction scope was extended with ketimines as directing group, which, after hydrolysis, gave arylated ketones.



Scheme S2.28: *Ruthenium catalyzed arylation of 2-phneyl pyridine with aryl chloride*

Subsequently, aryl tosylates have been also employed as electrophiles in the Ru-catalyzed direct arylation of arylpyridines (Scheme S2.29).[44] However the yields with aryl tosylates were less when compared with the aryl chloride and aryl bromides. The reaction was further extended to arylpyrazoles and aryloxazolines under similar condition and coupling partners.



Scheme S2.29: *Ruthenium catalyzed arylation of 2-phneyl pyridine with Ar-OTs*

In 2008, the Ackermann group first described the beneficial effect of carboxylic acids in the ruthenium-catalyzed direct arylation of arenes in the apolar, such as toluene. Among various carboxylate, 2,4,6-trimethylbenzoic acid (mesitylic acid, $MesCO_2H$) proved to be the best additive for the carboxylate-assisted direct arylation. Indeed, various arenes bearing nitrogen-containing directing groups such as pyridine, oxazolines, *N*-pyrazolyl, N-triazolyl as well as 1,4-disubstituted 1,2,3-triazoles were reacted smoothly with myriad aryl halides (X = Cl, Br) or pseudo halide (X = OTs) in the presence of 2,4,6-trimethylbenzoic acid (mesitylic acid, $MesCO_2H$) and K_2CO_3 in toluene at 100–120 °C to afford the corresponding mono and diarylated products in good to excellent yields.[45] In general, monoarylated products could be obtained chemoselectively when the substrates employed had *o*- or *m*-substituted arenes. Prades and Peris also explored the NHC-ruthenium catalyzed acetate-assisted arylation of 2-phenylpyridine in NMP.[46]

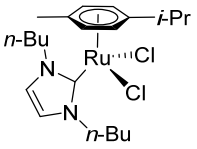


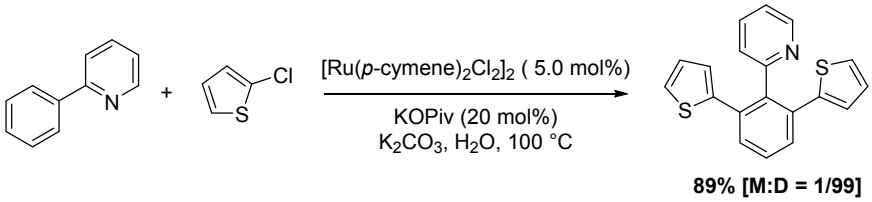
Figure S2.2

Next, this methodology was extended by Dixneuf for the diarylation of aryl- and heterohalides of arenes with an N-containing heterocycle as the directing group (pyridine, oxazoline, pyrazole) using such unusual ruthenium(II) precursors $[RuH(codyl)_2]BF_4$ in combination with various potassium carboxylates and K_2CO_3.[47]

Ouellet and co-workers also revealed that the common impurity present in NMP such as γ-butyrolactone or their carboxylates acted as a soluble carboxylate source which enhanced the reactivity in the same extent as KOAc.[48]

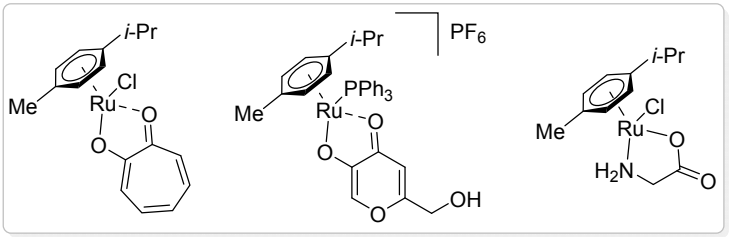
Most of reported direct arylations were performed either in NMP or toluene as solvents. However, the application of "green solvents" in direct C–H bond functionalizations was demanded for more user and environmental friendliness. First, in 2005, the Ackermann group reported the chemoselectivity of the ruthenium-catalyzed direct arylation and that water could be used as a cosolvent, still with a good yield of products.[43]

Since 2009, several ruthenium-catalyzed direct arylations in green solvents were reported by the Dixneuf group. The diarylation of 2-phenylpyridines with aryl chlorides employing $[RuCl_2(p\text{-cymene})]_2$/KOPiv catalytic system was reported in diethylcarbonate (DEC), an eco-friendly solvent, at 80 °C (Scheme S2.30).[49] Several arenes containing an N-heterocycle as a directing group have been diarylated and tolerating various functional groups like cyanide or ester. Remarkably, the arylation of 2-phenylpyridine with same catalytic system using water as the solvent found to be most effective under very mild reaction conditions.[50]



Scheme S2.30: *Ruthenium catalyzed direct arylation of 2-phneyl pyridine in H_2O*

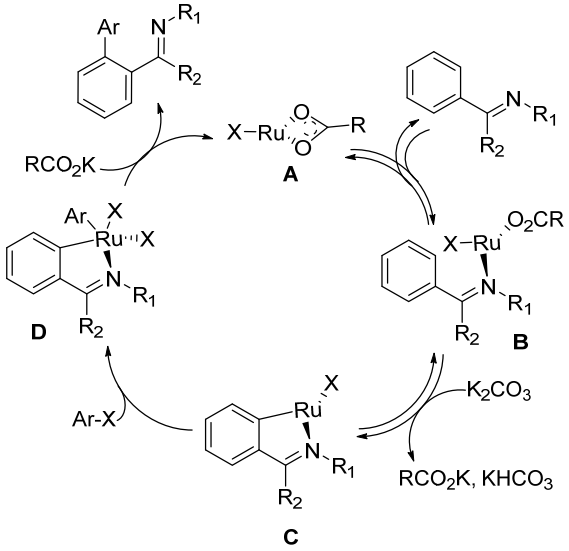
Recently, water-soluble (O,O)- and (O,N)-chelated ruthenium catalysts were prepared by Dixneuf through treatment of $[RuCl_2(p\text{-cymene})]_2$ with tropolone, sodiumglycinate or kojic acid respectively (Scheme S2.31).[51] These new Ru-complexes proved to be efficient for the direct arylation of 2-phenylpyridine with aryl chlorides or bromides in the presence of catalytic amounts of potassium acetate or pivalate in water.[52]



Scheme S2.31: *Water-soluble Ru-complex for direct arylations of 2-phenyl pyridine*

During the last decade, the mechanistic considerations of ruthenium-catalyzed direct arylation underwent rapid evolution, but yet still remain under investigation. Based on the experimental studies by various groups, the following mechanism has been proposed for the ruthenium catalyzed carboxylate-assisted direct arylation of arenes.[53] Initial ruthenium

carboxylate complex **A** coordination with the directed hetero atom to formed the complex **B**. Subsequently deprotonation and metal insertion gave complex **C**. Thereafter, complex **C** undergoes oxidative addition with the aryl halide Ar–X to yield the intermediate **D**. Finally, reductive elimination yields the product with regeneration of the catalytic species **A**.

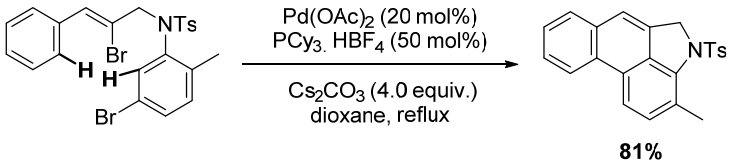


Scheme S2.32: *Proposed mechanism for the ruthenium-catalyzed direct arylation of arenes*

In summary, the C–H functionalization of the pyridine ring or pyridine directed *ortho* C–H activation has seen significant developments in recent years. As mentioned previously, the direct C–H functionalization of pyridine proceeds through either with an activated substrate like their N-oxides, N-iminopyridinium ylides, or using some Lewis acid which increases the acidity at the C2 or the metal complex coordinates with Lewis base nitrogen followed by C–H functionalization. On the other hand, the pyridine directed C–H activation proceeds a through five- or six-membered metallacycle *via* coordination of metal with an electron rich nitrogen atom. But both C–H activations *viz* direct or directed have been achieved separately either with the same metal complex or with different metal complex.[9-11, 21] However, to obtain molecular complexity and diversity from simple starting materials as well as to reduce the waste in the stepwise reaction, the necessity is towards developing a one pot approach for more than one C–H functionalization to form multiple C–C and C–X bonds using a single transition metal catalyst for a green and atom economical method. A few selected examples of sequential or cascade C–H activations using one metal and in one pot is given below.

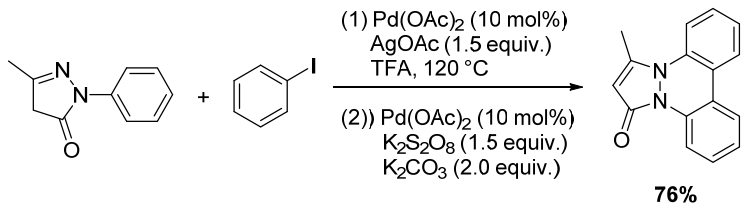
Direct or Directed Sequential/Cascade C–H activation:

In 2007, Tanaka *et al* reported the palladium catalyzed "zipper-mode" double C–H bond activation to construct fused aromatic/heteroaromatic compounds. Reaction of various (*Z*)-3-bromo-N-(2-bromo-3-phenylprop-2-enyl)anilines using catalytic $Pd(OAc)_2$ and $PCy_3.HBF_4$ in the presence of Cs_2CO_3 as a base in dioxane under reflux afforded indole derivatives in 42-93% yields. The reaction was also facile with heterocycles such as benzofuran, benzothiophene or indole (Scheme S2.33).[54]



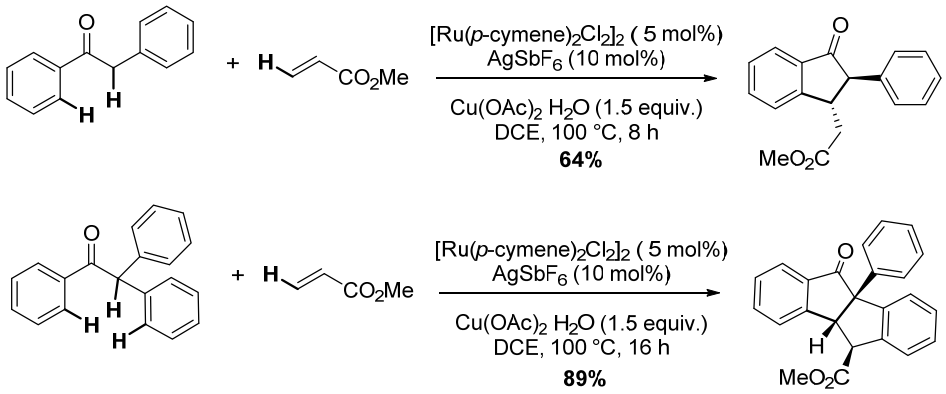
Scheme S2.33: *Palladium catalyzed Zipper-mode double C–H activation*

Palladium-catalyzed one-pot double C–H activation to construct benzo[c]pyrazolo[1,2-a]cinnolin-1-ones through sequential C–C/C–N bonds formation was developed by Zhang and co workers (Scheme S2.34).[55] The reaction comprised of the C–H arylation followed by the intramolecular C–N bond formation. This approach provides the flexible strategy to access this polycyclic skeleton using a pyrazolone moiety as an internal directing group for C–H activation.



Scheme S2.34: *Pd-catalyzed one-pot synthesis of benzo[c]pyrazolo[1,2-a]cinnolin-1-ones*

Greaney and co-workers have developed ruthenium-catalyzed sequential C–H activation cascades for the synthesis of 1-indanones and indenoindenes employing aryl acetophenones and a variety of Michael acceptors (acrylates) (Scheme S2.35).[56] The conditions employed involve the use of a cationic ruthenium complex derived from [{Ru(*p*-cymene)Cl_2}$_2$]/$AgSbF_6$, equimolar amounts of $Cu(OAc)_2$ in DCE as solvent at 100 °C. The initial carbonyl-directed dehydrogenative coupling of acrylate results in a cinnamate that subsequently undergoes the Michale addition in the same pot to provide the indanone. Various aryl acetophenones and diarylated acetophenone are found to be suitable with various Michael acceptors. However the substitution at the *ortho* position to the ketone proved sensitive to steric factors and led to a diminishing yield of the reaction.



Scheme S2.35: *Ru-catalyzed synthesis of Indanones and Indeno indenes via sequential C–H activation*

RESULT AND DISCUSSION

Introduction

The construction of C–C bonds through the transition-metal catalyzed functionalization of aryl/heteroaryl C–H bonds has recently attracted attention because these reactions provide more desirable step- and atom economy than those where prefunctionalization of aryl/heteroaryl rings is required.[57] Pyridine derivatives are interesting in this regard. On the one hand, the pyridine moiety is one of the conventional functional groups employed as a ligand for the directed catalytic functionalization of aryl C–H bonds.[58] On the other hand, catalytic C–H activation reactions that lead to functionalization of the pyridine moiety are important because the pyridine is a privileged substructure of biologically active small molecules, functional organic materials and ligands.[23] Generally, the direct C alkylation of pyridine moieties requires the nitrogen atom to be electron deficient in order to increase the acidity of the C–H bond at the C2 position. This requirement can be achieved by using N-oxides, N-iminopyridinium ylides and pyridine compounds in the presence of Lewis acids.[24] Conversely, in the case of directed alkylations, the pyridine moiety needs to be electron rich because the catalytic cycle involves the coordination of the nitrogen atom with a metal complex.[58] Therefore, the direct functionalization of pyridine moieties and pyridine-directed C–H activation reactions have, in general, been approached separately by using various transition-metal complexes, which are usually complexes of palladium, rhodium, ruthenium, and nickel.[9-11, 21, 57] In this regard, we have been interested in developing a one-pot sequential Ru-catalyzed directed propenylation and arylation of 2-phenyl pyridine derivatives.

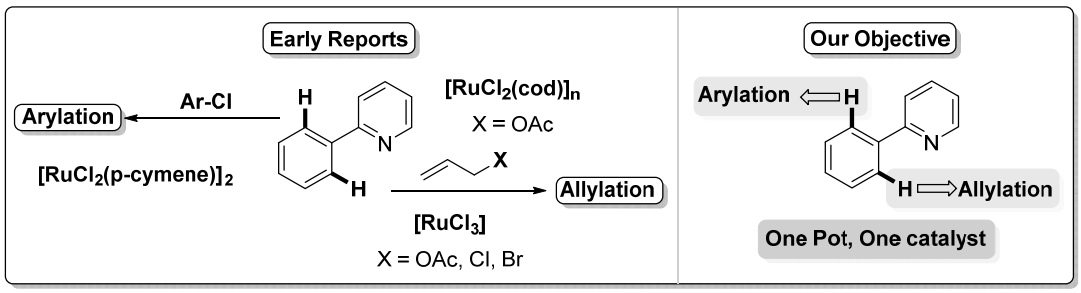
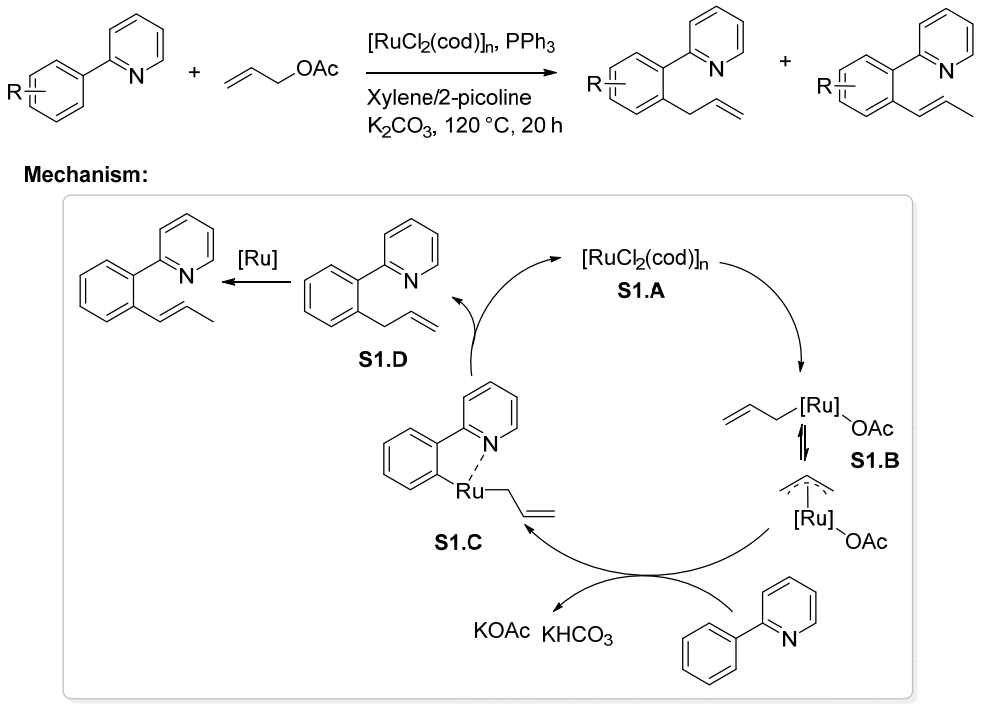


Figure 2.1: *Previous reports on C–H activation and our concept of sequential C–H activation*

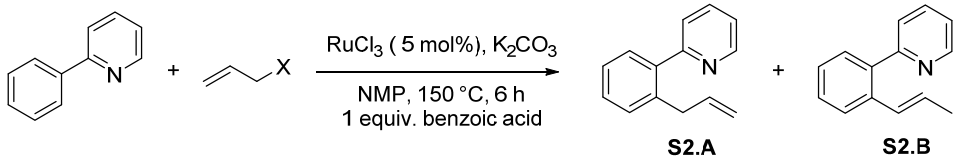
In 2006, Inoue *et al* developed the Ru-catalyzed *ortho*-selective C–H allylation of 2-pyridylarenes with allylacetates (Scheme 2.1).[59] The allylation of various 2-phenyl pyridine derivatives in the presence of a ruthenium(II)-phosphine complex afforded the corresponding selective *ortho* allylation with partial migration of the double bond. The proposed reaction mechanism involves, first the oxidative addition of the allyl acetate to the ruthenium complex

to afford a σ-allylruthenium intermediate, which subsequently undergoes *ortho*-ruthenation of **S1.B** with the elimination of AcOH, giving the corresponding ruthenacycle **S1.C**. Product **S1.D** is then formed through reductive elimination of **S1.C**, and regenerates the reactive catalyst.



Scheme 2.1: *Ruthenium-catalyzed ortho allylation of 2-arylpyridines*

In 2008, Zhang and co-workers described the Ru-catalyzed alkenylation of 2-arylpyridine with various allylic compounds such as allyl chloride, allyl bromide, and allylacetate (Scheme 2.2).[60] The regioisomeric products of **S2.A** and **S2.B** with migration of olefin (alkenylated isomer) was the major isomer.

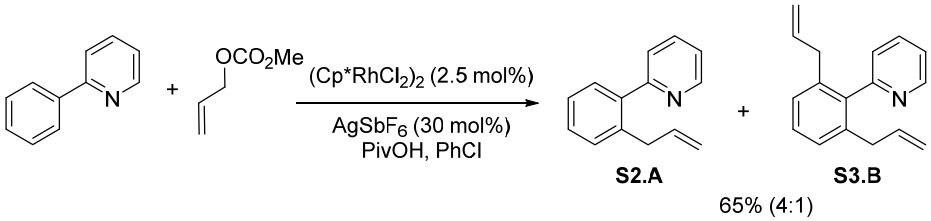


X	S2.A : S2.B	yield (%)
Cl	28 : 77	84
Br	18 : 82	76
OAc	21 : 79	73

Scheme 2.2: *Ruthenium-catalyzed ortho alkenylation of 2-arylpyridines*

Very recently, Glorius' group documented the rhodium(III)-catalyzed *ortho*-allylation of 2-phenylpyridines by using allyl carbonates (Scheme 2.3).[61] The reaction features complete γ-selectivity, a high isomeric ratio, good substrate scope, and functional group

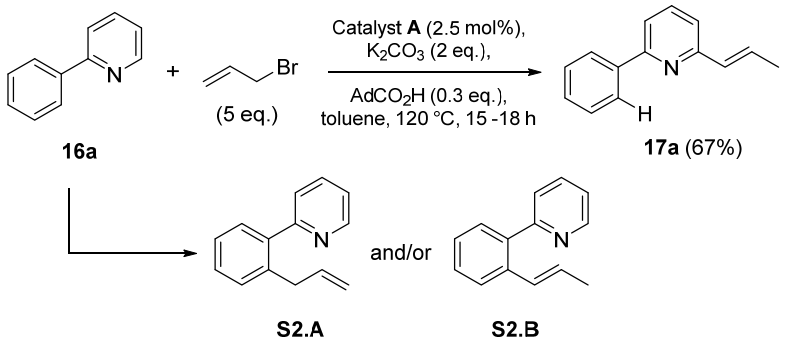
compatibility. Substrates with electron-withdrawing groups on the aryl ring were found to be not compatible. The use of a slight excess of the $AgSbF_6$ salt under mild reaction conditions improved both reactivity and selectivity.



Scheme 2.3: *Rh-catalyzed allylation of 2-arylpyridines with allyl carbonate*

Present Work:

Our initial working hypothesis was the checking of the possibility of the directed allylation reaction under the conditions prescribed for directed arylations[62] and sees whether these processes can be combined. The work in this direction started with the allylation of 2-phenyl pyridine (**16a**) under the arylation conditions reported by Ackermann. The allylation reaction was carried out using allyl bromide, K_2CO_3 (2.0 equiv), adamantane-1-carboxylic acid ($AdCO_2H$, 0.3 equiv), and $[Ru(p\text{-cymene})Cl_2]_2$ (**A**; 2.5 mol%) in toluene at 120 °C in a screw-capped sealed tube. The reaction was complete after 15 h and a single compound was isolated in 67% yield (Scheme 2.4).

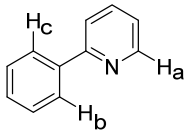
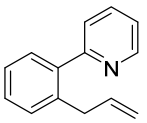
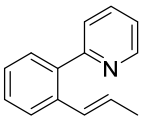
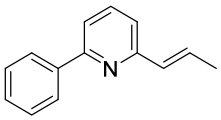


Scheme 2.4: *Initial attempt for allylation of 2-phenyl pyridine*

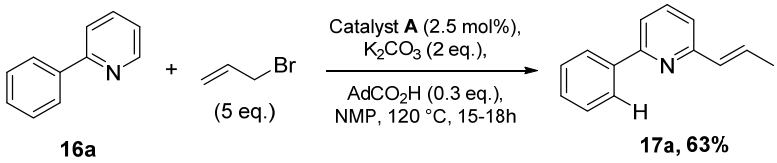
Quite interestingly, the spectral data of the isolated product **17a** was different from the data reported for the expected allyl products **S2.A** and **S2.B**. As shown in the Table 2.1, a comparison of ^{1}HNMR chemical shift of **16a**, **S2.A**, **S2.B** with the data of **17a** indicated that the phenyl ring protons are intact and that one of the C–H of pyridine ring is missing. In addition, the two olefin protons were seen to resonate at δ 6.58 (dq, J = 1.6, 15.5 Hz, 1H) and 6.91 (dq, J = 6.7, 15.5 Hz, 1H) ppm and the next is one methyl appearing as a doublet of doublets at δ 1.96 ppm with J = 1.6 and 6.7 Hz. In the ^{13}C NMR spectrum of compound **17a**, the C6-carbon of the pyridine ring, which usually resonates at $\delta \approx 149$ ppm as a doublet was

missing and a peak at δ 155.8 ppm as a singlet was observed that corresponds to the newly generated quaternary carbon. In addition the methyl carbon appeared at δ 18.3 ppm as a quartet. Furthermore, in the HRMS spectrum, the presence of a strong peak at m\z 196.1126 confirmed the compound **17a**.

Table 2.1: *^{1}H and ^{13}C NMR chemical shift for compound **16a**, **S2.A**, **S2.B** and **17a***

H	 **16a**	 **S2.A**	 **S2.B**	 **17a**
H_a	8.68 (dt, *J* = 4.8, 1.4 Hz)	8.69 (d, *J* = 4.4 Hz)	8.71 (d, *J* = 4.4 Hz)	---
H_b, H_c	7.97 (d, *J* = 7.0 Hz)	---	---	8.00–8.07 (m, 2H)
Ar–H Py–H	7.76–7.70 (m, 2H) 7.46 (t, 2H) 7.40 (t, 1H) 7.21 (ddd, 1H)	7.73 (t, 1 H) 7.39 (q, 2 H) 7.32 (m, 2 H) 7.25 (m, 2 H)	7.75 (t, 1H) 7.57 (d, 1H) 7.44 (q, 2H) 7.33 (m, 2H) 7.26 (m, 1H)	7.65 (t, 1H) 7.53 (dd, 1H) 7.39–7.50 (m, 3H) 7.15 (dd, 1H)
=CH	---	5.87 (m, 1H)	6.47 (d, *J* = 15.6 Hz, 1H) 6.19 (m, 1H)	6.91 (dq, *J* = 6.7, 15.5 Hz, 1H) 6.58 (dq, *J* = 1.6, 15.5 Hz, 1H)
$=CH_2$	---	4.96 (d, *J* = 9.6 Hz) 4.89 (d, *J* = 17.6 Hz)	---	---
$-CH_3$	---	---	1.82 (d, *J* = 6.0 Hz)	1.96 (dd, *J* = 1.6, 6.7 Hz)
$-CH_2$	---	3.49 (d, *J* = 6.4 Hz)	---	---

Next, we conducted the allylation reaction under similar conditions and replaced toluene with NMP (N-methyl-2-pyrrolidone). Even in this, the reaction provided **17a** exclusively in 63% yield (Scheme 2.5).

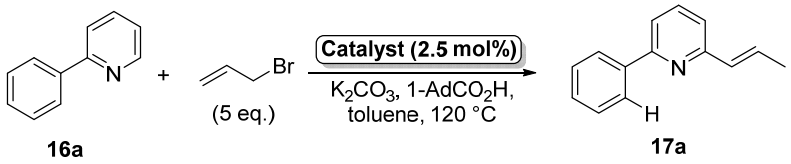


Scheme 2.5: *Ru-catalyzed C–H allylation in NMP*

Next, the other ruthenium complexes were explored under similar reaction conditions in order to examine how this selectivity of pyridine *vs* aryl C–H activation will be influenced by the nature of the ligand around [Ru]. As shown in Table 2.2, with a majority of the complexes, the direct allylation was the exclusive event. However the yields are poor. After successfully screening the catalyst, we proceeded for control experiments in order to understand the requirement of each component of the reaction. As shown in Table 2.2, the control experiments revealed that the presence of the base is essential. Furthermore, when the reaction was carried out in the absence of ruthenium complex **A** under otherwise similar

reaction conditions, the formation of **17a** was negligible (Table 2.2, entry 10). This result indicated that the ruthenium complex **A** is essential for the reaction.

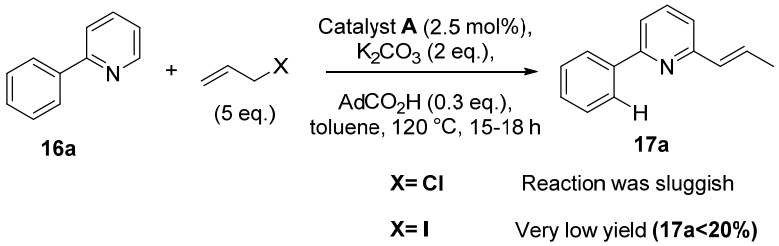
Table 2.2: Screening of Ru-catalysts for sp^2 C–H activation of 2-phenyl pyridine



Entry	Catalyst	Time/h	Yield (%)[a]
1	$[RuCl_2(NDB)]_n$	15	10%
2	RuO_2	15	30%
3	$RuCl_3{:}XH_2O$	15	10%
4	Grubbs I	15	NR
5	$RuH_2(CO)(PPh_3)_3$	15	28%[b]
6	$RuCl_2(Ph_3P)_3$	15	36%
7	$RuCl_2$(*p*-cymene)$_2$	18	72%[b,c]
8	$RuCl_2$(*p*-cymene)$_2$	18	17%[d]
9	$RuCl_2$(*p*-cymene)$_2$	18	28%
10	No catalyst	18	NR

[a] yields based on GC, [b] isolated yields, [c] reaction done without Ad-CO_2H,[d] reaction done without base, [e] reaction done without Ad-CO_2H and base

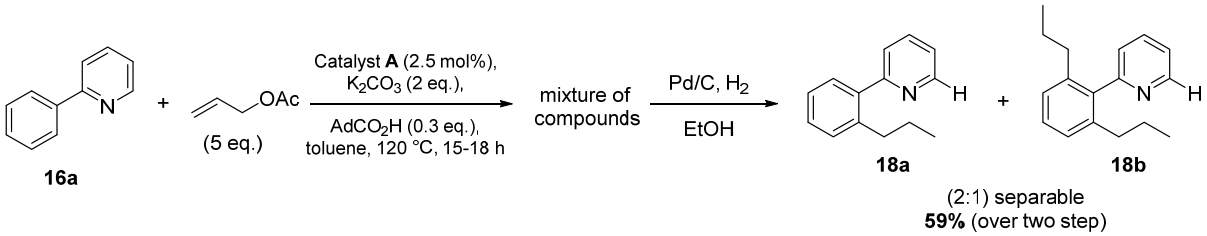
These initial results clearly indicated that the C–H activation was happening on the pyridine ring instead of the phenyl ring. Next, the scope of the other allylating agents in the C6–propenylation reaction of **16a** was examined using the same catalyst in toluene as the solvent. The reaction was found to be sluggish with allyl chloride and there was no reaction with crotyl bromide. When allyl iodide was employed, although complete consumption of **16a** was observed, but the product **17a** was isolated in poor yield (Scheme 2.6).



Scheme 2.6: *Reactivity of allyl chloride and allyl iodide*

Interestingly, the reaction with allyl acetate led to the isolation of a mixture of compounds resulting from the mono- and diallylation on the phenyl ring with a partial double bond migration. The separation of the product by column chromatography was found to be

difficult. In order to identify the distribution of the mono- and diallylation products, the crude mixture was subjected for hydrogenation. After hydrogenation, the mono- and the dialkylation products **18a** and **18b** were separable and characterized by extensive NMR data analysis (Scheme 2.7).

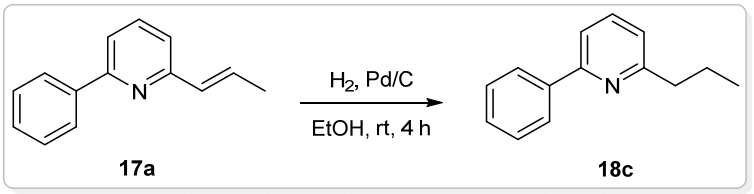


Scheme 2.7: *Reactivity of allyl acetate*

In the ^{1}H NMR spectrum of compound **18a**, two –CH_2 protons were seen to resonate at δ 1.44–1.52 and 2.66–2.69 ppm as multiplets. Most importantly, the characteristic C6-proton of the pyridine ring was seen to resonate at δ 8.68 ppm, indicating that the reaction occurs exclusively at the *ortho* C–H of phenyl ring. The –CH_3 protons appeared at δ 0.81 ppm as triplet with a coupling constant J = 7.3 Hz. In the ^{13}C NMR spectrum of compound **18a**, the two –CH_2 carbons were seen to resonate at δ 24.4, 35.0 ppm as triplets and methyl carbon at δ 14.0 ppm as quartet. A newly formed quaternary carbon appeared at δ 140.4 ppm and a characteristic C6 carbon of the pyridine ring was seen to resonate at δ 149.1 ppm as a doublet. Compound **18a** was further confirmed by the presence of strong mass peaks at m/z 198.1265 (100%, $[M+H]^+$) in the HRMS spectrum.

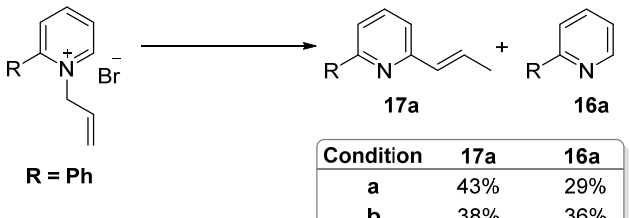
Similarly in the ^{1}H NMR spectrum of compound **18b**, one multiplet resonated at δ 1.36–1.49 ppm for two –CH_2 groups and the remaining four –CH_2 protons appeared as a doublet of triplet at δ 2.28 ppm with a coupling constant J = 1.6, 7.1 Hz. The characteristic C6-proton of pyridine ring was seen to resonate at δ 8.70 ppm and the methyl protons appeared at δ 0.76 ppm as a triplet with a coupling constant J = 7.3 Hz. In the ^{13}C NMR spectrum of compound **18b**, four –CH_2 carbons were seen to resonate at δ 24.1 (2C), 35.6 (2C) ppm as a triplets and two methyl carbons appeared at δ 14.1 (2C) ppm as a quartet. The newly formed quaternary carbon and the characteristic C6 carbon of the pyridine ring were seen to resonate at δ 140.4 and 149.6 ppm as singlet and doublet respectively. The presence of strong mass peaks at m/z 240.1754 (100%, $[M+H]^+$) in the HRMS spectrum further confirmed the compound **18b**.

Furthermore, the regioselectivity was also confirmed by comparing the NMR data of compound **18a** with **18c**. Compound **18c** was prepared by the hydrogenation of compound **17a** in the presence of catalytic Pd/C in EtOH (Scheme 2.8).



Scheme 2.8: *Hydrogenation of compound **17a***

The different reactivity of allyl bromide and allyl acetate suggests that the reaction might be proceeding through the N–allylation of pyridine in the case of allyl bromide, a transformation that would increase the acidity of the C–H bond at the C2 position. To check our hypothesis, we prepared the allyl bromide salt of **16a** by treating 2-phenyl pyridine with allyl bromide in toluene under reflux conditions. Then it was subjected for different reaction conditions as shown in Scheme 2.9. When the reaction of the N–allylpyridinium salt was performed under standard conditions (without any additional allyl bromide) gave **17a** was obtained in 43% yield along with **16a** (29%). Furthermore, when the reaction was conducted in absence of additive (1-Ad-CO_2H), as well as without any additional allyl bromide, the C6-propenylated product **17a** was obtained together with **16a** in 38% and 36% yields respectively; while less than 10% yield of **17a** and 49% yield of **16a** were obtained when the reaction was performed only in the presence of catalyst **A** and toluene at 120 °C for 15 h (Scheme 2.9). The results obtained from this control experiment using the N–allylpyridinium salt as a substrate supports our argument.



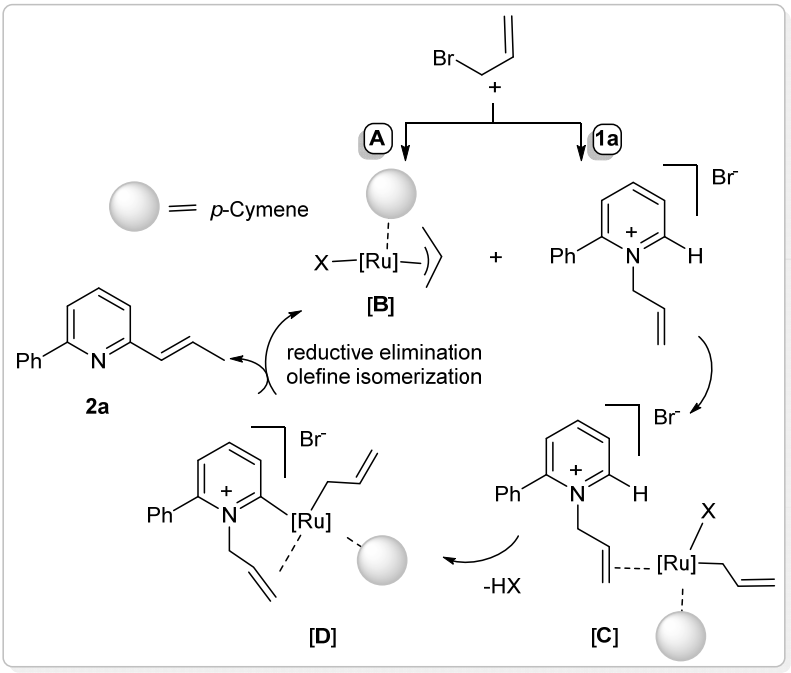
Condition	17a	16a
a	43%	29%
b	38%	36%
c	<10%	49%

Reagent and Condition: (a) catalyst A, K_2CO_3 (2 eq.), 1-Ad-CO_2H (0.3 eq.), Toluene, 120 °C, 15 h
(b) catalyst A, K_2CO_3 (2 eq.),Toluene, 120 °C, 15 h
(c) catalyst A, Toluene, 120 °C, 15 h

Scheme 2.9: *Control experiments using N–allylpyridinium salt*

Based on the complementary reactivity of allylbromide and allylacetate and result obtained from control experiments of the allyl bromide salt of **16a**, we extend the following tentative mechanism. We propose that, initially, the η3-allyl ruthenium complex [**B**] would be formed by the reaction between allyl bromide and catalyst (corresponding to the η3-allyl ruthenium mass peak at m/z 710.82, which was observed upon reaction of catalyst **A** with allyl bromide in toluene). This upon π-complexation with the pendant *N*–allyl unit of the

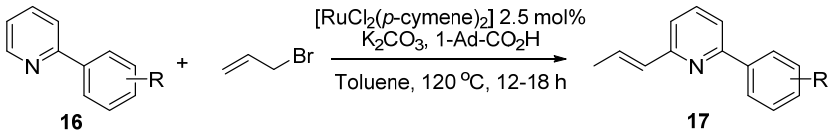
pyridine nitrogen should lead to the σ-allyl complex [**C**]. Next, the C6–H deprotonation and subsequent formation of the Ru(II)-intermediate [**D**], followed by reductive elimination concomitant with the *N*–deallylation, would regenerate the η3- allyl ruthenium complex [**B**] along with the formation of the intermediate C6-allylpyridine. This would undergo olefin migration in the presence of the ruthenium catalyst giving compound **17a**.



Scheme 2.10: *A tentative mechanism for the ruthenium catalyzed direct allylation of 2-phenyl pyridine*

After successfully optimizing the reaction conditions for the ruthenium catalyzed direct C6-propenylation, our next job was to investigate the substrate scope of the present reaction. Table 2.3 reveals the generality of the direct allylation reaction. Diverse 2-aryl pyridine derivatives have been employed. In the majority of the cases, the corresponding 2-substituted-6-(1*E*-prop-1-enyl)-pyridine derivatives were obtained in good to excellent yields. The propenylation of 2-aryl pyridine derivatives (aryl=4-MeC_6H_4 **16b**, 4-AcC_6H_4 **16c**, and 3,4-$(MeO)_2C_6H_3$ **16d**) proceeded smoothly and afforded the products (**17b–17d**) in 60–70% yields. In the ^{1}HNMR spectrum of all the three compounds **17b–17d**, the characteristic C6-pyridine ring proton was seen to disappear and olefinic protons were seen to resonate between 6.5–7.0 ppm as a doublet of quartets; whereas the newly formed quaternary carbon resonated at $\delta \approx$155–156 ppm as a singlet in the ^{13}C NMR spectra of compounds **17b–17d**.

Table 2.3: *The scope of the Ru-catalyzed propenylation reaction of substituted 2-phenyl pyridine derivatives*



Entry	Substrate	Product (Yield)	Entry	Substrate	Product (Yield)
1	**16a** (R = H) **16b** (R = Me)	**17a** (67%) **17b** (63%)	5	**16f**	**19**(63%)
2	**16c**	**17c** (66%)	6	**16f**	**17f** (62%)
3	**16d**	**17d** (62%)	7	**16g**	no reaction
4	**16e**	**17e** (61%)	8	**16h**	**17h** (<20%)

The reaction of 2-(3,4-dichlorophenyl)pyridine (**16e**) needs a special mention. In this case, the product **17e** resulting from one pot direct and directed C–H activation/allylation was obtained exclusively in 61% yield (Table 2.3, entry 4). The structure of compound **17e** was confirmed with the help of NMR and HRMS. In the ^{1}H NMR of compound **17e**, the two olefinic protons appeared at δ 6.53 and 6.79 as a doublet of quartet; one **Hd** at δ 5.84 as a ddt with J = 6.5, 10.1, 16.7 Hz and two protons (=CH_2, **He**) were seen to resonate at 4.93 and 5.01 as a ddd with $J \approx$ 1.6, 3.3, 17.0 Hz as well as one allylic –CH_2 (**Hc**) appeared at δ 3.46 as doublet of triplet with coupling constant J = 1.5, 6.4 Hz, which indicates that the presence of two olefin units, one internal and one terminal. The presence of one allylic moiety was further confirmed by two –CH_2 (**c** and **e**) carbons that resonated at δ 36.7 and 116.6 as a triplet in the ^{13}C NMR spectrum. The disappearance of the C6–H peak and the presence of a singlet for the new quaternary carbon at δ 155.8 indicate the presence of the propenyl unit at the C6 carbon of pyridine ring as our expected product. Furthermore, the presence of two singlets at δ 7.37 and 7.50 ppm suggested that the second allyl group is present at the *ortho*

carbon of the phenyl ring. This was further confirmed by the presence of a strong peak in HRMS: *m/z* 304.0662 ([M+H]$^+$, 100%).

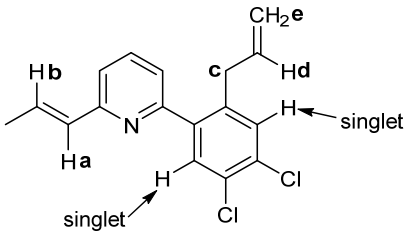
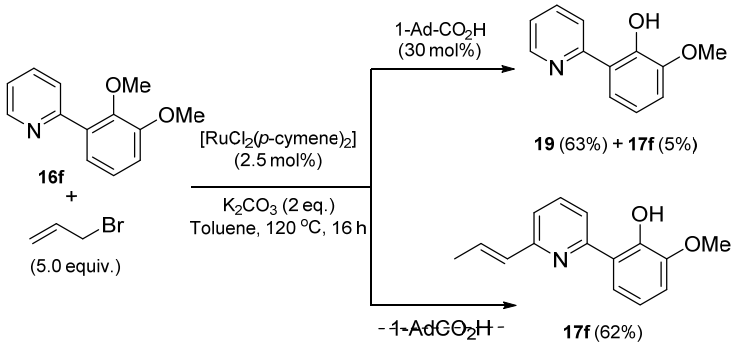


Figure 2.2

Surprisingly, the reaction of 2-(2,3-dimethoxyphenyl)pyridine under the standard reaction conditions gave the *ortho*-*O*-desmethyl compound **19** as the major product (isolated in 63% yield) and **17f** was obtained in less than 5% yield (Scheme 2.11).[63] The structure of the demethylated compound **19** was confirmed with the help of NMR and HRMS data. In the ^{1}H NMR spectrum of compound **19**, one methyl group was found to disappear and the other resonated at δ 3.92 ppm. The newly generated peak resonated at δ 14.75 (br s, 1H) ppm, indicating the presence of a phenolic –OH. In the ^{13}C NMR spectrum, the methyl carbon appeared at δ 56.0 ppm and the quaternary carbon attached to –OH and –OMe were seen to resonate at δ 149.4 and 150.2 ppm as a singlet. In the HRMS spectrum, the presence of a strong peak at 202.0889 ([M+H]$^+$, 100%) confirmed the compound **19**. It is believed that the deprotection was facile because of the presence of nitrogen atoms of the pyridine ring, with which the ruthenium would coordinate together with the oxygen of the –OMe and the presence of some nucleophile (like Cl) undergoes nucleophilic attack at the methyl carbon atom, providing the H_3C–O bond cleavage product.[63]



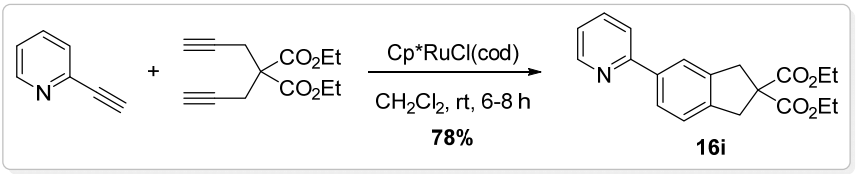
Scheme 2.11: *Ru-catalyzed propenylation reaction of compound **16f***

However, the same reaction in the absence of Ad-CO_2H gave the product **17f** in 62% yield (Table 2.3, entry 6); where *o*-demethylation was also found along with the required C6-propenylation (Scheme 2.11). In the ^{1}H NMR spectrum of compound **17f**, the olefinic protons were seen to resonate at δ 6.45 (dq, J = 1.6, 15.6 Hz, 1H), 6.83 (dq, J = 6.6, 15.7 Hz, 1H)

ppm, and $-CH_3$ protons at δ 1.93 ppm as doublet of doublet with J = 1.6, 6.7 Hz. The appearences of a singlet at δ 3.93 ppm integrating for three protons indicated that only one –OMe is present. The free –OH was seen to resonate at δ 15.63 ppm. In the ^{13}C NMR spectrum of compound **17f**, the characteristic C6 quaternary carbon resonated at δ 152.3 ppm and two methyl carbons at δ 18.4 and 56.0 ppm. The compound **17f** was further confirmed by HRMS, where the strong mass peak was observed at m/z 242.1196 corresponding to $[M+H]^+$.

Coming to the compatibility of substrates having an electron deficient pyridine ring such as 3-nitro-2-phenypyridine (**16g**). The reaction was sluggish and provided only small amounts of the directed *ortho* C–H allylation product **17h** with 5-nitro- 2-phenylpyridine (**16h**).

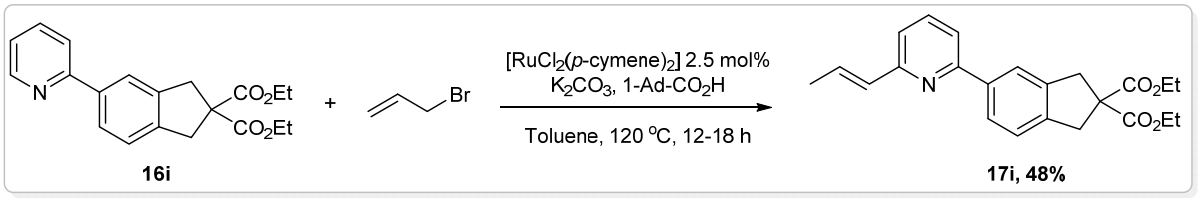
To look at the compatibility of an ester group, we prepared compound **16i** through the cyclotrimerization of 2-ethynylpyridine (1.0 eq.) and 2,2-di(prop-2-yn-1-yl)malonate (1.1 eq.) in the presence of Cp*Ru(cod)Cl (3 mol%) in dichloromethane at room temperature (Scheme 2.12). The compound **16i** was fully characterized with the help of NMR and HRMS. In the ^1H NMR spectrum of compound **16i**, the characteristic pyridine ring C6–H appeared at δ 8.66 ppm as a broad doublet, the two $-CH_2$ as well as the $-CH_3$ protons of diesters groups were seen to resonate at δ 4.20 and 1.25 ppm as a quartet and triplet with a coupling constant J = 7.02 Hz respectively. Most importantly, the disappearance of the alkyne proton was observed. The newly formed two benzylic $-CH_2$ groups appeared at δ 3.62 and 3.65 ppm as a singlet. On the other hand, the remaining aromatic protons together with newly formed rings were seen to resonate in the range of δ 7.19–7.83 ppm. In the ^{13}C NMR spectrum of compound **16i**, the two carbonyl carbons of the esters group resonated at δ 171 ppm and the C2–quaternary carbon of pyridine ring appeared at δ 157 ppm as a singlet. The presence of a strong peak in the HRMS: *m/z* 340.1524 ($[M+H]^+$, 100%) confirmed the compound **16i**.



Scheme 2.12: *Preparation of compound **16i** by trimerization*

Next, the compound **16i** was subjected for the direct allylation and the corresponding C6-propenylated product **17i** was obtained in 48% yield (Scheme 2.13). The structure of the compound **17i** was established with the help of NMR and HRMS data. In the ^1H NMR spectrum of the compound **17i**, the characteristic pyridine C6–H disappeared and two olefinic protons resonated at δ 6.55 (dq, J = 1.6, 15.6 Hz, 1H) and 6.89 (dq, J = 6.7, 15.5 Hz, 1H)

ppm as well as the methyl group at δ 1.95 ppm as doublet of doublet (J = 1.6, 6.7 Hz). In the ^{13}C NMR spectrum of compound **17i**, the newly generated quaternary carbon appeared at the δ 155.7 ppm. The peak resonated at δ 1.25 and 4.20 ppm as a triplet and quartet with net J = 7.20 Hz in ^{1}H NMR and the ester carbon at δ 171.6 ppm as singlet in the ^{13}C NMR confirmed that the ester groups are intact. The presence of a strong peak in the HRMS: *m/z* 380.1853 ([M+H]$^{+}$, 100%) supported the assigned structure **17i**.

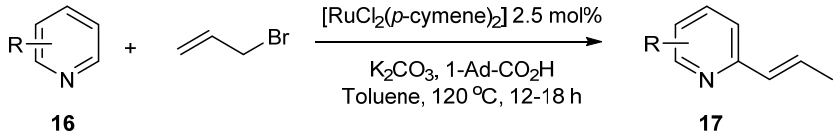


Scheme 2.13: *Ruthenium catalyzed propenylation reaction of compound **17i***

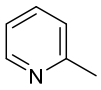
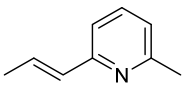
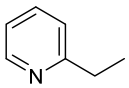
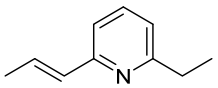
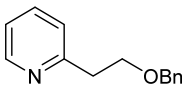
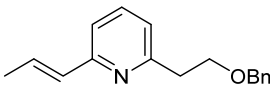
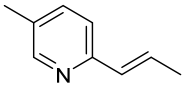
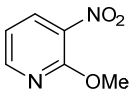
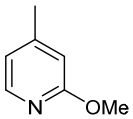
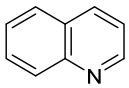
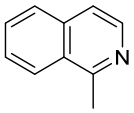
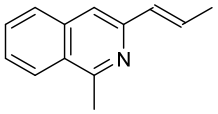
Next, the direct allylation of various pyridine and quinoline derivatives was examined. The reaction with simple alkyl pyridine derivatives such as 2-picoline (**16j**), 2-ethyl pyridine (**16k**), and 3-picoline (**16m**) gave exclusively the Csp2–H propenylation products **17j**, **17k**, and **17m**, respectively, with complete regio- and stereoselectivity (Table 2.4, entries 1, 2, and 4).[64] The regioselectivity of compound **17j**, **17k**, and **17m** was established with the help of NMR. For example, in the ^{1}H NMR spectrum of compound **17j** the two olefinic protons were seen to resonate at δ 6.51 (dq, J = 1.3, 15.6 Hz) and 6.65 (dq, J = 6.4, 15.6 Hz), whereas the characteristic C6-H disappeared. The C2–methyl group resonated at δ 2.52 ppm which shows that the reaction regioselectively is at the sp^2 C–H rather than at the sp^3 C–H. In the ^{13}C NMR spectrum of compound **17j**, two methyl carbons appeared at δ 18.3, 24.5 ppm and the two quaternary carbons of C2 and C6 carbon were seen to resonate at δ 157.8 and 155.5 ppm as singlet. Only the mono propenyl at the C6 position was observed when the reaction of 3-picoline was performed under the present condition.

In the ^{1}H NMR spectrum of compound **17m**, the C2–H resonated at δ 8.32 ppm as a broad singlet, whereas the remaining two aromatic protons C4/5–H appeared at 7.12 and 7.38 as doublets with $J \approx$ 8.0 Hz. In the ^{13}C NMR spectrum of compound **17m**, the C2 and C6 carbons appeared at δ 149.6 and 153.4 ppm as doublet and singlet respectively. The two methyl carbons appeared at δ 18.1 and 18.3 ppm, while the C3 quaternary carbon resonated at δ 130.8 ppm as a singlet.

Table 2.4: *Ru-catalyzed propenylation reaction of substituted pyridine derivatives*



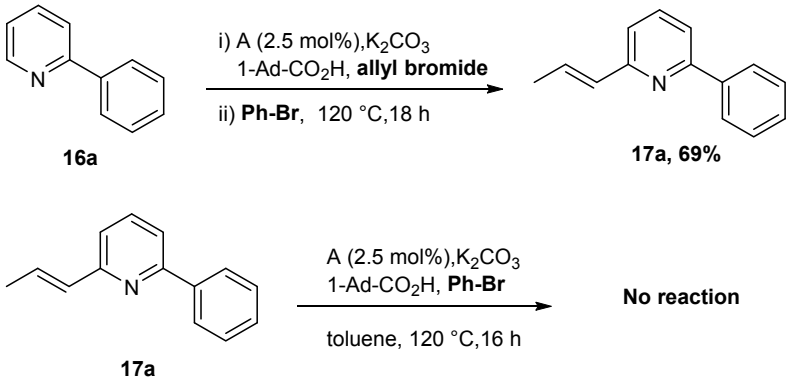
16 **17**

Entry	Substrate	Product	Yield
1	 **16j**	 **17j**	**67%**
2	 **16k**	 **17k**	**65%**
3	 **16l**	 **17l**	**22%**
4	 **16m**	 **17m**	**54%**
5	 **16n**	No Reaction	---
6	 **16o**	No Reaction	---
7	 **16p**	Starting Decompose	---
8	 **16q**	 **17q**	**42%**

However, pyridine **16l** having a 2-benzyloxyethyl group gave the corresponding product **17l** in poor yield (Table 2.4, entry 3). The reactions of disubstituted pyridine derivatives having either nitro or methoxy groups were found to be not compatible under these conditions (Table 2.4, entries 5 and 6). For example, 3-nitro- 2-methoxypyridine (**16n**)

and 2-methoxy-4-methylpyridine (**16o**) were intact under the standard reaction conditions. Next, we examined the possibility of the direct propenylation of quinoline and 1-methyl-isoquinoline. Surprisingly, quinoline (**16p**) decomposed under the standard reaction conditions and 1-methyl-isoquinoline (**16q**) gave the product **17q** in low yields (Table 2.4, entries 7 and 8). The structure of compound **17q** was confirmed by NMR and HRMS. In the ^{1}H NMR spectrum of compound **17q**, the two olefinic protons appeared at δ 6.58 (br dd, J = 1.4, 15.4 Hz, 1H), 6.90 (br dq, J = 6.8, 15.5 Hz, 1H) ppm and the two methyl groups resonated at δ 1.96 (dd, J = 1.3, 6.8 Hz, 3H) and 2.94 (s, 3H) ppm. In the ^{13}CNMR spectrum of compound **17q**, the methyl carbons resonated at δ 18.4, 22.6 ppm as a quartet and the four quaternary carbons, including newly formed ones, were seen to resonate at δ 126.5, 136.7, 148.6, 158.4 ppm. In the mass spectrum, the strong peak found at m/z 184.1121 confirmed the compound **17q**.

After having established an unprecedented direct allylation of pyridine derivatives, the initial objective of the sequential directed allylation and arylation has been revised to the sequential direct propenylation and directed arylation of 2-aryl pyridine derivatives in one pot using the same catalyst.[54-56] In this regard, using 2-phenyl pyridine as a model substrate, the propenylation reaction was carried out under the established reactions conditions and subsequently after complete consumption of the starting material (checked by TLC) bromobenzene (**20a**) was added to the reaction mixture and heating at 120 °C was continued for an additional 16 h. The characterization of the product formed from this reaction revealed that the propenylation product **17a** was obtained as the only product in 69% yield. Even after subjecting the isolated C6–propenylated product **17a** for direct arylation under these standard reaction conditions, the reaction was found to be unsuccessful and the starting material was recovered back (Scheme 2.14).



Scheme 2.14: *A one-pot sequential propenylation and arylation reaction of 2-phenyl pyridine*

This result might be due to the formation of either a stable N-coordinated ruthenacycle or a related π complex, which could undergo neither C–H bond ruthenation nor oxidative addition across the Ar–X bond. Another possibility might be the steric hindrance around the pyridine nitrogen atom (in **17a**, the pyridine moiety is 2,6-disubstituted), a characteristic that may prevent the pyridine nitrogen atom from acting as a directing group.[65]

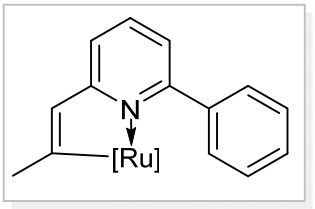
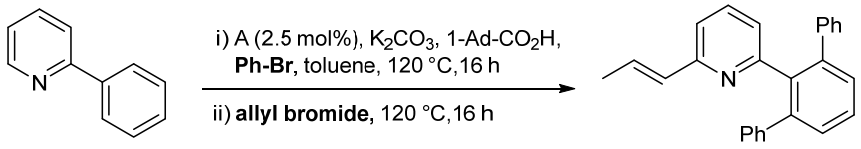


Figure 2.3

As a result, we changed the order of addition of the reactants, i.e. first arylation followed by propenylation. For example, the arylation of the phenyl ring was carried out using bromobenzene under the established reactions conditions (120 °C) and subsequently after complete consumption of the starting material (checked by TLC) allyl bromide was added and heating of the reaction mixture at 120 °C was continued for an additional 16 h. Surprisingly compound **21aa** was obtained in 89% yield through directed and direct C–H arylation followed by propenylation of 2-phenyl pyridine (Scheme 2.15).

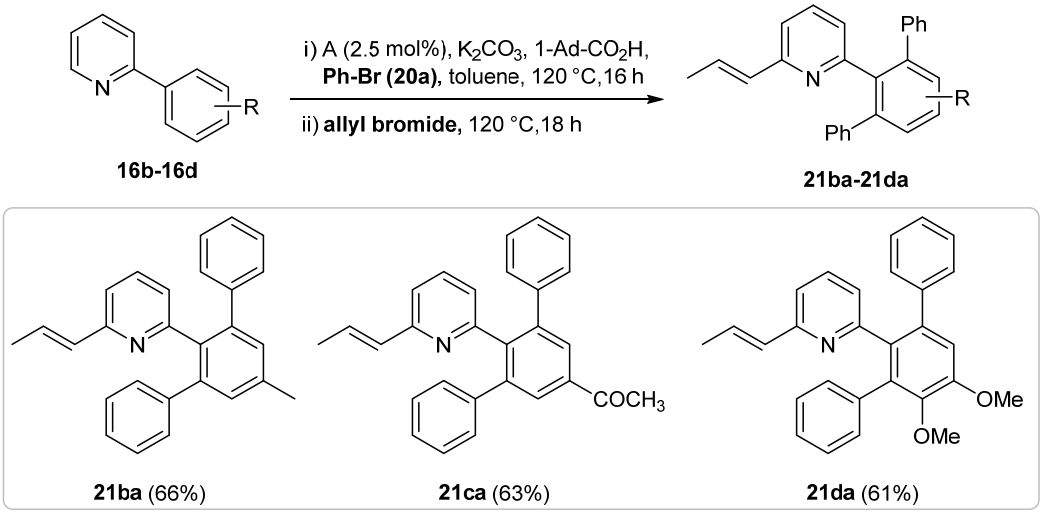


16a **21aa, 89%**

Scheme 2.15: *A one-pot sequential arylation and propenylation reaction of 2-phenyl pyridine*

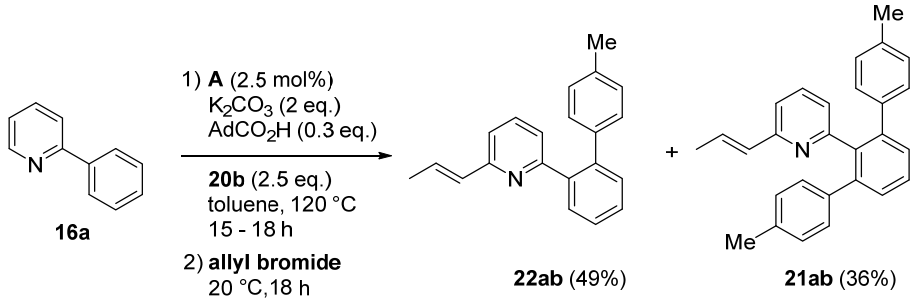
The compound **21aa** was fully characterized with the help of spectral and analytical data. In the ^{1}H NMR spectrum of compound **21aa**, the methyl protons resonated at δ 1.77 ppm as a broad doublet with J = 5.2 Hz. The two olefinic protons appeared at δ 6.05–6.30 ppm as a multiplet and the 10 protons of newly added two phenyl rings were seen to resonate at δ 7.07–7.22 ppm as a multiplet and, most importantly the C-6 proton of the pyridine ring was seen to disappear. In the ^{13}C NMR spectrum of compound **21aa**, the seven quaternary carbons at δ 141.8 (2C), 142.0 (3C), 155.0, 158.0 ppm were observed. The methyl carbon was seen to resonate at δ 18.2 ppm as a quartet. The constitution of the compound was further confirmed by HRMS, where a strong peak at m/z 348.1731 corresponding to $[M+H]^+$ was observed.

After successfully optimizing the reaction conditions for sequential directed and direct C–H activation, next the scope of this one-pot protocol has been explored by employing various 2-aryl pyridine derivatives and with three different aryl halides such as bromobenzene (**20a**), *p*-methyl iodobenzene (**20b**) and *p*-acetyl chlorobenzene (**20c**). The reaction of substrates **16b**, **16c,** and **16d** with bromobenzene as the arylating agent gave the diarylation and propenylation products **21ba–21da** in 60–70% yields (Scheme 2.16). Compound **21ba–21da** were fully analysed with help of NMR and HRMS similar to the previous compound **21aa**.



Scheme 2.16: *One-pot sequential arylation and propenylation reaction of **16b–16d** with **20a***

When 4-methyl-iodobenzene (**20b**) was employed, the reaction was slow and, even after 40 hours, was incomplete. The reaction afforded the mono- and diarylation products **22ab** (49%) and **21ab** (36%) respectively (Scheme 2.17).

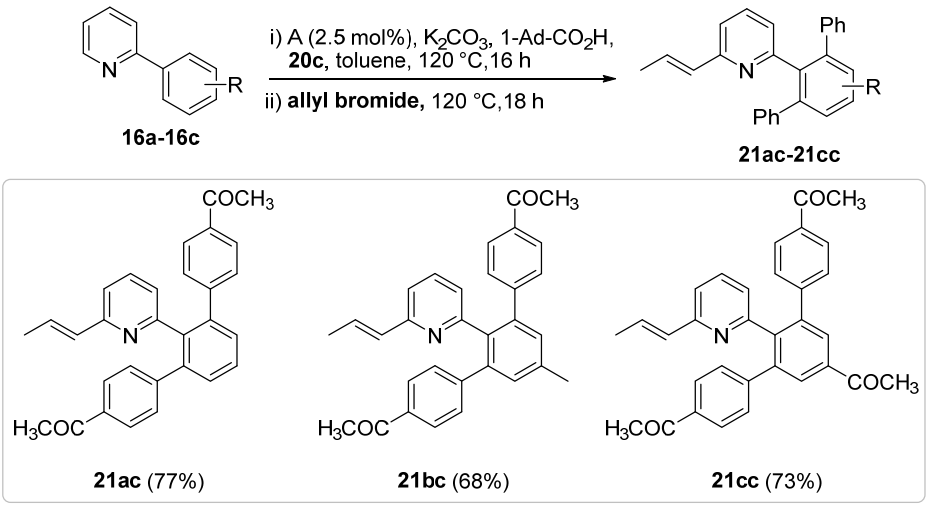


Scheme 2.17: *one-pot sequential arylation and propenylation reaction of **16a** with **20b***

Both the compounds were characterized by NMR and HRMS. In the ^{1}H NMR spectrum of compound **22ab**, the olefinic –CH appeared at δ 6.48–6.71 ppm as a multiplet and the methyl protons resonated at δ 1.92 (dd, J = 0.9, 6.2 Hz, propenyl unit) and at δ 2.31 ppm as a singlet from the toludine unit. This revealed that only one toludine group is present. In the ^{13}C NMR spectrum of compound **22ab**, two methyl carbons resonated at δ 18.3, 21.1

ppm as quartet. Most importantly, the disappearance of the pyridine ring C6 carbon doublet was observed and six quaternary carbons including newly formed ones were seen to resonate at δ 136.2, 138.6, 139.6, 140.6, 155.6, 158.7 ppm. The presence of a strong peak in the HRMS spectrum at m/z 286.1606 confirmed the compound **22ab**. However the NMR of compound **21ab** was almost similar to compound **22ab**; but a minor change was observed, for example, in the ^{1}H NMR spectrum of compound **21ab**, the two aromatic methyl groups resonated at δ 2.26 ppm as singlet and also in the ^{13}C NMR spectrum of compound **21ab** two new quaternary carbons were seen to resonate at δ 135.7 and 138.9 ppm as singlet. Compound **21ab** was also confirmed by HRMS, where a strong peak was observed at m/z 376.2022 corresponding to $[M+H]^{+}$.

Next, when the reactions of **16a**, **16b**, and **16c** were conducted with 4-acetylchlorobenzene (**20c**) as the arylating reagent, the reaction proceeded smoothly and gave the required diarylation and propenylation products **21ac–21cc** in 70–80% yields (Scheme 2.18). The compounds **21ac–21cc** were fully analysed with the help of NMR and HRMS. For example, in the ^{1}H NMR spectrum of compound **21ac**, two methyl groups attached to carbonyl group appeared at δ 2.55 ppm as singlet, one methyl of propenyl unit appeared at δ 1.76 ppm as a broad doublet with J = 5.2 Hz and the two alkene –CH resonated at δ 6.06–6.28 ppm as multiplets. In the ^{13}C NMR spectrum of compound **21ac**, one methyl carbon of the propenyl unit and the two methyl carbons attached to carbonyl were seen to resonate at δ 18.2 and 26.6 (2C) as quartets respectively. Two carbonyl carbons resonated at δ 197.9 (2C) ppm together with six other newly formed quaternary carbons appearing at δ 135.0 (2C), 135.5 (d), 141.0 (2C), 146.6 (2C) ppm as singlets. Compound **21ac** was further confirmed by HRMS, where the strong peak was found at m/z 432.1918 corresponding to $[M+H]^{+}$.

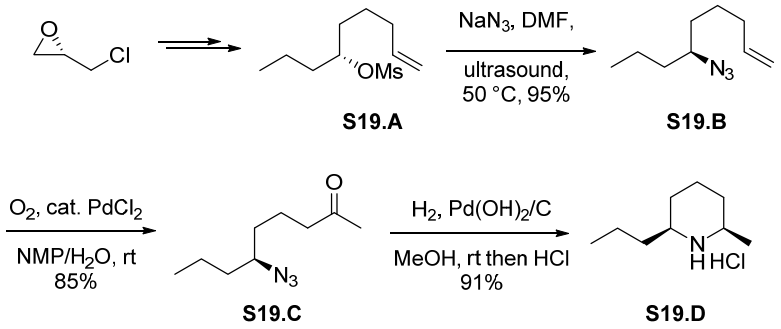


Scheme 2.18: *One-pot sequential arylation and propenylation reaction of **16a–16c** with **20c***

Synthesis of Dihydropinidine

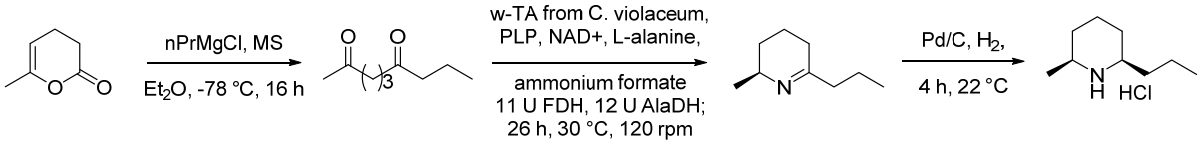
Having a simple catalytic method for the direct functionalization of pyridine derivatives with allyl bromide *via* C–H activation, next we looked at the possibility of extending the utilization of the resulting products, in this context, the dihydropinidine caught our attention. Dihydropinidine was isolated from the needles of Piceapungens, the bark of Picea sitchensis and the mexican bean beatle Epilachna varivestis as well.[66] Both the enantiomers of dihydropinidine are found to be potential antifeedant against the pine weevil Hylobius abietis.[67] In the literature numerous synthetic approaches have been explored for the synthesis of dihydropinidine.[68] The reported syntheses required long reaction sequences to construct the stereocenters selectively; moreover some of them suffer from low yield and the necessity of protecting groups. A couple of efficient synthesis of dihydropinidine has been described below.

In 2011, Szolcsányi's group has described the protecting group free total syntheses of 2,6-disubstituted piperidine alkaloids (+)-dihydropinidine from (*S*)-epichlorohydrin employing the regioselective Wacker–Tsuji oxidation of alkenyl azide and the diastereoselective reduction of cyclic imine as key steps. The key azido fragment (**S19.B**) was prepared from (*S*)-epichlorohydrin in seven steps and the subsequent Wacker–Tsuji oxidation gave azido ketone (Scheme 2.19). The azido ketone (**S19.C**) underwent intramolecular Staudinger-aza-Wittig condensation to furnish the cyclic imine, which upon C=N reduction gave (+)-dihydropinidine.[68d]



Scheme 2.19: *Synthesis of (+)-DihydropinidineHCl*

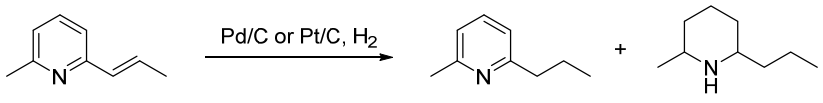
A seminal report from Kroutil and co-workers has documented the preparation of chiral 2,6-disubstituted piperidines through the regio- and stereoselective asymmetric monoamination of diketones using various ω-*trans* aminases. With this approach, synthesis of the alkaloid (+)-dihydropinidine has been achieved in three steps from diyhdropyrane-2-one (Scheme 2.20).[68e]



Scheme 2.20: *Chemoenzymatic total synthesis of (+)-dihydropinidine*

Considering the fact that the compound **17j** has the complete carbon framework of dihydropinidine, the exhaustive hydrogenolysis of compound **17j** was carried out under different reaction conditions, as shown in Table 2.5. However, the reduction of **17j** with the Pd/C or the Pt/C column using MeOH or H_2O as solvent found that the reaction ended up either with the olefin reduction only or with a mixture of both products (**18d** and **23**), but none of the conditions were able to give the completely reduced product.

Table 2.5: *Different reaction conditions for reduction of 2, 6-disubstituted pyridine*

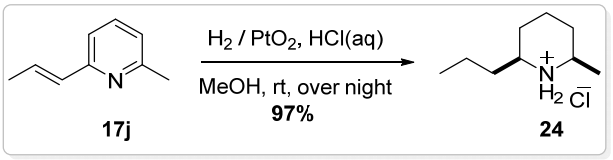


17j **18d** **23**

Entry	solvent	pressure	flow rate	temp (°C)	18d	23
1	MeOH	1 atm	—	rt	exclusive	not observed
2	MeOH	60 barr	0.7 mL/min	45	90-95%	5-10%
3	MeOH	70 barr	0.4 mL/min	80	**18d:23** mixture[a]	
4	H_2O/H^+	28 barr	—	80	—	—
5	MeOH	28 barr	—	80	—	—
6	MeOH	70 barr	0.5 mL/min	80	**18d:23** mixture[a]	
7	MeOH	70 barr	0.5 mL/min	80	**17j:18d** mixture[b]	

[a] Reaction mixture recycled 3 times. [b] Pt/C column used for reaction.

Surprisingly, when we performed the reduction employing a catalytic amount of PtO_2 in aq.HCl/EtOH at 50 bar H_2 pressure, the hydrochloric salt of (±)-dihydropinidine (**24**) was obtained in quantitative yield with complete selectivity for the 1,6-*cis*-disubstituted product (Scheme 2.21).



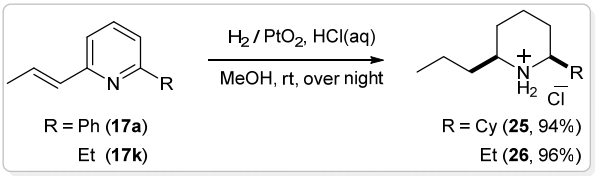
17j **24**

Scheme 2.21: *The synthesis of (±)-dihydropinidine*

The structure of the resultant product was confirmed with the help of NMR and HMRS. In the ^{1}H NMR spectrum of (±)-dihydropinidine (**24**), two olefinic and three aromatic C–H were seen to disappear, whereas newly formed five $-CH_2$ protons resonated between δ

1.23–2.10 ppm as multiplets and two N–H peaks appeared at δ 8.99 and 9.35 ppm as broad singlets. In the ^{13}C NMR spectrum of compound **24**, two –CH carbons were seen to resonate at δ 54.5 and 58.4 ppm as a doublet, two methyl carbons at δ 13.7 ad 19.4 ppm as quartet and the remaining five $-CH_2$ appeared at δ 18.8, 22.8, 27.4, 30.7, 35.1 ppm as triplet. The constitution of compound **24** was further confirmed by the presence of a strong peak in HMRS at 142.1598 ($[M+H]^+$, 100%).

Subsequently, the hydrogenation of compounds **17a** and **17k** was also performed under the same reduction conditions to afford fully reduced products **25** and **26** respectively in excellent yields (Scheme 2.22).



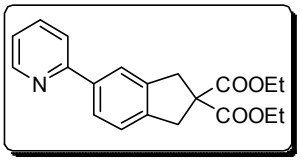
Scheme 2.22: *The synthesis of related analogues of (±)-dihydropinidine*

Conclusion

In conclusion, the direct C6 propenylation of pyridine and 2-aryl pyridine derivatives has been established. The [Ru(*p*-cymene)Cl_2]$_2$complex has been employed as the catalyst and the conditions employed are similar to those reported for the directed C–H activation of 2-aryl pyridines. Among the various allyl reagents screened, allyl bromide was found to be best for the direct propenylation, whereas with allyl acetate, the directed *ortho* C–H activation of the phenyl ring was found to be the predominant pathway. Subsequently, a one pot sequential directed and direct C–H activation of 2-phenyl pyridine derivatives has been executed successfully. The synthetic potential of this direct allylation method has been manifested by preparing (±)-dihydropinidine and its derivatives in two catalytic steps, including this propenylation.

EXPERIMENTAL

A. Procedure for the synthesis of Diethyl 5-(pyridin-2-yl)-1H-indene-2,2(3H)-dicarboxylate (16i):

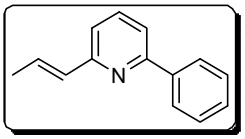


A solution of 2-ethynylpyridine (100 mg, 1.0 mmol) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (252 mg, 1.1 mmol) in CH_2Cl_2 (8 mL) was degassed with dry argon for 20 min. To this, Cp*RuCl(cod) catalyst (0.03 mmol) was added, and the mixture was stirred for 6-8 h at room temperature. The solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography to procure the cyclotrimerization product **16i** (258 mg, 78%) as colourless liquid; R_f 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 2981, 2925, 1732, 1588, 1466, 1366, 1245, 1156, 1067, 860, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 6H), 3.62 (s, 2H), 3.65 (s, 2H), 4.20 (q, J = 7.1 Hz, 4H), 7.19–7.21 (m, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.67 (br d, J = 7.9 Hz, 1H) 7.71–7.74 (m, 1H), 7.76 (br d, J = 7.9 Hz, 1H), 7.83 (br s, 1H), 8.66 (d, J = 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0 (q, 2C), 40.3 (t), 40.4 (t), 60.6 (s), 61.7 (t, 2C), 120.6 (d), 122.0 (d), 122.8 (d), 124.5 (d), 125.9 (d), 136.9 (d), 138.2 (s), 140.9 (s), 141.2 (s), 149.3 (d), 157.4 (s), 171.5 (s, 2C) ppm; ESI-MS: 340.10 (25%, $[M+H]^+$), 362.05 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{20}H_{21}NO_4H^+$ 340.1549, found 340.1524.

B. Representative Procedure for C6–H 1-propenylation of pyridines derivatives:

$[Ru(p\text{-cymene})Cl_2]_2$ (9.8 mg, 0.016 mmol) was added to suspension of 2-phenylpyridine (100 mg, 0.64 mmol), K_2CO_3 (180 mg, 1.3 mmol), 1-$AdCO_2H$ (35 mg, 0.2 mmol) in dry toluene (2 ml). The reaction mixture was degassed with argon for 10 min and allyl bromide (0.3 ml, 3.2 mmol) was added and the resulting solution was stirred at 120 °C for 18–20 h. The reaction mixture was poured into mixture of ice cold diethyl ether and water. The organic layer was separated and the aqueous layer was extracted (3 x 10 mL) with ether. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified over silica gel column (5→7 % ethyl acetate and pet ether) to afford compound **17a** (84 mg, 67%) as yellow liquid.

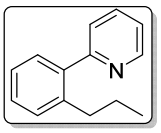
(*E*)-2-Phenyl-6-(prop-1-en-1-yl) pyridine (17a):



The general procedure B was followed using 2-phenyl pyridine **16a** (100 mg, 0.64 mmol) as a substrate procured **17a** (84 mg, 67%) as a yellow liquid; R_f 0.5 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3061, 3029, 2962, 2851, 1658, 1565, 1442, 1259, 1159, 965, 771, 754, 622 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.96

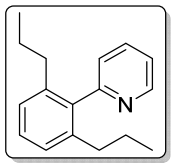
(dd, *J* = 1.6, 6.7 Hz, 3H), 6.58 (dq, *J* = 1.6, 15.5 Hz, 1H), 6.91 (dq, *J* = 6.7, 15.5 Hz, 1H), 7.15 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.39–7.50 (m, 3H), 7.53 (dd, *J* = 1.0, 7.9 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 8.00–8.07 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 (q), 118.3 (d), 119.2 (d), 126.9 (d, 2C), 128.6 (d, 2C), 128.8 (d), 130.9 (d), 131.4 (d), 137.0 (d), 139.6 (s), 155.8 (s), 156.7 (s) ppm; ESI-MS: 196.06 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{14}H_{13}NH^+$ 196.1126, found 196.1120.

2-(2-Propylphenyl) pyridine (18a):



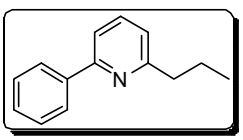
Colorless liquid; R_f 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 2959, 2928, 2869, 1586, 1562, 1425, 1149, 1023, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.3 Hz, 3H), 1.44–1.52 (m, 2H), 2.66–2.69 (m, 2H), 7.24–7.30 (m, 3H), 7.32–7.34 (m, 2H), 7.38 (br dt, *J* = 0.9, 7.8 Hz, 1H), 7.74 (dt, *J* = 1.9, 7.7 Hz, 1H), 8.68 (ddd, *J* = 0.9, 1.8, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0 (q), 24.4 (t), 35.0 (t), 121.6 (d), 124.1 (d), 125.8 (d), 128.2 (d), 129.7 (d), 129.7 (d), 136.1 (d), 140.4 (s), 140.5 (s), 149.1 (d), 160.4 (s) ppm; ESI-MS (*m/z*): 198.07 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{14}H_{15}NH^+$ 198.1282, found 198.1265**.**

(*E*)-2-Ethyl-6-(prop-1-en-1-yl)pyridine (18b):



Colorless liquid; R_f 0.4 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 2958, 2929, 2869, 1584, 1464, 1377, 1146, 1092, 1024, 789, 751 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.76 (t, *J* = 7.3 Hz, 6H), 1.36–1.49 (m, 4H), 2.28 (dt, *J* = 1.6, 7.1 Hz, 4H), 7.09–7.13 (m, 2H), 7.22–7.30 (m, 3H), 7.74 (dt, *J* = 1.9, 7.7 Hz, 1H), 8.7 (ddd, *J* = 1.1, 1.8, 4.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q, 2C), 24.1 (t, 2C), 35.6 (t, 2C), 121.6 (d), 124.9 (d), 126.5 (d, 2C), 127.8 (d), 135.7 (d), 139.9 (s), 140.4 (s, 2C), 149.6 (d), 159.7 (s) ppm; ESI-MS (*m/z*): 240.06 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{17}H_{21}NH^+$ 240.1752, found 240.1754.

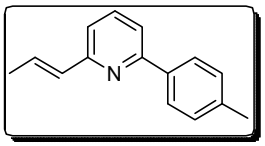
2-Phenyl-6-propylpyridine (18c):



To a solution of (*E*)-2-phenyl-6-(prop-1-en-1-yl) pyridine **17a** in EtOH and catalytic Pd/C were added and the resulting mixture was stirred under H_2 atm. for overnight. Then reaction mixture was filtered through ceilite and concentrated under reduced pressure. The resulting crude was purified over silica gel to afford **18c** in quantitative yield; R_f 0.4 (10% ethyl acetate/pet. ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.4 Hz, 3H), 1.74–1.92 (m, 2H), 2.8 (t, *J* = 7.6 Hz,

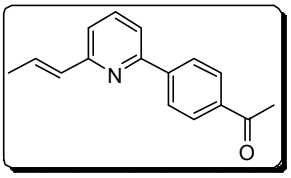
2H), 7.06 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.33–7.52 (m, 4H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.96–8.02 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 23.0 (t), 40.5 (t), 117.7 (d), 121.0 (d), 126.9 (d, 2C), 128.6 (d, 3C), 136.7 (d), 139.9 (s), 156.8 (s), 162.1 (s) ppm.

(*E*)-2-(Prop-1-en-1-yl)-6-(*p*-tolyl) pyridine (17b):



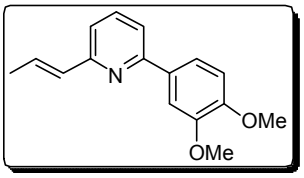
The general procedure B was followed using 2-(*p*-tolyl)pyridine **16b** (100 mg, 0.6 mmol) as a substrate yielded **17b** (78 mg, 63%) as a yellow solid; R_f 0.5 (10% ethyl acetate/pet. ether); mp: 50–51 °C; IR ($CHCl_3$)v: 3027, 2915, 1735, 1615, 1565, 1449, 1241, 1019, 966, 819, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (dd, *J* = 1.6, 6.7 Hz, 3H), 2.40 (s, 3H), 6.57 (dq, *J* = 1.5, 15.5 Hz, 1H), 6.9 (dq, *J* = 6.7, 15.5 Hz, 1H), 7.12 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.24–7.29 (m, 2H), 7.51 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.91–7.96 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 (q), 21.3 (q), 118.0 (d), 118.9 (d), 126.8 (d, 2C), 129.3 (d, 2C), 130.7 (d), 131.4 (d), 136.8 (s), 137.0 (d), 138.7 (s), 155.7 (s), 156.7 (s) ppm; ESI-MS: 210.06 (65%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{15}H_{15}NH^+$ 210.1283, found 210.1265.

(*E*)-2-(4-Acetylphenyl)-6-(prop-1-en-1-yl)pyridine (17c):



The general procedure B was followed using 2-(4-acetyl phenyl)pyridine **16c** (100 mg, 0.5 mmol) as a substrate afforded **17c** (80 mg, 66%) as a yellow syrup; R_f 0.4 (20% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 2924, 1682, 1605, 1584, 1451, 1356, 1014, 965 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.96 (dd, *J* = 1.5, 6.7 Hz, 3H), 2.63 (s, 3H), 6.57 (dq, *J* = 1.5, 15.5 Hz, 1H), 6.91 (dq, *J* = 6.7, 15.5 Hz, 1H), 7.19 (dd, *J* = 0.9, 7.6 Hz, 1H), 7.57 (dd, *J* = 1.0, 7.7 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 8.01–8.05 (m, 2H), 8.11–8.15 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.4 (q), 26.7 (q), 118.7 (d), 120.0 (d), 127.0 (d, 2C), 128.7 (d, 2C), 131.1 (d), 131.4 (d), 136.9 (s), 137.2 (d), 143.8 (s), 155.2 (s), 156.0 (s), 197.9 (s) ppm; ESI-MS: 237.96 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{16}H_{15}NOH^+$ 238.1232, found 238.1226.

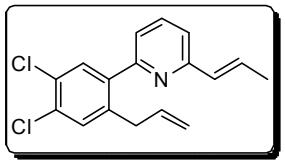
(*E*)-2-(3,4-Dimethoxyphenyl)-6-(prop-1-en-1-yl)pyridine (17d):



The general procedure B was followed using 2-(3,4-dimethoxyphenyl)pyridine **16d** (100 mg, 0.46 mmol) as a substrate yielded **17d** (74 mg, 62%) as a yellow liquid; R_f 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3001, 2957, 2836, 1657, 1578, 1515, 1439, 1330, 1270, 1026, 967, 780 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (dd, *J* = 1.6, 6.7 Hz, 3H), 3.92 (s,

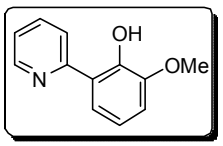
3H), 3.99 (s, 3H), 6.56 (dq, *J* = 1.6, 15.5 Hz, 1H), 6.87 (dq, *J* = 6.7, 15.5 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 0.9, 7.6 Hz, 1H), 7.48 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.54 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 (q), 55.9 (q, 2C), 110.0 (d), 111.0 (d), 117.7 (d), 118.7 (d), 119.4 (d), 130.6 (d), 131.5 (d), 132.6 (s), 137.0 (d), 149.1 (s), 149.8 (s), 155.6 (s), 156.3 (s) ppm; ESI-MS: 256.02 (25%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{16}H_{17}NO_2H^+$ 256.1338, found 256.1368.

(*E*)-2-(2-Allyl-4,5-dichlorophenyl)-6-(prop-1-en-1-yl)pyridine (17e):



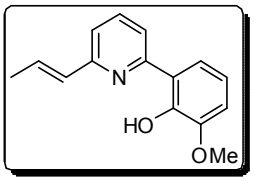
The general procedure B was followed using 2-(3,4-dichlorophenyl)pyridine **16e** (100 mg, 0.45 mmol) as a substrate afforded **17e** (83 mg, 61%) as a colourless liquid; R_f 0.4 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3077, 2961, 2928, 1658, 1567, 1446, 1138, 965, 784, 682 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.93 (dd, *J* = 1.5, 6.6 Hz, 3H), 3.46 (dt, *J* = 1.5, 6.4 Hz, 2H), 4.93 (ddd, *J* = 1.6, 3.3, 17.0 Hz, 1H), 5.01 (ddd, *J* = 1.4, 3.1, 10.1 Hz, 1H), 5.84 (ddt, *J* = 6.5, 10.1, 16.7 Hz, 1H), 6.53 (dq, *J* = 1.5, 15.5 Hz, 1H), 6.79 (dq, *J* = 6.8, 15.8 Hz, 1H) 7.15 (dd, *J* = 0.8, 7.7 Hz, 1H), 7.19 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.37 (s, 1H), 7.50 (s, 1H), 7.65 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.4 (q), 36.7 (t), 116.6 (t), 119.3 (d), 121.7 (d), 124.2 (s), 131.0 (d), 131.5 (d), 131.6 (d), 131.8 (d), 132.1 (s), 136.4 (d), 136.8 (d), 138.1 (s), 140.4 (s), 155.8 (s), 156.9 (s) ppm; ESI-MS: 304.03 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{17}H_{15}Cl_2NH^+$ 304.0660, found 304.0662.

2-Methoxy-6-(pyridin-2-yl)phenol (19):



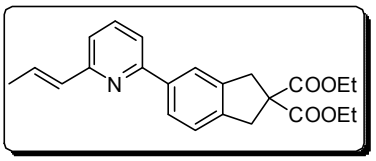
Yellow solid; mp: 100–102 °C; R_f 0.2 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3019, 2937, 2839, 1597, 1451, 1432, 1249, 1095, 828, 757, 667 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 6.84 (t, *J* = 7.8 Hz, 1H), 6.92 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.24 (ddd, *J* = 1.4, 5.1, 7.1 Hz, 1H), 7.41 (dd, *J* = 1.9, 7.8 Hz, 1H), 7.82 (dt, *J* = 1.8, 7.2 Hz, 1H), 7.91 (dt, *J* = 1.1, 8.4 Hz, 1H) 8.51 (ddd, *J* = 1.0, 1.8, 5.1 Hz, 1H), 14.75 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.0 (q), 112.7 (d), 117.8 (d), 117.9 (d), 118.7 (s), 119.3 (d), 121.5 (d), 137.7 (d), 145.7 (d), 149.4 (s), 150.2 (s), 157.9 (s) ppm; ESI-MS: 223.99 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{12}H_{11}NO_2H^+$ 202.0868, found 202.0889.

(*E*)-2-(2-Hydroxy-3-methoxy phenyl)-6-(prop-1-en-1-yl) pyridine (17f):



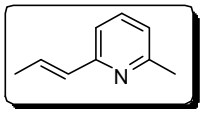
The general procedure B was followed using 2-(2,3-dimethoxyphenyl)pyridine **16f** (100 mg, 0.46 mmol) as a substrate procured **17f** (74 mg, 62%) as a yellow solid; R_f 0.4 (15% ethyl acetate/pet. ether); mp: 61–62 °C; IR ($CHCl_3$)*v*: 3019, 2938, 2837, 1660, 1585, 1462, 1417, 1215, 1181, 1050, 963, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.93 (dd, *J* = 1.6, 6.7 Hz, 3H), 3.93 (s, 3H), 6.45 (dq, *J* = 1.6, 15.6 Hz, 1H), 6.83 (dq, *J* = 6.6, 15.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.92 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.07 (dd, *J* = 2.5, 6.2 Hz, 1H), 7.41 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.67–7.78 (m, 2H), 15.63 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.4 (q), 56.0 (q), 112.4 (d), 117.1 (d), 117.7 (d), 117.9 (d), 118.5 (s), 119.3 (d), 129.0 (d), 132.4 (d), 138.3 (d), 149.4 (s), 150.5 (s), 152.3 (s), 157.4 (s) ppm; ESI-MS: 264.01 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{15}H_{15}NO_2H^+$ 242.1181, found 242.1196.

(*E*)-Diethyl 5-(6-(prop-1-en-1-yl)pyridin-2-yl)-1H-indene-2,2(3H)-dicarboxylate (17i):



The general procedure B was followed using diethyl 5-(pyridin-2-yl)-1H-indene-2,2(3H)-dicarboxylate **16i** (100 mg, 0.29 mmol) as a substrate afforded **17i** (54 mg, 48%) as a yellow liquid; R_f 0.4 (20% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3019, 2978, 1731, 1427, 1215, 759, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.0 Hz, 6H), 1.95 (dd, *J* = 1.6, 6.7 Hz, 3H), 3.61 (s, 2H), 3.65 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 4H), 6.55 (dq, *J* = 1.6, 15.6 Hz, 1H), 6.89 (dq, *J* = 6.7, 15.5 Hz, 1H), 7.13 (dd, *J* = 0.8, 7.7 Hz, 1H), 7.26 (d, *J* = 6.8 Hz, 1H), 7.48 (dd, *J* = 0.8, 7.8 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.80 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.88 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q, 2C), 18.3 (q), 40.2 (t), 40.4 (t), 60.6 (s), 61.7 (t, 2C), 118.2 (d), 119.0 (d), 122.8 (d), 124.3 (d), 125.9 (d), 130.7 (d), 131.4 (d), 137.0 (d), 138.7 (s), 140.6 (s), 140.9 (s), 155.7 (s), 156.8 (s), 171.6 (s, 2C) ppm; ESI-MS: 380.16 (15%, $[M+H]^+$), 402.12 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{23}H_{25}NO_4H^+$ 380.1862, found 380.1853.

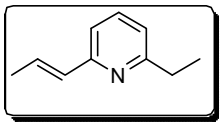
(*E*)-2-Methyl-6-(prop-1-en-1-yl) pyridine (17j):



The general procedure B was followed using 2-picoline **16j** (100 mg, 1.07 mmol) as a substrate yielded **17j** (96 mg, 67%) as a yellow liquid; R_f 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3019, 1577, 1457, 1218, 968, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.91 (dd, *J* = 1.4, 6.5 Hz, 3H), 2.52 (s, 3H), 6.51 (dq, *J* = 1.3, 15.6 Hz,

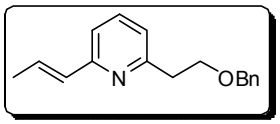
1H), 6.65 (dq, *J* = 6.4, 15.6 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 (q), 24.5 (q), 117.6 (d), 121.0 (d), 130.3 (d), 131.4 (d), 136.5 (d), 155.5 (s), 157.8 (s) ppm; ESI-MS (*m/z*): 134.15 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_9H_{11}NH^+$ 134.0970, found 134.0930**.**

(*E*)-2-Ethyl-6-(prop-1-en-1-yl)pyridine (17k):



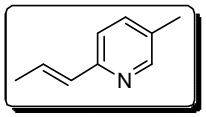
The general procedure B was followed using 2-ethyl pyridine **16k** (100 mg, 0.93 mmol) as a substrate procured **17k** (90 mg, 65%) as a yellow liquid; R_f 0.5 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3020, 1454, 1215, 758, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.4 Hz, 3H), 1.92 (dd, *J* = 1.3, 6.4 Hz, 3H), 2.79 (q, *J* = 7.7 Hz, 2H), 6.49 (dq, *J* = 1.5, 15.7 Hz, 1H), 6.72 (dq, *J* = 6.5, 15.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 18.3 (q), 31.4 (t), 117.8 (d), 119.7 (d), 130.2 (d), 131.6 (d), 136.6 (d), 155.5 (s), 163.0 (s) ppm; ESI-MS (*m/z*): 148.13 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{10}H_{13}NH^+$ 148.1126, found 148.1154.

(*E*)-2-(2-(Benzyloxy)ethyl)-6-(prop-1-en-1-yl)pyridine (17l):



The general procedure B was followed using 2-(2-(benzyloxy)ethyl)pyridine **16l** (100 mg, 0.5 mmol) as a substrate yielded **17l** (27 mg, 22%) as a colorless liquid; R_f 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3019, 1589, 1455, 1215, 760, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.93 (dd, *J* = 1.3, 6.6 Hz, 3H), 3.08 (t, *J* = 6.7 Hz, 2H), 3.87 (t, *J* = 6.8 Hz, 2H), 4.53 (s, 2H), 6.49 (dq, *J* = 1.3, 15.6 Hz, 1H), 6.72 (dq, *J* = 6.5, 15.3 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.36–7.25 (m, 5H), 7.51 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 (q), 38.7 (t), 69.7 (t), 72.9 (t), 118.3 (d), 121.3 (d), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 130.4 (d), 131.5 (d), 136.5 (d), 138.4 (s), 155.7 (s), 158.6 (s) ppm; ESI-MS: 276.10 (30%, $[M+Na]^+$), 292.06 (100%, $[M+K]^+$); HRMS (ESI+): calcd. for $C_{17}H_{19}NOH^+$ 254.1545, found 254.1534.

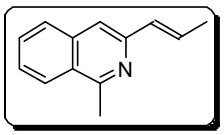
(*E*)-5-Methyl-2-(prop-1-en-1-yl)pyridine (17m):



The general procedure B was followed using 3-picoline **16m** (100 mg, 1.07 mmol) as a substrate afforded **17m** (77 mg, 54%) as a yellow liquid; R_f 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3019, 1577, 1457, 1218, 968, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.91 (dd, *J* = 1.1, 6.4 Hz, 3H), 2.28 (s, 3H), 6.45 (dq, *J* = 1.2, 15.6 Hz,

1H), 6.66 (dq, J = 6.4, 15.6 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 7.38 (dd, J = 1.8, 8.0 Hz, 1H), 8.32 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1 (q), 18.3 (q), 120.1 (d), 129.5 (d), 130.8 (s), 131.0 (d), 136.9 (d), 149.6 (d), 153.4 (s) ppm; ESI-MS (*m/z*): 134.16 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_9H_{11}NH^+$ 134.0970, found 134.0999.

(*E*)-1-Methyl-3-(prop-1-en-1-yl)isoquinoline (17q):

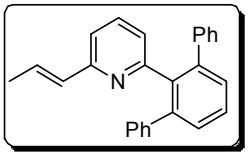


The general procedure B was followed using 1-methyl isoquinoline **16q** (100 mg, 1.07 mmol) as a substrate afforded **17q** (54 mg, 42%) as a yellow liquid; R_f 0.5 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 2925, 2852, 1655, 1570, 1448, 1388, 1030, 966, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (dd, J = 1.3, 6.8 Hz, 3H), 2.94 (s, 3H), 6.58 (br dd, J = 1.4, 15.4 Hz, 1H), 6.90 (br dq, J = 6.8, 15.5 Hz, 1H), 7.31 (s, 1H), 7.48 (dd, J = 0.8, 7.5 Hz, 1H), 7.60 (dd, J = 0.9, 7.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4 (q), 22.6 (q), 115. 7 (d), 125.7 (d), 126.2 (d), 126.5 (s), 127.2 (d), 129.4 (d), 129.9 (d), 131.1 (d), 136.7 (s), 148.6 (s), 158.4 (s) ppm; ESI-MS (*m/z*): 184.15 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{13}H_{13}NH^+$ 184.1126, found 184.1121.

C. **Representative Procedure for Sequential C–H activations:**

To a suspension of 2-phenylpyridine (100 mg, 0.64 mmol), K_2CO_3 (180 mg, 1.3 mmol), 1-AdCO_2H (35 mg, 0.2 mmol) in dry toluene (2 mL), [Ru(p-cymene)Cl_2]$_2$ (9.8 mg, 0.016 mmol) was added and the reaction mixture was flushed with argon for 10 min. To this, bromobenzene (0.17 ml, 1.6 mmol) was added and the contents were heated at 120 ^{o}C for 18 h. To this allyl bromide (0.09 ml, 1.0 mmol) was added and the heating was continued at 120 ^{o}C for additional 15–18 h. The reaction mixture was diluted with diethyl ether and water. Separated the organic layer and the aqueous layer was extracted 3 times with ether. Combined organic layer was dried (Na_2SO_4) and solvent was removed under reduced pressure. The crude was purified over silica gel (8→9 % ethyl acetate in pet ether) to procure compound **21aa** (199 mg, 89%) as white solid.

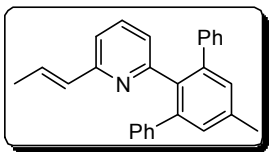
(*E*)-2-([1,1':3',1''-Terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21aa):



The general procedure C was followed using 2-phenyl pyridine **16a** (100 mg, 0.64 mmol) as a substrate yielded **21aa** (199 mg, 89%) as a white solid; R_f 0.4 (10% ethyl acetate/pet. ether); mp: 115–117 °C; IR ($CHCl_3$)v: 3058, 3026, 2930, 2851, 1660, 1578, 1456, 1442, 1217, 969, 758, 701 cm^{-1}; ^{1}H

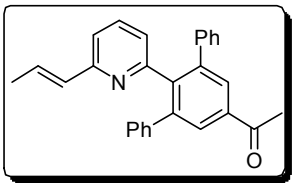
NMR (200 MHz, $CDCl_3$): δ 1.77 (br d, J = 5.2 Hz, 3H), 6.05–6.30 (m, 2H), 6.63 (dd, J = 0.8, 7.7 Hz, 1H), 6.82 (dd, J = 0.8, 7.8 Hz, 1H), 7.07–7.22 (m, 11H), 7.41–7.55 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 117.8 (d), 124.6 (d), 126.2 (d, 2c), 127.5 (d, 4C), 128.1 (d), 129.6 (d, 2C), 129.7 (d, 4C), 130.6 (d), 130.9 (d), 135.1 (d), 141.8 (s, 2C), 142.0 (s, 3C), 155.0 (s), 158.0 (s) ppm; ESI-MS: 348.12 (100%, $[M+H]^+$), 370.01 (55%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{26}H_{21}NH^+$ 348.1752, found 348.1731.

(*E*)-2-(5'-Methyl-[1,1':3',1''-terphenyl]-2'-yl)-6(prop-1-en-1-yl) pyridine (21ba):



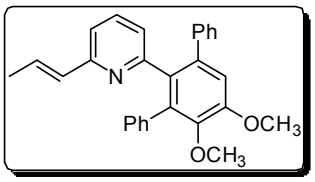
The general procedure C was followed using 2-(*p*--tolyl)pyridine **16b** (100 mg, 0.6 mmol) as a substrate yielded **21ba** (142 mg, 66%) as a yellow syrup; R_f 0.4 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 3058, 2931, 2853, 1600, 1564, 1447, 1216, 966, 757, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76 (d, J = 5.3 Hz, 3H), 2.46 (s, 3H), 6.05–6.29 (m, 2H), 6.61 (dd, J = 0.8, 7.7 Hz, 1H), 6.79 (dd, J = 0.8, 7.8 Hz, 1H), 7.06–7.24 (m, 11H), 7.27 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 21.2 (q), 117.6 (d), 124.7 (d), 126.1 (d, 2C), 127.5 (d, 4C), 129.7 (d, 4C), 130.3 (d, 2C), 130.5 (d), 130.9 (d), 135.0 (d), 135.9 (s), 137.7 (s), 141.8 (s, 2C), 141.9 (s, 2C), 154.8 (s), 158.0 (s) ppm; ESI-MS: 361.12 (100%, $[M+H]^+$), 384.04 (15%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{27}H_{23}NH^+$ 362.1909, found 362.1921.

(*E*)-2-(5'-Acetyl-[1,1':3',1''-terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21ca):



The general procedure C was followed using 2-(4-acetyl phenyl)pyridine **16c** (100 mg, 0.5 mmol) as a substrate yielded **21ca** (127 mg, 63%) as a white solid; R_f 0.3 (15% ethyl acetate/pet. ether); mp: 123–125 °C; IR ($CHCl_3$)v: 3019, 2929, 1685, 1566, 1358, 1215, 759, 668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77 (d, J = 5.1 Hz, 3H), 2.67 (s, 3H), 6.08–6.30 (m, 2H), 6.62 (br d, J = 7.7 Hz, 1H), 6.84 (br d, J = 7.8 Hz, 1H), 7.10–7.24 (m, 11H), 8.03 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 26.8 (q), 118.2 (d), 124.2 (d), 126.6 (d, 2C), 127.7 (d, 4C), 129.3 (d, 2C), 129.6 (d, 4C), 130.7 (d), 131.0 (d), 135.3 (d), 136.4 (s), 140.9 (s, 2C), 142.6 (s, 2C), 142.9 (s), 155.1 (s), 157.0 (s), 197.8 (s) ppm; ESI-MS: 390.12 (30%, $[M+H]^+$), 412.07 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{28}H_{23}NOH^+$ 390.1858, found 390.1844.

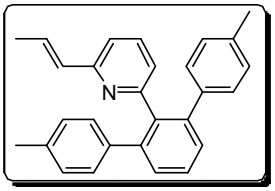
(*E*)-2-(4',5'-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21da):



The general procedure C was followed using 2-(3,4-dimethoxyphenyl)pyridine **16d** (100 mg, 0.46 mmol) as a substrate yielded **21da** (116 mg, 61%) as a brown syrup; R_f 0.4 (15% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3057, 2933, 2850, 1577, 1566, 1476, 1454, 1346, 1244, 1147, 965, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.77 (d, *J* = 4.9 Hz, 3H), 3.55 (s, 3H), 3.95 (s, 3H), 6.07–6.27 (m, 2H), 6.52 (dd, *J* = 0.7, 7.7 Hz, 1H), 6.73 (dd, *J* = 0.8, 7.8 Hz, 1H), 7.01 (s, 1H), 7.06–7.21 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 56.0 (q), 60.6 (q), 113.6 (d), 117.4 (d), 124.6 (d), 126.2 (d), 126.2 (d), 127.1 (d, 2C), 127.5 (d, 2C), 129.7 (d, 2C), 130.4 (d), 130.6 (d, 2C), 130.9 (d), 132.8 (s), 134.9 (d), 136.5 (s), 136.9 (s), 137.7 (s), 141.8 (s), 146.0 (s), 152.3 (s), 154.6 (s), 157.6 (s) ppm; ESI-MS: 408.09 (20%, $[M+H]^+$), 430.13 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{28}H_{25}NO_2H^+$ 408.1964, found 408.1936.

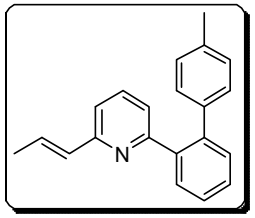
(*E*)-2-(4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21ab):

The general procedure C was followed using 2-phenyl pyridine **16a** (100 mg, 0.64 mmol) as a substrate yielded **21ab** (81 mg, 36%) and **22ab** (86 mg, 49%) respectively.



colorless liquid; R_f 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3054, 2921, 2854, 1566, 1514, 1431, 1157, 966, 798, 752 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.78 (dd, *J* = 0.9, 6.3 Hz, 3H), 2.26 (s, 6H), 6.05–6.33 (m, 2H), 6.64 (dd, *J* = 0.8, 7.7 Hz, 1H), 6.84 (dd, *J* = 0.8, 7.8 Hz, 1H), 6.93–7.03 (m, 8H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.37–7.51 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 21.0 (q, 2C), 117.7 (d), 124.6 (d), 128.0 (d), 128.2 (d, 4C), 129.4 (d, 2C), 129.6 (d, 4C), 130.6 (d), 131.0 (d), 135.2 (d), 135.7 (s, 2C), 138.5 (s), 138.9 (s, 2C), 141.8 (s, 2C), 154.9 (s), 158.3 (s) ppm; ESI-MS: 376.12 (45%, $[M+H]^+$), 398.09 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{28}H_{25}NH^+$ 376.2065, found 376.2022.

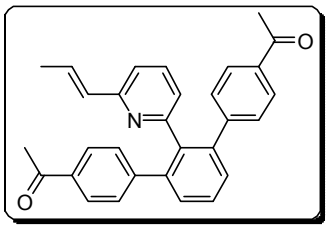
(*E*)-2-(4'-Methyl-[1,1'-biphenyl]-2-yl)-6-(prop-1-en-1-yl)pyridine (22ab):



colourless liquid; R_f 0.4 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)*v*: 3024, 2962, 2852, 1656, 1566, 1453, 1159, 1006, 967, 820, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.92 (dd, *J* = 0.9, 6.2 Hz, 3H), 2.31 (s, 3H), 6.48–6.71 (m, 2H), 6.72 (dd, *J* = 0.8, 7.8 Hz, 1H), 6.99–7.10 (m, 5H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.39–7.47 (m, 3H), 7.68–7.76 (m, 1H); ^{13}C NMR (50 MHz,

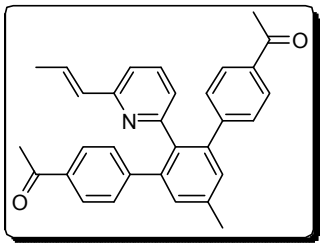
$CDCl_3$): δ 18.3 (q), 21.1 (q), 118.2 (d), 123.1 (d), 127.4 (d), 128.4 (d), 128.7 (d, 2C), 129.6 (d, 2C), 130.5 (d), 130.6 (d), 130.7 (d), 131.3 (d), 135.5 (d), 136.2 (s), 138.6 (s), 139.6 (s), 140.6 (s), 155.6 (s), 158.7 (s) ppm; ESI-MS: 286.09 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{21}H_{19}NH^+$ 286.1596, found 286.1606.

(*E*)-2-(4,4''-Diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21ac):



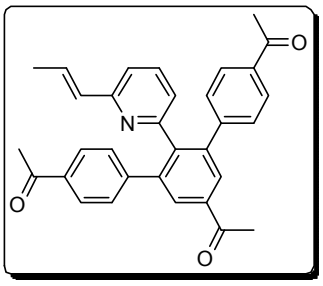
The general procedure C was followed using 2-phenyl pyridine **16a** (100 mg, 0.64 mmol) as a substrate yielded **21ac** (214 mg, 77%) as a white solid; R_f 0.3 (15% ethyl acetate/pet. ether); mp: 183–184 °C; IR ($CHCl_3$)*v*: 3018, 2965, 1681, 1565, 1433, 1358, 1216, 965, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.76 (br d, *J* = 5.2 Hz, 3H), 2.55 (s, 6H), 6.06–6.28 (m, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.17–7.27 (m, 5H), 7.45–7.60 (m, 3H), 7.75 (br s, 2H), 7.79 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 26.6 (q, 2C), 118.3 (d), 124.4 (d), 127.7 (d, 4C), 128.4 (d), 129.8 (d, 4C), 129.9 (d, 2C), 130.7 (d), 131.0 (d), 135.0 (s, 2C), 135.5 (d), 138.5 (s), 141.0 (s, 2C), 146.6 (s, 2C), 155.2 (s), 157.0 (s), 197.9 (s, 2C) ppm**;** ESI-MS: 432.05 (65%, $[M+H]^+$), 454.13 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{30}H_{25}NO_2H^+$ 432.1964, found 432.1918.

(*E*)-2-(5'-Methyl-4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21bc):



The general procedure C was followed using 2-(*p*-tolyl)pyridine **16b** (100 mg, 0.6 mmol) as a substrate yielded **21bc** (180 mg, 68%) as a white solid; R_f 0.4 (20% ethyl acetate/pet. ether); mp: 68–71 °C; IR ($CHCl_3$)*v*: 3031, 2980, 2922, 2853, 1737, 1682, 1564, 1436, 1266, 1045, 959, 829, 710, 602 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.76 (d, *J* = 5.3 Hz, 3H), 2.49 (s, 3H), 2.55 (s, 6H), 6.05–6.27 (m, 2H), 6.56 (dd, *J* = 0.8, 7.7 Hz, 1H), 6.83 (dd, *J* = 0.8, 7.8 Hz, 1H), 7.16–7.30 (m, 5H), 7.30 (br s, 2H), 7.73–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 21.2 (q), 26.6 (q, 2C), 118.2 (d), 124.5 (d), 127.7 (d, 4C), 129.8 (d, 4C), 130.6 (d, 2C), 130.8 (d), 130.9 (d), 135.0 (d), 135.5 (s), 135.9 (s), 138.2 (s, 2C), 141.0 (s, 2C), 146.9 (s, 2C), 155.2 (s), 157.1 (s), 198.0 (s, 2C) ppm; ESI-MS: 446.16 (25%, $[M+H]^+$), 468.18 (100%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{31}H_{27}NO_2H^+$ 446.2120, found 446.2118.

(*E*)-2-(4,4'',5'-Triacetyl-[1,1':3',1''-terphenyl]-2'-yl)-6-(prop-1-en-1-yl)pyridine (21cc):

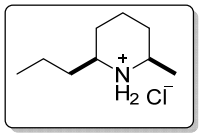


The general procedure C was followed using 2-(4-acetyl phenyl)pyridine **16c** (100 mg, 0.5 mmol) as a substrate yielded **21cc** (176 mg, 73%) as a white solid; R_f 0.3 (30% ethyl acetate/pet. ether); mp: 192–193 °C; IR ($CHCl_3$)ν: 3020, 1682, 1566, 1524, 1338, 1215, 1016, 928, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.77 (dd, J = 1.4, 3.8 Hz, 3H), 2.57 (s, 6H), 2.70 (s, 3H), 6.09–6.29 (m, 2H), 6.61 (dd, J = 0.8, 7.7 Hz, 1H), 6.89 (dd, J = 0.8, 7.9 Hz, 1H), 7.20–7.30 (m, 5H), 7.77–7.83 (m, 4H), 8.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.2 (q), 26.6 (q, 2C), 26.8 (q), 118.8 (d), 124.0 (d), 127.8 (d, 3C), 127.9 (d), 129.6 (d, 2C), 129.8 (d, 4C), 130.6 (d), 131.3 (d), 135.5 (s, 2C), 135.7 (d), 136.8 (s), 141.7 (s, 2C), 142.9 (s), 145.7 (s, 2C), 155.5 (s), 156.2 (s), 197.2 (s), 197.7 (s, 2C) ppm; ESI-MS: 474.18 (100%, $[M+H]^+$), 496.12 (45%, $[M+Na]^+$); HRMS (ESI+): calcd. for $C_{32}H_{27}NO_3H^+$ 474.2069, found 474.2026.

D. Representative Procedure for exhaustive hydrogenation:

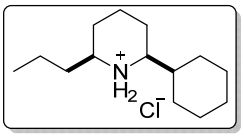
To a solution of (*E*)-2-methyl-6-(prop-1-en-1-yl) pyridine **17j** in MeOH, HCl (3 equiv.) and catalytic Adams catalyst (PtO_2) were added and the resulting mixture was stirred at 50 bar under H_2 atm. for overnight. Then reaction mixture was filtered through ceilite and concentrated under reduced pressure. The resulting solid was washed with diethyl ether (20 ml x 3) to afford **24** in quantitative yield.

(±)-Dihydropinidine hydrochloride (24):



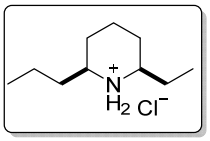
The general procedure D was followed using (*E*)-2-methyl-6-(prop-1-en-1-yl)pyridine **17j** (50 mg, 0.37 mmol) as a substrate yielded **24** (64 mg, 97%) as a white solid; R_f 0.3 (5% MeOH/DCM); mp: 213–214 °C; IR ($CHCl_3$)ν: 3610, 3546, 3503, 3019, 2975, 1747, 1641, 1541, 1215, 929, 757, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.3 Hz, 3H), 1.23–1.34 (m, 1H), 1.39–1.50 (m, 2H), 1.55 (d, J = 6.2 Hz, 3H), 1.58–1.64 (m, 1H), 1.73–1.79 (m, 3H), 1.87–1.95 (m, 2H), 2.05–2.13 (m, 1H), 2.88–2.92 (m, 1H), 3.07 (br s, 1H), 8.99 (br s, 1H), 9.35 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7 (q), 18.8 (t), 19.4 (q), 22.8 (t), 27.4 (t), 30.7 (t), 35.1 (t), 54.5 (d), 58.4 (d) ppm; ESI-MS: 142.15 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_9H_{19}NH^+$ 142.1590, found 142.1598.

(±)-2-Cyclohexyl-6-propylpiperidine hydrochloride (25):



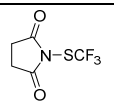
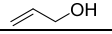
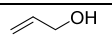
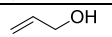
The general procedure D was followed using (*E*)-2-phenyl-6-(prop-1-en-1-yl)pyridine **17a** (50 mg, 0.26 mmol) as a substrate afforded **25** (59 mg, 94%) as a white solid; R_f 0.3 (5% MeOH/DCM); mp: 214–215 °C; IR ($CHCl_3$)*v*: 3020, 2934, 2856, 1427, 1215, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, J = 7.3 Hz, 3H), 1.09–1.15 (m, 2H), 1.28–1.43 (m, 4H), 1.62–1.65 (m, 1H), 1.72–1.75 (m, 4H), 1.80 (br s, 4H), 1.92–1.95 (m, 3H) 2.03–2.08 (m, 2H), 2.23–2.25 (m, 1H), 2.77 (br s, 1H), 2.97–2.99 (br s, 1H), 8.47 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4 (q), 18.8 (t), 23.3 (t), 24.8 (t), 25.7 (t), 25.8 (t), 26.1 (t), 27.7 (t), 27.8 (t), 30.4 (t), 34.4 (t), 39.5 (d), 59.9 (d), 64.9 (d) ppm; ESI-MS: 210.18 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{14}H_{27}NH^+$ 210.2216, found 210.2203.

(±)-2-Ethyl-6-propylpiperidine hydrochloride (26):



The general procedure D was followed using (*E*)-2-ethyl-6-(prop-1-en-1-yl)pyridine **17k** (50 mg, 0.33 mmol) as a substrate procured **26** (62 mg, 96%) as a white solid; R_f 0.3 (5% MeOH/DCM); mp: 224–226 °C; IR ($CHCl_3$)*v*: 3684, 3020, 2964, 2739, 1589, 1459, 1215, 759, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88–0.98 (m, 6H), 1.28–1.51 (m, 4H), 1.69–2.03 (m, 6H), 2.11–2.36 (m, 2H), 2.79–2.98 (m, 2H), 9.03 (br s, 1H), 9.23 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.0 (q), 13.8 (q), 18.8 (t), 22.8 (t), 26.3 (t), 27.4 (t), 27.9 (t), 35.2 (t), 58.9 (d), 60.3 (d) ppm; ESI-MS: 156.20 (100%, $[M+H]^+$); HRMS (ESI+): calcd. for $C_{10}H_{21}NH^+$ 156.1747, found 156.1750.

Metal Complex	R-X	Arylation	Alkylation	Allylation	Amination	Amidation	Cyanation	Alkenylation	Carboxylation	Halogenation	Nitration	Alkoxylation	Borylation	Acylation	Azidation	Benzoxylation	References
$[RhCp^*(CH_3CN)_3](SbF_6)_2$	N-hydroxycarbamates					√											OL, 2014, 2, 592
	Ar-N=O				√												OL, 2013, 24, 6302
	2-cyclohexenone		√														OBC, 2011, 9, 7176
	N-Sulfonyl Aldimines	√															ACIE, 2011, 9, 2115
	Cyclic Imines		√														OL, 2014, 9, 2538
	2-Vinyloxirane			√													OL, 2014, 4, 1200
	$PhSO_2$-NH-SO_2Ph					√											ASC, 2013, 5, 869
	Ethyl glyoxylate/ Ar CHO		√														ASC, 2011, 8, 1269
$Pd(OAc)_2$	Ar–O–Ar													√			JOC, 2014, 1, 275
	R-OH								√								Synlett 2013, 24, 2274 and 2008, 18, 2841
	Ar-$B(OH)_2$	√															Synlett 2013, 24, 2153
	NaN_3														√		OL, 2013, 16, 4262
	$AgNO_2$										√						JOC, 2013, 12, 5932
	aryl acyl peroxide															√	Molecules 2013, 18, 4403
	BR_2												√				ACIE, 2013, 16, 4431
	Ar-CH_3													√			OL, 2012, 20, 5294
	t-BuCN						√										OL, 2012, 18, 4966, and 2012, 17, 4614
	α-Diketones													√			OL, 2012, 17, 4594
	Ar-CO_2H															√	TL, 2012, 53, 2465
	Ar-$Si(OMe)_3$	√															JOC, 2011, 20, 8543
	NH_3+DMF						√										JACS, 2010, 30, 10272
	CF_3 Source		√														JACS, 2010, 11, 3648
	Ar-BF_3K	√															Synthesis, 2009, 22, 3757
	$K_3[Fe(CN)_6]$						√										JOC, 2009, 24, 9470
	CuCN						√										OL, 2009, 20, 4716
	HX									√							JACS, 2009, 32, 11310
	Aryl Acyl peroxide	√															OL, 2009, 15, 3174
	PhCHO													√			OL, 2009, 14, 3120
	4-Iodo anisole	√															CC, 2008, 6312
	dicumylperoxide		√														JACS, 2008, 10, 2900
	Methylboroxine		√														JACS, 2006, 39, 12634

		Trifluoromethylthiolation														OL, 2014, 16, 2046
	$PhCO_2H$													√		ASC, 2013, 2-3, 529
	PhCHO													√		ASC, 2010, 7, 1145
	α-Keto esters								√							ASC, 2013, 7, 1145
$[RuCl_2(p\text{-cymene})]_2$				√												OBC, 2013, 11, 8009
	$R\text{-}N_3$					√										OL, 2013, 13, 3286
	$Ts\text{-}N_3$					√										CEJ, 2013,19, 7328
	2°-alkyl halide		√													JACS, 2013, 15, 5877
	Alkene		√													ACIE, 2013, 14, 3977
	Alkyne							√								Synlett, 2012, 23, 2763
	Isocyanate					√										OL, 2012, 16, 4262
	Ts-Cl	Sulfonation														JACS, 2011, 48, 19298
	Het-X	√														ACIE, 2010, 37, 6629
	Ar-Cl	√														Green Chem, 2009, 11, 1871
	BnCl		√													OL, 2009, 21, 4966
	R-X		√													ACIE, 2009, 33, 6045
	cyclo alkane		√													ACIE, 2008, 33, 6278
	Ar-OTs/Cl	√														ACIE, 2006, 16, 2619 & OL, 2005, 14, 3123
	$RCON_3$					√										OL, 2014, 16, 2022
	Homo coupling	√														ASC, 2009, 13, 2071
	Het/Ar-X	√														ASC, 2009, 11-12, 1737
$[Cp^*RhCl_2]_2$			√													OBC, 2013, 11, 8009
			√													CC, 2013, 49, 6489
	Allyl Carbonates			√												ACIE, 2013, 20, 5386
	Het-X	√														OL, 2013, 6, 1290
	$Ar\text{-}N_3$				√											EJOC, 2013, 7480
	NaN_3, $NaNO_2$										√				√	ACIE, 2013, 45, 11862
	$Ar\text{-}NH_2$					√										OL, 2013, 19, 5106
	PhNCNTs						√									OL, 2013, 19, 4960
	N-Arenesulfonated Imides					√										OL, 2013, 14, 3706
	RO-NHBoc					√										OL, 2013, 12, 3014
	aziridine		√													ACIE, 2013, 9, 2577
	Het-H	√														ACIE, 2013, 2, 580
	α,β-unsaturated ketone		√													CEJ, 2012, 18, 9511
	$Ts\text{-}N_3$					√										JACS, 2012, 22, 9110
	NXS									√						JACS, 2012, 20, 8298

	Boc-Imines	√															JACS, 2011, 5, 1248
	Vinyl							√									JOC, 2009, 74, 7094
	$RCON_3$					√											OL, 2014, 16, 2022
	Cyclopropenones													√			OL, 2014, 16, 1220
CuBr	NBS, NCS									√							CCC, 2014, 6, 123
	BnCN						√										CC, 2012, 48, 9933
						√											ASC, 2010, 4, 632
$[IrCp^*Cl_2]_2$	$R\text{-}N_3$				√												JOC, 2013, 21, 11102
$RuCl_3\ nH_2O$	Ar-Cl	√															CC, 2013, 49, 8320, CEJ, 2010, 10, 787, Tetrahedron, 2008, 64, 6115
	ArOTs	√															Syn Comm, 2013, 43, 2110
	Alkyne							√									OL, 2008, 22, 5309
	Ar-I/Br	√															Synlett 2008, 9, 1325 & 2007, 18, 2833
$[Ru(MesCO_2)_2(p\text{-cymene})]$			√														OL, 2013, 17, 4482
$Cu(OAc)_2$	ROH											√					ACIE, 2013, 35, 9279
	AIBN						√										OL, 2013, 13, 3354
	ArCHO															√	Synlett 2011, 16, 2407
	$AgNO_3$										√						OL, 2011, 24, 6536
	RNH_2					√											JOC, 2011, 10, 4158
	RCOCl													√			CC, 2011, 47, 3978
	Het-H	√															JACS, 2011, 7, 2160, Tetrahedron, 2009, 65 3085
	Anhydrid															√	JOC, 2010, 7, 2415
	Aniline				√												Chem Lett, 2006, 8, 842
	alkyne and alkene															√	OL, 2014, 16, 1614
$PdCl_2$	$ArCH_2NH_2$													√			CC, 2013, 49, 6837
	O_2											√					ACIE, 2013, 22, 5827
	Oxaziridine								√								OL, 2011, 19, 5244
	RCH_2OH													√			OL, 2011, 7, 1614
$Co(acac)_2$	Ar-Cl	√															CEJ, 2013,19, 10605
	aryl sulfamates	√															ACIE, 2012, 33, 8251
	EtMgCl		√														OL, 2011, 12, 3232
	RMgBr	√															ACIE, 2011, 5, 1109
$[\{RuCl_2(cod)\}n]$	Ar-I													√			ACIE, 2013, 24, 6293
	Methylenecyclopropane		√														OL, 2008, 16, 3409
	Allyl Acetates			√													Org. Met. 2006, 25, 4773
$Cu(NO_3)_2{\cdot}3H_2O$	LiCl									√							OBC, 2013, 11, 2756, Synlett 2011, 7, 1038

$MnBr(CO)_5$	Alkyne							√									JACS, 2013, 4, 1264
$RuCl_2(PPh_3)(p\text{-cymene})$	Ar-X	√															Green Chem., 2013, 15, 67
$[RuCl_2(\eta^6\text{-benzene})\text{-MOTPP}]$	Ar-X	√															EJOC, 2012, 6702
$Rh(acac)_3$	Alkene		√														JACS, 2012, 42, 17778
$CoBr_2$	Aldimine		√														CC, 2012, 36, 4305
	$SiMe_3$		√														ACIE, 2011, 30, 6888
	Ph		√														JACS, 2011, 3, 400
	Alkyne							√									JACS, 2010, 35, 12249
FeI_2	CuCN						√										Synlett 2011, 20, 2991
$[Cp^*Rh(CH_3CN)_3][BF_4]_2$	Ar-CHO		√														OL, 2012, 2, 636
AgOTf	*t*-BuOCl									√							Chin. J. Chem. 2011, 29, 2809
$[Rh(OH)(cod)]_2$	pinB-pinB												√				JACS, 2011, 48, 19310
$[RuCl_2(PPh_3)_3]$	RCOCl												√				Chem. Lett. 2011, 40, 1018
	Carbamoyl Chlorides Alkyl Chloroformates																JACS, 2009, 8, 2792
$Fe(acac)_3$	ArMgBr	√															CAJ. 2011, 6, 3059 and JACS, 2008, 18, 5858
	Ar-Br	√															ASC, 2012, 4, 593
$[RuH(codyl)_2]BF_4$	Het-X	√															Green Chem, 2011, 13, 2315
$[Rh(coe)_2Cl]_2$	CO_2								√								JACS, 2011, 5, 1251
$(CO)_2Rh(acac)$	Ar-CHO	√															JACS, 2010, 35, 12212
$Pd(PhCN)_2Cl_2$	α-Oxocarboxylic Acids													√			OL, 2010, 15, 3464
CuF_2	Methylthiolation		√														OL, 2010, 7, 1644
$FeCl_3$	ArMgBr	√															Synlett 2010, 2, 313
$[Rh(cod)Cl]_2$	RCO_2H								√								OL, 2009, 17, 3974
	Anhydride	√						√									OL, 2009, 6, 1317
	R-OH								√								JACS, 2009, 2, 729
	ArCOCl	√															JACS, 2008, 26, 8136
$Pd(CH_3CN)_2Cl_2$	$ArSO_2Cl$	Sulfonylation															JACS, 2009, 10, 3466
$[RuCl_2(\eta^6\text{-benzene})]_2$	Het-X	√															Tetrahedron, 2008, 64,6051
	ArBr	√															OL, 2001, 16, 2579
$[RhCl(C_2H_4)_2]_2$	$ArB(OH)_2$	√															OL, 2008, 1, 129
$CuCl_2$	$CuCl_2$									√							JACS, 2006, 21, 6790
$[RhCl(PPh_3)_3]$	alkyne							√									TL, 2001, 42, 7609
	Ph_4Sn	√															CC, 1998, 2439
	R		√														J. Chem. Soc., Chem. Commun, 1994, 2267
$Ru_3(CO)_{12}$	R													√			JOC, 1997, 62, 2604

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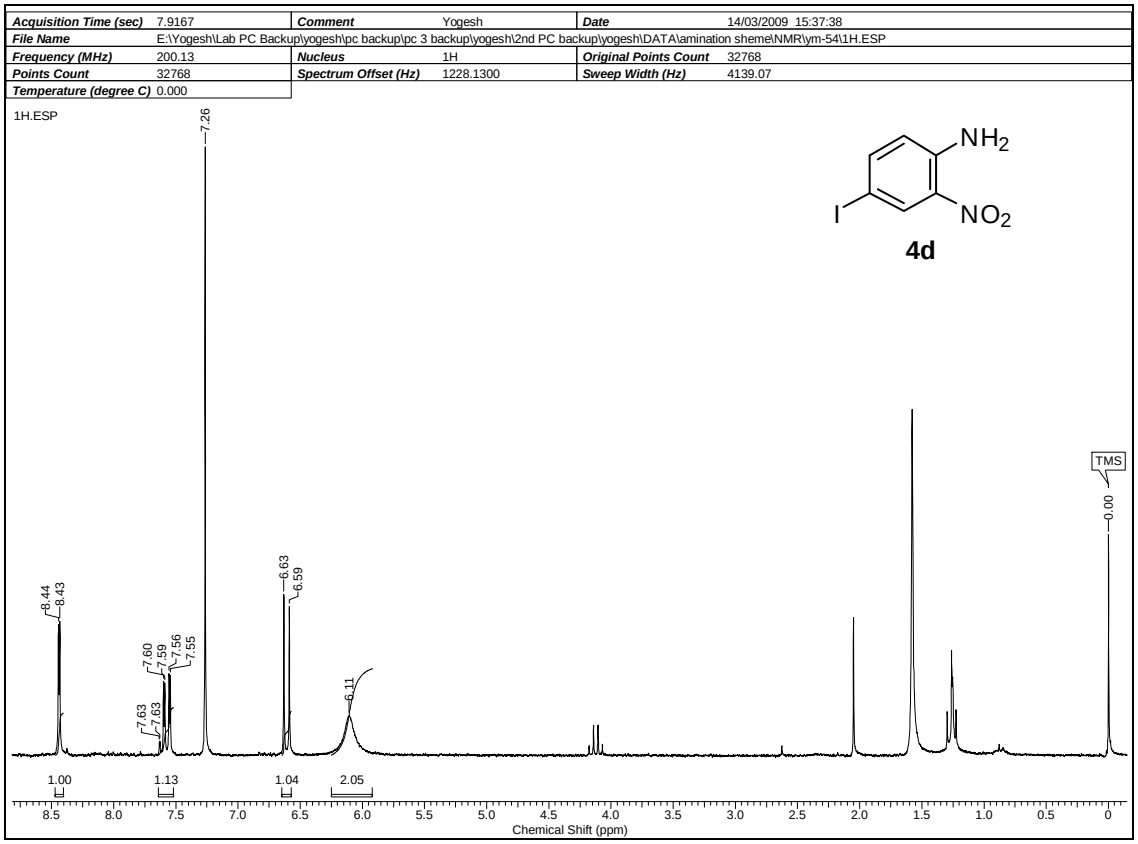
SPECTRA



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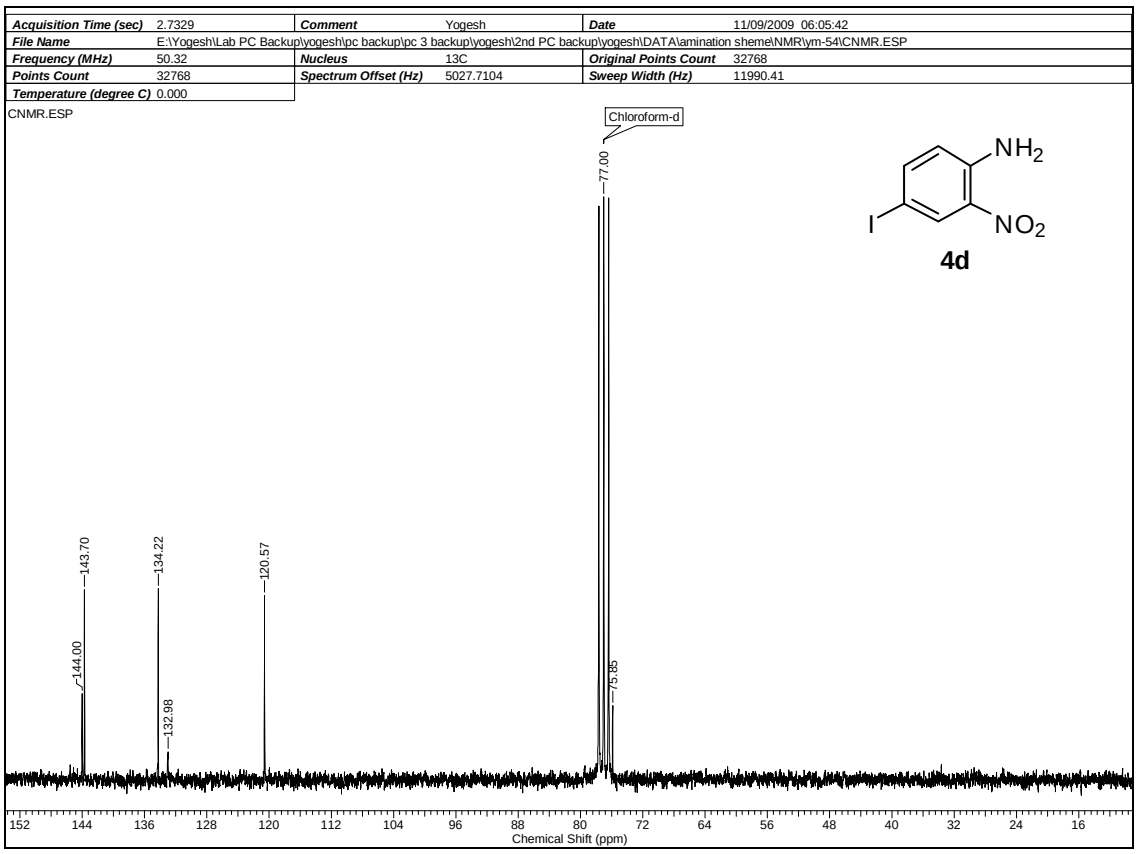

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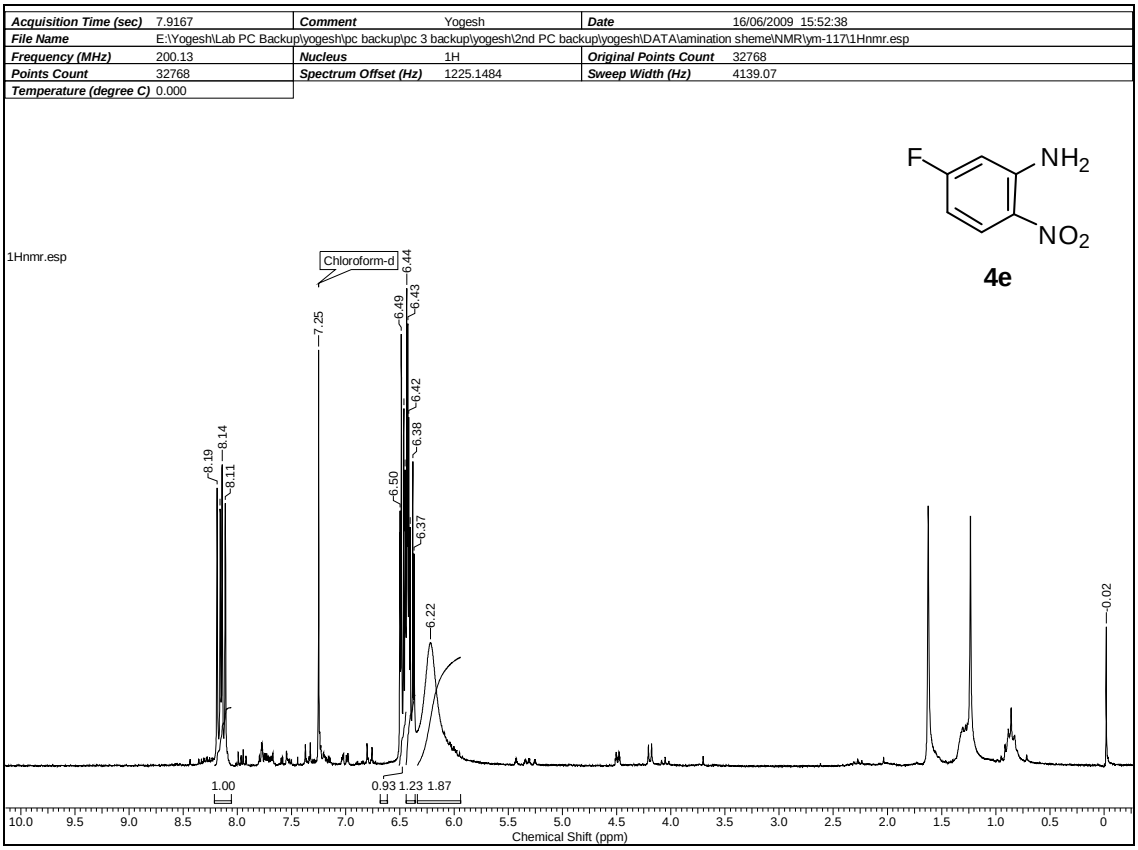

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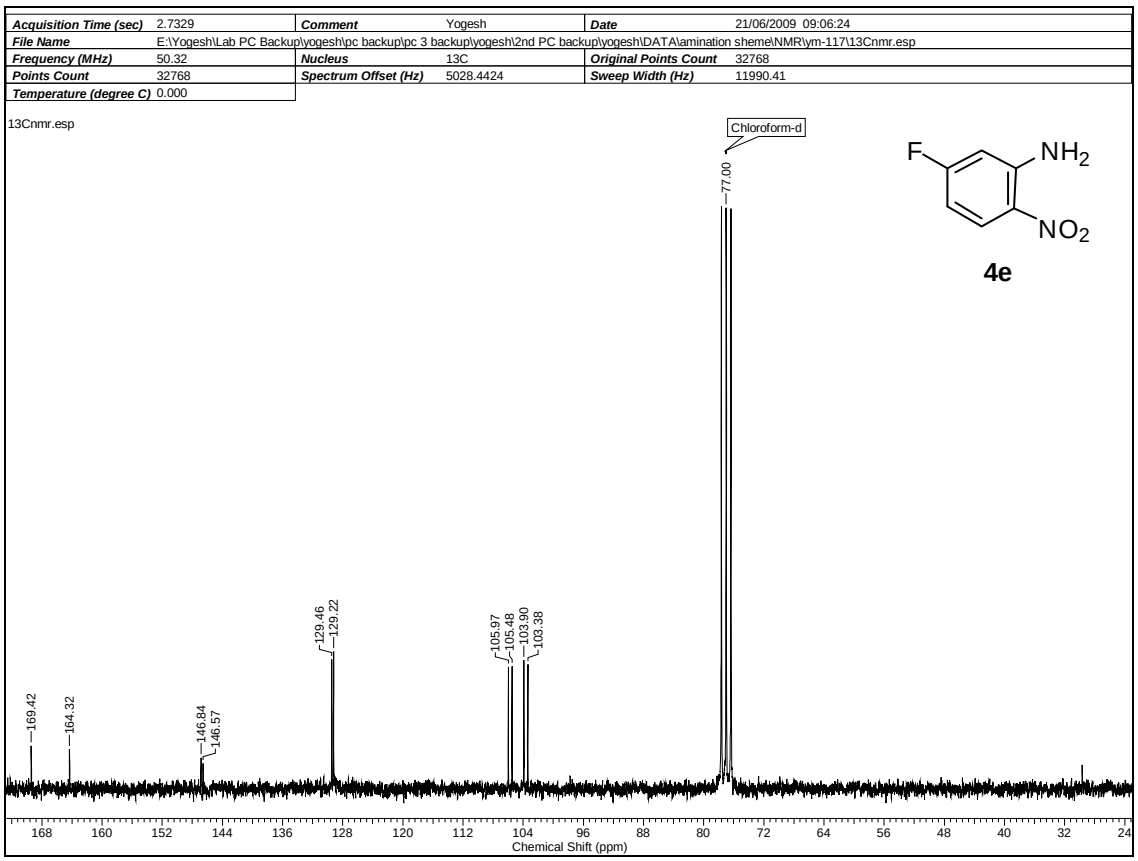
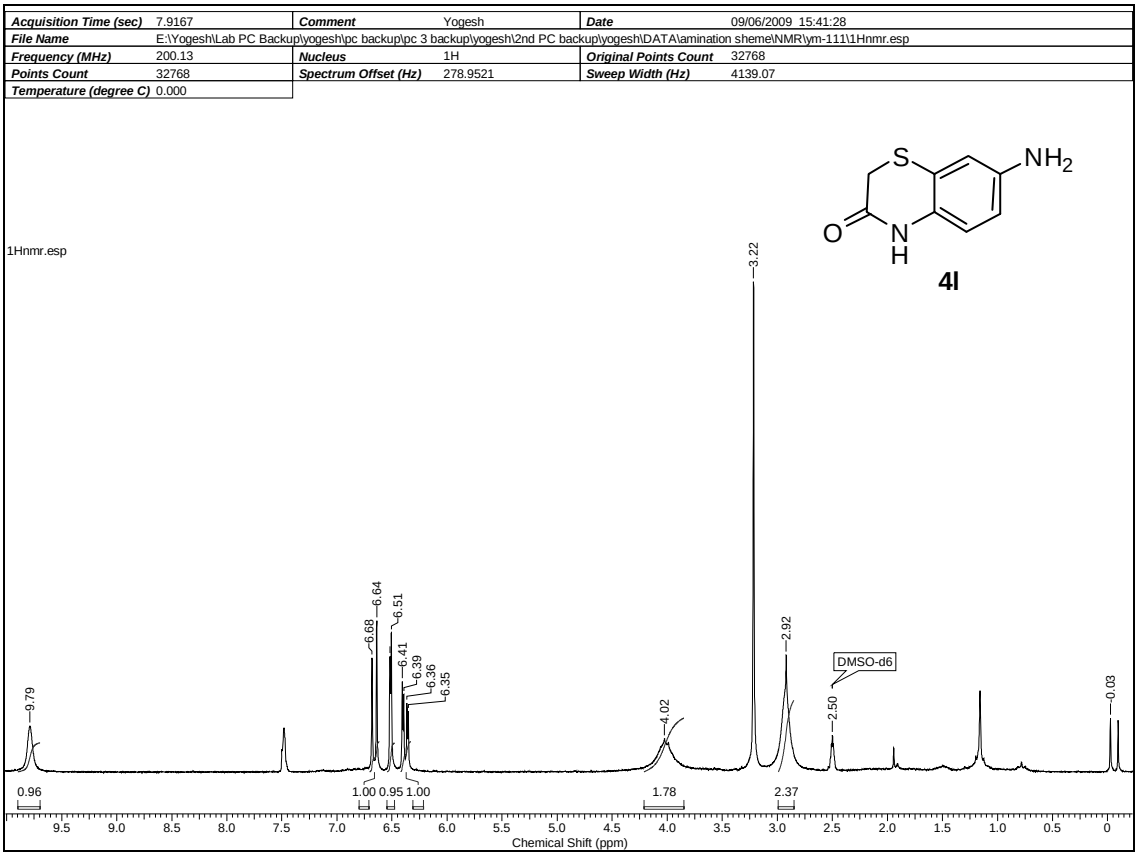
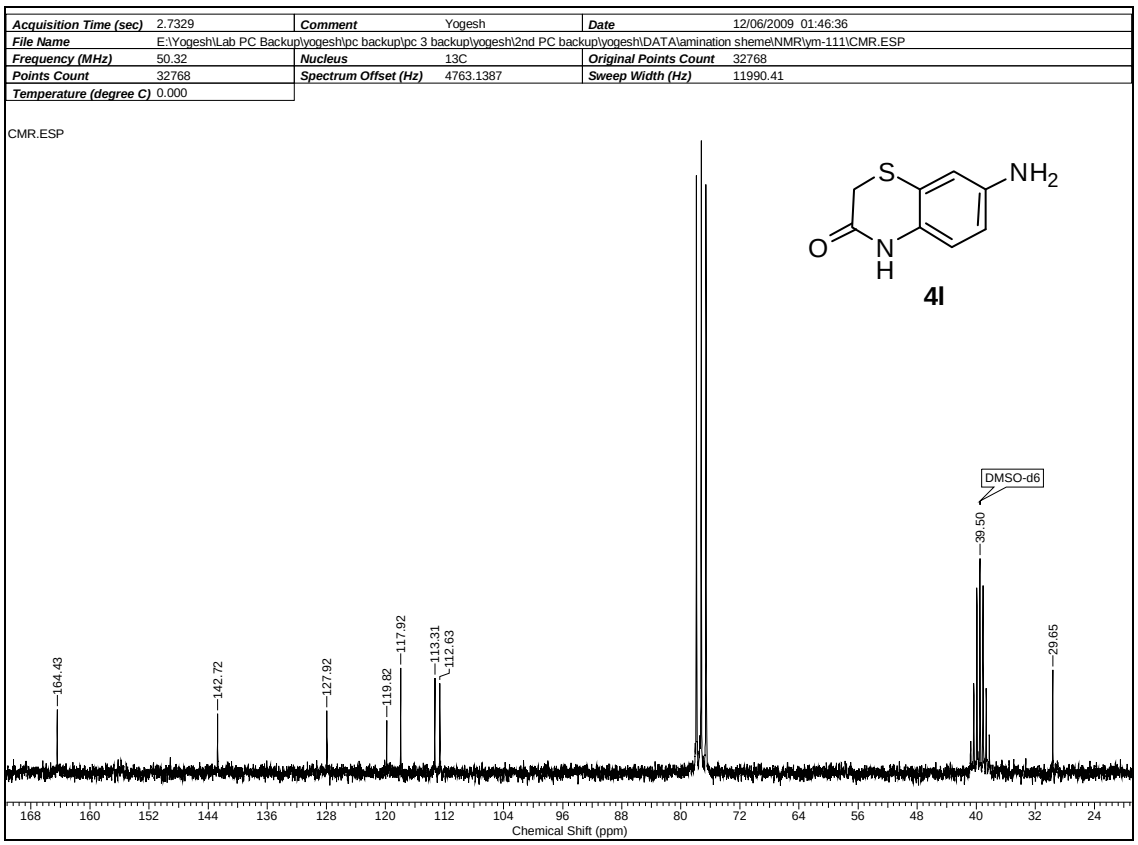


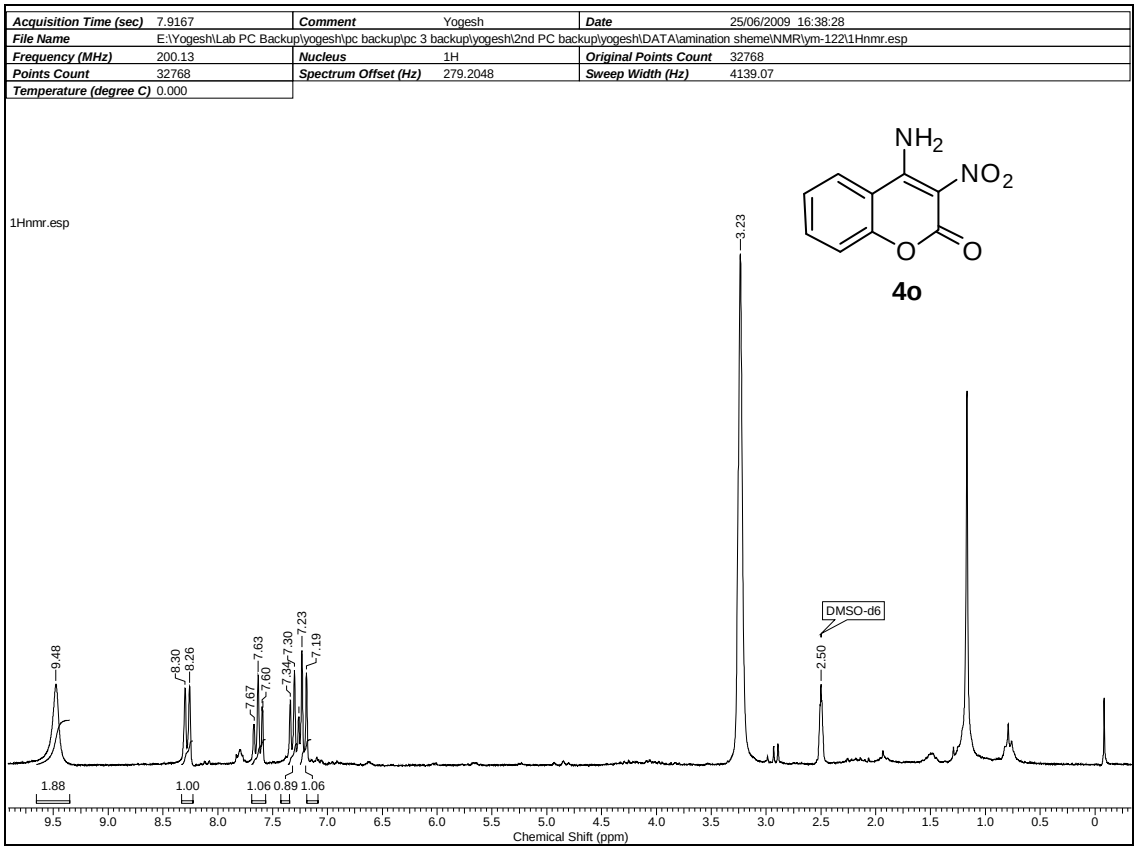
^{13}C NMR Spectrum of 4e in $CDCl_3$



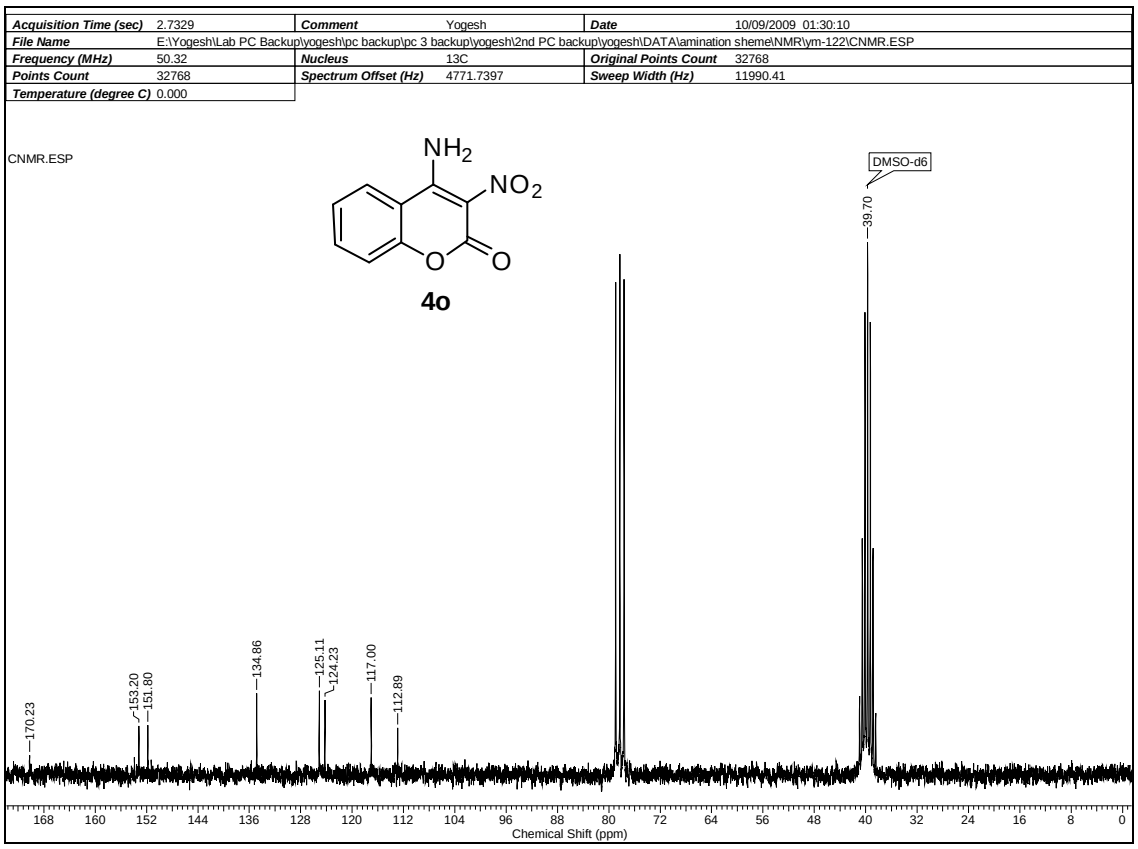
^{1}H NMR Spectrum of 4l in DMSO-d6



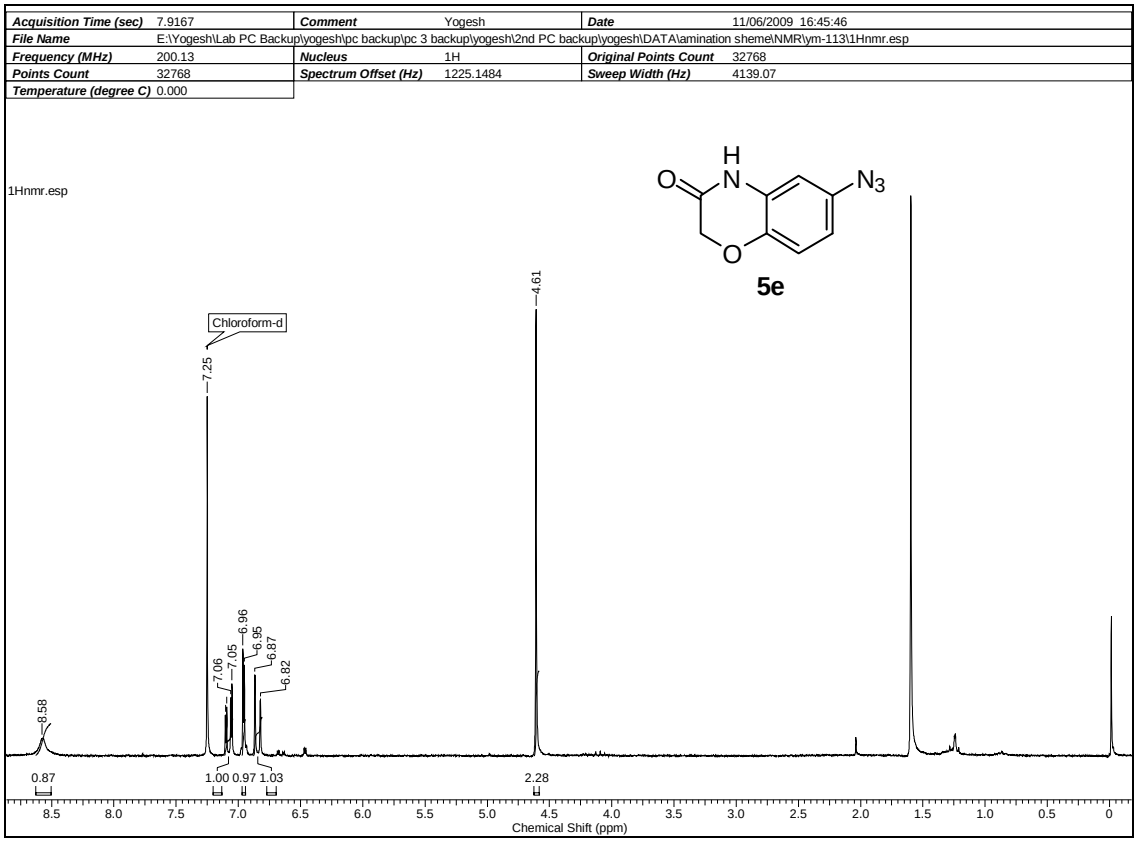
^{13}C NMR Spectrum of 4l in DMSO-d6



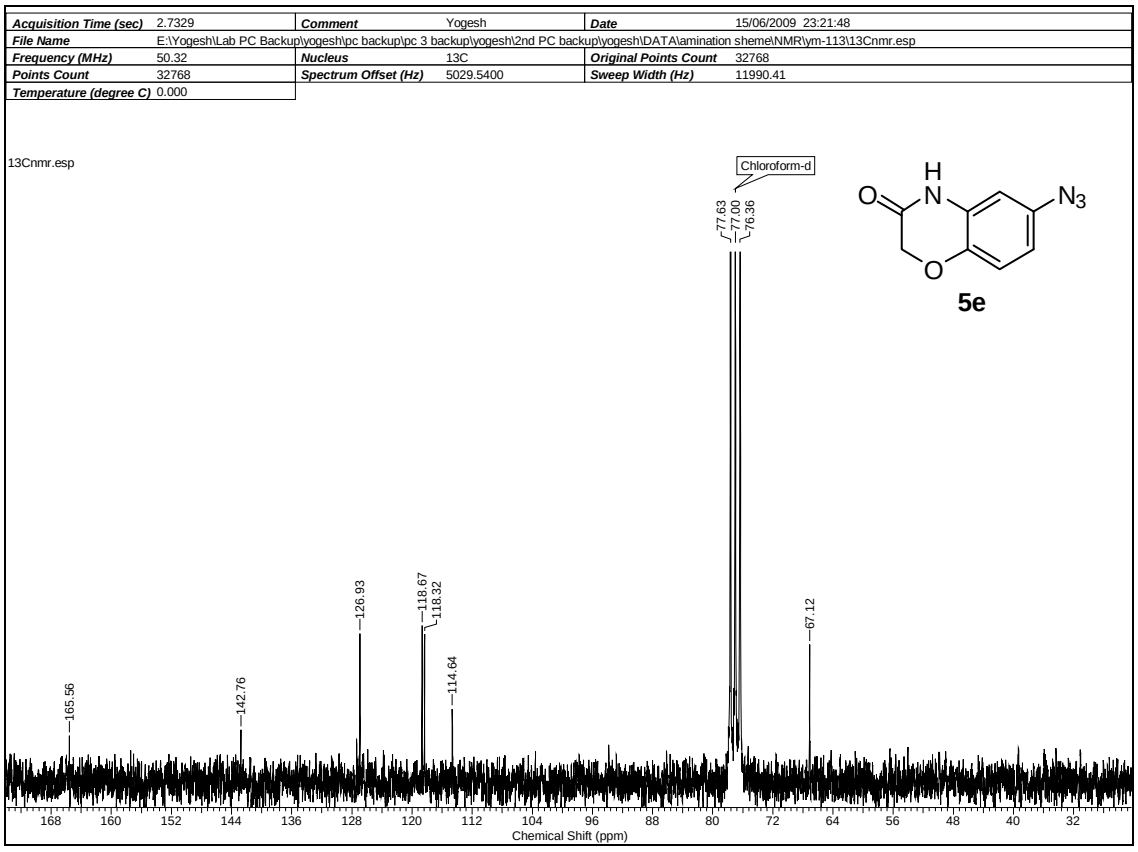
^{1}H NMR Spectrum of 4o in DMSO-d6



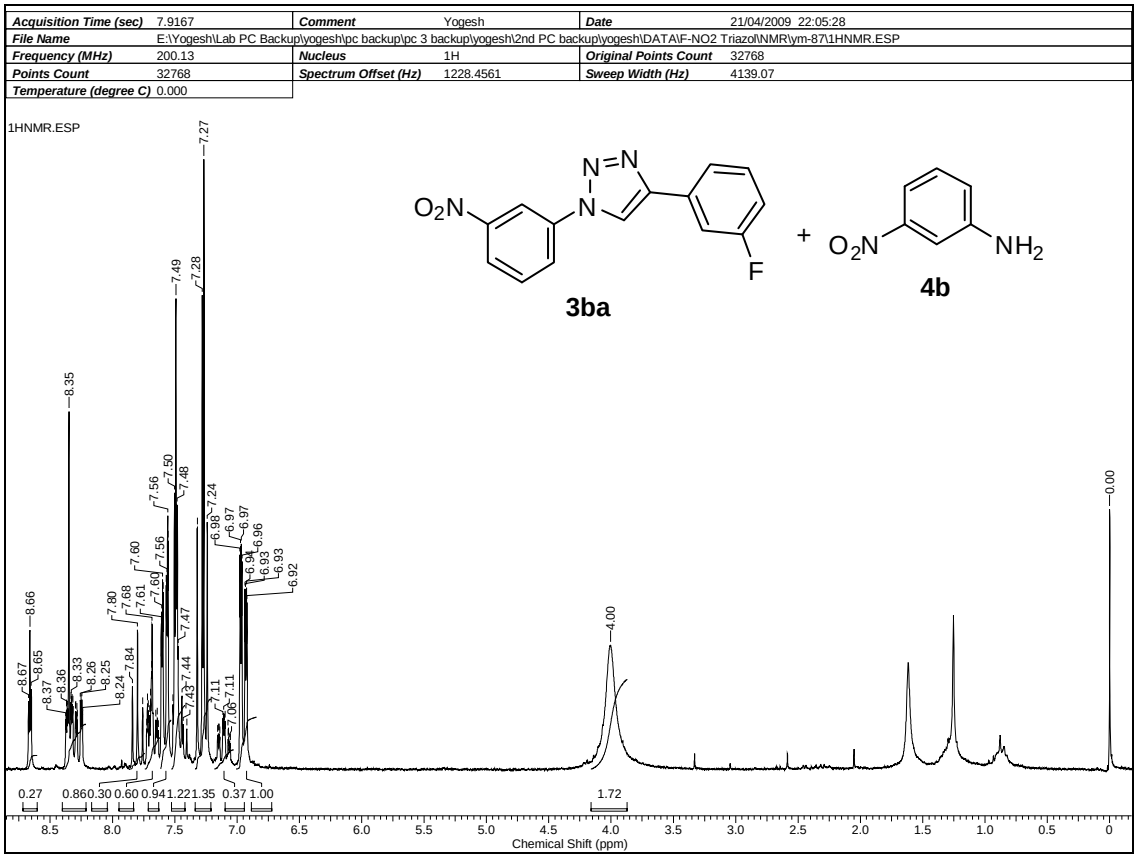
^{13}C NMR Spectrum of 4o in DMSO-d6



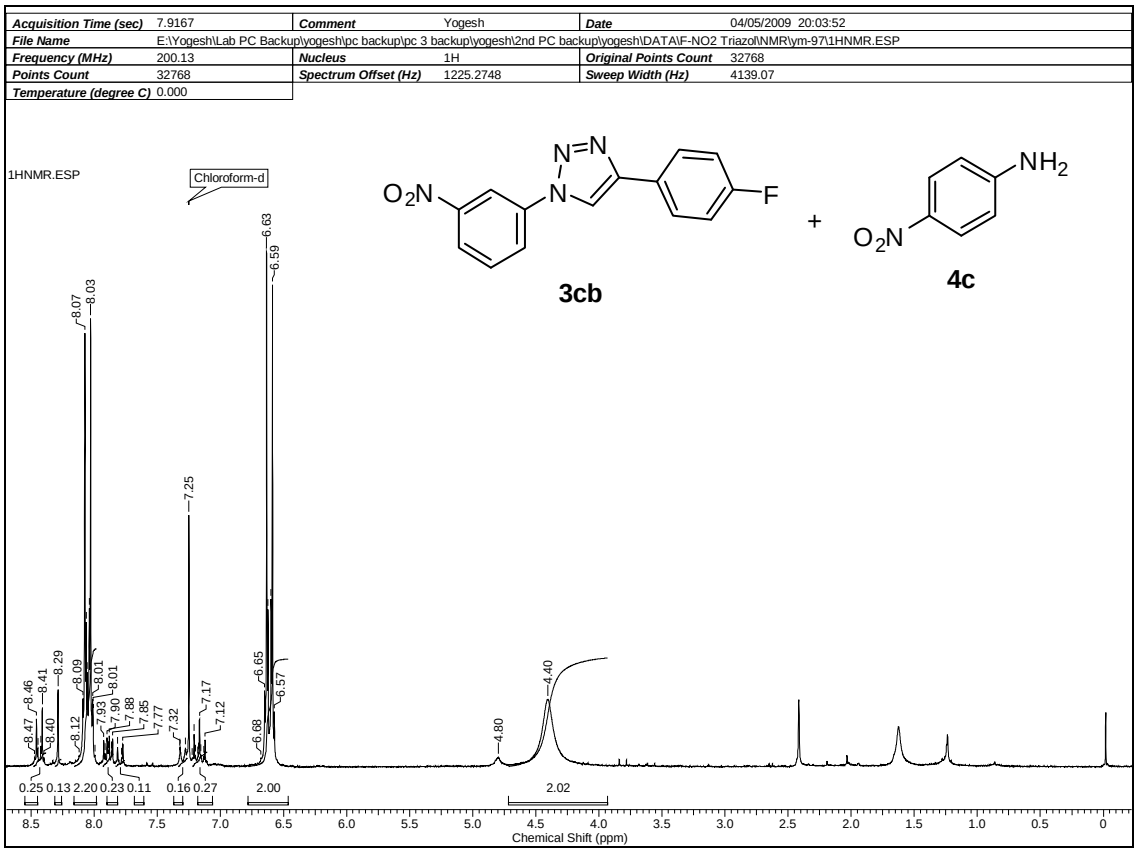
^{1}H NMR Spectrum of 5e in $CDCl_3$



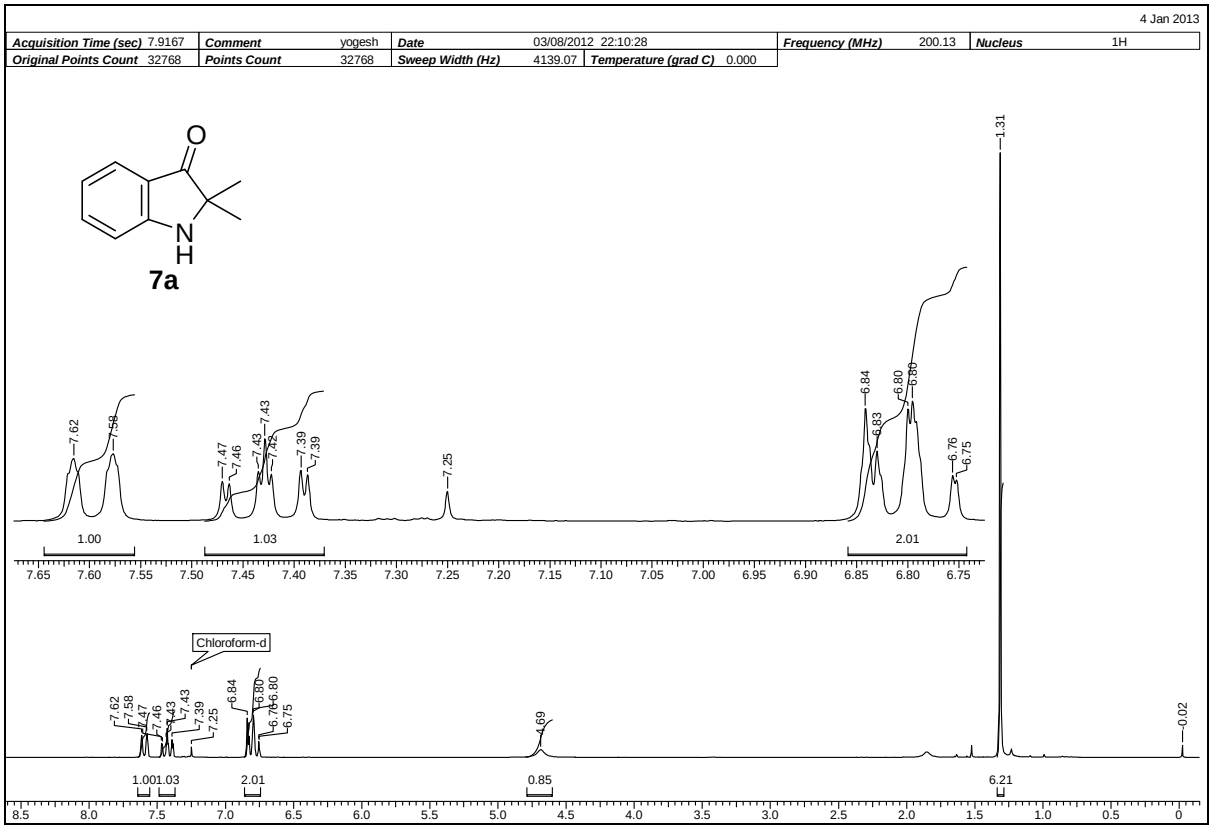
^{13}C NMR Spectrum of 5e in $CDCl_3$



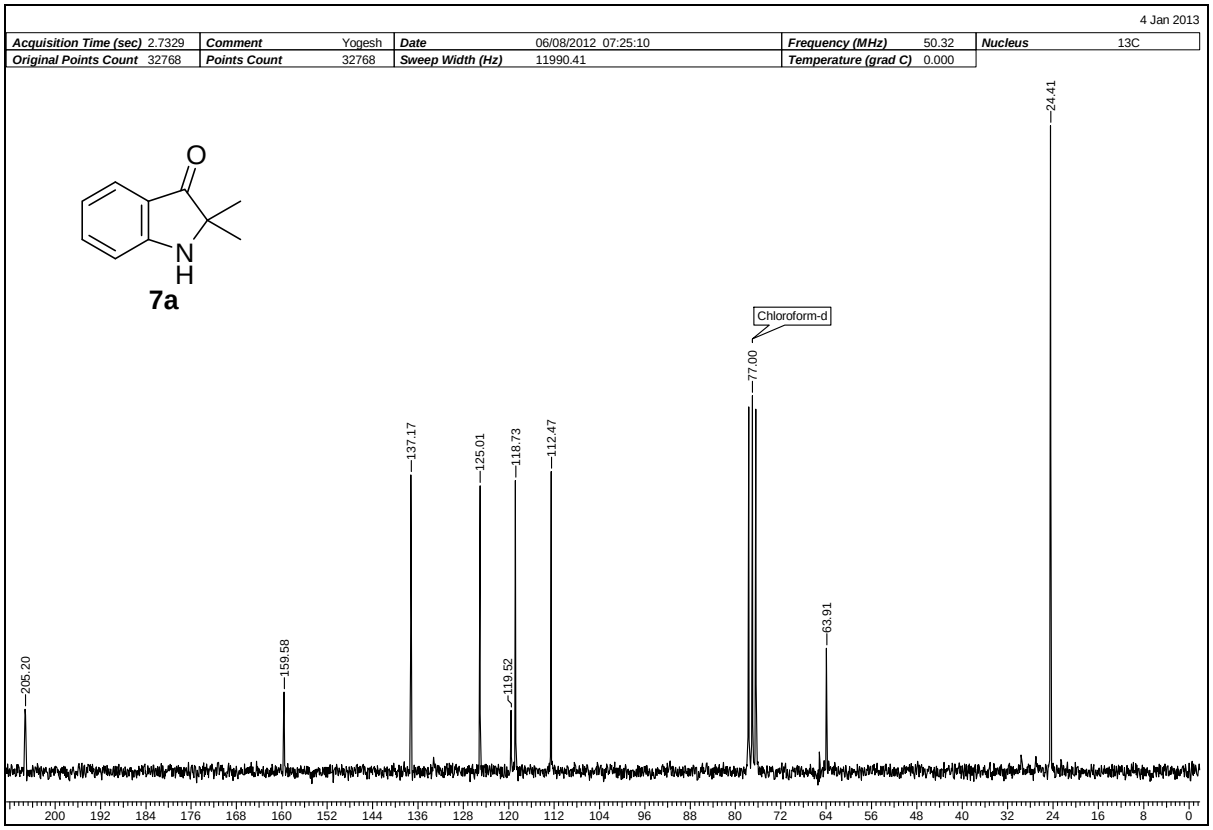
^{1}H NMR Spectrum of 3ba+4b in $CDCl_3$



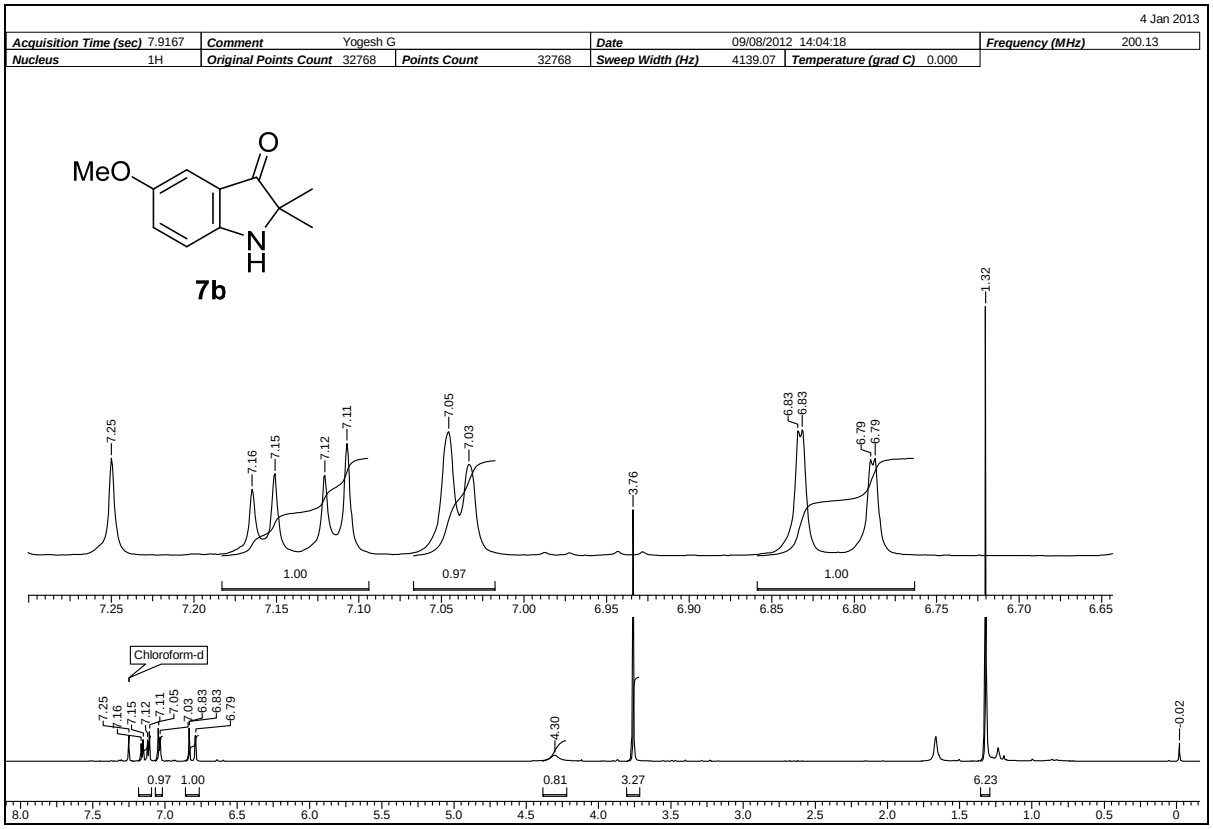
^{1}H NMR Spectrum of 3cb+4c in $CDCl_3$



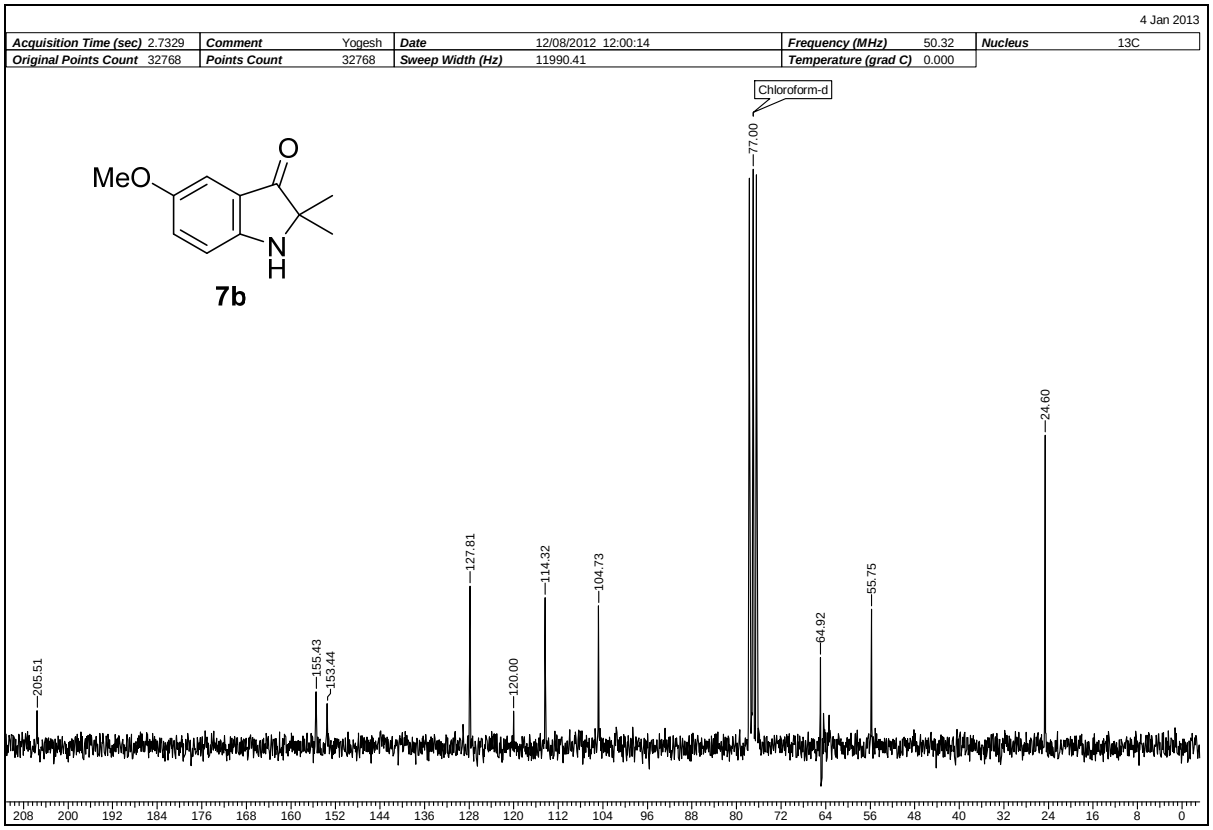
^{1}H NMR Spectrum of 7a in $CDCl_3$



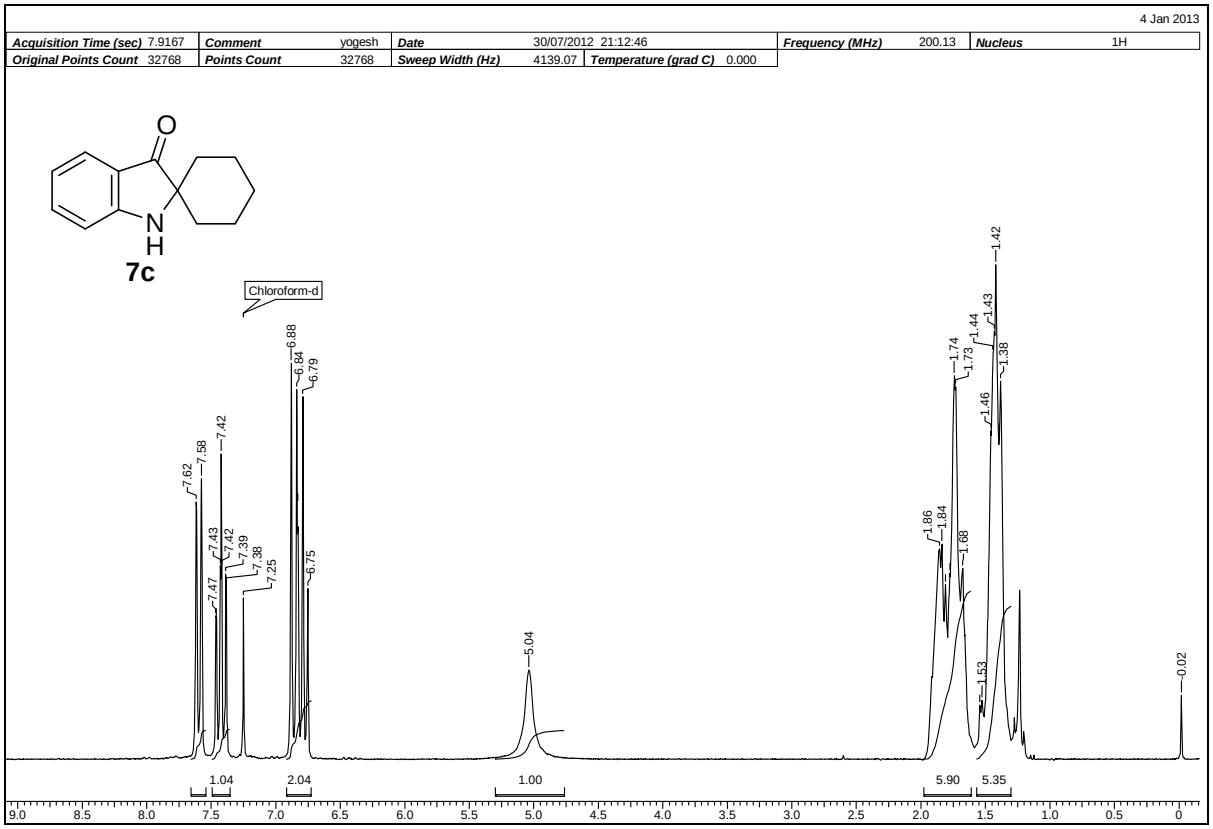
^{13}C NMR Spectrum of 7a in $CDCl_3$



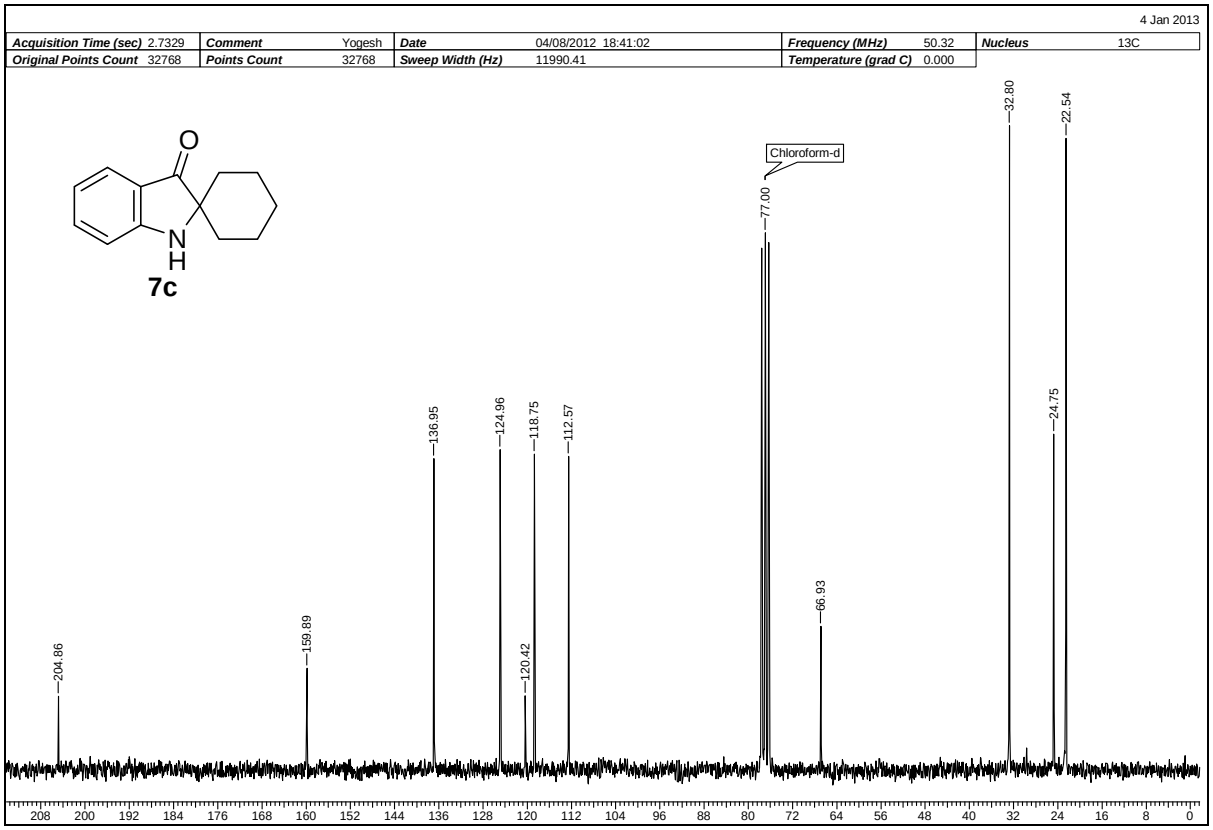
^{1}H NMR Spectrum of 7b in $CDCl_3$



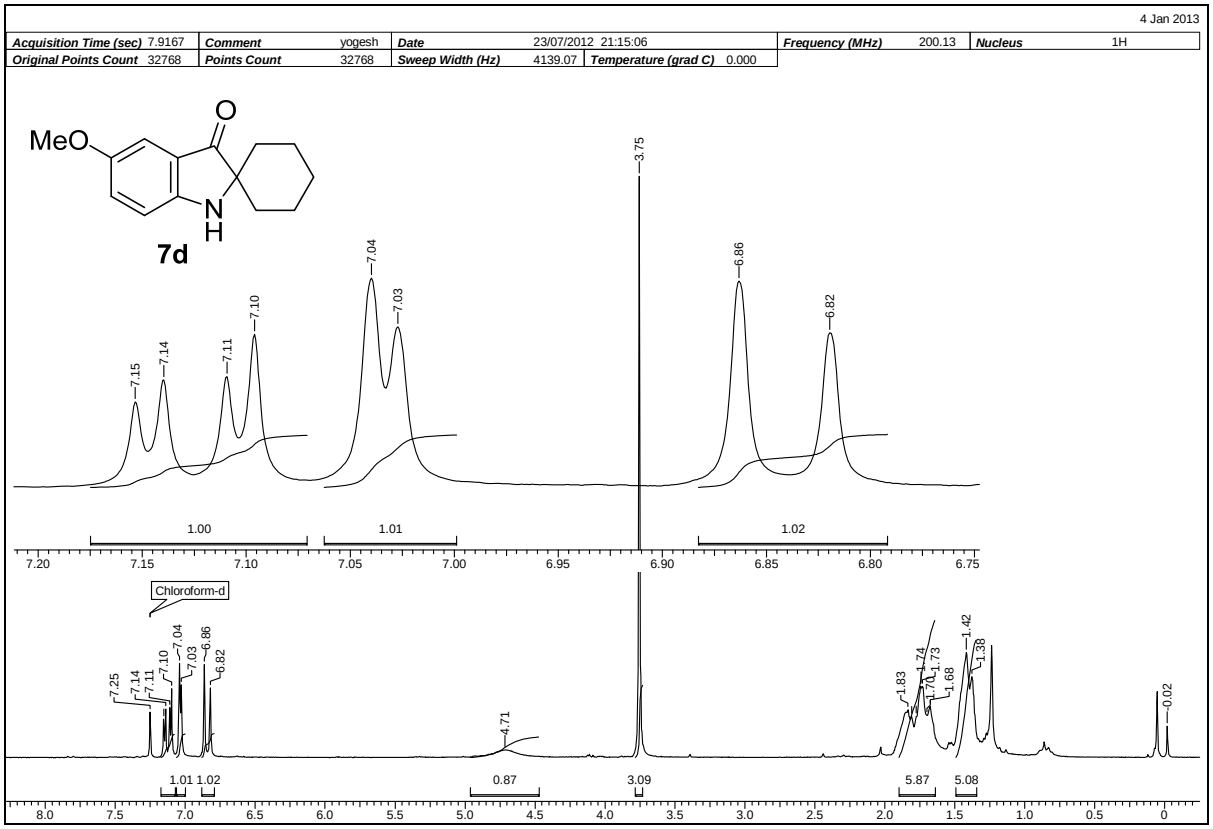
^{13}C NMR Spectrum of 7b in $CDCl_3$



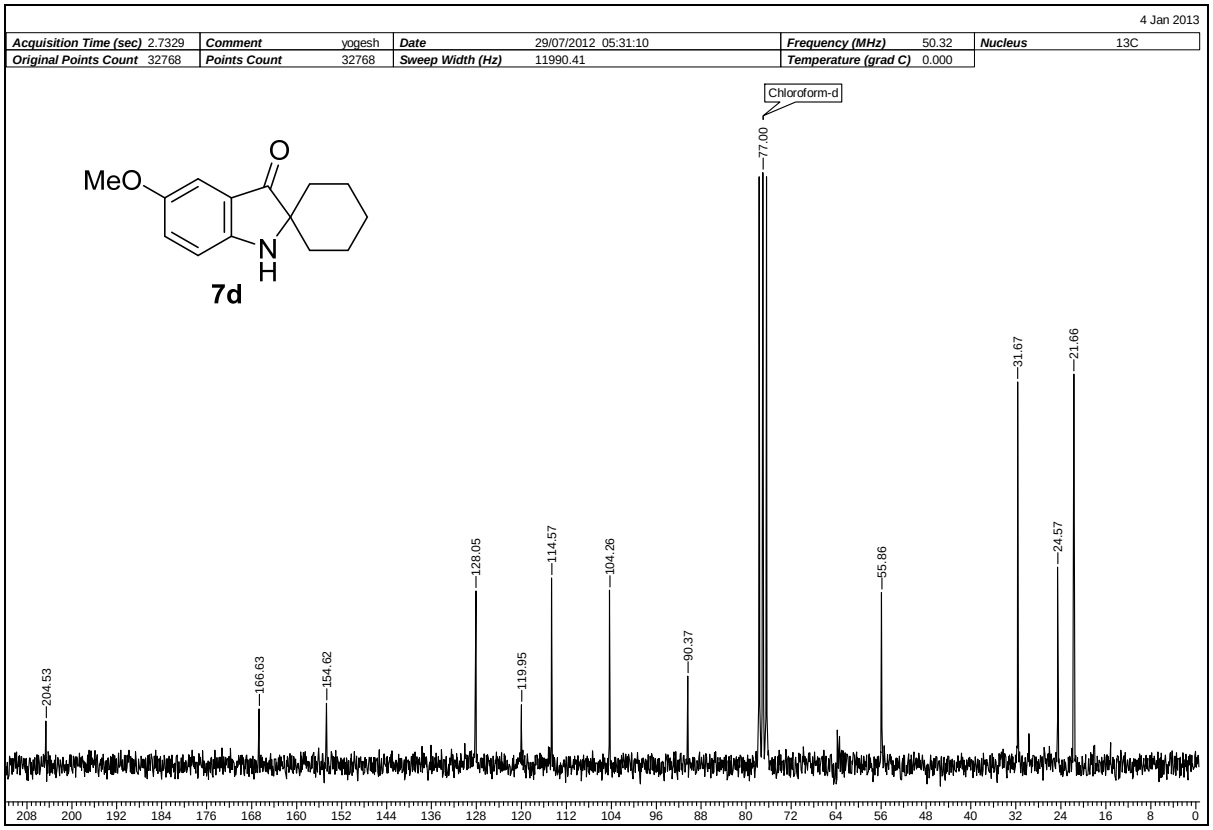
^{1}H NMR Spectrum of 7c in $CDCl_3$



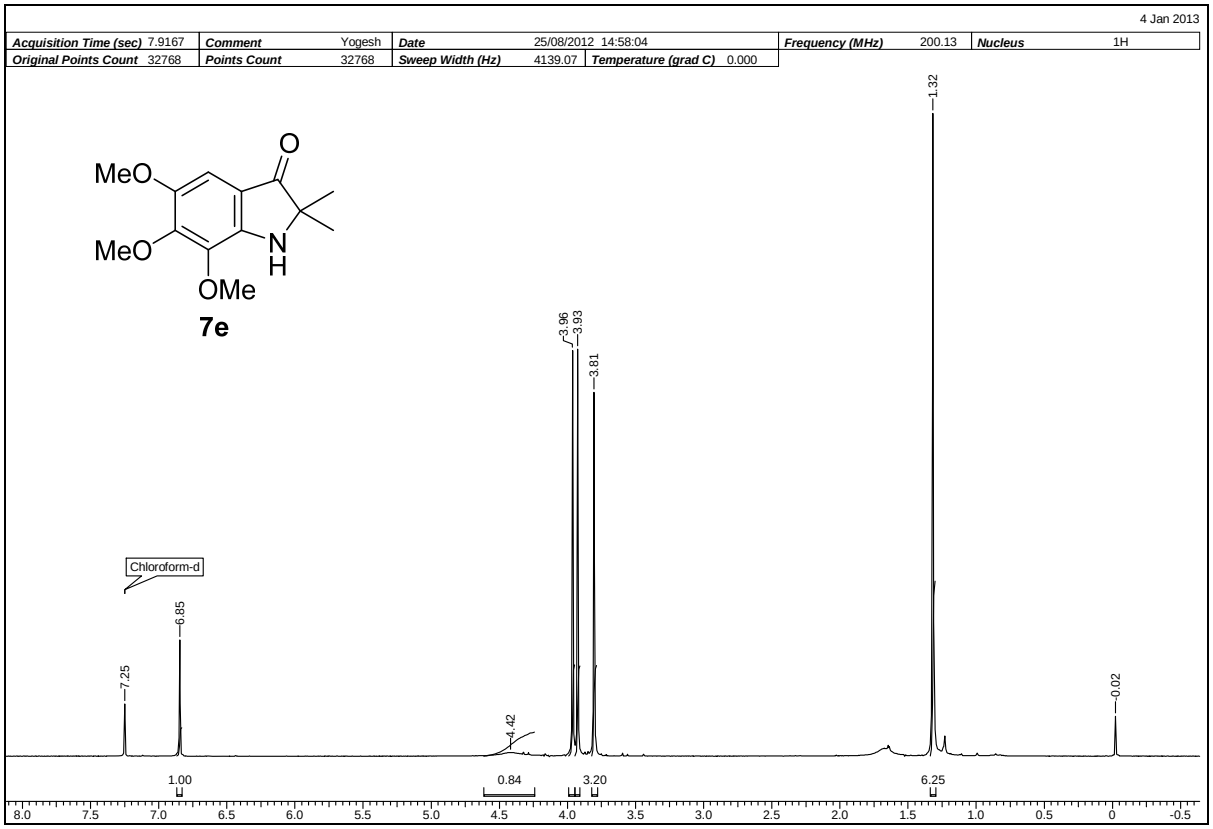
^{13}C NMR Spectrum of 7c in $CDCl_3$



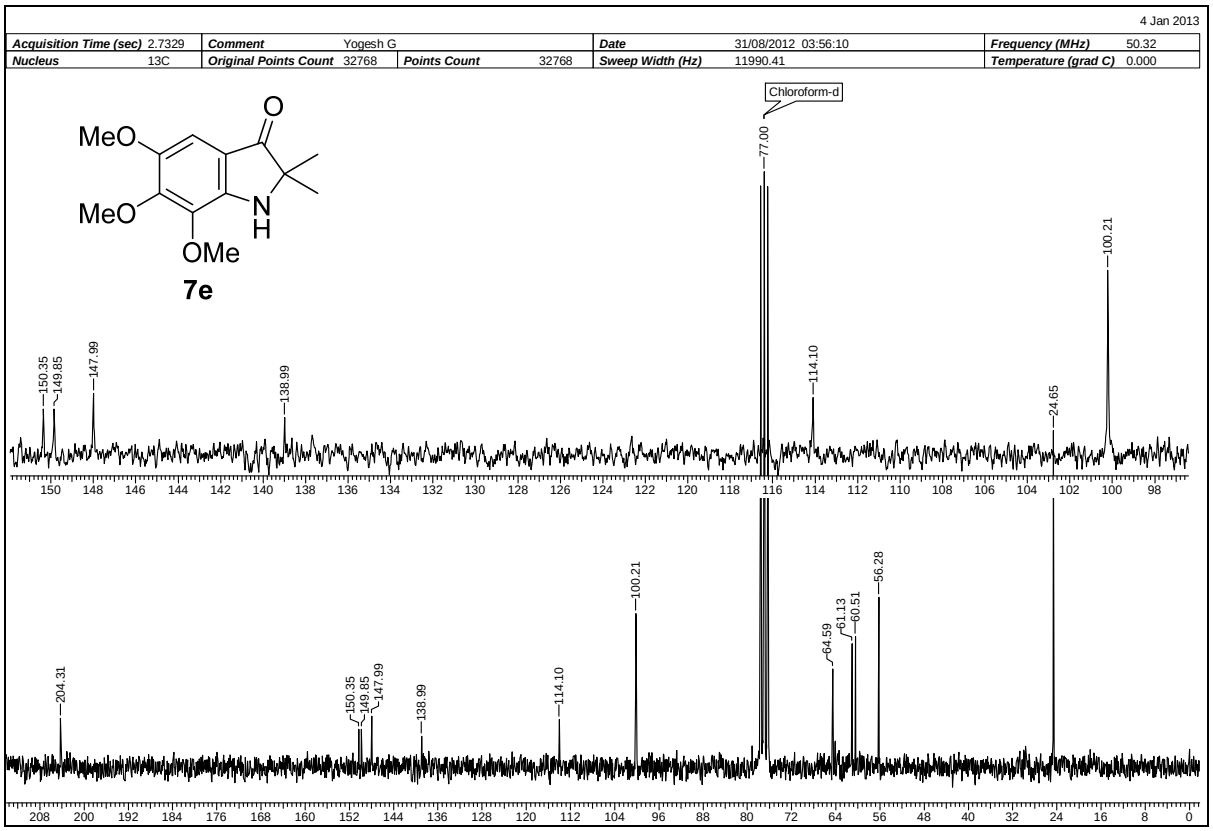
^{1}H NMR Spectrum of 7d in $CDCl_3$



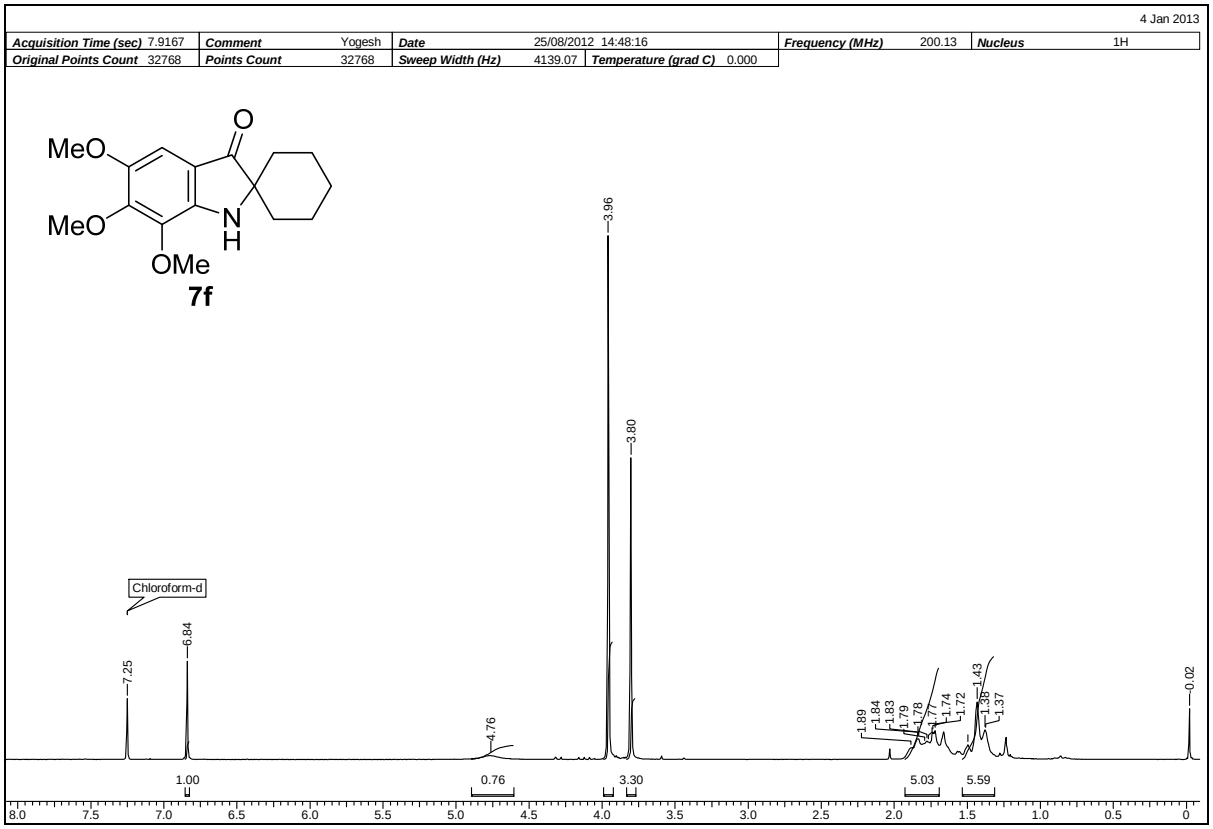
^{13}C NMR Spectrum of 7d in $CDCl_3$



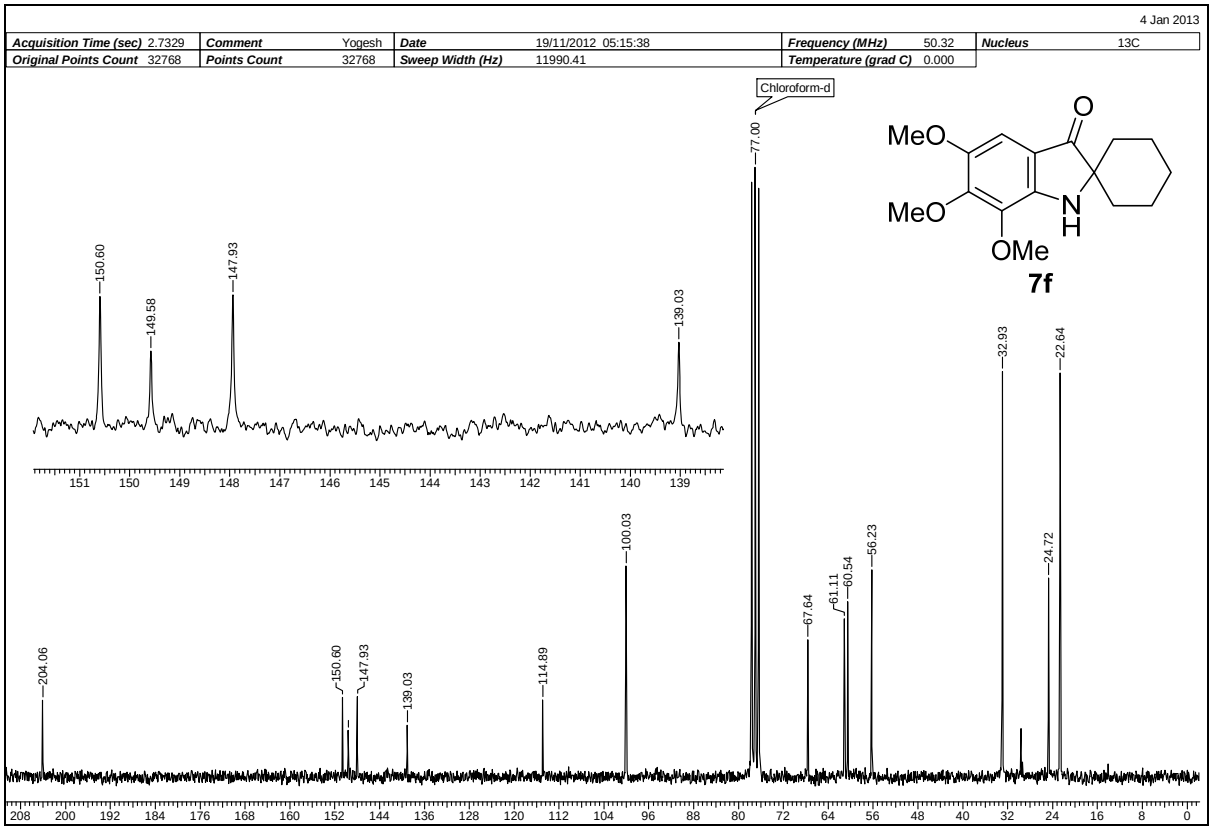
^{1}H NMR Spectrum of 7e in $CDCl_3$



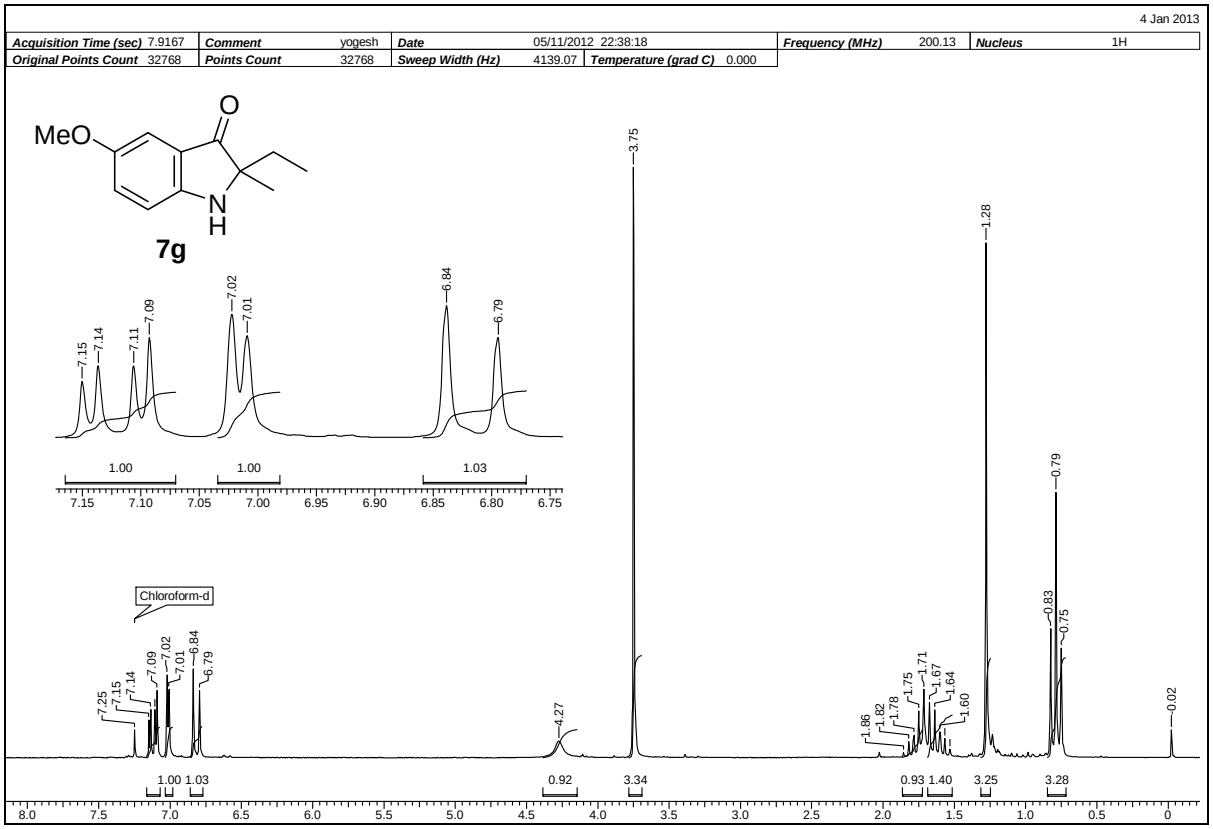
^{13}C NMR Spectrum of 7e in $CDCl_3$



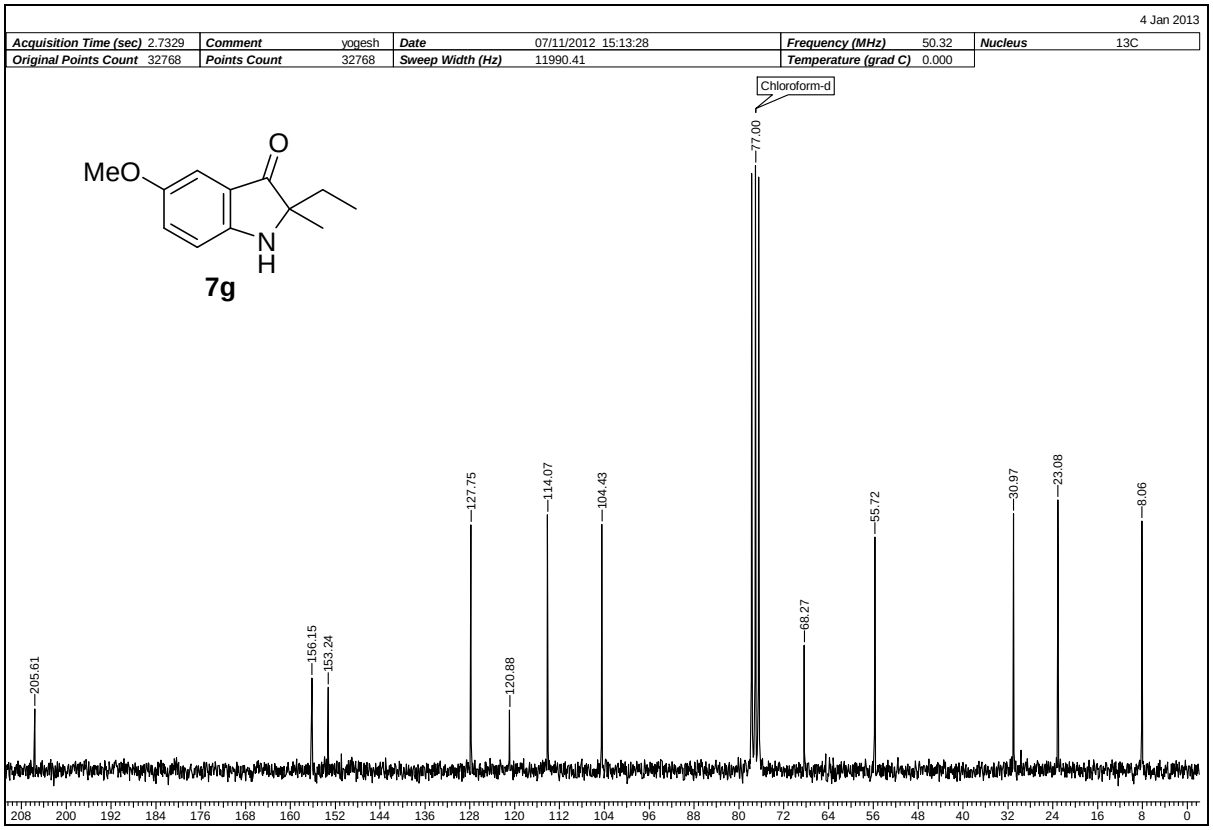
^{1}H NMR Spectrum of 7f in $CDCl_3$



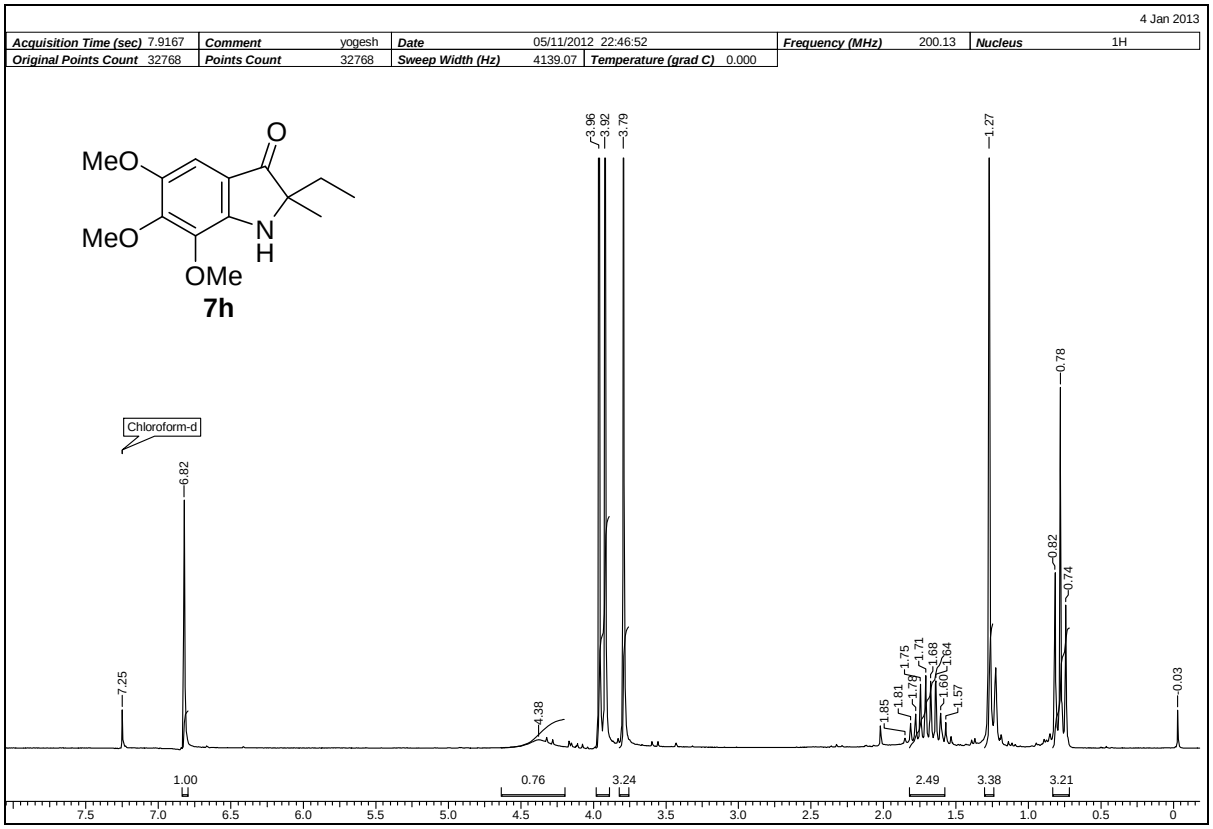
^{13}C NMR Spectrum of 7f in $CDCl_3$



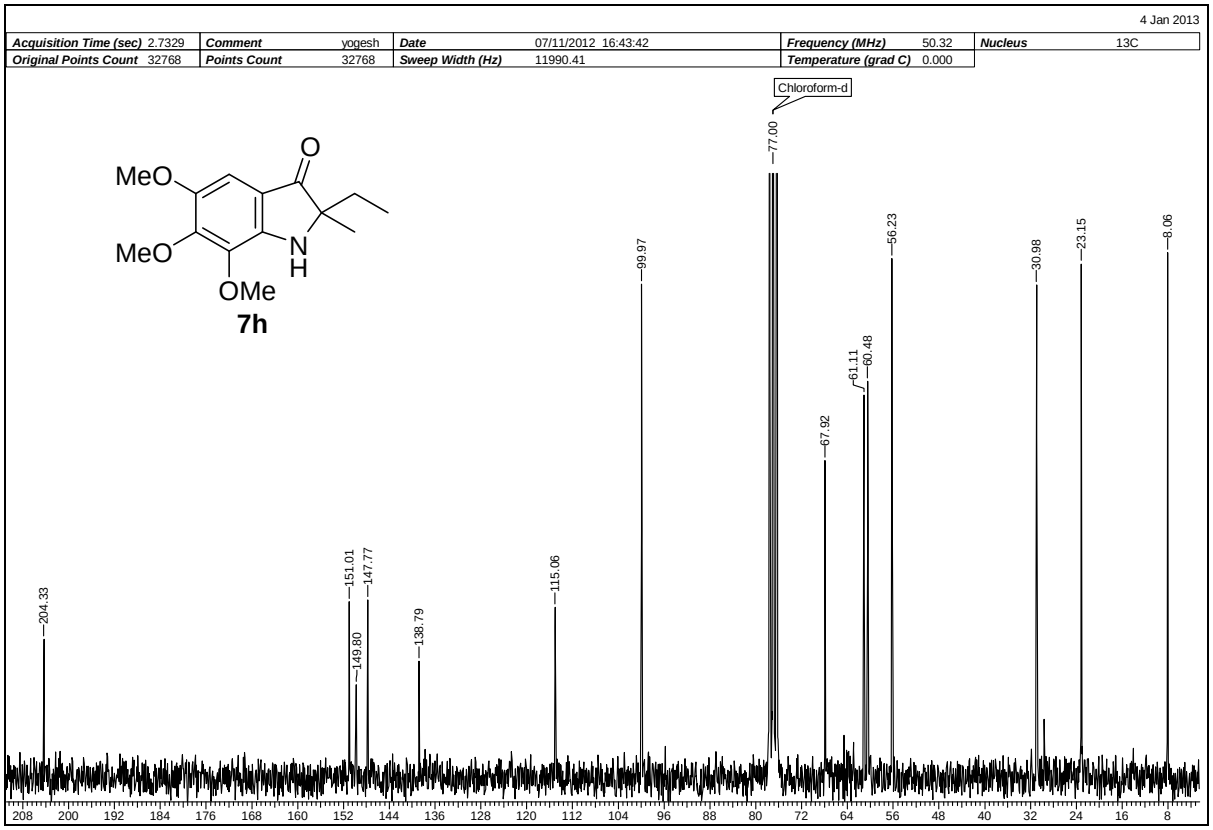
^{1}H NMR Spectrum of 7g in $CDCl_3$



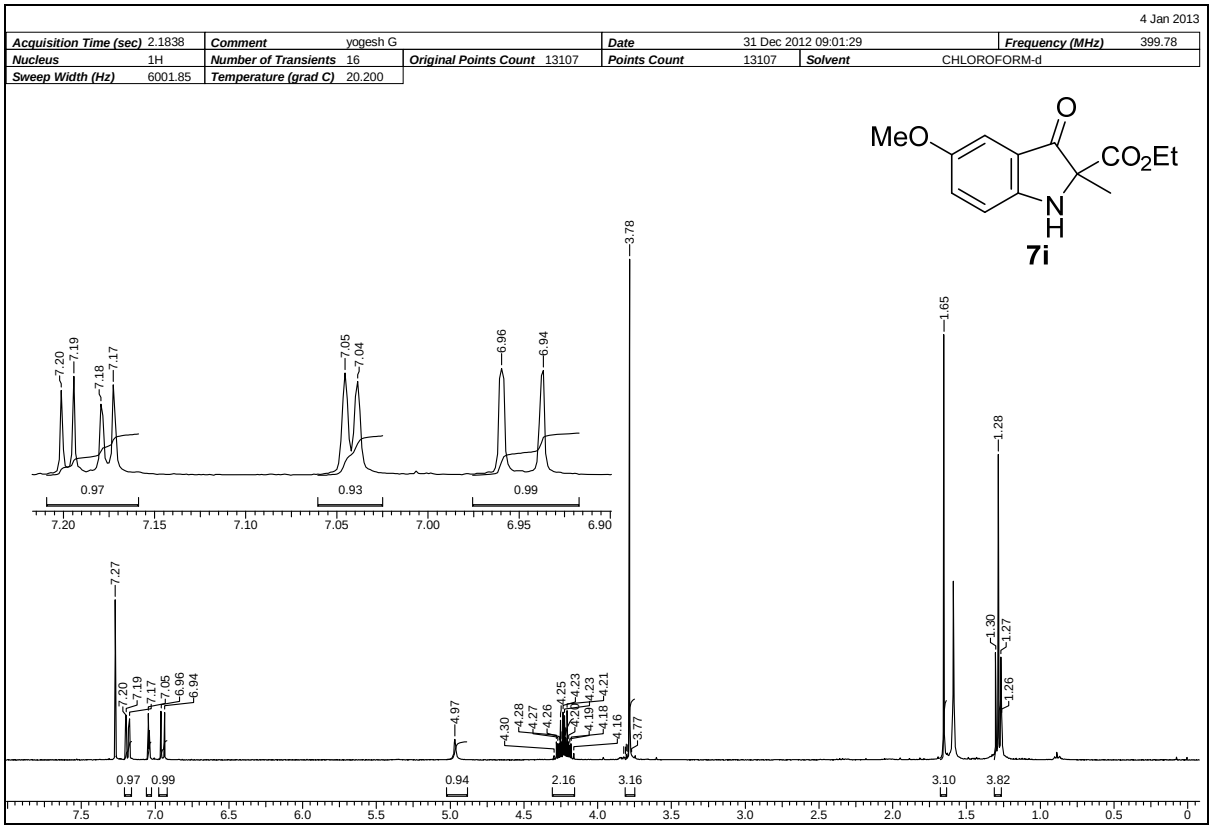
^{13}C NMR Spectrum of 7g in $CDCl_3$



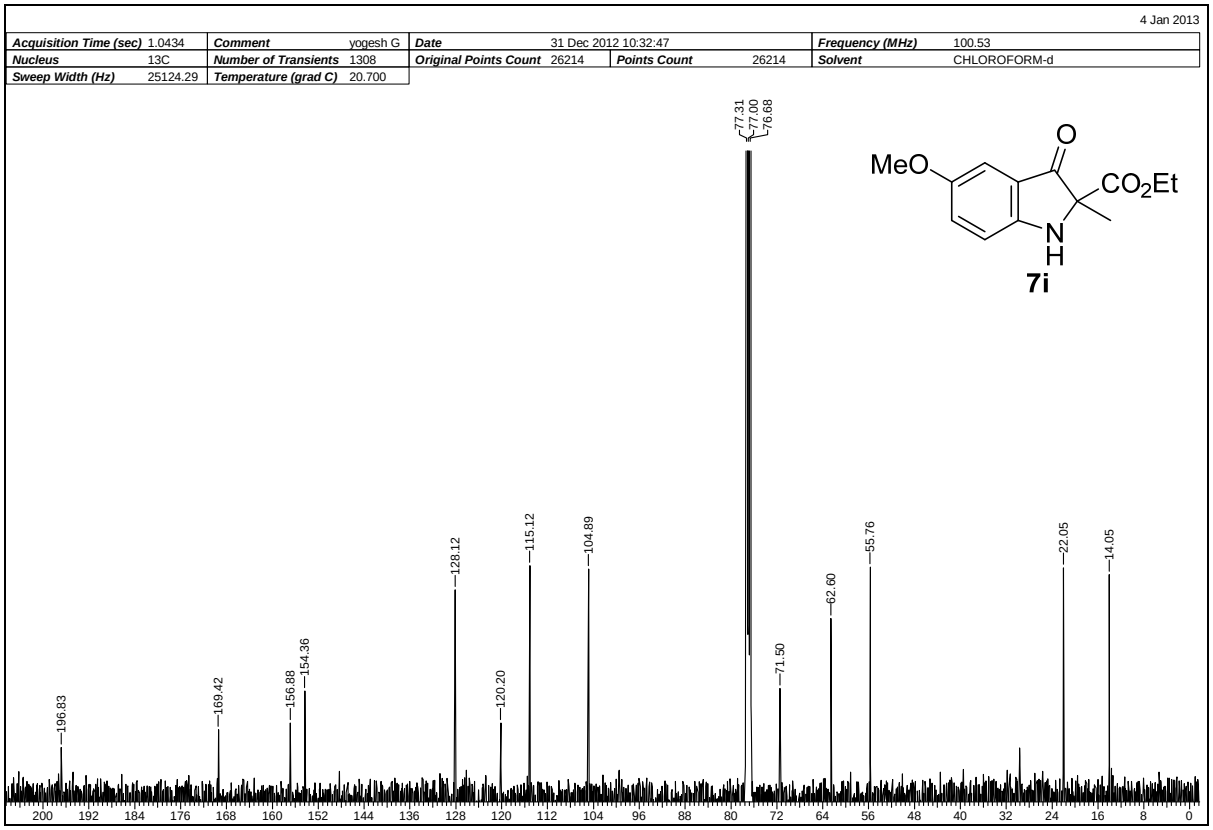
^{1}H NMR Spectrum of 7h in $CDCl_3$



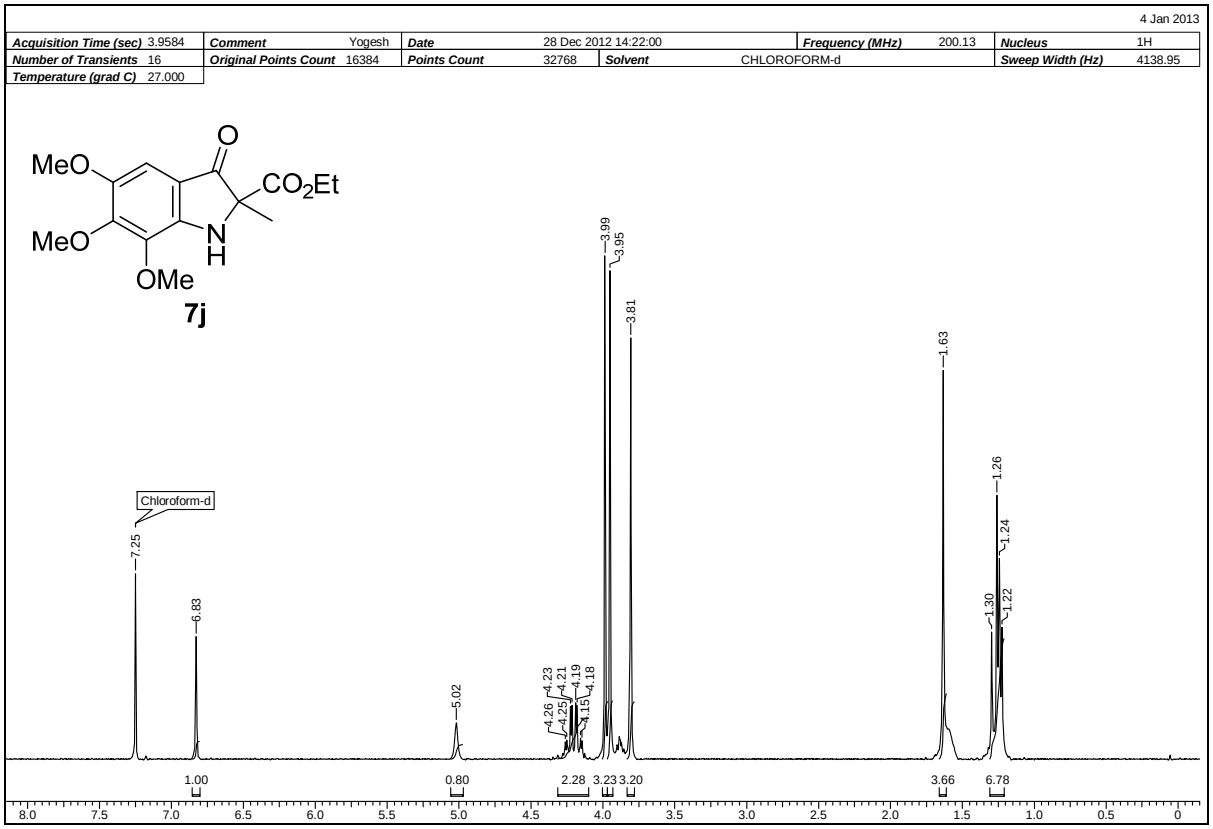
^{13}C NMR Spectrum of 7h in $CDCl_3$



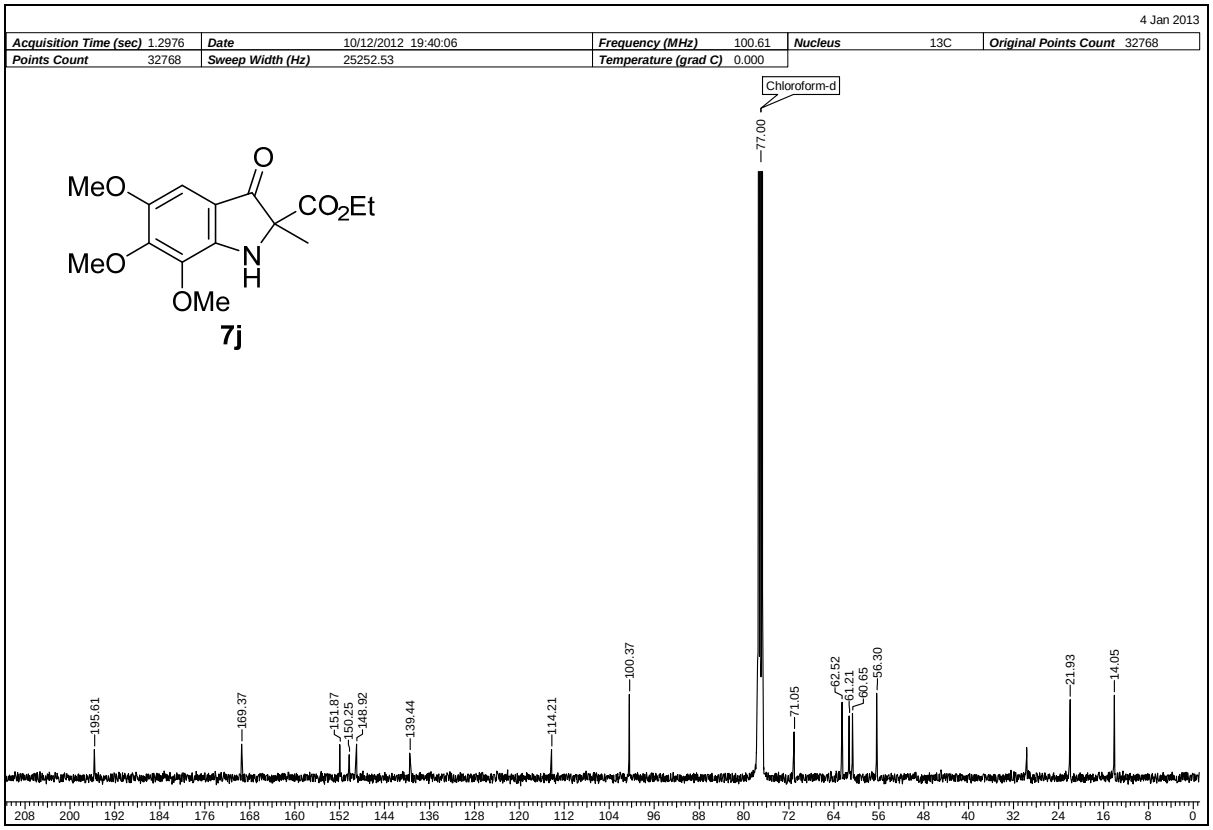
^{1}H NMR Spectrum of 7i in $CDCl_3$



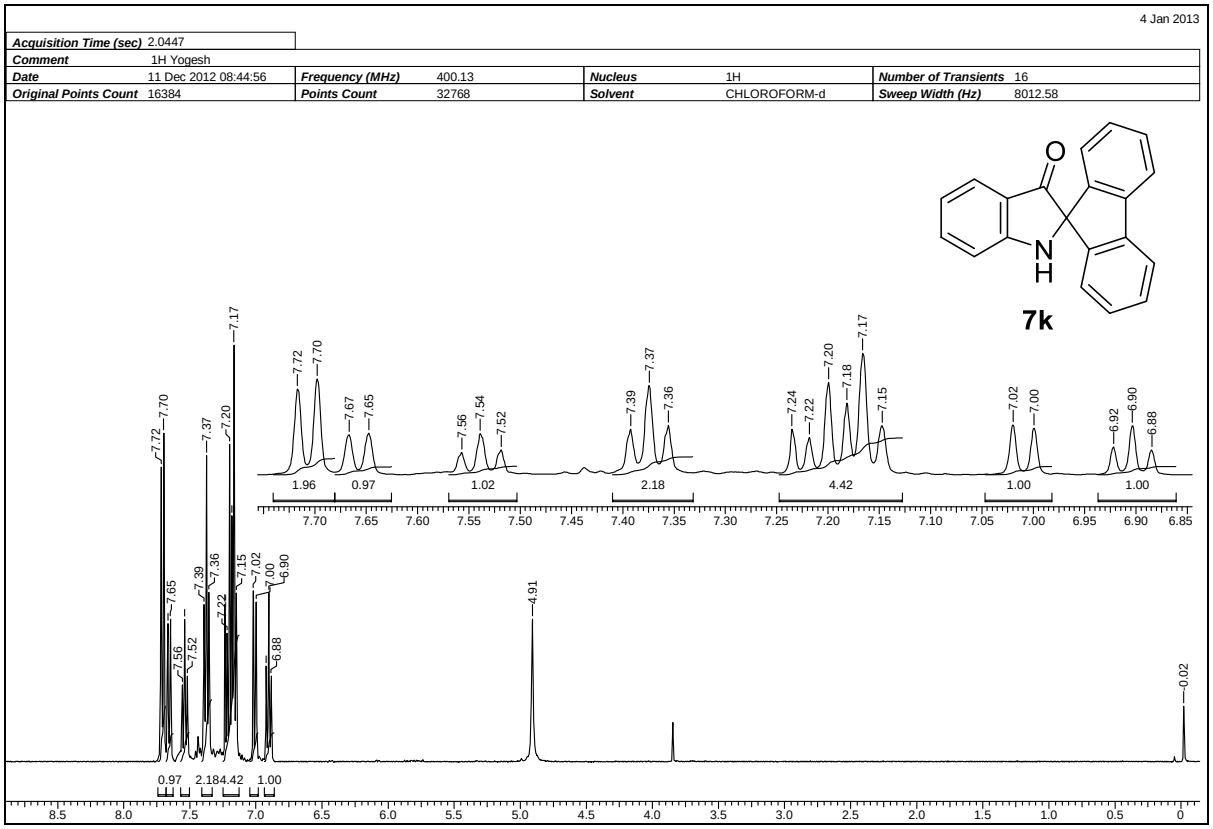
^{13}C NMR Spectrum of 7i in $CDCl_3$



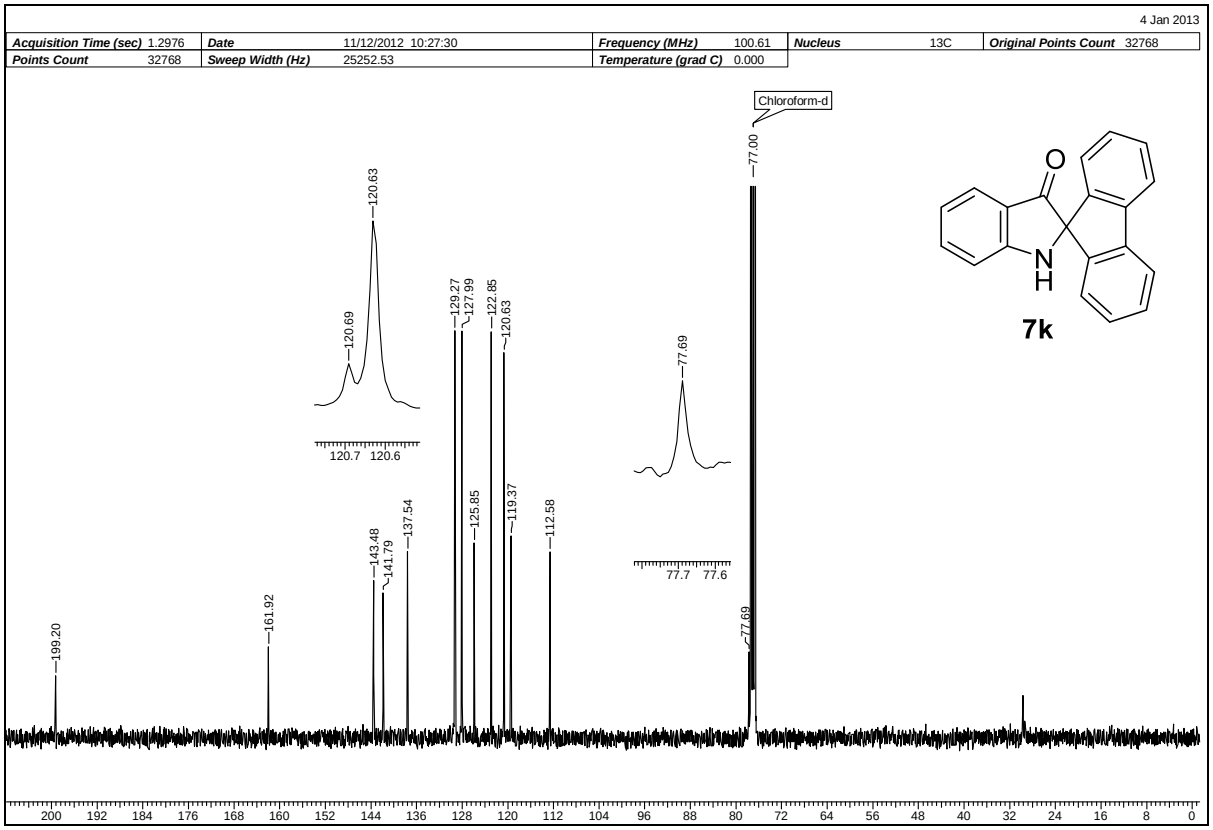
^{1}H NMR Spectrum of 7j in $CDCl_3$



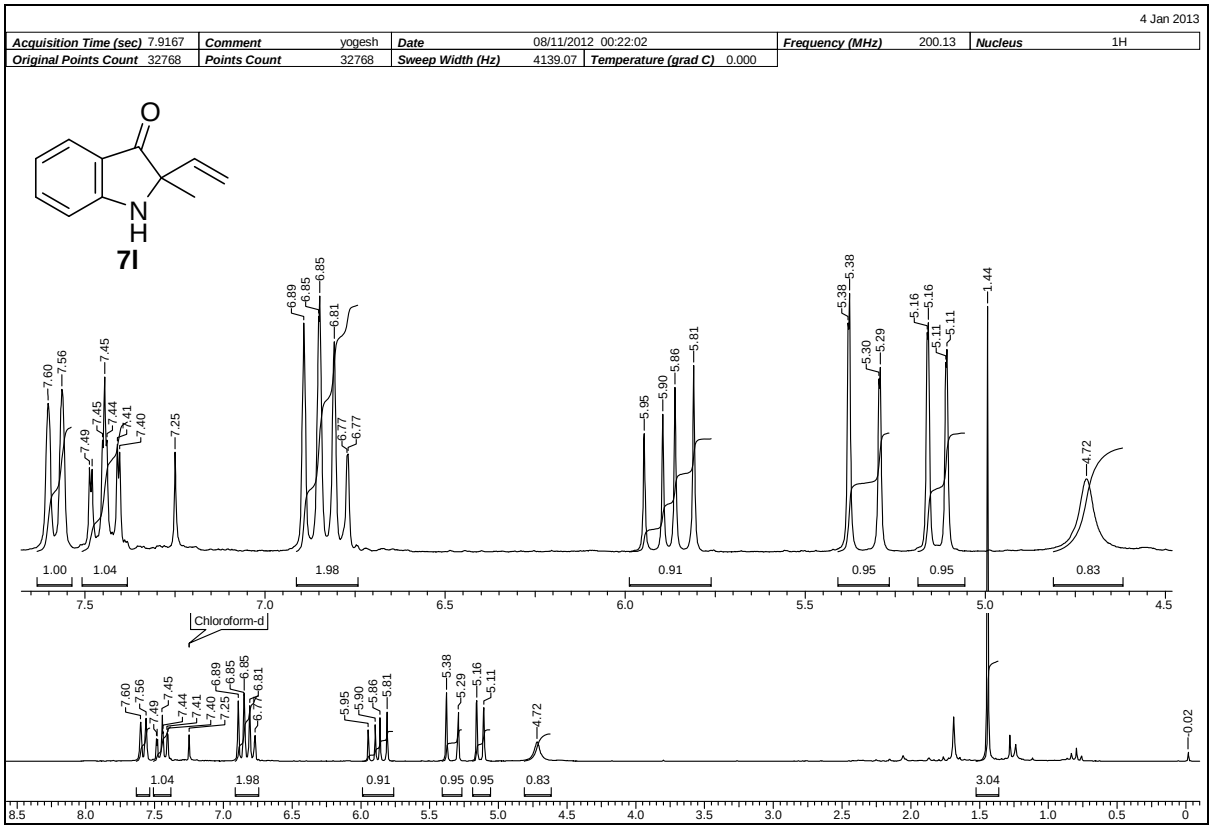
^{13}C NMR Spectrum of 7j in $CDCl_3$



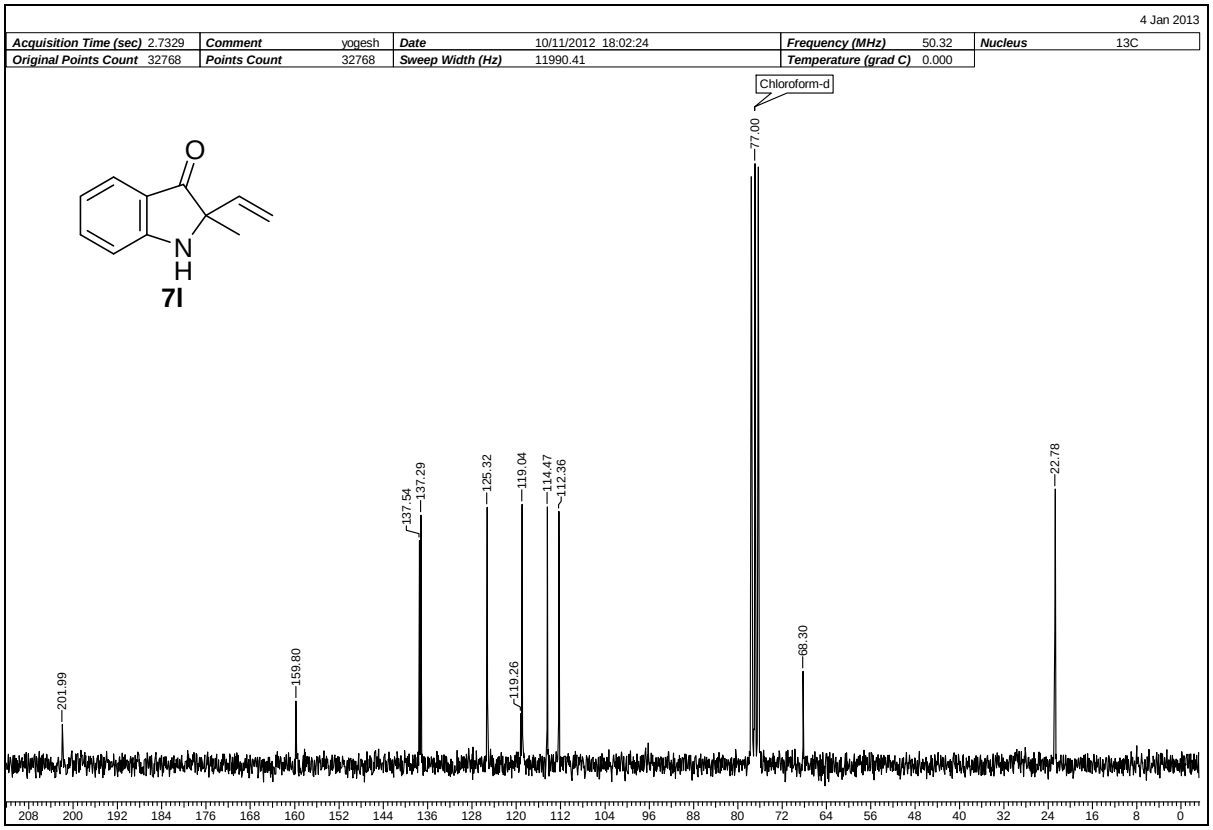
^{1}H NMR Spectrum of 7k in $CDCl_3$



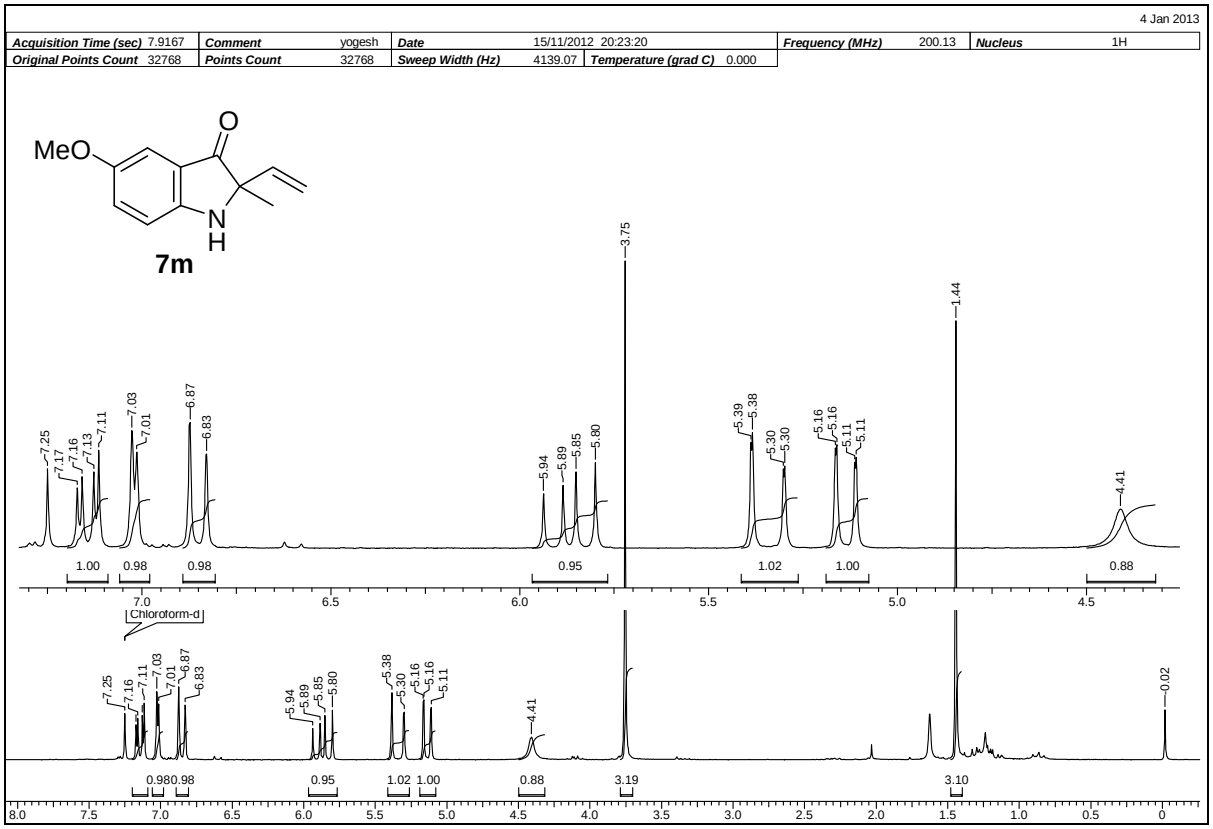
^{13}C NMR Spectrum of 7k in $CDCl_3$



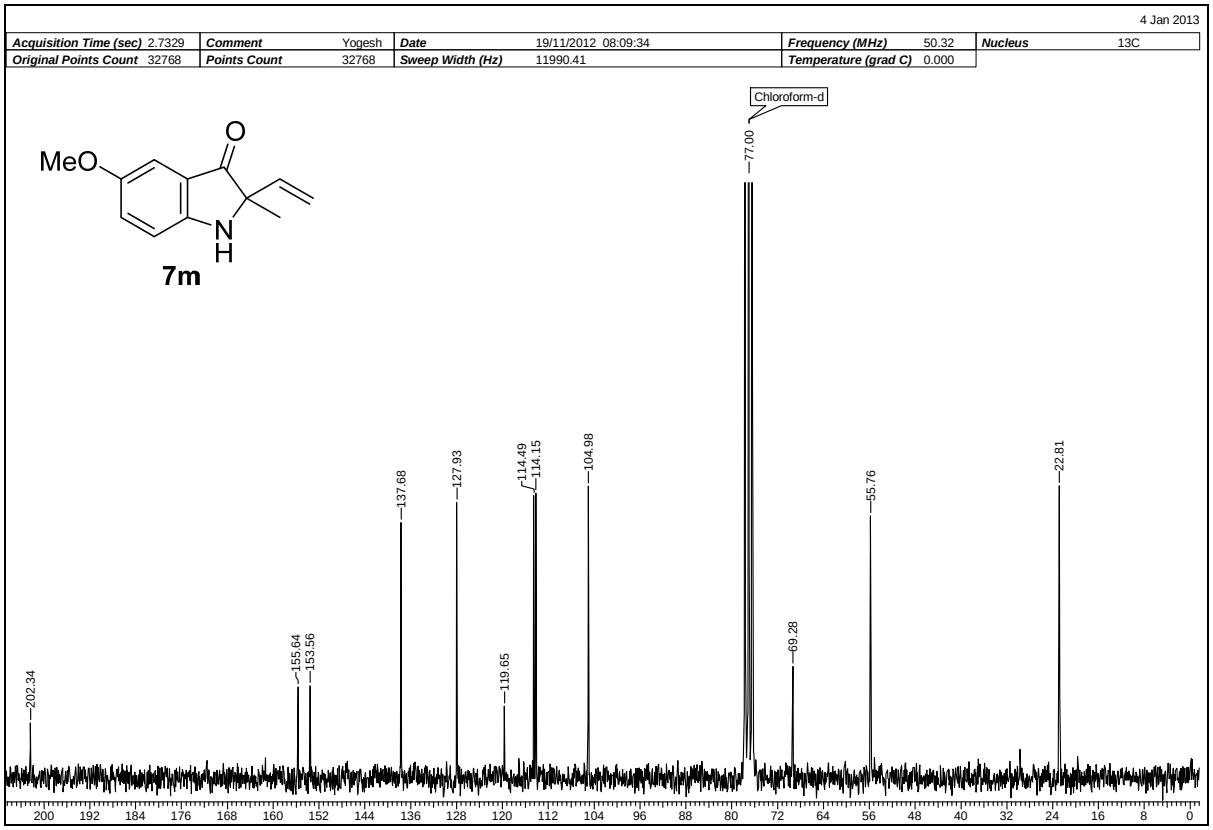
^{1}H NMR Spectrum of 7l in $CDCl_3$



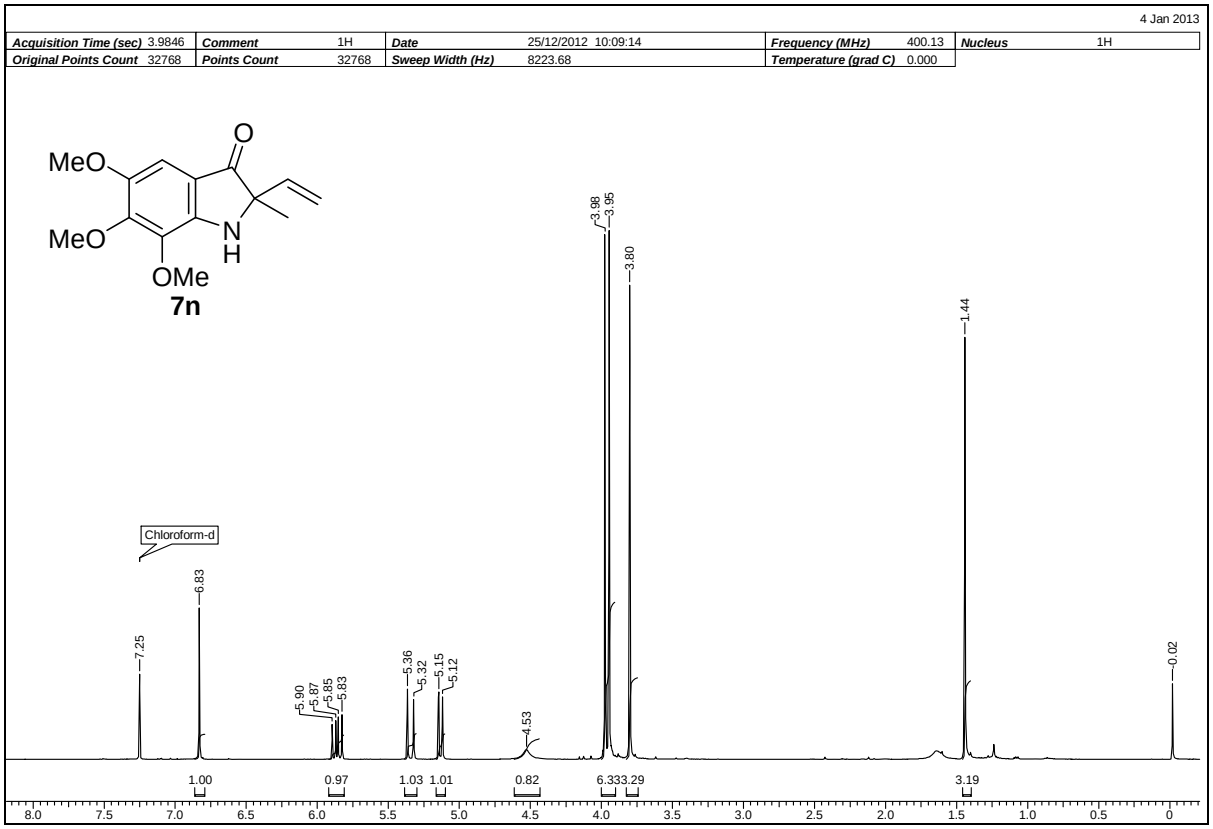
^{13}C NMR Spectrum of 7l in $CDCl_3$



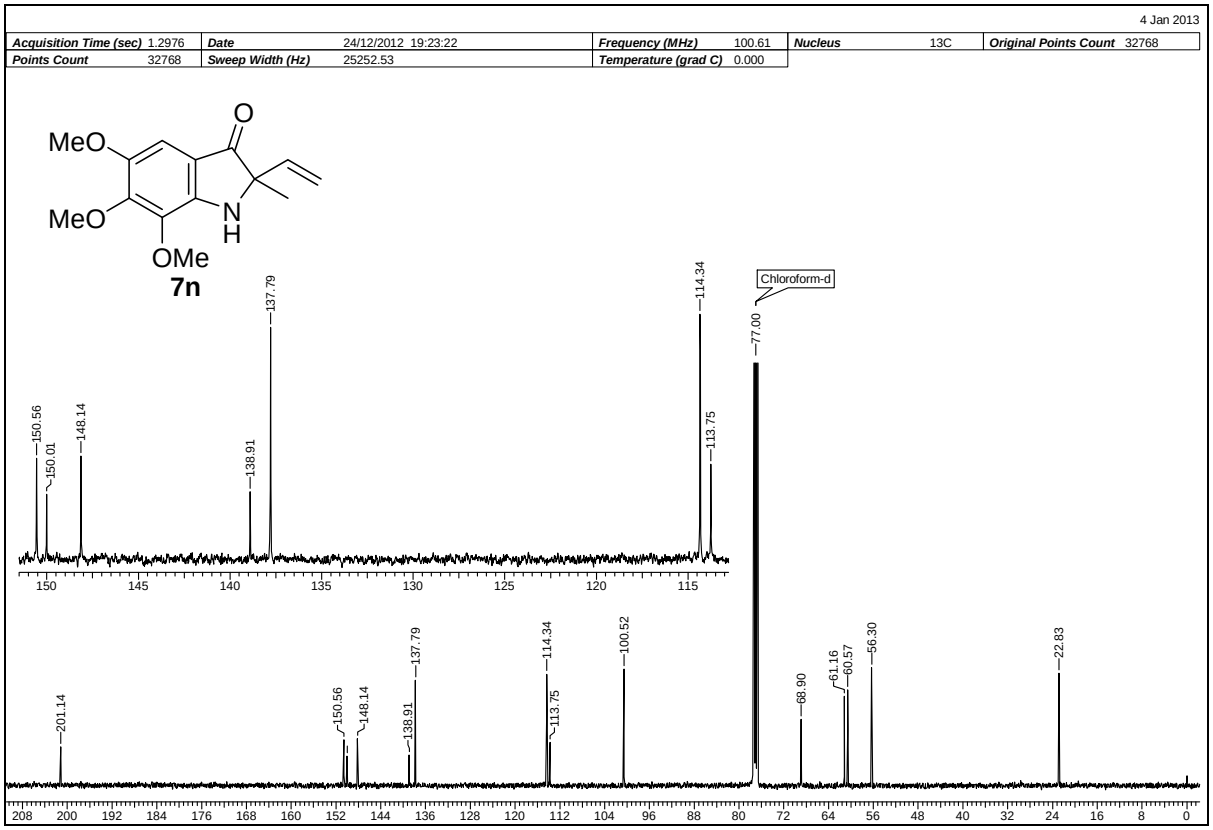
^{1}H NMR Spectrum of 7m in $CDCl_3$



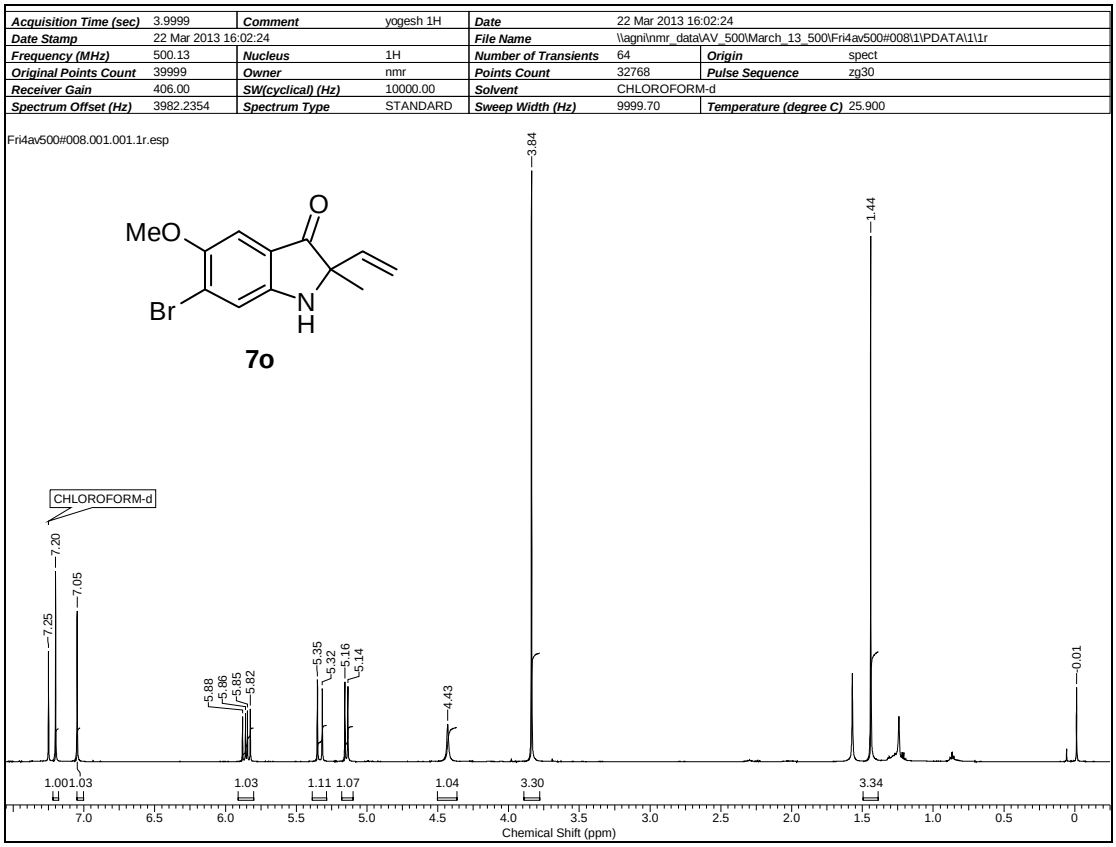
^{13}C NMR Spectrum of 7m in $CDCl_3$



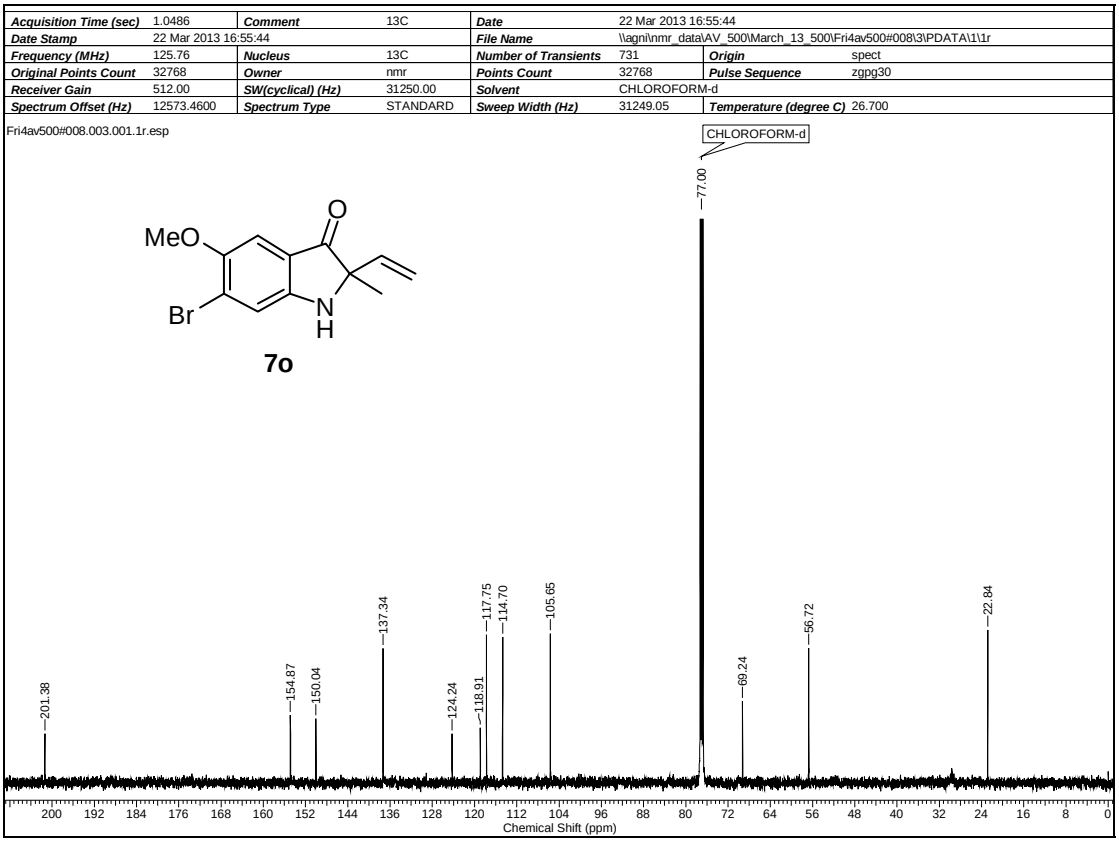
^{1}H NMR Spectrum of 7n in $CDCl_3$



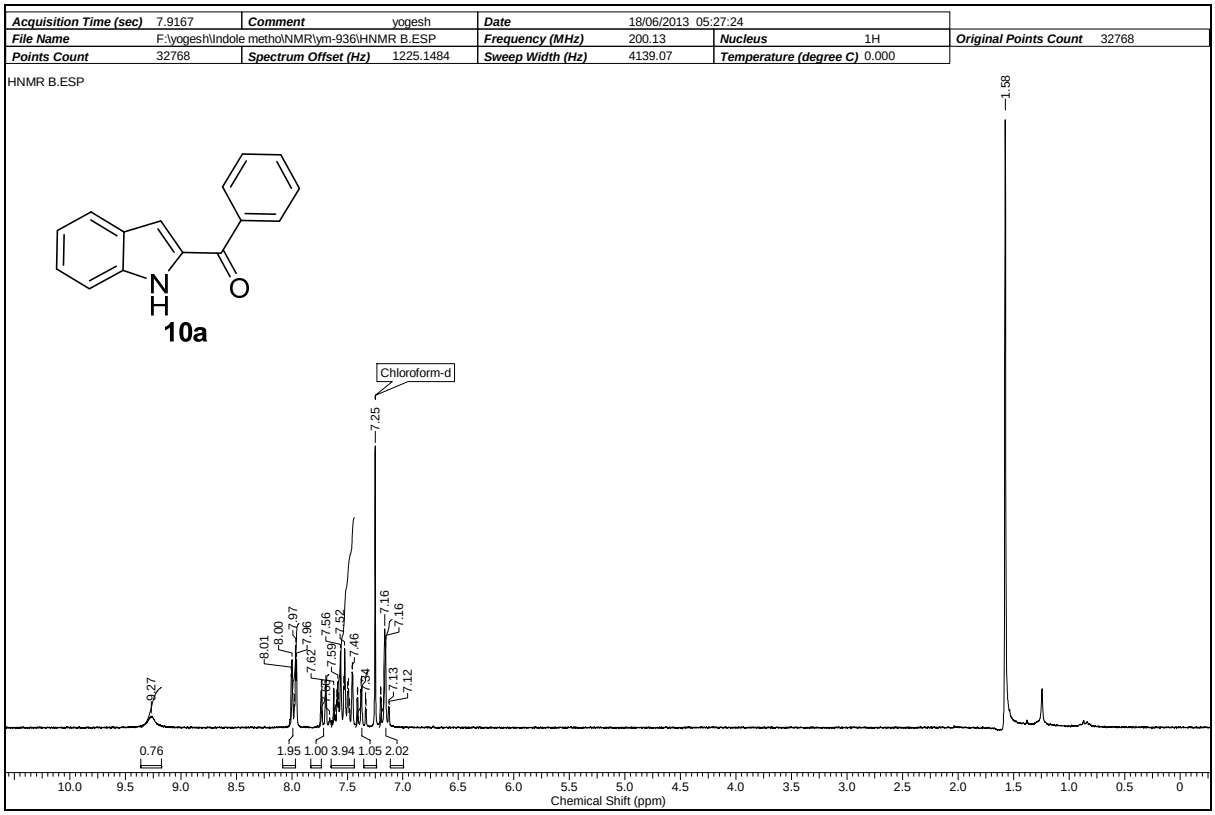
^{13}C NMR Spectrum of 7n in $CDCl_3$



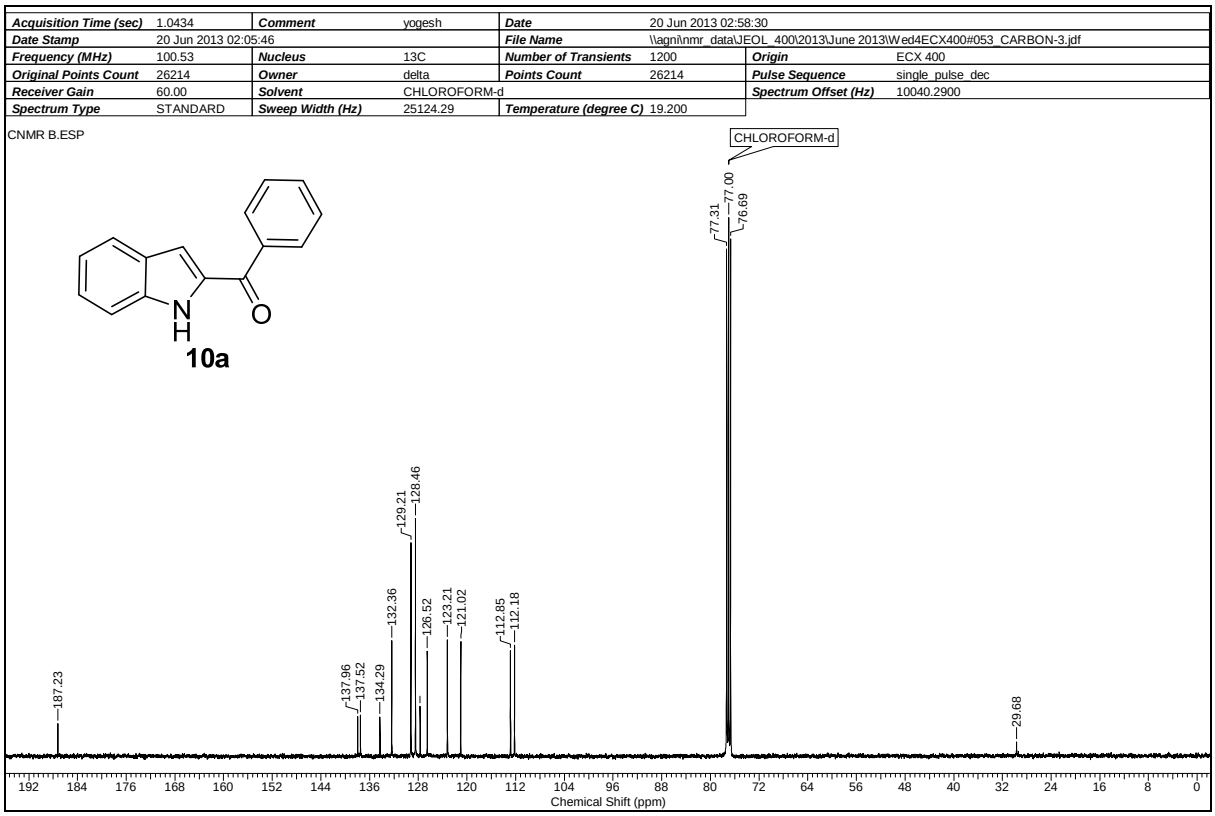
^{1}H NMR Spectrum of 7o in $CDCl_3$



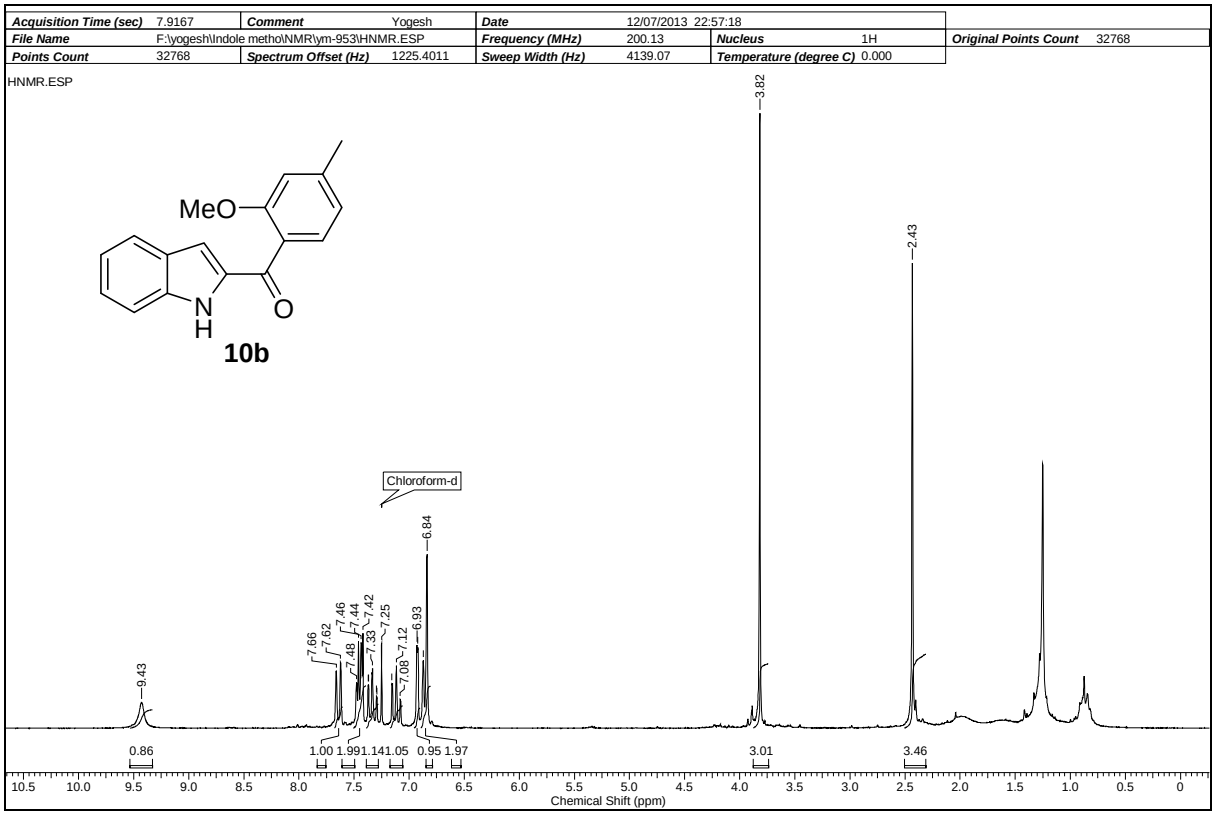
^{13}C NMR Spectrum of 7o in $CDCl_3$



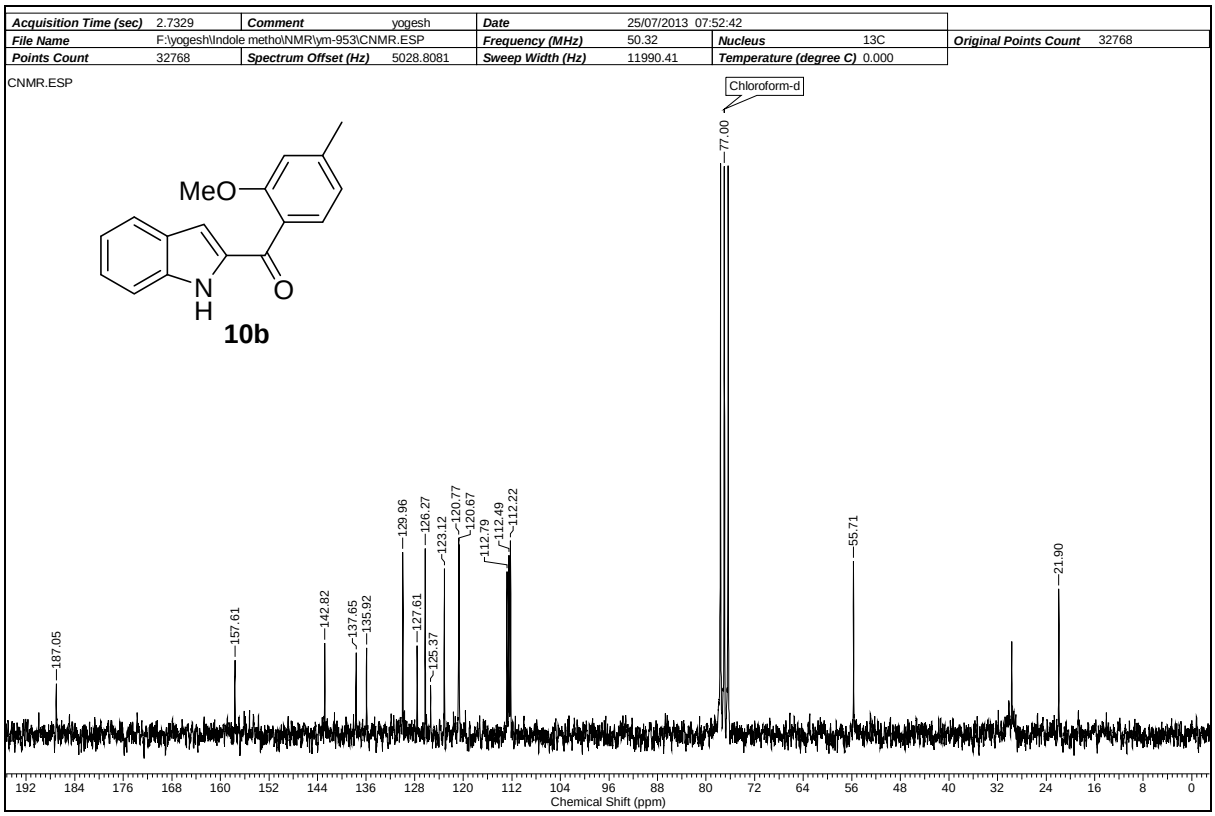
^{1}H NMR Spectrum of 10a in $CDCl_3$



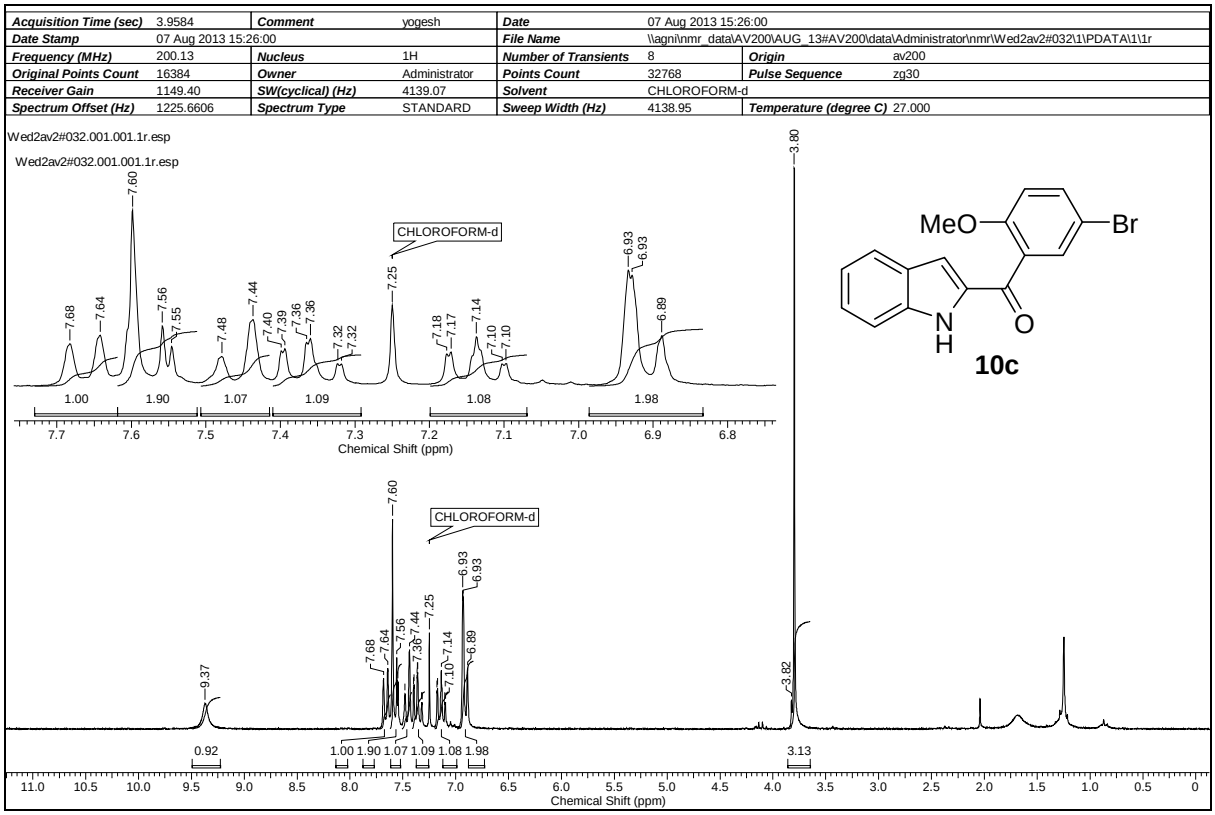
^{13}C NMR Spectrum of 10a in $CDCl_3$



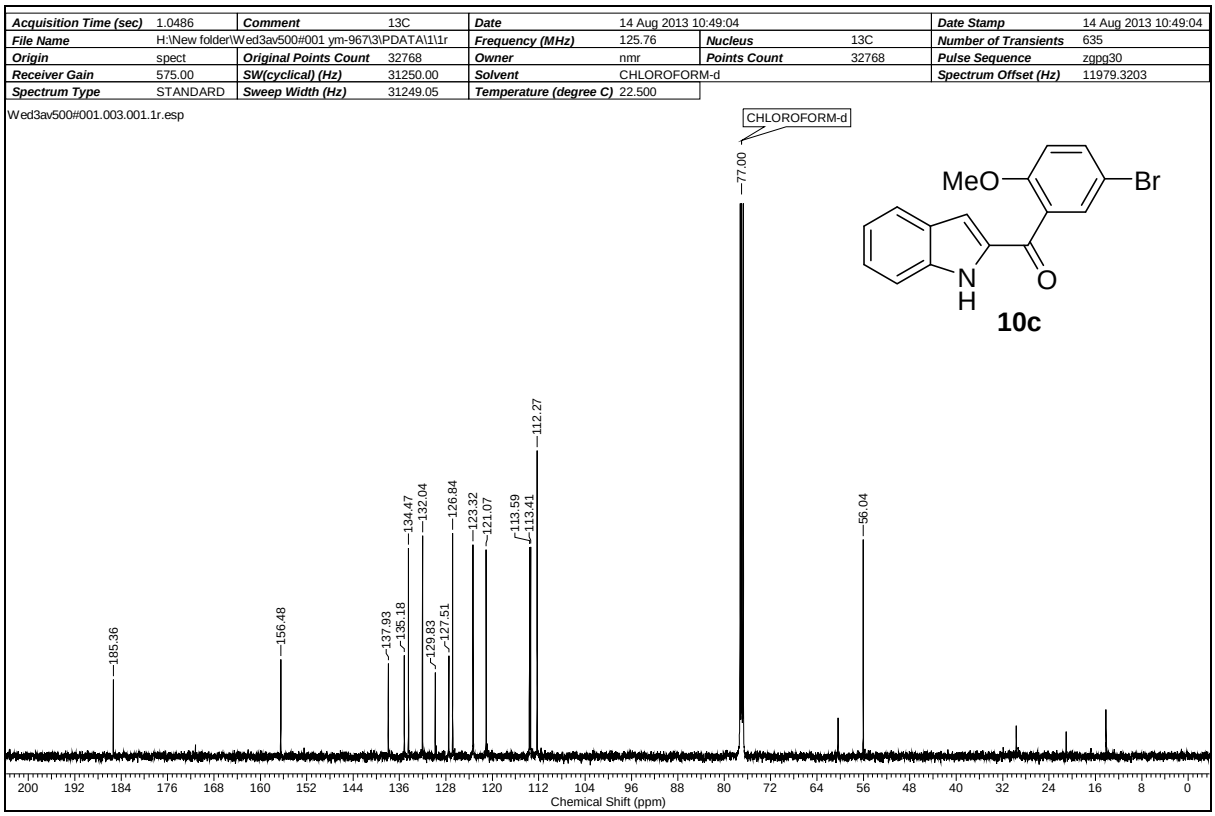
^{1}H NMR Spectrum of 10b in $CDCl_3$



^{13}C NMR Spectrum of 10b in $CDCl_3$



^{1}H NMR Spectrum of 10c in $CDCl_3$



^{13}C NMR Spectrum of 10c in $CDCl_3$

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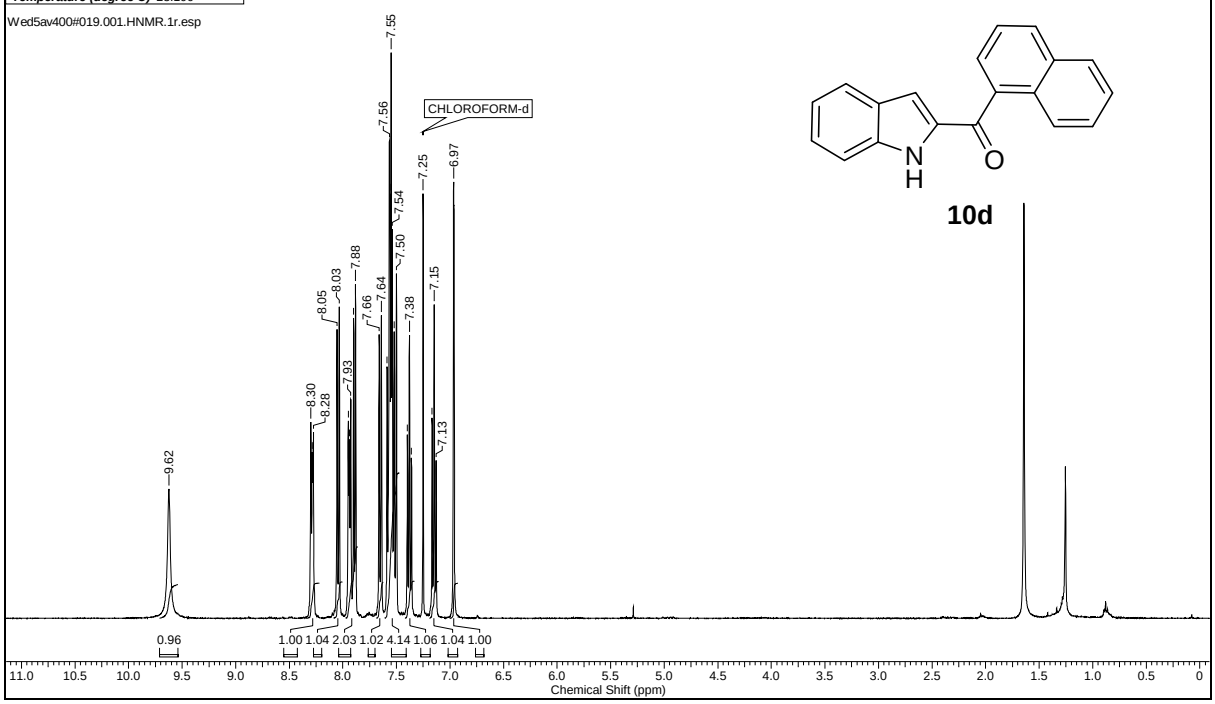

^{1}H NMR Spectrum of 10d in $CDCl_3$

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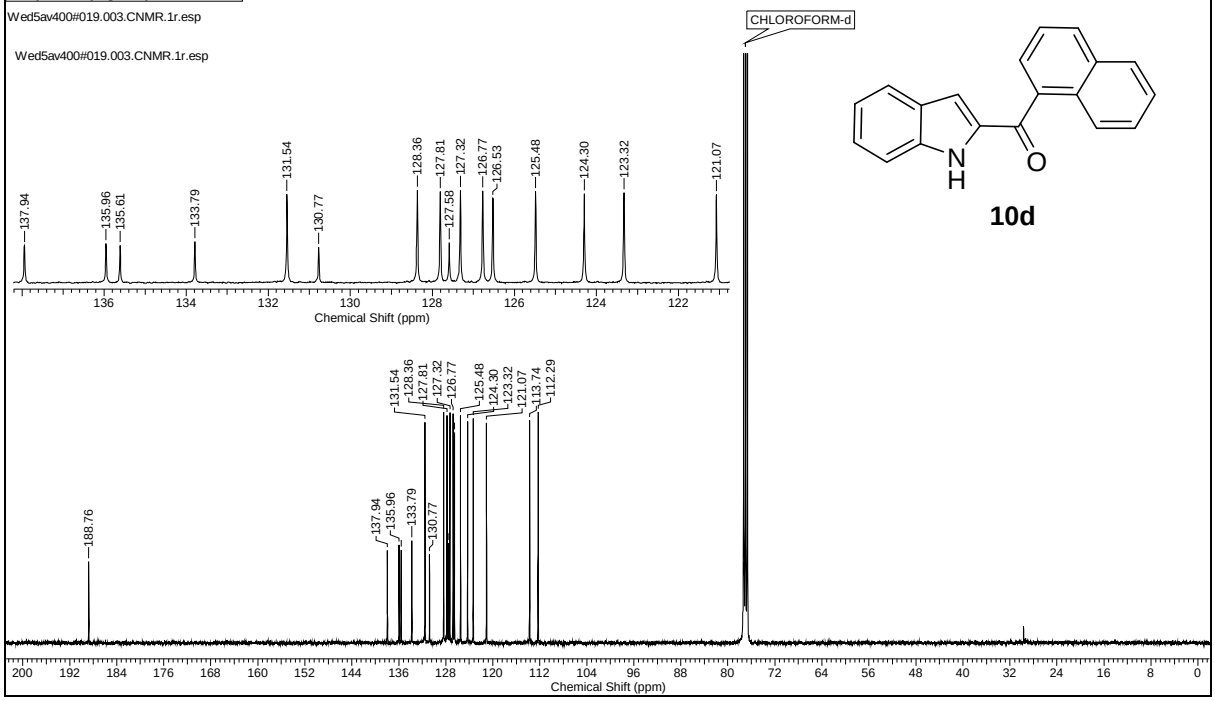
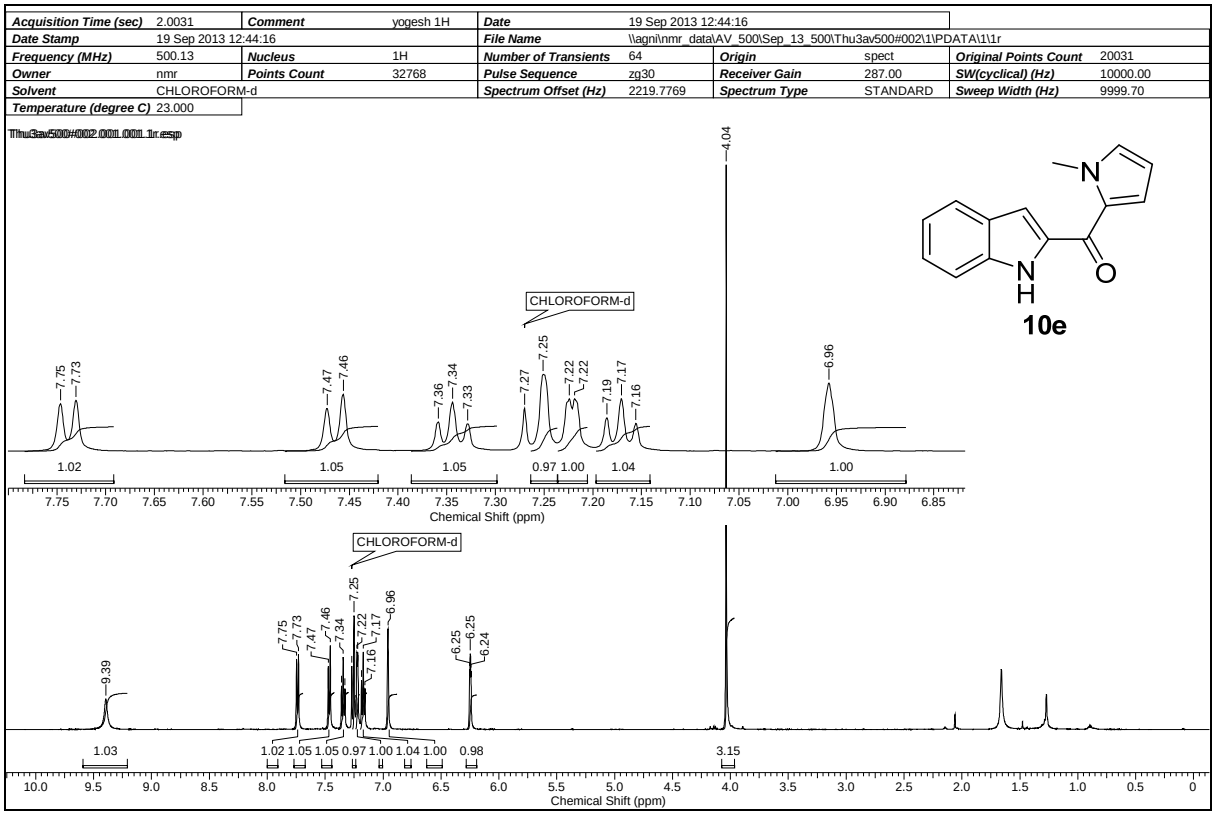
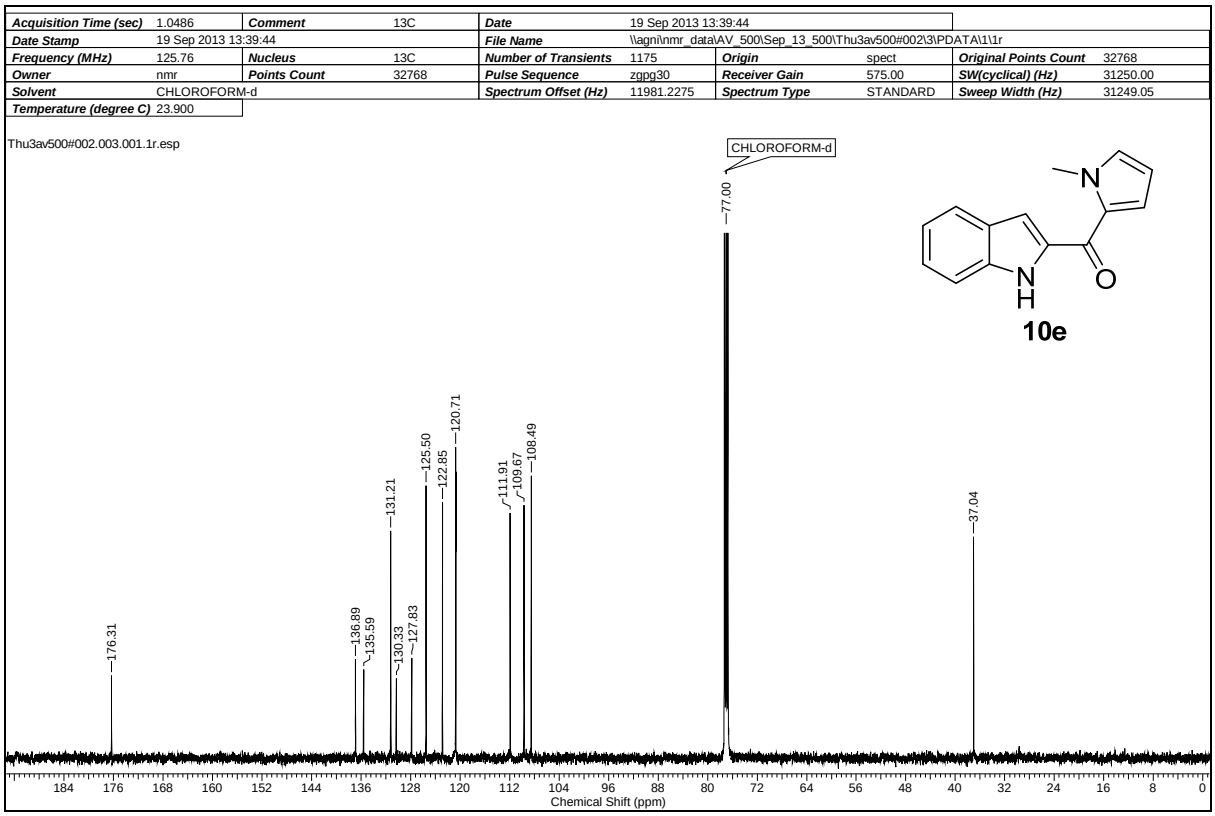


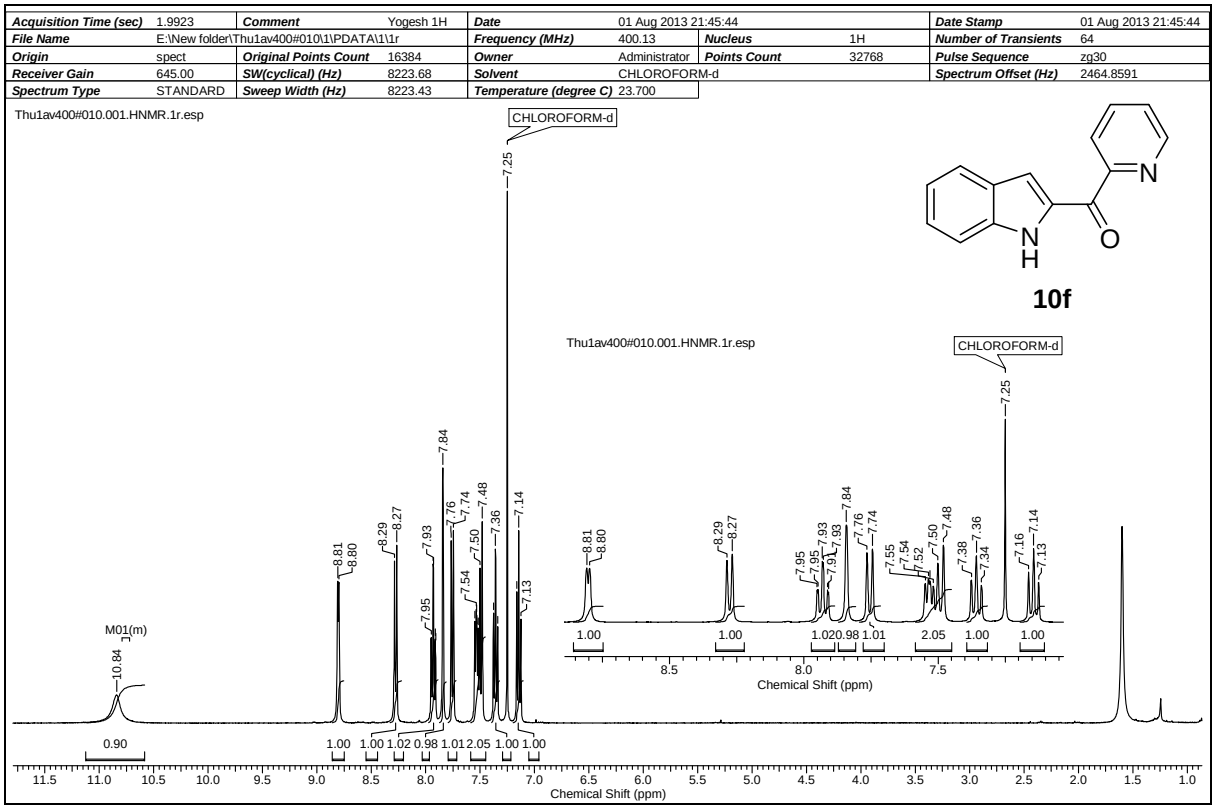
^{13}C NMR Spectrum of 10d in $CDCl_3$



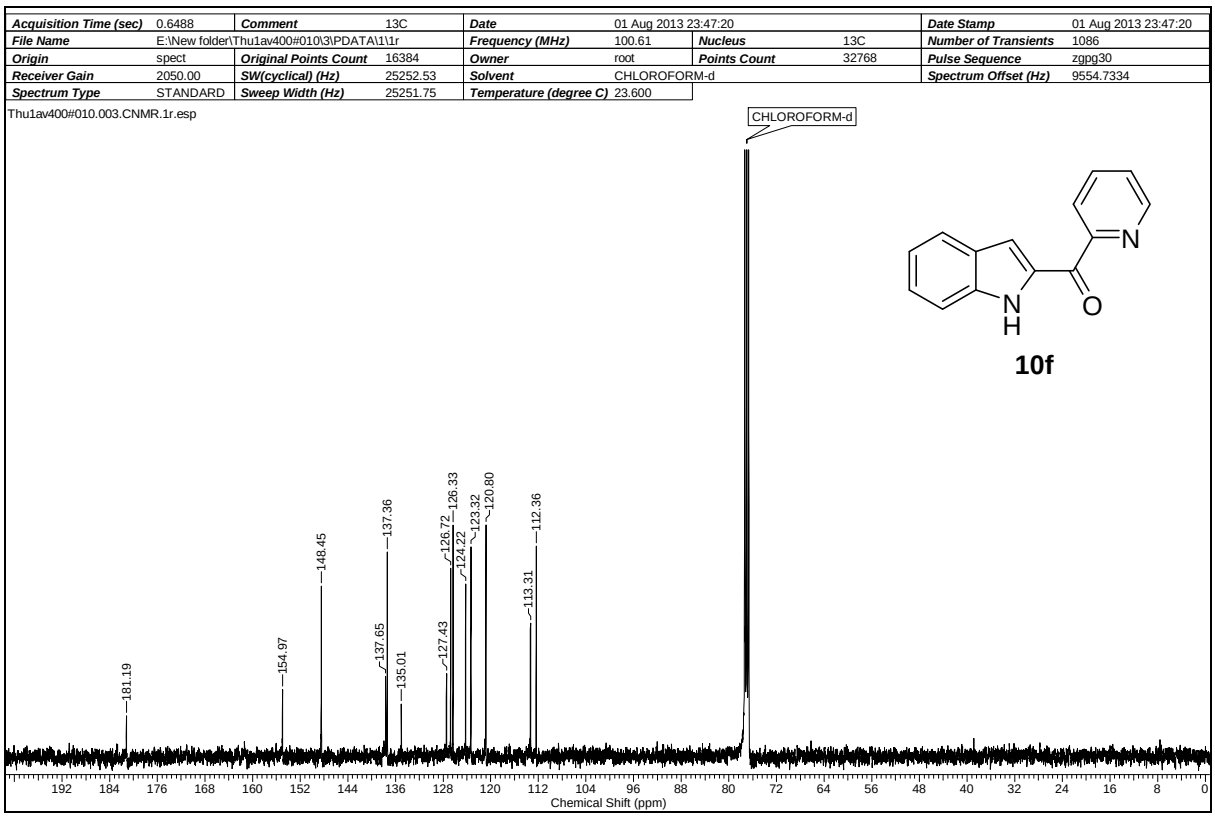
^{1}H NMR Spectrum of 10e in $CDCl_3$



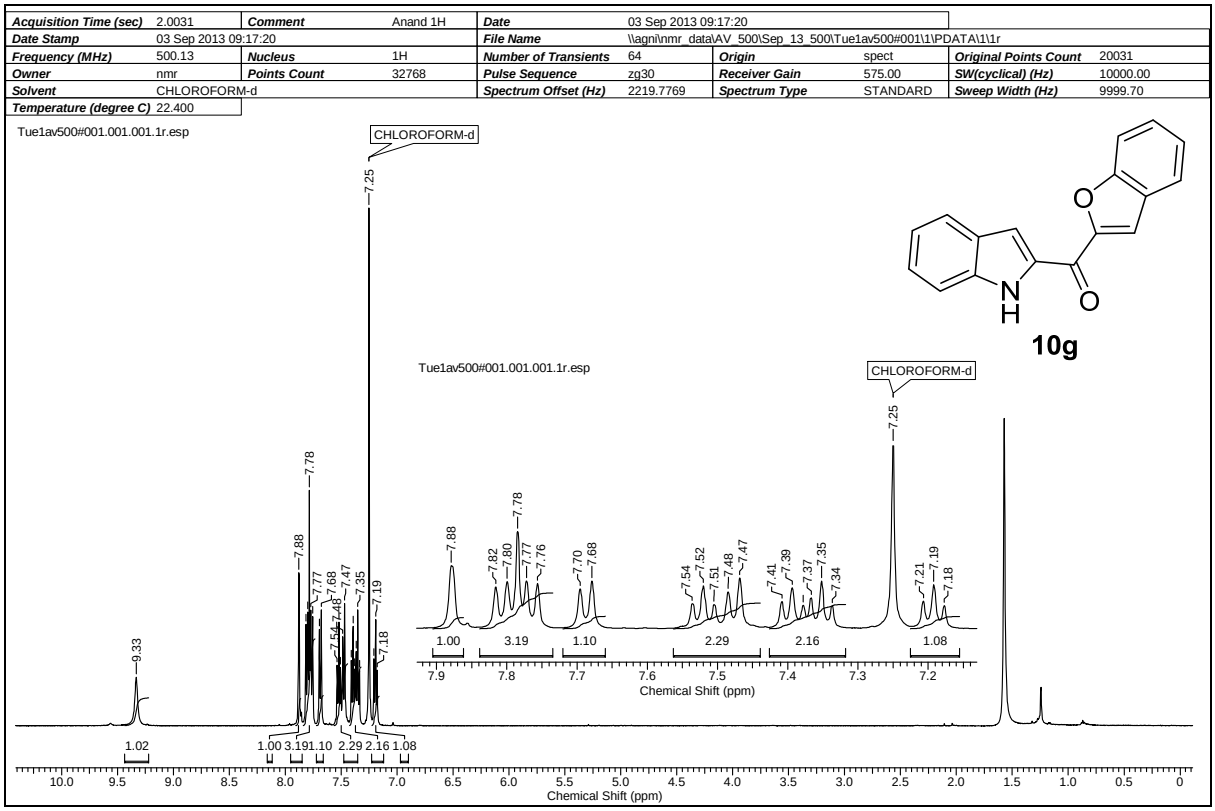
^{13}C NMR Spectrum of 10e in $CDCl_3$



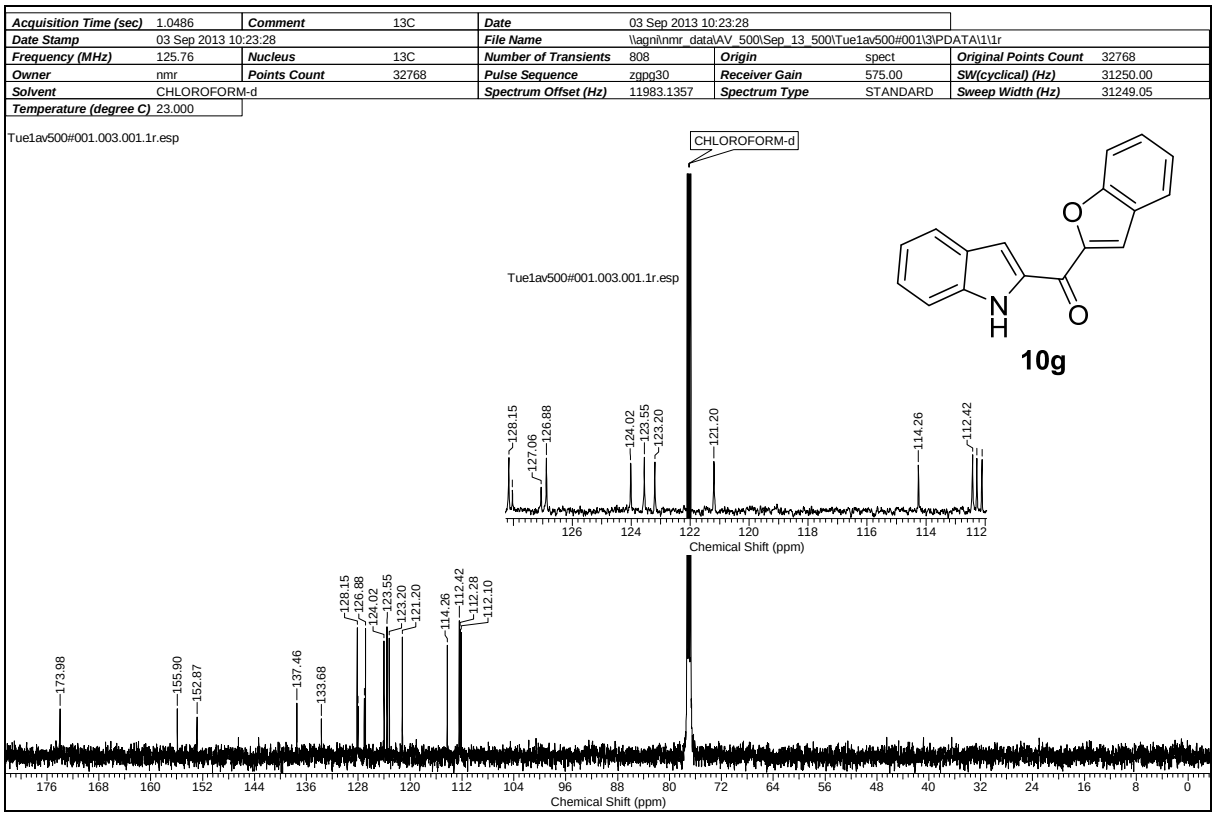
^{1}H NMR Spectrum of 10f in $CDCl_3$



^{13}C NMR Spectrum of 10f in $CDCl_3$

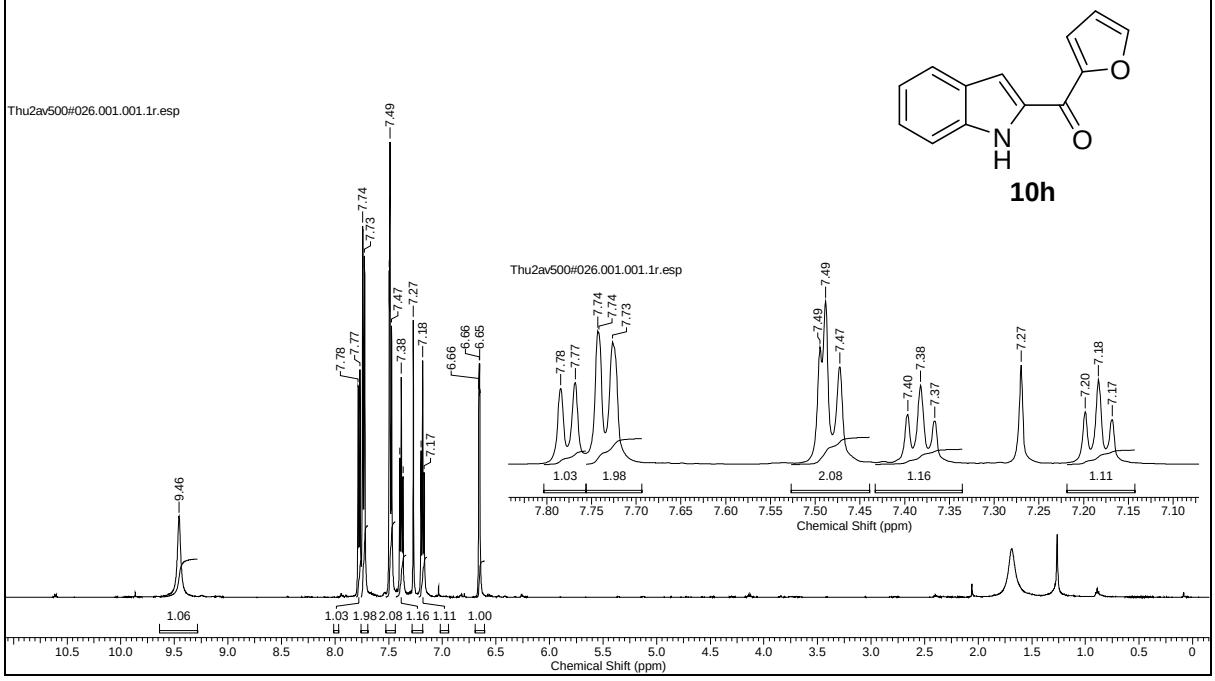


^{1}H NMR Spectrum of 10g in $CDCl_3$



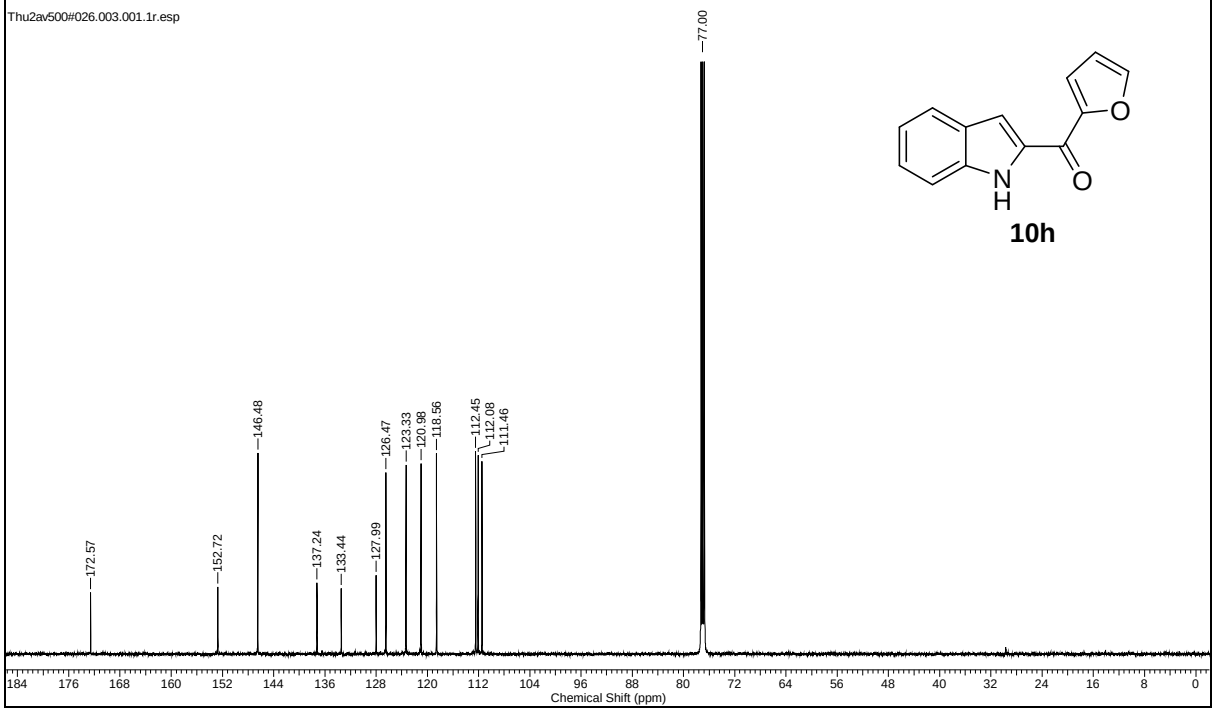
^{13}C NMR Spectrum of 10g in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	Yogesh 1H	***Date***	08 Aug 2013 23:09:20			***Date Stamp***	08 Aug 2013 23:09:20
File Name	H:\New folder\Thu2av500#026\1\PDATA\1\1r			***Frequency (MHz)***	500.13	***Nucleus***	1H	***Number of Transients***	64
Origin	spect	***Original Points Count***	20031	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	256.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2219.7769
Spectrum Type	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	21.900				

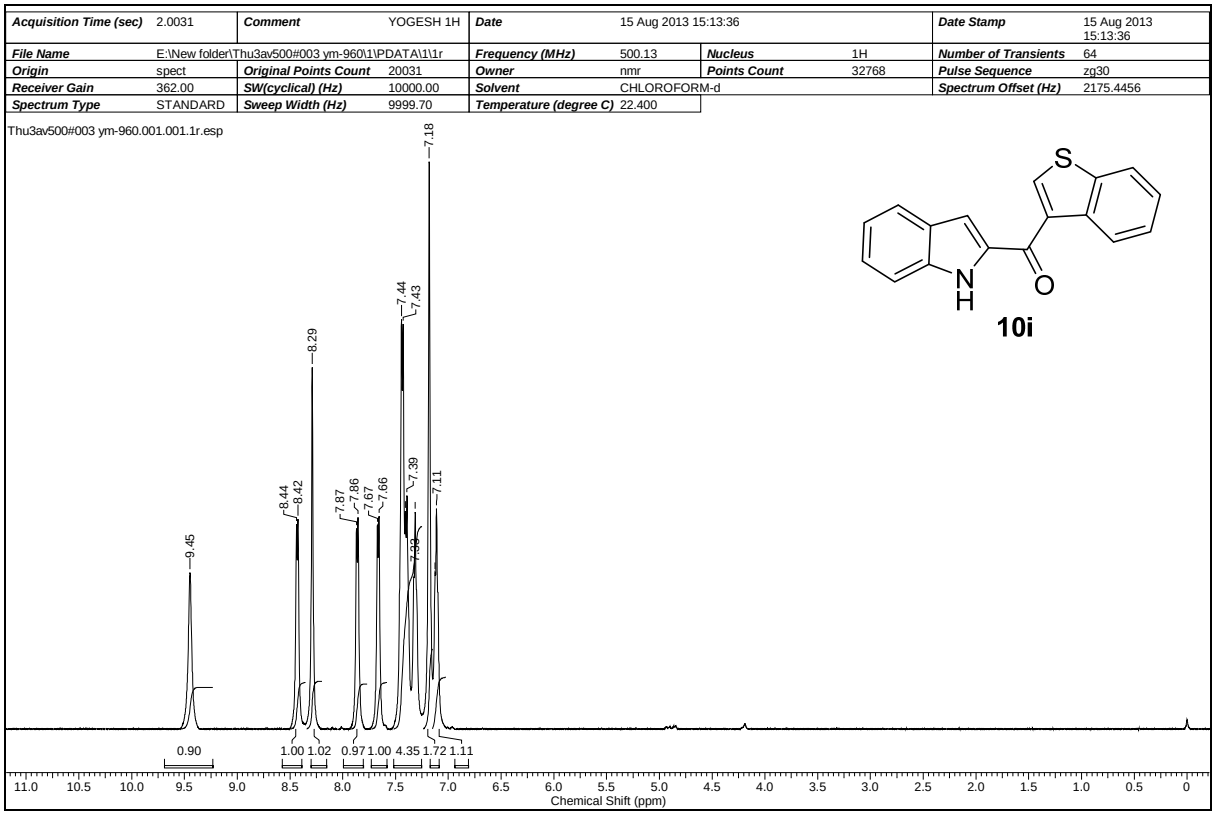


^{1}H NMR Spectrum of 10h in $CDCl_3$

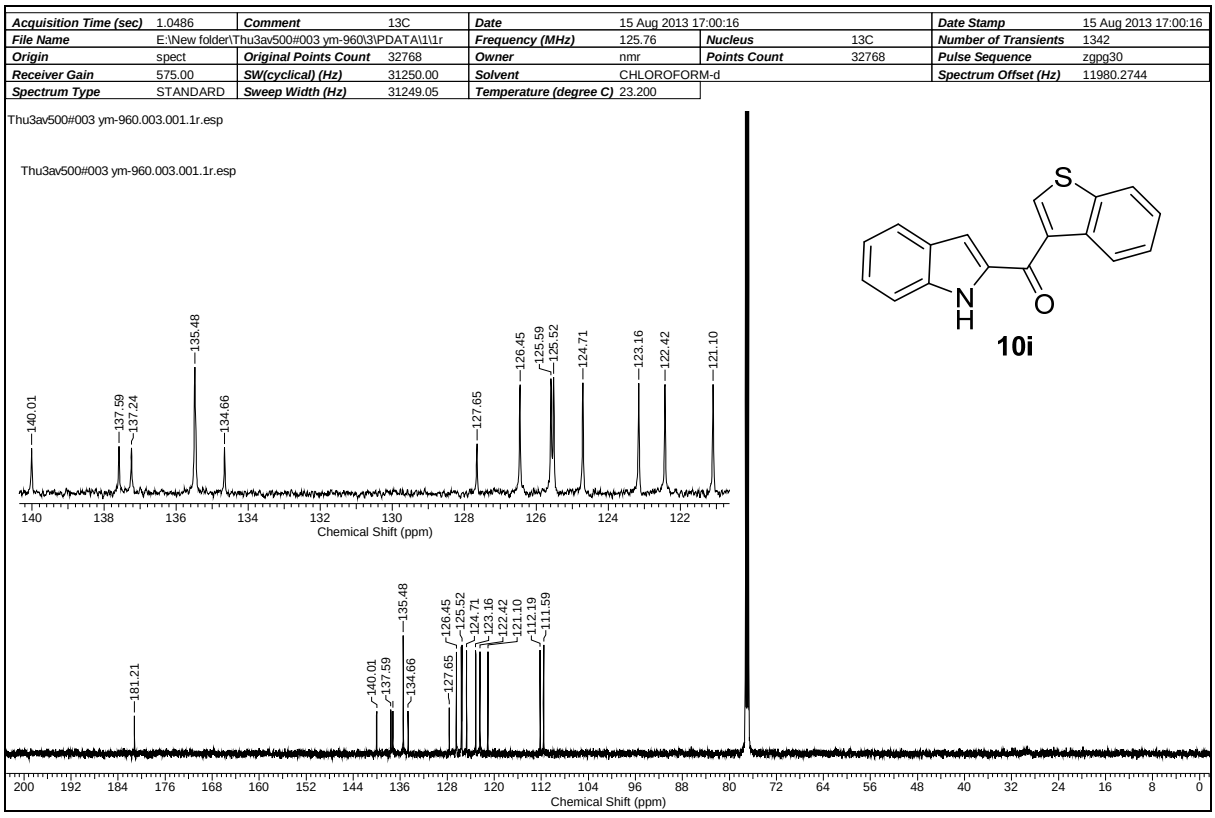
Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	09 Aug 2013 09:40:48			***Date Stamp***	09 Aug 2013 09:40:48
File Name	H:\New folder\Thu2av500#026\3\PDATA\1\1r			***Frequency (MHz)***	125.76	***Nucleus***	13C	***Number of Transients***	9471
Origin	spect	***Original Points Count***	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	575.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	11981.2275
Spectrum Type	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	22.400				



^{13}C NMR Spectrum of 10h in $CDCl_3$

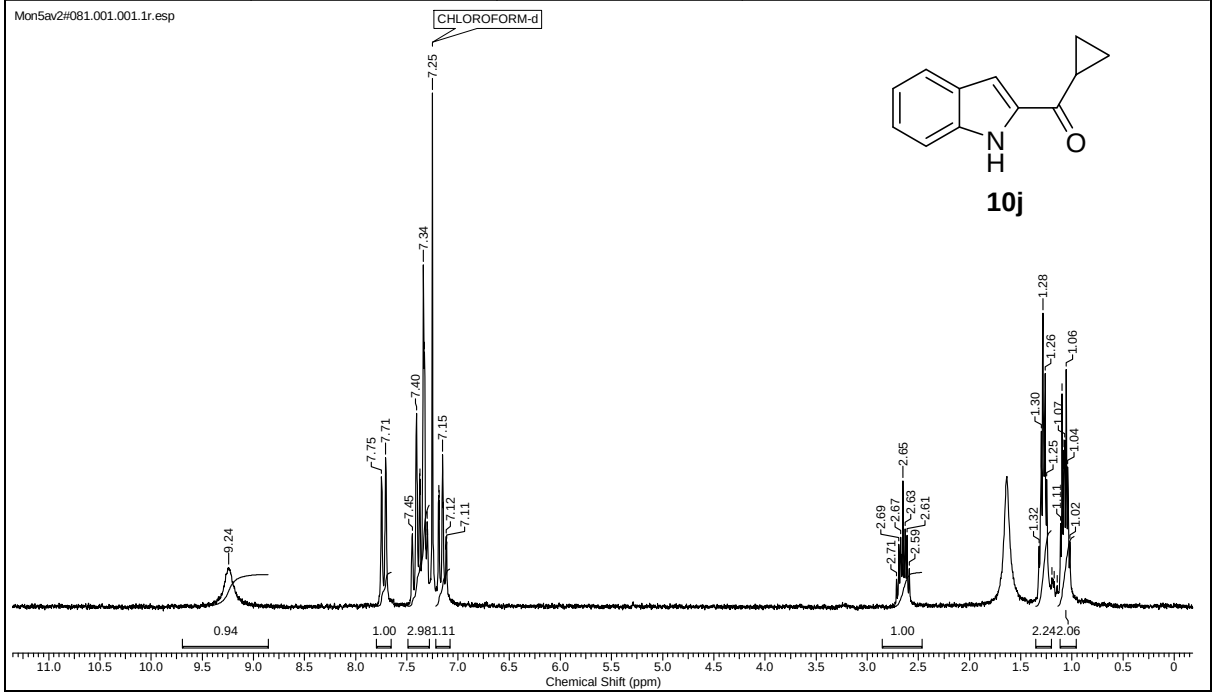


^{1}H NMR Spectrum of 10i in $CDCl_3$



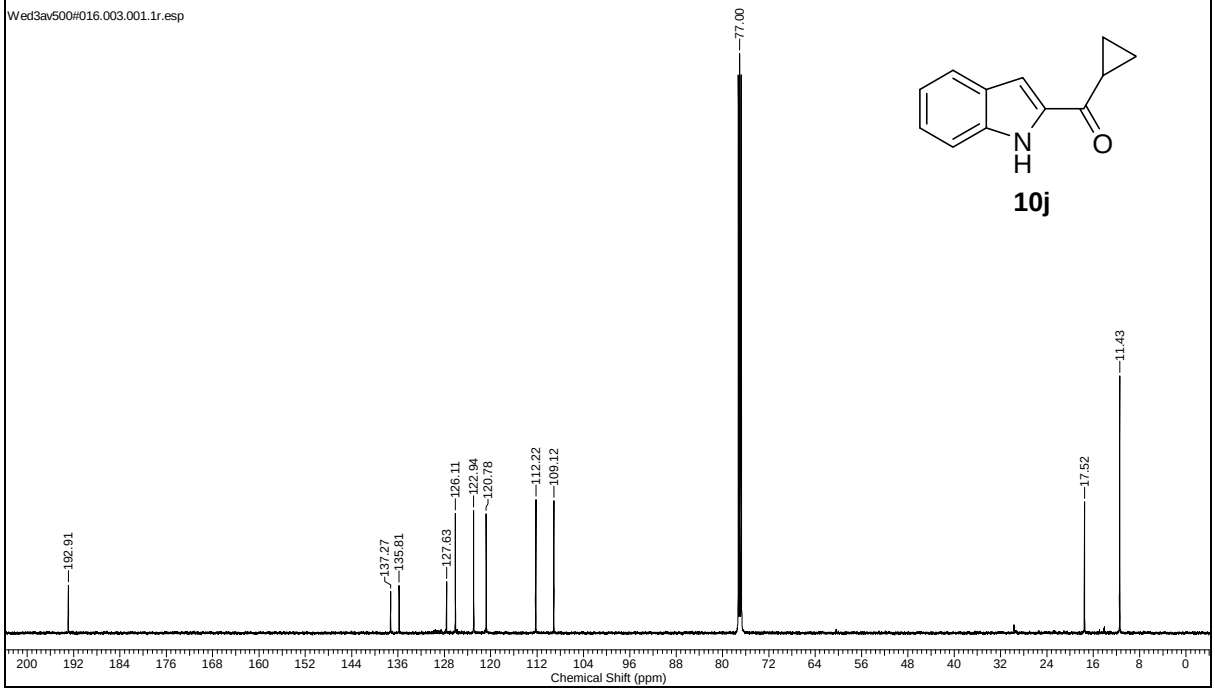
^{13}C NMR Spectrum of 10i in $CDCl_3$

Acquisition Time (sec)	3.9584	***Comment***	Yogesh	***Date***	26 Aug 2013 23:17:28		
Date Stamp	26 Aug 2013 23:17:28			***File Name***	\\agni\nmr_data\AV200\AUG_13#AV200\data\Administrator\nmr\Mon5av2#081\1\PDATA\1\1r		
Frequency (MHz)	200.13	***Nucleus***	1H	***Number of Transients***	8	***Origin***	av200
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	1149.40	***SW(cyclical) (Hz)***	4139.07	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	1229.5370	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4138.95	***Temperature (degree C)***	27.000



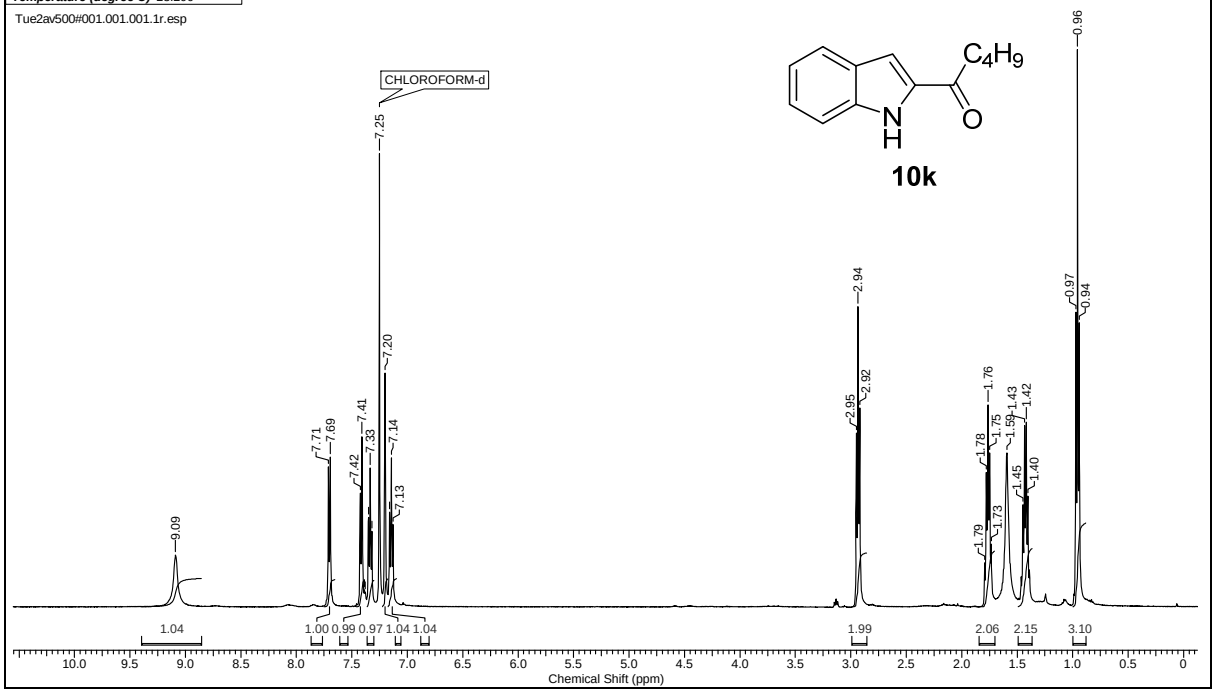
^{1}H NMR Spectrum of 10j in $CDCl_3$

Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	14 Aug 2013 20:46:24			***Date Stamp***	14 Aug 2013 20:46:24
File Name	H:\New folder\Wed3av500#016 ym-962\3\PDATA\1\1r			***Frequency (MHz)***	125.76	***Nucleus***	13C	***Number of Transients***	2043
Origin	spect	***Original Points Count***	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	575.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	11980.2744
Spectrum Type	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	22.800				



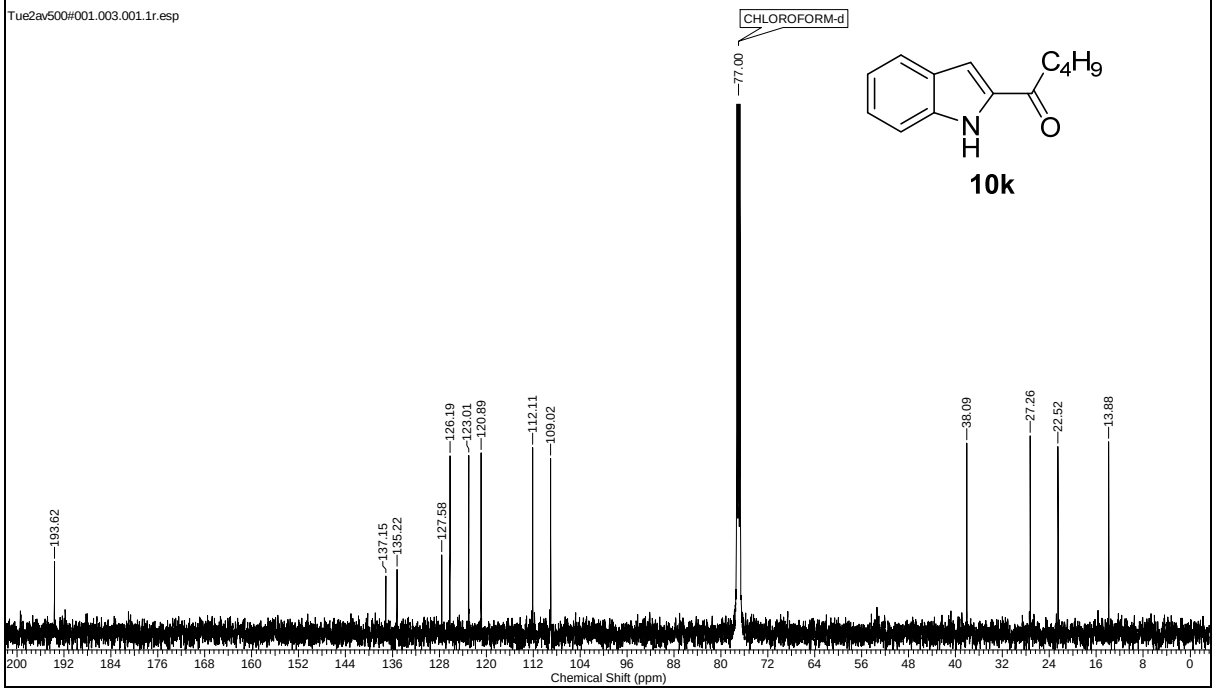
^{13}C NMR Spectrum of 10j in $CDCl_3$

Acquisition Time (sec)	2.0031	**Comment**	Yogesh 1H	**Date**	10 Sep 2013 09:57:52				
Date Stamp	10 Sep 2013 09:57:52			**File Name**	\\agni\nmr_data\AV_500\Sep_13_500\Tue2av500#001\1\PDATA\1\1r				
Frequency (MHz)	500.13	**Nucleus**	1H	**Number of Transients**	64	**Origin**	spect	**Original Points Count**	20031
Owner	nmr	**Points Count**	32768	**Pulse Sequence**	zg30	**Receiver Gain**	575.00	**SW(cyclical) (Hz)**	10000.00
Solvent	CHLOROFORM-d			**Spectrum Offset (Hz)**	2219.7769	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	9999.70
Temperature (degree C)	23.200								

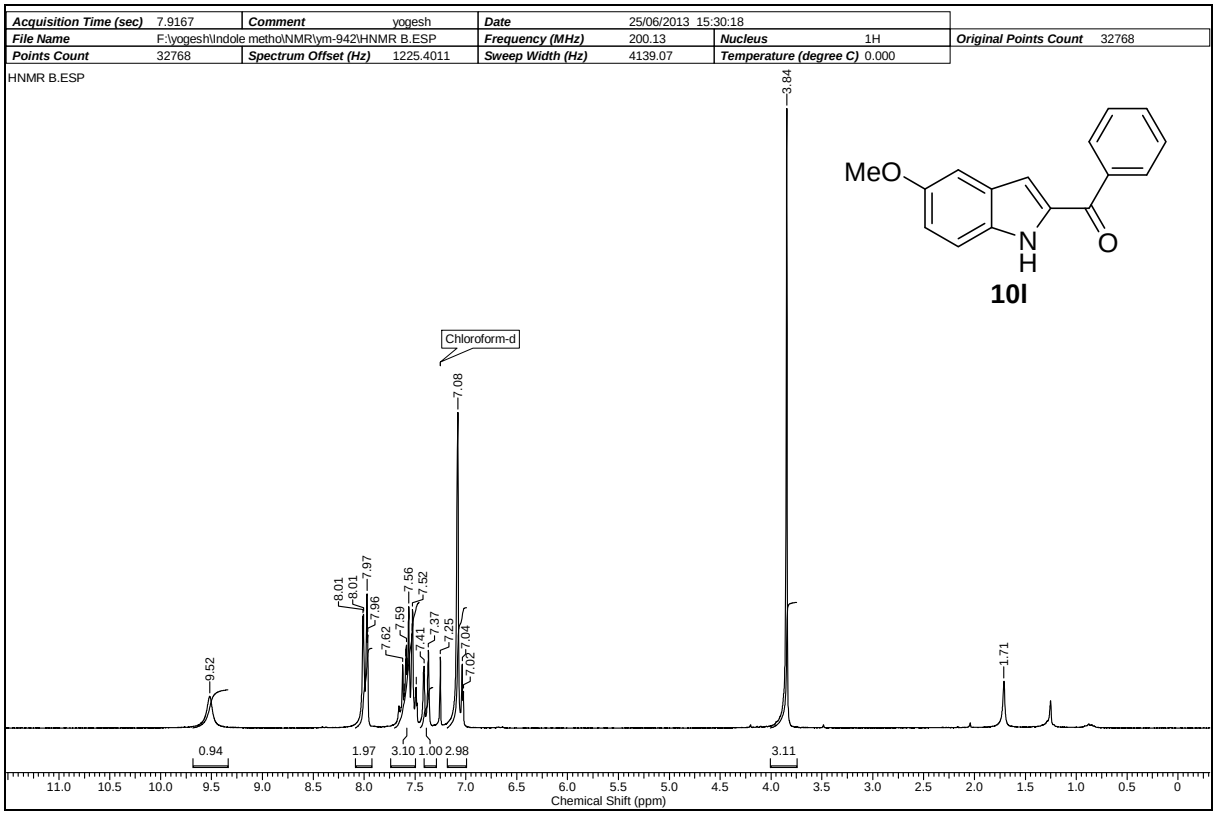


^{1}H NMR Spectrum of 10k in $CDCl_3$

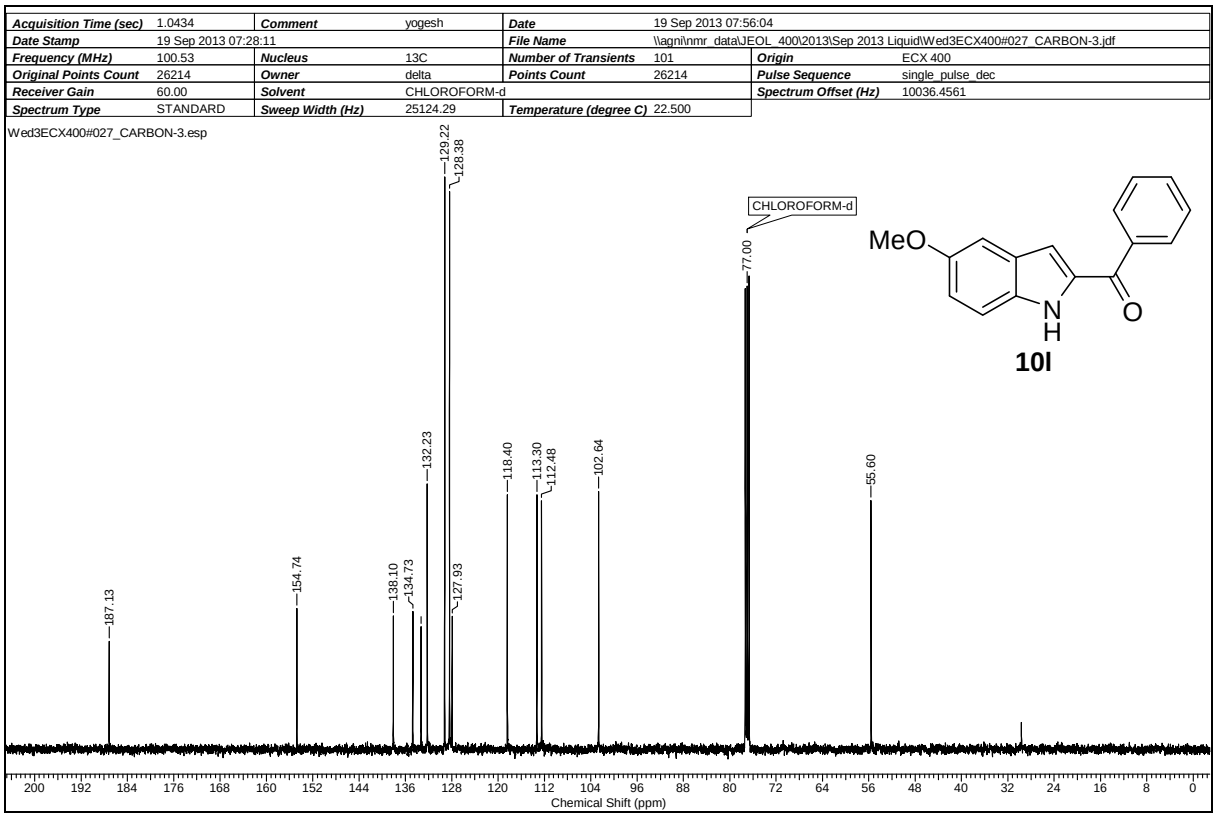
Acquisition Time (sec)	1.0486	**Comment**	13C	**Date**	10 Sep 2013 10:46:56				
Date Stamp	10 Sep 2013 10:46:56			**File Name**	\\agni\nmr_data\AV_500\Sep_13_500\Tue2av500#001\3\PDATA\1\1r				
Frequency (MHz)	125.76	**Nucleus**	13C	**Number of Transients**	522	**Origin**	spect	**Original Points Count**	32768
Owner	nmr	**Points Count**	32768	**Pulse Sequence**	zgpg30	**Receiver Gain**	575.00	**SW(cyclical) (Hz)**	31250.00
Solvent	CHLOROFORM-d			**Spectrum Offset (Hz)**	11982.1826	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	31249.05
Temperature (degree C)	24.100								



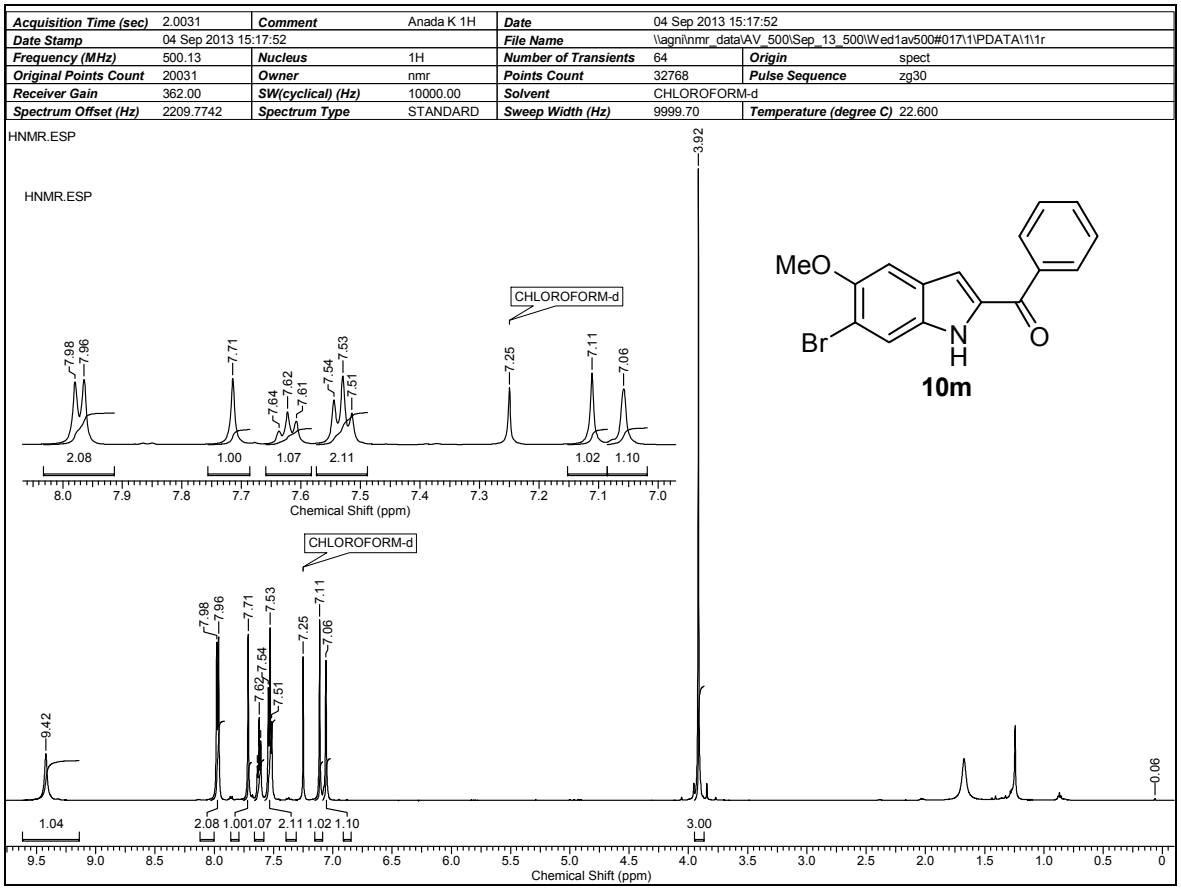
^{13}C NMR Spectrum of 10k in $CDCl_3$



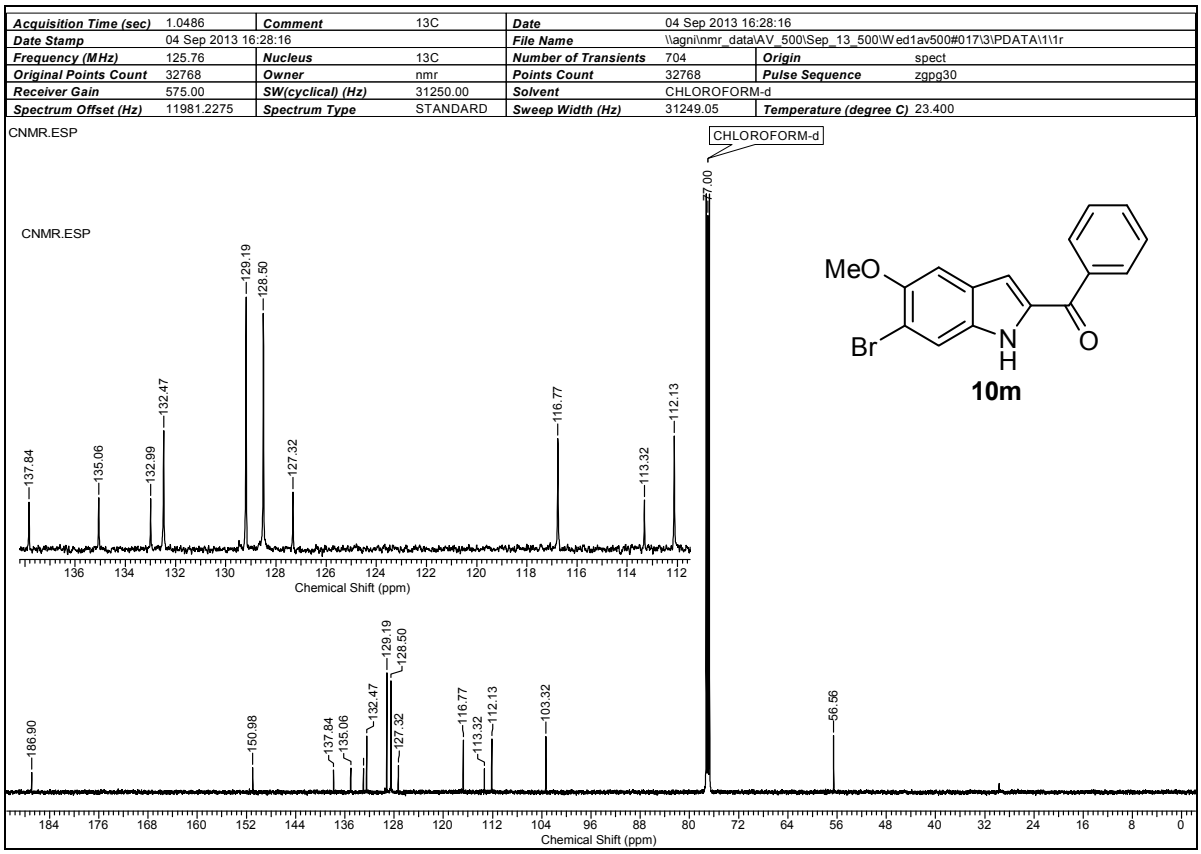
^{1}H NMR Spectrum of 10l in $CDCl_3$



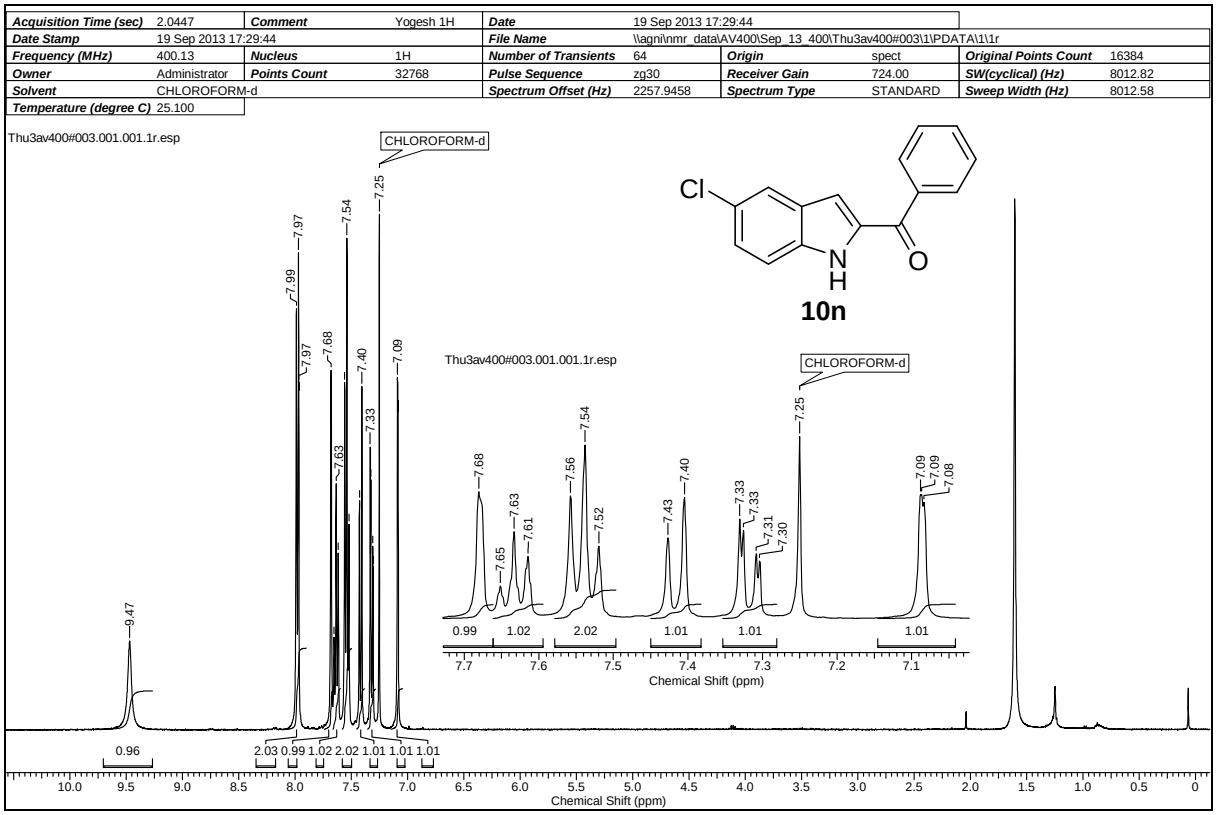
^{13}C NMR Spectrum of 10l in $CDCl_3$



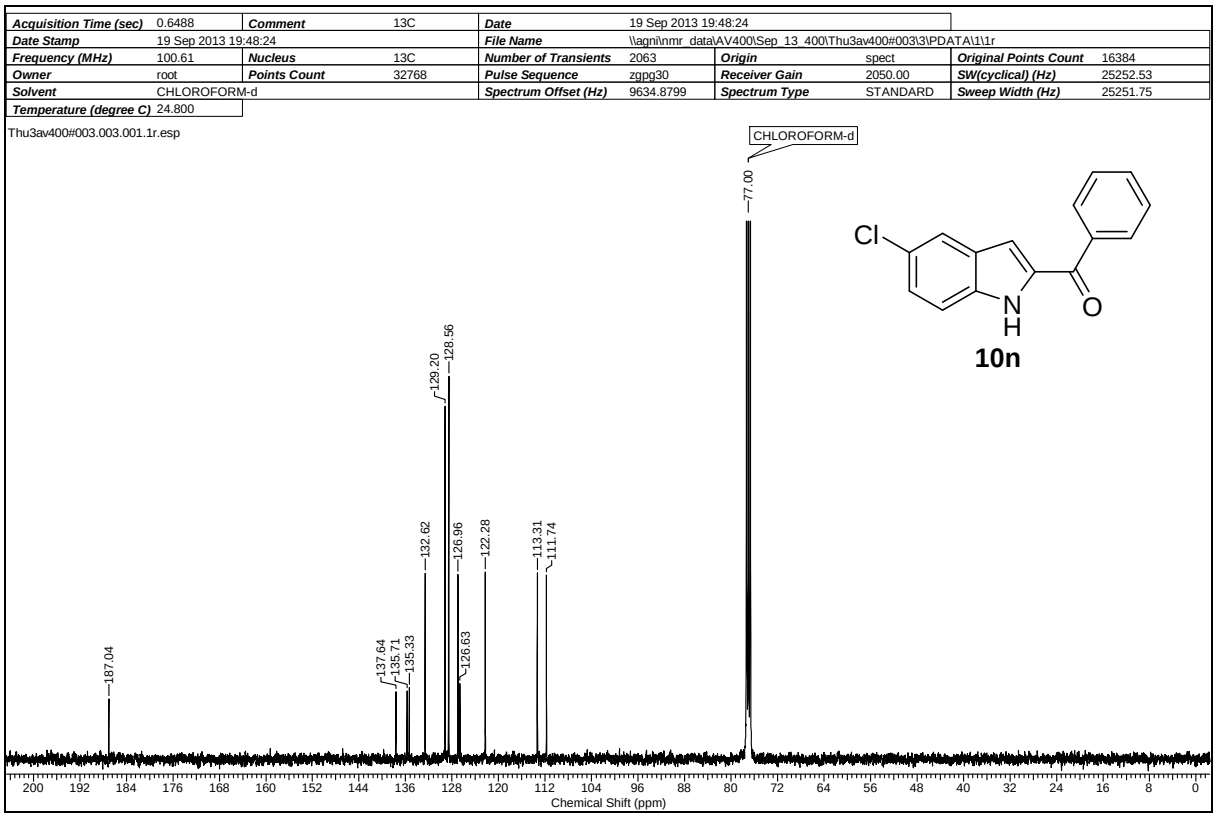
^{1}H NMR Spectrum of 10m in $CDCl_3$



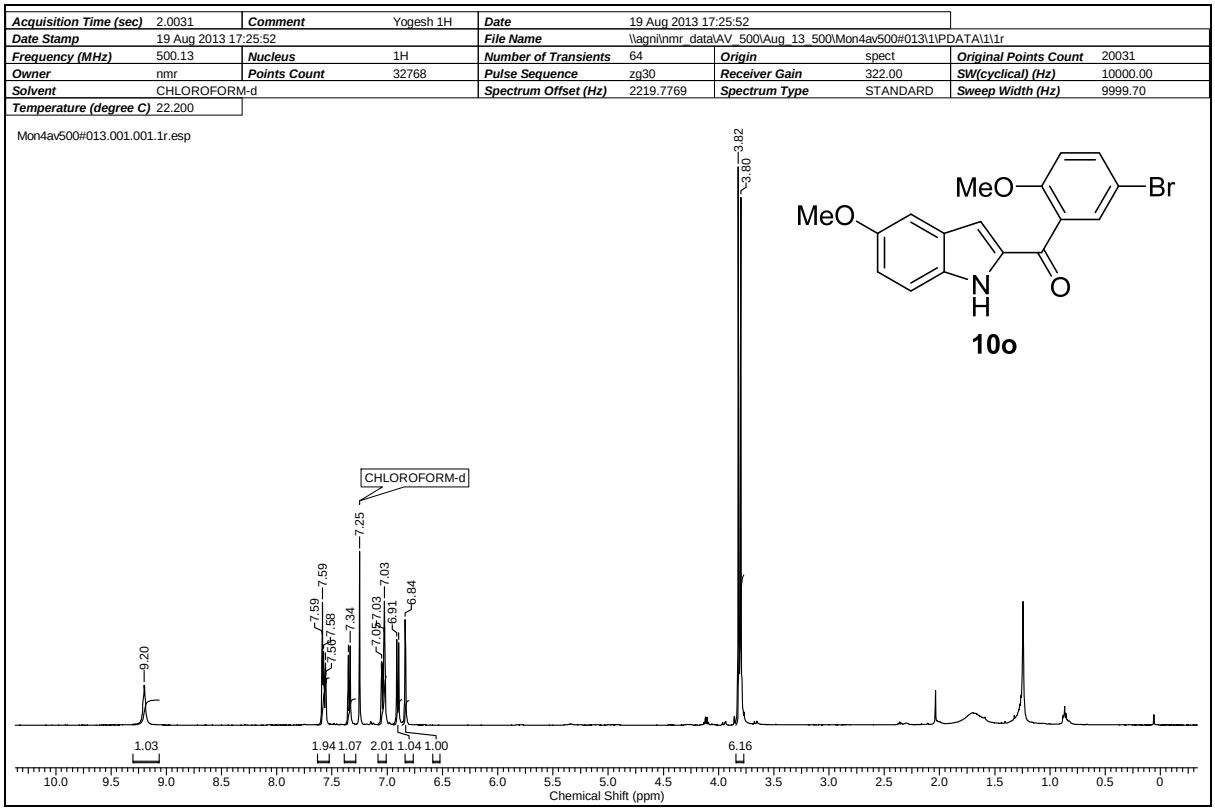
^{13}C NMR Spectrum of 10m in $CDCl_3$



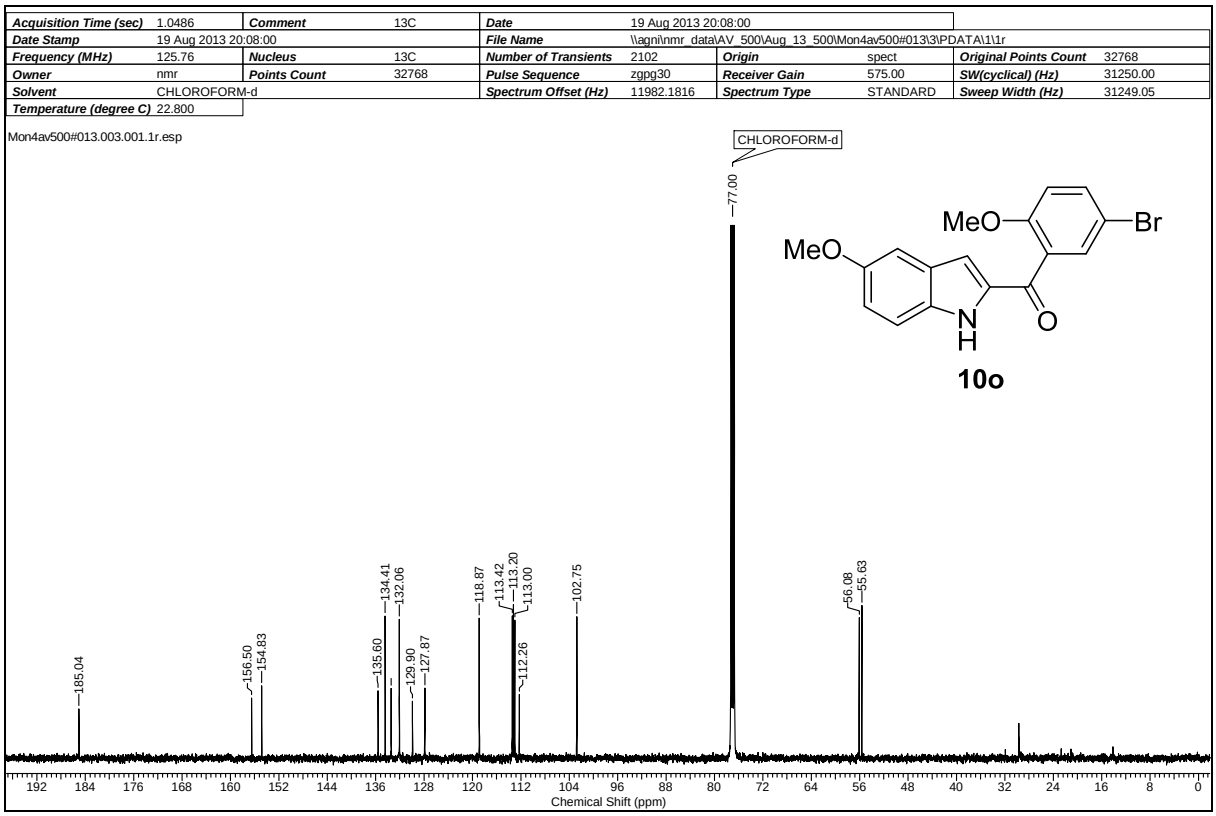
^{1}H NMR Spectrum of 10n in $CDCl_3$



^{13}C NMR Spectrum of 10n in $CDCl_3$

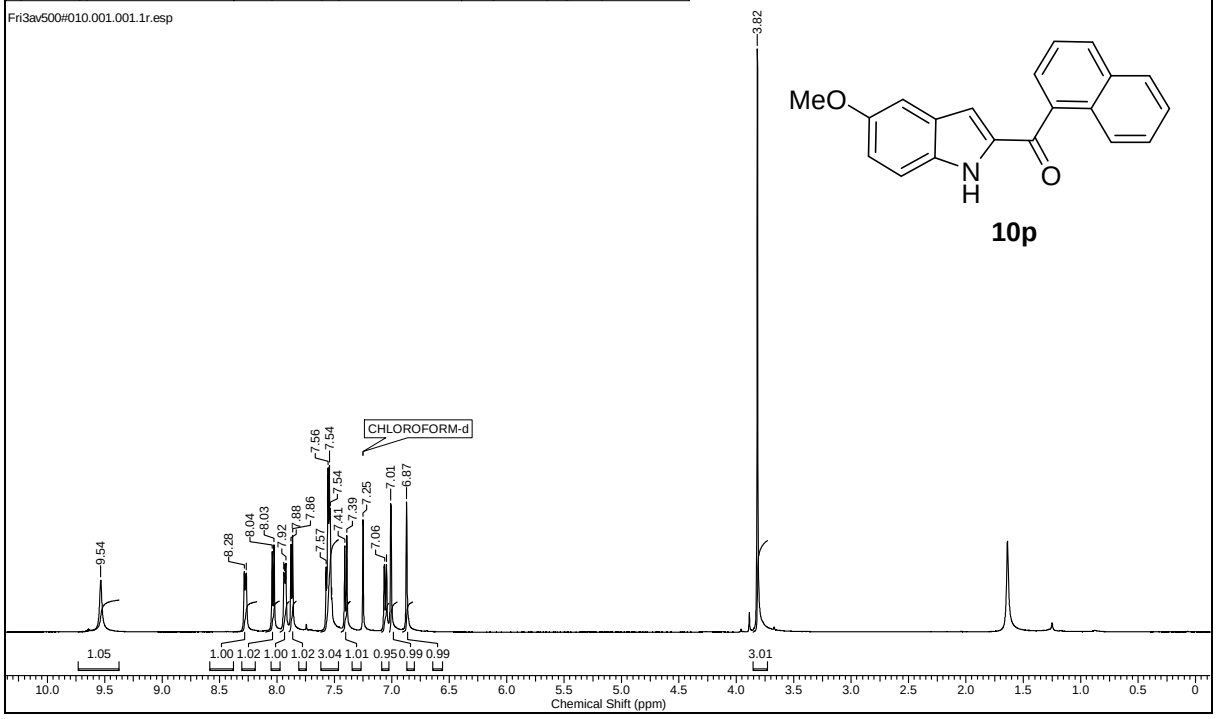


^{1}H NMR Spectrum of 10o in $CDCl_3$



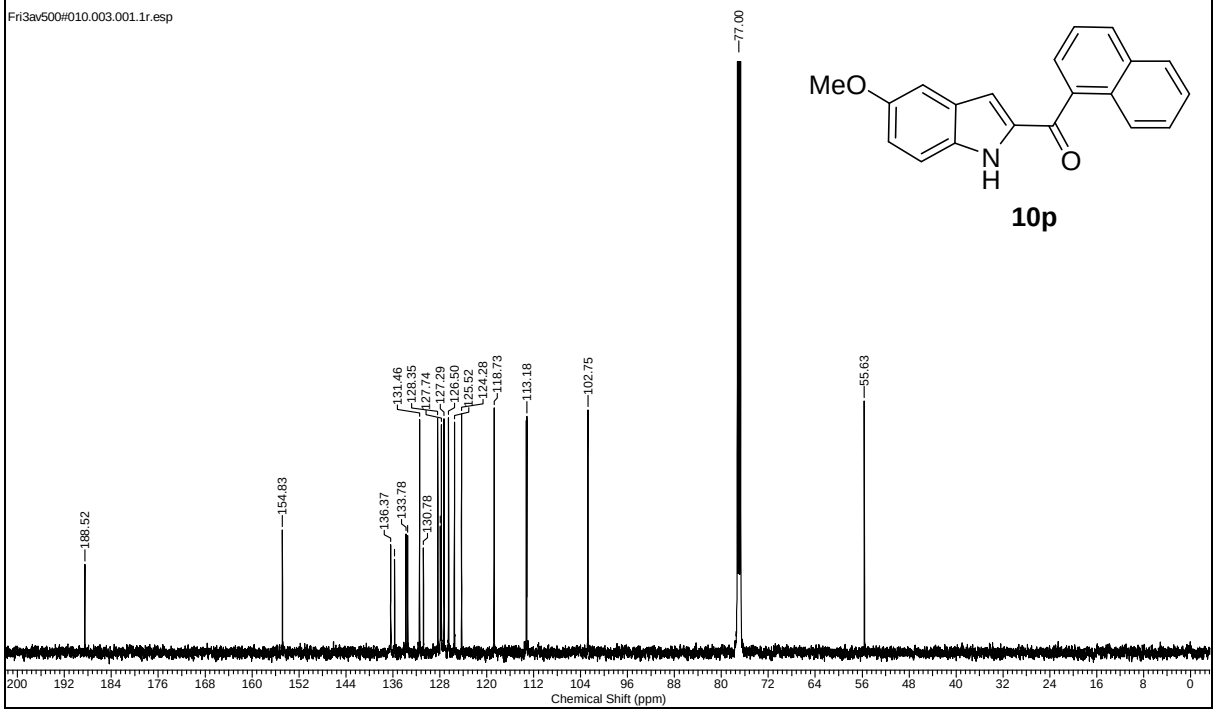
^{13}C NMR Spectrum of 10o in $CDCl_3$

Acquisition Time (sec)	2.0031	***Comment***	yogesh 1H	***Date***	16 Aug 2013 13:29:04			***Date Stamp***	16 Aug 2013 13:29:04
File Name	H:\New folder\Fri3av500#010\1\PDATA\1\1r			***Frequency (MHz)***	500.13	***Nucleus***	1H	***Number of Transients***	64
Origin	spect	***Original Points Count***	20031	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	322.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2209.7742
Spectrum Type	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	22.400				

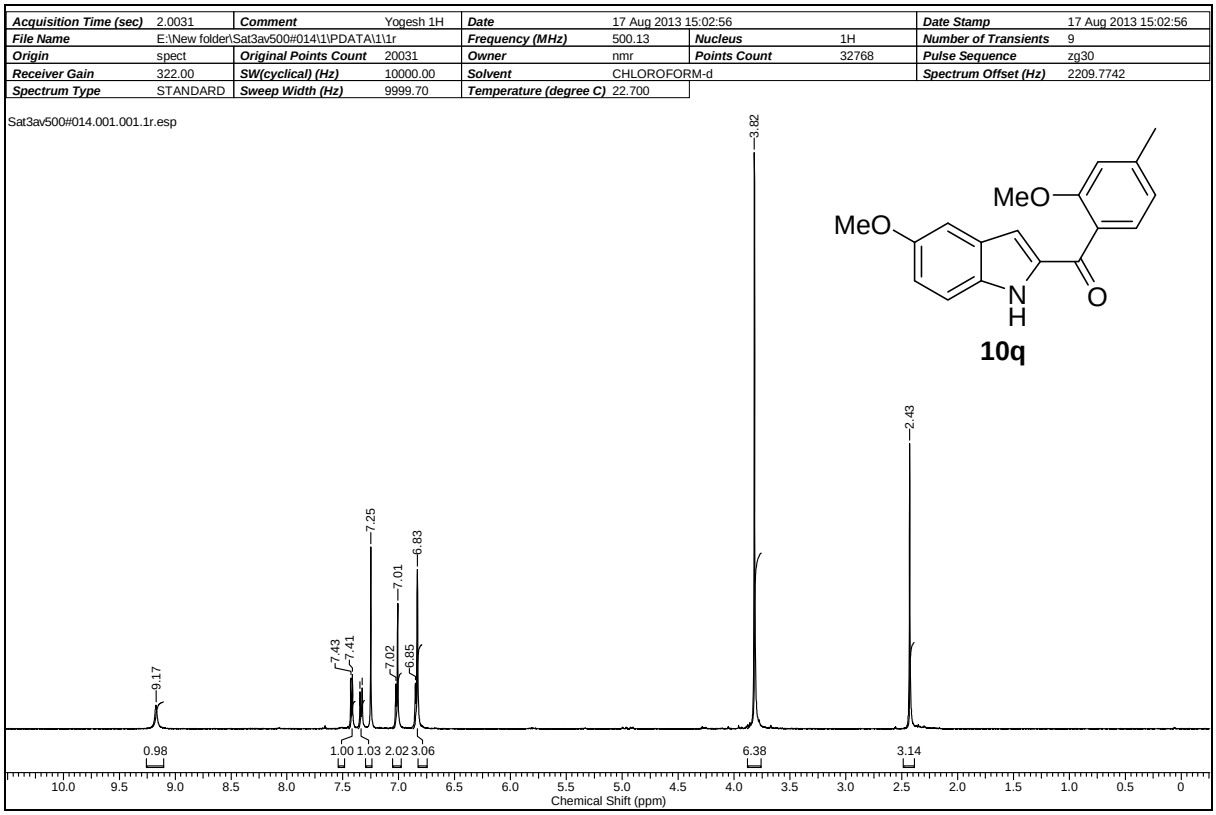


^{1}H NMR Spectrum of 10p in $CDCl_3$

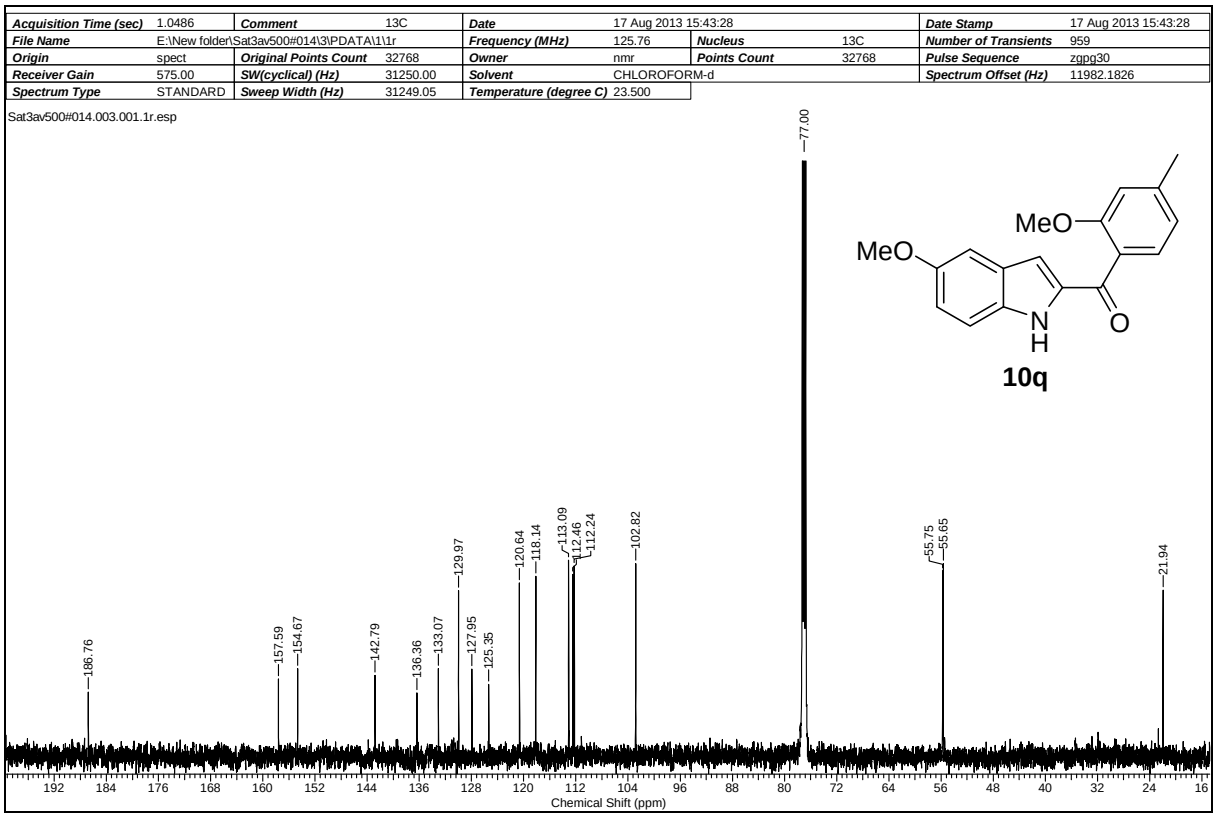
Acquisition Time (sec)	1.0486	***Comment***	13C	***Date***	16 Aug 2013 15:00:48			***Date Stamp***	16 Aug 2013 15:00:48
File Name	H:\New folder\Fri3av500#010\3\PDATA\1\1r			***Frequency (MHz)***	125.76	***Nucleus***	13C	***Number of Transients***	1172
Origin	spect	***Original Points Count***	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	575.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	11981.2275
Spectrum Type	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	23.400				



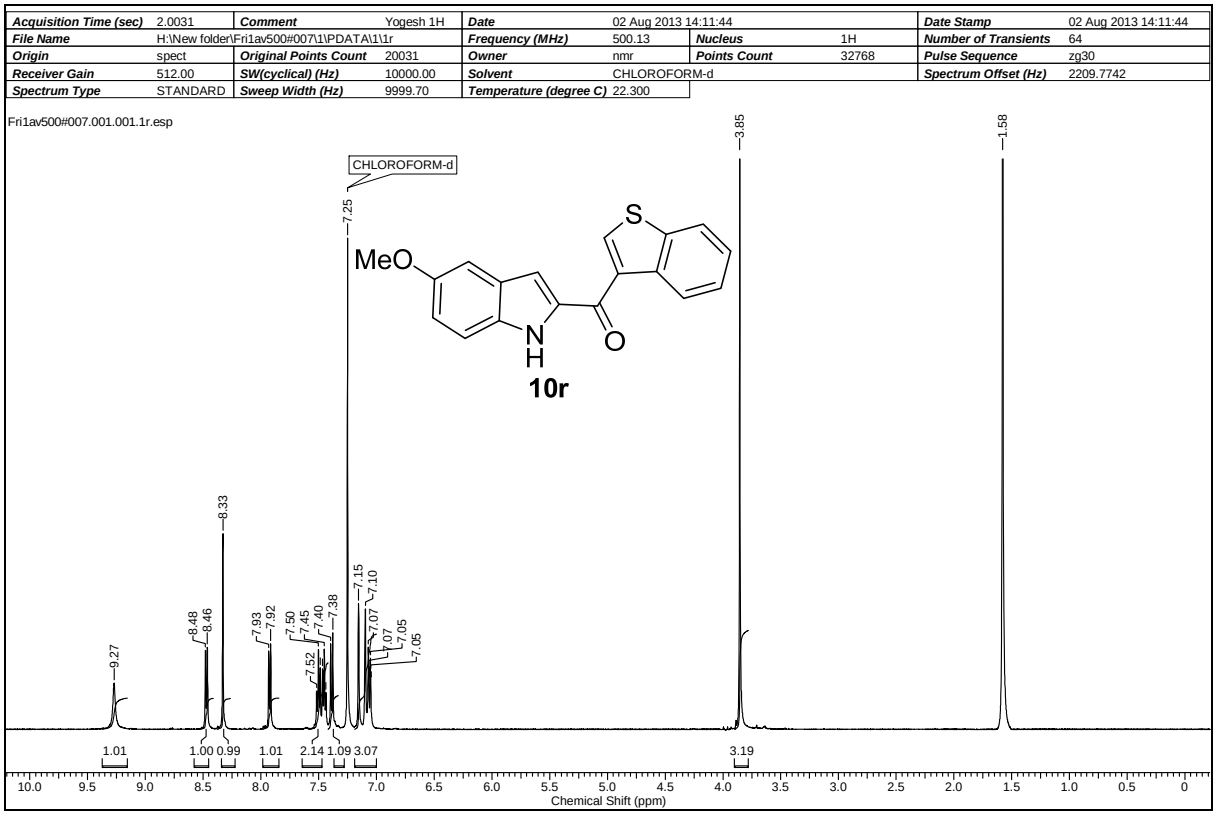
^{13}C NMR Spectrum of 10p in $CDCl_3$



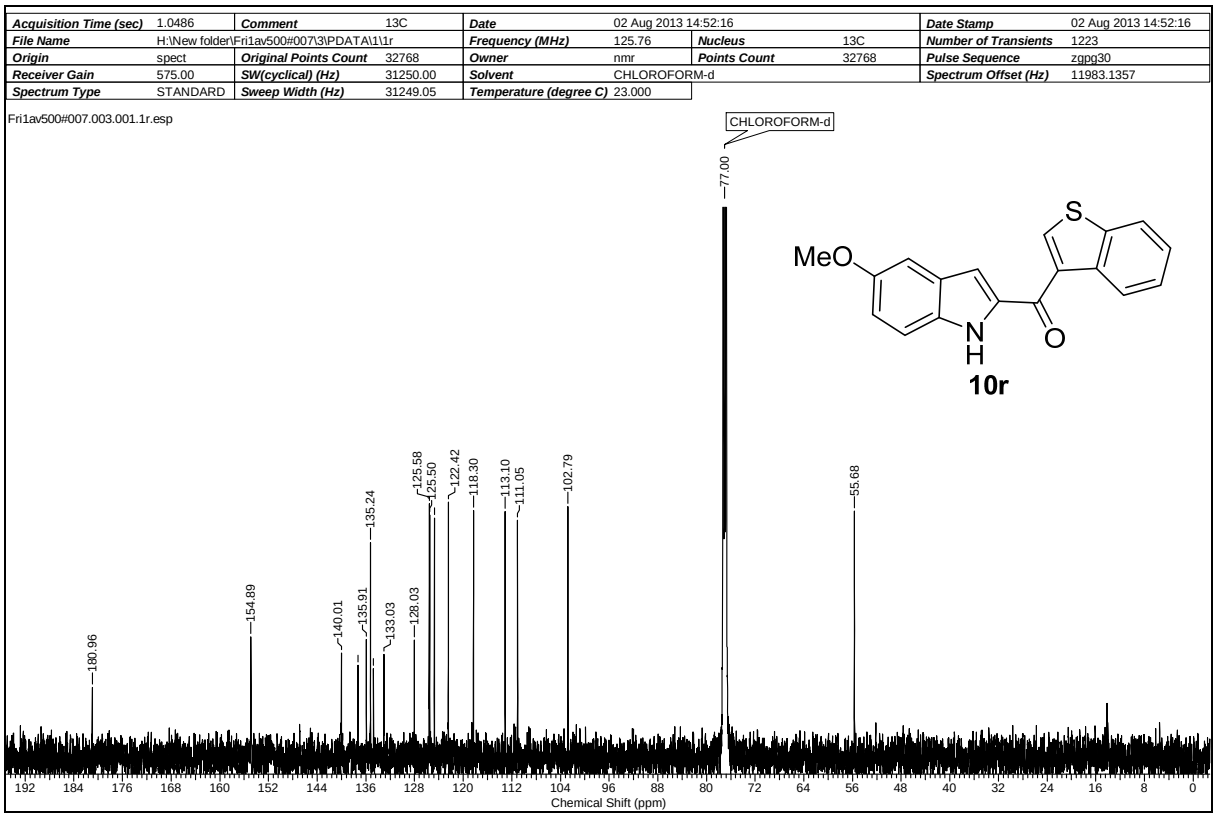
^{1}H NMR Spectrum of 10q in $CDCl_3$



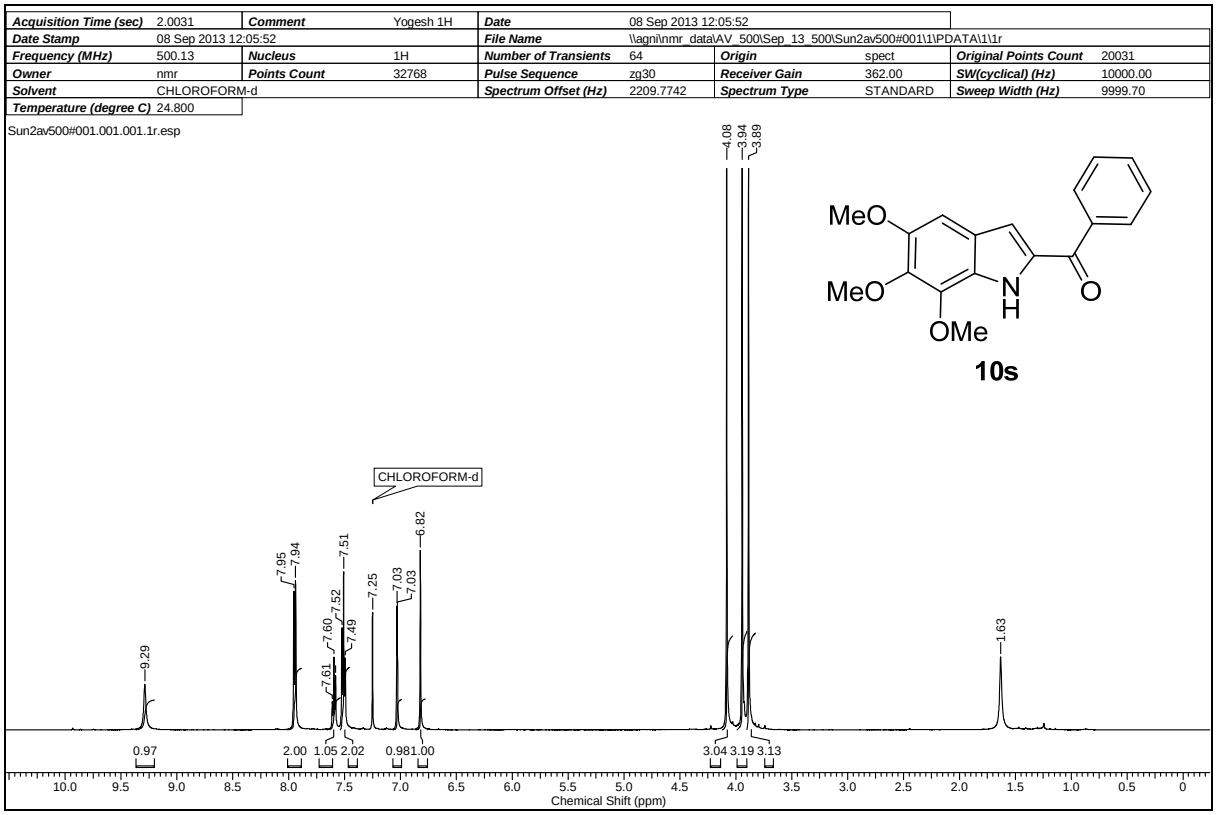
^{13}C NMR Spectrum of 10q in $CDCl_3$



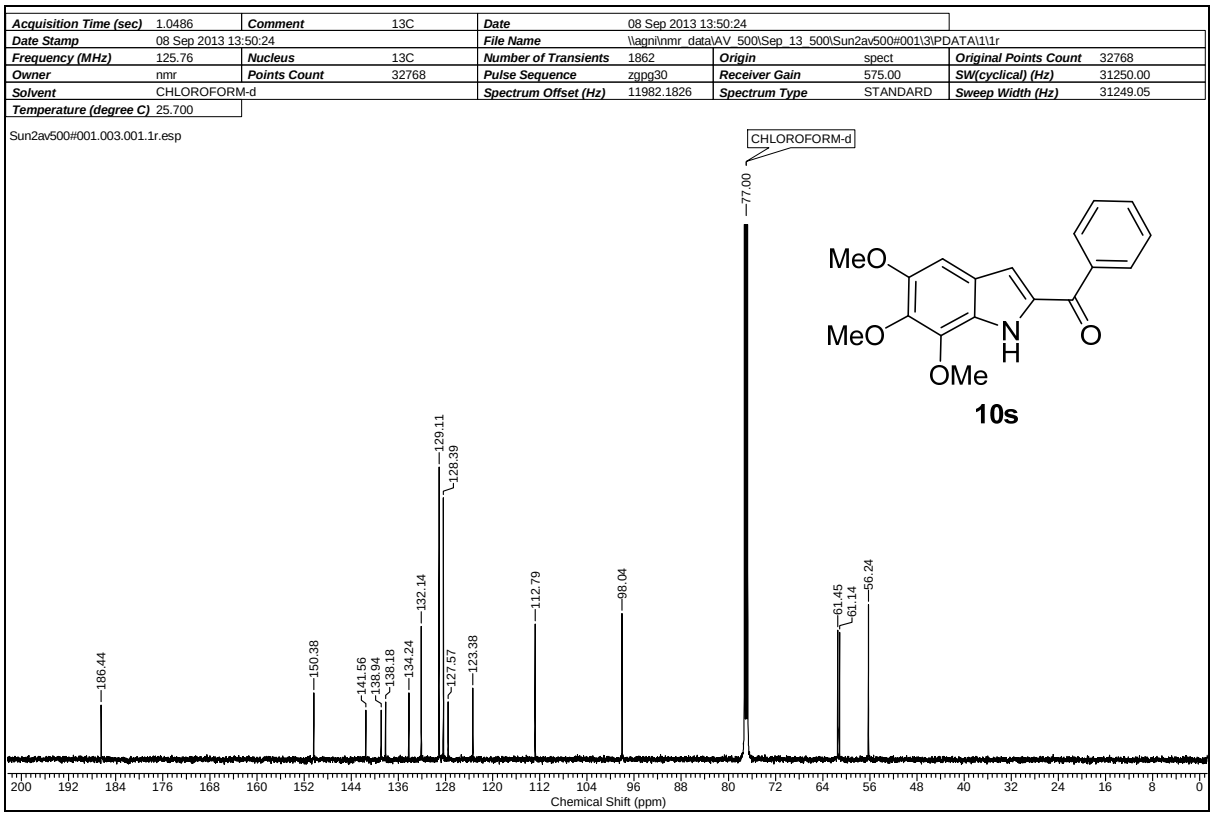
^{1}H NMR Spectrum of 10r in $CDCl_3$



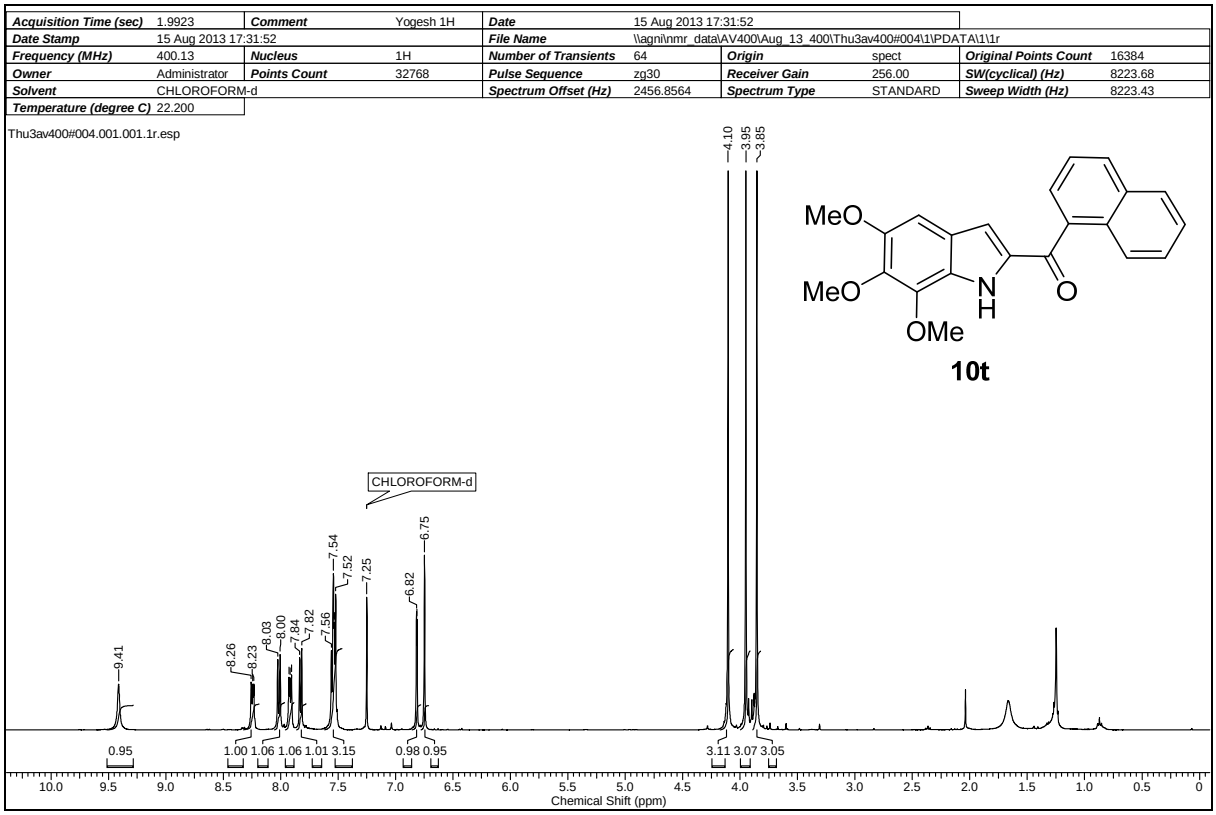
^{13}C NMR Spectrum of 10r in $CDCl_3$



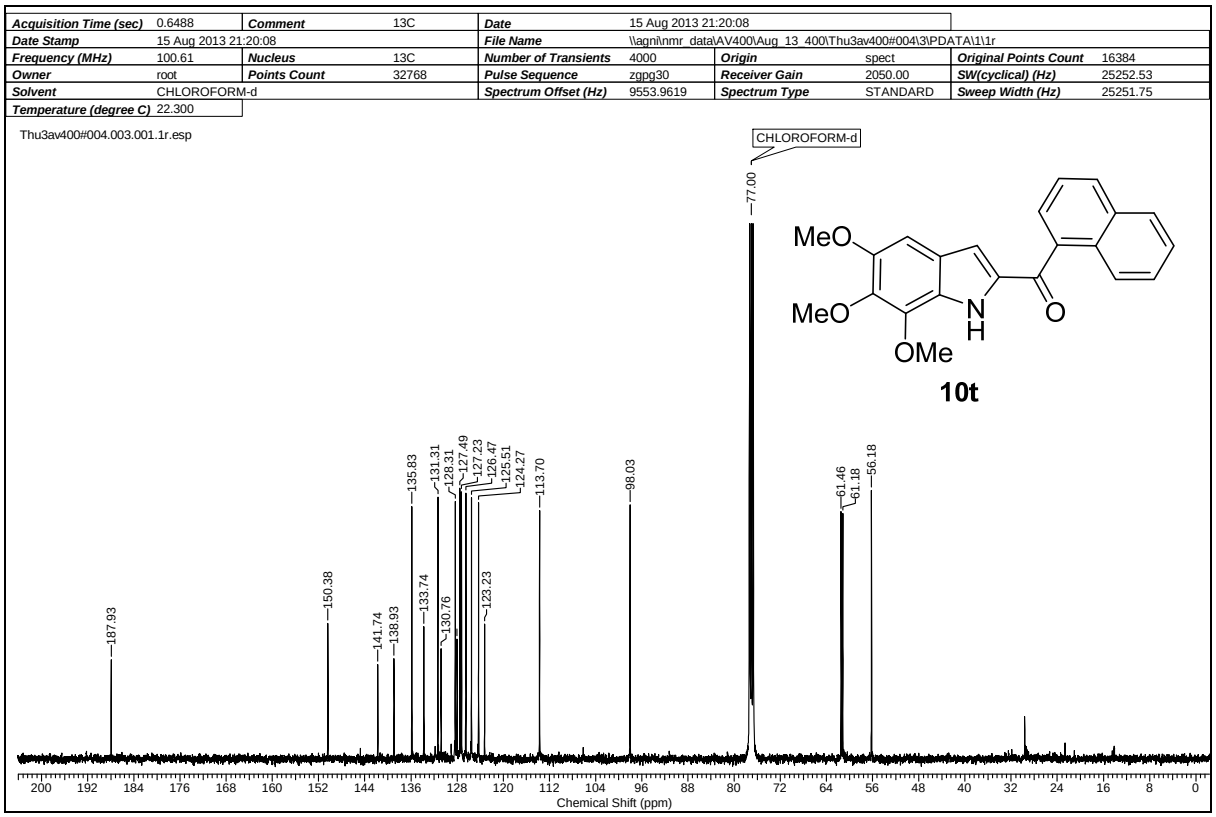
^{1}H NMR Spectrum of 10s in $CDCl_3$



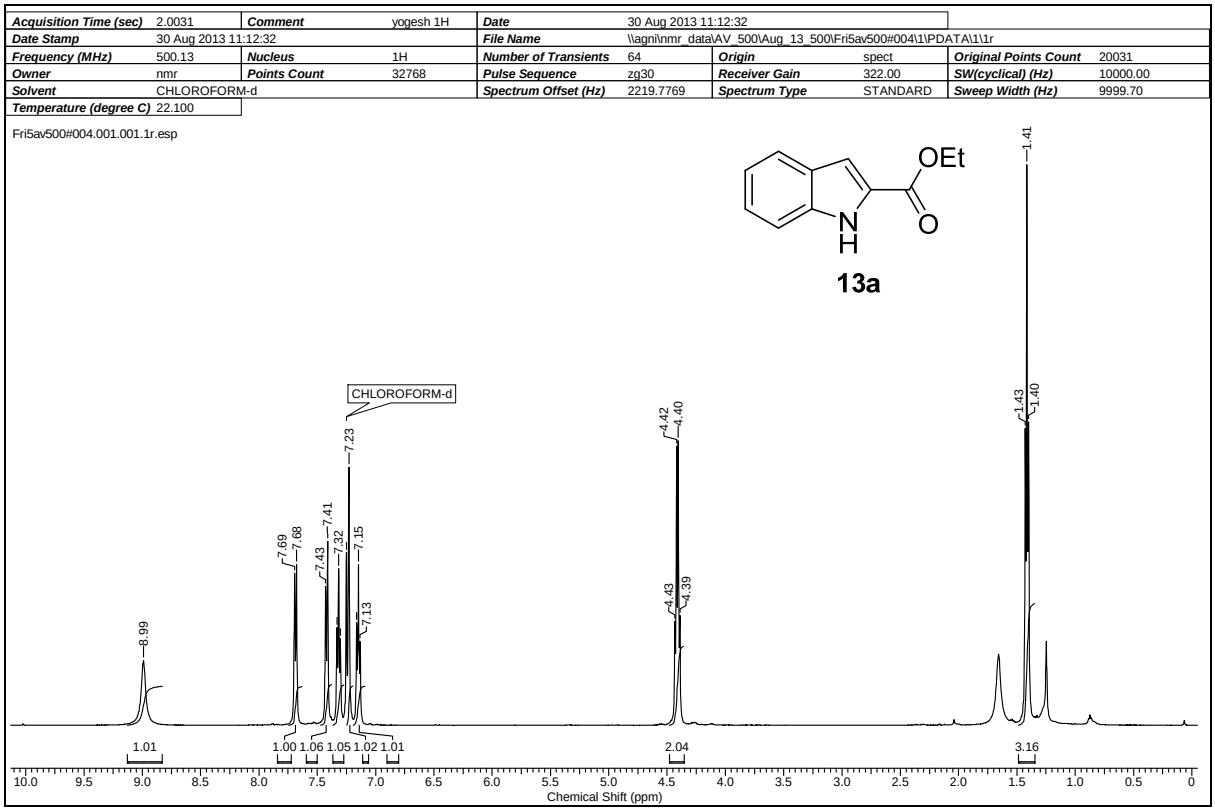
^{13}C NMR Spectrum of 10s in $CDCl_3$



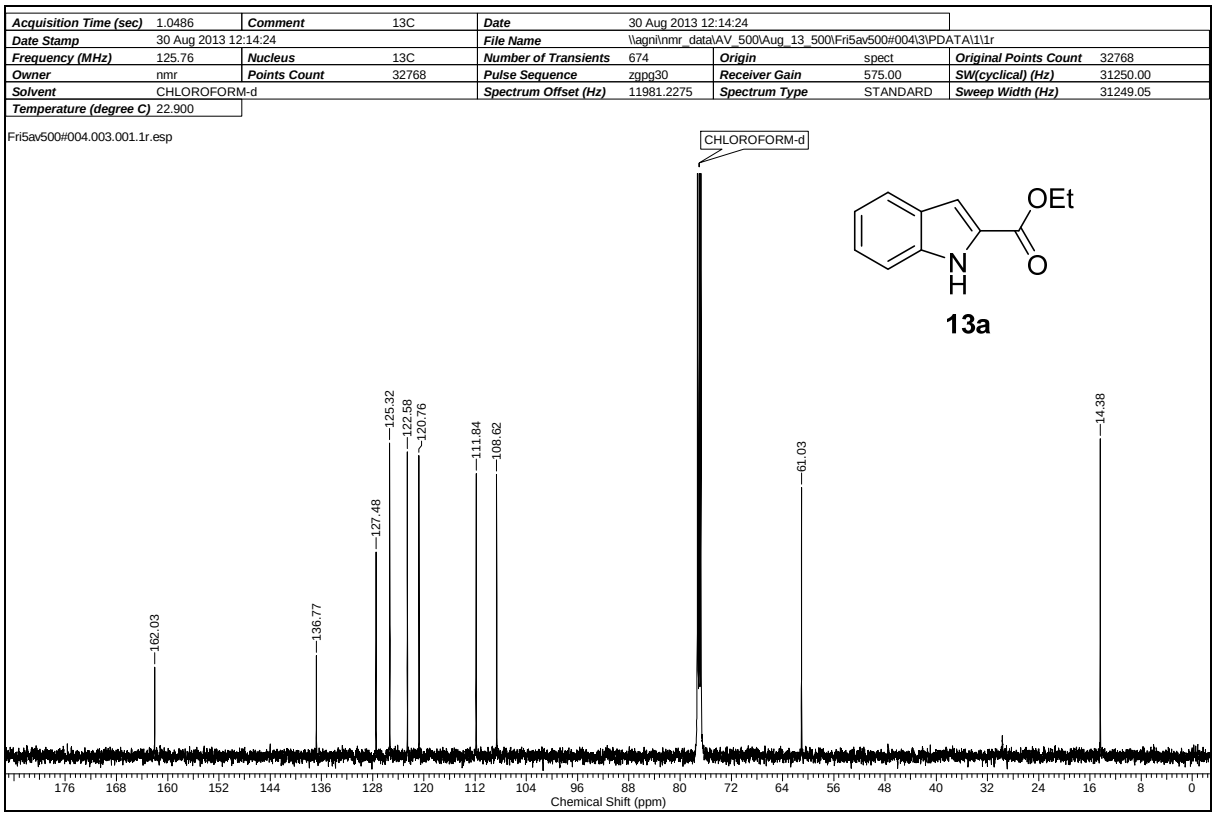
^{1}H NMR Spectrum of 10t in $CDCl_3$



^{13}C NMR Spectrum of 10t in $CDCl_3$



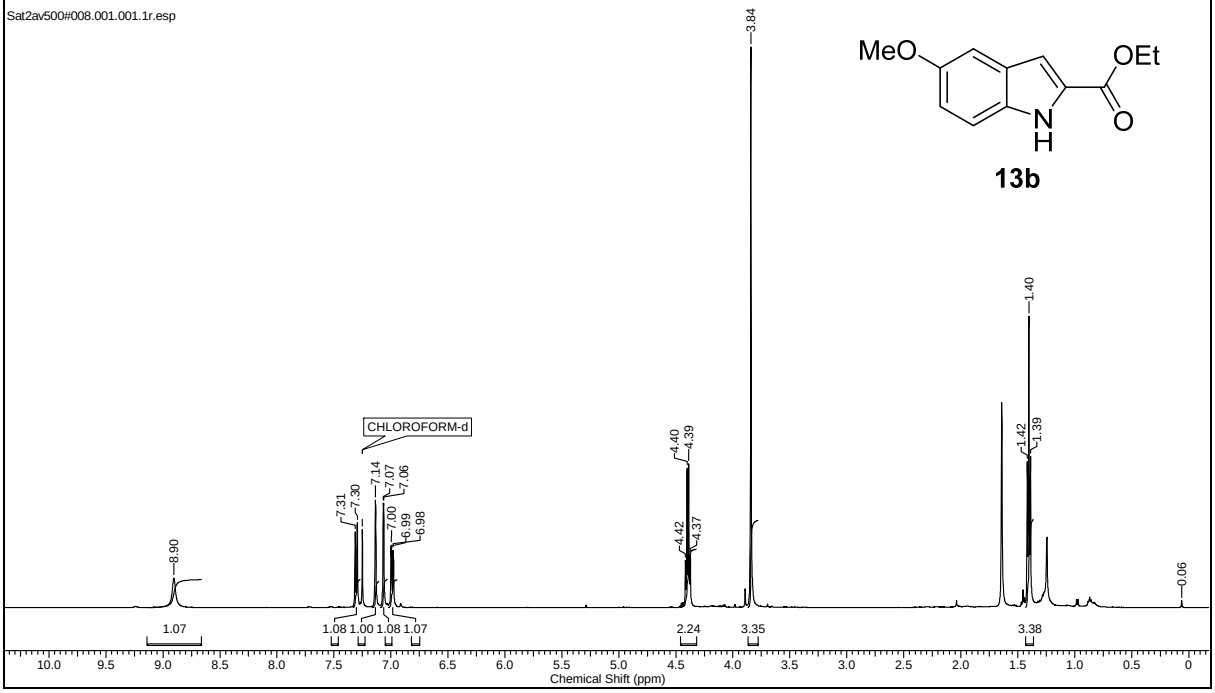
^{1}H NMR Spectrum of 13a in $CDCl_3$



^{13}C NMR Spectrum of 13a in $CDCl_3$

Acquisition Time (sec)	2.0031	**Comment**	yogesh 1H	**Date**	14 Sep 2013 13:22:40				
Date Stamp	14 Sep 2013 13:22:40			**File Name**	\\agni\nmr_data\AV_500\Sep_13_500\Sat2av500#008\1\PDATA\1\1r				
Frequency (MHz)	500.13	**Nucleus**	1H	**Number of Transients**	64	**Origin**	spect	**Original Points Count**	20031
Owner	nmr	**Points Count**	32768	**Pulse Sequence**	zg30	**Receiver Gain**	287.00	**SW(cyclical) (Hz)**	10000.00
Solvent	CHLOROFORM-d			**Spectrum Offset (Hz)**	2209.7742	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	9999.70
Temperature (degree C)	22.100								

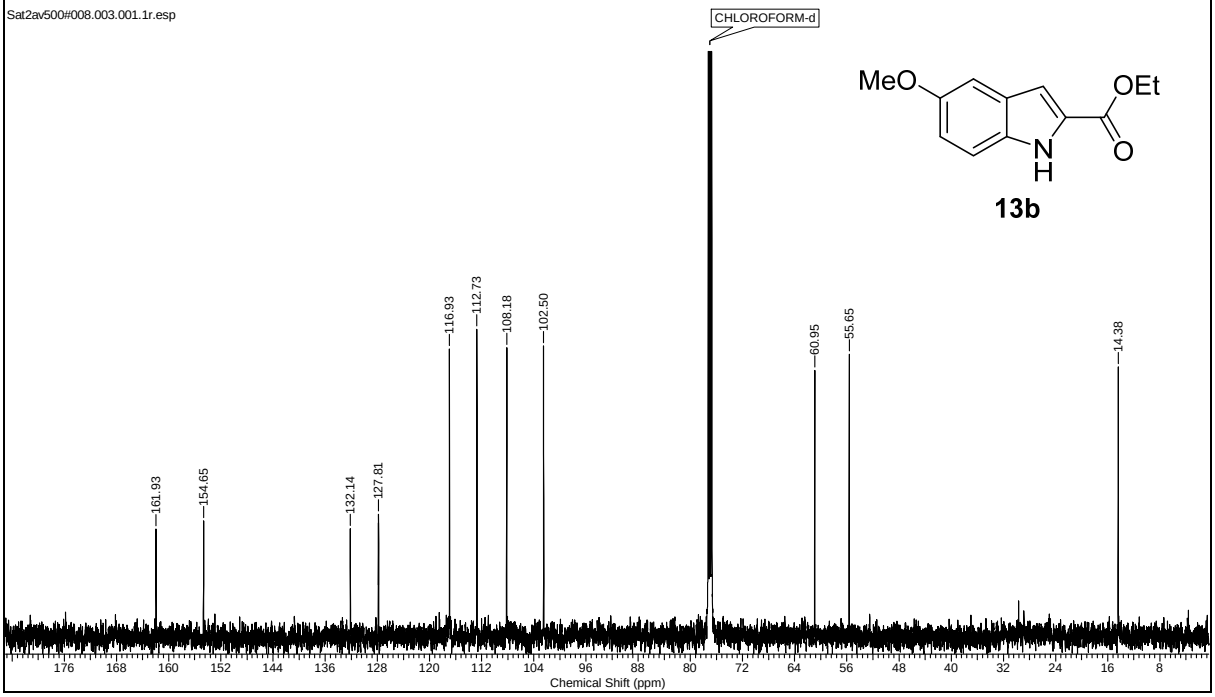
Sat2av500#008.001.001.1r.esp



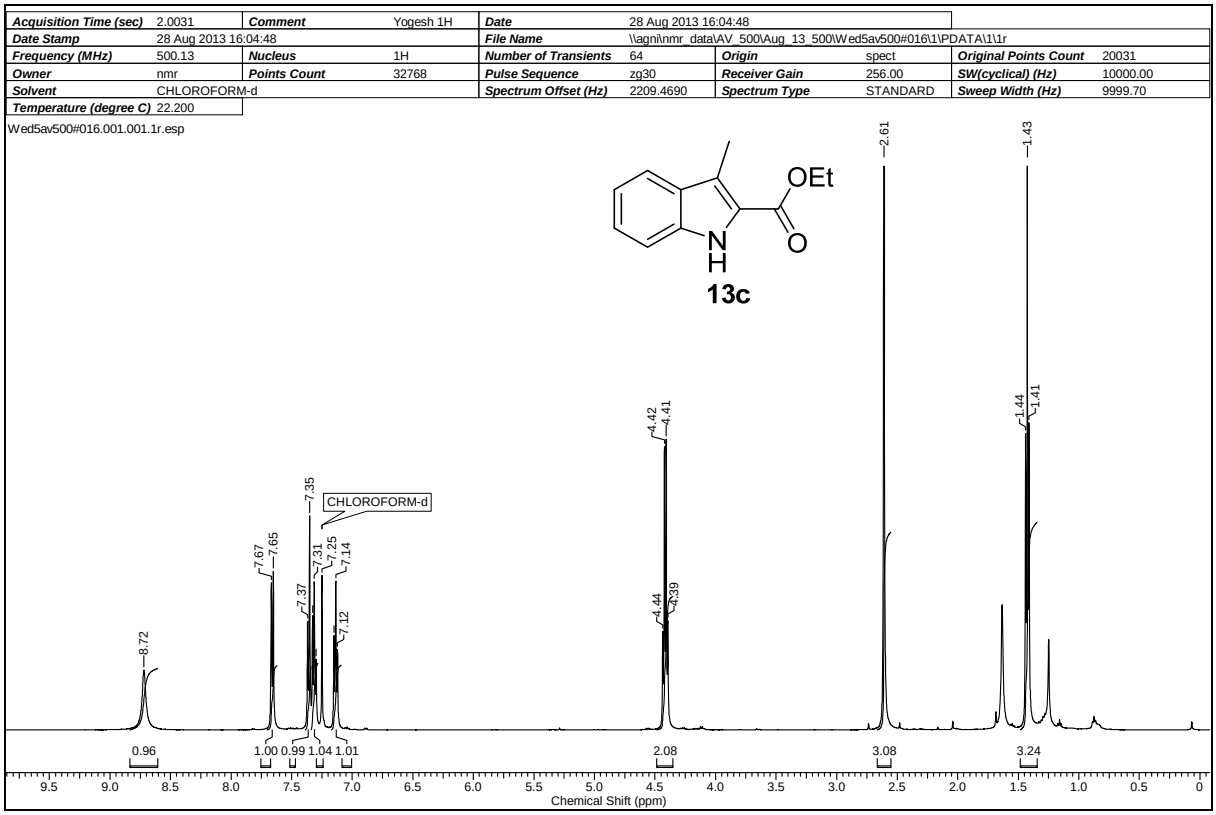
^{1}H NMR Spectrum of 13b in $CDCl_3$

Acquisition Time (sec)	1.0486	**Comment**	13C	**Date**	14 Sep 2013 13:58:56				
Date Stamp	14 Sep 2013 13:58:56			**File Name**	\\agni\nmr_data\AV_500\Sep_13_500\Sat2av500#008\3\PDATA\1\1r				
Frequency (MHz)	125.76	**Nucleus**	13C	**Number of Transients**	223	**Origin**	spect	**Original Points Count**	32768
Owner	nmr	**Points Count**	32768	**Pulse Sequence**	zgpg30	**Receiver Gain**	575.00	**SW(cyclical) (Hz)**	31250.00
Solvent	CHLOROFORM-d			**Spectrum Offset (Hz)**	11981.2275	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	31249.05
Temperature (degree C)	23.000								

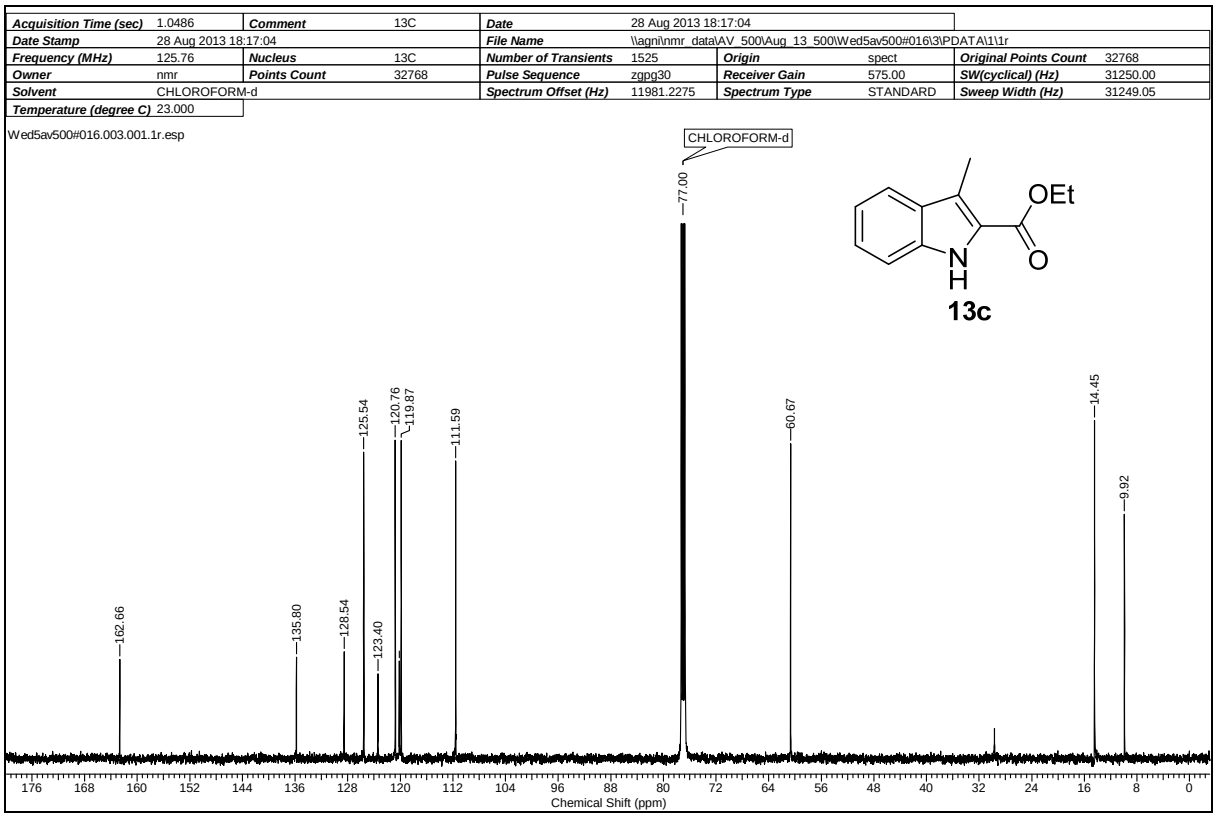
Sat2av500#008.003.001.1r.esp



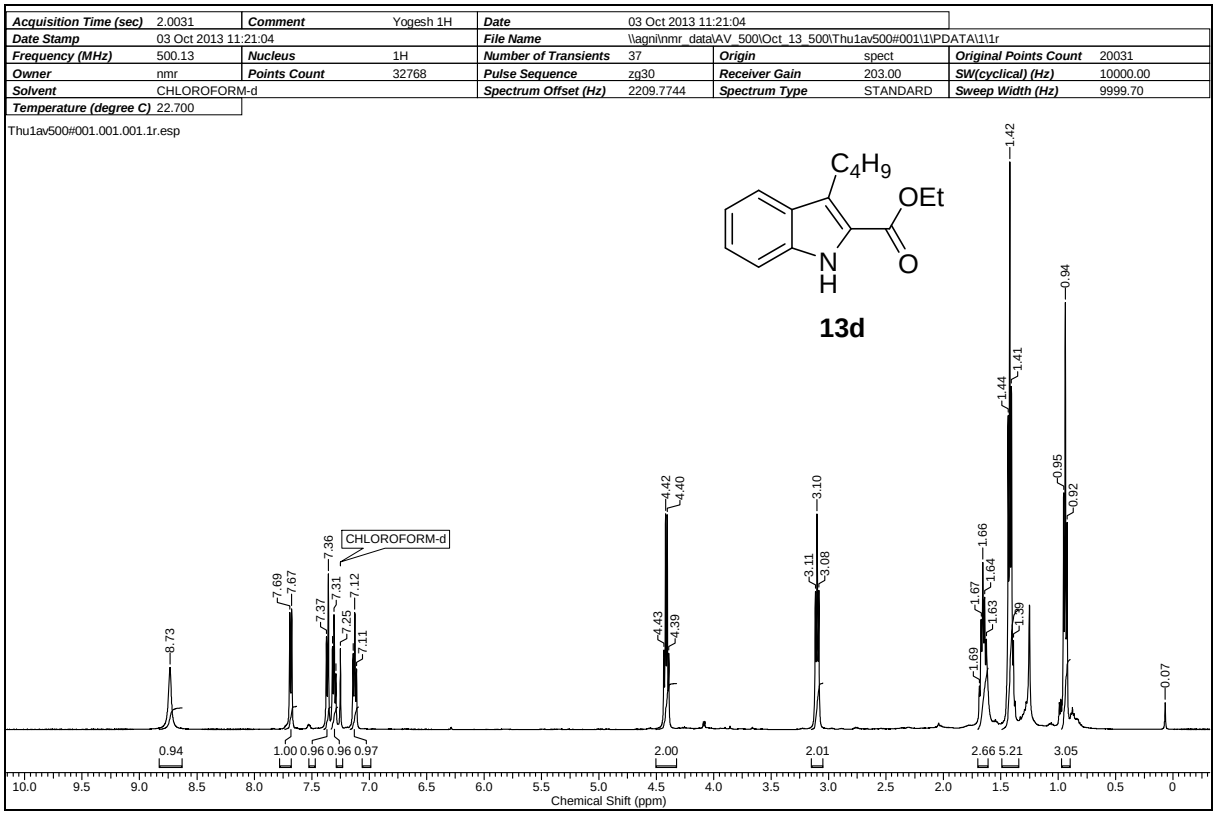
^{13}C NMR Spectrum of 13b in $CDCl_3$



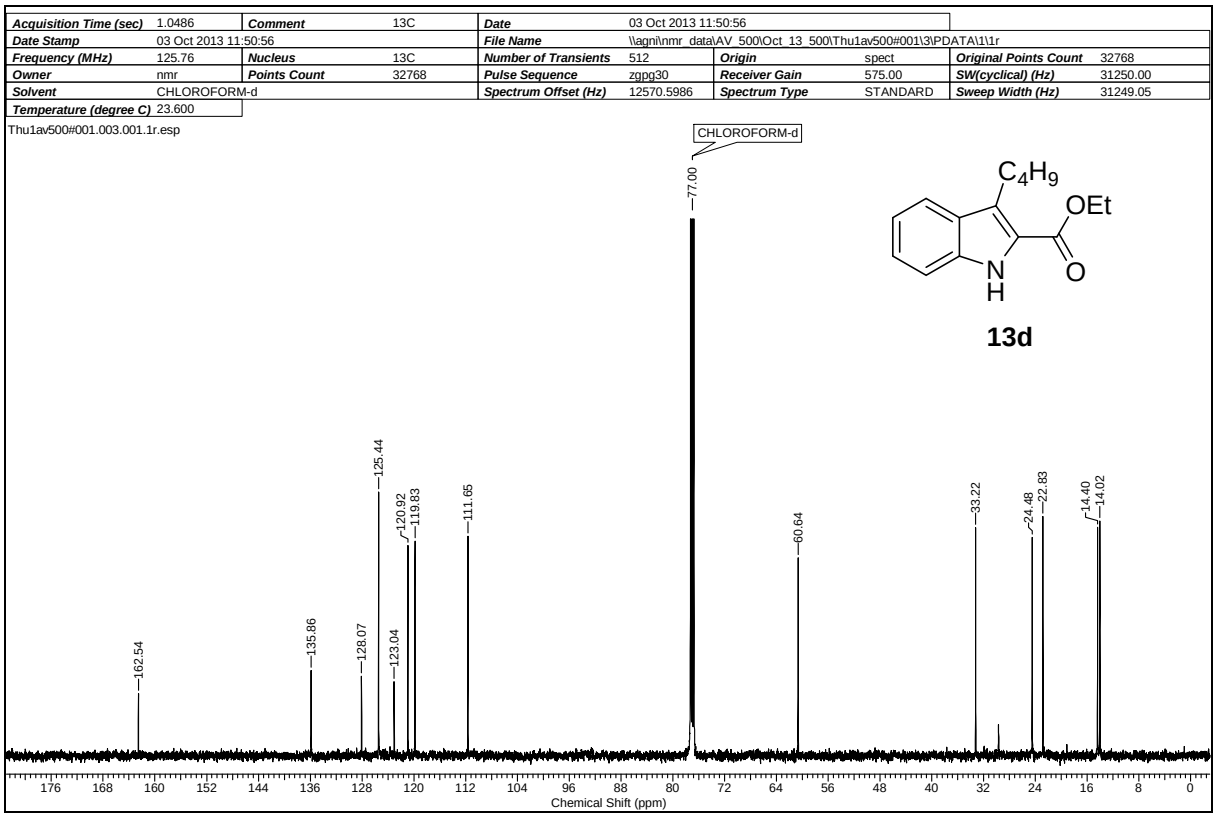
^{1}H NMR Spectrum of 13c in $CDCl_3$



^{13}C NMR Spectrum of 13c in $CDCl_3$

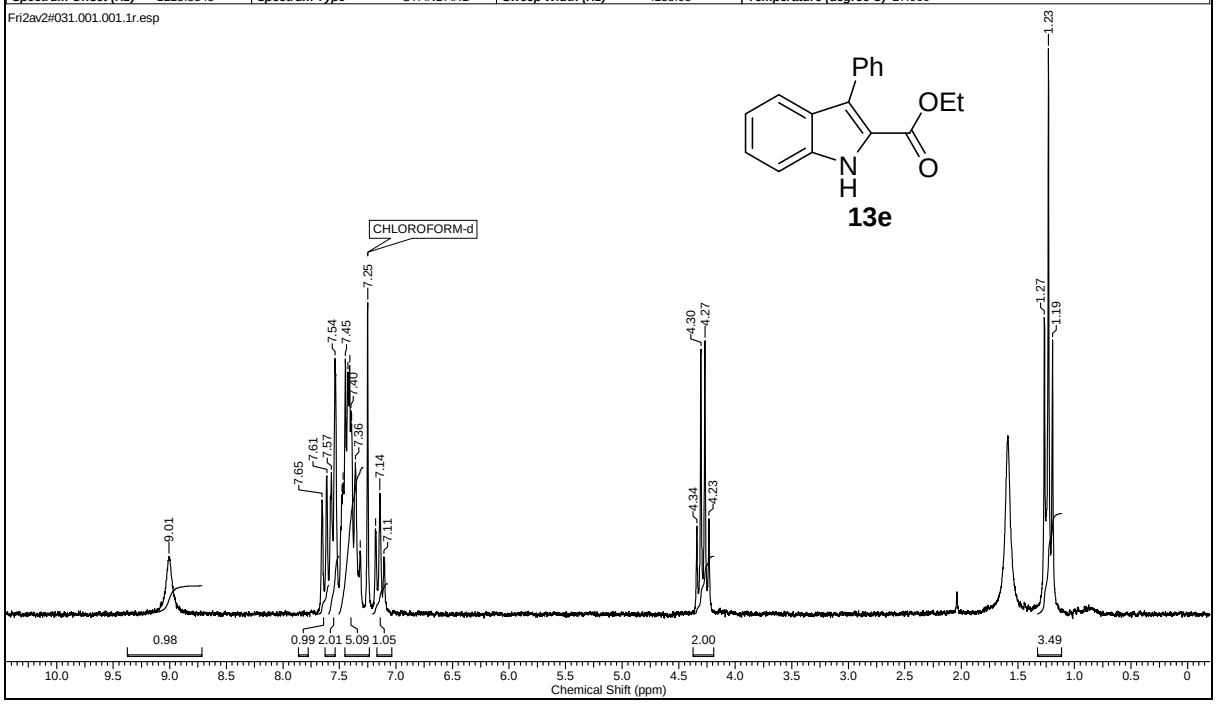


^{1}H NMR Spectrum of 13d in $CDCl_3$



^{13}C NMR Spectrum of 13d in $CDCl_3$

Acquisition Time (sec)	3.9584	**Comment**	Yogesh	**Date**	13 Sep 2013 15:04:40		
Date Stamp	13 Sep 2013 15:04:40			**File Name**	\\agni\nmr_data\AV200\SEPT_13#AV200\data\Administrator\nmr\Fri2av2#031\1\PDATA\1\1r		
Frequency (MHz)	200.13	**Nucleus**	1H	**Number of Transients**	8	**Origin**	av200
Original Points Count	16384	**Owner**	Administrator	**Points Count**	32768	**Pulse Sequence**	zg30
Receiver Gain	1149.40	**SW(cyclical) (Hz)**	4139.07	**Solvent**	CHLOROFORM-d		
Spectrum Offset (Hz)	1225.5343	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	4138.95	**Temperature (degree C)**	27.000



^{1}H NMR Spectrum of 13e in $CDCl_3$

Acquisition Time (sec)	0.6832	**Comment**	yogesh	**Date**	14 Sep 2013 21:39:20		
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Frequency (MHz)	50.32	**Nucleus**	13C	**Number of Transients**	1600	**Origin**	av200
Original Points Count	8192	**Owner**	Administrator	**Points Count**	32768	**Pulse Sequence**	zgpg30
Receiver Gain	812.70	**SW(cyclical) (Hz)**	11990.41	**Solvent**	CHLOROFORM-d		
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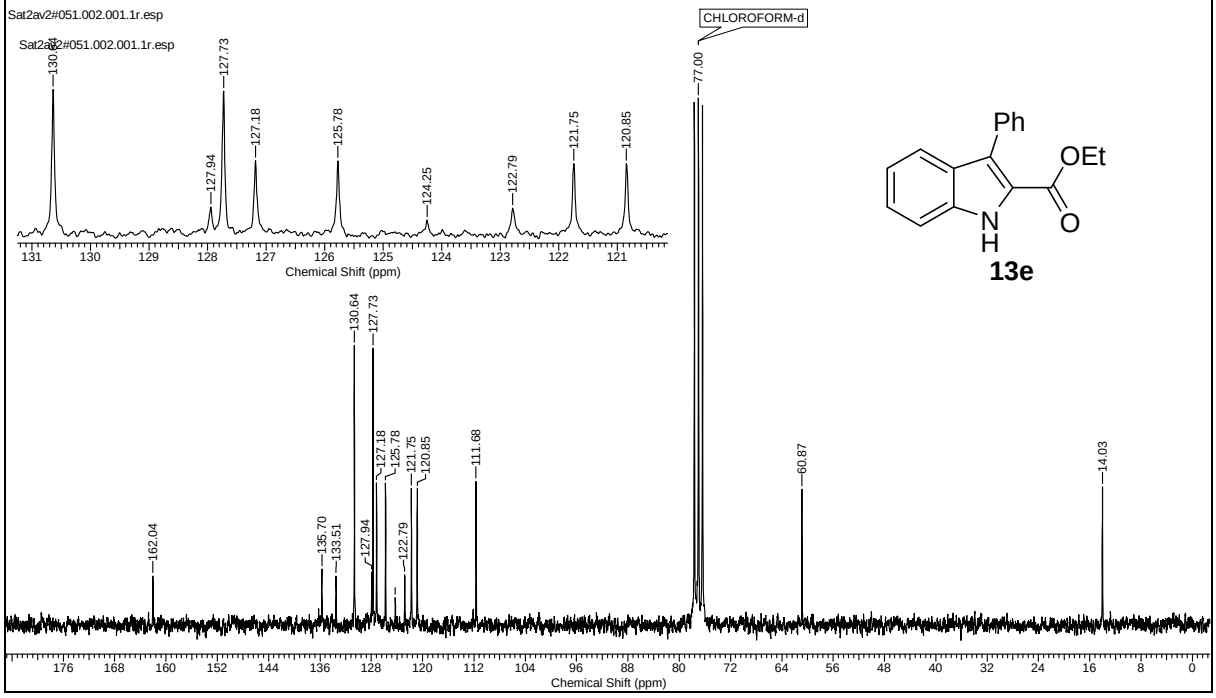
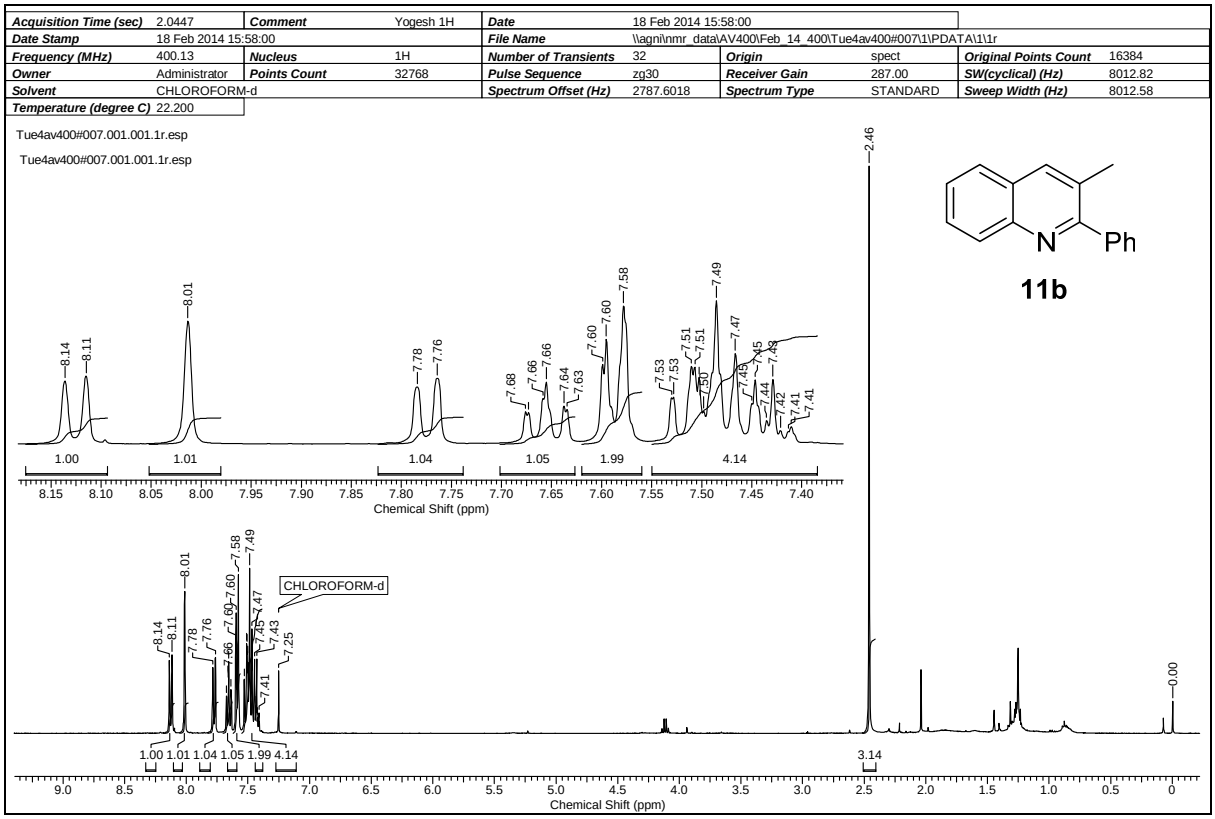
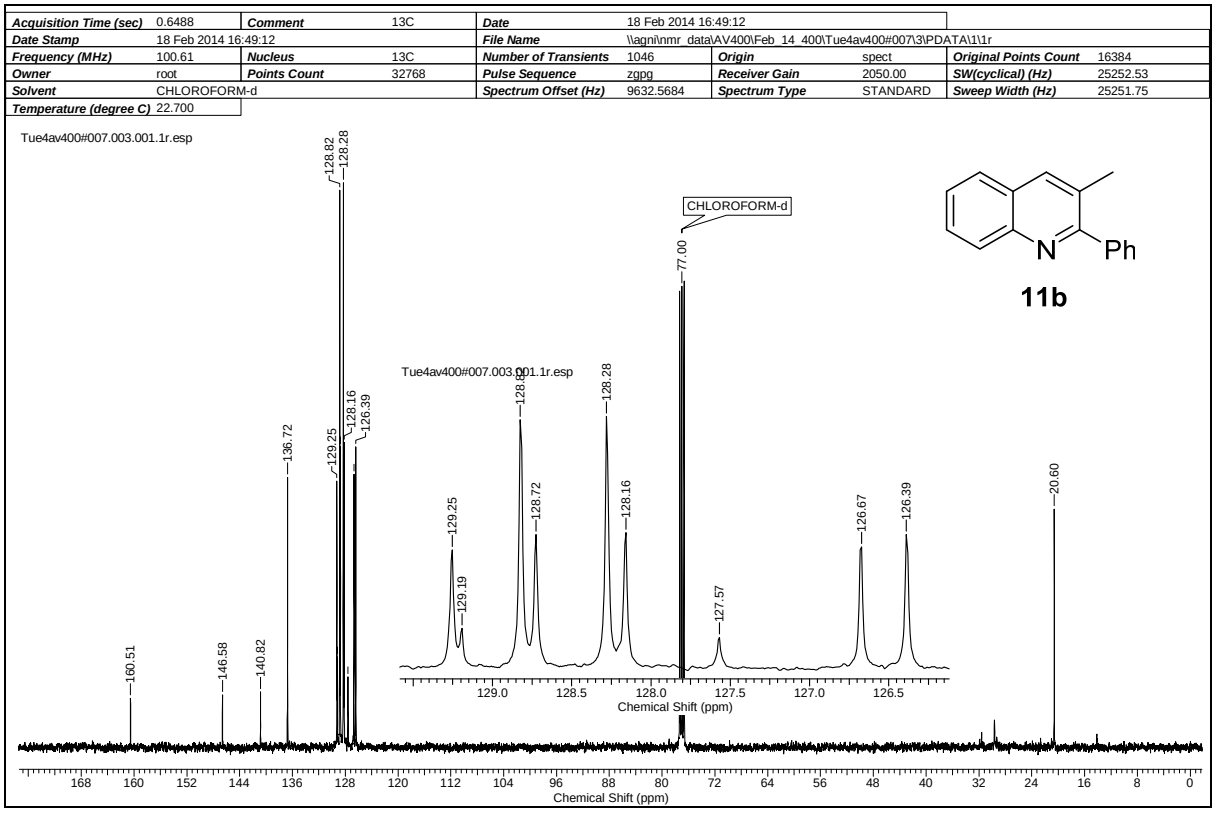


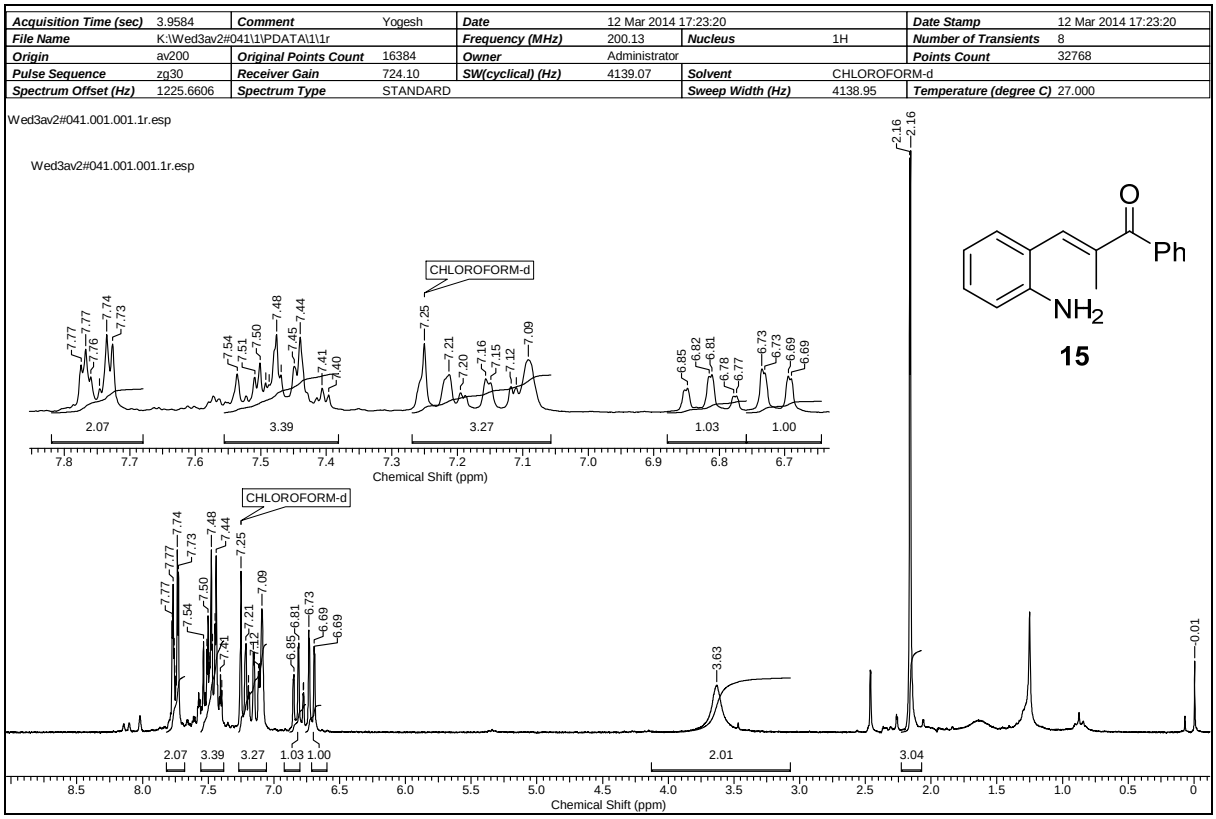
^{13}C NMR Spectrum of 13e in $CDCl_3$



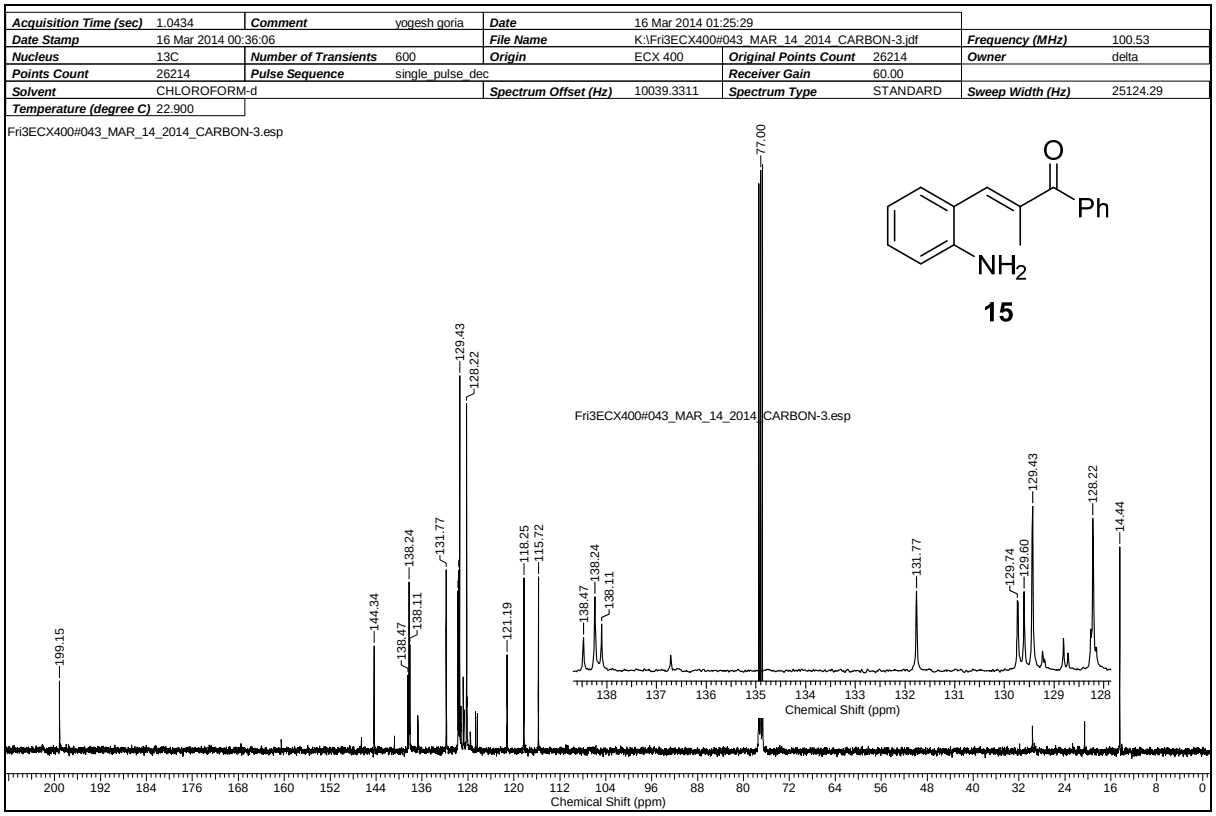
^{1}H NMR Spectrum of 11b in $CDCl_3$



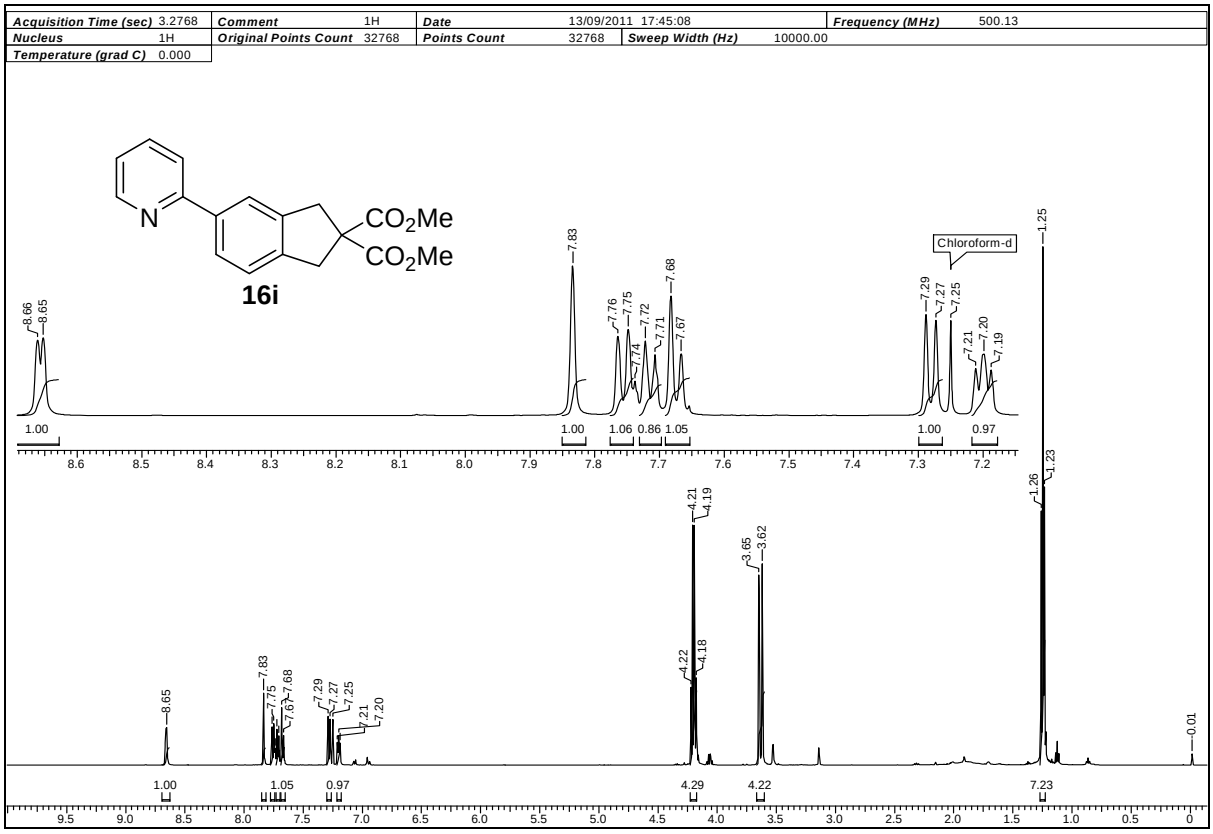
^{13}C NMR Spectrum of 11b in $CDCl_3$



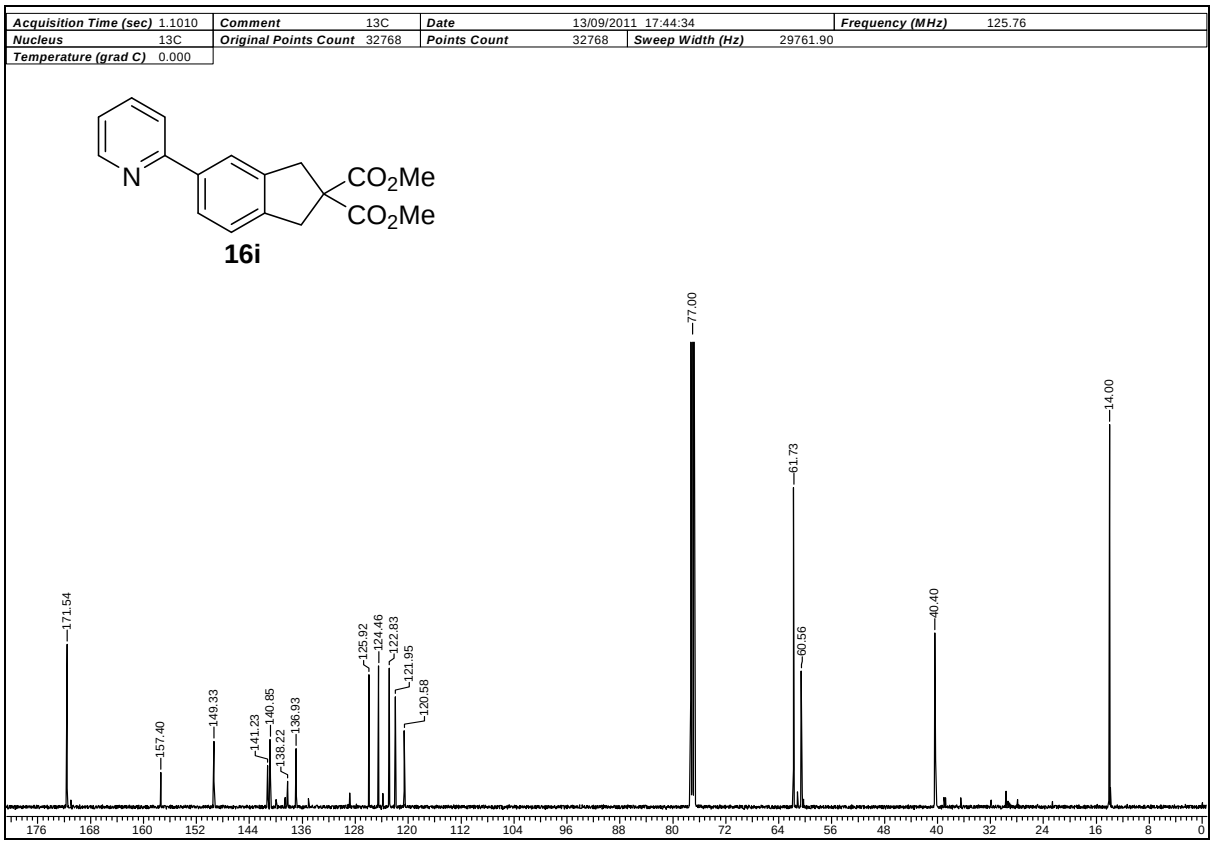
^{1}H NMR Spectrum of 15 in $CDCl_3$



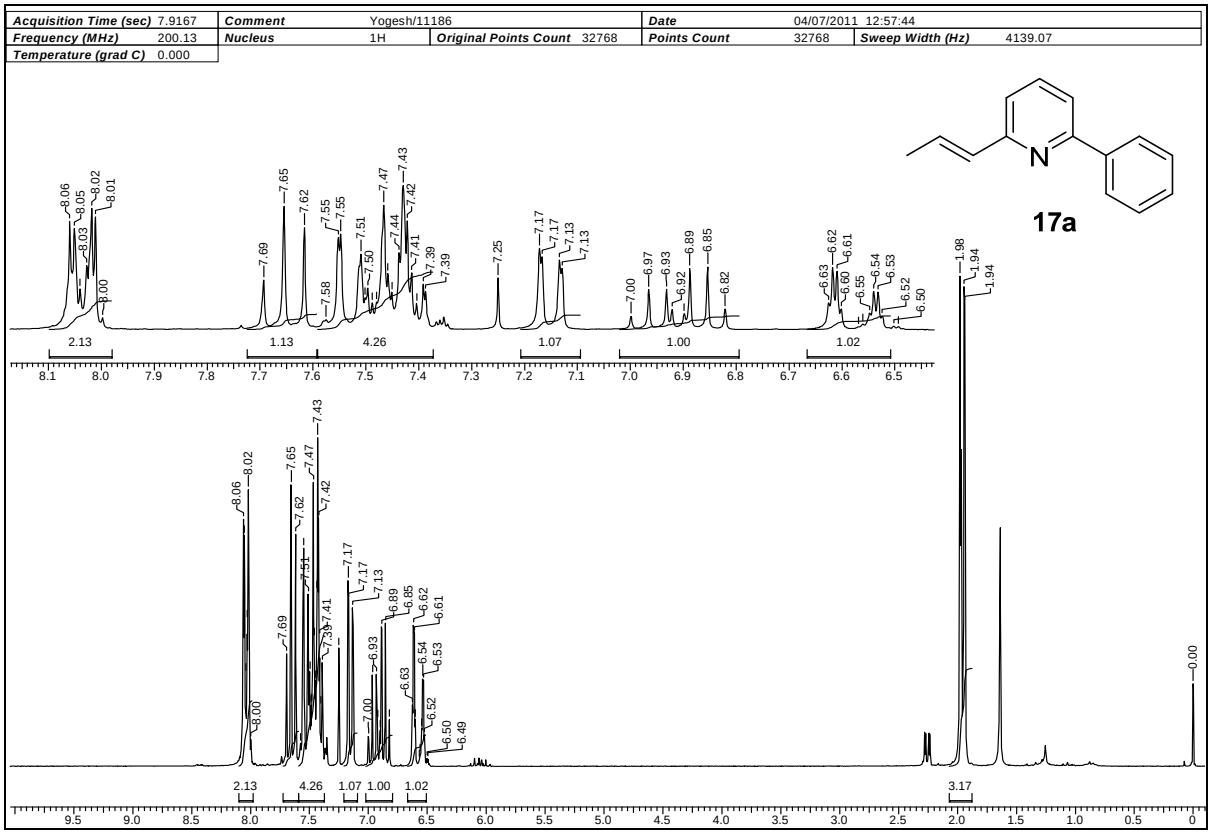
^{13}C NMR Spectrum of 15 in $CDCl_3$



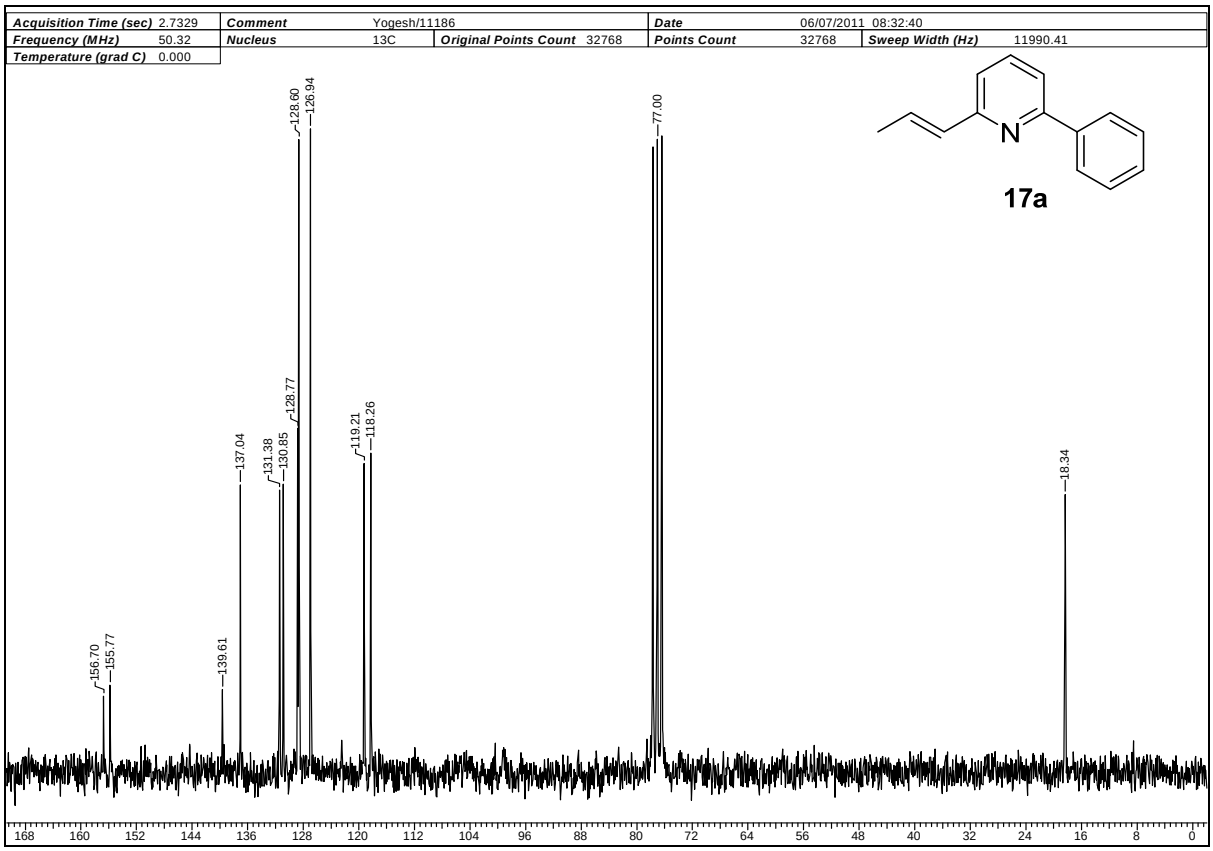
^{1}H NMR Spectrum of 16i in $CDCl_3$



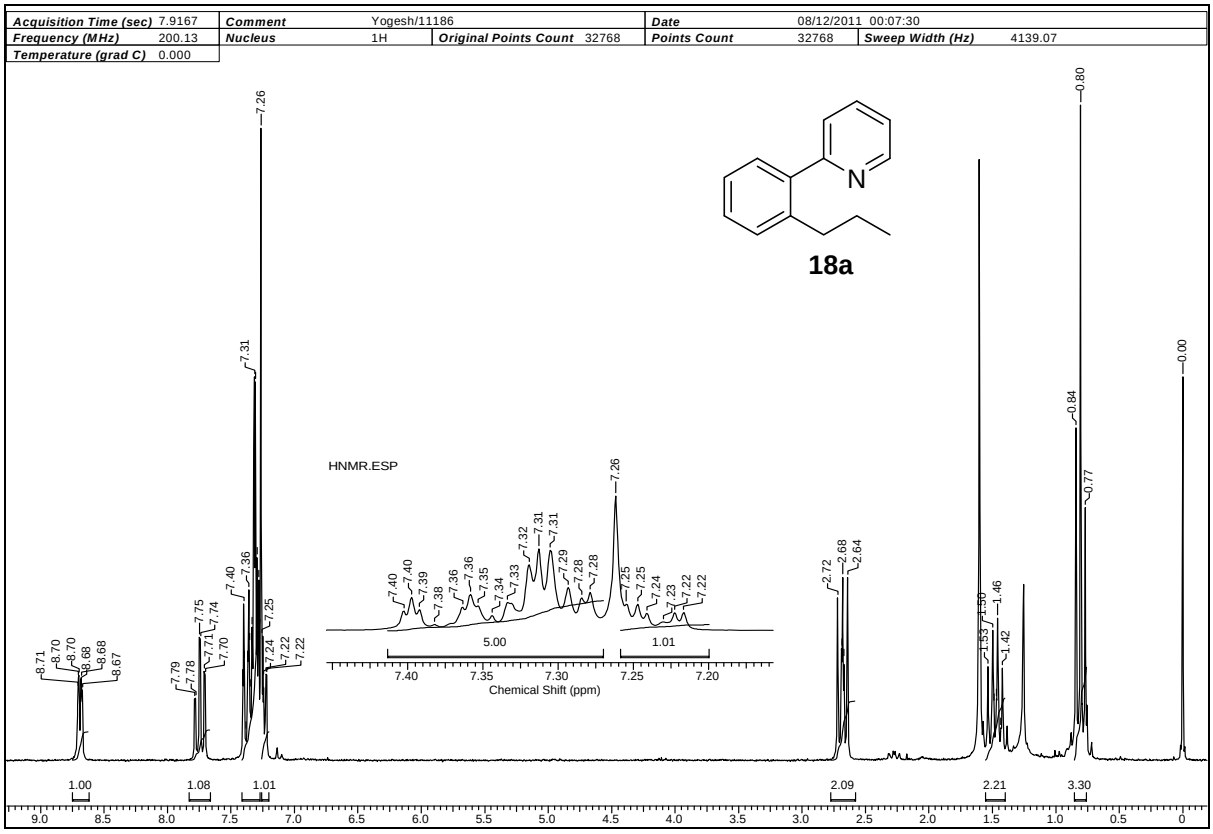
^{13}C NMR Spectrum of 16i in $CDCl_3$



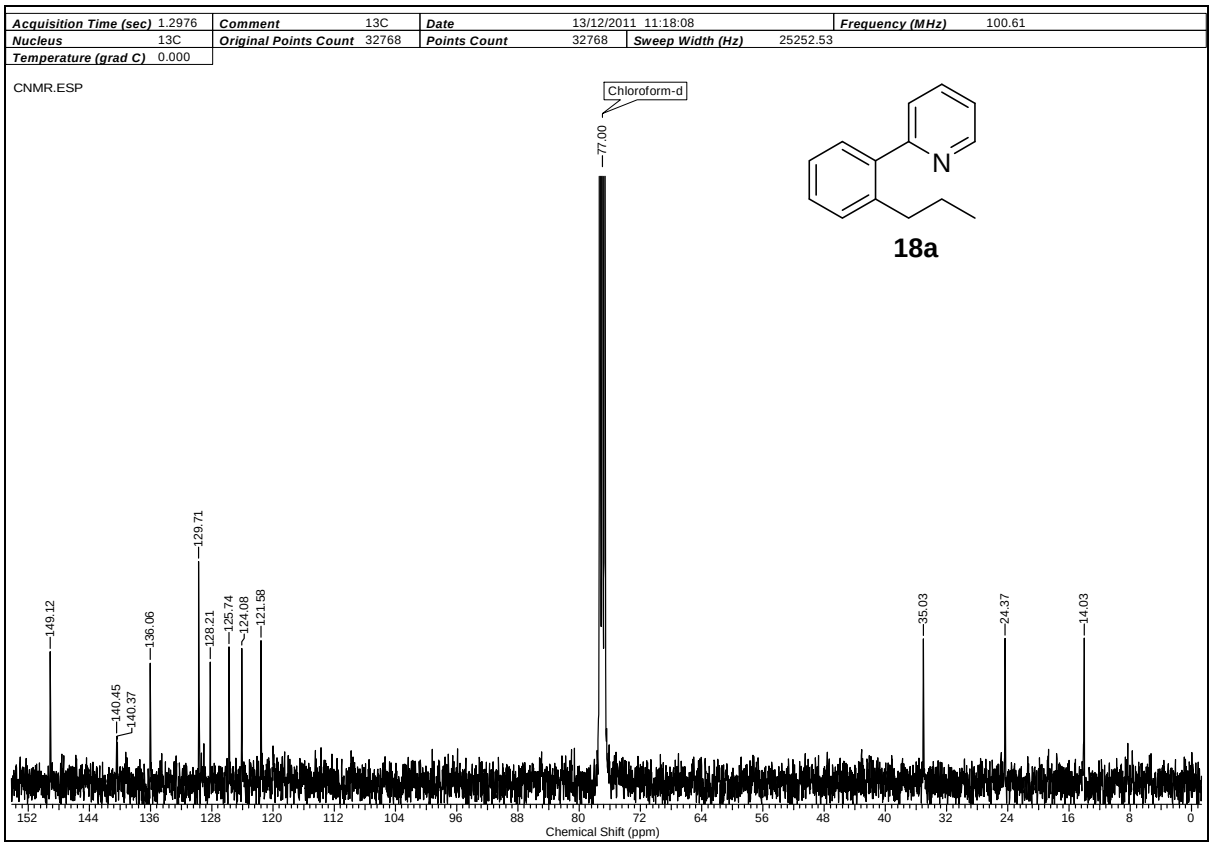
^{1}H NMR Spectrum of 17a in $CDCl_3$



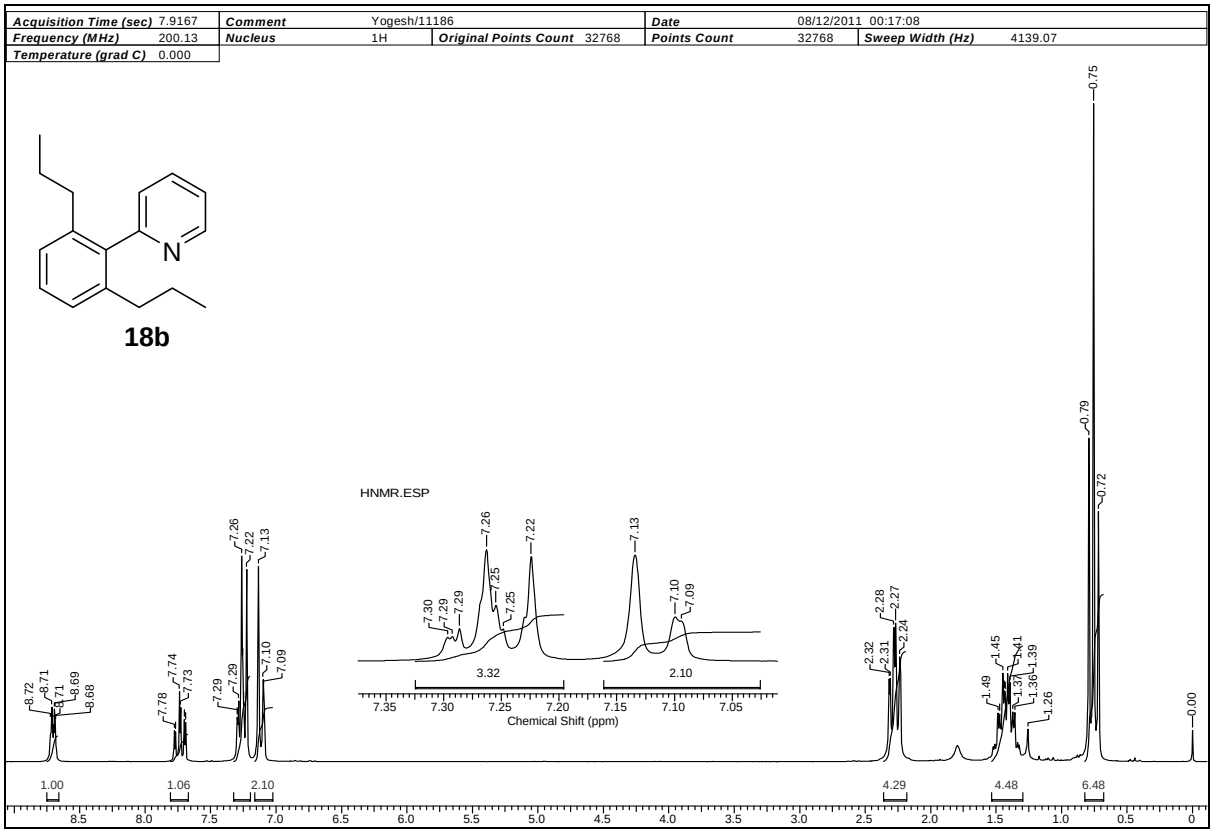
^{13}C NMR Spectrum of 17a in $CDCl_3$



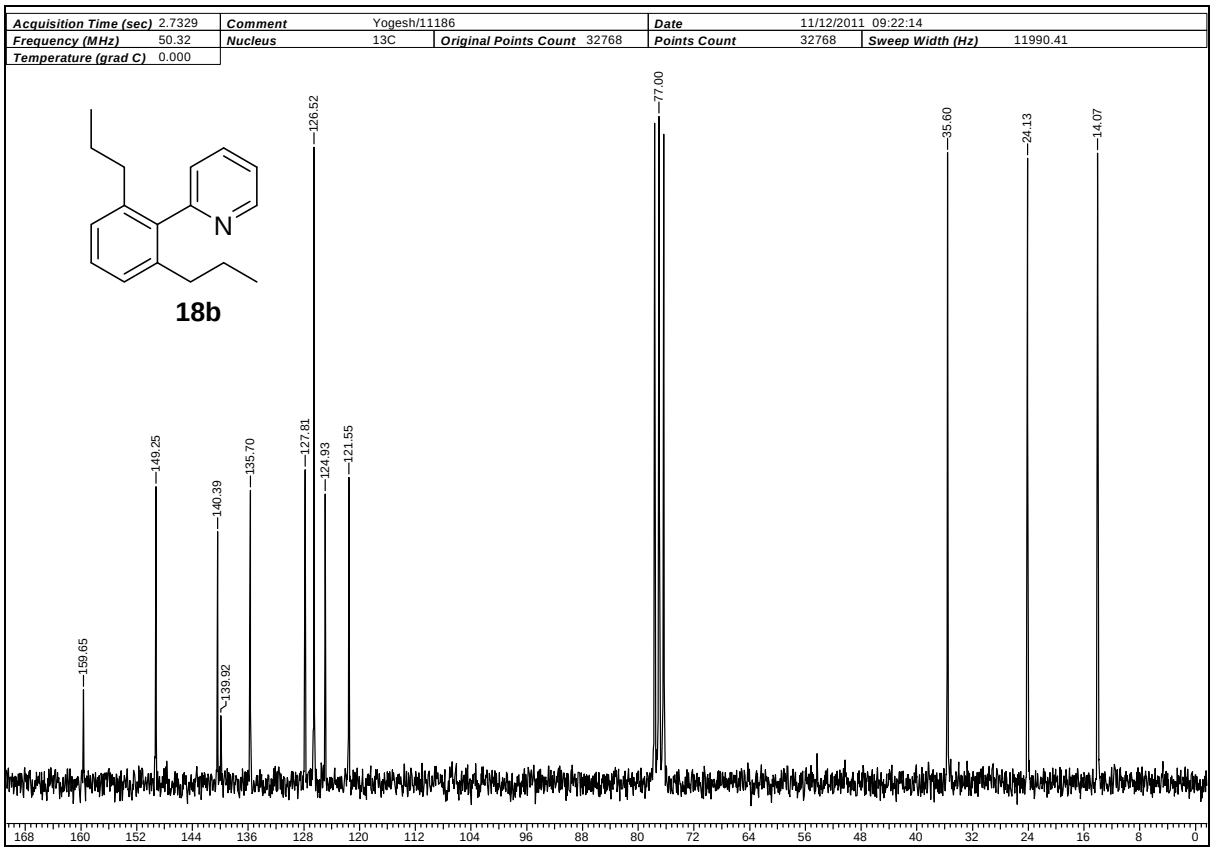
^{1}H NMR Spectrum of 18a in $CDCl_3$



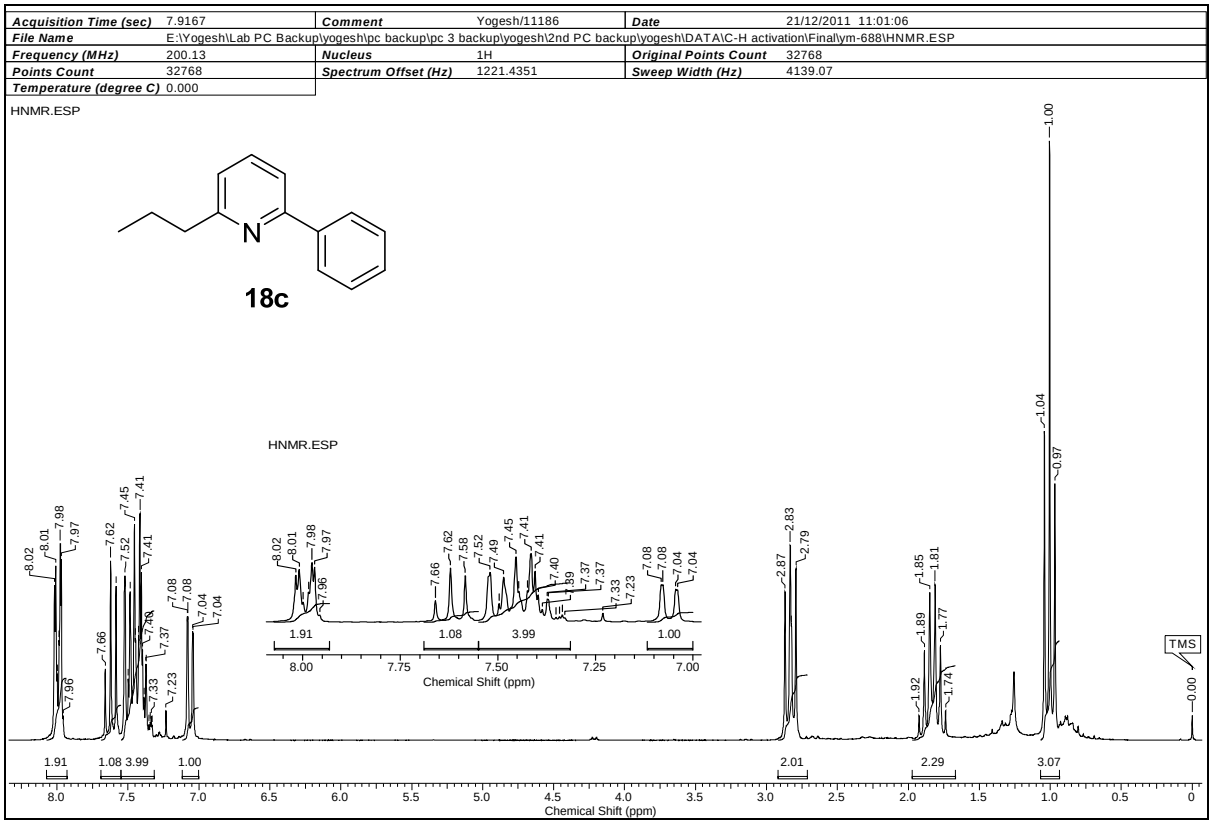
^{13}C NMR Spectrum of 18a in $CDCl_3$



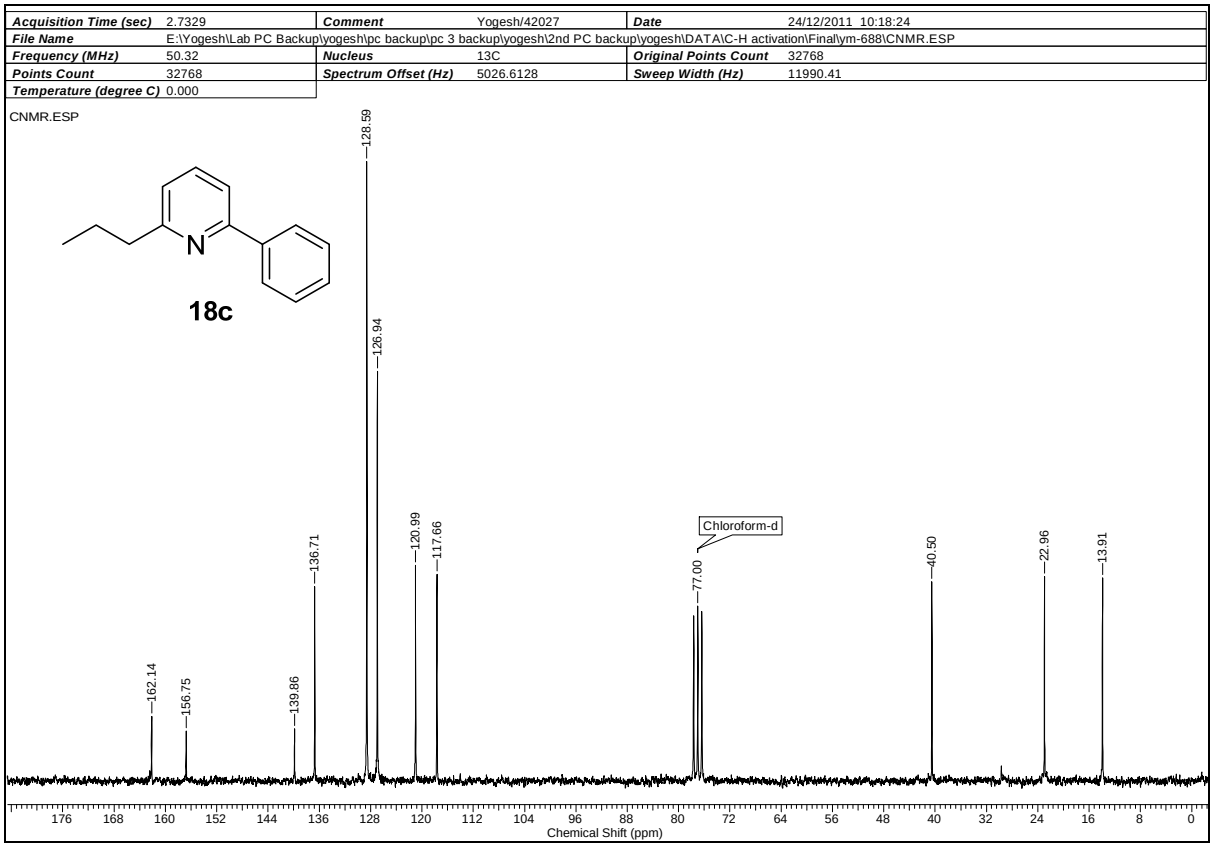
^{1}H NMR Spectrum of 18b in $CDCl_3$



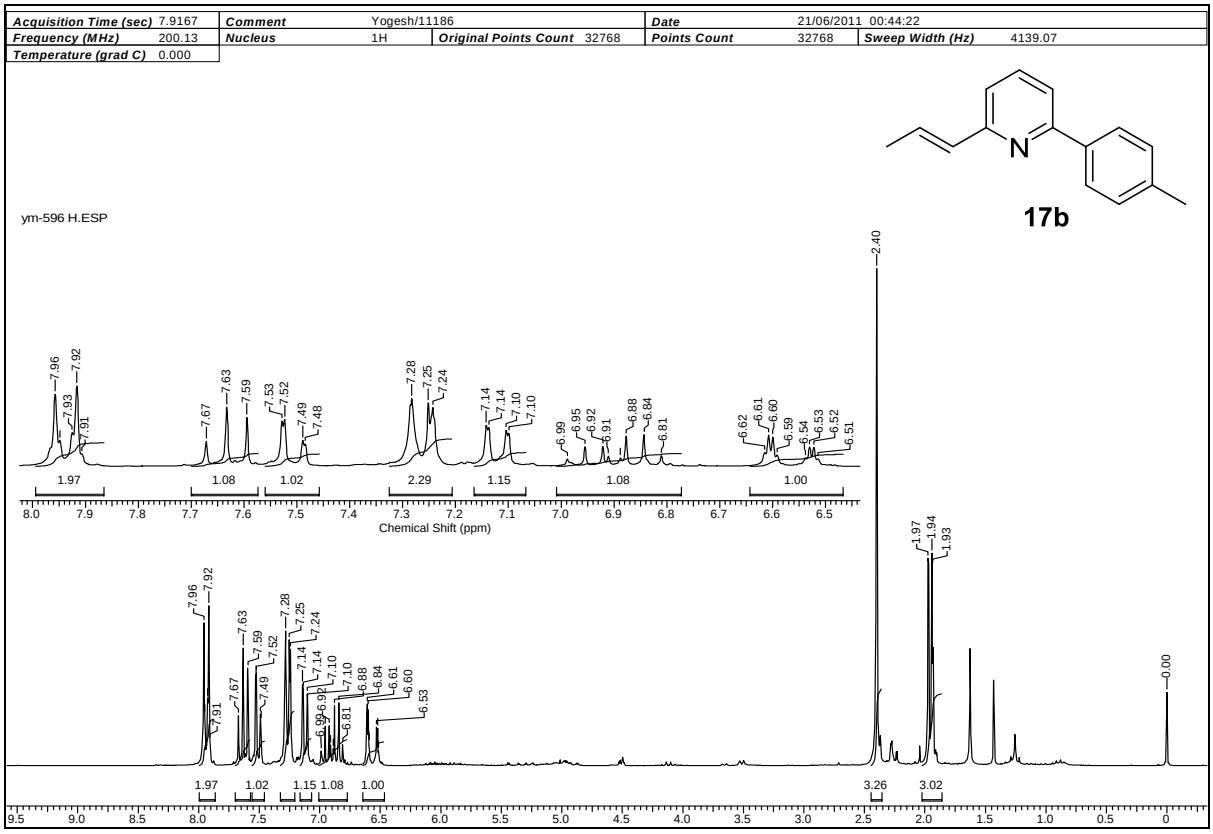
^{13}C NMR Spectrum of 18b in $CDCl_3$



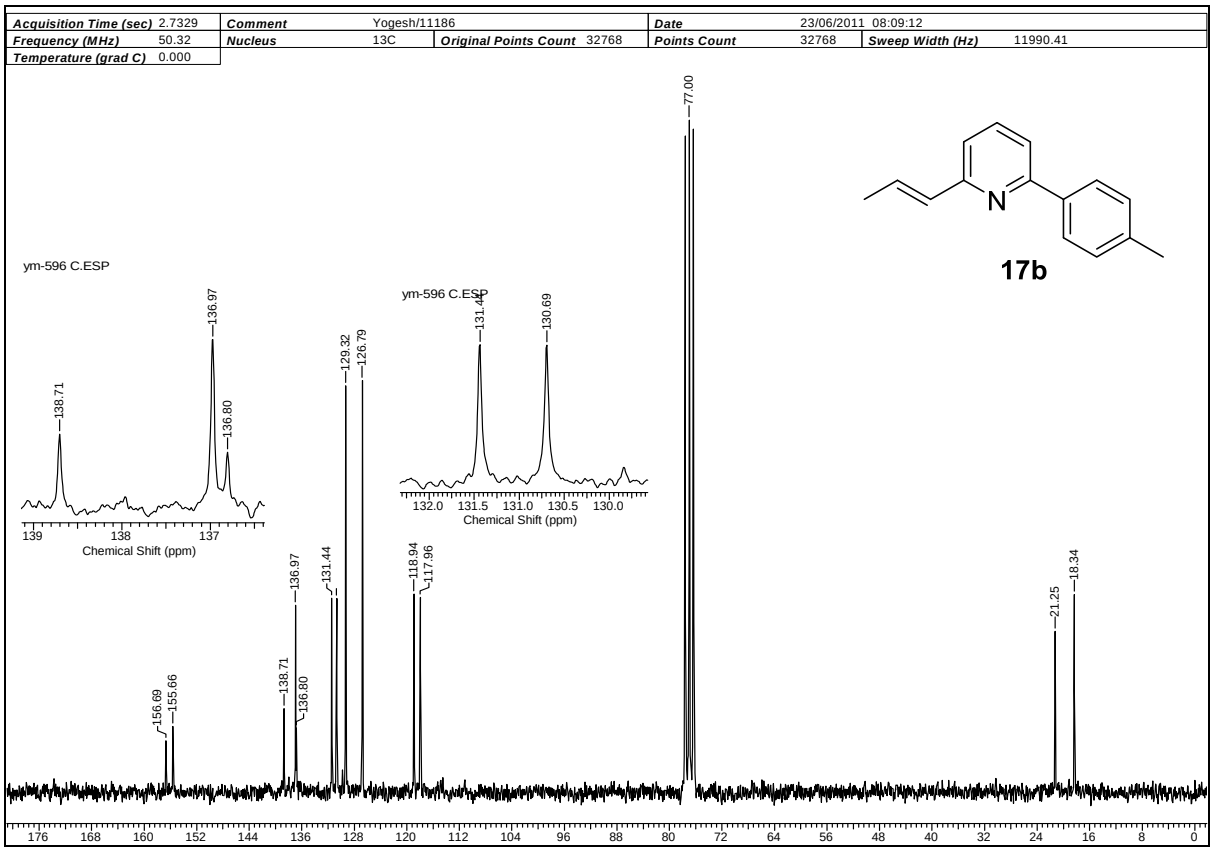
^{1}H NMR Spectrum of 18c in $CDCl_3$



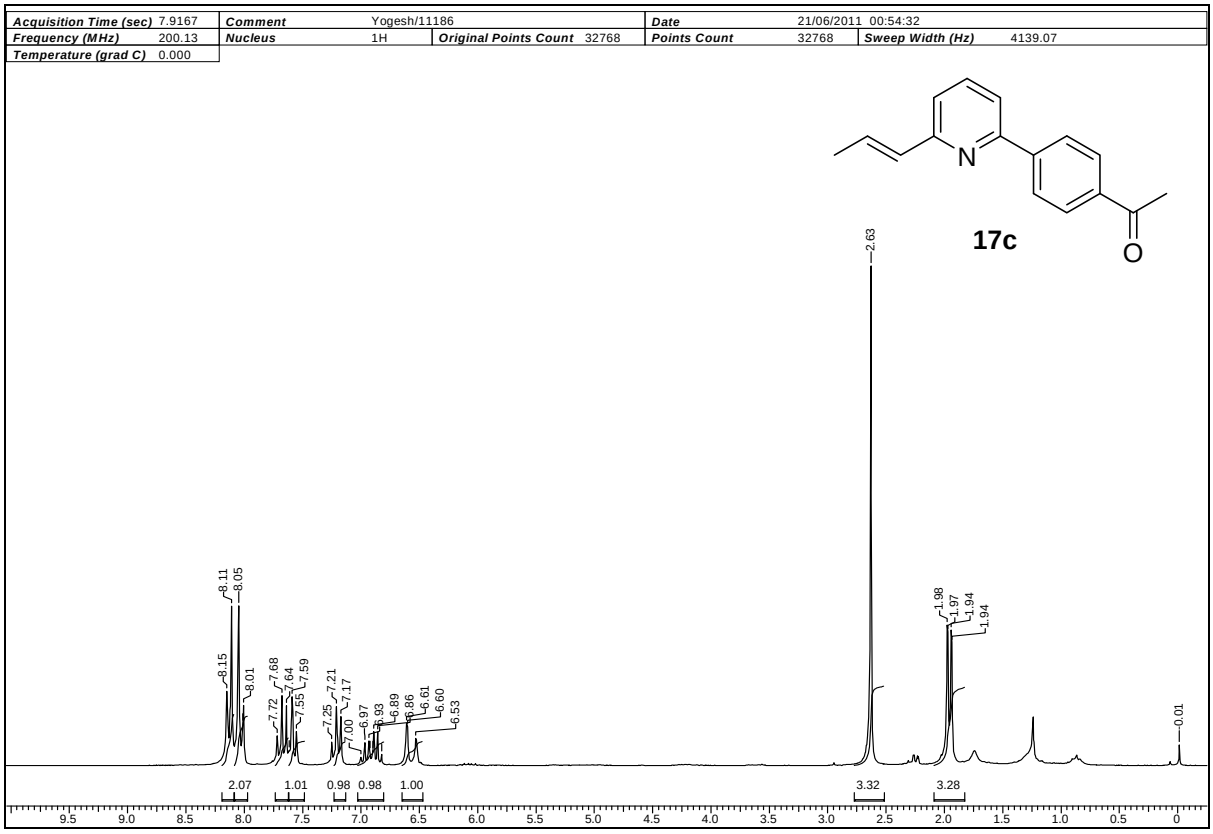
^{13}C NMR Spectrum of 18c in $CDCl_3$



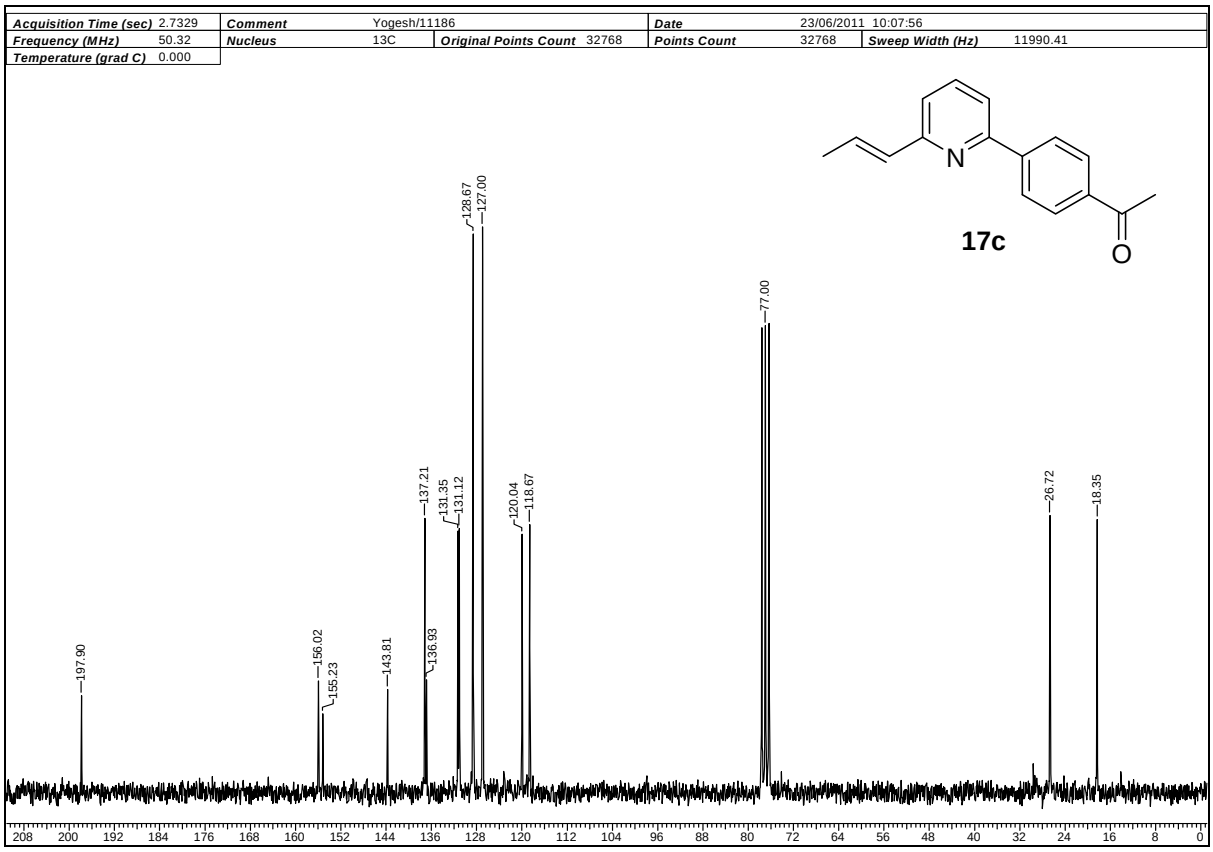
^{1}H NMR Spectrum of 17b in $CDCl_3$



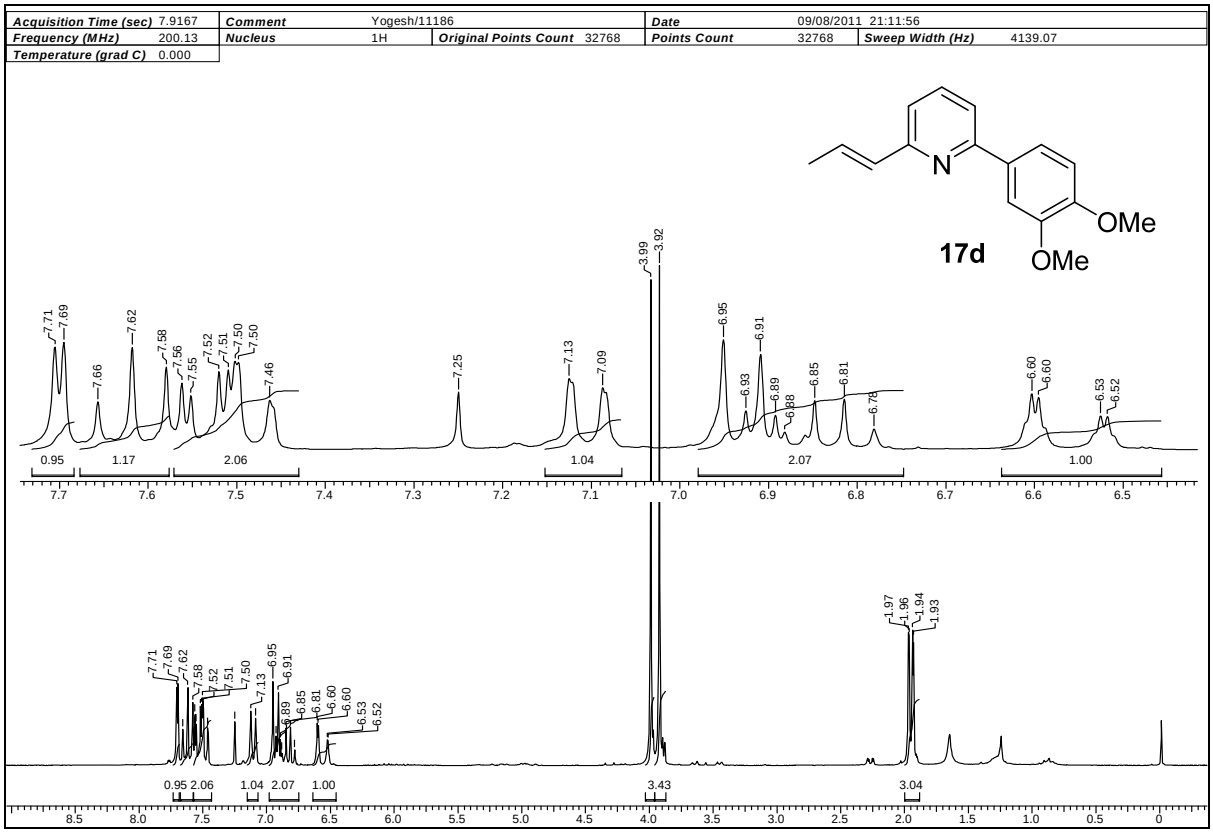
^{13}C NMR Spectrum of 17b in $CDCl_3$



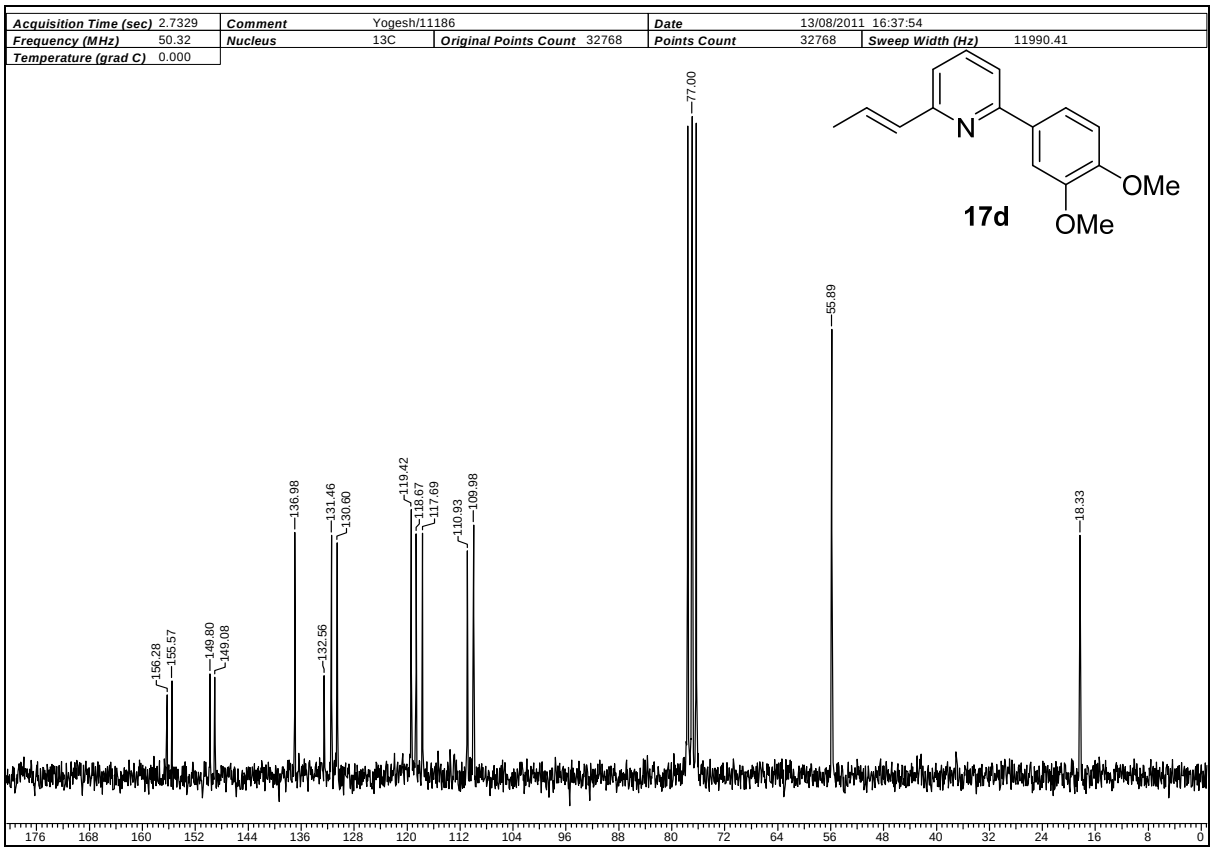
^{1}H NMR Spectrum of 17c in $CDCl_3$



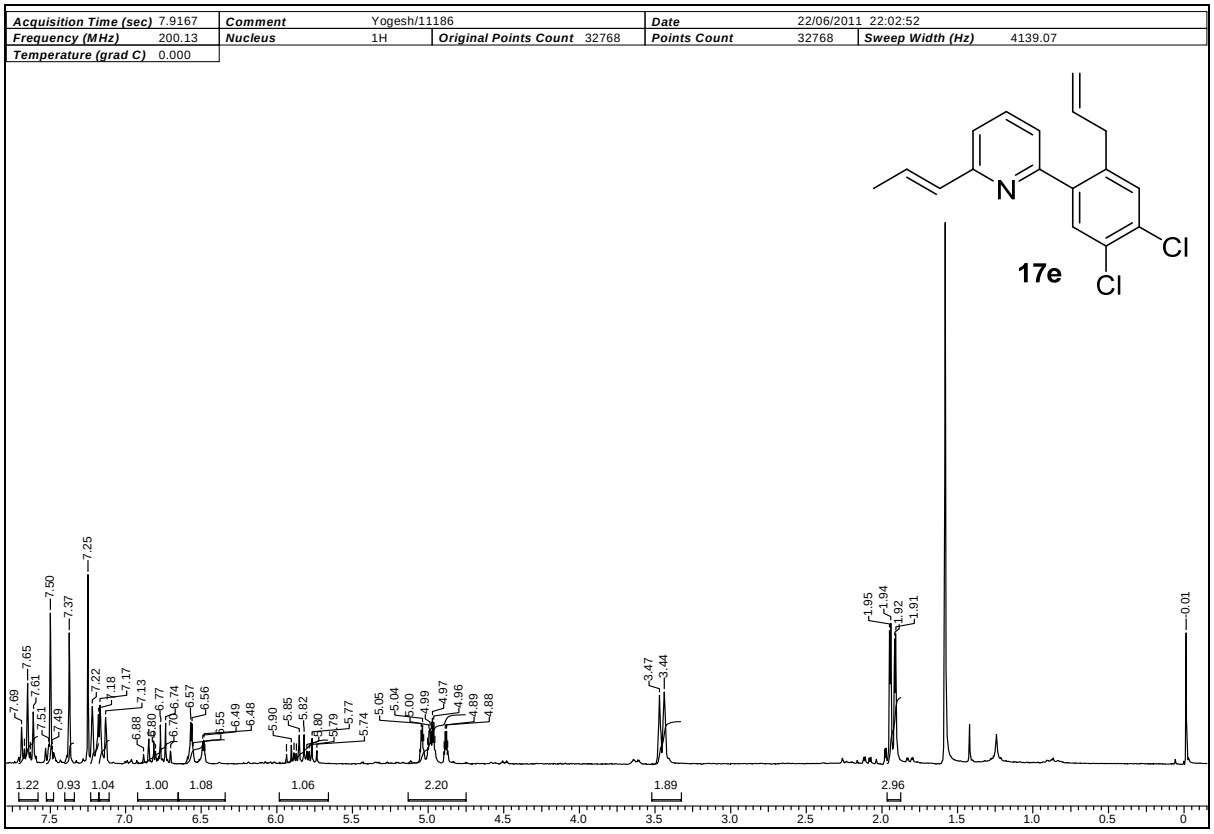
^{13}C NMR Spectrum of 17c in $CDCl_3$



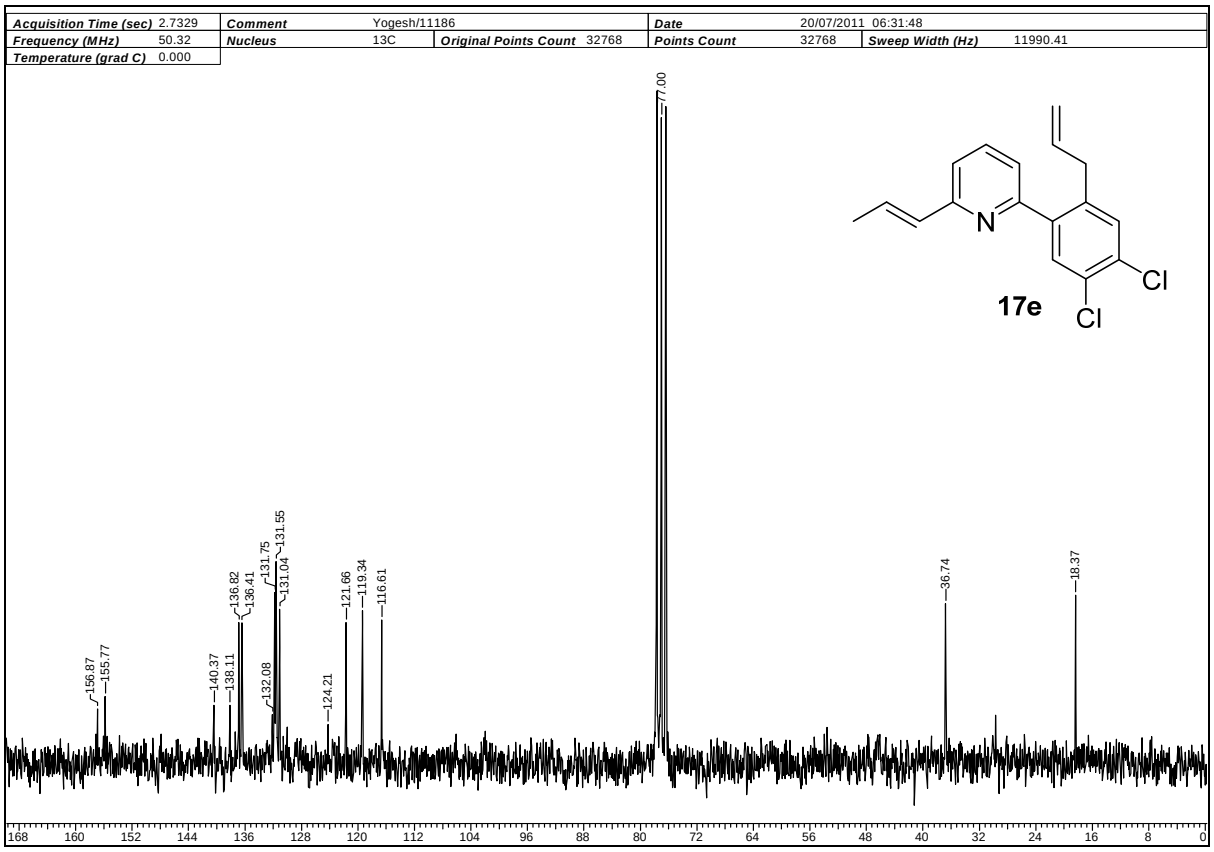
^{1}H NMR Spectrum of 17d in $CDCl_3$



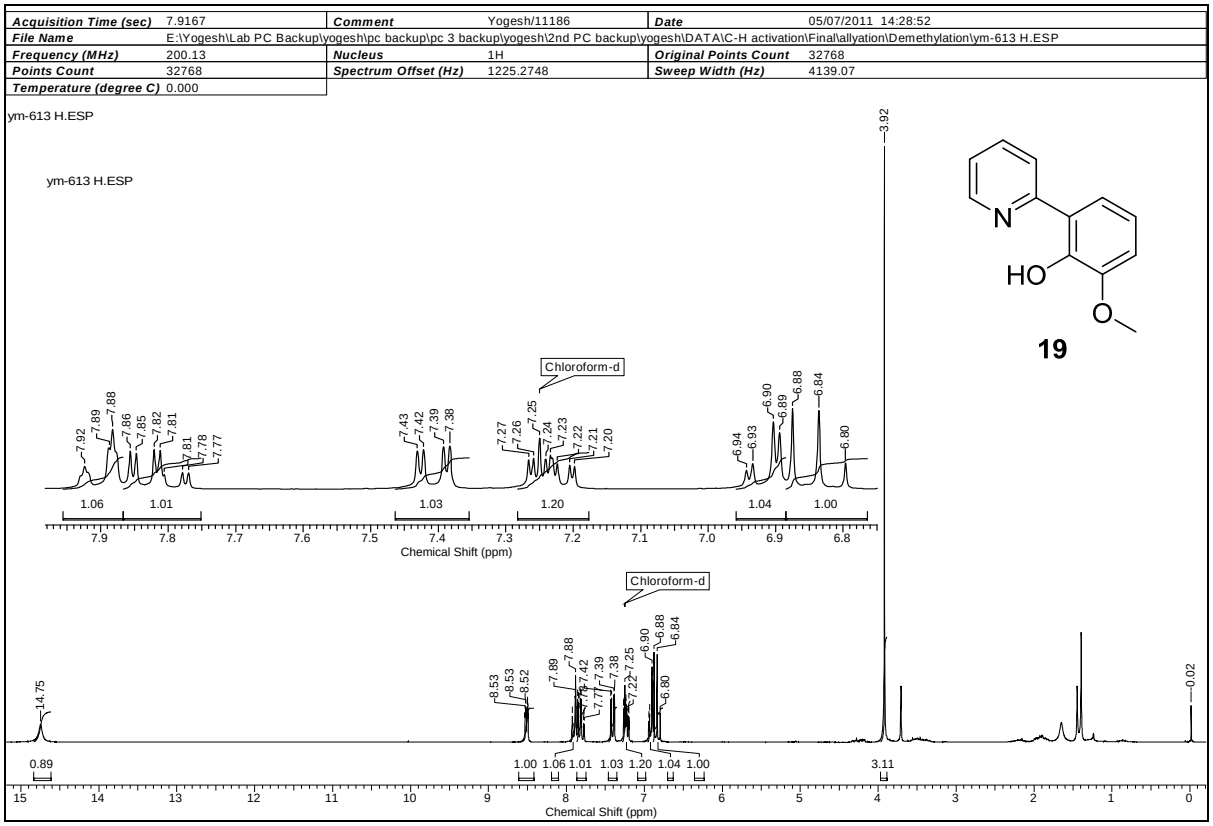
^{13}C NMR Spectrum of 17d in $CDCl_3$



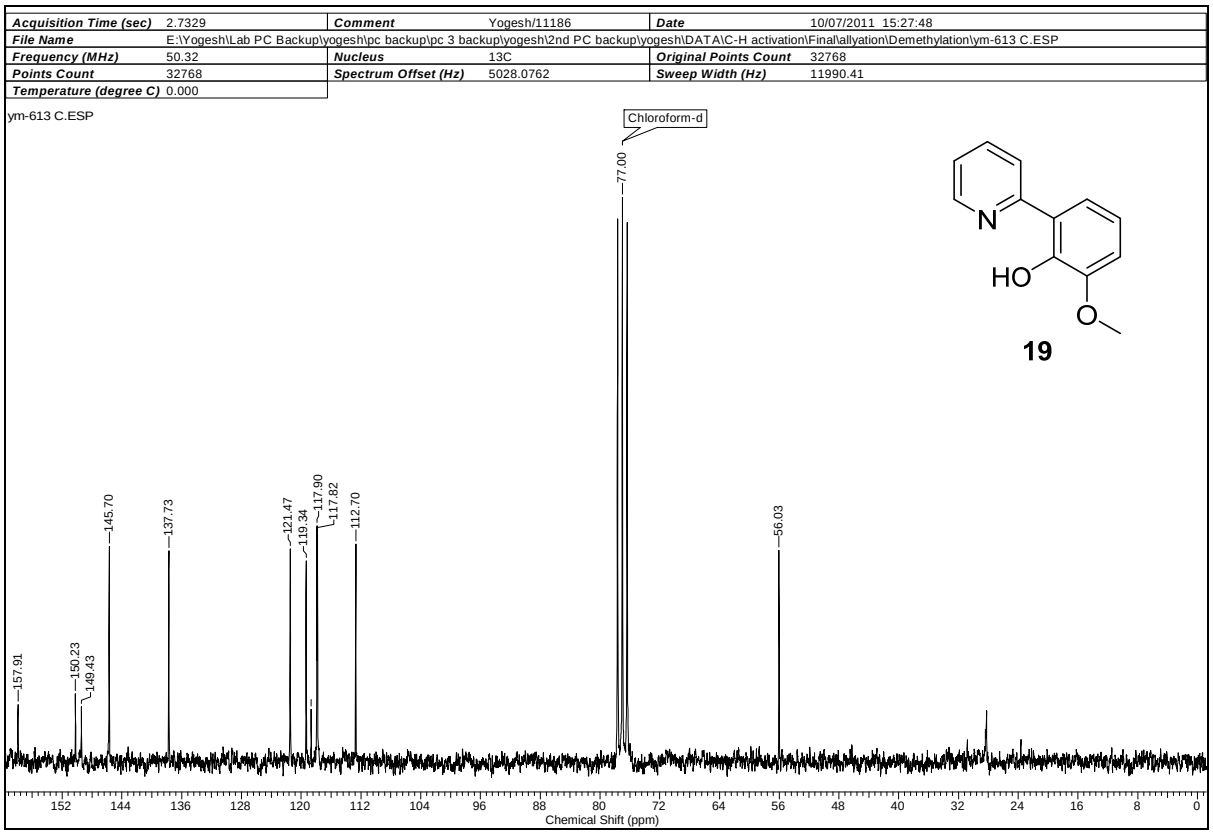
^{1}H NMR Spectrum of 17e in $CDCl_3$



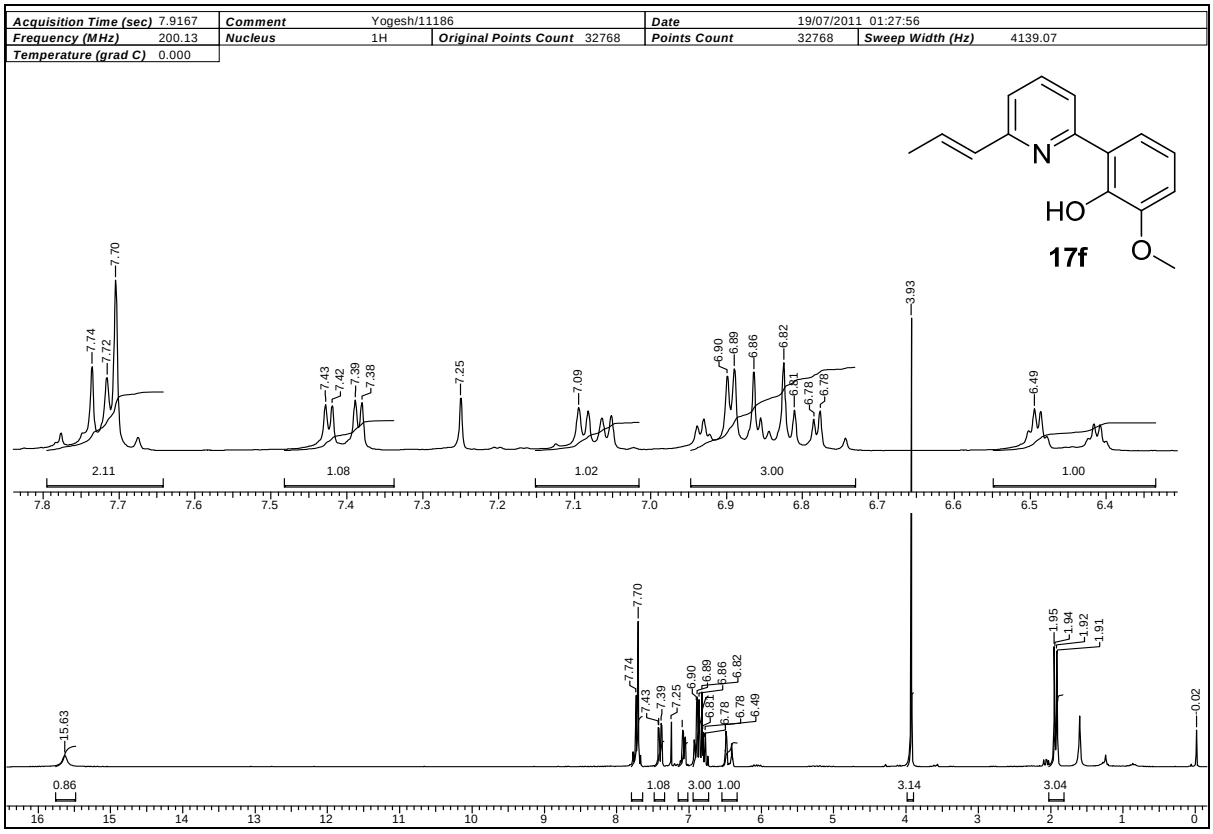
^{13}C NMR Spectrum of 17e in $CDCl_3$



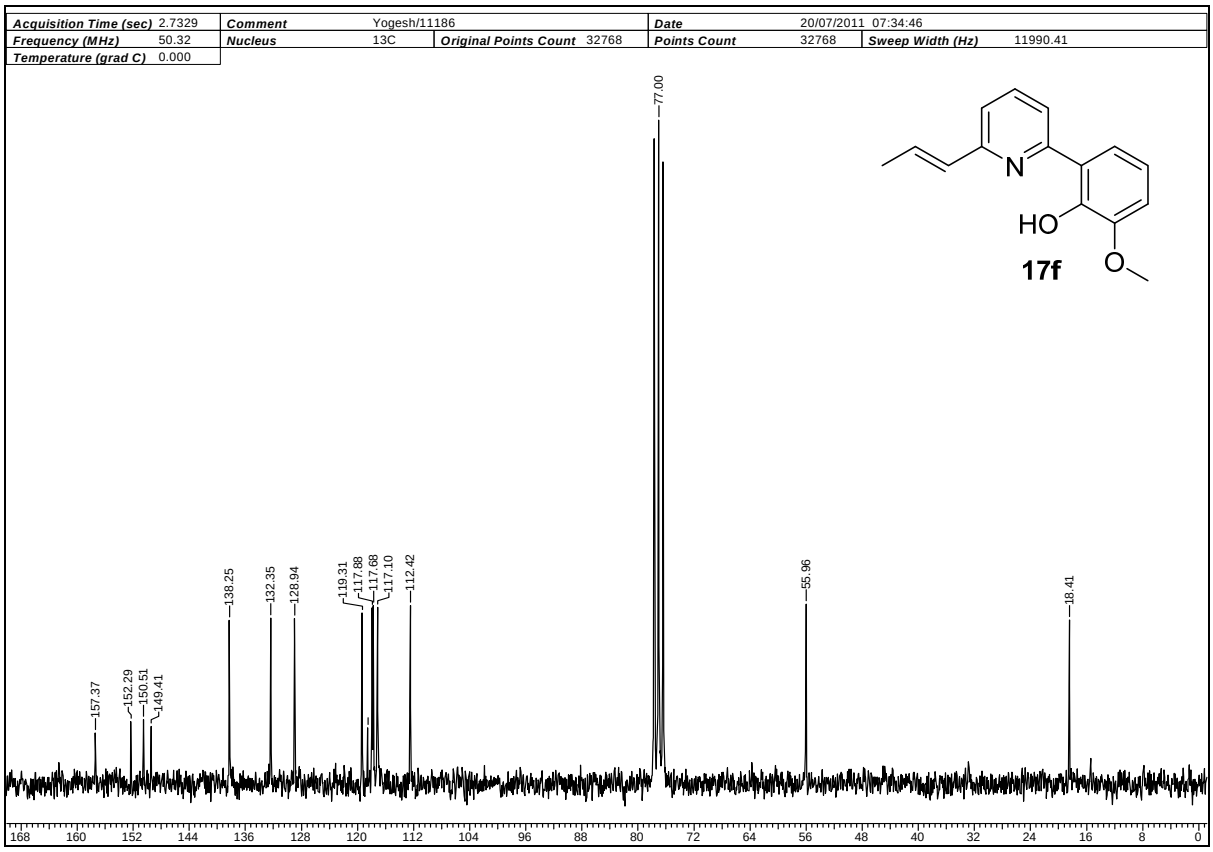
^{1}H NMR Spectrum of 19 in $CDCl_3$



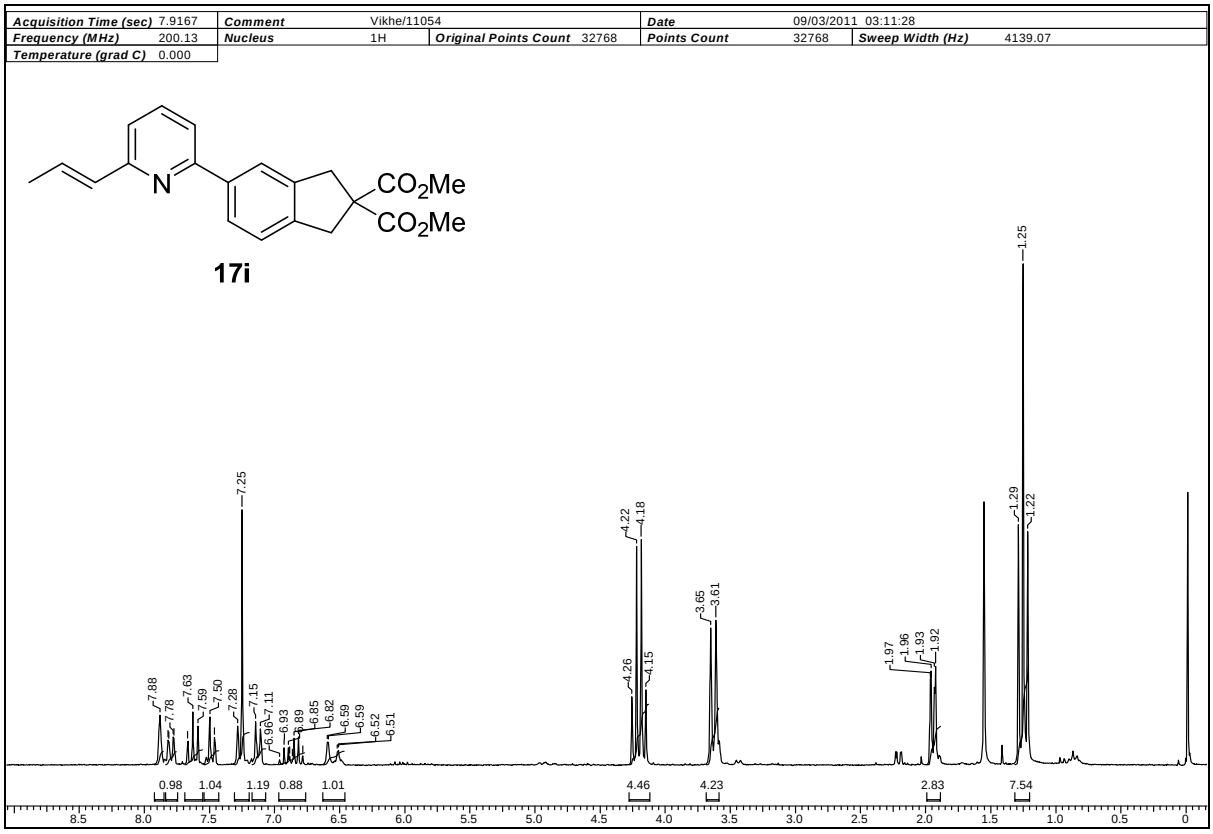
^{13}C NMR Spectrum of 19 in $CDCl_3$



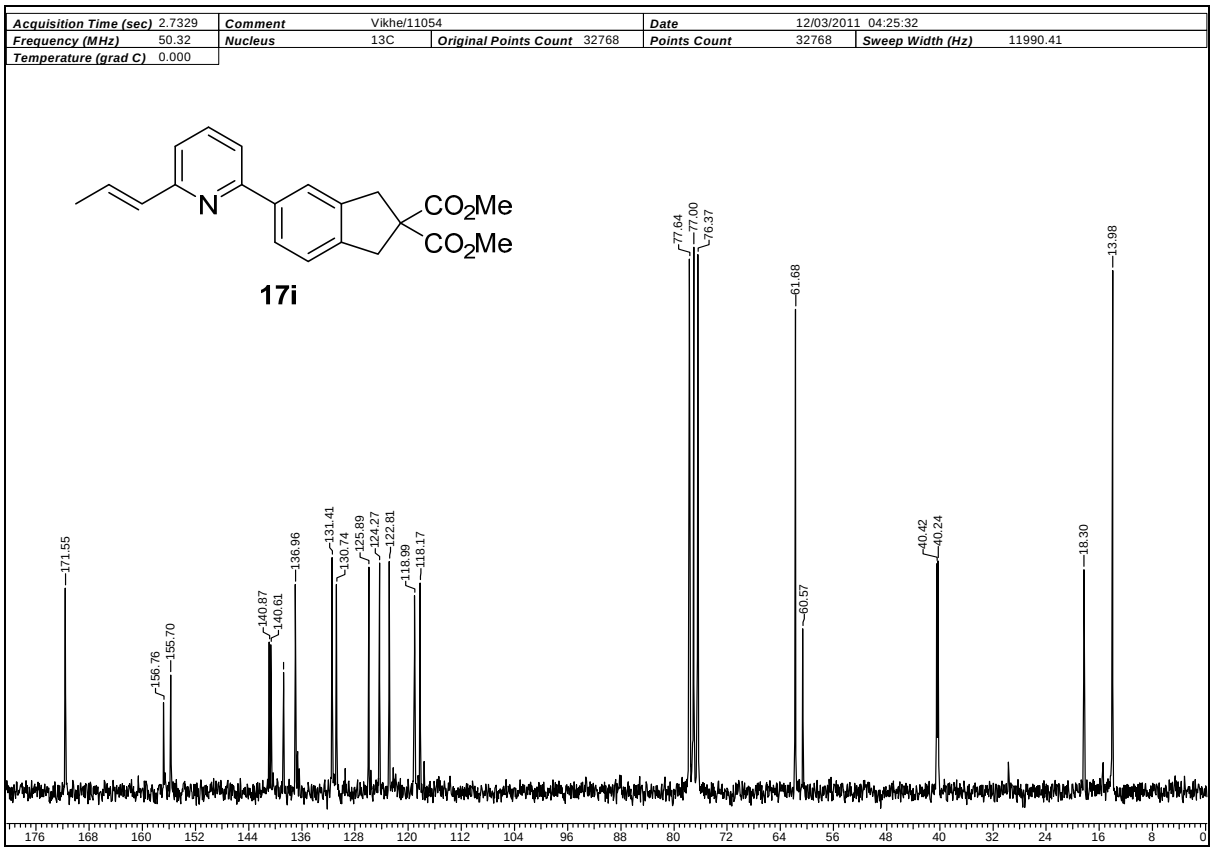
^{1}H NMR Spectrum of 17f in $CDCl_3$



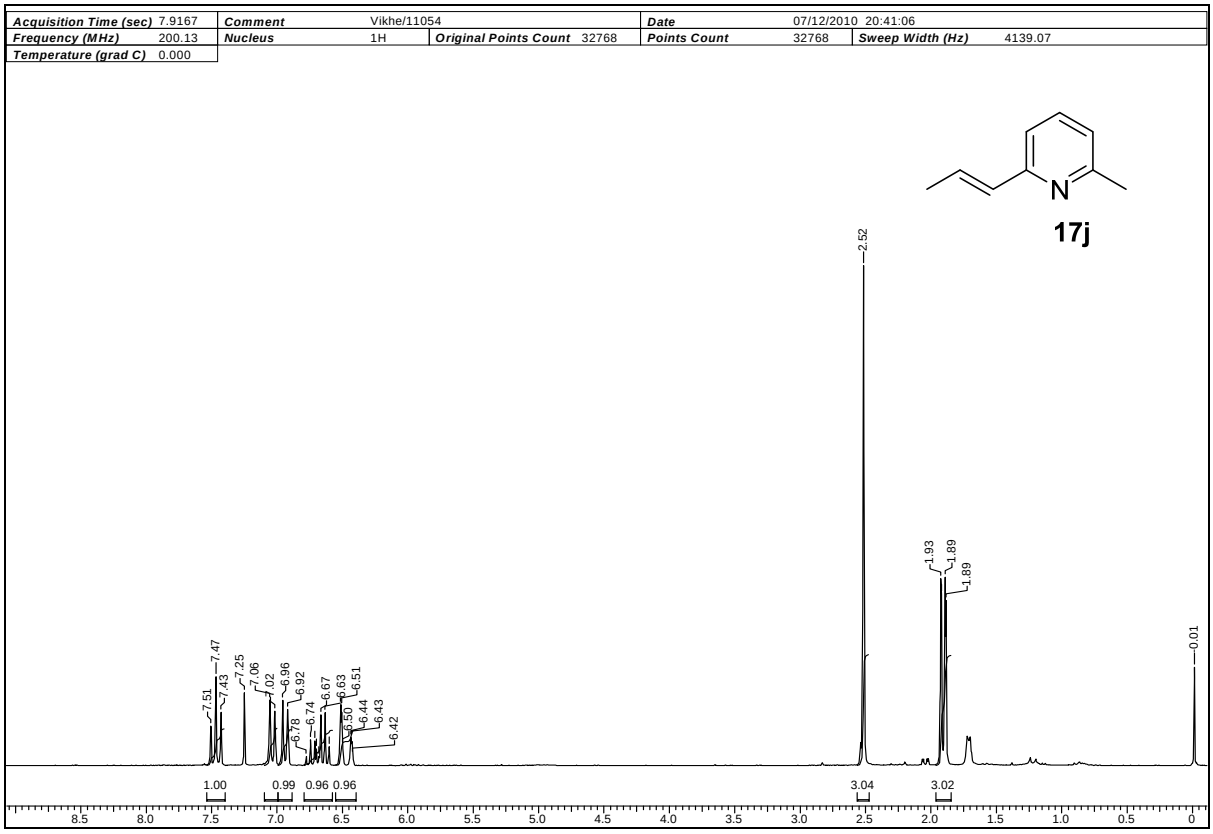
^{13}C NMR Spectrum of 17f in $CDCl_3$



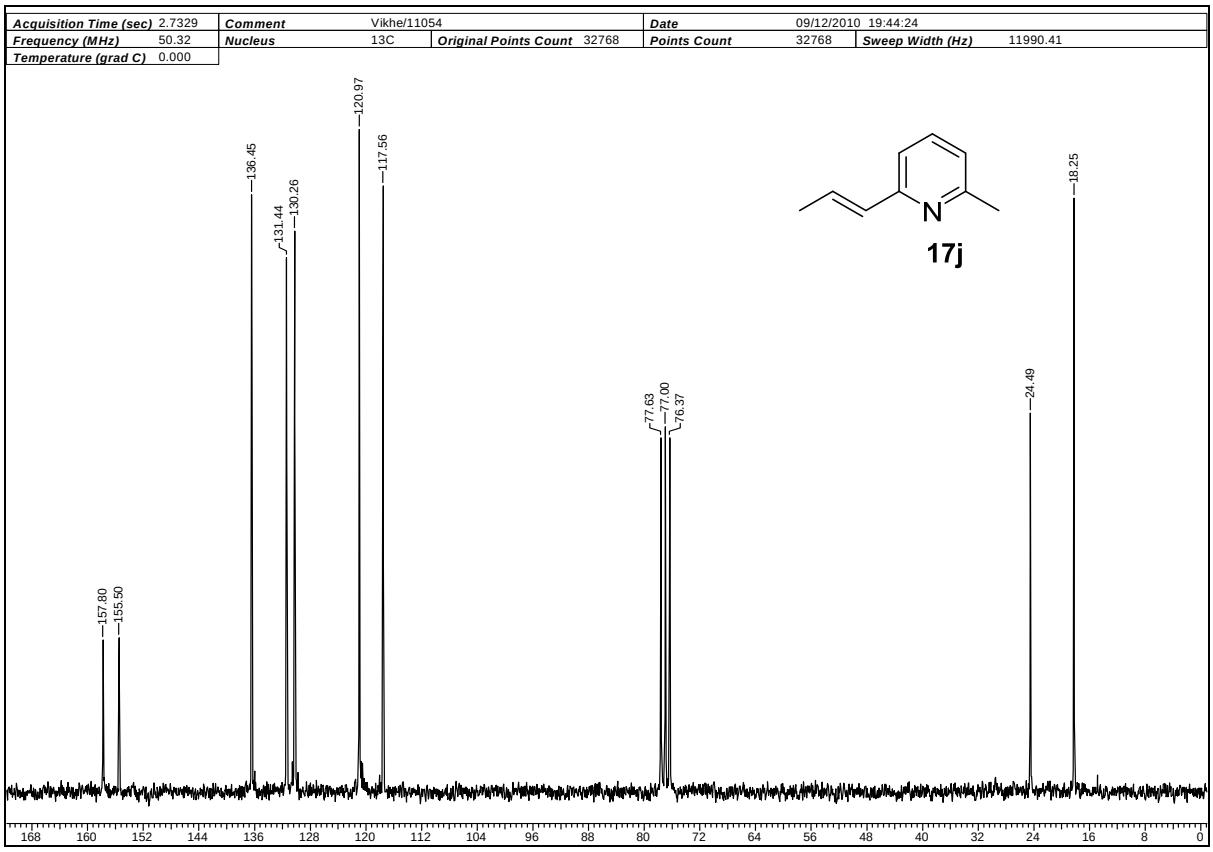
^{1}H NMR Spectrum of 17i in $CDCl_3$



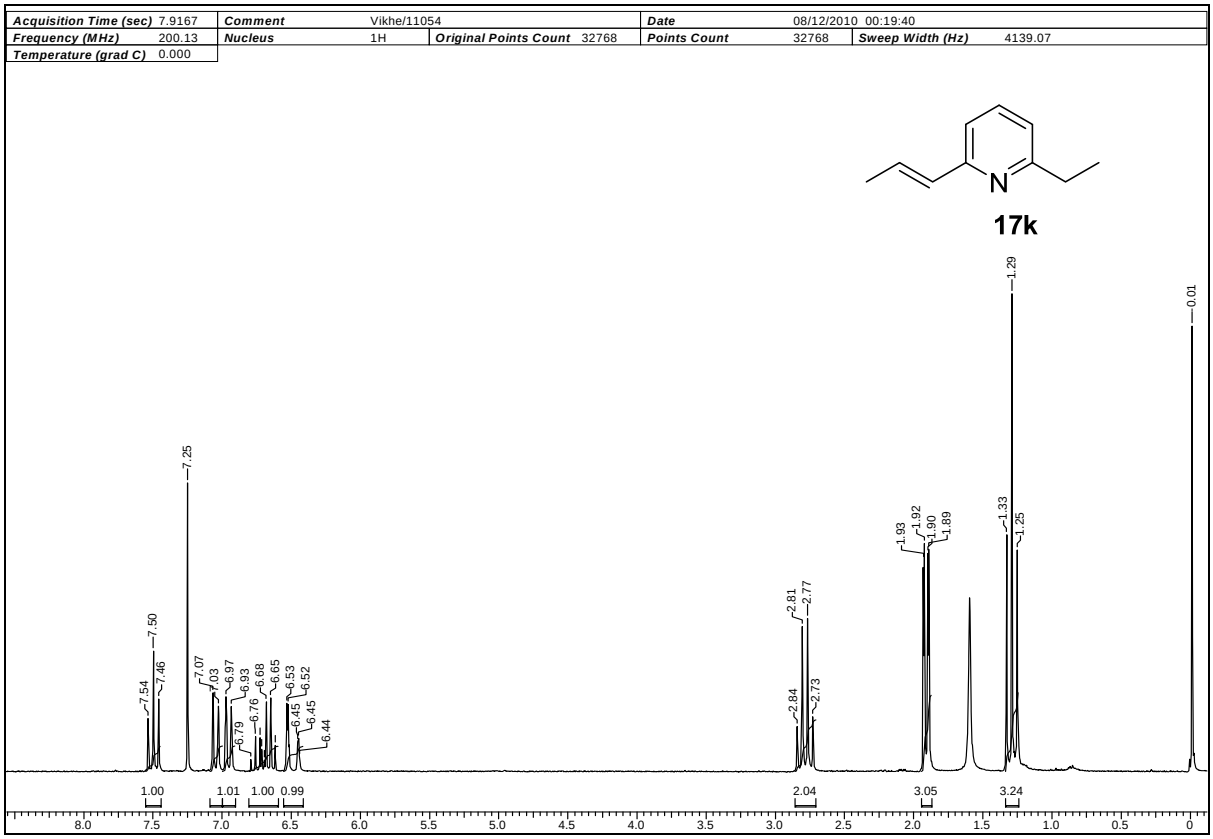
^{13}C NMR Spectrum of 17i in $CDCl_3$



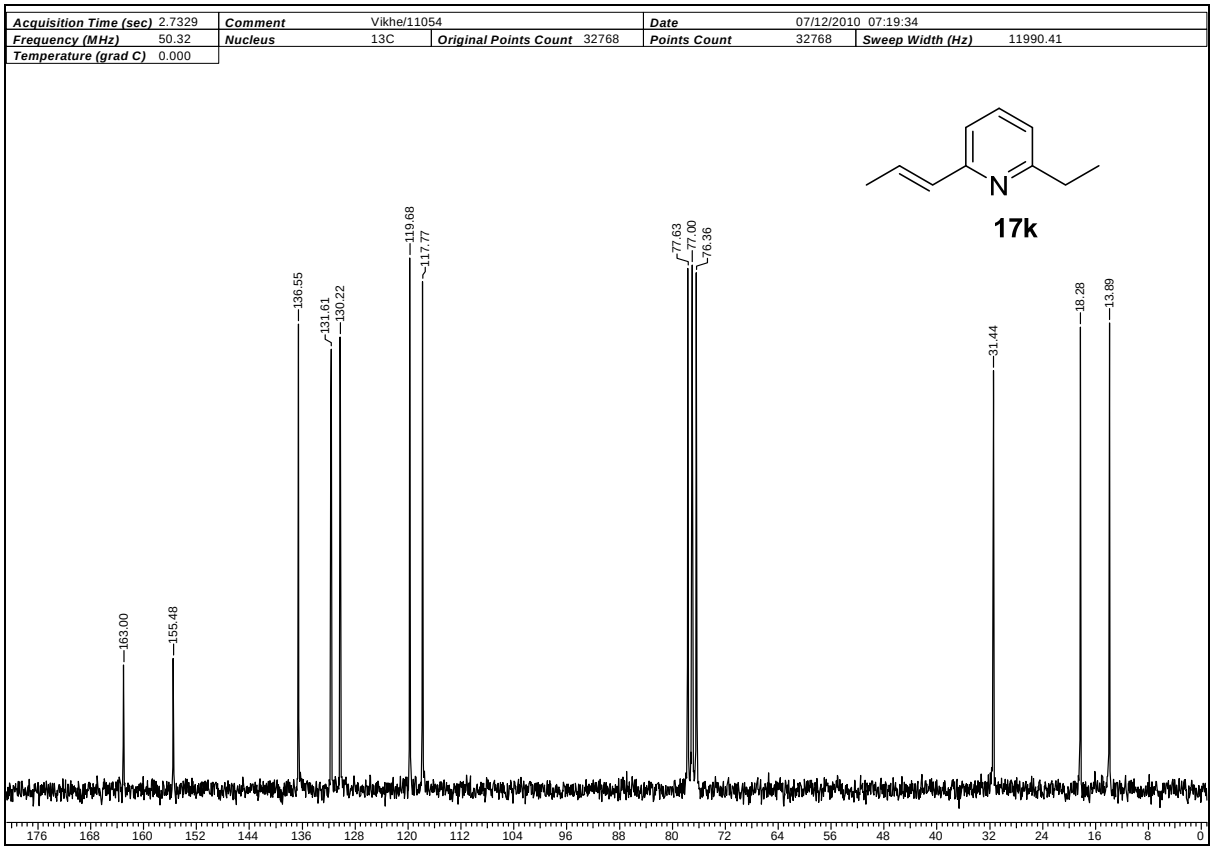
^{1}H NMR Spectrum of 17j in $CDCl_3$



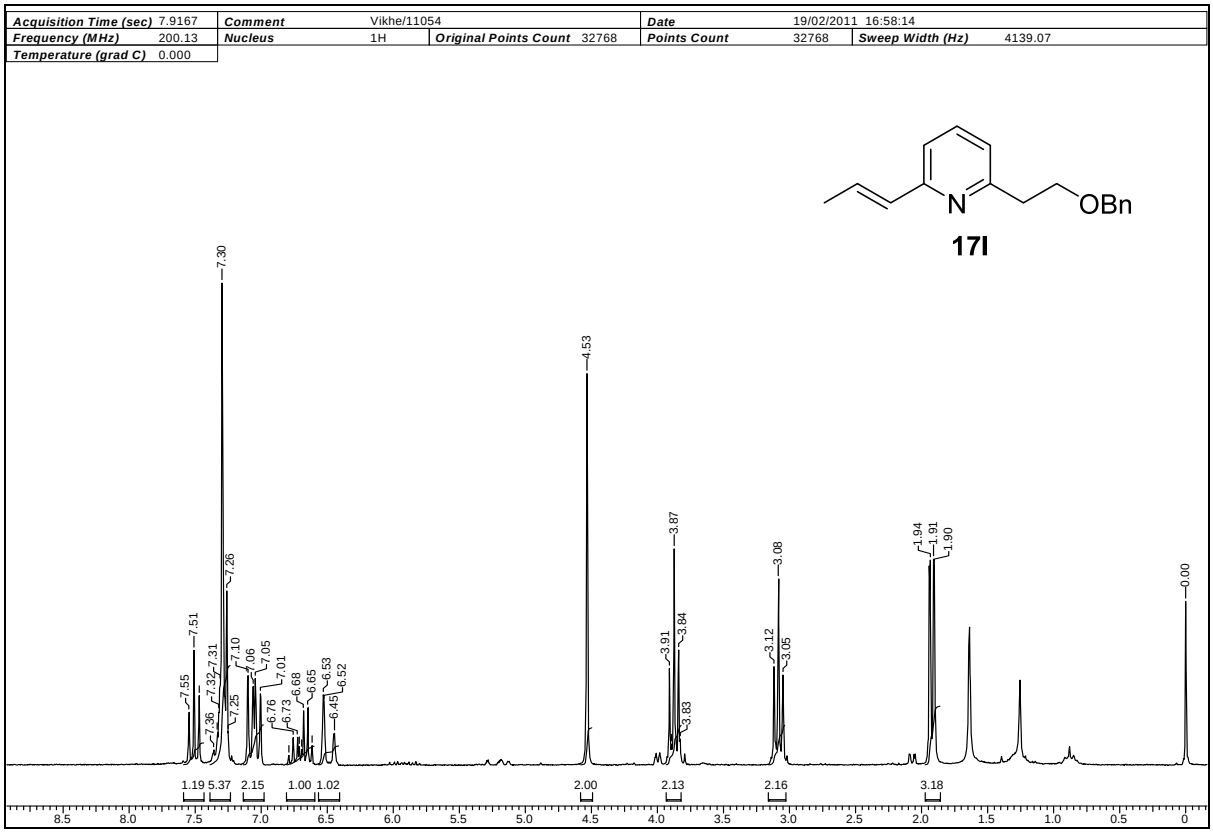
^{13}C NMR Spectrum of 17j in $CDCl_3$



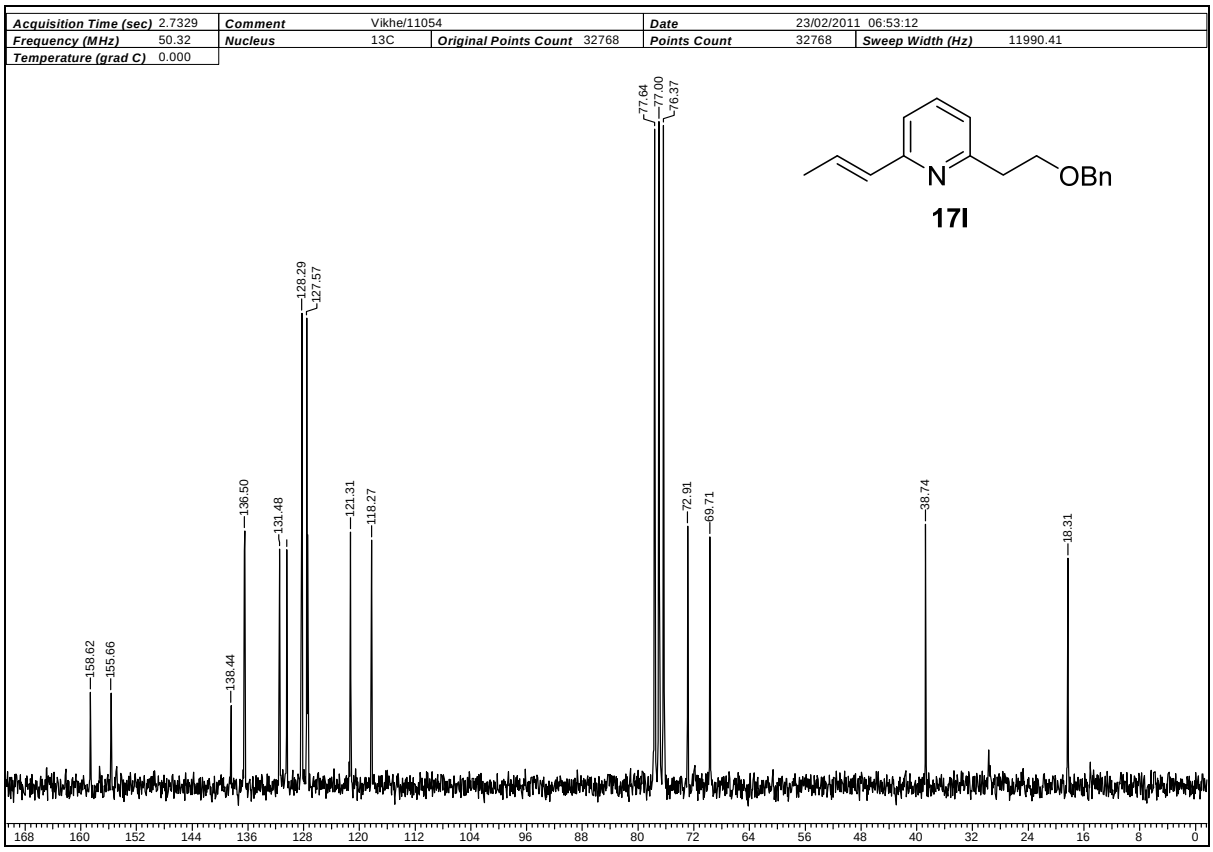
^{1}H NMR Spectrum of 17k in $CDCl_3$



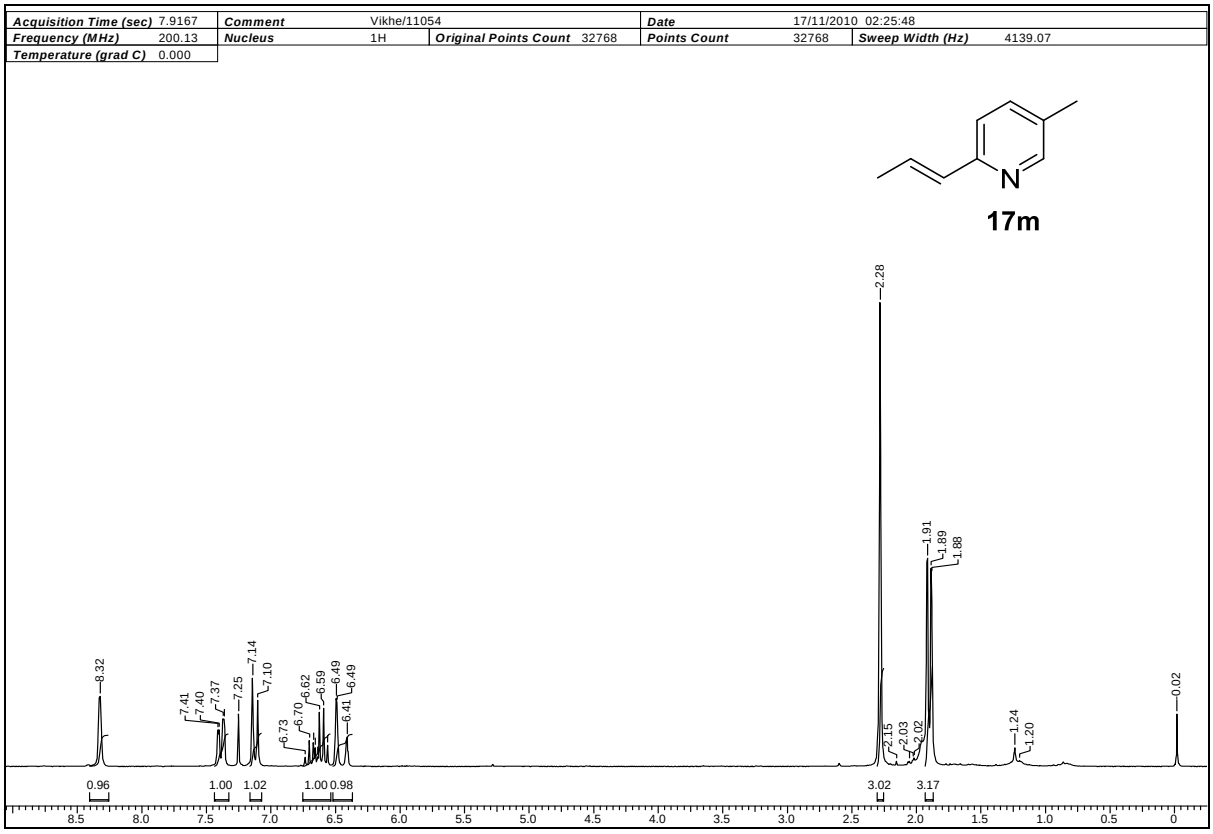
^{13}C NMR Spectrum of 17k in $CDCl_3$



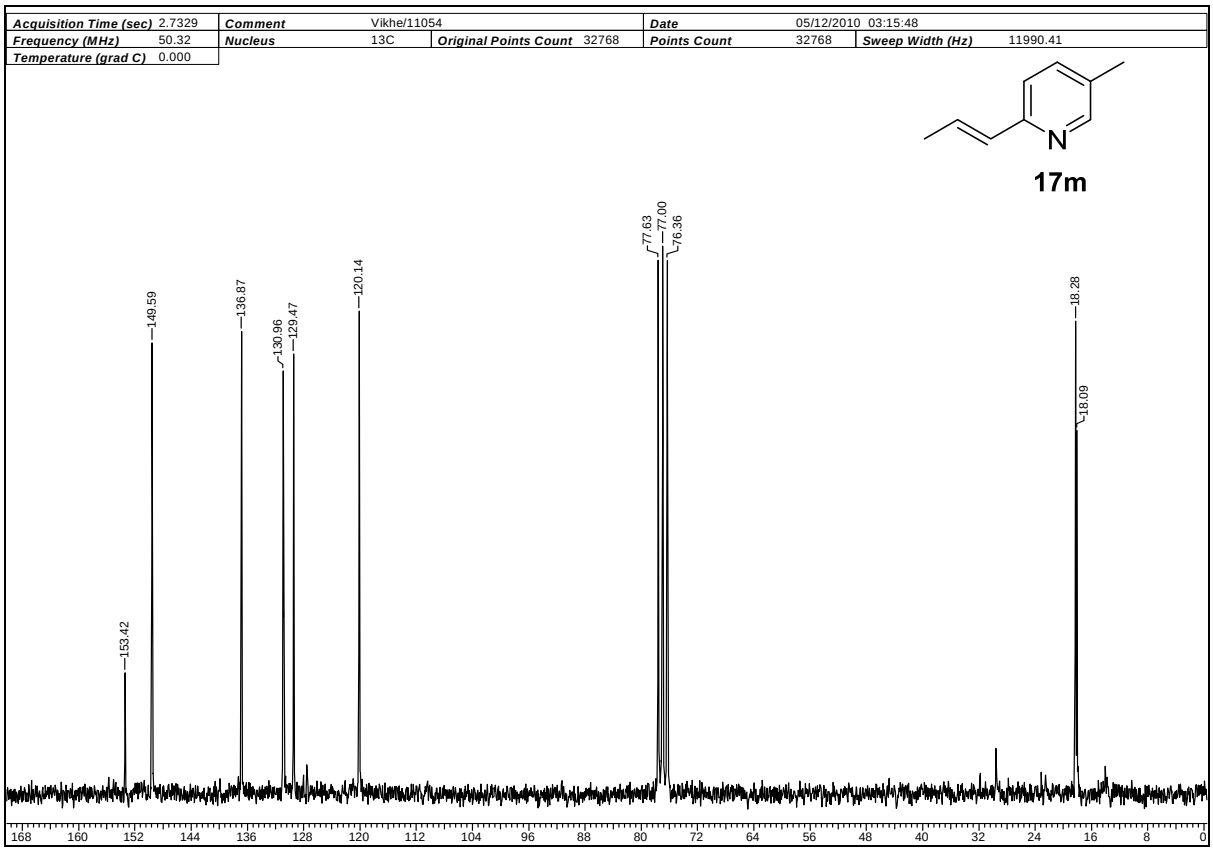
^{1}H NMR Spectrum of 17l in $CDCl_3$



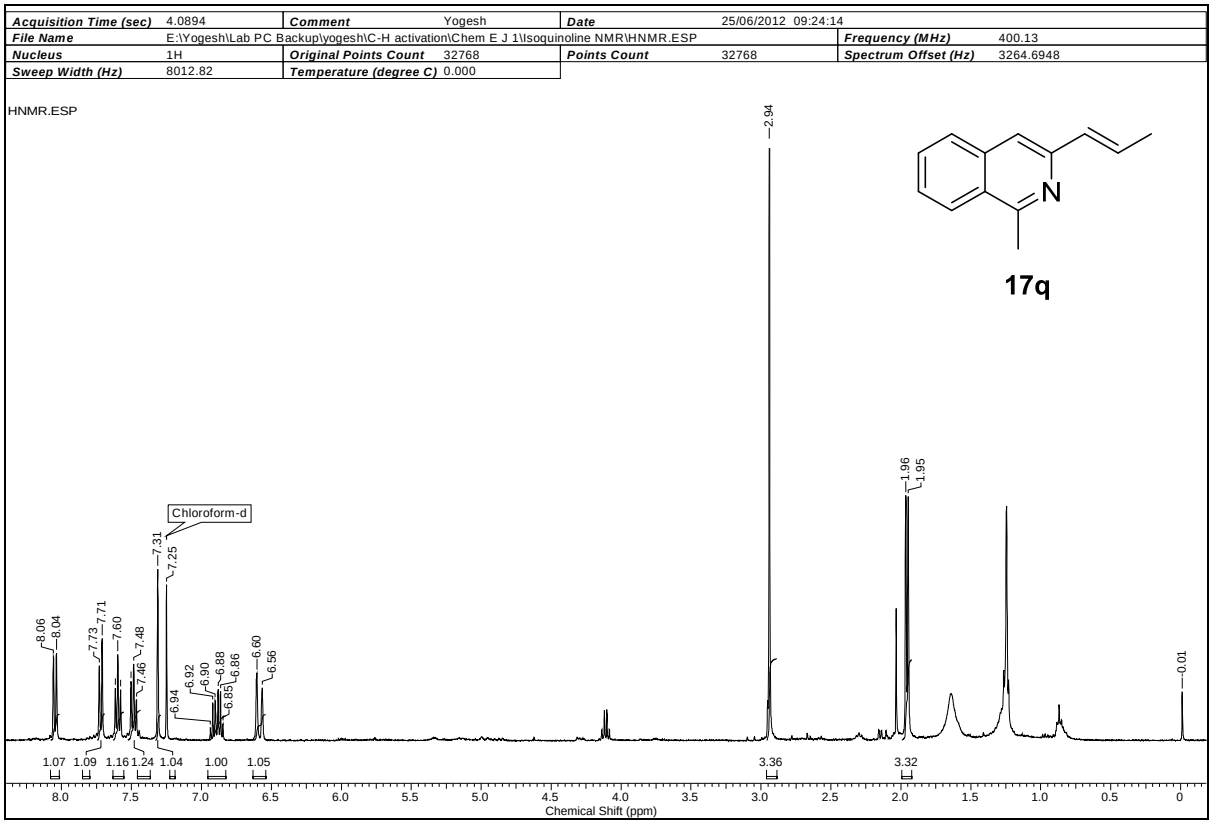
^{13}C NMR Spectrum of 17l in $CDCl_3$



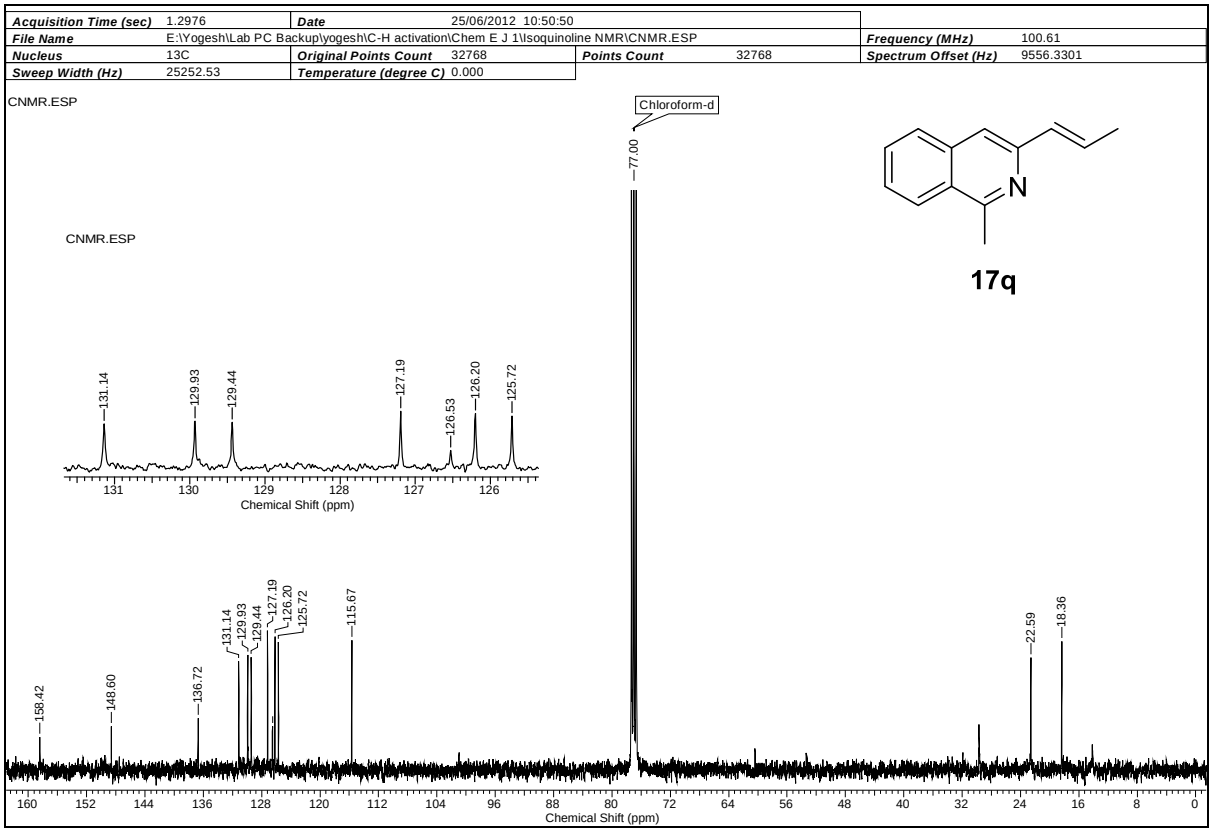
^{1}H NMR Spectrum of 17m in $CDCl_3$



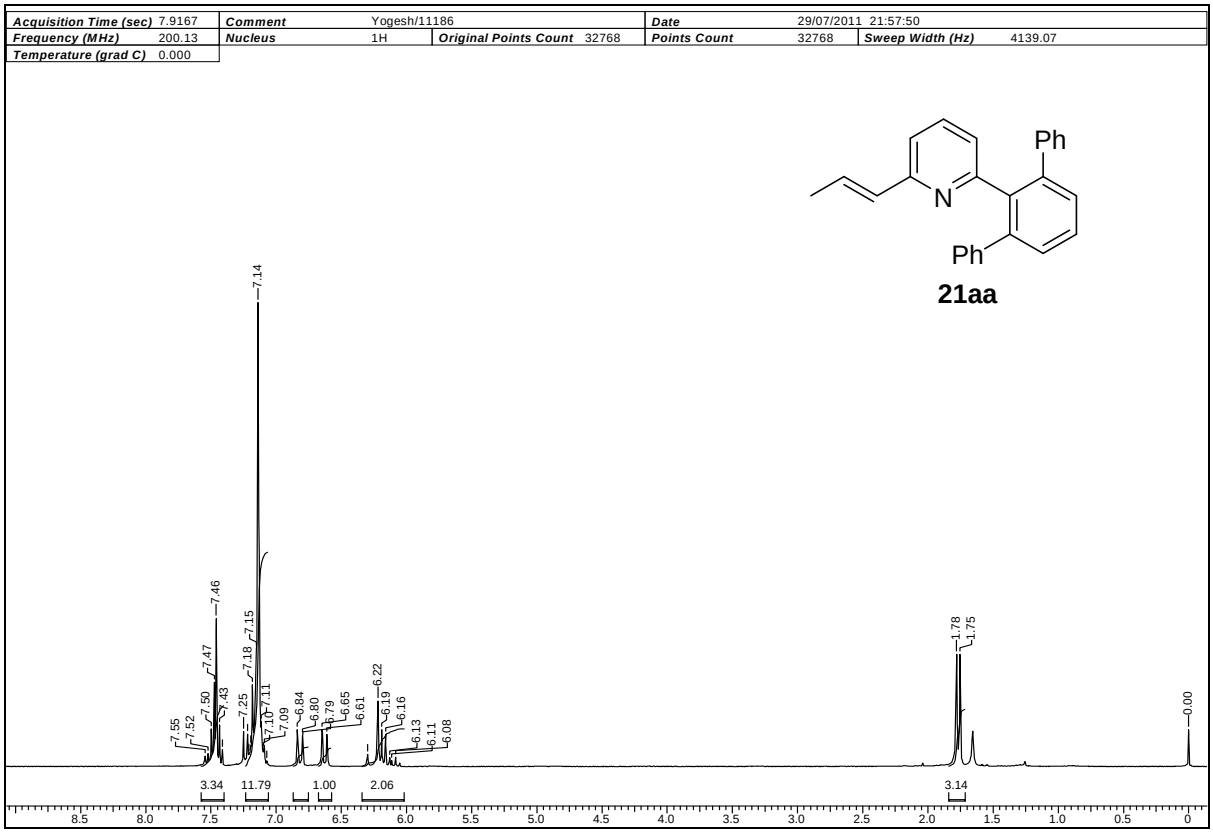
^{13}C NMR Spectrum of 17m in $CDCl_3$



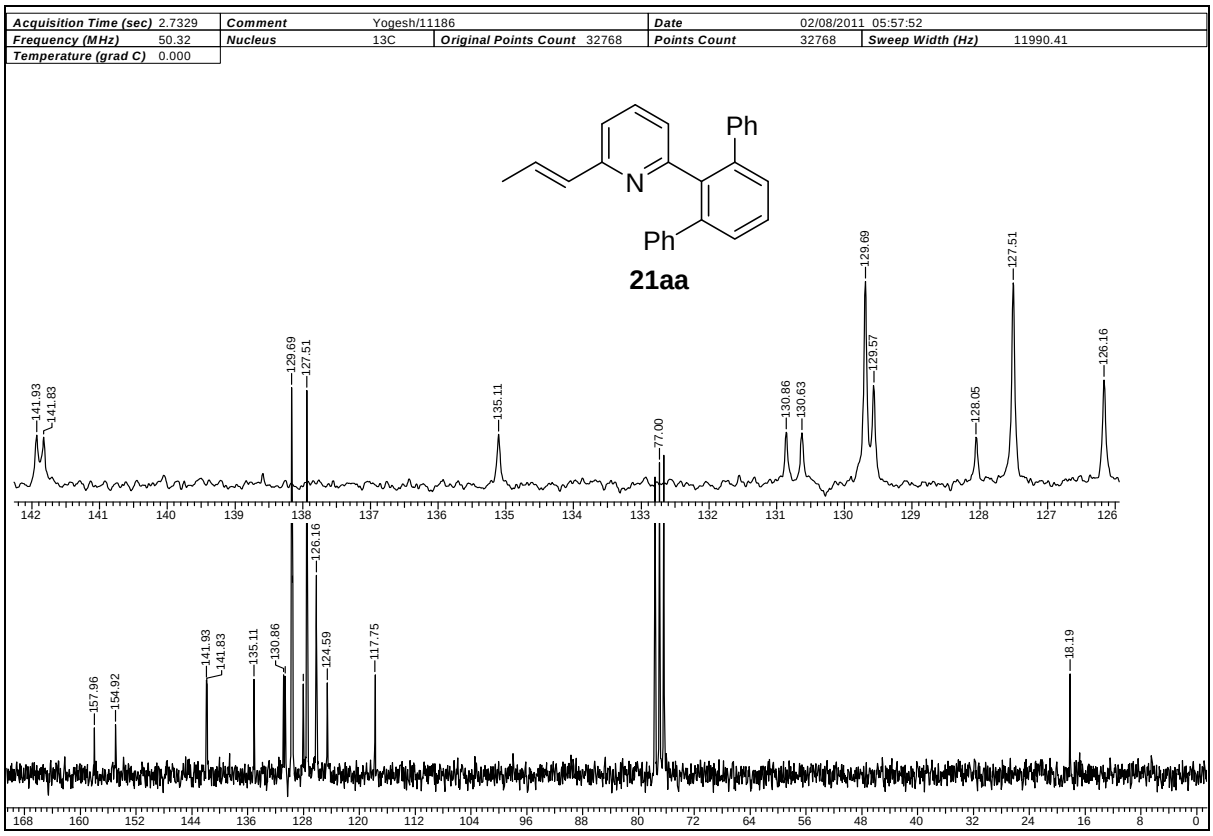
^{1}H NMR Spectrum of 17q in $CDCl_3$



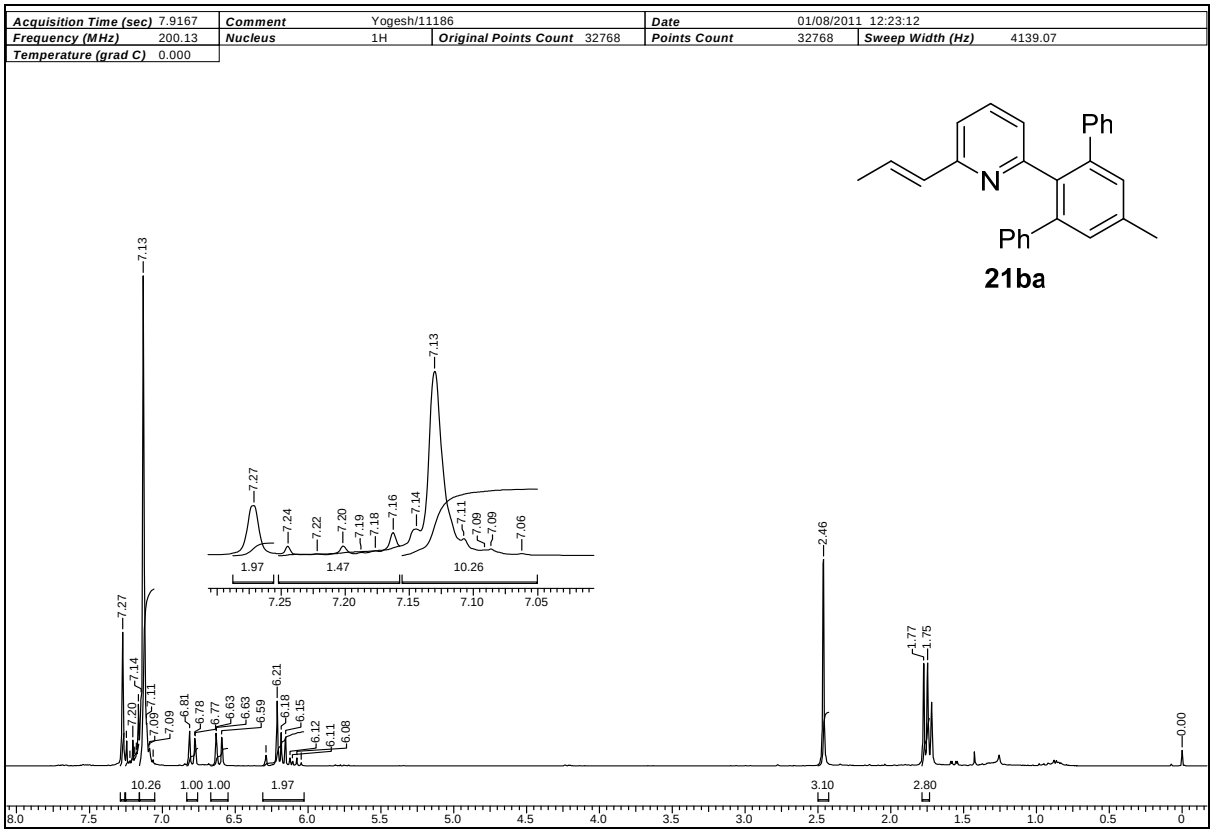
^{13}C NMR Spectrum of 17q in $CDCl_3$



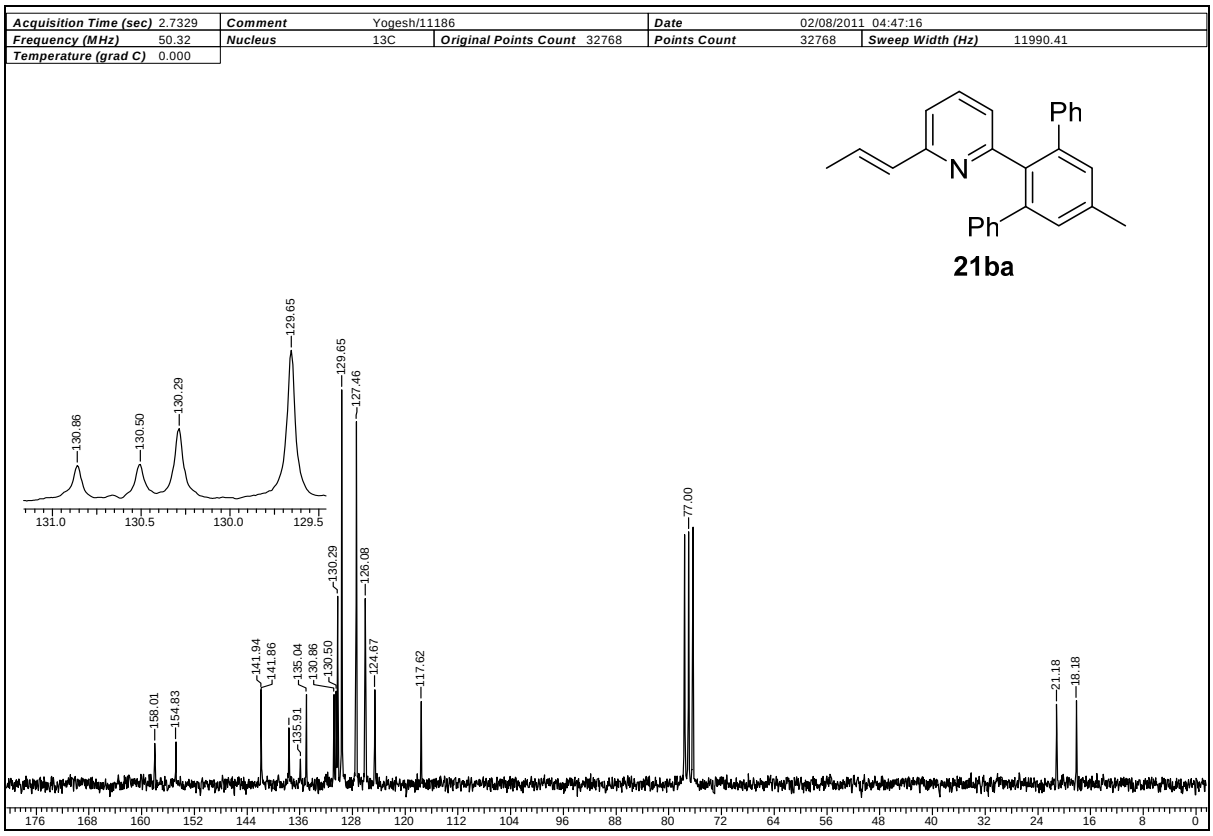
^{1}H NMR Spectrum of 21aa in $CDCl_3$



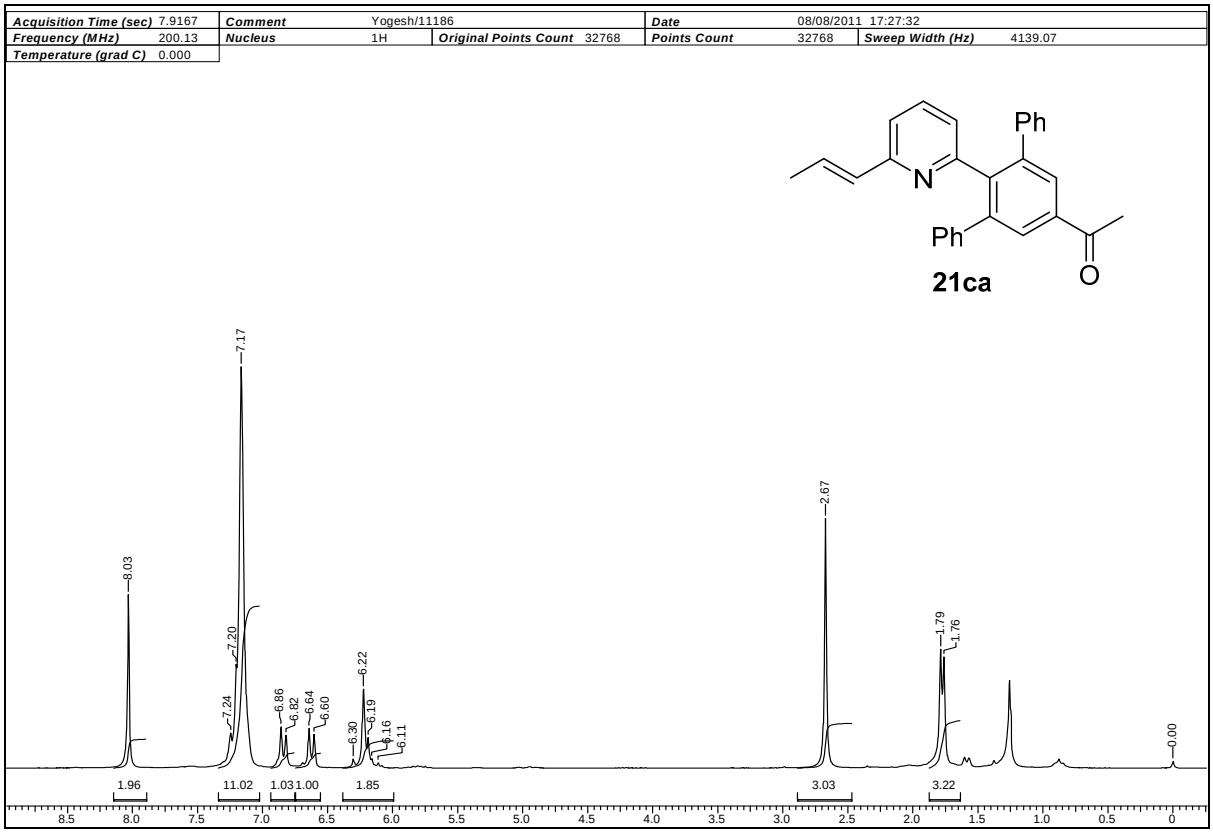
^{13}C NMR Spectrum of 21aa in $CDCl_3$



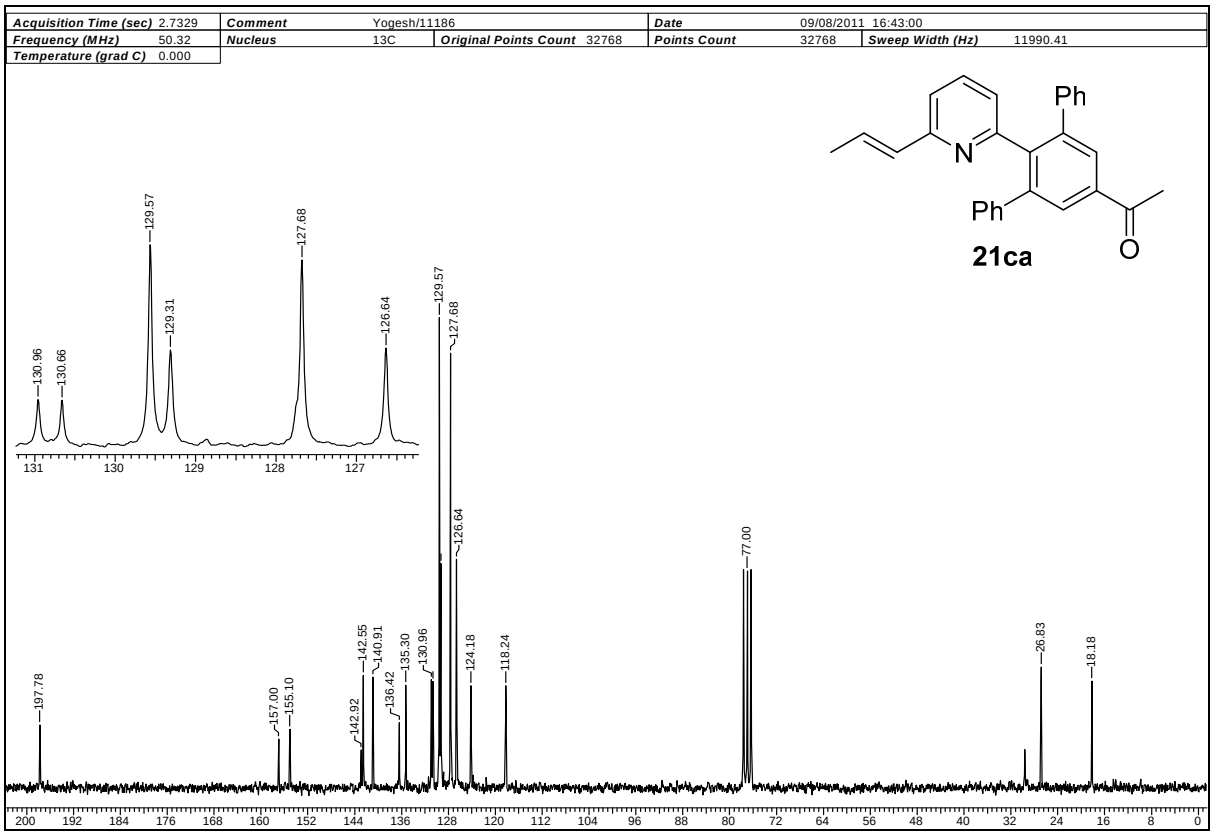
^{1}H NMR Spectrum of 21ba in $CDCl_3$



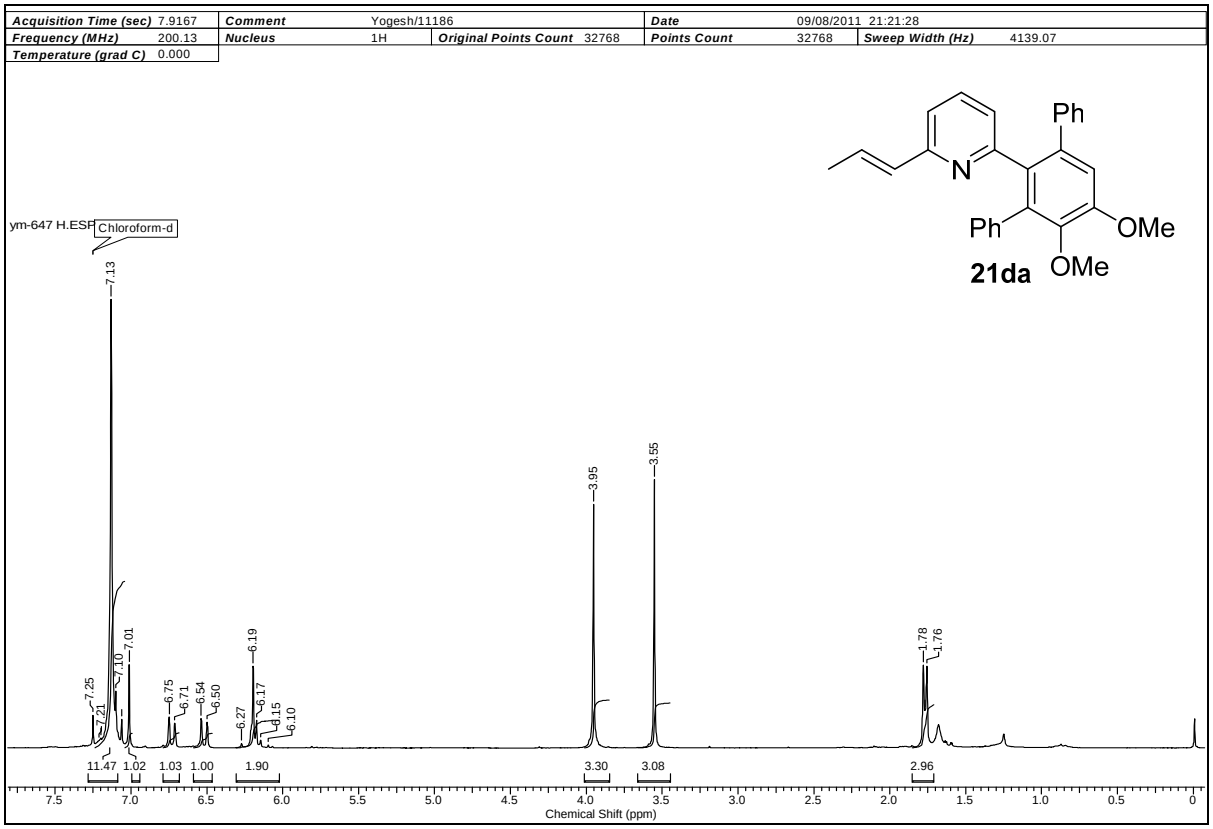
^{13}C NMR Spectrum of 21ba in $CDCl_3$



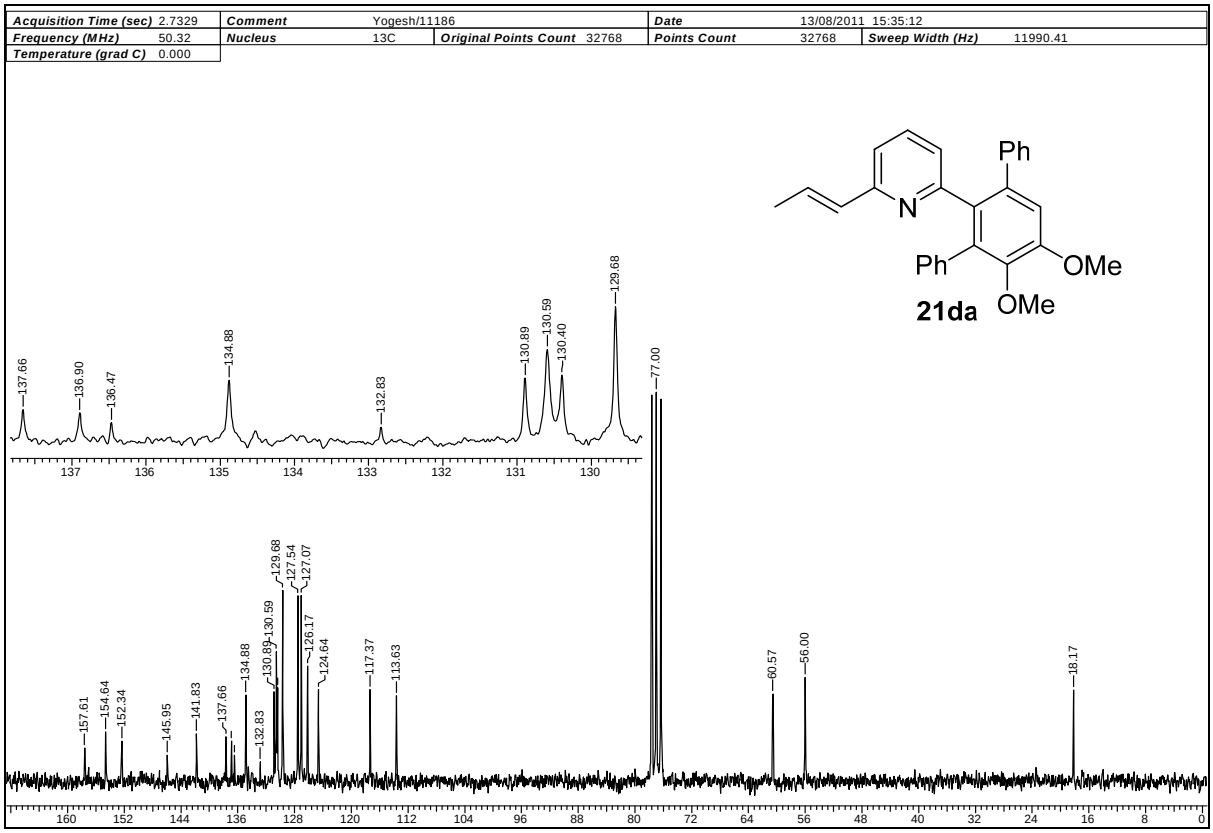
^{1}H NMR Spectrum of 21ca in $CDCl_3$



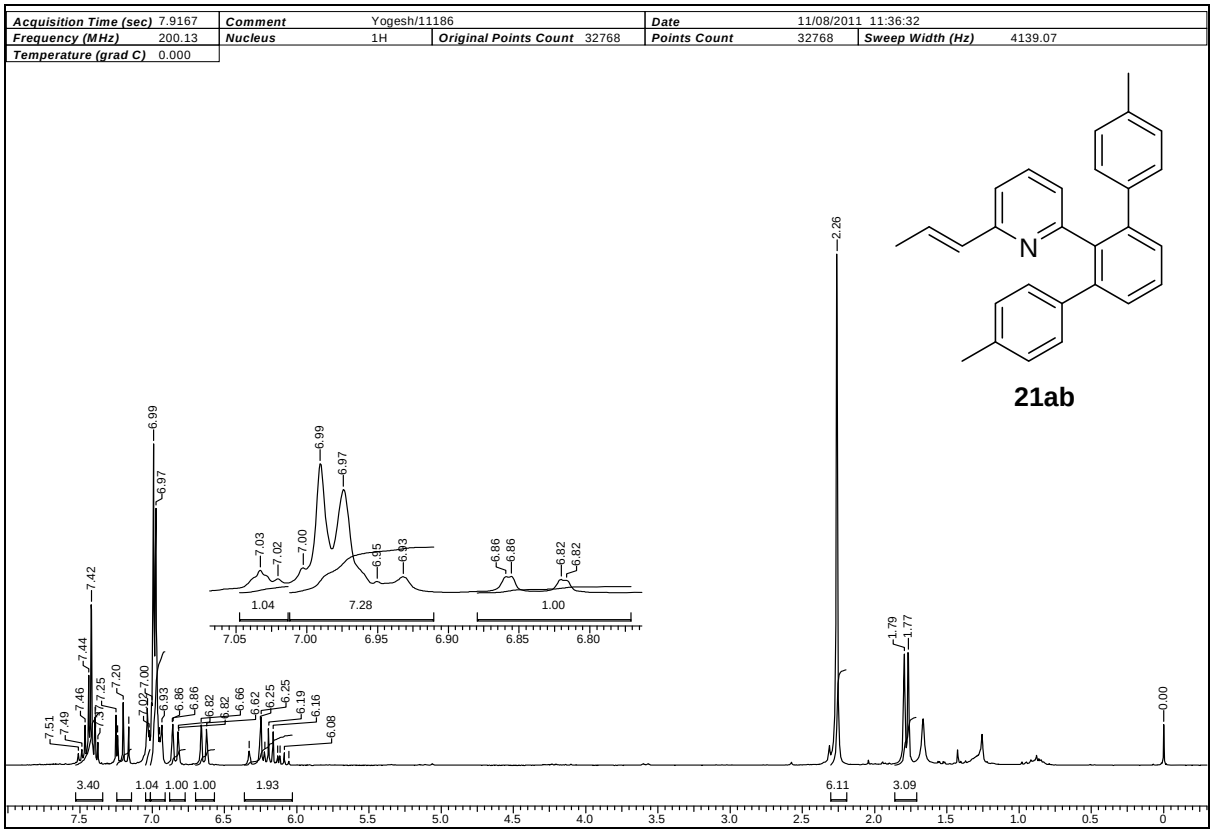
^{13}C NMR Spectrum of 21ca in $CDCl_3$



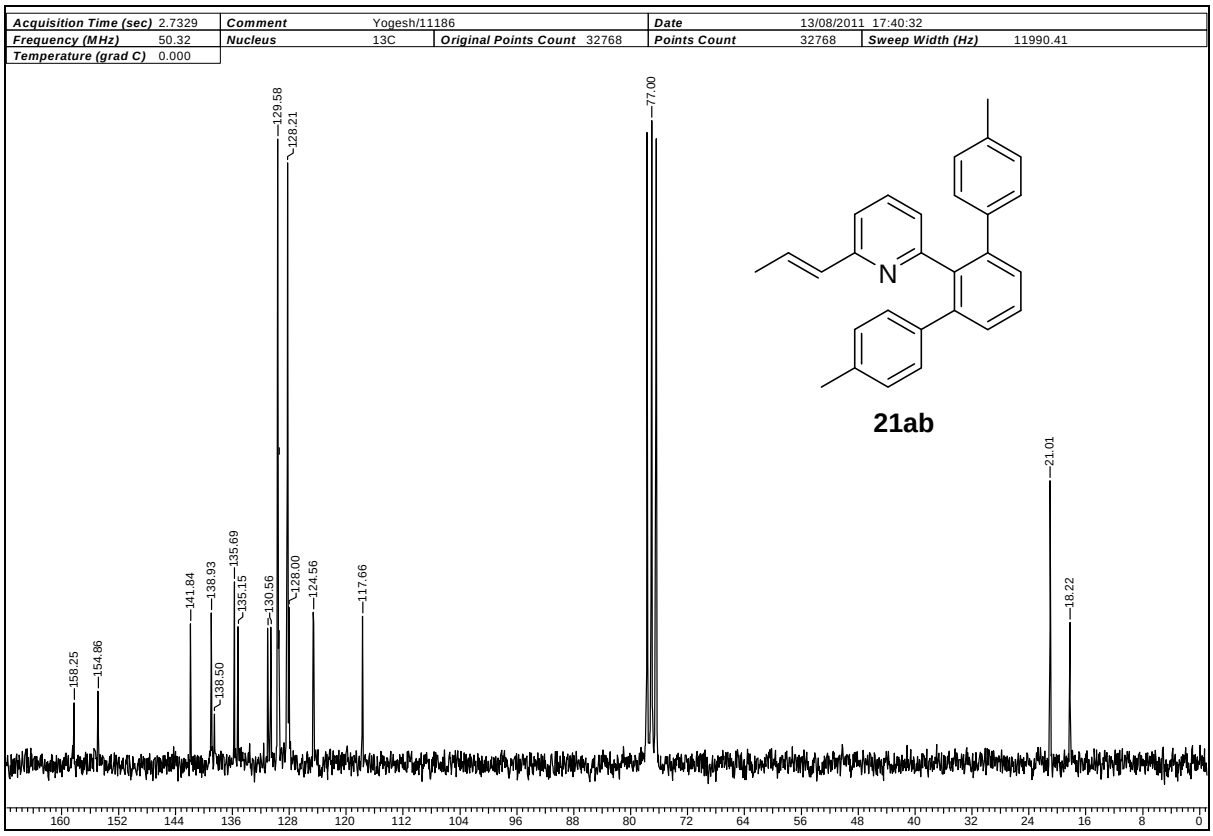
^{1}H NMR Spectrum of 21da in $CDCl_3$



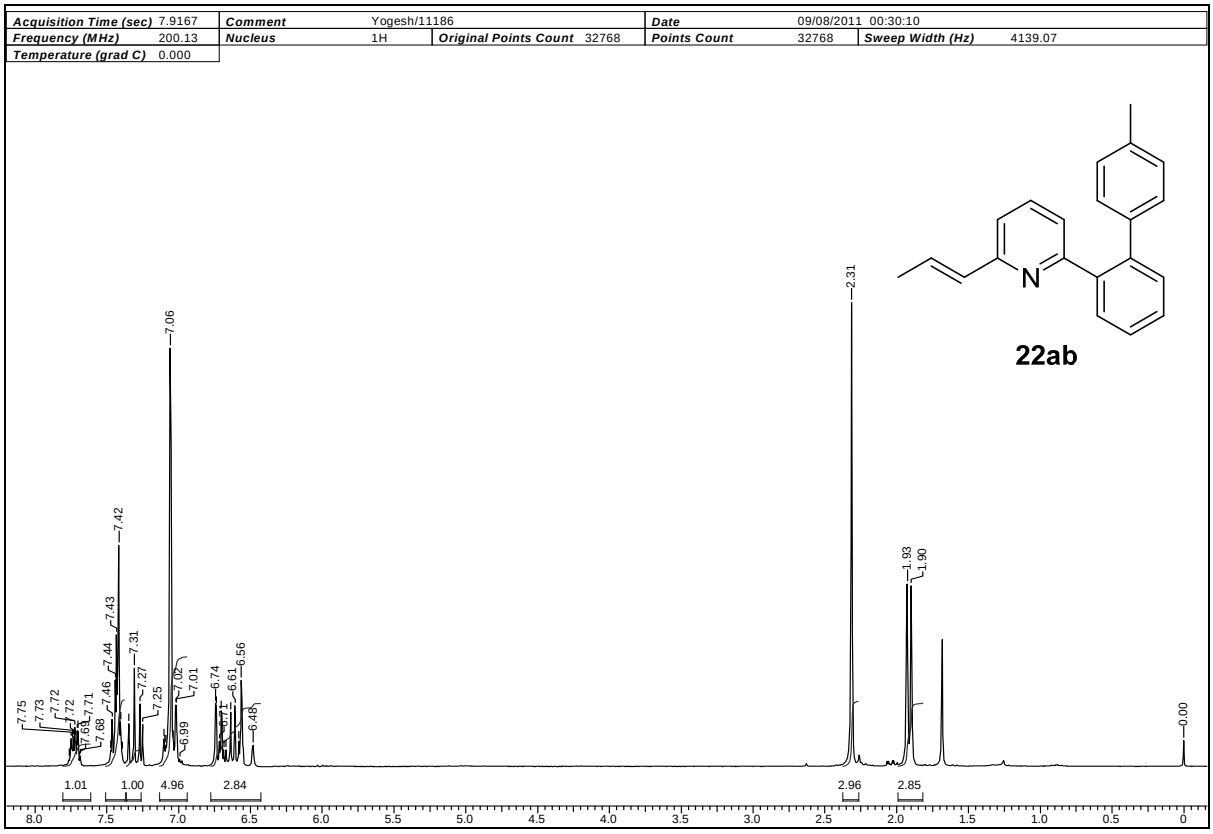
^{13}C NMR Spectrum of 21da in $CDCl_3$



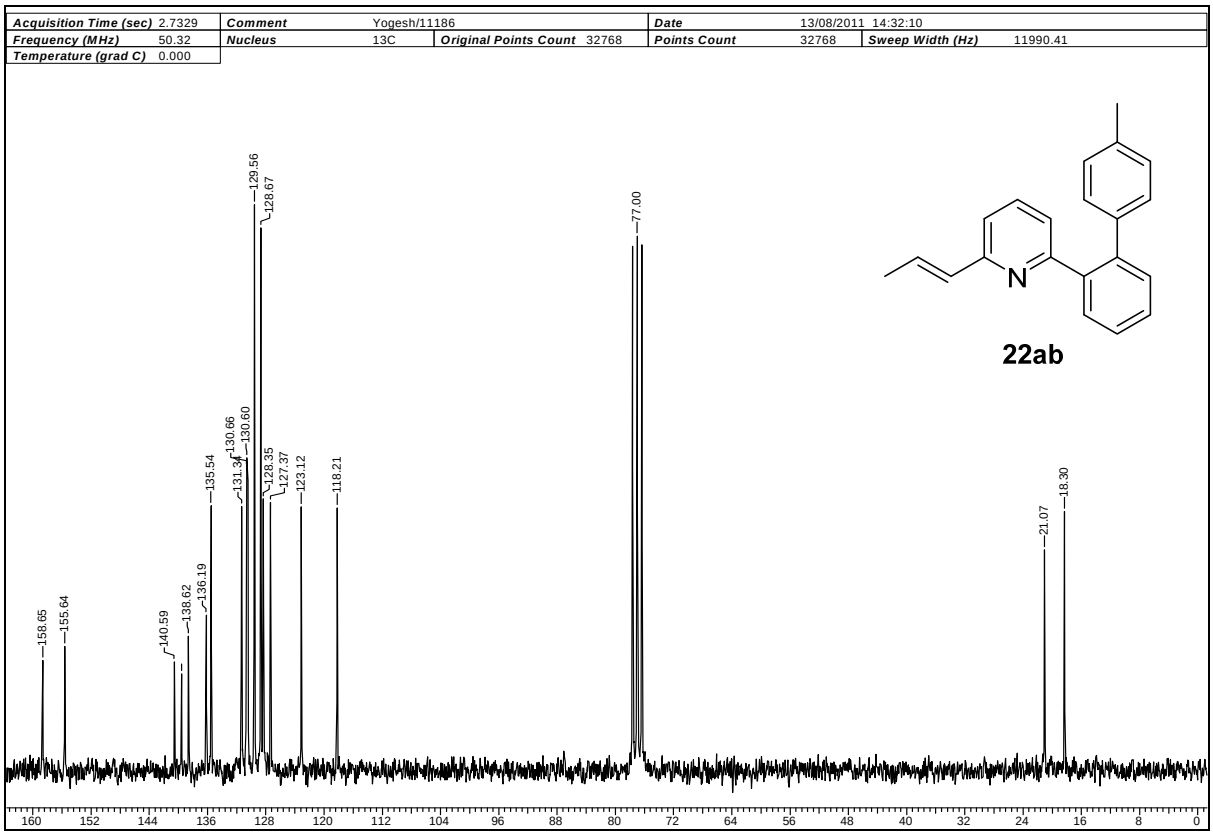
^{1}H NMR Spectrum of 21ab in $CDCl_3$



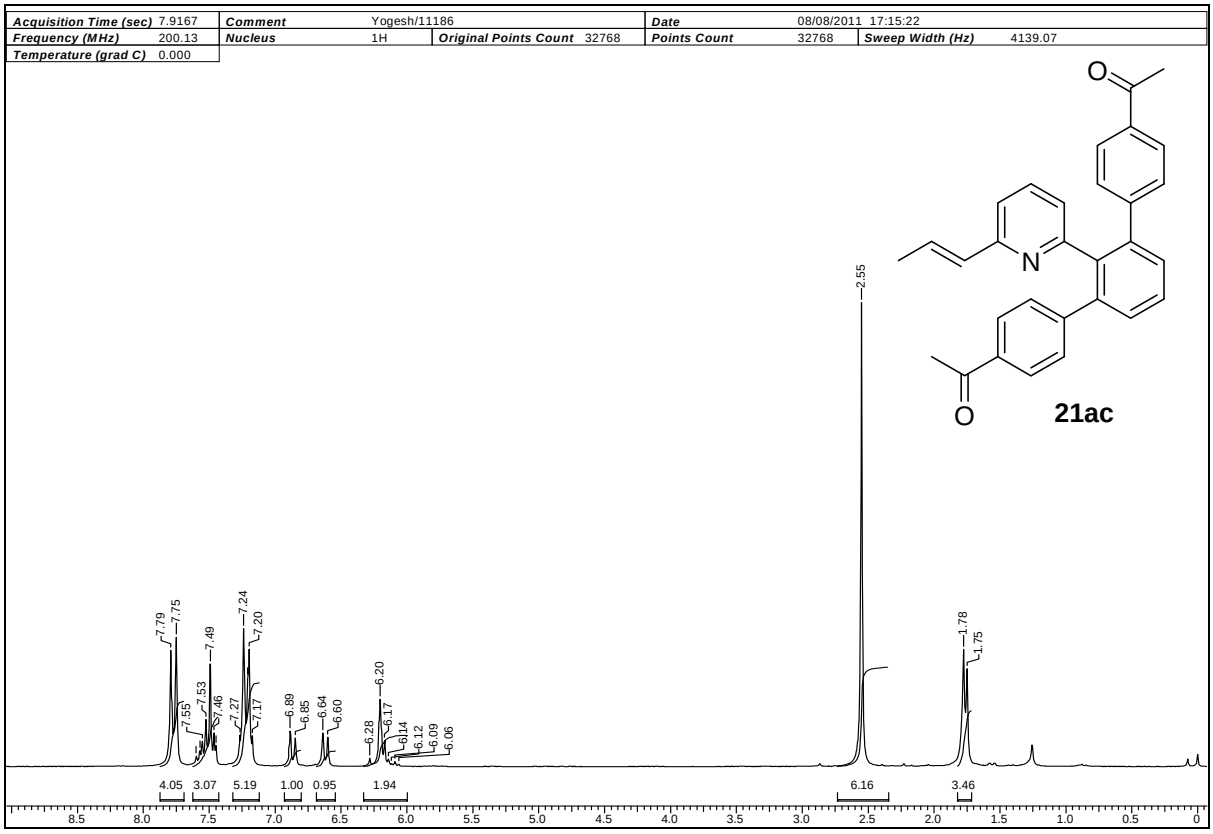
^{13}C NMR Spectrum of 21ab in $CDCl_3$



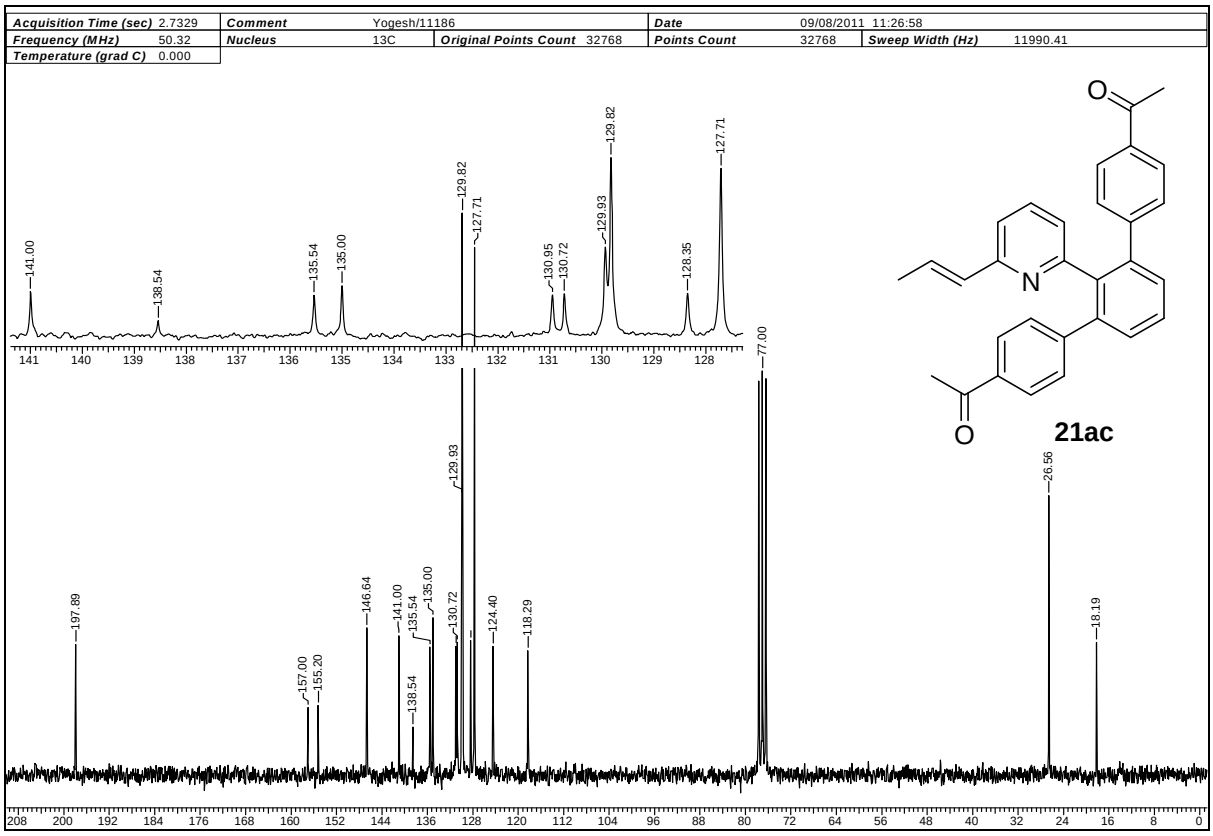
^{1}H NMR Spectrum of 22ab in $CDCl_3$



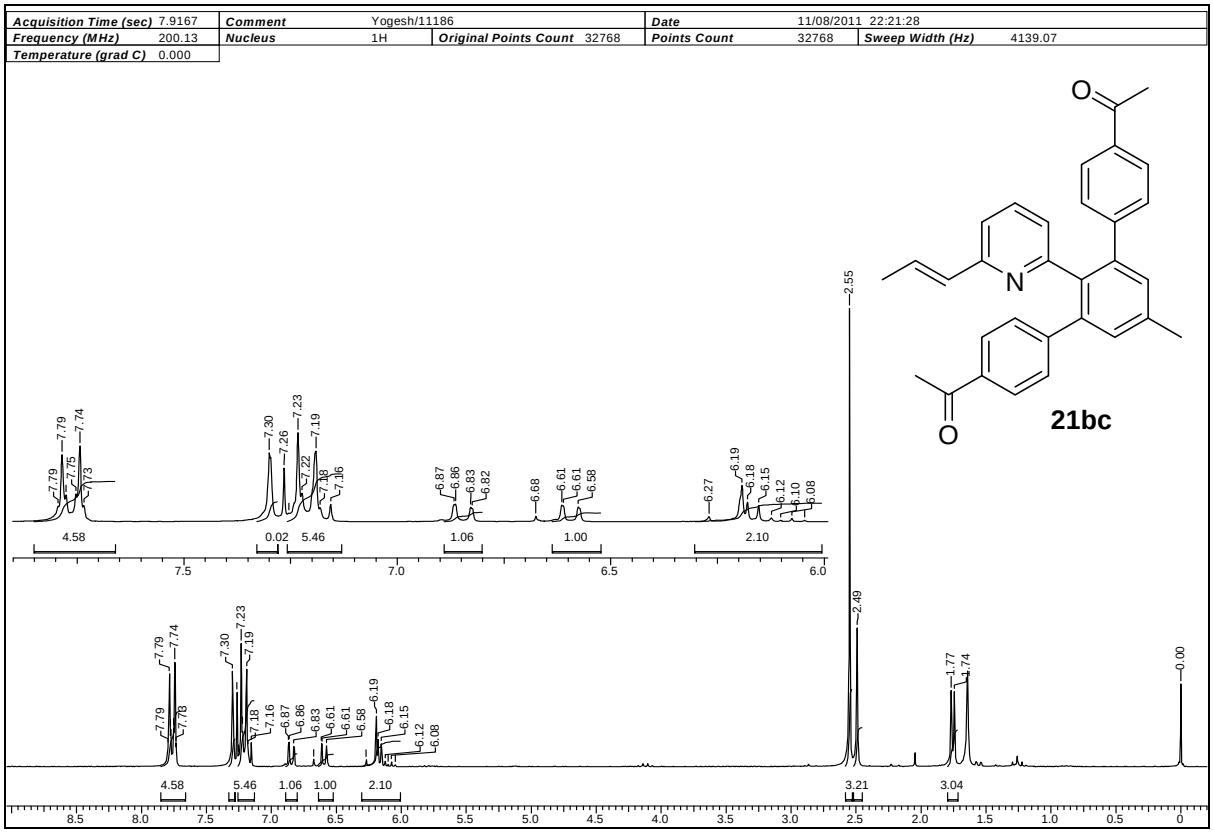
^{13}C NMR Spectrum of 22ab in $CDCl_3$



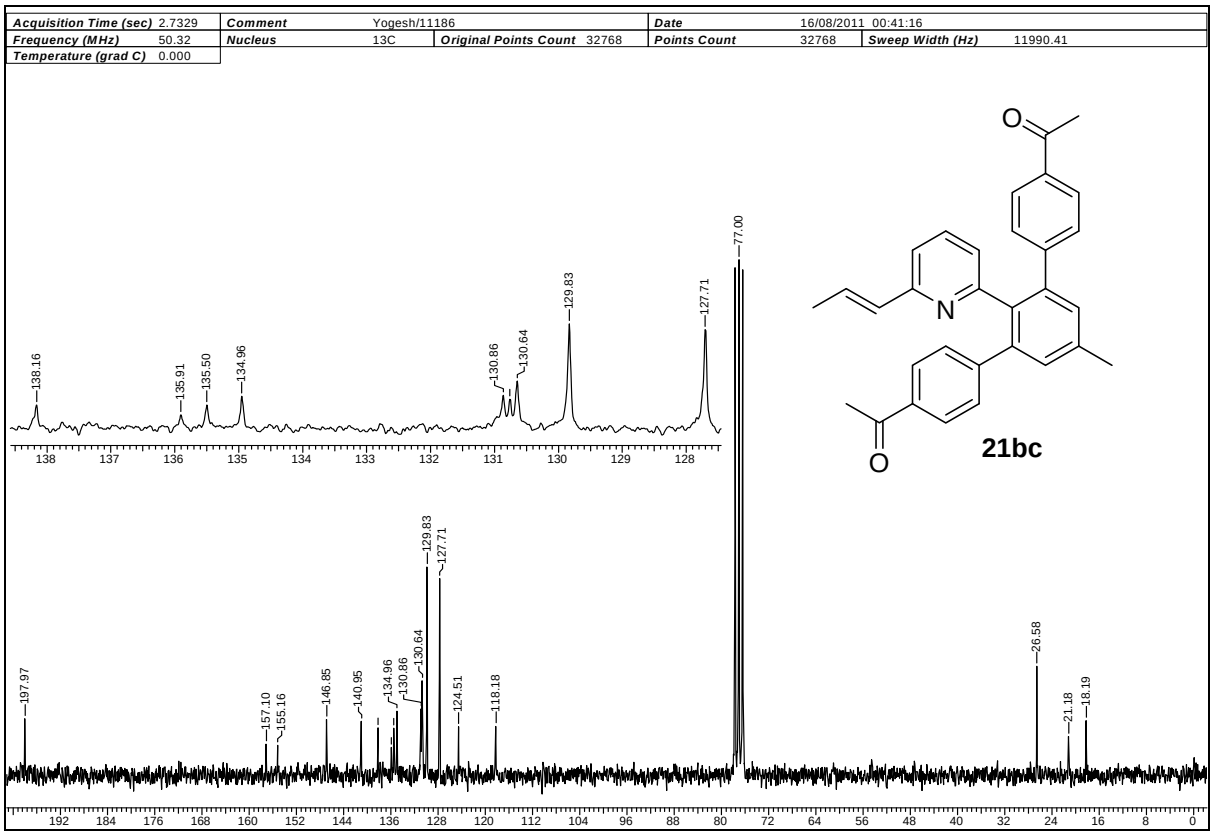
^{1}H NMR Spectrum of 21ac in $CDCl_3$



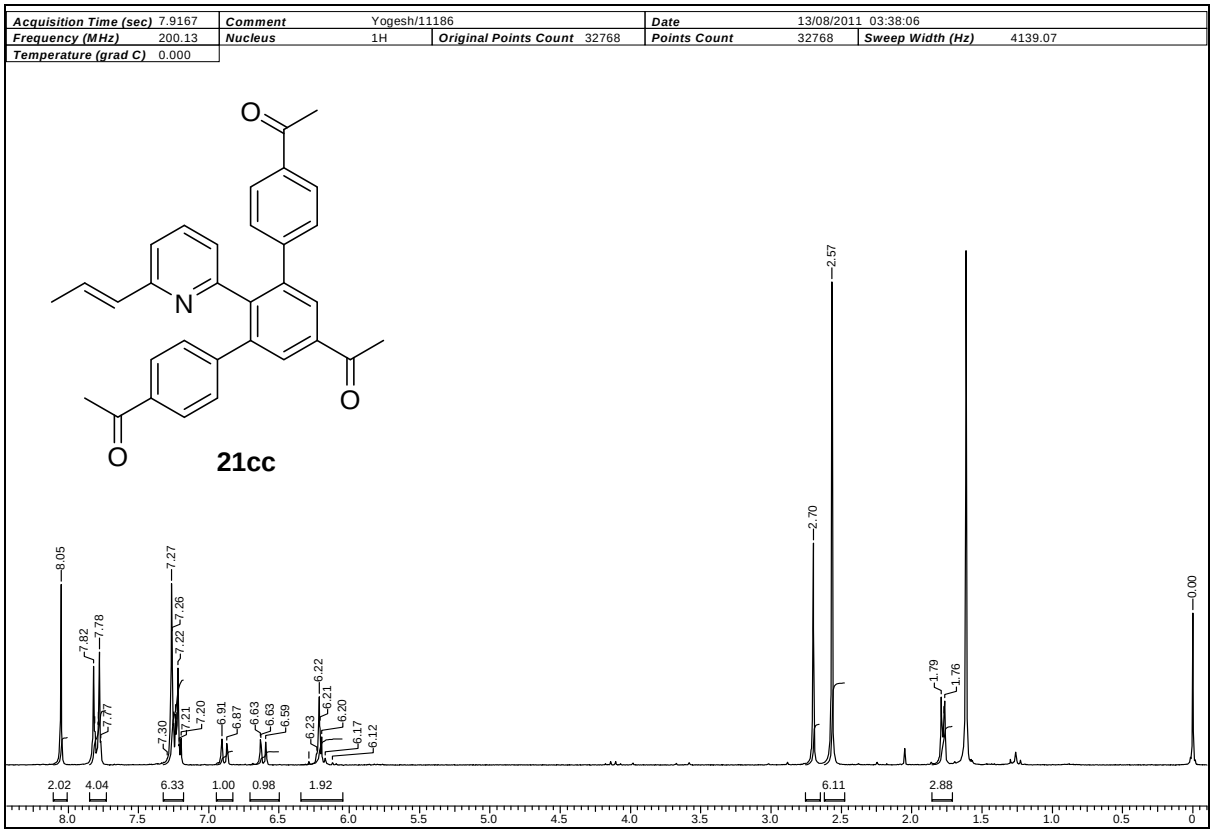
^{13}C NMR Spectrum of 21ac in $CDCl_3$



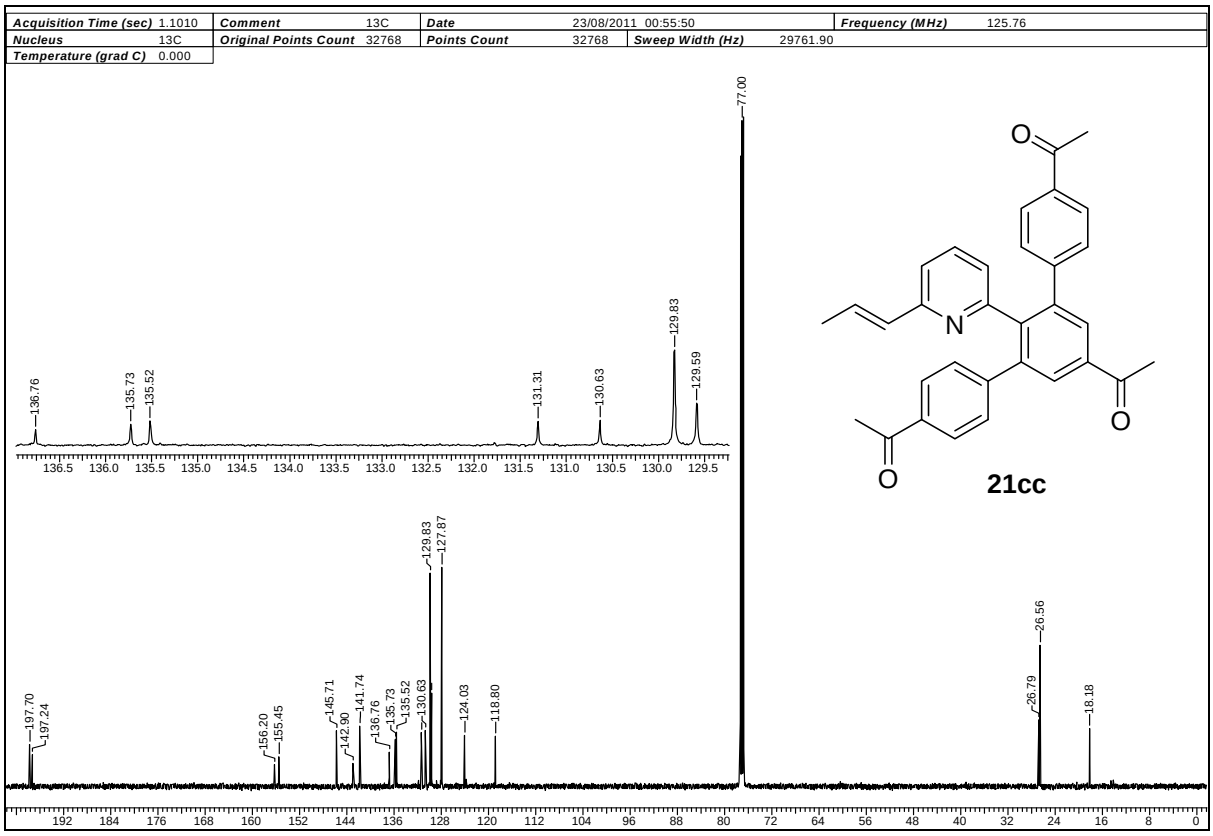
^{1}H NMR Spectrum of 21bc in $CDCl_3$



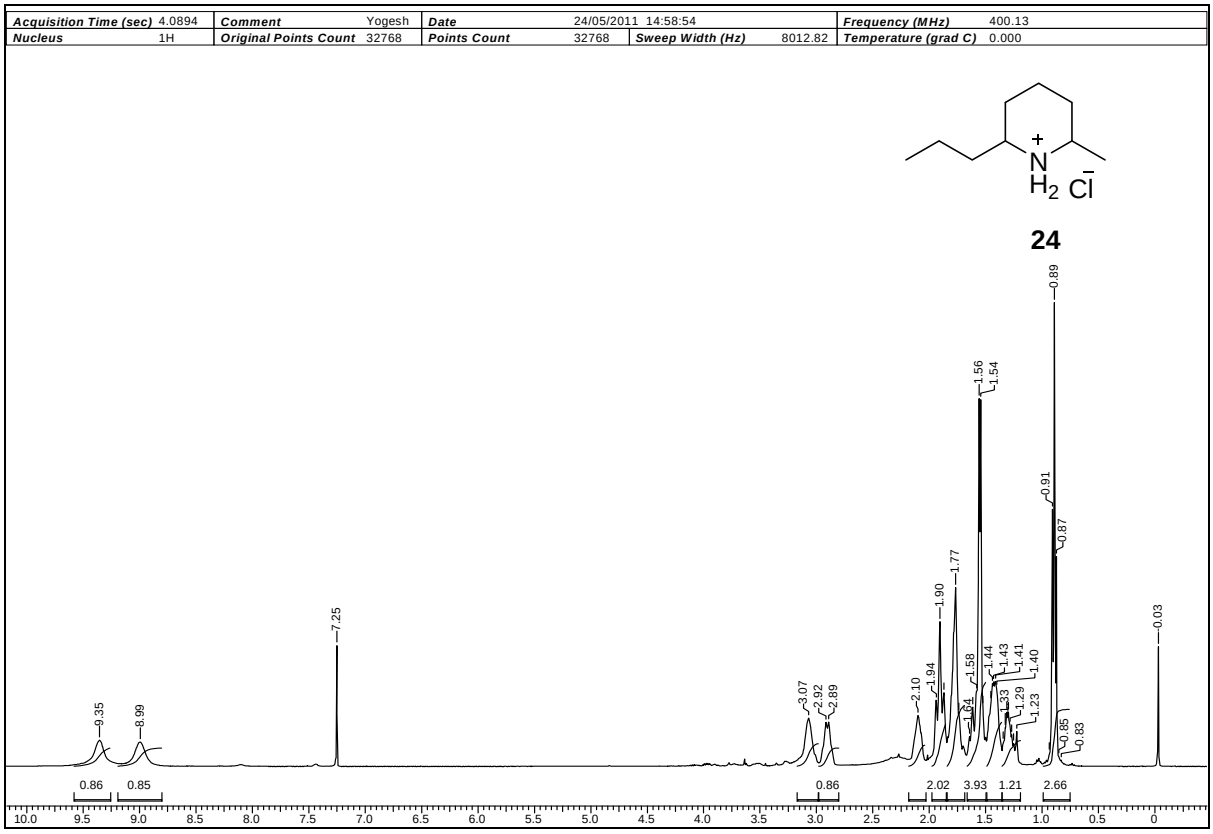
^{13}C NMR Spectrum of 21bc in $CDCl_3$



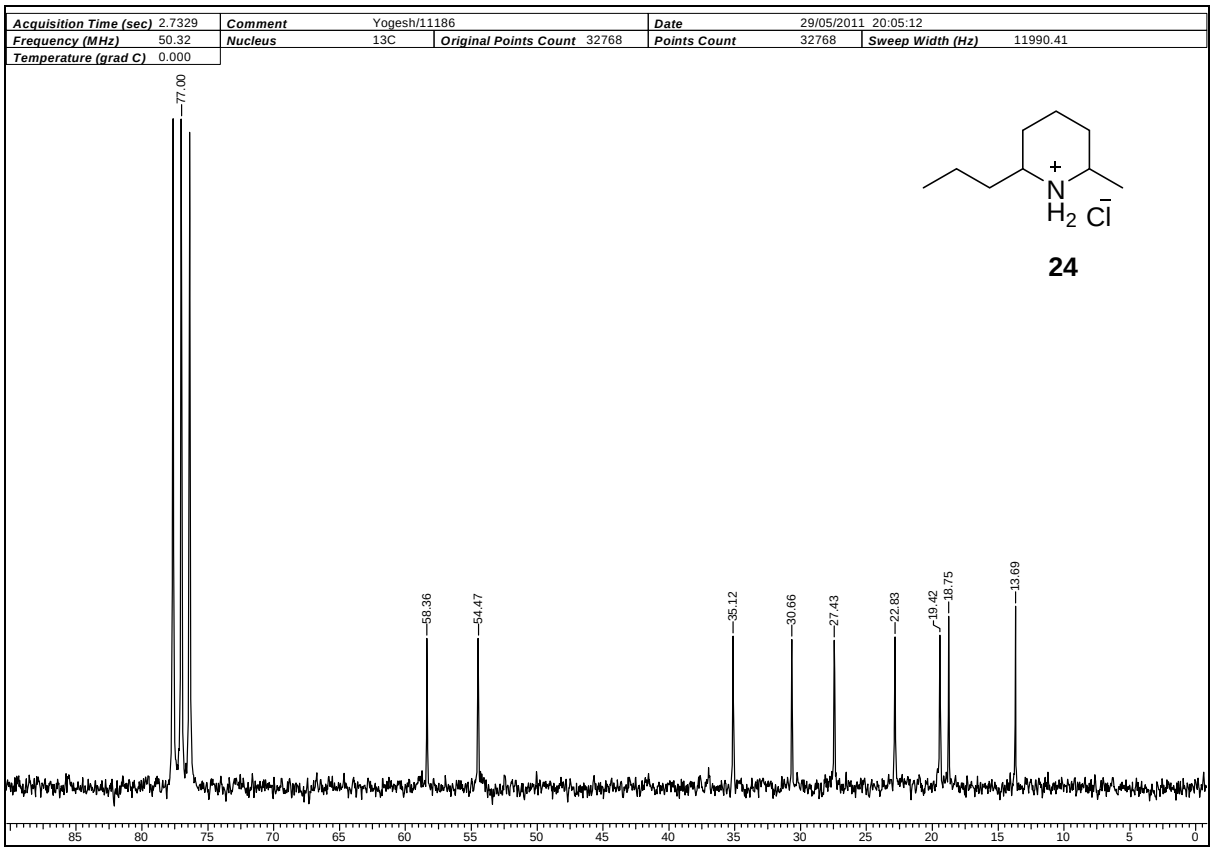
^{1}H NMR Spectrum of 21cc in $CDCl_3$



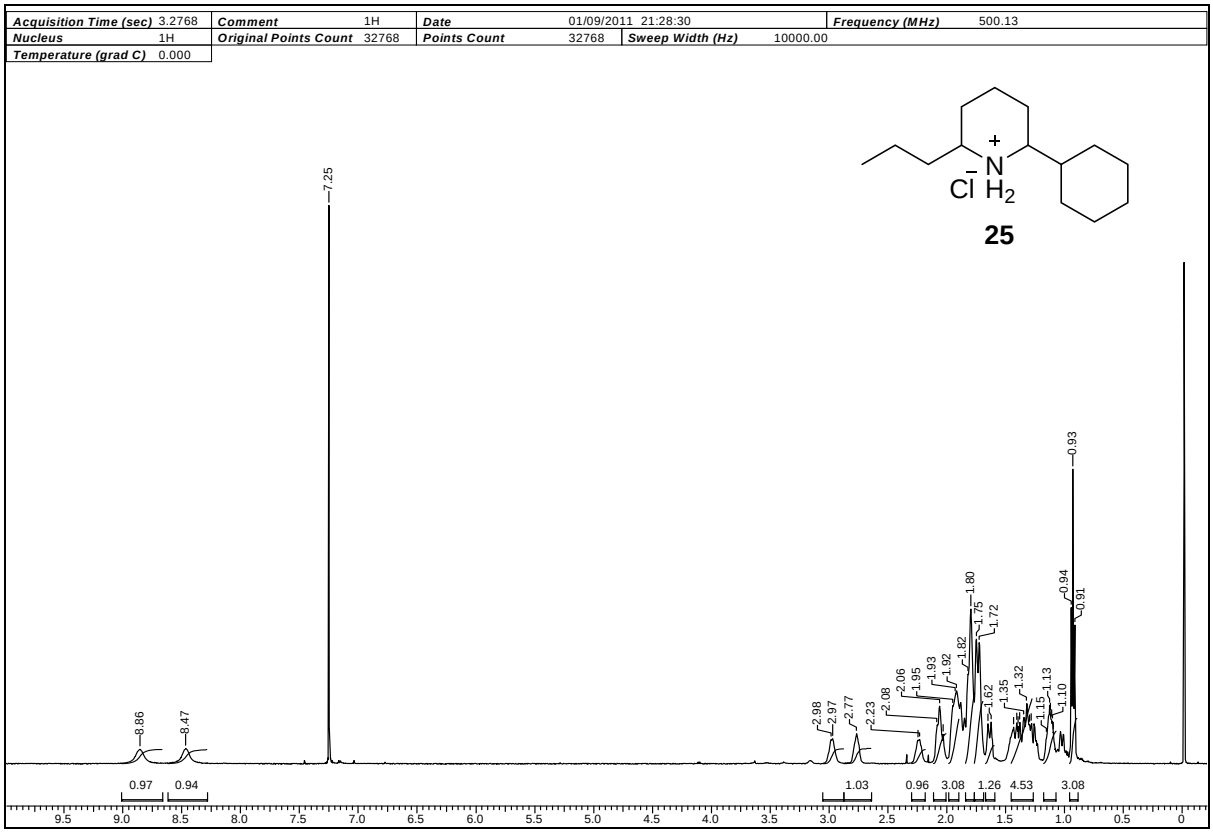
^{13}C NMR Spectrum of 21cc in $CDCl_3$



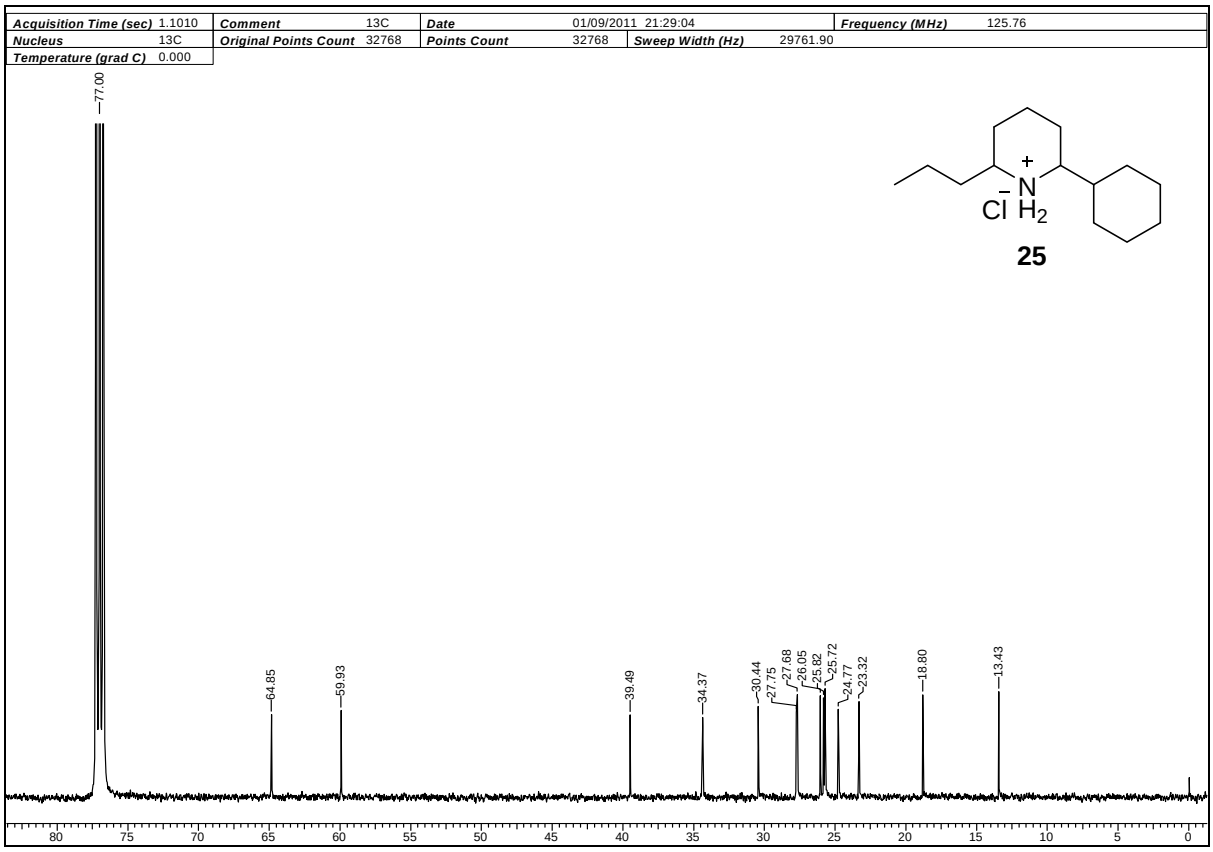
^{1}H NMR Spectrum of 24 in $CDCl_3$



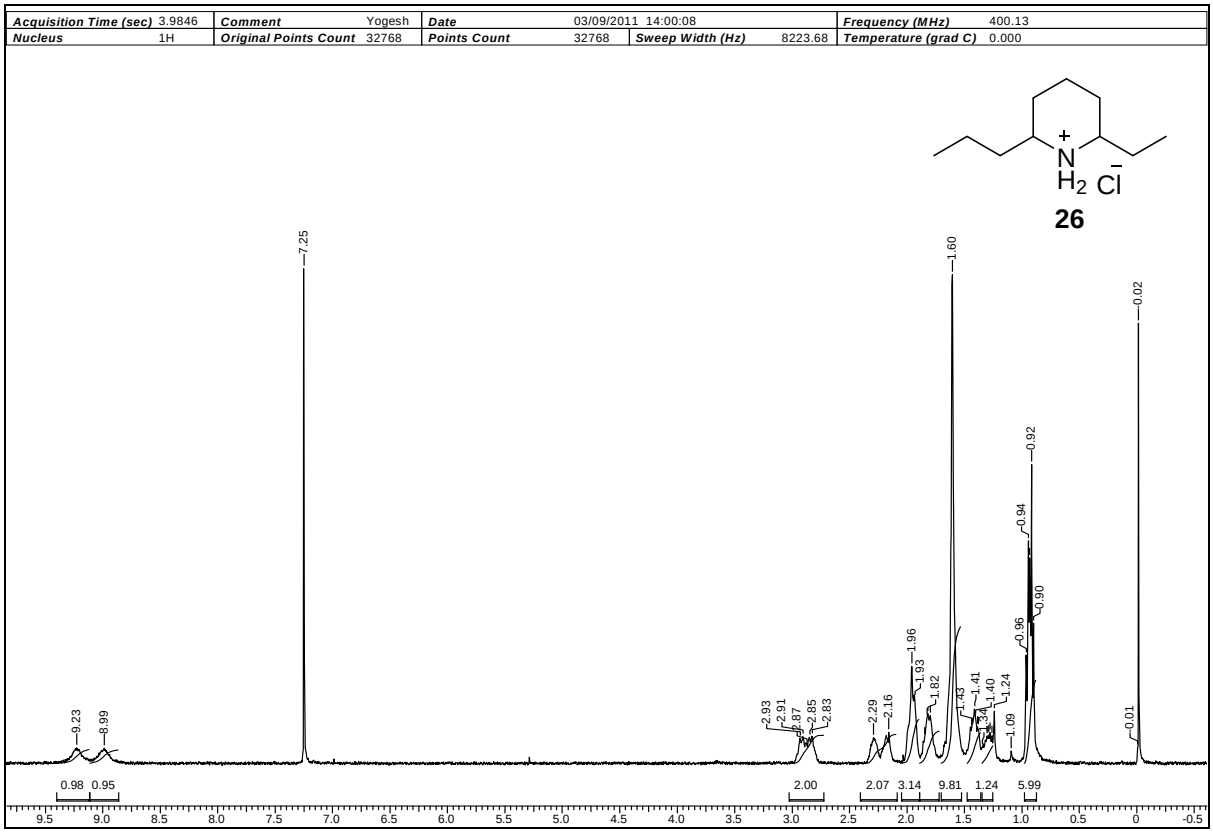
^{13}C NMR Spectrum of 24 in $CDCl_3$



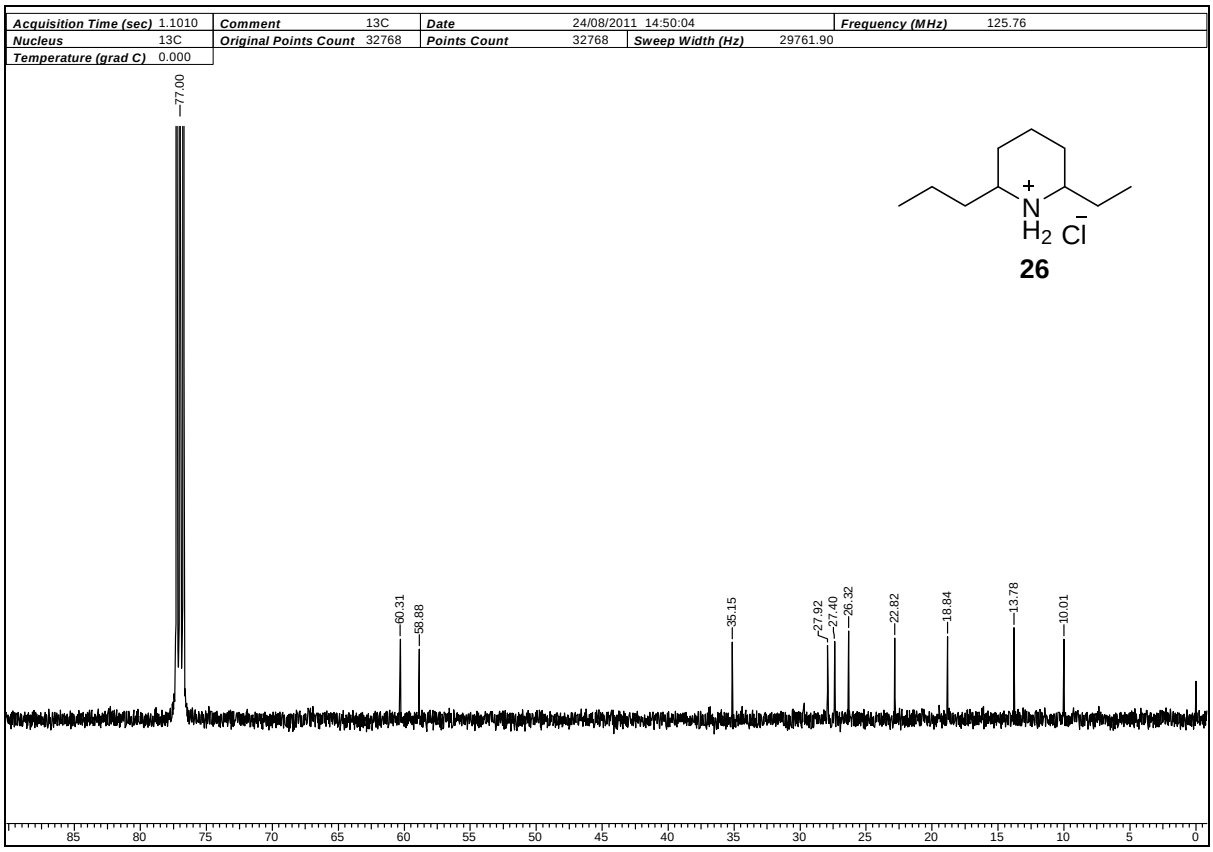
^{1}H NMR Spectrum of 25 in $CDCl_3$



^{13}C NMR Spectrum of 25 in $CDCl_3$



^{1}H NMR Spectrum of 26 in $CDCl_3$



^{13}C NMR Spectrum of 26 in $CDCl_3$

LIST OF PUBLICATIONS

1. "The [Cu]-catalyzed S_NAR reactions: Direct amination of electron deficient aryl halides with sodium azide and the synthesis of arylthioethers under Cu(II)-ascorbate redox system" **Yogesh Goriya** and C. V. Ramana, *Tetrahedron*, **2010**, *66*, 7642–7650.

2. "Ruthenium-Catalyzed C6-Propenylation Reactions of Substituted Pyridine Derivatives: Directed and Direct C–H Activation" **Yogesh Goriya** and C. V. Ramana, *Chem. Eur. J.*, **2012**, *18*, 13288–13292.

3. "Synthesis of pseudo-indoxyl derivatives *via* sequential Cu-catalyzed S_NAr and Smalley cyclization" **Yogesh Goriya** and C. V. Ramana, *Chem. Commun.*, **2013**, *49*, 6376–6378.

4. "Evaluation of viability of halogen…O_2N interactions: Insight from crystal packing in a series of isomeric halo and nitro substituted triaryl compounds with modular positioning of halogen and NO_2 groups" C. V. Ramana, **Yogesh Goriya**, Kulbhushan A. Durugkar, Soumitra Chatterjee, Shobhana Krishnaswamy and Rajesh G. Gonnade, *CrystEngComm*, **2013**, *15*, 5283–5300.

5. "2-Aroylindoles from *o*-bromochalcones *via* Cu(I)-catalyzed S_NAr with an azide and intramolecular nitrene C–H insertion" **Yogesh Goriya** and C. V. Ramana, *Chem. Commun.*, **2014**, *50*, 7790–7792.

List of Patents:

1. Synthesis of pseudo-indoxyl derivatives *via* sequential Cu-catalyzed S_NAr and Smalley cyclization, C. V. Ramana and **Yogesh Goriya** (US provisional patent has filed).