Functionalizations of Oxindoles and Thio-oxindoles Under Metal-Free Conditions

Doctoral Thesis

by

Manisha Lamba

(2018CYZ0001)

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY, ROPAR

August, 2024

Manisha Lamba: *Functionalizations of Oxindoles and Thio-oxindoles Under Metal-Free Conditions*

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A Thesis Submitted

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

by

Manisha Lamba

2018CYZ0001

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY ROPAR

August, 2024

Dedicated to My Mumma, Daddy, Bhai

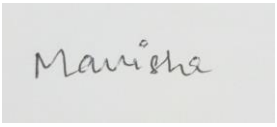
and Lord Shiva

Indian Institute of Technology Ropar

Department of Chemistry

DECLARATION BY THE CANDIDATE

I, Ms. Manisha Lamba, hereby declare that the work presented in the thesis entitled "*Functionalizations of Oxindoles and Thio-oxindoles Under Metal-Free Conditions*", submitted for the degree of **Doctor of Philosophy** in Chemistry to the Indian Institute of Technology Ropar, Rupnagar, India has been carried out by me under the supervision of **Dr. Avijit Goswami** in the Department of Chemistry, Indian Institute of Technology Ropar, Rupnagar, India. The work is original, based on experimental findings and has not been submitted in part or full by me elsewhere for a degree. In keeping parity with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.



IIT Ropar
August, 2024

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Functionalizations of Oxindoles and Thio-oxindoles Under Metal-Free Conditions***" was carried out by the candidate, Ms. Manisha Lamba under my supervision in the Department of Chemistry, Indian Institute of Technology Ropar, Rupnagar, India. I am forwarding the above-mentioned thesis of her being submitted for the degree of **Doctor of Philosophy** in **Chemistry** of this Institute. To the best of my knowledge, the present work or any part thereof has not been submitted elsewhere for a degree.

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August, 2024

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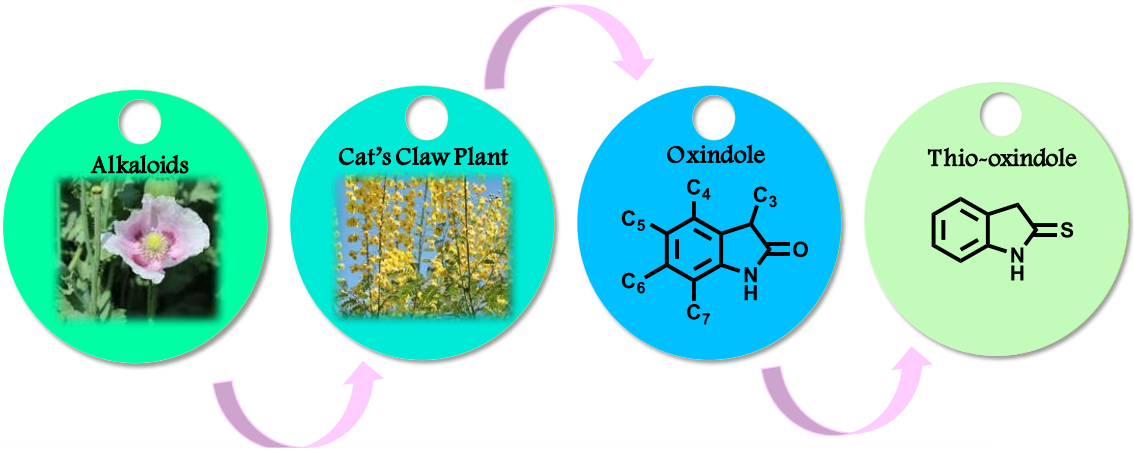
Manisha Lamba

ABSTRACT

This thesis aims to modify oxindoles and thio-oxindoles, which are important scaffolds with biological significance, in order to enhance their functional properties.

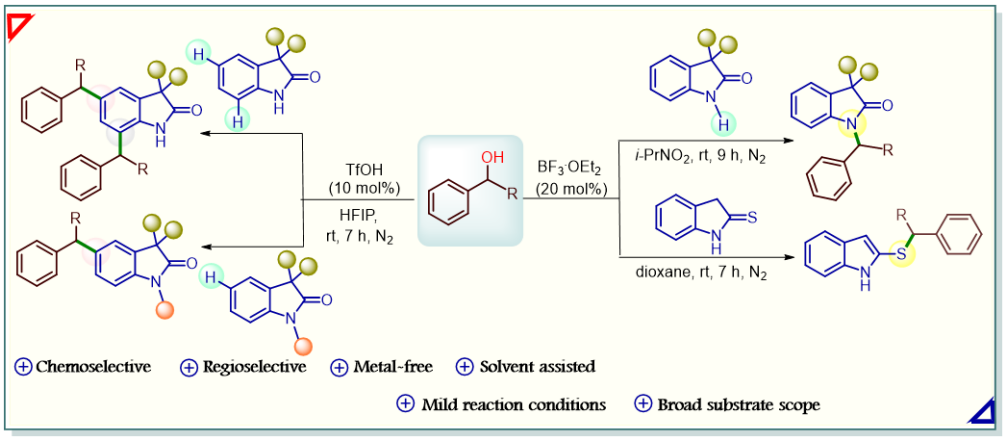
Chapter-1: Introduction

The text discusses alkaloids, which are naturally occurring organic molecules produced by plants for self-protection against pathogens and herbivores. It focuses on oxindole, an alkaloid derived from the Cat's Claw plant, which has traditionally been used in medicine for treating various diseases and infections. The chapter explores the diverse biological effects of these compounds and their correlation with the position of substituents on oxindole. It also delves into the development of methods for constructing oxindoles and different protocols for their functionalization. Additionally, it highlights the synthesis and biological activities of thio-oxindoles, emphasizing their growing importance in constructing indole-fused and spiro organosulfur compounds.



Chapter-2 In this study, we have disclosed N-alkylation and C-alkylation reactions of 2-oxindoles and S-alkylation of thio-oxindoles with secondary alcohols. Interestingly, these chemoselective reactions are tunable by changing the reaction conditions. Utilization of protic solvent and Brønsted acid catalyst afforded C-alkylation, whereas, aprotic solvent and Lewis acid catalyst afforded N-alkylation of 2-oxindoles in good to excellent yields. Regioselectivity is achieved by protecting the N-centre of the oxindole and C5 alkylated product is furnished exclusively. This protocol is notable because it demonstrates functionalization at the C7 position

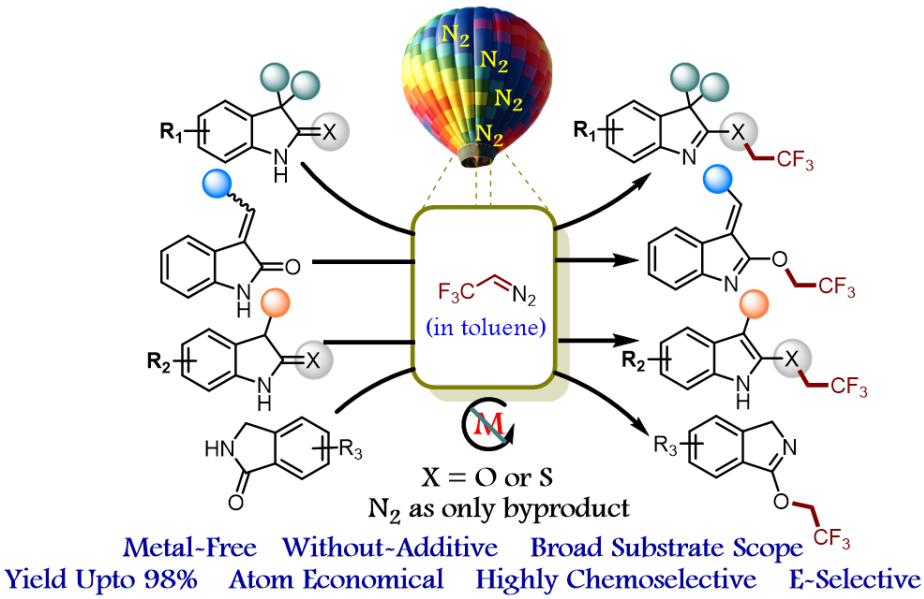
of oxindole without the need for any directing group at the N-centre. Further, a new protocol has been reported for C-H oxygenation at the benzylic position of one of the C5 alkylated derivative.



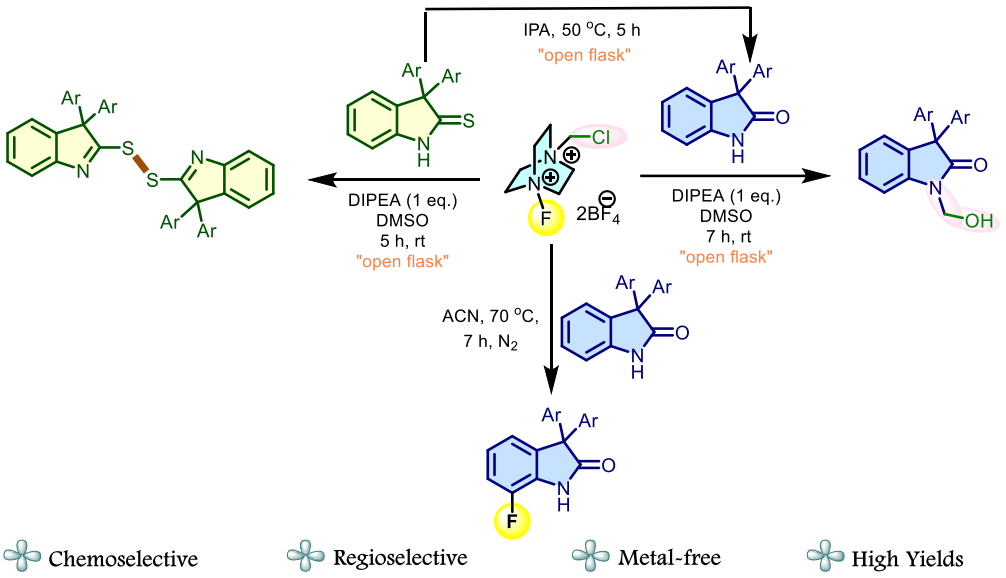
Chapter 3:

Fluorine-containing moieties are of great interest in the development of new synthetic methods due to their considerable medicinal value. In this regard, researchers have explored the direct trifluoroethylation using CF_3CH_2-containing precursors, however, the high cost, prolonged synthesis time, toxic nature, and instability towards transition metal catalysis of these precursors have proven to be a challenge. As an alternative, generating trifluoroethylation by in situ production of 2,2,2-trifluorodiazoethane (CF_3CHN_2) from $CF_3CH_2NH_2 \cdot HCl$ in solution is comparatively easy, safe, and a greener approach. But, previous reports using 2,2,2-trifluorodiazoethane in solution also demonstrate the use of transition metal-catalyzed pathways under harsh reaction conditions and hazardous solvents. Herein, we have developed a triflic acid (commercially available and cheap Brønsted acid) catalyzed protocol for O-trifluoroethylation of 3,3-disubstituted, monosubstituted, unsubstituted, chalcone-based oxindoles, isoindolines, and S-trifluoroethylation of thio-oxindoles in the presence of in situ generated 2,2,2-trifluorodiazoethane in solution. This highly efficient metal- and additive-free strategy offers a mild and feasible approach to access chemoselective trifluoroethylation in good to excellent yields in a very short reaction time (10 minutes). This methodology exhibits a wide range of substrate scope, rendering it a versatile approach that can be effectively employed for all types of cyclic amides. Additionally, the method is scalable for larger operations. The calculation of various green chemistry metrics, such as high atom economy (93%), carbon efficiency (100%), reaction mass efficiency (74%), and lower E-factor (0.40 kg waste/ 1kg

product) confirms the eco-friendliness of this approach. The EcoScale evaluation showcases the simplicity, effectiveness, and eco-friendliness of this approach.



Chapter 4: This research has led to a significant advancement in the field of organic synthesis. We have successfully developed a method to directly fluorinate the C7-H position of oxindoles, N-hydroxymethylate oxindole, form dithianes, and transform thio-oxindole to oxindole. This breakthrough was the result of thorough experimentation involving the testing of various solvents, bases, and reaction temperatures. A key element in this process is the dual role played by selectfluor, acting as both an oxidant and a fluorine source. Our innovative protocol offers a practical and efficient approach to synthesizing oxindole analogs under mild conditions, resulting in good to excellent yields of the desired products. Significantly, our method demonstrates exceptional regioselectivity, high tolerance to functional groups, and is free of additives, making it an enticing option for researchers and practitioners in organic synthesis and pharmaceutical chemistry.



Chapter 5. In this chapter, I provide a detailed overview of the work that has been accomplished in the thesis entitled as "*Functionalizations of Oxindoles and Thio-oxindoles Under Metal-Free Conditions*".

Keywords: Oxindoles, Thio-oxindoles, alkaloids, Lewis acids, Brønsted acids, Metal-free, HFIP, alcohols, fluorination, hydroxymethylation, dithianes.

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List of Abbreviations

Ac	acetyl
ACN/MeCN	acetonitrile
$AlCl_3$	aluminium trichloride
aq	aqueous
atm	atmospheric
$AuCl_3$	gold trichloride
α	alfa
BA	Brønsted Acid
BF_4	tetrafluoroborate
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Br_2/H_2O	bromine water
brs	broad singlet
^{n}Bu	butyl
^{t}Bu	*tert*-butyl
calcd.	calculated
Cy	cyclohexyl
CuO	copper oxide
CO_2	carbon dioxide
d	doublet

DABCO	1,4-diazabicyclo[2.2.2]octane
DAC	donor-acceptor cyclopropanes
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of a doublet
DIPEA	N,N-Diisopropylethylamine
DKR	dynamic kinetic resolution
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*'-dimethyl formamide
DMSO	dimethyl sulfoxide
dq	doublet of a quartet
dr	diastereomeric ratio
dt	doublet of a triplet
DFT	density functional theory
ee	enantiomeric excess
eq.	equivalents
ESI	electron spray ionization
EtOH	ethanol
FC	Friedel-Crafts
Gem	geminal

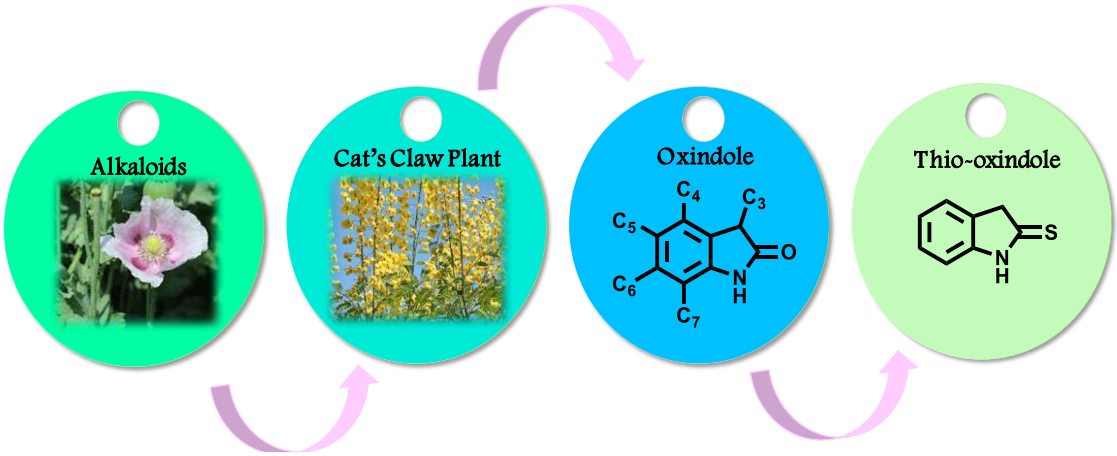
h	hour(s)
HCl	hydrochloric acid
HF	hydrogen fluoride
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HNO_3	nitric acid
H_2O_2	hydrogen peroxide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
H_2SO_4	sulphuric acid
Hz	Hertz
I_2	Iodine
IPA	Isopropyl alcohol
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LDA	lithium diisopropylamide
LA	Lewis Acid
LHMDS	lithium hexamethyldisilazide
LED	light-emitting diode
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
mg	milligram(s)

MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
m.p.	melting point
MS	molecular sieves
m/z	mass/charge
NaOH	sodium hydroxide
Na-Hg	sodium-mercury amalgam
NMR	Nuclear Magnetic Resonance
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine bis(trifluoroacetate)
$POCl_3$	Phosphorus oxychloride
ppm	parts per million
^{n}Pr	*n*-propyl
^{i}Pr	isopropyl
p-TSA	*para*-toluenesulfonic acid
q	quartet
rt	room temperature
s	singlet
SCF_3	scandium fluoride
sept	septet

SFOH	trifluoromethanesulfonic acid
t	triplet
TBHP	*tert*-Butyl hydroperoxide
*t*BuOH	*tert*-butanol
td	triplet of a doublet
tert	tertiary
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography

Chapter 1

Introduction: Essence of Oxindoles and Thio-oxindoles



Chapter 1

1. Introduction

1.1 Significance of Bioactive Compounds

Bioactive compounds are compounds which impart certain biological effects, beyond their nutritional value, and have a positive impact on a patient's health. These bioactive compounds are harnessed not only from plants however, many of these can be obtained from animals in the form of dairy products and meat. Apart from these, eatable fungi and mushrooms are also capable of supplying bioactive compounds.[1] Without going into detail about all bioactive compounds, I am going to discuss the bioactive compounds that can be obtained through food. Most of the bioactive compounds are extracted from plants, nevertheless, they are also found in animals, fungi, and bacteria. Important bioactive compounds found in food are grouped as- Polyphenols (e.g. blueberry fruits), polysterols (e.g. soybean), terpenoids (e.g. citrus fruits), polysaccharides (e.g. flax seeds), tocopherols and carotenoids (e.g. carrot), glucosilonates (e.g.,broccoli), triterpenes (e.g. olive oil), alkaloids (e.g. coffee beans), capsaicinoids (e.g. peppers), peptides (e.g. red meat) and poly-unsaturated fatty acids (e.g. fishes).[2]

1.2 Alkaloids: Basis for many Biologically Active Compounds

Alkaloids are an assembly of small naturally occurring organic molecules, mainly they are produced by plants to protect themselves against pathogens and herbivores. They are purified through an acid-base extraction process and contain nitrogen atoms in the ring. They generally are solid in nature. These metabolites are known to show many pharmacological actions like, antimalarial, anticancer, stimulant, anesthetic, etc. Most of them are obtained from nature, for instance, nicotine, **1** is extracted from Nicotiana Tobacum plant, Caffeine, **2** is obtained from Coffee Arabica, Opium seeds are the source of morphine, **3** and Cat's Claw plant generates oxindole, **4,** etc. (Figure 1.1), a few of them can be obtained synthetically.[3]

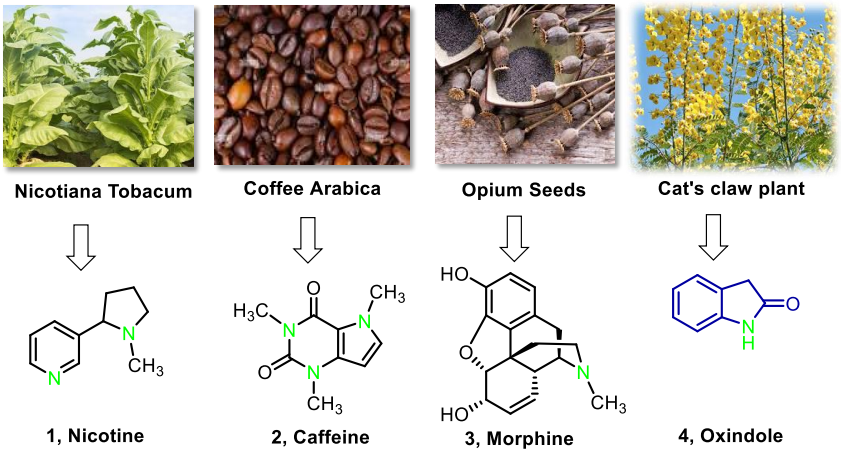
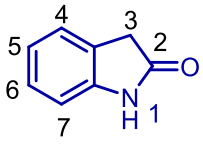


Figure 1.1: Representative examples of some alkaloids.

1.3 Oxindoles

1.3.1 Introduction

Oxindole is made-up of a five-membered pyrrole ring which is fused with a six-membered benzene ring and at the C2 position, a carbonyl group is placed as depicted below. C_8H_7NO is the chemical formula and 1,3-dihydro-2*H*-indole-2-one is the IUPAC name of oxindole. 2-Indolinone is its another name commonly used because it is believed that it is the modified form of indole.[4]



4, Oxindole

1.3.2 Oxindole: Origin

Oxindoles are defined as endogenous hetero-aromatics which are found in bodily fluids and tissues of various mammals. They can also be obtained from plants and the first derivative of oxindole was obtained from Cat's claw plant in the form of alkaloids.

Traditionally, it found its root in medicine where it was used in therapies and treatment of various diseases and infections. These multifaceted compounds possess various biological effects and their pharmacological activities have direct relation with the substituent position at oxindole. For example, substitution at –NH position exhibits activities like anticancer, antibacterial, glucosidase and kinase inhibitor. Similarly, substitution at C5-position offers activities like progesterone antagonists, NMDA blockers as shown in the Figure 1.2.[5]

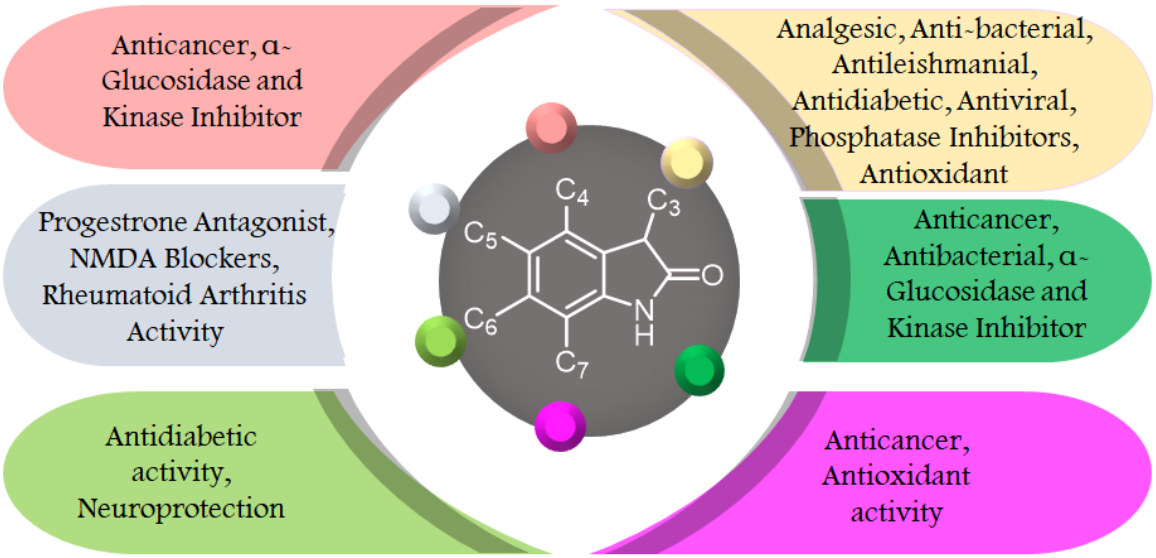


Figure 1.2: Pharmacological activities of oxindole on varying substituent positions.

1.3.3 Oxindole: Biological Importance

Oxindole plays an important role in designing and fabricating new drugs by its ability to get modified by different functional groups and generates advanced biological functions. Some of the examples of very useful drugs showcasing substituent variation at different positions of oxindole are demonstrated in Figure 1.3.[6]

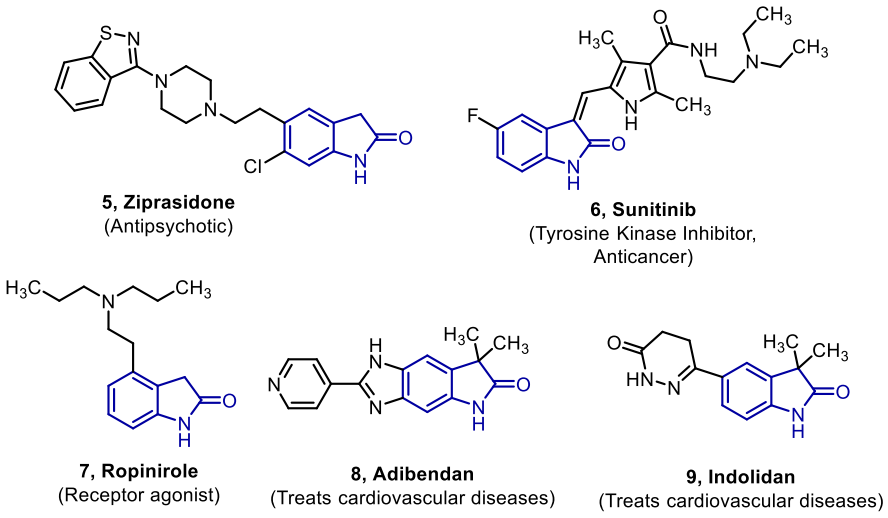


Figure 1.3: Substituent-dependent Food and Drug Administration (FDA) approved oxindole-containing drugs.

1.3.4 Tautomerism in Oxindole

Because of the presence of an amide functional group, oxindoles tend to show keto-enol tautomerism as illustrated in Figure 1.4. Migration of hydrogen from NH- to oxygen results in lactim. Similarly, hydrogen migration or enol formation also occurs with the C2 position resulting in the formation of O-substituted indole derivatives, and this conversion is known as amide-imidol interconversion.[7]

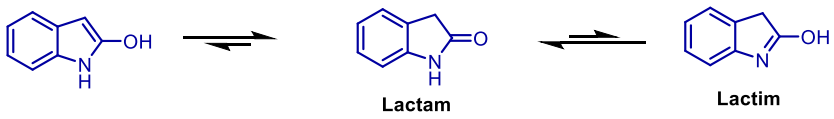


Figure 1.4: Tautomeric forms of oxindole.

1.3.5 Acidities of Oxindole Derivatives

Furthermore, Bordwell and co-workers suggested that the substitution at NH- and C3 positions has a direct relation with the acidity (Figure 1.5). Unsubstituted NH and C3 of **4** give pKa of 18.2, however, nitrogen protection by methyl **10** slightly enhances the acidity, on the other hand, pKa gets slightly decreased on placing the electron-withdrawing group at the nitrogen, **11**.[8]

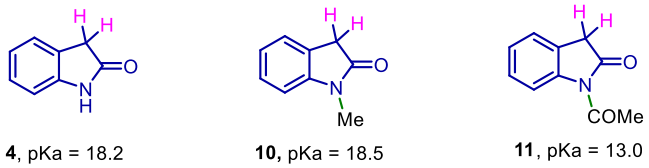


Figure 1.5: Comparison of acidities of oxindole derivatives.

1.3.6 Oxindole and thio-oxindole: A Comparison

Oxindole and thio-oxindole can be compared with each other in terms of their reactivity, based on their Mulliken charge distribution (Figure 1.6). The charge distribution of these compounds is such that the α-carbon of thio-oxindole, **12** is more electron-dense than sulfur, and hence, it has the capability to act as a better nucleophile. Similarly, the α-carbon of thio-oxindole is more electron-dense than the α-carbon of oxindole, and hence, it can be a better nucleophile than oxindole. This tendency arises from the strong resonance between the nitrogen atom and the carbonyl group in oxindole, **10** which makes it less likely to act as a nucleophile. Conversely, in thio-oxindole, **13** there is a good resonance between the α-carbon and the thiocarbonyl group, making it a more effective nucleophile.[9]

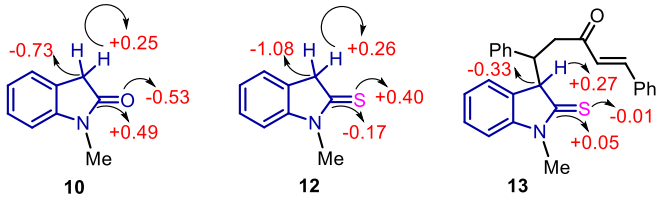
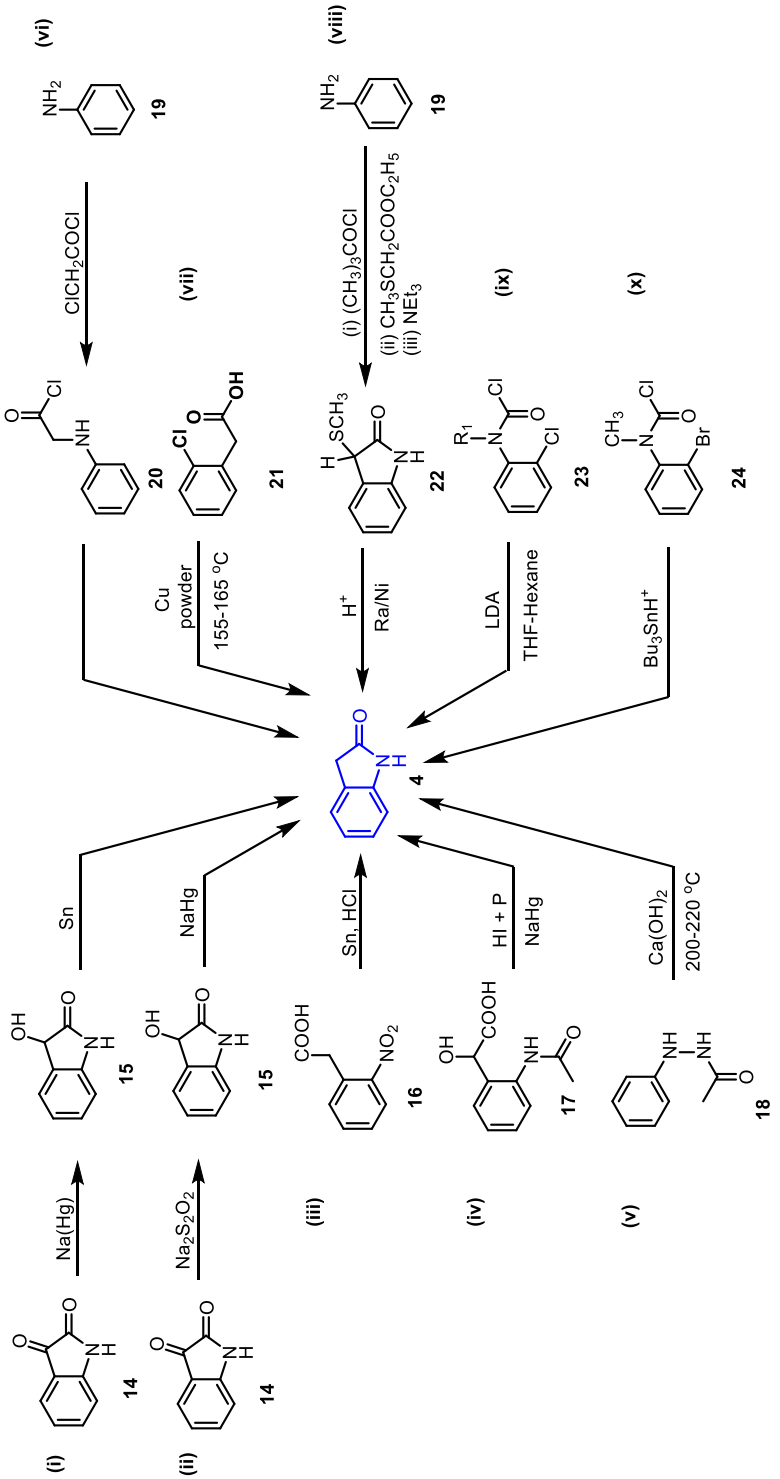


Figure 1.6: Charge distribution on C3 and carbonyl part of N-methyl oxindole and C3 and thiocarbonyl part of N-methyl thio-oxindole.

1.3.7 Synthesis of Oxindoles

2-Oxindoles can be synthesized in various ways, however, Bayer and Knop were the first who initiated its synthesis in 1866. They treated isatin, **14** with sodium amalgam, and furnished dioxindole, **15** which on further reaction with acidic Sn^{2+} produced the first non-natural oxindole compound, **4** (Scheme 1.1 (i)). Similarly, Marschalk *et al.* harvested oxindole from isatin and sodium hydrosulfite ($Na_2S_2O_4$), which directly gave oxindole. They used Na metal in amalgam in the presence of gaseous CO_2 (Scheme 1.1 (ii)). Several successful synthetic strategies have been attempted to produce the oxindole scaffold. One such procedure involved the reduction of 2-nitrophenylacetic acid, **16** using tin and HCl (Scheme 1.1 (iii)). Out of all these methods, this reaction is established as the most useful, straightforward and convenient method for synthesizing oxindole in terms of cost, accessibility and viability. This is because 2-nitrophenylacetic acid, which is used as a precursor, is readily available. Furthermore, it is a single-step protocol and the aggregate yield of the reaction is approximately 80%, which is exceptional. Another method involved the reduction of 2-acetaminomandelic acid, **17** with Na-Hg (Scheme 1.1 (iv)). Oxindole was also produced by Brunner using slaked lime on β-acetylphenylhydrazine, **18** at high temperature (Scheme 1.1 (v)). Additionally, a relevant method for preparing oxindole involved using chloroacetyl chloride, **20** to condense with an aromatic amine and amide. This mixture was then cyclized to oxindole with the addition of a Lewis acid such as $AlCl_3$



Scheme 1.1: Synthesis of 2-oxindole *via* various methods.

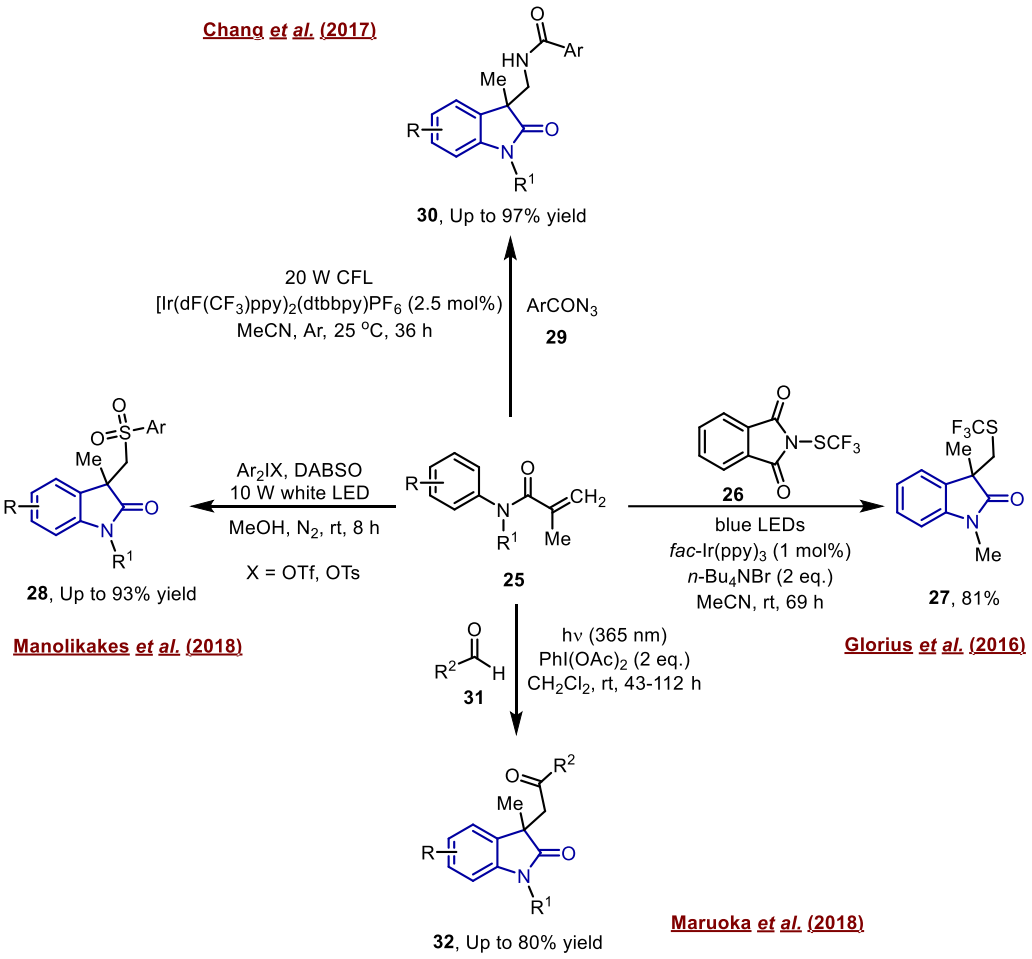
(Scheme 1.1 (vi)). Afterward, in 1952, Oxindole was synthesized by heating *o*-chloro-phenyl-acetic acid, **21** and ammonium hydroxide (Scheme 1.1 (vii)).[10] Later on, Bergen and Gassman developed another method to prepare oxindole by reacting aniline, **19** with ethyl methylthioacetate, *tert*-butyl hypochlorite, and triethylamine simultaneously to obtain amino ester, **22**. This amino ester was then acidified, which was further reduced with Raney Nickel, resulting in oxindole (Scheme 1.1 (viii)).[11] Another method involved treating N-acyl-*o*-chloroanilines, **23** with LDA in a THF-hexane to obtain oxindole (Scheme 1.1 (ix)).[12] Similarly, the association of tributylstannane and *o*-bromo-N-methylanilides, **24** at high temperature following homolytic translocation generated oxindole scaffold (Scheme 1.1 (x)).

Oxindoles have garnered significant interest due to their intriguing biological and physiological activities. Over the years, various methods have been devised for their construction. Notably, in the past decade, visible light-mediated strategies have appeared as a promising approach for synthesizing oxindoles, attracting considerable attention. Scheme 1.2 provides a short description for the synthesis of oxindole from *N*-substituted acrylamides, **25** *via* different visible light-mediated protocols. In 2016, Glorius *et al.* devised an innovative method for creating SCF_3 radicals from **26** by combining photoredox catalysis and halides. This groundbreaking approach marks the first instance of using visible-light photocatalysis for trifluoromethylthiolation. It enables the efficient addition of the SCF_3 group to heteroaryl- and aryl-substituted alkenes, resulting in the production of vinyl–SCF_3 compounds, **27**. Additionally, authors have developed radical-polar crossover processes that lead to the formation of oxindole scaffolds. These derivatives boast a quaternary center alongwith a $C(sp^3)$–SCF_3 bond. These reactions all take advantage of the gentle conditions provided by visible-light photocatalysis.[13]

Later in 2017, Chang *et al.* introduced a gentle and effective method for synthesizing oxindole and spirooxindole scaffolds. This method harnesses the power of visible light photocatalysis to bring about a reaction between N-arylmethacrylamides, **25** and benzoyl azides, **29** to form **30**. Through mechanistic studies, they proposed that this process operates through a triplet energy transfer mechanism using $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ in catalytic quantity. Importantly, this cyclization process works well with a wide variety of substrates and reactants, without leading to any competing decomposition pathways.[14]

Manolikakes and co-workers developed an innovative method for creating sulfonylated oxindoles, **28** using visible light. This process involves the direct use of sulfur dioxide as the main component for adding the sulfonyl functionality. This methodology enables the easy and efficient preparation of oxindole scaffolds that are important for pharmaceutical applications. Importantly, the reaction occurs under room temperature conditions and consistently produces high yields. It is also notable for its broad tolerance towards various functional groups and its ability to proceed without the need for any external photosensitizer or catalyst. The process relies on the formation of *in situ* sulfonyl radicals from sulfur dioxide and aryl radicals, and it makes use of environmentally friendly diaryliodonium salts as radical precursors. The entire process is driven solely by visible light, allowing for the straightforward assimilation of sulfur dioxide into small but important organic molecules.[15]

Afterward, Maruoka *et al.* have disclosed an innovative method for the radical acylarylation of N-arylacrylamides, **25** using hypervalent iodine(III) reagents, and UV light. This technique enables the use of a wide range of aliphatic aldehydes, **31** resulting in the production of 3,3-disubstituted 2-oxindoles with carbonyl groups, **32**.[16]

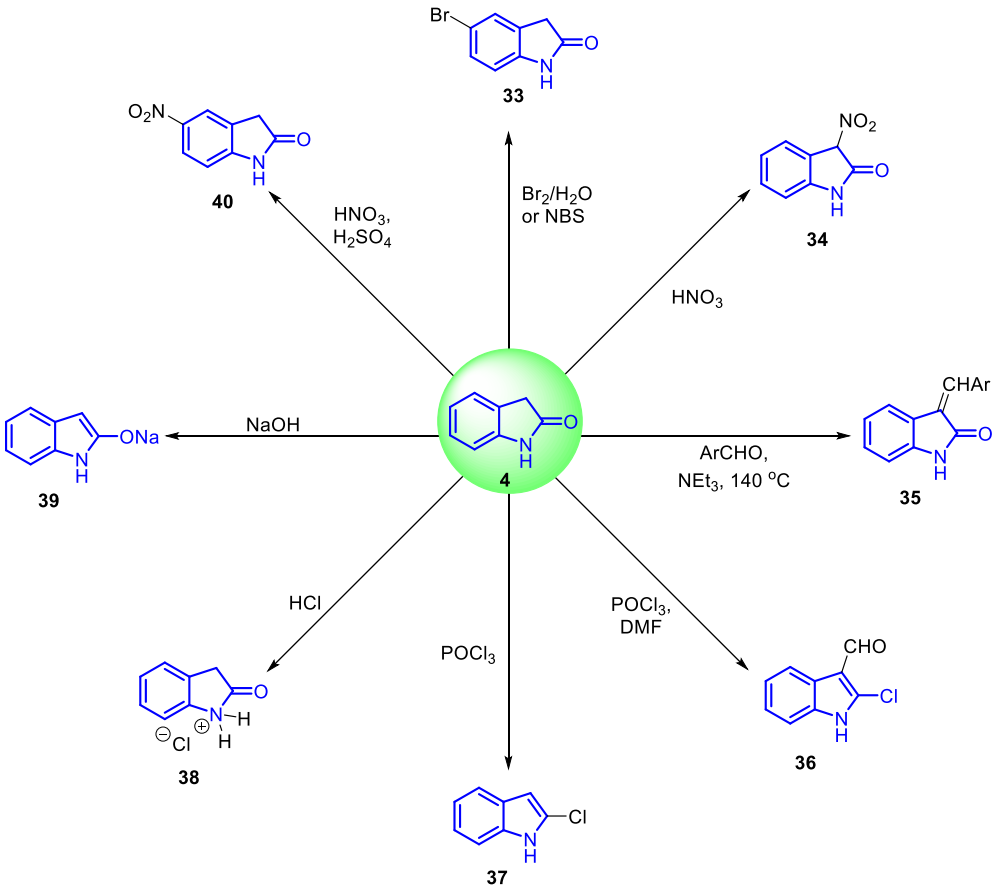


Scheme 1.2: Synthesis of 2-oxindole *via* visible light-mediated methodologies.

1.3.8 Fundamental reactions of Oxindole

It is essential to take into account the feasibility of reactions and chemical reactivity when dealing with oxindole's five-membered lactam isomers. Among these isomers, the β-carbon atom is typically more reactive than the amide, except for amine-deprotonation. The anion that forms is stabilized because of the secure aromatic properties of the oxindole enolate that is created. This feature is the primary cause of several reactions undergone by oxindole

and its derivatives, such as acylation, alkylation, and prompt condensation reactions with ketones and aldehydes.



Scheme 1.3: Electrophilic reactions of 2-Oxindole.

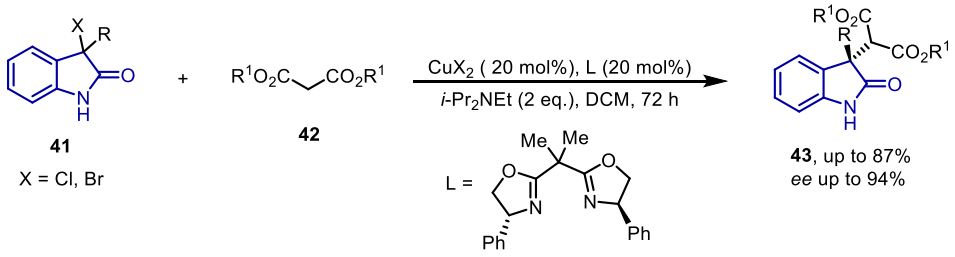
Oxindole based compounds undergo various chemical reactions, which are briefly described in Scheme 1.3. Oxindole exhibits typical electrophilic aromatic substitution (EAS) reactions, such as acid-catalyzed halogenation, nitration, *etc.*, due to its basic nature. However, it has been observed that electrophilic substitution at the C-5 position is more favored than the C-3 position. Example, when oxindole is treated with bromine water or

N-bromo succinimide (NBS), 5-bromo-2-oxindole, **33** is obtained instead of 3-bromo-2-oxindole. Similarly, on nitration with concentrated HNO_3 and H_2SO_4, 5-nitro-2-oxindole, **40** is produced, whereas nitric acid alone yields only 3-nitro-2-oxindole, **34**. When $POCl_3$ is used as a reagent with DMF, oxindole undergoes Vilsmeier-hack formylation to give 2-chloro-3-formylindole, **36** which upon further reaction with $POCl_3$ at reflux temperature gives 2-chloro indole, **37**. Under base-catalyzed reaction conditions, substitution occurs preferentially at the C-3 position rather than the C-1 center. The lactim isomer of oxindole forms sodium-1*H*-indole-2-olate salt, **39** with NaOH. Lastly, when aryl-substituted aldehydes undergo aldol condensation with oxindole at 140 ºC under base-catalyzed conditions, 3-arylidene-2-oxindole derivatives, **35** are furnished. [17]

1.4 Reactivity of Oxindoles

1.4.1 Oxindole as an Electrophile

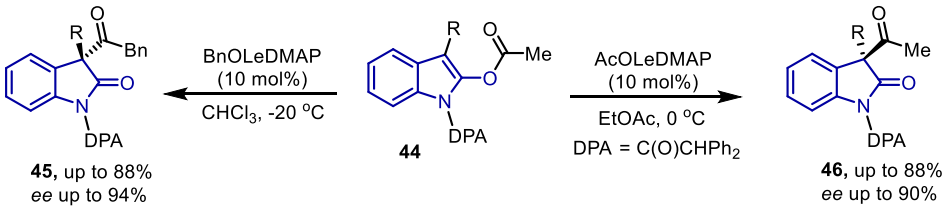
The reactivity of oxindoles as an electrophile has been observed in only a few instances. In 2009, Stoltz provided an example of using oxindoles as electrophile with 1,3-dicarbonyl compounds. The reaction required a halooxindole, **41** a base, and activated malonate esters, **42,** chiral copper(II)-BOX complex to produce a C3 quaternary stereocenter, **43** (Scheme 1.4).[18]



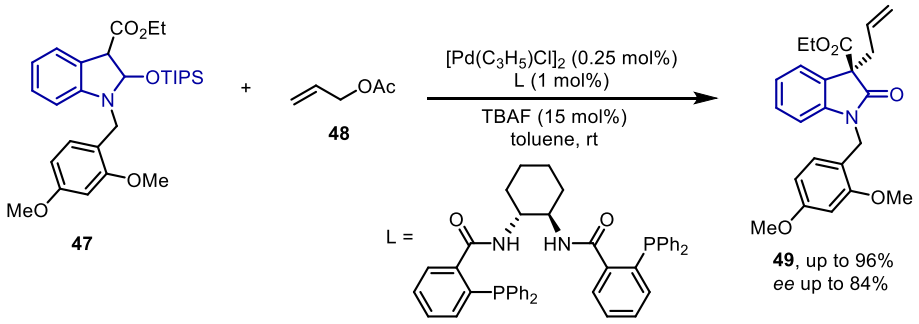
Scheme 1.4: Electrophilic reaction of oxindole with 1,3-dicarbonyl substrates.

1.4.2 Rearrangement Reactions of Oxindole

O-substituted 2-oxindoles derivatives, **44** are incredibly significant due to their remarkable ability to construct C-3 quaternary stereocenters in 2-oxindoles, **46**. Indolyl acetates, esters, and carbonates serve as ideal substrates for intramolecular catalytic rearrangements (Scheme 1.5).[19] These rearrangements have proven to be extremely useful in the development of new compounds with diverse applications in the pharmaceutical field. Trost *et al.* in 2006, developed a highly effective protocol and synthesized C-3 quaternary centers of 2-oxindoles, **49** through intramolecular reaction of O-substituted 2-oxindoles, **47** *via* palladium-catalyzed asymmetric allylic alkylation (AAA) method (Scheme 1.6). With this breakthrough methodology, they successfully synthesized the enantioenriched naturally occurring alkaloid (–)-horsfiline in an impressively satisfactory yield.[20]



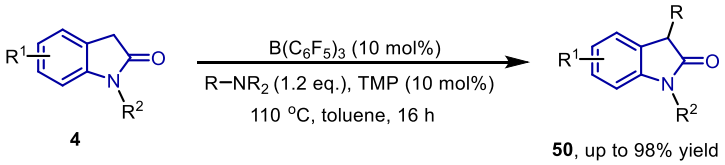
Scheme 1.5: Intramolecular rearrangement of O-substituted 2-oxindole.



Scheme 1.6: Pd-Asymmetric allylic alkylation-based synthesis of C-3 enantioenriched 2-oxindoles.

1.4.3 Reaction at C3 Center

N-substituted oxindoles, **4** are often used as primary starting materials in numerous protocols. This is due to the high acidities of the hydrogens as well as the availability of softer bases that can be used for deprotonation and simultaneous enolate formation. In this regard, many studies have been performed at C3 center of 2-oxindole, **50**. For instance, a new methodology was introduced for the C3 alkylation by using $B(C_6F_5)_3$ as the catalyst and an amine-based alkylating agent.[21] Here, boranes behaved differently and cleaved α-N C(sp^3)-H bond heterolytically which ultimately results into the making of C-C bond as shown in the scheme 1.7 below.



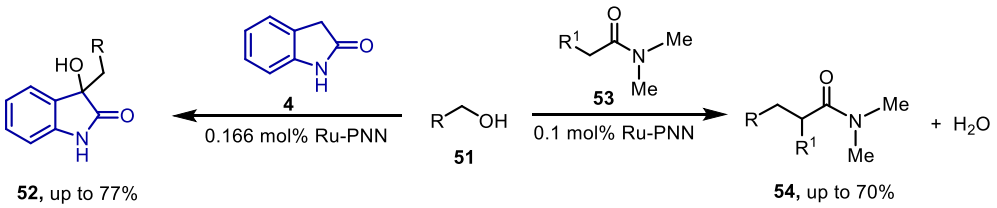
Scheme 1.7: C3-alkylation of oxindoles by using $B(C_6F_5)_3$ as the catalyst.

Spirooxindoles, have become a subject of intense interest in drug discovery and its development due to their vast prevalence in organic chemistry and natural products. They possess a sp^3-hybridized C-3 carbon at the bicyclic structure, making them the primary building blocks for a wide range of pharmaceutical molecules. Furthermore, they serve as the major unit of many alkaloids, which are of immense importance in the field of medicine.[22]

C3-fluorinated oxindoles have captured the interest of researchers in recent years due to their remarkable array of biological properties. Beyond their significance in medicinal chemistry, these structural motifs are also employed in crafting intricate molecular frameworks adorned with fluorine atoms under specific reaction conditions. Furthermore, C3-difluorinated oxindoles are harnessed as nucleophilic catalysts for regenerative

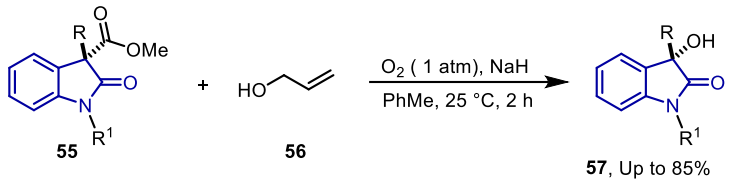
glycosylation. This class of compounds is intriguing due to its wide-ranging biological activities, placing it at the forefront of research in medicinal chemistry. Furthermore, they are valuable building blocks for creating complex structures that contain fluorine atoms, and are thus used in the synthesis of novel materials. Notably, C3-difluorinated oxindoles act as catalysts for regenerative glycosylation, a key process in the biosynthesis of carbohydrates. Overall, the multifaceted properties of C3-fluorinated oxindoles make them a promising area of research with significant potential for future applications.[23]

The process of direct α-alkylation by employing alcohols with high TON (turnover number) is efficiently achieved with Ru-PNN catalysts. This is made possible through a series of steps including dehydrogenation, condensation, and hydrogenation under simple and facile reaction conditions. The use of a phosphine-based pincer complex has proven to be highly effective for α-alkylation reactions of various amides with a wide range of alcohols, distinguishing it from other Ru-catalysts (as shown in Scheme 1.8). Additionally, the combination of alcohol, **51**, and Ru-PNN catalysts has resulted in a new method for synthesizing C3-hydroxy-2-oxindole, **52** directly from 2-oxindole through double functionalization in a single step, without the need for any oxidant. The resulting products have been thoroughly characterized and supported by X-ray structures. This method is highly valued for its straightforwardness, its ability to work with a wide range of substrates, and its high atom efficiency. As a result, it presents an appealing alternative approach for the synthesis of both α-alkylated amides and C3-alkylated-3-hydroxyindolin-2-one, **52**.[24]



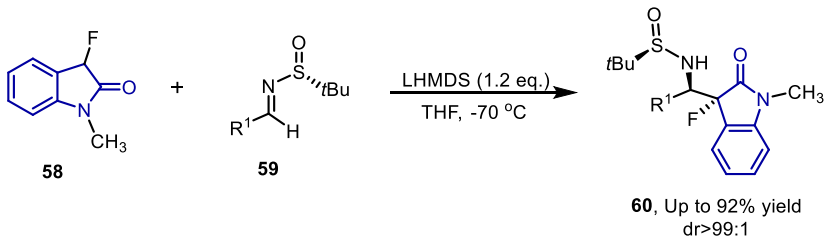
Scheme 1.8: α-Alkylation of amides by the use of alcohols and Ru-catalysis.

In 2017, Bisai *et al.* presented a highly efficient strategy for synthesizing 3-hydroxy-2-oxindoles, **57** using oxygen gas as an eco-friendly source of oxidants (Scheme 1.9). This is achieved by taking advantage of deacylative oxidation *via* retro-Claisen condensation.[25]



Scheme 1.9: Deacylative oxygenation (DaO) leading to the production of 3-hydroxy 2-oxindoles.

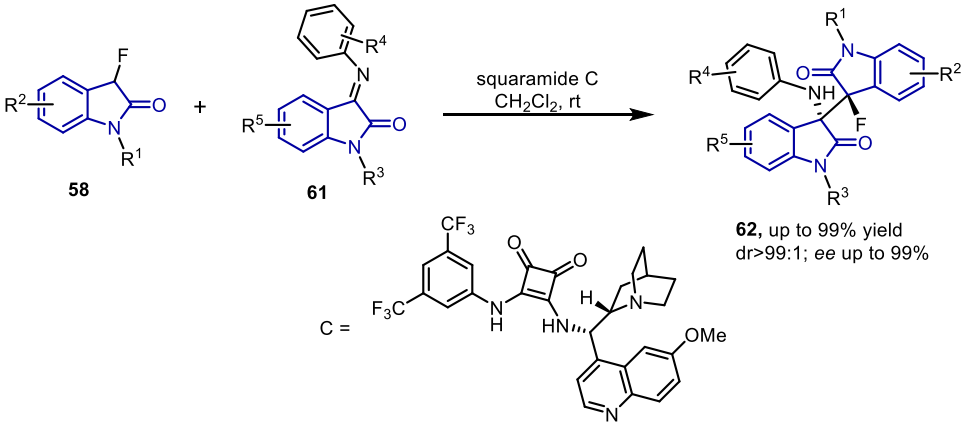
A new method has been developed to create stereogenic C-F units through a diastereoselective Mannich reaction (Scheme 1.10). This involves the use of α-fluorosubstituted amides, including 3-fluoro-oxindoles, **58** with N-*tert*-butylsulfinylimines, **59** and fluoroacetamides, to provide α-fluoro-β-amino amides, **60** with stereogenic fluorinated C3 position. This method is advantageous because it uses easily accessible starting reagents and is simple in operation.[26]



Scheme 1.10: Synthesis of C3 quaternary stereocenter by the Mannich reaction between Fluoroacetamides, 3-Fluorooxindoles and N-(*tert*-Butylsulfinyl)imines.

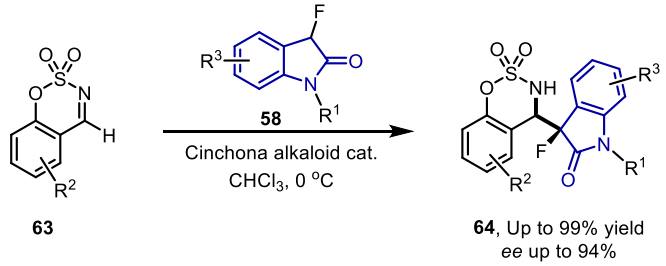
Later, in 2018, Du *et al.* documented a new method for synthesizing fluorinated 3,3'-bisoxindoles, **62** with adjacent stereocenters (Scheme 1.11). This method involves using

squaramide catalyst to carry out an asymmetric Mannich reaction between isatin-derived imines, **61** and 3-fluorooxindoles, **58**. The resulting 3,3'-bisoxindoles were obtained in 99% yield, with dr >99:1 and >99% *ee*.[27]



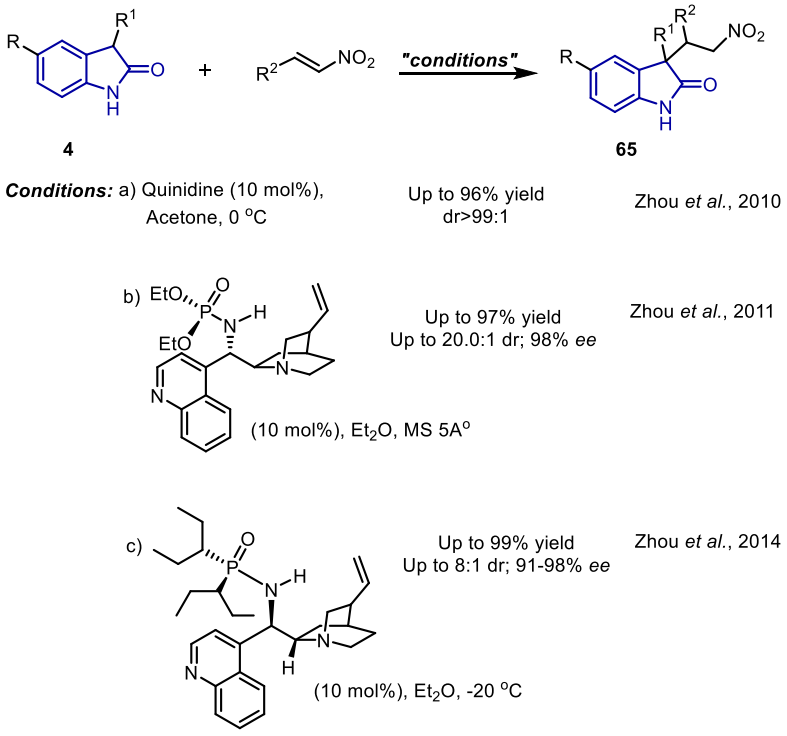
Scheme 1.11: Harnessing fluorinated 3,3'-bisoxindoles *via* asymmetric Mannich reactions

On the same note, using alkaloid catalyst- cinchona, Li *et al.* have developed a synthesis method for C3-fluorinated benzo-fused sulfamidate moiety, **64** with high enantioselectivity (Scheme 1.12). This method involves adding C3-fluorinated oxindoles, **58** to cyclic N-sulfamidate aldimines, **63** and an alkaloid catalyst- cinchona.[28]



Scheme 1.12: Synthesis of C3-fluorinated benzo-fused sulfamidate derivatives from 3-Fluorooxindoles and N-Sulfamidate Aldimines.

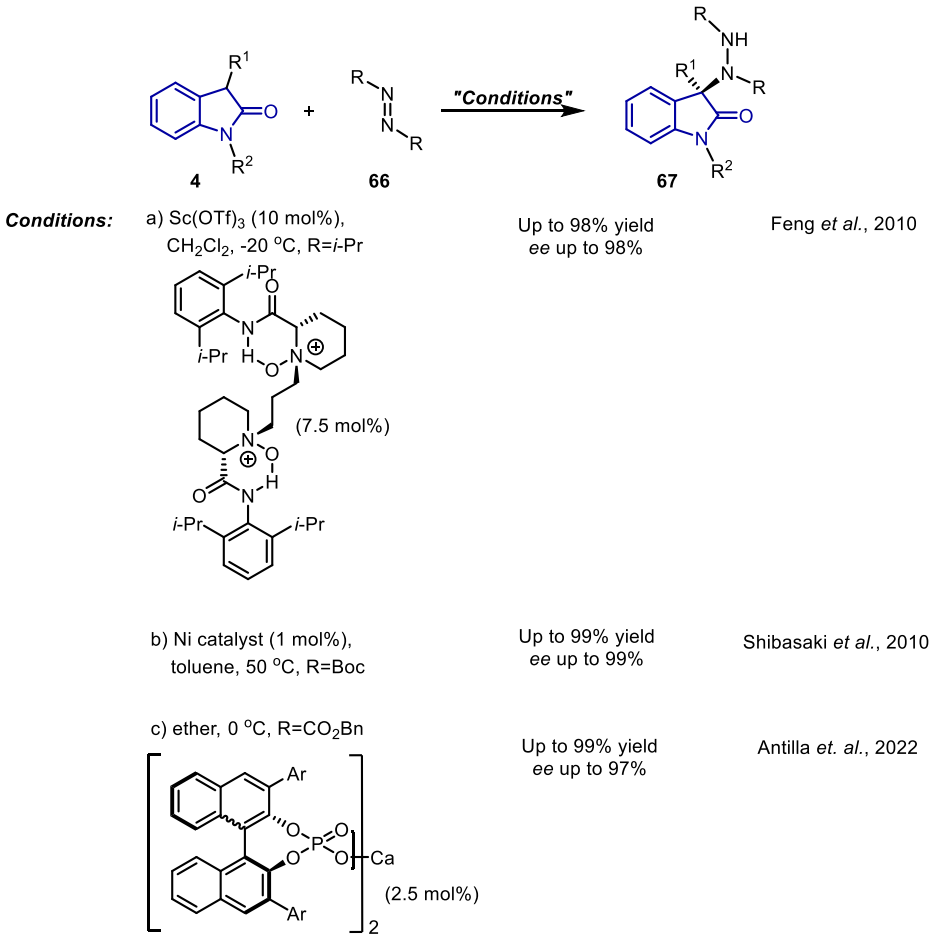
In 2010, Zhou *et al.* reported a quinidine-catalyzed Michael addition of N-unprotected C3-substituted oxindoles, **4** and nitroolefins (Scheme 1.13 a). Later, in 2011 and 2014, the same group developed a range of phosphoramide catalysts based on cinchona alkaloid that are easily accessible and simple (Scheme 1.13 b and c). Out of all these catalysts, they identified that cinchonidine-alkaloid hinged bifunctional phosphoramide is appreciably enantioselective and diastereoselective for the reaction of nitroalkenes and unprotected 3-prochiral oxindoles to form **65**.[29]



Scheme 1.13: Michael addition of N-unprotected C3-substituted oxindoles with nitro-olefins.

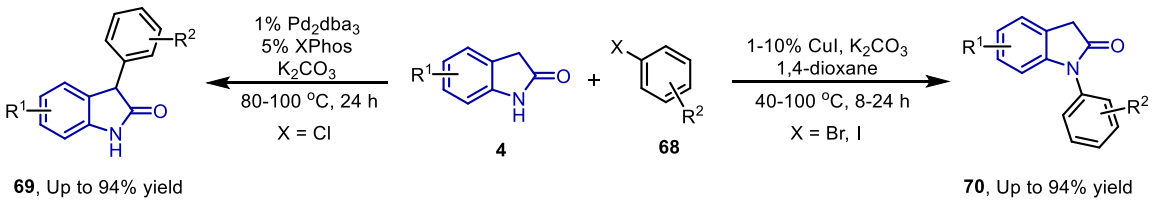
A new process is hosted for the highly selective amination of C3-substituted oxindoles, **4** with azodicarboxylates, **66**. This process is catalyzed by a chiral $Sc(OTf)_3$/N,N'-dioxide complex (Tf: triflate) and results in the production of the 3-amino-2-oxindole derivatives,

67. The protocol offers a wide variety of substrates in high yields and high enantioselectivities (92–96% ee) (Scheme 1.14 a).[30] In the same year, Shibasaki and co-workers also reported the synthesis of chiral 3-aminooxindoles, **67** by using a complex of Ni_2-Schiff base and azodicarboxylates, **66** (Scheme 1.14 b).[31] Similarly, Antilla *et al.* also synthesized the same compound with dibenzyl azodicarboxylate and chiral calcium phosphate catalyst, offering a wide range of substrate scope in good yields and high enantioselectivity (Scheme 1.14 c).[32]



Scheme 1.14: Selective amination of C3-substituted oxindoles with azodicarboxylates.

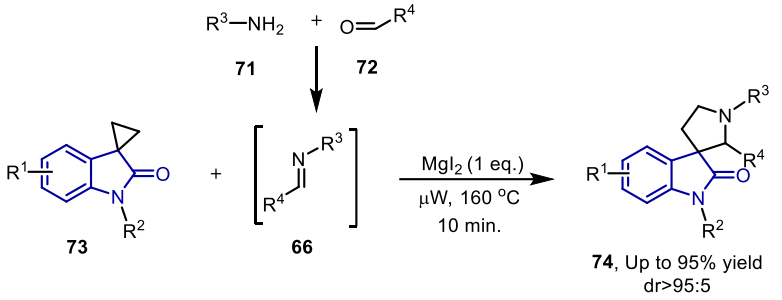
In the field of organic chemistry, cross-coupling reactions have become a powerful tool for constructing complex organic molecules. In this context, unprotected oxindoles, **4** are combined with aryl halides, **68** to form new compounds. However, the chemoselectivity of the reaction can vary depending on the type of catalyst system used. In this study, two different catalyst systems were investigated: one based on Pd-dialkylbiarylphosphine and the other on Cu-diamine. The Pd-based system selectively arylated oxindole at the C3 position, **69** while the Cu-based system exclusively arylated at the nitrogen site, **70** (Scheme 1.15). This orthogonal chemoselectivity of the two catalyst systems provides an exciting opportunity to selectively modify oxindoles and could potentially be applied in the synthesis of novel pharmaceuticals and natural products.[33]



Scheme 1.15: Orthogonal C- and N- arylation of Oxindole using Pd and Cu catalyst respectively.

1.4.4 Ring-expansion and ring-contraction on oxindole

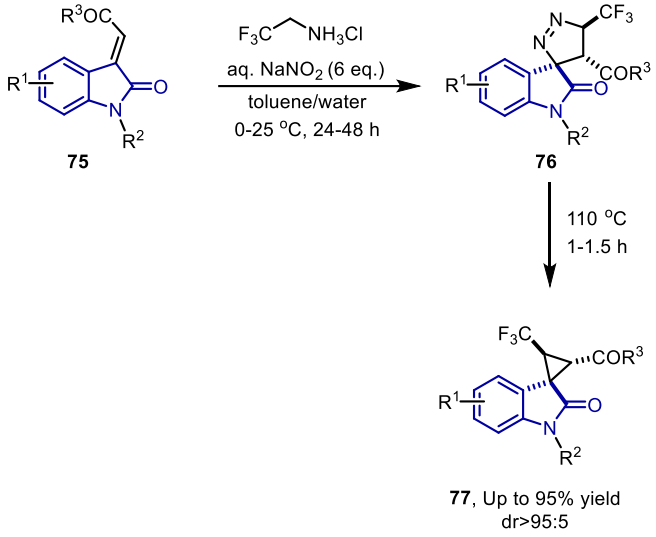
A novel three-component synthesis method utilizing magnesium iodide (MgI_2) has been described for the preparation of molecules having the 3,3'-pyrrolidinyl-spirooxindole core,



Scheme 1.16: Ring-expansion on oxindole- Synthesis of Spiro[pyrrolidin-3,3'-oxindoles].

74 (Scheme 1.16). In this method, a variety of aldehydes, **72** and amines, **71** are combined correspondent of a natural product-like core. This approach has the potential to significantly expand the chemical space for the preparation of biologically relevant compounds.[34]

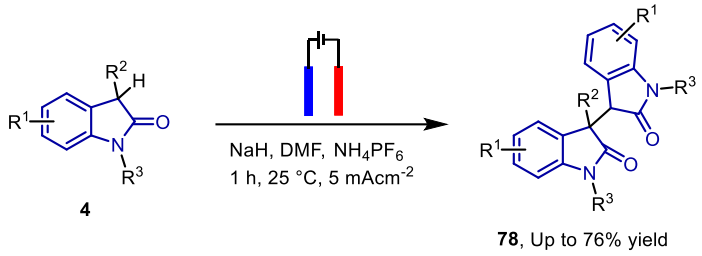
Research by Xiao and the team utilized 3-ylideneoxindoles, **75** with in situ-prepared CF_3CHN_2 which led to the development of a process showing a [3 + 2] cycloaddition followed by ring contraction reaction (Scheme 1.17). This innovative metal-free approach efficiently produces CF_3-functionalized 3,3′-cyclopropyl spirooxindole compounds, **77** in exceptional yields, while maintaining excellent diastereoselectivities. Notably, this method enables the one-step synthesis of a CF_3-decorated representative compound of an HIV-1 NNRTI, demonstrating its practical significance. These findings open up newer possibilities for the synthesis of valuable compounds with potential applications in pharmaceutical and materials science.[35]



Scheme 1.17: Ring contraction on oxindole: Synthesis of CF_3-decorated 3,3'-cyclopropyl spirooxindoles.

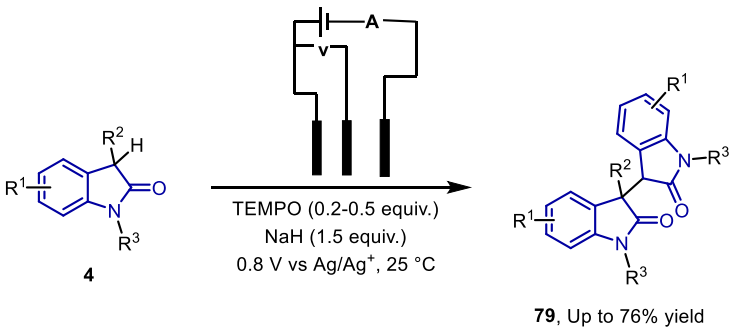
1.4.5 Electrochemical reactions of Oxindoles

Paul and coworkers gave an account of an electro-oxidative preparation for dimeric 2-oxindoles with vicinal C3 quaternary centers, **78** (Scheme 1.18). It can be produced through three ways, *viz.* (a) reaction between two radicals, (b) base-assisted PT-ET-ET reaction pathway between an enolate and carbocation, (c) reaction following an ET-PT-ET pathway between an enolate anion and carbocation. An appropriate base choice can show an increment in the kinetics of electro-organic protocols remarkably. Their study shows the advantages of proton-coupled electron transfer (PCET) in electro-organic procedures, providing a significant direction in this field.[36]



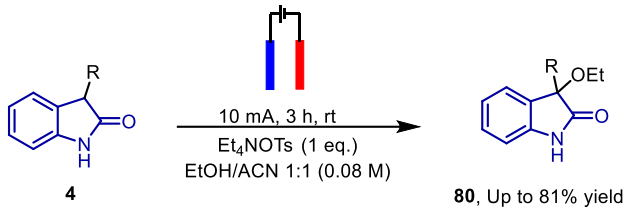
Scheme 1.18: Electrochemical oxidative coupling of oxindole by sharing vicinal quaternary centers.

Recently in 2023, the same group of researchers developed an innovative method for dimerizing 3-substituted-2-oxindoles, **4** using an indirect electrocatalytic process (Scheme 1.19). This process involved using a redox mediator- TEMPO to prevent electrode passivation and lower the activation barrier. To carry out the synthesis, an undivided cell was used and charged with a constant voltage of 0.8 V *vs* the Ag/Ag+ reference electrode, allowing for greener electrochemical conditions. Through this method, the team was able to successfully dimerize three different types of 3-substituted-2-oxindoles, resulting in moderate to good yields of dimeric 2-oxindoles, **79**. This groundbreaking research has the potential to greatly impact the field of organic synthesis.[37]



Scheme 1.19: Dimerization of C3-substituted oxindoles electrochemically.

In 2022, Maulide and co-authors proclaimed a highly efficient and versatile electrochemical method that allows for the direct functionalization of the C-H bond to access unsymmetrical 3,3-disubstituted oxindoles, **80** (Scheme 1.20). This method omits the use of stoichiometric oxidants and can be carried out under mild and environmentally benign conditions, making it a highly attractive option for sustainable chemical synthesis. One of the key advantages of this method is its ability to facilitate the functionalization of oxindoles through C-O bond formation, which can be easily extended to C-C or even C-N bond formation. This opens up new opportunities for the synthesis of complex and diverse organic molecules, which can have significant implications in the fields of drug discovery and materials science.[38]

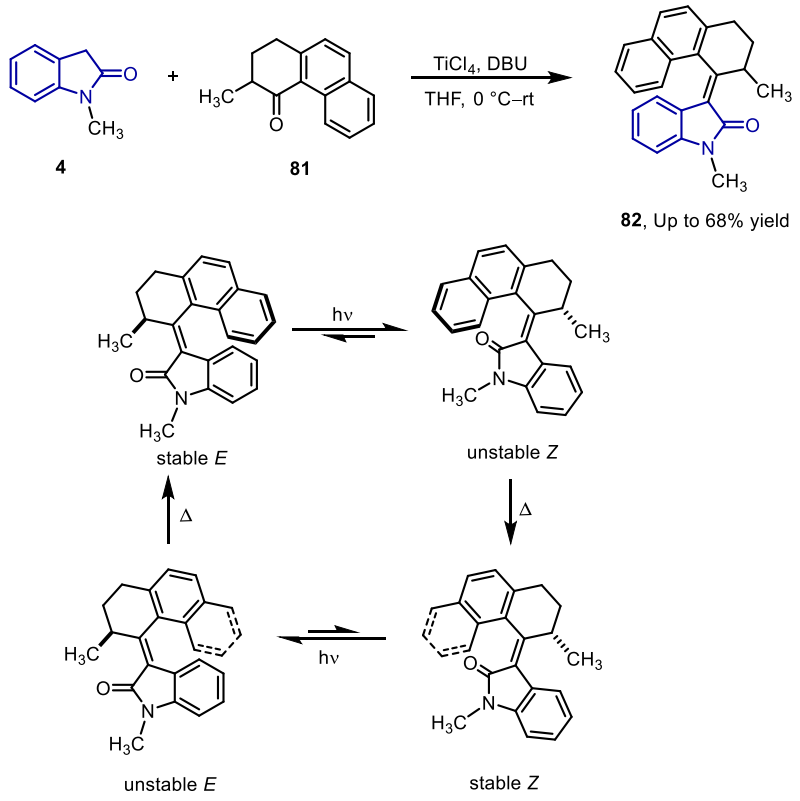


Scheme 1.20: Electrochemical C-H functionalization of oxindole at the C-3 carbon.

1.4.6 Light-mediated Reactions of Oxindoles

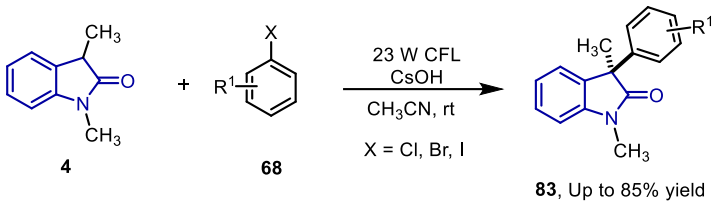
Researchers have developed molecular motors associated with oxindole, which are smoothly accessible and can be powered by visible light. These motors have a 4 step rotation cycle, which is proposed using DFT calculations. The motors can be easily synthesized with four different upper halves using Knoevenagel condensation. Moreover, the oxindole scaffold is free for further functionalization, which could open up new possibilities for the application of these motors in biology and materials science. With these

motors, the field of nanotechnology could be revolutionized, leading to new and exciting discoveries (Scheme 1.21).[39]



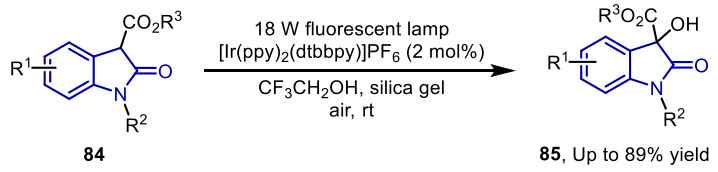
Scheme 1.21: Oxindole-based motors powered by visible light.

Xia *et al.* charted a transition-metal-free reaction for coupling of aryl halides, **68** with oxindoles, **4** under irradiation of visible-light (Scheme 1.22). No external photoredox catalysts are needed, and for the light source, a simple household CFL bulb was used at the room temperature. The process is highly efficient and produces only the halogen anion as a byproduct. This redox neutral method is a useful and efficient way to produce 3-aryloxindole products, **83**. It involves a radical chain propagation pathway and can be used to create a variety of 3-aryloxindole derivatives that are of importance in the pharmaceutical industry, all in a single step.[40]



Scheme 1.22: α-Arylation of oxindoles powered by visible.

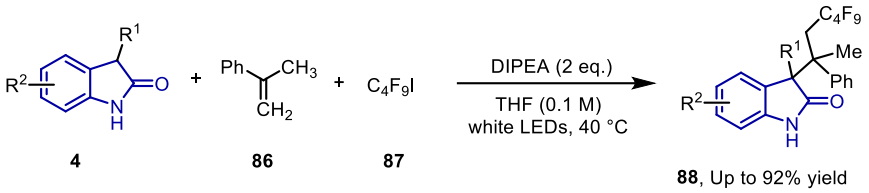
The same group presented a photocatalytic system to obtain 3-ester-3-hydroxy-2-oxindoles, **85** which are potentially important molecules in biology (Scheme 1.23). The yield of this process can reach up to 89%. The reaction can be performed at room temperature and exposed to air under visible light. Additionally, the optimized conditions do not require the addition of a base, making this method suitable for unprotected as well as N-allyl protected compounds, **84**. This process can also be scaled up to a gram level without complication.[41]



Scheme 1.23: Hydroxylation of 2-oxindoles *via* visible light-promoted aerobic oxidation.

Later in 2021, Zheng and co-authors developed a method for assembling oxindole derivatives having fluoroalkyl groups, **87** to produce **88** through a three-component photocatalytic radical coupling reaction where fluoro-benzyl iodides are found to be the key intermediates (Scheme 1.24). This process uses readily available materials to produce a range of structural and functional oxindoles with adjacent quaternary centers. These centers are difficult to achieve using other methods. This method works effectively with a wide range of alkenes, *viz.*, conjugated dienes, and enynes, terminal and non-terminal

alkenes, **86**. This method is useful for synthesizing known pharmaceutical analogs in a rapid and scalable way.[42]



Scheme 1.24: 3-Component reaction of oxindole with fluoroalkyls and alkenes.

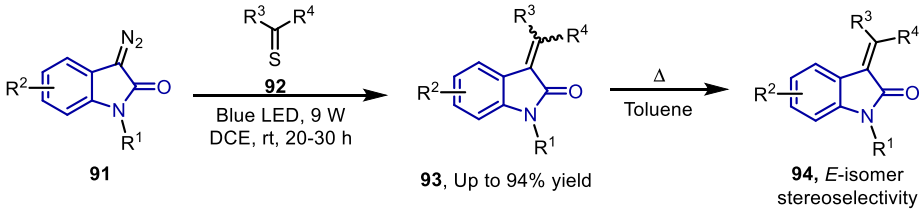
A new metal-free and chemoselective hydrogenation method *via* photoredox catalysis using Eosin Y as the catalyst was achieved by Bhat and co-authors (Scheme 1.25). Here, DIPEA was utilized as a sacrificial electron donor, followed by in-situ generation of cationic radical which is used as a reductant to synthesize **90**. The method is practical,

Scheme 1.25: Reduction of α-Alkylidene Oxindoles.

scalable, and can reduce a variety of substrates having activated double bonds, **89**. Mechanistic studies show that the activated double bond systematically quenches the photocatalyst through oxidation.[43]

A fascinating study has demonstrated a novel method for the synthesis of diverse symmetrical and unsymmetrical 3-arylidene oxindoles (Scheme 1.26). The process involves a cross-coupling olefination reaction, which uses diazoindolones, **91** and

diphenylmethanethiones, **92** along with blue LED irradiation. In addition to the successful synthesis of the oxindoles, the process also eliminates elemental sulfur while generating tetrasubstituted olefins, **94**. The study also showed that this process has other potential applications, including thermal olefin isomerization, gram-scale synthesis, and stereoselective synthesis, all in good yield. Overall, this research has opened up new avenues for the synthesis of complex molecules, with potential benefits in the fields of chemistry, medicine, and materials science.[44]



Scheme 1.26: Preparation of 3-Arylidene Oxindoles by using Blue LED.

1.5. Thio-oxindoles

Like oxindole, their sulfur analogs (thio-oxindole) also exhibit many biological activities. Over the past few years, thio-oxindole has become increasingly recognized as a valuable component in constructing indole-fused and spiro organosulfur compounds, **95-100**. Figure 1.7 showcases a variety of thio-oxindole-based drugs, each known for their anti-tumor, antibacterial, antifungal, analgesic, and melanogenesis inhibitor properties.[45] It is worth noting that, at present, only a limited number of methodologies exist for the functionalizations of thio-oxindole which I have discussed in the sections below:

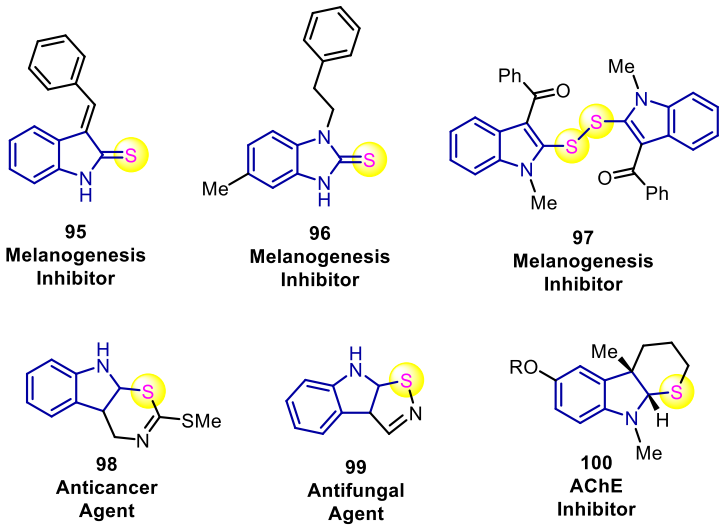
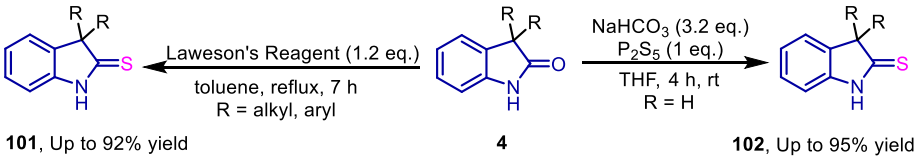


Figure 1.7: Representative examples of biologically active thio-oxindoles and their derivatives.

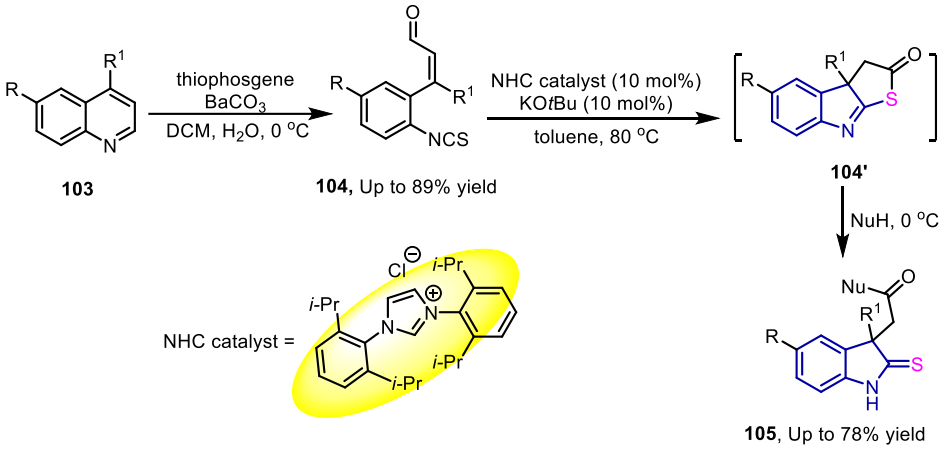
1.6 Synthesis of Thio-oxindoles

The reaction involved the addition of sulfur to C3-unsubstituted oxindoles, **4** using phosphorous pentasulfide (P_2S_5) to produce the corresponding 2-indolinethiones, **102**. If the 2-indolinone at C3-position had more than one hydrogen, it reacted with P_2S_5 to yield indoline-2-thione. However, when the C3-substituted oxindole is treated with P_2S_5, it turned out to be unreactive.[46] Furthermore, the reaction of C3 substituted oxindole with Lawesson's reagent produced the corresponding thio-oxindole, **101** in appreciable yields as represented in Scheme 1.27.[47]



Scheme 1.27: Synthesis of C3-substituted and unsubstituted thio-oxindoles from oxindole.

In 2014, Taekmoto *et al.* developed an innovative process that involves a NHC-catalyzed formation of 2*H*-thienoindolones and a subsequent nucleophilic ring-opening reaction (Scheme 1.28). This method utilizes α,β-unsaturated aldehydes containing an isothiocyanato moiety, **104**. As a result, it allows for the efficient synthesis of different 3,3-disubstituted indoline-2-thiones, **105**. These indoline-2-thiones hold a quaternary center at the C-3 position and are produced in appreciable yields.[48]



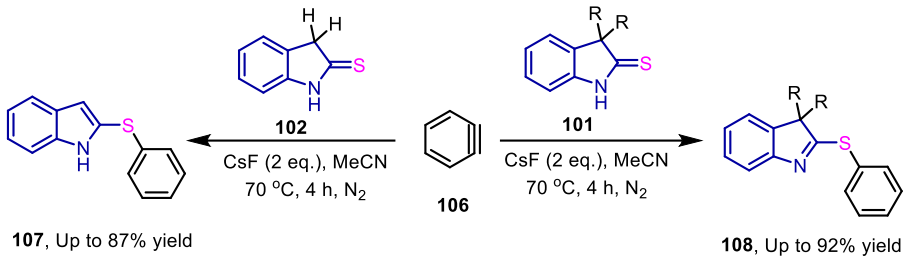
Scheme 1.28: Synthesis of thio-oxindoles with a quaternary center at C3 position by using an NHC catalyst.

1.7 Reactivity of thio-oxindoles

1.7.1 Reaction of thio-oxindole with arynes

Tan and co-workers in 2020, demonstrated a highly selective S-arylation of thio-oxindoles, **107, 108** that omits the use of transition metals (Scheme 1.29). This innovative method has been successfully utilized with a wide array of building blocks, and it has proven to be

effective even at a gram scale. To further investigate their protocol robustness and broader derivatizations, authors showcased its potential in medicinal chemistry. In this regard, the simplicity of this operational procedure and its wide tolerance for different functional groups make it an ideal choice for carrying out this synthesis on both small as well as industrial scale.[49]

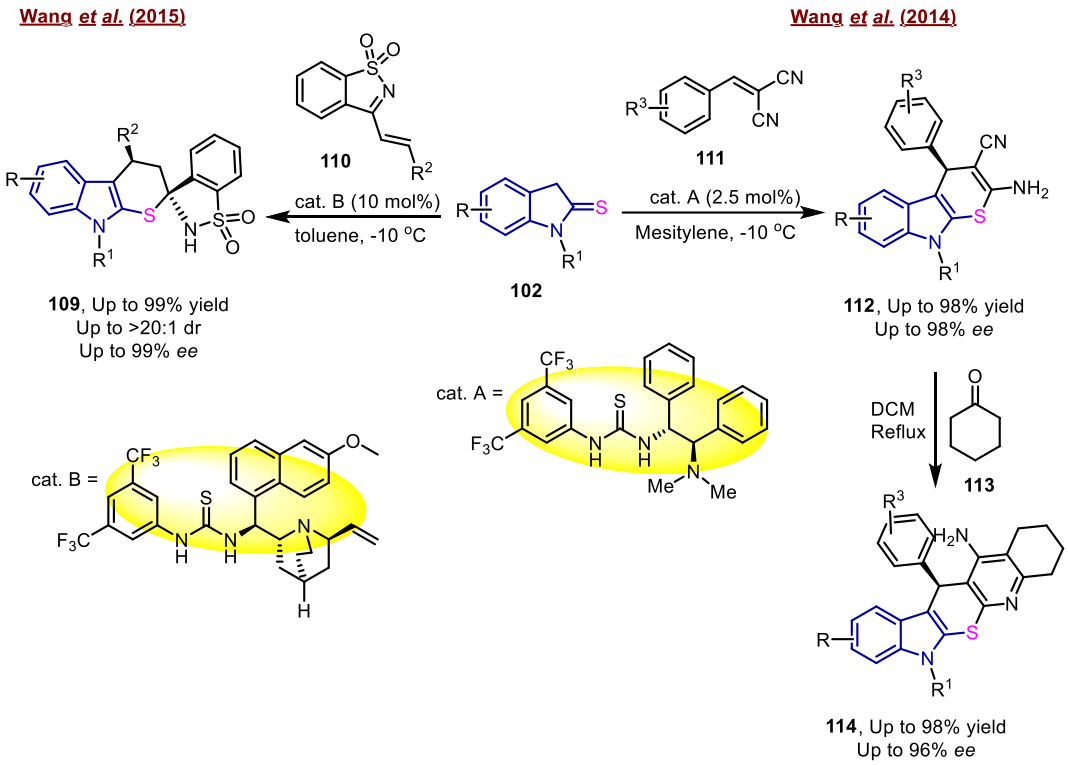


Scheme 1.29: Arylation of C3 unsubstituted and substituted thio-oxindoles.

1.7.2 Cycloaddition Reactions of thio-oxindole

Wang *et al.* made significant progress in designing cascade thio-Michael-cyclization reaction *via* asymmetric organocatalysis (Scheme 1.30). This method aimed at producing crucial thiopyranoindole annulated heterocyclic derivatives. The group has revealed a notable reactivity between 2-benzylidenemalononitrile, **111** and indoline-2-thione, **102** (keto-S), and elaborated by density functional theory (DFT) calculations.[50] Later, the same group introduced a novel method for creating a series of complex spiro[thiopyranoindole-benzoisothiazole] heterocyclic derivatives, **109**. This was achieved through an innovative formal [3 + 3] cycloaddition reaction by using asymmetric organocatalysis, in the sight of a 3° amine-thiourea catalyst. Here, the process yielded these compounds in high yields with impressive diastereo- and enantioselectivities. This approach represents a significant advancement in the enantioselective synthesis of spiro[thiopyranoindole-benzoisothiazole] heterocycle compounds, which are characterized by a spiro quaternary stereogenic center

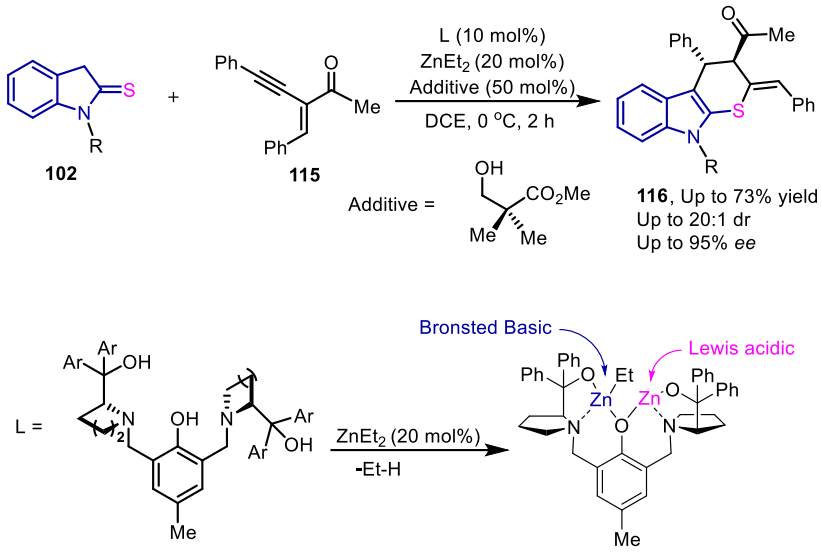
involving C−S/C−N bonds. The resulting products exhibit a unique structure that holds promise for potential drug discovery endeavors.[51]



Scheme 1.30: [3+3] Annulation reactions of indoline-2-thiones.

Recently, Jia *et al.* reported a new method using zinc catalyst to asymmetrically join indoline-2-thiones to yne-enones, **115** in a [3 + 3] annulation manner. This method allows for the creation of tetrahydrothiopyrano[2,3-*b*]indole compounds, **102** with an exocyclic double bond. The process delivers moderate yields and exceptional stereoselectivity, as shown in the scheme 1.31. This innovative transformation has a variety of substrate scope and enables the synthesis of complex molecules on a larger scale. Additionally, it allows for late-stage functionalization. Further authors mentioned that they are delving deeper into

the reaction mechanism and exploring the potential applications of this protocol for constructing other intricate chiral heterocycles, **116**.[52]

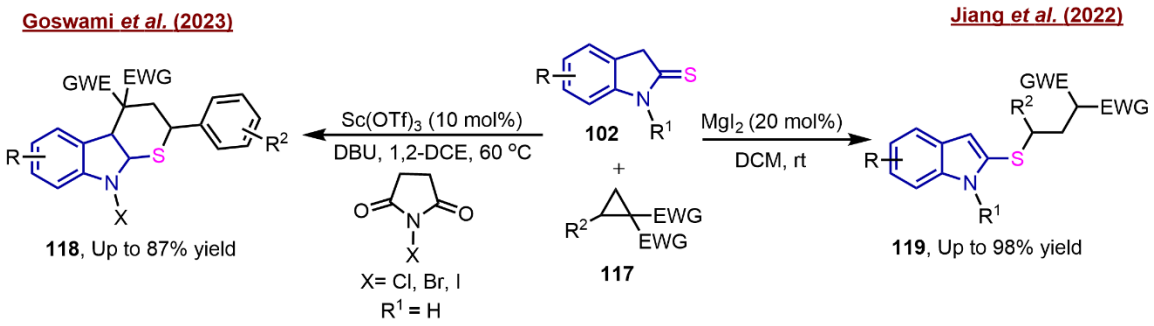


Scheme 1.31: Synthesis of tetrahydrothiopyrano[2,3-*b*]indole derivatives *via* [3+3] annulation of yne-enones and indoline-2-thiones.

1.7.3 Reactions of thio-oxindole with donor-acceptor cyclopropanes (DACs)

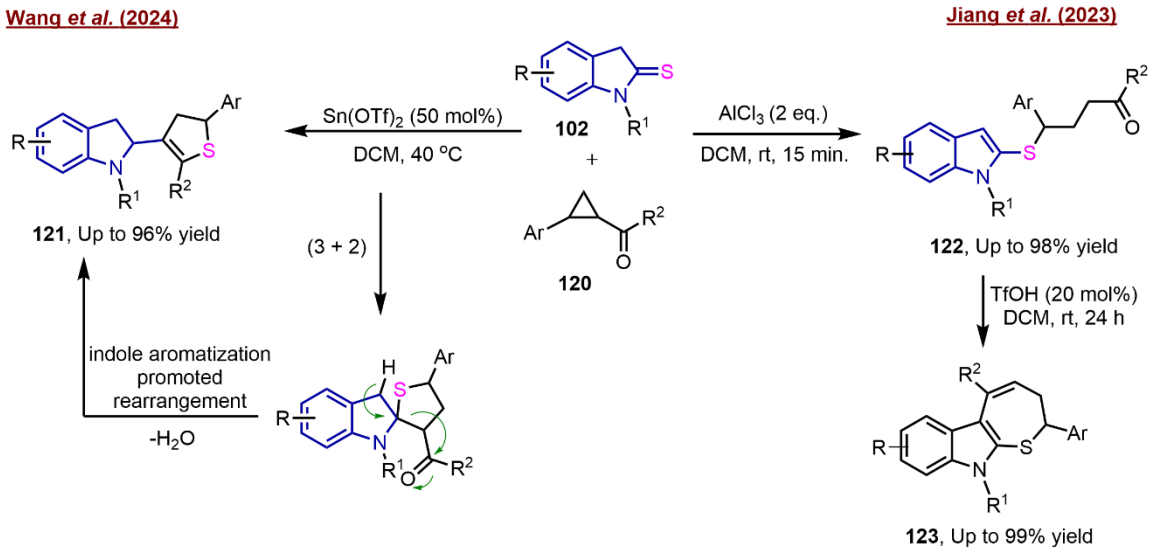
Using a chemoselective MgI_2-catalyst-based ring-opening reaction, Jiang *et al.* developed a method to react indoline-2-thiones, **102** with DACs, **117** (Scheme 1.32). This innovative method enables the efficient production of a range of γ-thioether tethered butyric acid scaffolds, **119** hosting a 2-indole group, with appreciable yields. Furthermore, the resulting products can be readily transformed into methionine and sulfone analogs, allowing for a wide range of potential applications and further chemical synthesis.[53] In a similar fashion, a highly effective and direct approach has been devised by our team (Goswami *et al.* in 2023) for creating N-halo indole-fused dihydrothiopyrano derivatives, **118**. This method involves using $Sc(OTf)_3$ as a catalyst to facilitate (3 + 3)-annulation reactions between

indoline-2 thiones and DACs under mild conditions, resulting in consistently high yields. These derivatives hold significant promise for synthesizing targeted biologically important molecules, and we are actively pursuing this avenue for further research and development.[54]



Scheme 1.32: Ring-opening and annulation reaction of indoline-2-thiones with DACs

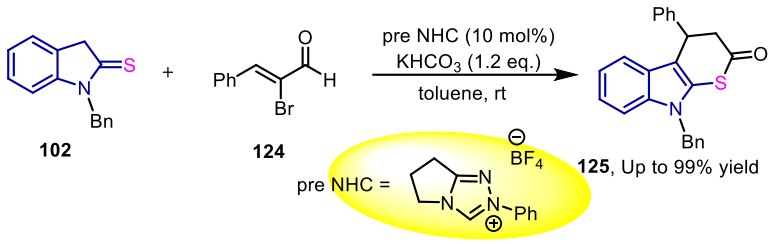
Jiang and co-authors reported a new method for opening the ring of bi-cyclopropanes, acyl cyclopropanes and spirocyclic cyclopropanes using $AlCl_3$ in combination with various indoline-2-thiones (Scheme 1.33). This method allows for the synthesis of 4-heptanones and 4-thiobutan-1-ones that contain a 2-indole group with good yields. Additionally, the resulting ring-opening products, 4-thiobutan-1-ones, can undergo intramolecular cyclization to form 3,10-dihydro-2*H*-thiepino[2,3-*b*]indoles, **123** and further oxidation to sulfones is also achievable.[55] Very recently, Wang *et al.* have successfully conducted a chemical reaction utilizing $Sn(OTf)_2$ as a catalyst. This reaction involved a (3 + 2) cycloaddition followed by sulfur rearrangement of thio-oxindole with cyclopropyl ketone. This innovative method enables the efficient production of a variety of functionalized 3-indolyl-4,5-dihydrothiophenes, **121** with yields ranging from good to excellent. The process consists of a (3 + 2) cycloaddition reaction between indoline-2-thione and cyclopropane having a keto acceptor, followed by a sulfur rearrangement and nucleophilic addition reaction promoted by indole aromatization.[56]



Scheme 1.33: Reactions of indoline-2-thiones with cyclopropyl ketone.

1.7.4 Reaction of thio-oxindole with NHC catalyst

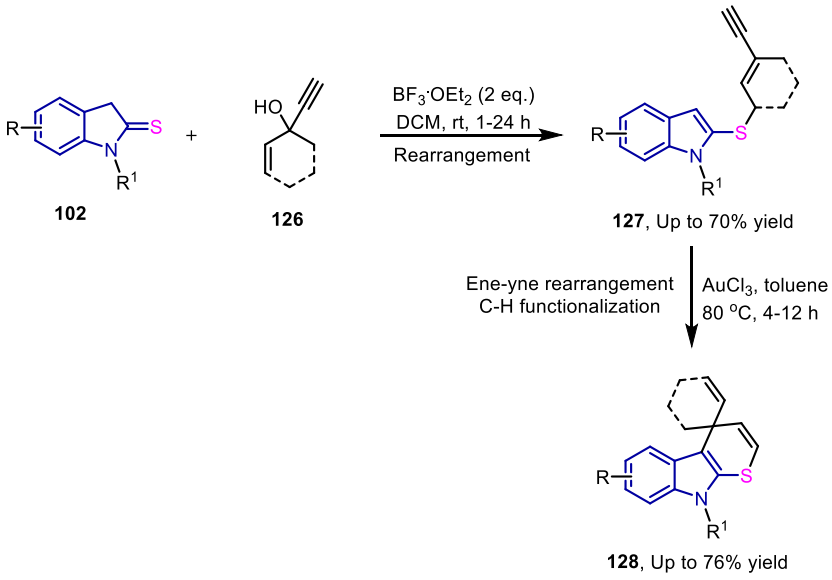
In 2016, a new method has been reported for synthesizing indolo[2,3-*b*]dihydrothiopyranones, **125** by using NHC-catalyst to give [3 + 3] annulation of indoline-2-thiones, **102** and bromoenals, **124**. The process has shown good to high yields with both aliphatic and aryl bromoenals (Scheme 1.34). Furthermore, a preliminary experiment using chiral NHCs displayed encouraging enantioselectivity.[57]



Scheme 1.34: NHC-catalyzed [3 + 3] annulation of bromoenals with indoline-2-thiones.

1.7.5 Other reactions of thio-oxindole

Kumar and group disclosed an efficient method for synthesizing dihydrothiopyrano[2,3-*b*]indole, **128** initiating from indoline-2-thione as represented in scheme 1.35. This process involves two main steps. First, they use $BF_3{\cdot}OEt_2$ to conduct a alkylation reaction that changes the structure of the indoline-2-thione, resulting in a new compound called 2-(2-alkenylthio)indole, **127**. Then, another chemical reaction, involving a specific type of gold as a catalyst, helps them to transform the 2-(2-alkenylthio)-indole into the final product, which is the indole-fused dihydrothiopyran framework, **128**. This transformation happens in a series of steps, involving changes in the arrangement of certain parts of the molecule (ene-yne chain) and the formation of new chemical bonds.[58]



Scheme 1.35: Synthetic route for dihydrothiopyrano[2,3-*b*]indole *via* S-alkylation followed by hydroarylation.

Chapter 1

Aim of the thesis

Oxindole derivatives are widely present in pharmaceuticals and natural products with potential bioactivity. Researchers have been constructing oxindole frameworks for decades and introducing diverse functional groups on the nucleus to expand the drug candidate library. In this regard, I envisioned developing green and efficient methodologies to access different functionalized oxindoles. The following points are kept in mind while conducting research discussed in this thesis:

Literature survey: I have read and thoroughly discussed all the available research and review articles related to oxindole in this thesis. This compilation will be helpful for researchers working on oxindole as it presents a comprehensive discussion of the topic. The thesis provides an extensive elaboration on oxindole, covering both previously known and newly established methods.

Reactivity of Oxindole: The primary objective of this thesis is to delve into the intricate details of 2-oxindoles, as it is of great interest to the scientific community due to their unique chemical properties and potential synthetic applications. Through a comprehensive investigation of its reactivity and interactions with other moieties, this study aims to unearth the full extent of its synthetic potential. This research will provide valuable insights into their chemical transformations and pave the way for the development of innovative synthetic strategies.

Methodology development: The primary goal of this research is to exploit the chemical reactivity of oxindoles. These functionalized oxindoles are indispensable building blocks in the fields of pharmaceuticals and agrochemicals, as they are utilized in the synthesis of various biologically active compounds. The focus of this research is to synthesize compounds with C5, C7, N- and O- functionalization, as these are crucial for the formation of novel and diverse chemical structures. The thesis aims to develop innovative synthetic

methods that can be used to create these compounds efficiently, while also exploring the potential of these compounds for new applications. By making a significant contribution to the advancement of chemical research, this research has the potential to impact various fields that rely on organic synthesis.

Mechanistic studies: In the realm of chemical synthesis, the ability to create functionalized heterocycles is of paramount importance. These molecules are essential building blocks for many pharmaceuticals and complex organic compounds. The chemical reactions that involve oxindoles are particularly challenging due to their complex mechanisms and unpredictable outcomes. The goal of this thesis is to delve into the molecular-level mechanisms of these reactions, intending to provide insights into the complexities of these transformations. By better understanding these mechanisms, I can improve our ability to synthesize functionalized heterocycles with greater efficiency and accuracy.

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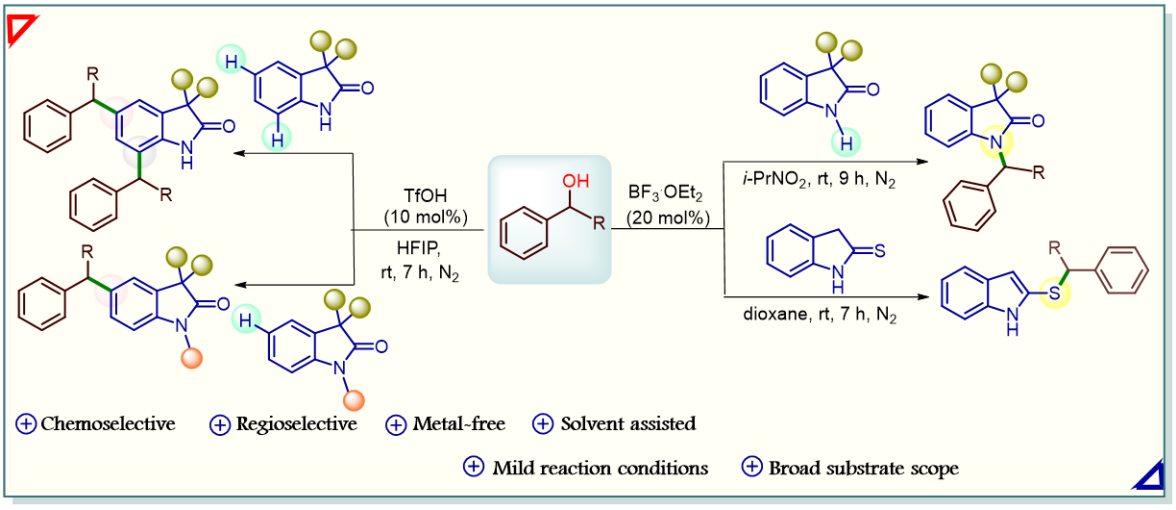
Chapter 2

Metal-Free Switchable Chemo- and Regioselective Alkylation of Oxindoles and Thio-oxindoles using Secondary Alcohols



Chapter 2

2.1 Introduction

As I have discussed in the previous chapter, oxindole is a heterocyclic organic compound that has gained considerable attention for its pharmacological and medicinal properties. Its widespread occurrence in natural plant-based alkaloids further reinforces its potential as a valuable and versatile scaffold that can be modified by various chemical groups to generate novel biological functions, making it an attractive platform for drug development. The simplicity and ease of functionalization of oxindole make it a promising candidate for synthesizing a diverse range of biologically active compounds (Figure 2.1).[1] The inherent characteristics of oxindole like directing group ability, amide-iminol tautomerism, and cross-reactivity offer both challenges and opportunities, making their synthetic transformations appealing.[2]

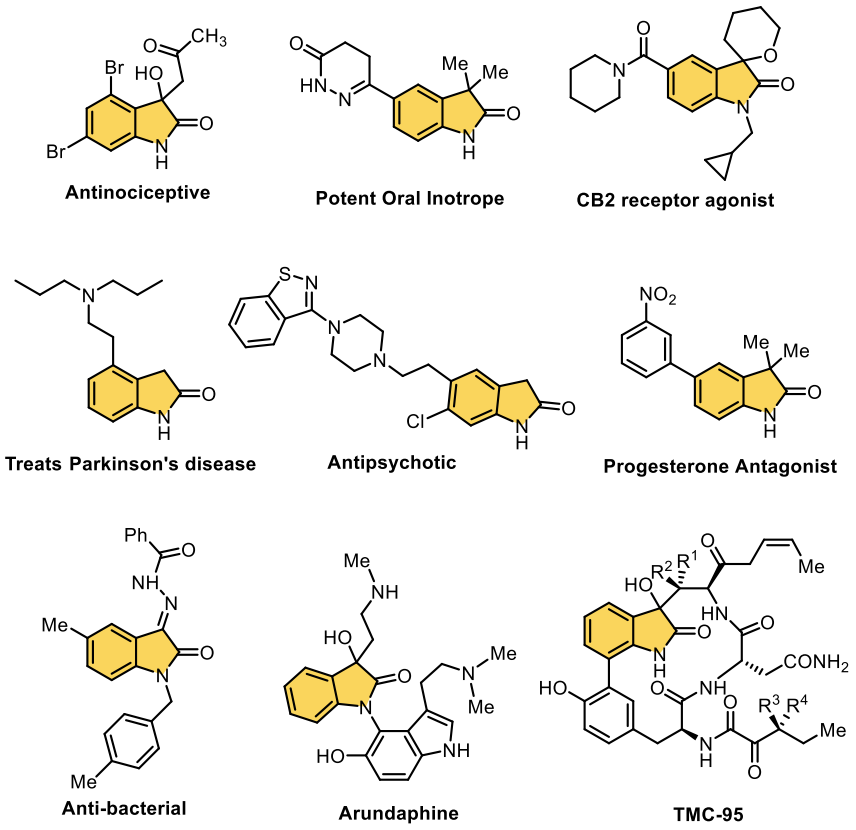
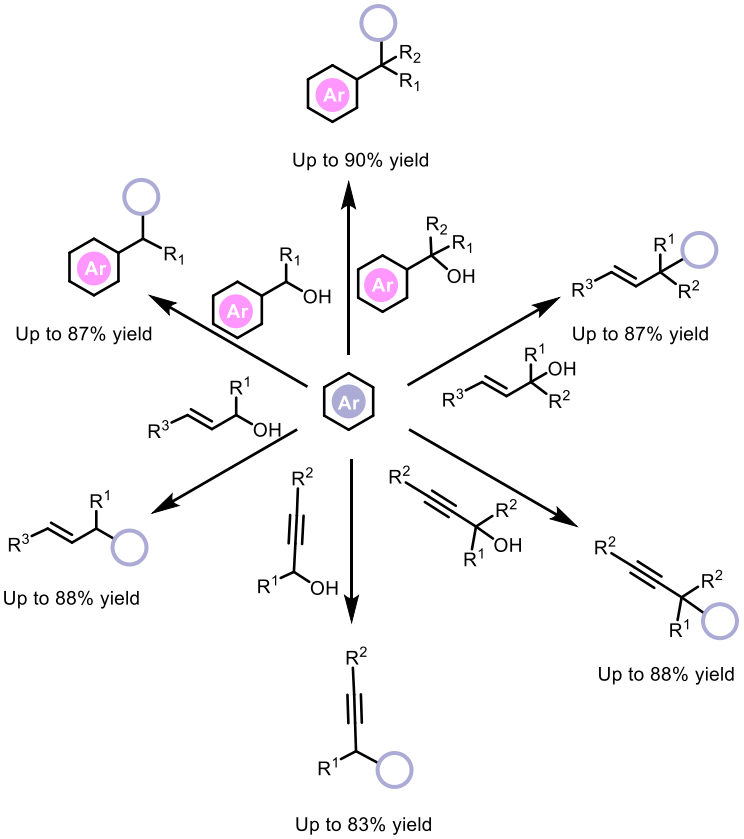


Figure 2.1: Representative examples of biologically active oxindoles.

Chemo- and regioselective Friedel-Crafts (FC) alkylation is one of the efficient tools for increasing molecular complexity.[3] Despite the numerous attempts to improve FC alkylation reactions, they still have significant drawbacks. These include poor regioselectivity and chemoselectivity, low functional group affinity with Lewis acid catalysts, generation of deadly hydrogen halides, and harsh reaction conditions.[4] Although there are plenty of examples of alkylation, the low toxicity and higher stability of alcohols make them a wise alternative to traditional substrates.[5] As hydroxyl groups do not have a strong leaving ability, the reaction totally depends on the compatibility of the alcohol and

Niggemann (2010)



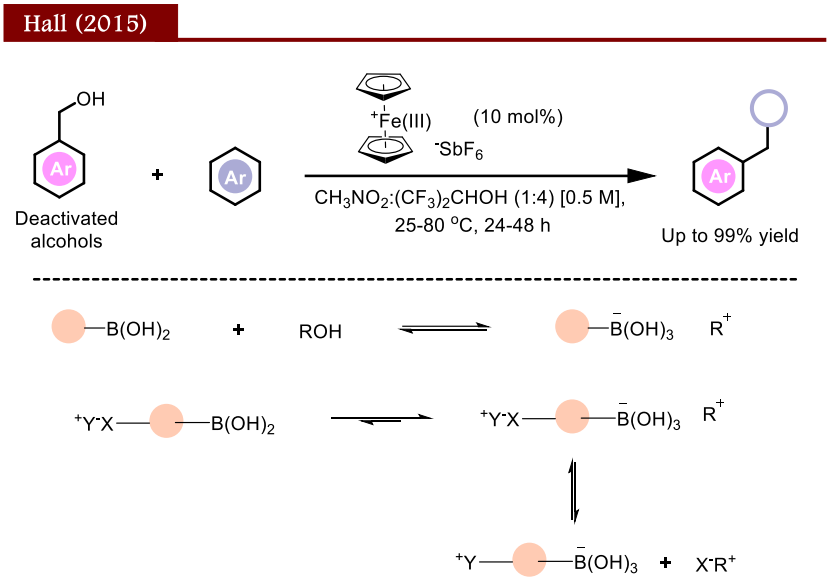
Reaction Conditions: $Ca(NTf_2)_2/Bu_4NPF_6$ (5 mol%), DCM, rt, 2-5 h

Scheme 2.1: Arylation of secondary and tertiary alcohols using a calcium-based catalyst.

the catalyst used. In this regard, FC alkylation reactions have been documented using alcohol. For instance, in 2010, Niggemann *et al.* developed a groundbreaking method for selective alkylation of benzylic, propargylic, and allylic alcohols using calcium-catalyst (Scheme 2.1). This innovative approach significantly expands the scope of the reaction, and what's remarkable is that typical reactions can take place at room temperature without the need for additional strong acids and bases. The mild reaction conditions also permit the presence of moieties such as thiophenes, furans, ethers and phenolic hydroxy groups. This discovery has identified calcium as an appropriate Lewis acid for catalyzing the arylation reaction, opening up new possibilities in the field.[6]

Afterward, in 2015, Hall and co-authors reported a groundbreaking boron-based catalyst of ferrocene known as ferroceniumboronic acid hexafluoroantimonate salt, which has proved to be a highly effective and versatile catalyst for FC alkylations (Scheme 2.2). This catalyst enables the direct transformation of a diverse range of arenes using easily available 1^o and 2^o benzylic alcohols. By avoiding the use of toxic and corrosive benzylic halides, this protocol offers a much more environmentally friendly approach, under remarkably mild conditions, to produce different unsymmetrical diarylmethanes with consistently high yields and regioselectivity. The use of ferroceniumboronic acid-based salt in HFIP under optimal reaction conditions allows for a wide variety of substrates in comparison to the catalysts in the literature. Notably, this boronic acid catalyst has been shown to effectively activate 1^o deactivated benzylic alcohols. When applied on a gram-scale (up to 1 M), the catalyst can be recovered for reuse, demonstrating practicality and cost-effectiveness. Mechanistic studies have revealed the significance of the oxidized cationic behavior of the boronic acid-based catalyst, and have proposed a mechanism in which ion exchange leads to the formation of a carbocation in conjunction with the non-coordinating SbF_6^- anion. This breakthrough in boronic acid catalysis opens up exciting new avenues for the

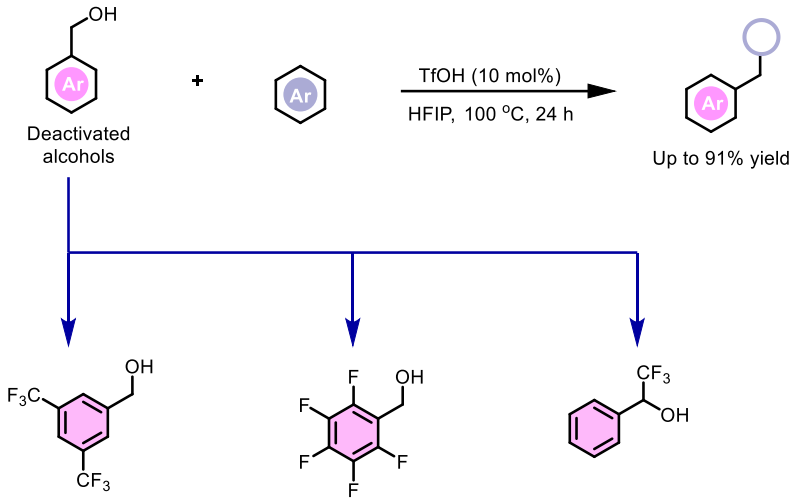
transformation of alcohols, offering a promising route for future research and development.[7]



Scheme 2.2: Arylation of deactivated alcohols by using ion-exchange method.

Later in 2017, Moran and team hosted an innovative catalytic system that significantly extended the scope of the dehydrative Friedel-Crafts reaction, allowing for the incorporation of highly electron-deficient benzylic alcohols, even those having a CF_3 group next to the OH-containing carbon (Scheme 2.3). Through the interaction of the HFIP and Brønsted acid, catalytically activated aggregates are formed, with the HFIP's hydrogen-bonding ability playing a crucial role. This research aims to capitalize on the straightforward approach to facilitate different TfOH-catalyzed transformations that are typically not achievable in normally used solvents.[8]

Moran (2017)

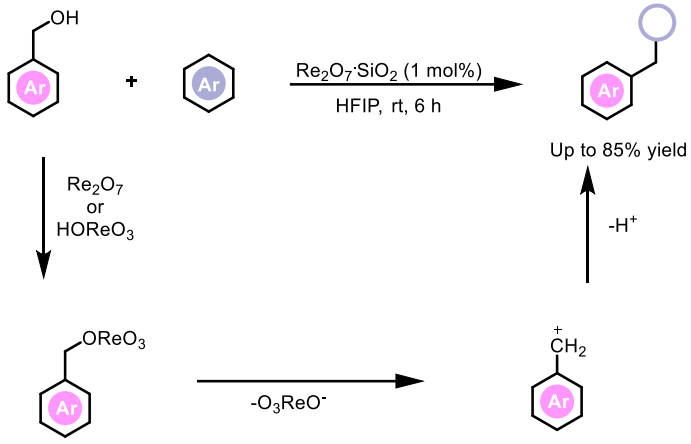


Scheme 2.3: Arylation of deactivated alcohols by using HFIP-TfOH system.

Floreancig *et al.* introduced an efficient method for producing diaryl methanes by using FC reactions involving arenes and alcohols (Scheme 2.4). Re_2O_7, in crystalline form as well as adsorbed on silica, serves as a potent catalyst for these types of reactions. The protocol involves a wide scope, encompassing electronically poor alcohols, and works well with lower catalyst loading. The use of HFIP is vital for accelerating rates and reducing the nucleophilicity of –OH moiety. Perrhenic acid can be used as an alternative to Re_2O_7 to cut down costs and enable easier handling. Based on mechanistic studies, it has been confirmed that the reactions do not propagate through protonation, however, proceed with the formation of intermediates as depicted in scheme 2.4 below.[9]

Crousse and team have successfully developed a gentle, effective, and environmentally-benign protocol that utilizes bisulfate salt as a catalyst for the FC reaction of arenes (Scheme 2.5). This system has demonstrated impressive versatility, accommodating a wide range of arenes and alcohols. Under these mild conditions, they generated a diverse array of unsymmetrical diarylmethanes with high yields and regioselectivity. The researchers

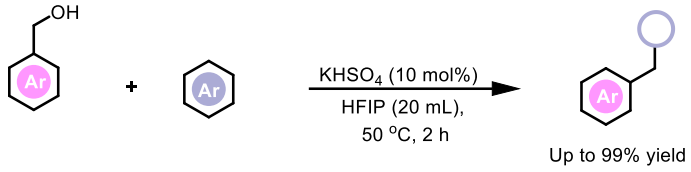
Floreancig (2018)



Scheme 2.4: Arylation using Re_2O_7 catalysis.

proposed an S_N1 mechanism that involves the activation of the –OH moiety through a H-bond with HFIP. One of the key advantages of this approach is its successful implementation on a large scale. Moreover, the environmentally friendly nature, cost-effectiveness, ready availability, and ease of removal of bisulfate salt in water workup make this protocol highly appealing for arylation.[10]

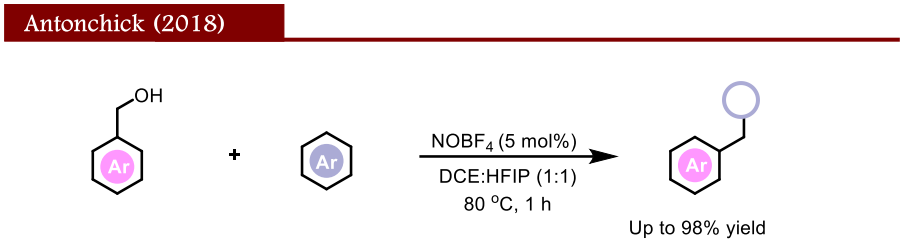
Crousse (2018)



Scheme 2.5: Arylation using bisulfate salt as a catalyst.

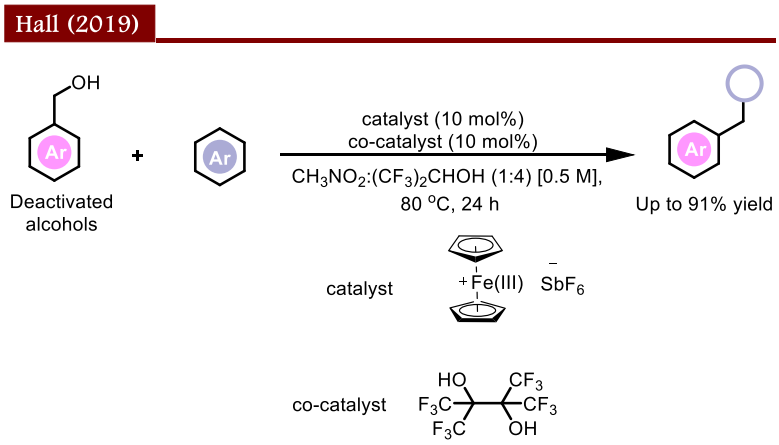
Antonchick and co-workers have successfully developed a revolutionary metal-free arylation protocol (Scheme 2.6). This process utilizes mild reaction conditions and a lower loading (5 mol%) of nitrosonium tetrafluoroborate ($NOBF_4$). They demonstrated that this

method has a wide substrate scope, showing excellent tolerance towards various functional groups, and a rapid reaction rate.[11]



Scheme 2.6: Arylation using nitrosonium tetrafluoroborate as a catalyst.

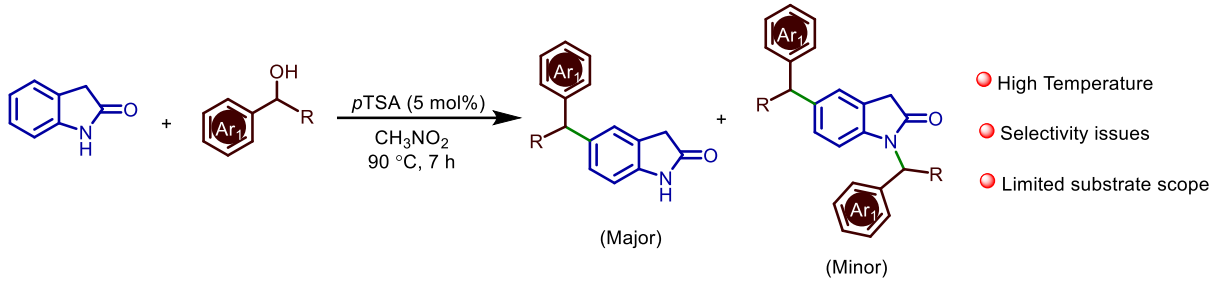
In this insightful article, the authors discussed the utilization of perfluoropinacol to enhance the reactivity of a boron-based catalyst (as discussed in scheme 2.2) in the FC alkylation reaction of deactivated alcohols (Scheme 2.7). The co-catalyst formed a Lewis-acidic system of boronic ester, leading to the creation of a hydronium boronate functionality. This species ultimately produces the corresponding carbocations.[12]



Scheme 2.7: Alkylation of arenes using deactivated alcohols by utilizing ferrocenium boronic acid as the catalyst and perfluoropinacol as the co-catalyst.

Similarly, alkylation using alcohols is also experimented with the less activated rings but the selectivity between proximal and distal centers could not be achieved (Scheme 2.8).

Reddy (2011)

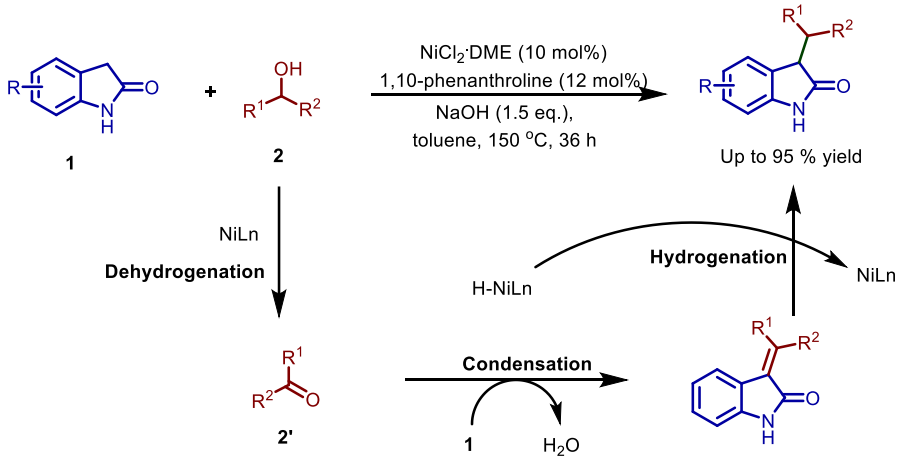


Scheme 2.8: Alkylation of oxindoles using alcohol and *p*TSA as the catalyst.

For example, the reaction of alcohol with oxindole delivered two products- C- alkylation and C- and N-alkylation, which is too under harsh reaction conditions, raising the selectivity issues.[13]

Contrary to this, C3 alkylation of oxindole using alcohols is well explored. Banerjee *et al.* in 2023, developed a method for the alkylation of indoline-2-ones by using a wide range of secondary alcohols, and nickel catalyst (Scheme 2.9). It is noteworthy that this alkylation process can occur even in the company of reducible alkenes, demonstrating the exciting

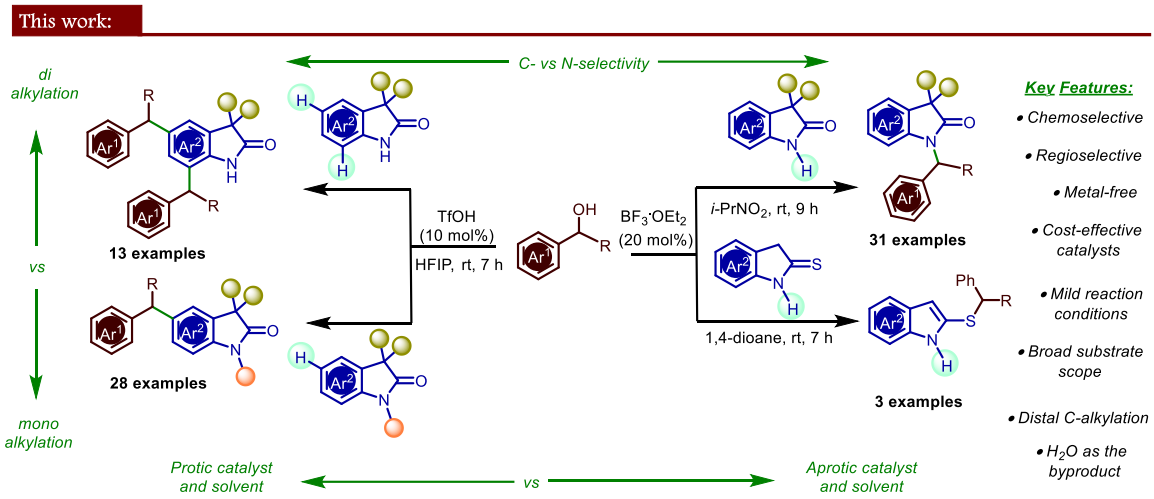
Banerjee (2023)



Scheme 2.9: C3-alkylation of oxindole by using the hydrogen-borrowing technique

potential for synthetic applications. Additionally, authors have achieved late-stage alkylation of the cholesterol.[14]

In spite of the synthetic advancement in the field of alkylation using alcohols, the switchable alkylation of heterocyclic scaffolds using alcohols remains limited. Given our ongoing interest in the reactivity of oxindole and thio-oxindole, herein, I delineate catalyst- and solvent-controlled tunable chemo- and regioselective alkylation protocol of oxindoles and thio-oxindoles by using secondary alcohols. This methodology is noteworthy due to its ability to perform functionalization at the C7 position of oxindole without requiring any directing group at the N-centre (Scheme 2.10).



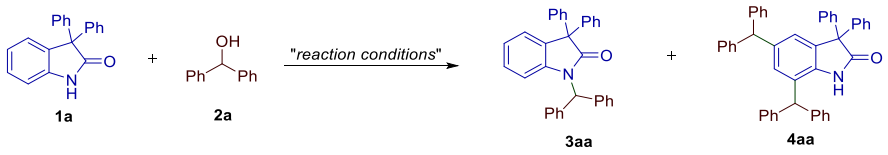
Scheme 2.10: C5-, N-, C5- & C7-, S- alkylation of oxindole and thio-oxindole.

2.2 Results and Discussion

I commenced my investigation for the alkylation of oxindoles by taking oxindole **1a** and diphenyl methanol **2a** as the model substrates. Initially, the reaction was carried out in the presence of aluminum trichloride in toluene and DMF, the yield of **3aa** was less than 10% (Table 1, entries 1-2). The reaction was further carried out in the presence of $FeCl_3$ in HFIP and a new product **4aa** was encountered instead of **3aa**, although, the yield was poor (Table

1, entry 3). Meanwhile, switching to another Lewis acid catalyst, $BF_3{\cdot}OEt_2$ offered us a better yield of **4aa** using HFIP as reaction media, although it was noticed that enhancing the reaction temperature decreased the yield (Table 1, entries 4-5). Several organic solvents like DMSO, DMF, and DCE were examined for the transformation, and in all cases, **3aa** was found in the reaction mixture (Table 1, entries 6-8). From these findings, it was clear that not only the catalyst but also the solvent plays an important role in this reaction. Next, nitromethane was tried and found useful for the transformation of substrates into **3aa** (Table 1, entry 9). The desired compound **3aa** was obtained in excellent yield at room temperature under a nitrogen atmosphere when the reaction was performed in nitropropane (Table 1, entry 10). Utilization of tris(pentafluorophenyl)borane [$B(C_6H_5)_3$] didn't show the transformation at room temperature, however, on heating it offered **3aa** in 65% yield (Table 1, en-tries 11-12). Changing the Lewis acid catalysts like $Yb(OTf)_3$ didn't give us success in accessing C-alkylated product **4aa** in good yield (Table 1, entries 13). On the other hand, Brønsted acid-based catalysts like *p*TSA and TFA delivered the product **4aa**, however, the yields were not acceptable (Table 1, entries 14-15). Later, attempting the reaction with TfOH in HFIP afforded the product **4aa** in 80% yield (Table 1, entry 16). Despite changing the solvent used, there was no discernible improvement in the yield of product **4aa** (Table 1, entries 17, 18).

Table 2.1. Optimization table[a]



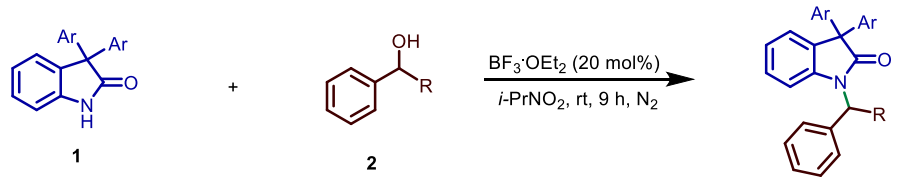
No.	Catalysts	Solvent	T (°C)	Time (h)	Yield % (3aa)[b]	Yield % (4aa)[b]
1	$AlCl_3$	toluene	80	16	-	-

2	$AlCl_3$	DMF	rt	16	<10	-
3	$FeCl_3$	HFIP	50	16	trace	<15
4	$BF_3{\cdot}OEt_2$	HFIP	50	12	trace	38
5	$BF_3{\cdot}OEt_2$	HFIP	100	10	trace	20
6	$BF_3{\cdot}OEt_2$	DMSO	rt	16	20	-
7[c]	$BF_3{\cdot}OEt_2$	DMF	40	10	40	-
8[c]	$BF_3{\cdot}OEt_2$	DCE	60	10	30	-
9[c]	$BF_3{\cdot}OEt_2$	$MeNO_2$	rt	10	75	-
10[c]	**$BF_3{\cdot}OEt_2$**	***i*-PrNO$_2$**	**rt**	**9**	**77**	**-**
11[c]	$B(C_6H_5)_3$	*i*-PrNO$_2$	rt	10	-	-
12[c]	$B(C_6H_5)_3$	*i*-PrNO$_2$	80	7	65	-
13	$Yb(OTf)_3$	HFIP	60	10	<12	32
14	*p*-TSA	HFIP	rt	10	-	39
15	TFA	HFIP	rt	10	-	43
16	**TfOH**	**HFIP**	**rt**	**7**	**-**	**80**
17	TfOH	*i*-PrOH	rt	10	-	20
18	TfOH	DMF	50	10	-	15

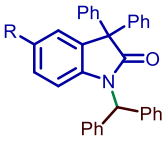
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.24 mmol), catalyst (10 mol%), solvent, N_2 atmosphere. [b]Isolated yield. [c]**2a** (0.12 mmol) and catalyst (20 mol%).

With the optimized conditions in hand, I initiated the explorations of the substrate scope for N-alkylated products **3** by employing different 3,3-diphenyl oxindole scaffolds (Scheme 2.11). The treatment of 3,3-diphenyl indoline-2-one **1a** with diphenylmethanol **2a** provided the respective product **3aa** in 75% yield. Oxindoles possessing substituents

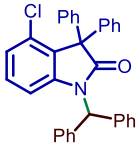
like -OMe, -F, -Br at the C5 position furnished the anticipated products **3ba**, **3ca**, and **3da** in moderate to good yields. However, the reactivity of oxindole got arrested in the presence of -NO_2 substituent at the C5 position, and as a result, the formation of **3ea** was not observed. Oxindole having -Cl at the C4 position also furnished the product **3fa** in 68% yield. Moreover, C6 substituted oxindoles with –F and –Br proved beneficial for the targeted transformation and gave **3ga** and **3ha** in good yields. Next, the reaction was performed with C7 methyl substituted oxindole **1i**, however, in this case, I did not observe the product formation due to the methyl obesity at the C7 position. Variations in 3,3-disubstituted aryls including *p*-methyl and *p*-fluoro afforded the corresponding products **3ja** and **3ka** in excellent yields. Thereafter, I checked the reactivity of C3 alkyl substituted oxidoles, and gratifyingly, **3daa** was obtained in 73% yield. Influenced by the formation of this product, functionalization of spiro-oxindoles was attempted and to our delight, I harnessed the products **3faa** and **3gaa** in good yields. Then, I planned to check the requirement of C3 substitution at oxindole and I observed that C3 substitution is not necessary for the reaction to occur. In this respect, I employed several C3 unsubstituted oxindoles in the reaction and surprisingly reaction performed well under the optimized reaction conditions and delivered the products **3aaa**, **3baa**, **3caa,** and **3aal** in excellent yields. Next, different benzylic alcohols were screened, in this series, variants of less reactive alcohol like 1-phenylethanol **2b**, 1,2-diphenylethanol **2g**, 1-phenylprop-2-yn-1-ol **2h**, and cyclohexyl(phenyl)methanol **2i** furnished the respective products **3ab**, **3ag**, **3ah** and **3ai** in moderate to good yields. Other substrates like 4-Methyl thiophenylethanol **2e**, 1-(naphthalen-2-yl)ethan-1-ol **2f**, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol **2j** and naphthalen-2-yl(phenyl)methanol **2k** reacted with **1a** and offered the desired products **3ae**, **3af**, **3aj** and **3ak** in 55-85% yield. Analogously, *p*-substituted diarylmethanols smoothly transformed in their corresponding N-alkylated products **3al-3ap** with satisfactory yields. On the other hand, alcohol with a strong electron-withdrawing group (-NO_2 and -CN) didn't show the transformation, **3aq** and **3at**. The alcohol with a methyl group positioned



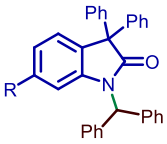
Scope of 3,3-disubstituted oxindoles:



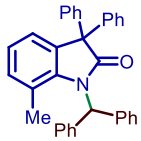
3aa: R = H, 75%
3ba: R = OMe, 84%
3ca: R = F, 70%
3da: R = Br, 72%
3ea: R = NO_2, 0%



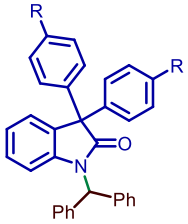
3fa, 68%



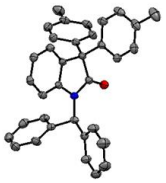
3ga, R = F, 67%
3ha, R = Br, 69%



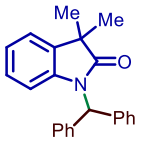
3ia, 0%



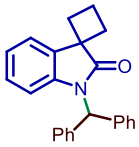
3ja, R = Me, 80%
3ka, R = F, 72%



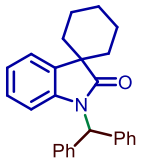
SCXRD of **3ja**
CCDC No.:**2269433**



3daa, 73%

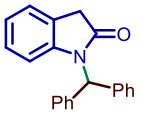


3faa, 75%

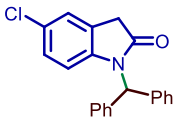


3gaa, 77%

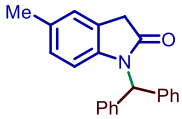
Scope of C3-unsubstituted oxindoles:



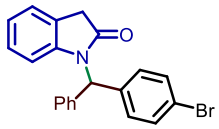
3aaa, 90%



3baa, 87%

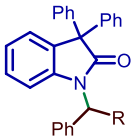


3caa, 92%

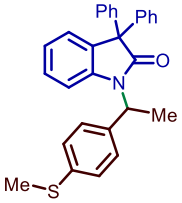


3aal, 86%

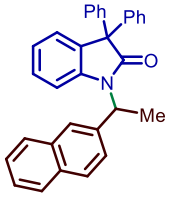
Scope of alcohols:



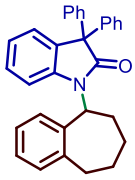
3ab, R = Me, 54%
3ag, R = Bn, 68%
3ah, R = C_2H_2, 70%
3ai, R = Cy, 60%



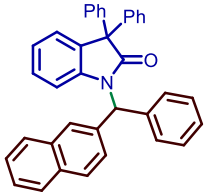
3ae, 55%



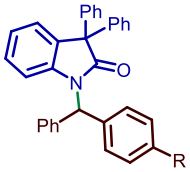
3af, 68%



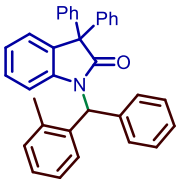
3aj, 62%



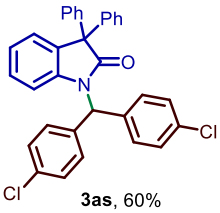
3ak, 85%



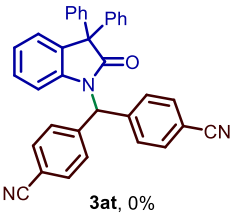
3al, R = Me, 82%
3am, R = F, 68%
3an, R = Cl, 65%
3ao, R = Br, 66%
3ap, R = CF_3, 61%
3aq, R = NO_2, 0%



3ar, 74%



3as, 60%



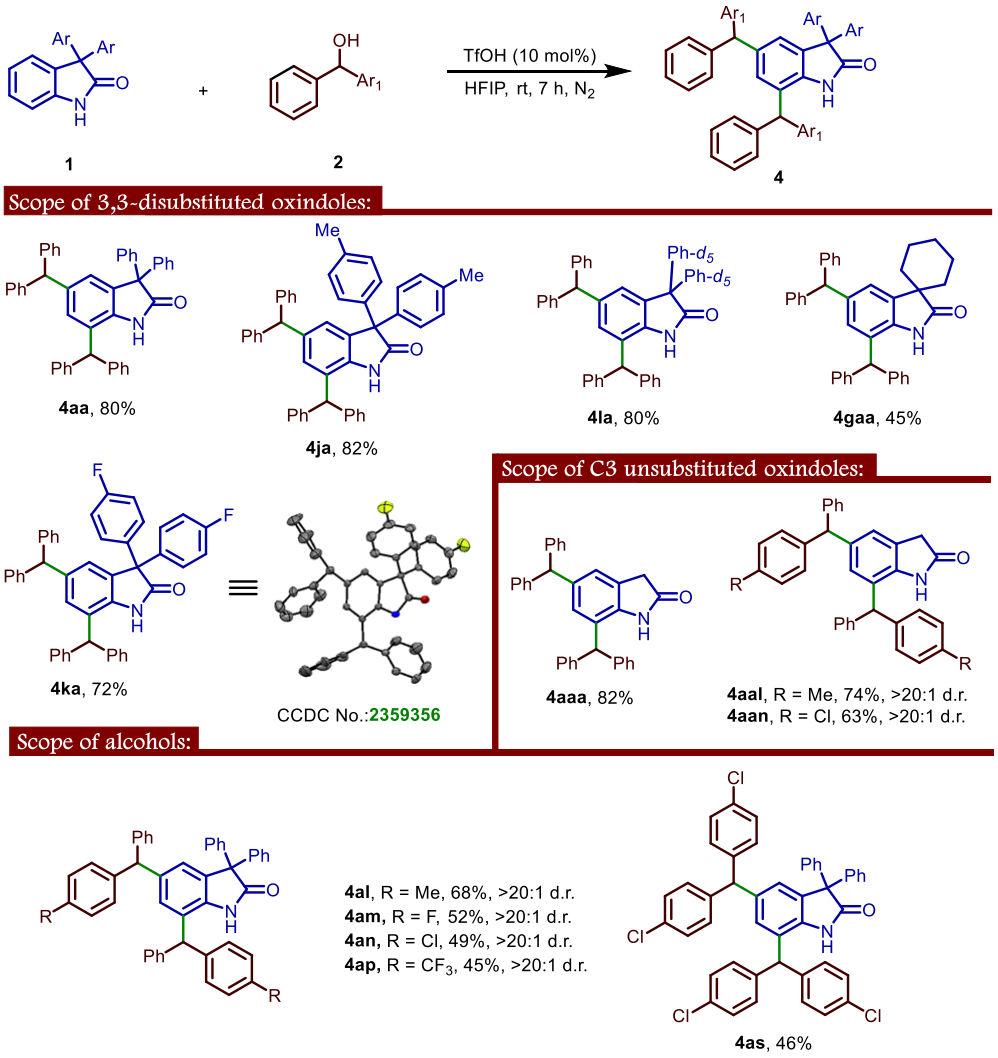
3at, 0%

Scheme 2.11: Substrate scope for the synthesis of N-alkylated product 3.[a,b] [a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), $BF_3 \cdot OEt_2$ (20 mol%), *i*-$PrNO_2$ (0.8 mL), N_2 atmosphere. [b]Isolated yield.

at the ortho position (**2r**), and the dichloro-decorated alcohol (**2s**), have both shown to be beneficial for the transformation process and be-stowed us with the product **3ar** and **3as** in 74% and 60% yield respectively.

Encouraged by the presented results, I attempted the synthesis of bis C-alkylated products **4** by conducting reactions between oxindoles and diphenylmethanols under the optimized reaction conditions (Scheme 2.12). In the course of studies, I began with 3,3-diphenyl oxindole **1a** and **2a** and it delivered us the desired product **4aa** with 80% yield. Next, I explored variation in 3,3-diaryl substitution and found that both –Me and –F substituents at the para-position of the phenyl ring granted us the respective products **4ja** and **4ka** in acceptable yields. Further, the deuterated substrate also offered the product **4la** in excellent yield. Even, spiro-oxindole handed over the product **4gaa** in 45% yield, which proved that the methodology is not limited to 3,3-diaryl substituted oxindoles. Like C3 disubstituted oxindoles, unsubstituted oxindoles also led to the corresponding products **4aaa**, **4aal,** and **4aan** in very good yield under the optimized conditions. Finally, variations in alcohol were explored and it was found that the electronically rich as well as electronically deficient alcohols like **2l**, **2m**, **2n,** and **2p** worked well in the transformation of **4al**, **4am**, **4an** and **4ap**. The alcohol with dichloro decoration also successfully underwent the trans-formation and produced a 46% yield of product **4as**.

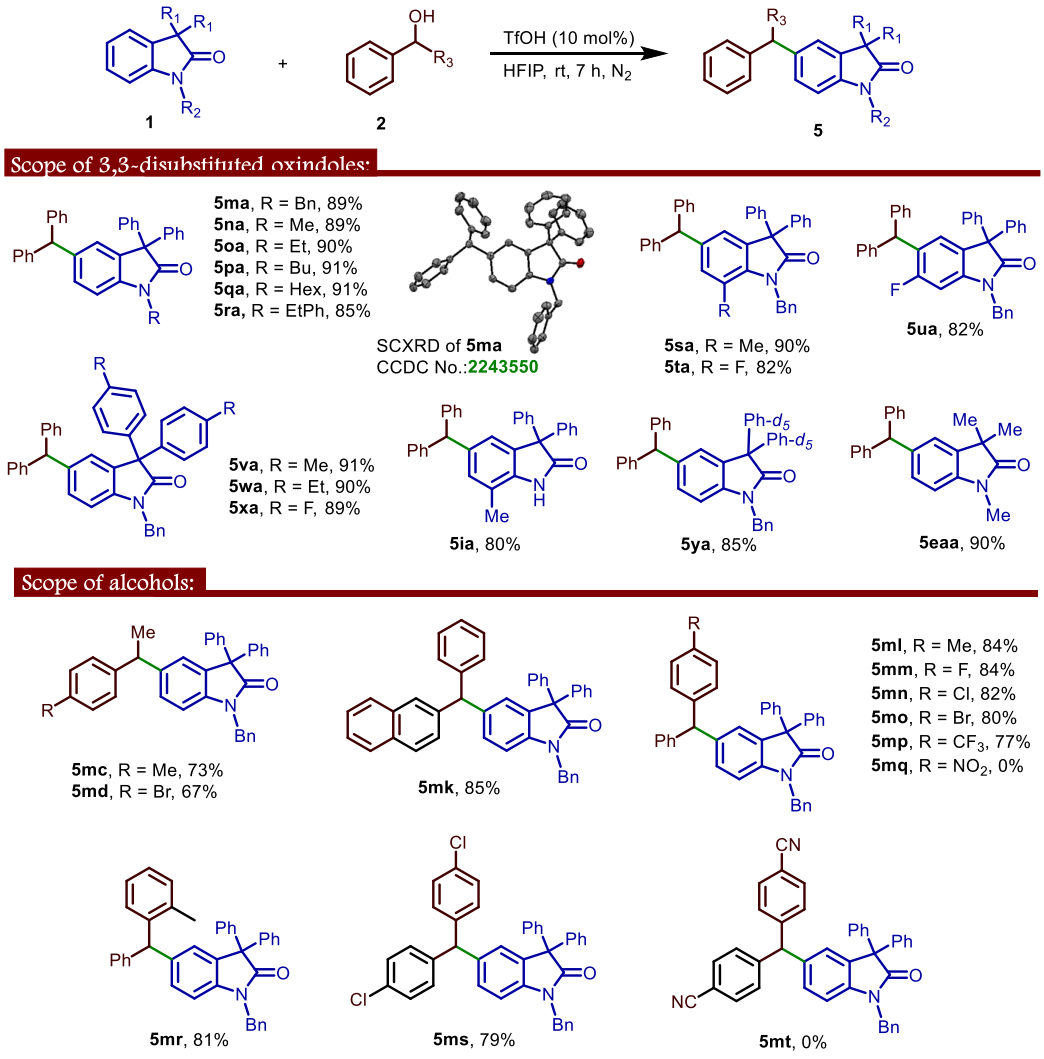
Interestingly, when N-protected oxindoles were subjected to the optimized reaction conditions, it was observed that due to the steric effect at the C7 position of oxindoles, it exclusively delivered C5 alkylated oxindole products **5** (Scheme 2.13). N-centre bearing –benzyl, -methyl, -ethyl, -butyl, -hexyl, -ethanephenyl precursors **1m-1r** delivered the desired product **5ma-5ra** in excellent yields. Oxindoles having electron-donating and



Scheme 2.12: Synthesis of bis C-alkylated oxindoles 4.[a,b] [a]Reaction conditions: **1** (0.1 mmol), **2** (0.24 mmol), TfOH (10 mol%), HFIP (0.7 mL), N_2. [b]Isolated yield.

electron-withdrawing substituents **1s** and **1t** at the C7 position also furnished the products **5sa** and **5ta** in good to excellent yields. In addition, C6-substituted oxindole was also found to be capable of furnishing the desired product **5ua** with a 82% yield. Later, variation in 3,3-dialkyl/diaryl substitution on oxindole ring having 3,3-dimethyl, and *p*-substituted diphenyl rings with electron-enriched and electron-deficient groups -Me, -Et, and -F were

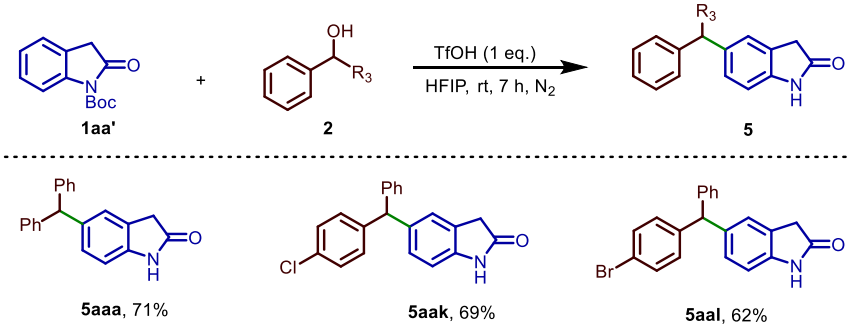
also found suitable candidates for the said reaction and gave access to the corresponding products **5va-5xa** in satisfactory yield. Gratifyingly, the deuterated diphenyl rings in the third position of oxindole led to the corresponding product **5ya** in 85% yield. Moreover, N-unprotected C7 substituted oxindole also served the C5 alkylated product **5ia** in 80% yield. Also,the dialkyl-substituted oxindole bestowed us with a 90% yield of **5eaa**. Next, I evaluated the substrate scope of alcohols with a methyl group at the benzylic position. To our delight,



Scheme 2.13: Substrate scope for C5-alkylation[a,b] [a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), TfOH (10 mol %), HFIP (0.7 mL), N_2. [b]Isolated yield.

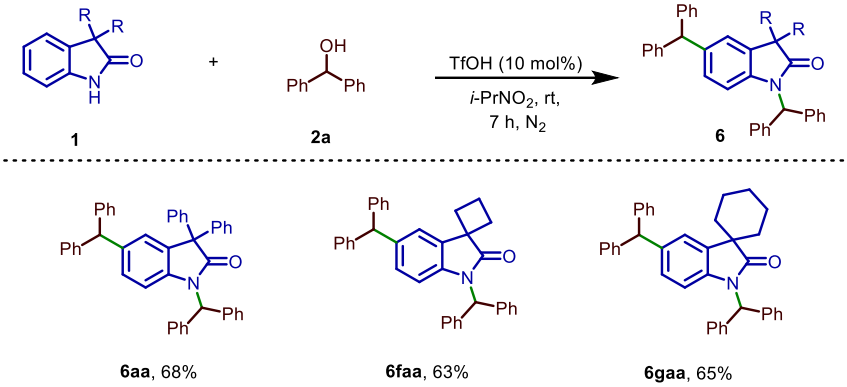
the substrates with substituted phenyl ring (–Me and –Br group) proved appropriate in the transformation of **5mc** and **5md** with appreciable yields. Upon subjecting naphthalen-2-yl(phenyl)methanol **2k** to the carefully optimized reaction conditions, I successfully obtained the corresponding product **5mk** with a high yield of 85%. Even, substituted diphenyl alcohols were tested under the optimized reaction conditions, and –Me, halo-substituted, -CF_3 substituted alcohols, **2l-2p** successfully handed over the products **5ml-5mp**. The alcohol containing a methyl group at the ortho position (**2r**) and the dichloro-decorated alcohol (**2s**) have both been found to positively influence the transformation process, resulting in the production of **5mr** and **5ms** at yields of 81% and 79% respectively. However, no product formation was observed on reactions of oxindole **1a** with primary and tertiary alcohols.

Oxindole bearing a –Boc substituent on the nitrogen rendered the product **5aaa** in 71% yield (Scheme 2.14). It is important to mention that, in this reaction, TfOH served two purposes- it catalyzed the C-alkylation reaction and subsequently deprotected the Boc group from **1aa'**. Then I extended the methodology to different alcohols and they granted us the products **5aak** and **5aal** in good yields.



Scheme 2.14: Synthesis of C5-alkylated products using N-boc-protected and C3 unsubstituted oxindoles and alcohols[a,b] [a]Reaction conditions: **1aa'** (0.1 mmol), **2** (0.12 mmol), TfOH (1 eq.), HFIP (0.7 mL), N_2 atmosphere. [b]Isolated yield.

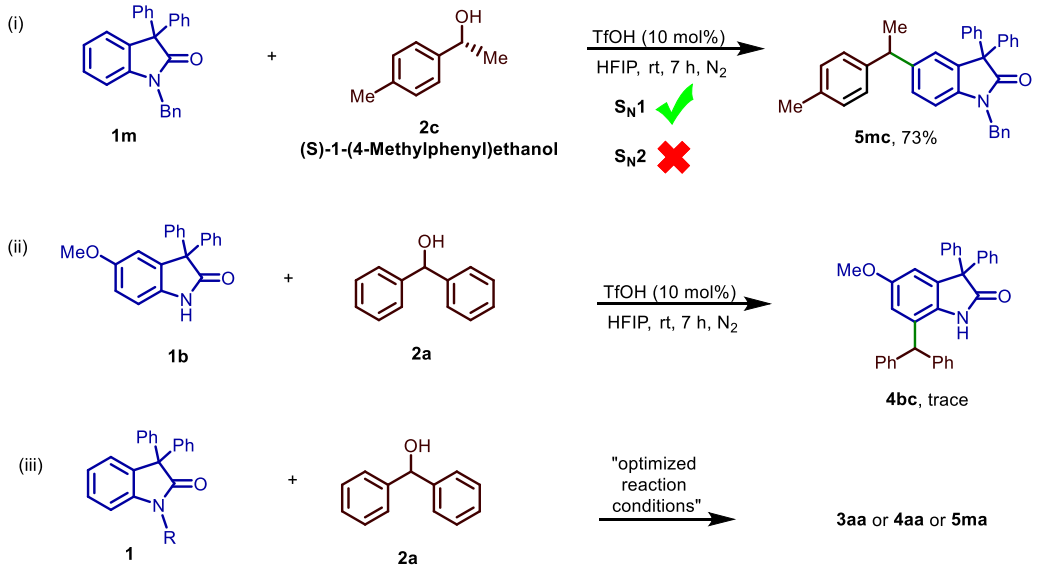
Further, a reaction was performed between **1** and **2a** in the presence of a protic catalyst (TfOH) and aprotic solvent (*i*-PrNO$_2$), and products **6aa**, **6faa**, and **6gaa** were encountered in 68%, 63%, and 65% yields respectively (Scheme 2.15). From here it can be inferred that protic catalyst and solvent are the requirements for C-alkylation of oxindoles, whereas, aprotic catalyst and solvent are the necessity for the corresponding N-alkylation.



Scheme 2.15: Substrate scope for N- and C5 alkylation of oxindole[a,b] [a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), TfOH (10 mol%), *i*-PrNO$_2$ (0.8 mL), N_2 atmosphere. [b]Isolated yield.

Following our initial experiments, I sought to gain deeper insights into the underlying mechanism. Hence, I performed a series of reactions as depicted in Scheme 2.16. To start, I subjected oxindole to the optimized reaction conditions with chiral alcohol **2c**. This led to the complete erasure of stereochemical information in the resulting product **5mc**, providing compelling evidence for the S_N1 pathway as the operative mechanism. The outcomes concurs with the results identified by the study conducted by Moran and colleagues.[8] Following this, our objective was to investigate the feasibility of C7

monoalkylation. In pursuit of this, I conducted a reaction involving C5-substituted oxindole **1b** and **2a**. Unfortunately, I observed only a trace amount of product **4bc**. This leads us to conclude that alkylation occurs concurrently at the C5 and C7 centers. In the next step, I carried out all three reactions without an inert atmosphere, catalyst, and solvent. The outcomes of these reactions are presented in scheme 2.16.

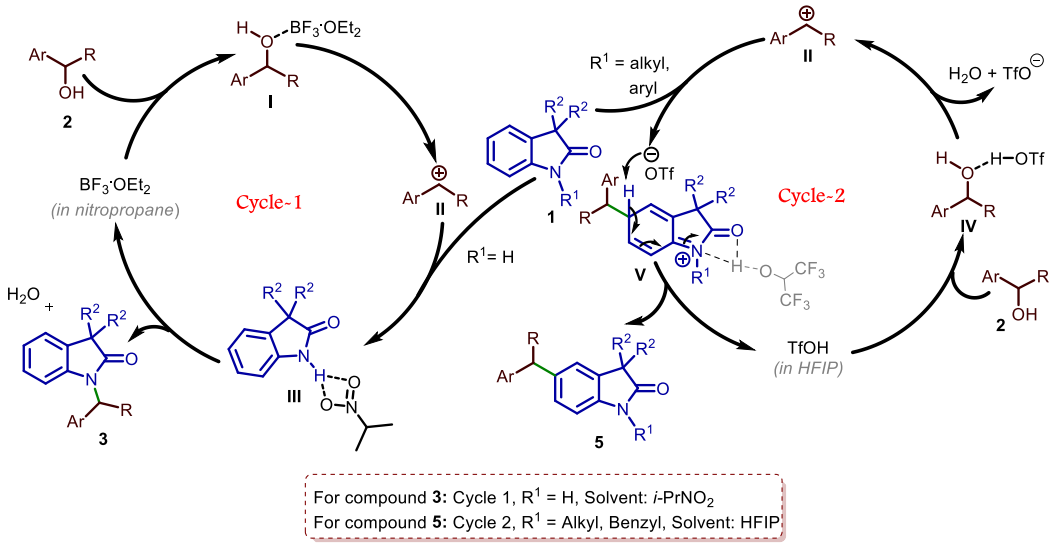


	Optimized Reaction conditions	Without N_2	Without Catalyst	Without Solvent
3aa	77%	65%	0%	21%
4aa	80%	66%	0%	7%
5ma	89%	70%	0%	13%

Scheme 2.16: Control Experiments

Based on these experiments, I proposed the reaction pathways for N- and C5-alkylation of 2-oxindoles which are depicted in Scheme 2.17. For N-alkylation as represented in cycle 1, catalyst $BF_3 \cdot OEt_2$ in nitropropane coordinated to the secondary alcohol **2** and led to the formation of intermediate **I**, followed by dehydration of **I** resulting in the formation of carbocationic intermediate **II** (Cycle 1). Meanwhile, 2-oxindole got polarized in the

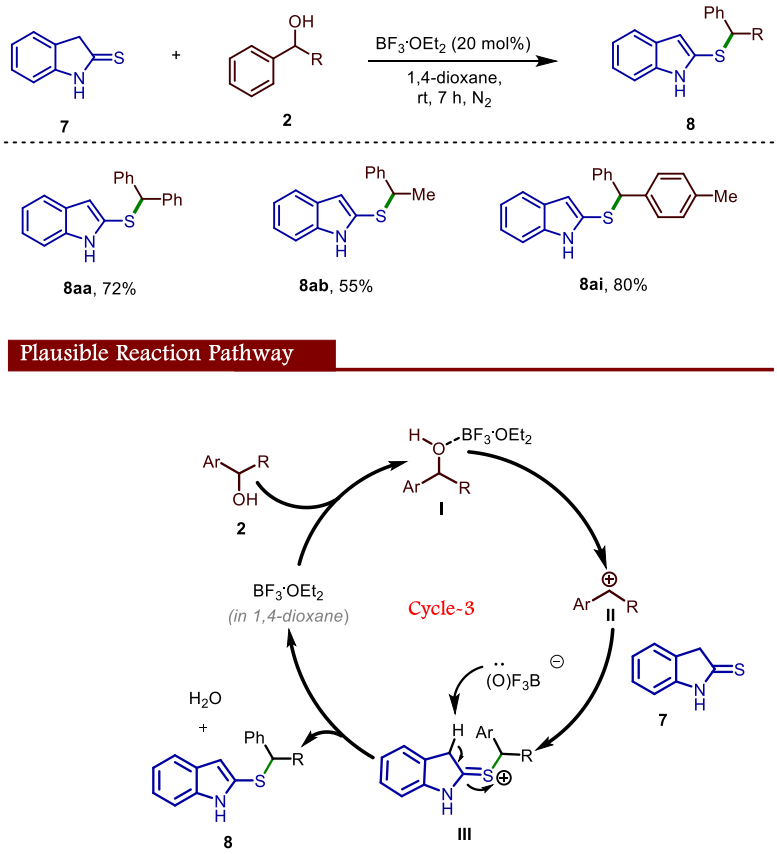
presence of *i*-PrNO$_2$, and formed the intermediate **III**. The intermediate **II** further reacted with the intermediate **III** and eventually led to the formation of N-alkylated product, **3**. On the other hand, in cycle 2, TfOH dehydrated the alcohol **2** as depicted in intermediate **IV** and resulted in the formation of of a new C-C bond at the C5 position of oxindole (intermediate **V**). Finally, in situ generated triflate ion abstracted the proton from the C5 position, and rearomatization yielded the desired product **5**.



Scheme 2.17: Plausible reaction mechanism.

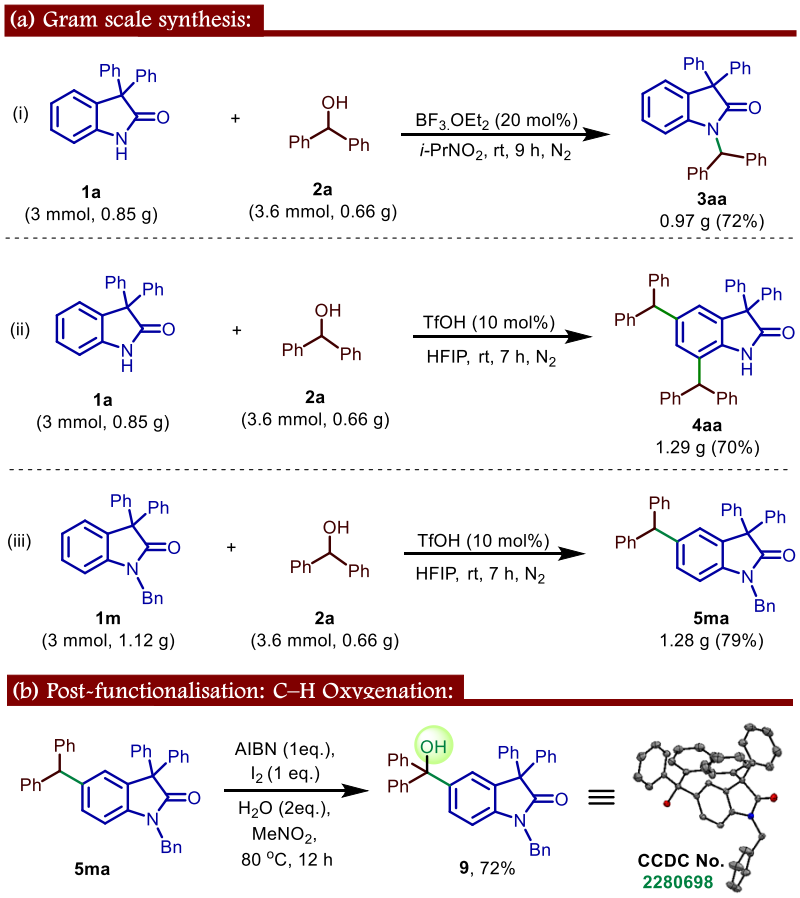
After that, I developed a new method for the selective addition of benzyl alcohol to a specific position on a molecule called indoline-2-thione, **7** (Scheme 2.18). This reaction is catalyzed by Lewis acid ($BF_3.OEt_2$) at room temperature conditions. After conducting thorough experimental adjustments to the reaction conditions, I determined that using a small amount of the catalyst, $BF_3.OEt_2$ (20 mol%) is effective in enabling the transformation. However, when dealing with C3 substituted thio-oxindoles, we encountered the production of a complex mixture, indicating a more intricate reaction pathway. From a mechanistic standpoint, the synthesis of an S-alkylated product indicates

the participation of a carbocation stabilized through resonance as an intermediate in the reaction.



Scheme 2.18: S-alkylation of thio-oxindole with plausible reaction mechanism.

To further exhibit the practicality and synthetic utility of the developed methodologies, preparative-scale experiments were conducted to obtain **3aa**, **4aa** and **5ma** in 72% (0.97 g), 70% (1.29 g) and 79% (1.28 g) yields, respectively (Scheme 2.19 a). The compound **5ma** was subjected to undergo C-H oxygenation at the benzylic carbon using AIBN and iodine as the oxidant, resulting in the synthesis of compound **9** in 72% yield (Scheme 2.19 b).



Scheme 2.19: Gram-scale synthesis and synthetic application.

2.3 Conclusions

I have developed an efficient and user-friendly protocol for the chemo- and regioselective alkylation (C- and N-alkylation) of oxindoles and S-alkylation of thio-oxindoles by using secondary alcohols. Furthermore, regioselectivity in C-alkylation was achieved just by protecting the N-centre of the amide moiety of the oxindoles. This report demonstrates the C7 functionalization of oxindoles without the N-directing group. The practicality of the strategies was confirmed by the gram scale experiments. One of the C5 alkylated oxindoles

was further derivatized and subjected to a novel protocol for C-H oxygenation at the benzylic position.

2.4 Experimental Section

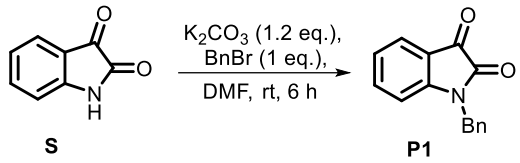
Unless otherwise noted, all reactions were performed on a Schlenk vacuum line or in a glovebox using oven-dried glassware and were stirred with teflon-coated magnetic stirring bars. All the chemicals and reagents were purchased from commercial suppliers Sigma Aldrich, GLR Innovations, BLD Pharma, Spectrochem and used without further purification. Solvents were dried and stored over molecular sieves under an argon atmosphere prior to use. All work-up and purification procedures were done with reagent-grade solvents in an air atmosphere. Reaction temperatures above 25 °C refer to temperatures of an aluminum heating block or a silicon oil bath, which were controlled by an electronic temperature modulator from Heidolph. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh). ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded in $CDCl_3$ and d_6-DMSO, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz {^{1}H} or 101 MHz {^{13}C} as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent ($CDCl_3$, δ= 7.26 for ^{1}H NMR and 77.16 for ^{13}C NMR, d_6-DMSO: δ = 2.50 for ^{1}H NMR and δ = 39.52 for ^{13}C NMR) and coupling constants (*J*) in Hz. Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet, dt for doublet of triplet, and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF). The data

collection for single crystal S-3 X-ray was performed at a 298 K on a CMOS-based Bruker D8 Venture PHOTON 100 diffractometer equipped with INCOATEC micro-focus source with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA.

2.4.1 Preparation of Starting Materials

Synthesis of Precursors (P1)[15]:

In a 100 mL Schlenk round-bottom flask equipped with a magnetic stir bar, the required amount of isatin (1 eq., 10 mmol) was added to 12 mL of DMF, and stirred for 5 minutes under nitrogen atmosphere. Then, benzyl bromide (1 eq., 10 mmol) was added dropwise in the mixture and the reaction mixture was stirred at room temperature until the starting material was completely consumed. Next, ice-cold water was added and stirred for 15 minutes before vacuum filtration of the precipitates and their subsequent washing with water several times. Finally, the resulting product was left to dry for a while.

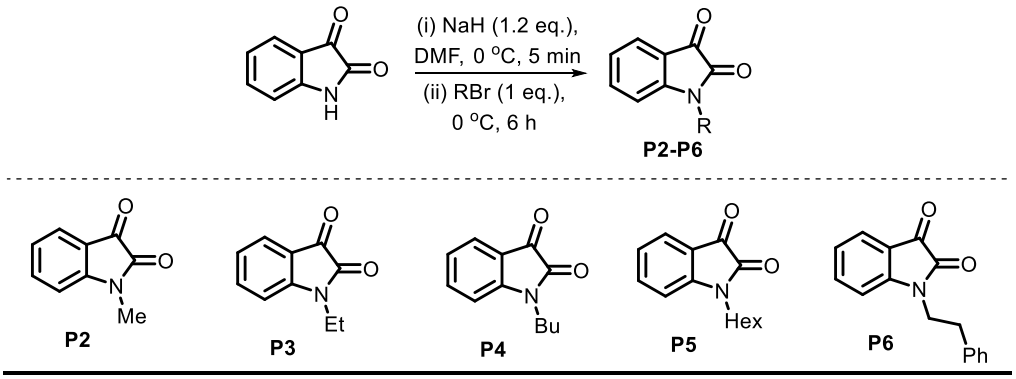


Scheme 2.20: Synthesis of N-benzylated isatin from isatin.

Synthesis of Precursors (P2-P6)[16]:

A 100 mL schlenk rbf was equipped with a magnetic bar, charged with isatin (1 eq., 10 mmol), DMF (12 mL), and nitrogen was purged into it. These were allowed to stir at 0 °C for 5 minutes which was followed by the addition of NaH (1.2 eq., 12 mmol) in three portions. After the complete addition of NaH in one hour, respective alkyl bromide (1 eq.,

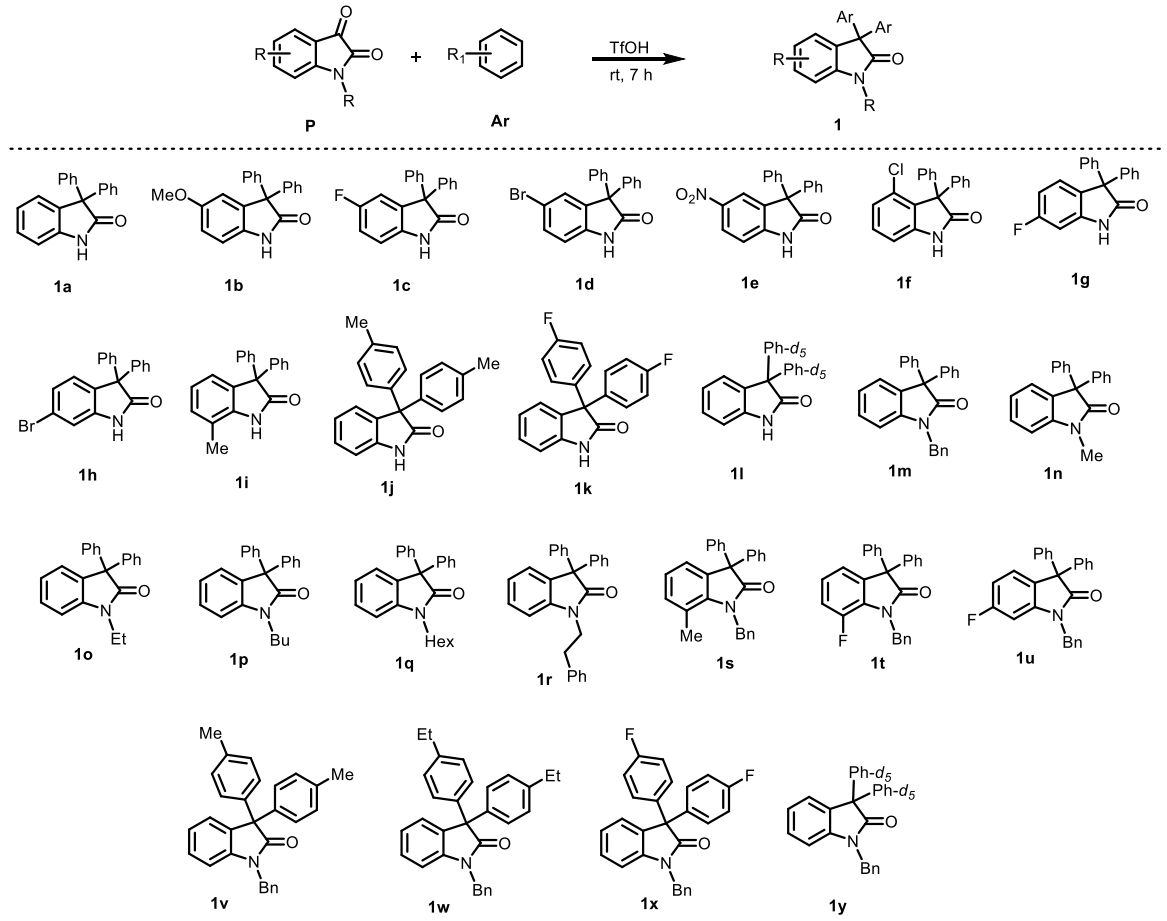
10 mmol) was added dropwise and the reaction mixture was left for stirring at 0 °C for 6 h. After the complete consumption of the starting materials, the ice-cold water was added to the reaction mixture and stirred for 15 minutes, and the resulted precipitate was filtered under vacuum and washed several times with water, and kept for drying.



Scheme 2.21: Synthesis of N-substituted isatin from isatin.

Synthesis of 3,3 disubstituted 2-oxindole derivatives (1)[17]:

In order to synthesize 3,3 disubstituted 2-oxindoles, a solution of isatin derivatives **P** (1 eq.) was prepared in freshly distilled triflic acid. Subsequently, the respective arene (2.5 eq.) was introduced to the solution at room temperature. The reaction was closely monitored using thin-layer chromatography (TLC) until it reached completion. Once the reaction was finalized, crushed ice was added to the mixture, followed by extraction with ethyl acetate. The resultant organic layer was washed with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained compound underwent further purification *via* silica gel column chromatography using hexane and ethyl acetate (8:2) as the eluent. Ultimately, the final product was successfully obtained in good yield, and it was identified as 3,3 disubstituted 2-oxindoles, **1**.

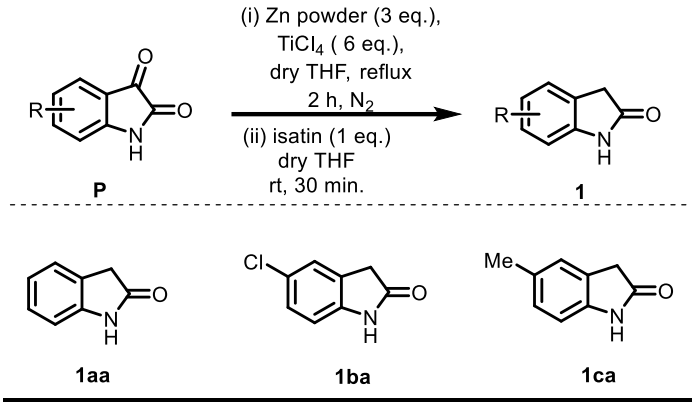


Scheme 2.22: Synthesis of 3,3-diaryl substituted oxindole from isatin.

Synthesis of C3 unsubstituted 2-oxindole derivatives (1)[18]:

A two-neck rbf was charged with a magnetic bead and a condenser was fixed on the one neck of the rbf. After that, Zn powder (0.78 g, 12 mmol) followed by dry THF and $TiCl_4$ (0.7 mL, 6 mmol) were added to the rbf at room temperature under a dry N_2 atmosphere. The mixture was refluxed for 2 hours. Then the resulting suspension was cooled to room temperature and a solution of respective isatin (2 mmol) in THF was added slowly. Thereafter, the reaction mixture was allowed to stir at room temperature for 30 minutes.

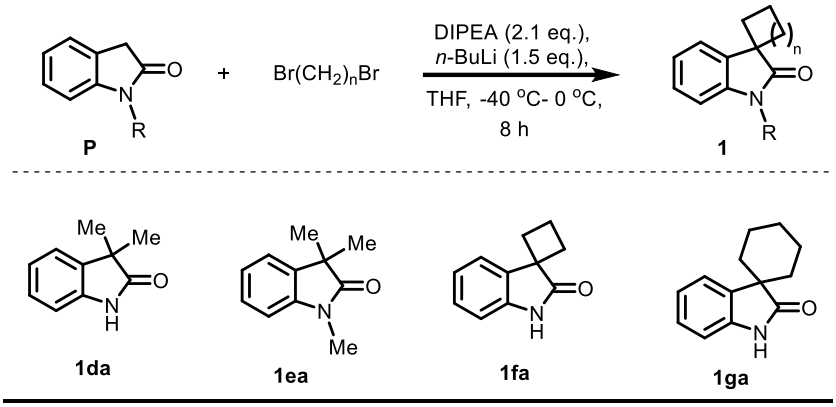
The reaction mixture was quenched with 3% HCl (15 mL), extracted with DCM and dried over anhydrous Na_2SO_4. After the solvent was evaporated under reduced pressure, the crude product was purified by column chromatography (hexane/ethyl acetate = 5:1) to obtain the pure products.



Scheme 2.23: Synthesis of C3-unsubstituted oxindole from isatin.

Synthesis of C3 alkyl substituted or spirocyclic 2-oxindole derivatives (1)[19]:

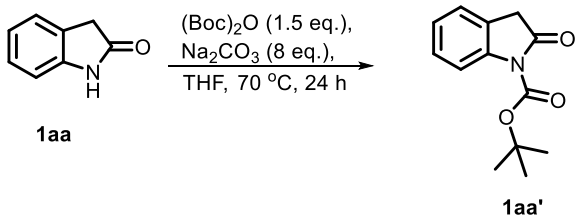
To an oven-dried schlenk round-bottomed flask, indoline-2-one was dissolved in freshly dried THF and nitrogen gas was purged. The reaction mixture was transferred to the chiller having -40 ^oC temperature and DIPEA (2.1 eq.) was added to the solution followed by *n*-BuLi (1.5 eq.). After that, dibromopropane or dibromopentane or methyl iodide (3 eq.) was added slowly and allowed to stir at 0 ^oC for 8 hours. Upon completion of the reaction as monitored by TLC, THF was recovered back by evaporating on rota-vapor and ice was added to the reaction mixture. The crude product was extracted with ethyl acetate and purified through silica gel chromatography to afford compound **1**.



Scheme 2.24: Synthesis of 3,3-dimethyl substituted and spiro-oxindole.

Synthesis of *tert*-butyl 2-oxoindoline-1-carboxylate (1aa')[20]

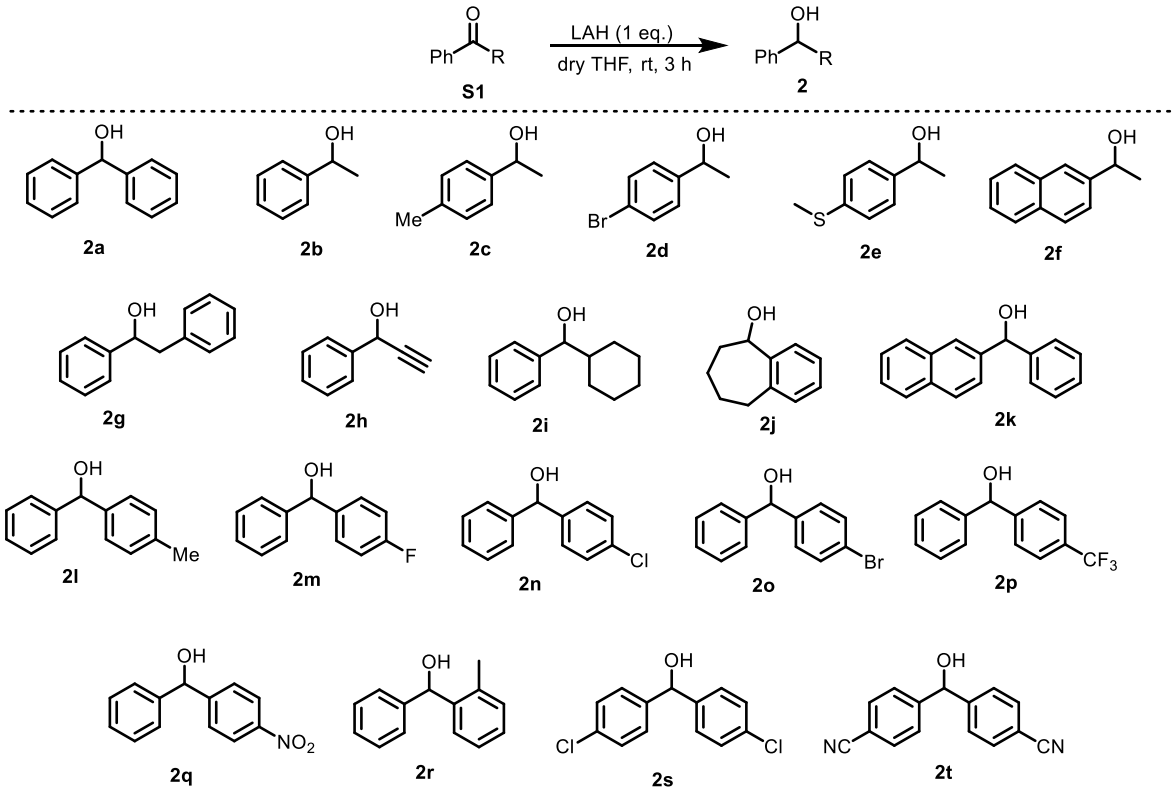
In a Schlenk reaction flask equipped with a magnetic stir bar, THF was added, followed by indoline-2-one (1 eq.), and nitrogen gas was purged. After that, Na_2CO_3 (8 eq.) was added to the stirred mixture. Next, an ice bath was placed under the flask, and boc anhydride (1.5 eq.) was added dropwise. The reaction mixture was then stirred at 70°C for 24 hours. After the reaction was complete, water was added to the mixture, and the resulting mixture was extracted with ethyl acetate. The combined organic layer was then dried over sodium sulfate and evaporated under reduced pressure. The crude product obtained was purified using silica gel column chromatography.



Scheme 2.25: Synthesis of Boc-substituted oxindole from 2-oxindole.

Synthesis of alcohols (2)[21]:

Ketone (1 eq.) underwent a reaction with $LiAlH_4$ (1 eq.) in THF for 4 hours. The reaction mixture was promptly quenched with water and THF was swiftly removed under high pressure. The resulting mixture was rigorously extracted three times with diethyl ether and the ether washings were thoroughly dried using $MgSO_4$. Finally, the ether was expeditiously evaporated under high pressure.

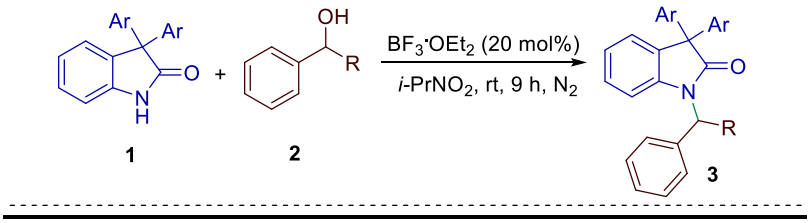


Scheme 2.26: Reduction of ketones to alcohols.

2.4.2 General Procedures

General procedure for N-alkylation of oxindoles (3):

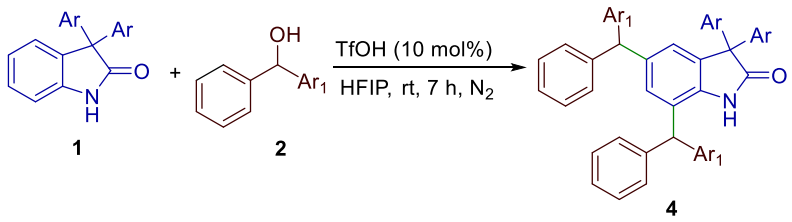
A vial containing Oxindole **1** (0.1 mmol) and alcohol **2** (0.12 mmol) was purged with N_2 gas. Then, nitropropane ([0.125 M], 0.8 mL), and $BF_3{\cdot}OEt_2$ (2.5 µL, 20 mol%) were added to the reaction mixture. The reaction was stirred vigorously at room temperature and monitored using TLC. After completion, the reaction mixture was treated with water and extracted three times with ethyl acetate. The entire organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography to yield product **3**.



Scheme 2.27: N-alkylation of oxindoles.

General procedure for C5- and C7- dialkylation of oxindoles (4):

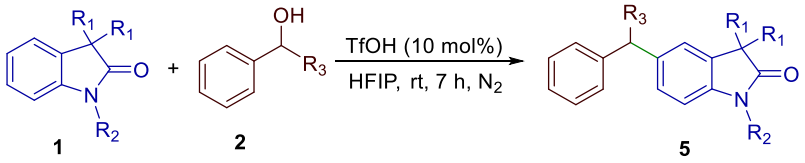
Oxindole **1** (0.1 mmol) and alcohol **2** (0.24 mmol) were taken into a vial. Subsequently, HFIP ([0.14 M], 0.7 mL), and TfOH (0.9 µL, 10 mol%) were added to the reaction mixture. The mixture was vigorously stirred at room temperature in N_2 atmosphere and monitored using TLC. Upon completion, the reaction mixture was treated with cold water and extracted with ethyl acetate. The organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography, resulting in the formation of product **4**.



Scheme 2.28: C5- & C7- alkylation of oxindoles.

General procedure for C5-alkylation of oxindoles (5):

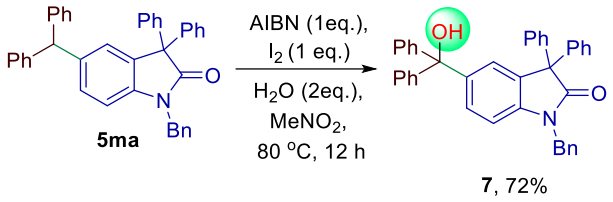
A vial was charged with a magnetic bead and N-protected oxindole, **1** (0.1 mmol) and alcohol, **2** (0.12 mmol) were added to it. Thereafter, the reaction mixture was supplemented by HFIP ([0.14 M], 0.7 mL), which was followed by the addition of TfOH (0.9 µL, 10 mol%). The reaction mixture was allowed to stir at room temperature in N_2 atmosphere and the reaction progress was monitored through TLC. Upon completion in 7 hours, cold water was added to the reaction mixture and was extracted with ethyl acetate three times. The complete organic layer was collected, dried over sodium sulfate and evaporated under reduced pressure. The obtained crude product was further purified through silica gel chromatography to afford product **5**.



Scheme 2.29: C5-alkylation of oxindoles.

General procedure for C-H Oxygenation of 5ma (7):

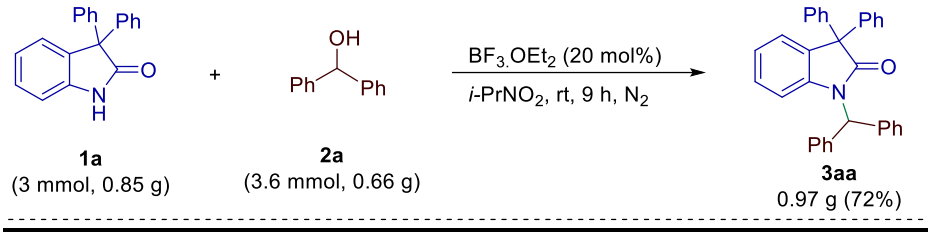
A reaction vial was dried in an oven and a magnetic stir bar was added. Next, AIBN (16.5 mg, 0.1 mmol), I_2 (25 mg, 0.1 mmol), $MeNO_2$ (1 mL), H_2O (3.6 µL), and substrate **5ma** (54 mg, 0.1 mmol) were added to the vial. After purging the vial with N_2 and sealing it with a screw cap, the reaction mixture was stirred at 80 °C for 12 hours. On completion of reaction, the solution was passed through a celite band using EtOAc as the eluent. The solution was then extracted with ethyl acetate and concentrated under reduced pressure to obtain the crude product, which was then purified by using silica gel column chromatography.



Scheme 2.30: Oxygenation at the benzylic position of oxindole.

Gram-scale synthesis of 3aa:

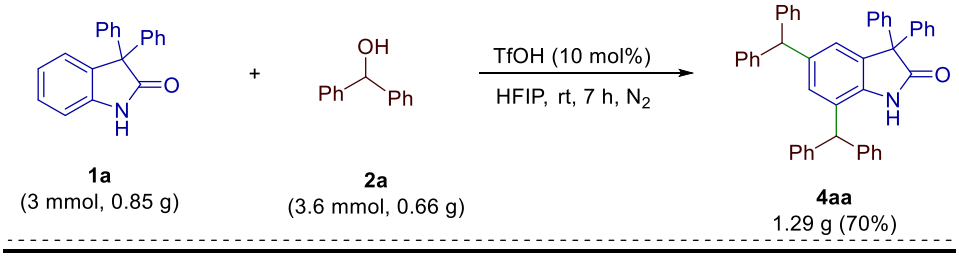
A vial containing Oxindole **1a** (0.85 g, 3 mmol) and alcohol **2a** (0.66 g, 3.6 mmol) was purged with N_2 gas. Then, nitropropane ([0.125 M], 24 mL), and $BF_3{\cdot}OEt_2$ (75 µL, 20 mol%) were added to the reaction mixture. The reaction was stirred vigorously at room temperature and monitored using TLC. After completion, the reaction mixture was treated with water and extracted three times with ethyl acetate. The entire organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography to yield product **3aa** (0.97 g, 72%).



Scheme 2.31: Gram-scale synthesis of N-alkylated oxindole, **3aa**.

Gram-scale synthesis of 4aa:

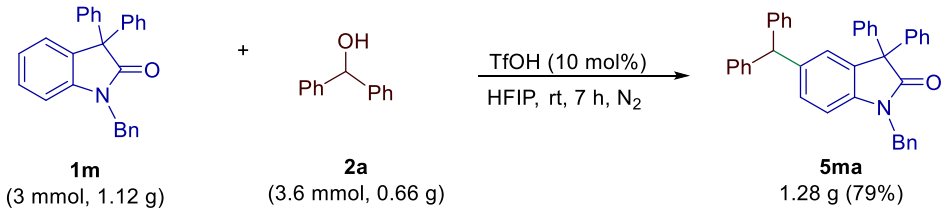
Oxindole **1a** (0.85 g, 3 mmol) and alcohol **2a** (0.66 g, 3.6 mmol) were taken into a vial. Subsequently, HFIP ([0.14 M], 21 mL), and TfOH (27 µL, 10 mol%) were added to the reaction mixture. The mixture was vigorously stirred at room temperature in N_2 atmosphere and monitored using TLC. Upon completion, the reaction mixture was treated with cold water and extracted with ethyl acetate. The organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography, resulting in the formation of product **4aa** (1.29 g, 70%).



Scheme 2.32: Gram-scale synthesis of C5- & C7- substituted oxindole, **4aa.**

Gram-scale synthesis of 5ma:

A vial was charged with a magnetic bead and N-protected oxindole, **1m** (1.12 g, 3 mmol) and alcohol, **2a** (0.66 g, 3.6 mmol) were added to it. Thereafter, the reaction mixture was supplemented by HFIP ([0.14 M], 21 mL), which was followed by the addition of TfOH (27 µL, 10 mol%). The reaction mixture was allowed to stir at room temperature in N_2 atmosphere and the reaction progress was monitored through TLC. Upon completion in 7 hours, cold water was added to the reaction mixture and was extracted with ethyl acetate three times. The complete organic layer was collected, dried over sodium sulfate and evaporated under reduced pressure. The obtained crude product was further purified through silica gel chromatography to afford product **5ma** (1.28 g, 79%).



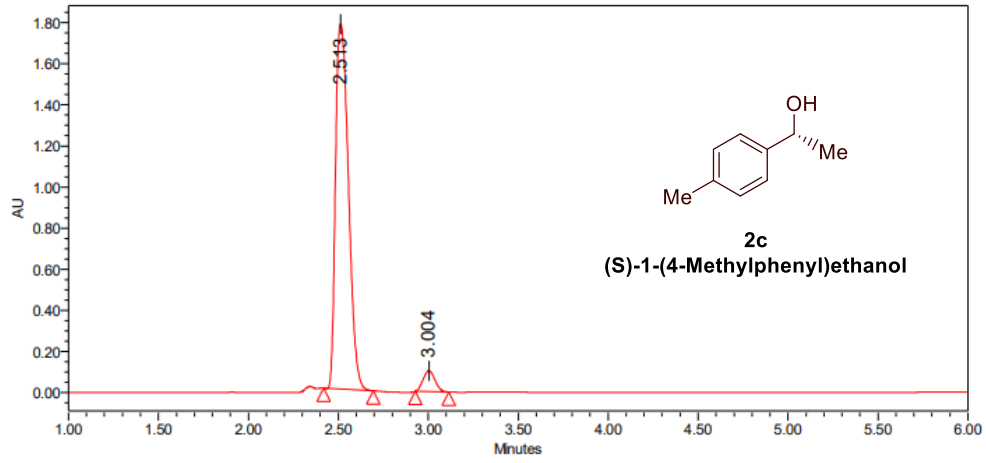
1m
(3 mmol, 1.12 g)

2a
(3.6 mmol, 0.66 g)

5ma
1.28 g (79%)

Scheme 2.33: Gram-scale synthesis of C5-alkylated oxindole, **5ma**

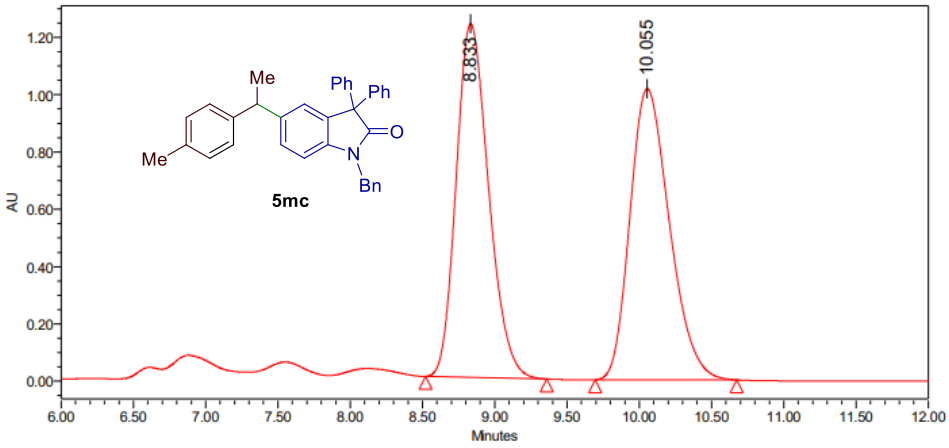
2.4.3 HPLC Traces



Peak Results

	Name	RT	Area	% Area
1		2.513	8854394	95.00
2		3.004	466222	5.00

HPLC: Ash Column, i-PrOH/hexanes = 20/80, flow rate = 1 mL/min; *ee* = 90%



Peak Results

	Name	RT	Area	% Area
1		8.833	19227821	49.91
2		10.055	19297451	50.09

HPLC: Ash Column, i-PrOH/hexanes = 20/80, flow rate = 0.3 mL/min; *ee* = 0.15%

2.4.4 Characterization data

1-benzhydryl-3,3-diphenylindolin-2-one, 3aa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 150-153 °C. **Yield:** 77%, 35 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.33 (m, 2H), 7.33 – 7.30 (m, 6H), 7.30 – 7.28 (d, J = 2.2 Hz, 6H), 7.28 – 7.27 (m, 2H), 7.26 (s, 2H), 7.25 – 7.24 (m, 3H), 7.11 (s, 1H), 7.02 – 6.97 (m, 2H), 6.54 – 6.48 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.0, 142.3, 141.9, 137.8, 133.3, 128.72, 128.66, 128.59, 128.5, 127.9, 127.8, 127.5, 126.1, 122.7, 112.5, 62.4, 58.6. **HRMS:** m/z calculated for $C_{33}H_{26}NO$ $[M+H]^+$ = 452.2014, found 452.1992.

1-benzhydryl-5-methoxy-3,3-diphenylindolin-2-one, 3ba

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 152-156 °C. **Yield:** 84%, 40 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.31 (m, 8H), 7.30 – 7.28 (m, 7H), 7.28 – 7.26 (m, 4H), 7.25 (d, *J* = 1.8 Hz, 1H), 7.09 (s, 1H), 6.84 (d, *J* = 2.6 Hz, 1H), 6.54 – 6.52 (m, 1H), 6.39 (d, *J* = 8.7 Hz, 1H), 3.68 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 155.8, 142.3, 137.9, 135.3, 134.7, 128.70, 128.67, 128.60, 128.5, 127.9, 127.5, 113.2, 112.9, 112.1, 62.8, 58.5, 55.7. **HRMS:** m/z calculated for $C_{34}H_{28}NO_2$ $[M+H]^+$ = 482.2120, found 482.2127.

1-benzhydryl-5-fluoro-3,3-diphenylindolin-2-one, 3ca

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 142-147 °C. **Yield:** 70%, 33 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.33 (m, 10H), 7.32 (d, *J* = 1.0 Hz, 1H), 7.31 – 7.26 (m, 9H), 7.14 (s, 1H), 7.04 – 7.01 (m, 1H), 6.75 – 6.70 (m, 1H), 6.48 – 6.45 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 160.3, 157.9, 141.7, 137.6 (d, *J* = 31.1 Hz), 135.0 (d, *J* = 7.7 Hz), 128.8, 128.4 (d, *J* = 3.0 Hz), 128.0, 127.7, 114.3 (d, *J* = 23.1 Hz), 113.78 (d, *J* = 24.7 Hz),

113.08 (d, *J* = 7.7 Hz), 62.7, 58.6. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -119.92. **HRMS:** m/z calculated for $C_{30}H_{19}N_4OF$ $[M+H]^+$ = 470.1543, found 470.1534.

1-benzhydryl-5-bromo-3,3-diphenylindolin-2-one, 3da

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 146-149 °C. **Yield:** 72%, 38 mg. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.37 – 7.29 (m, 13H), 7.27 – 7.22 (m, 8H), 7.13 – 7.11 (m, 1H), 7.10 (s, 1H), 6.37 (d, *J* = 8.5 Hz, 1H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 177.4, 141.5, 141.0, 137.3, 135.4, 130.8, 129.0, 128.8, 128.5, 128.4, 128.1, 127.8, 115.7, 113.9, 62.4, 58.5. **HRMS:** m/z calculated for $C_{33}H_{25}BrNO$ $[M+H]^+$ = 530.1120, found 530.1109.

1-benzhydryl-4-chloro-3,3-diphenylindolin-2-one, 3fa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 144-145 °C. **Yield:** 68%, 33 mg. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.38 – 7.31 (m, 16H), 7.29 – 7.27 (m, 4H), 7.08 (s, 1H), 7.03 – 6.92 (m, 2H), 6.52 – 6.50 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 178.3, 143.9, 138.0, 137.4, 132.5, 130.4, 129.5, 129.2, 128.8, 128.4, 128.2, 128.0, 127.8, 124.3, 111.1, 63.2, 58.8. **HRMS:** m/z calculated for $C_{33}H_{25}NOCl$ $[M+H]^+$ = 486.1625, found 486.1604.

1-benzhydryl-6-fluoro-3,3-diphenylindolin-2-one, 3ga

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 142-146 °C. **Yield:** 67%, 31 mg. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.37 – 7.32 (m, 7H), 7.31 – 7.27 (m, 6H), 7.26 – 7.20 (m, 7H), 7.18 – 7.14 (m, 1H), 7.07 (s, 1H), 6.72 – 6.65 (m, 1H), 6.23 – 6.20 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 178.3, 143.2 (d, *J* = 11.6 Hz), 142.0, 137.3, 128.8 (d, *J* = 13.3 Hz), 128.5, 128.4 (d, *J* = 2.9 Hz), 127.6, 126.9 (d, *J* = 9.4 Hz), 109.2 (d, *J* = 22.3 Hz), 101.0 (d, *J* = 27.2 Hz), 61.9, 58.7. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -112.68. **HRMS:** m/z calculated for $C_{30}H_{19}N_4OF$ $[M+H]^+$ = 470.1543, found 470.1541.

1-benzhydryl-6-bromo-3,3-diphenylindolin-2-one, 3ha

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 147-150 °C. **Yield:** 69%, 36 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.33 (m, 6H), 7.32 – 7.28 (m, 6H), 7.28 – 7.24 (m, 4H), 7.24 – 7.20 (m, 4H), 7.15 – 7.12 (m, 1H), 7.10 (s, 1H), 7.08 (d, *J* = 6.5 Hz, 1H), 6.63 (d, *J* = 1.6 Hz, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.8, 143.3, 141.6, 137.2, 132.3, 128.88, 128.78, 128.44, 128.41, 128.1, 128.0, 127.3, 125.7, 121.4, 115.5, 62.1, 58.8. **HRMS:** m/z calculated for $C_{33}H_{25}BrNO$ $[M+H]^+$ = 530.1120, found 530.1128.

1-benzhydryl-3,3-di-*p*-tolylindolin-2-one, 3ja

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 132-136 °C. **Yield:** 80%, 38 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.30 (m, 6H), 7.29 – 7.26 (m, 4H), 7.26 – 7.22 (m, 1H), 7.15 – 7.09 (m, 9H), 6.99 – 6.96 (m, 2H), 6.50 – 6.47 (m, 1H), 2.32 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.2, 141.9, 139.5, 137.8, 137.1, 133.7, 129.3, 128.7, 128.5, 128.4, 127.8, 127.6, 125.9, 122.7, 112.5, 61.7, 58.5, 21.2. **HRMS:** m/z calculated for $C_{35}H_{29}NO$ $[M+H]^+$ = 480.2327, found 480.2301.

1-benzhydryl-3,3-bis(4-fluorophenyl)indolin-2-one, 3ka

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 134-138 °C. **Yield:** 72%, 35 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.30 (m, 5H), 7.26 – 7.24 (m, 5H), 7.22 – 7.16 (m, 5H), 7.06 (s, 1H), 7.04 – 6.95 (m, 6H), 6.55 – 6.50 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.8, 163.5, 161.0, 141.8, 137.8 (d, *J* = 3.1 Hz), 137.6, 132.9, 130.2 (d, *J* = 8.3 Hz), 128.8, 128.4, 128.1 (d, *J* = 10.9 Hz), 125.9, 122.9, 115.6 (d, *J* = 21.4 Hz), 112.7, 61.1, 58.7. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.86. **HRMS:** m/z calculated for $C_{33}H_{24}NOF_2$ $[M+H]^+$ = 488.1826, found 488.1806.

1-benzhydryl-3,3-dimethylindolin-2-one, 3daa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 125-128 °C. **Yield:** 73%, 23 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.27 (m, 10H), 7.24 – 7.20 (m, 1H), 7.05 (s, 1H), 7.02 – 6.93 (m, 2H), 6.46 (dd, *J* = 7.0, 1.6 Hz, 1H), 1.45 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 181.7, 141.3, 138.0, 136.0, 128.7, 128.5, 127.8, 127.2, 122.3, 122.3, 112.1, 57.9, 43.9, 24.8. **HRMS:** m/z calculated for $C_{23}H_{22}NO$ $[M+H]^+$ = 328.1701, found 328.1710.

1'-benzhydrylspiro[cyclobutane-1,3'-indolin]-2'-one, 3faa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 127-131 °C. **Yield:** 75%, 25 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53-7.50 (m, 1H), 7.36 – 7.25 (m, 10H), 7.06 – 6.93 (m, 3H), 6.40 (dd, *J* = 7.5, 0.9 Hz, 1H), 2.76 – 2.66 (m, 2H), 2.49 – 2.37 (m, 3H), 2.30 – 2.20 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 180.7, 141.7, 138.0, 134.4, 128.63, 128.56, 127.7, 127.3, 122.4, 122.4, 111.6, 58.1, 47.9, 31.8, 16.8. **HRMS:** m/z calculated for $C_{24}H_{22}NO$ $[M+H]^+$ = 340.1701, found 340.1692

1'-benzhydrylspiro[cyclohexane-1,3'-indolin]-2'-one, 3gaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 127-133 °C. **Yield:** 77%, 28 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 – 7.42 (m, 1H), 7.35 – 7.25 (m, 10H), 7.05 (s, 1H), 6.99 – 6.93 (m, 2H), 6.48 – 6.42 (m, 1H), 2.00 (qd, *J* = 11.4, 6.1 Hz, 2H), 1.90 (ddd, *J* = 12.8, 8.8, 3.8 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.73 – 1.63 (m, 3H), 1.63 – 1.56 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 180.9, 141.5, 138.1, 135.6, 128.6, 128.5, 127.7, 127.0, 123.8, 121.8, 111.9, 57.7, 46.9, 33.5, 25.3, 21.2. **HRMS:** m/z calculated for $C_{26}H_{26}NO$ $[M+H]^+$ = 368.2014, found 368.2019

1-benzhydrylindolin-2-one, 3aaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 10 : 1. **Physical State:** White solid, **m.p.:** 116-118 °C. **Yield:** 90%, 27 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.28 (m, 10H), 7.27 – 7.23 (m, 1H), 7.07 (s, 1H), 6.97 (dt, *J* = 9.7, 4.6 Hz, 2H), 6.50 – 6.41 (m, 1H), 3.67 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 175.4, 143.9, 137.8, 129.5, 128.7, 128.6, 128.5, 128.4, 127.8, 127.4, 126.5, 125.4, 124.6, 124.5, 122.1, 112.0, 58.2, 35.7. **HRMS:** m/z calculated for $C_{21}H_{18}NO$ $[M+H]^+$ = 300.1388, found 300.1397

1-benzhydryl-5-chloroindolin-2-one, 3baa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 10 : 1. **Physical State:** White solid, **m.p.:** 117-121 °C. **Yield:** 87%, 29 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.30 (m, 6H), 7.29 – 7.25 (m, 4H), 7.24 – 7.21 (m, 1H), 7.05 (s, 1H), 6.95 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 3.65 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 174.7, 142.4, 137.5, 128.8, 128.5, 128.0, 127.6, 127.4, 126.3, 124.9, 112.8, 58.2, 35.6. **HRMS:** m/z calculated for $C_{21}H_{17}ClNO$ $[M+H]^+$ = 334.0999, found 334.0986

1-benzhydryl-5-methylindolin-2-one, 3caa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 10 : 1. **Physical State:** White solid, **m.p.:** 118-123 °C. **Yield:** 92%, 29 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.25 (m, 10H), 7.06 (d, *J* = 12.5 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 3.63 (s, 2H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 175.4, 141.5, 137.9, 131.7, 128.64, 128.59, 127.8, 127.7, 125.3, 124.7, 111.8, 58.1, 35.8, 21.0. **HRMS:** m/z calculated for $C_{22}H_{20}NO$ $[M+H]^+$ = 314.1545, found 314.1559.

1-((4-bromophenyl)(phenyl)methyl)indolin-2-one, 3aal

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 10 : 1. **Physical State:** White solid, **m.p.:** 116-118 °C. **Yield:** 86%, 32 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 – 7.42 (m, 1H), 7.38 – 7.22 (m, 7H), 7.21 – 7.12 (m, 2H), 7.07 – 6.92 (m, 3H), 6.46 – 6.38 (m, 1H), 3.65 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 175.4, 143.6, 137.3, 137.0, 131.8, 130.3, 128.8, 128.7, 128.6, 128.5, 128.1, 127.5, 124.6, 122.4, 111.9, 57.7, 35.7. **HRMS:** m/z calculated for $C_{21}H_{17}BrNO$ $[M+H]^+$ = 378.0494, found 378.0484

3,3-diphenyl-1-(1-phenylethyl)indolin-2-one, 3ab

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 125-127 °C. **Yield:** 54%, 21 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.24 (m, 16H), 7.08 – 6.98 (m, 2H), 6.57 (d, *J* = 7.4 Hz, 1H), 5.96 (q, *J* = 7.2 Hz, 1H), 1.87 (d, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 142.4, 142.1, 141.0, 139.2, 133.4, 128.82, 128.67, 128.61, 128.58, 128.56, 127.9, 127.5, 127.5, 127.4, 126.7, 126.2, 122.6, 111.5, 62.5, 49.3, 16.5. **HRMS:** m/z calculated for $C_{28}H_{24}NO$ $[M+H]^+$ = 390.1858, found 390.1876.

1-(1-(4-(methylthio)phenyl)ethyl)-3,3-diphenylindolin-2-one, 3ae

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 127-130 °C. **Yield:** 55%, 24 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.27 (m, 8H), 7.26 – 7.18 (m, 7H), 7.08 – 7.14 (m, 1H), 7.01 - 6.97 (m, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 5.90 (q, *J* = 7.2 Hz, 1H), 2.46 (s, 3H), 1.83 (d, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 142.4, 142.1, 141.0, 137.8, 136.1, 133.5, 128.68, 128.63, 128.58, 128.55, 127.9, 127.5, 127.4, 127.2, 126.8, 126.2, 122.7, 111.5, 62.5, 49.0, 16.5, 15.8. **HRMS:** m/z calculated for $C_{29}H_{26}NOS$ $[M+H]^+$ = 436.1735, found 436.1743.

1-(1-(naphthalen-2-yl)ethyl)-3,3-diphenylindolin-2-one, 3af

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 129-132 °C. **Yield:** 68%, 30 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.86 – 7.74 (m, 4H), 7.54 – 7.46 (m, 2H), 7.39 – 7.29 (m, 11H), 7.26 – 7.23 (m, 1H), 7.02 – 6.94 (m, 2H), 6.61 – 6.57 (m, 1H), 6.10 (q, J = 7.0 Hz, 1H), 1.99 (d, J = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.8, 142.4, 142.2, 141.0, 136.9, 133.4 (d, J = 8.7 Hz), 132.7, 128.70, 128.65, 128.58, 128.11, 128.0, 127.8, 127.5, 127.4, 126.4, 126.2 (d, J = 8.7 Hz), 125.1 (d, J = 10.3 Hz), 122.7, 111.4, 62.6, 49.5, 16.5. **HRMS:** m/z calculated for $C_{32}H_{26}NO$ $[M+H]^+$ = 440.2014, found 440.2020.

1-(1,2-diphenylethyl)-3,3-diphenylindolin-2-one, 3ag

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 128-132 °C. **Yield:** 68%, 32 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.28 (m, 5H), 7.27 – 7.24 (m, 3H), 7.19 – 7.09 (m, 12H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.1 Hz, 2H), 6.12 – 6.08 (m, 1H), 3.72 (dd, *J* = 8.5, 5.5 Hz, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.8, 142.3, 141.0, 141.3, 138.7, 137.3, 133.2, 129.4, 128.85, 128.71, 128.66, 128.4, 128.3, 127.9, 127.7, 127.4, 127.0, 126.9, 126.8, 126.2, 122.6, 111.0, 62.3, 55.1, 36.0. **HRMS:** m/z calculated for $C_{34}H_{28}NO$ $[M+H]^+$ = 466.2171, found 466.2177.

3,3-diphenyl-1-(1-phenylprop-2-yn-1-yl)indolin-2-one, 3ah

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 122-127 °C. **Yield:** 70%, 28 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 – 7.48 (m, 2H), 7.34 – 7.28 (m, 13H), 7.25 – 7.23 (m, 1H), 7.14 – 7.10 (m, 1H), 7.06 – 7.02 (m, 1H), 6.95 – 6.92 (m, 1H), 6.82 – 6.80 (m, 1H), 2.63 (d, *J* = 2.6 Hz, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.2, 142.0, 141.7, 139.9, 134.9, 133.0, 128.88, 128.69, 128.63, 128.6, 128.4, 127.9, 127.6, 127.5, 126.9, 126.0, 123.2, 112.1, 78.3,

75.6, 62.5, 45.7. **HRMS:** m/z calculated for $C_{29}H_{22}NO$ $[M+H]^+$ = 400.1701, found 400.1718.

1-(cyclohexyl(phenyl)methyl)-3,3-diphenylindolin-2-one, 3ai

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 126-129 °C. **Yield:** 60%, 27 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 (d, J = 7.3 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.20 (m, 7H), 7.18 – 7.14 (m, 6H), 7.06 – 6.96 (m, 2H), 5.16 (d, J = 10.4 Hz, 1H), 2.85 – 2.74 (m, 1H), 1.84 (dd, J = 13.1, 3.8 Hz, 1H), 1.68 (ddd, J = 15.2, 8.5, 3.9 Hz, 3H), 1.28 – 1.35 (m, 2H), 1.23 – 1.11 (m, 2H), 1.04 – 0.95 (m, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.79, 144.62, 144.58, 142.61, 142.50, 142.40, 142.30, 140.42, 138.74, 138.31, 133.26, 133.20, 128.92, 128.65, 128.59, 128.55, 128.49, 128.43, 128.41, 128.14, 128.12, 127.88, 127.82, 127.70, 127.23, 127.20, 127.15, 127.11, 126.05, 125.82, 125.74, 110.10, 62.45, 59.00, 41.76, 32.1, 31.8, 26.6, 26.3, 25.9. **HRMS:** m/z calculated for $C_{33}H_{32}NO$ $[M+H]^+$ = 458.2484, found 458.2492.

3,3-diphenyl-1-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)indolin-2-one, 3aj

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 130-133 °C. **Yield:** 62%, 27 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.30 (m, 5H), 7.30 – 7.26 (m, 5H), 7.26 – 7.22 (m, 1H), 7.22 – 7.16 (m, 2H), 7.15 – 7.08 (m, 2H), 7.04 – 6.94 (m, 3H), 5.88 (d, J = 10.6 Hz, 1H), 3.03 – 2.86 (m, 2H), 2.42 – 2.31 (m, 1H), 2.15 – 2.04 (m, 3H), 1.95 – 1.82 (m, 1H), 1.53 – 1.38 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.2, 142.9, 142.3, 142.0, 141.1, 140.1, 133.2, 130.4, 128.8, 128.7, 128.6, 128.4, 128.0, 127.6, 127.3, 127.1, 126.4, 126.2, 124.6, 122.8, 112.6, 62.6, 55.8, 36.5, 33.8, 30.8, 27.4. **HRMS:** m/z calculated for $C_{31}H_{28}NO$ $[M+H]^+$ = 430.2171, found 430.2181.

1-(naphthalen-2-yl(phenyl)methyl)-3,3-diphenylindolin-2-one, 3ak

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 150-153 °C. **Yield:** 85%, 43 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.87 – 7.78 (m, 2H), 7.71 – 7.69 (m, 2H), 7.52 – 7.43 (m, 2H), 7.42 – 7.39 (m, 1H), 7.37 – 7.34 (m, 5H), 7.33 – 7.26 (m, 12H), 7.03 – 6.94 (m, 2H), 6.61 – 6.57 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.0, 142.3, 141.9, 137.6, 135.4, 133.3 (d, J = 3.5 Hz), 132.9, 128.79, 128.68, 128.61, 128.54, 128.22, 127.96, 127.85, 127.75, 127.48 (d, J = 3.8 Hz), 127.39, 126.4, 126.1, 122.8, 112.5, 62.4, 58.7. **HRMS:** m/z calculated for $C_{37}H_{28}NO$ $[M+H]^+$ = 502.2171, found 502.2183.

3,3-diphenyl-1-(phenyl(*p*-tolyl)methyl)indolin-2-one, 3al

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 145-148 °C. **Yield:** 82%, 38 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.21 (m, 16H), 7.18 – 7.12 (q, *J* = 8.2 Hz, 4H), 7.08 (s, 1H), 7.03 – 6.97 (m, 2H), 6.57 – 6.51 (m, 1H), 2.35 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.9, 142.3, 142.0, 137.9, 137.6, 134.7, 133.3, 129.4, 128.66, 128.63, 128.60, 128.46, 128.45, 127.76, 127.74, 127.42, 126.0, 122.7, 112.6, 62.4, 58.3, 21.2. **HRMS:** m/z calculated for $C_{34}H_{28}NO$ $[M+H]^+$ = 466.2171, found 466.2174.

1-((4-fluorophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 3am

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 149-153 °C. **Yield:** 68%, 32 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.31 (m, 4H), 7.30 – 7.26 (m, 7H), 7.25 – 7.21 (m, 7H), 7.06 (s, 1H), 7.03 – 6.99 (m, 4H), 6.52 – 6.46 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.0, 163.6, 161.1, 142.1 (d, *J* = 6.0 Hz), 141.7, 137.5, 133.6 (d, *J* = 3.2 Hz), 133.3, 130.2 (d, *J* = 8.1 Hz), 128.8, 128.7, 128.5, 128.4, 127.9 (d, *J* = 18.7 Hz), 127.5 (d, *J* = 2.0 Hz), 126.2,

122.9, 115.7 (d, *J* = 21.5 Hz), 112.3, 62.4, 58.0. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.31. **HRMS:** m/z calculated for $C_{33}H_{25}NOF$ $[M+H]^+$ = 470.1920, found 470.1926.

1-((4-chlorophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 3an

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 156-159 °C. **Yield:** 65%, 31 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.29 (m, 10H), 7.29 – 7.23 (m, 9H), 7.21 (d, *J* = 1.3 Hz, 1H), 7.06 (s, 1H), 7.04 – 7.00 (m, 2H), 6.53 – 6.48 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.0, 142.2, 142.1, 141.6, 137.2, 136.4, 133.8, 133.3, 129.9, 128.93, 128.86, 128.69, 128.54, 128.53, 128.39, 128.09, 127.9, 127.6, 127.5, 126.2, 122.9, 112.3, 62.4, 58.0. **HRMS:** m/z calculated for $C_{33}H_{25}NOCl$ $[M+H]^+$ = 486.1625, found 486.1633.

1-((4-bromophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 3ao

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 160-163 °C. **Yield:** 66%, 35 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 – 7.42 (m, 2H), 7.37 – 7.28 (m, 9H), 7.27 – 7.21 (m, 7H), 7.18 – 7.13 (m, 2H), 7.04 (s, 1H), 7.04 – 6.99 (m, 2H), 6.53 – 6.47 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.0, 142.2, 142.1, 141.6, 137.2, 136.9, 133.3, 131.9, 130.2, 128.9, 128.7, 128.5, 128.4, 128.1, 127.9, 127.6, 127.5, 126.2, 122.9, 122.0, 112.3, 62.4, 58.1. **HRMS:** m/z calculated for $C_{33}H_{25}NOBr$ $[M+H]^+$ = 530.1120, found 530.1122.

3,3-diphenyl-1-(phenyl(4-(trifluoromethyl)phenyl)methyl)indolin-2-one, 3ap

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 169-172 °C. **Yield:** 61%, 32 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.33 – 7.29 (m, 6H), 7.27 – 7.24 (m, 7H), 7.14 (s, 1H), 7.07 – 7.00 (m, 2H), 6.53 – 6.48 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.0, 142.1 (d, *J* = 8.1 Hz), 141.9, 141.5, 136.9,

133.3, 130.1 (q, *J* = 32.5 Hz), 128.9, 128.8, 128.7, 128.5, 128.3, 127.9, 127.6 (d, *J* = 3.3 Hz), 126.3, 125.74 (d, *J* = 3.5 Hz), 125.69, 125.46, 123.1, 122.8, 112.1, 62.4, 58.2. **HRMS:** m/z calculated for $C_{34}H_{25}NOF_3$ $[M+H]^+$ = 520.1888, found 520.1889.

3,3-diphenyl-1-(phenyl(*o*-tolyl)methyl)indolin-2-one, 3ar

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 142-145 °C. **Yield:** 74%, 34 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.29 (m, 6H), 7.29 – 7.23 (m, 9H), 7.21 – 7.12 (m, 5H), 7.07 (s, 1H), 7.03 – 6.94 (m, 2H), 6.47 – 6.41 (m, 1H), 2.12 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 142.6 (d, *J* = 2.8 Hz), 142.2, 137.8, 137.5, 136.6, 133.1, 131.0, 128.8, 128.7, 128.6 (d, *J* = 1.5 Hz), 128.3, 128.1 (d, *J* = 4.9 Hz), 127.9 (d, *J* = 3.7 Hz), 127.4, 126.2 (d, *J* = 5.7 Hz), 122.7, 112.1, 62.2, 57.1, 19.5. **HRMS:** m/z calculated for $C_{34}H_{28}NO$ $[M+H]^+$ = 466.2171, found 466.2177.

1-(bis(4-chlorophenyl)methyl)-3,3-diphenylindolin-2-one, 3as

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 162-165 °C. **Yield:** 60%, 31 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.29 (m, 10H), 7.29 – 7.26 (m, 2H), 7.25 – 7.21 (m, 6H), 7.19 (s, 1H), 7.08 – 7.03 (m, 2H), 7.02 (s, 1H), 6.52 – 6.48 (m, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.9, 142.0, 141.3, 135.8, 134.0, 133.3, 129.8, 129.1, 128.7, 128.5, 128.0, 127.6, 126.3, 123.1, 112.1, 62.4, 57.5. **HRMS:** m/z calculated for $C_{33}H_{24}NOCl_2$ $[M+H]^+$ = 520.1235, found 520.1227.

5,7-dibenzhydryl-3,3-diphenylindolin-2-one, 4aa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 186-190 °C. **Yield:** 80%, 49 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.29 – 7.27 (m, 2H), 7.25 – 7.22 (m, 11H), 7.21 – 7.19 (m, 4H), 7.18 – 7.14 (m, 6H), 7.05 – 7.02 (m, 4H), 6.98 – 6.94 (m, 5H), 6.46 (d, *J* = 1.2 Hz, 1H), 5.41 (s, 1H), 5.37

(s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 179.0, 144.0, 141.8, 141.4, 138.6, 136.9, 133.7, 130.4, 129.3, 129.1, 128.9, 128.62, 128.56, 128.5, 128.3, 127.40, 127.2, 126.4, 126.0, 125.4, 62.8, 56.4, 53.1. **HRMS:** m/z calculated for $C_{46}H_{36}NO$ $[M+H]^+$ = 618.2797, found 618.2792.

5,7-dibenzhydryl-3,3-di-*p*-tolylindolin-2-one, 4ja

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 193-196 °C. **Yield:** 82%, 53 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.25 (m, 19H), 7.14 – 7.12 (m, 5H), 7.10 – 7.05 (m, 6H), 6.54 (d, *J* = 1.3 Hz, 1H), 5.51 (s, 1H), 5.48 (s, 1H), 2.41 (s, 6H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 179.3, 144.1, 141.5, 139.0, 138.5, 137.0, 136.9, 134.1, 130.3, 129.3, 129.2, 129.1, 128.9, 128.3, 127.1, 126.3, 125.9, 125.3, 62.2, 56.4, 53.0, 21.2. **HRMS:** m/z calculated for $C_{48}H_{40}NO$ $[M+H]^+$ = 646.3110, found 646.3104.

5,7-dibenzhydryl-3,3-bis(4-fluorophenyl)indolin-2-one, 4ka

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 195-197 °C. **Yield:** 72%, 47 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.30 – 7.27 (m, 1H), 7.25 – 7.22 (m, 4H), 7.21 – 7.15 (m, 7H), 7.13 – 7.09 (m, 5H), 7.05 – 6.99 (m, 4H), 6.98 – 6.91 (m, 8H), 6.87 (d, *J* = 1.5 Hz, 1H), 6.51 – 6.48 (m, 1H), 5.41 (s, 1H), 5.37 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 178.8, 163.4, 161.0, 143.9, 141.3, 138.9, 137.4 (d, *J* = 2.7 Hz), 136.8, 133.4, 130.7, 130.1 (d, *J* = 7.9 Hz), 129.0 (d, *J* = 12.1 Hz), 128.9, 128.4, 127.4, 127.3, 126.5, 125.8, 115.5 (d, *J* = 21.6 Hz), 61.5, 56.4, 53.0. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.90. **HRMS:** m/z calculated for $C_{46}H_{34}NOF_2$ $[M+H]^+$ = 654.2608, found 654.2607.

5,7-dibenzhydryl-3,3-bis(phenyl-d_5)indolin-2-one, 4la

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 200-204 °C. **Yield:** 80%, 37 mg. **^{1}H NMR (400 MHz,**

$CDCl_3$): δ 7.25 – 7.21 (m, 7H), 7.21 – 7.16 (m, 5H), 7.15 – 7.11 (m, 2H), 7.05 – 7.03 (m, 4H), 6.97 – 6.95 (m, 4H), 6.45 (d, *J* = 1.0 Hz, 1H), 5.41 (s, 1H), 5.37 (s, 1H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):** δ 178.9, 144.0, 141.4, 138.6, 136.9, 133.8, 130.4, 129.3, 129.1, 129.0, 128.3, 127.2, 126.4, 126.0, 125.4, 56.4, 53.1. **HRMS:** m/z calculated for $C_{45}H_{41}N_2O$ $[M+H]^+$ = 625.3219, found 625.3215.

5',7'-dibenzhydrylspiro[cyclohexane-1,3'-indolin]-2'-one, 4gaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 168-172 °C. **Yield:** 45%, 24 mg. **^1H NMR (400 MHz, $CDCl_3$):** δ 7.30 – 7.15 (m, 13H), 7.08 – 7.00 (m, 8H), 6.86 (s, 1H), 6.50 (d, *J* = 1.5 Hz, 1H), 5.41 (s, 1H), 5.37 (s, 1H), 1.91 – 1.82 (m, 2H), 1.81 – 1.72 (m, 2H), 1.54 (dd, *J* = 15.7, 2.1 Hz, 6H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):** δ 182.4, 144.3, 141.6, 137.5, 136.5, 136.3, 129.7, 129.6, 129.3, 129.4, 128.9, 128.4, 128.03, 128.00, 127.1, 126.3, 124.7, 123.6, 56.7, 53.2, 47.6, 33.3, 25.2, 21.1. **HRMS:** m/z calculated for $C_{39}H_{36}NO$ $[M+H]^+$ = 534.2797, found 534.2809

5,7-dibenzhydrylindolin-2-one, 4aaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 150-154 °C. **Yield:** 82%, 38 mg. **^1H NMR (400 MHz, $CDCl_3$):** δ 7.87 (s, 1H), 7.29 – 7.24 (m, 8H), 7.23 – 7.17 (m, 4H), 7.09 – 7.03 (m, 8H), 6.87 (s, 1H), 6.63 (s, 1H), 5.46 (s, 1H), 5.42 (s, 1H), 3.42 (s, 2H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.3, 144.1, 141.7, 139.4, 138.1, 130.2, 129.3, 129.2, 128.8, 128.4, 127.0, 126.4, 125.7, 125.4, 123.9, 56.5, 52.7, 36.3. **HRMS:** m/z calculated for $C_{34}H_{28}NO$ $[M+H]^+$ = 466.2171, found 466.2156.

5,7-bis(phenyl(*p*-tolyl)methyl)indolin-2-one, 4aal

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 152-156 °C. **Yield:** 74%, 36 mg, >20 : 1 dr. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.29 – 7.27 (m, 1H), 7.28 – 7.16 (m, 5H), 7.09 – 7.01 (m, 8H), 6.92 (t, *J* = 7.4 Hz, 5H), 6.85 (s, 1H), 6.61 – 6.56 (m, 1H), 5.35 (s, 1H), 5.33 (s, 1H), 3.41 (s, 2H), 2.32 (s, 3H), 2.31 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 176.7, 144.3, 141.7, 141.1, 139.1, 138.4, 138.4, 136.8, 135.9, 130.3, 129.7, 129.3, 129.2, 129.1, 129.0, 128.9, 128.4, 127.1, 126.3, 125.7, 125.3, 124.0, 56.1, 53.0, 36.2, 21.2. **HRMS:** m/z calculated for $C_{39}H_{32}NO$ $[M+H]^+$ = 494.2484, found 494.2495.

5,7-bis((4-chlorophenyl)(phenyl)methyl)indolin-2-one, 4aan

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 166-169 °C. **Yield:** 63%, 34 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.48 (s, 1H), 7.30 – 7.19 (m, 10H), 7.10 – 7.00 (m, 5H), 6.99 – 6.94 (m, 3H), 6.91 – 6.83 (m, 1H), 6.59 – 6.44 (m, 1H), 5.48 (d, J = 16.2 Hz, 1H), 5.40 (d, J = 14.3 Hz, 1H), 3.44 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.8, 144.0, 143.4, 142.6, 142.5, 141.2, 140.2, 139.6, 138.2, 137.7, 132.7, 132.2, 130.6, 130.1, 129.9, 129.3, 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 127.2, 127.0, 126.6, 126.4, 125.9, 125.1, 124.0, 123.9, 123.8, 55.7, 51.5, 36.4. **HRMS:** m/z calculated for $C_{34}H_{26}NOCl_2$ $[M+H]^+$ = 534.1391, found 534.1385.

3,3-diphenyl-5,7-bis(phenyl(*p*-tolyl)methyl)indolin-2-one, 4al

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 208-211 °C. **Yield:** 68%, 44 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.26 – 7.20 (m, 7H), 7.19 – 7.13 (m, 8H), 7.07 – 6.99 (m, 8H), 6.98 – 6.90 (m, 5H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.43 – 6.42 (m, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.8, 144.4, 141.9, 141.8, 141.6, 141.1,

138.7, 138.4, 136.8, 135.8, 133.7, 130.5, 129.7, 129.3, 129.2, 129.1, 129.01, 129.0, 128.9, 128.54, 128.51, 128.3, 127.4, 127.1, 126.2, 126.0, 125.5, 62.7, 56.0, 52.9, 21.2, 21.2. **HRMS:** m/z calculated for $C_{48}H_{40}NO$ $[M+H]^+$ = 646.3110, found 646.3104.

5,7-bis(-(4-fluorophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 4am

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 211-214 °C. **Yield:** 52%, 34 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 (d, *J* = 2.8 Hz, 1H), 7.26 – 7.23 (m, 6H), 7.22 – 7.13 (m, 9H), 7.02 -6.98 (m, 3H), 6.97 – 6.86 (m, 11H), 6.29 – 6.28 (m, 1H), 5.40 (s, 1H), 5.35 (s, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.9, 143.7, 141.8, 141.71, 141.66, 141.6, 141.1, 139.7, 138.6, 136.9, 133.8, 130.74, 130.66, 130.6, 130.1, 129.2, 129.1, 129.0, 128.6, 128.5, 127.5, 127.4, 126.6, 126.0, 125.2, 115.8, 115.7, 115.2, 115.0, 62.8, 55.5, 52.2. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -115.51, -116.77. **HRMS:** m/z calculated for $C_{46}H_{34}NOF_2$ $[M+H]^+$ = 654.2608, found 654.2593.

5,7-bis((4-chlorophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 4an

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 218-221 °C. **Yield:** 49%, 34 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.83 (d, J = 31.0 Hz, 1H), 7.31 – 7.24 (m, 12H), 7.21 (dd, J = 6.9, 2.4 Hz, 8H), 7.12 – 7.02 (m, 4H), 7.02 – 6.97 (m, 4H), 6.86 (d, J = 0.9 Hz, 2H), 5.53 – 5.37 (m, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 180.0, 143.5, 142.6, 141.6, 138.8, 138.3, 134.3, 133.9, 132.3, 130.8, 129.5, 129.4, 129.1, 128.6, 128.5, 127.7, 127.5, 126.7, 126.5, 110.1, 63.1, 55.8, 55.4. **HRMS:** m/z calculated for $C_{46}H_{34}NOCl_2$ $[M+H]^+$ =686.2017, found 686.2026.

3,3-diphenyl-5,7-bis(phenyl(4-(trifluoromethyl)phenyl)methyl)indolin-2-one, 4ap

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 227-230 °C. **Yield:** 45%, 34 mg. **^{1}H NMR (400 MHz,**

$CDCl_3$): δ 8.27 (d, *J* = 13.7 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 4H), 7.29 – 7.26 (m, 5H), 7.25 – 7.22 (m, 4H), 7.21 – 7.14 (m, 7H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.08 – 7.03 (m, 2H), 7.01 – 6.96 (m, 2H), 6.96 – 6.90 (m, 3H), 6.25 (dd, *J* = 14.4, 0.9 Hz, 1H), 5.52 (s, 1H), 5.44 (s, 1H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):** δ 179.54, 147.98 (d, *J* = 9.2 Hz), 145.51, 142.90 (d, *J* = 5.6 Hz), 141.60 (dd, *J* = 13.5, 11.8 Hz), 140.53, 137.81, 137.35, 134.11, 130.04, 129.59 (d, *J* = 1.2 Hz), 129.20, 129.07, 128.62, 128.45, 127.57, 126.89, 126.18, 125.67, 125.31 (d, *J* = 3.5 Hz), 124.83 (d, *J* = 3.5 Hz), 122.87 (d, *J* = 10.1 Hz), 63.02, 56.07 (d, *J* = 5.9 Hz), 52.22. **HRMS:** m/z calculated for $C_{48}H_{34}NOF_6$ $[M+H]^+$ =754.2545, found 754.2549.

5,7-bis(bis(4-chlorophenyl)methyl)-3,3-diphenylindolin-2-one, 4as

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 235-237 °C. **Yield:** 46%, 35 mg. **^1H NMR (400 MHz, $CDCl_3$):** δ 9.73 (s, 1H), 7.33 – 7.26 (m, 6H), 7.22 – 7.12 (m, 12H), 6.94 – 6.81 (m, 9H), 6.24 (d, *J* = 1.2 Hz, 1H), 5.50 (s, 1H), 5.33 (s, 1H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):** δ 180.0, 141.9, 141.6, 139.6, 137.8, 137.4, 134.2, 133.1, 132.6, 130.5, 129.9, 129.0, 128.6, 128.4, 127.6, 125.9, 125.0, 63.2, 55.0, 50.9. **HRMS:** m/z calculated for $C_{46}H_{32}NOCl_4$ $[M+H]^+$ =754.1238, found 754.1235.

5-benzhydryl-1-benzyl-3,3-diphenylindolin-2-one, 5ma

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 172-175 °C. **Yield:** 89%, 48 mg. **^1H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.26 (m, 9H), 7.26 – 7.17 (m, 12H), 7.11 – 7.04 (m, 5H), 6.84 – 6.82 (m, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 5.47 (s, 1H), 4.97 (s, 2H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.7, 144.0, 142.0, 140.7, 139.0, 136.0, 133.1, 129.5, 129.1, 128.9, 128.6, 128.4, 127.8, 127.6, 127.5, 127.4, 126.5, 109.2, 62.6, 56.4, 44.3. **HRMS:** m/z calculated for $C_{40}H_{32}NO$ $[M+H]^+$ =542.2484, found 542.2484.

5-benzhydryl-1-methyl-3,3-diphenylindolin-2-one, 5na

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 165-169 °C. **Yield:** 89%, 41 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31 - 7.24 (m, 11H), 7.24 – 7.19 (m, 5H), 7.14 – 7.07 (m, 5H), 7.01 - 6.98 (m, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.54 (s, 1H), 3.29 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.6, 144.1, 141.9, 141.6, 138.9, 133.0, 129.5, 129.2, 128.5, 128.5, 128.4, 127.6, 127.3, 126.5, 108.2, 62.6, 56.4, 26.8. **HRMS:** m/z calculated for $C_{34}H_{28}NO$ $[M+H]^+$ = 466.2171, found 466.2177.

5-benzhydryl-1-ethyl-3,3-diphenylindolin-2-one, 5oa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 158-162 °C. **Yield:** 90%, 43 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.28 (m, 3H), 7.28 – 7.23 (m, 8H), 7.23 – 7.19 (m, 5H), 7.13 – 7.07 (m, 5H), 6.98 – 6.96 (m, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 5.52 (s, 1H), 3.83 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 181.6, 158.3, 152.3, 145.4, 133.7, 132.7, 131.7, 128.3, 127.2, 122.8, 114.1, 55.5, 27.8, 27.0, 18.1. **HRMS:** m/z calculated for $C_{35}H_{30}NO$ $[M+H]^+$ = 480.2327, found 480.2324.

5-benzhydryl-1-butyl-3,3-diphenylindolin-2-one, 5pa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 166-170 °C. **Yield:** 91%, 46 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41 – 7.29 (m, 16H), 7.28 – 7.20 (m, 5H), 7.10 - 7.08 (m, 1H), 6.95 (d, J = 8.1 Hz, 1H), 5.64 (s, 1H), 3.89 (t, J = 7.3 Hz, 2H), 1.88 – 1.77 (m, 2H), 1.51 (dq, J = 14.7, 7.4 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.3, 144.0, 142.0, 140.9, 138.5, 133.2, 129.4, 129.0, 128.4, 128.3, 127.7, 127.2, 126.4, 108.4, 62.4, 56.3, 40.2, 29.5, 20.2, 13.8. **HRMS:** m/z calculated for $C_{37}H_{34}NO$ $[M+H]^+$ = 508.2640, found 508.2654.

5-benzhydryl-1-hexanoyl-3,3-diphenylindolin-2-one, 5qa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 168-171 °C. **Yield:** 91%, 50 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.26 (m, 8H), 7.26 – 7.20 (m, 8H), 7.12 (d, *J* = 6.9 Hz, 5H), 7.02 – 6.94 (m, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 5.54 (s, 1H), 3.78 (t, *J* = 7.3 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.44 – 1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.4, 144.1, 142.1, 141.0, 138.6, 133.3, 129.5, 129.1, 128.5, 128.5, 128.4, 128.0, 127.7, 127.3, 126.5, 108.5, 62.5, 56.4, 40.5, 31.5, 27.5, 26.6, 22.6, 14.1. **HRMS:** m/z calculated for $C_{39}H_{38}NO$ $[M+H]^+$ =536.2953, found 536.2958.

5-benzhydryl-1-phenethyl-3,3-diphenylindolin-2-one, 5ra

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 172-174 °C. **Yield:** 85%, 47 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31 – 7.26 (m, 4H), 7.24 – 7.17 (m, 13H), 7.09 – 7.06 (m, 9H), 6.92 – 6.90 (m, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 5.50 (s, 1H), 4.04 – 3.98 (m, 2H), 3.03 – 2.97 (m, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.3, 144.1, 142.0, 140.7, 138.7, 138.0, 133.0, 129.5, 129.1, 129.0, 128.7, 128.51, 128.45, 127.8, 127.3, 126.8, 126.5, 108.3, 62.5, 56.4, 41.8, 33.7. **HRMS:** m/z calculated for $C_{41}H_{34}NO$ $[M+H]^+$ = 556.2640, found 556.2659.

5-benzhydryl-1-benzyl-7-methyl-3,3-diphenylindolin-2-one, 5sa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 168-174 °C. **Yield:** 90%, 50 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.26 (m, 15H), 7.25 – 7.20 (m, 4H), 7.15 – 7.08 (m, 6H), 6.99 – 6.96 (m, 1H), 6.70 – 6.67 (m, 1H), 5.46 (s, 1H), 5.27 (s, 2H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 178.7, 144.0, 142.3, 138.8, 138.8, 137.9, 133.8, 133.1, 129.4, 128.9, 128.7, 128.5, 128.4, 127.3, 127.3, 126.5, 125.8, 125.7, 119.8, 62.2, 56.3, 45.4, 29.8, 19.1. **HRMS:** m/z calculated for $C_{41}H_{34}NO$ $[M+H]^+$ = 556.2640, found 556.2664.

5-benzhydryl-1-benzyl-7-fluoro-3,3-diphenylindolin-2-one, 5ta

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 170-173 °C. **Yield:** 82%, 46 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.28 (m, 5H), 7.27 (d, *J* = 1.1 Hz, 4H), 7.25 (d, *J* = 1.7 Hz, 4H), 7.23 – 7.20 (m, 3H), 7.19 – 7.14 (m, 5H), 7.07 – 7.02 (m, 4H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.63 – 6.60 (m, 1H), 5.44 (s, 1H), 5.09 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.5, 143.4, 141.5, 140.4 (d, *J* = 5.0 Hz), 137.3, 135.7 (d, *J* = 2.6 Hz), 129.4, 128.7, 128.64, 128.57, 128.50, 127.70, 127.67, 127.6, 126.8, 123.4 (d, *J* = 2.0 Hz), 117.3 (d, *J* = 20.3 Hz), 62.9, 56.1, 45.8. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -133.24. **HRMS:** m/z calculated for $C_{40}H_{31}NOF$ $[M+H]^+$ = 560.2390, found 560.2384.

5-benzhydryl-1-benzyl-6-fluoro-3,3-diphenylindolin-2-one, 5ua

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 171-174 °C. **Yield:** 82%, 46 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.30 (m, 3H), 7.29 – 7.28 (m, 3H), 7.28 – 7.26 (m, 5H), 7.26 – 7.25 (m, 2H), 7.24 – 7.20 (m, 4H), 7.19 – 7.15 (m, 4H), 7.07 – 7.03 (m, 4H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 9.8 Hz, 1H), 5.74 (s, 1H), 4.96 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 161.8, 159.3, 142.6, 142.1 (d, *J* = 11.7 Hz), 141.8, 135.5, 129.2, 129.1, 128.6, 128.5, 128.3, 128.1, 128.1, 128.0, 127.4 (d, *J* = 6.6 Hz), 126.6, 125.4 (d, *J* = 15.4 Hz), 98.2 (d, *J* = 29.0 Hz), 62.2, 49.1 (d, *J* = 2.4 Hz), 44.4. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.76. **HRMS:** m/z calculated for $C_{40}H_{31}NOF$ $[M+H]^+$ = 560.2390, found 560.2383.

5-benzhydryl-1-benzyl-3,3-di-*p*-tolylindolin-2-one, 5va

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 165-168 °C. **Yield:** 91%, 52 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.29 (m, 9H), 7.27 – 7.22 (m, 2H), 7.19 – 7.17 (m, 5H), 7.15 – 7.10 (m, 8H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 5.53 (s, 1H), 5.01 (s, 2H), 2.36 (s,

6H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.9, 144.0, 140.7, 139.1, 138.8, 137.0, 136.0, 133.4, 129.5, 129.2, 128.89, 128.86, 128.4, 127.7, 127.5, 127.4, 126.4, 109.1, 62.0, 56.4, 44.1, 21.1. **HRMS:** m/z calculated for $C_{42}H_{36}NO$ $[M+H]^+$ = 570.2797, found 570.2788.

5-benzhydryl-1-benzyl-3,3-bis(4-ethylphenyl)indolin-2-one, 5wa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 161-163 °C. **Yield:** 90%, 54 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.29 (m, 9H), 7.28 – 7.24 (m, 2H), 7.23 – 7.16 (m, 8H), 7.15 – 7.11 (m, 5H), 6.87 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.53 (s, 1H), 5.01 (s, 2H), 2.67 (q, *J* = 7.6 Hz, 4H), 1.27 (t, *J* = 7.6 Hz, 6H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 178.0, 144.0, 143.2, 140.6, 139.3, 138.7, 136.0, 133.5, 129.5, 128.9, 128.4, 128.4, 128.0, 127.7, 127.6, 127.4, 126.4, 109.1, 62.1, 56.4, 44.2, 28.5, 15.5. **HRMS:** m/z calculated for $C_{44}H_{40}NO$ $[M+H]^+$ = 598.3110, found 598.3108.

5-benzhydryl-1-benzyl-3,3-bis(4-fluorophenyl)indolin-2-one, 5xa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 169-173 °C. **Yield:** 89%, 51 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.31 (m, 1H), 7.30 – 7.26 (m, 8H), 7.24 – 7.16 (m, 6H), 7.09 – 7.05 (m, 5H), 7.01 – 6.94 (m, 4H), 6.90 - 6.88 (m, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 5.50 (s, 1H), 4.97 (s, 2H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.5, 163.4, 160.9, 143.8, 140.5, 139.2, 137.5 (d, *J* = 3.0 Hz), 135.8, 132.8, 130.1 (d, *J* = 8.1 Hz), 129.4, 129.0, 128.5, 127.9 (d, *J* = 11.2 Hz), 127.4 (d, *J* = 6.7 Hz), 126.6, 115.5 (d, *J* = 21.6 Hz), 109.5, 61.3, 56.4, 44.3. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.90. **HRMS:** m/z calculated for $C_{40}H_{30}NOF_2$ $[M+H]^+$ = 578.2295, found 578.2292.

5-benzhydryl-1-benzyl-3,3-bis(phenyl-*d*$_5$)indolin-2-one, 5ya

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 174-177 °C. **Yield:** 85%, 47 mg. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.33 – 7.26 (m, 10H), 7.25 – 7.20 (m, 2H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.11 – 7.08 (m, 3H), 6.88 – 6.86 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.51 (s, 1H), 5.00 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 177.7, 144.0, 141.9, 141.9, 141.8, 140.7, 138.9, 136.0, 133.1, 129.5, 129.1, 128.9, 128.4, 128.1, 128.0, 127.7, 127.6, 127.4, 127.3, 127.1, 126.5, 109.2, 62.6, 56.4, 44.3. **HRMS:** m/z calculated for $C_{39}H_{39}N_2O$ $[M+H]^+$ = 551.3062, found 551.3028.

5-benzhydryl-7-methyl-3,3-diphenylindolin-2-one, 5ia

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 138-141 °C. **Yield:** 80%, 74 mg. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 9.84 (s, 1H), 7.34 – 7.30 (m, 4H), 7.28 (s, 9H), 7.26 – 7.21 (m, 3H), 7.14 – 7.10 (m, 4H), 6.91 (s, 1H), 6.77 (s, 1H), 5.50 (s, 1H), 2.22 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 181.1, 144.2, 141.8, 138.7, 137.7, 133.3, 130.6, 129.5, 128.6, 128.4, 128.4, 127.3, 126.4, 125.2, 123.7, 122.8, 119.8, 63.6, 56.5, 16.8. **HRMS:** m/z calculated for $C_{34}H_{28}NO$ $[M+H]^+$ = 466.2171, found 466.2159.

5-benzhydryl-1,3,3-trimethylindolin-2-one, 5eaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 122-126 °C. **Yield:** 90%, 31 mg. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.35 – 7.29 (m, 4H), 7.27 – 7.22 (m, 2H), 7.16 – 7.14 (m, 4H), 7.04 (d, *J* = 1.8 Hz, 1H), 7.00 – 6.98 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.58 (s, 1H), 3.22 (s, 3H), 1.35 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 181.5, 144.11, 141.10, 138.5, 136.0, 129.4, 128.7, 128.4, 126.4, 123.6, 107.8, 56.6, 44.4, 26.3, 24.5. **HRMS:** m/z calculated for $C_{24}H_{24}NO$ $[M+H]^+$ = 342.1855, found 342.1858.

1-benzyl-3,3-diphenyl-5-(1-(*p*-tolyl)ethyl)indolin-2-one, 5mc

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 155-157 °C. **Yield:** 73%, 36 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.24 (m, 16H), 7.21 (d, *J* = 1.7 Hz, 1H), 7.09 (d, *J* = 3.1 Hz, 3H), 7.04 – 7.02 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 4.99 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 1H), 2.33 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 143.5, 142.2, 142.1, 141.6, 140.3, 136.1, 135.7, 132.9, 129.2, 128.9, 128.6, 127.7, 127.5, 127.4, 127.3, 125.6, 109.5, 62.8, 44.2, 44.1, 22.3, 21.1. **HRMS:** m/z calculated for $C_{36}H_{32}NO$ $[M+H]^+$ = 494.2484, found 494.2486.

1-benzyl-5-(1-(4-bromophenyl)ethyl)-3,3-diphenylindolin-2-one, 5md

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 159-163 °C. **Yield:** 67%, 37 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 – 7.34 (m, 2H), 7.34 – 7.26 (m, 11H), 7.26 – 7.20 (m, 4H), 7.12 (d, *J* = 1.6 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.99 – 6.96 (m, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 4.97 (s, 2H), 4.04 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 145.5, 142.1, 142.0, 140.6, 136.0, 133.2, 131.5, 129.4, 128.9, 128.61, 128.57, 128.54, 128.48, 127.8, 127.6, 127.5, 127.4, 127.3, 125.6, 120.0, 109.5, 62.8, 44.3, 44.0, 22.1. **HRMS:** m/z calculated for $C_{35}H_{29}NOBr$ $[M+H]^+$ = 558.1433, found 558.1425.

1-benzyl-5-(naphthalen-2-yl(phenyl)methyl)-3,3-diphenylindolin-2-one, 5mk

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 171-173 °C. **Yield:** 85%, 50 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 – 7.79 (m, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.70 - 7.66 (m, 1H), 7.48 – 7.41 (m, 3H), 7.36 – 7.25 (m, 12H), 7.23 (d, *J* = 8.9 Hz, 7H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 2H), 6.88 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 5.64 (s, 1H), 4.99 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 143.7, 142.0, 141.9, 141.6, 140.8,

138.7, 136.0, 133.4, 133.1, 132.2, 129.6, 129.2, 128.9, 128.6, 128.54, 128.49, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.5, 127.4, 126.6, 126.2, 125.8, 109.3, 62.6, 56.5, 44.3. **HRMS:** m/z calculated for $C_{44}H_{34}NO$ $[M+H]^+$ = 592.2640, found 592.2651.

1-benzyl-3,3-diphenyl-5-(phenyl(p-tolyl)methyl)indolin-2-one, 5ml

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 172-175 °C. **Yield:** 84%, 47 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.26 (m, 14H), 7.26 – 7.24 (m, 3H), 7.22 – 7.20 (m, 1H), 7.13 (d, *J* = 1.7 Hz, 1H), 7.11 – 7.06 (m, 4H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.89 – 6.82 (m, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 5.46 (s, 1H), 4.99 (s, 2H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 144.3, 142.0, 141.0, 140.6, 139.1, 136.0, 133.0, 129.4, 129.3, 129.1, 129.0, 128.9, 128.6, 128.4, 127.7, 127.6, 127.43, 127.37, 126.4, 109.2, 62.6, 56.0, 44.3, 21.1. **HRMS:** m/z calculated for $C_{41}H_{34}NO$ $[M+H]^+$ = 556.2640, found 556.2661.

1-benzyl-5-((4-fluorophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 5mm

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 175-178 °C. **Yield:** 84%, 47 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 – 7.29 (m, 12H), 7.27 – 7.22 (m, 6H), 7.11 – 7.01 (m, 5H), 6.99 – 6.93 (m, 2H), 6.85 – 6.83 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.48 (s, 1H), 4.99 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.6, 162.7, 160.3, 143.8, 141.9 (d, *J* = 1.5 Hz), 140.8, 139.7 (d, *J* = 3.2 Hz), 138.7, 136.0, 133.2, 130.9 (d, *J* = 7.9 Hz), 129.4, 129.0, 128.9, 128.6, 128.5, 127.8, 127.5, 127.4, 126.6, 115.2 (d, *J* = 21.2 Hz), 109.3, 62.6, 55.6, 44.3. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -116.64. **HRMS:** m/z calculated for $C_{46}H_{34}NOF_2$ $[M+H]^+$ = 654.2608, found 654.2599.

1-benzyl-5-((4-chlorophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 5mn

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 176-180 °C. **Yield:** 82%, 47 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.26 (m, 12H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.24 – 7.19 (m, 7H), 7.08 – 7.01 (m, 3H), 7.01 – 6.96 (m, 2H), 6.82 – 6.79 (m, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 5.44 (s, 1H), 4.97 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.6, 143.5, 142.6, 141.9, 140.9, 138.4, 135.9, 133.2, 132.3, 130.8, 129.4, 129.0, 128.96, 128.60, 128.55, 128.51, 127.8, 127.5, 126.7, 109.3, 62.6, 55.8, 44.3. **HRMS:** m/z calculated for $C_{40}H_{31}NOCl$ $[M+H]^+$ = 576.2094, found 576.2092.

1-benzyl-5-((4-bromophenyl)(phenyl)methyl)-3,3-diphenylindolin-2-one, 5mo

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 183-187 °C. **Yield:** 80%, 50 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 – 7.39 (m, 2H), 7.35 – 7.28 (m, 17H), 7.27 – 7.24 (m, 1H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.11 – 7.06 (m, 2H), 7.01 – 6.95 (m, 2H), 6.87 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.47 (s, 1H), 5.02 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.5, 143.3, 143.0, 141.8, 140.8, 138.2, 135.8, 133.2, 131.4, 131.1, 129.4, 129.3, 128.96, 128.87, 128.53, 128.48, 128.43, 128.35, 127.7, 127.39, 127.35, 120.4, 109.3, 62.6, 55.7, 44.2. **HRMS:** m/z calculated for $C_{40}H_{31}NOBr$ $[M+H]^+$ = 620.1589, found 620.1574.

1-benzyl-3,3-diphenyl-5-(phenyl(4-(trifluoromethyl)phenyl)methyl)indolin-2-one, 5mp

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 193-197 °C. **Yield:** 77%, 47 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.26 (m, 17H), 7.22 (d, *J* = 8.0 Hz, 3H), 7.15 – 7.05 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.77 (dd, *J* = 8.0, 3.3 Hz, 1H), 5.56 (s, 1H), 5.01 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.6, 148.1, 143.0, 141.9, 141.0, 137.9, 135.9,

133.4, 129.8, 129.5, 129.4, 129.0, 128.9, 128.6, 128.5, 127.8, 127.5 (d, *J* = 5.6 Hz), 126.9, 125.4 (d, *J* = 3.5 Hz), 109.4, 62.6, 56.2, 44.3. **HRMS:** m/z calculated for $C_{41}H_{31}NOF_3$ $[M+H]^+$ = 610.2358, found 610.2363.

1-benzyl-3,3-diphenyl-5-(phenyl(o-tolyl)methyl)indolin-2-one, 5mr

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 168-171 °C. **Yield:** 81%, 45 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.19 (m, 19H), 7.17 – 7.13 (m, 2H), 7.08 (d, *J* = 1.6 Hz, 1H), 7.05 – 7.01 (m, 2H), 6.82 – 6.78 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 4.99 (d, *J* = 2.7 Hz, 2H), 2.18 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.7, 143.3, 142.5, 142.1, 141.8, 140.7, 138.5, 136.7, 136.0, 133.1, 130.5, 129.6, 129.4, 129.2, 128.9, 128.6, 128.5, 128.4, 127.8, 127.7, 127.5, 127.4, 127.3, 126.6, 126.4, 125.8, 109.2, 62.6, 53.1, 44.3, 20.0. **HRMS:** m/z calculated for $C_{41}H_{34}NO$ $[M+H]^+$ = 556.2640, found 556.2646.

1-benzyl-5-(bis(4-chlorophenyl)methyl)-3,3-diphenylindolin-2-one, 5ms

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 196-198 °C. **Yield:** 79%, 48 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.29 (m, 11H), 7.28 – 7.25 (m, 5H), 7.25 (d, *J* = 1.9 Hz, 3H), 7.09 (d, *J* = 1.6 Hz, 1H), 7.00 (t, *J* = 5.2 Hz, 4H), 6.83 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.44 (s, 1H), 5.00 (s, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 177.5, 142.0, 141.8, 141.0, 137.8, 135.8, 133.4, 132.5, 130.6, 128.9, 128.63, 128.58, 128.4, 127.8, 127.5, 127.4, 127.3, 109.4, 62.6, 55.1, 44.3. **HRMS:** m/z calculated for $C_{40}H_{30}NOCl_2$ $[M+H]^+$ = 610.1704, found 610.1712.

5-benzhydrylindolin-2-one, 5aaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 141-144 °C. **Yield:** 71%, 21 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.59 (s, 1H), 7.32 – 7.27 (m, 4H), 7.25 – 7.20 (m, 2H), 7.14 – 7.08 (m, 4H),

6.98 – 6.96 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.52 (s, 1H), 3.48 (s, 2H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.7, 144.0, 140.8, 138.5, 129.5, 129.1, 128.5, 126.5, 125.9, 125.6, 109.5, 56.6, 36.4. **HRMS:** m/z calculated for $C_{21}H_{18}NO$ $[M+H]^+$ = 300.1388, found 300.1379.

5-((4-chlorophenyl)(phenyl)methyl)indolin-2-one, 5aak

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 147-151 °C. **Yield:** 69%, 23 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.29 (s, 1H), 7.33 – 7.22 (m, 5H), 7.11 – 7.01 (m, 4H), 6.93 (dd, *J* = 5.2, 4.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.48 (s, 1H), 3.49 (s, 2H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.5, 143.5, 142.6, 140.9, 137.9, 132.4, 130.8, 129.4, 129.0, 128.6, 128.1, 126.8, 125.8, 125.7, 122.5, 109.5, 55.9, 36.3. **HRMS:** m/z calculated for $C_{21}H_{17}ClNO$ $[M+H]^+$ = 334.0999, found 334.0986.

5-((4-bromophenyl)(phenyl)methyl)indolin-2-one, 5aal

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 5 : 1. **Physical State:** White solid, **m.p.:** 153-157 °C. **Yield:** 62%, 23 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.75 (s, 1H), 7.33 – 7.23 (m, 5H), 7.08 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 7.1 Hz, 2H), 6.81 (d, J = 8.6 Hz, 1H), 5.48 (s, 1H), 3.49 (s, 2H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 178.0, 143.5, 142.6, 141.1, 137.9, 132.3, 130.8, 129.5, 129.4, 129.0, 128.6, 128.5, 126.7, 126.5, 125.7, 125.7, 109.7, 55.9, 36.4. **HRMS:** m/z calculated for $C_{21}H_{17}BrNO$ $[M+H]^+$ = 378.0494, found 378.0481.

1,5-dibenzhydryl-3,3-diphenylindolin-2-one, 6aa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 202-205 °C. **Yield:** 68%, 42 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.29 (m, 6H), 7.29 – 7.22 (m, 14H), 7.21 – 7.16 (m, 6H), 7.09 – 7.02 (m, 6H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.40 – 6.38 (m, 1H), 5.42 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz,**

$CDCl_3$): δ 177.9, 144.0, 142.3, 140.3, 138.4, 137.8, 129.5, 128.7, 128.6, 128.4, 127.9, 127.4, 126.5, 111.8, 58.7, 56.4. **HRMS:** m/z calculated for $C_{46}H_{36}NO$ $[M+H]^+$ = 618.2797, found 618.2795.

1',5'-dibenzhydrylspiro[cyclobutane-1,3'-indolin]-2'-one, 6faa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 182-186 °C. **Yield:** 63%, 32 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.18 (m, 18H), 7.10 – 7.12 (m, 3H), 6.96 (s, 1H), 6.63 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.28 (d, *J* = 8.2 Hz, 1H), 5.49 (s, 1H), 2.63 (ddd, *J* = 11.6, 8.6, 6.1 Hz, 2H), 2.44 – 2.28 (m, 3H), 2.09 (ddd, *J* = 13.5, 9.2, 5.5 Hz, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 180.90, 144.14, 140.01, 138.12, 138.04, 134.45, 129.53, 128.65, 128.63, 128.46, 128.31, 127.74, 126.47, 123.56, 111.06, 58.26, 56.69, 47.93, 31.85, 16.68. **HRMS:** m/z calculated for $C_{37}H_{32}NO$ $[M+H]^+$ = 506.2484, found 506.2499.

1',5'-dibenzhydrylspiro[cyclohexane-1,3'-indolin]-2'-one, 6gaa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 20 : 1. **Physical State:** White solid, **m.p.:** 192-196 °C. **Yield:** 65%, 35 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.16 (m, 18H), 7.13 – 7.07 (m, 3H), 6.99 (s, 1H), 6.65 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.33 (d, *J* = 8.2 Hz, 1H), 5.45 (s, 1H), 1.87 (ddd, *J* = 13.3, 11.6, 5.7 Hz, 4H), 1.65 – 1.53 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 181.0, 144.2, 139.8, 138.2, 137.3, 135.7, 129.5, 128.63, 128.56, 128.4, 127.9, 127.7, 126.4, 124.8, 111.3, 57.8, 56.7, 46.9, 33.5, 25.2, 21.1. **HRMS:** m/z calculated for $C_{39}H_{36}NO$ $[M+H]^+$ = 534.2797, found 534.2811.

2-(benzhydrylthio)-1*H*-indole, 8aa

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 9 : 1. **Physical State:** Greenish yellow solid, **m.p.:** 69-72 °C. **Yield:** 72%, 23 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 (s, 1H), 7.54 – 7.48 (m, 1H), 7.45 – 7.40 (m, 4H), 7.36 – 7.31 (m,

4H), 7.29 – 7.26 (m, 2H), 7.16 – 7.13 (m, 2H), 7.09 – 7.02 (m, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 5.43 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 141.20, 137.11, 128.80, 128.44, 128.24, 128.00, 127.65, 122.87, 120.53, 120.08, 110.69, 110.35, 59.87, 29.85. **HRMS:** m/z calculated for $C_{21}H_{18}NS$ $[M+H]^+$ = 316.1160, found 316.1169.

2-((1-phenylethyl)thio)-1*H*-indole, 8ab

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 9 : 1. **Physical State:** Greenish yellow solid, **m.p.:** 51-54 °C. **Yield:** 55%, 14 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 (s, 1H), 7.57 – 7.51 (m, 1H), 7.32 – 7.26 (m, 3H), 7.26 – 7.22 (m, 2H), 7.21 – 7.13 (m, 2H), 7.10 – 7.06 (m, 1H), 6.61 – 6.60 (m, 1H), 4.24 (q, *J* = 7.0 Hz, 1H), 1.65 (d, *J* = 7.0 Hz, 4H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 143.43, 137.22, 128.68, 128.45, 128.38, 127.56, 127.32, 122.88, 120.56, 120.09, 111.07, 110.71, 49.63, 31.58, 30.33, 21.79. **HRMS:** m/z calculated for $C_{16}H_{16}NS$ $[M+H]^+$ = 254.1003, found 254.1010.

2-((phenyl(p-tolyl)methyl)thio)-1*H*-indole, 8ai

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 9 : 1. **Physical State:** Greenish yellow solid, **m.p.:** 77-80 °C. **Yield:** 80%, 26 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.63 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42- 7.39 (m, 2H), 7.35 – 7.29 (m, 4H), 7.29 – 7.24 (m, 1H), 7.16 – 7.10 (m, 4H), 7.07 – 7.03 (m, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 5.40 (s, 1H), 2.34 (s, 3H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 141.46, 138.18, 137.39, 137.11, 129.48, 128.77, 128.41, 128.30, 128.26, 127.56, 122.79, 120.50, 120.05, 110.67, 110.16, 59.60, 21.24. **HRMS:** m/z calculated for $C_{22}H_{20}NS$ $[M+H]^+$ = 330.1316, found 330.1322.

1-benzyl-5-(hydroxydiphenylmethyl)-3,3-diphenylindolin-2-one, 9

Purification: Silica gel Column chromatography, eluted with *n*-hexane : EtOAc = 10 : 1. **Physical State:** White solid, **m.p.:** 177-181 °C. **Yield:** 72%, 39 mg. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 1.8 Hz, 1H), 7.33 (q, *J* = 2.7 Hz, 5H), 7.30 – 7.24 (m, 20H), 7.05 –

7.03 (m, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.00 (s, 2H), 2.94 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 177.7, 146.8, 142.0, 141.8, 141.4, 135.8, 132.7, 128.9, 128.52, 128.46, 128.1, 127.95, 127.86, 127.7, 127.39, 127.37, 127.3, 126.4, 108.6, 81.9, 62.6, 44.3. **HRMS:** m/z calculated for $C_{40}H_{32}NO$ $[M+H]^+$ = 542.2484, found 542.2458.

2.5 References

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N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611–1641; c) Hie, L.; Chang, J. J.; Garg, N. K. Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling in a Green Alcohol Solvent for an Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2015**, *92*, 571–574; d) Contente, M. L.; Marzuoli, I.; Iding, H.; Wetzl, D.; Puentener, K.; Hanlon, S. P.; Paradisi, F. Screening methods for enzyme-mediated alcohol oxidation. *Sci. Rep.* **2022**, *12*, 3019.

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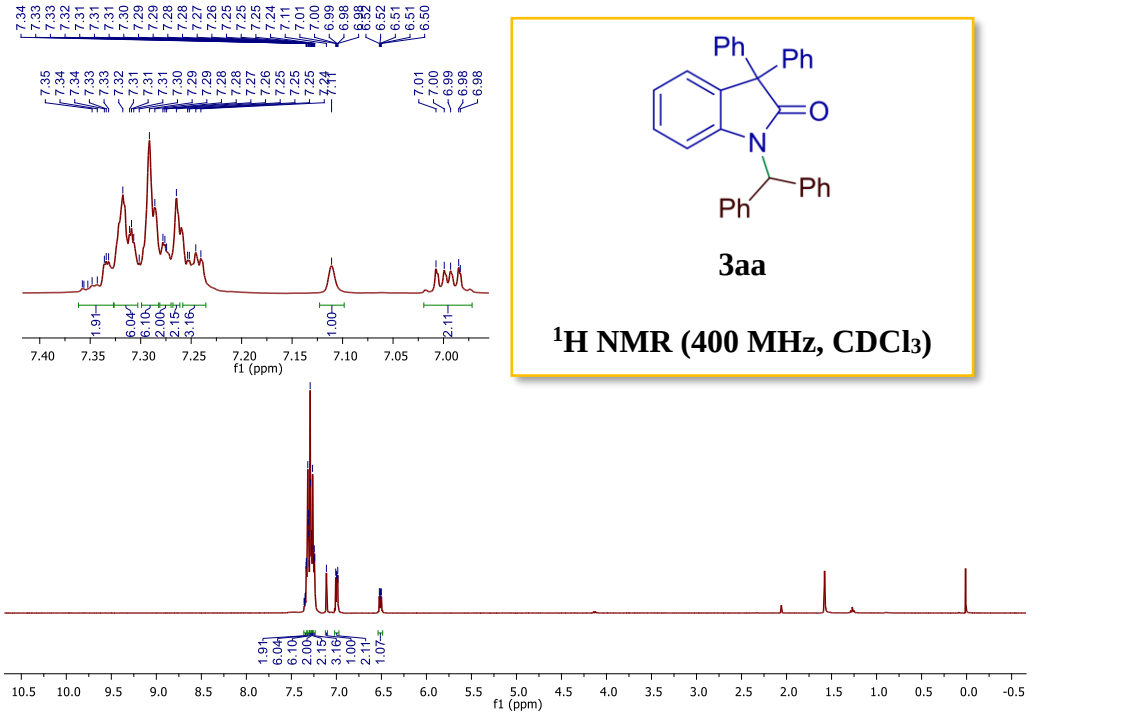
2.6 NMR Spectras of Compounds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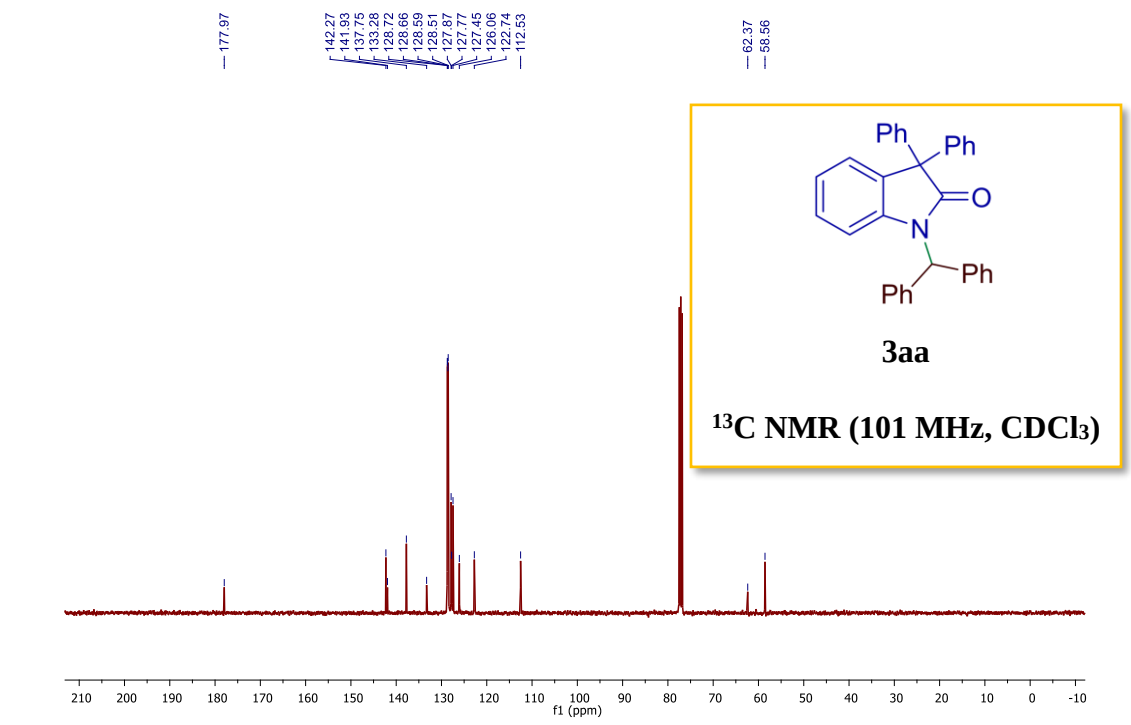
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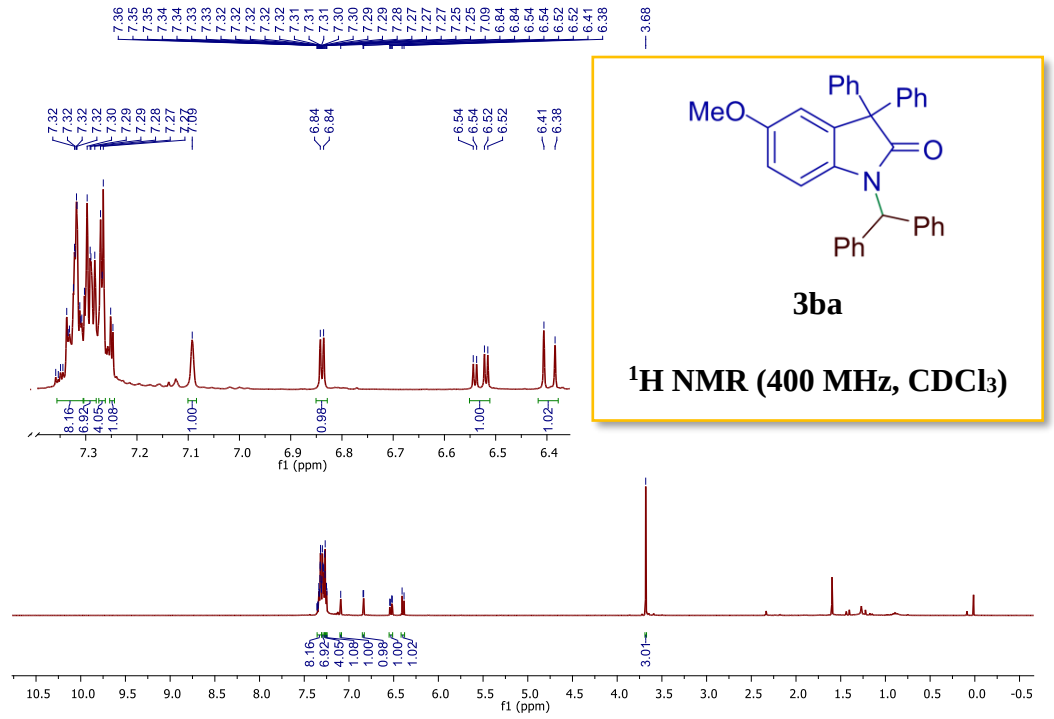
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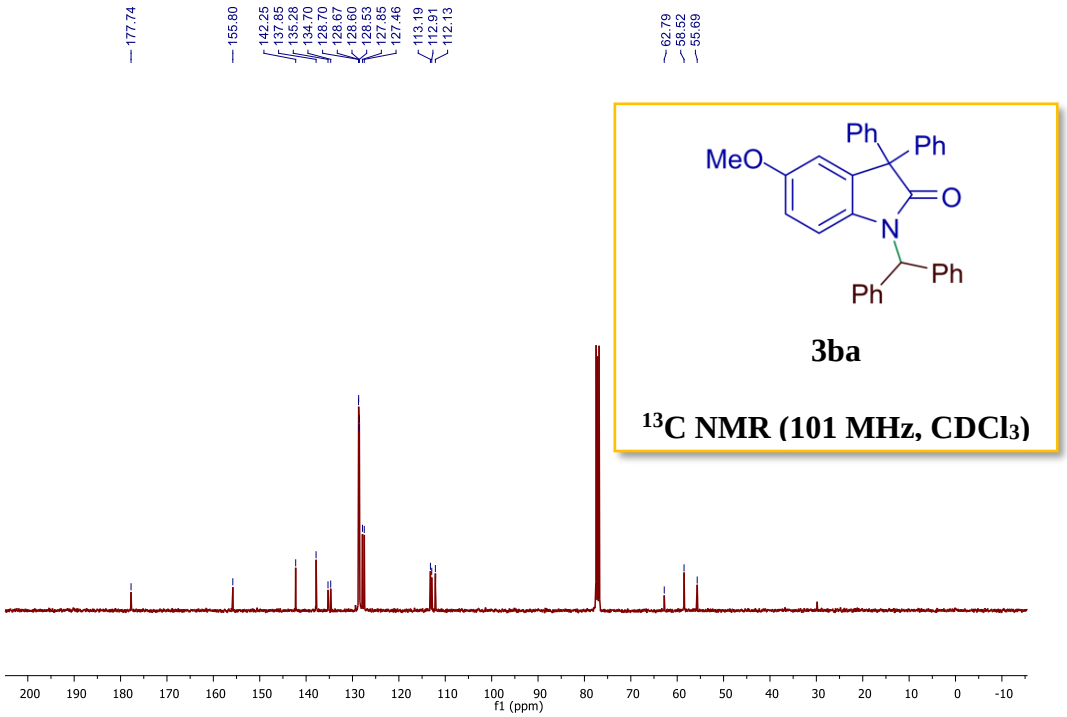
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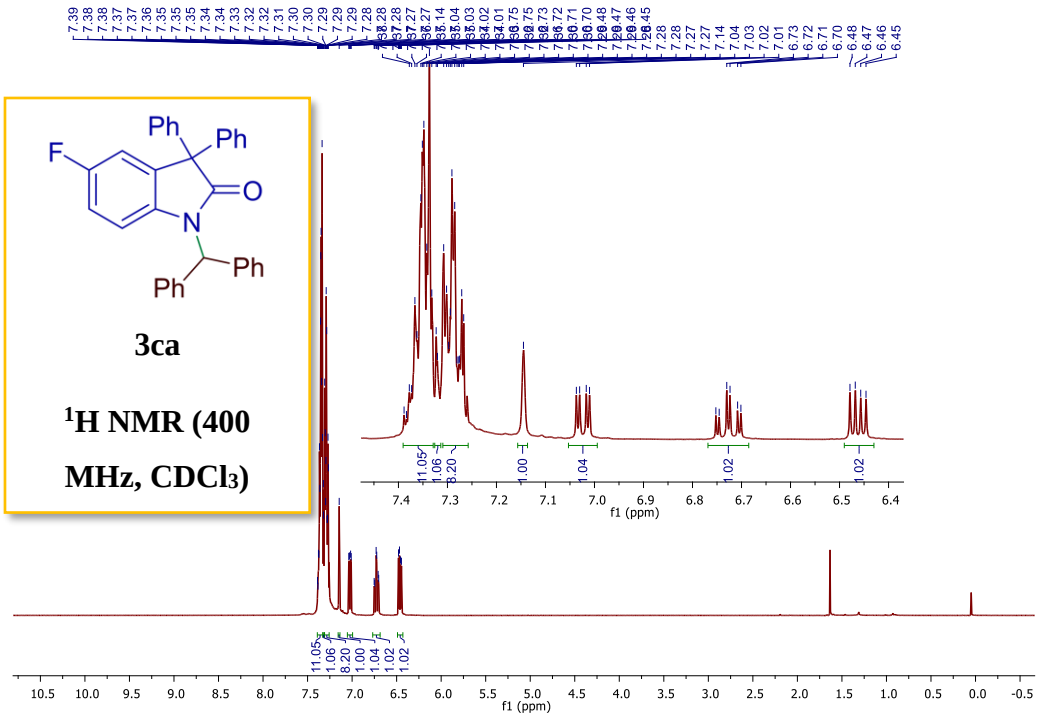
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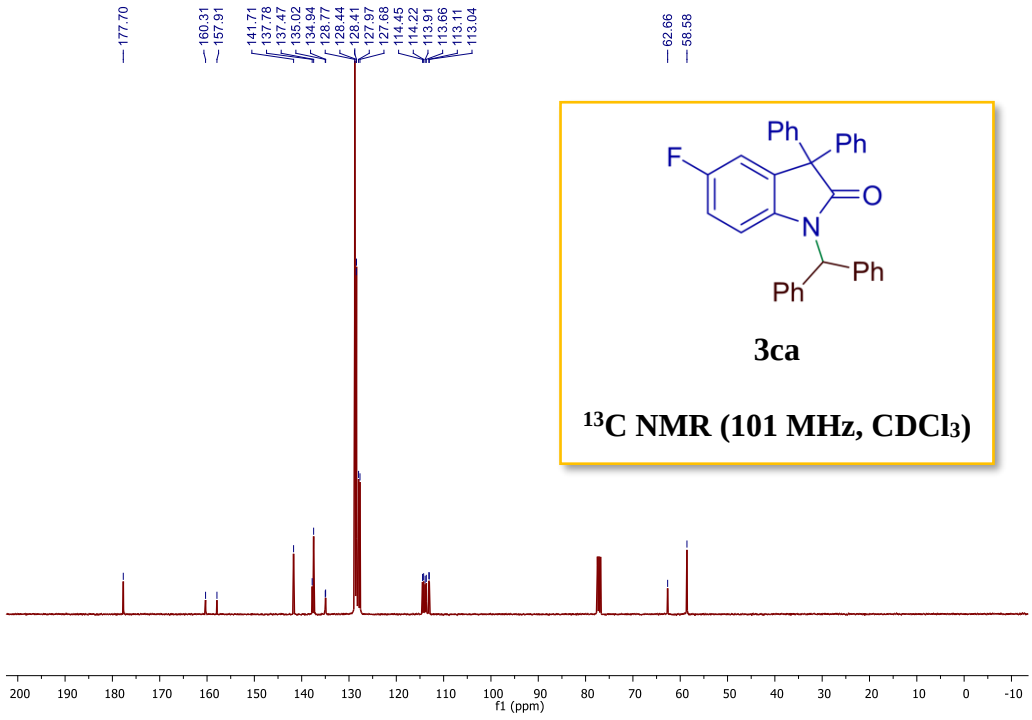
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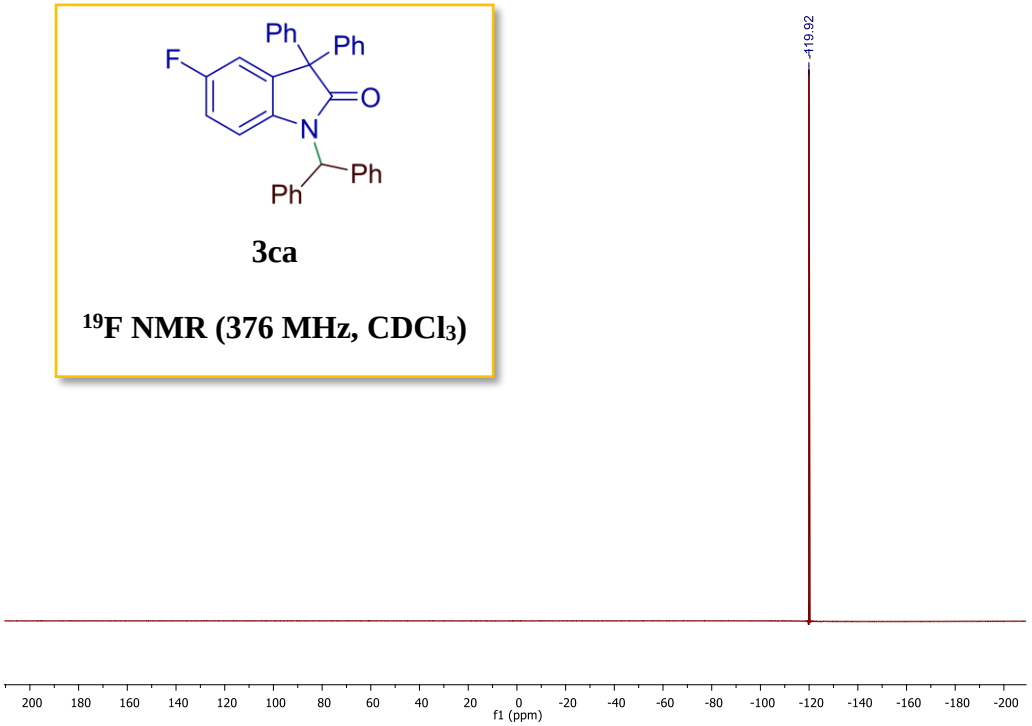

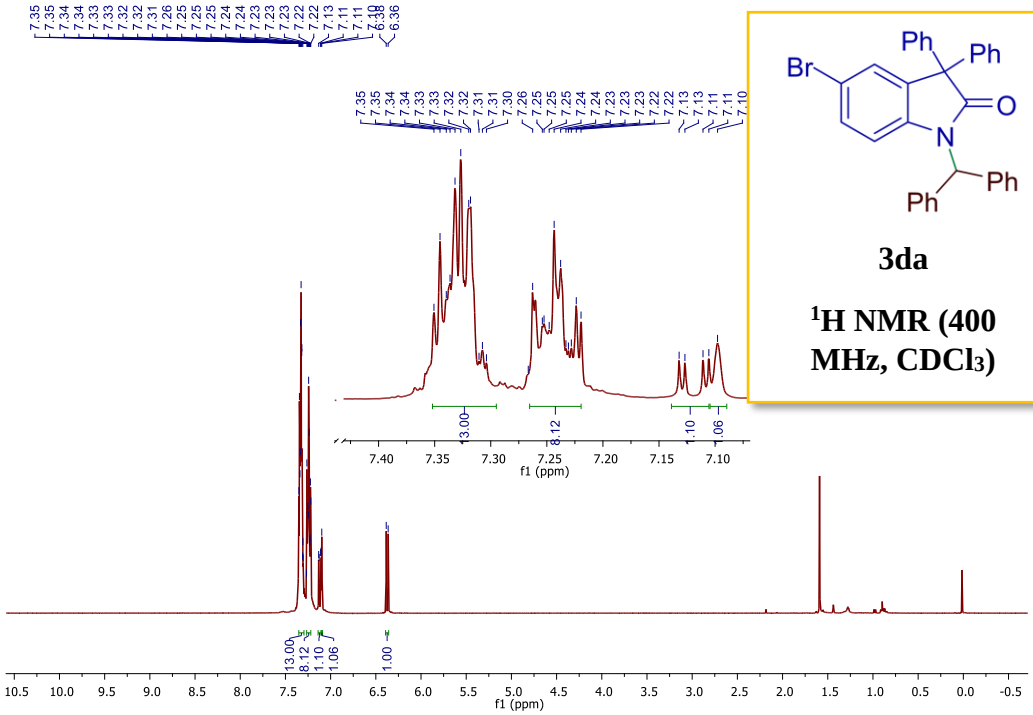

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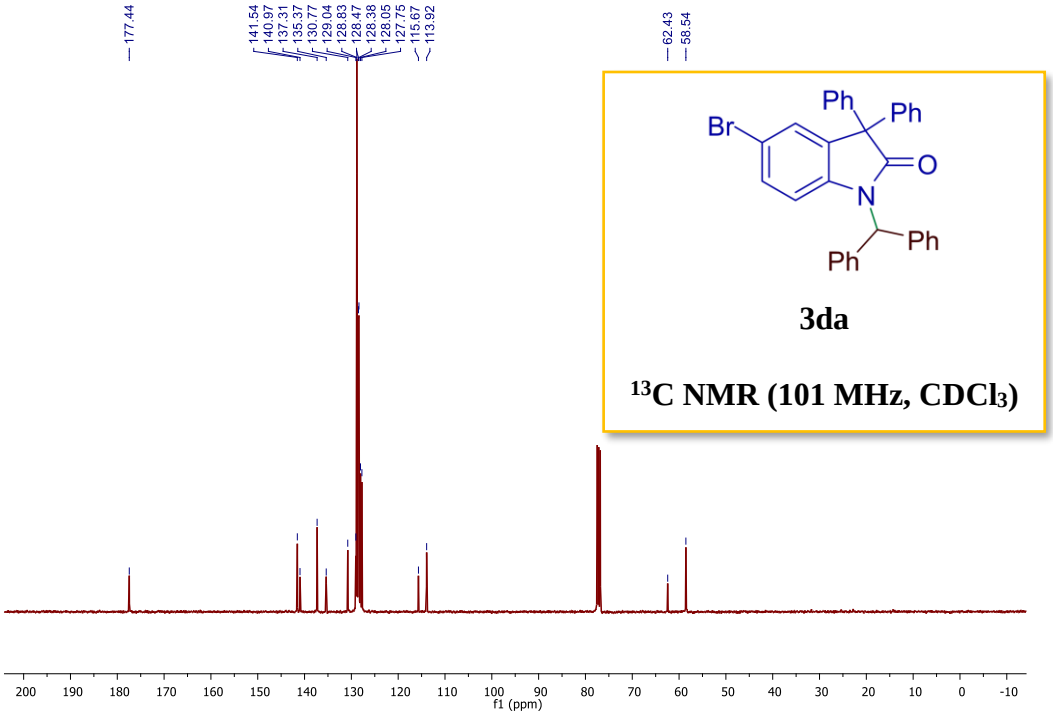
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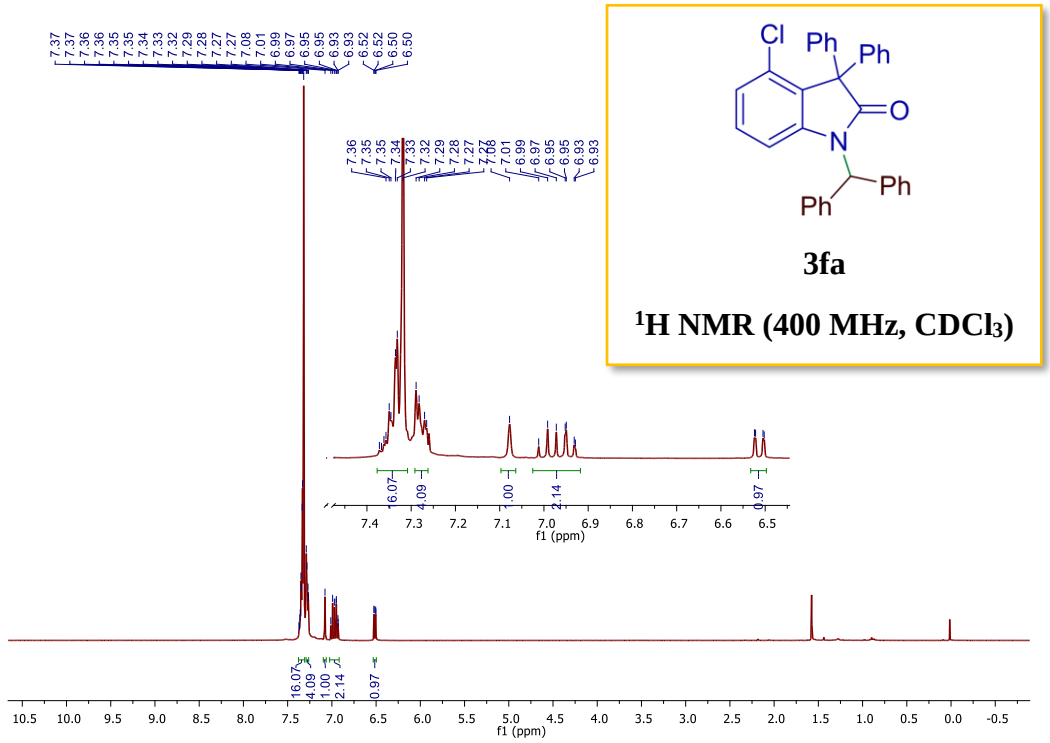
f1 (ppm)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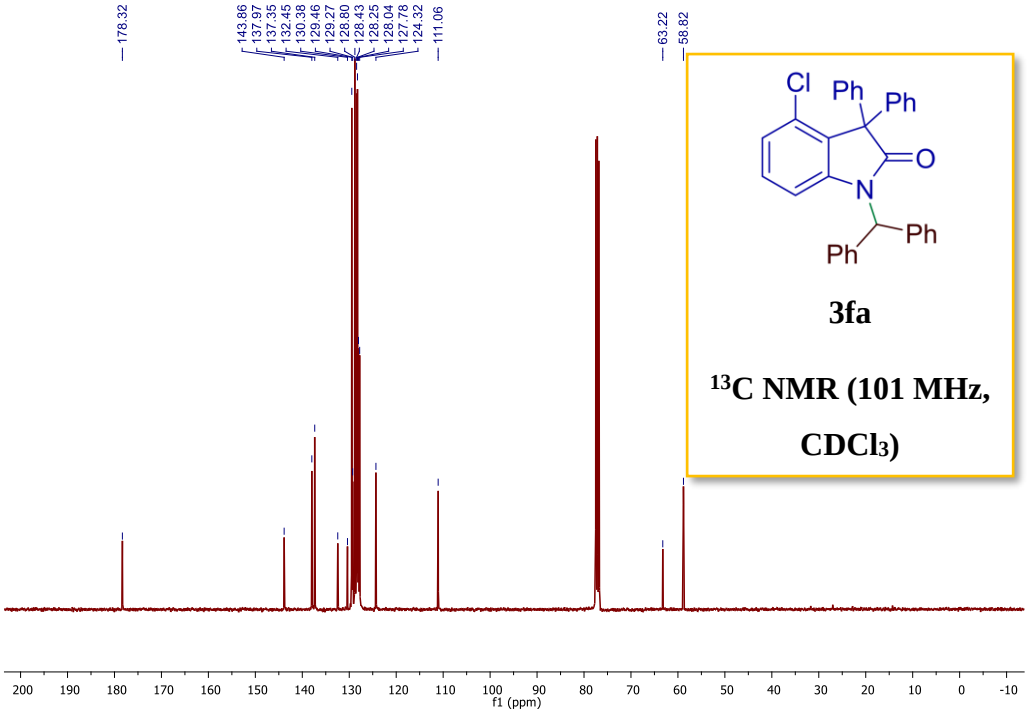
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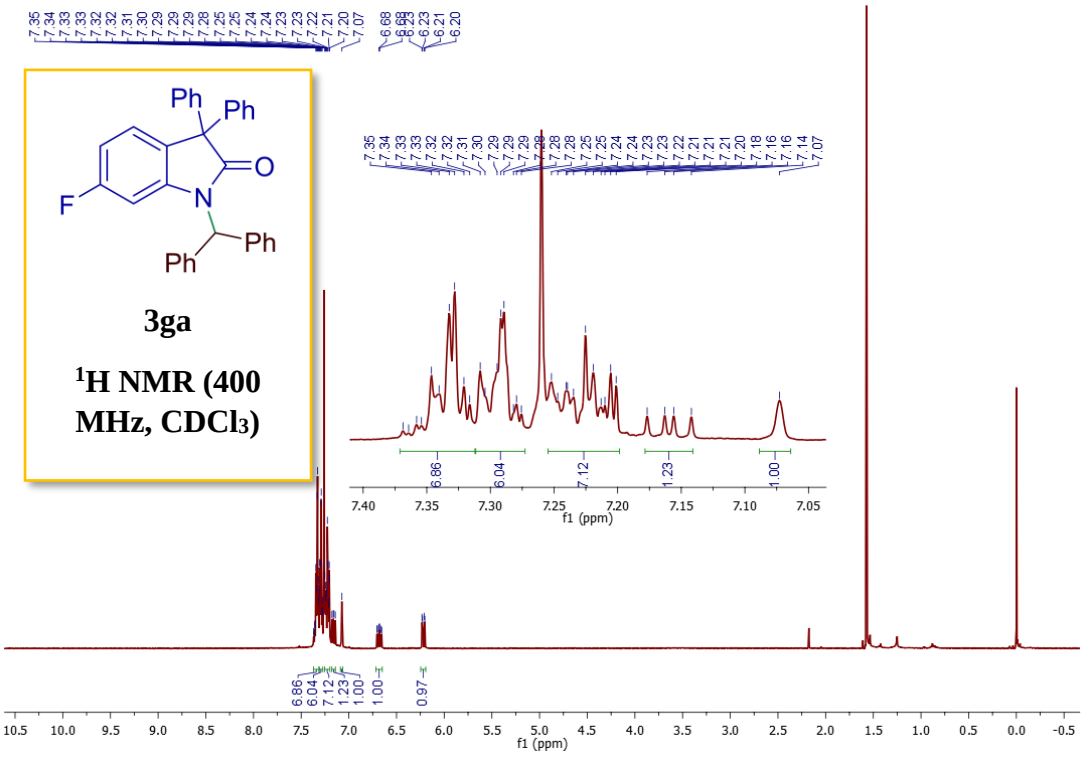
f1 (ppm)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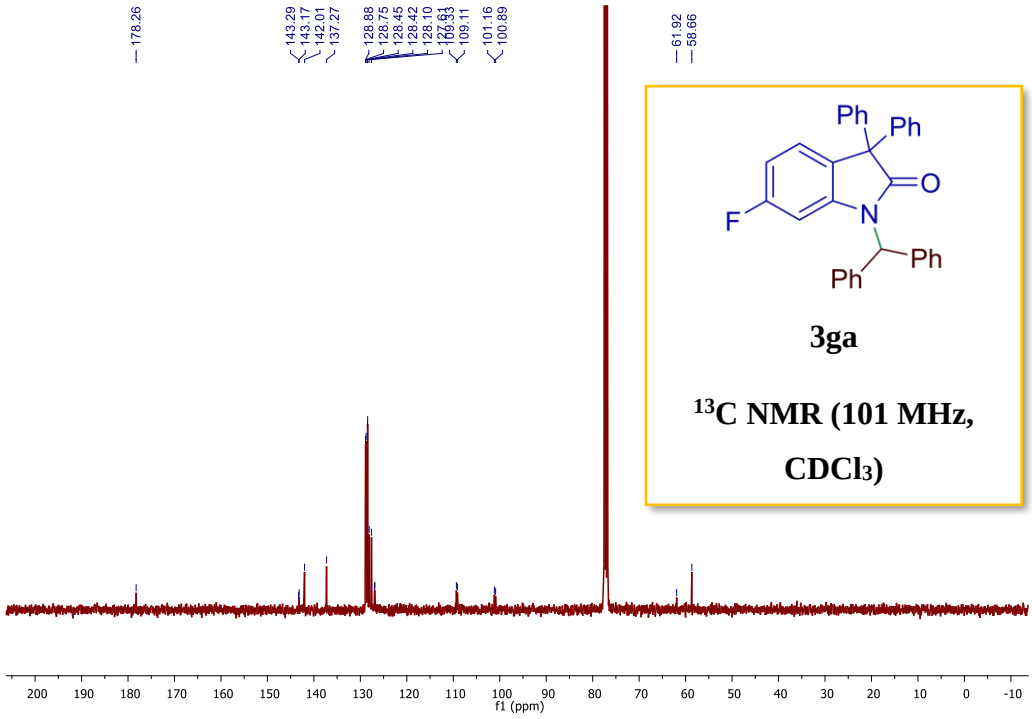
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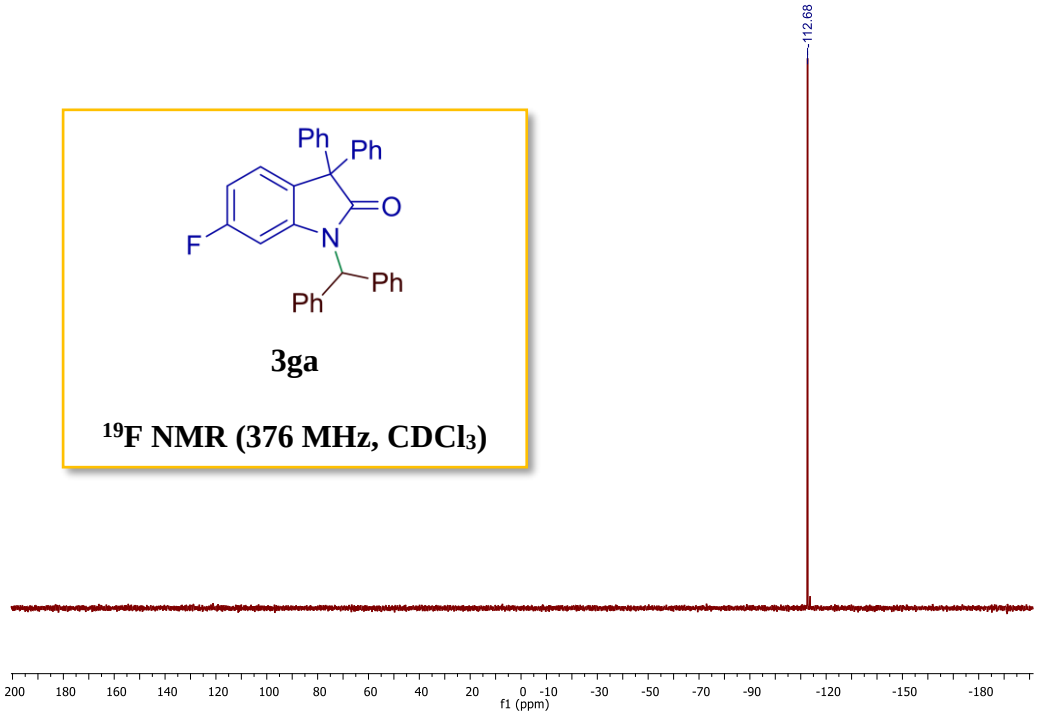
f1 (ppm)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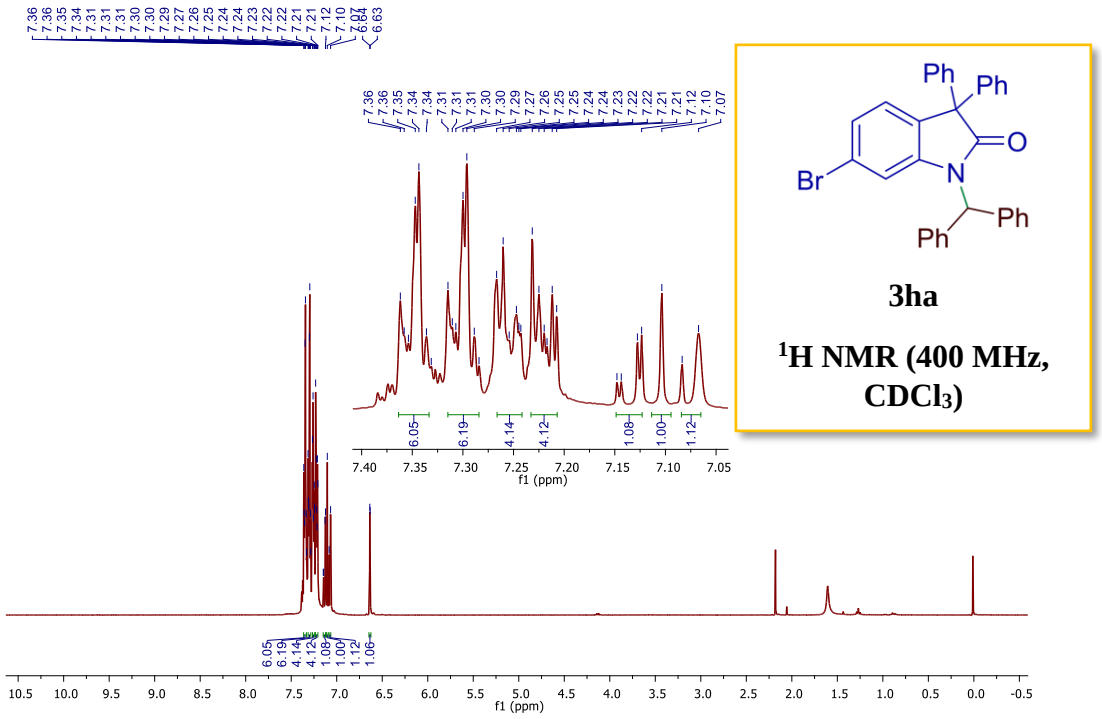
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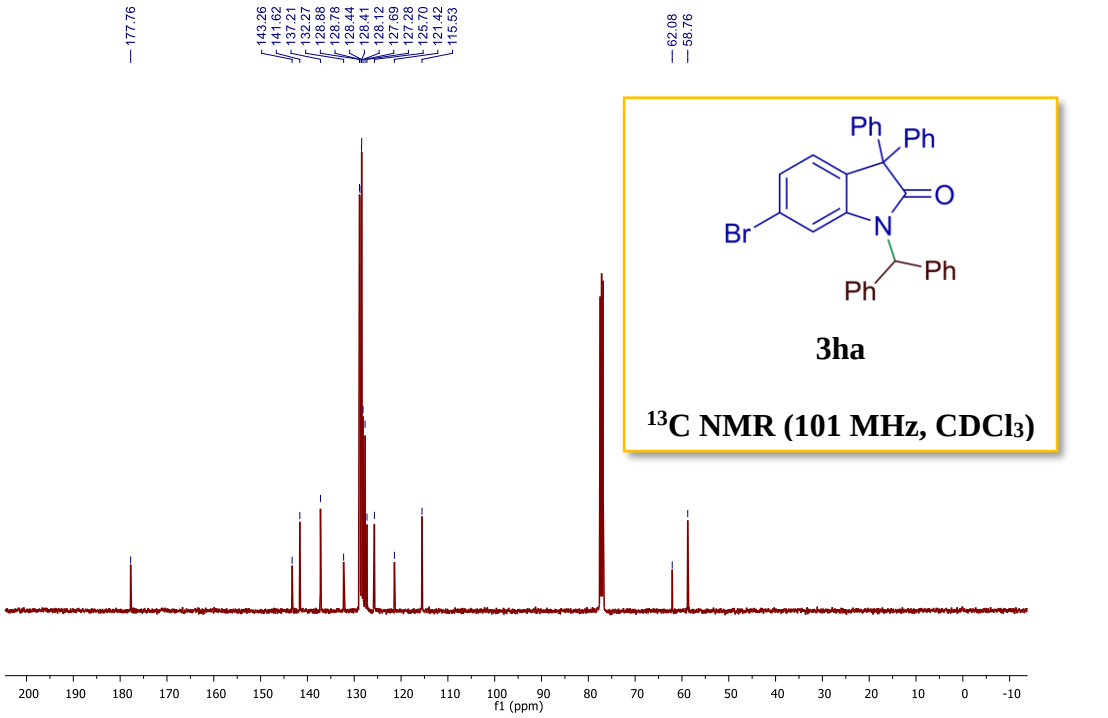
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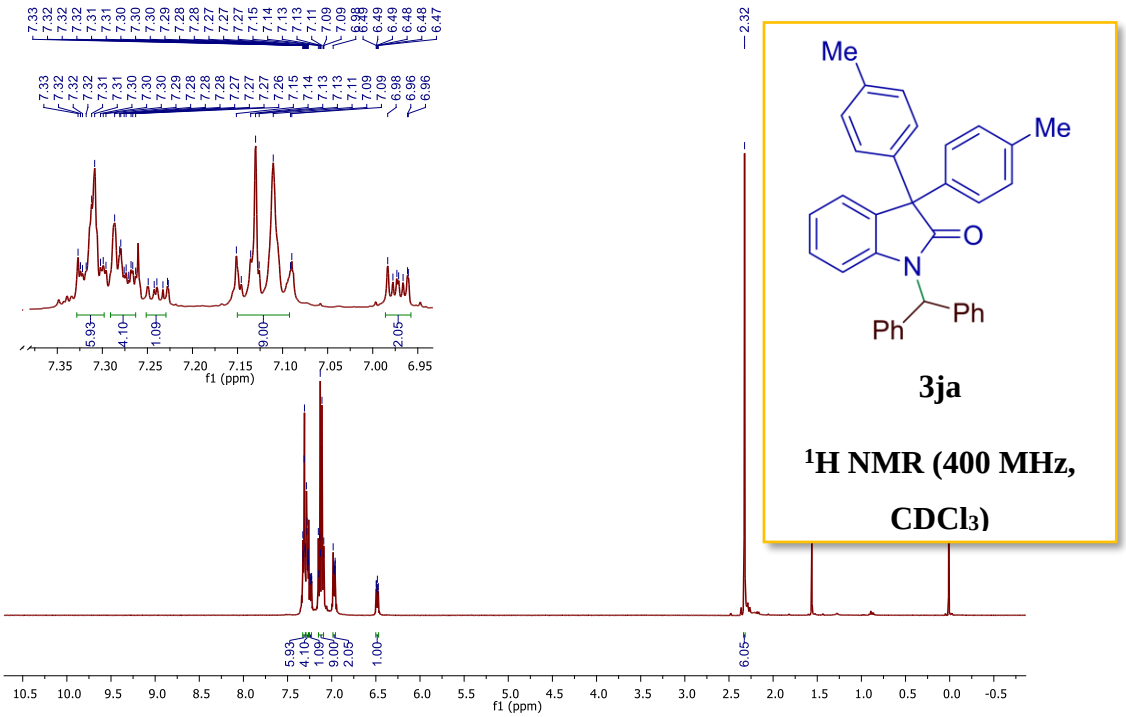
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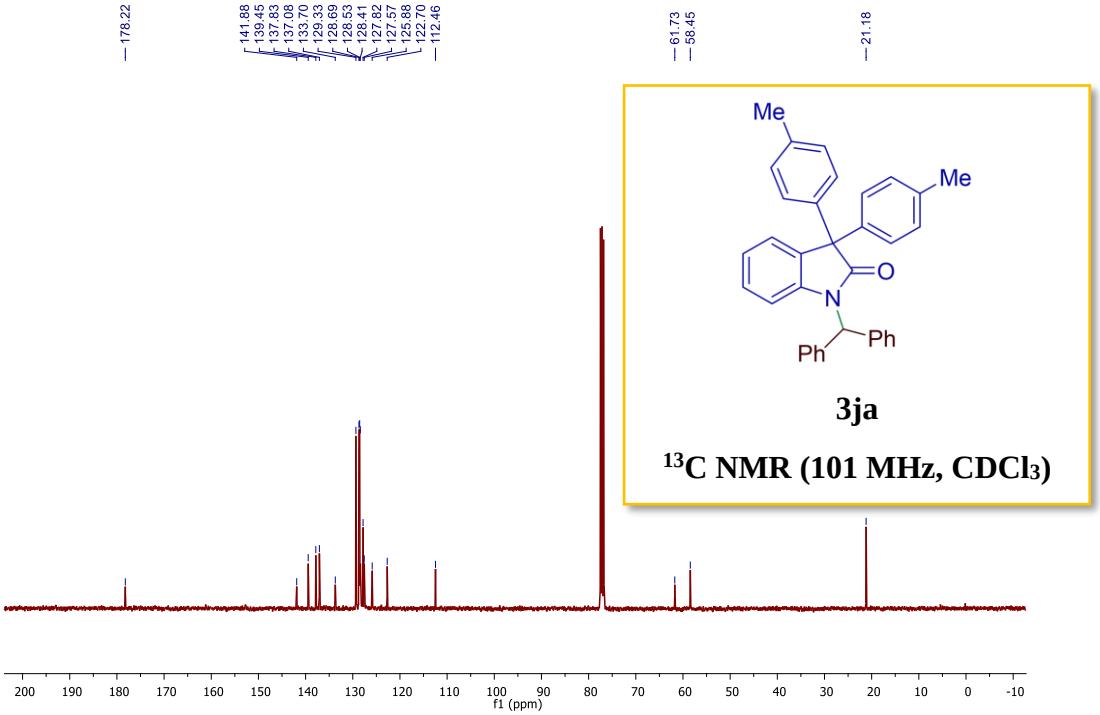
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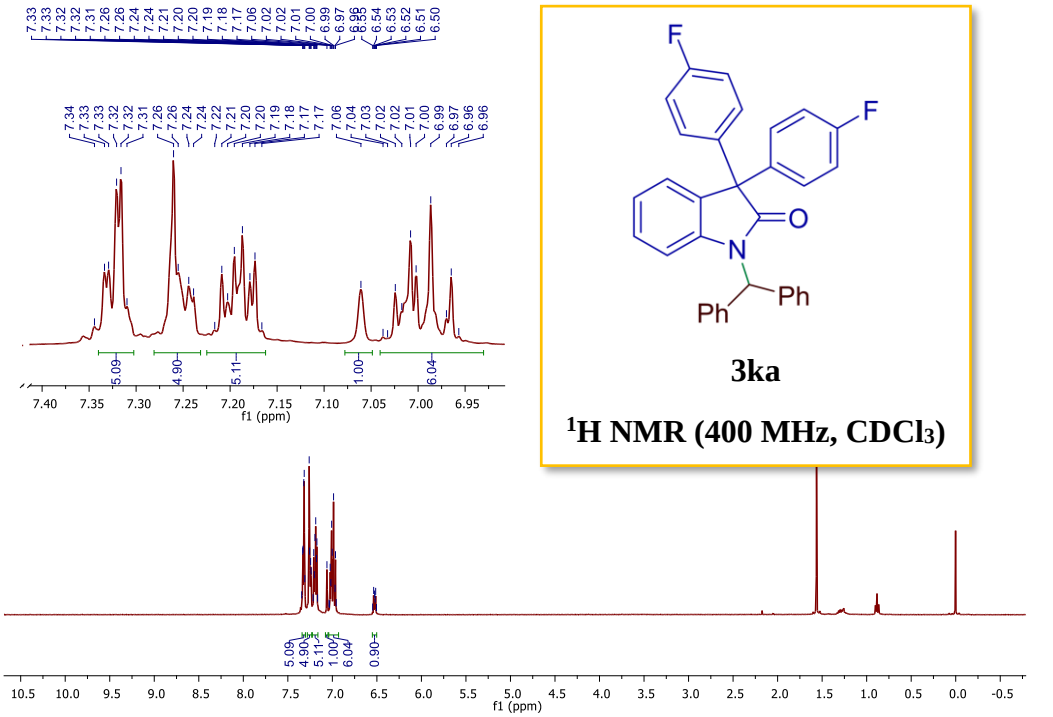
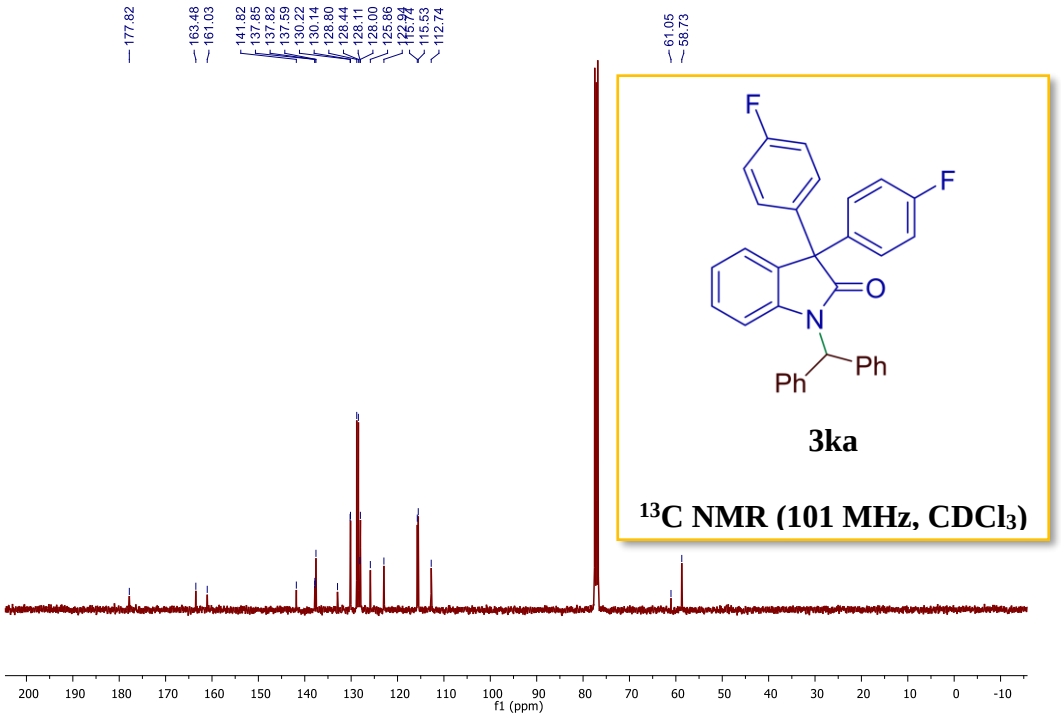
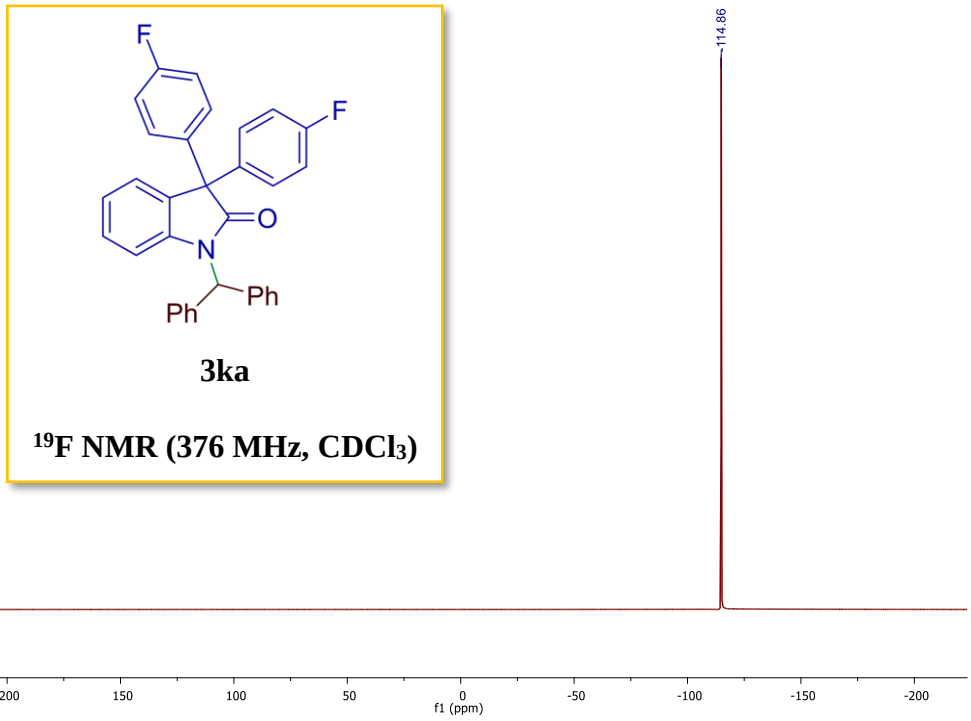
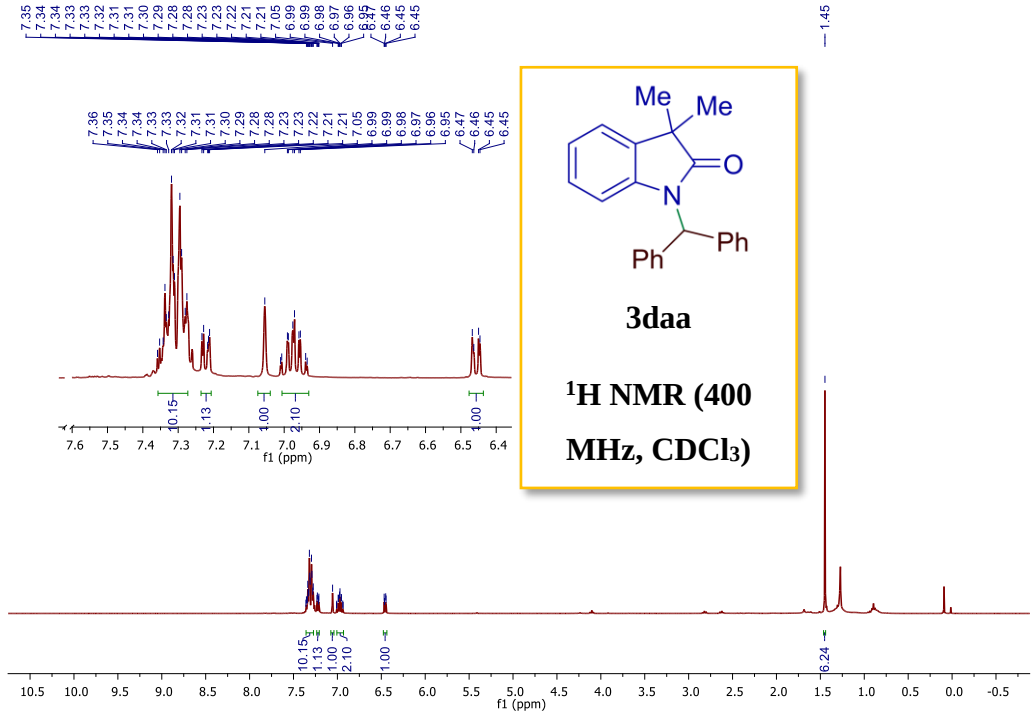
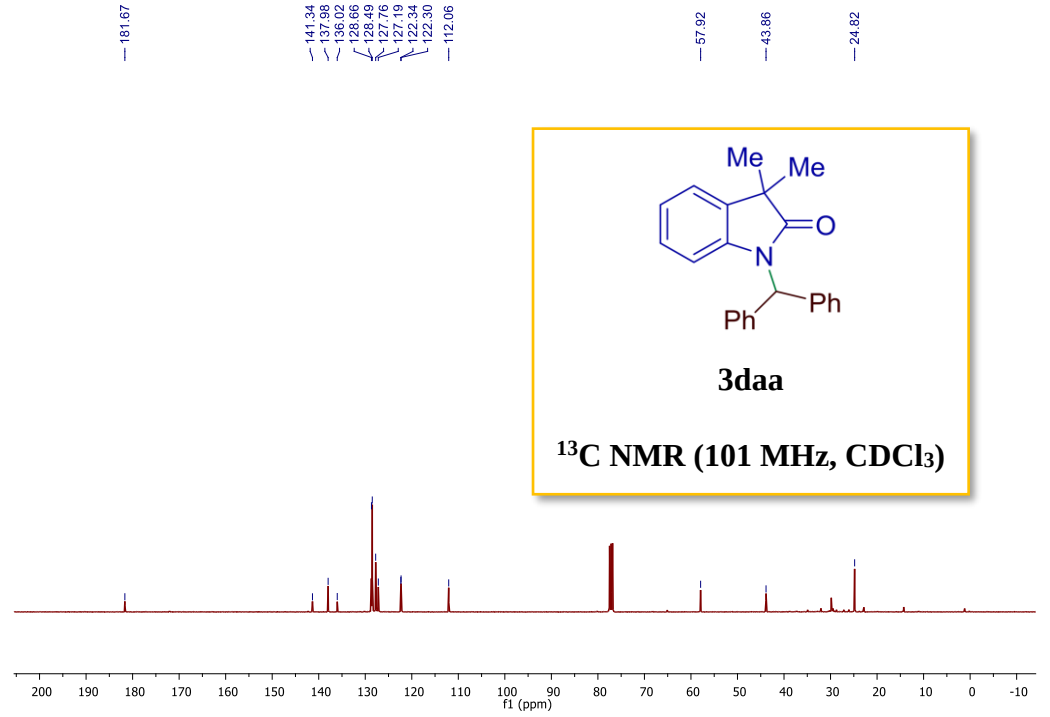
Ph
3ja
^{13}C NMR (101 MHz, CDCl$_3$)

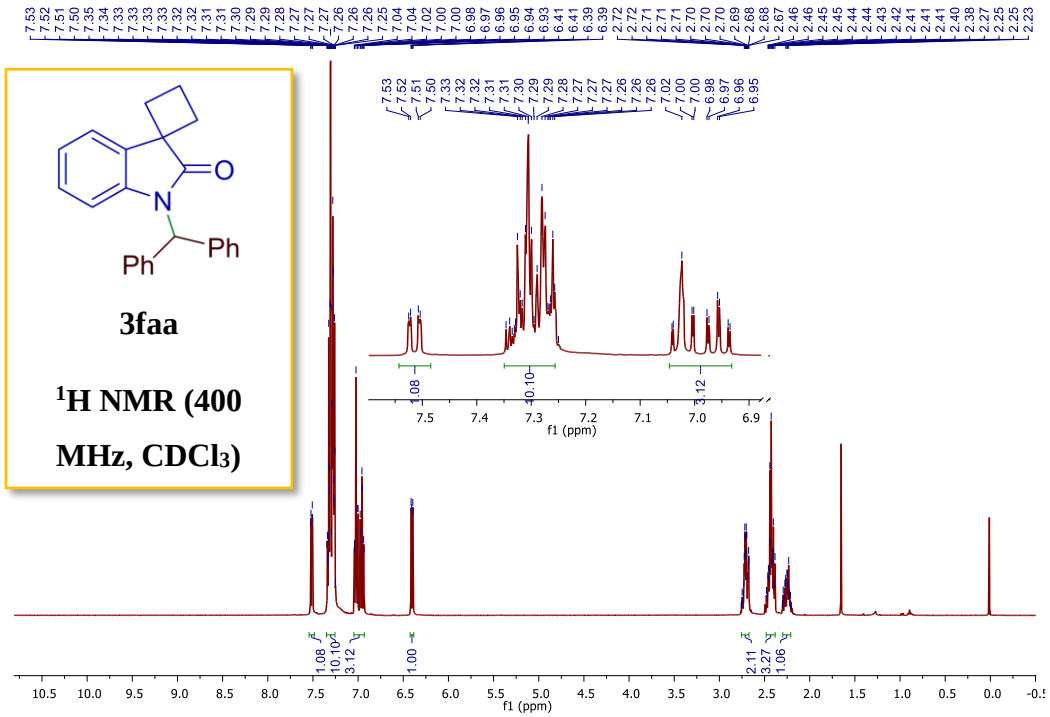

F
F
O
N
Ph
Ph
3ka
1H NMR (400 MHz, CDCl3)
f1 (ppm)

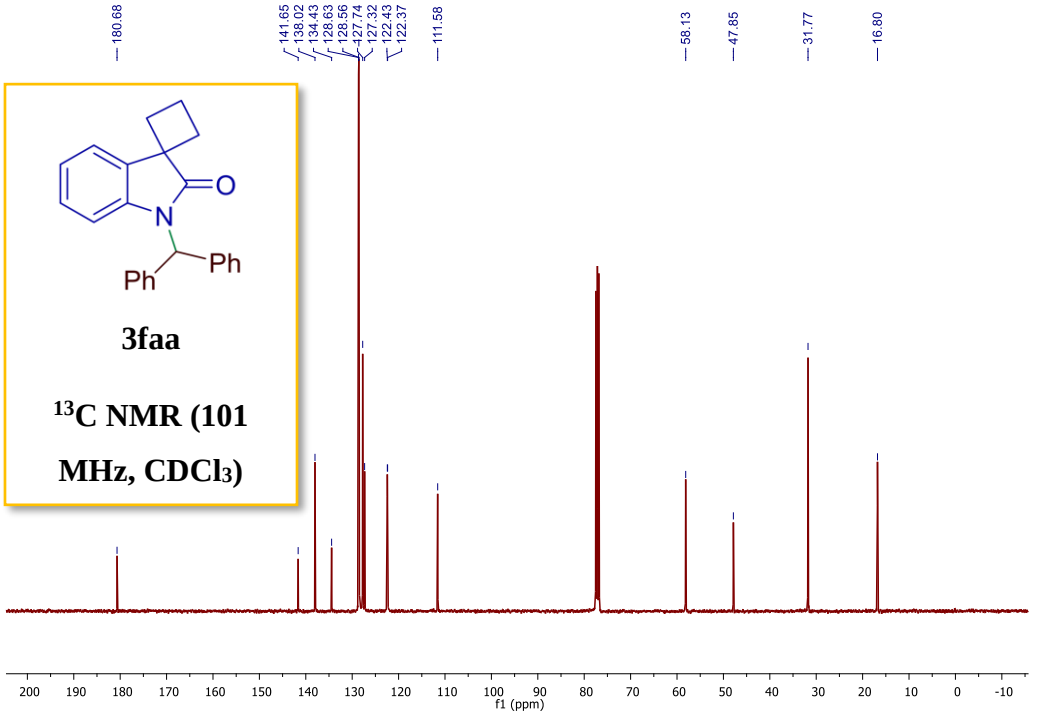

F
F
O
N
Ph
Ph
3ka
13C NMR (101 MHz, CDCl3)
f1 (ppm)

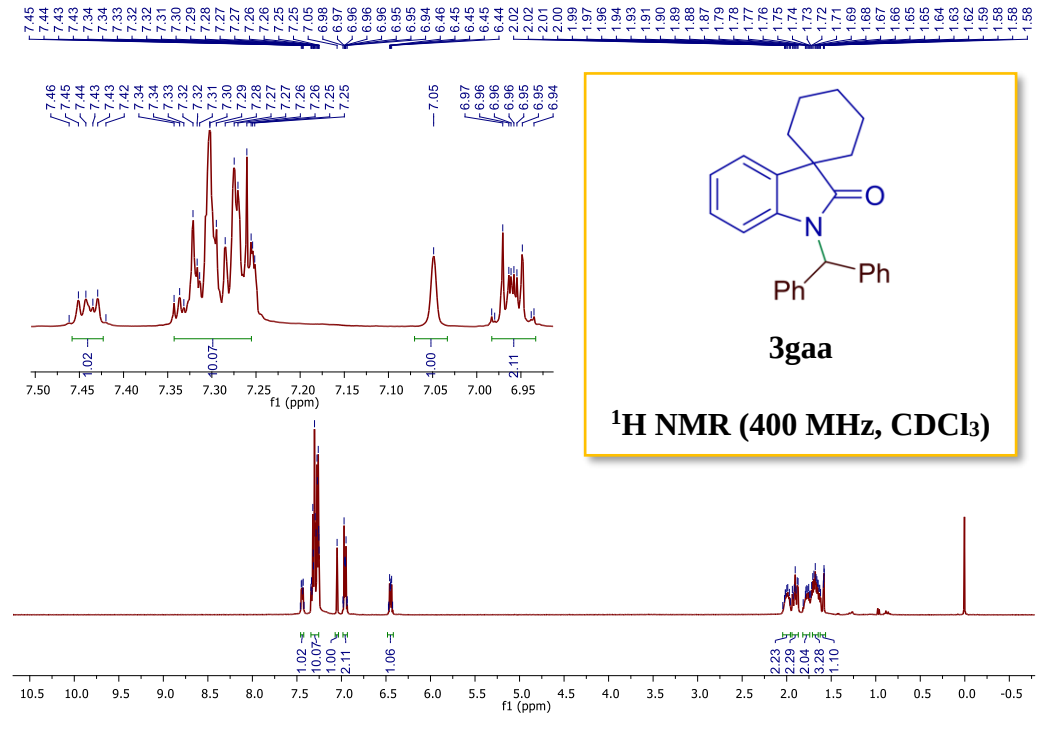

F
F
O
N
Ph
Ph
3ka
19F NMR (376 MHz, CDCl3)
114.86
200
150
100
50
0
-50
-100
-150
-200
f1 (ppm)

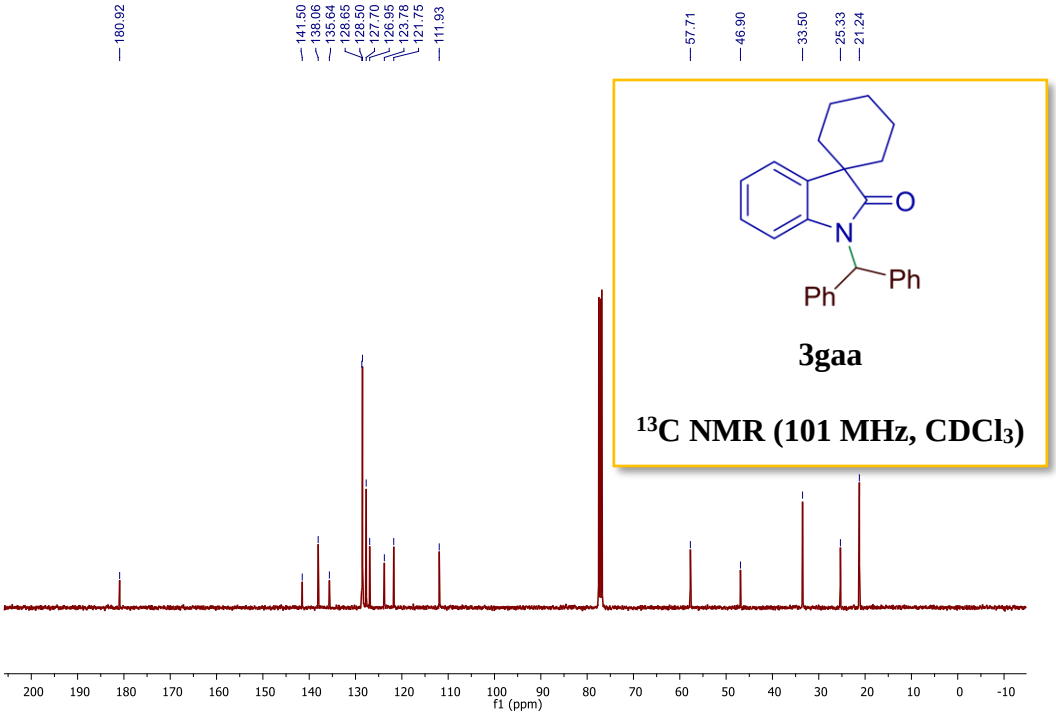

Me
Me
O
N
Ph
Ph
3daa
1H NMR (400 MHz, CDCl3)
1.45
6.24
f1 (ppm)


181.67
141.34
137.98
136.02
128.66
128.49
127.76
127.19
122.34
122.30
112.06
57.92
43.86
24.82
Me
Me
O
N
Ph
Ph
3daa
13C NMR (101 MHz, CDCl3)
f1 (ppm)


O
N
Ph
Ph
3faa
1H NMR (400 MHz, CDCl3)
f1 (ppm)

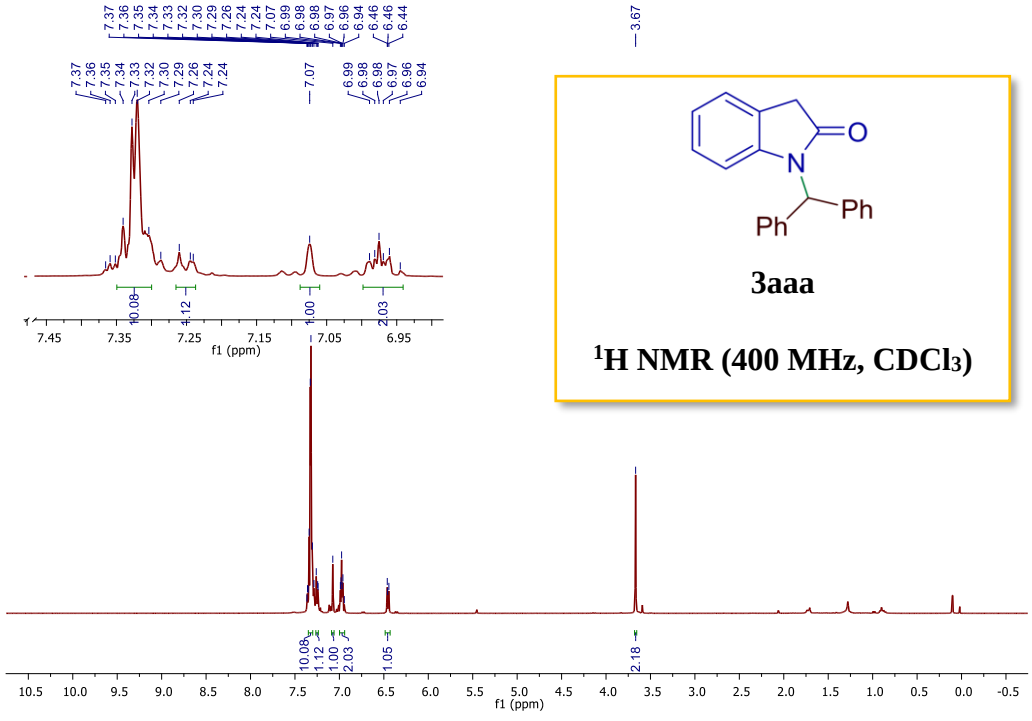

180.68
141.65
138.02
134.43
128.63
128.56
127.74
127.32
122.43
122.37
111.58
58.13
47.85
31.77
16.80
O
N
Ph
Ph
3faa
13C NMR (101 MHz, CDCl3)
f1 (ppm)


O
N
Ph
Ph
3gaa
1H NMR (400 MHz, CDCl3)
f1 (ppm)



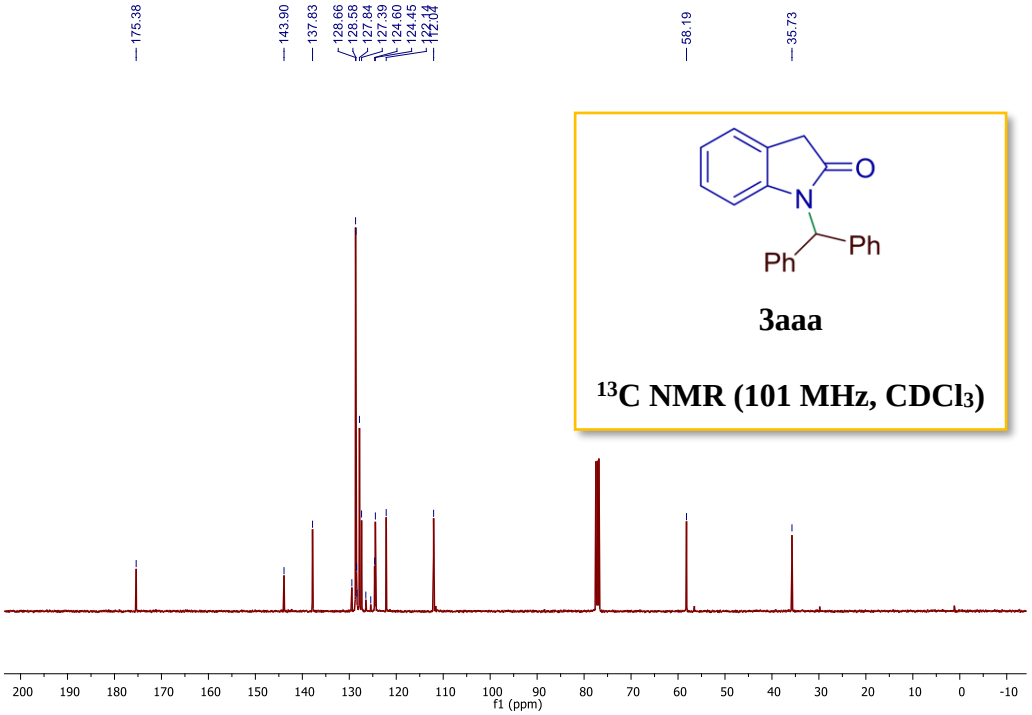
3gaa

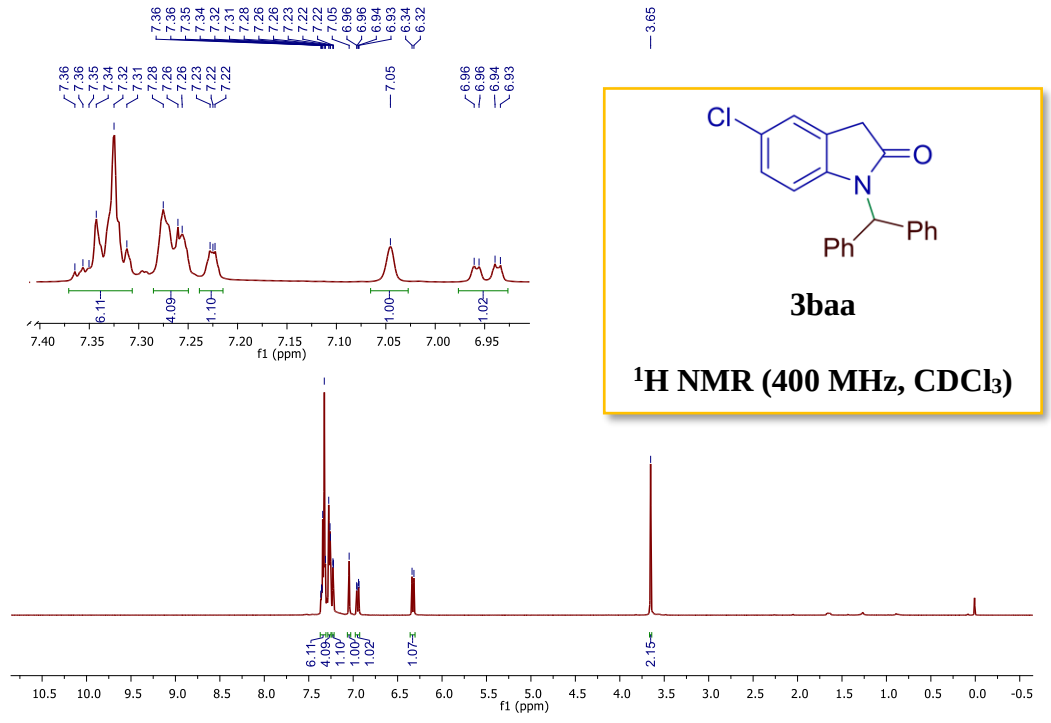
^{13}C NMR (101 MHz, $CDCl_3$)

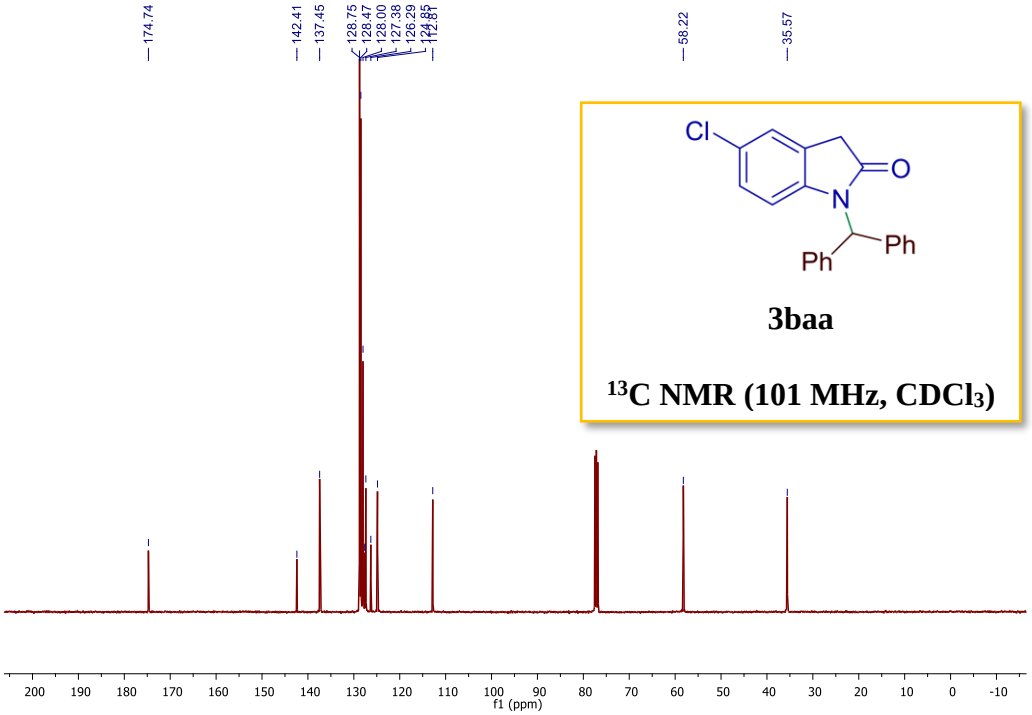


3aaa

^{1}H NMR (400 MHz, $CDCl_3$)

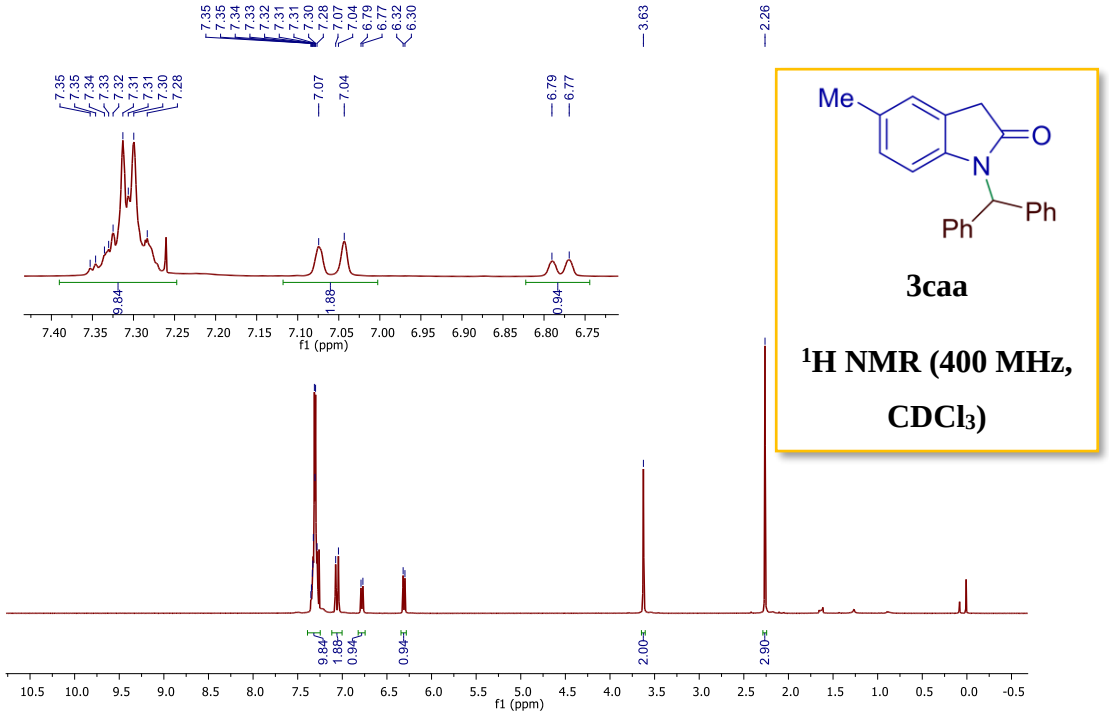

175.38
143.90
137.83
128.66
128.58
127.84
127.39
124.60
124.45
122.14
112.04
58.19
35.73
O
N
Ph
Ph
3aaa
13C NMR (101 MHz, CDCl3)
f1 (ppm)


7.36
7.35
7.34
7.32
7.31
7.28
7.26
7.23
7.22
7.05
6.96
6.94
6.93
6.34
6.32
3.65
6.11
4.09
1.10
1.00
1.02
1.07
2.15
Cl
O
N
Ph
Ph
3baa
1H NMR (400 MHz, CDCl3)
f1 (ppm)



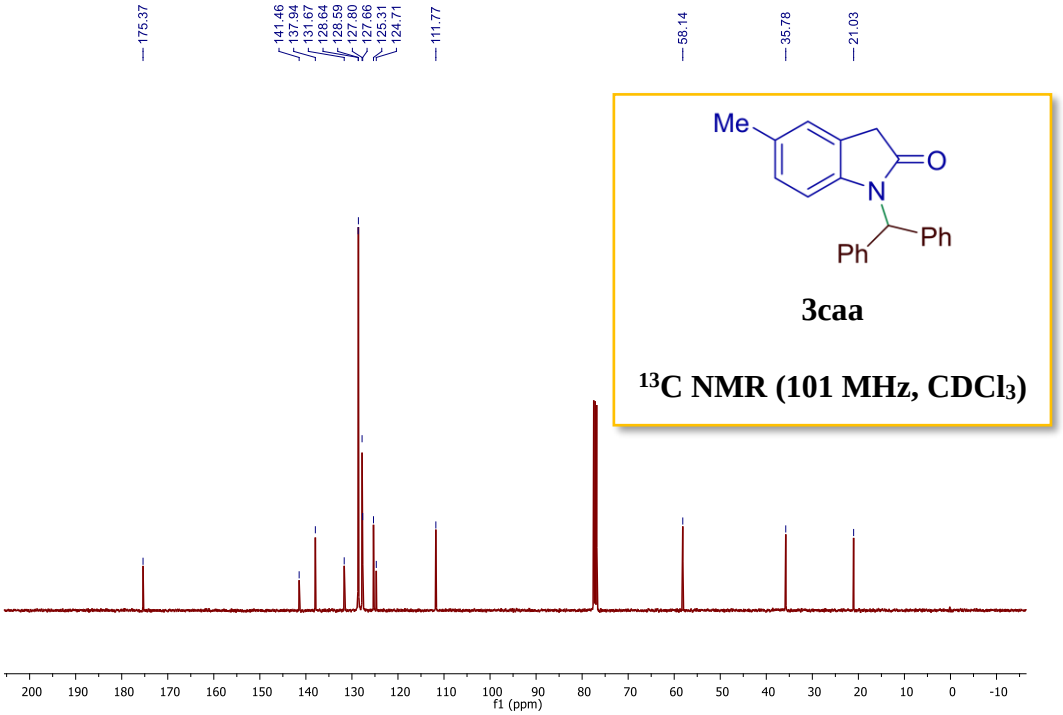
3baa

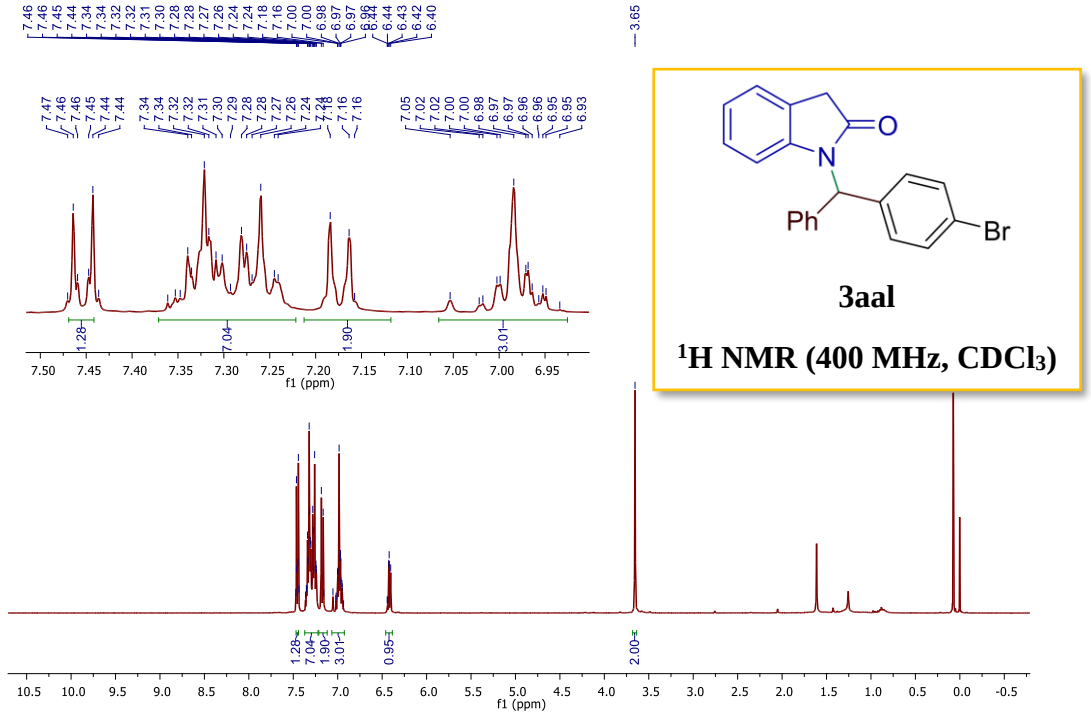
^{13}C NMR (101 MHz, $CDCl_3$)

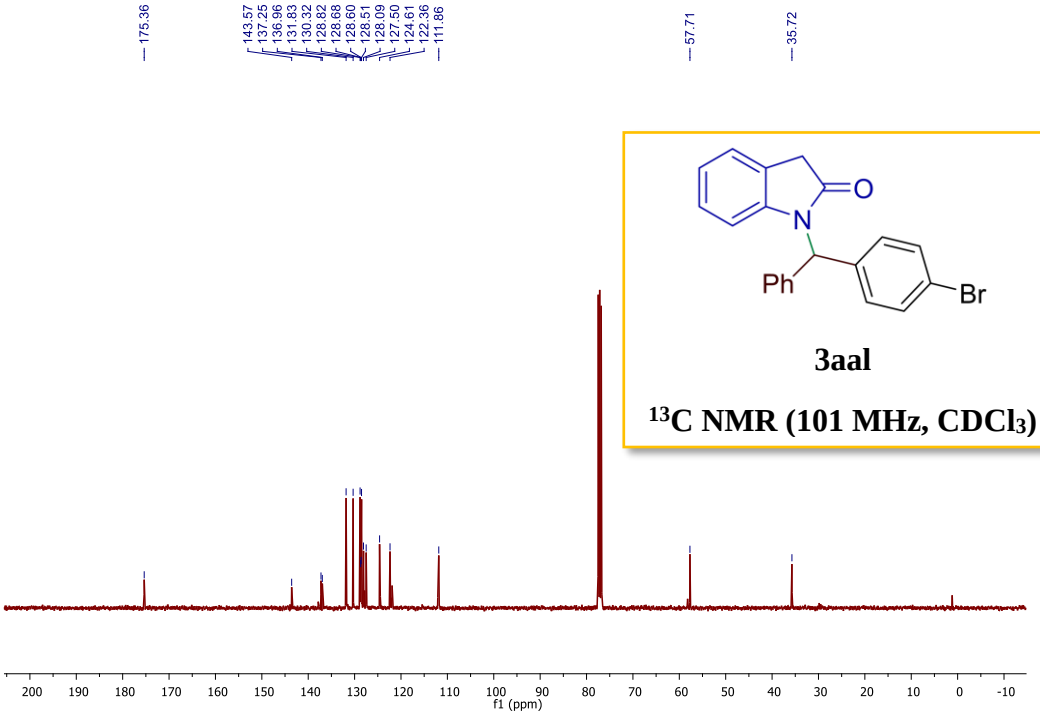


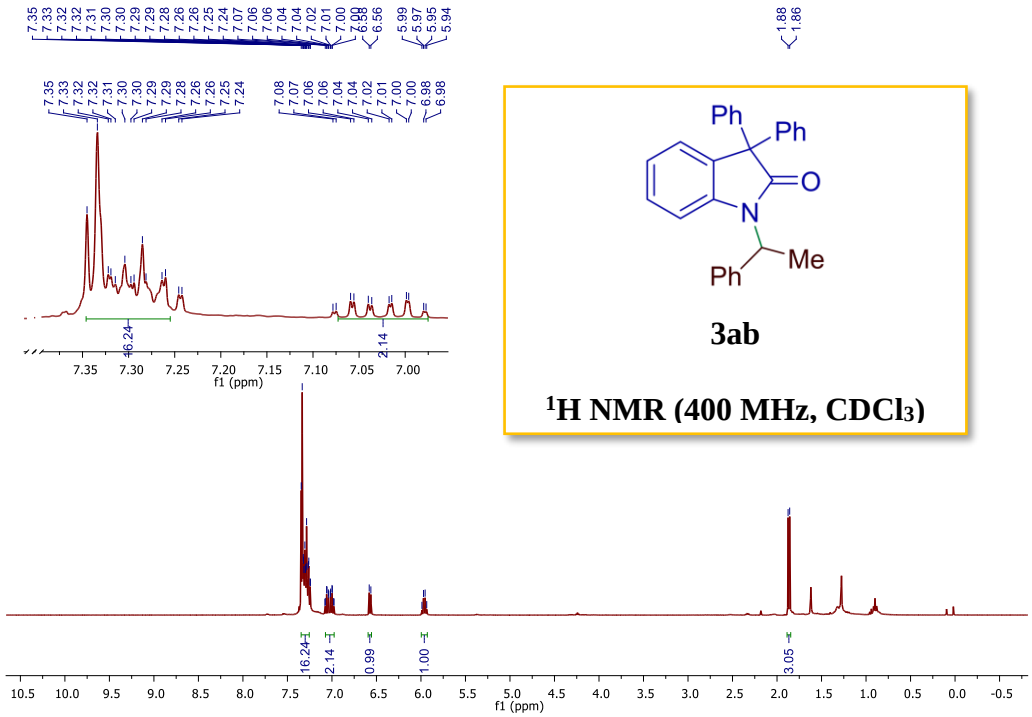
3caa

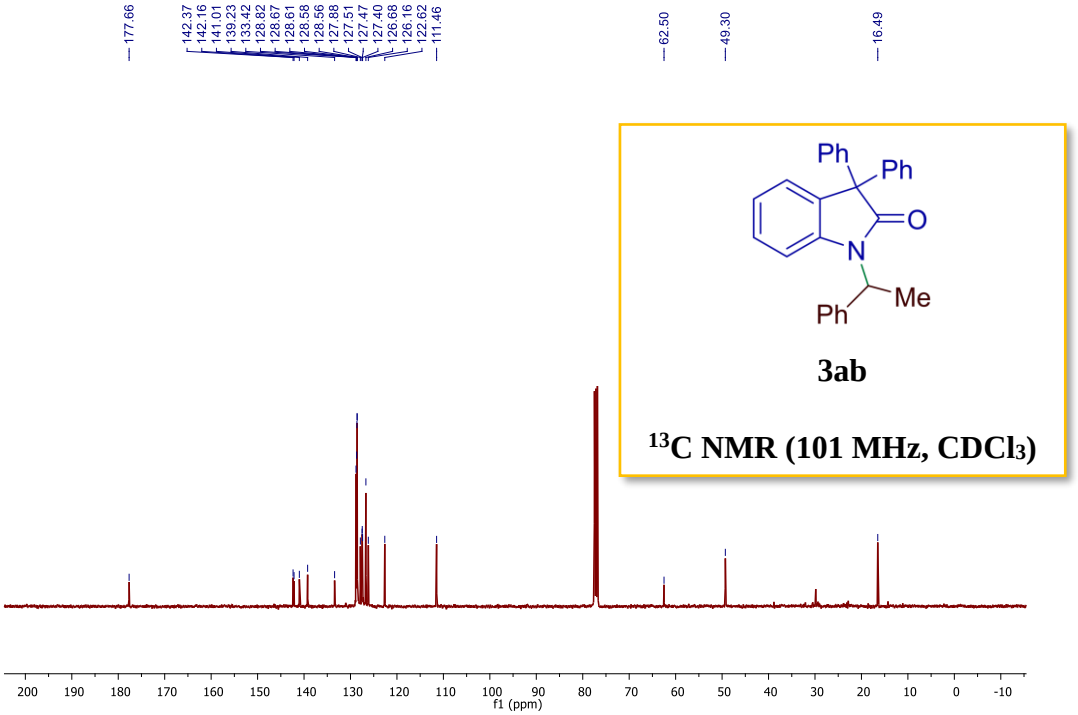
^{1}H NMR (400 MHz, $CDCl_3$)

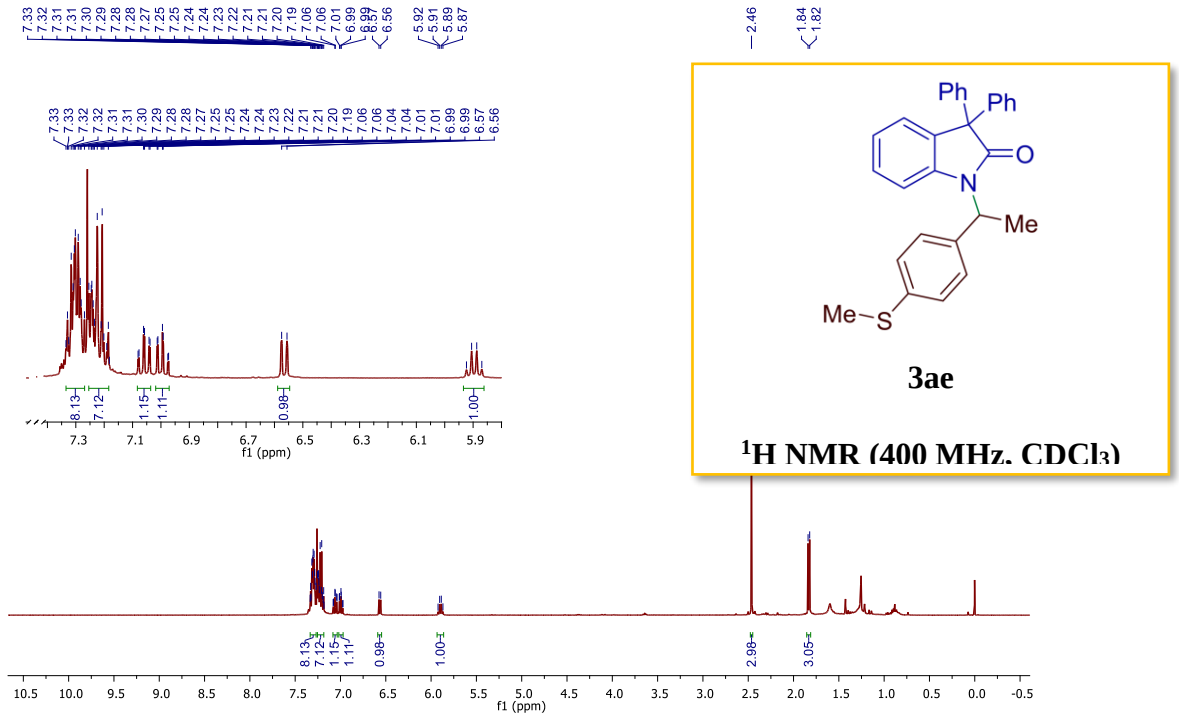

175.37
141.46
137.94
131.67
128.64
128.59
127.80
127.66
125.31
124.71
111.77
58.14
35.78
21.03
Me
O
N
Ph
Ph
3caa
13C NMR (101 MHz, CDCl3)
f1 (ppm)

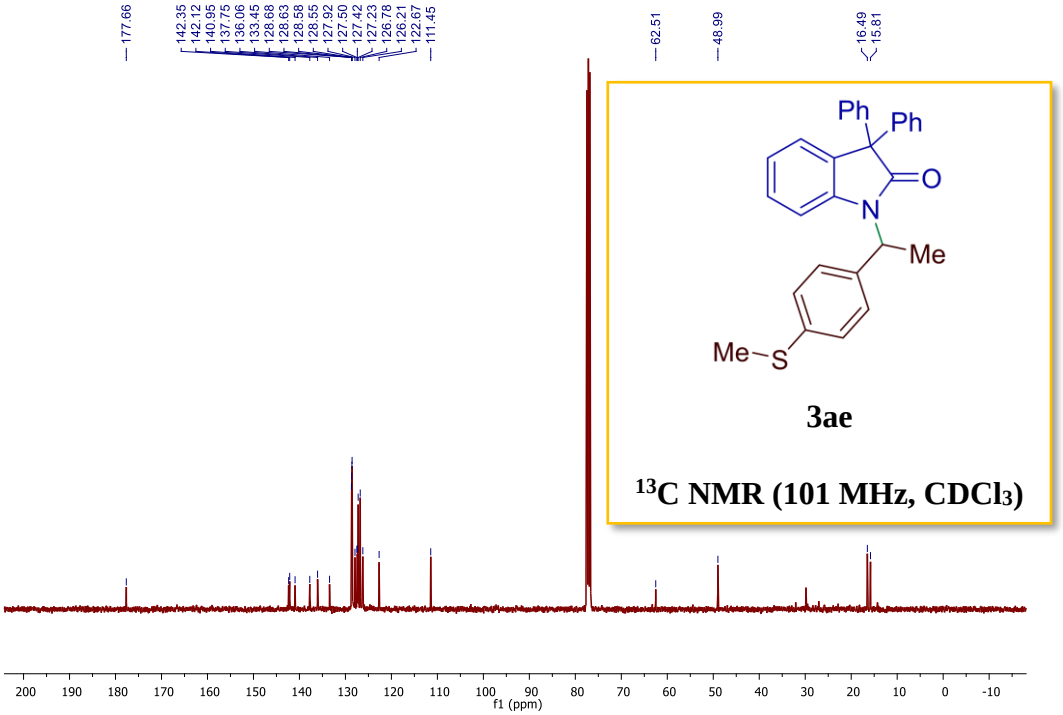

3.65
O
N
Ph
Br
3aal
1H NMR (400 MHz, CDCl3)
1.28
7.04
1.90
3.01
0.95
2.00
f1 (ppm)

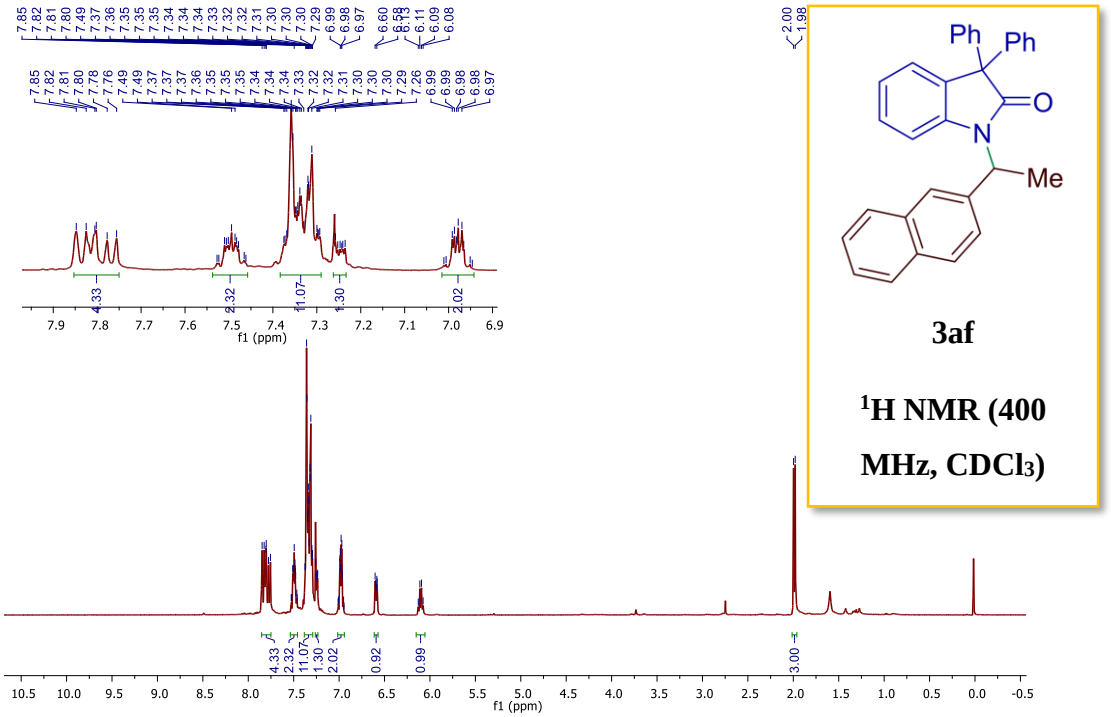

175.36
143.57
137.25
136.96
131.83
130.32
128.82
128.68
128.60
128.51
128.09
127.50
124.61
122.36
111.86
57.71
35.72
O
N
Ph
Br
3aal
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

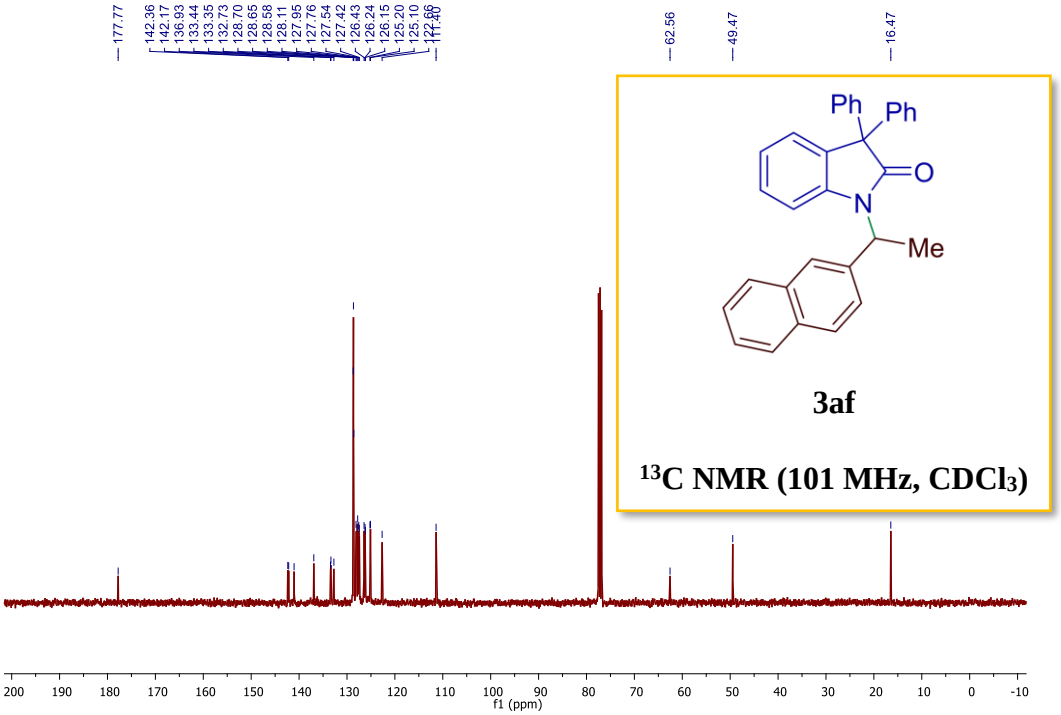

7.35
7.33
7.32
7.31
7.30
7.29
7.28
7.26
7.25
7.24
7.08
7.07
7.06
7.04
7.02
7.01
7.00
6.99
6.98
6.56
5.99
5.97
5.95
5.94
1.88
1.86
16.24
2.14
0.99
1.00
3.05
Ph
Ph
O
N
Ph
Me
3ab
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

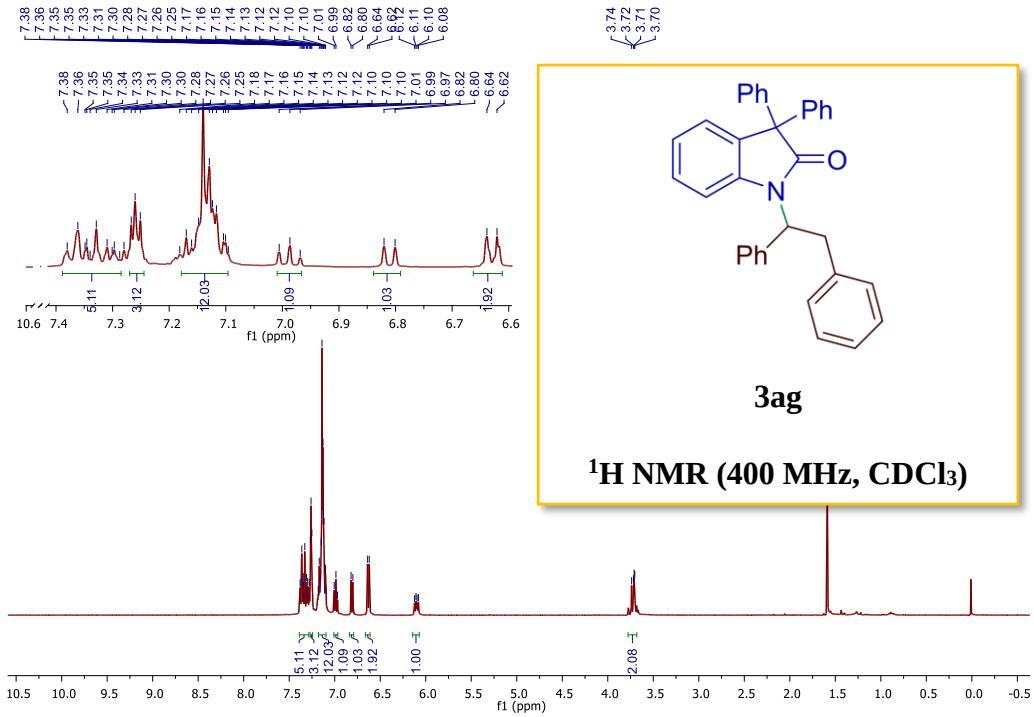

177.66
142.37
142.16
141.01
139.23
133.42
128.82
128.67
128.61
128.58
128.56
127.88
127.51
127.47
127.40
126.68
126.16
122.62
111.46
62.50
49.30
16.49
Ph
Ph
O
N
Me
Ph
3ab
13C NMR (101 MHz, CDCl3)
f1 (ppm)

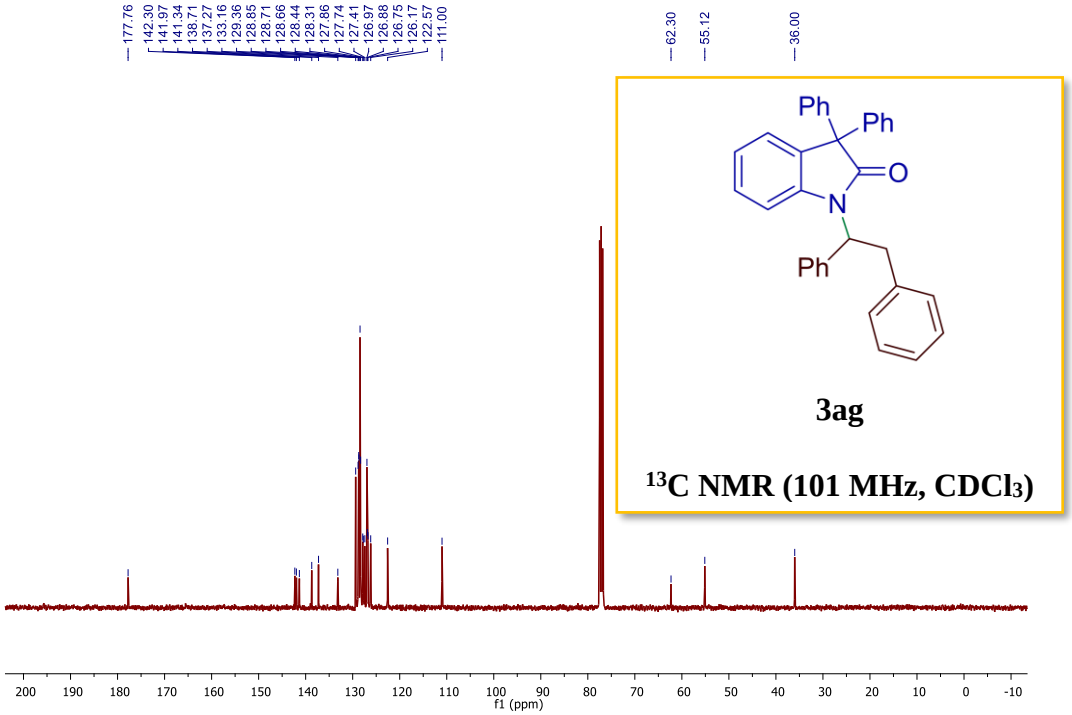

2.46
1.84
1.82
Ph
Ph
O
N
Me
Me–S
3ae
1H NMR (400 MHz, CDCl3)
f1 (ppm)

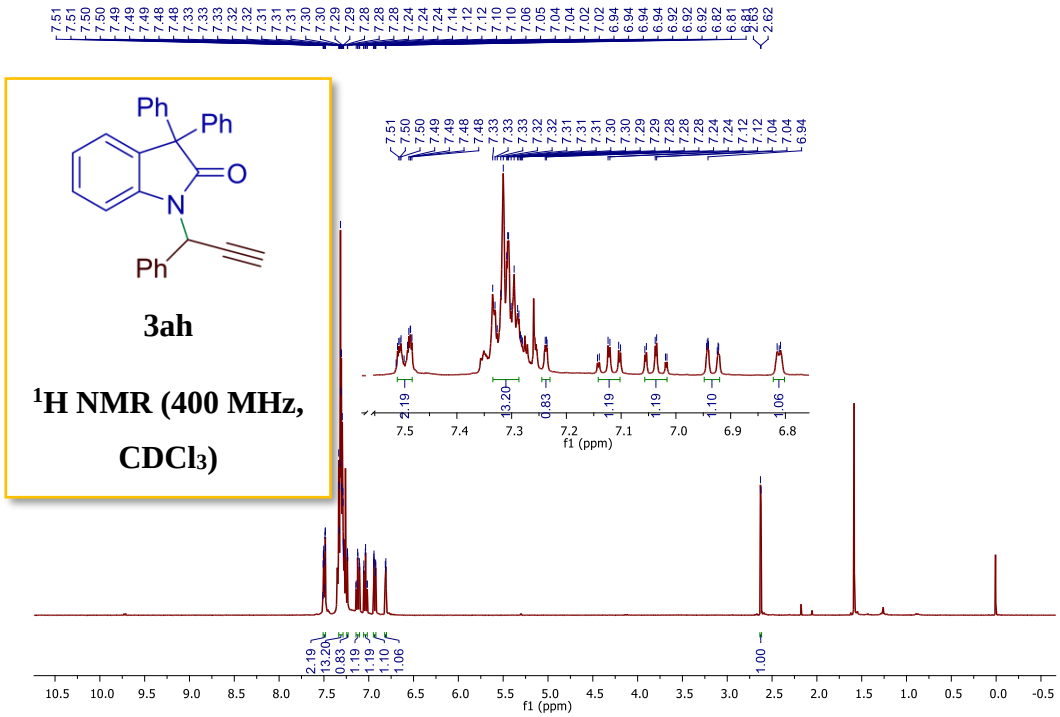

Ph
Ph
O
N
Me
Me–S
3ae
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

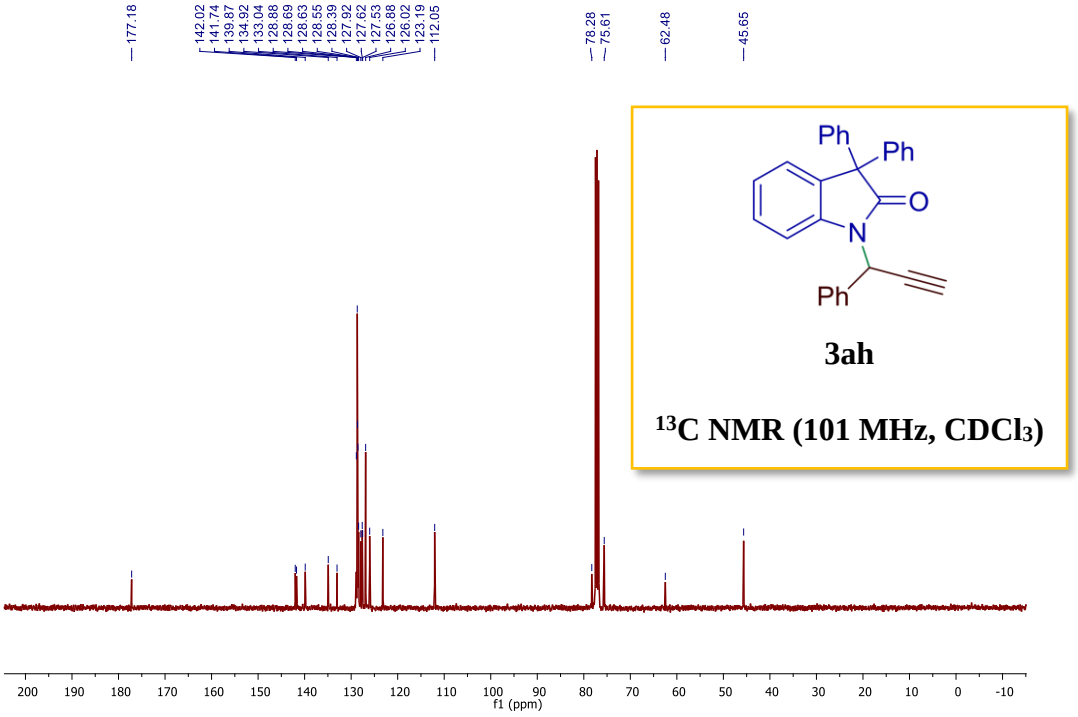

Ph
Ph
O
N
Me
3af
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

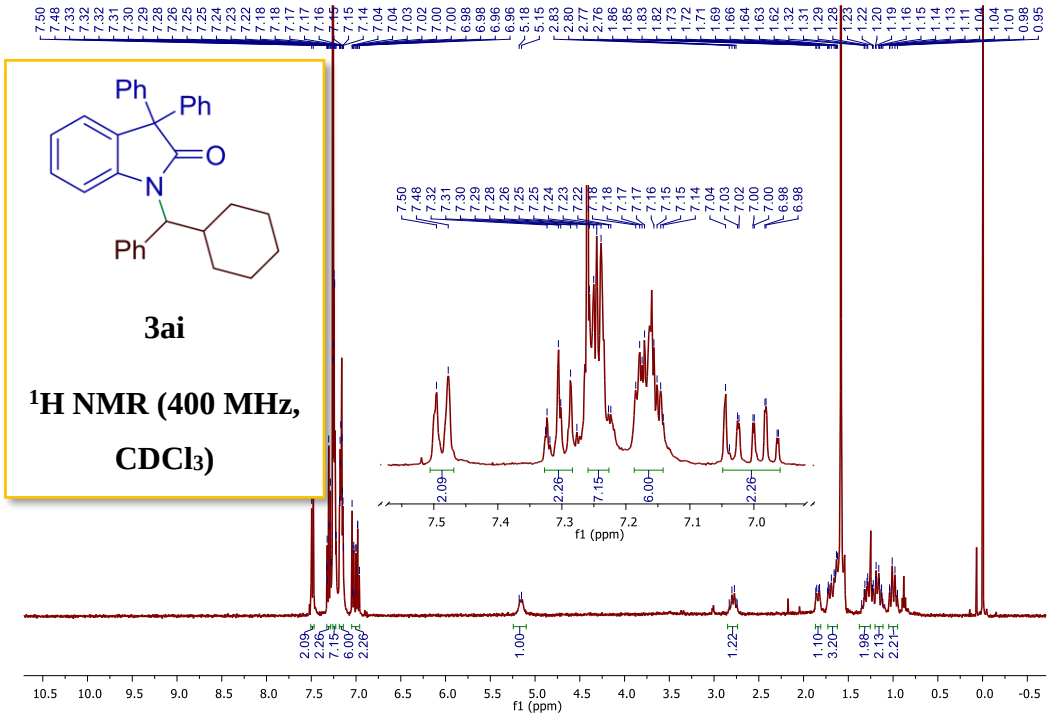

177.77
142.36
142.17
136.93
133.44
133.35
132.73
128.70
128.65
128.58
128.11
127.95
127.76
127.54
127.42
126.43
126.24
126.15
125.20
125.10
122.66
111.40
62.56
49.47
16.47
Ph
Ph
O
N
Me
3af
13C NMR (101 MHz, CDCl3)
f1 (ppm)

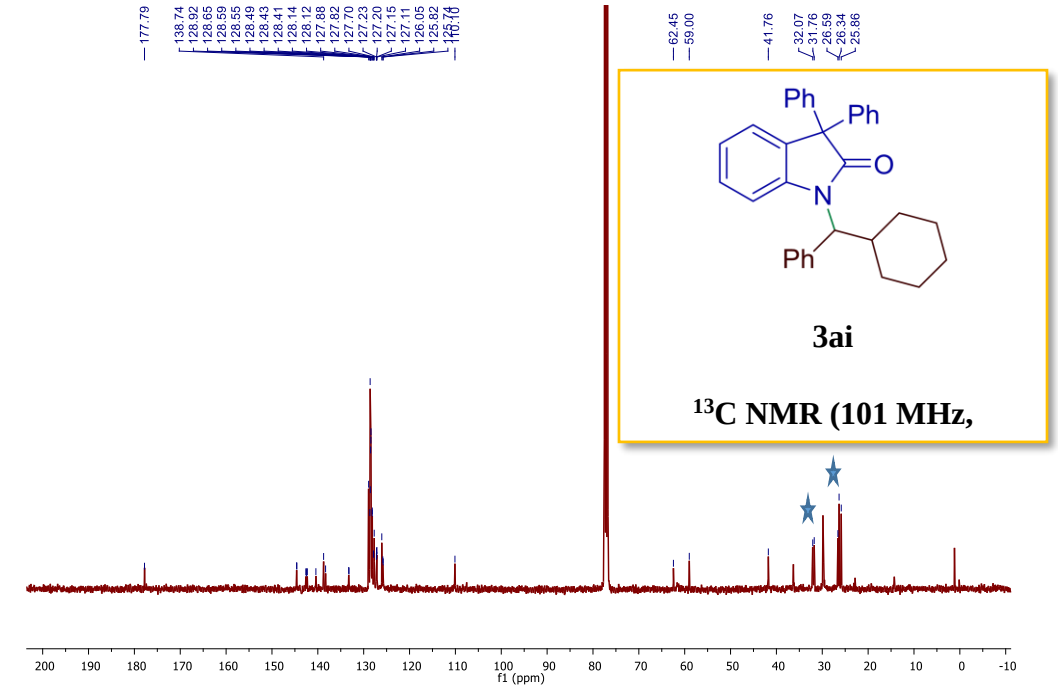

7.38
7.36
7.35
7.35
7.33
7.31
7.30
7.28
7.27
7.26
7.25
7.17
7.16
7.15
7.14
7.13
7.12
7.12
7.10
7.10
7.10
7.01
6.99
6.82
6.80
6.64
6.62
6.11
6.10
6.08
3.74
3.72
3.71
3.70
5.11
3.12
12.03
1.09
1.03
1.92
1.00
2.08
Ph
Ph
O
N
Ph
3ag
1H NMR (400 MHz, CDCl3)
f1 (ppm)


177.76
142.30
141.97
141.34
138.71
137.27
133.16
129.36
128.85
128.71
128.66
128.44
128.31
127.86
127.74
127.41
126.97
126.88
126.75
126.17
122.57
111.00
62.30
55.12
36.00
Ph
Ph
O
N
Ph
3ag
13C NMR (101 MHz, CDCl3)
f1 (ppm)

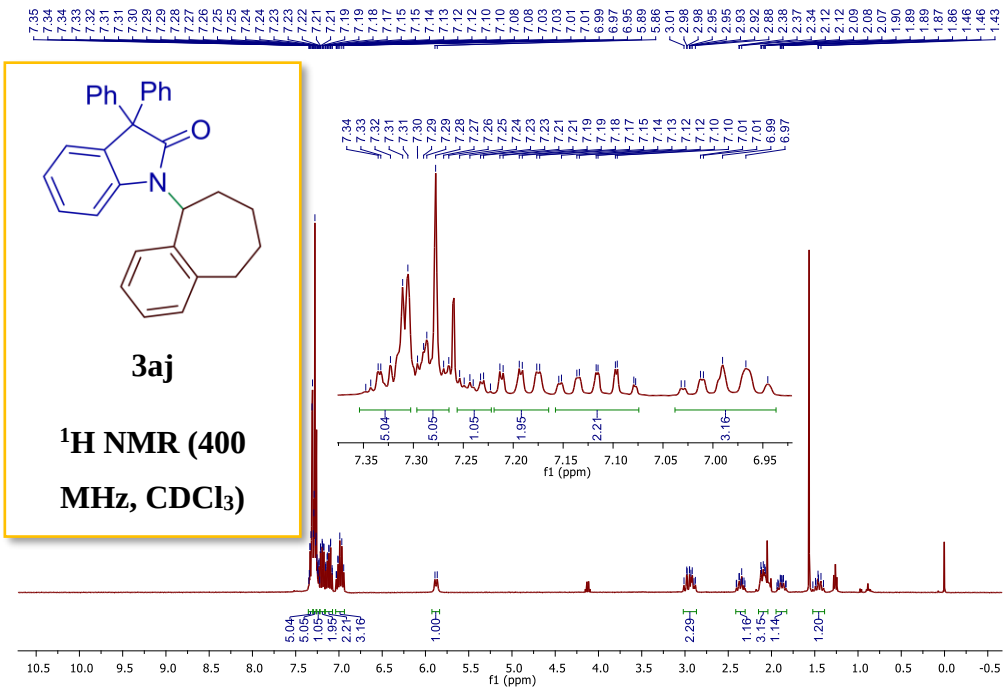

Ph
Ph
O
N
Ph
3ah
1H NMR (400 MHz, CDCl3)
f1 (ppm)

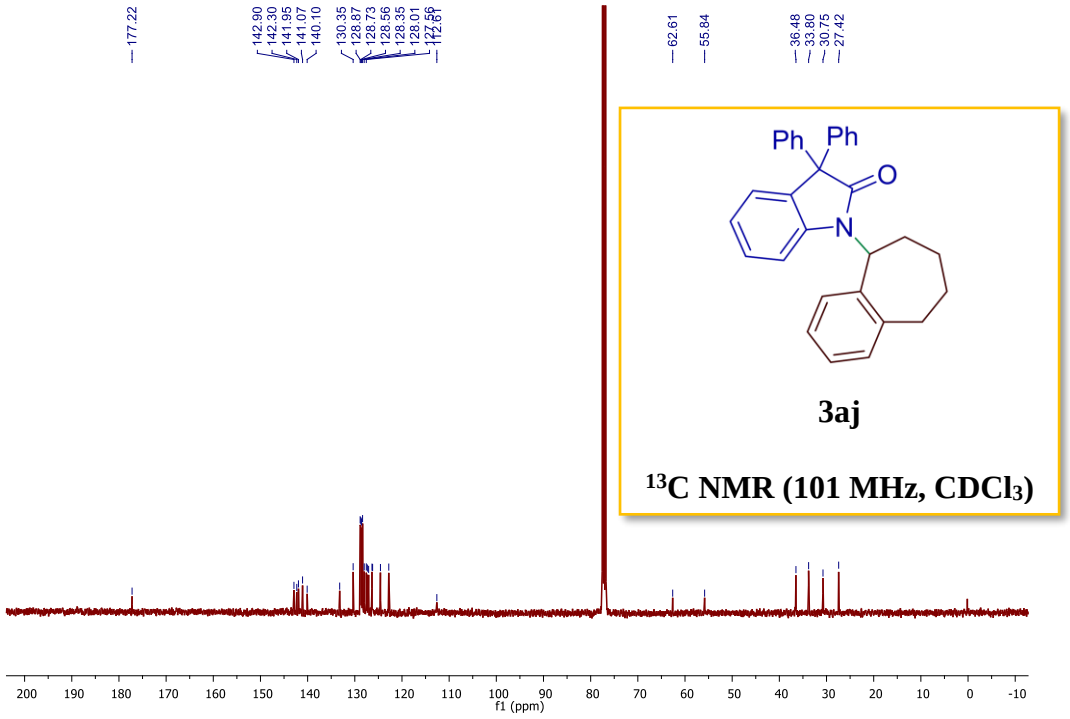

177.18
142.02
141.74
139.87
134.92
133.04
128.88
128.69
128.63
128.55
128.39
127.92
127.62
127.53
126.88
126.02
123.19
112.05
78.28
75.61
62.48
45.65
Ph
Ph
O
N
Ph
3ah
13C NMR (101 MHz, CDCl3)
f1 (ppm)

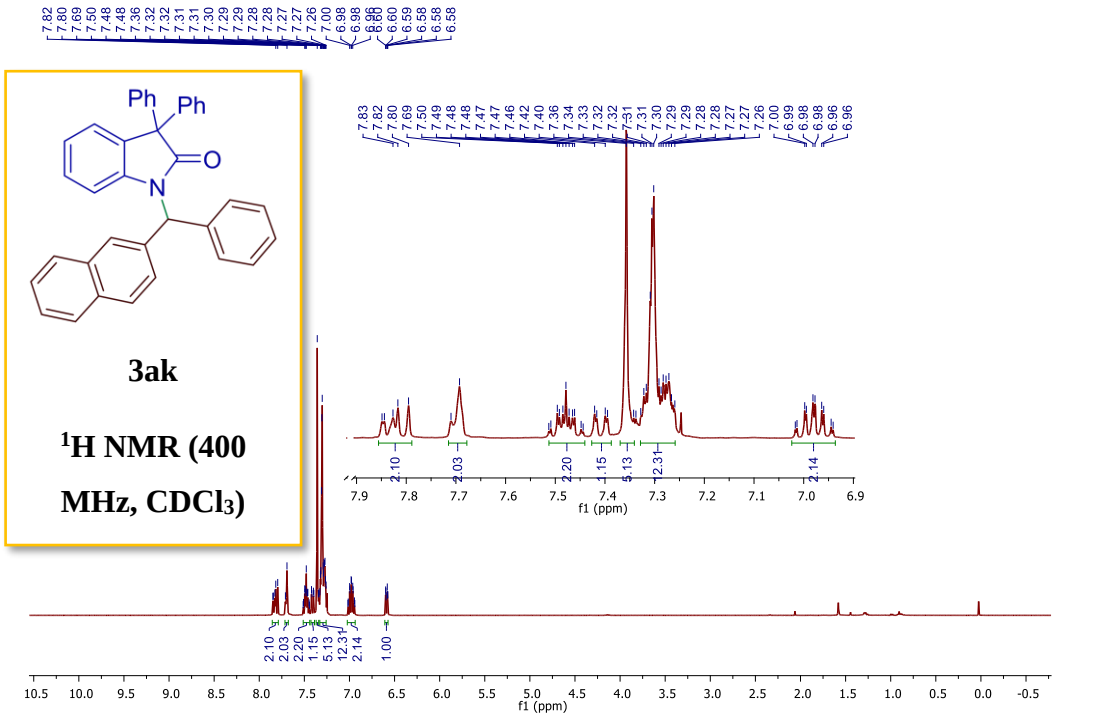

Ph
Ph
O
N
Ph
3ai
1H NMR (400 MHz, CDCl3)
f1 (ppm)

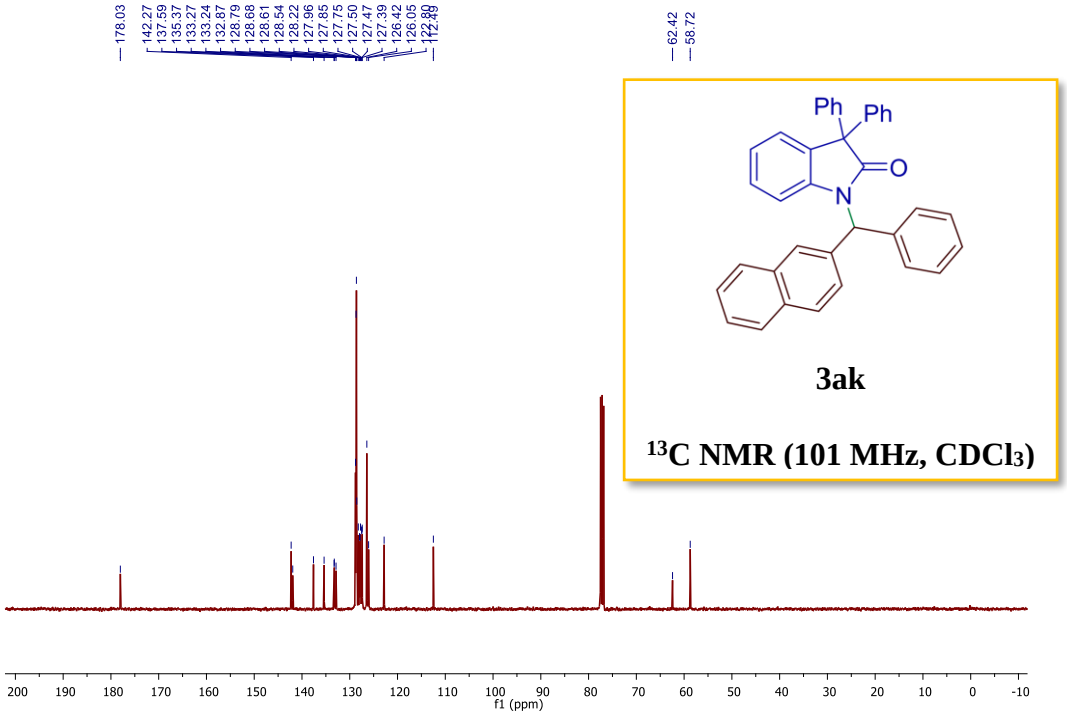


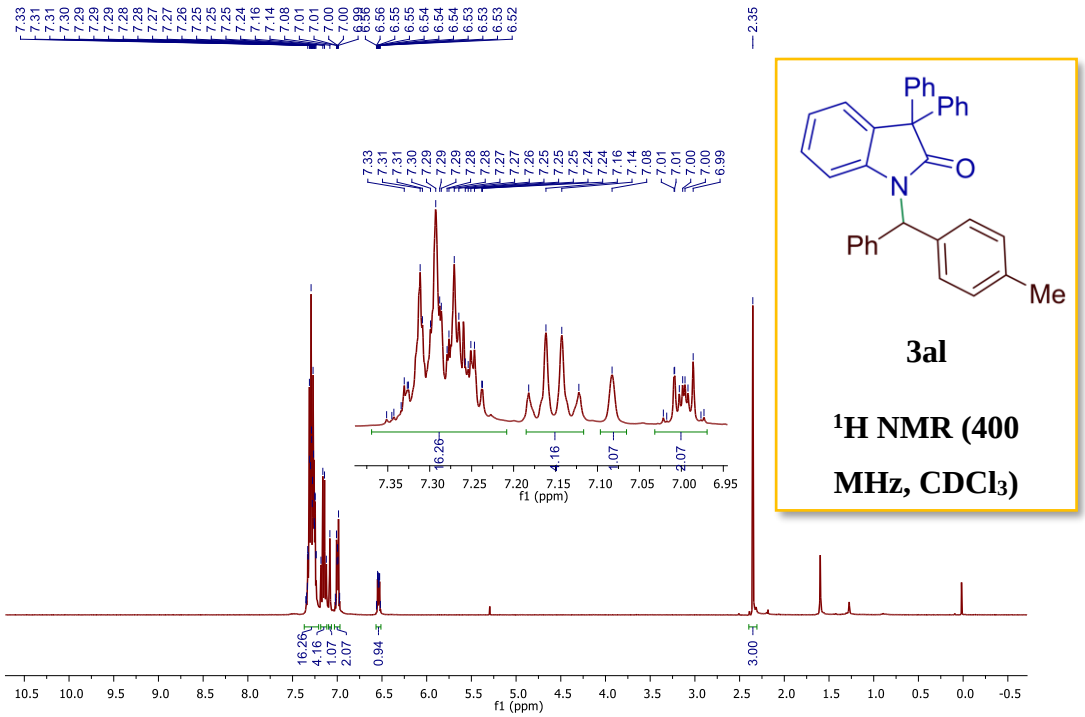
★- Unidentified impurities

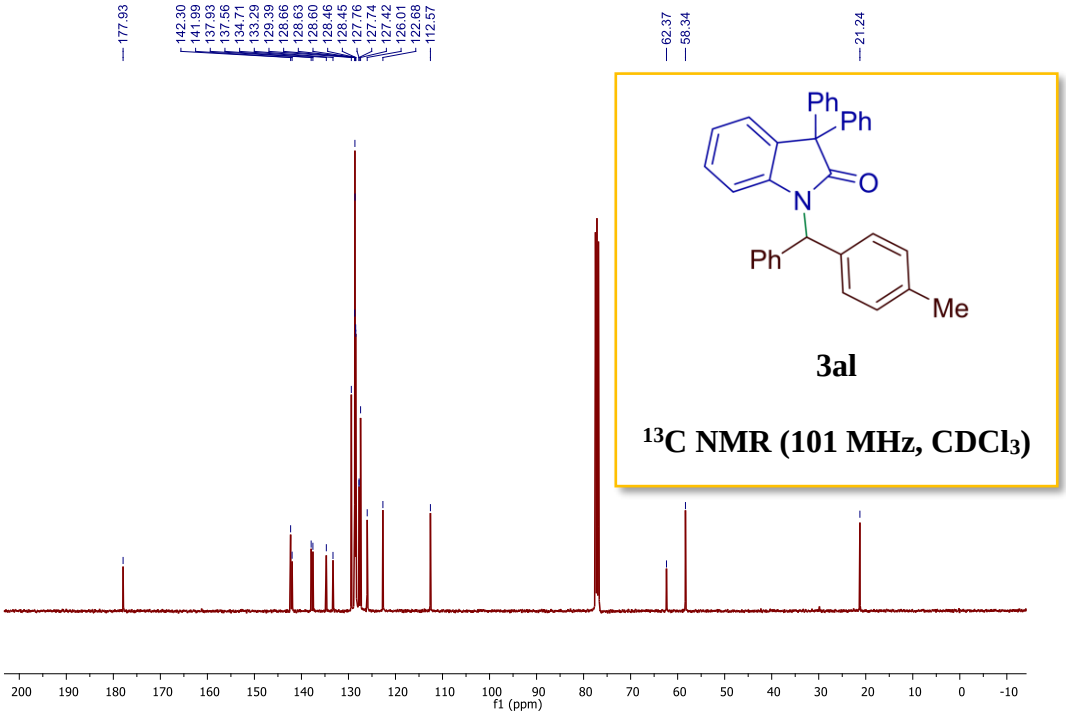



Ph
Ph
O
N
3aj
^{13}C NMR (101 MHz, CDCl$_3$)


Ph
Ph
O
N
3ak
^{1}H NMR (400 MHz, CDCl$_3$)

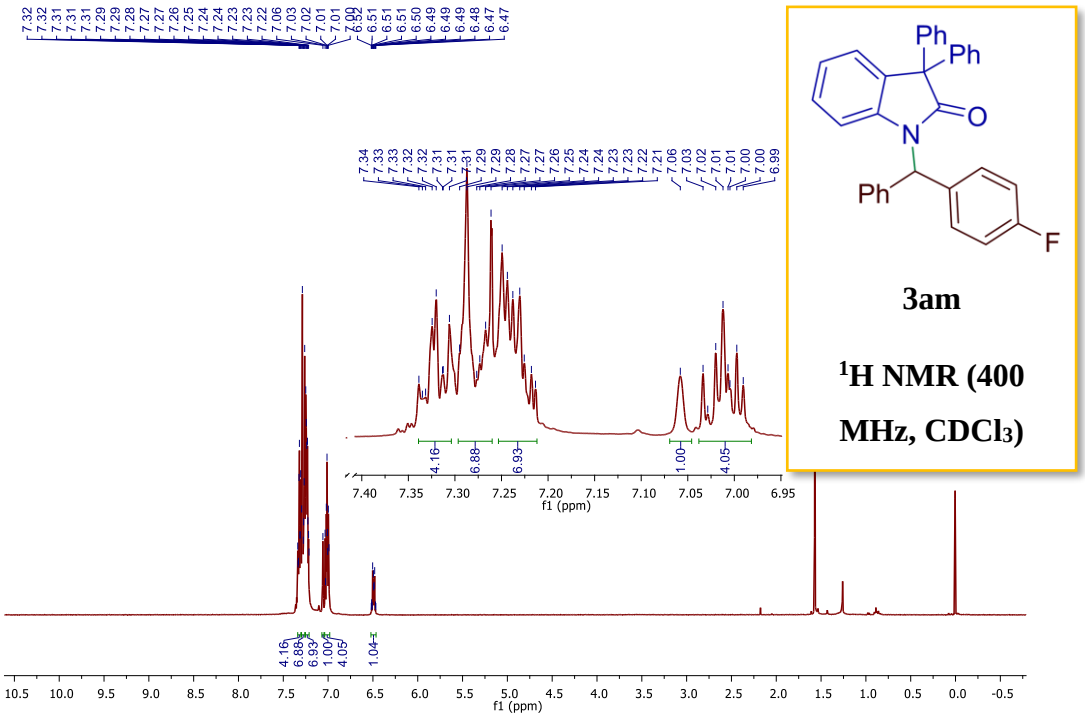

Ph
Ph
O
N
3ak
13C NMR (101 MHz, CDCl3)
f1 (ppm)


Ph
Ph
O
N
Ph
Me
3al
1H NMR (400 MHz, CDCl3)
f1 (ppm)



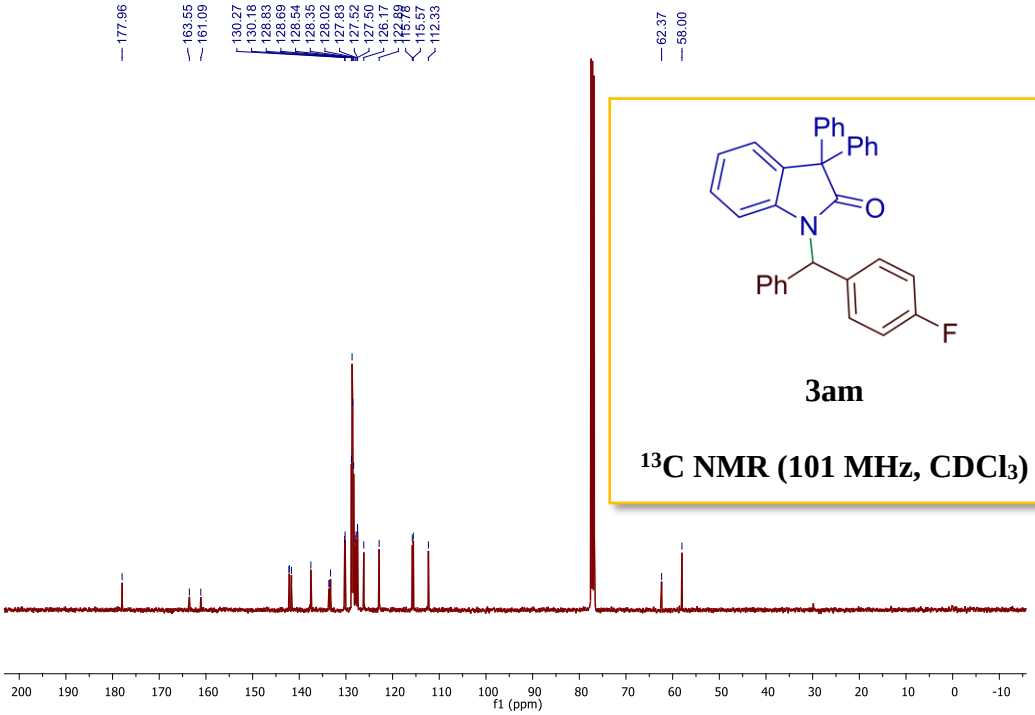
3al

^{13}C NMR (101 MHz, $CDCl_3$)



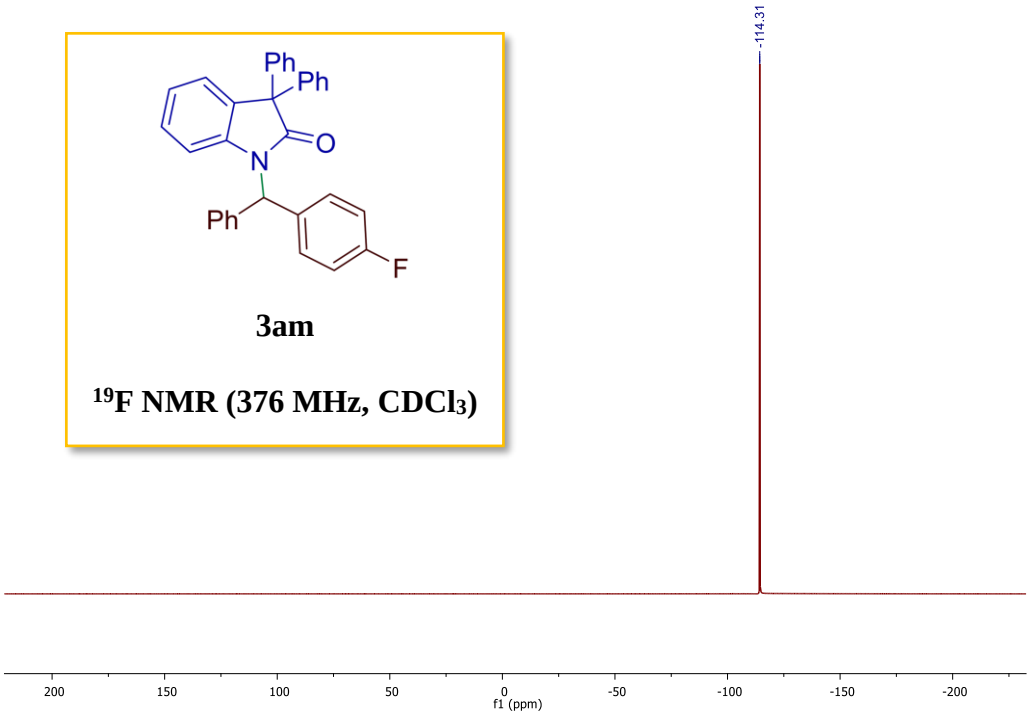
3am

^{1}H NMR (400 MHz, $CDCl_3$)



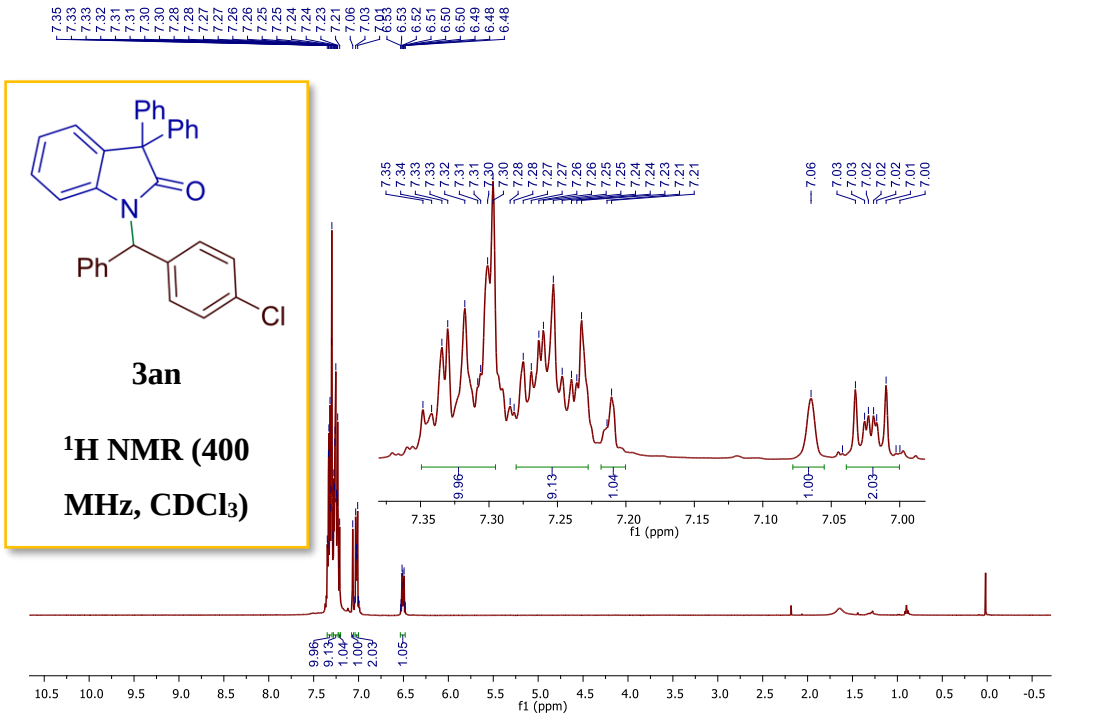
3am

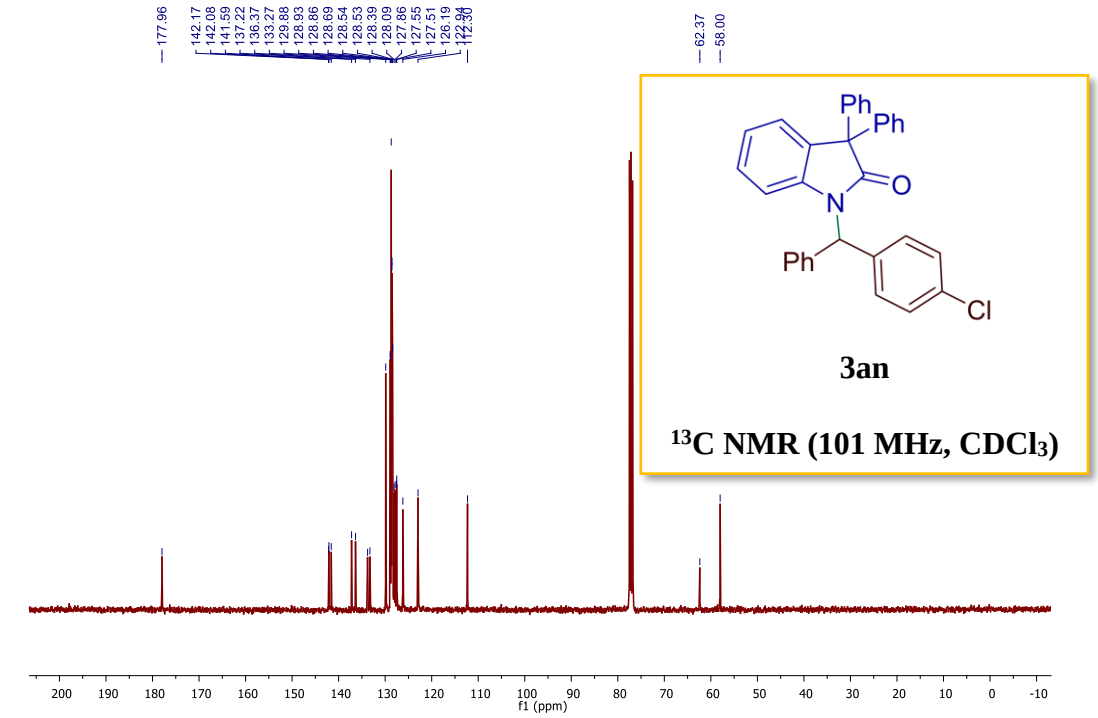
^{13}C NMR (101 MHz, $CDCl_3$)

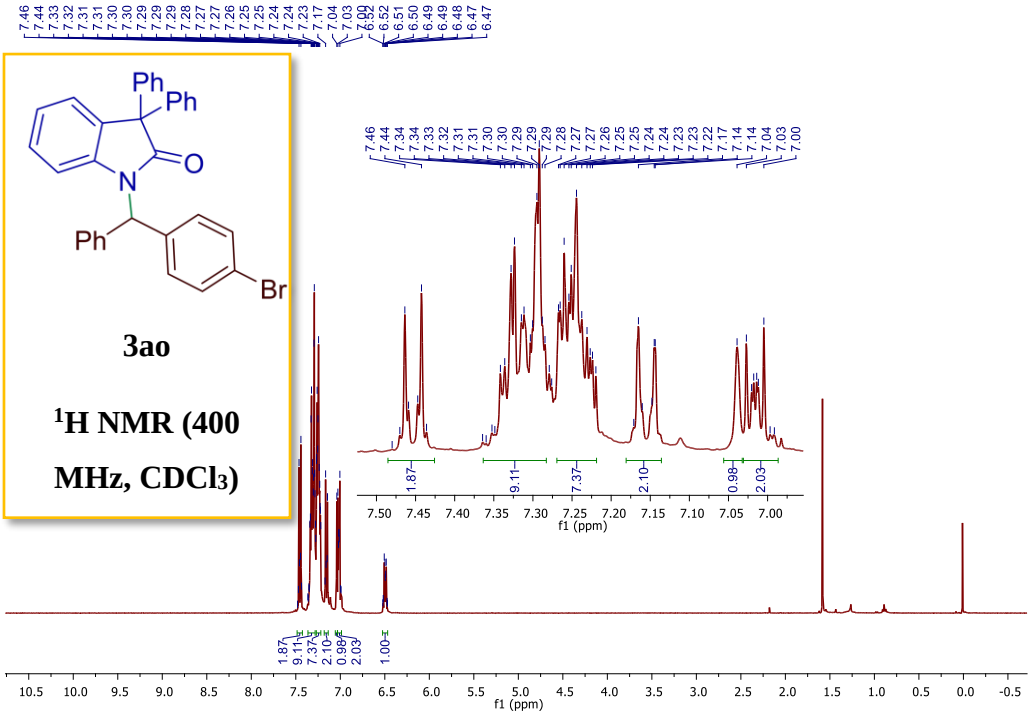


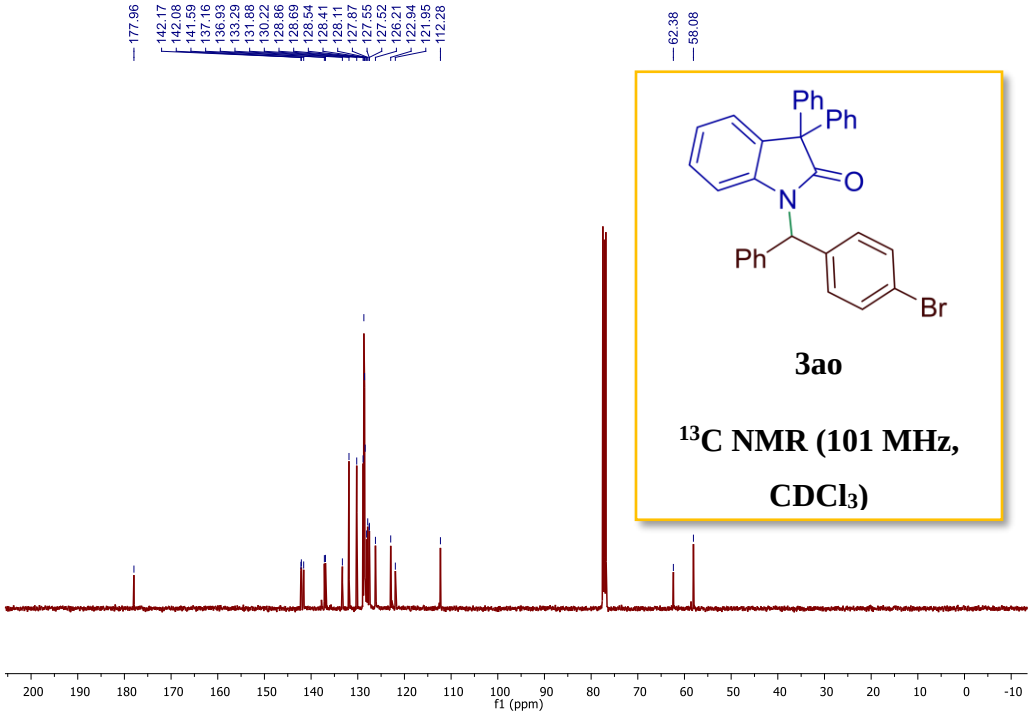
3am

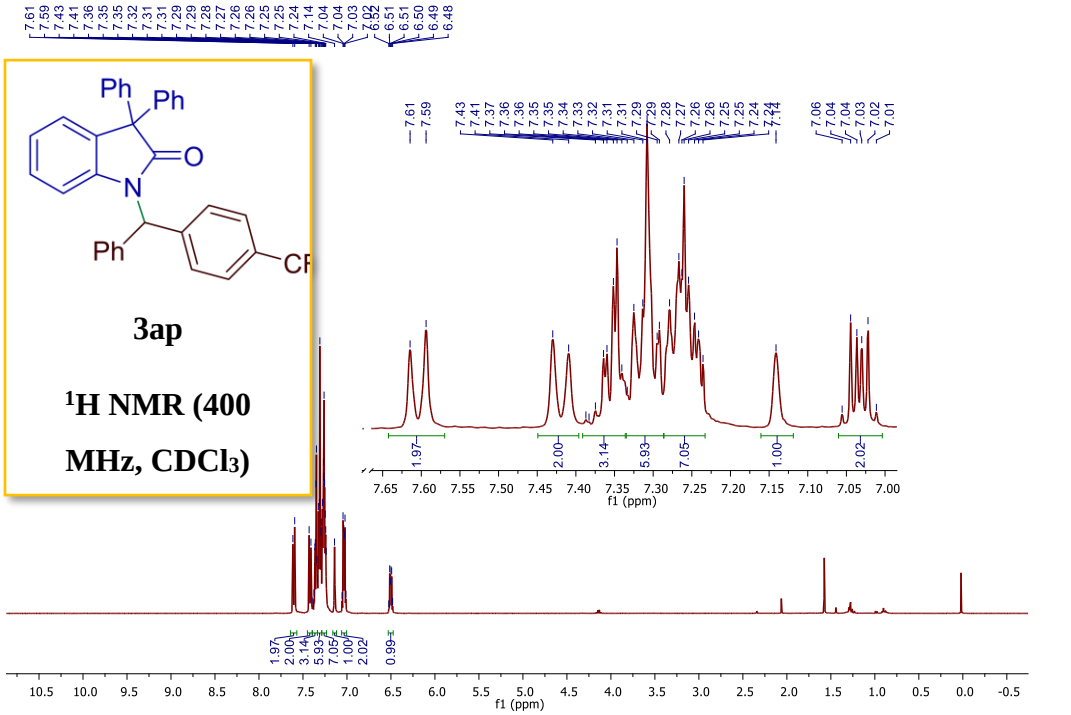
^{19}F NMR (376 MHz, $CDCl_3$)

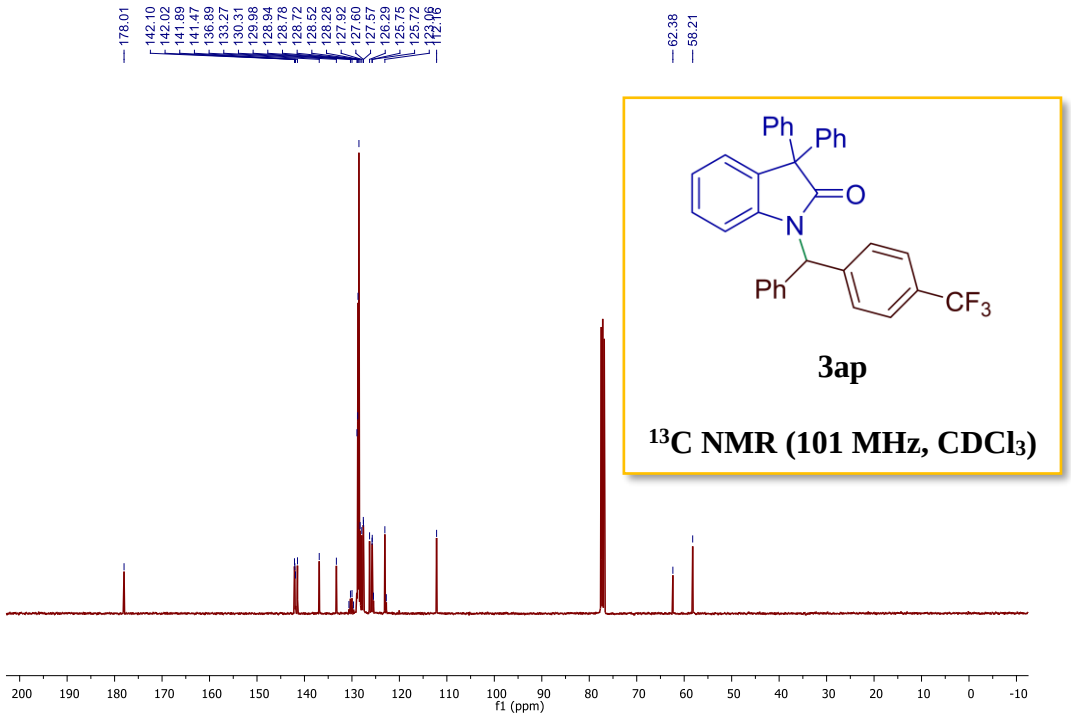

Ph
Ph
O
N
Ph
Cl
3an
^{1}H NMR (400 MHz, CDCl$_3$)

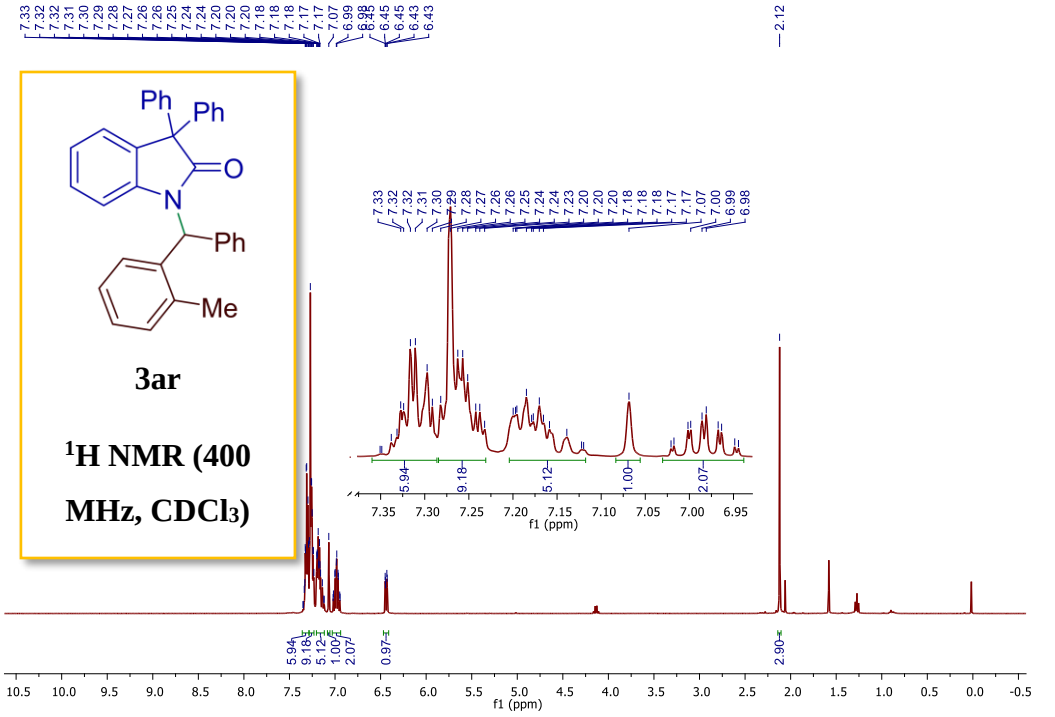

Ph
Ph
O
N
Ph
Cl
3an
^{13}C NMR (101 MHz, CDCl$_3$)

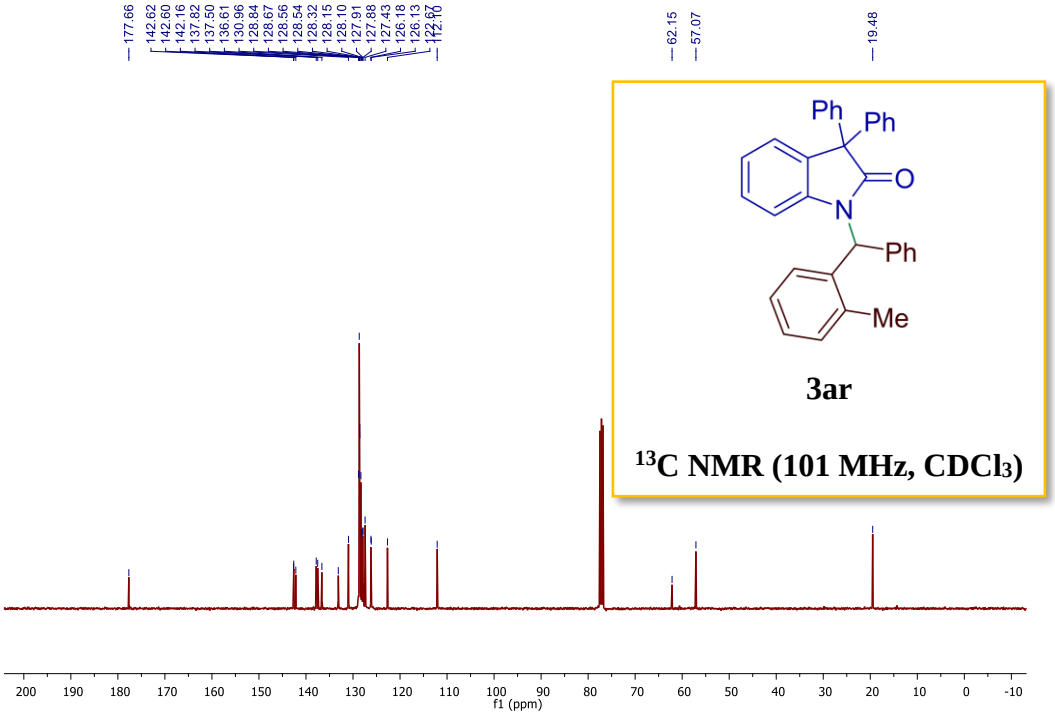

Ph
Ph
O
N
Ph
Br
3ao
1H NMR (400 MHz, CDCl3)
f1 (ppm)

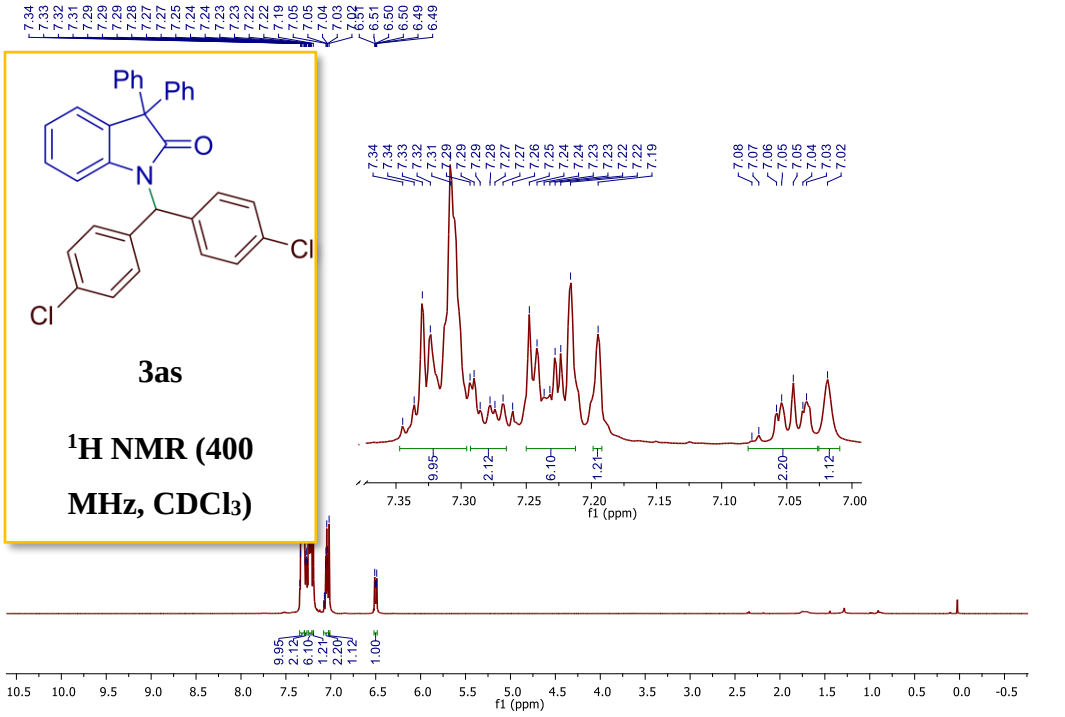

Ph
Ph
O
N
Ph
Br
3ao
13C NMR (101 MHz, CDCl3)
f1 (ppm)

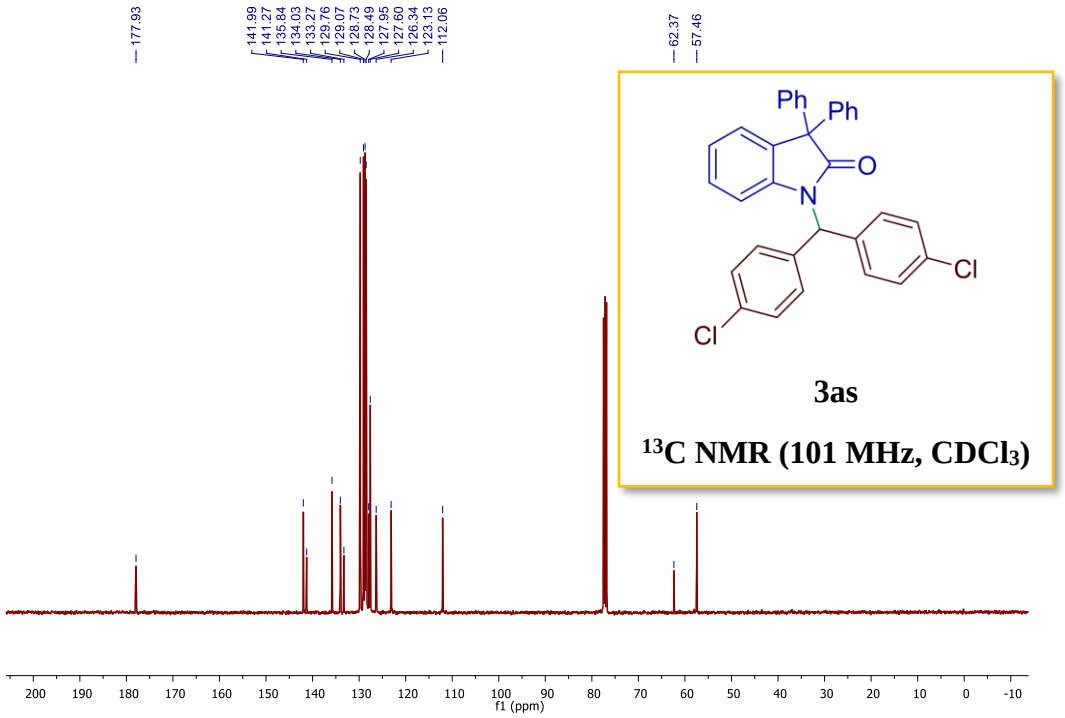

Ph
Ph
O
N
Ph
CF
3ap
1H NMR (400 MHz, CDCl3)
f1 (ppm)

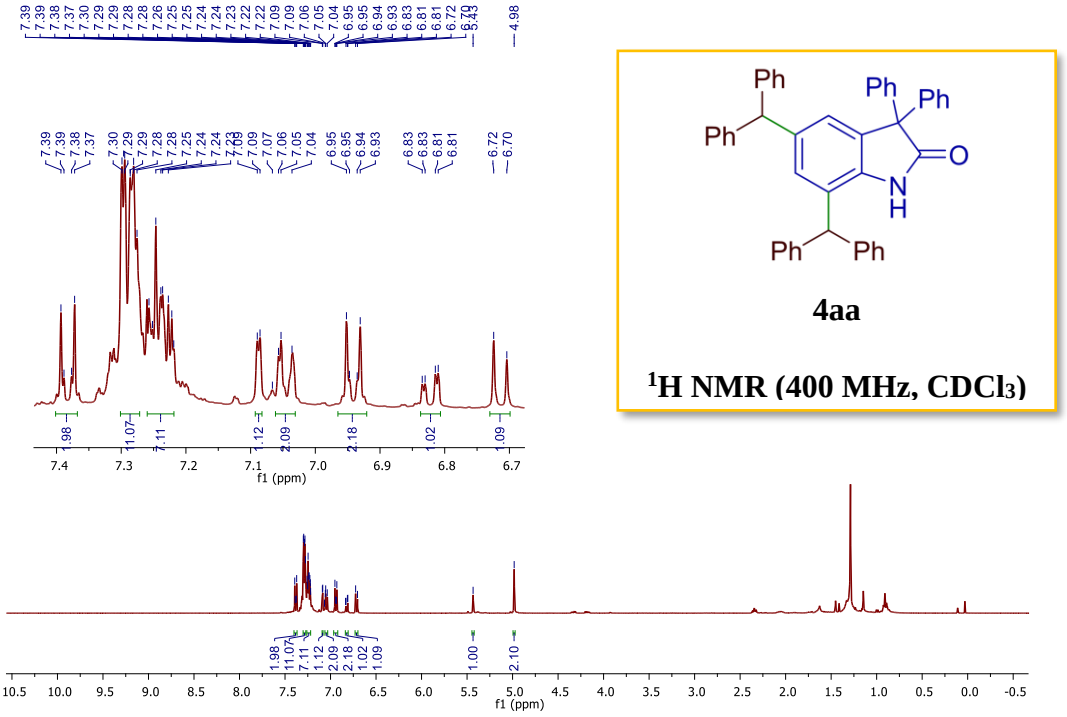

Ph
Ph
O
N
Ph
CF3
3ap
13C NMR (101 MHz, CDCl3)
f1 (ppm)


Ph
Ph
O
N
Ph
Me
3ar
1H NMR (400 MHz, CDCl3)
f1 (ppm)


Ph
Ph
O
N
Ph
Me
3ar
13C NMR (101 MHz, CDCl3)
f1 (ppm)

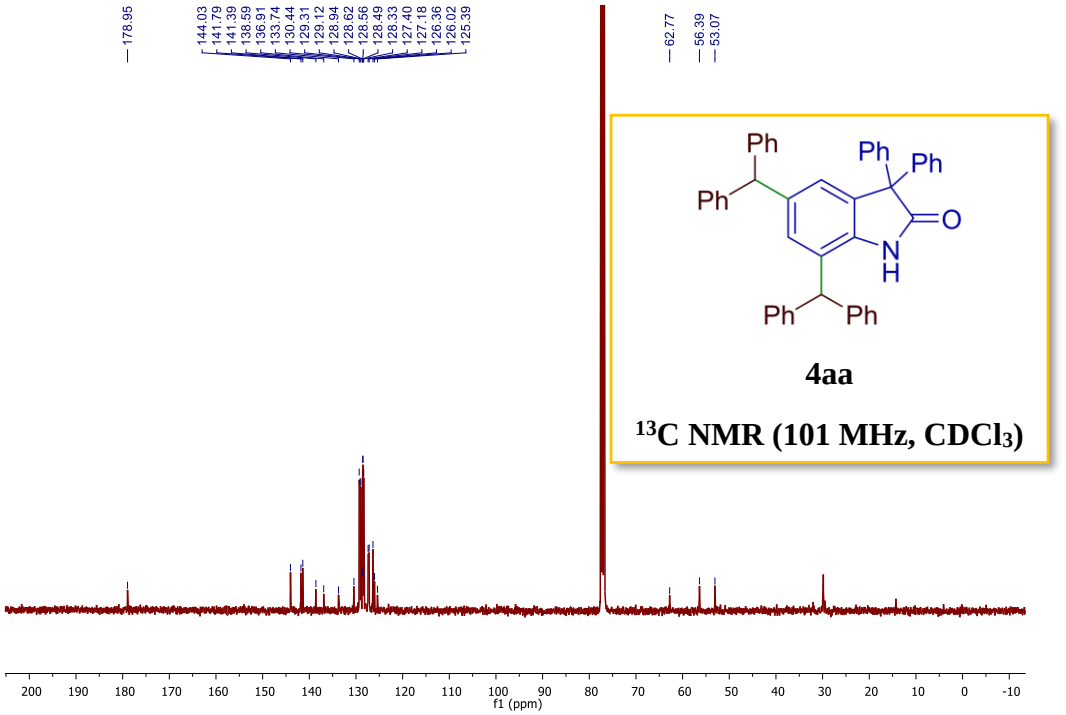

Ph
Ph
O
N
Cl
Cl
3as
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)


Ph
Ph
O
N
Cl
Cl
3as
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)



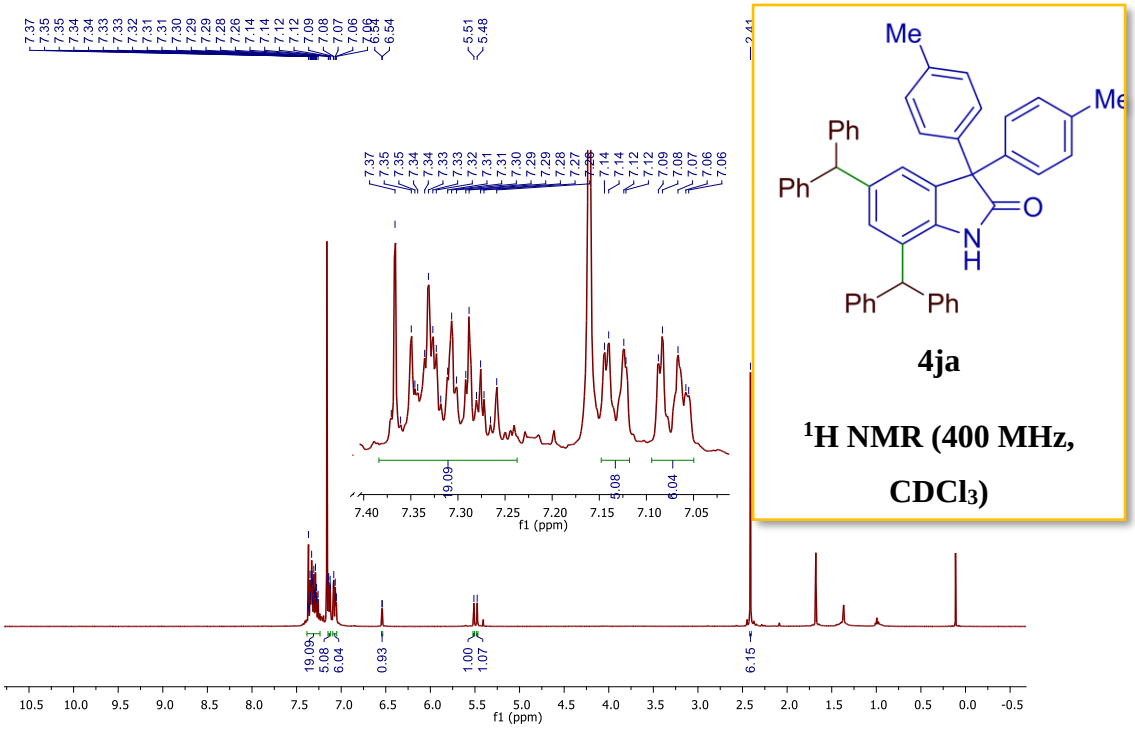
4aa

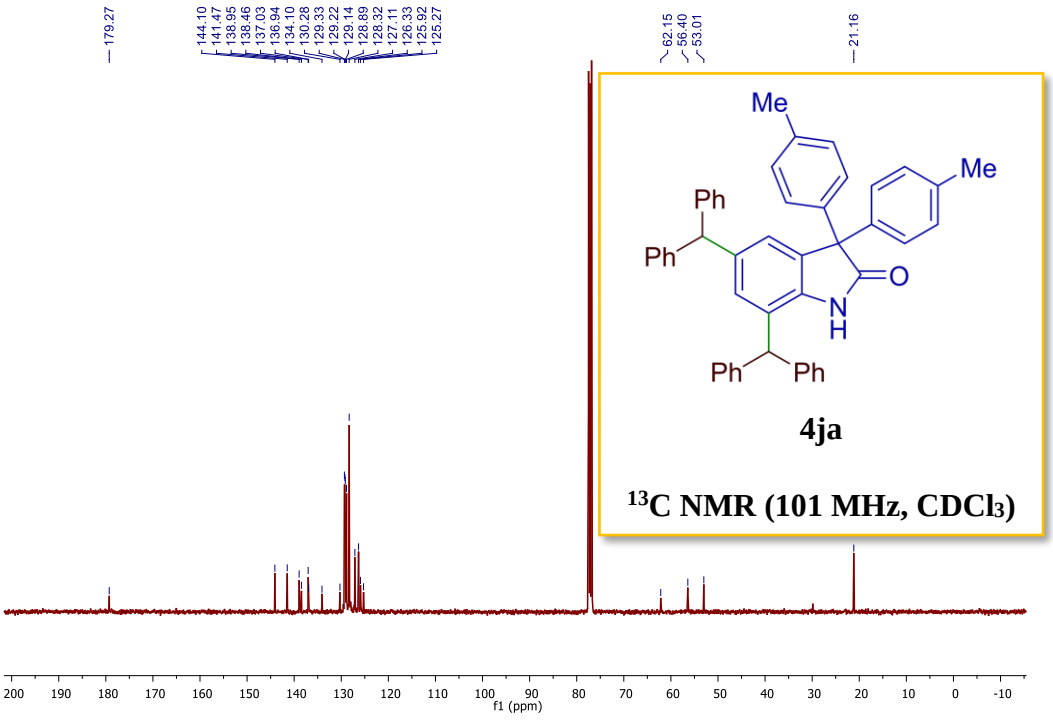
^{1}H NMR (400 MHz, $CDCl_3$)

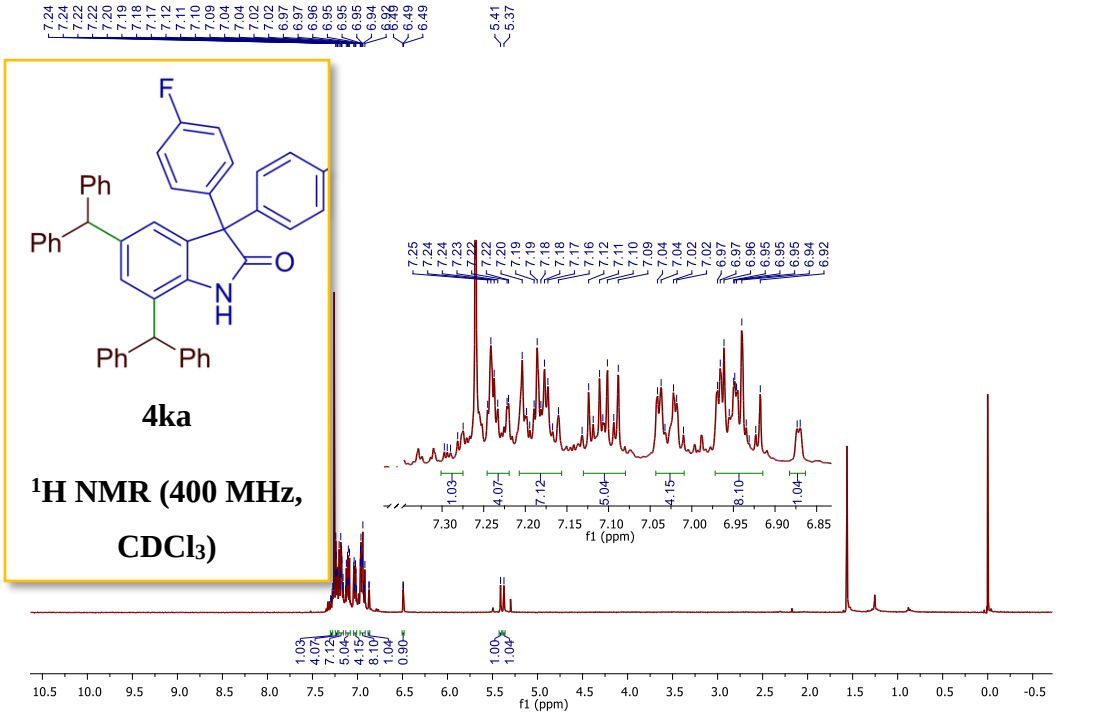


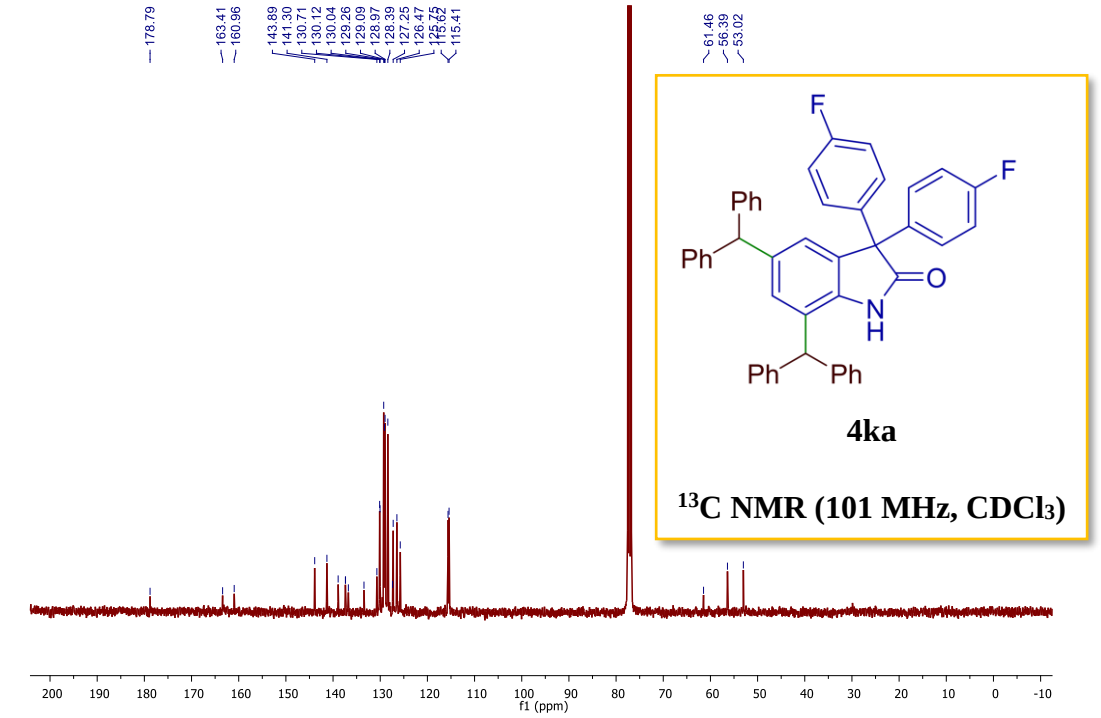
4aa

^{13}C NMR (101 MHz, $CDCl_3$)


Me
Me
Ph
Ph
O
N
H
Ph
Ph
4ja
^{1}H NMR (400 MHz, CDCl$_3$)

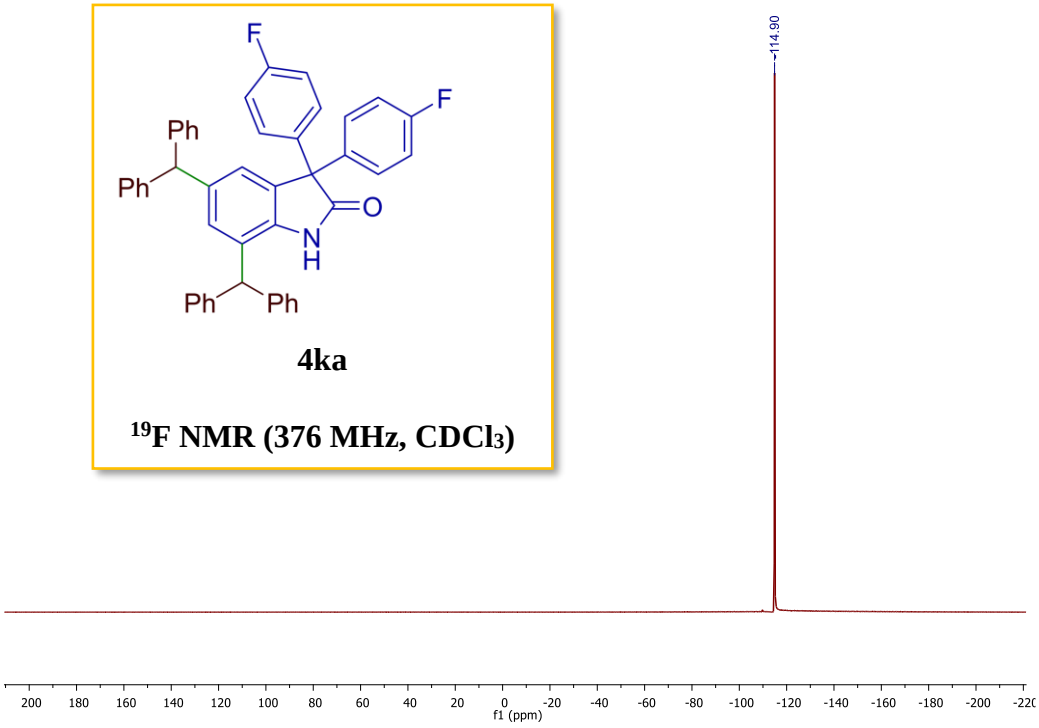

Me
Me
Ph
Ph
O
N
H
Ph
Ph
4ja
^{13}C NMR (101 MHz, CDCl$_3$)

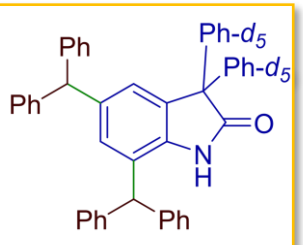

F
Ph
Ph
O
N
H
Ph
Ph
4ka
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)


F
F
Ph
Ph
O
N
H
Ph
Ph
4ka
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

4ka

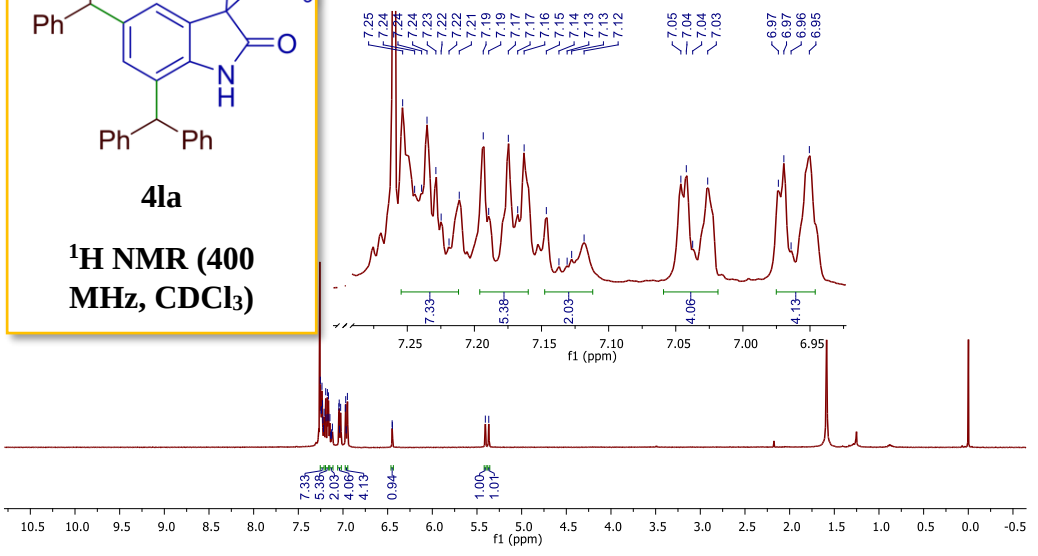
^{19}F NMR (376 MHz, $CDCl_3$)

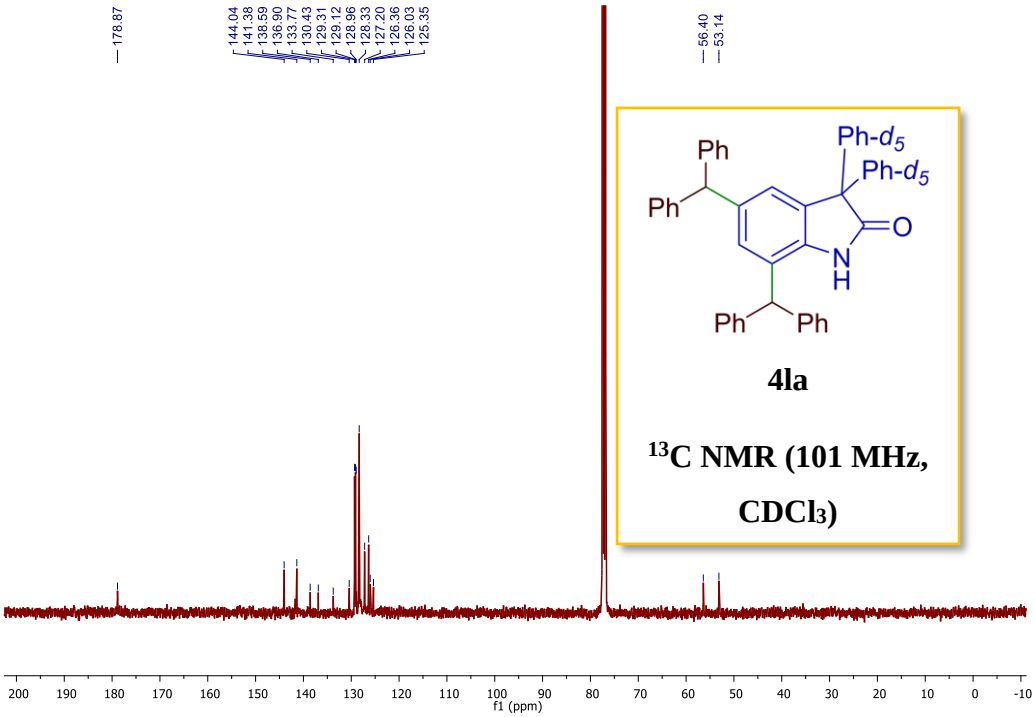


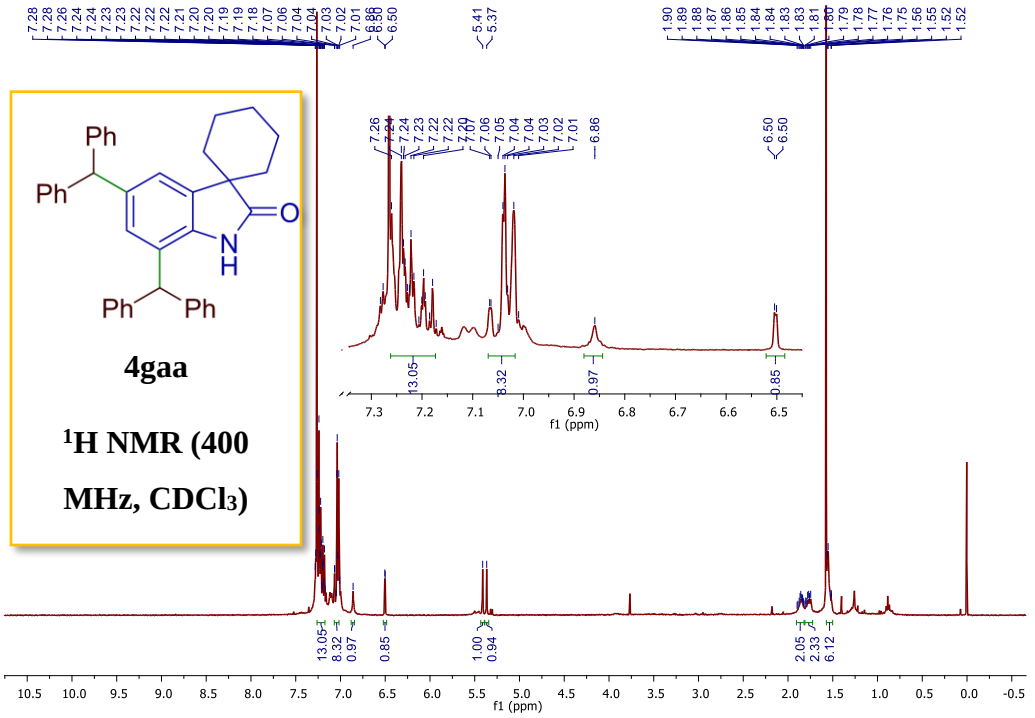


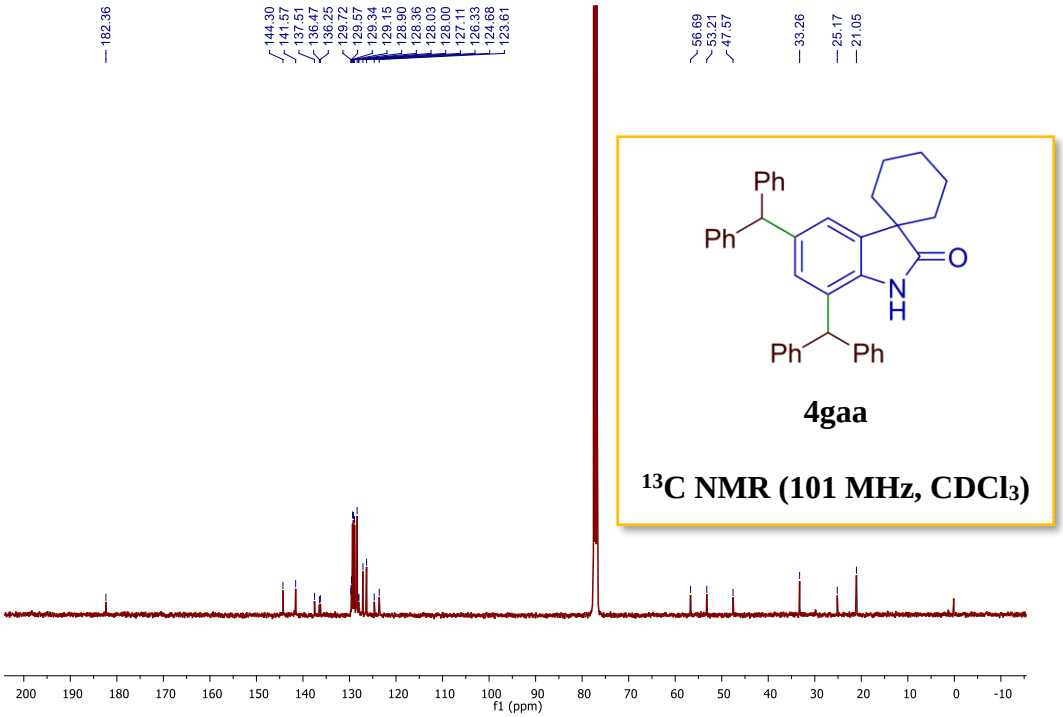
4la

^{1}H NMR (400 MHz, $CDCl_3$)



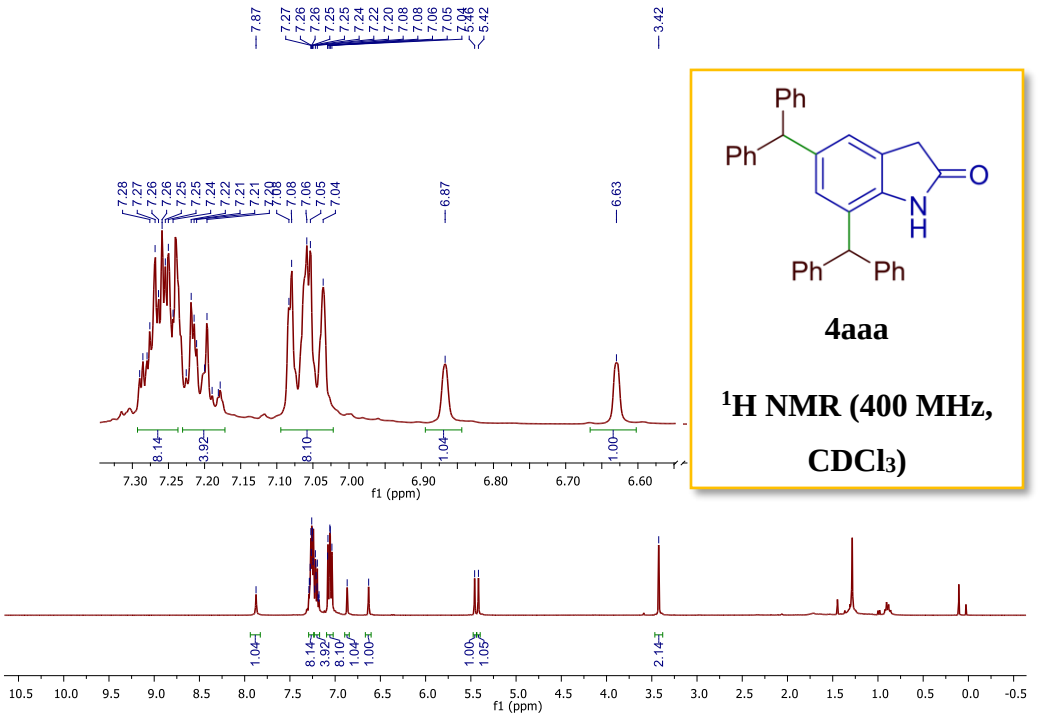

Ph
Ph
Ph-d_5
Ph-d_5
O
N
H
Ph
Ph
4la
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)


Ph
Ph
O
N
H
Ph
Ph
4gaa
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)



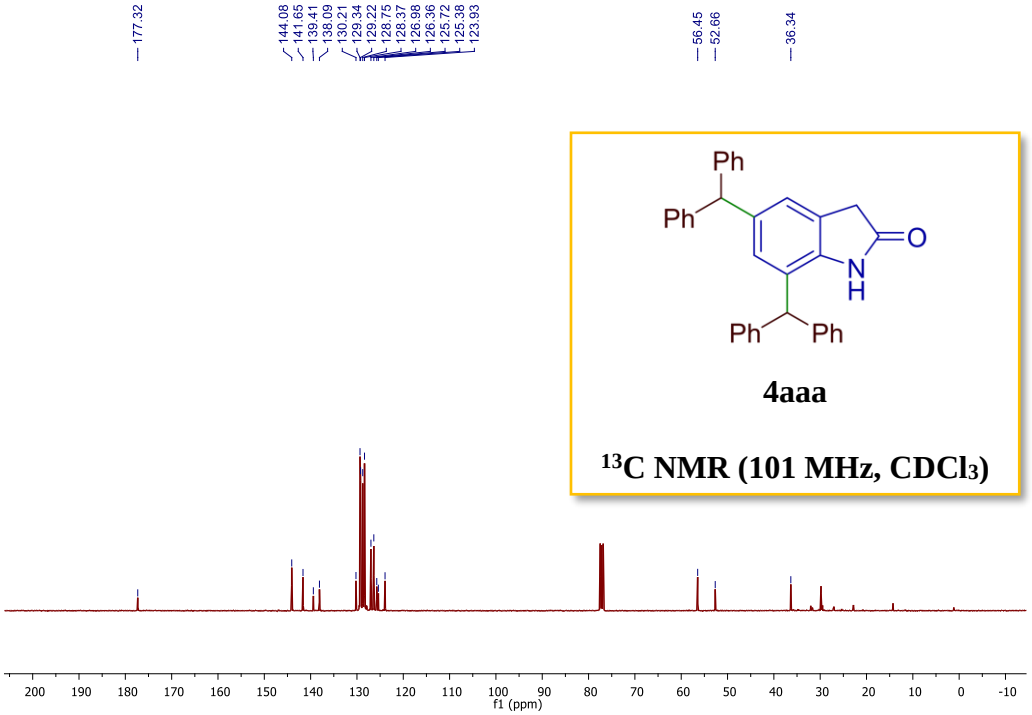
4gaa

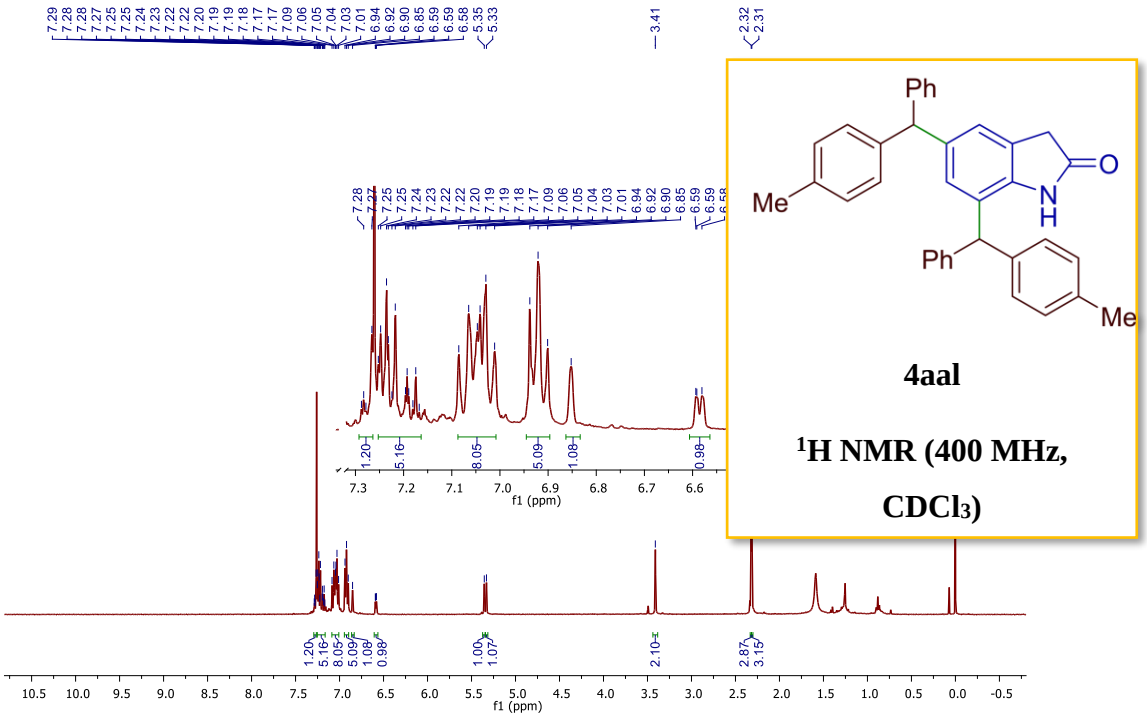
^{13}C NMR (101 MHz, $CDCl_3$)

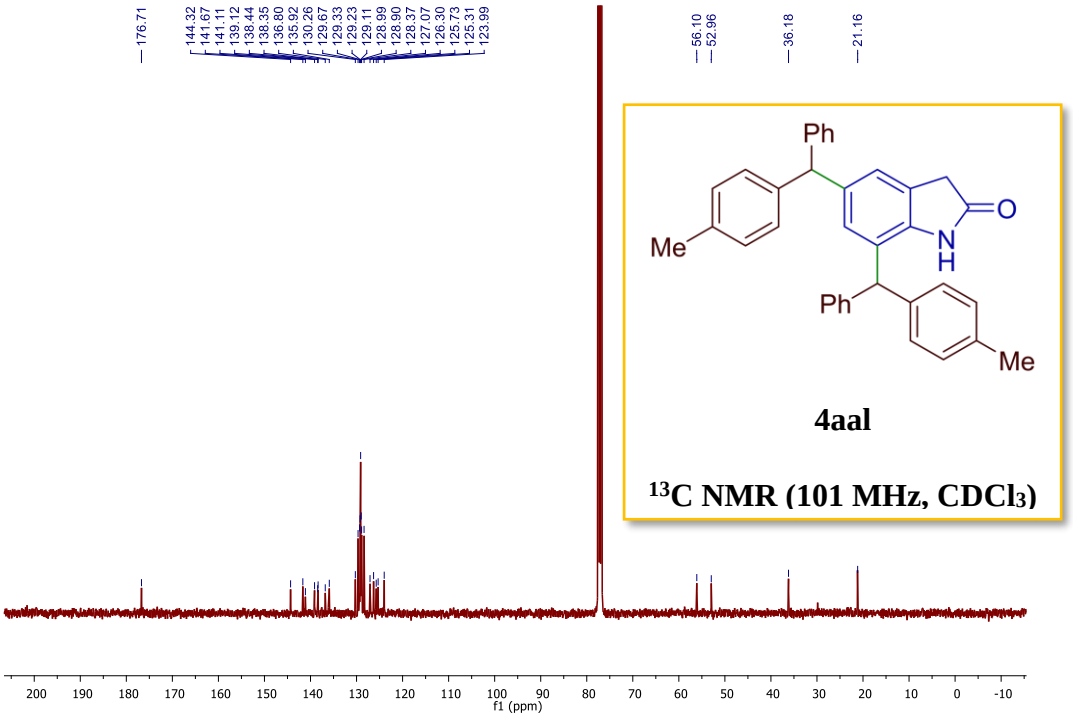


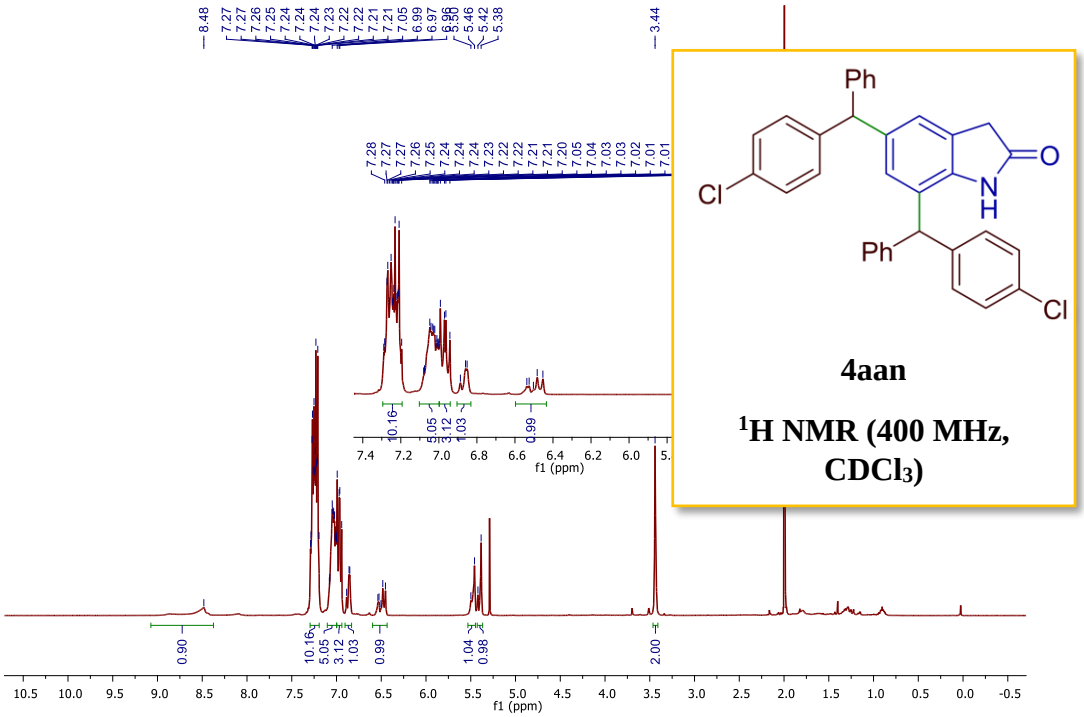
4aaa

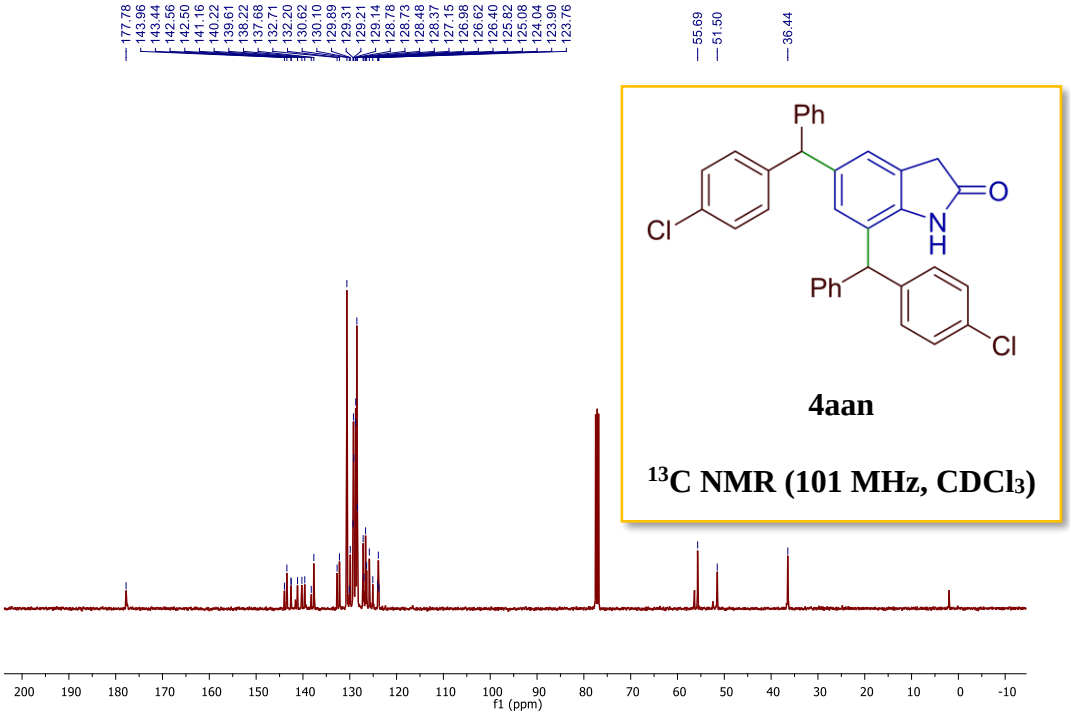
^{1}H NMR (400 MHz, $CDCl_3$)

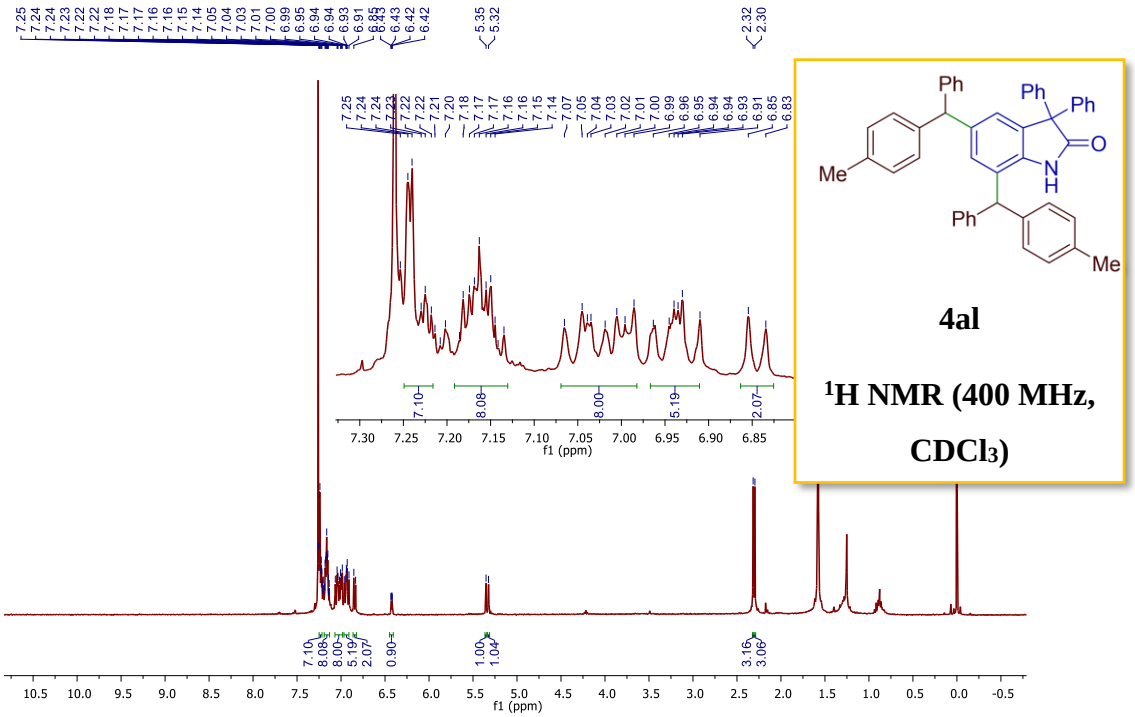

177.32
144.08
141.65
139.41
138.09
130.21
129.34
129.22
128.75
128.37
126.98
126.36
125.72
125.38
123.93
56.45
52.66
36.34
Ph
Ph
O
N
H
Ph
Ph
4aaa
13C NMR (101 MHz, CDCl3)
f1 (ppm)

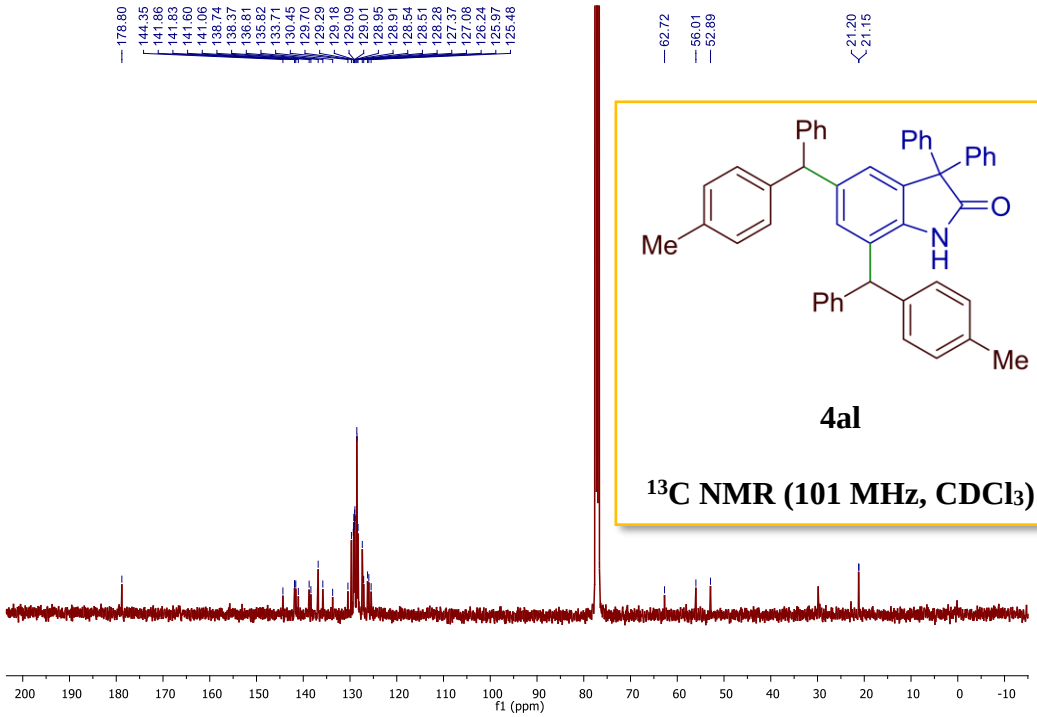

7.29
7.28
7.28
7.27
7.25
7.25
7.24
7.23
7.22
7.22
7.20
7.19
7.19
7.18
7.17
7.17
7.09
7.06
7.05
7.04
7.03
7.01
6.94
6.92
6.90
6.85
6.59
6.59
6.58
5.35
5.33
3.41
2.32
2.31
1.20
5.16
8.05
5.09
1.08
0.98
1.00
1.07
2.10
2.87
3.15
f1 (ppm)
Ph
Me
O
N
H
Ph
Me
4aal
1H NMR (400 MHz, CDCl3)

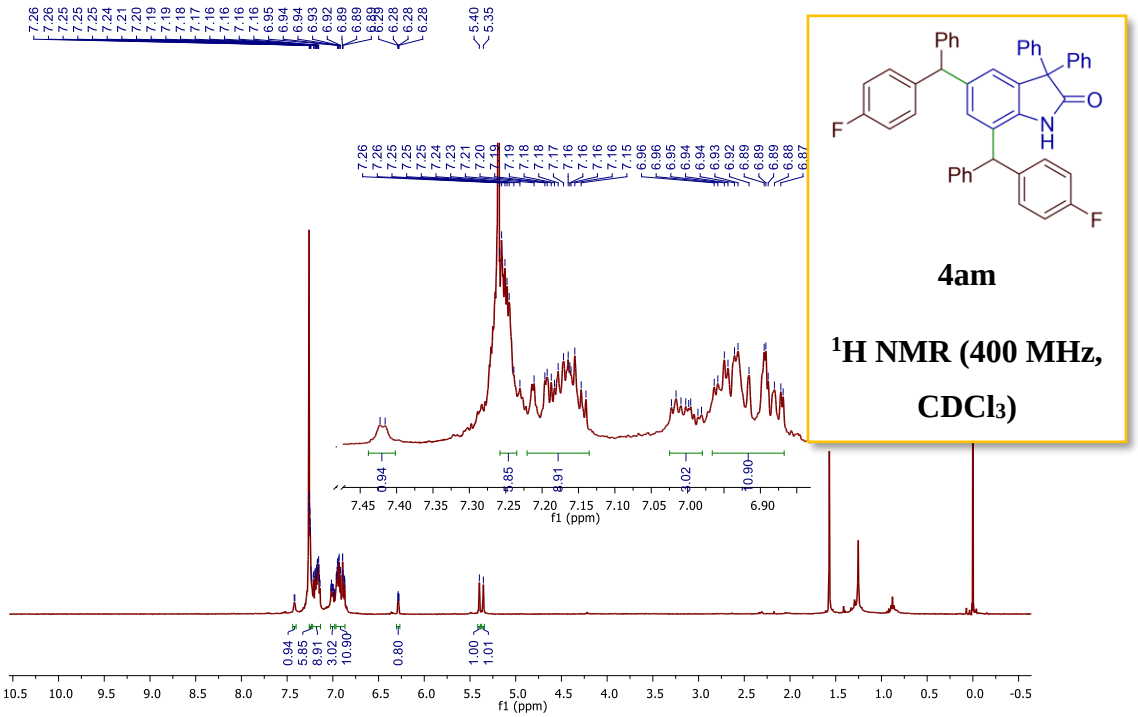

Ph
Me
O
N
H
Ph
Me
4aal
13C NMR (101 MHz, CDCl3)

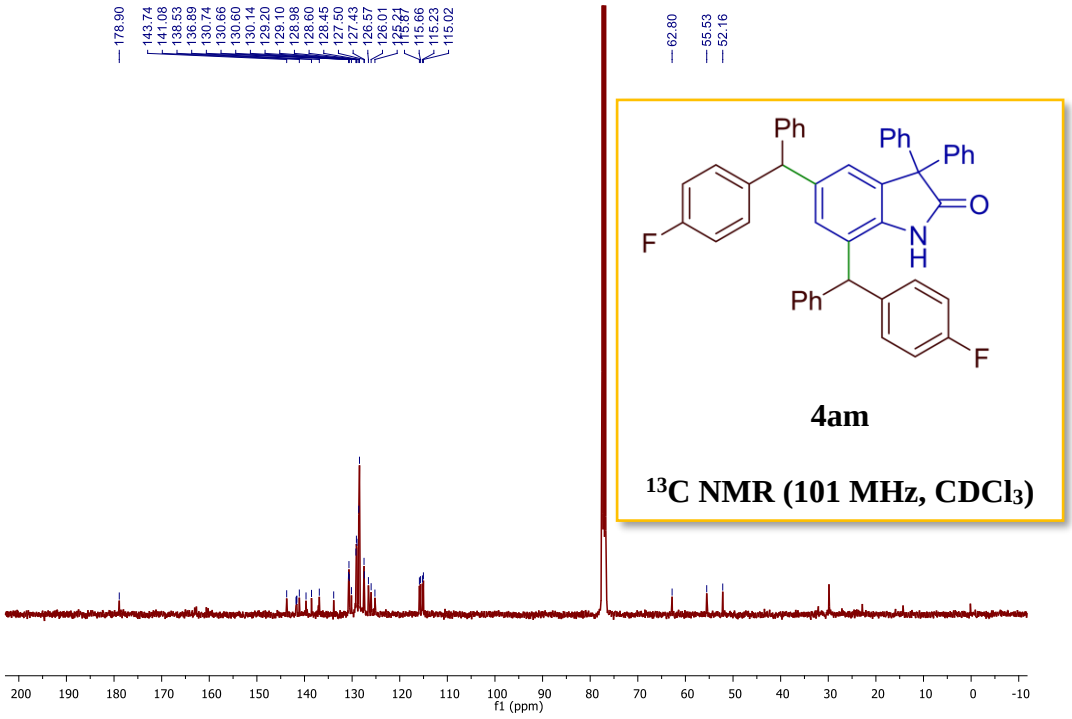

Ph
Cl
O
N
H
Ph
Cl
4aan
1H NMR (400 MHz, CDCl3)

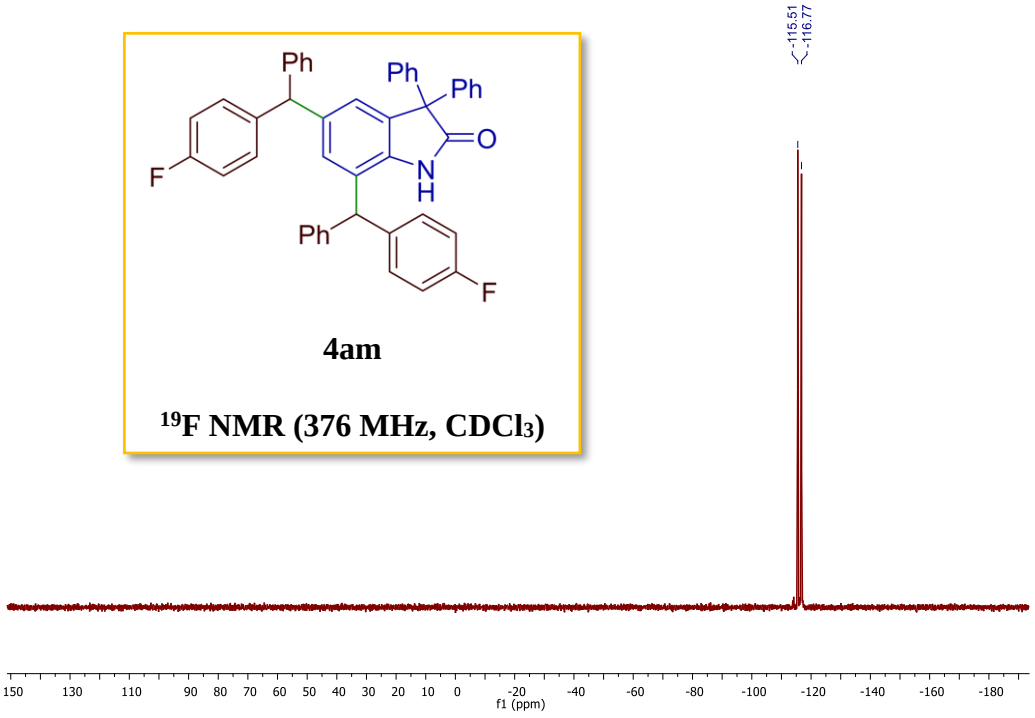

Ph
Cl
O
N
H
Ph
Cl
4aan
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

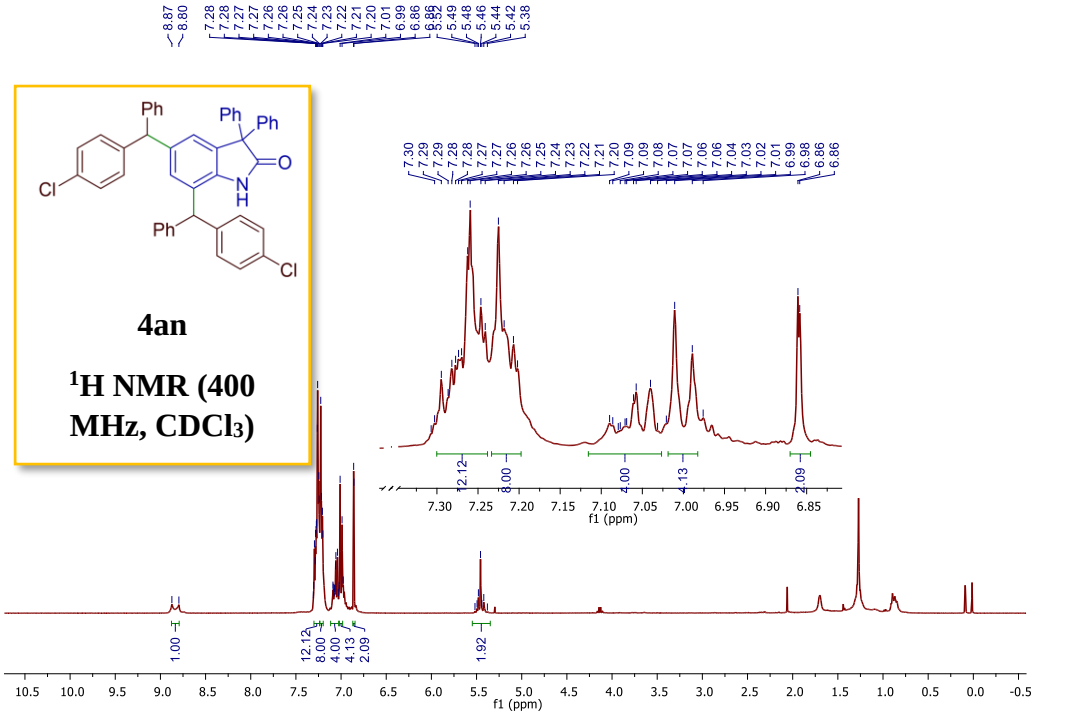

Ph
Ph
Ph
Me
O
N
H
Ph
Me
4al
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

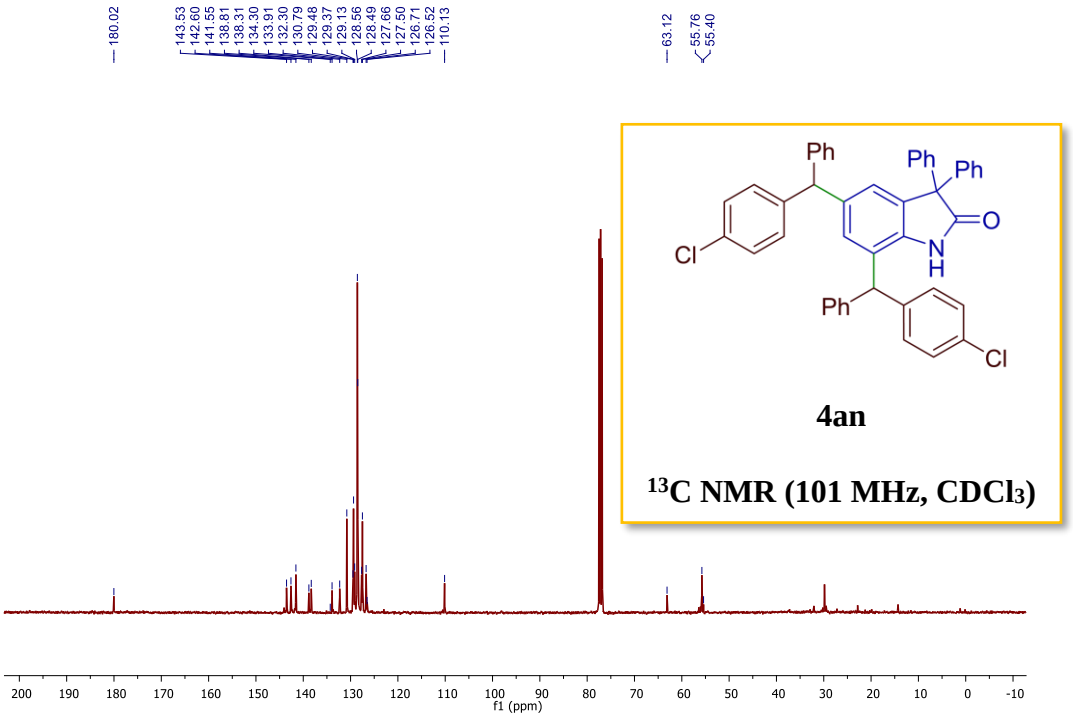

Ph
Ph
Ph
O
N
H
Me
Ph
Me
4al
13C NMR (101 MHz, CDCl3)

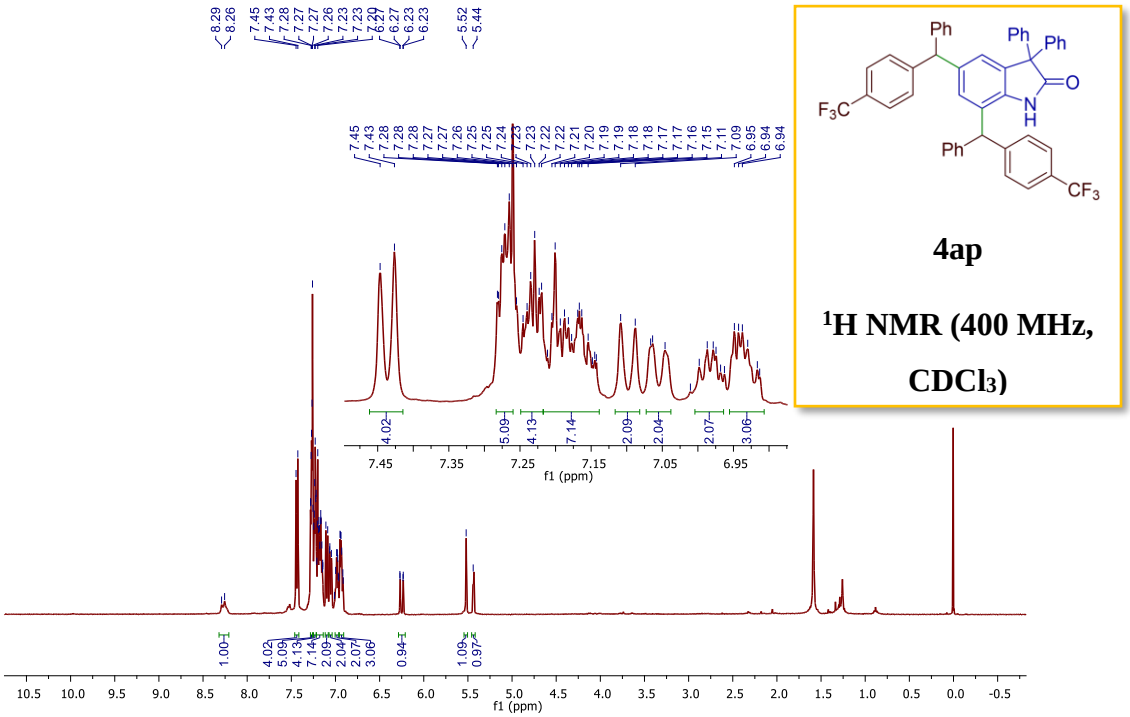

Ph
Ph
Ph
O
N
H
F
Ph
F
4am
1H NMR (400 MHz, CDCl3)

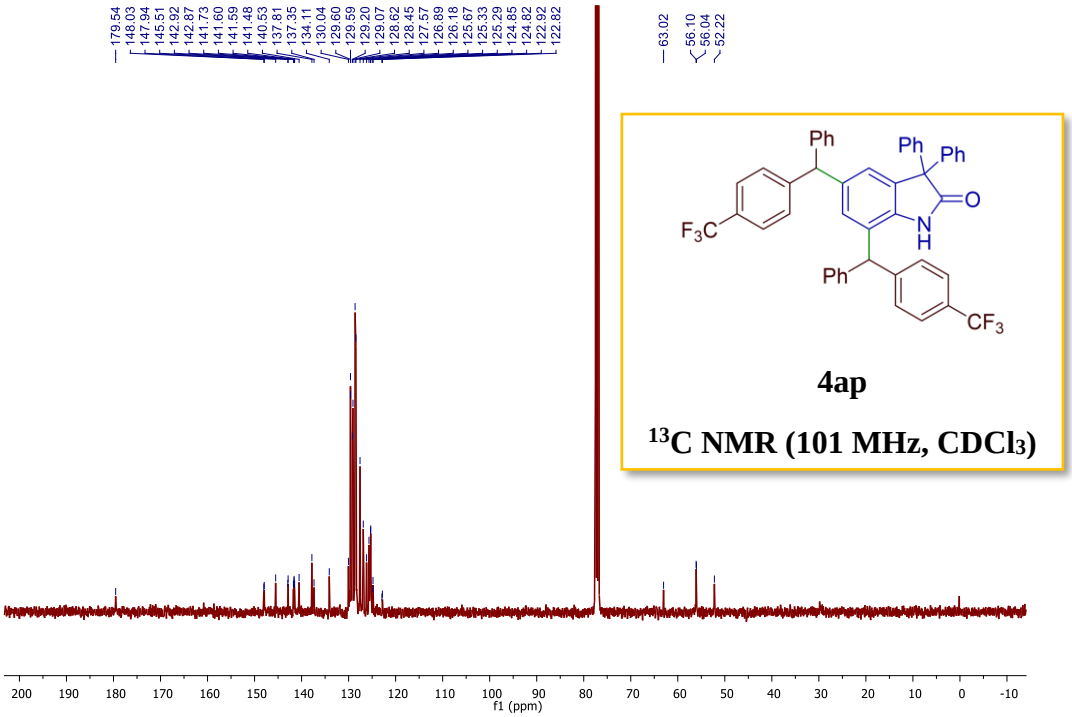

178.90
143.74
141.08
138.53
136.89
130.74
130.66
130.60
130.14
129.20
129.10
128.98
128.60
128.45
127.50
127.43
126.57
126.01
115.66
115.23
115.02
62.80
55.53
52.16
Ph
Ph
Ph
O
N
H
F
Ph
F
4am
13C NMR (101 MHz, CDCl3)
f1 (ppm)

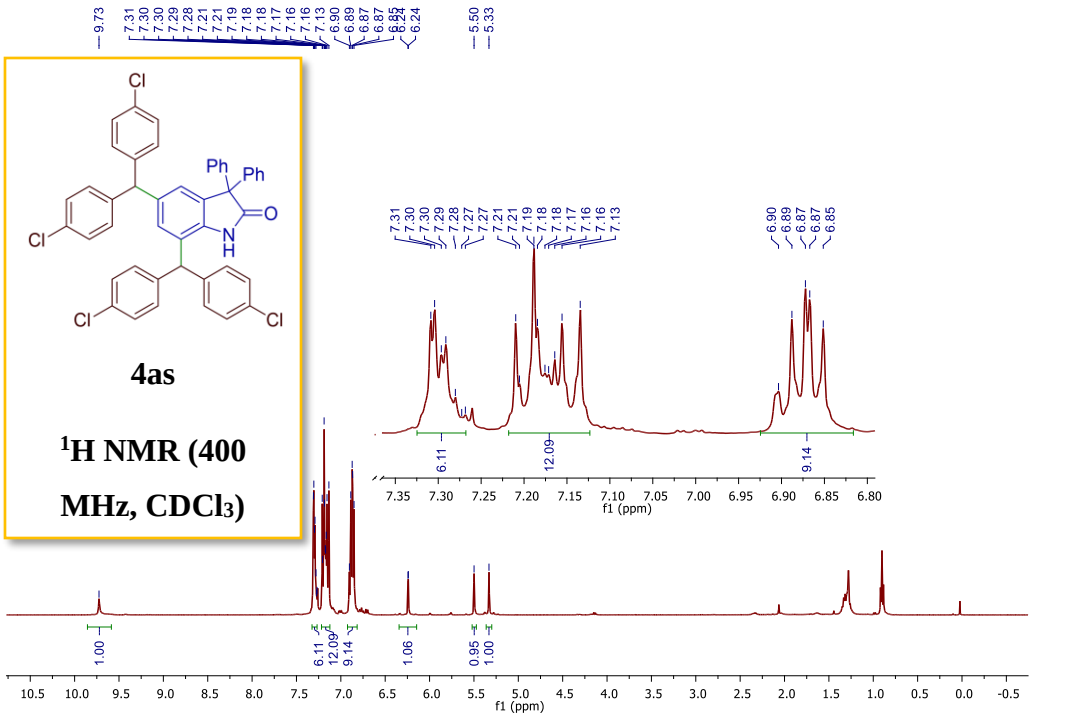

-115.51
-116.77
Ph
Ph
Ph
O
N
H
F
Ph
F
4am
19F NMR (376 MHz, CDCl3)
f1 (ppm)

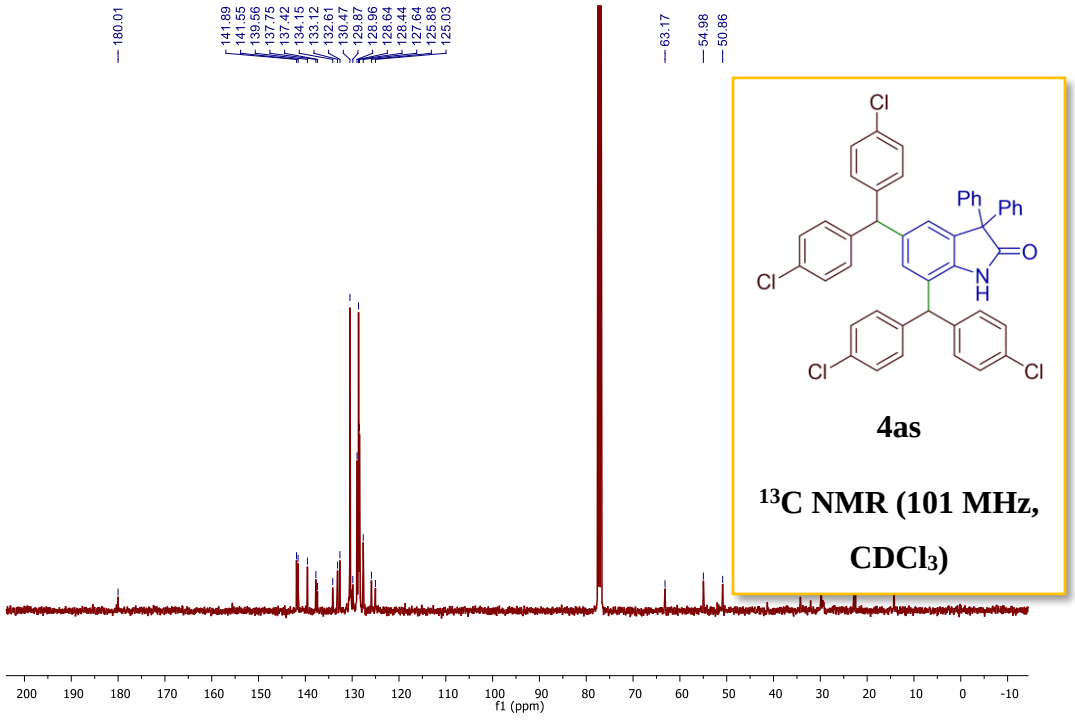

4an
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

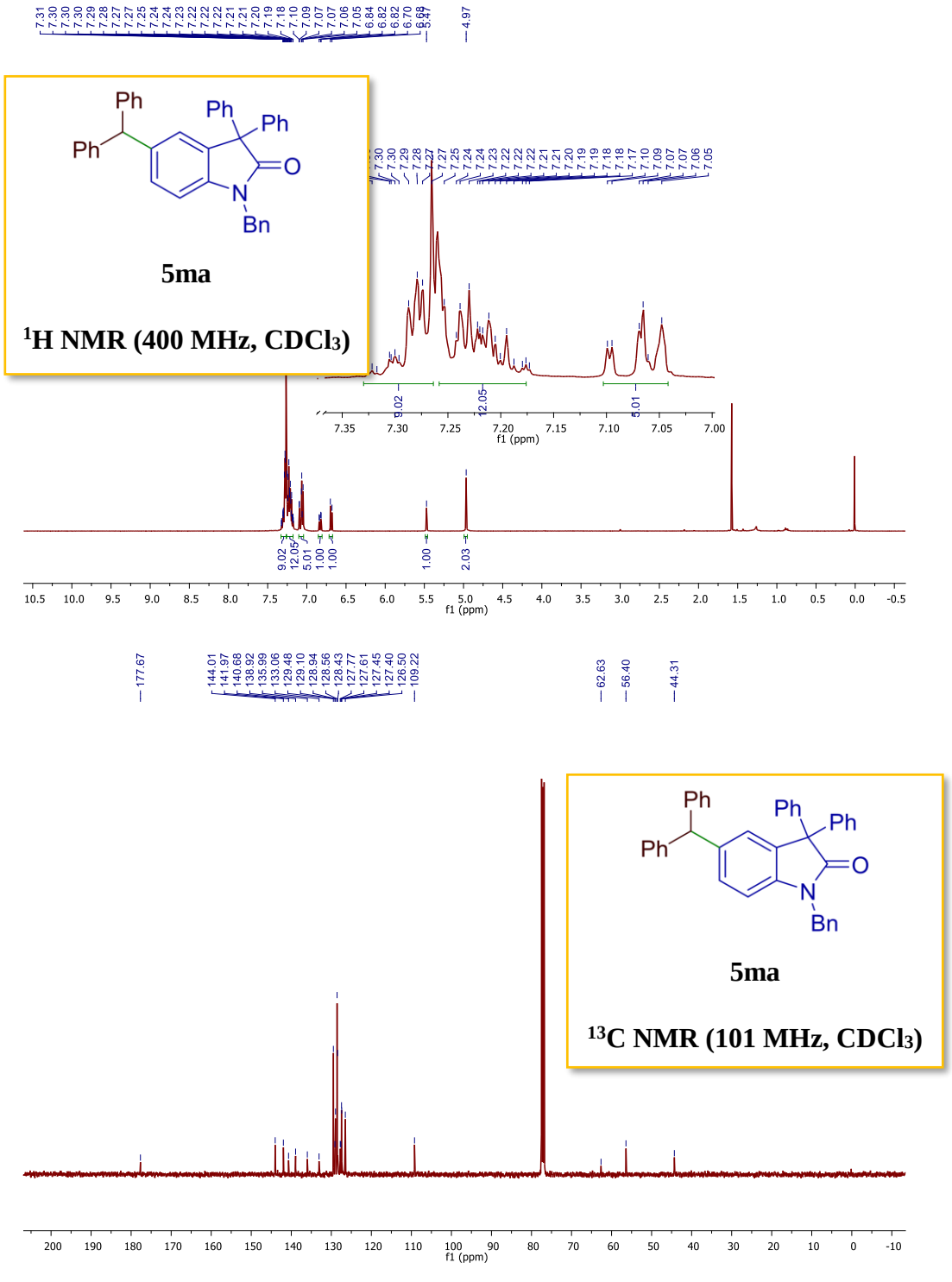

4an
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

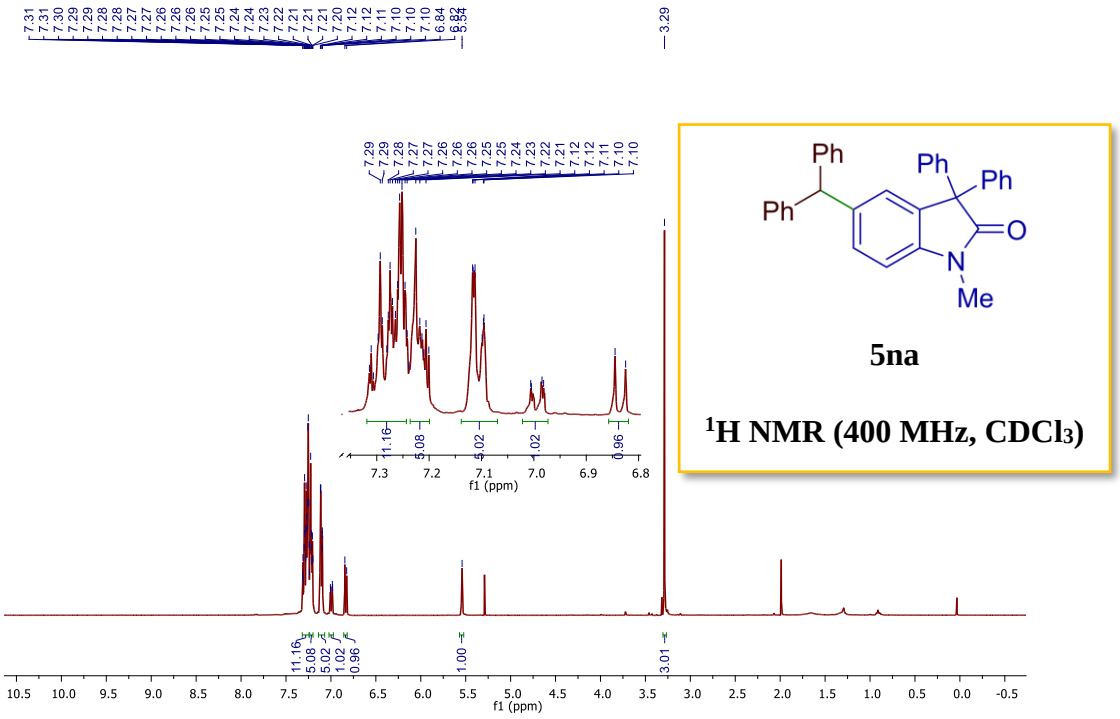

4ap
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

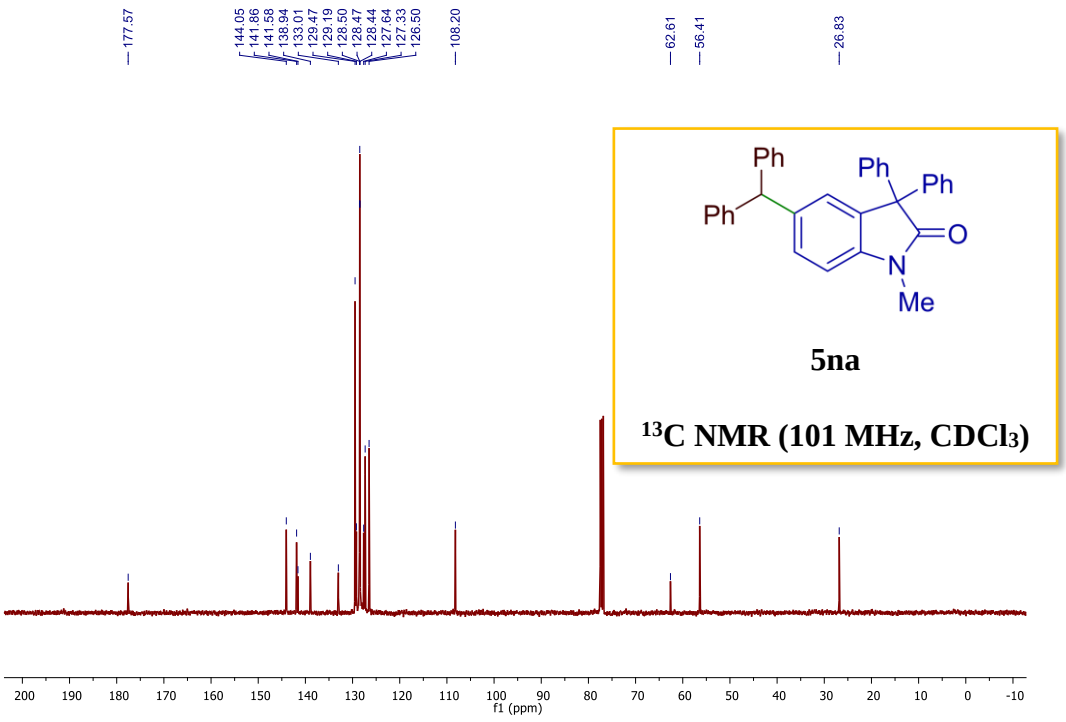

4ap
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

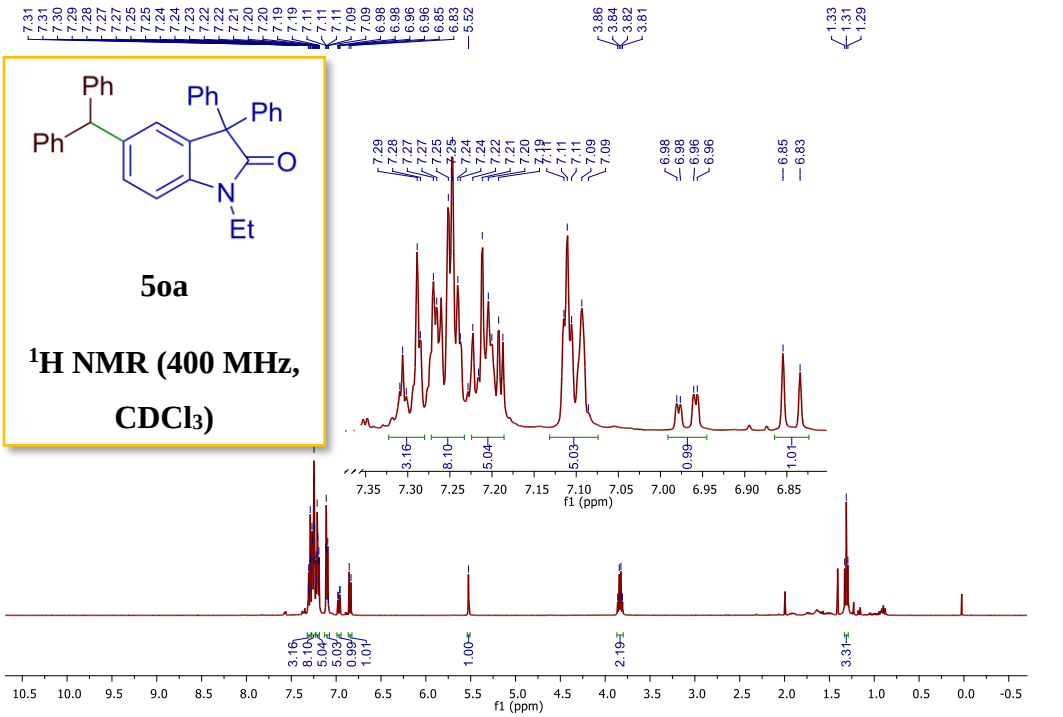

4as
^{1}H NMR (400 MHz, CDCl$_3$)

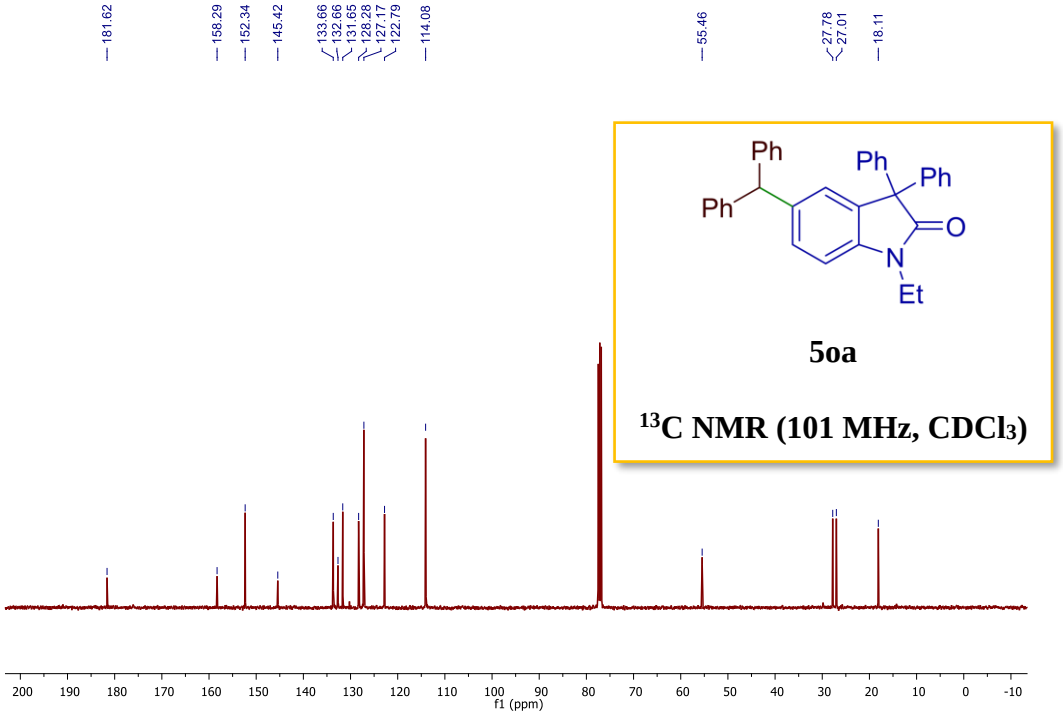

4as
^{13}C NMR (101 MHz, CDCl$_3$)

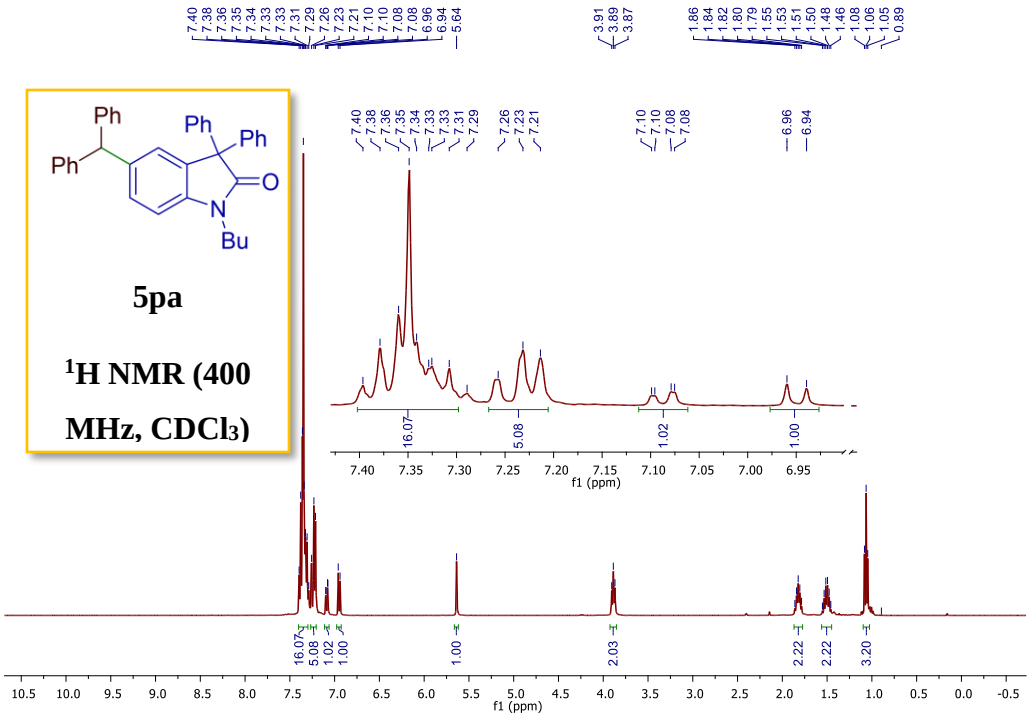

Ph
Ph
Ph
Ph
O
N
Bn
5ma
1H NMR (400 MHz, CDCl3)
f1 (ppm)
5ma
13C NMR (101 MHz, CDCl3)
f1 (ppm)

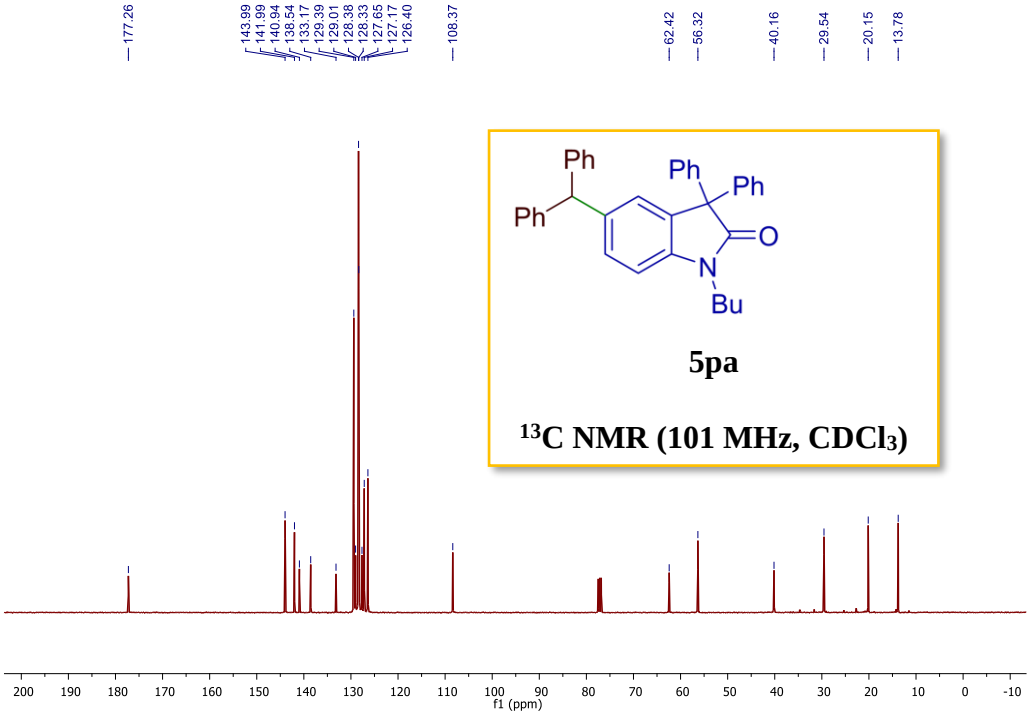

Ph
Ph
Ph
Ph
O
N
Me
5na
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

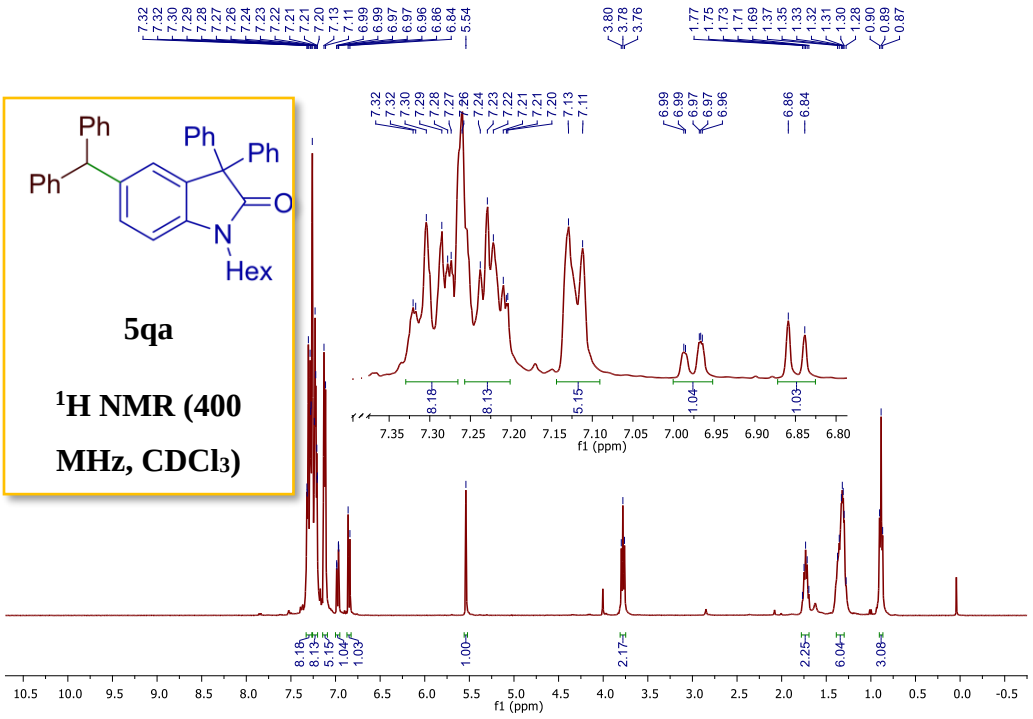

Ph
Ph
Ph
Ph
O
N
Me
5na
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

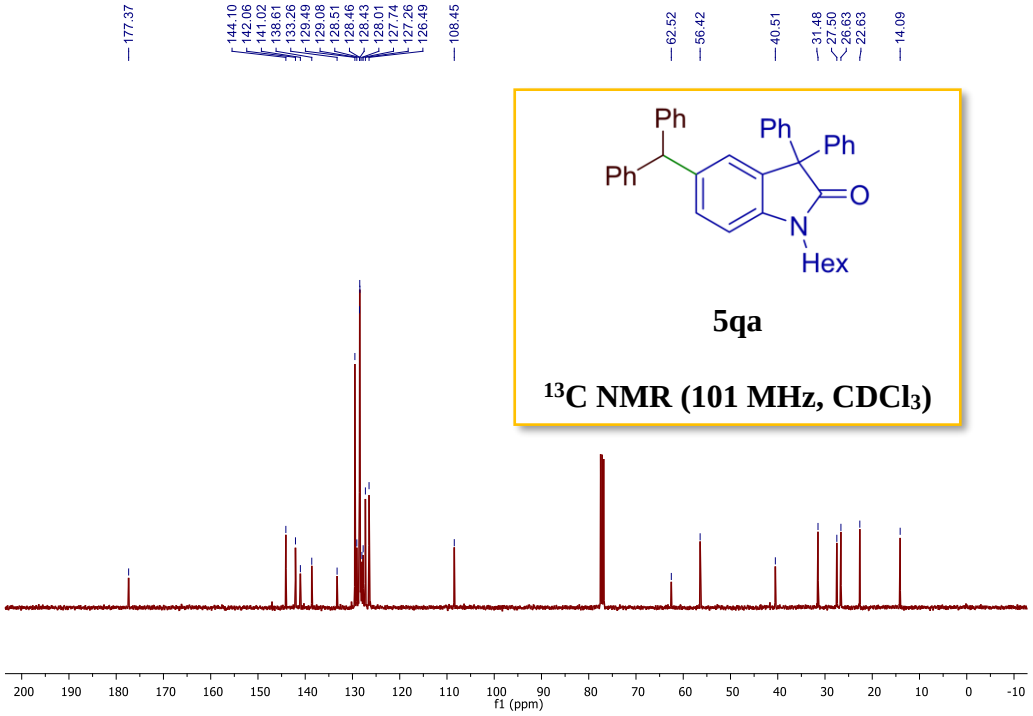

Ph
Ph
Ph
Ph
O
N
Et
5oa
1H NMR (400 MHz, CDCl3)

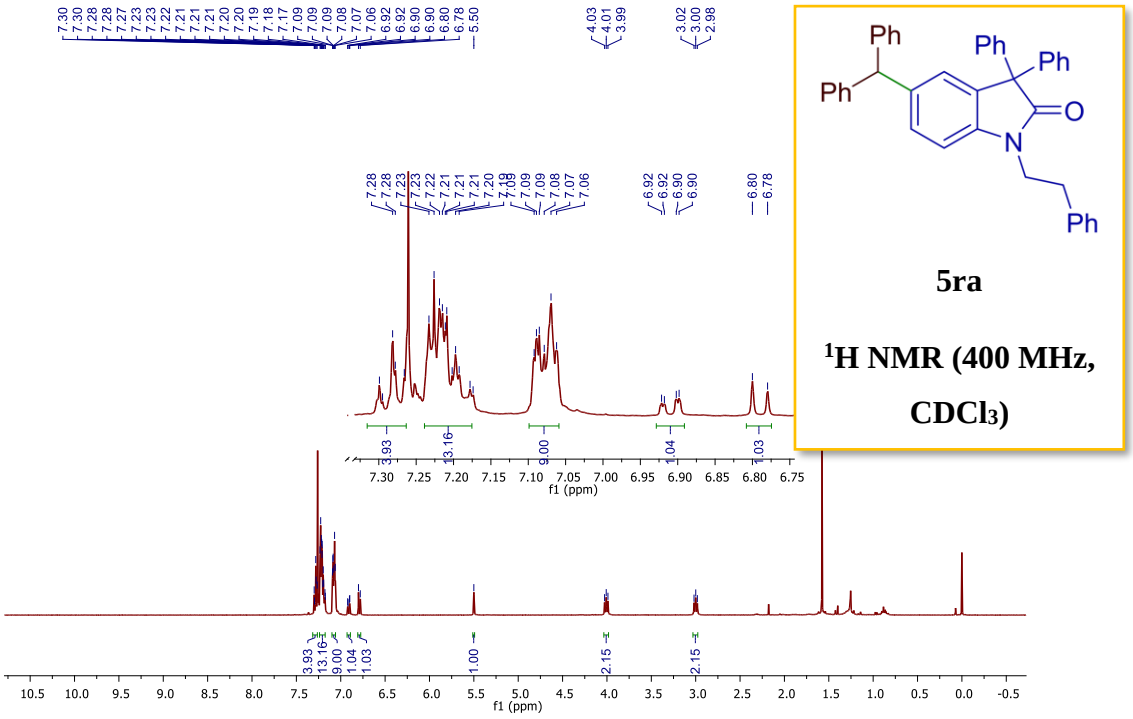

Ph
Ph
Ph
Ph
O
N
Et
5oa
13C NMR (101 MHz, CDCl3)

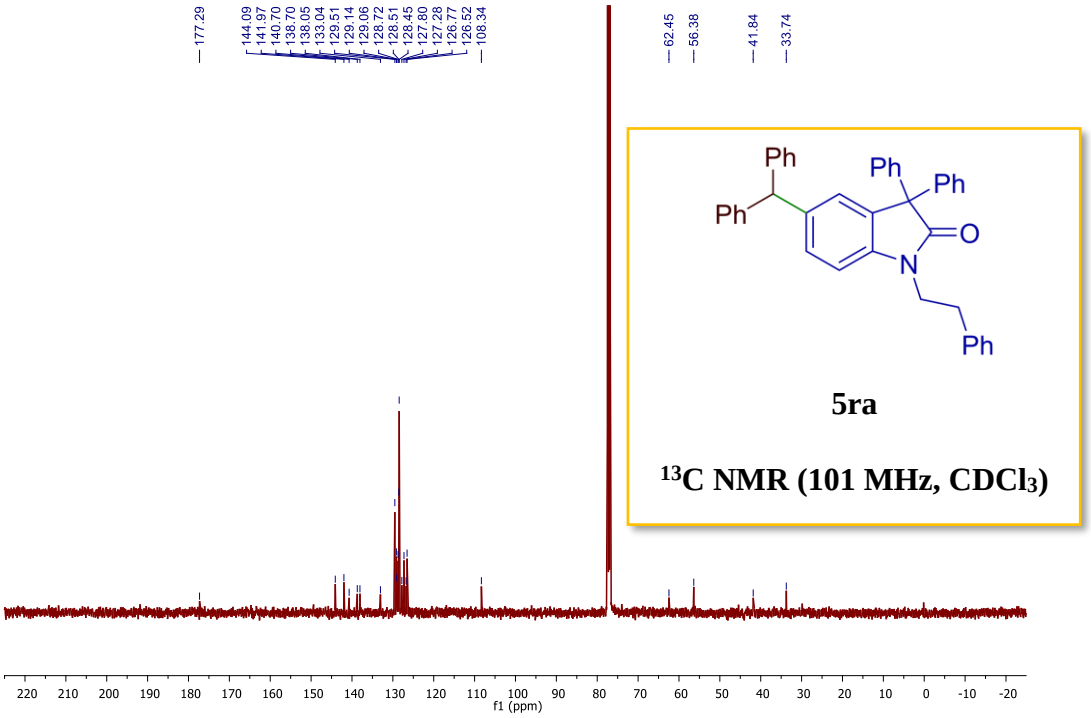

Ph
Ph
Ph
Ph
O
N
Bu
5pa
1H NMR (400 MHz, CDCl3)
f1 (ppm)

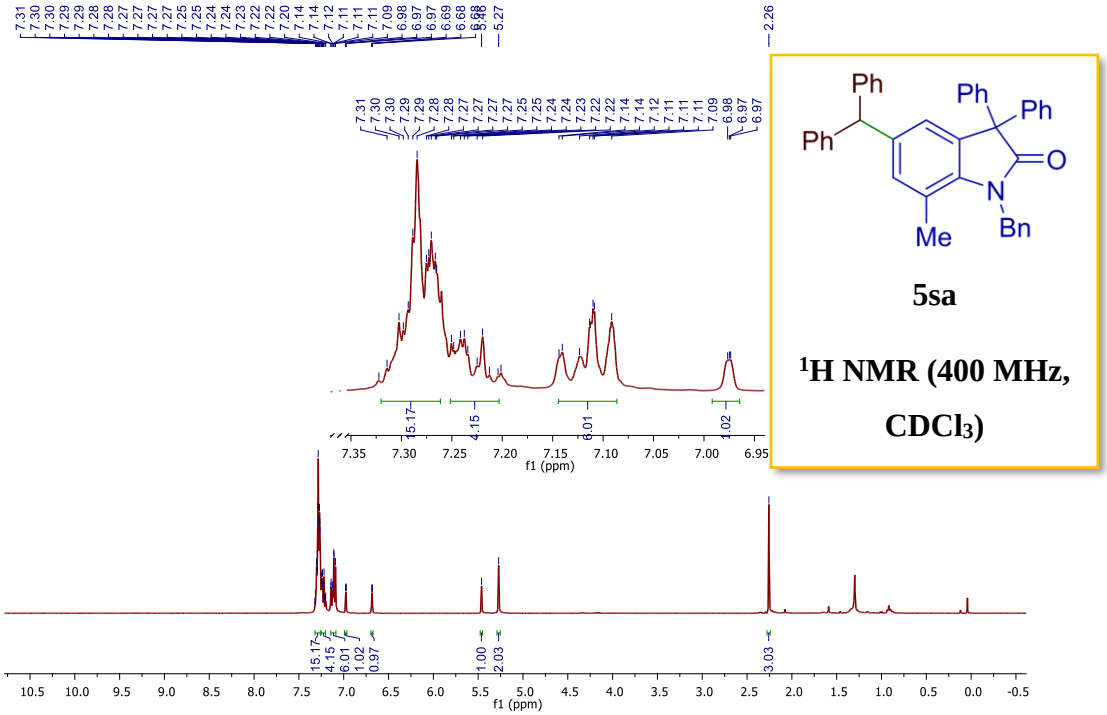

Ph
Ph
Ph
Ph
O
N
Bu
5pa
13C NMR (101 MHz, CDCl3)
f1 (ppm)

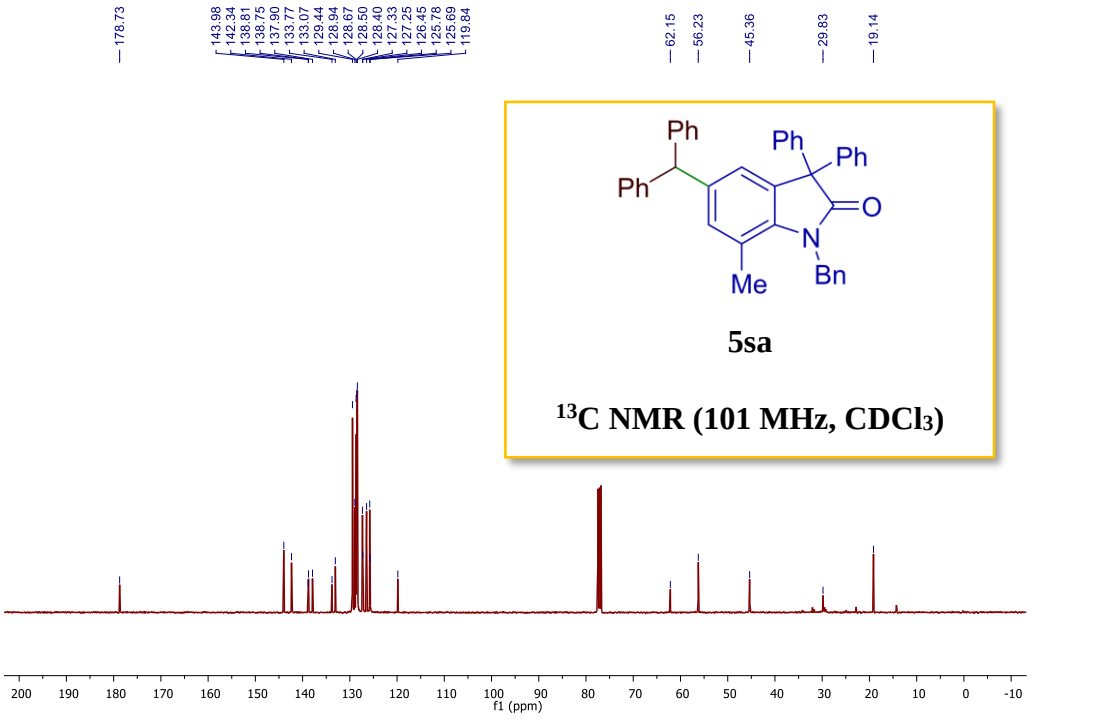

Ph
Ph
Ph
Ph
O
N
Hex
5qa
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

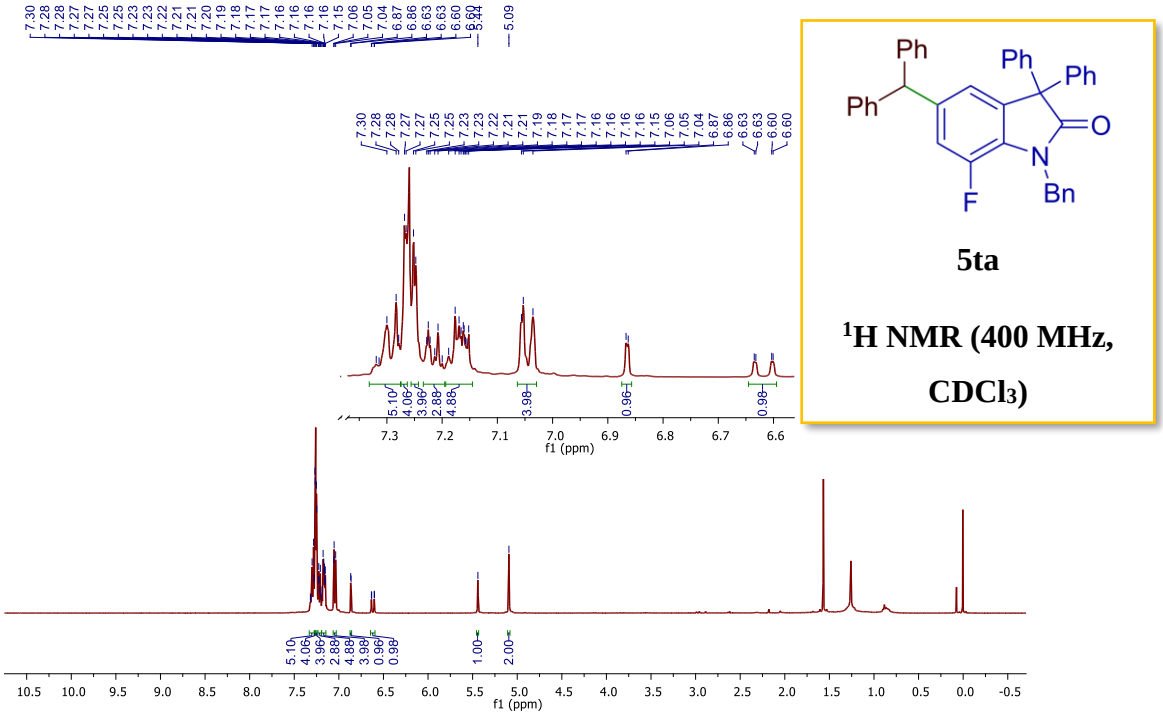

Ph
Ph
Ph
Ph
O
N
Hex
5qa
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)


Ph
Ph
Ph
Ph
O
N
Ph
5ra
1H NMR (400 MHz, CDCl3)
f1 (ppm)


Ph
Ph
Ph
Ph
O
N
Ph
5ra
13C NMR (101 MHz, CDCl3)
f1 (ppm)

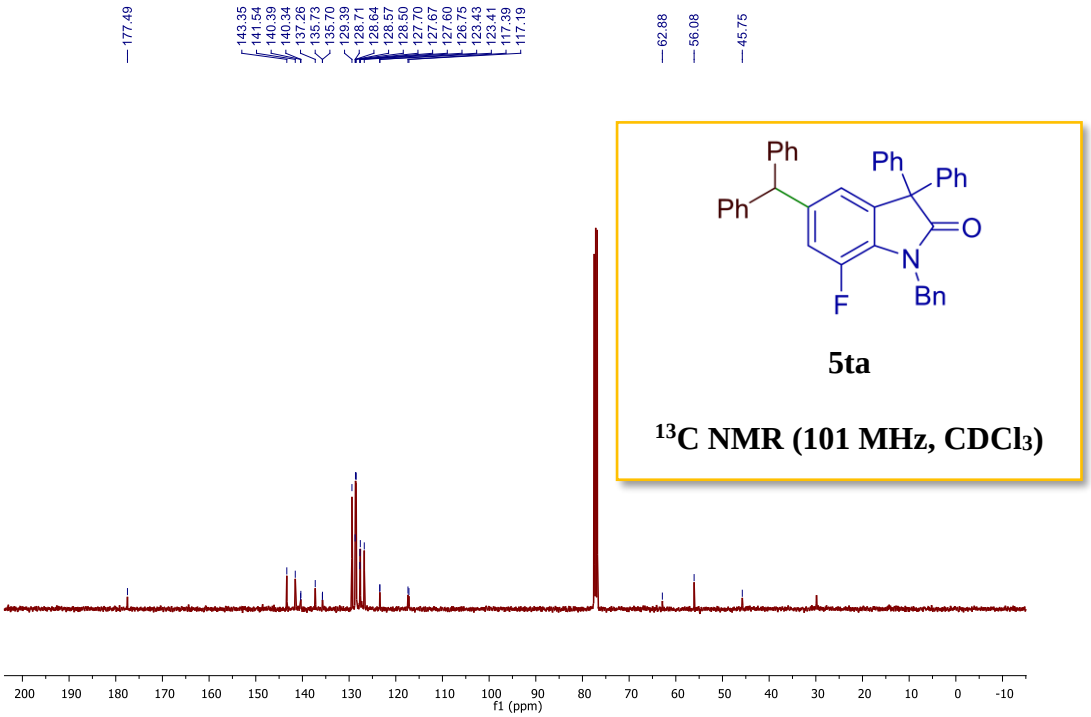

Ph
Ph
Ph
Ph
O
N
Me
Bn
5sa
1H NMR (400 MHz, CDCl3)


Ph
Ph
Ph
Ph
O
N
Me
Bn
5sa
13C NMR (101 MHz, CDCl3)



5ta

^{1}H NMR (400 MHz, $CDCl_3$)

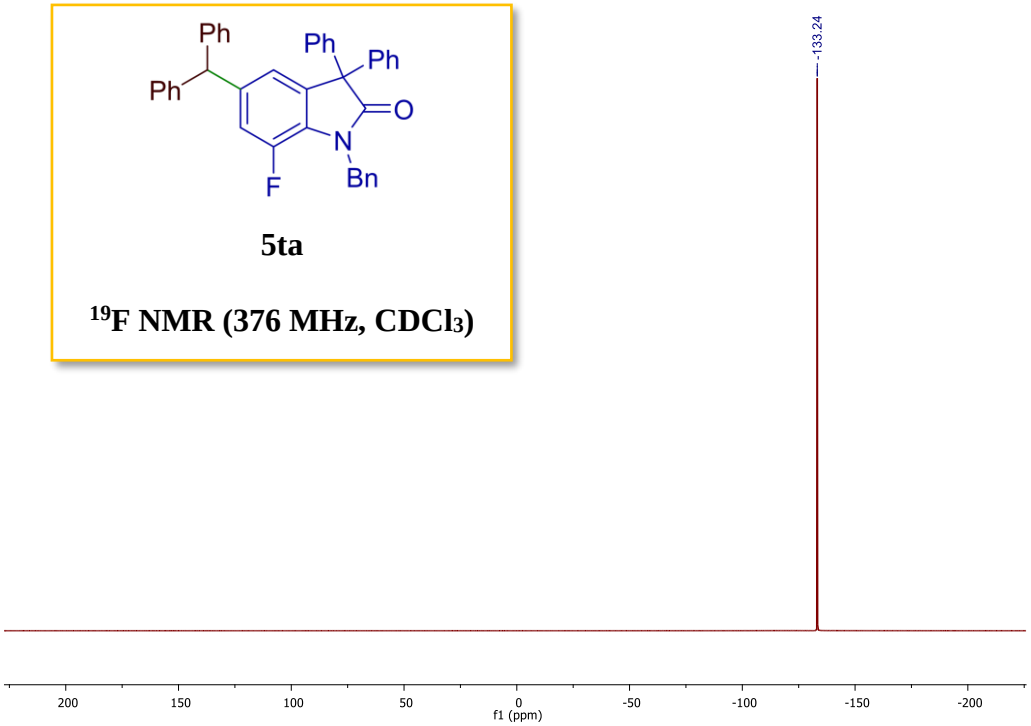


5ta

^{13}C NMR (101 MHz, $CDCl_3$)

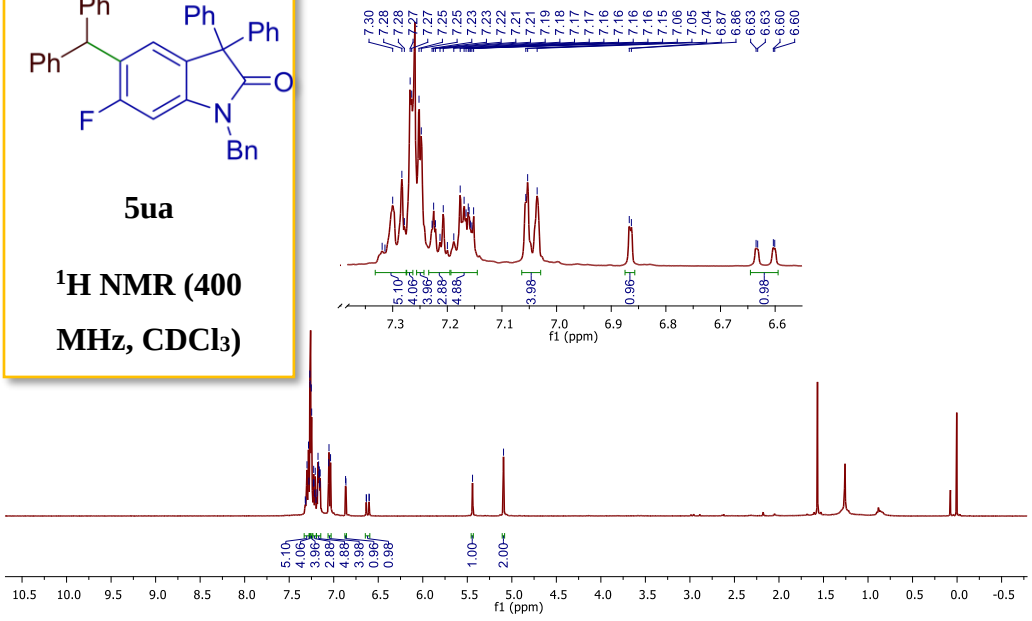
5ta

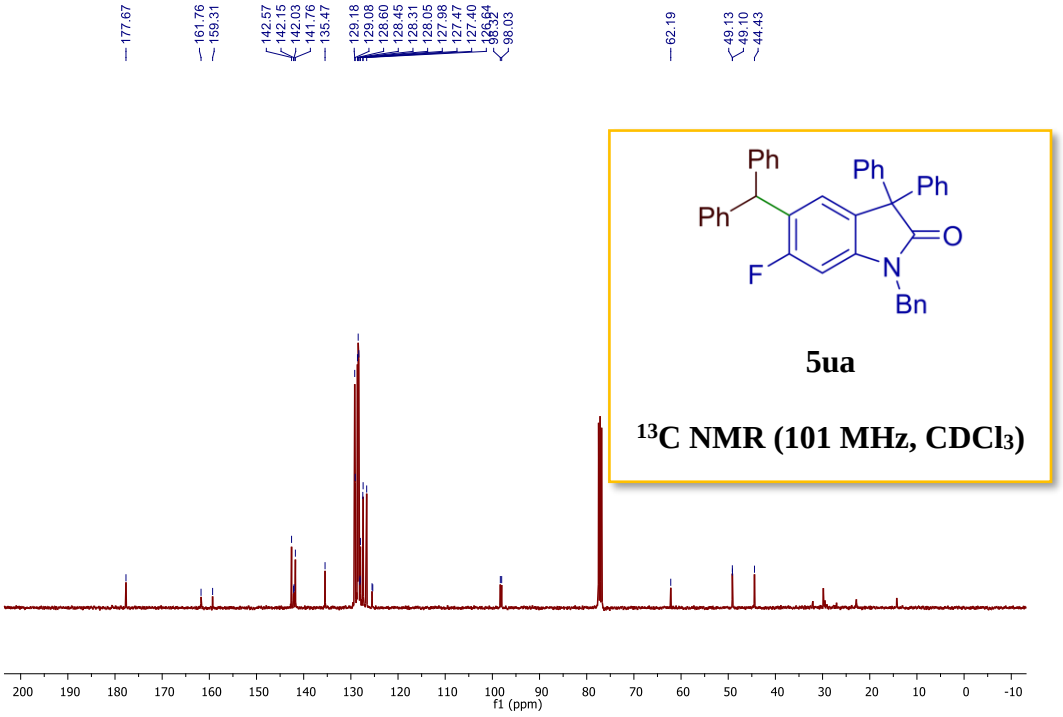
^{19}F NMR (376 MHz, $CDCl_3$)

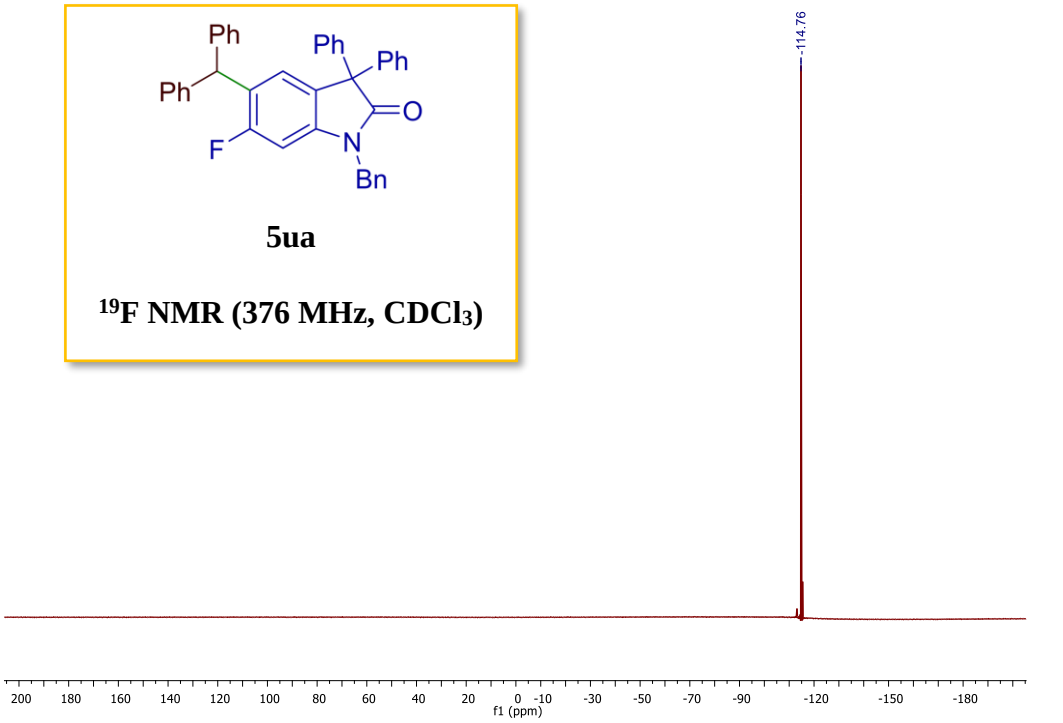


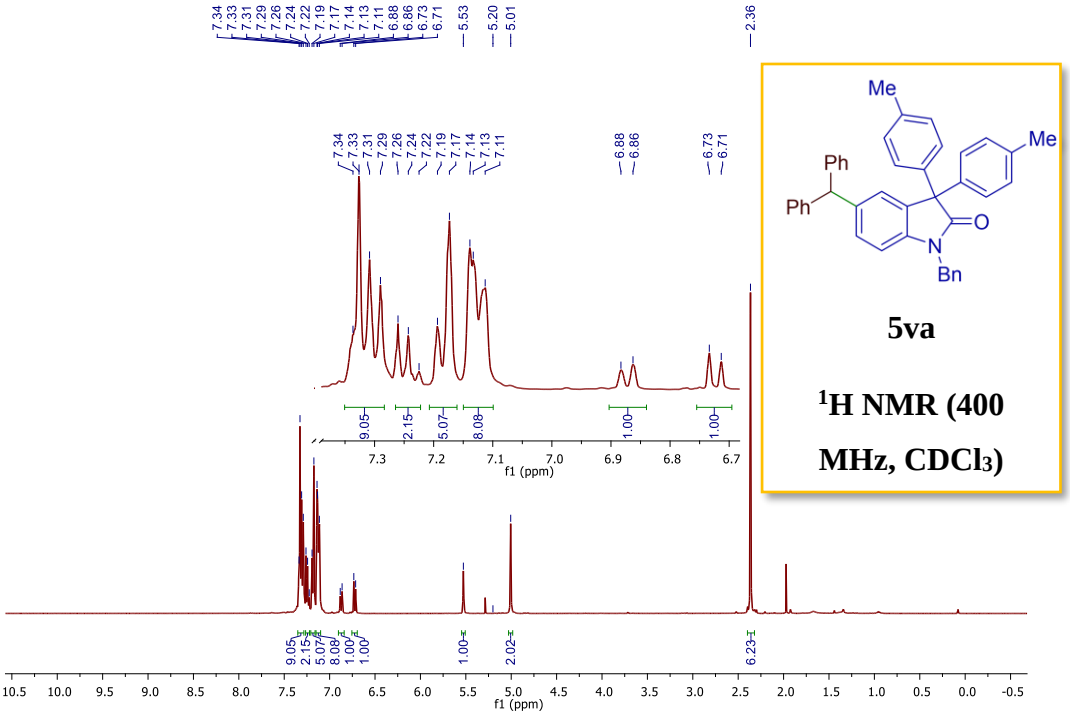
5ua

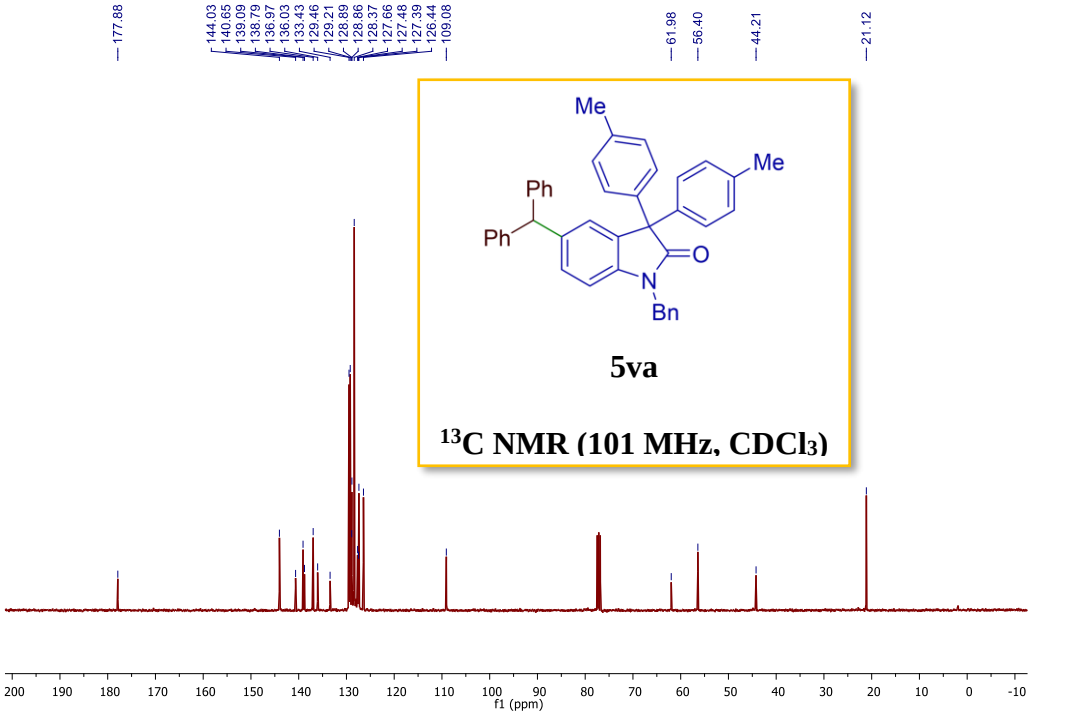
^{1}H NMR (400 MHz, $CDCl_3$)

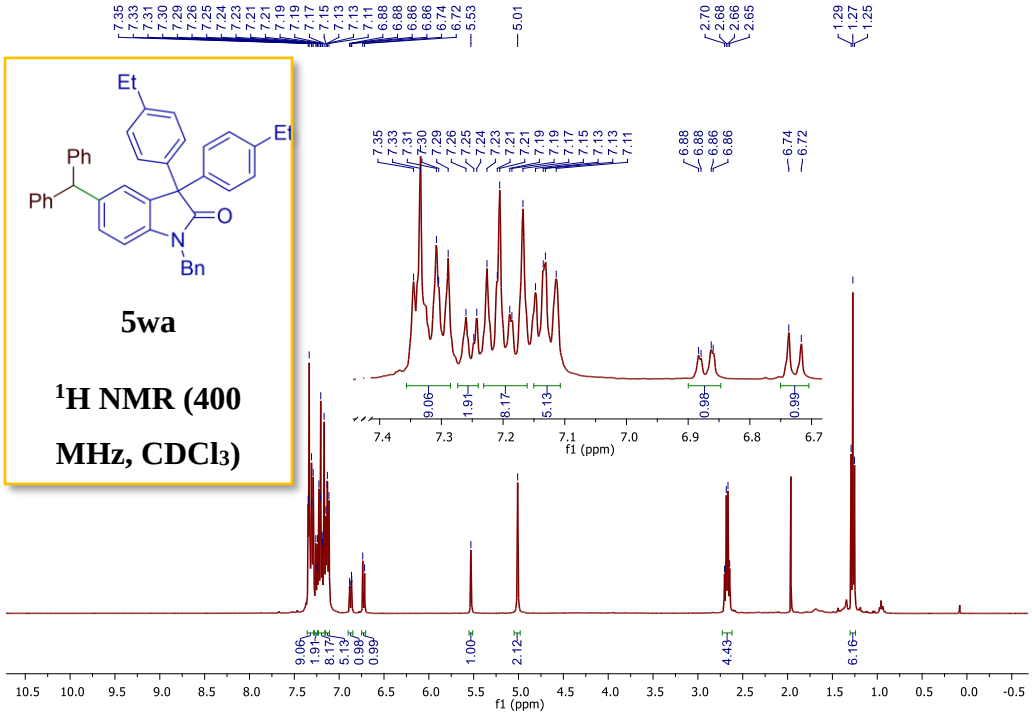


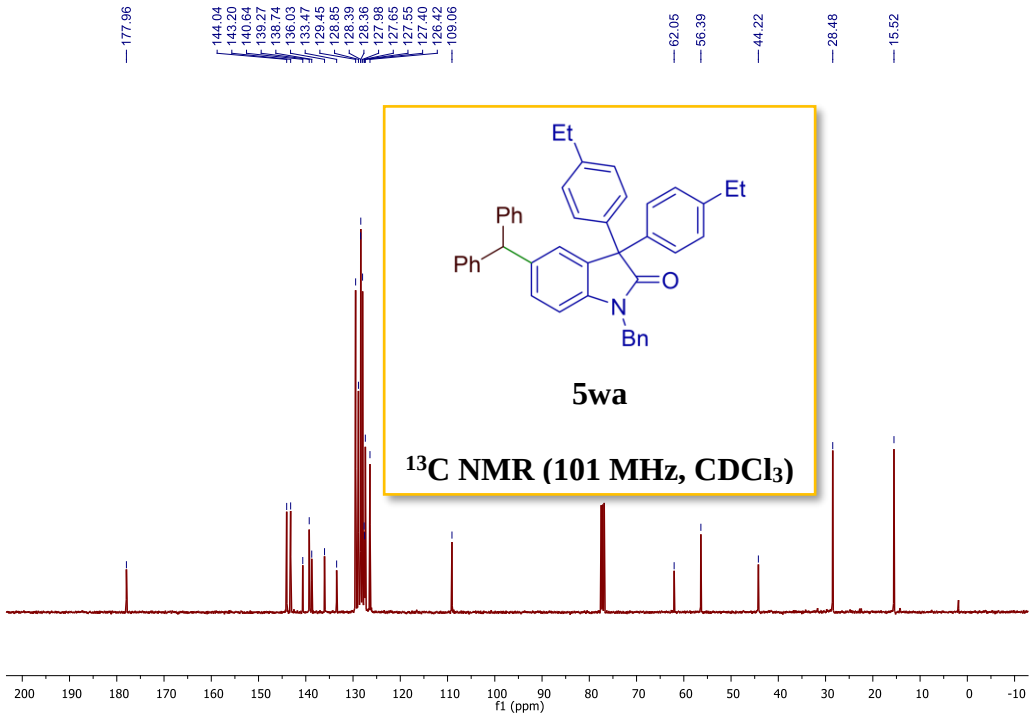

177.67
161.76
159.31
142.57
142.15
142.03
141.76
135.47
129.18
129.08
128.60
128.45
128.31
128.05
127.98
127.47
127.40
126.64
98.32
98.03
62.19
49.13
49.10
44.43
Ph
Ph
Ph
Ph
O
F
N
Bn
5ua
13C NMR (101 MHz, CDCl3)
f1 (ppm)

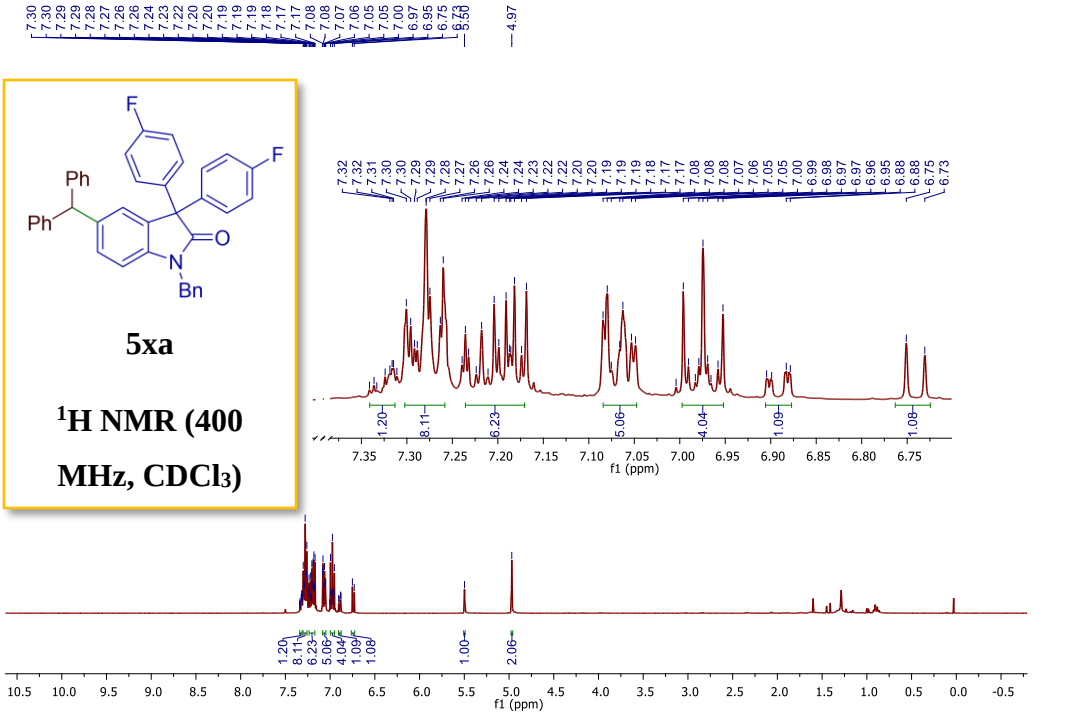

-114.76
Ph
Ph
Ph
Ph
O
F
N
Bn
5ua
19F NMR (376 MHz, CDCl3)
f1 (ppm)

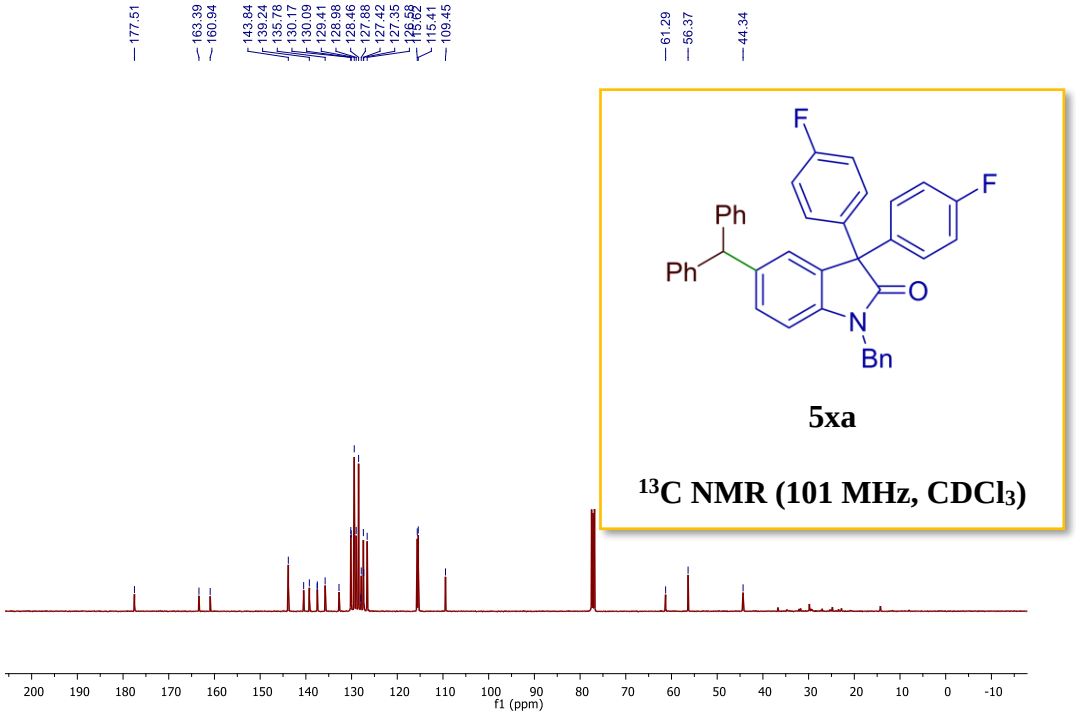

Me
Me
Ph
Ph
O
N
Bn
5va
^{1}H NMR (400 MHz, CDCl$_3$)

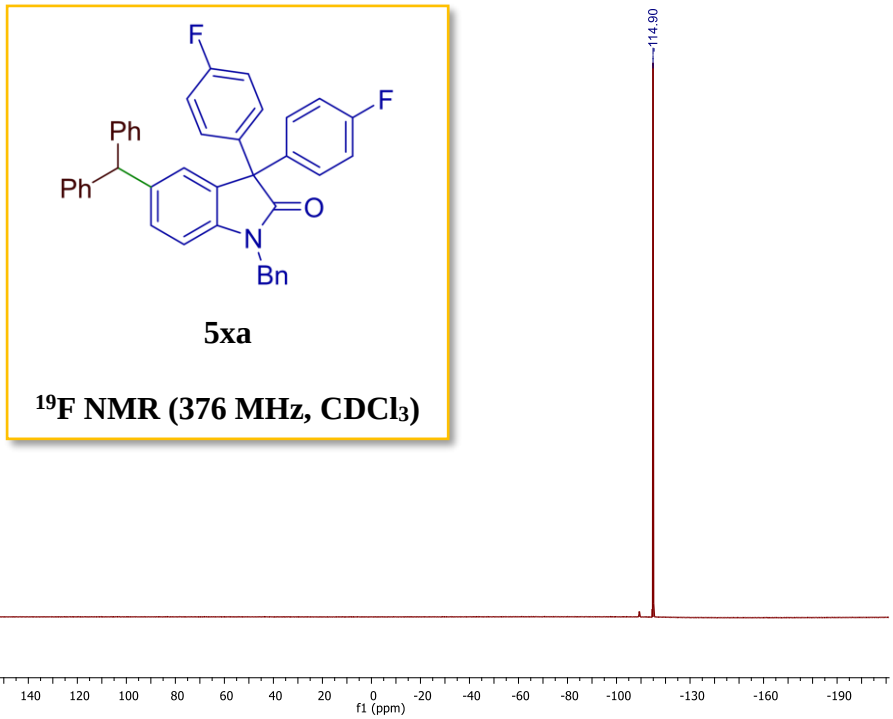

Me
Me
Ph
Ph
O
N
Bn
5va
^{13}C NMR (101 MHz, CDCl$_3$)

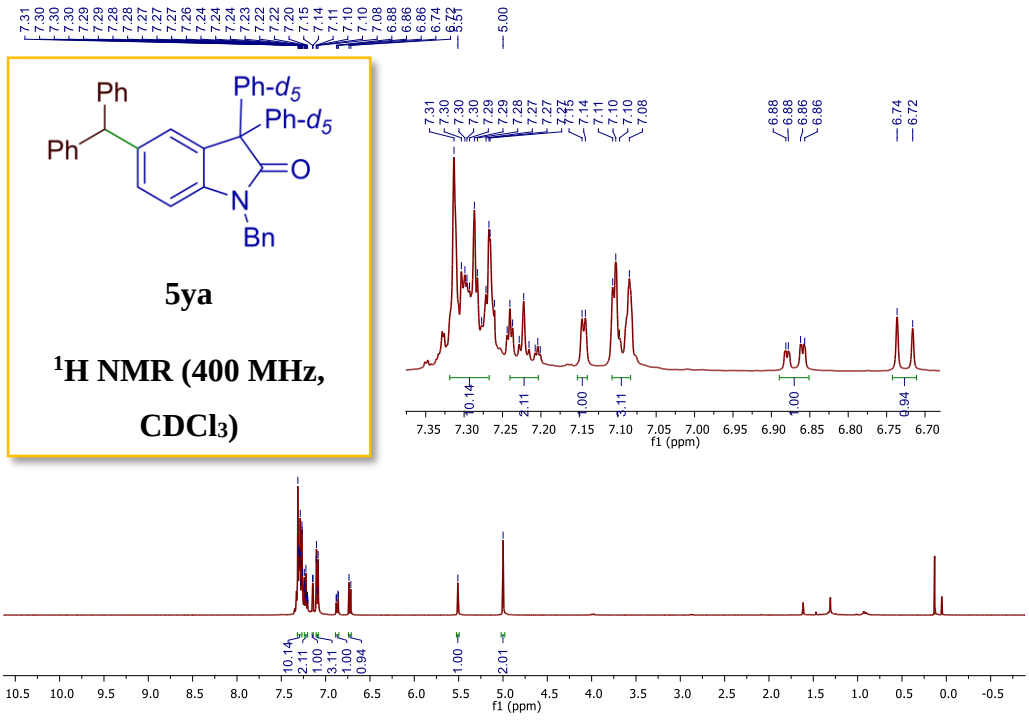

Et
Et
Ph
Ph
O
N
Bn
5wa
^{1}H NMR (400 MHz, CDCl$_3$)

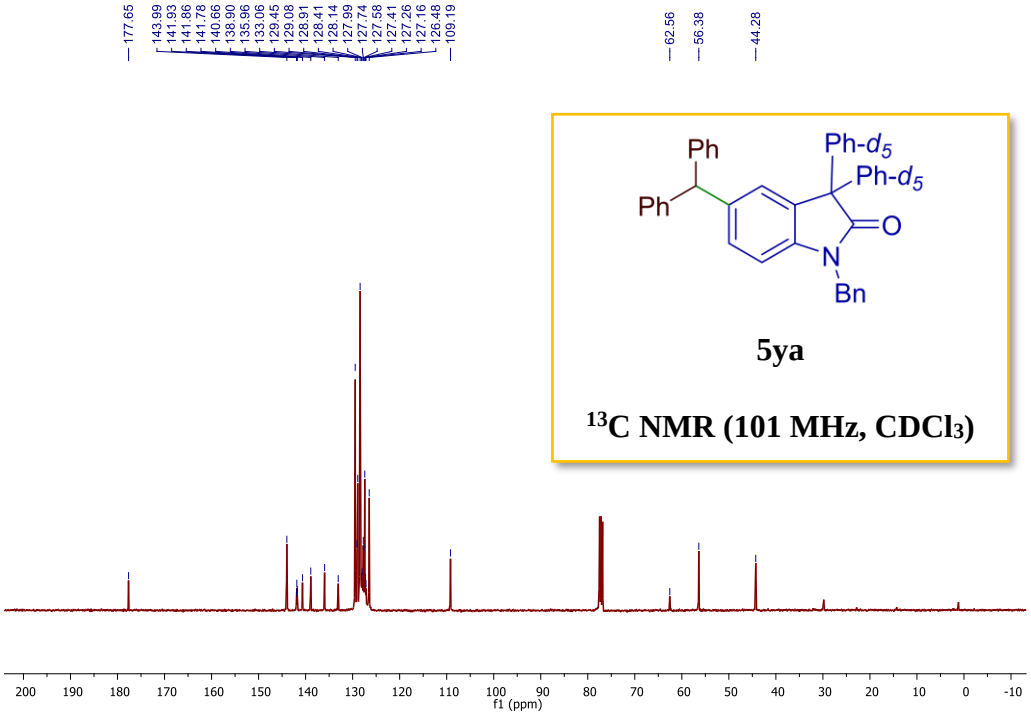

Et
Et
Ph
Ph
O
N
Bn
5wa
^{13}C NMR (101 MHz, CDCl$_3$)

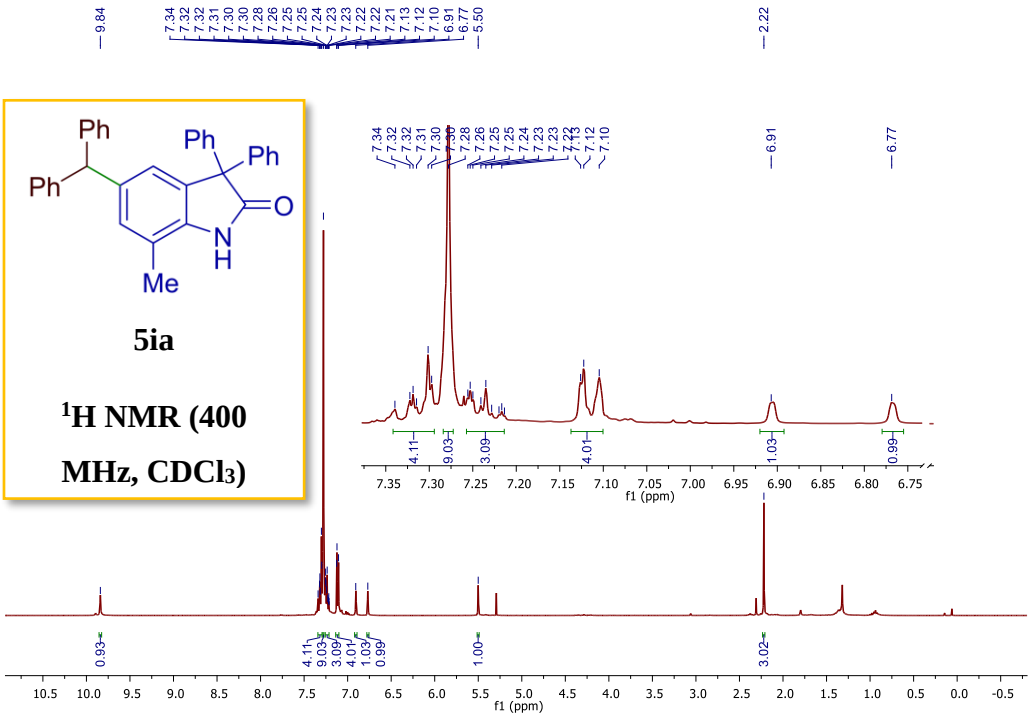

5xa
1H NMR (400 MHz, CDCl3)

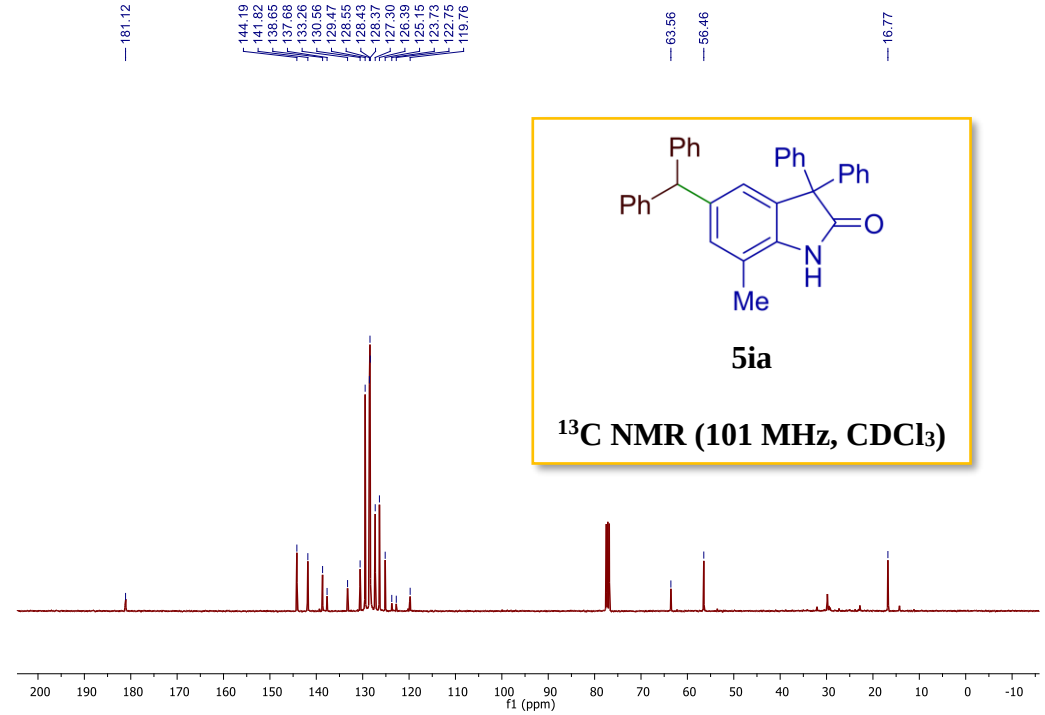

5xa
13C NMR (101 MHz, CDCl3)

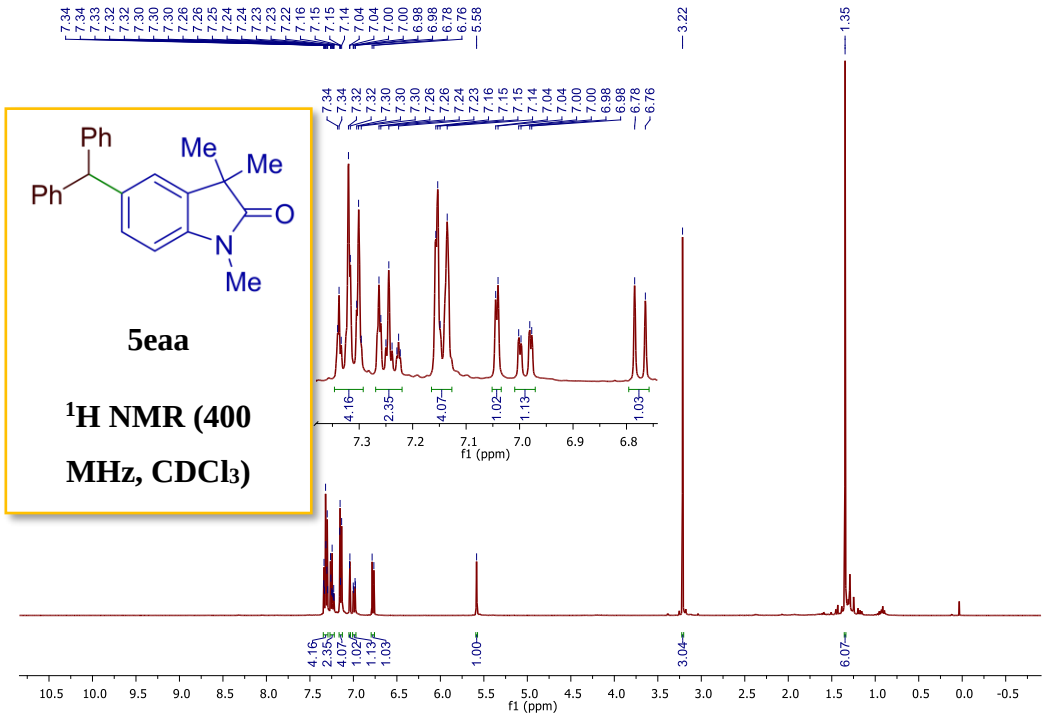

F
F
Ph
Ph
O
N
Bn
5xa
19F NMR (376 MHz, CDCl3)
114.90
f1 (ppm)

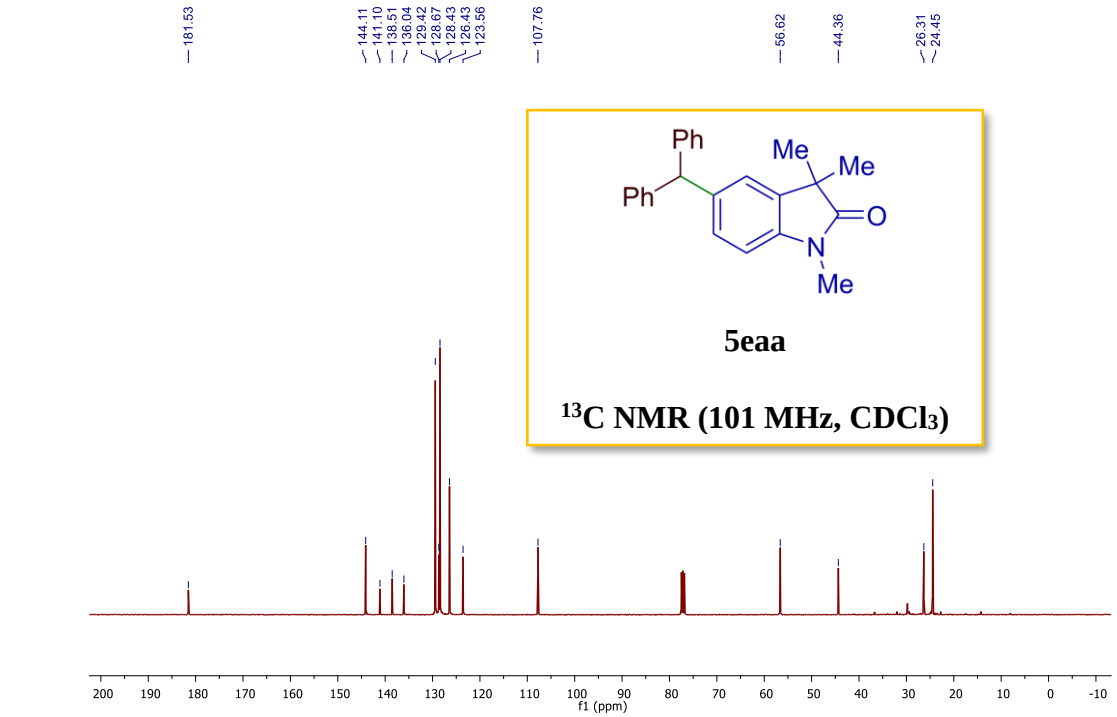

Ph
Ph
Ph-d5
Ph-d5
O
N
Bn
5ya
1H NMR (400 MHz, CDCl3)
f1 (ppm)


177.65
143.99
141.93
141.86
141.78
140.66
138.90
135.96
133.06
129.45
129.08
128.91
128.41
128.14
127.99
127.74
127.58
127.41
127.26
127.16
126.48
109.19
62.56
56.38
44.28
Ph
Ph
Ph-d5
Ph-d5
O
N
Bn
5ya
13C NMR (101 MHz, CDCl3)
f1 (ppm)


9.84
7.34
7.32
7.32
7.31
7.30
7.30
7.28
7.26
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.21
7.13
7.12
7.10
6.91
6.77
5.50
2.22
Ph
Ph
Ph
Ph
O
N
H
Me
5ia
1H NMR (400 MHz, CDCl3)
4.11
9.03
3.09
4.01
1.03
0.99
0.93
1.00
3.02
f1 (ppm)

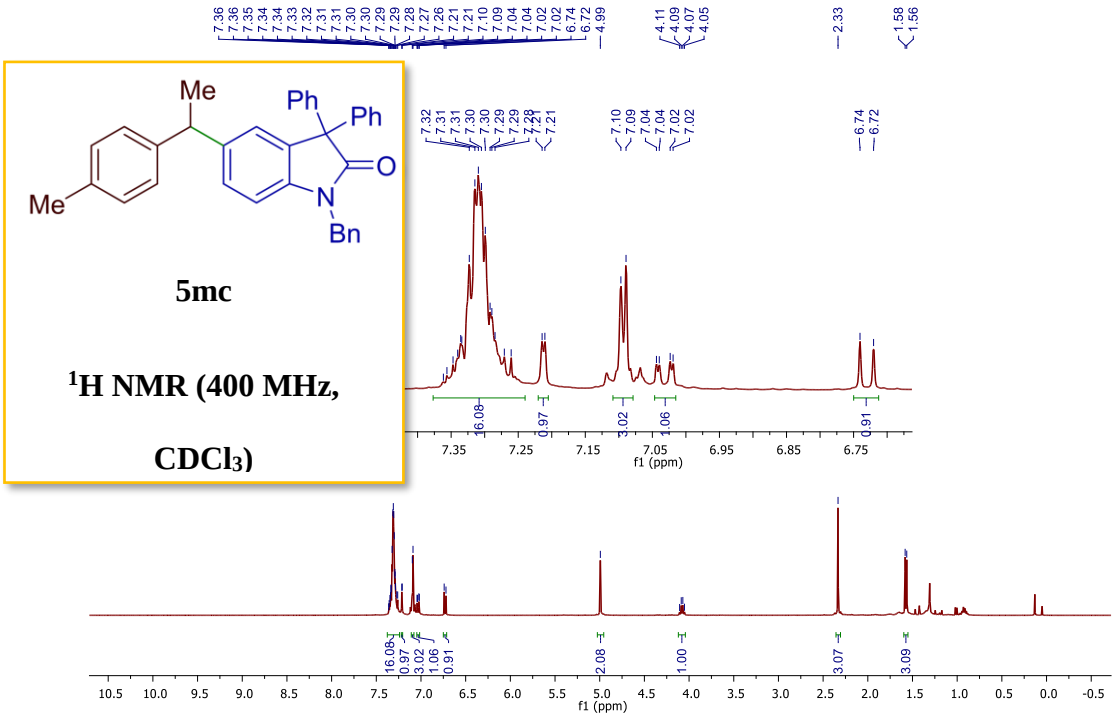

181.12
144.19
141.82
138.65
137.68
133.26
130.56
129.47
128.55
128.43
128.37
127.30
126.39
125.15
123.73
122.75
119.76
63.56
56.46
16.77
Ph
Ph
Ph
Ph
O
N
H
Me
5ia
13C NMR (101 MHz, CDCl3)
f1 (ppm)


7.34
7.34
7.33
7.32
7.32
7.30
7.30
7.30
7.30
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.16
7.15
7.15
7.14
7.04
7.04
7.00
7.00
6.98
6.98
6.78
6.76
5.58
3.22
1.35
Ph
Ph
Me
Me
O
N
Me
5eaa
1H NMR (400 MHz, CDCl3)
4.16
2.35
4.07
1.02
1.13
1.03
1.00
3.04
6.07
f1 (ppm)



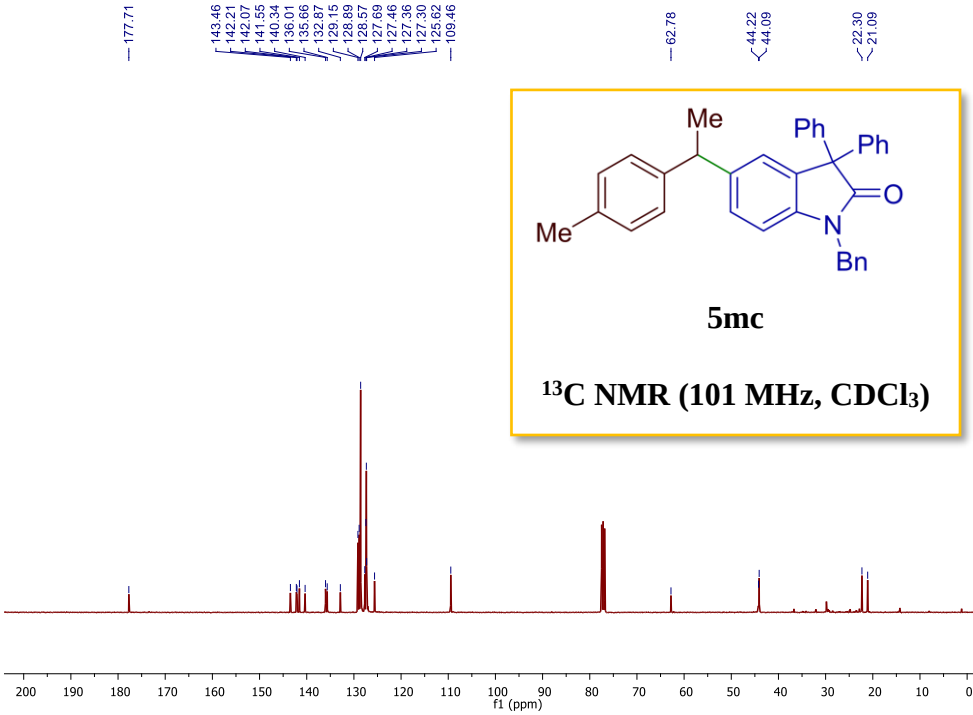
5eaa

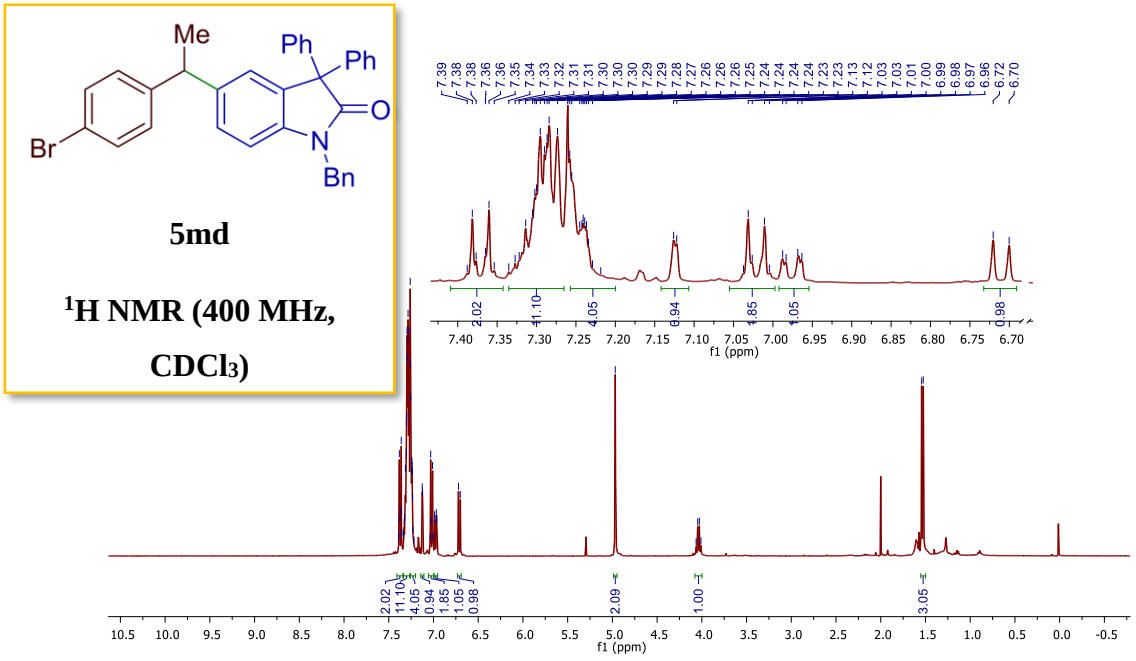
^{13}C NMR (101 MHz, $CDCl_3$)

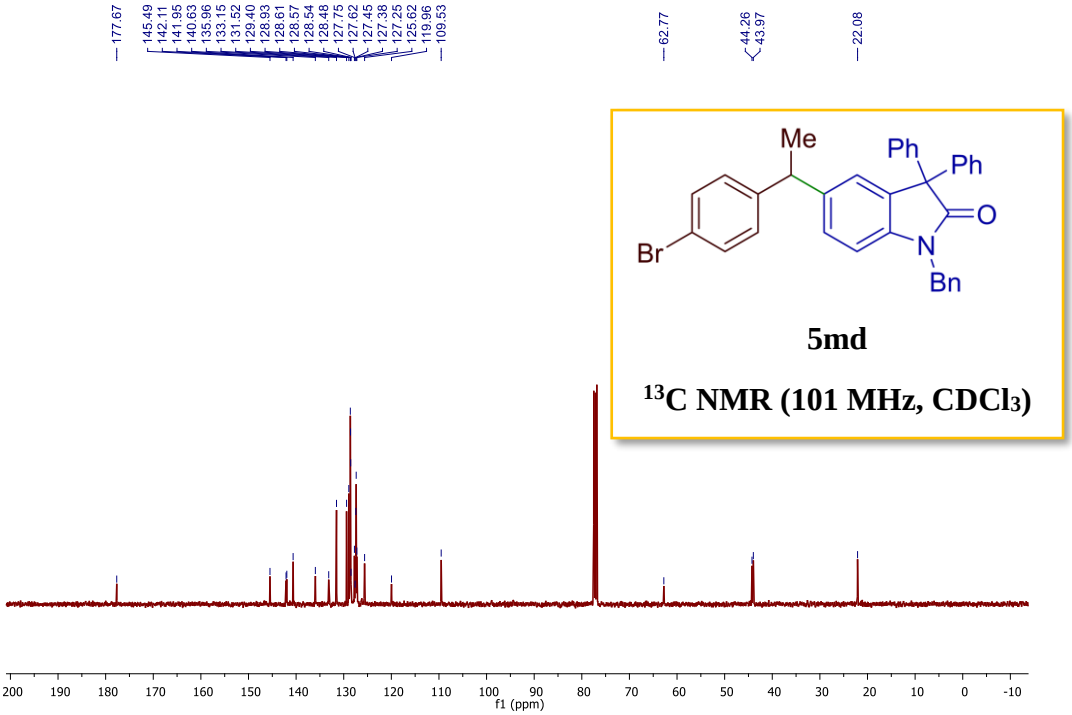


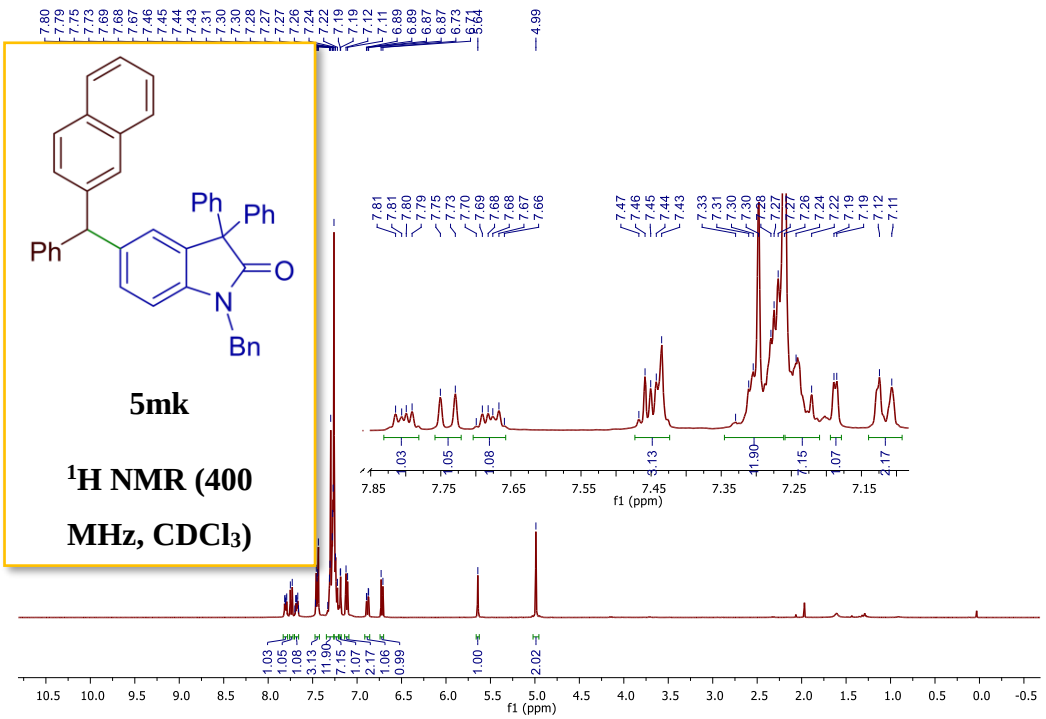
5mc

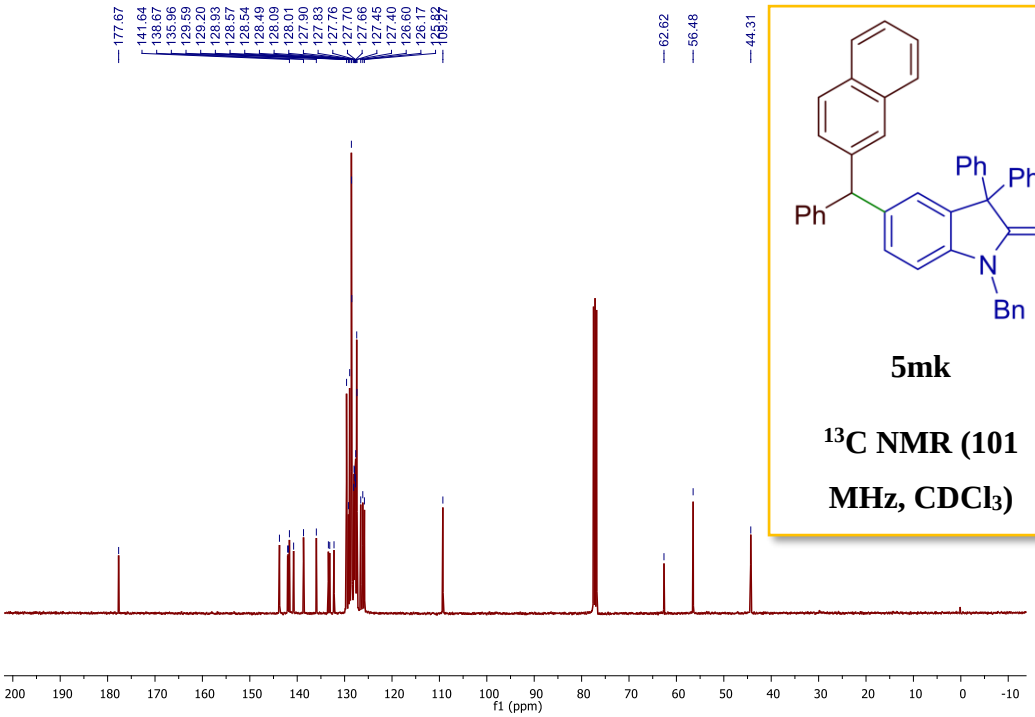
^{1}H NMR (400 MHz, $CDCl_3$)


Me
Ph
Ph
O
N
Bn
Me
5mc
13C NMR (101 MHz, CDCl3)
f1 (ppm)


Me
Ph
Ph
O
N
Bn
Br
5md
1H NMR (400 MHz, CDCl3)
f1 (ppm)

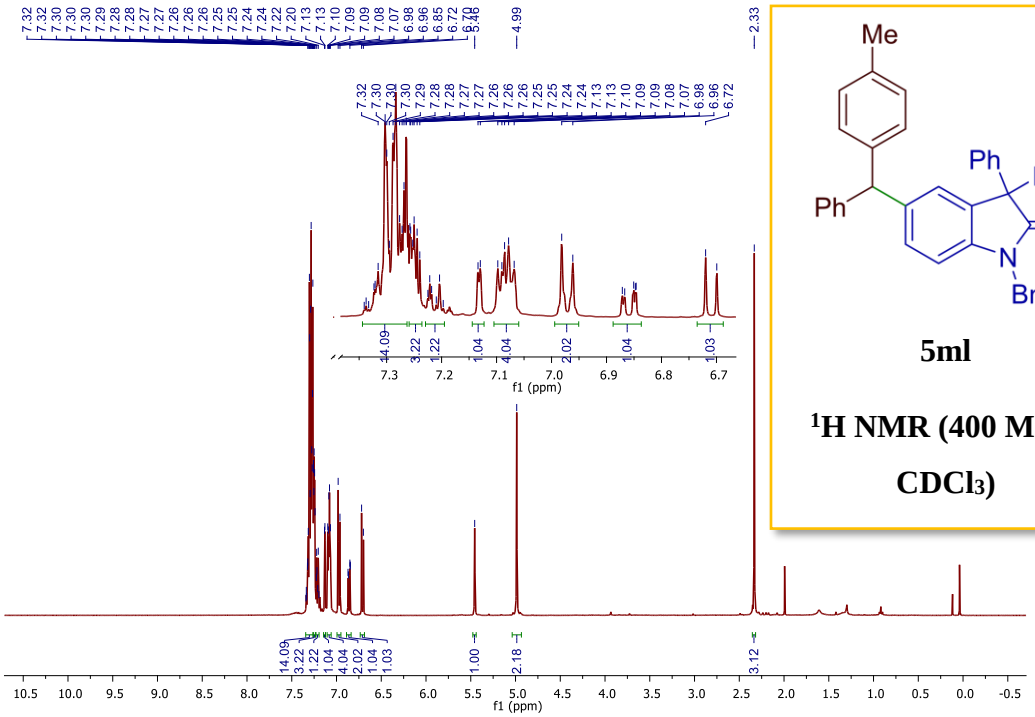

Me
Ph
Ph
O
N
Bn
Br
5md
13C NMR (101 MHz, CDCl3)
f1 (ppm)


Ph
Ph
Ph
O
N
Bn
5mk
1H NMR (400 MHz, CDCl3)
f1 (ppm)



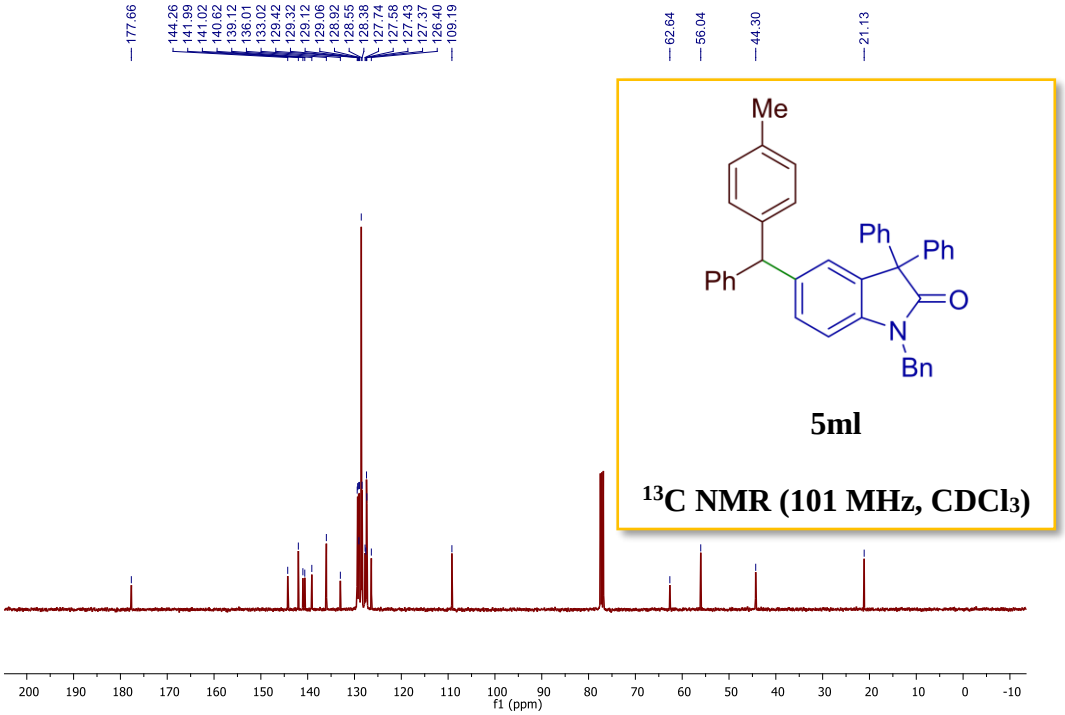
5mk

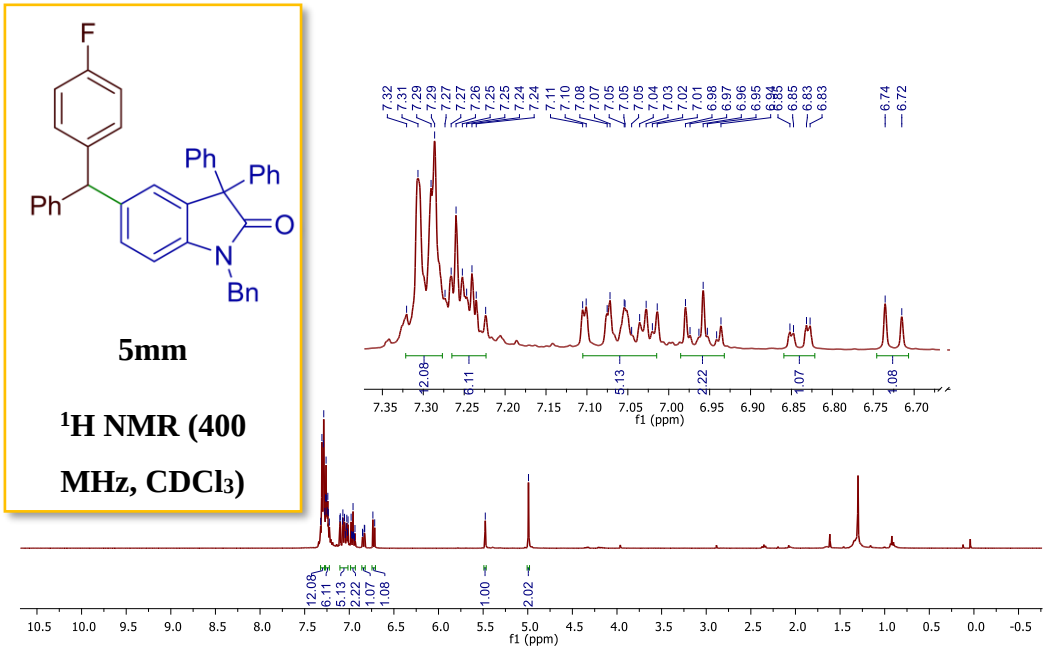
^{13}C NMR (101 MHz, $CDCl_3$)

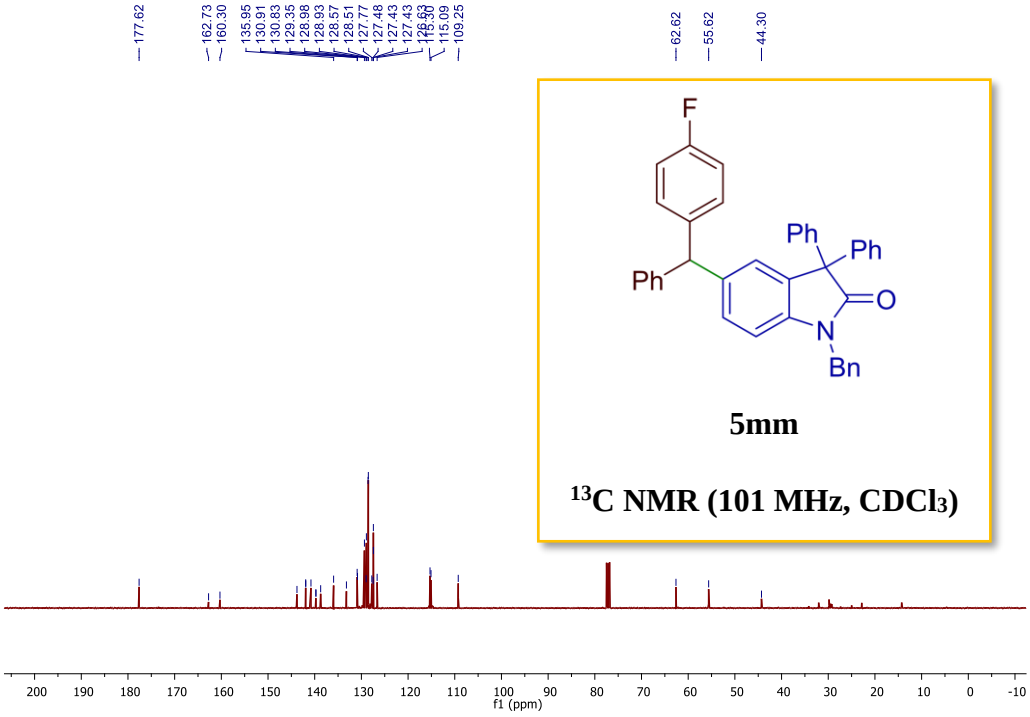


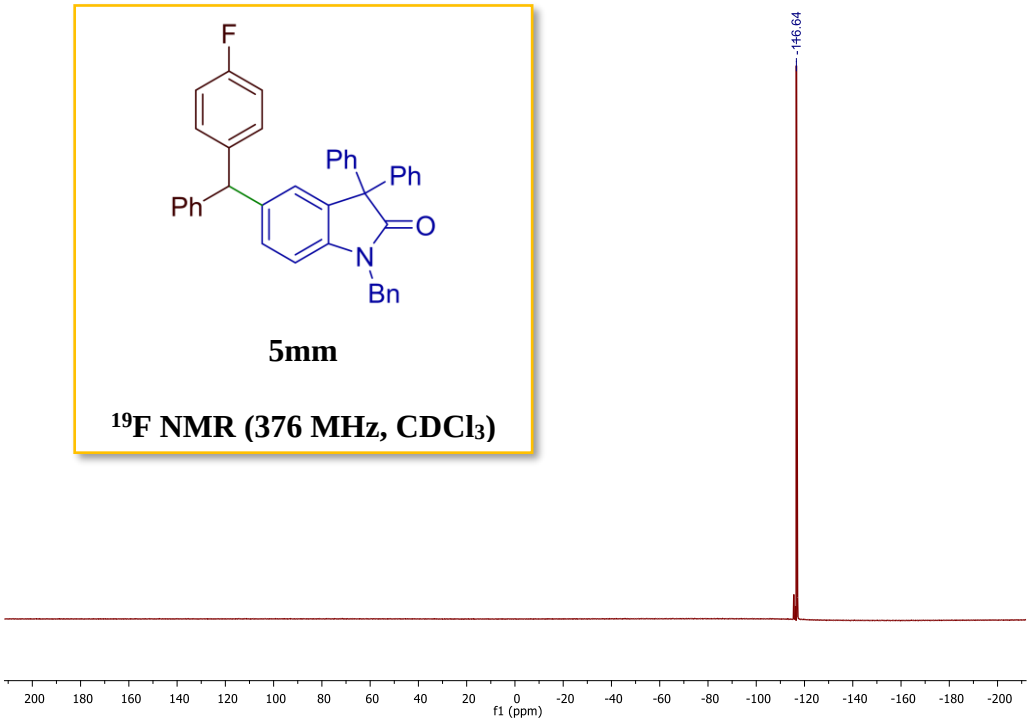
5ml

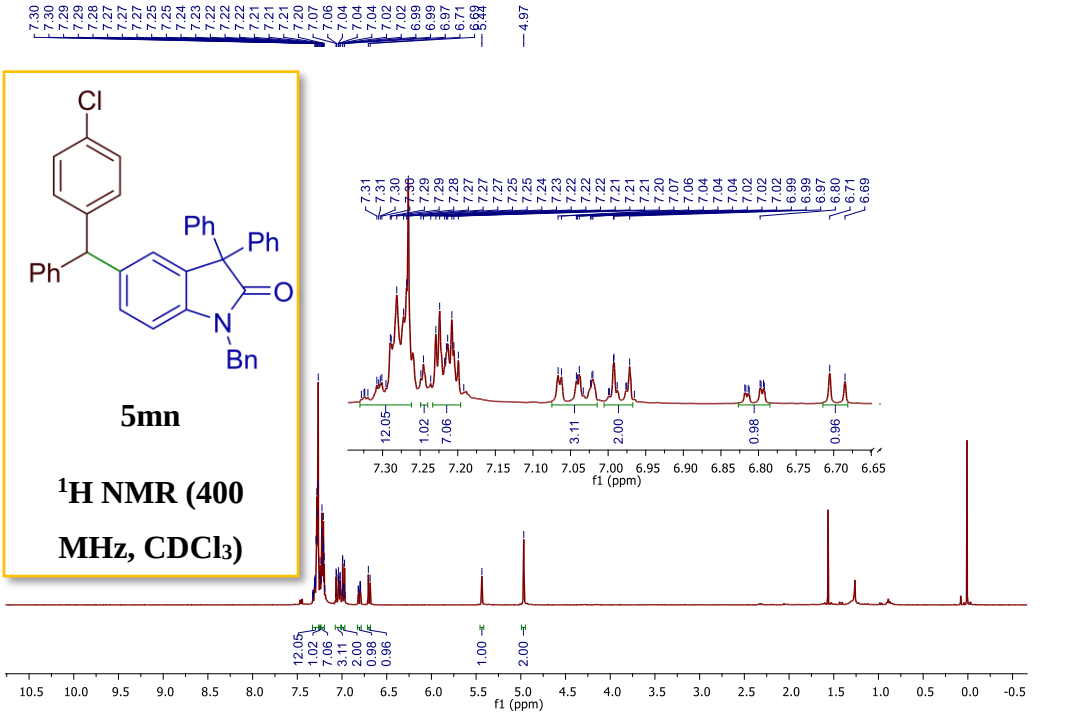
^{1}H NMR (400 MHz, $CDCl_3$)

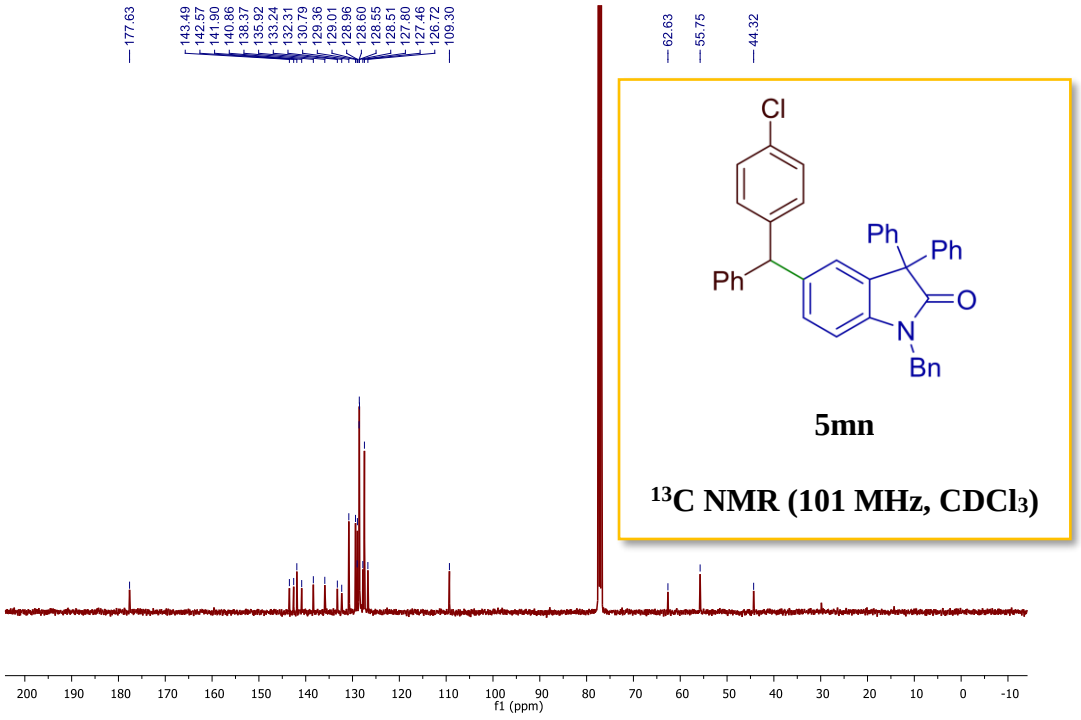

Me
Ph
Ph
Ph
O
N
Bn
5ml
^{13}C NMR (101 MHz, CDCl$_3$)

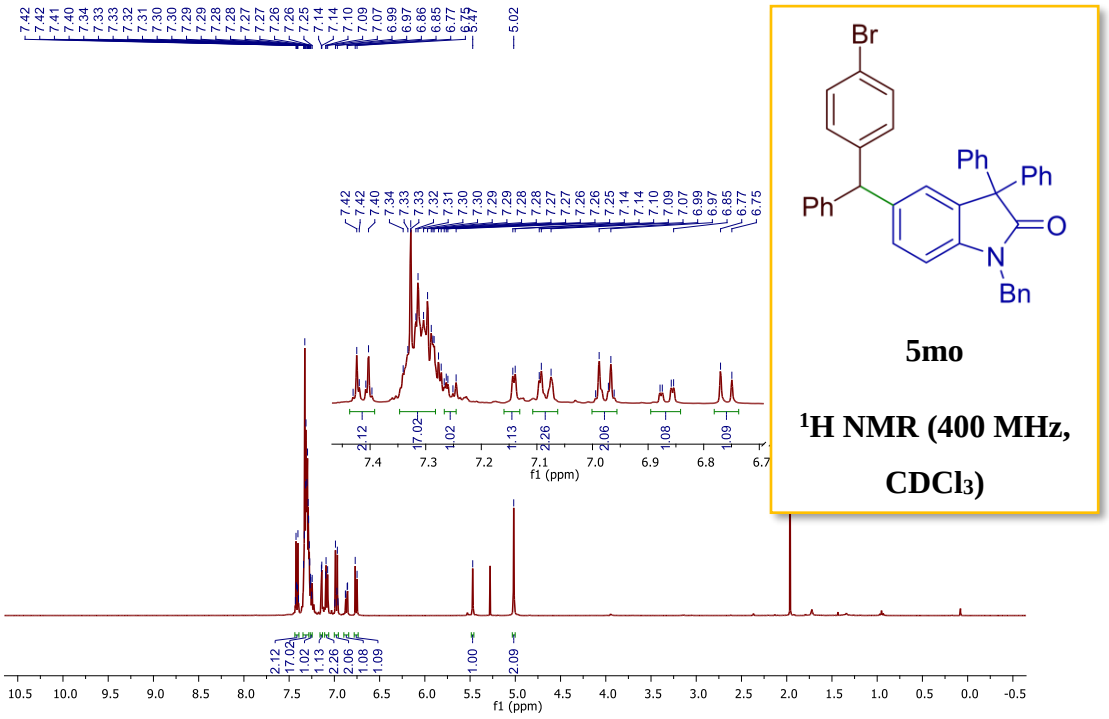

F
Ph
Ph
Ph
O
N
Bn
5mm
^{1}H NMR (400 MHz, CDCl$_3$)


177.62
162.73
160.30
135.95
130.91
130.83
129.35
128.98
128.93
128.57
128.51
127.77
127.48
127.43
127.43
115.09
109.25
62.62
55.62
44.30
F
Ph
Ph
Ph
O
N
Bn
5mm
13C NMR (101 MHz, CDCl3)
f1 (ppm)


F
Ph
Ph
Ph
O
N
Bn
5mm
19F NMR (376 MHz, CDCl3)
-146.64
f1 (ppm)


Cl
Ph
Ph
Ph
O
N
Bn
5mn
1H NMR (400 MHz, CDCl3)


Cl
Ph
Ph
Ph
O
N
Bn
5mn
13C NMR (101 MHz, CDCl3)


Br
Ph
Ph
Ph
O
N
Bn
5mo
1H NMR (400 MHz, CDCl3)
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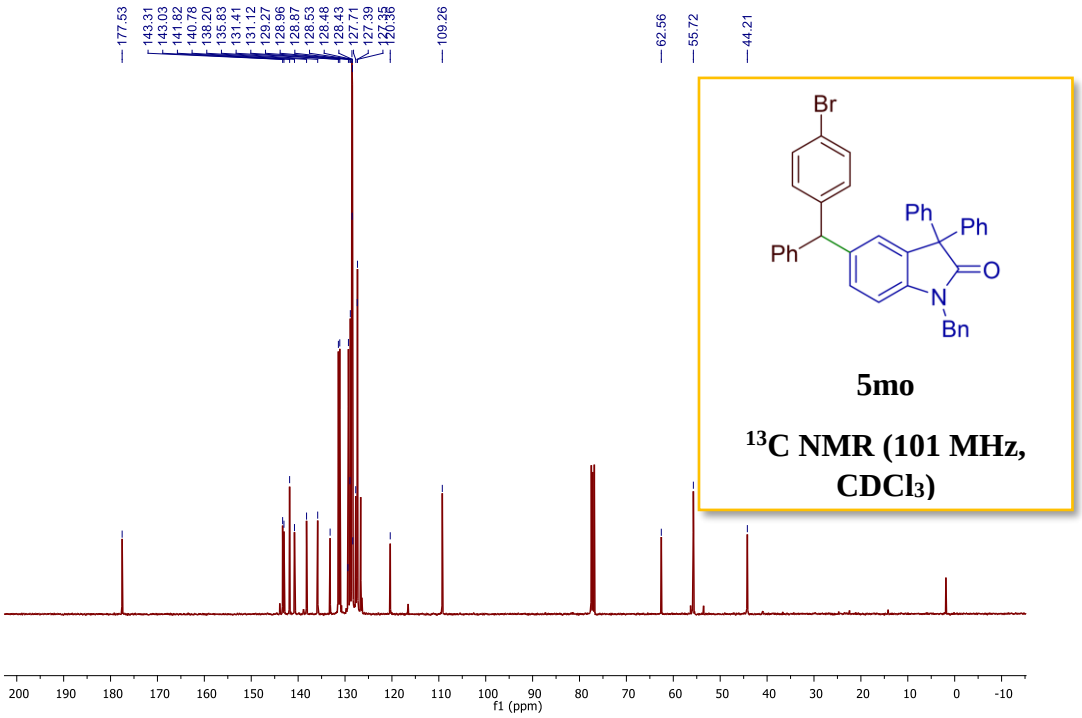
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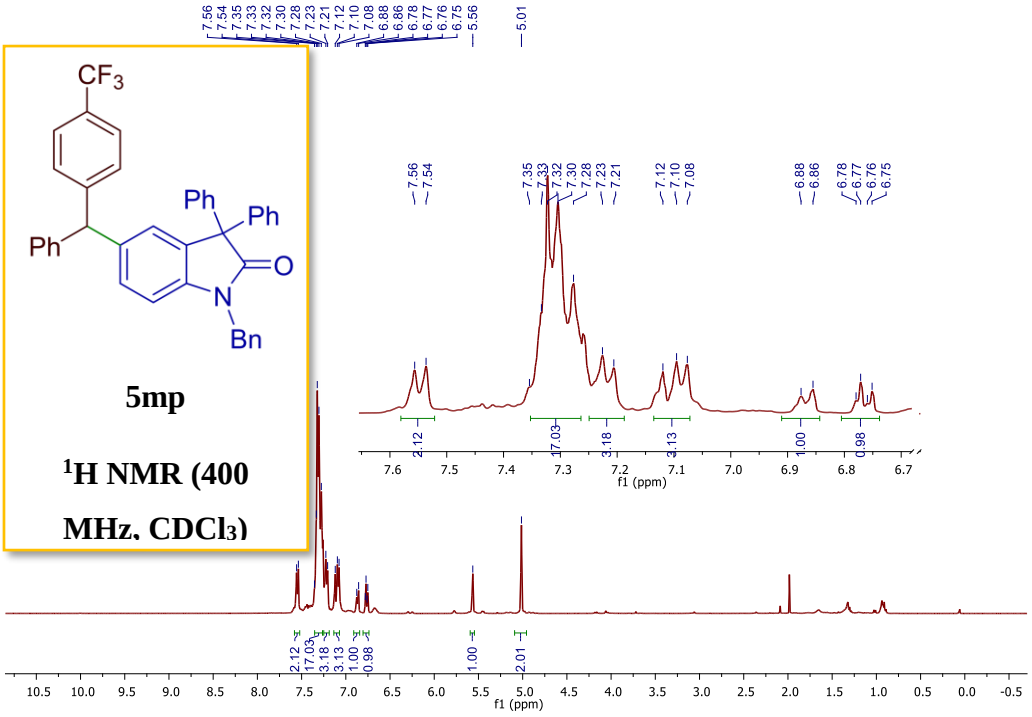
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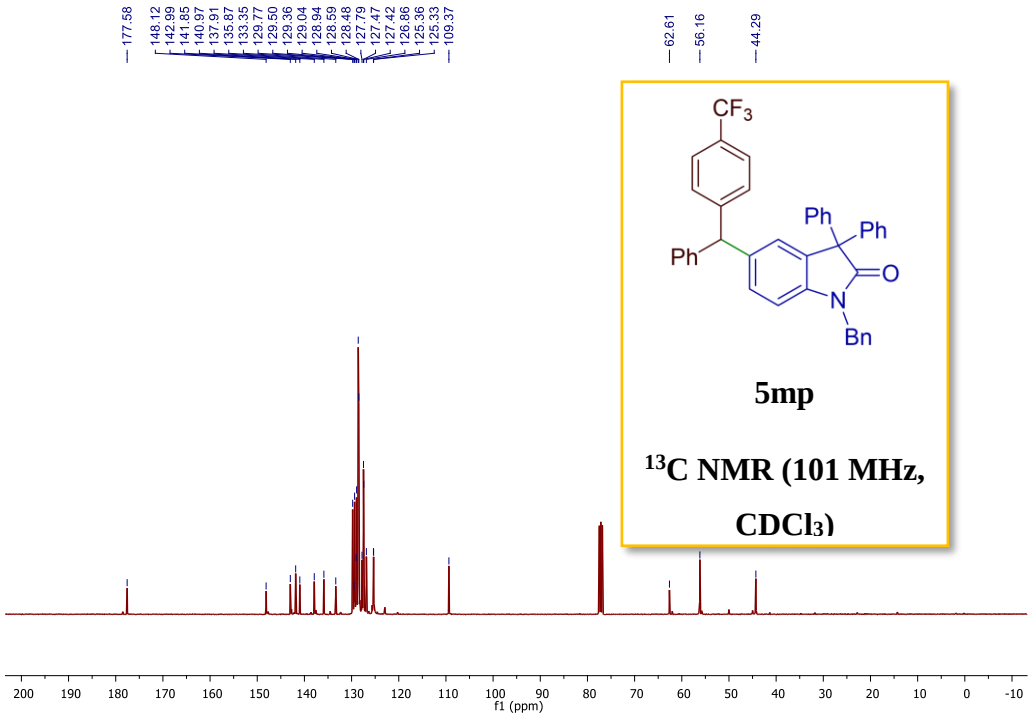
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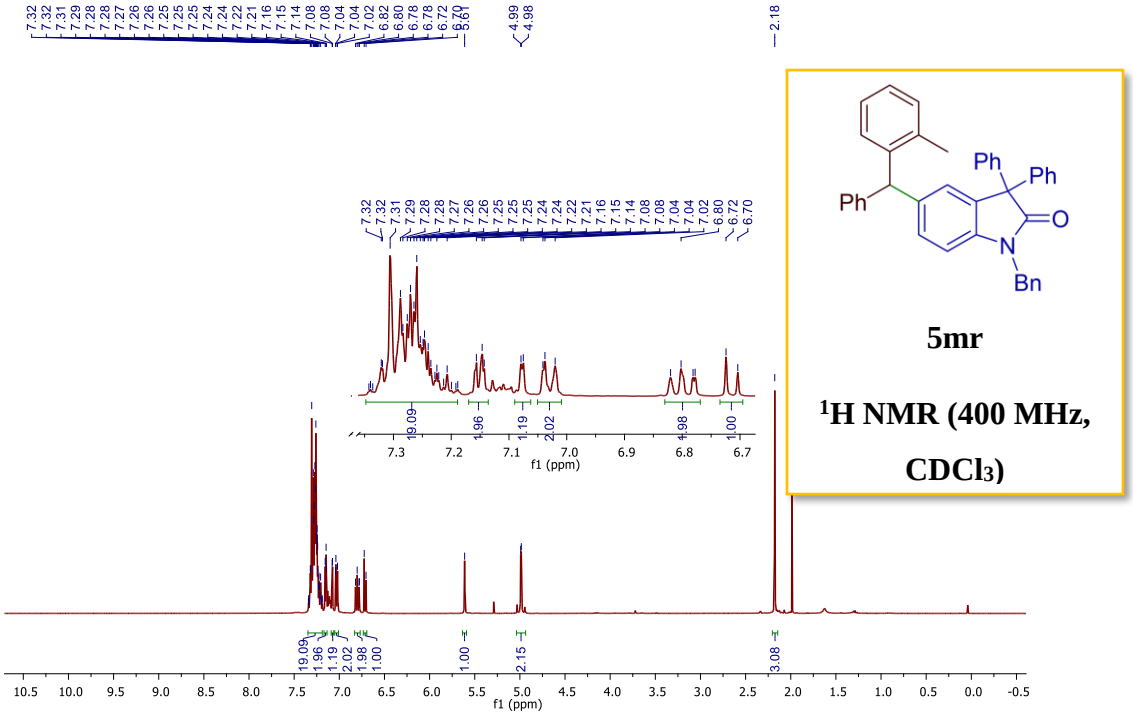
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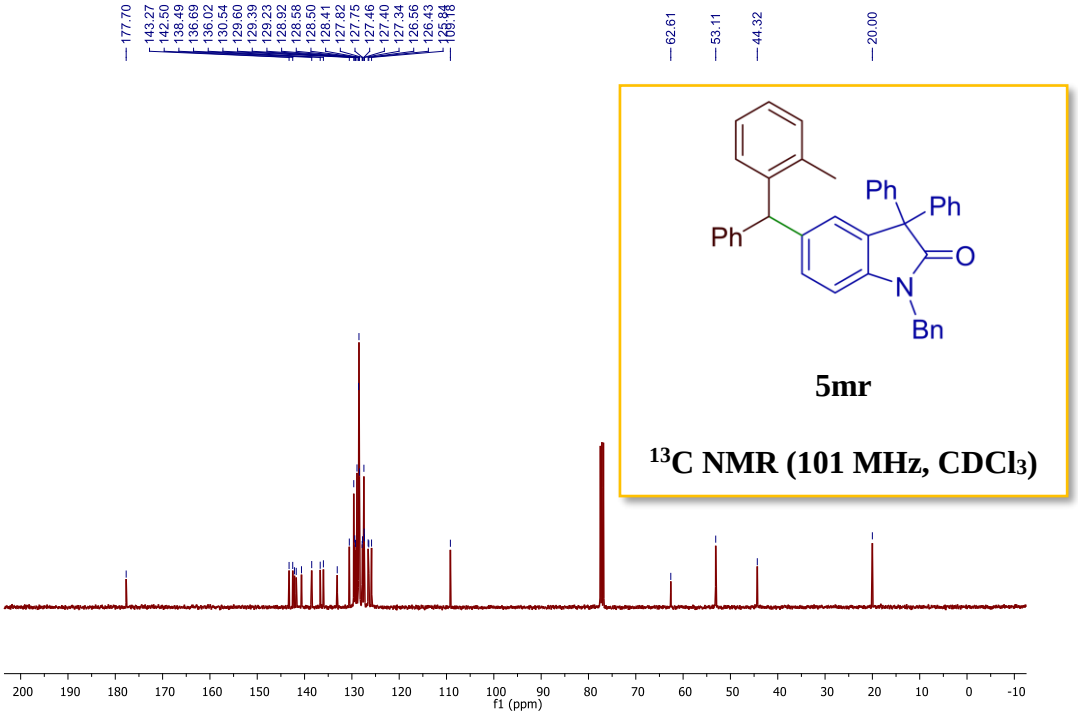
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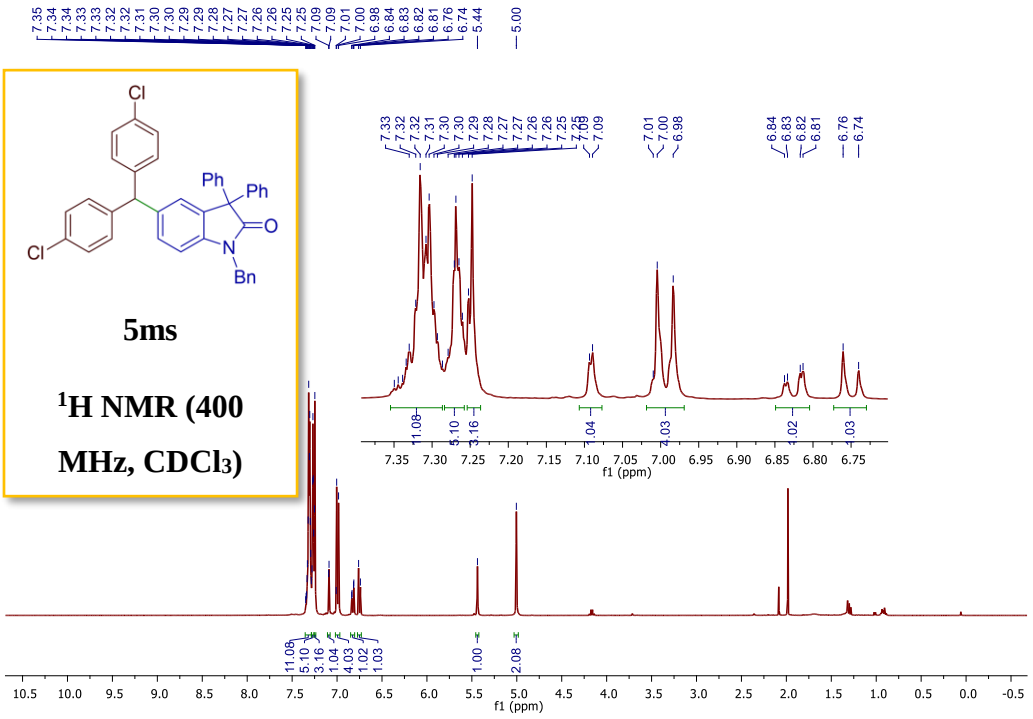
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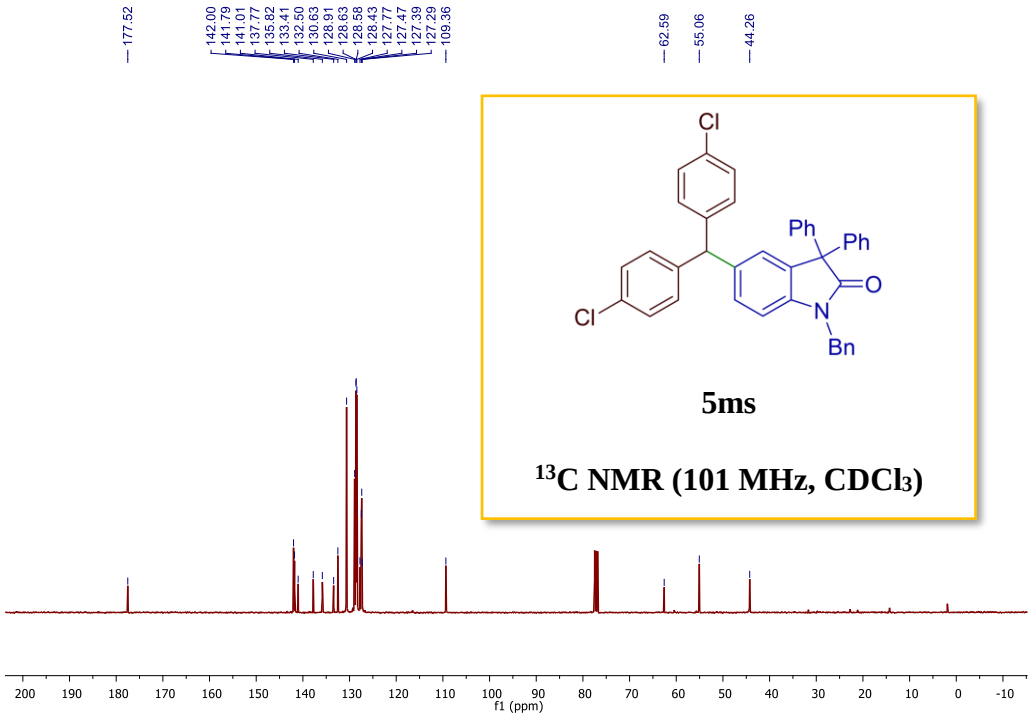
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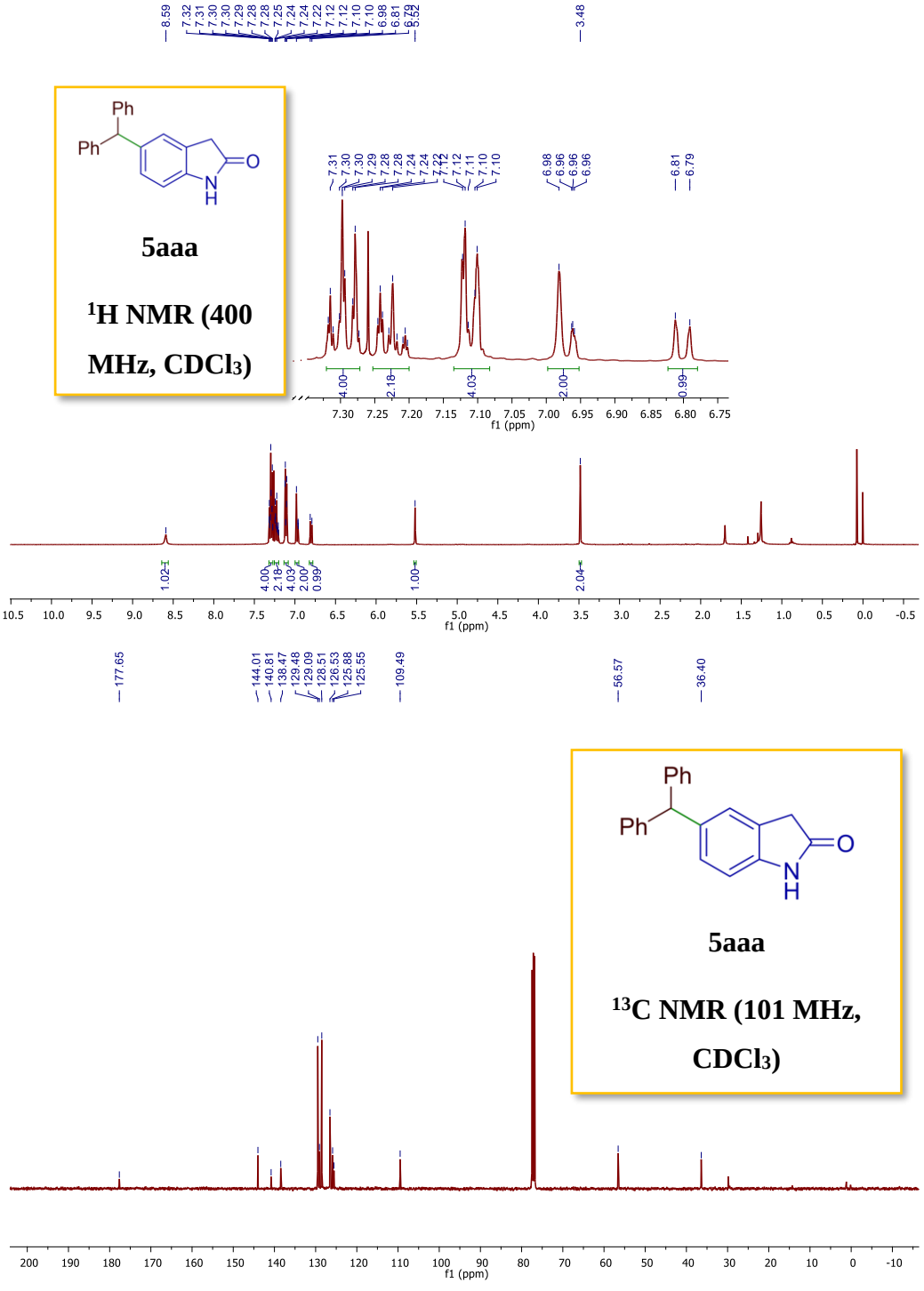
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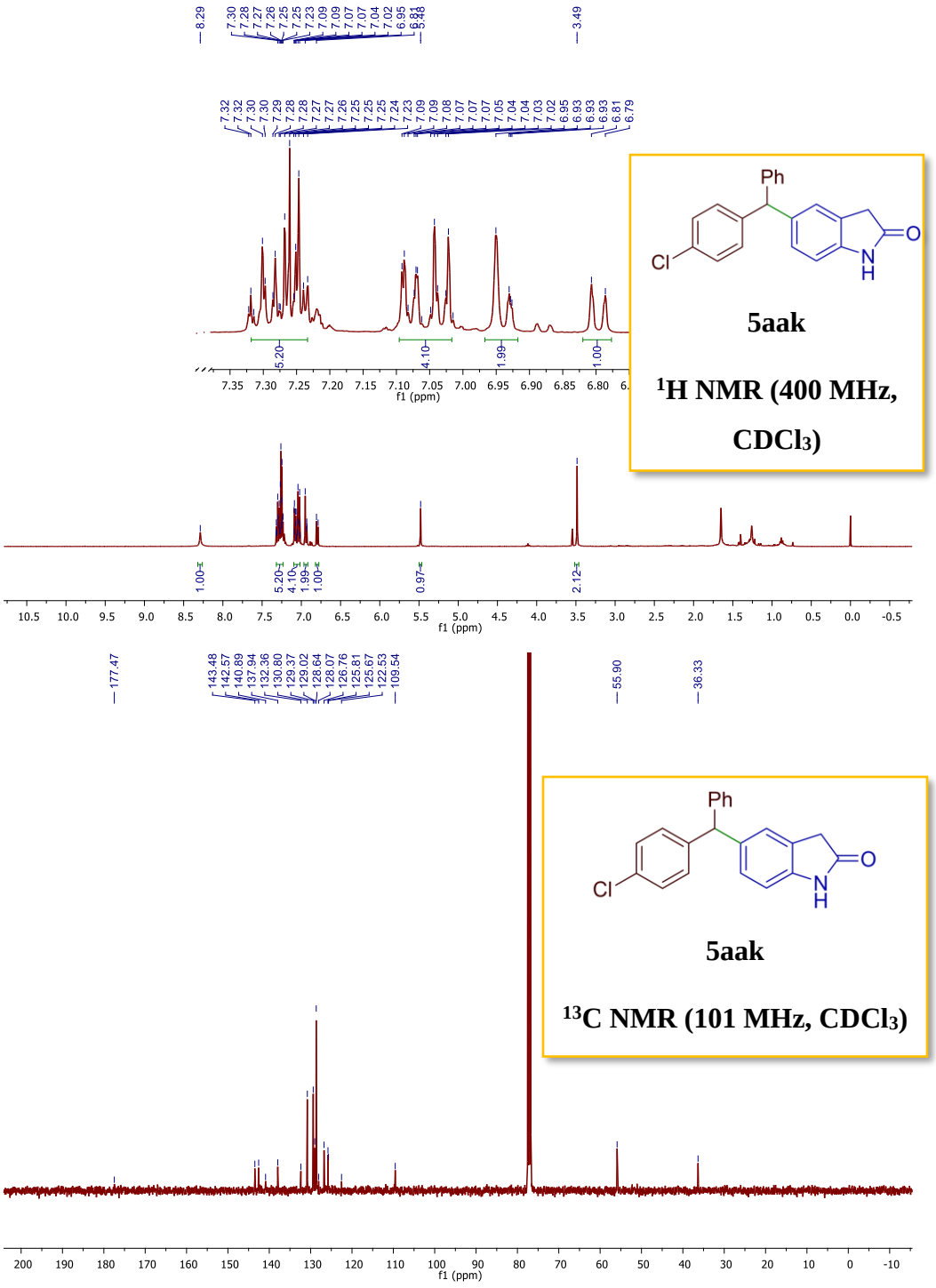
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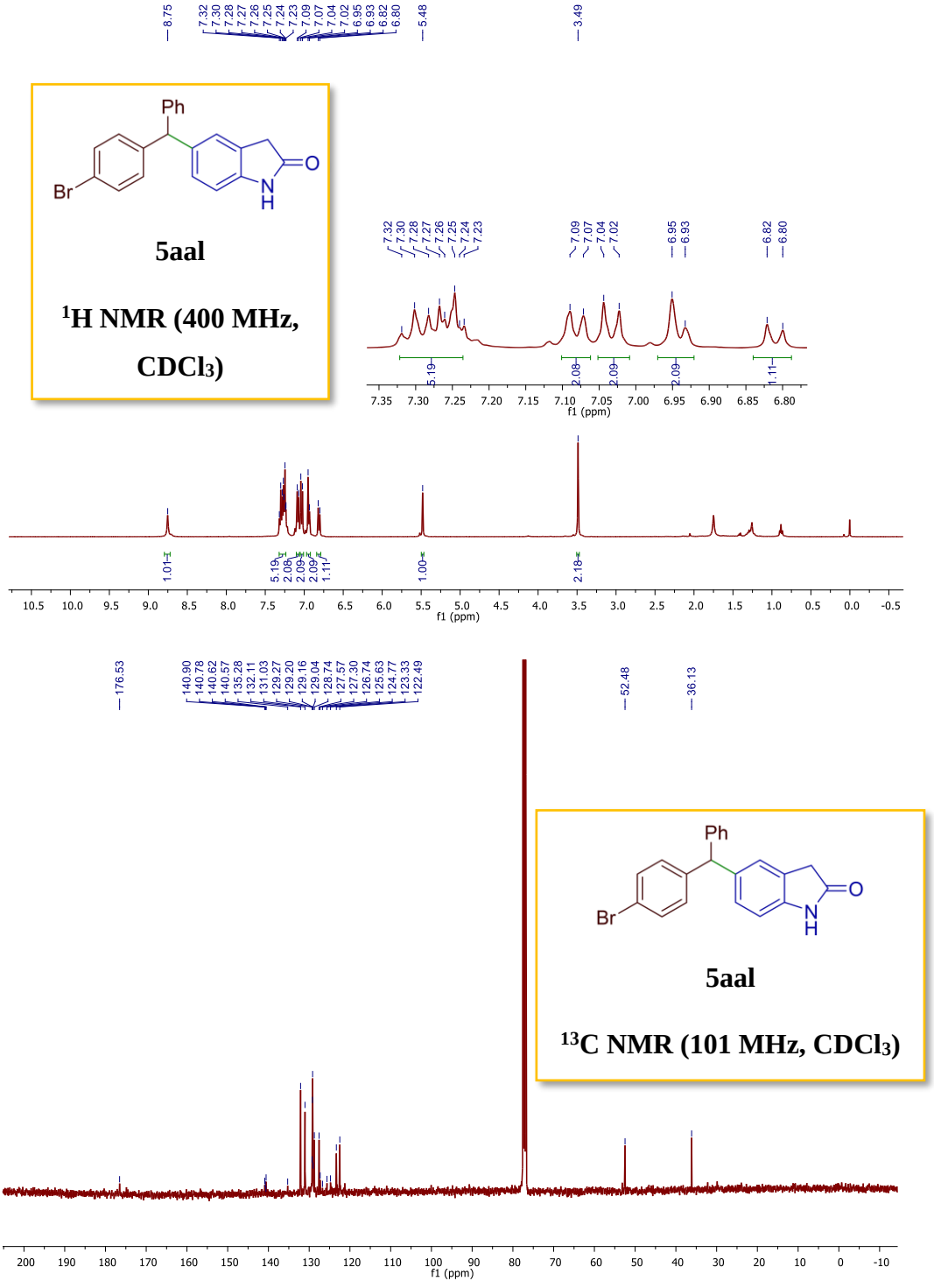
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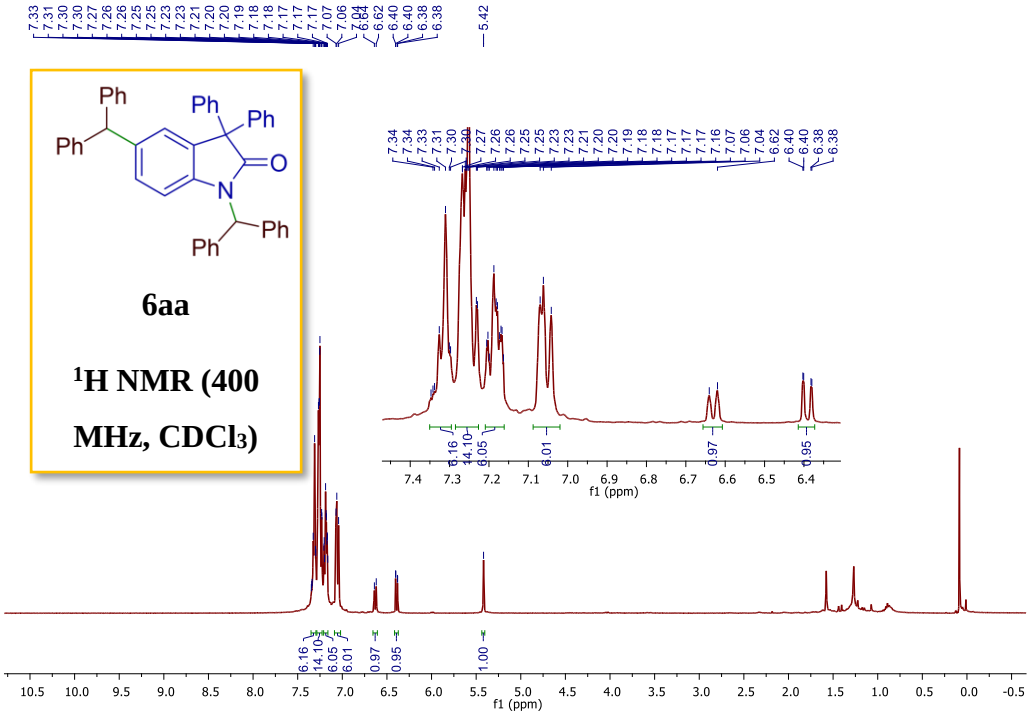
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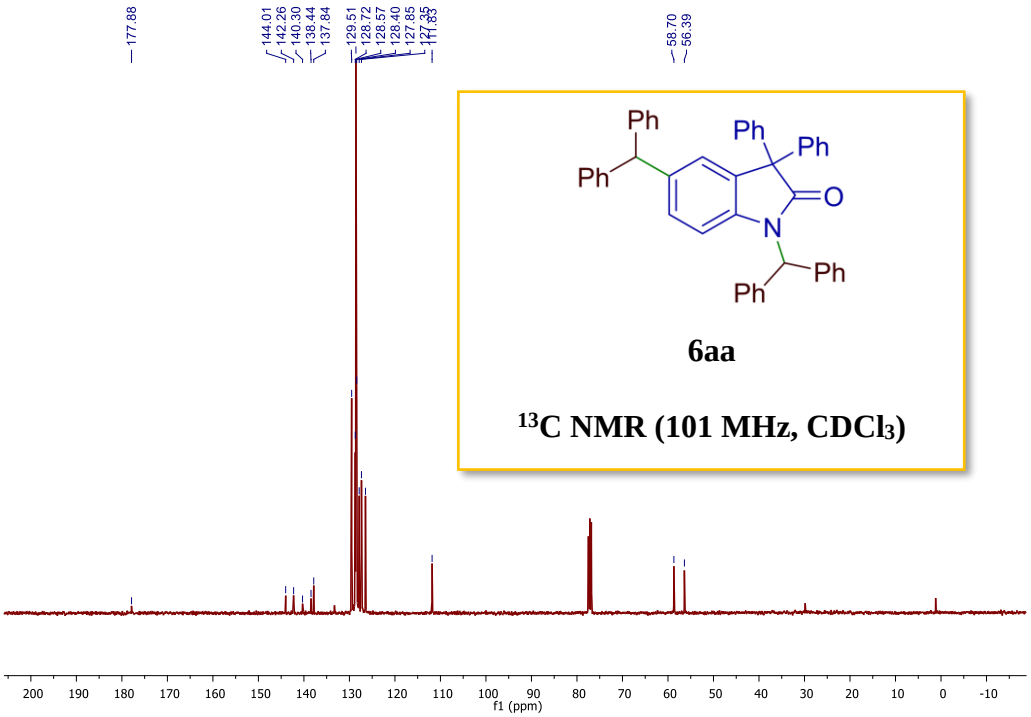
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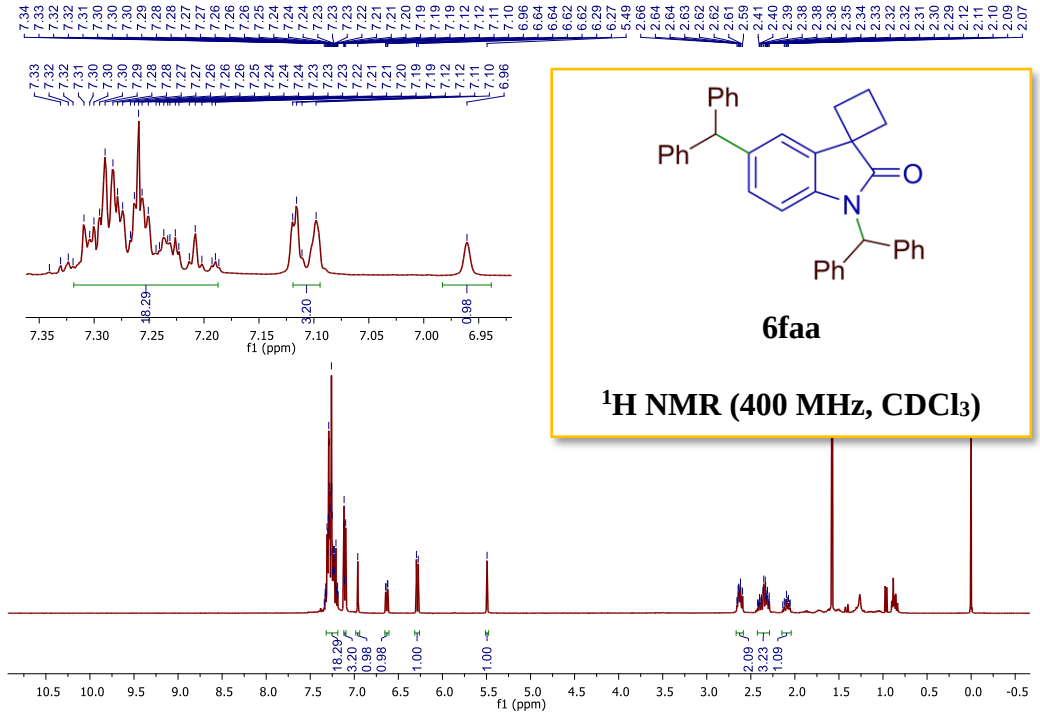
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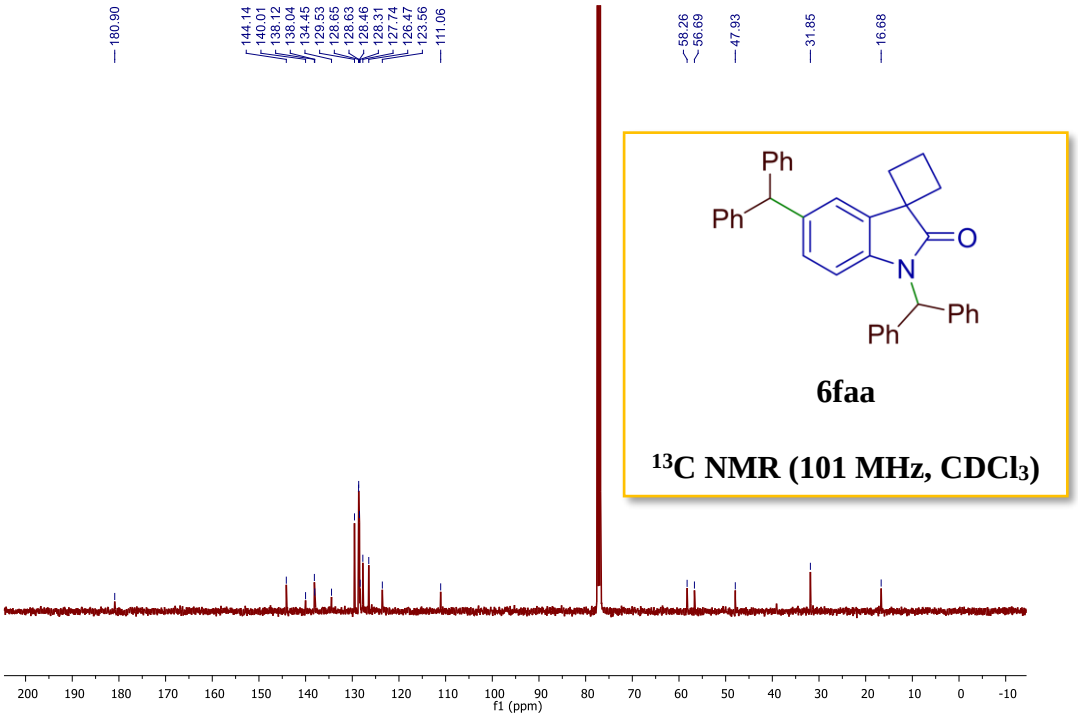
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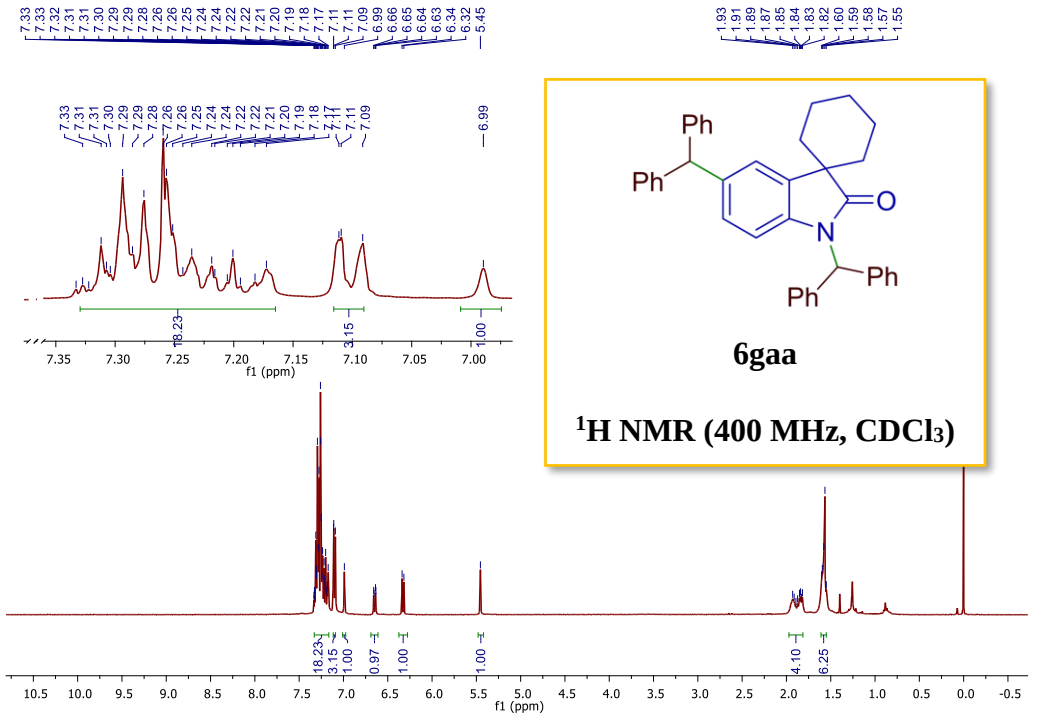
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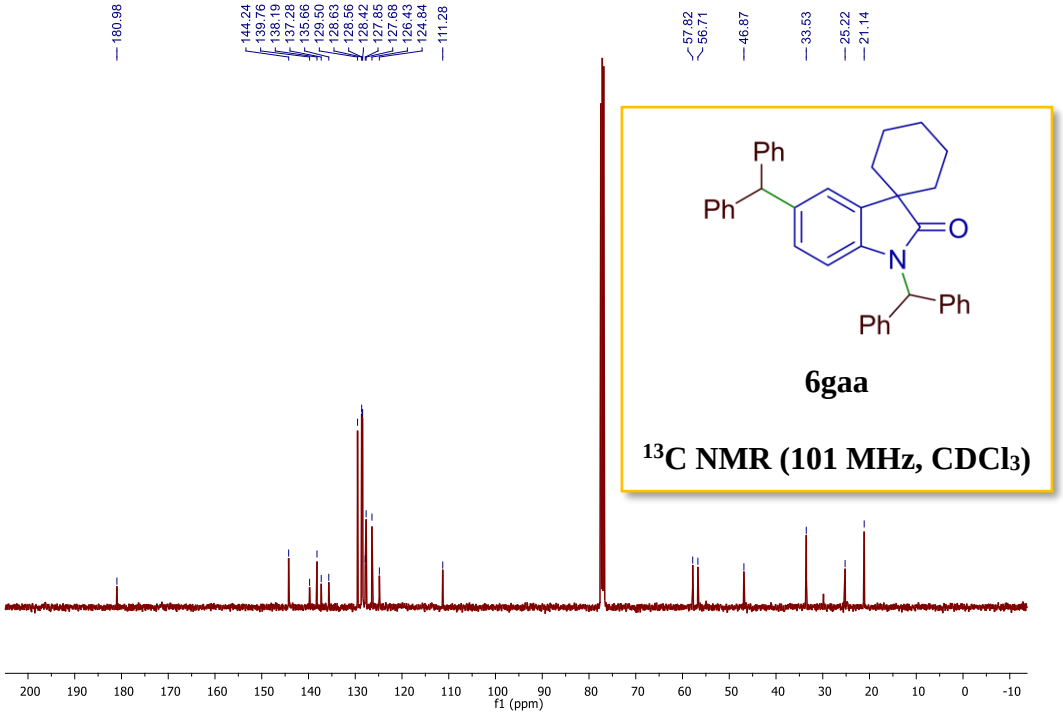
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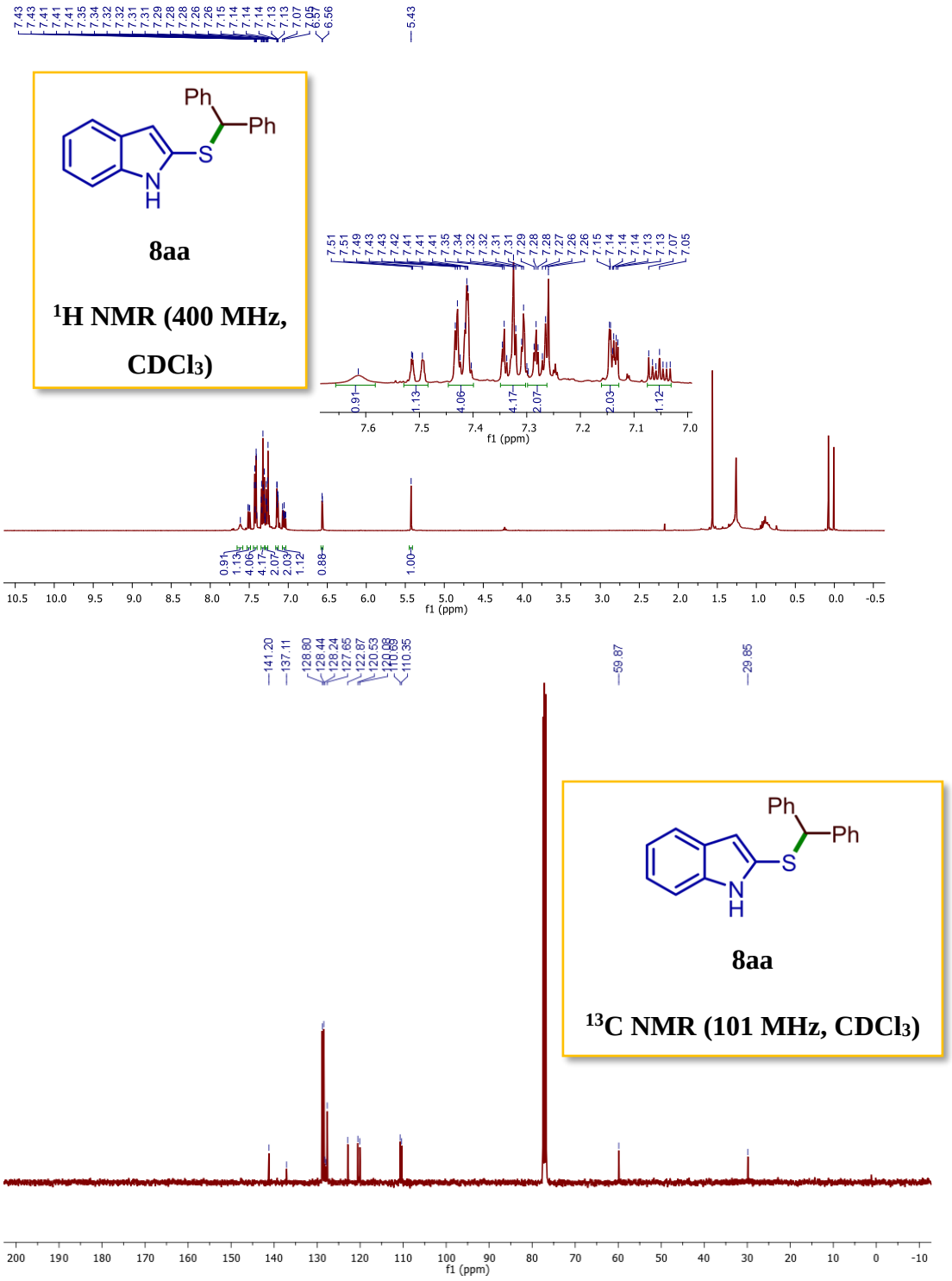
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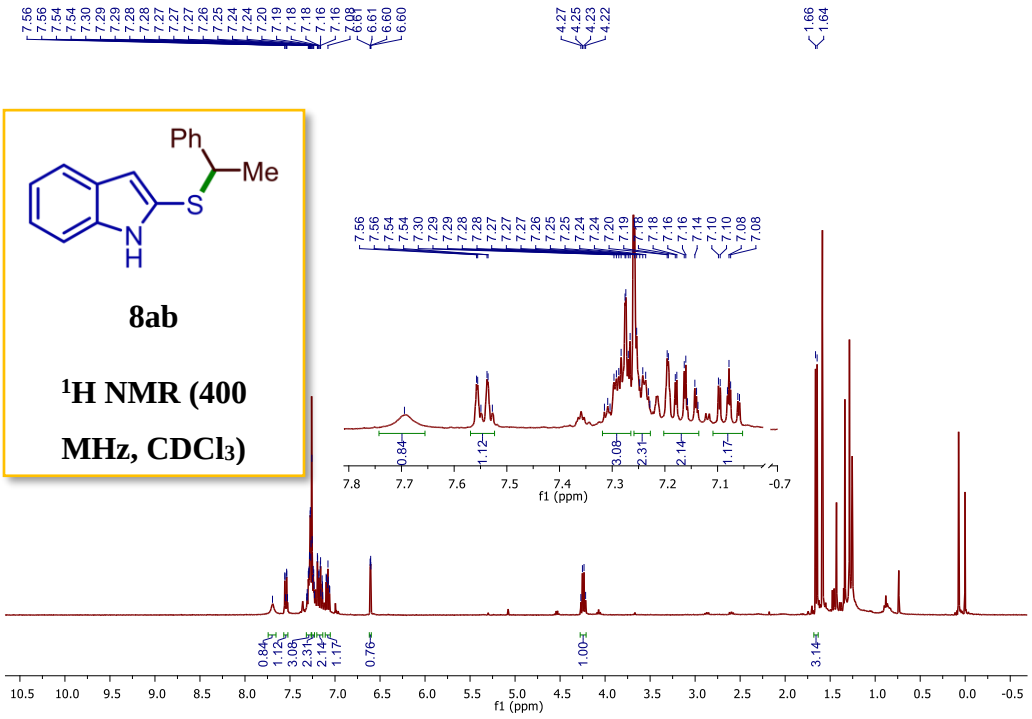
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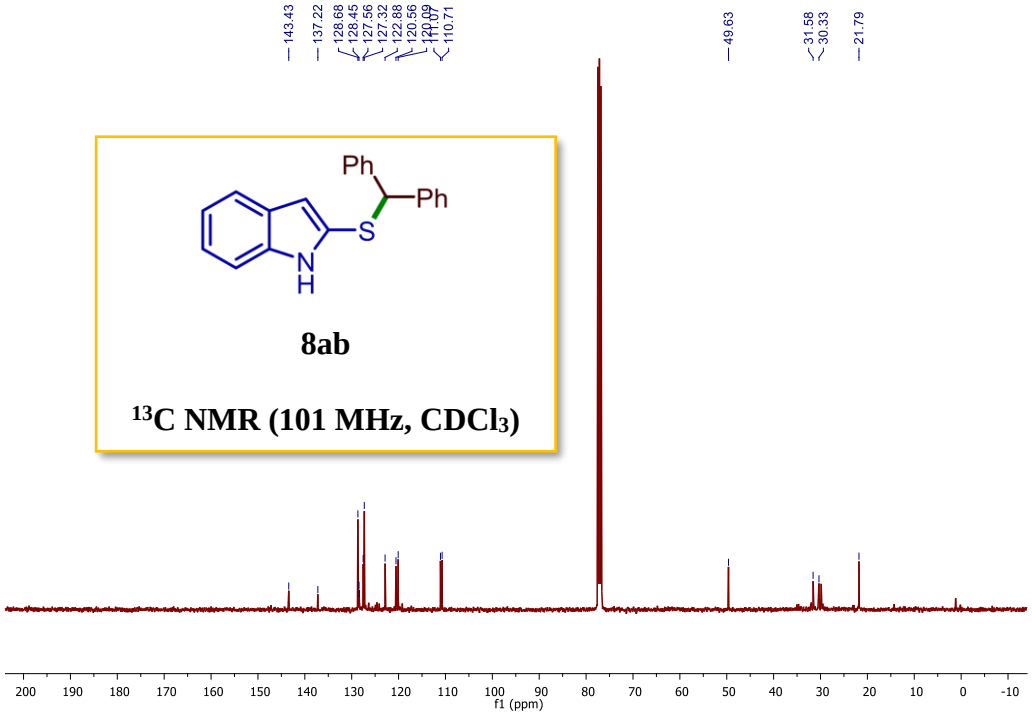
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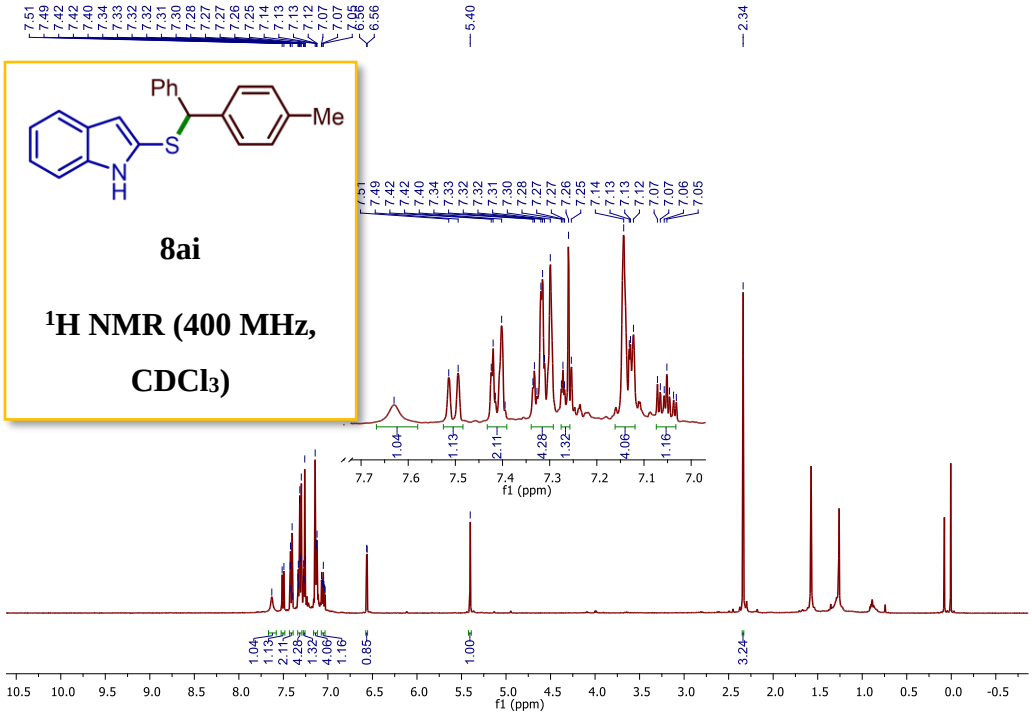
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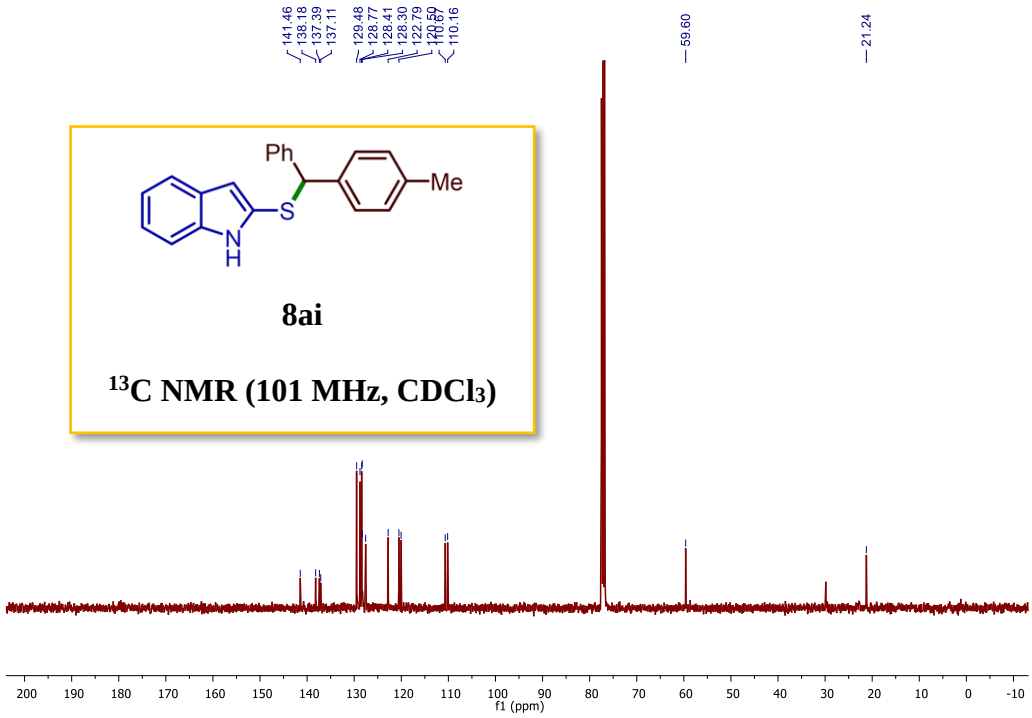
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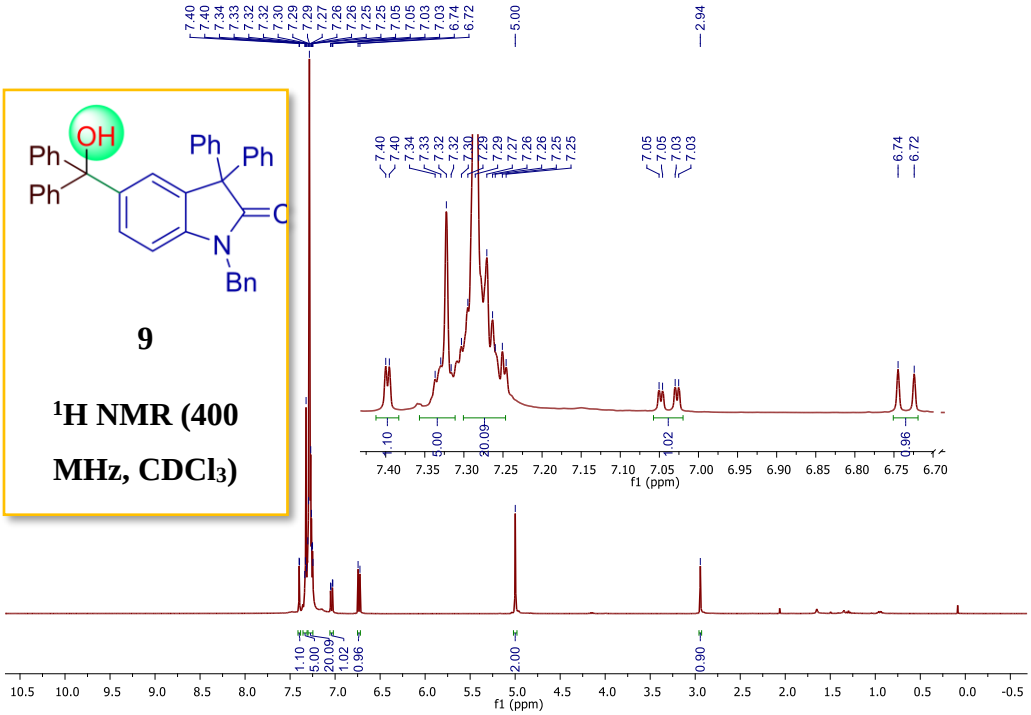
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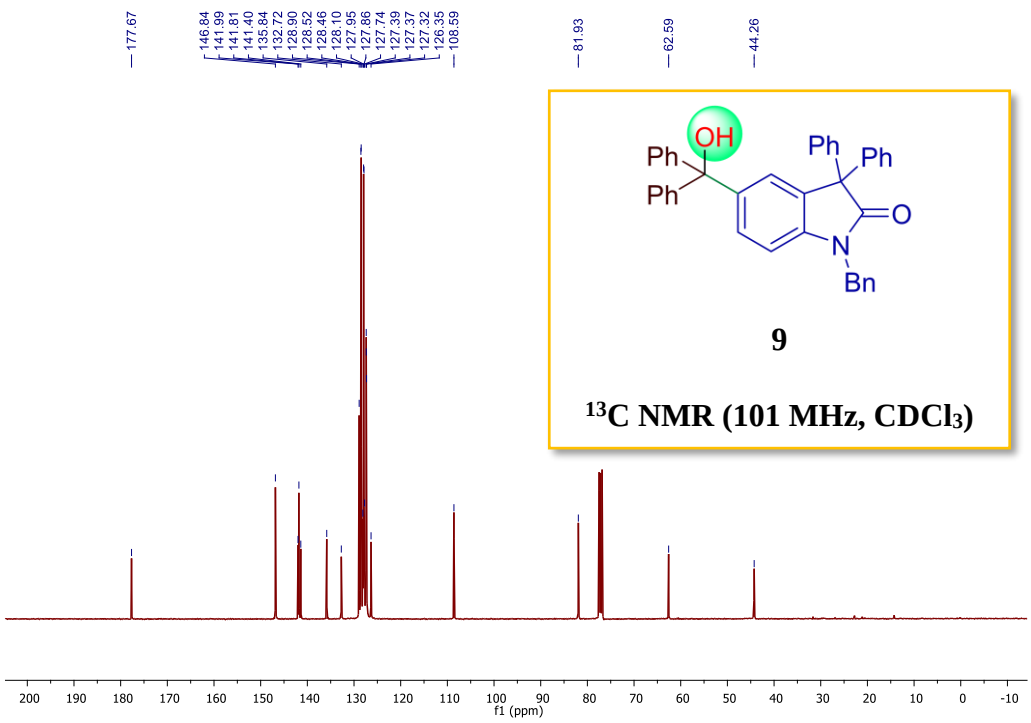
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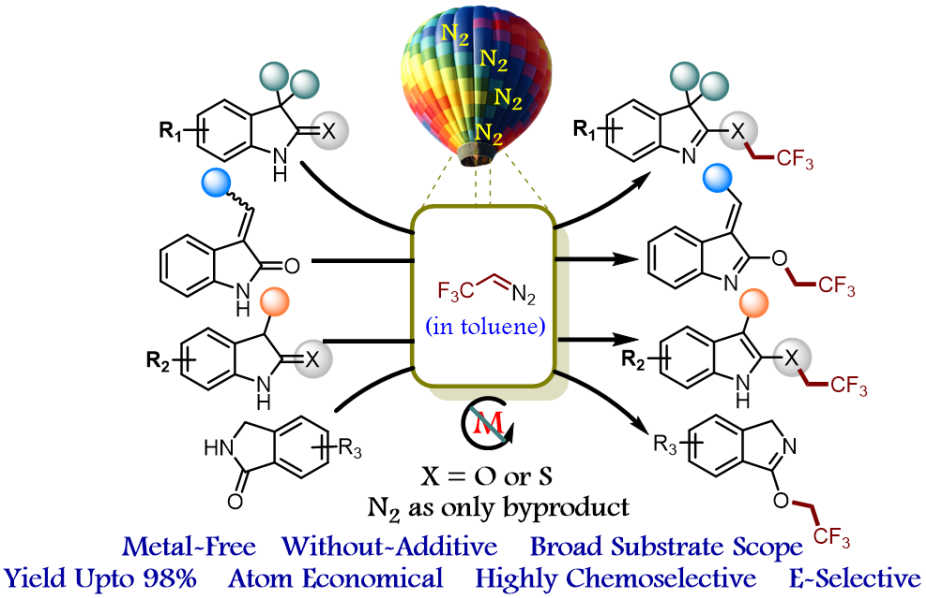
Chapter 3

Metal- and Additive-Free TfOH Catalyzed Chemoselective O- and S-Trifluoroethylation of Oxindoles, Isoindolines and Thio-oxindoles



Chapter 3

3.1 Introduction

In the preceding chapter, I covered the C- and N- functionalization of oxindole. Now, in this chapter, I will delve into the O-functionalization of oxindole. In the preceding chapter, alcohols were shown to act as soft electrophiles, engaging with the soft centers (C- and N-centers) of oxindole. In contrast, this chapter delves into the reactivity of 2,2,2-trifluorodiazoethane as a hard electrophile, which interacts with the hard center (O-center) of the oxindole. This demonstrates the application of the hard-soft acid-base (HSAB) principle in this context. The trifluoromethyl moiety (-CF_3) is a prevalent bioisostere in several natural and agrochemical products and plays multifarious roles. In particular, the introduction of fluorine in a compound has the capability of influencing its physiochemical properties and bioactivity such as metabolic stability, acidity or basicity, and lipophilicity.[1] Many CF_3-containing drugs are under clinical trials,[2] while many more are already approved by the Food and Drug Administration (FDA).[3] Especially, interest in these functionalities has greatly enhanced after recognizing the extensive involvement of isotopically labeled fluorine groups in biomolecules for imaging purposes.[4] Positron emission tomography (PET) has several utilities in the medicinal fields like oncology, neurology, and cardiology. It is an efficient tool for detecting diverse tumor stages, examining brain functions, and detecting inflammation and infections related to the heart. The ^{18}F radiolabeled biomolecules viz., carbohydrates, lipids, amino acids, oligonucleotides, peptides, and protein molecules have shown promise for PET imaging in recent decades. These ^{18}F-labeled biomolecules enable the detection of metabolic changes at the cellular level and the

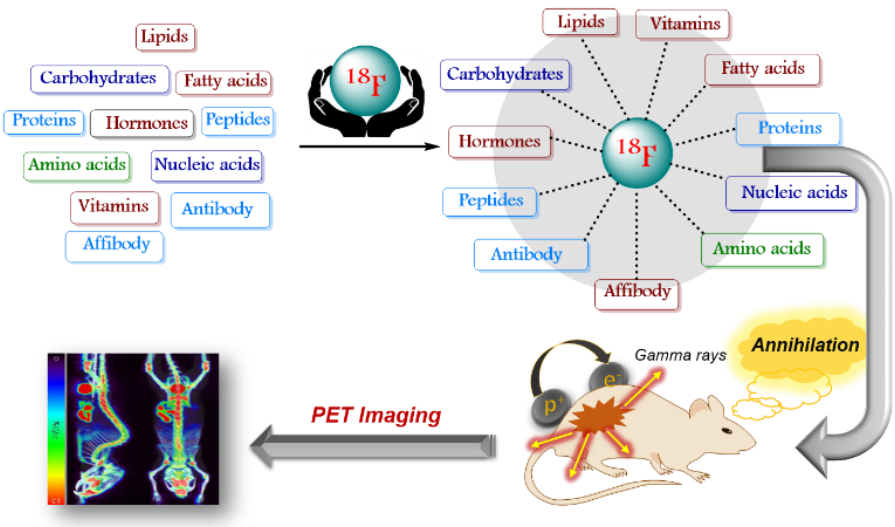


Figure 3.1: Role of biomolecules in PET.

imaging of gross anatomical localization selectively *via* PET imaging (Figure 3.1).[5] Besides their roles in active pharmaceutical ingredient (APIs) and radiolabeling, these moieties are widely accepted as solvents or additives [*e.g.*, hexfluoroisopropanol (HFIP), trifluoroethanol (TFE) and trifluoroethanedithiol (TFET)] used extensively in various chemical and biological transformations.[6]

In this regard, protocols for trifluoromethylation are extensively explored.[7] In sharp contrast to it, the corresponding homologous trifluoroethylation is relatively less reported. Furthermore, chemoselective trifluoroethylation is more challenging for amides, thioamides, enolates, oximes, nitrites, etc. due to the presence of more than one reaction center. Despite various potential utilities of the trifluoroethyl group in many biologically active compounds (Figure 3.2(i)),[8] strategies for introducing them are rare. In order to enhance the triumph in the ongoing drug discovery studies, it is highly demanding to synthesize a library of molecules that can imitate the structural and functional characteristic features found in many pharmaceutical and natural products. Oxindoles

are one of these classes of cyclic amides which are naturally occurring alkaloids and have potential for various bioactivities (Figure 3.2(ii)).[9] These amide frameworks offer both opportunities and challenges for late-stage functionalization as they have intrinsic directing group capacity as well as show amide-iminol tautomerism.

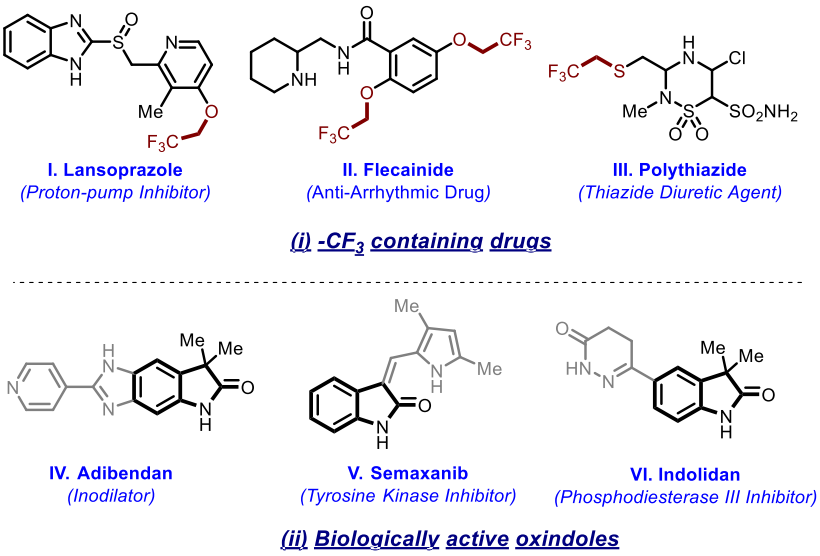


Figure 3.2. Representative examples of (i) $–CF_3$-containing drugs and biomarkers, (ii) biologically active 2-oxindoles.

In the context of fluorine-containing moieties and developing new modes of synthesizing them, the direct trifluoroethylation using CF_3CH_2-containing precursors *viz.*, CF_3CHCl_2, CF_3CH_2I, $[ArI(CH_2CF_3)]^+(OTf)^-$ etc. have been mainly explored, but either these motifs are expensive or require days for their synthesis (Figure 3.3).[10] Moreover, the instability of these alkyl electrophiles towards transition metal-catalyzed pathways (CF_3CH_2-M) leads to hydrodehalogenation (CF_3CH_3) or β-F elimination ($CF_2=CH_2$) in coupling reactions.[11] On the other hand, trifluoroethylation can easily be obtained by *in situ* generating 2,2,2-trifluorodiazoethane (CF_3CHN_2) in solution from

$CF_3CH_2NH_2 \cdot HCl$.[12] Albeit safety studies specific to CF_3CHN_2 in solution have not been carried out to our knowledge, Pavel K. Mykhailiuk suggests "*it is safer to use its diluted solutions in organic solvents generated either in situ or in flow.*"[13]

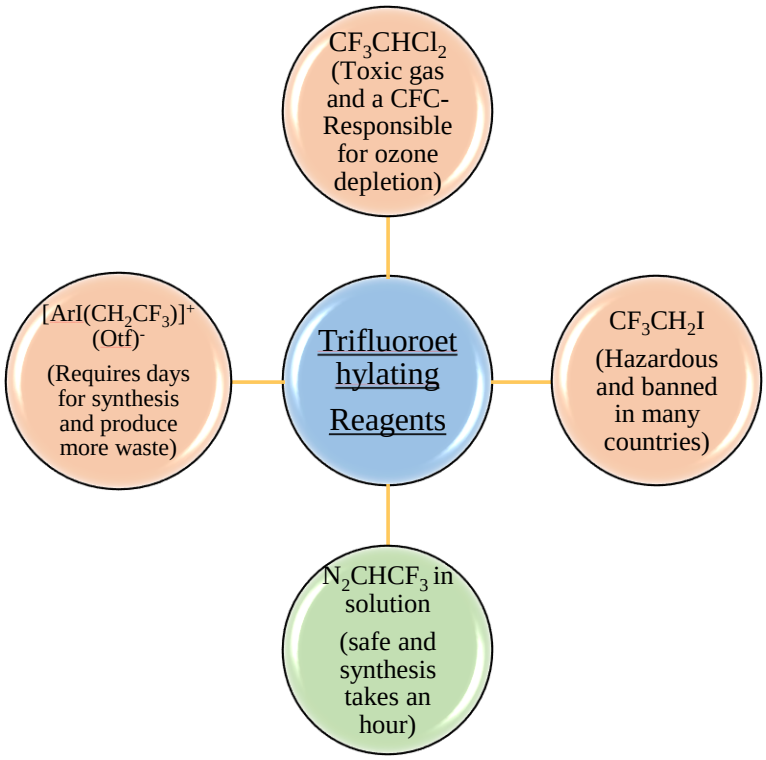
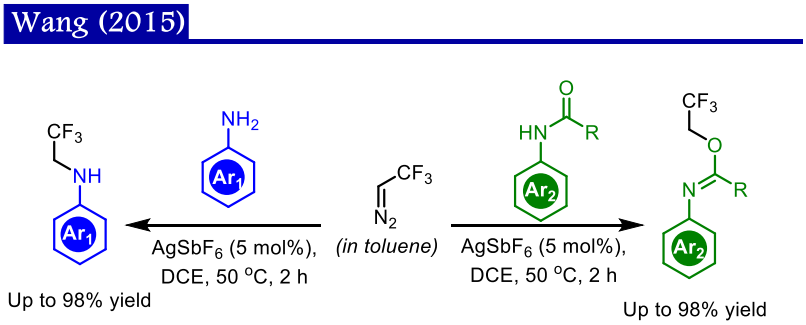


Figure 3.3. Different trifluorinating reagents used in chemical transformations.

CF_3CHN_2 shows a variety of reactivity modes and tends to react as *N*-Electrophile and *C*-Nucleophile. In addition, it also exhibits reactivity *via* CF_3CH:-carbene and undergoes cycloadditions.[13] Wang *et al.* developed a method for N-trifluoroethylation of anilines using CF_3CHN_2 from $CF_3CH_2NH_2 \cdot HCl$. The reaction involved Ag^I/carbene formation and a subsequent insertion mechanism (Scheme 3.1). Similarly, O-trifluoroethylation products were obtained with

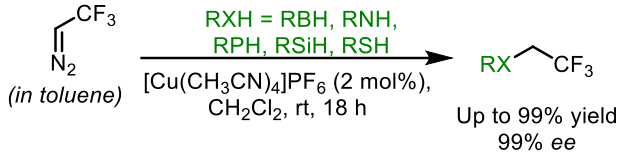
amides as substrates. To date, only this report illustrated the trifluoroethylation of acyclic amides using CF_3CHN_2 in the presence of a silver (I) catalyst.[14] The protocol offered mild reaction conditions with a wide range of functional groups, making it a promising technique for drug discovery in medicinal chemistry.



Scheme 3.1. Silver(I)-catalyzed trifluoroethylation of anilines and acyclic amides.

Gouverneur and co-workers developed a highly innovative method that enables the insertion of 1-aryl-2,2,2-trifluoro-1-diazoalkanes into a range of different bonds, including Si-H, B-H, P-H, S-H, and N-H bonds, using a catalytic process (Scheme 3.2). This groundbreaking transformation opens up new possibilities for synthesizing a diverse and extensive range of chiral CF_3-substituted molecules that were previously unavailable. Additionally, by using enantioselective Si-H and B-H insertion reactions, which are catalyzed by CuI complexes based on chiral bisoxazoline ligands, high yields with exceptional enantioselectivity were obtained, making this process an exciting prospect for future research and development.[15]

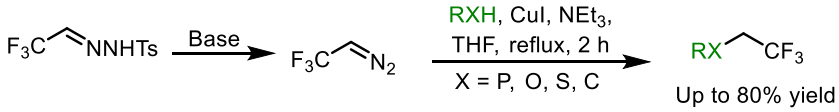
Gouverneur (2016)



Scheme 3.2. Trifluoroethylation of RBH, RNH, RPH, RSiH, RSH using copper-catalyzed insertion.

In 2019, Titanyuk reported a stable precursor, trifluoroacetaldehyde N-tosylhydrazone (TFHZ-Tfs), which was then used to generate CF_3CHN_2 under mild basic conditions. This method was much safer than using a hazardous diazo compound. They further showed a simple and easy method that could be used to directly and efficiently add a trifluoroethyl group to dialkyl phosphonates, thiols, carboxylic acids, and terminal alkynes using copper(I) as a catalyst (Scheme 3.3).[16]

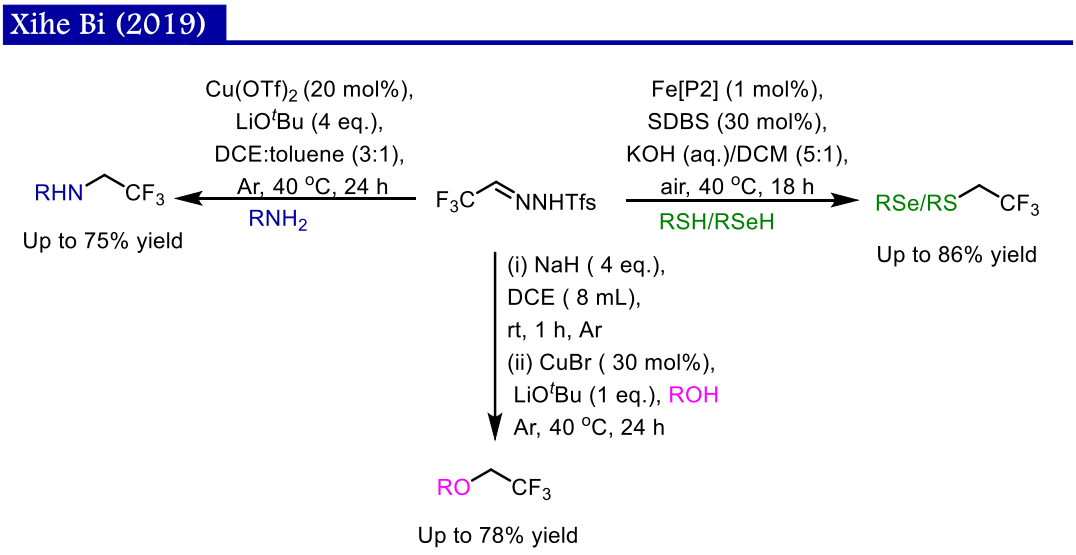
Titanyuk (2019)



Scheme 3.3. Trifluoroethylation of RPH, ROH, RSH, and RCH *via* carbene insertion using trifluoroacetaldehyde N-tosylhydrazone.

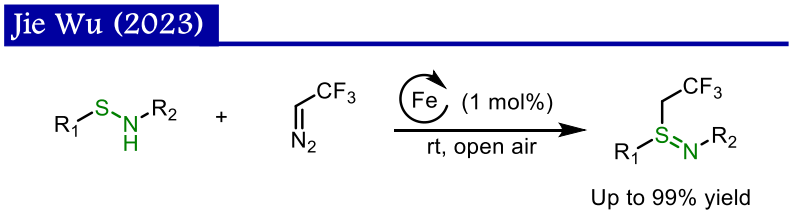
Furthermore, the researchers employed the same stable precursor- TFHZ-Tfs to facilitate the controlled release of CF_3CHN_2 into the reaction system. This strategy involved the decomposition of TFHZ-Tfs under basic conditions, which eliminated the need for the slow addition of CF_3CHN_2.

This approach not only minimized the exposure risk but also reduced the explosion risk associated with CF_3CHN_2. In addition, the authors reported the novel reactivity of CF_3CHN_2, which was used in the difluoroalkenylation of X-H bonds, where X can be N, O, S, or Se (Scheme 3.4). This method overcame the challenges and limitations of previous routes. Moreover, CF_3CHN_2 demonstrated excellent stereoselectivity and high yields when used in Doyle-Kirmse and cyclopropanation reactions, which suggested its potential utility as a trifluorodiazoethane surrogate. Overall, this study highlighted the significance of TFHZ-Tfs as a bench-stable CF_3CHN_2 precursor and the base-mediated approach as a safe and efficient method to release CF_3CHN_2 into the reaction system. The findings also shed light on the promising reactivity of CF_3CHN_2 in various synthetic applications.[17]



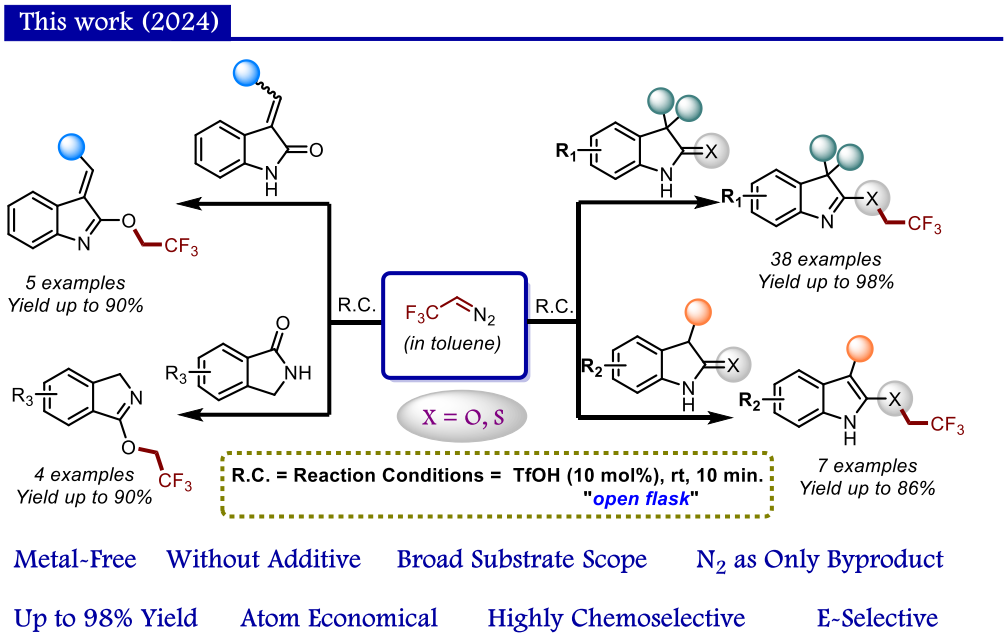
Scheme 3.4. Trifluoroethylation of RNH_2, ROH, RSH, and RSeH using trifluoroacetaldehyde N-tosylhydrazone.

In the year 2023, a team led by Wu developed a highly efficient method for synthesizing trifluoroethylated sulfilimines. Their process involved using sulfenamides and 2,2,2-trifluorodiazoethane with an inexpensive and green iron(II) phthalocyanine catalyst (Scheme 3.5). The process was characterized by its ease-of-use, operation under mild conditions and had broad substrate scope. It was also able to accommodate the presence of various functional groups. Through the use of this process, the team was able to obtain various trifluoroethylated sulfilimines in high yields of up to 99% with high chemoselectivity. Furthermore, diazoacetonitrile or diazomethylphosphonate were also employed as diazo reagents to extend the methodology for the synthesis of respective sulfilimines derivatives.[18]



Scheme 3.5. Trifluoroethylation of thioamides using iron-catalysis.

On the other hand, the chemoselective installation of trifluoroethyl moiety in cyclic amides and cyclic thioamides is still unexplored. As a part of our ongoing research on exploring the reactivity of oxindoles and thio-oxindoles, I have unfolded the metal- and additive-free TfOH-catalyzed chemoselective trifluoroethylation of oxindoles, isoindolines, and thio-oxindoles (Scheme 3.6).



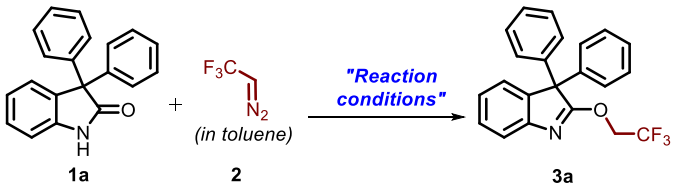
Scheme 3.6. Trifluoroethylation of oxindoles, thio-oxindoles and isoindolines.

3.2 Results and Discussions

In the course of obtaining the optimized reaction conditions for the O-trifluoroethylation of oxindoles, I commenced a reaction by taking 3,3-diphenyl indoline-2-one **1a** as the model substrate for screening various initiators in the presence of *in situ* generated 2,2,2-trifluorodiazoethane **2** in toluene (Table 3.1). At the onset, the reaction showed good results under transition metal catalysts through carbene formation (CuI and CuO) but I wanted to introduce trifluoroethyl group under metal-free conditions as it is the need of the hour to advance not only selective, efficient, and high-yielding but also environment-friendly, green, and safe approaches for organic reactions. Initially, nitrogenous bases like 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, 2,6-di-*tert*-butyl-pyridine (DTBPy), 4-(Dimethylamino)pyridine (DMAP) and quinolone were employed as initiators in this survey, however, in all these cases, either reaction went sluggish or a complex

mixture was observed (Table 3.1, entries 1-5). Interestingly, when DIPEA was utilized as a base, the desired product, **3a** was observed in 70% yield (Table 3.1, entry 6). The reaction was further explored with tertiary amines like NEt_3, NPh_3, and NBn_3, however, further improvement in the yield was not observed (Table 3.1, entries 7-9). Moreover, an array of inorganic bases like NaH, *t*-BuOK, K_2CO_3, and Cs_2CO_3 were also investigated; unfortunately, none of these could offer us the desired product (Table 3.1, entries 10-13). Afterward, I turned my attention toward Lewis and Brønsted acids as reaction promoters for the mentioned reaction. Lewis acids like $AlCl_3$ and $BF_3{\cdot}OEt_2$ were noticed completely ineffective for the said reaction (Table 3.1, entries 14-15). At this point, we enquired about the proton source of trifluoroethylation in the case of base and performed a reaction in the presence of a drop of D_2O and found the formation of O-$CHDCF_3$ (see experimental section). In order to provide a better proton source, I performed the reaction in acidic conditions, and to our delight, the use of Brønsted acids like *p*-TSA and trifluoroacetic acid (TFA) furnished the product, **3a** with moderate yields (Table 3.1, entries 16-17). In the process of enhancing the yield, the reaction was further performed using TfOH, and to our delight, targeted product **3a** was obtained in excellent yield within 10 minutes at ambient temperature (Table 3.1, entries 18-19). Further screening of other reaction parameters like varying solvents from toluene to benzene, DCM, DCE, $CHCl_3$ could not prove to be effective.

Table 3.1 Optimization of the reaction conditions[a,b]



Entry	Initiator	Temp.	Time	Yield **3a**[b]

1	DBU	80 ºC	24 h	n.r.
2	Pyridine	80 ºC	10 h	c.m.
3	DTBPy	80 ºC	24 h	n.r.
4	DMAP	80 ºC	24 h	n.r.
5	Quinoline	80 ºC	20 h	n.r.
6	DIPEA	80 ºC	5 h	70 %
7	NEt_3	80 ºC	10 h	60 %
8	NPh_3	80 ºC	8 h	30 %
9	NBn_3	80 ºC	8 h	47 %
10	NaH	rt	8 h	c.m.
11	KO*t*-Bu	80 ºC	8 h	n.r.
12	K_2CO_3	80 ºC	10 h	c.m.
13	Cs_2CO_3	80 ºC	10 h	c.m.
14[c]	$AlCl_3$	80 ºC	10 h	n.r.

15[c]	$BF_3 \cdot OEt_2$	80 ºC	24 h	n.r.
16[c]	*p*-TSA	rt	2 h	67%
17[d]	TFA	rt	2 h	42 %
18[c]	TfOH	rt	10 min.	89 %
19[c, e]	**TfOH**	**rt**	**10 min.**	**90 %**

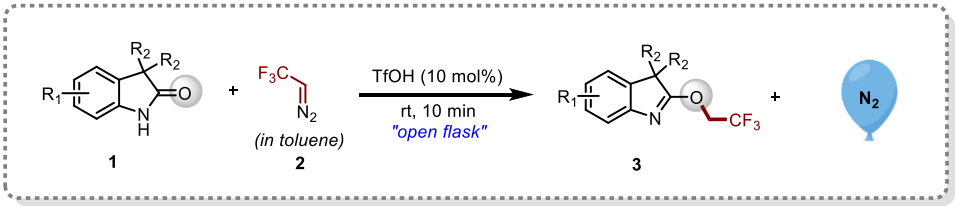
n.r. = no reaction, c.m. = complex mixture, [a]Reaction conditions: **1a** (0.2 mmol, 1 eq.), **2** ([0.5 M], 1.1 eq.), initiator = (2 eq.), N_2 atmosphere, neat. [b]isolated yield, [c]initiator used 10 mol%, [d]initiator used 20 mol%, [e]reaction performed in an open flask.

Having optimal reaction conditions in hand, I further explored several oxindoles **1** with *in situ* generated 2,2,2-trifluorodiazoethane (in toluene) **2** to determine the substrate scope and generality of the proposed protocol as shown in Scheme 3.7. In this context, I began my study with 3,3 diphenyl substituted oxindole **1a** and afforded the desired product **3a** in 90% yield. Afterward, different halide (-F, -Cl, -Br, -I) substituted oxindole derivatives (**1b-1m**) were investigated, and it was found that all of them furnished the product **(3b-3m)** in good to excellent yields. Next, the electron-donating groups (-Me and –OMe) on oxindole, were carried out and the desired compounds **3n-3r** were obtained in good yields. Analogously, the reaction worked well with 5-NO_2 substituted oxindole **1s** and furnished the corresponding desired product **3s** in 82% yield, which indicated the incredible functional group tolerance of the developed protocol. Further, the 3,3-substituted dibenzyl oxindole **1t** also delivered the chemoselective product **3t** in good yield. Meanwhile, substituents at the C3 position having *p*-EDG and *p*-EWG attached to the aryl group on the oxindoles were also exploited under optimized reaction conditions and achieved the targeted

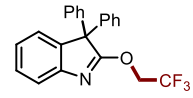
products **3u-3x** with high yields. Remarkably, 2-oxindole having deuterated diphenyl groups at the C3 position delivered O-trifluoroethylated derivative **3y** in 90% yield. The structure of compound **3y** was unambiguously determined using a single crystal XRD analysis. Next, I explored the scope of 3,3 dialkyl substituted oxindoles under the standard reaction conditions, and product **3z** was obtained with an 82% yield. Similarly, spiro derivatives also behaved well in the reaction and furnished the products **3aa** and **3ab** with excellent yields.

To establish the potential of the newly developed methodology, I applied the same reaction protocol for thio-oxindoles and as expected, I observed the chemoselective S-trifluoroethylation product **5a** in almost quantitative yield (Scheme 3.8). Initially, I explored halide substituted thio-oxindole derivatives and it is worth noting that the compounds **5b-5e** were successfully furnished in good to excellent yields. The reaction went well with various methyl-substituted thio-oxindole derivatives **4f** and **4g** and afforded corresponding S-trifluoroethyl decorated oxindole derivatives **5f** and **5g,** respectively. In addition, the formation

Chapter 3



Varition in 3,3 disubstituted 2-oxindoles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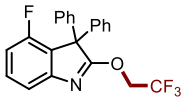
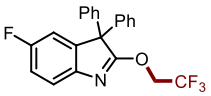

3b, 92%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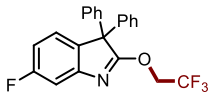
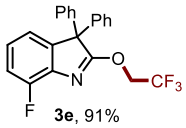
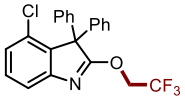

3d, 93%


3e, 91%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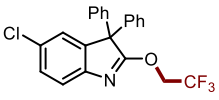
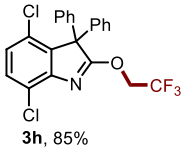

3g, 90%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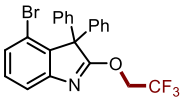
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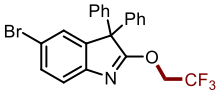
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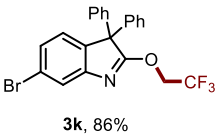
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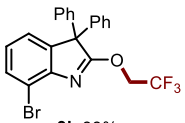
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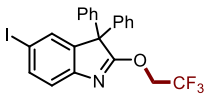
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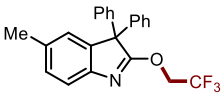
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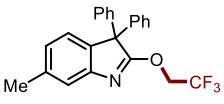
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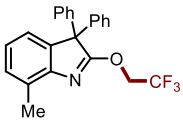
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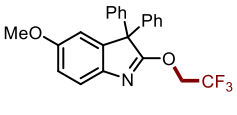
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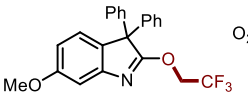
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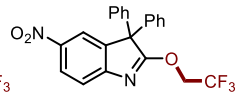
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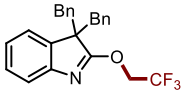
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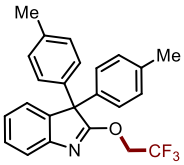
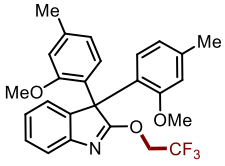

3u, 91%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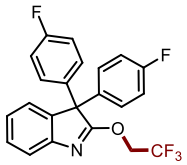
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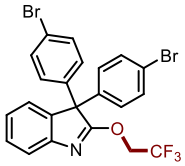
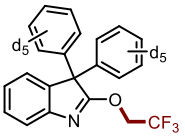
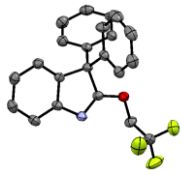

3x, 87%


3y, 90%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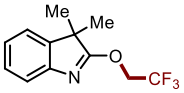
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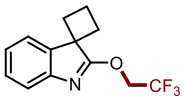
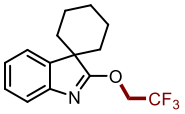
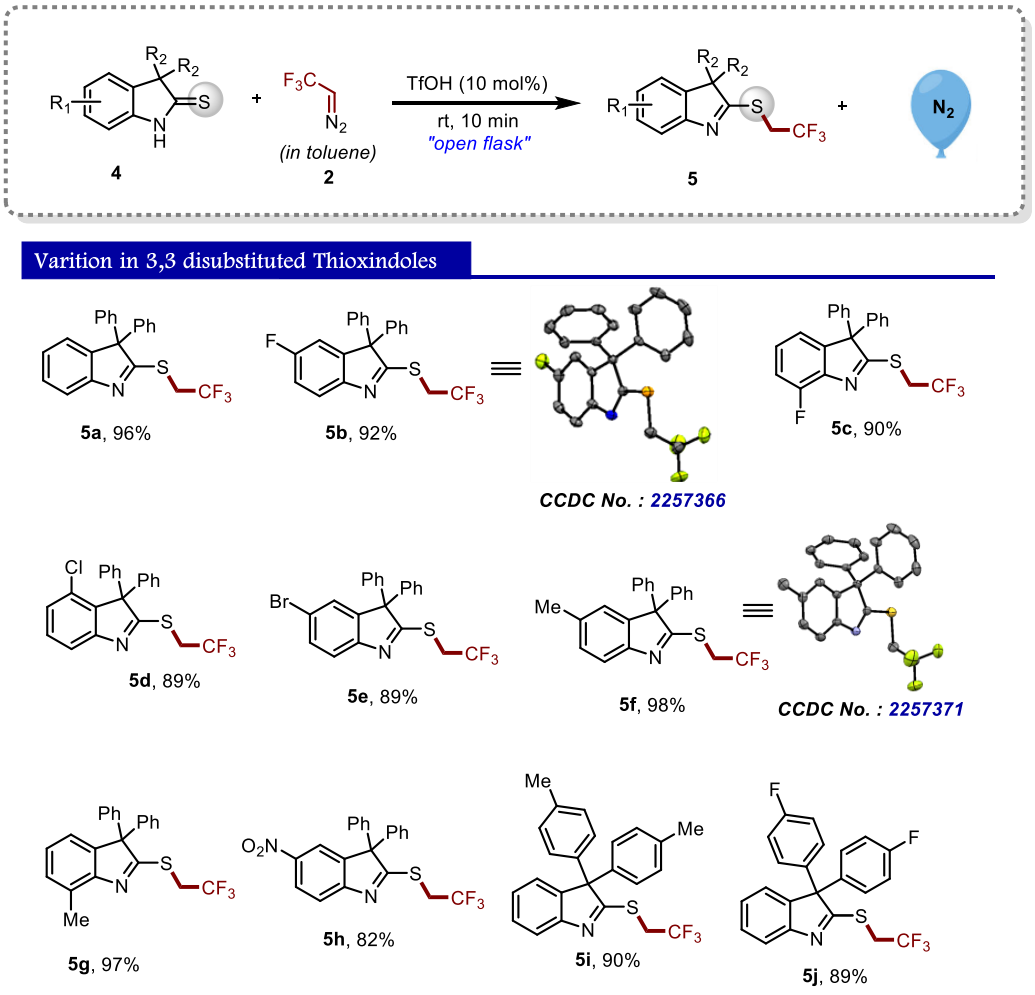

3aa, 85%


3ab, 87%

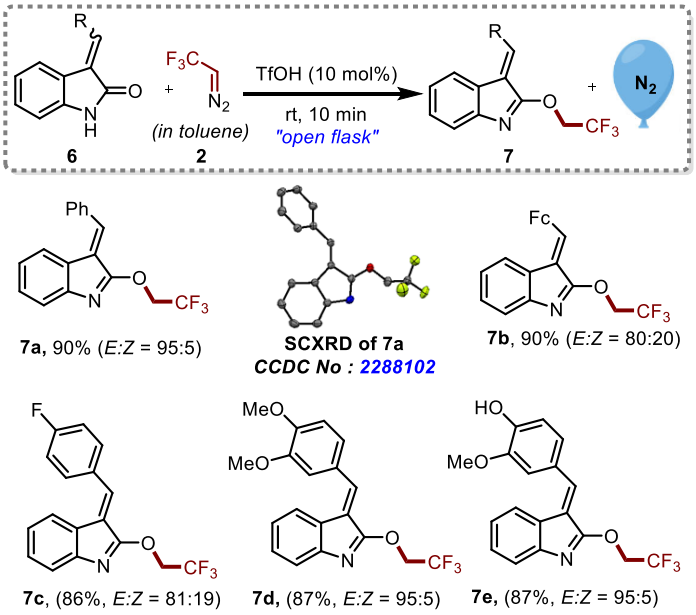
Scheme 3.7. Synthesis of O-trifluoroethylated oxindole derivatives.[a,b] [a]Reaction conditions: **1** (0.2 mmol, 1 eq.), **2** ([0.5 M], 1.1 eq.), TfOH (10 mol%). [b]Isolated yield.

of compound **5h** demonstrated that the reaction was not limited to electron-donating derivatives, but also worked well for electron-withdrawing substituents. In a similar fashion, introducing the –Me and –F moieties on the phenyl ring at the third position of the thio-oxindole, furnished the products, **5i, 5j** in good yields.



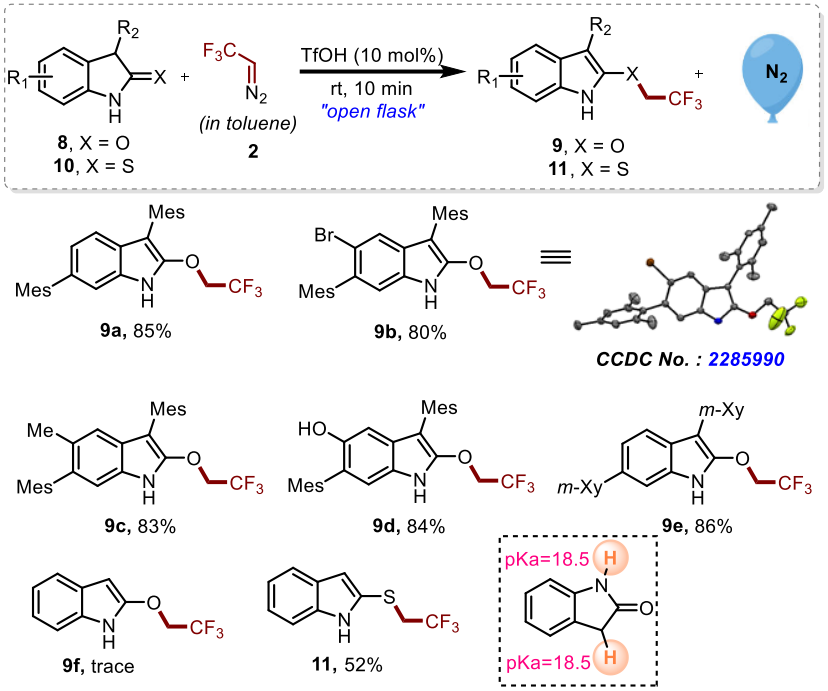
Scheme 3.8. Synthesis of S-trifluoroethylated thio-oxindole derivatives.[a,b] [a]Reaction conditions: **4** (0.2 mmol, 1 eq.), **2** ([0.5 M], 1.1 eq.), TfOH (10 mol%). [b]Isolated yield.

Emboldened by the efficiency of this protocol, I further explored the possibility of the O-trifluoroethylation on several oxindole-based chalcones **6a-e,** which are known to inhibit Melanogenesis (production of extra pigment melanin).[19] Besides this, **6e** is also known to exhibit biological activities as an entrenched anti-oxidative agent as well as tyrosinase inhibitor.[20] A mixture of cis and trans isomers of the compounds **6** were subjected to this approach to furnish the desired products **7a-e** with *E*-isomer as the major product, as represented in Scheme 3.9. It is noteworthy that, even in the presence of hydroxyl substituent in **6e**, I was able to obtain the O-trifluoroethylation of amide exclusively.

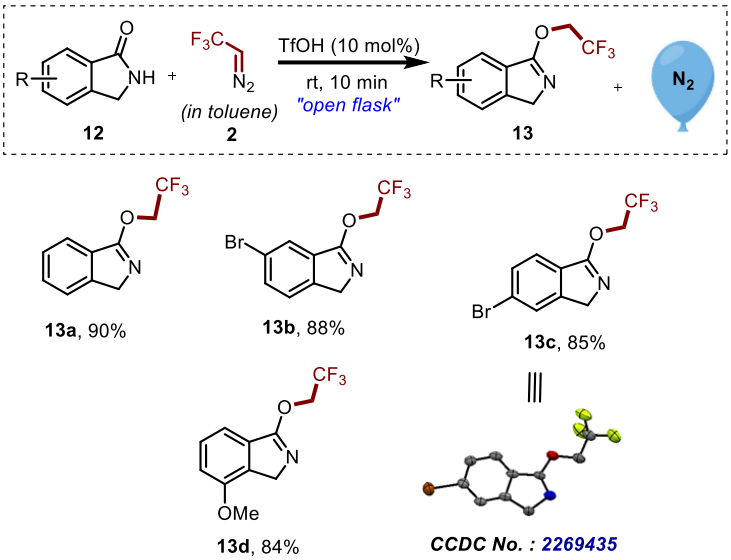


Scheme 3.9. Synthesis of trifluoroethylated oxindole-based chalcone derivatives.[a,b,c] [a]Reaction conditions: **6** (0.2 mmol, 1 eq.), **2** ([0.5 M], 1.1 eq.), TfOH (10 mol%). [b]Isolated yield. [c]*E:Z* was determined through crude NMR.

In order to investigate the effect of substituents at the C3 position of oxindoles and thio-oxindole, monosubstituted and unsubstituted oxindoles and thio-oxindole were tested under the established reaction conditions (Scheme 3.10). By utilizing the optimized reaction conditions, 2-trifluoroethyoxy indole derivatives **9a-e** were afforded due to the chemoselective proton abstraction from the C3 position of oxindoles over NH proton present on **8a-e**. On the other hand, C3 unsubstituted 2-oxindole **8f** offered the product **9f** only in trace amount and that might be due to identical pKa values of C3-H and NH as represented in Scheme 3.10.[21] Luckily, with C3 unsubstituted thio-oxindole **10**, I was able to access the corresponding trifluoroethylated derivative **11** in good yield.



Scheme 3.10. Exploration of mono- and unsubstituted oxindoles and thio-oxindoles for chemoselective trifluoroethylation.[a,b] [a]Reaction conditions: **8** or **10** (0.2 mmol, 1 eq.), **2** ([0.5 M], 1.1 eq.), TfOH (10 mol%). [b]Isolated yield.

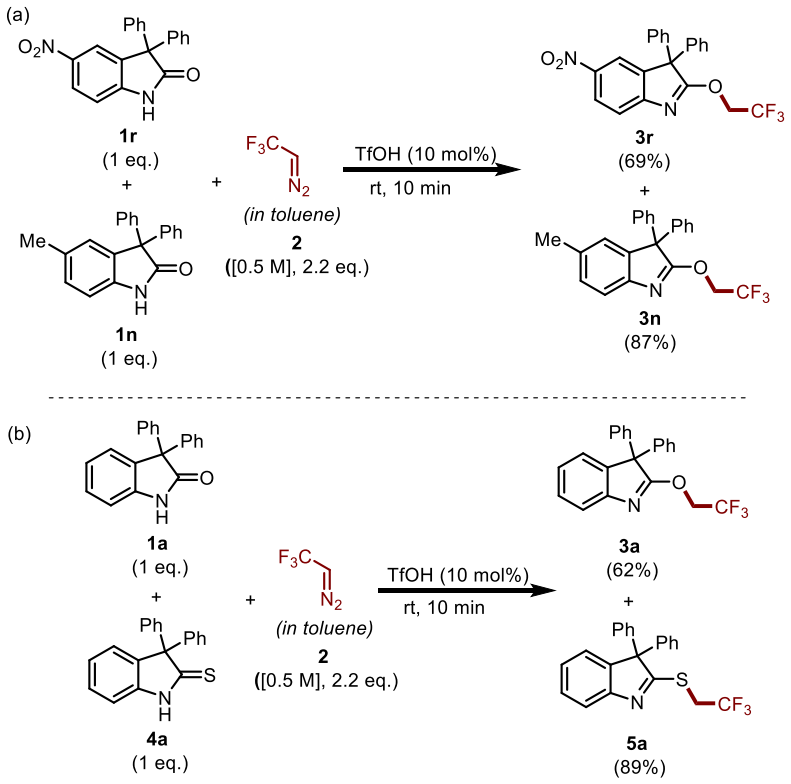


Scheme 3.11. Synthesis of 3-(2,2,2-trifluoroethoxy)-1*H*-isoindole derivatives **13a-d**.[a,b] [a]Reaction conditions: **12** (0.3 mmol, 1 eq.), **2** ([0.5 M], 1.1 eq.), TfOH (10 mol%). [b]Isolated yield.

In the course of in-depth studies, I focused my attention on analyzing the conjugation effect of the aromatic ring on the carbonyl part of compound **12** and checked the practicality of the established strategy. To our surprise, an exclusive chemoselective O-trifluoroethylation over N-trifluoroethylation was observed and as a result, a library of substituted isoindoline derivatives **13a-d** were synthesized in good to excellent yields as exhibited in Scheme 3.11.

To gain the reaction insight, I carried out two competitive experiments which are summarized in Scheme 3.12. Initially, I performed an experiment with a mixture of electron-rich oxindole **1n** and an electron-deficient oxindole **1r** under the standard reaction conditions and achieved compound **3n** in 87% yield and compound **3r** in 69% yield. This result suggested that **1n** is more reactive than **1r** in the reaction medium. On the same note, another experiment was performed between

oxindole **1a** and thio-oxindole **4a**, it demonstrated the synthesis of S-trifluoroethylated product **5a** in major amounts as compared to that of O-trifluoroethylated product **3a**.

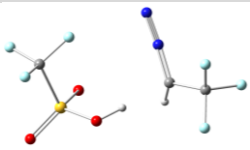
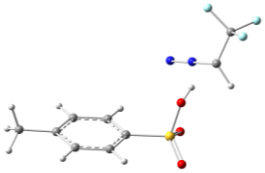
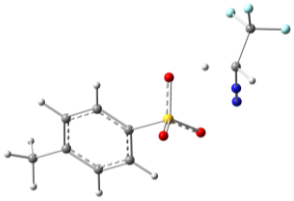
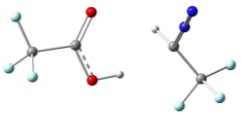
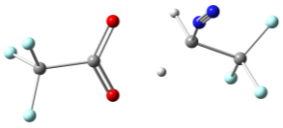


Scheme 3.12. Competitive experiments: (a) electron-deficient *vs* electron-rich oxindoles; (b) oxindole *vs* thio-oxindole.

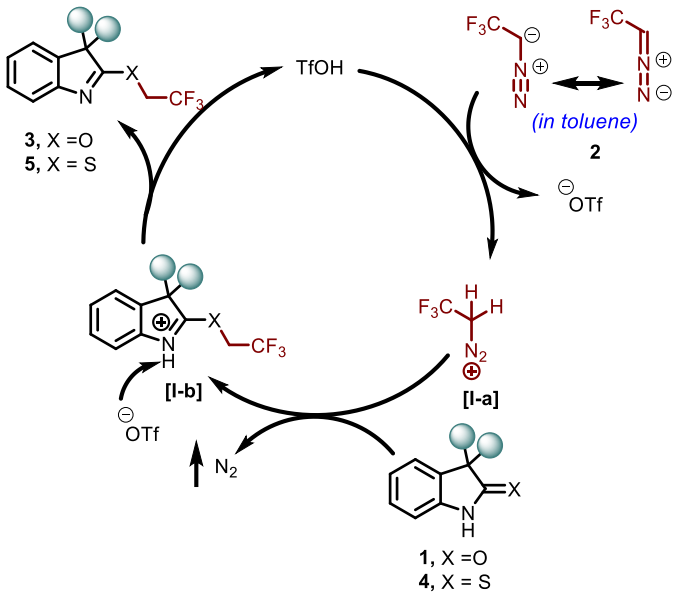
To gain deeper mechanistic insights, I conducted theoretical studies of different acids at the B3LYP/6-31G(d) level to examine my hypothesis. All structures have been optimized at B3LYP/6-31G(d) level and the details are presented in Table 3.2 of the experimental section. During the preliminary examination, it was found that the process of abstracting a proton from a Brønsted acid is thermodynamically endergonic, which demands an input of energy. As a result,

this step is a rate-determining step for the reaction. In this context, I specifically focused on the proton abstraction capability of three Brønsted acids *i.e*. TfOH, TFA, and *p*-TSA by N_2CHCF_3 **2**, and the results are summarized in Table 3.2. The data presented in Table 2

Table 3.2 GS structure, TS structure and Gibbs free energy ($\Delta G^{\ddagger}$) for H-abstraction.

2 + Acid	**Ground State (GS)**	**Transition State (TS)**	**$\Delta G^{\ddagger}$**
2 + TfOH			7.13 kcal/mol
2 + *p*-TSA			14.83 kcal/mol
2 + TFA			17.51 kcal/mol

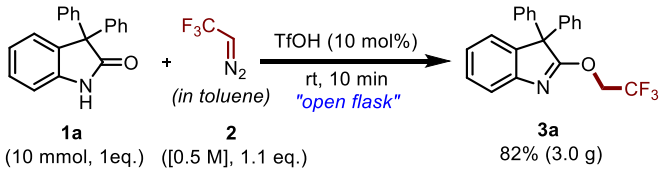
indicates that the H-abstraction from TfOH results in the lowest energy barrier, whereas TFA has the highest. It is noteworthy that all the reactions are thermodynamically feasible, as the transition state is attainable at room temperature. Nevertheless, the kinetics of the reaction varies depending on the reaction pathway. In this process, the transition states (TS) of complex (**2**+TfOH) have been also verified by the imaginary frequency and intrinsic reaction coordinate (IRC) calculations as shown in experimental section. The ground state (GS) and transition state (TS) of complex (**2** + TfOH) are located at 4 and 0 respectively, however, protonated **2** ($N_2CH_2CF_3$) is located at -4. The uphill trajectory, observable in the reaction, plays a crucial role in governing its kinetics. This trajectory is consistent with the other two acids as well. As a result, the reaction involving TfOH delivers the corresponding product fastest compared to the other two Brønsted acids.



Scheme 3.13. Plausible mechanistic pathway.

Next, based on these studies and previous report,[22] a plausible reaction mechanism for the chemoselective O- and S-trifluoroethylation of oxindoles **1** and thio-oxindoles **4** respectively, is outlined in Scheme 3.13. Initially, catalyst TfOH protonated 2,2,2-trifluorodiazomethane **2** and formed an activated intermediate **I-a**. A nucleophilic attack on the intermediate **I-a** through the O or S-centre (chemoselectively) of the compounds **1** or **4** resulted in a new intermediate **I-b**. Finally, proton abstraction from **1-b** by the triflate ion leads to the formation of the final products **3** or **5**.

To investigate the applicability of the proposed methodology, a preparative-scale synthesis of compound **3a** was conducted. To our delight, I afforded 3.0 g of the desired product with magnificent chemoselectivity (Scheme 3.14).



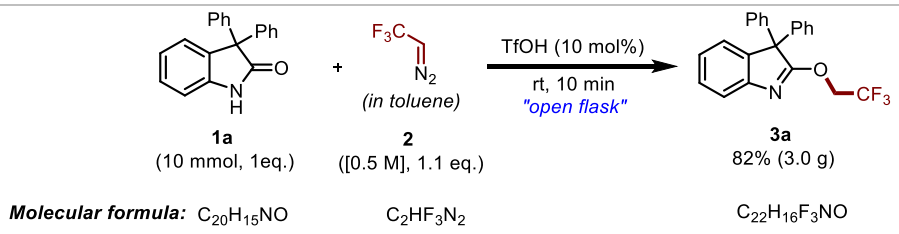
Scheme 3.14. Gram scale synthesis of **3a**.

Thereafter, I determined the various green chemistry metrics (E factor, atom economy, carbon efficiency, and reaction mass efficiency) for the reaction protocol taking compound **1a** as a model substrate (Table 3.3). Gratifyingly, the developed approach has high atom economy (93%), carbon efficiency (100%), reaction mass efficiency (74%), and lower E-factor (0.40 kg waste/1kg product) indicating the greenness of the methodology.

In addition, I conducted an EcoScale evaluation based on six parameters, namely yield, temperature/time, price of reaction components, technical setup, safety, workup, and

purification.[23] The result of this evaluation, as presented in Table 3.4, indicates a remarkable EcoScale value of 86, signifying the implementation of an excellent green synthesis protocol that is safe, technically sound, and environmentally friendly. This C-O bond-forming chemoselective transformation does not generate any hazardous by-products, rendering it a viable option for green synthesis protocols. Furthermore, the reaction requires none of the expensive metals, or harsh reaction conditions commonly employed in many synthetic methods, making it a cost-effective and safe approach.[24] The reaction setup is straightforward, and the reaction can be executed efficiently at room temperature within a few minutes. These key features make this process an exemplary and eco-friendly green process.

Table 3.3. Evaluation of green chemistry metrics in the synthesis of 3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole.



	Chemicals	Molecular weight (g/mol)	Weight (mg)
Substrate **1a**	3,3-diphenylindolin-2-one	285.1154	2850.1 mg
Substrate **2**	2,2,2,-trifluorodiazoethane	110.0092	1210.1 mg

Catalyst	Trifluoromethanesulfonic acid	150.08	150 mg
Solvent used	toluene	92.14	1724 mg
Solvent recovered	toluene	92.14	1720 mg
Product **3a**	3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole	367.1184	3009.4 mg (82%)
Waste (byproducts)	-	-	1204.1 mg (18%)

E-factor = (Total mass of waste from process / Total mass of product)

= (1204.1/ 3009.4) = **0.40 kg waste/1kg product**

Atom Economy = (Molecular mass of product / Molecular masses of substrates) × 100

= (367.1184 / 395.1246) × 100 = **93%**

Atom Efficiency = (% yield of product x % atom economy)/100

= (82 x 93)/100 = **76.26 %**

Carbon Efficiency = (Amount of carbon in product / Amount of carbon in reactants) × 100

= {22/ (20 + 2)} × 100 = **100 %**

Reaction mass efficiency (RME) = {Mass of **3a** / (Mass of **1a** + Mass of **2a**)} × 100

= {3009.4 / (2850.1 + 1210.1)} × 100 = **74 %**

Table 3.4. EcoScale penalty points in the synthesis of 3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole, **3a**

	Parameter	Penalty points
1	Yield (100–82 % yield)/2 = 9	= 9
2	Total cost of synthesis of 10 mmol of **3a** <$50	= 0
3	Safety	
	2,2,2-trifluorodiazoethane	= 5
4	Technical setup (Simple setup)	= 0

5	Temperature/time (Room temperature, <1h)	= 0
6	Workup and purification	
	(Classical chromatography)	= 0
	Total of individual penalties	= 14

EcoScale calculation = 100 – sum of individual penalities = 100 – 14 = **86**

Following scores: **>75, excellent**; >50, acceptable; and <50, inadequate

3.3 Conclusions

In this study, I have successfully introduced a straightforward and effective procedure for the chemoselective O-trifluoroethylation of 3,3-disubstituted, monosubstituted, unsubstituted, chalcone-based oxindoles, isoindolines, and S-trifluoroethylation of thio-oxindoles under mild reaction conditions, without the need of hazardous fluorinating reagents. The products are achieved in excellent yields and in the case of chalcone-based oxindoles, *E*-selective products were obtained. Remarkable functional group compatibility and exclusive chemoselectivity clearly indicate the potentiality of the protocol. This is the first time such a method has been developed as I used an environmentally benign catalyst, such as TfOH. Unlike previous trifluoroethylation synthetic protocols, our method involves the use of renewable, inexpensive feedstock chemicals without solvent, making it more sustainable. Furthermore, I calculated various green chemistry metrics, such as high atom economy (93%), carbon efficiency (100%), reaction mass efficiency (74%), and lower E-

factor (0.40 kg wastw/1 kg product), all of which indicate the protocol's "greenness." The EcoScale evaluation demonstrates the simplicity, efficacy, and environmental friendliness of this methodology.

3.4 Experimental Section

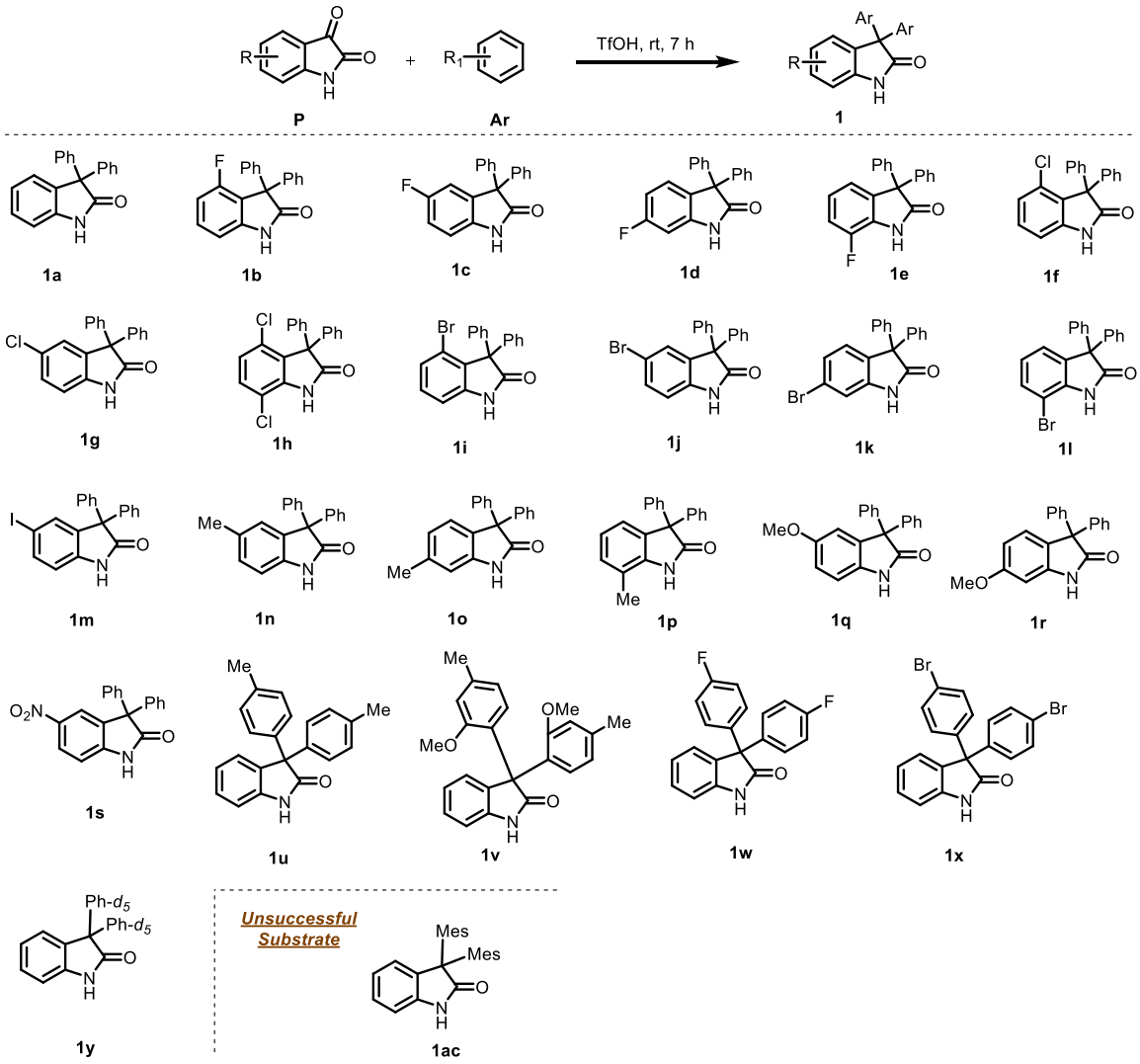
Unless otherwise noted, all reactions were performed on a Schlenk vacuum line or in a glovebox using oven-dried glassware and were stirred with teflon-coated magnetic stirring bars. All the chemicals and reagents were purchased from commercial suppliers Sigma Aldrich, GLR Innovations, BLD Pharma, Spectrochem and used without further purification. Solvents were dried and stored over molecular sieves under an argon atmosphere prior to use. All work-up and purification procedures were done with reagent-grade solvents in an air atmosphere. Reaction temperatures above 25 °C refer to temperatures of an aluminum heating block or a silicon oil bath, which were controlled by an electronic temperature modulator from Heidolph. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh). ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded in $CDCl_3$ and d_6-DMSO, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz {^{1}H} or 101 MHz {^{13}C} as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million (ppm) relative to residual solvent ($CDCl_3$, δ= 7.26 for ^{1}H NMR and 77.16 for ^{13}C NMR, d_6-DMSO: δ = 2.50 for ^{1}H NMR and δ = 39.52 for ^{13}C NMR) and coupling constants (J) in Hz. Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet, dt for doublet of triplet, and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF). The data

collection for single crystal S-3 X-ray was performed at a 298 K on a CMOS-based Bruker D8 Venture PHOTON 100 diffractometer equipped with INCOATEC micro-focus source with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. All solvents used for work-up and column chromatography were recovered by evaporation using a rota-vapor.

3.4.1 Preparation of Starting Materials

Synthesis of 3,3 diaryl substituted 2-oxindole derivatives (1)[25]:

To a solution of Indoline-2,3-dione or isatin, **P** (1 eq.) in freshly distilled triflic acid, respective arene (2.5 eq.) was added at room temperature. Monitored the reaction progress with thin-layer chromatography (TLC). Upon completion (as determined by TLC analysis) of the reaction, several grams of crushed ice were added to the reaction mixture and extracted with ethyl acetate. The combined organic layer was washed once with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure, which was further purified by silica gel column chromatography using hexane and ethyl acetate (8:2) as the eluent to afford 3,3 diaryl substituted 2-oxindoles, **1**.



Scheme 3.15. Synthesis of 3,3-aryl substituted oxindoles from isatins.

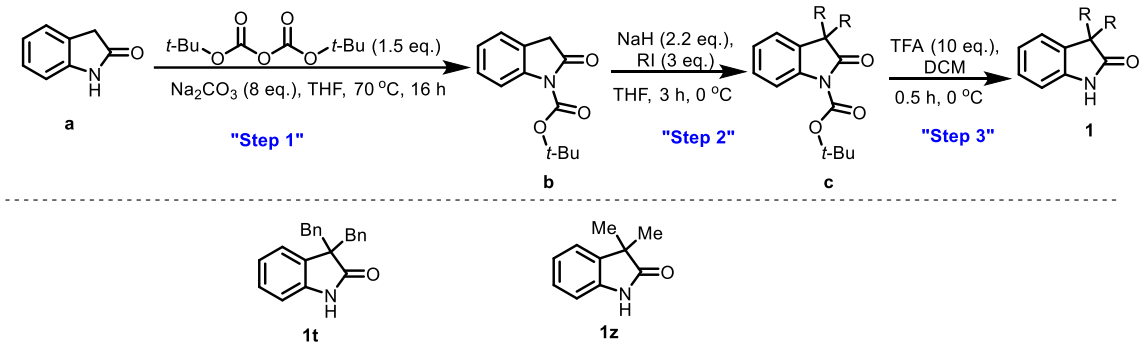
Synthesis of 3,3 dialkyl substituted 2-oxindole derivatives (1)[26]:

Step 1: To an oven-dried schlenk round-bottomed flask, indoline-2-one (1 eq.) was added and nitogen was purged. After that, freshly distilled THF was added and allowed to stir for

2 minutes. To this solution, Na_2CO_3 (8 eq.) was added and an ice bath was placed under the schlenk rbf. After cooling for 10 minutes, boc anhydride (1.5 eq.) was added dropwise and the ice bath was removed. Then the reaction mixture was placed over an oil bath and the reaction temperature was maintained up to 70 ^oC in the oil bath. Upon completion of the reaction, THF was recovered by evaporating on rota vapor and the reaction mixture was extracted with ethyl acetate. The crude mixture was purified through column chromatography using hexane and ethyl acetate as the eluent to obtain compound N-boc oxindole, **b** in 75 % yield.

Step 2: In an oven-dried schlenk round-bottomed flask, compound **b** (1 eq.) was added to freshly dried THF and nitrogen gas was purged. To this solution, methyl iodide or benzyl bromide (3 eq.) was added and the rbf was placed over an ice bath. Then, NaH (60 wt% mineral oil dispersion, 2.2 eq.) was added in three installments over a time lap of 15 minutes. After completion of reaction in 3 hours as monitored by TLC, THF was recovered by evaporating on rota vapor and cold water was added to the rbf. The product was extracted three times with DCM and the crude was further purified with column chromatography to afford N-boc 3,3-dialkyl oxindole, **c** in 65% yield.

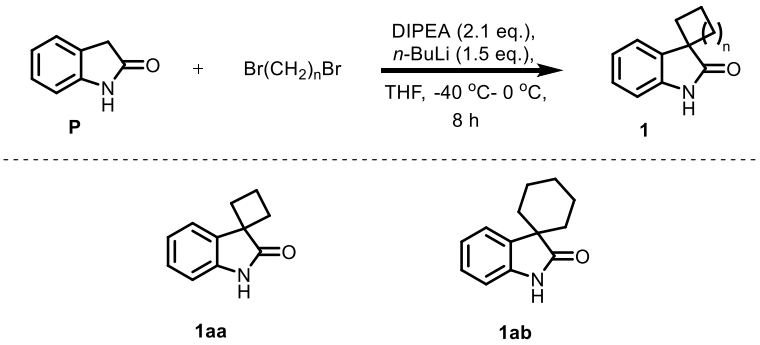
Step 3: To a solution of compound **c** (1 eq.) in DCM, TFA (10 eq.) was added dropwise while placing the rbf over ice bath and the reaction mixture was allowed to stir at room temperature for half an hour. After completion of the reaction as monitored by TLC, the solvent was collected back using rota-vapor and the crude product was purified using silica gel column chromatography to afford the final compound **1.**



Scheme 3.16. Synthesis of 3,3 dialkyl substituted 2-oxindole derivatives from 2-oxindole.

<u>Synthesis of spirocyclic 2-oxindole derivatives (1)[27]</u>:

To an oven-dried schlenk round-bottomed flask, indoline-2-one was dissolved in freshly dried THF and nitrogen gas was purged. The reaction mixture was transferred to the chiller having -40 °C temperature and DIPEA (2.1 eq.) was added to the solution followed by *n*-BuLi (1.5 eq.). After that, dibromopropane or dibromopentane (3 eq.) was added slowly and allowed to stir at 0 °C for 8 hours. Upon completion of the reaction as monitored by

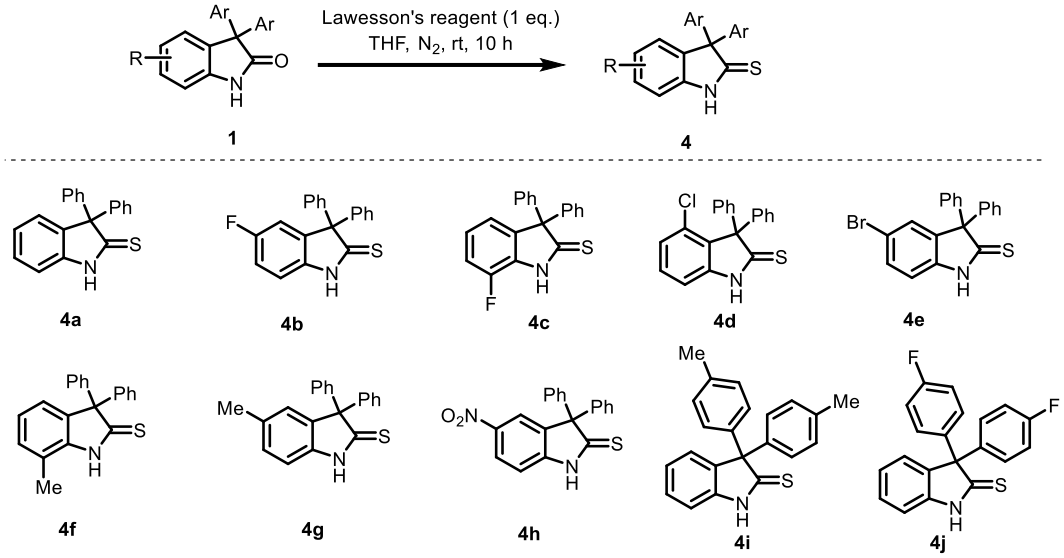


Scheme 3.17. Synthesis of spirocyclic 2-oxindole derivatives from 2-oxindole.

TLC, THF was recovered back by evaporating on rota-vapor and ice was added to the reaction mixture. The crude product was extracted with ethyl acetate and purified through silica gel chromatography to afford compound **1**.

Synthesis of 3,3-disubstituted thioindolin-2-one derivatives (4)[28]:

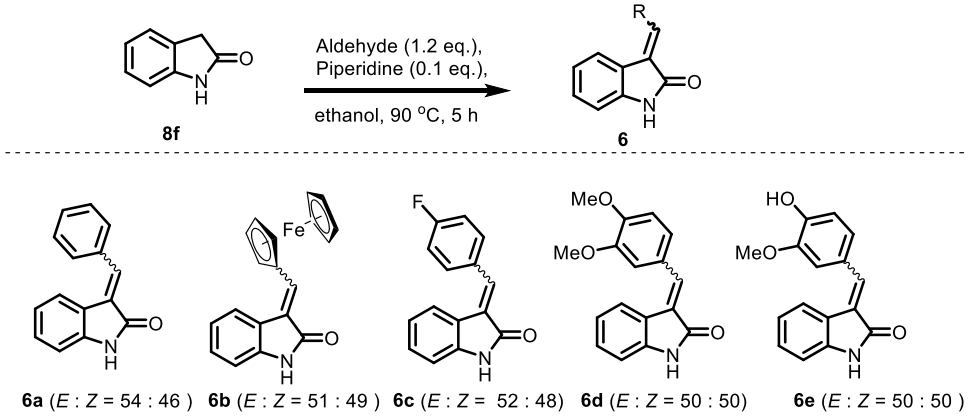
To a solution of 3,3-disubstituted indoline-2-one, **1** (1.5 eq.) in freshly dried THF, Lawesson's reagent (1 eq.) was added. The resulting reaction mixture was stirred under an argon atmosphere at ambient temperature for 10 hours. After completion of the reaction, THF was recovered through evaporation using rota-vapor, cold water was added to it and extracted with ethyl acetate. The complete organic layer was washed with brine and dried over sodium sulfate. Upon evaporation of the organic solvent under reduced pressure, a crude product was obtained which was further purified through silica gel column chromatography.



Scheme 3.18. Synthesis of thio-oxindole from 2-oxindole.

Synthesis of 3-Arylidenindolin-2-one derivatives (6)[29]:

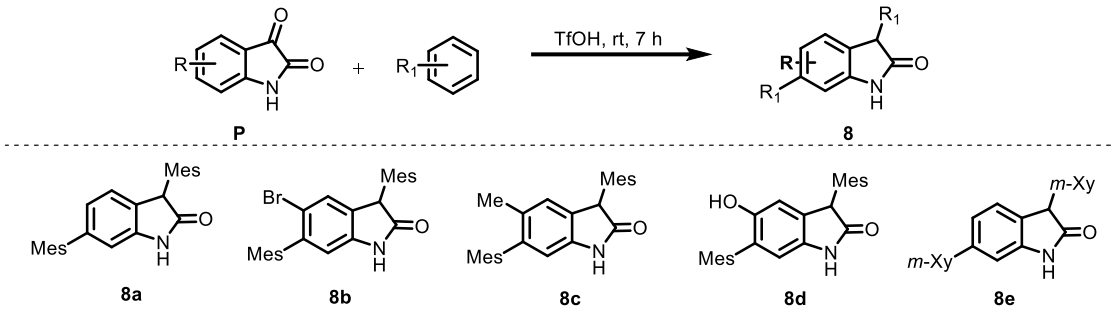
To a solution of indolin-2-one (1 eq.) in ethanol, aldehyde (1.2 eq.), piperidine (0.1 eq.) were added and stirred at 90 ^{o}C. After the completion of the reaction in 5 hours, the reaction mixture was cooled to room temperature and ethanol was recovered through evaporation using rota-vapor. The organic layer was extracted using ethyl acetate and dried over sodium sulfate. Upon evaporation of the solvent, a crude product was obtained as diastereomers and was used for the next step.



Scheme 3.19. Synthesis of 3-arylidenindoline-2-one derivatives from 2-oxindole.

Synthesis of 3,6-substituted indolin-2-one derivatives (8):

To a solution of isatin, P (1 eq.) in TfOH under an N_2 atmosphere, bulky arene was added and the resulting reaction mixture was stirred for 7 hours at ambient temperature. After analyzing the TLC, crushed ice was added to the reaction mixture and extracted with ethyl acetate. The complete organics were washed with brine once and dried over Na_2SO_4. The final product was isolated with excellent yield on purification through silica gel column chromatography.



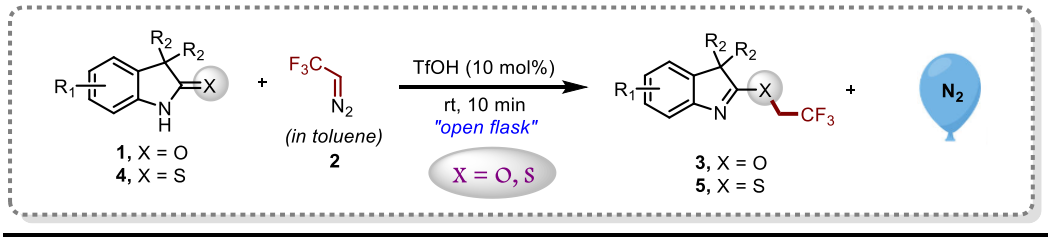
Scheme 3.19. Synthesis of 3,6- diaryl substituted 2-oxindole derivatives from isatin.

Preparation of (trifluoromethyl)diazomethane [CF_3CHN_2] in toluene (2)[30]:

A solution of $CF_3CH_2NH_2.HCl$ (100 mmol, 1 eq.) and $NaNO_2$ (125 mmol, 1.25 eq.) in toluene (200 mL) were prepared in a 500 mL round-bottomed flask (RBF) and immediately placed in an ice bath. After stirring the mixture for 15 minutes, water (20 mL) was added to it dropwise and stirred for an additional hour in the ice bath. The reaction was successful, resulting in the clear formation of aqueous and organic layers. Then, the aqueous layer was frozen in the freezer overnight at approximately -18°C and organic layer was extracted using a Teflon needle and transferred to a flame-dried round bottom flask and stored in a bottle in the freezer at -20 °C for further use.

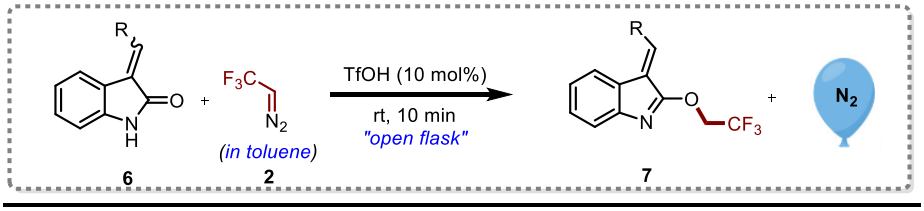
3.4.2 General Procedures

General procedure for O- and S- trifluoroethylation of 3,3-disubstituted oxindoles and thio-oxindoles (GP-1):



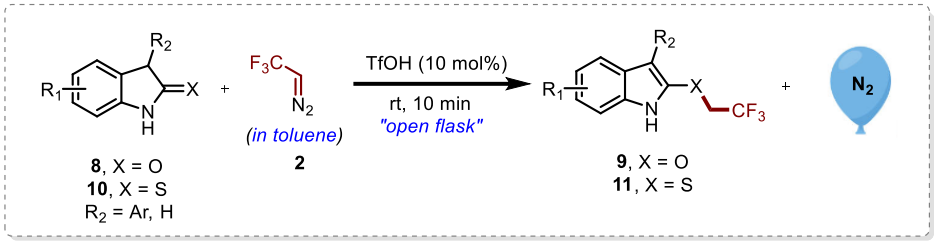
A vial was charged with a magnetic bead and the required amount of 3,3-disubstituted oxindole **1** or thio-oxindole **4** (0.2 mmol, 1 eq.) was added to it. Thereafter, CF_3CHN_2 **2** (0.22 mmol, 1.1 eq.) solution in toluene was added to the vial and after stirring for 2 minutes, catalyst triflic acid (10 mol %) was added and the reaction mixture was allowed to stir at room temperature for 10 minutes. After completion of the reaction, toluene used in the reaction was recovered through evaporation using rota-vapor. Then cold water was added to the reaction mixture and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated and the product **3** or **5** was purified through silica gel column chromatography using hexane as the eluent.

General procedure for O- trifluoroethylation of oxindole-based chalcone derivatives (GP-2):



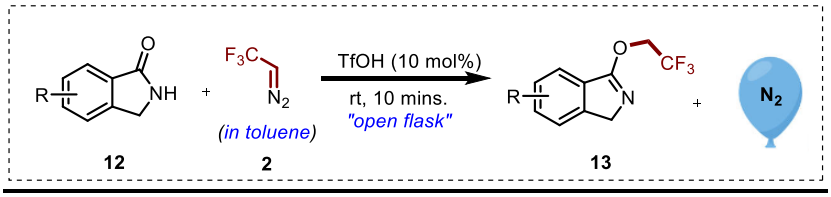
A vial was charged with a magnetic bead and the required amount of (*E* and *Z*) oxindole-based chalcone derivative **6** (0.2 mmol, 1 eq.) was added to it. Thereafter, CF_3CHN_2 **2** (0.22 mmol, 1.1 eq.) solution in toluene was added to the vial and after stirring for 2 minutes, catalyst triflic acid (10 mol %) was added and the reaction mixture was allowed to stir at room temperature for 10 minutes. After completion of the reaction, toluene used in the reaction was recovered through evaporation using rota-vapor. Then cold water was added to the reaction mixture and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated and the product **7** was purified through silica gel column chromatography using hexane as the eluent.

General procedure for O- trifluoroethylation of mono-substituted oxindoles, unsubstituted oxindoles, and thio-oxindoles (GP-3):



A vial was charged with a magnetic bead and the required amount of respective oxindole derivative **8/10** (0.2 mmol, 1 eq.) was added to it. Thereafter, CF_3CHN_2 **2** (0.22 mmol, 1.1 eq.) solution in toluene was added to the vial and after stirring for 2 minutes, catalyst triflic acid (10 mol %) was added and the reaction mixture was allowed to stir at room temperature for 10 minutes. After completion of the reaction, toluene used in the reaction was recovered through evaporation using rota-vapor. Then cold water was added to the reaction mixture and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated and the product **9 or 11** was purified through silica gel column chromatography using hexane as the eluent.

General procedure for O- trifluoroethylation of isoindolines (GP-4):



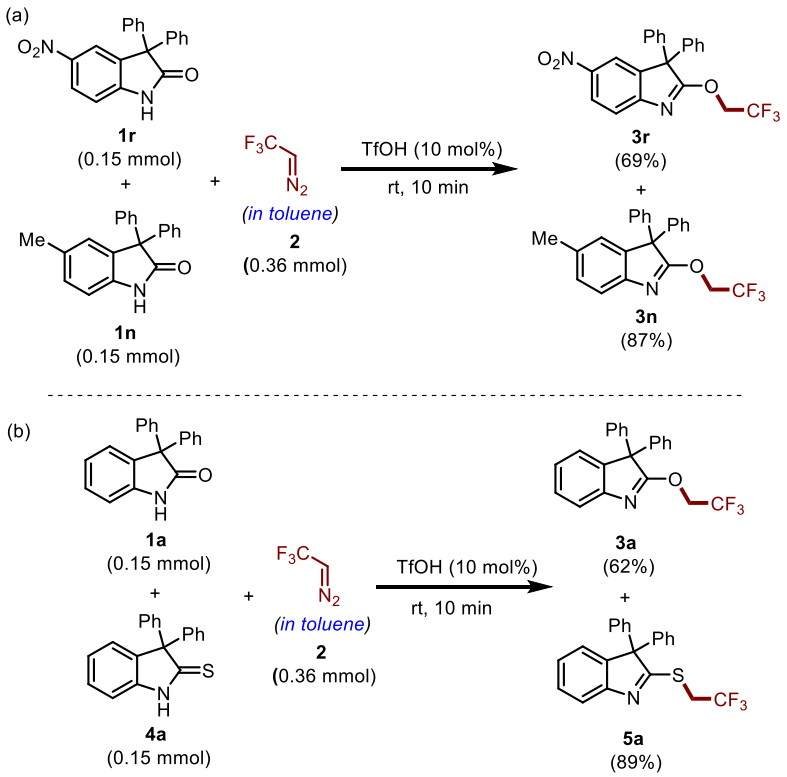
A vial was charged with a magnetic bead and the required amount of isoindoline derivative **12** (0.3 mmol, 1 eq.) was added to it. Thereafter, CF_3CHN_2 **2** (0.33 mmol, 1.1 eq.) solution in toluene was added to the vial and after stirring for 2 minutes, catalyst triflic acid (10 mol

%) was added and the reaction mixture was allowed to stir at room temperature for 10 minutes. After completion of the reaction, toluene used in the reaction was recovered through evaporation using rota-vapor. Then cold water was added to the reaction mixture and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated and the product **13** was purified through silica gel column chromatography using hexane as the eluent.

3.4.3 **Mechanistic Studies**

Competitive Experiments : a) Electron-rich *vs* electron-deficient oxindoles

A vial was charged with a magnetic bead and the required amount of **1r** (0.15 mmol, 1 eq.) and **1n** (0.15 mmol, 1 eq.) was added to it. Thereafter, CF_3CHN_2 (0.33 mmol, 2.2 eq.) solution in toluene was added to the vial and after stirring for 2 minutes, catalyst triflic acid (10 mol %) was added and the reaction mixture was allowed to stir at room temperature for 10 minutes. After completion of the reaction, toluene used in the reaction was recovered through evaporation using rota-vapor. Then cold water was added to the reaction mixture and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated and the crude product was analyzed through NMR spectroscopy. Then the mixture of products was separated through silica gel column chromatography by using hexane as the eluent. The effect of the substituents on the phenyl ring of oxindole was examined, and the product ratio illustrated that the -Me group on the C5 position of the oxindole facilitated the reaction while the $-NO_2$ group slowed down the reaction, **3n** was formed as the major product while **3r** was the minor.

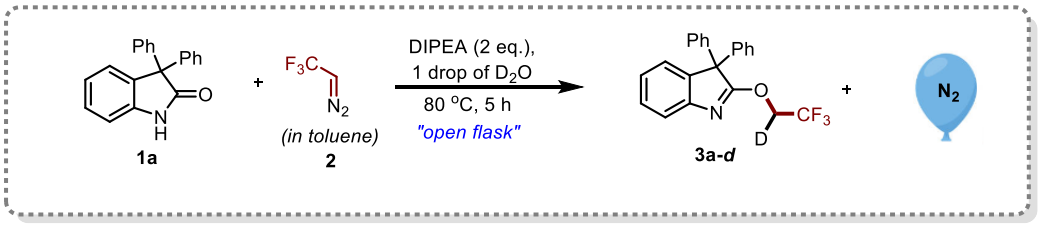


b) Oxindole *vs* Thioxindole

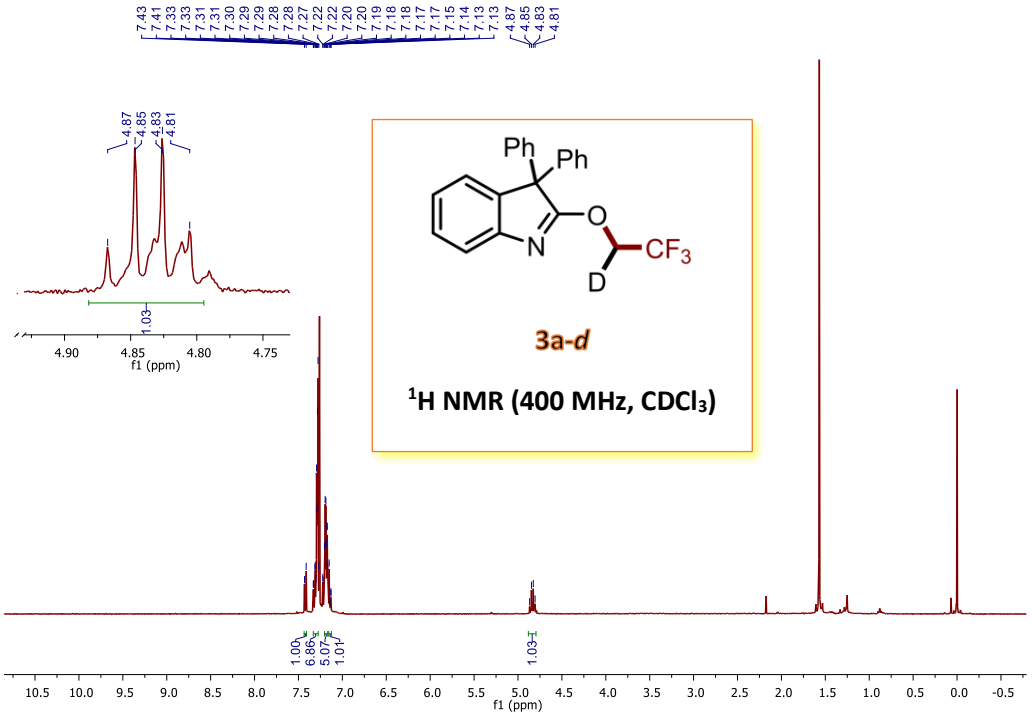
A vial was charged with a magnetic bead and the required amount of **1a** (0.15 mmol, 1 eq.) and **4a** (0.15 mmol, 1 eq.) was added to it. Thereafter, CF_3CHN_2 (0.33 mmol, 2.2 eq.) solution in toluene was added to the vial and after stirring for 2 minutes, catalyst triflic acid (10 mol %) was added and the reaction mixture was allowed to stir at room temperature for 10 minutes. After completion of the reaction, toluene used in the reaction was recovered through evaporation using rota-vapor. Then cold water was added to the reaction mixture and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated and the crude product was analyzed through NMR spectroscopy. Then the mixture of products was separated through silica gel column chromatography by using hexane as the eluent. The effect of oxygen and sulfur on the protocol was examined, and the product ratio demonstrated that

the reaction with thioxindole was comparatively faster and **5a** was formed as the major product in a competitive experiment with **3a**.

c) Deuterium labeling by using D_2O under basic condition



During optimization, I enquired about the proton source of trifluoroethylation in the case of base and performed a reaction in a drop of D_2O and I found through ^1H NMR that deuterium got labeled and formed O-$CHDCF_3$ (Table 1, entry 6 in main document).



3.4.4 Characterization data

3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3a)

Following the general procedure (GP-1), treatment of 3,3-diphenylindolin-2-one, **1a** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3a** as viscous liquid (0.066 g, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 – 7.42 (m, 1H), 7.35 – 7.27 (m, 7H), 7.25 – 7.14 (m, 6H), 4.85 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.50, 151.15, 141.27, 140.40, 129.99, 128.69, 128.59, 128.20, 127.77, 127.09, 124.92, 124.82, 121.73 (q, *J* = 277.45 Hz), 119.64, 66.76, 65.31 (q, *J* = 36.6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.57. **HRMS:** m/z calculated for $C_{22}H_{17}NOF_3$ $[M+H]^+$ = 368.1262, found 368.1262.

4-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3b)

Following the general procedure (GP-1), treatment of 4-fluoro-3,3-diphenylindolin-2-one, **2b** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 4-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3b** as viscous liquid (0.070 g, 92% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.27 (m, 6H), 7.20 – 7.10 (m, 6H), 6.82 – 6.87 (m, 1H), 4.83 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.87, 164.45, 162.01, 152.63 (d, *J* = 11.7 Hz), 140.00, 136.84, 128.79, 128.09, 127.92, 126.99, 125.50, 125.41, 121.78 (q, *J* = 277.55 Hz), 111.48 (d, *J* = 22.9 Hz), 107.72 (d, *J* = 24.7 Hz), 66.39, 65.47 (q, *J* = 36.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.35, -112.22. **HRMS:** m/z calculated for $C_{22}H_{17}NOF_3$ $[M+H]^+$ = 386.1168, found 386.1176.

5-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3c)

Following the general procedure (GP-1), treatment of 5-fluoro-3,3-diphenylindolin-2-one, **1c** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3c** as viscous liquid (0.070 g, 91% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.34 (m, 1H), 7.32 – 7.29 (m, 6H), 7.19 – 7.16 (m, 4H), 7.04 – 6.92 (m, 2H), 4.82 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.19, 161.75, 159.34, 146.93, 142.89 (d, *J* = 9.2 Hz), 139.73, 128.84, 128.75, 128.08, 128.02, 121.69 (q, *J* = 275.7 Hz), 120.39, 120.31, 115.17 (d, *J* = 21.5 Hz), 112.59 (d, *J* = 25.5 Hz), 67.21, 65.27 (q, *J* = 36.2 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.58, -115.95. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_4$ $[M+H]^+$ = 386.1168, found 386.1182.

6-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3d)

Following the general procedure (GP-1), treatment of 6-fluoro-3,3-diphenylindolin-2-one, **1d** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 6-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3d** as viscous liquid (0.071 g, 93% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 – 7.27 (m, 6H), 7.18 – 7.14 (m, 4H), 7.13 – 7.11 (m, 2H), 6.87 – 6.82 (m, 1H), 4.83 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.25, 164.27, 161.99, 152.60 (d, *J* = 11.6 Hz), 140.08, 137.41, 128.78, 128.09, 127.92, 125.50, 125.40, 120.67 (q, *J* = 276.1 Hz), 111.48 (d, *J* = 23.0 Hz), 107.71 (d, *J* = 24.7 Hz), 66.37, 65.49 (q, *J* = 36.7 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.60, -112.13. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_4$ $[M+H]^+$ = 386.1168, found 386.1167.

7-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3e)

Following the general procedure (GP-1), treatment of 7-fluoro-3,3-diphenylindolin-2-one, **1e** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 7-fluoro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3e** as viscous liquid (0.070 g, 91% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.36 (m 1H), 7.35 – 7.27 (m, 6H), 7.22 – 7.19 (m, 4H), 7.05 – 6.94 (m, 2H), 4.84 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.20, 161.77, 159.35, 146.97, 142.93 (d, *J* = 8.5 Hz), 139.74, 128.84, 128.09, 128.01, 122.90 (q, *J* = 277.6 Hz), 120.37 (d, *J* = 8.6 Hz), 115.17 (d, *J* = 23.4 Hz), 112.59 (d, *J* = 25.3 Hz), 67.23, 65.32 (q, *J* = 37.0 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.60, -116.81. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_4$ $[M+H]^+$ = 386.1168, found 386.1166.

4-chloro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3f)

Following the general procedure (GP-1), treatment of 4-chloro-3,3-diphenylindolin-2-one, **1f** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 4-chloro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3f** as viscous liquid (0.074 g, 92% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.35 (m, 1H), 7.33 – 7.29 (m, 6H), 7.28 – 7.23 (m, 5H), 7.09 – 7.07 (m, 1H), 4.77 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.21, 153.20, 138.43, 135.60, 130.94, 130.16, 129.15, 128.34, 128.12, 126.33, 124.15 (q, *J* = 263.7 Hz), 118.31, 68.03, 65.36 (q, *J* = 36.9 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.21. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3Cl$ $[M+H]^+$ = 402.0873, found 402.0867.

5-chloro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3g)

Following the general procedure (GP-1), treatment of 5-chloro-3,3-diphenylindolin-2-one, **1g** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-chloro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3g** as viscous liquid (0.072 g, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.29 (m, 6H), 7.27 – 7.26 (m, 1H), 7.19 – 7.13 (m, 5H), 4.82 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.69, 149.68, 142.88, 139.56, 130.35, 128.87, 128.79, 128.10, 125.16, 122.65 (q, *J* = 278 Hz), 67.07, 65.33 (q, *J* = 36.7 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.33. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3Cl$ $[M+H]^+$ = 402.0873, found 402.0868.

4,7-dichloro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3h)

Following the general procedure (GP-1), treatment of 4,7-dichloro-3,3-diphenylindolin-2-one, **1h** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 4,7-dichloro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3h** as viscous liquid (0.074 g, 85% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.28 (m, 7H), 7.25 – 7.21 (m, 4H), 7.04 – 7.01 (m, 1H), 4.84 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.73, 150.02, 139.64, 134.92, 130.53, 129.33, 129.07, 128.46, 128.39, 127.14, 123.34, 121.95 (q, *J* = 279.5 Hz), 69.20, 65.74 (q, *J* = 36.1 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.61. **HRMS:** m/z calculated for $C_{22}H_{15}Cl_2F_3NO$ $[M+H]^+$ = 436.0483, found 436.0491.

4-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3i)

Following the general procedure (GP-1), treatment of 4-bromo-3,3-diphenylindolin-2-one, **1i** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with

TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 4-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3i** as off white solid (0.077 g, 87% yield), m.p. 87-89 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 – 7.40 (m, 1H), 7.35 – 7.26 (m, 11H), 7.25 – 7.20 (m, 1H), 4.77 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.26, 153.58, 140.30, 135.02, 130.32, 129.48, 129.41, 128.27, 128.13, 123.63 (q, *J* = 183.0 Hz), 119.89, 118.86, 68.60, 65.31 (q, *J* = 36.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.62. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3Br$ $[M+H]^+$ = 446.0367, found 446.0366.

5-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3j)

Following the general procedure (GP-1), treatment of 5-bromo-3,3-diphenylindolin-2-one, **1j** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3j** as off white solid (0.072 g, 82% yield) m.p. 87-88 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45 (m, 1H), 7.37 – 7.28 (m, 8H), 7.21 – 7.14 (m, 4H), 4.84 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.67, 150.18, 143.28, 139.53, 131.71, 128.87, 128.10, 128.07, 127.94, 122.83 (q, *J* = 277.6 Hz), 121.45, 118.03, 67.07, 65.42 (q, *J* = 36.7 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.57. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3Br$ $[M+H]^+$ = 446.0367, found 446.0368.

6-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3k)

Following the general procedure (GP-1), treatment of 6-bromo-3,3-diphenylindolin-2-one, **1k** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 6-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3k** as off white solid (0.076g, 83% yield), m.p. 88-90 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 – 7.6 (m, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.26 (m,

6H), 7.22 – 7.10 (m, 5H), 4.82 (q, *J* = 8.2 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.58, 150.88, 143.57, 139.53, 137.73, 133.58, 128.87, 128.11, 128.06, 122.95 (q, *J* = 275.8 Hz), 121.66, 88.70, 66.91, 65.43 (q, *J* = 37.1 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.58. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3Br$ $[M+H]^+$ = 446.0367, found 446.0372.

7-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3l)

Following the general procedure (GP-1), treatment of 7-bromo-3,3-diphenylindolin-2-one, **1l** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 7-bromo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3l** as off white solid (0.076 g, 83% yield) m.p. 86-88 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 (m, 1H), 7.34 – 7.27 (m, 6H), 7.21 – 7.12 (m, 5H), 7.05 – 6.99 (m, 1H), 4.91 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.96, 149.86, 142.69, 139.64, 131.97, 128.80, 128.13, 128.04, 126.20, 123.80, 122.86 (q, *J* = 277.3 Hz), 113.26, 68.13, 65.67 (q, *J* = 37.2 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.58. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3Br$ $[M+H]^+$ = 446.0367, found 446.0370.

5-iodo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3m)

Following the general procedure (GP-1), treatment of 5-iodo-3,3-diphenylindolin-2-one, **1m** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-iodo-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3m** as off white solid (0.082 g, 84% yield), m.p. 91-93 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 – 7.45 (m, 1H), 7.35 – 7.31 (m, 8H), 7.22 – 7.16 (m, 4H), 4.85 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.66, 150.16, 143.25, 139.52, 131.71, 128.87, 128.09, 127.93, 122.82 (q, *J* = 277.2 Hz), 121.11, 118.03, 67.05, 65.42 (q, *J* = 36.7 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.56. **HRMS:** m/z calculated for $C_{22}H_{16}NOF_3I$ $[M+H]^+$ = 494.0229, found 494.0225.

5-methyl-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3n)

Following the general procedure (GP-1), treatment of 5-methyl-3,3-diphenylindolin-2-one, **1n** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-methyl-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3n** as viscous liquid (0.074 g, 97% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.26 (m, 7H), 7.23 – 7.16 (m, 4H), 7.13 – 7.09 (m, 1H), 7.01 (m, 1H), 4.82 (q, *J* = 8.3 Hz, 2H), 2.33 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.86, 148.57, 141.22, 140.43, 134.63, 129.12, 128.66, 128.23, 127.69, 125.49, 122.96 (q, *J* = 277.5 Hz), 119.18, 66.69, 65.22 (q, *J* = 36.7 Hz), 21.66. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.70. **HRMS:** m/z calculated for $C_{23}H_{19}F_3NO$ $[M+H]^+$ = 332.1419, found 332.1424.

6-methyl-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3o)

Following the general procedure (GP-1), treatment of 6-methyl-3,3-diphenylindolin-2-one, **1o** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 6-methyl-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3o** as viscous liquid (0.072 g, 96% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 – 7.27 (m, 7H), 7.20 (m, 4H), 7.13 – 7.09 (m, 1H), 7.02 (s, 1H), 4.82 (q, *J* = 8.3 Hz, 2H), 2.33 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.88, 148.60, 141.26, 140.44, 134.63, 129.12, 128.66, 128.24, 127.69, 125.49, 122.97 (q, *J* = 277.6 Hz), 118.83, 66.71, 65.23 (q, *J* = 36.6 Hz), 21.65. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.62. **HRMS:** m/z calculated for $C_{23}H_{19}F_3NO$ [M+H]+ = 332.1419, found 332.1423.

7-methyl-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3p)

Following the general procedure (GP-1), treatment of 7-methyl-3,3-diphenylindolin-2-one, **1p** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with

TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 7-methyl-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3p** as viscous liquid (0.073 g, 96% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.27 (m, 6H), 7.24 – 7.19 (m, 4H), 7.15 – 7.13 (m, 1H), 7.09 – 7.05 (m, 2H), 4.88 (q, *J* = 8.4 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.37, 149.58, 141.06, 140.58, 129.80, 129.37, 128.61, 128.24, 127.62, 124.70, 123.09 (q, *J* = 277.9 Hz), 122.15, 66.92, 65.13 (q, *J* = 36.5 Hz).16.89. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.09. **HRMS:** m/z calculated for $C_{23}H_{19}NOF_3$ $[M+H]^+$ = 381.1419, found 381.1413.

5-methoxy-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3q)

Following the general procedure (GP-1), treatment of 5-methoxy-3,3-diphenylindolin-2-one, **1q** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (99/1) afforded 5-methoxy-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3q** as viscous liquid (0.078 g, 98% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.27 (m, 6H), 7.22 – 7.17 (m, 4H), 6.84 – 6.81 (m, 1H), 6.78 (d, *J* = 2.6 Hz, 1H), 4.80 (q, *J* = 8.3 Hz, 2H), 3.76 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.31, 160.37, 152.25, 140.58, 133.18, 129.35, 128.65, 128.11, 127.66, 125.14, 122.90 (q, *J* = 277.6 Hz), 110.41, 105.82, 66.27, 65.30 (q, *J* = 36.7 Hz), 55.62. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -72.72. **HRMS:** m/z calculated for $C_{23}H_{19}NO_2F_3$ $[M+H]^+$ = 398.1368, found 398.1384

6-methoxy-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3r)

Following the general procedure (GP-1), treatment of 6-methoxy-3,3-diphenylindolin-2-one, **1r** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (99/1) afforded 6-methoxy-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3r** as viscous liquid (0.075 g, 95%

yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.27 (m, 6H), 7.24 – 7.18 (m, 4H), 6.86 – 6.78 (m, 2H), 4.81 (q, *J* = 8.4 Hz, 2H), 3.77 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.08, 157.42, 144.29, 142.62, 140.30, 128.70, 128.21, 127.75, 124.36, 121.60 (q, *J* = 278.4 Hz), 112.77, 111.90, 67.06, 65.64 (q, *J* = 36.1 Hz), 55.76. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.64. **HRMS:** m/z calculated for $C_{23}H_{19}NO_2F_3$ $[M+H]^+$ = 398.1368, found 398.1376.

5-nitro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3s)

Following the general procedure (GP-1), treatment of 5-nitro-3,3-diphenylindolin-2-one, **1s** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (98/2) afforded 5-nitro-3,3-diphenyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3s** as off white solid (0.067 g, 82% yield), m.p. 101-103 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.29 – 8.27 (m, 1H), 8.09 (d, *J* = 2.3 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.31 (m, 6H), 7.20 – 7.13 (m, 4H), 4.90 (q, *J* = 8.2 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.04, 157.31, 145.97, 145.27, 143.90, 142.39, 140.23, 138.67, 134.53, 129.12, 129.05, 128.48, 128.33, 128.23, 127.97, 126.81, 125.47, 122.57 (q, *J* = 277.9 Hz), 120.49, 119.81, 110.22, 67.13, 65.86 (q, *J* = 35.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.27. **HRMS:** m/z calculated for $C_{22}H_{16}N_2O_3F_3$ $[M+H]^+$ = 413.1113, found 413.1113.

3,3-dibenzyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3t)

Following the general procedure (GP-1), treatment of 3,3-dibenzylindolin-2-one, **1t** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-dibenzyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3t** as viscous liquid (0.070 g, 89% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31 – 7.27 (m, 1H), 7.20 – 7.14 (m, 2H), 7.11 – 7.02 (m, 6H), 6.95 – 6.91 (m, 1H), 6.82 – 6.80

(m, 4H), 4.53 (q, *J* = 8.4 Hz, 2H), 3.29 (q, *J* = 13.2 Hz, 4H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 179.22, 151.79, 137.87, 135.47, 129.52, 128.36, 127.89, 127.37, 123.80, 123.24 (q, *J* = 277.0 Hz), 123.15, 118.65, 64.78 (q, *J* = 36.5 Hz), 59.95, 42.59. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -73.31. **HRMS:** m/z calculated for $C_{24}H_{21}NOF_3$ $[M+H]^+$ = 396.1575, found 396.1566.

3,3-di-*p*-tolyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3u)

Following the general procedure (GP-1), treatment of 3,3-di-*p*-tolylindolin-2-one, **1u** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-di-*p*-tolyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3u** as viscous liquid (0.072 g, 91% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.43 (m, 1H), 7.42 – 7.37 (m, 1H), 7.34 – 7.24 (m, 9H), 5.02 (q, *J* = 8.3 Hz, 2H), 2.50 (s, 6H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 179.82, 151.06, 141.66, 137.41, 129.35, 128.40, 128.05, 124.84, 124.68, 123.00 (q, *J* = 277.3 Hz), 119.55, 66.13, 65.24 (q, *J* = 36.7 Hz), 21.10. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -73.48. **HRMS:** m/z calculated for $C_{24}H_{21}F_3NO$ $[M+H]^+$ = 396.1324, found 396.1290

3,3-bis(2-methoxy-4-methylphenyl)-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3v)

Following the general procedure (GP-1), treatment of 3,3-bis(2-methoxy-4-methylphenyl)indolin-2-one, **1v** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (95/5) afforded 3,3-bis(2-methoxy-4-methylphenyl)-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3v** as pale yellow solid (0.084 g, 92% yield), m.p. 81-83 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.35 (d, *J* = 6.8 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.11 – 6.94 (m, 3H), 6.86 – 6.68 (m, 3H), 6.63 (d, *J* = 2.0 Hz, 1H), 4.83 – 4.68 (m, 2H), 3.53 (s, 3H), 3.44 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 181.48, 156.62, 155.03, 151.54, 141.52,

129.92, 129.42, 129.35, 129.29, 128.74, 128.38, 128.32, 128.03, 127.29, 124.73, 124.32, 123.07 (q, *J* = 276.5 Hz), 118.53, 112.26, 112.12, 65.29 (q, *J* = 36.0 Hz), 62.88, 55.87, 55.51, 20.80. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -73.62. **HRMS:** m/z calculated for $C_{26}H_{25}F_3NO_3$ $[M+H]^+$ = 456.1787, found 456.1792.

3,3-bis(4-fluorophenyl)-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3w)

Following the general procedure (GP-1), treatment of 3,3-bis(4-fluorophenyl)indolin-2-one, **1w** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-bis(4-fluorophenyl)-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3w** as viscous liquid (0.070g, 88% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.27 – 7.18 (m, 6H), 7.07 – 6.99 (m, 4H), 4.92 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 179.16, 163.66, 161.20, 150.98, 141.15, 135.86 (d, *J* = 2.8 Hz).129.82 (d, *J* = 8.0 Hz), 128.88, 125.13, 124.84 (d, *J* = 58.7 Hz), 122.96 (q, *J* = 277.6 Hz), 119.94, 115.70 (d, *J* = 21.7 Hz), 65.33 (q, *J* = 36.52 Hz). **^{19}F NMR (376 MHz, CDCl$_3$):** δ -73.65, -114.13. **HRMS:** m/z calculated for $C_{22}H_{15}NO_5$ $[M+H]^+$ = 404.1074, found 404.1087.

3,3-bis(4-bromophenyl)-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3x)

Following the general procedure (GP-1), treatment of 3,3-bis(4-bromophenyl)indolin-2-one, **1x** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-bis(4-bromophenyl)-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3x** as off white solid (0.090 g, 87% yield), m.p. 89-91 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.45 – 7.39 (m, 5H), 7.36 – 7.31 (m, 1H), 7.20 – 7.12 (m, 2H), 7.06 – 7.01 (m, 4H), 4.83 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 178.45, 150.91, 140.29, 138.79, 131.99, 129.80, 129.09, 125.27, 124.53, 122.25, 122.93

(q, *J* = 276.4 Hz), 119.99, 65.98, 65.88 (q, *J* = 36.1 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.21. **HRMS:** m/z calculated for $C_{22}H_{15}NOF_3Br_2$ $[M+H]^+$ = 525.9429, found 525.9451.

3,3-bis(phenyl-*d*$_5$)-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3y)

Following the general procedure (GP-1), treatment of 3-(1 λ^5-phenyl-d_5)-3-(phenyl-d_5)indolin-2-one, **1y** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-bis(phenyl-*d*$_5$)-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3y** as off white solid (0.068 g, 90% yield), m.p. 77-79 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.13 (m, 3H), 4.85 (q, *J* = 8.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.51, 151.07, 141.28, 140.18, 140.08, 128.69, 128.58, 128.47, 128.18, 128.07, 127.76, 127.65, 127.54, 124.92, 124.81, 124.70, 122.94 (q, *J* = 277.6 Hz), 119.63, 66.70, 65.30 (q, *J* = 36.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.15. **HRMS:** m/z calculated for $C_{22}H_{17}NOF_3$ $[M+H]^+$ = 378.1842, found 378.1873.

3,3-dimethyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole (3z)

Following the general procedure (GP-1), treatment of 3,3-dimethylindolin-2-one **1z** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-dimethyl-2-(2,2,2-trifluoroethoxy)-3*H*-indole **3z** as off white solid (0.040 g, 82% yield), m.p. 70-73 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.33 (m, 1H), 7.29 – 7.24 (m, 1H), 7.23 – 7.19 (m, 1H), 7.16 – 7.14 (m, 1H), 4.82 (q, *J* = 8.3 Hz, 1H), 1.39 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.39, 150.62, 143.20, 128.05, 124.38, 123.31 (q, *J* = 218.3 Hz), 121.31, 118.94, 64.88 (q, *J* = 36.5 Hz), 48.20, 23.05. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.00. **HRMS:** m/z calculated for $C_{12}H_{13}NOF_3$ $[M+H]^+$ = 244.0949, found 244.0957.

2'-(2,2,2-trifluoroethoxy)spiro[cyclobutane-1,3'-indole] (3aa)

Following the general procedure (GP-1), treatment of spiro[cyclobutane-1,3'-indolin]-2'-one **1aa** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 2'-(2,2,2-trifluoroethoxy)spiro[cyclobutane-1,3'-indole] **3aa** as off white solid (0.043 g, 85% yield), m.p. 72-74 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 - 7.50 (m, 1H), 7.34 – 7.25 (m, 2H), 7.20 – 7.16 (m, 1H), 4.87 (q, *J* = 8.3 Hz, 2H), 2.68 – 2.59 (m, 2H), 2.50 – 2.43 (m, 2H), 2.40 – 2.23 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.40, 150.84, 141.27, 128.11, 124.45, 123.16 (q, *J* = 277.2 Hz), 121.39, 118.45, 64.95 (q, *J* = 36.4 Hz), 51.67, 29.49, 16.94. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.98. **HRMS:** m/z calculated for $C_{13}H_{13}NOF_3$ $[M+H]^+$ = 256.0949, found 256.0960.

2'-(2,2,2-trifluoroethoxy)spiro[cyclohexane-1,3'-indole] (3ab)

Following the general procedure (GP-1), treatment of spiro[cyclohexane-1,3'-indolin]-2'-one **1ab** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 2'-(2,2,2-trifluoroethoxy)spiro[cyclohexane-1,3'-indole] **3ab** as off white solid (0.049 g, 87% yield), m.p. 72-74 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.14 – 7.10 (m, 1H), 4.81 (q, *J* = 8.4 Hz, 2H), 1.91 – 1.78 (m, 6H), 1.70 – 1.54 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.20, 150.80, 142.72, 127.89, 123.84, 123.17 (q, *J* = 218.3 Hz), 123.12, 118.95, 64.92 (q, *J* = 36.4 Hz), 51.94, 31.87, 25.17, 21.54. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.92. **HRMS:** m/z calculated for $C_{15}H_{17}NOF_3$ $[M+H]^+$ = 284.1262, found 284.1268.

3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5a)

Following the general procedure (GP-1), treatment of 3,3-diphenylindoline-2-thione, **4a** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole, **5a** as pale yellow solid (0.073 g, 96% yield), m.p. 96-98 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.27 (m, 7H), 7.24 – 7.13 (m, 6H), 4.08 (q, *J* = 10.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.98, 153.37, 145.32, 140.76, 128.87, 128.48, 128.38, 127.89, 125.59, 124.84 (q, *J* = 216.4 Hz) 124.38, 119.80, 73.21, 32.61 (q, *J* = 33.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -64.79. **HRMS:** m/z calculated for $C_{22}H_{17}NSF_3$ $[M+H]^+$ = 384.1034, found 384.1030.

5-fluoro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5b)

Following the general procedure (GP-1), treatment of 5-fluoro-3,3-diphenylindoline-2-thione, **4b** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-fluoro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole, **5b** as pale yellow solid (0.076 g, 92% yield), m.p. 97-99 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 – 7.48 (m, 1H), 7.35 – 7.31 (m, 6H), 7.20 – 7.17 (m, 4H), 7.05 – 7.00 (m, 1H), 6.93 – 6.91 (m, 1H), 4.05 (q, *J* = 9.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.65, 162.27, 159.83, 149.45, 147.08 (d, *J* = 8.6 Hz), 140.20, 129.02, 128.27, 128.14, 124.67 (q, *J* = 216.9 Hz), 120.48 (d, *J* = 8.9 Hz), 115.23 (d, *J* = 23.7 Hz), 112.12 (d, *J* = 25.2 Hz), 73.52, 32.57 (q, *J* = 33.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.02, -115.91. **HRMS:** m/z calculated for $C_{22}H_{16}NSF_4$ $[M+H]^+$ = 402.0940, found 402.0938.

7-fluoro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5c)

Following the general procedure (GP-1), treatment of 7-fluoro-3,3-diphenylindoline-2-thione, **4c** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 7-fluoro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole, **5c** as pale yellow solid (0.074 g, 90% yield), m.p. 97-98 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.28 (m, 6H), 7.20 – 7.16 (m, 4H), 7.14 – 7.03 (m, 2H), 7.00 - 6.98 (m, 1H), 4.10 (q, *J* = 10.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 182.89, 154.40, 151.87, 148.47 (d, *J* = 2.7 Hz), 140.21, 128.98, 128.33, 128.14, 126.88 (d, *J* = 6.4 Hz), 124.68 (q, *J* = 207.3 Hz), 120.12 (d, *J* = 3.1 Hz), 115.70 (d, *J* = 18.5 Hz), 73.79, 32.71 (q, *J* = 33.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.61, -126.85. **HRMS:** m/z calculated for $C_{22}H_{16}NSF_4$ $[M+H]^+$ = 402.0940, found 402.0938.

4-chloro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5d)

Following the general procedure (GP-1), treatment of 4-chloro-3,3-diphenylindoline-2-thione, **4d** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 4-chloro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5d** as pale yellow solid (0.074 g, 89% yield), m.p. 100-102 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (m, 1H), 7.37 (m, 11H), 7.14 (m, 1H), 4.07 (q, *J* = 9.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.96, 155.18, 141.85, 135.76, 130.62, 130.16, 129.14, 128.54, 128.23, 126.81, 124.43 (q, *J* = 208.1 Hz), 118.58, 74.50, 32.43 (q, *J* = 33.9 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -66.07. **HRMS:** m/z calculated for $C_{22}H_{16}NSClF_3$ $[M+H]^+$ = 418.0644, found 418.0644.

5-bromo-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5e)

Following the general procedure (GP-1), treatment of 5-bromo-3,3-diphenylindoline-2-thione, **4e** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-bromo-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5e** as pale yellow solid (0.082 g, 89% yield), m.p. 103-105 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 – 7.46 (m, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.29 (m, 7H), 7.21 – 7.14 (m, 4H), 4.05 (q, *J* = 9.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 182.77, 152.37, 147.29, 140.03, 131.66, 129.05, 128.28, 128.18, 127.57, 124.75 (q, *J* = 219.8 Hz), 121.10, 119.17, 73.45, 32.62 (q, *J* = 33.9 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.33. **HRMS:** m/z calculated for $C_{22}H_{16}NSBrF_3$ $[M+H]^+$ = 462.0139, found 462.0113.

5-methyl-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5f)

Following the general procedure (GP-1), treatment of 5-methyl-3,3-diphenylindoline-2-thione, **4f** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 5-methyl-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5f** as pale yellow solid (0.078 g, 98% yield), m.p. 98-100 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.28 (m, 6H), 7.23 – 7.17 (m, 4H), 7.15 – 7.11 (m, 1H), 7.01 (s, 1H), 4.06 (q, *J* = 10.0 Hz, 2H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.71, 151.25, 145.39, 140.89, 135.46, 129.09, 128.84, 128.41, 127.81, 125.04, 124.49 (q, *J* = 219.3 Hz), 119.32, 73.06, 32.56 (q, *J* = 33.6 Hz), 21.63. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -66.21. **HRMS:** m/z calculated for $C_{23}H_{19}NSF_3$ $[M+H]^+$ = 398.1190, found 398.1181.

7-methyl-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5g)

Following the general procedure (GP-1), treatment of 7-methyl-3,3-diphenylindoline-2-thione, **4g** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 7-methyl-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5g** as pale yellow solid (0.076 g, 97% yield), m.p. 99-101 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 – 7.26 (m, 6H), 7.22 – 7.15 (m, 4H), 7.12 – 7.14 (m, 1H), 7.07 – 6.99 (m, 2H), 4.09 (q, *J* = 10.0 Hz, 2H), 2.59 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.22, 151.92, 145.12, 140.99, 129.70, 128.80, 128.40, 127.77, 125.45, 125.19 (q, *J* = 220.2 Hz), 121.74, 73.39, 31.40 (q, *J* = 34.2 Hz), 16.87. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.69. **HRMS:** m/z calculated for $C_{23}H_{19}NSF_3$ $[M+H]^+$ = 398.1190, found 398.1190.

5-nitro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5h)

Following the general procedure (GP-1), treatment of 5-nitro-3,3-diphenylindoline-2-thione, **4h** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (97/3) afforded 5-nitro-3,3-diphenyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5h** as pale yellow solid (0.070 g, 82% yield), m.p. 105-107 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30 – 8.28 (m, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.37 – 7.32 (m, 6H), 7.20 – 7.14 (m, 4H), 4.08 (q, *J* = 9.8 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 188.79, 158.25, 146.44, 145.62, 139.34, 129.31, 128.59, 128.18, 125.43, 124.30 (q, *J* = 219.2 Hz), 119.98, 119.89, 73.62, 32.84 (q, *J* = 33.5 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.67. **HRMS:** m/z calculated for $C_{22}H_{16}N_2O_2SF_3$ $[M+H]^+$ = 429.0885, found 429.0863.

3,3-di-*p*-tolyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5i)

Following the general procedure (GP-1), treatment of 3,3-di-*p*-tolylindoline-2-thione, **4i** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-di-*p*-tolyl-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5i** as pale yellow solid (0.074 g, 90% yield), m.p. 102-104 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.31 – 7.18 (m, 9H), 4.20 (q, *J* = 10.0 Hz, 2H), 2.46 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 182.30, 153.28, 145.69, 137.80, 137.56, 129.54, 129.30, 128.27, 125.50, 125.19 (q, *J* = 218.4 Hz), 124.19, 119.71, 72.57, 32.41 (q, *J* = 33.9 Hz), 21.07. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.49. **HRMS:** m/z calculated for $C_{24}H_{21}NSF_3$ $[M+H]^+$ = 412.1347, found 412.1345.

3,3-bis(4-fluorophenyl)-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole (5j)

Following the general procedure (GP-1), treatment of 3,3-bis(4-fluorophenyl)indoline-2-thione, **4j** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3,3-bis(4-fluorophenyl)-2-((2,2,2-trifluoroethyl)thio)-3*H*-indole **5j** as pale yellow solid (0.074 g, 89% yield), m.p. 103-105 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.24 – 7.11 (m, 6H), 7.08 – 6.94 (m, 4H), 4.09 (q, *J* = 9.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.63, 163.70, 161.23, 153.14, 145.09, 136.30 (d, *J* = 3.3 Hz), 128.78, 125.82, 125.06 (q, *J* = 276.2 Hz), 124.11, 120.04, 115.92 (d, *J* = 21.5 Hz), 71.86, 32.50 (q, *J* = 34.0 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -65.78, -113.89. **HRMS:** m/z calculated for $C_{22}H_{15}NSF_5$ $[M+H]^+$ = 420.0845, found 420.0844.

(*E*)-3-benzylidene-2-(2,2,2-trifluoroethoxy)-3*H*-indole (7a)

Following the general procedure (GP-2), treatment of 3-benzylideneindolin-2-one **6a** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded (*E*)-3-benzylidene-2-(2,2,2-trifluoroethoxy)-3*H*-indole **7a** as yellow solid (0.054 g, 90% yield), m.p. 87-88 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.73 – 7.62 (m, 4H), 7.54 – 7.43 (m, 3H), 7.32 – 7.25 (m, 2H), 6.99 – 6.95 (m, 1H), 4.90 (q, *J* = 8.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.17, 152.93, 137.28, 134.34, 130.19, 130.00, 129.78, 128.81, 126.87, 123.97, 123.08 (q, *J* = 282.7 Hz), 122.52, 119.09, 64.90 (q, *J* = 36.6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.69. **HRMS:** m/z calculated for $C_{17}H_{13}NOF_3$ $[M+H]^+$ = 304.0979, found 304.0949.

(*E*)-3-ferrocenylidene-2-(2,2,2-trifluoroethoxy)-3*H*-indole (7b)

Following the general procedure (GP-2), treatment of 3-ferrocenylideneindolin-2-one **6b** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded (*E*)-3-ferrocenylidene-2-(2,2,2-trifluoroethoxy)-3*H*-indole **7b** as yellow solid (0.074 g, 90% yield), m.p. 96-98 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.54 (s, 1H), 7.34 – 7.28 (m, 2H), 7.08 (t, *J* = 7.0 Hz, 1H), 4.90 (q, *J* = 7.8 Hz, 2H), 4.83 – 4.82 (m, 2H), 4.67 – 4.63 (m, 2H), 4.24 (s, 5H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.94, 151.94, 138.51, 128.53, 126.31 (q, *J* = 279.7 Hz), 124.04, 123.59, 122.30, 118.90, 78.16, 72.30, 71.81, 70.22, 64.73 (q, *J* = 36.1 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.71. **HRMS:** m/z calculated for $C_{21}H_{17}NOF_3Fe$ $[M+H]^+$ = 412.0624, found 412.0612.

(*E*)-3-(4-fluorobenzylidene)-2-(2,2,2-trifluoroethoxy)-3*H*-indole (7c)

Following the general procedure (GP-2), treatment of 3-(4-fluorobenzylidene)indolin-2-one **6c** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded (*E*)-3-(4-fluorobenzylidene)-2-(2,2,2-trifluoroethoxy)-3*H*-indole **7c** as yellow solid (0.055 g, 86% yield), m.p. 89-91 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.70 – 7.63 (m, 2H), 7.61 – 7.59 (m, 2H), 7.33 – 7.25 (m, 2H), 7.21 – 7.14 (m, 2H), 7.00 – 6.96 (m, 1H), 4.88 (q, *J* = 8.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.05, 164.88, 162.37, 152.94, 135.93, 131.90 (d, *J* = 8.4 Hz), 130.10, 127.37 (q, *J* = 275.2 Hz), 124.00, 122.28, 119.18, 116.04 (d, *J* = 21.9 Hz), 64.89 (q, *J* = 37.9 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.68, -108.90. **HRMS:** m/z calculated for $C_{17}H_{12}NOF_4$ $[M+H]^+$ = 322.0855, found 322.0884.

(*E*)-3-(3,4-dimethoxybenzylidene)-2-(2,2,2-trifluoroethoxy)-3*H*-indole (7d)

Following the general procedure (GP-2), treatment of 3-(3,4-dimethoxybenzylidene)indolin-2-one **6d** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (95/5) afforded (*E*)-3-(3,4-dimethoxybenzylidene)-2-(2,2,2-trifluoroethoxy)-3*H*-indole **7d** as yellow solid (0.063 g, 87% yield), m.p. 90-92 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.36 – 7.24 (m, 4H), 7.03 – 6.96 (m, 2H), 4.88 (q, *J* = 8.4 Hz, 2H), 3.97 (s, 3H), 3.91 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.35, 152.78, 151.05, 148.96, 137.75, 129.62, 127.05, 126.98, 126.88, 124.19, 123.76, 122.31, 122.01 (q, *J* = 244.2 Hz), 118.65, 112.71, 111.10, 64.91 (q, *J* = 36.3 Hz), 56.16. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.71. **HRMS:** m/z calculated for $C_{19}H_{17}N_3OF_3$ $[M+H]^+$ = 365.1182, found 365.1161.

(*E*)-2-methoxy-4-((2-(2,2,2-trifluoroethoxy)-3*H*-indol-3-ylidene)methyl)phenol (7e)

Following the general procedure (GP-2), treatment of 3-(4-hydroxy-3-methoxybenzylidene)indolin-2-one **6e** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (90/10) afforded (*E*)-2-methoxy-4-((2-(2,2,2-trifluoroethoxy)-3*H*-indol-3-ylidene)methyl)phenol **7e** as yellow solid (0.061 g, 87% yield), m.p. 89-91 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.34 – 7.23 (m, 4H), 7.02 – 6.94 (m, 2H), 5.86 (s, 1H), 4.88 (q, *J* = 8.4 Hz, 2H), 3.98 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.33, 152.68, 148.53, 145.81, 137.66, 129.60, 127.62, 127.12, 126.97, 123.92, 123.41, 123.08 (q, *J* = 242.2 Hz), 122.48, 118.98, 116.02, 110.63, 64.90 (q, *J* = 36.2 Hz), 56.16. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.69. **HRMS:** m/z calculated for $C_{18}H_{15}NO_3F_3$ $[M+H]^+$ = 350.1004, found 350.1029.

3,6-dimesityl-2-(2,2,2-trifluoroethoxy)-1*H*-indole (9a)

Following the general procedure (GP-3), treatment of 3,6-dimesitylindolin-2-one, **8a** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (85/15) afforded 3,6-dimesityl-2-(2,2,2-trifluoroethoxy)-1*H*-indole **9a** as off white solid (0.076 g, 85% yield), m.p. 97-99 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 4.2 Hz, 3H), 7.03 (s, 2H), 6.88 – 6.85 (m, 1H), 4.15 (q, *J* = 8.3 Hz, 2H), 2.42 (d, *J* = 7.3 Hz, 6H), 2.23 (s, 6H), 2.11 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 145.81, 140.07, 138.79, 137.40, 136.72, 136.35, 134.30, 130.47, 128.50, 128.09, 126.35, 123.32 (q, *J* = 243.2 Hz), 121.95, 118.84, 110.92, 95.26, 68.55 (q, *J* = 35.4 Hz). 21.26, 21.14, 21.06, 20.67. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.66. **HRMS:** m/z calculated for $C_{28}H_{29}NOF_3$ $[M+H]^+$ = 452.2201, found 452.2207.

5-bromo-3,6-dimesityl-2-(2,2,2-trifluoroethoxy)-1*H*-indole (9b)

Following the general procedure (GP-3), treatment of 5-bromo-3,6-dimesitylindolin-2-one, **8b** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (85/15) afforded 5-bromo-3,6-dimesityl-2-(2,2,2-trifluoroethoxy)-1*H*-indole **9b** as off white solid (0.084 g, 80% yield), m.p. 103-105 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.90 (s, 1H), 7.34 (s, 1H), 7.05 – 6.94 (m, 5H), 4.09 (q, *J* = 8.2 Hz, 2H), 2.37 (d, *J* = 5.2 Hz, 6H), 2.16 (s, 6H), 2.00 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 146.61, 139.03, 138.76, 137.84, 137.06, 136.70, 134.29, 129.86, 128.63, 127.99, 127.35, 123.12 (q, *J* = 298.5 Hz), 122.22, 115.73, 112.07, 94.74, 68.49 (q, *J* = 35.2 Hz), 21.33, 21.30, 20.70, 20.59. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.72. **HRMS:** m/z calculated for $C_{28}H_{28}NOFBr$ $[M+H]^+$ = 530.1306, found 530.1309.

3,6-dimesityl-5-methyl-2-(2,2,2-trifluoroethoxy)-1*H*-indole (9c)

Following the general procedure (GP-3), treatment of 3,6-dimesityl-5-methylindolin-2-one, **8c** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (85/15) afforded 3,6-dimesityl-5-methyl-2-(2,2,2-trifluoroethoxy)-1*H*-indole **9c** as off white solid (0.077 g, 83% yield), m.p. 99-101 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.74 (s, 1H), 6.95 (m, 6H), 4.08 (q, *J* = 8.3 Hz, 2H), 2.37 (d, *J* = 9.9 Hz, 6H), 2.18 (s, 6H), 1.95 (s, 6H), 1.92 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 145.86, 139.29, 138.83, 137.34, 136.55, 136.22, 134.39, 129.25, 128.47, 128.40, 128.02, 127.98, 127.01, 120.45 (q, *J* = 266.0 Hz), 119.58, 110.51, 94.99, 68.62 (q, *J* = 35.4 Hz), 21.31, 21.23, 20.73, 20.57, 19.84. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.74. **HRMS:** m/z calculated for $C_{29}H_{31}NOF_3$ $[M+H]^+$ = 466.2358, found 466.2357.

3,6-dimesityl-2-(2,2,2-trifluoroethoxy)-1*H*-indol-5-ol (9d)

Following the general procedure (GP-3), treatment of 5-hydroxy-3,6-dimesitylindolin-2-one, **8d** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (82/18) afforded 3,6-dimesityl-2-(2,2,2-trifluoroethoxy)-1*H*-indol-5-ol **9d** as off white solid (0.078 g, 84% yield), m.p. 98-100 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 4H), 6.87 (s, 1H), 6.63 (s, 1H), 4.30 (s, 1H), 4.07 (q, *J* = 8.3 Hz, 2H), 2.35 (d, *J* = 3.5 Hz, 6H), 2.16 (s, 6H), 2.05 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 147.27, 146.66, 138.74, 138.49, 137.93, 137.38, 132.86, 128.77, 128.63, 128.46, 128.08, 125.44, 123.52 (q, *J* = 298.8 Hz), 121.45, 111.04, 103.71, 95.29, 68.485 (q, *J* = 35.1 Hz), 21.28, 21.24, 20.68, 20.59. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.76. **HRMS:** m/z calculated for $C_{28}H_{29}NO_2F_3$ $[M+H]^+$ = 468.2150, found 468.2169.

3,6-bis(2,4-dimethylphenyl)-2-(2,2,2-trifluoroethoxy)-1*H*-indole (9e)

Following the general procedure (GP-3), treatment of 3,6-bis(3,5-dimethylphenyl)indolin-2-one, **8e** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (85/15) afforded 3,6-bis(2,4-dimethylphenyl)-2-(2,2,2-trifluoroethoxy)-1*H*-indole **9e** as off white solid (0.036 g, 86% yield), m.p. 93-95 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.94 (s, 1H), 7.32 – 7.27 (m, 2H), 7.22 – 7.18 (m, 2H), 7.13 - 7.04 (m, 5H), 4.14 (q, *J* = 8.3 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 146.50, 140.75, 139.99, 137.84, 137.42, 136.61, 135.72, 135.53, 131.36, 131.19, 130.30, 126.81, 126.53, 124.58 (q, *J* = 268.5 Hz), 122.34, 118.52, 111.12, 97.64, 68.52 (q, J = 35.5 Hz), 21.36, 21.19, 20.77, 20.18. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -74.66. **HRMS:** m/z calculated for $C_{26}H_{25}NOF_3$ $[M+H]^+$ = 424.1901, found 424.1888.

2-((2,2,2-trifluoroethyl)thio)-1*H*-indole (11)

Following the general procedure (GP-3), treatment of indolin-2-thione, **10** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (85/15) afforded 2-((2,2,2-trifluoroethyl)thio)-1*H*-indole **11** as yellow solid (0.024 g, 52% yield), m.p. 93-95 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.20 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.31 – 7.23 (m, 1H), 6.96 – 6.87 (m, 1H), 3.39 (q, *J* = 9.8 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.41, 128.26, 125.66, 125.34 (q, *J* = 276.0 Hz), 123.69, 120.89, 120.58, 111.30, 111.08, 39.83 (q, *J* = 32.3 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -66.60. **HRMS:** m/z calculated for $C_{10}H_9NF_3S$ $[M+H]^+$ = 232.0408, found 232.0441.

3-(2,2,2-trifluoroethoxy)-1*H*-isoindole (13a)

Following the general procedure (GP-4), treatment of isoindolin-1-one, **12a** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 3-(2,2,2-trifluoroethoxy)-1*H*-isoindole **13a** as viscous liquid (0.038 g, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 – 7.63 (m, 1H), 7.56 – 7.52 (m, 1H), 7.48 – 7.40 (m, 2H), 4.86 (q, *J* = 8.5 Hz, 2H), 4.63 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 168.92, 150.91, 131.60, 129.69, 127.44, 123 (q, *J* = 298.1 Hz), 122.63, 120.89, 64.24 (q, *J* = 36.4 Hz), 58.23. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.31. **HRMS:** m/z calculated for $C_{10}H_8F_3NO$ [M+H]+ = 216.0636, found 216.0632.

5-bromo-3-(2,2,2-trifluoroethoxy)-1*H*-isoindole (13b)

Following the general procedure GP-4), treatment of 5-bromoisoindolin-1-one, **12b** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction

mixture using silica gel in hexane afforded 5-bromo-3-(2,2,2-trifluoroethoxy)-1*H*-isoindole **13b** as off white solid (0.051 g, 88% yield), m.p. 80-82 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.68 (s, 1H), 7.54 (m, 2H), 4.84 (q, *J* = 8.4 Hz, 2H), 4.60 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 168.20, 152.95, 130.86, 126.18 (q, *J* = 310.1 Hz), 126.13, 124.64, 122.02, 64.33 (q, *J* = 36.6 Hz), 57.97. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.81. **HRMS:** m/z calculated for $C_{10}H_8NOBrF_3$ $[M+H]^+$ = 293.9741, found 293.9742.

6-bromo-3-(2,2,2-trifluoroethoxy)-1*H*-isoindole (13c)

Following the general procedure (GP-4), treatment of 6-bromoisoindolin-1-one, **12c** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane afforded 6-bromo-3-(2,2,2-trifluoroethoxy)-1*H*-isoindole **13c** as off white solid (0.049 g, 85% yield), m.p. 79-81 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 – 7.77 (m, 1H), 7.59 – 7.55 (m, 1H), 7.42 – 7.37 (m, 1H), 4.84 (q, *J* = 8.4 Hz, 2H), 4.59 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.66, 149.79, 133.64, 132.64, 124.12, 124.02, 121.42, 64.36 (q, *J* = 37.1 Hz), 58.11. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.81. **HRMS:** m/z calculated for $C_{10}H_8NOBrF_3$ $[M+H]^+$ = 293.9741, found 293.9731.

7-methoxy-3-(2,2,2-trifluoroethoxy)-1*H*-isoindole (13d)

Following the general procedure (GP-4), treatment of 7-methoxyisoindolin-1-one, **12d** (0.2 mmol, 1 eq.) and 2,2,2-trifluorodiazoethane **2** in toluene (0.24 mmol, 1.2 eq.) with TfOH (10 mol %) at rt for 10 minutes followed by column chromatography of the crude reaction mixture using silica gel in hexane/ethyl acetate (99/1) afforded 7-methoxy-3-(2,2,2-trifluoroethoxy)-1*H*-isoindole **13d** as viscous liquid (0.040 g, 84% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.84 (q, *J* = 8.4 Hz, 2H), 4.59 (s, 2H), 3.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 168.75, 154.61, 138.64, 133.40, 129.50, 123.36 (q, *J* = 277.2 Hz), 113.21, 111.22, 64.28

(q, *J* = 36.4 Hz), 56.23, 55.47, 55.46. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -73.81. **HRMS**: m/z calculated for $C_{11}H_{11}NO_2F_3$ $[M+H]^+$ = 246.0742, found 246.0730.

3.5 References

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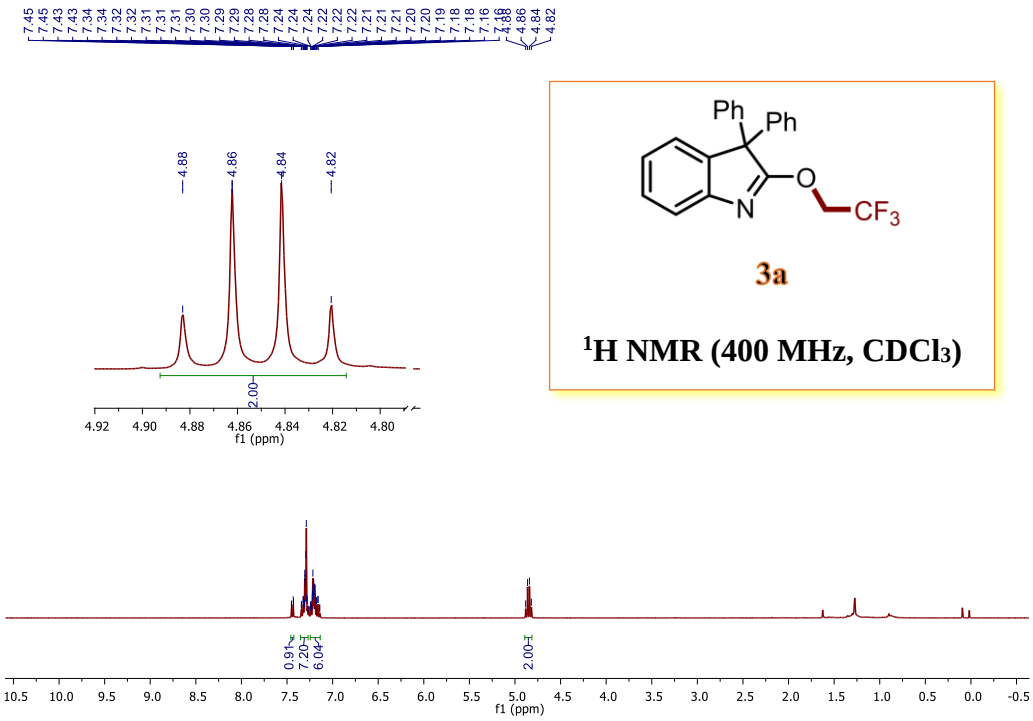
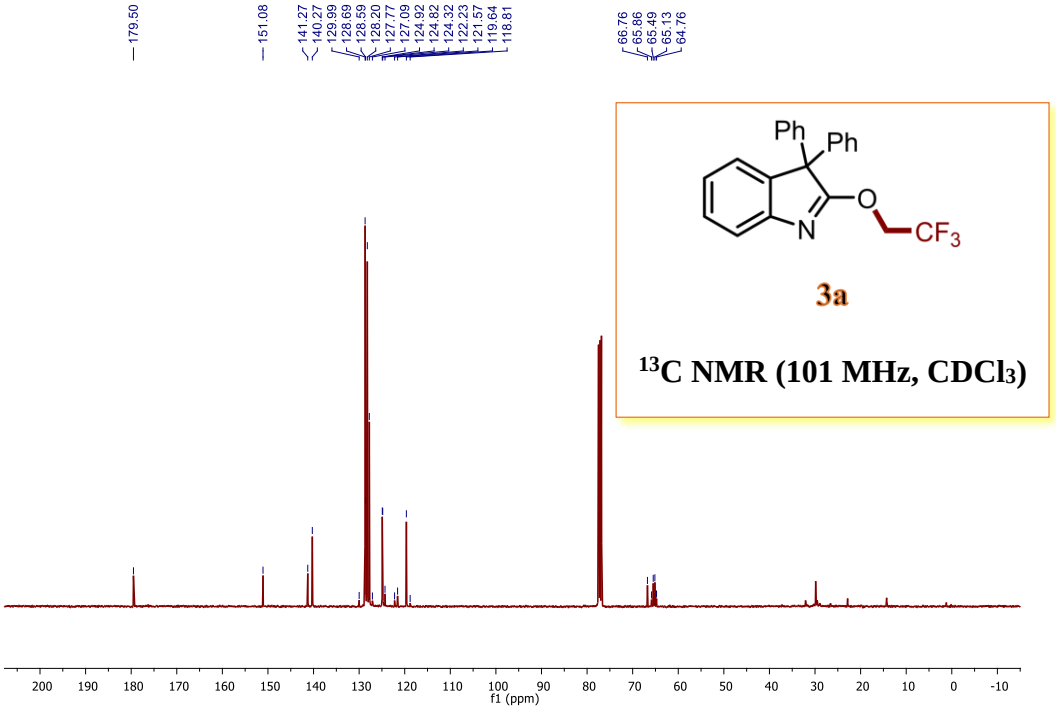
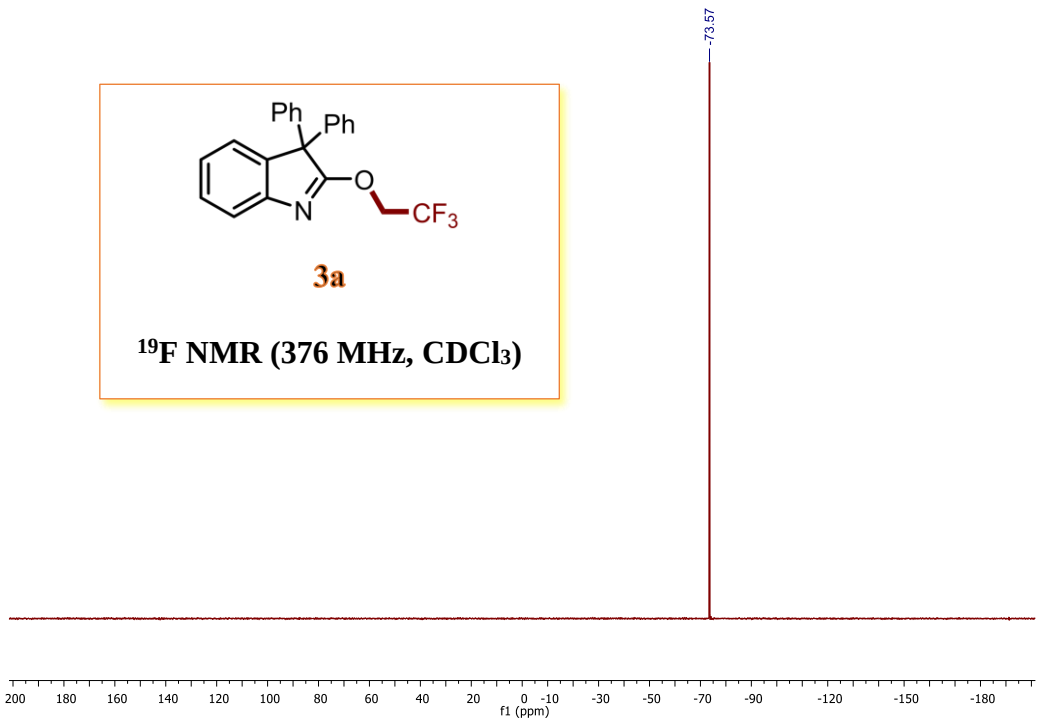
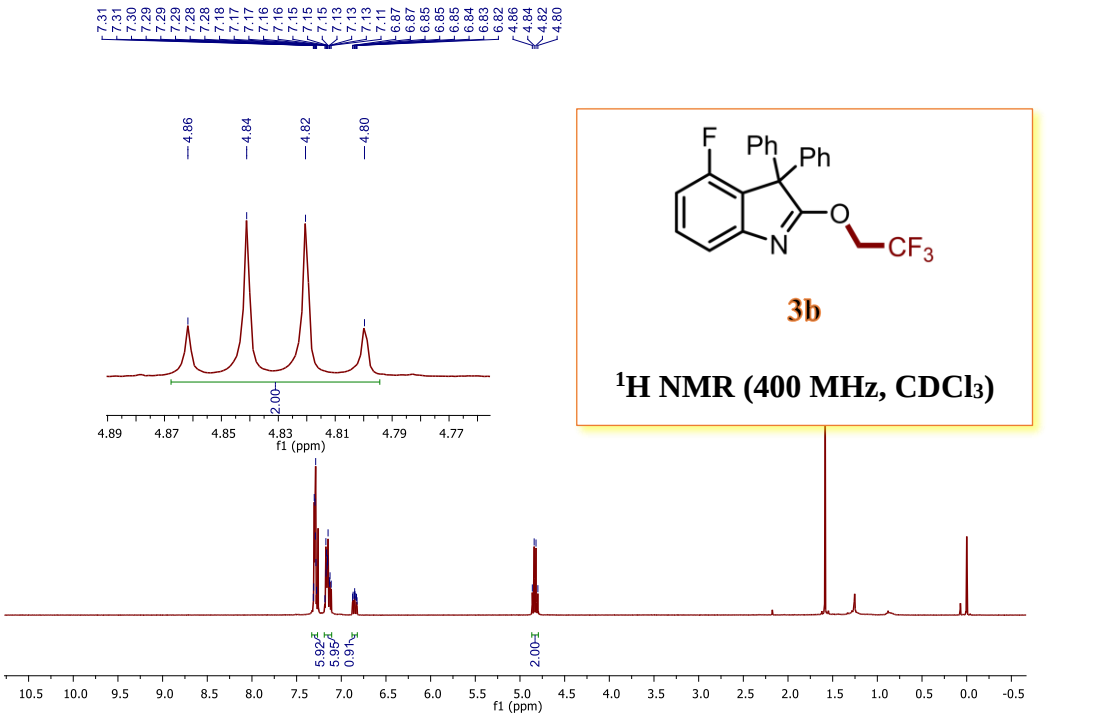
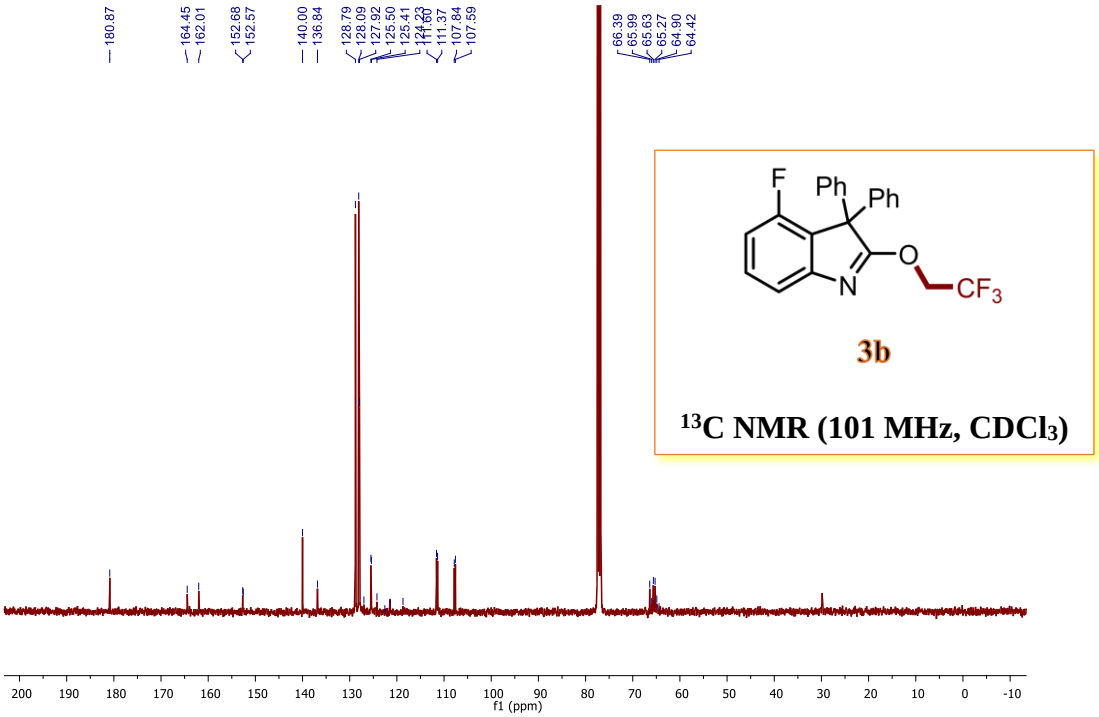
3.6 NMR Spectras of Compounds

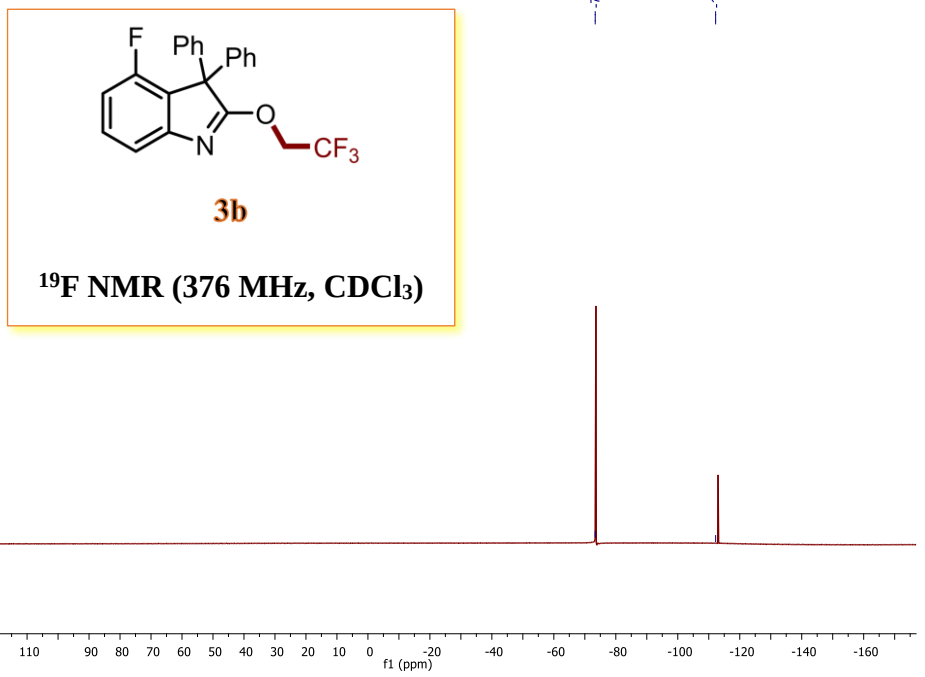


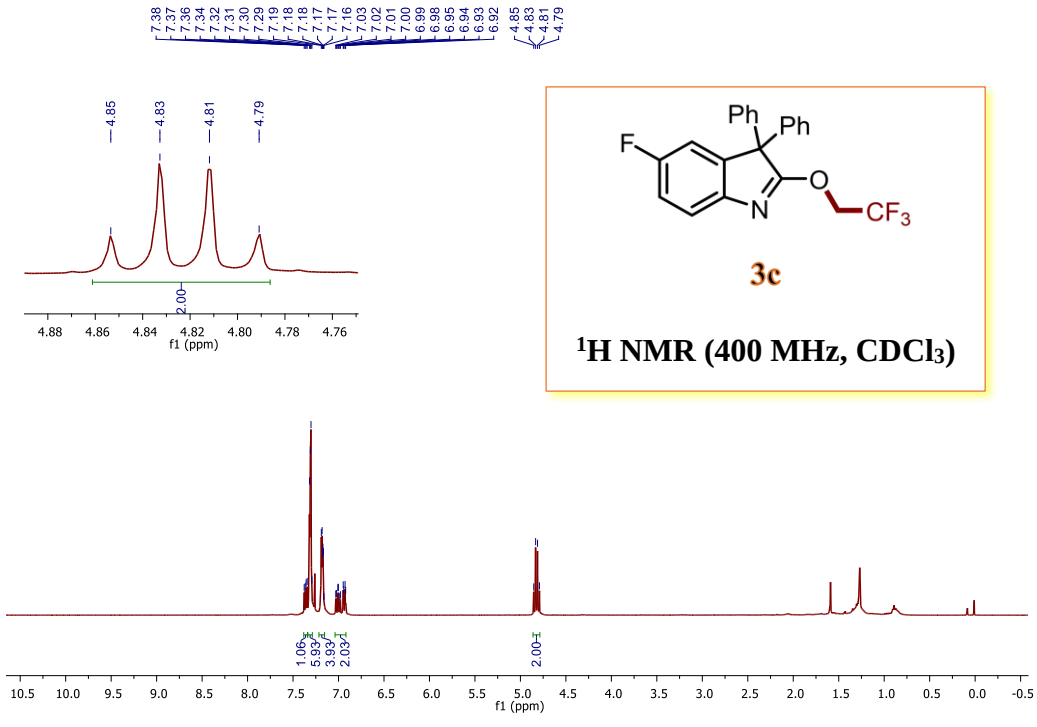

179.50
151.08
141.27
140.27
129.99
128.69
128.59
128.20
127.77
127.09
124.92
124.82
124.32
122.23
121.57
119.64
118.81
66.76
65.86
65.49
65.13
64.76
Ph
Ph
O
N
CF3
3a
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

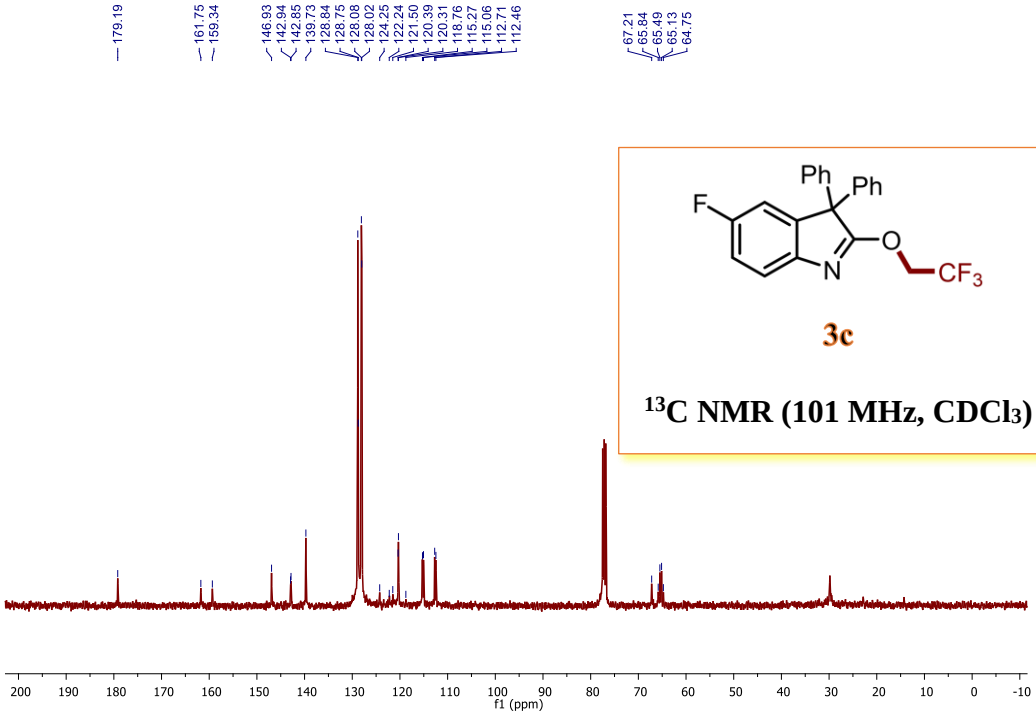

-73.57
Ph
Ph
O
N
CF3
3a
19F NMR (376 MHz, CDCl3)
200 180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180
f1 (ppm)

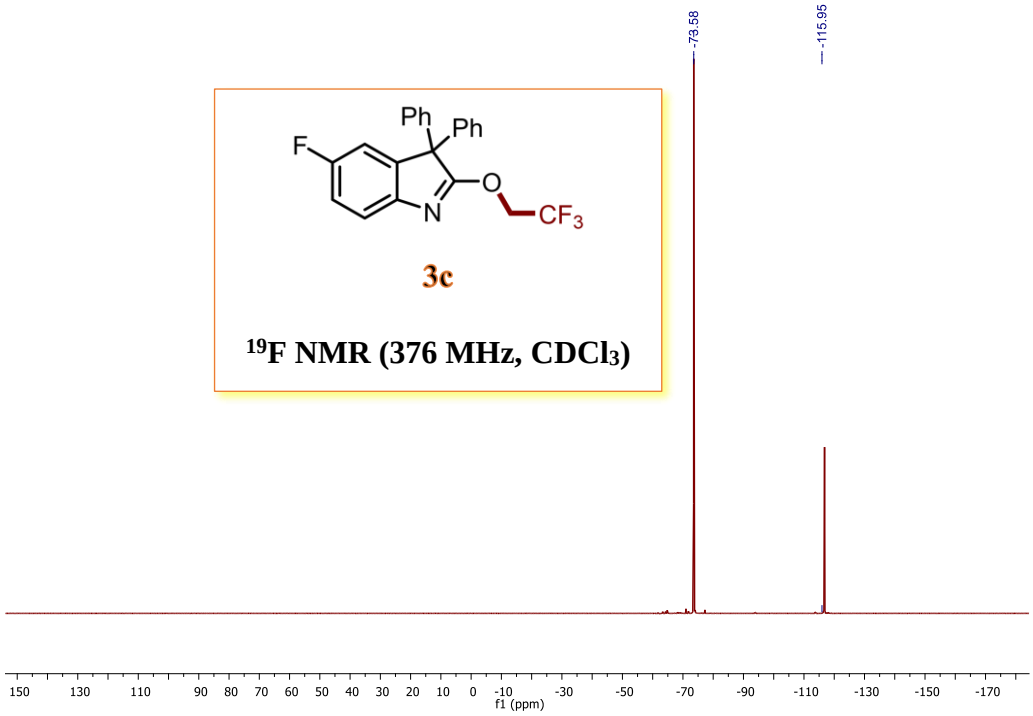

F
Ph
Ph
O
N
CF3
3b
1H NMR (400 MHz, CDCl3)

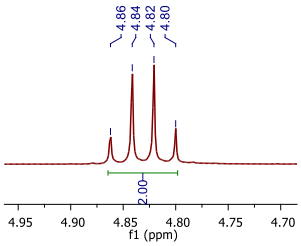

F
Ph
Ph
O
N
CF3
3b
13C NMR (101 MHz, CDCl3)

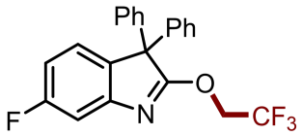

F
Ph
Ph
O
N
CF3
3b
19F NMR (376 MHz, CDCl3)
-73.35
-112.22
f1 (ppm)


7.38
7.37
7.36
7.34
7.32
7.31
7.30
7.29
7.19
7.18
7.18
7.17
7.17
7.16
7.03
7.02
7.01
7.00
6.99
6.98
6.95
6.94
6.93
6.92
4.85
4.83
4.81
4.79
2.00
f1 (ppm)
F
Ph
Ph
O
N
CF3
3c
1H NMR (400 MHz, CDCl3)
1.06
5.93
3.93
2.03
2.00
f1 (ppm)


179.19
161.75
159.34
146.93
142.94
142.85
139.73
128.84
128.75
128.08
128.02
124.25
122.24
121.50
120.39
120.31
118.76
115.27
115.06
112.71
112.46
67.21
65.84
65.49
65.13
64.75
Ph
Ph
F
O
N
CF3
3c
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

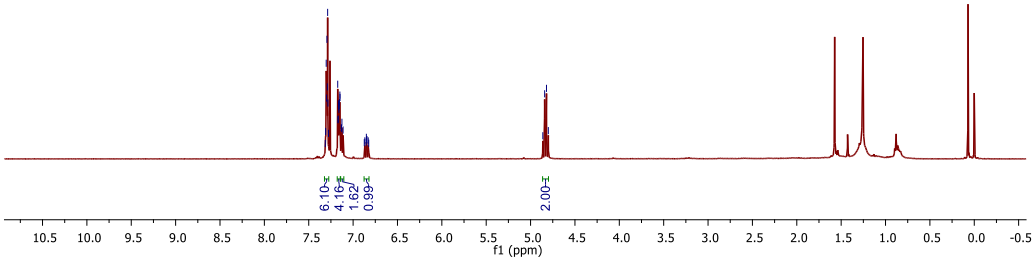

-79.58
-115.95
Ph
Ph
F
O
N
CF3
3c
19F NMR (376 MHz, CDCl3)
150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170
f1 (ppm)





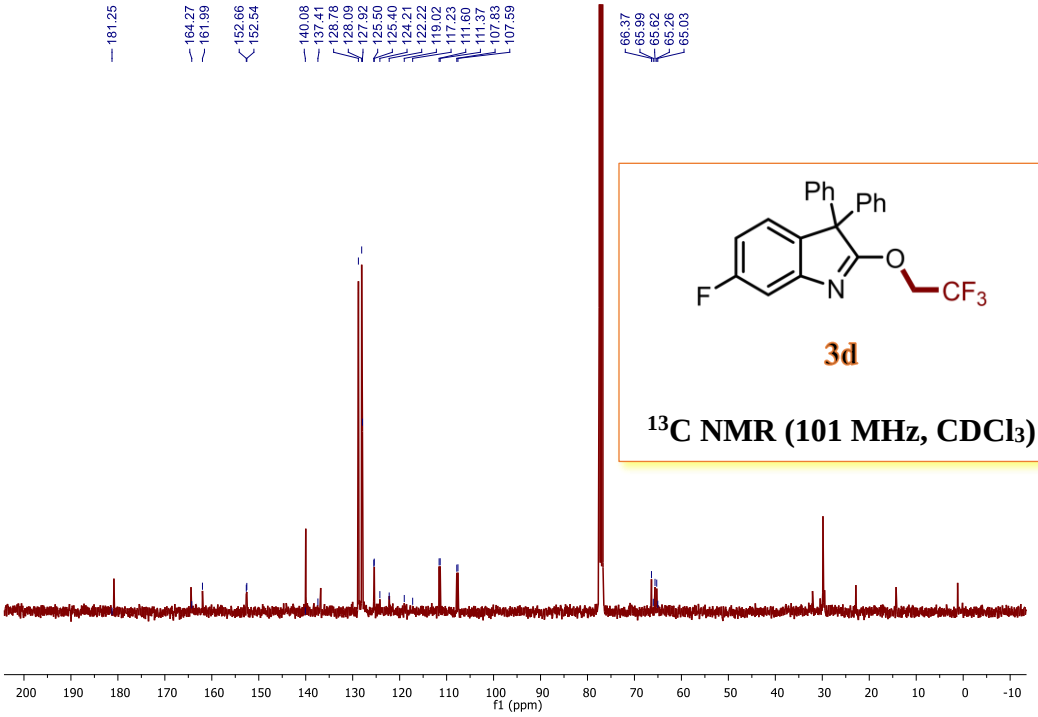
3d

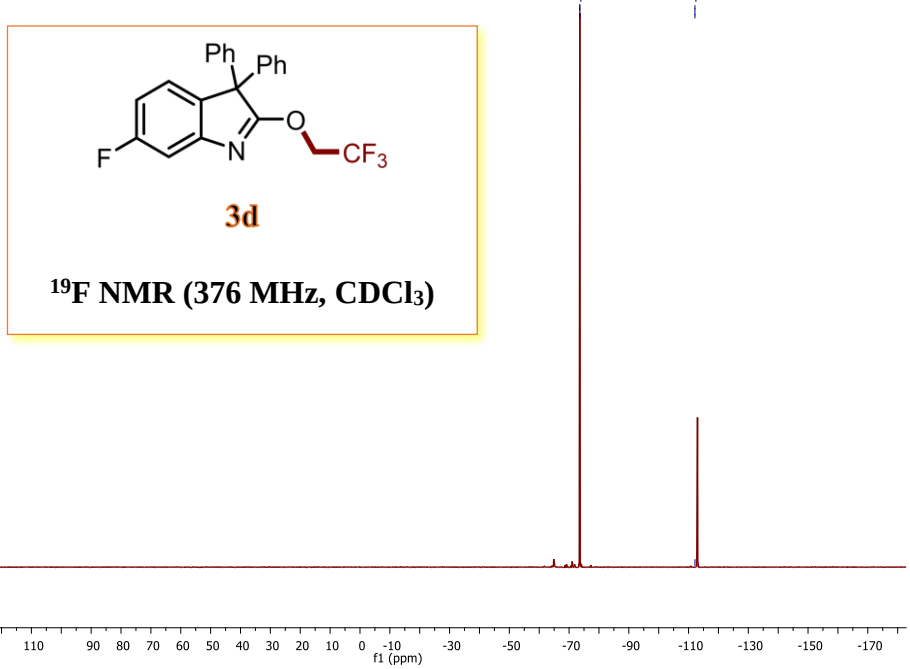
^{1}H NMR (400 MHz, $CDCl_3$)



3d

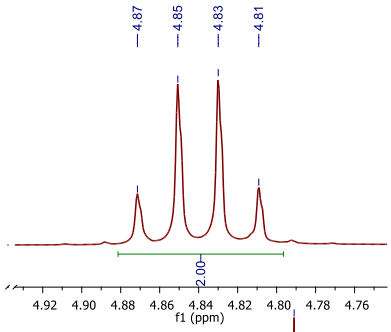
^{13}C NMR (101 MHz, $CDCl_3$)

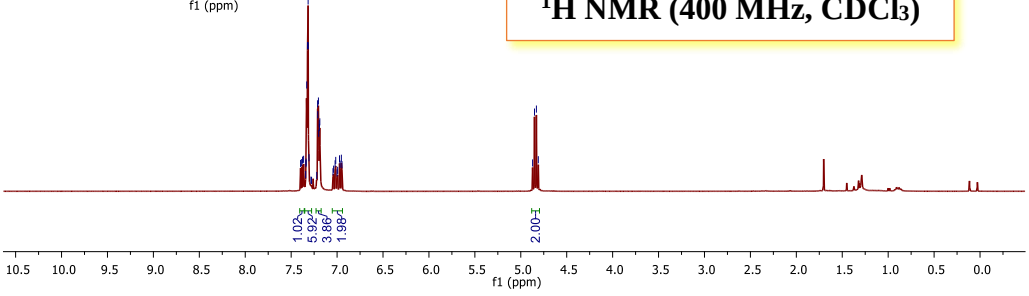


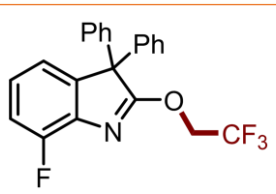


3d

^{19}F NMR (376 MHz, $CDCl_3$)

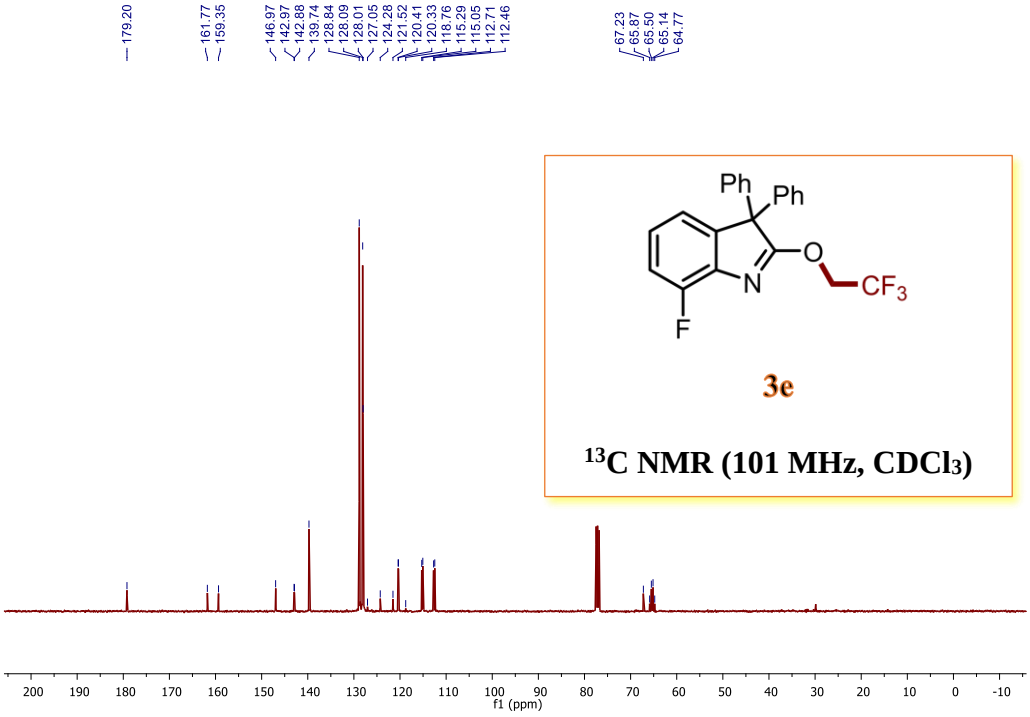


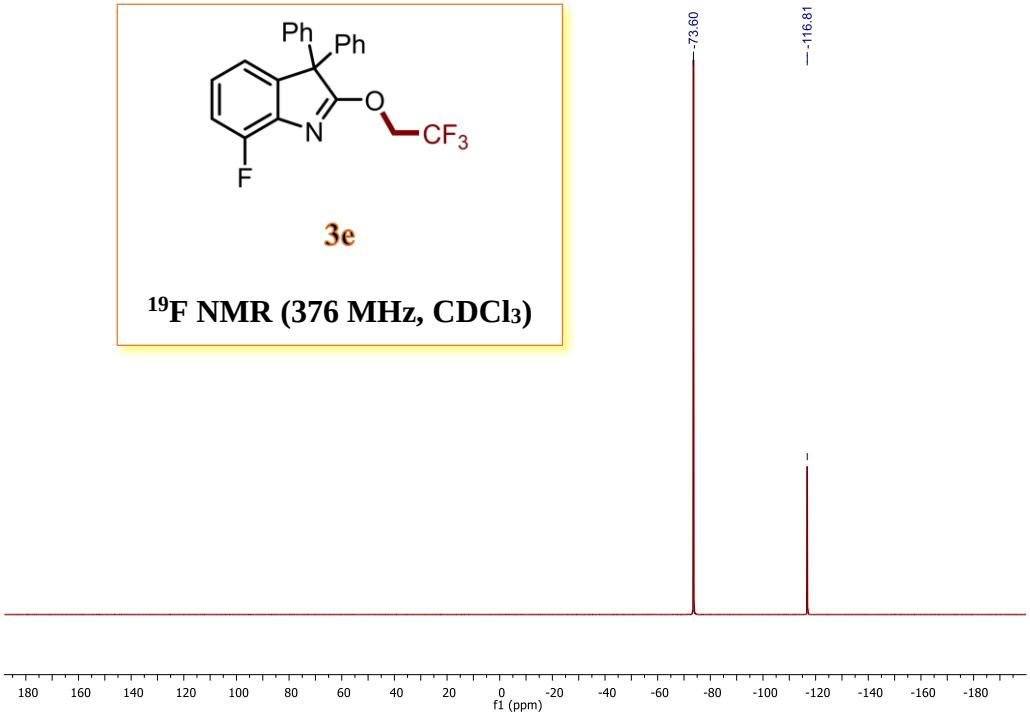


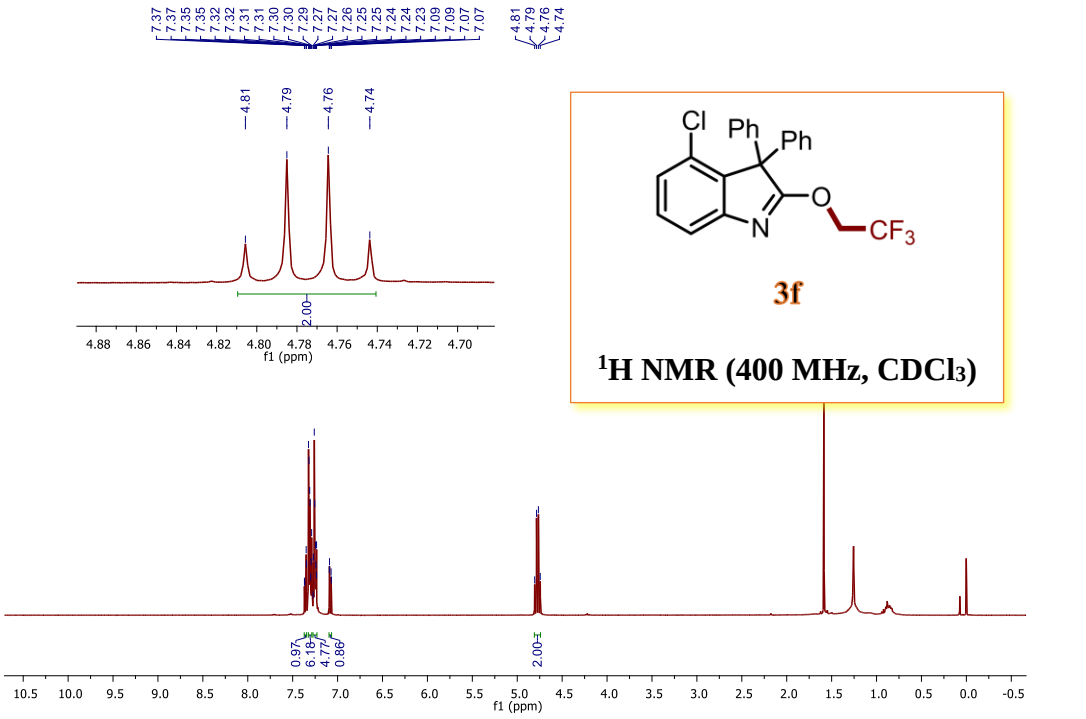


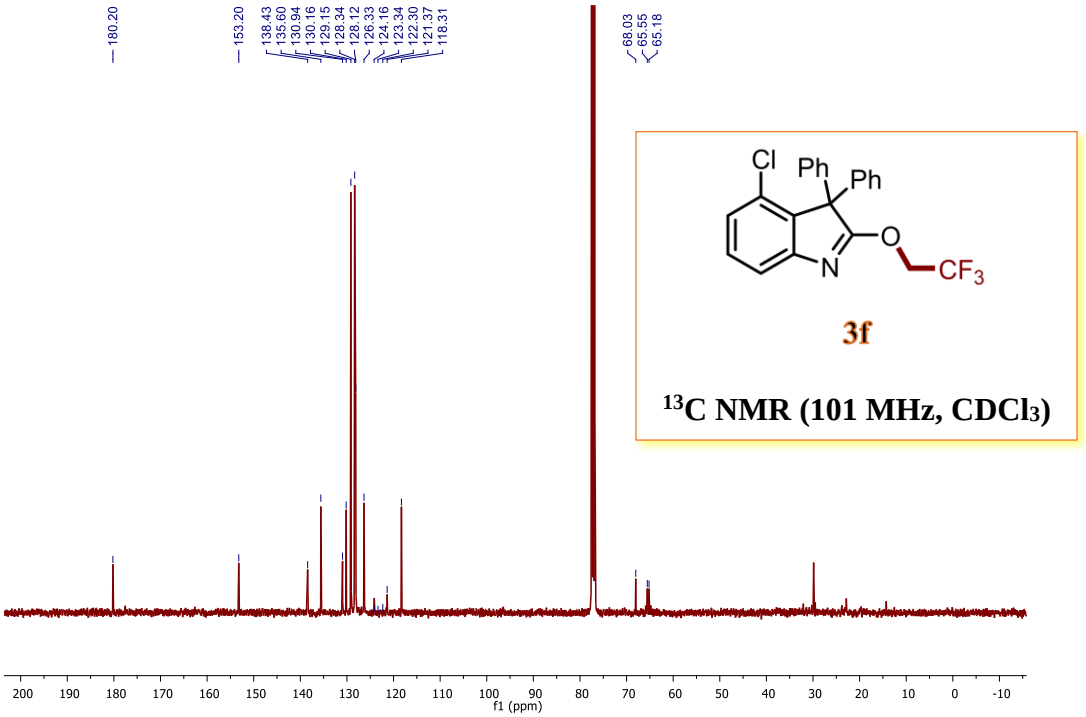
3e

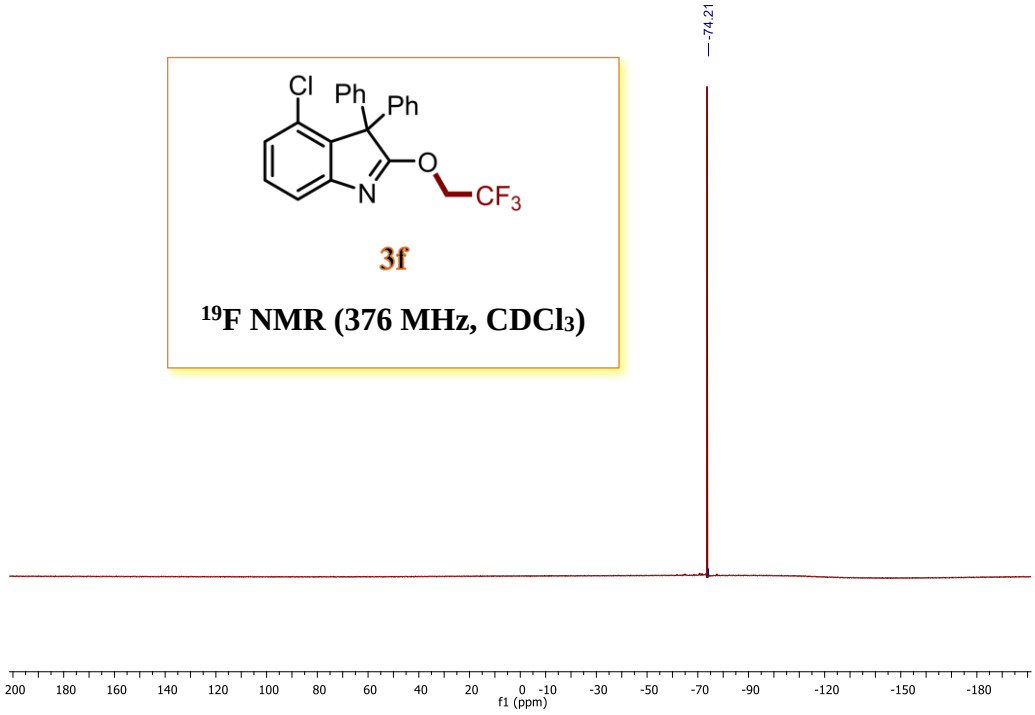
^{1}H NMR (400 MHz, $CDCl_3$)

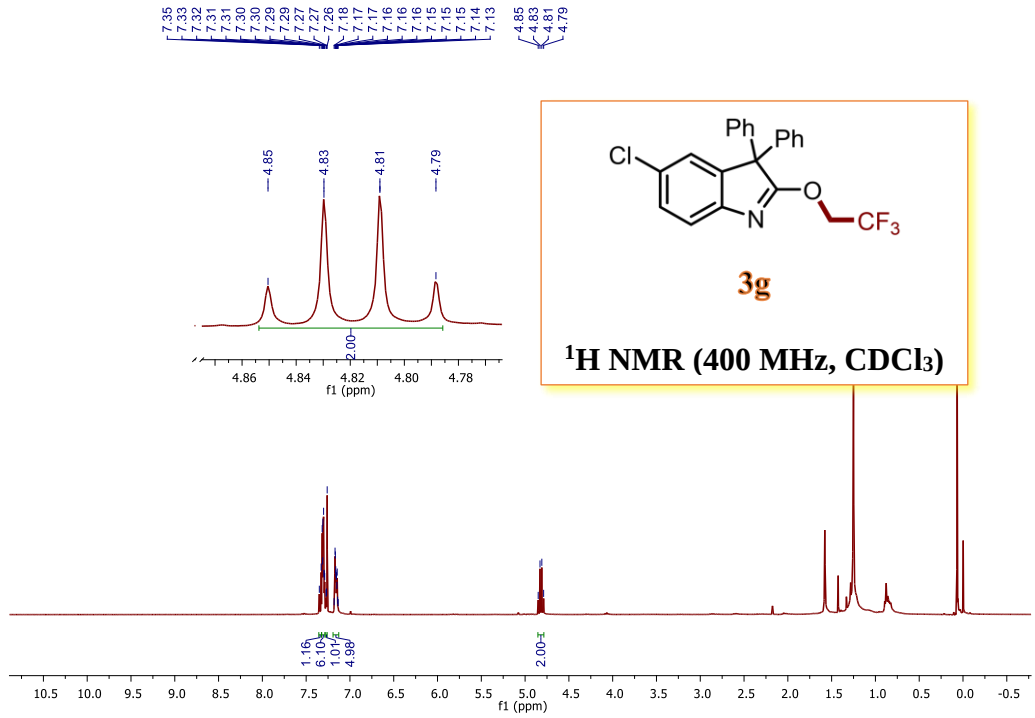

179.20
161.77
159.35
146.97
142.97
142.88
139.74
128.84
128.09
128.01
127.05
124.28
121.52
120.41
120.33
118.76
115.29
115.05
112.71
112.46
67.23
65.87
65.50
65.14
64.77
Ph
Ph
O
N
CF3
F
3e
13C NMR (101 MHz, CDCl3)
f1 (ppm)

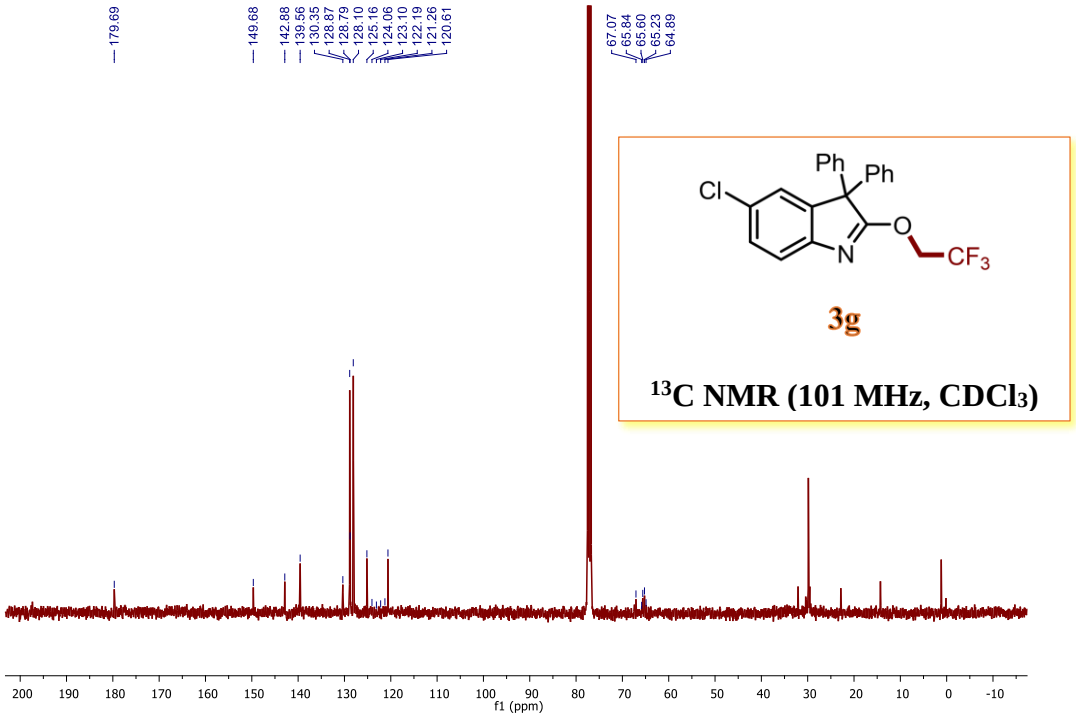

-73.60
-116.81
Ph
Ph
O
N
CF3
F
3e
19F NMR (376 MHz, CDCl3)
f1 (ppm)

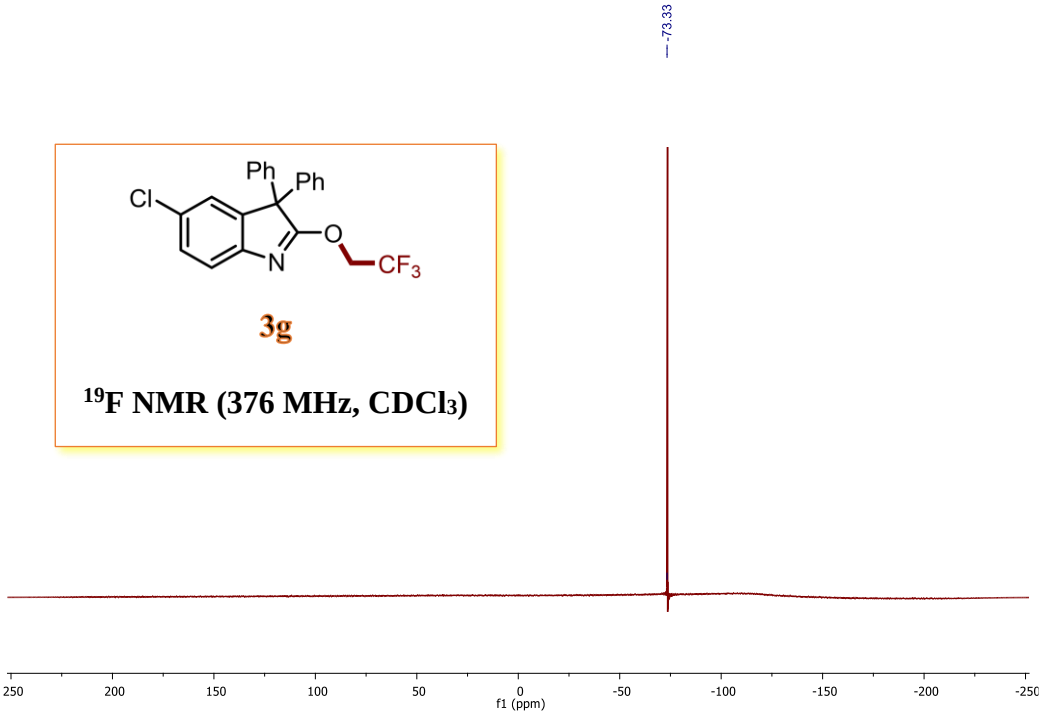

Cl
Ph
Ph
O
N
CF3
3f
1H NMR (400 MHz, CDCl3)

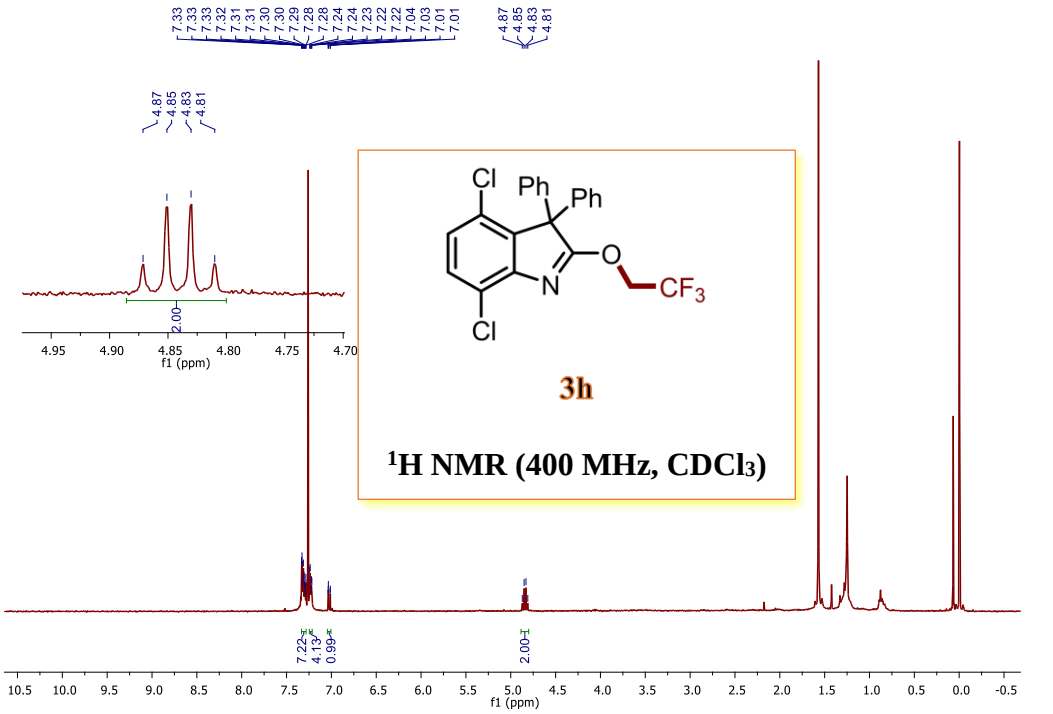

Cl
Ph
Ph
O
N
CF3
3f
13C NMR (101 MHz, CDCl3)

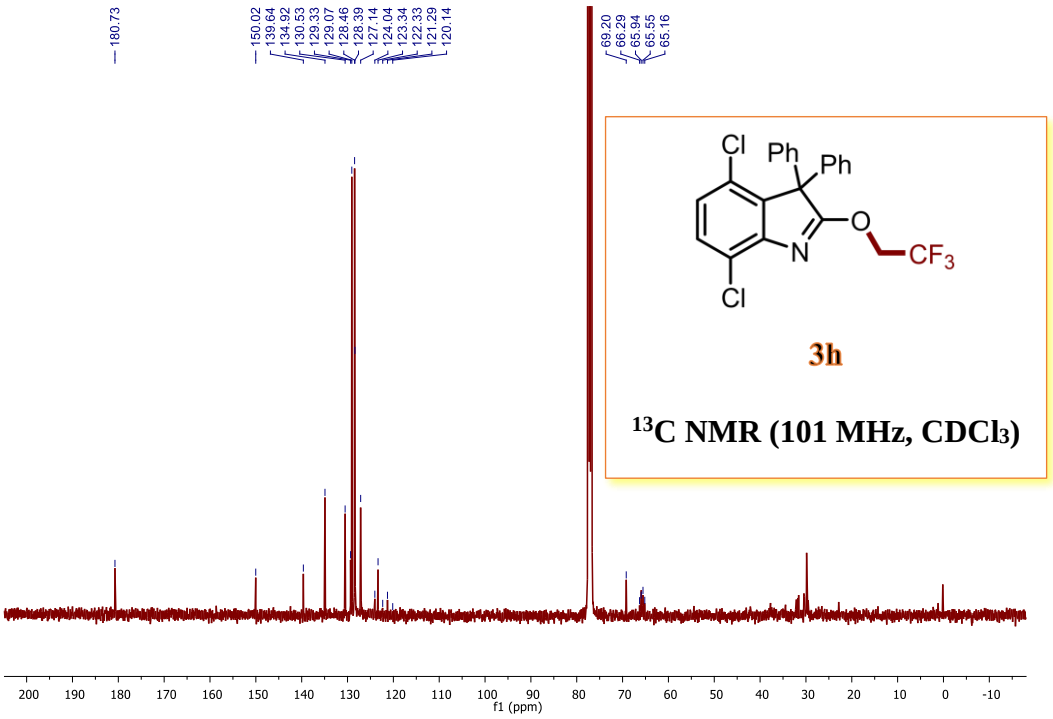

Cl
Ph
Ph
O
N
CF3
3f
19F NMR (376 MHz, CDCl3)
-74.21
200 180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180
f1 (ppm)


7.35 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.27 7.27 7.26 7.18 7.17 7.17 7.16 7.16 7.16 7.15 7.15 7.15 7.15 7.14 7.13
4.85 4.83 4.81 4.79
4.85 4.83 4.81 4.79
2.00
4.86 4.84 4.82 4.80 4.78
f1 (ppm)
Cl
Ph
Ph
O
N
CF3
3g
1H NMR (400 MHz, CDCl3)
1.16 6.10 1.01 4.98 2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


179.69
149.68
142.88
139.56
130.35
128.87
128.79
128.10
125.16
124.06
123.10
122.19
121.26
120.61
67.07
65.84
65.60
65.23
64.89
Ph
Ph
Cl
O
N
CF3
3g
13C NMR (101 MHz, CDCl3)
f1 (ppm)

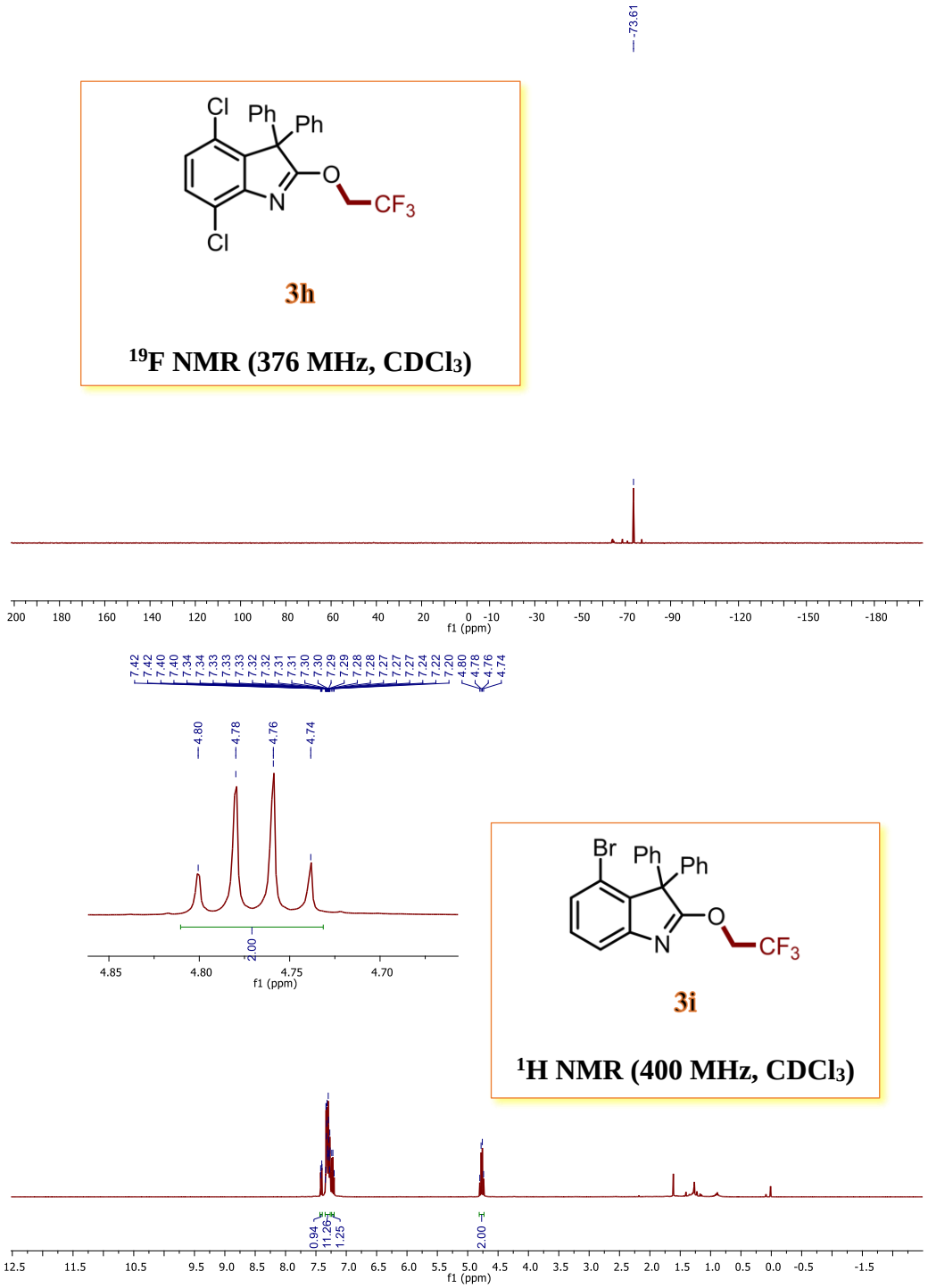

-73.33
Ph
Ph
Cl
O
N
CF3
3g
19F NMR (376 MHz, CDCl3)
f1 (ppm)


Cl
Ph
Ph
O
N
CF3
Cl
3h
1H NMR (400 MHz, CDCl3)
f1 (ppm)


Cl
Ph
Ph
O
N
CF3
Cl
3h
13C NMR (101 MHz, CDCl3)
f1 (ppm)

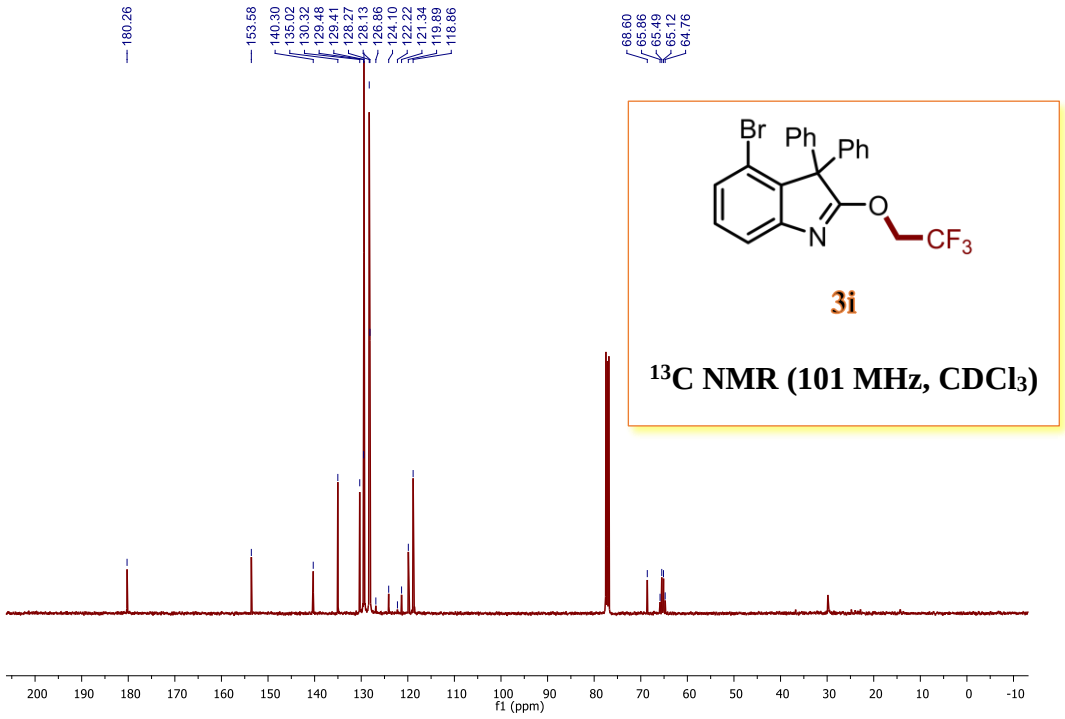
3h

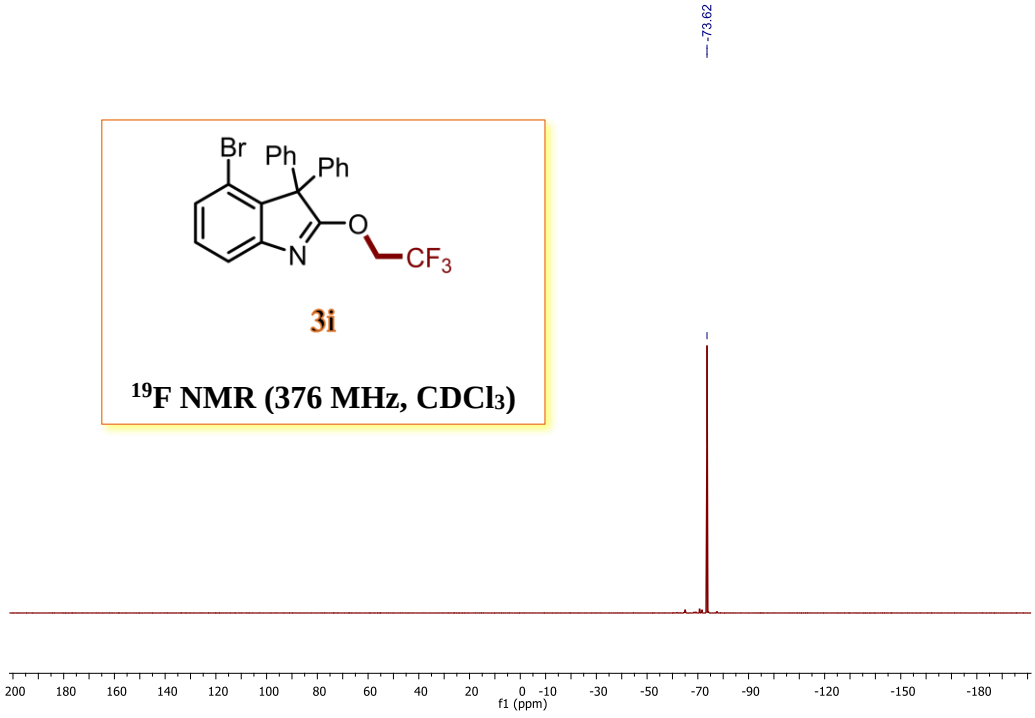
^{19}F NMR (376 MHz, $CDCl_3$)

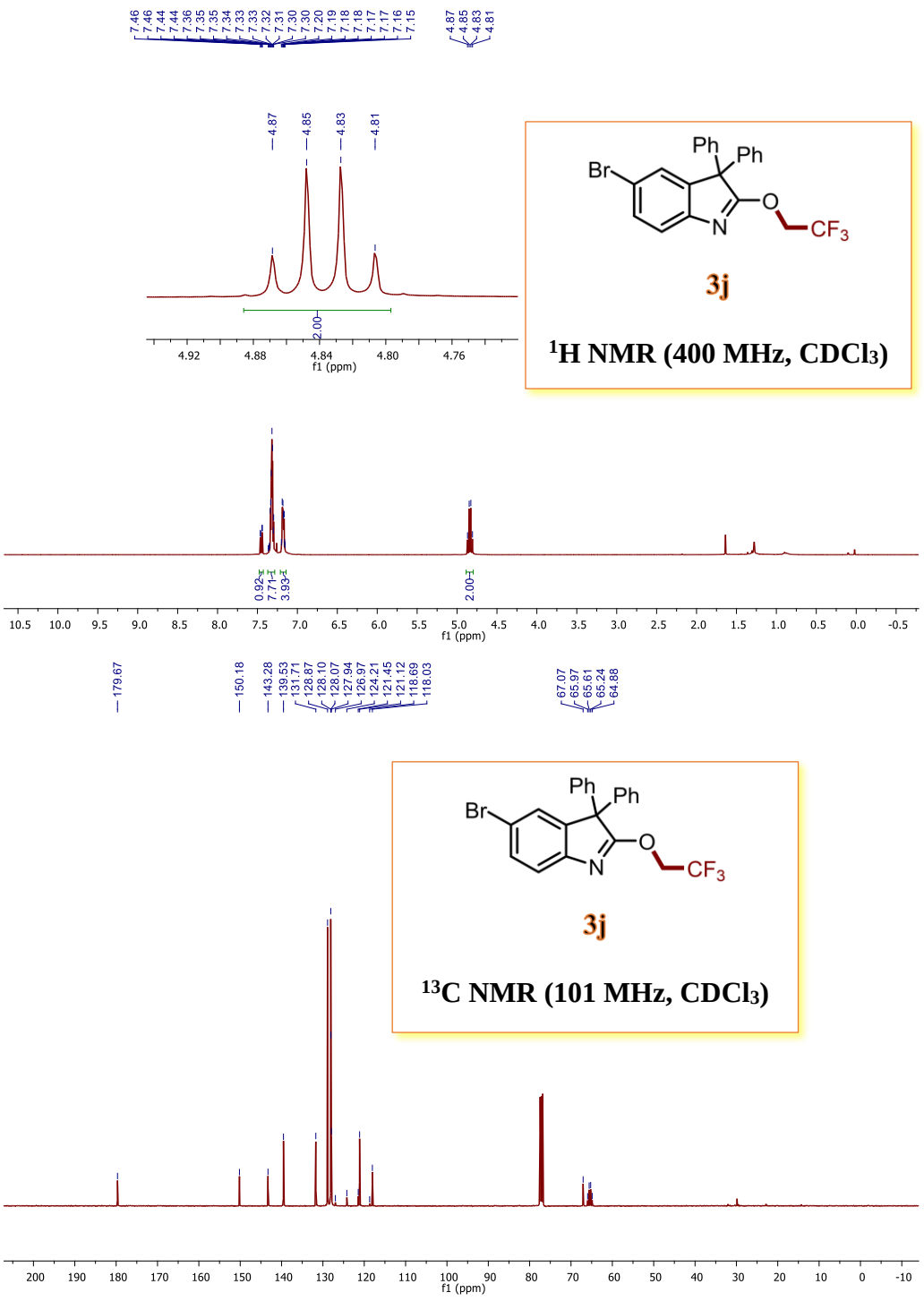


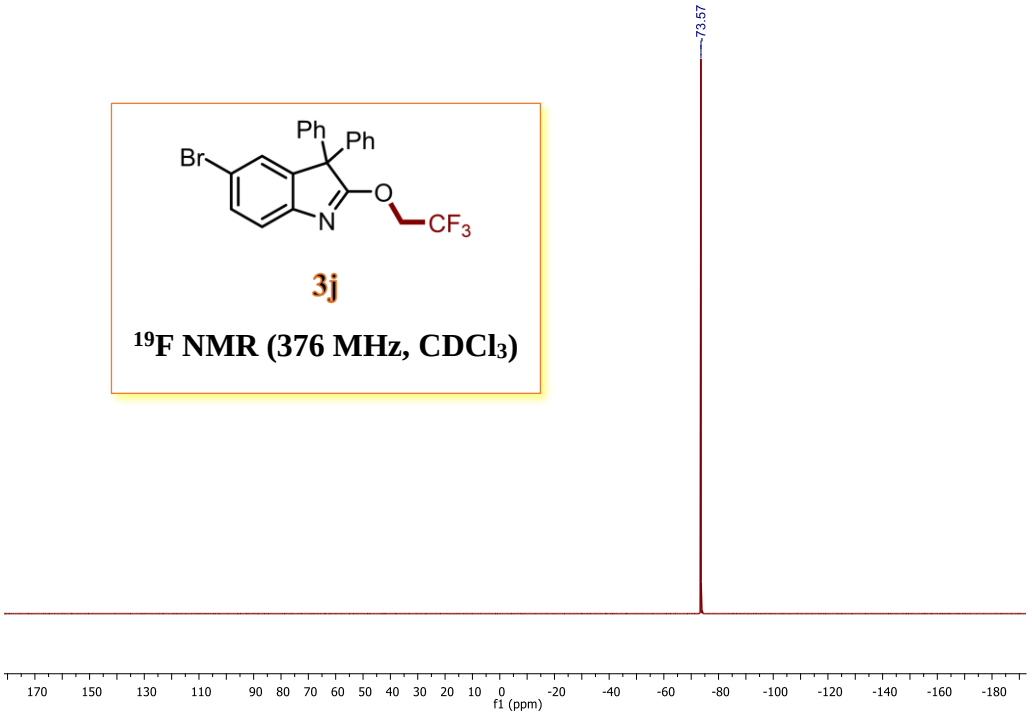
3i

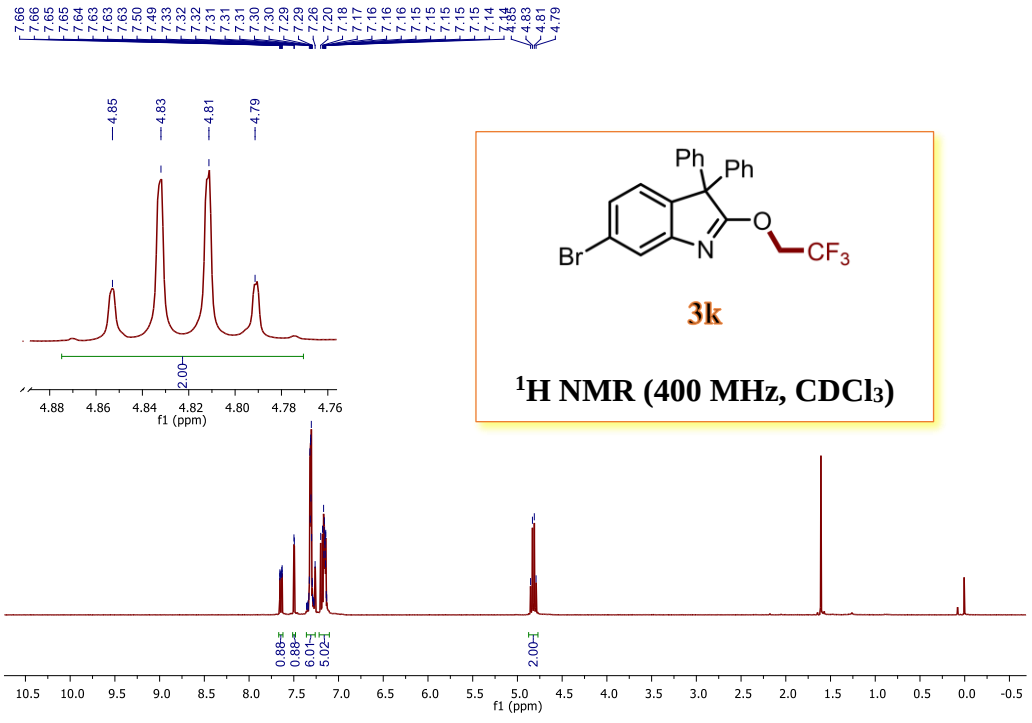
^{1}H NMR (400 MHz, $CDCl_3$)

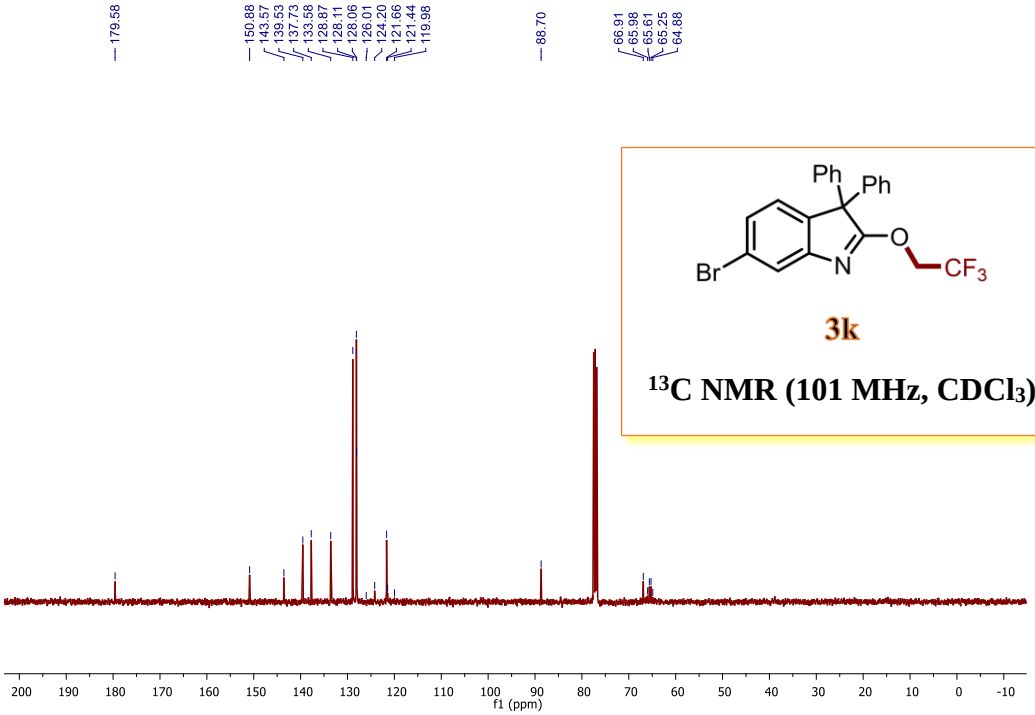

180.26
153.58
140.30
135.02
130.32
129.48
129.41
128.27
128.13
126.86
124.10
122.22
121.34
119.89
118.86
68.60
65.86
65.49
65.12
64.76
Br
Ph
Ph
O
N
CF3
3i
13C NMR (101 MHz, CDCl3)
f1 (ppm)

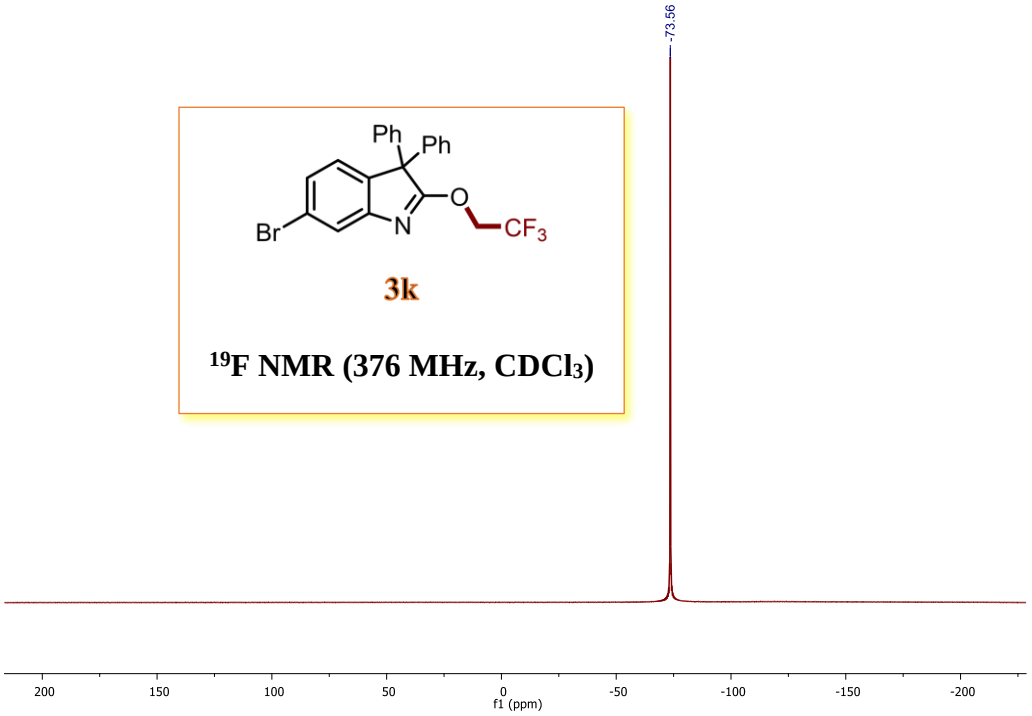

-73.62
Br
Ph
Ph
O
N
CF3
3i
19F NMR (376 MHz, CDCl3)
f1 (ppm)

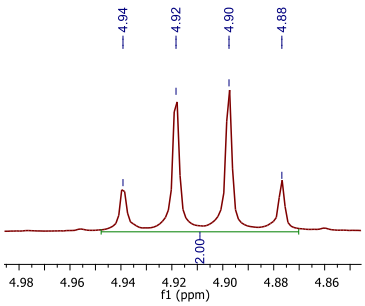

7.46
7.46
7.44
7.44
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.30
7.30
7.20
7.19
7.18
7.18
7.17
7.17
7.16
7.15
4.87
4.85
4.83
4.81
4.87
4.85
4.83
4.81
2.00
4.92
4.88
4.84
4.80
4.76
f1 (ppm)
Ph
Ph
Br
O
N
CF3
3j
1H NMR (400 MHz, CDCl3)
0.92
7.71
3.93
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
179.67
150.18
143.28
139.53
131.71
128.87
128.10
128.07
127.94
126.97
124.21
121.45
121.12
118.69
118.03
67.07
65.97
65.61
65.24
64.88
Ph
Ph
Br
O
N
CF3
3j
13C NMR (101 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

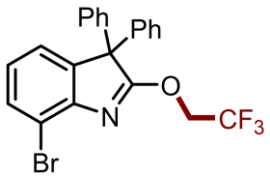

Ph
Ph
Br
O
N
CF3
3j
19F NMR (376 MHz, CDCl3)
73.57
f1 (ppm)


7.66
7.66
7.65
7.65
7.64
7.63
7.63
7.63
7.50
7.49
7.33
7.32
7.32
7.31
7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.26
7.20
7.18
7.17
7.16
7.16
7.16
7.15
7.15
7.15
7.15
7.15
7.14
4.85
4.83
4.81
4.79
4.83
4.81
4.79
2.00
f1 (ppm)
Ph
Ph
Br
O
N
CF3
3k
1H NMR (400 MHz, CDCl3)
0.88
0.88
6.01
5.02
2.00
f1 (ppm)


179.58
150.88
143.57
139.53
137.73
133.58
128.87
128.11
128.06
126.01
124.20
121.66
121.44
119.98
88.70
66.91
65.98
65.61
65.25
64.88
Ph
Ph
O
N
Br
CF3
3k
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

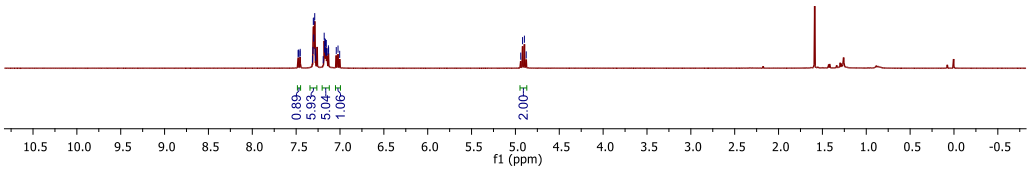

-73.56
Ph
Ph
O
N
Br
CF3
3k
19F NMR (376 MHz, CDCl3)
200 150 100 50 0 -50 -100 -150 -200
f1 (ppm)

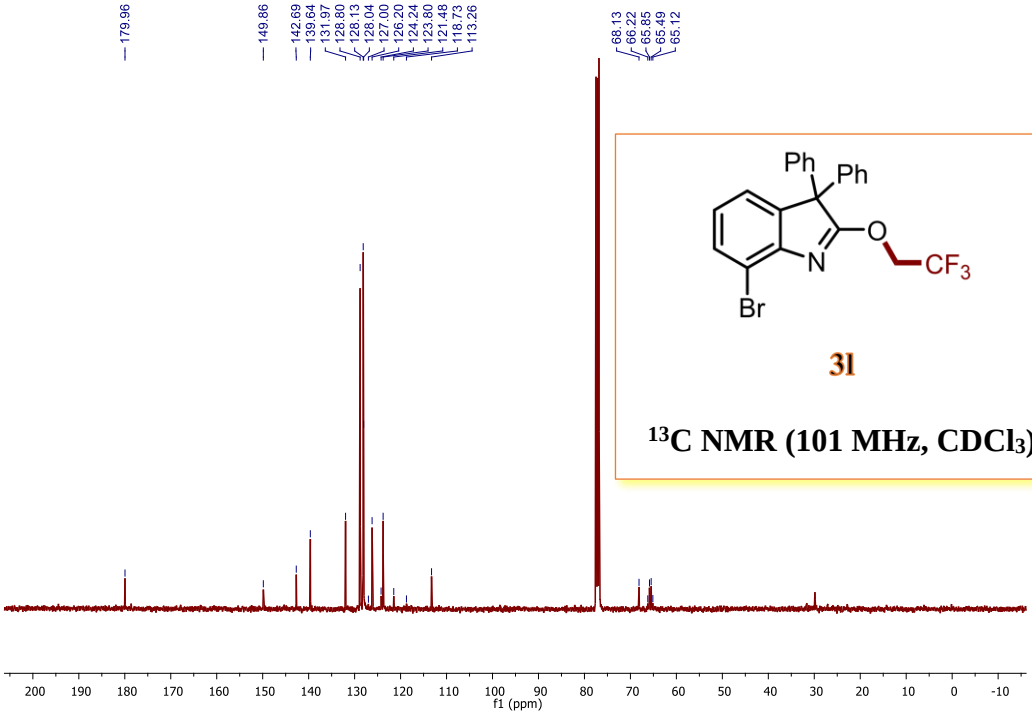




3l

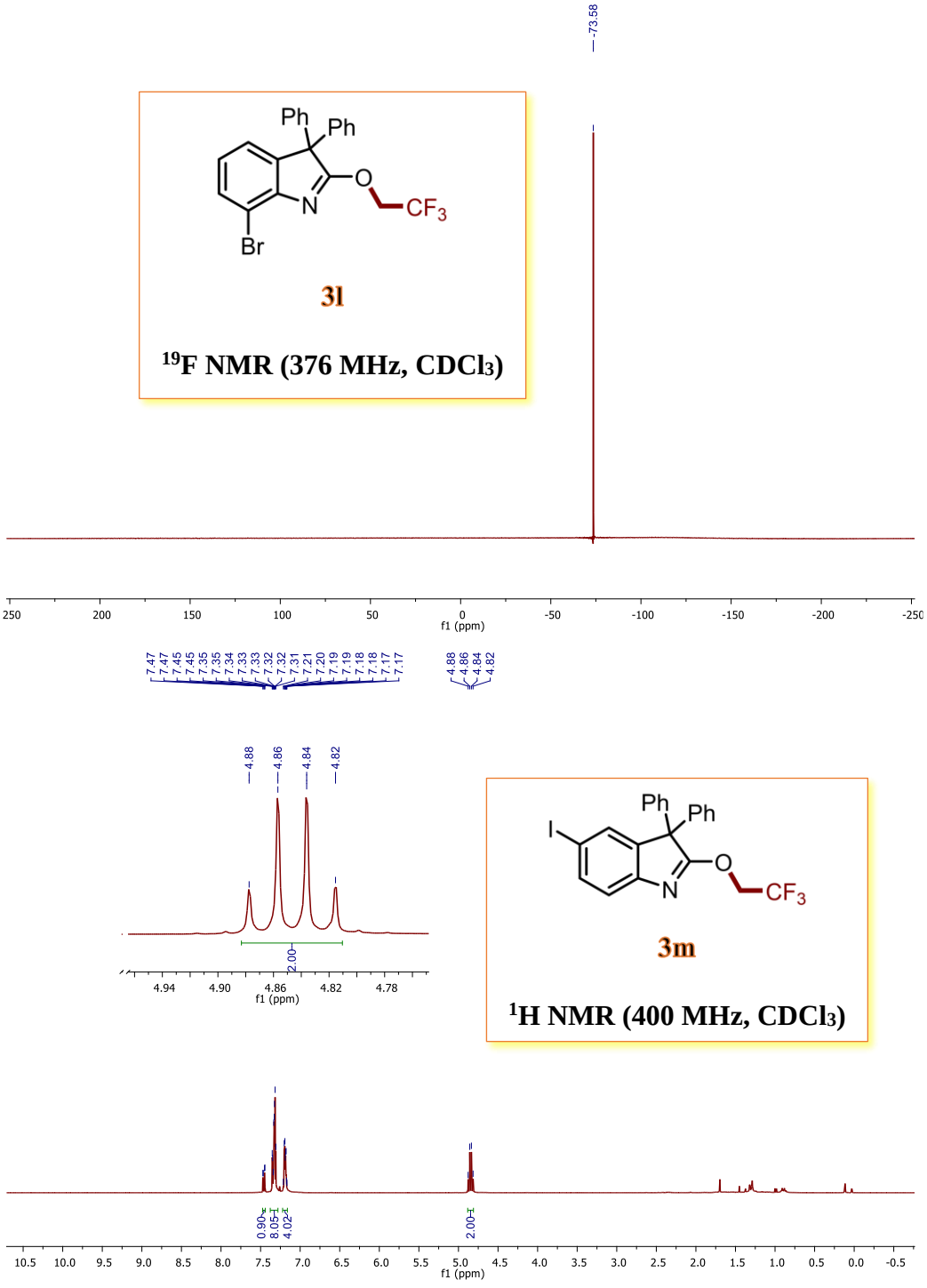
^{1}H NMR (400 MHz, $CDCl_3$)

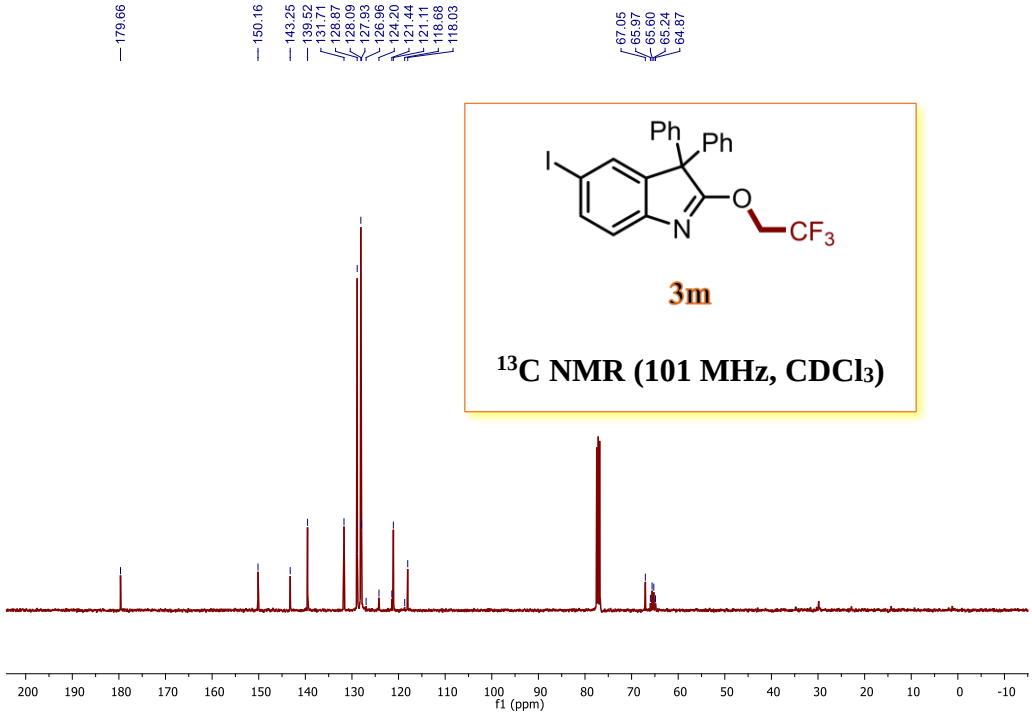


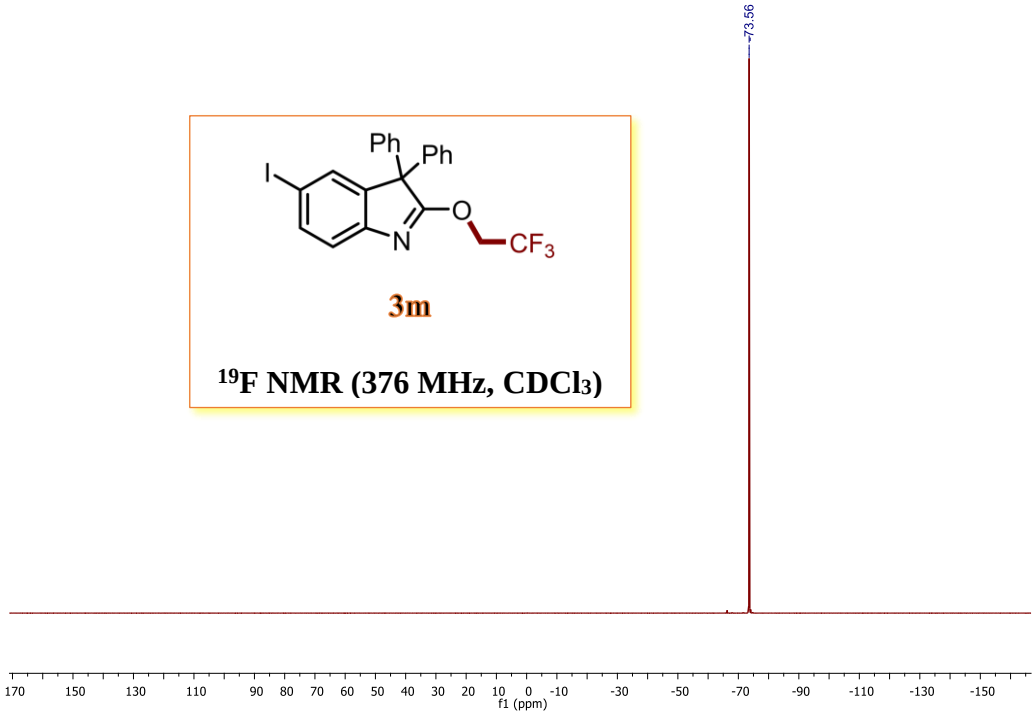


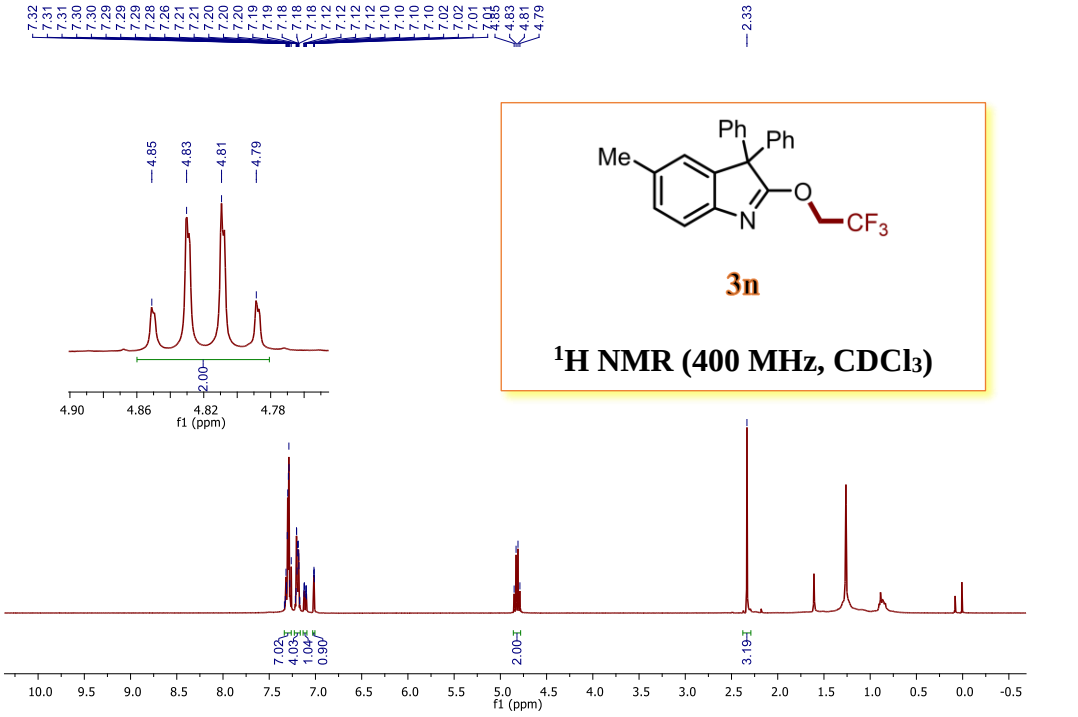
3l

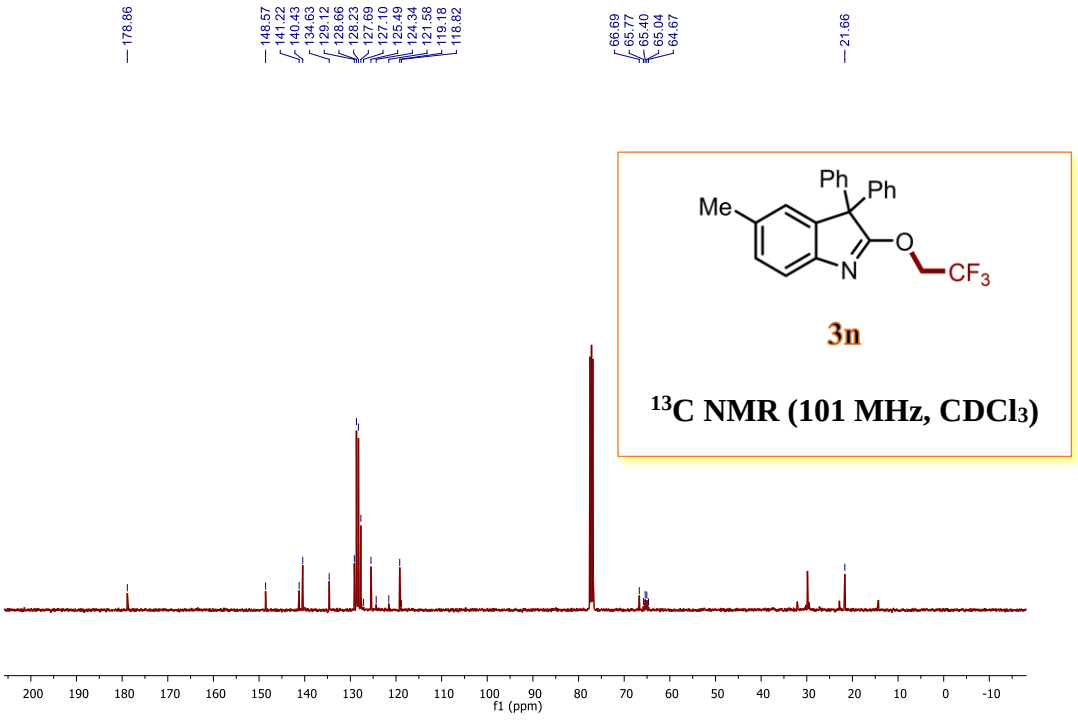
^{13}C NMR (101 MHz, $CDCl_3$)


Ph
Ph
O
N
CF3
Br
3l
19F NMR (376 MHz, CDCl3)
-73.58
f1 (ppm)
7.47
7.47
7.45
7.45
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.21
7.20
7.19
7.19
7.18
7.18
7.17
7.17
4.88
4.86
4.84
4.82
2.00
Ph
Ph
I
O
N
CF3
3m
1H NMR (400 MHz, CDCl3)
0.90
8.05
4.02
2.00


179.66
150.16
143.25
139.52
131.71
128.87
128.09
127.93
126.96
124.20
121.44
121.11
118.68
118.03
67.05
65.97
65.60
65.24
64.87
Ph
Ph
I
O
N
CF3
3m
13C NMR (101 MHz, CDCl3)
f1 (ppm)

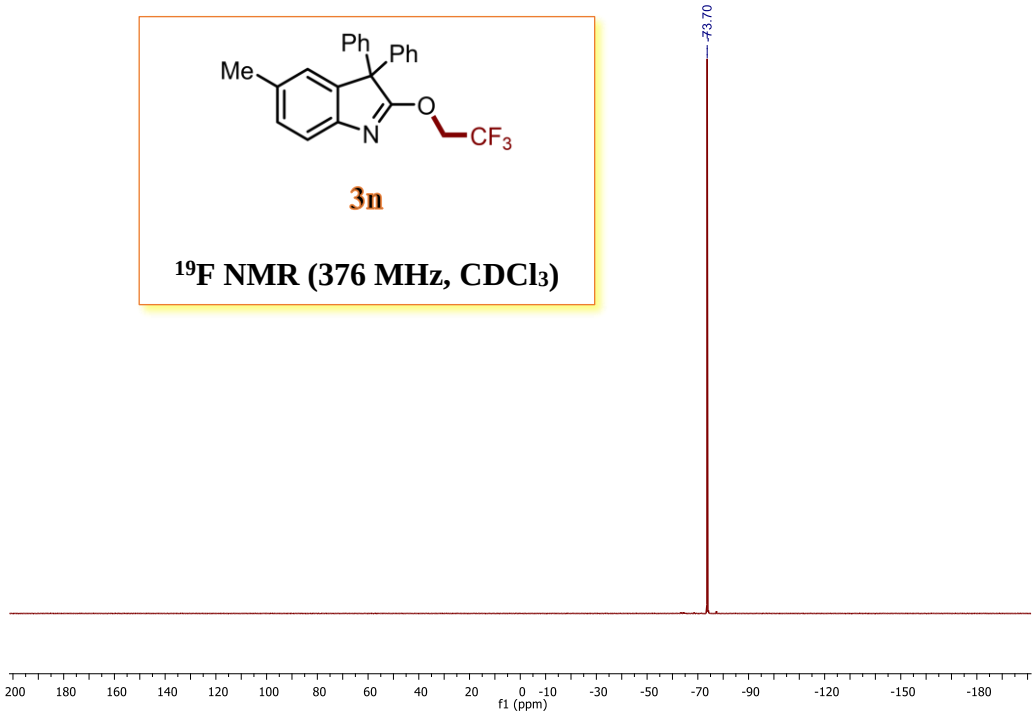

-73.56
Ph
Ph
I
O
N
CF3
3m
19F NMR (376 MHz, CDCl3)
f1 (ppm)

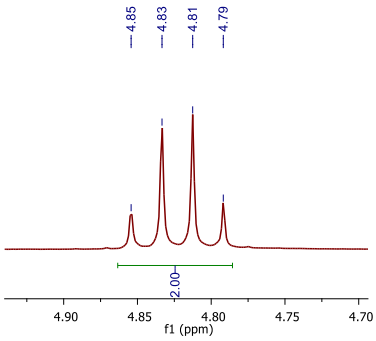

Ph
Ph
Me
O
N
CF3
3n
1H NMR (400 MHz, CDCl3)

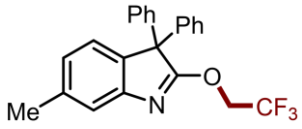

Ph
Ph
Me
O
N
CF3
3n
13C NMR (101 MHz, CDCl3)

3n

^{19}F NMR (376 MHz, $CDCl_3$)

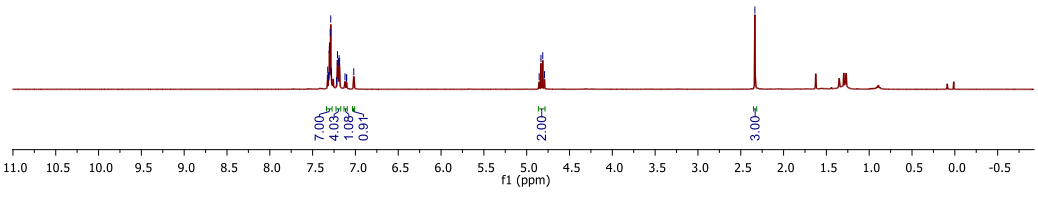


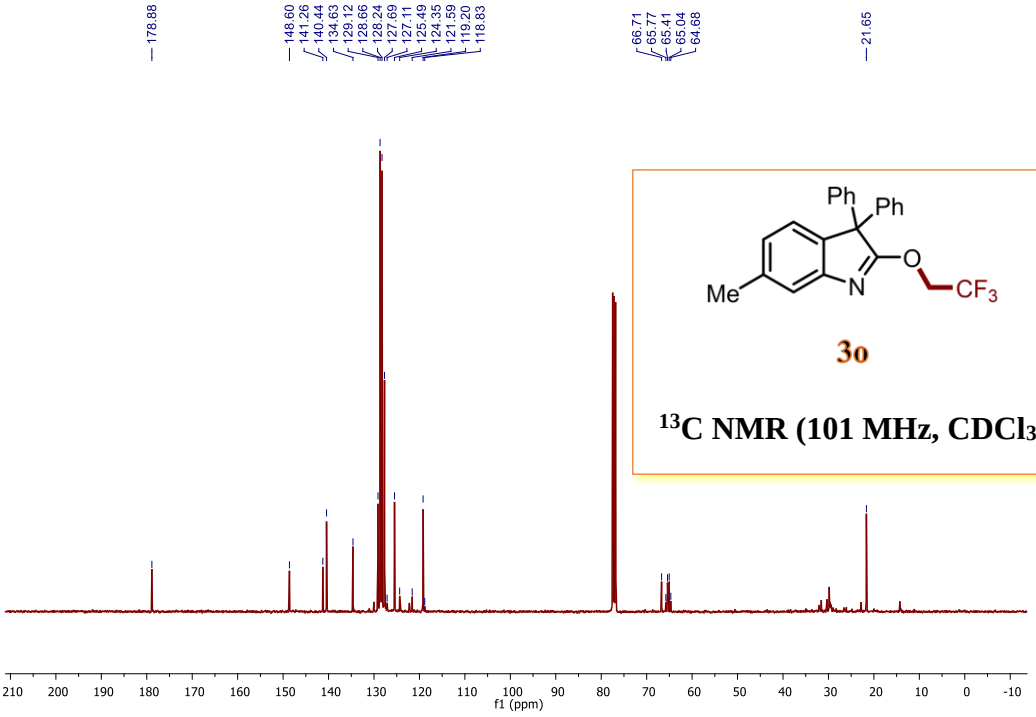


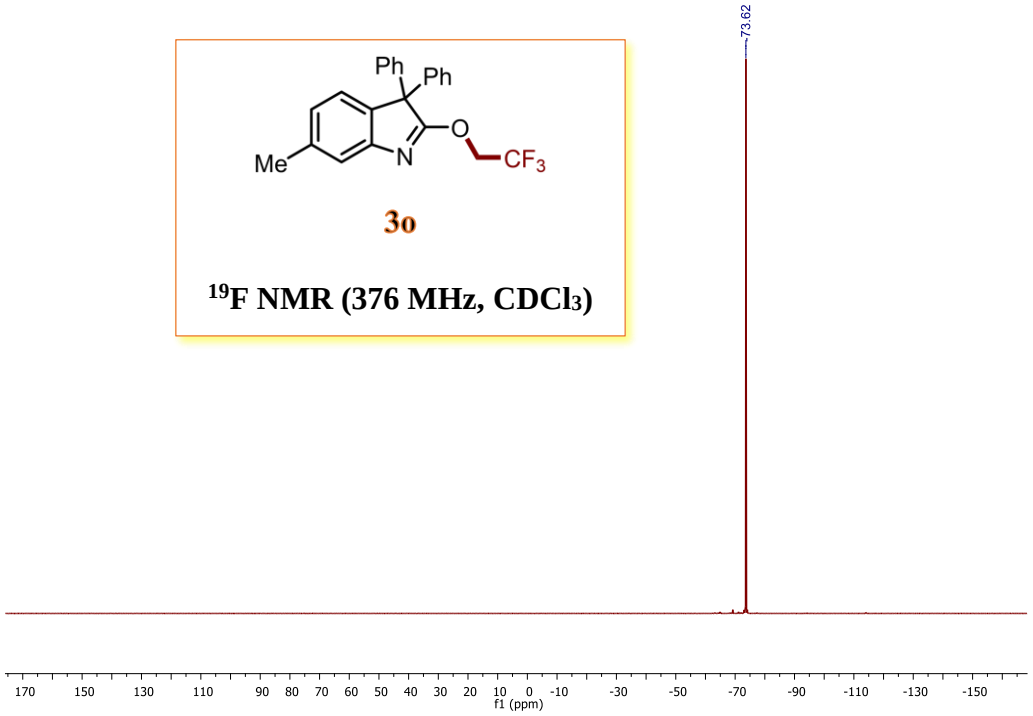


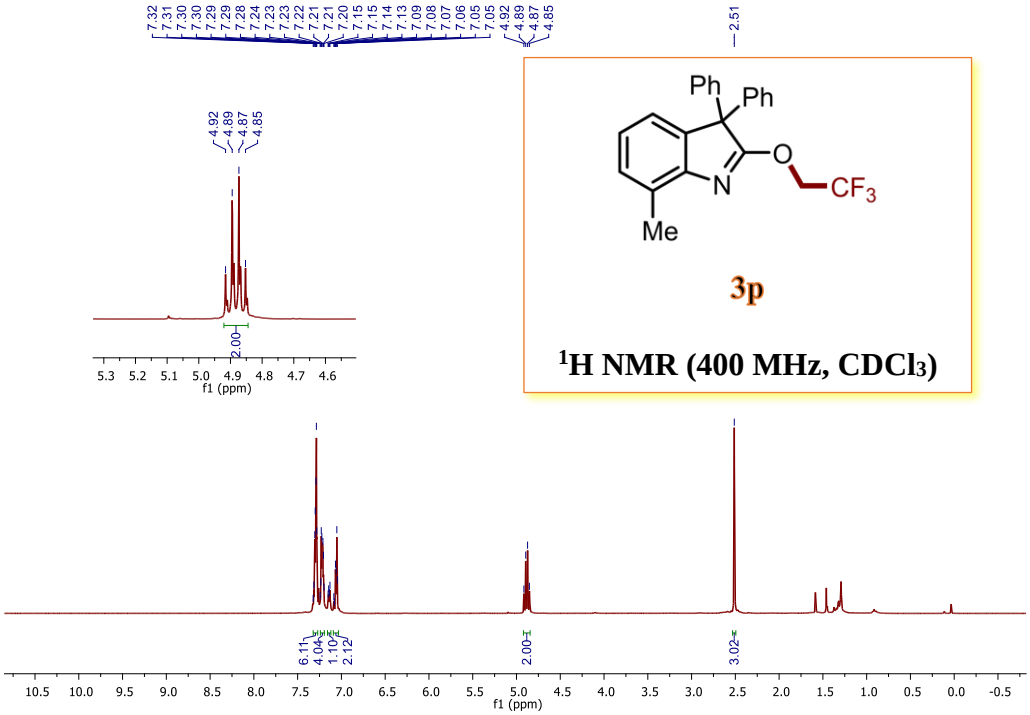
3o

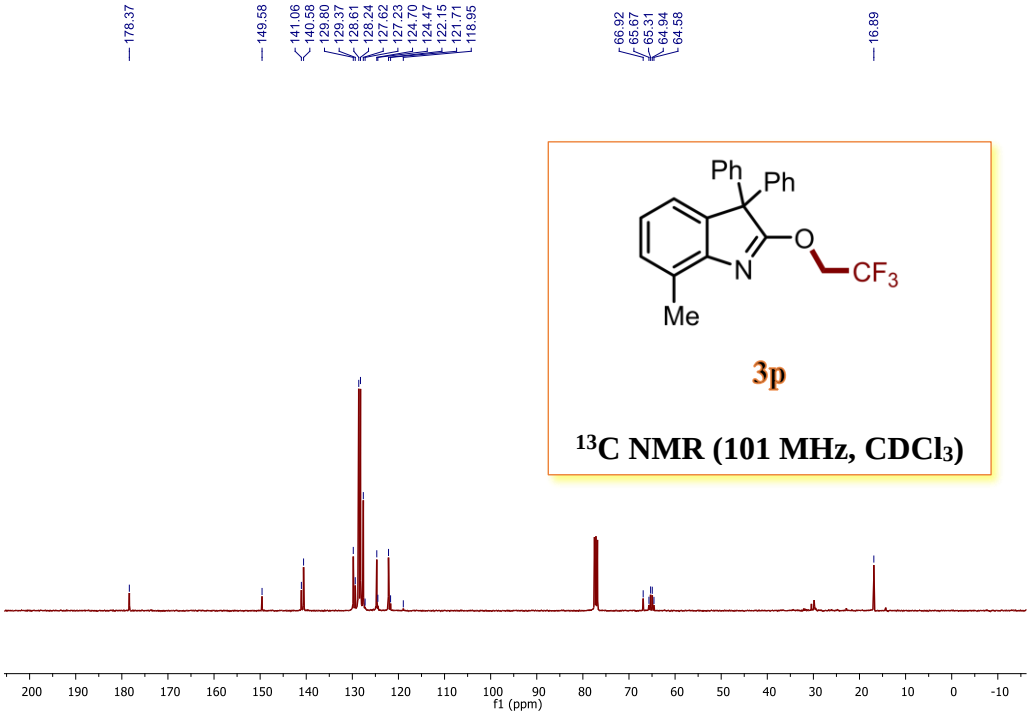
^{1}H NMR (400 MHz, $CDCl_3$)




178.88
148.60
141.26
140.44
134.63
129.12
128.66
128.24
127.69
127.11
125.49
124.35
121.59
119.20
118.83
66.71
65.77
65.41
65.04
64.68
21.65
Ph
Ph
Me
N
O
CF3
3o
13C NMR (101 MHz, CDCl3)
f1 (ppm)

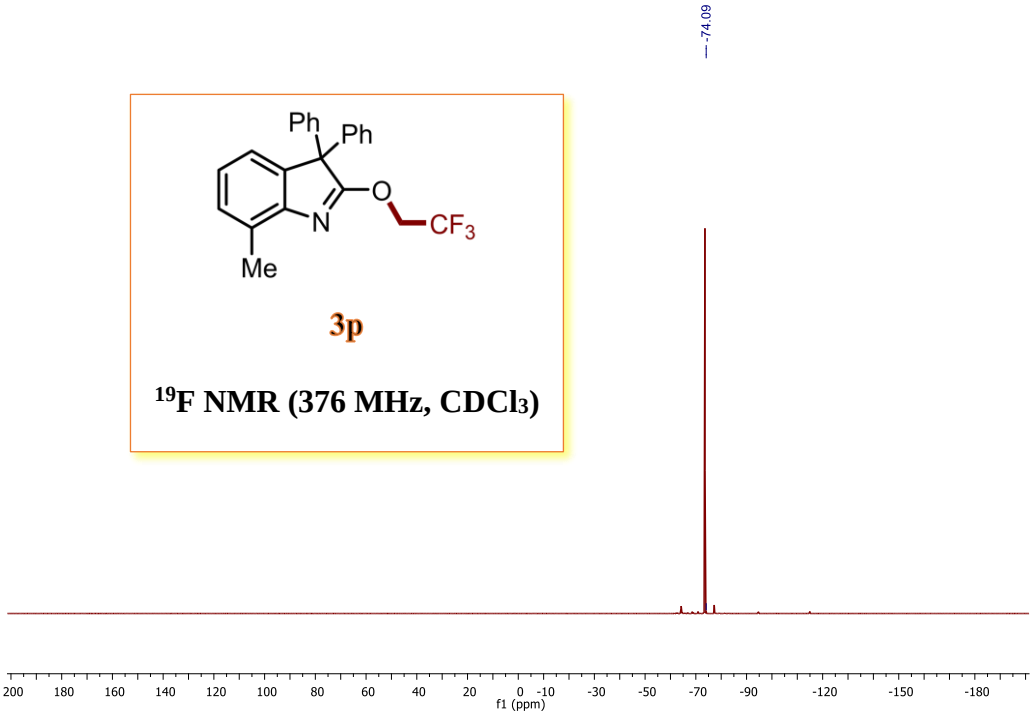

73.62
Ph
Ph
Me
N
O
CF3
3o
19F NMR (376 MHz, CDCl3)
f1 (ppm)


7.32
7.31
7.30
7.30
7.29
7.29
7.28
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.15
7.15
7.14
7.13
7.09
7.08
7.07
7.06
7.05
7.05
4.92
4.89
4.87
4.85
2.51
Ph
Ph
O
N
CF3
Me
3p
1H NMR (400 MHz, CDCl3)
2.00
f1 (ppm)
6.11
4.04
1.10
2.12
2.00
3.02


178.37
149.58
141.06
140.58
129.80
129.37
128.61
128.24
127.62
127.23
124.70
124.47
122.15
121.71
118.95
66.92
65.67
65.31
64.94
64.58
16.89
Ph
Ph
O
N
CF3
Me
3p
13C NMR (101 MHz, CDCl3)
f1 (ppm)

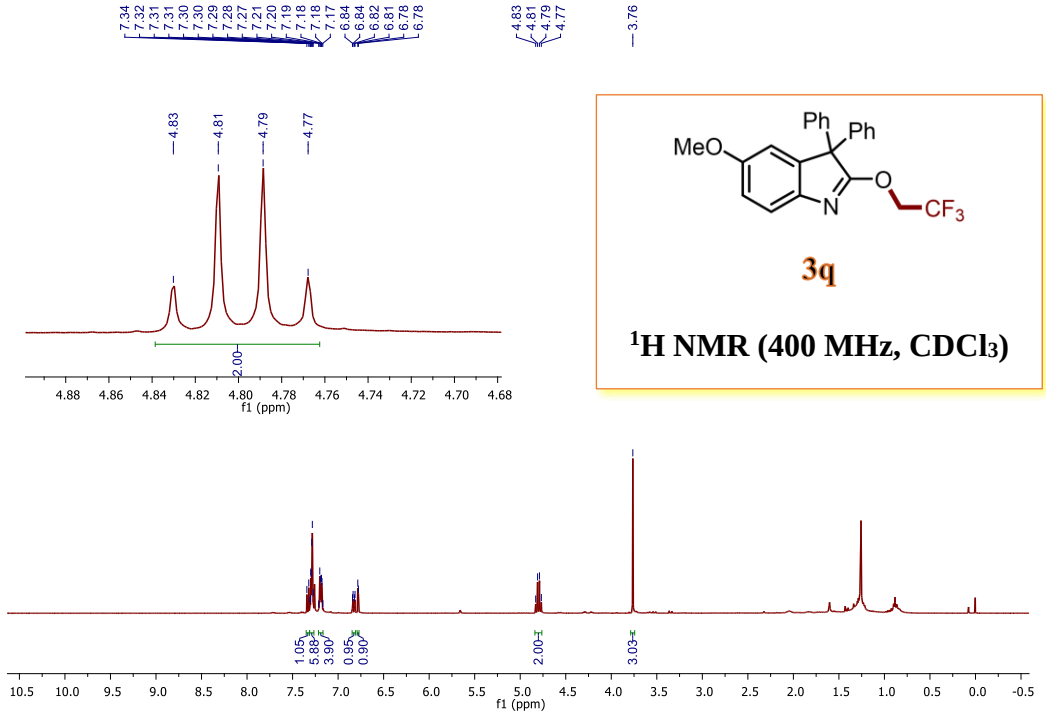
3p

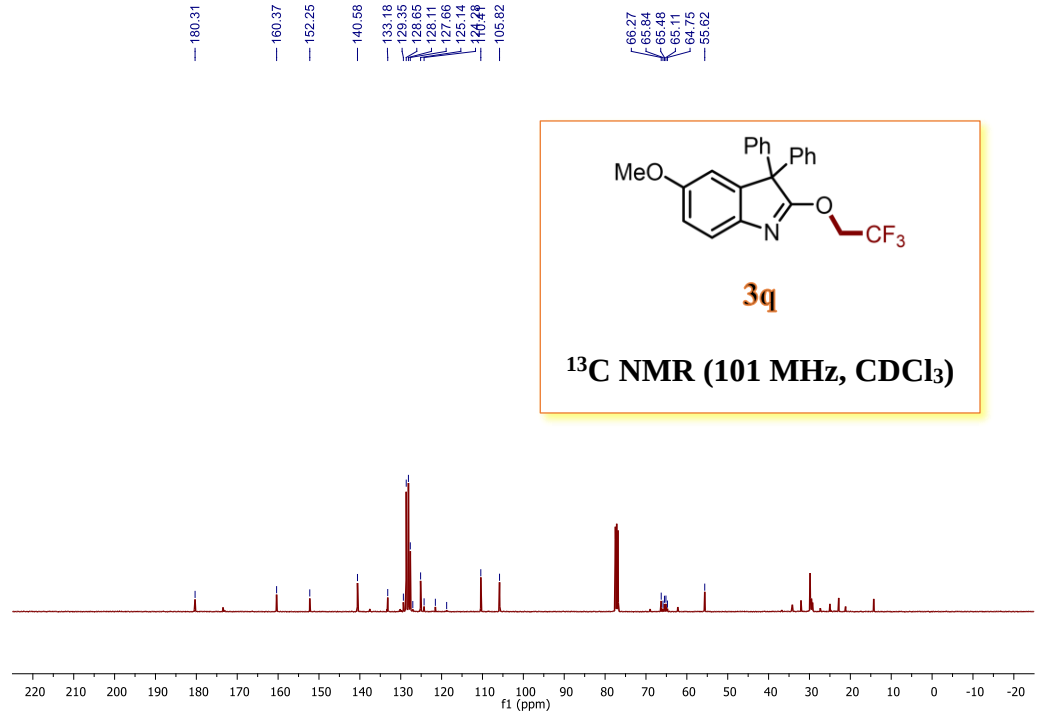
^{19}F NMR (376 MHz, $CDCl_3$)

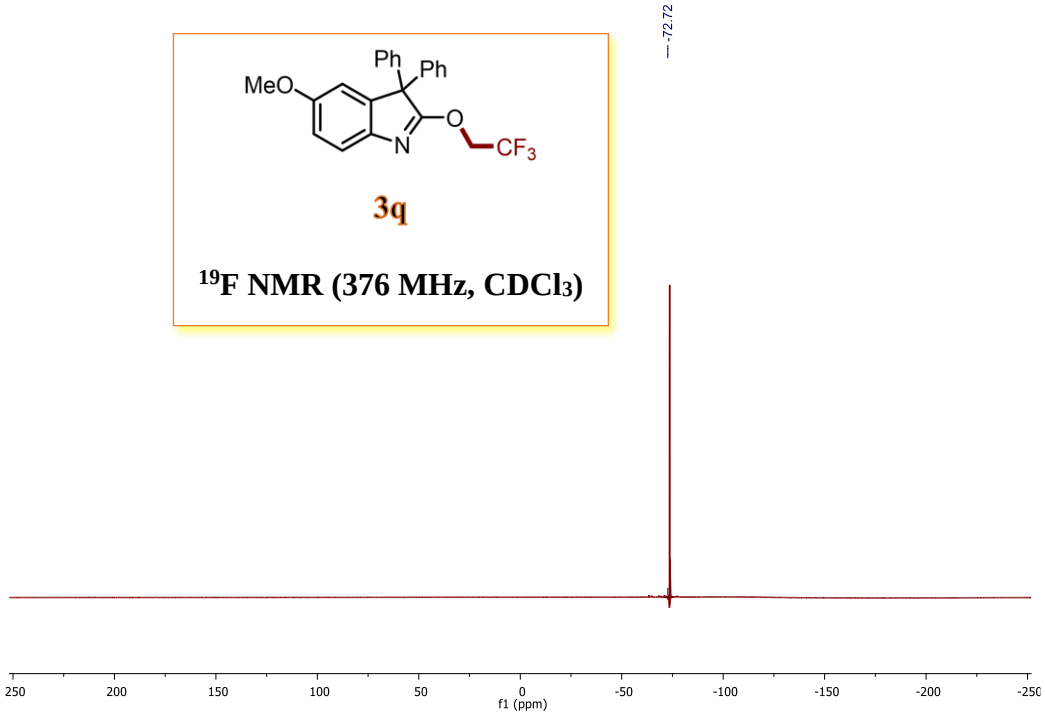


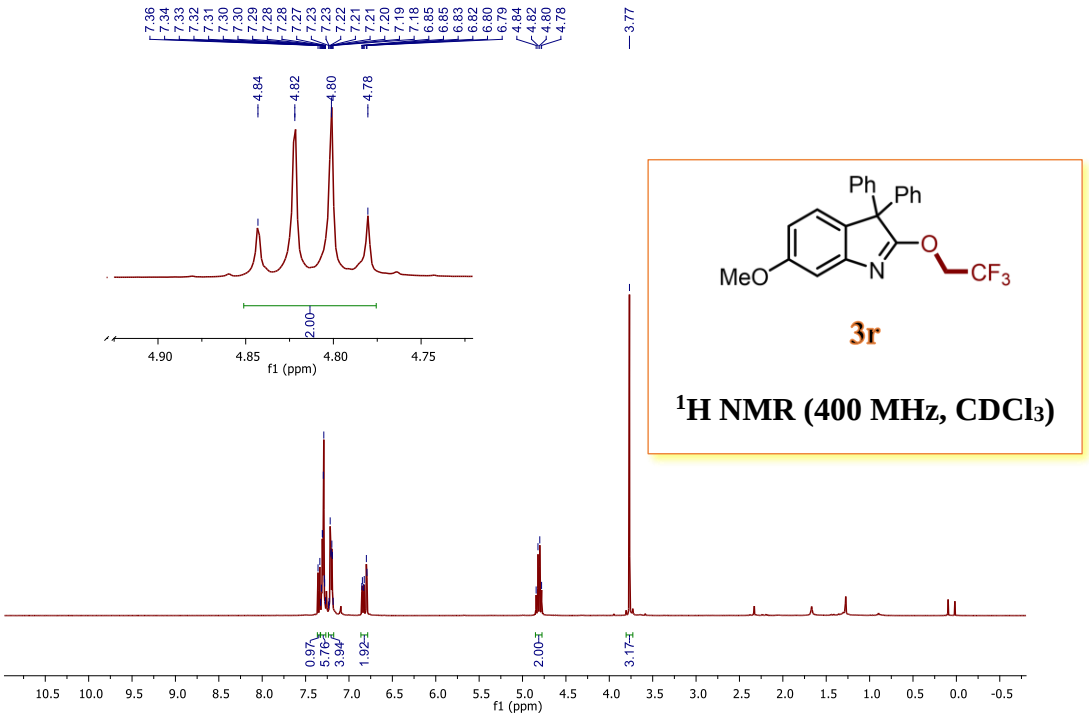
3q

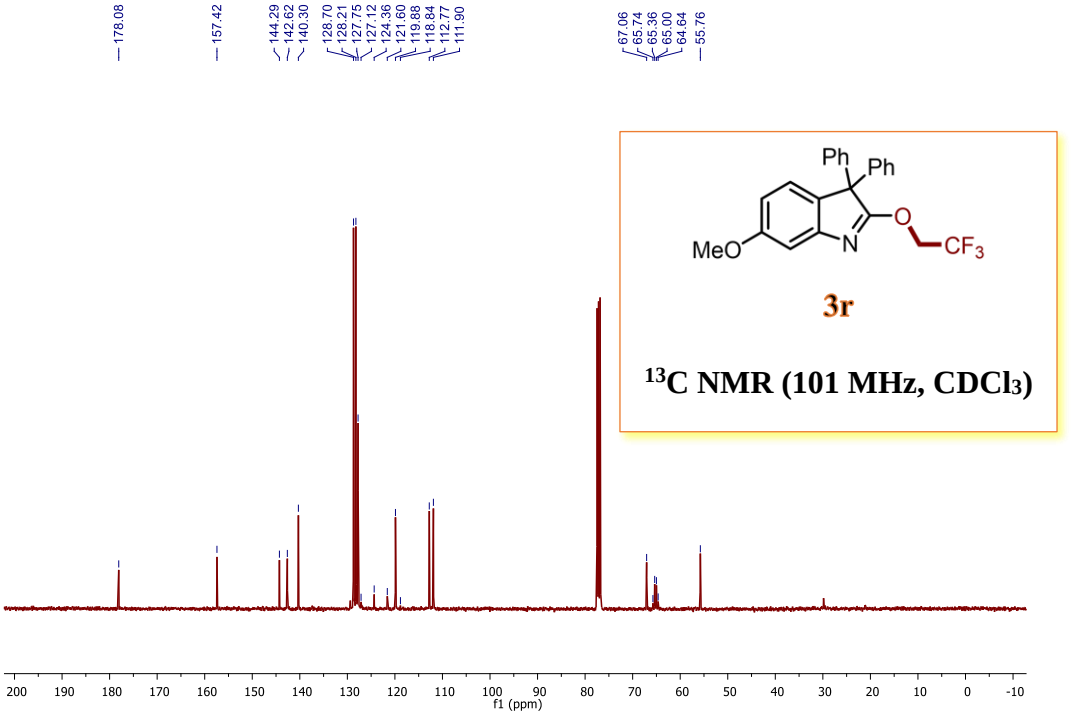
^{1}H NMR (400 MHz, $CDCl_3$)

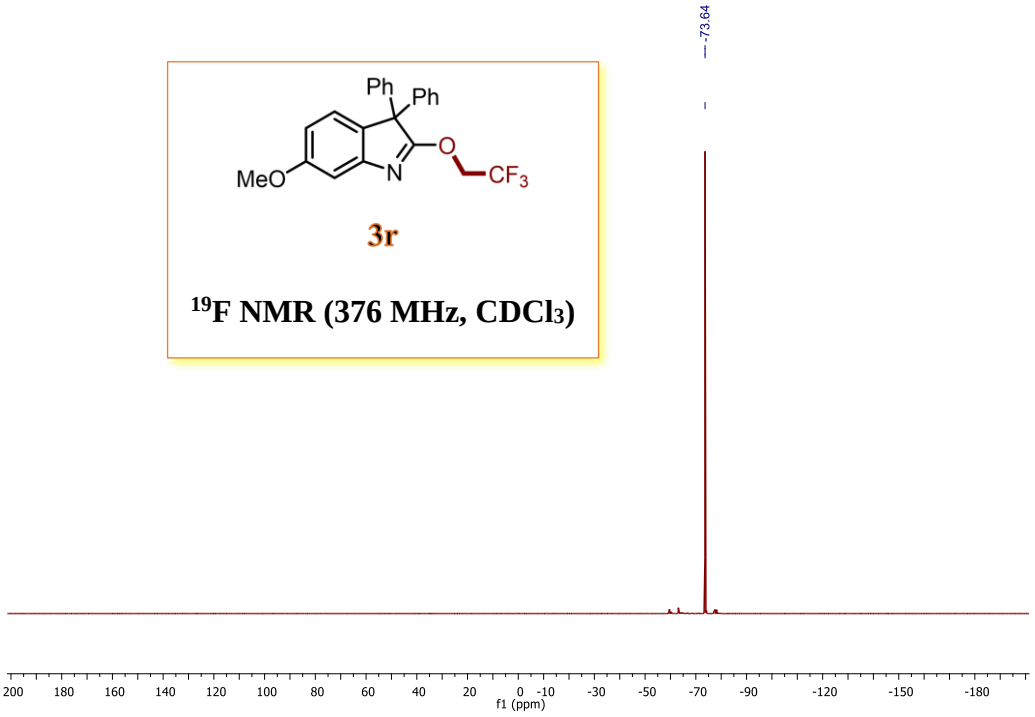


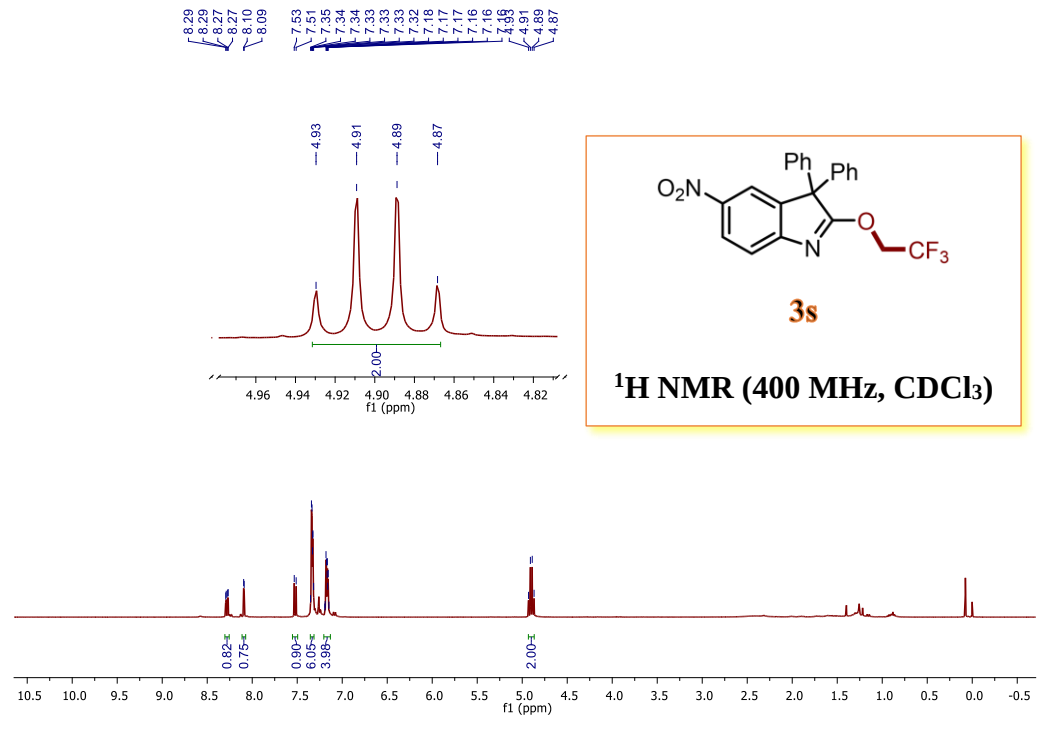

180.31
160.37
152.25
140.58
133.18
129.35
128.65
128.11
127.66
125.14
105.82
66.27
65.84
65.48
65.11
64.75
55.62
Ph
Ph
MeO
O
N
CF3
3q
13C NMR (101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

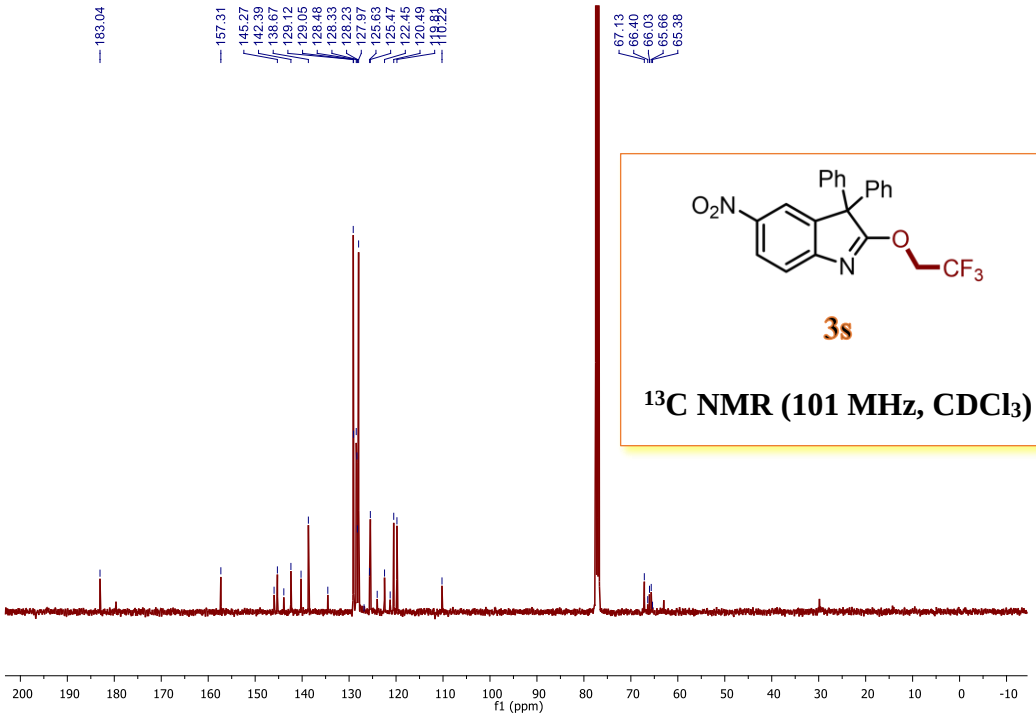

-72.72
Ph
Ph
MeO
O
N
CF3
3q
19F NMR (376 MHz, CDCl3)
250 200 150 100 50 0 -50 -100 -150 -200 -250
f1 (ppm)

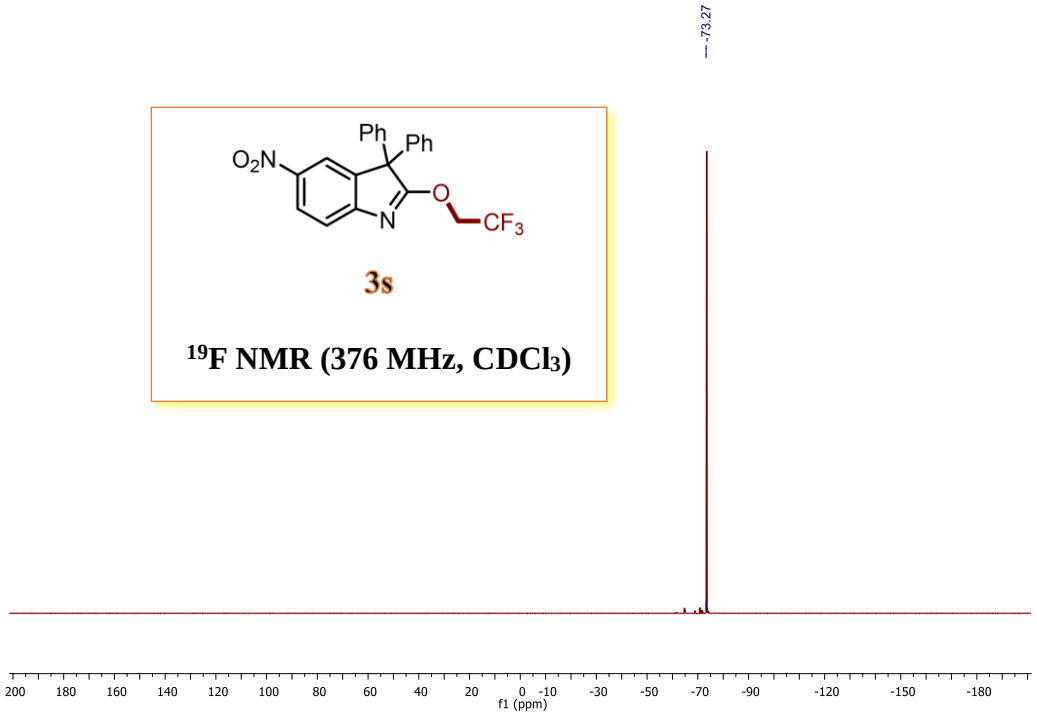

Ph
Ph
MeO
O
N
CF3
3r
1H NMR (400 MHz, CDCl3)

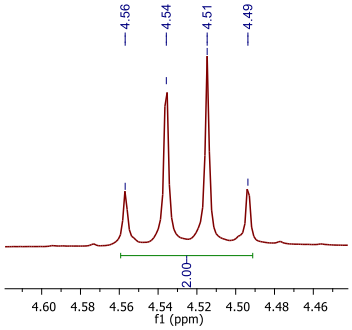

Ph
Ph
MeO
O
N
CF3
3r
13C NMR (101 MHz, CDCl3)

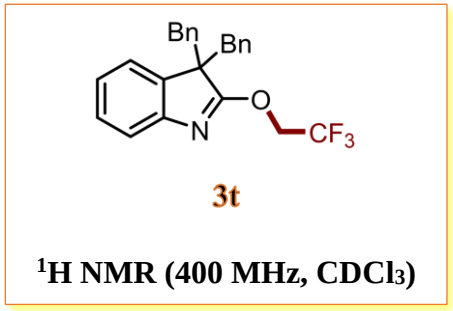

Ph
Ph
MeO
N
O
CF3
3r
19F NMR (376 MHz, CDCl3)
-73.64
f1 (ppm)


8.29
8.27
8.10
8.09
7.53
7.51
7.35
7.34
7.33
7.32
7.18
7.17
7.16
4.93
4.91
4.89
4.87
2.00
4.96 4.94 4.92 4.90 4.88 4.86 4.84 4.82
f1 (ppm)
O2N
Ph
Ph
N
O
CF3
3s
1H NMR (400 MHz, CDCl3)
0.82
0.75
0.90
6.05
3.98
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


183.04
157.31
145.27
142.39
138.67
129.12
129.05
128.48
128.33
128.23
127.97
125.63
125.47
122.45
120.49
67.13
66.40
66.03
65.66
65.38
Ph
Ph
O2N
O
N
CF3
3s
13C NMR (101 MHz, CDCl3)
f1 (ppm)

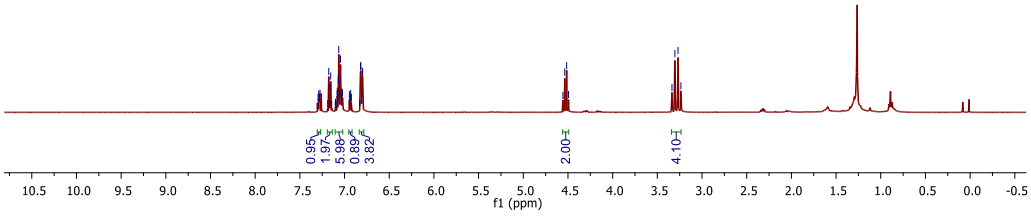

-73.27
Ph
Ph
O2N
O
N
CF3
3s
19F NMR (376 MHz, CDCl3)
f1 (ppm)

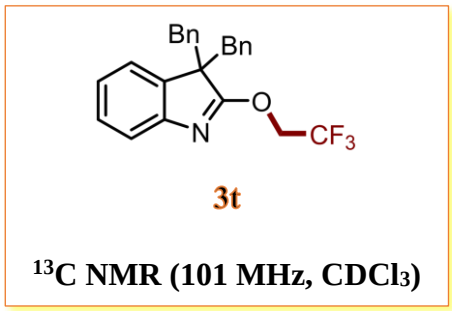




3t

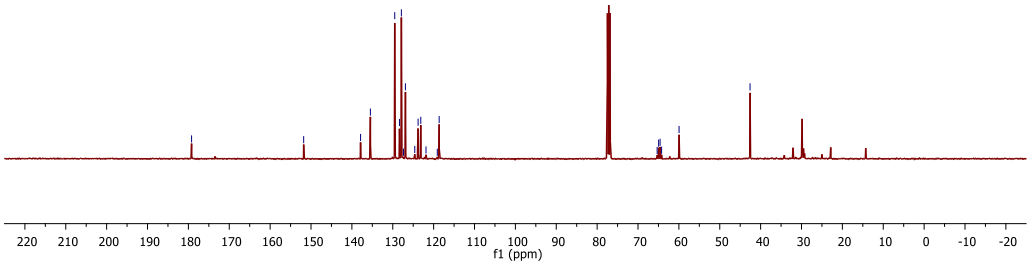
^{1}H NMR (400 MHz, $CDCl_3$)

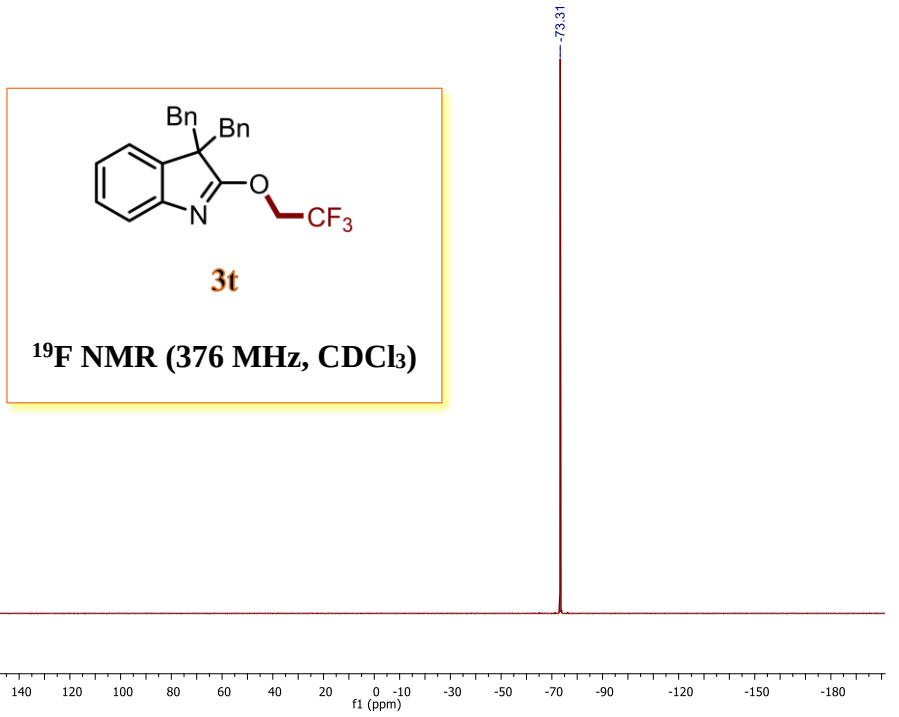


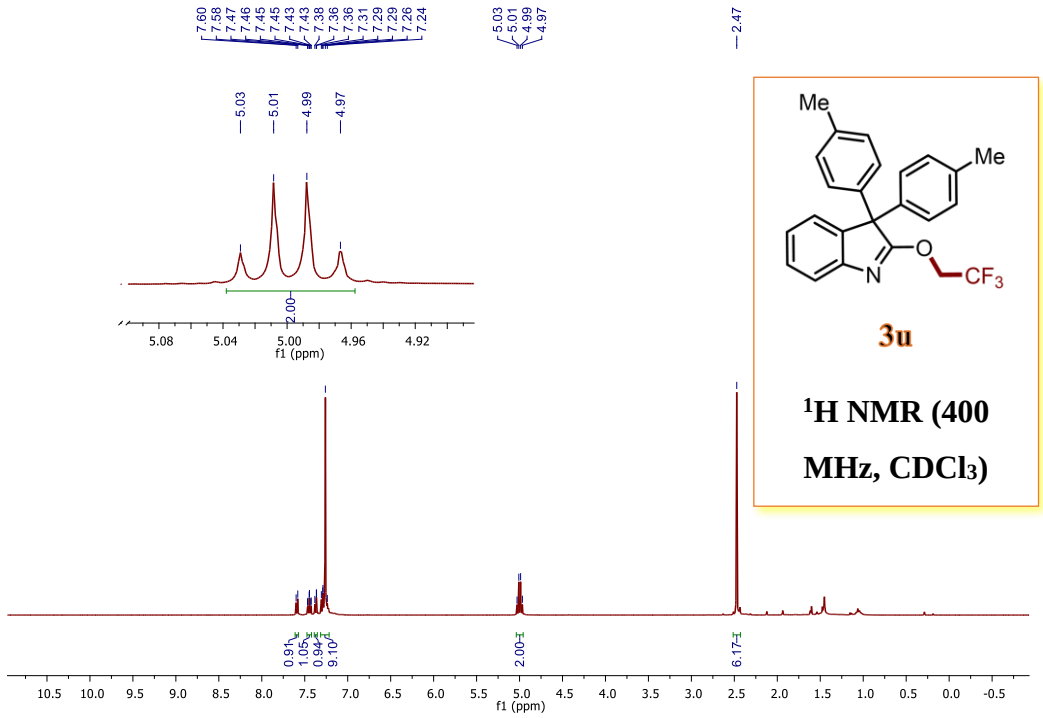


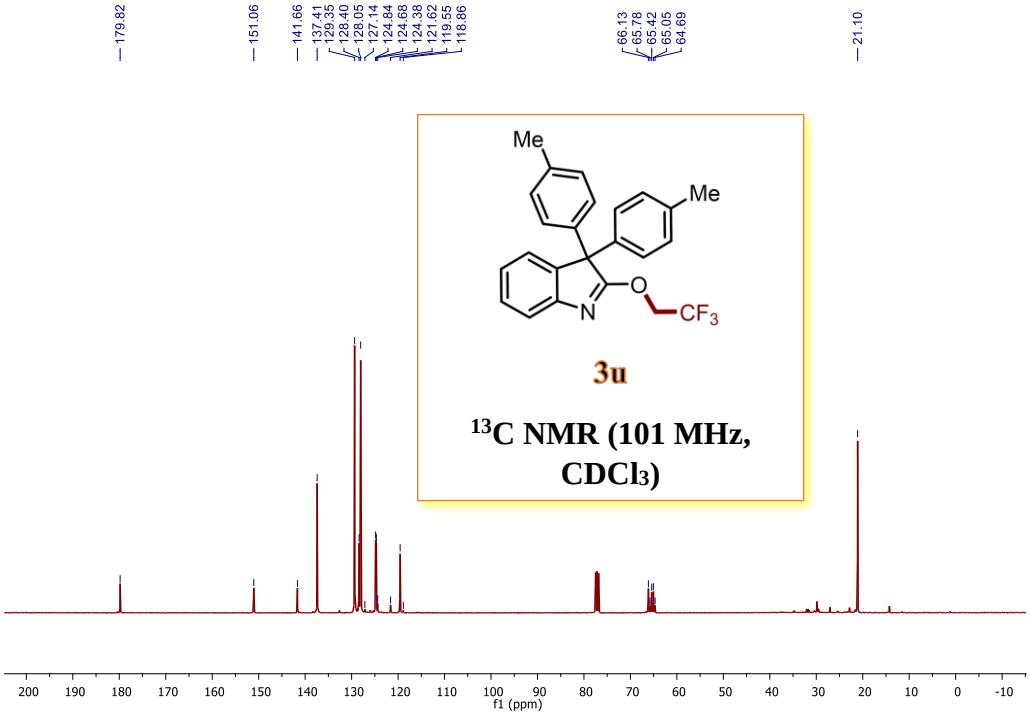
3t

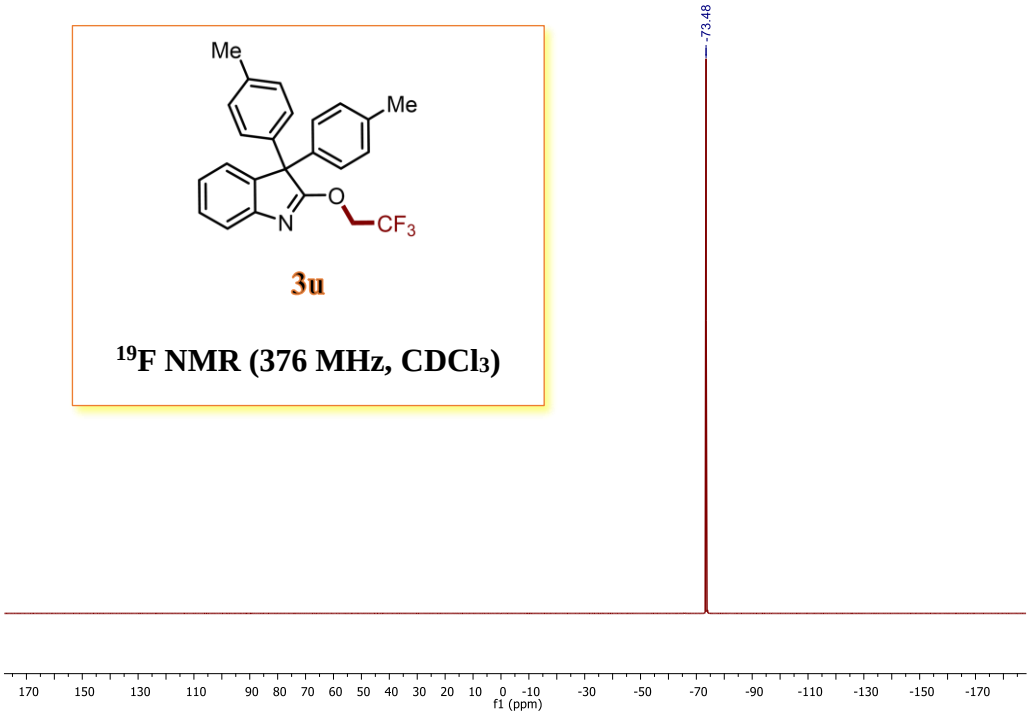
^{13}C NMR (101 MHz, $CDCl_3$)

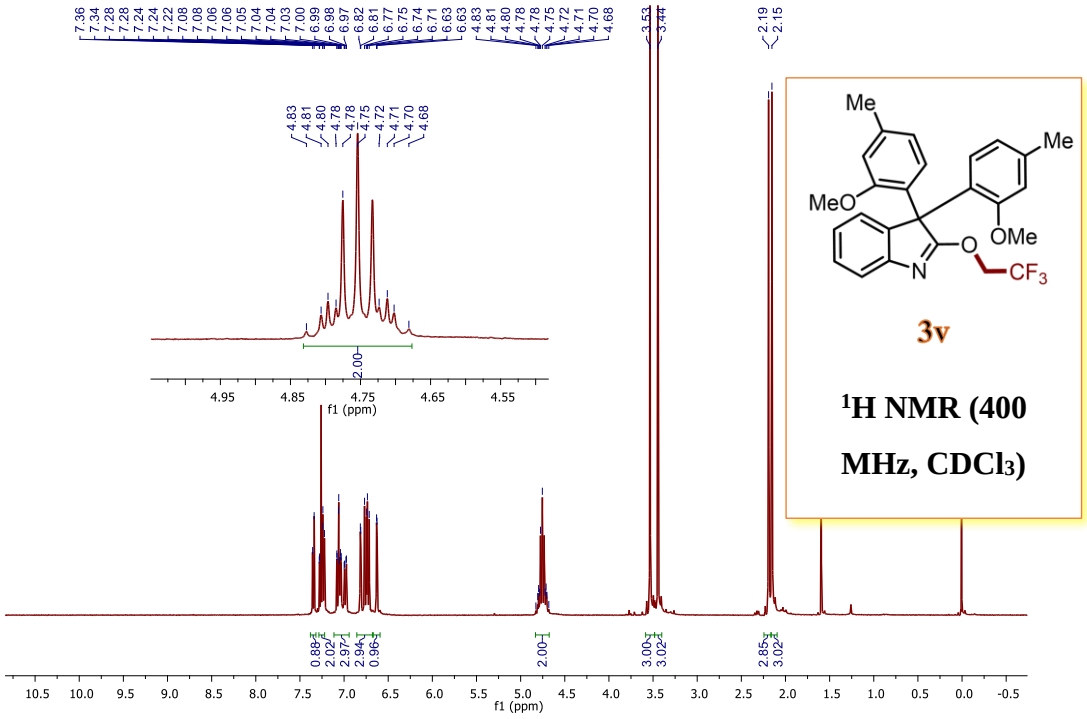


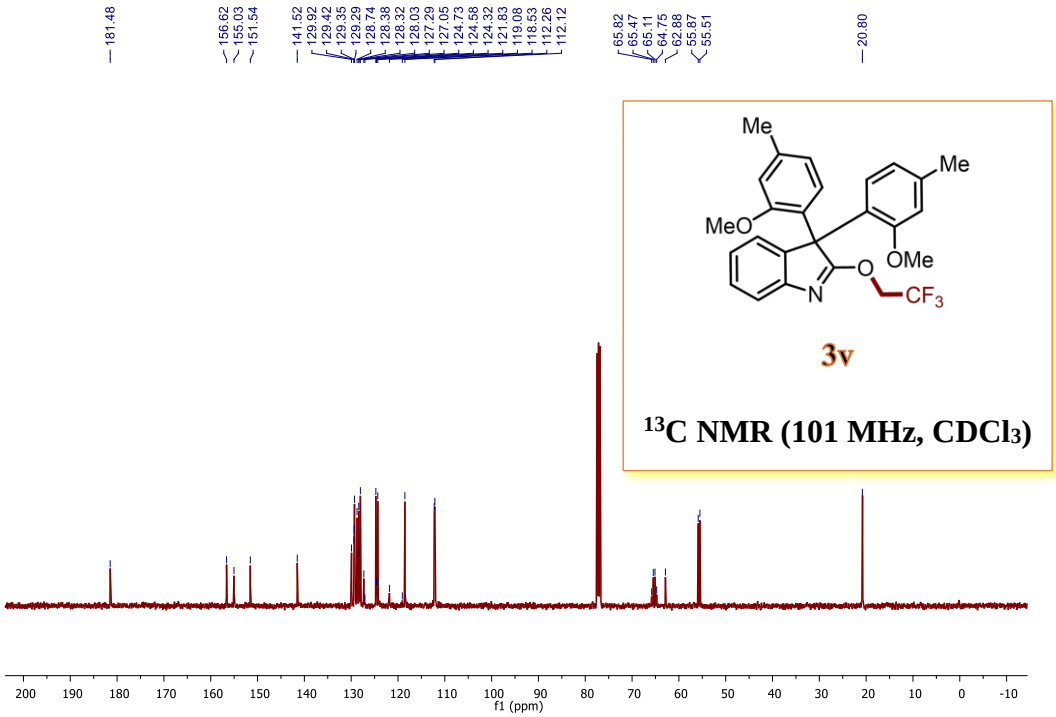

Bn
Bn
O
N
CF3
3t
19F NMR (376 MHz, CDCl3)
-73.31
f1 (ppm)


7.60
7.58
7.47
7.46
7.45
7.45
7.43
7.43
7.38
7.36
7.36
7.31
7.29
7.29
7.26
7.24
5.03
5.01
4.99
4.97
2.47
2.00
f1 (ppm)
Me
Me
O
N
CF3
3u
1H NMR (400 MHz, CDCl3)
0.91
1.05
0.94
9.10
2.00
6.17
f1 (ppm)


179.82
151.06
141.66
137.41
129.35
128.40
128.05
127.14
124.84
124.68
124.38
121.62
119.55
118.86
66.13
65.78
65.42
65.05
64.69
21.10
Me
Me
O
N
CF3
3u
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

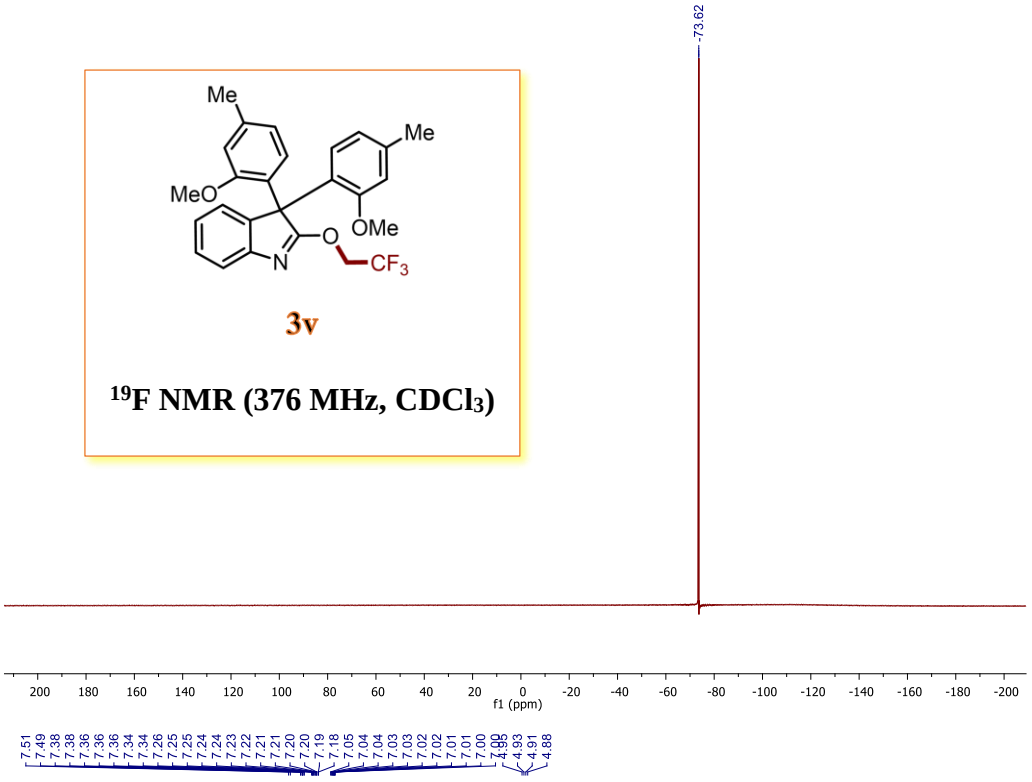

-73.48
Me
Me
O
N
CF3
3u
19F NMR (376 MHz, CDCl3)
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170
f1 (ppm)

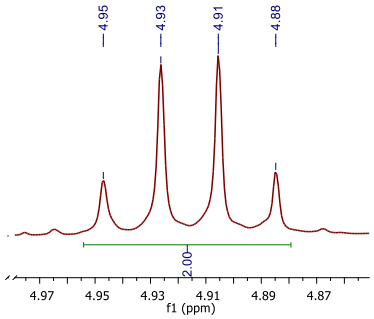

Me
Me
MeO
OMe
O
N
CF3
3v
1H NMR (400 MHz, CDCl3)
f1 (ppm)

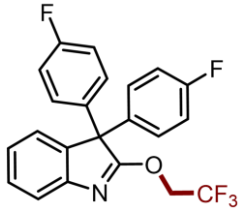

Me
Me
MeO
OMe
O
N
CF3
3v
13C NMR (101 MHz, CDCl3)
f1 (ppm)

3v

^{19}F NMR (376 MHz, $CDCl_3$)

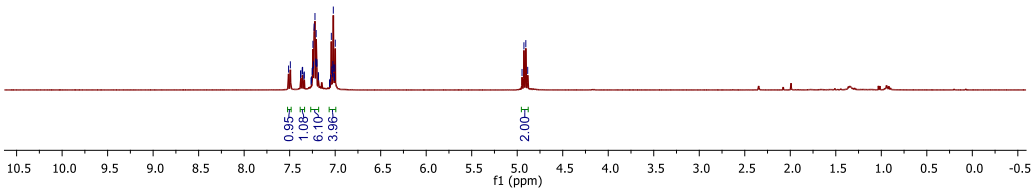


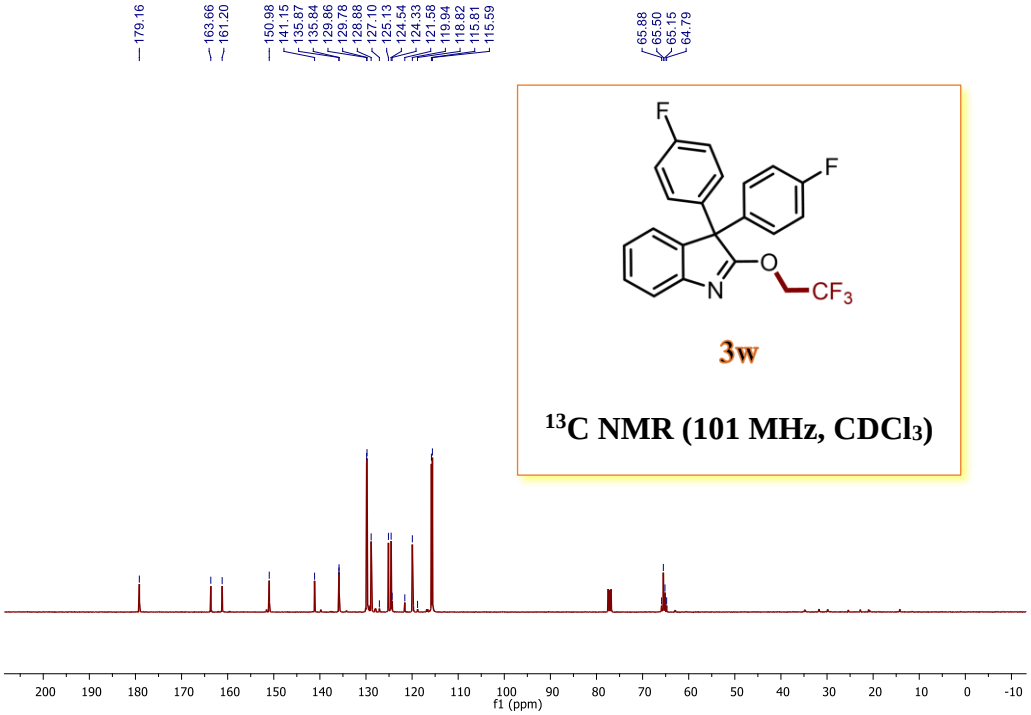


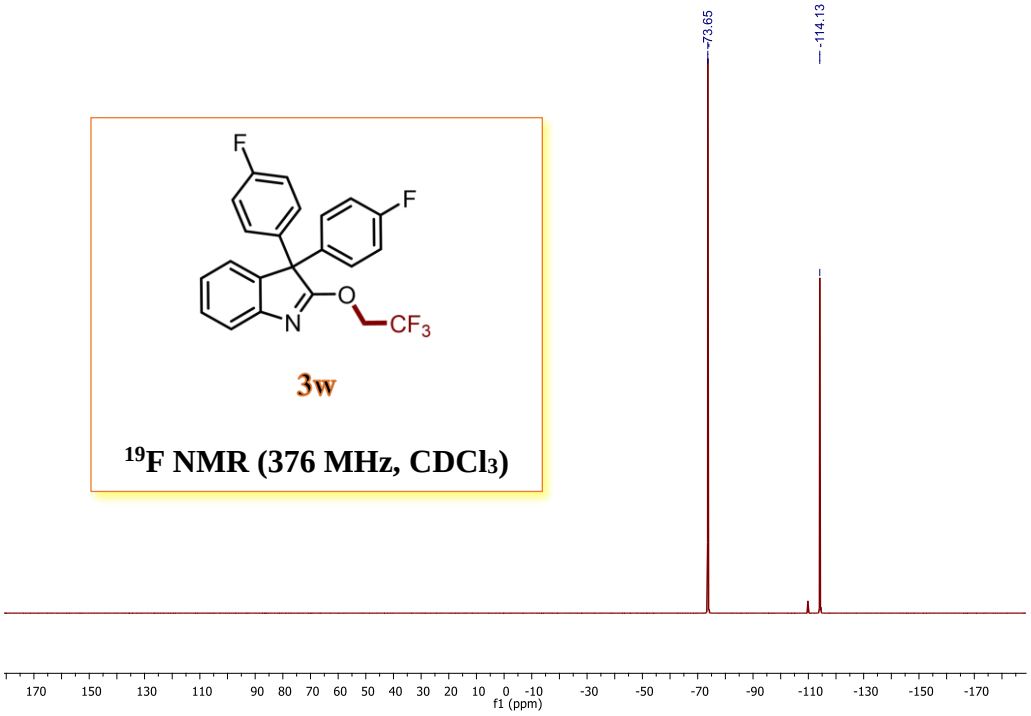


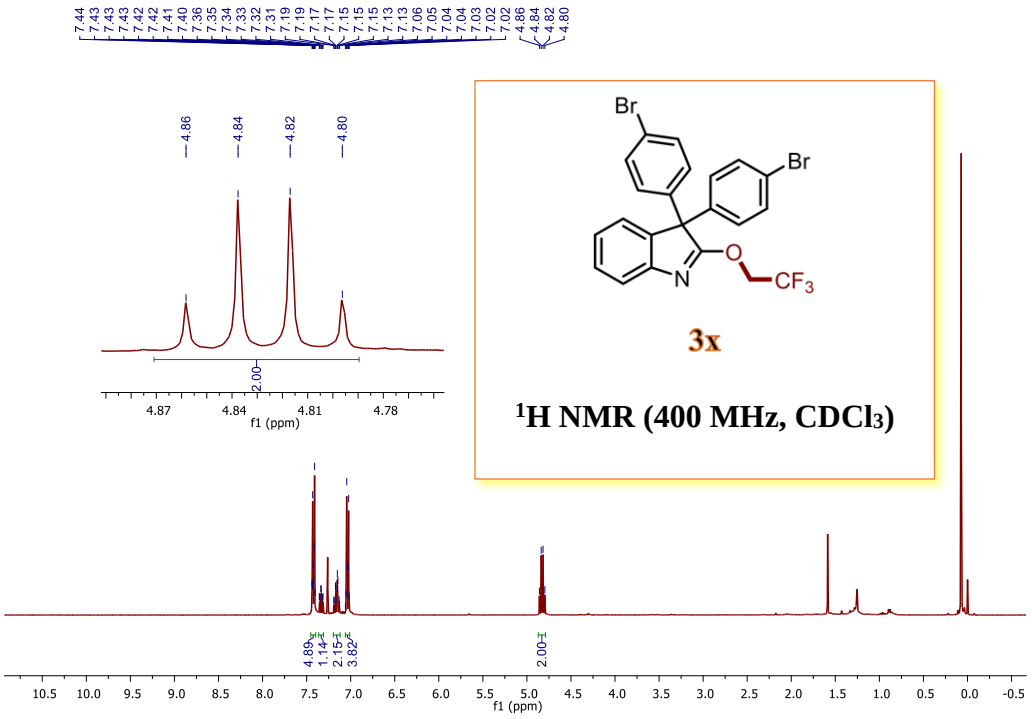
3w

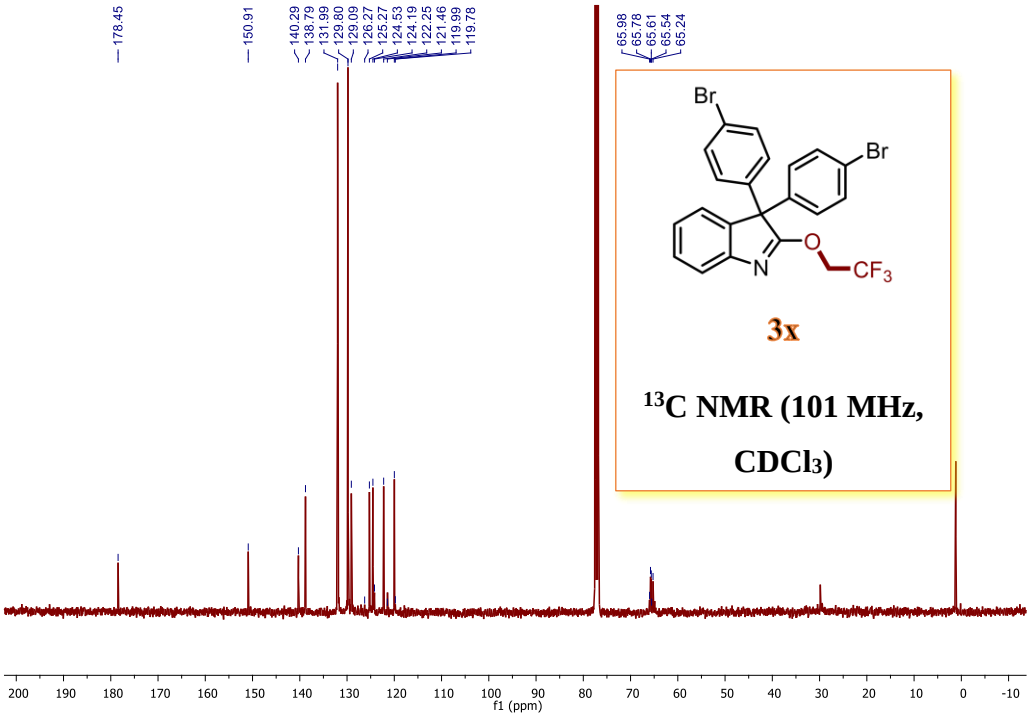
^{1}H NMR (400 MHz, $CDCl_3$)




179.16
163.66
161.20
150.98
141.15
135.87
135.84
129.86
129.78
128.88
127.10
125.13
124.54
124.33
121.58
119.94
118.82
115.81
115.59
65.88
65.50
65.15
64.79
F
F
O
N
CF3
3w
13C NMR (101 MHz, CDCl3)
f1 (ppm)

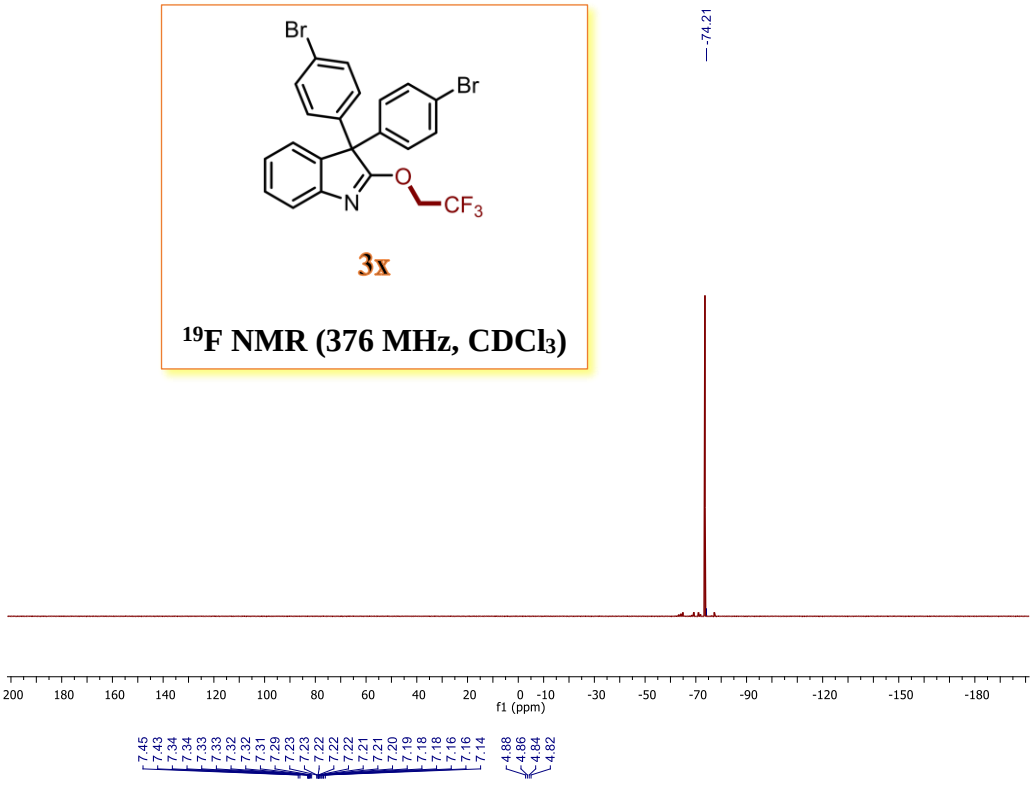

-73.65
-114.13
F
F
O
N
CF3
3w
19F NMR (376 MHz, CDCl3)
f1 (ppm)

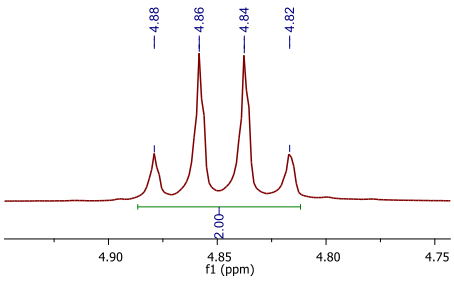

Br
Br
O
N
CF3
3x
1H NMR (400 MHz, CDCl3)

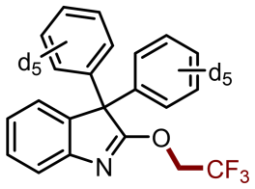

Br
Br
O
N
CF3
3x
13C NMR (101 MHz, CDCl3)

3x

^{19}F NMR (376 MHz, $CDCl_3$)

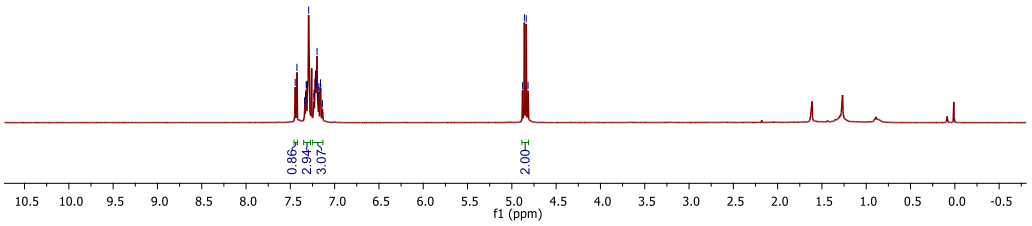


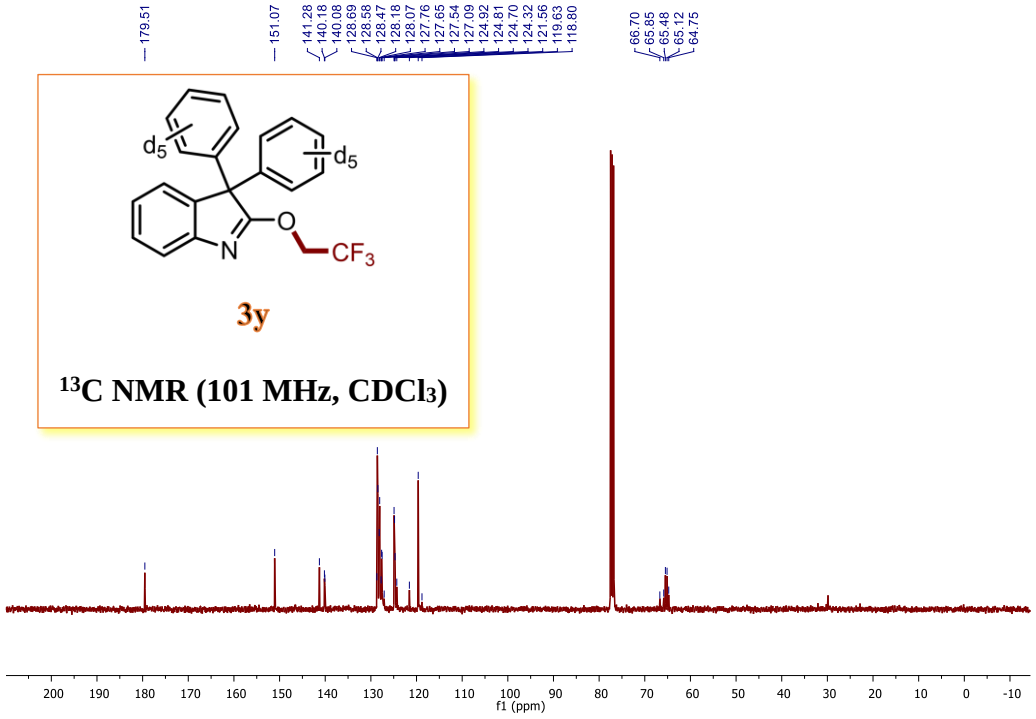


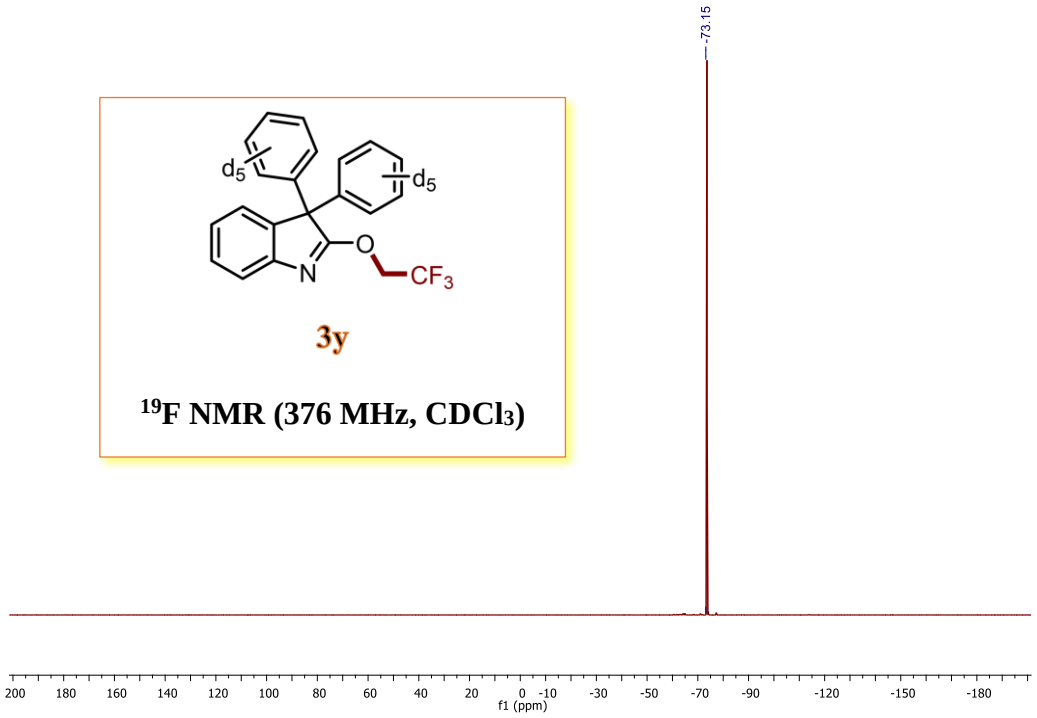


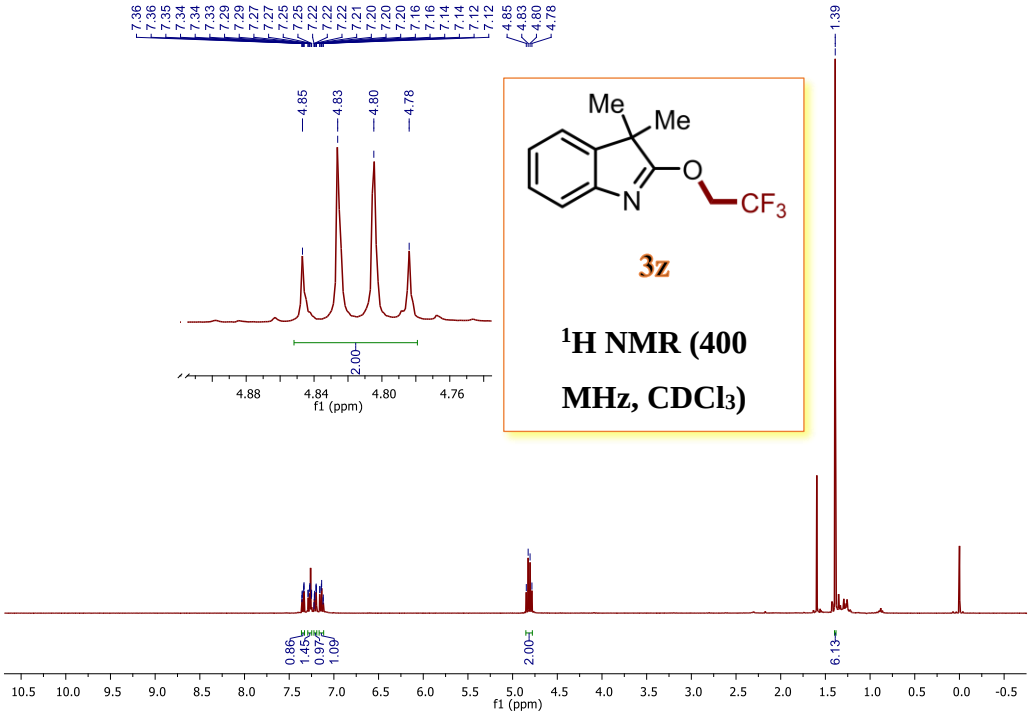
3y

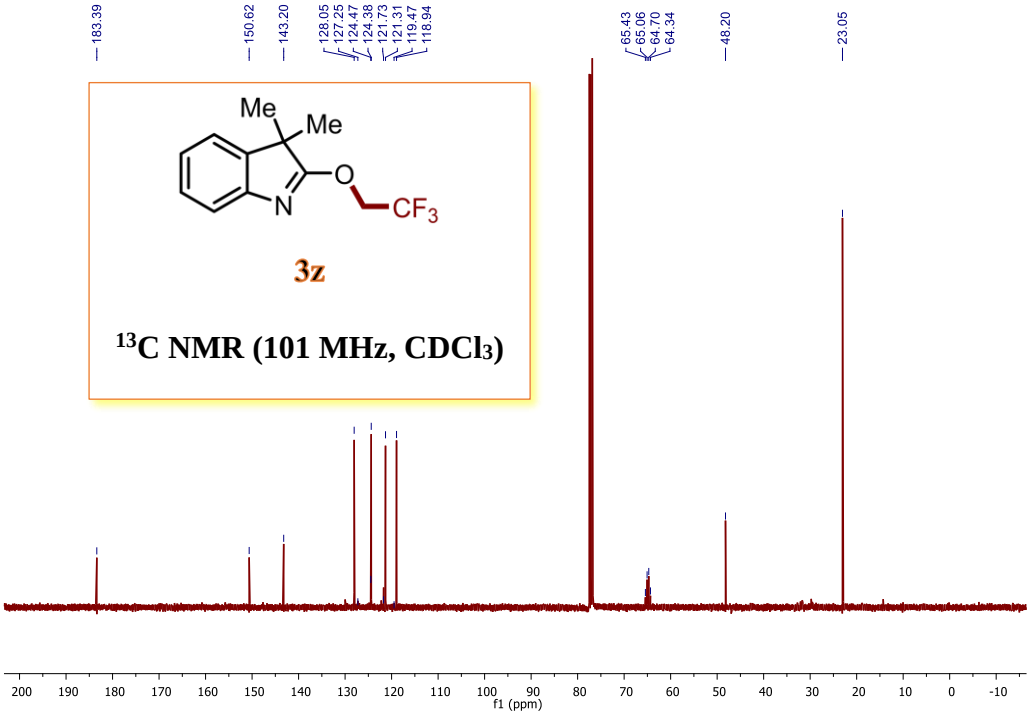
^{1}H NMR (400 MHz, $CDCl_3$)

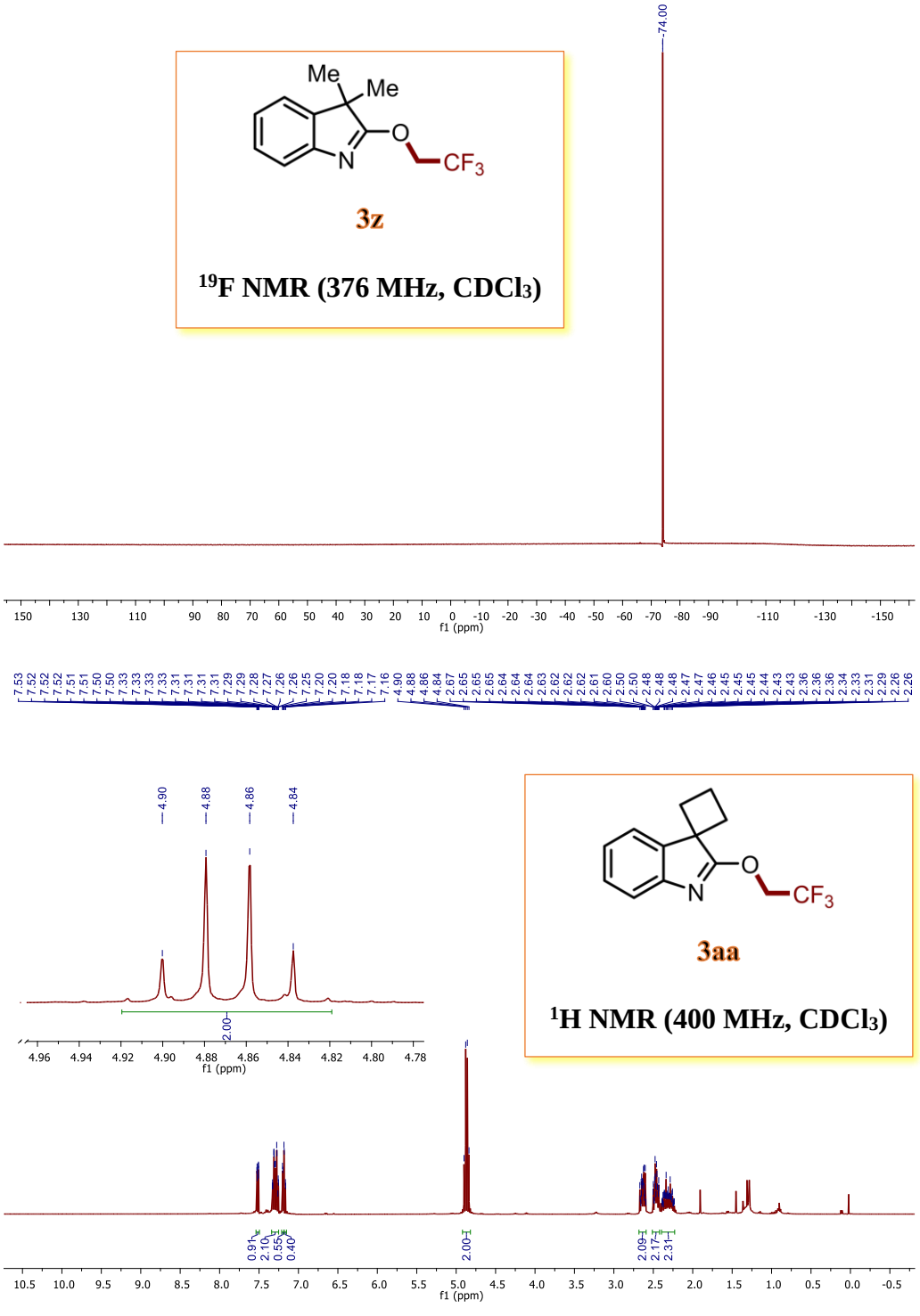


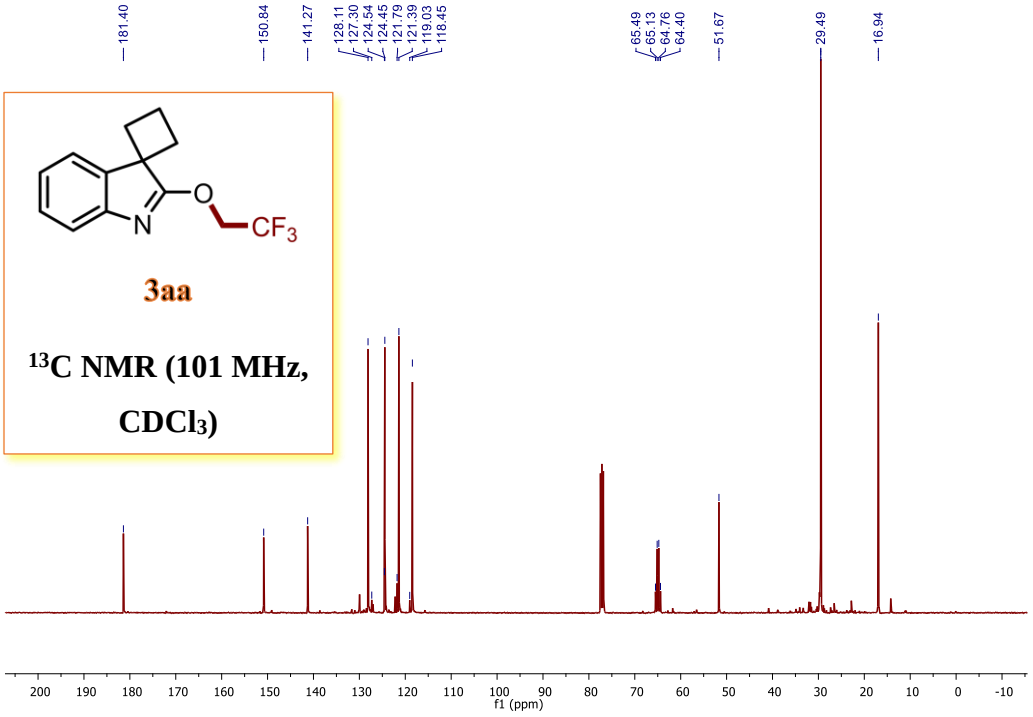

179.51
151.07
141.28
140.18
140.08
128.69
128.58
128.47
128.18
128.07
127.76
127.65
127.54
127.09
124.92
124.81
124.70
124.32
121.56
119.63
118.80
66.70
65.85
65.48
65.12
64.75
d5
d5
O
N
CF3
3y
13C NMR (101 MHz, CDCl3)
f1 (ppm)

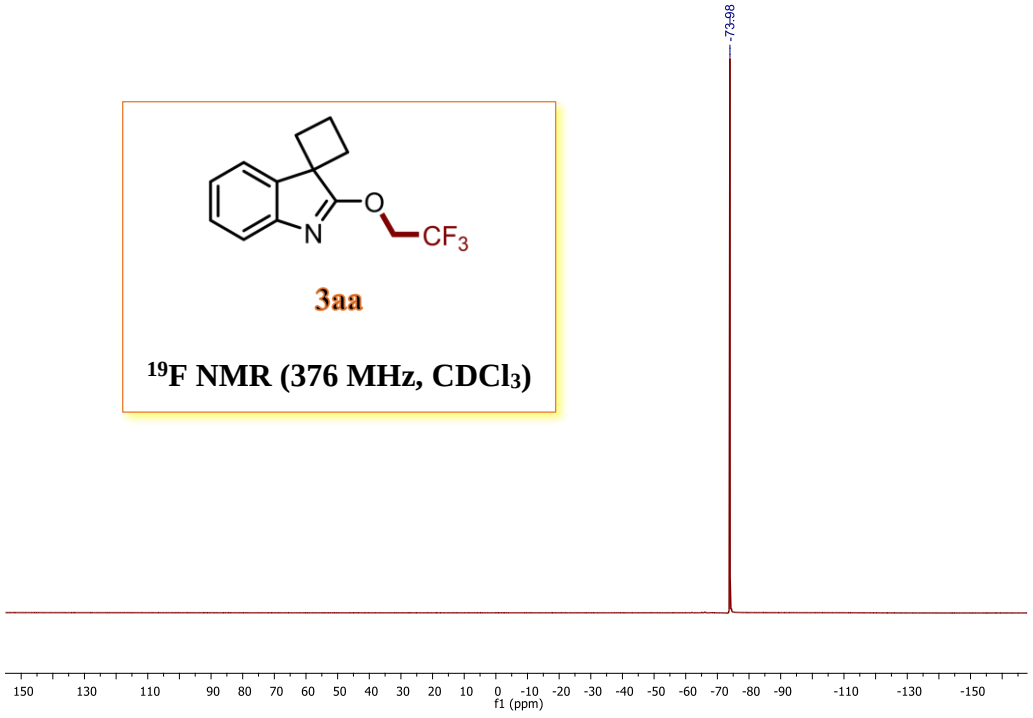

-73.15
d5
d5
O
N
CF3
3y
19F NMR (376 MHz, CDCl3)
f1 (ppm)

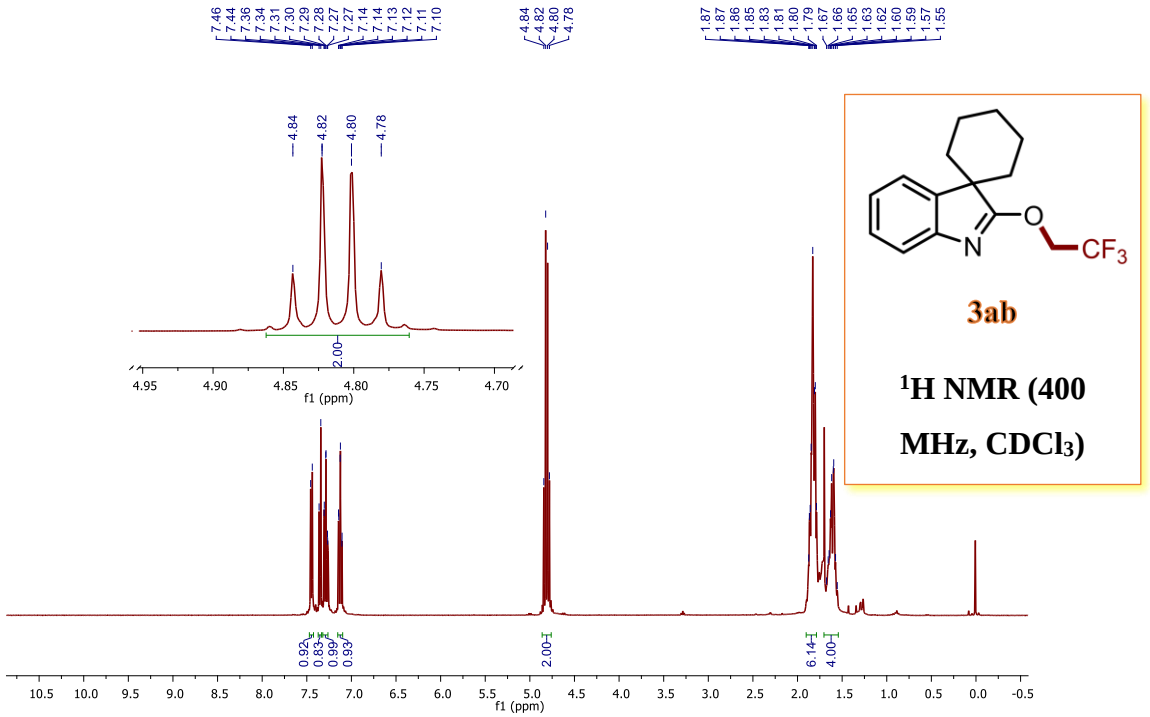

Me
Me
O
N
CF3
3z
1H NMR (400 MHz, CDCl3)

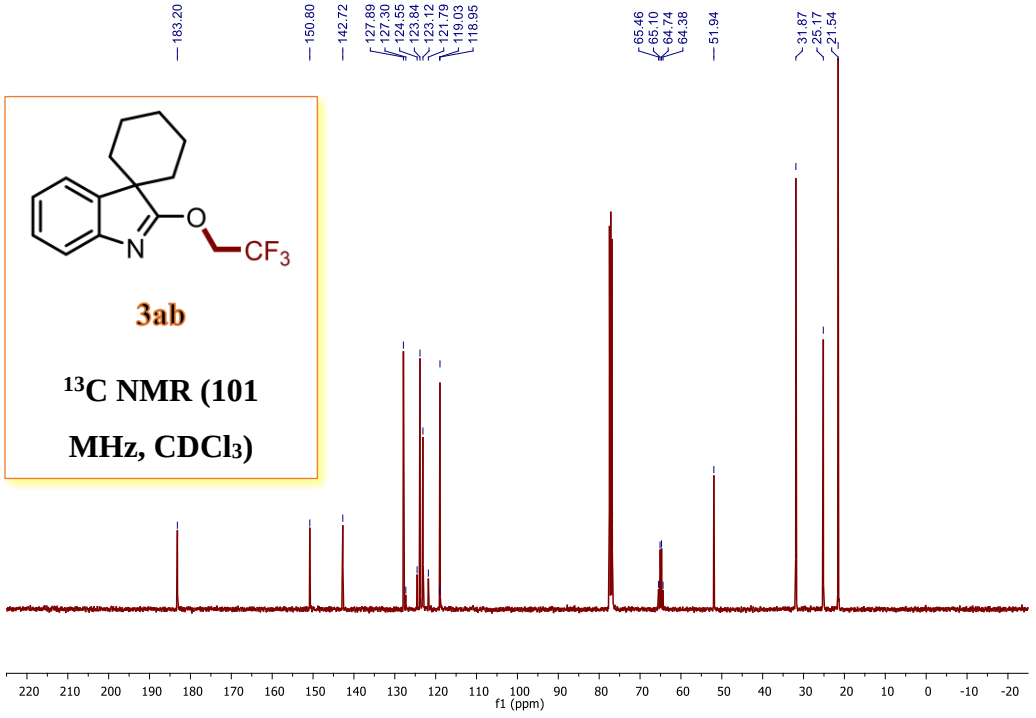

Me
Me
O
N
CF3
3z
13C NMR (101 MHz, CDCl3)

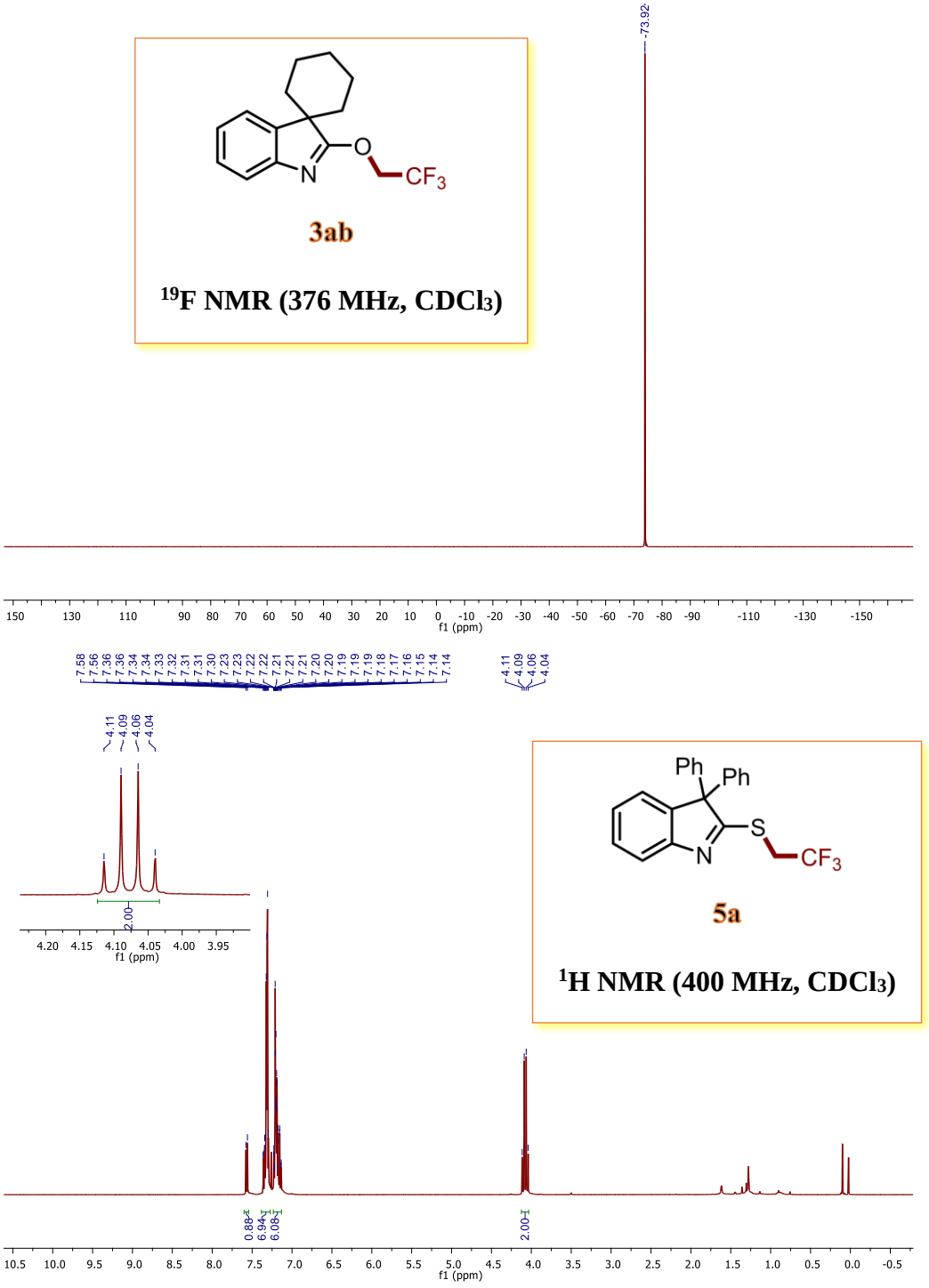

Me
Me
O
N
CF3
3z
19F NMR (376 MHz, CDCl3)
-74.00
f1 (ppm)
4.90
4.88
4.86
4.84
2.00
3aa
1H NMR (400 MHz, CDCl3)
0.91
2.10
0.55
0.40
2.00
2.09
2.17
2.31

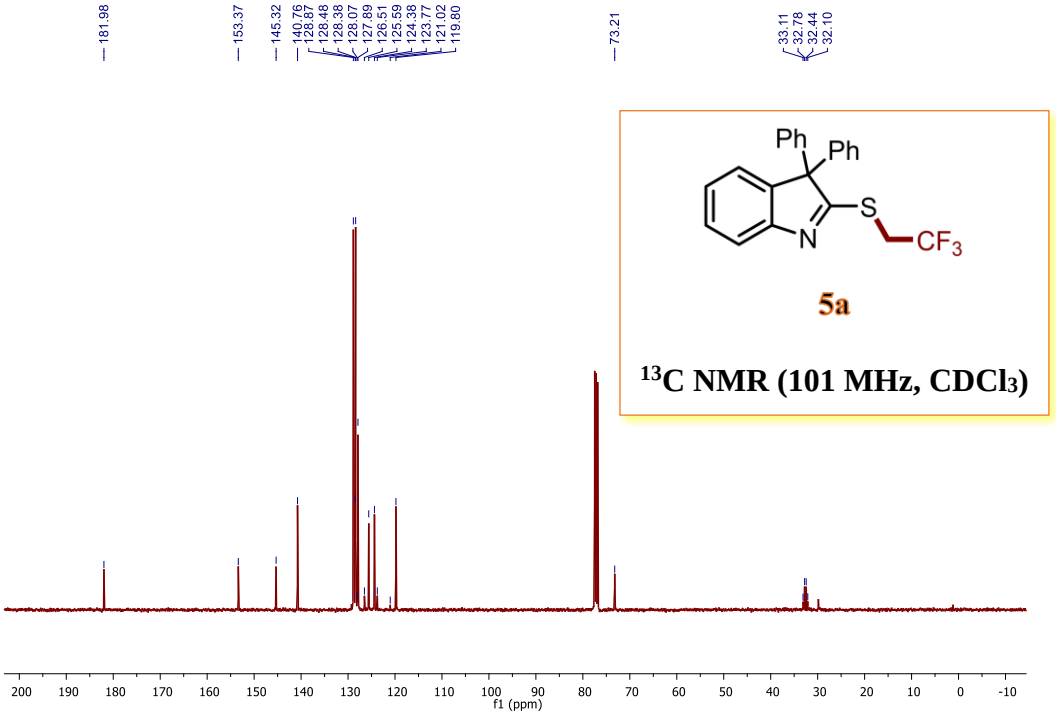

181.40
150.84
141.27
128.11
127.30
124.54
124.45
121.79
121.39
119.03
118.45
65.49
65.13
64.76
64.40
51.67
29.49
16.94
O
N
CF3
3aa
13C NMR (101 MHz, CDCl3)
f1 (ppm)

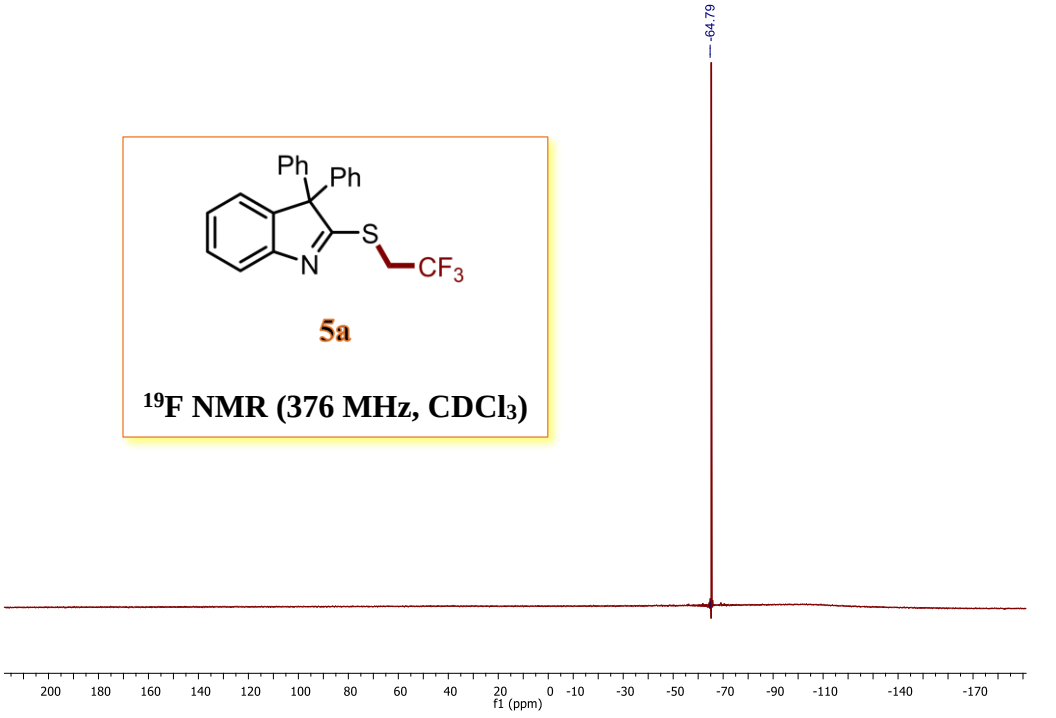

-73.98
O
N
CF3
3aa
19F NMR (376 MHz, CDCl3)
f1 (ppm)

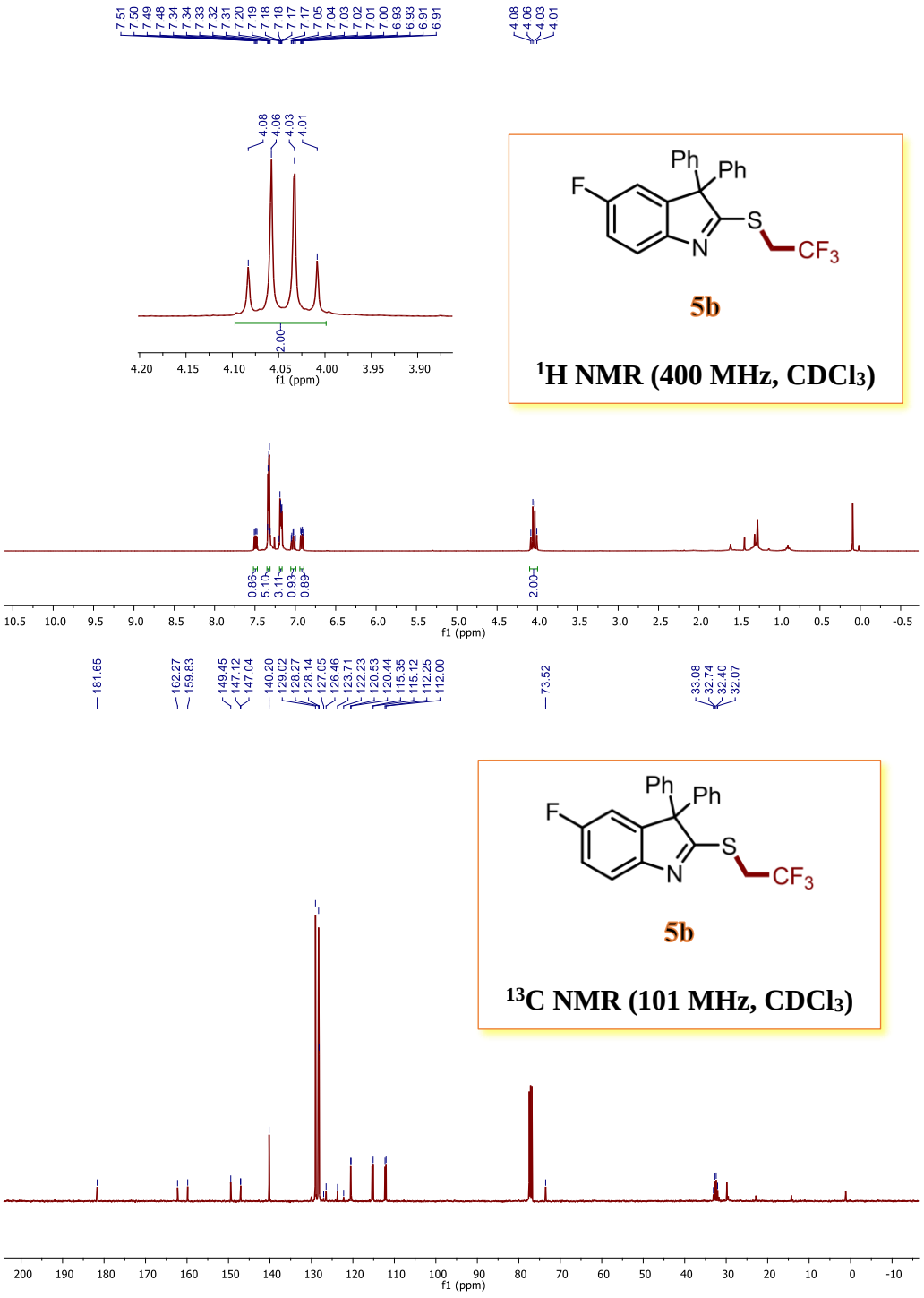

3ab
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)

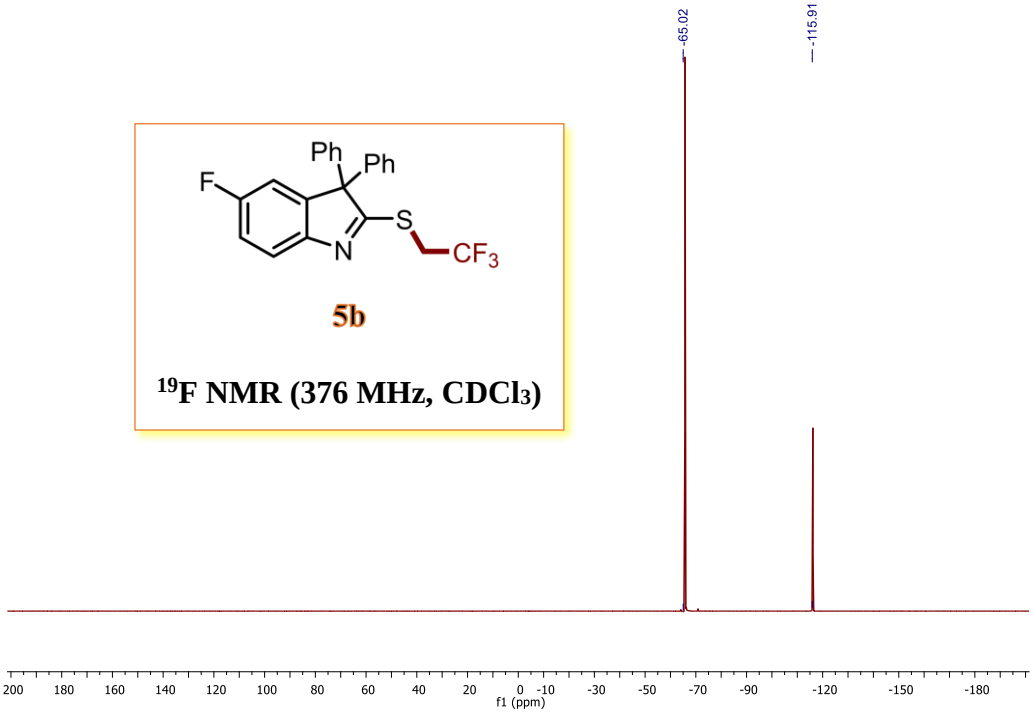

3ab
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)


-73.92
3ab
19F NMR (376 MHz, CDCl3)
f1 (ppm)
7.58
7.56
7.36
7.34
7.33
7.32
7.31
7.30
7.23
7.22
7.21
7.20
7.19
7.18
7.17
7.16
7.15
7.14
4.11
4.09
4.06
4.04
2.00
Ph
Ph
S
N
CF3
5a
1H NMR (400 MHz, CDCl3)
0.88
6.94
6.08
2.00


181.98
153.37
145.32
140.76
128.87
128.48
128.38
128.07
127.89
126.51
125.59
124.38
123.77
121.02
119.80
73.21
33.11
32.78
32.44
32.10
Ph
Ph
S
N
CF3
5a
13C NMR (101 MHz, CDCl3)
f1 (ppm)

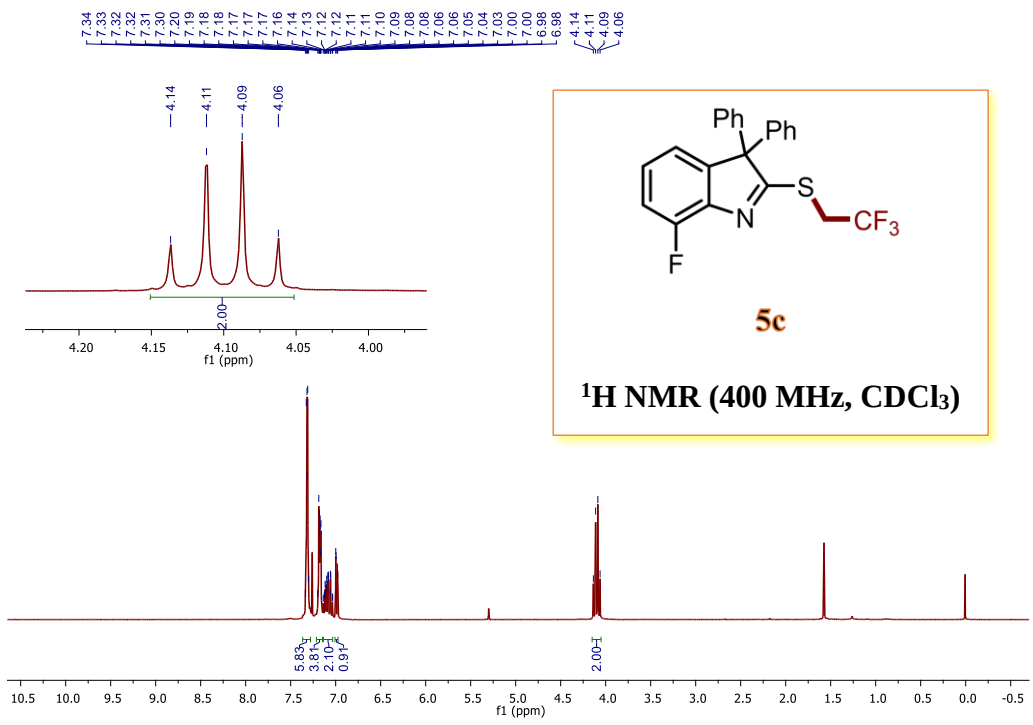

-64.79
Ph
Ph
S
N
CF3
5a
19F NMR (376 MHz, CDCl3)
f1 (ppm)


7.51
7.50
7.49
7.48
7.34
7.34
7.33
7.32
7.31
7.20
7.19
7.18
7.18
7.17
7.17
7.05
7.04
7.03
7.02
7.01
7.00
6.93
6.93
6.91
6.91
4.08
4.06
4.03
4.01
4.08
4.06
4.03
4.01
2.00
4.20 4.15 4.10 4.05 4.00 3.95 3.90
f1 (ppm)
Ph
Ph
F
S
N
CF3
5b
1H NMR (400 MHz, CDCl3)
0.86
5.10
3.11
0.93
0.89
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
181.65
162.27
159.83
149.45
147.12
147.04
140.20
129.02
128.27
128.14
127.05
126.46
123.71
122.23
120.53
120.44
115.35
115.12
112.25
112.00
73.52
33.08
32.74
32.40
32.07
Ph
Ph
F
S
N
CF3
5b
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



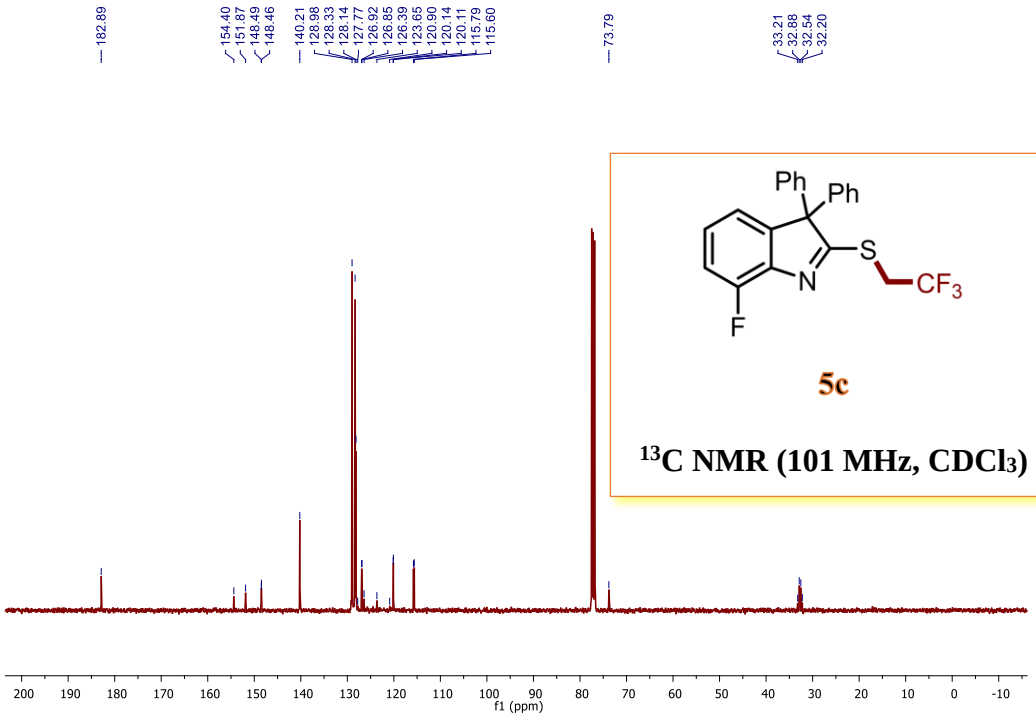
5b

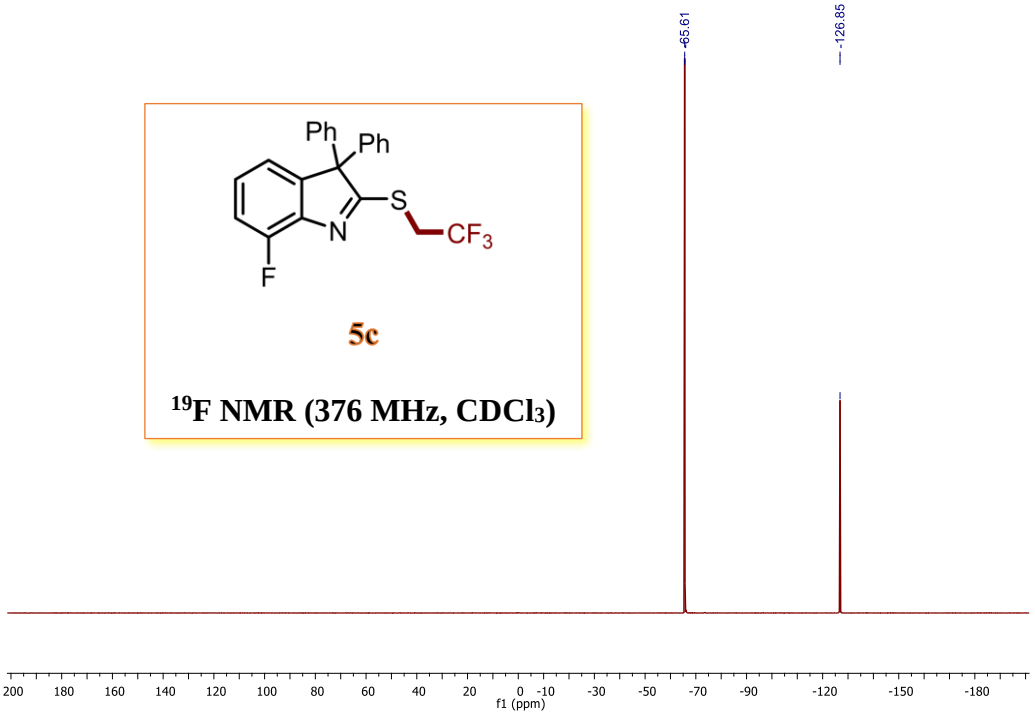
^{19}F NMR (376 MHz, $CDCl_3$)

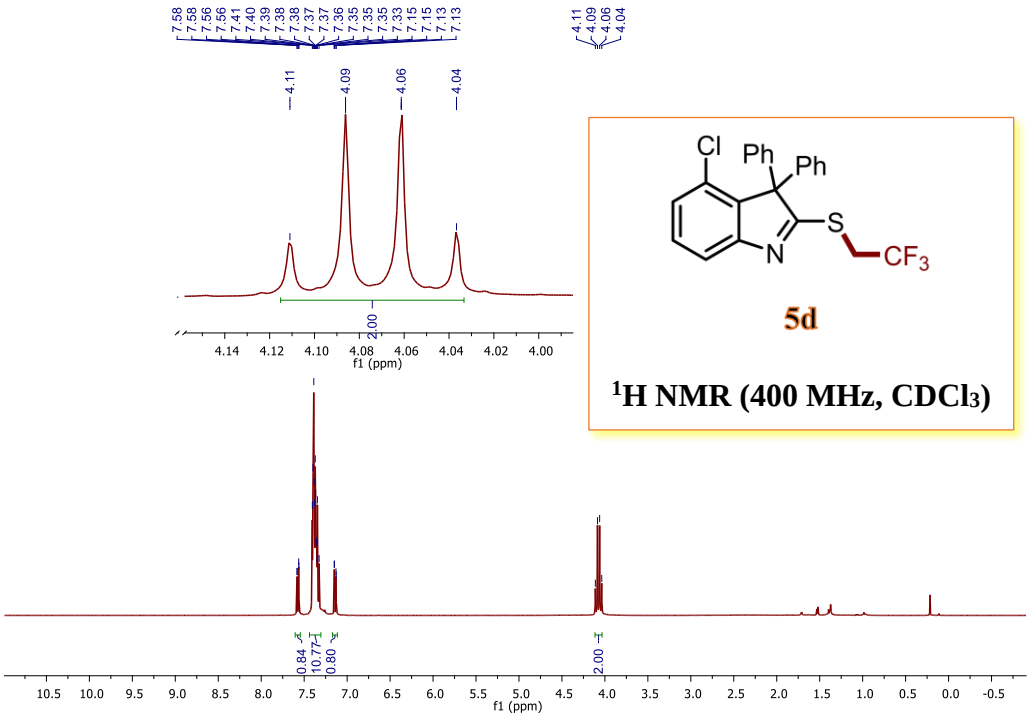


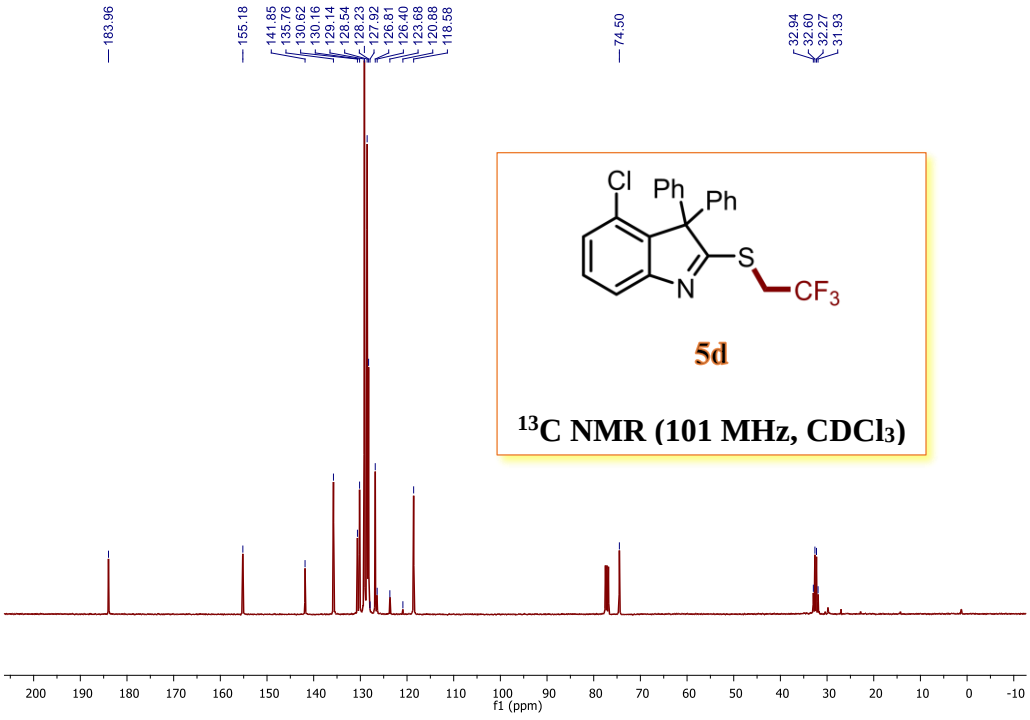
5c

^{1}H NMR (400 MHz, $CDCl_3$)


182.89
154.40
151.87
148.49
148.46
140.21
128.98
128.33
128.14
127.77
126.92
126.85
126.39
123.65
120.90
120.14
120.11
115.79
115.60
73.79
33.21
32.88
32.54
32.20
Ph
Ph
S
N
F
CF3
5c
13C NMR (101 MHz, CDCl3)
f1 (ppm)

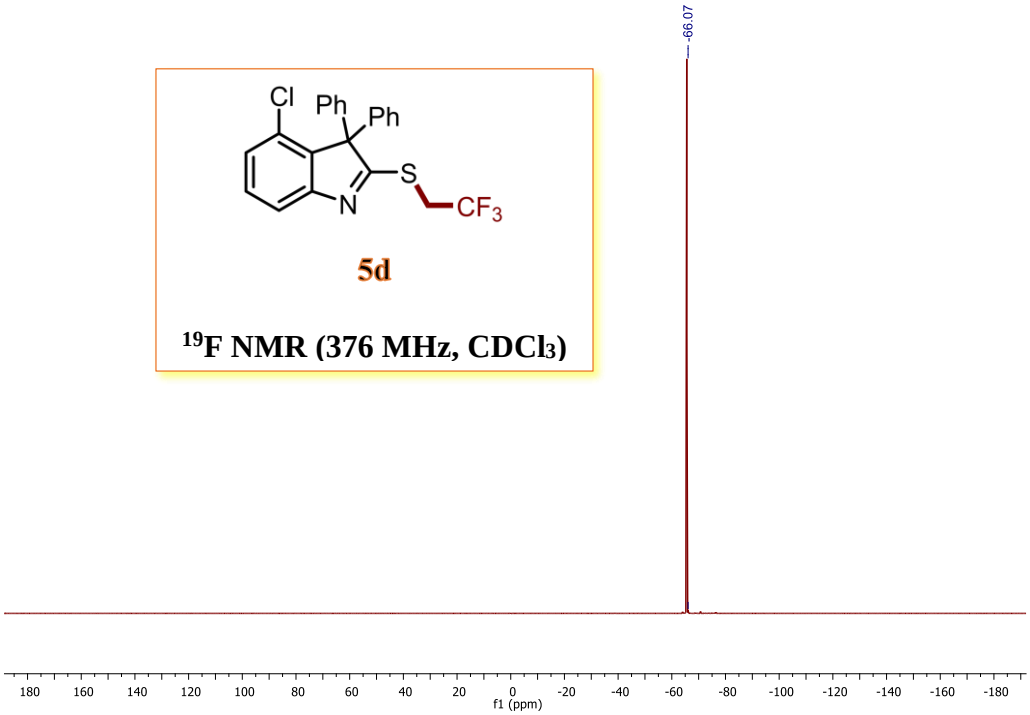

-65.61
-126.85
Ph
Ph
S
N
F
CF3
5c
19F NMR (376 MHz, CDCl3)
f1 (ppm)

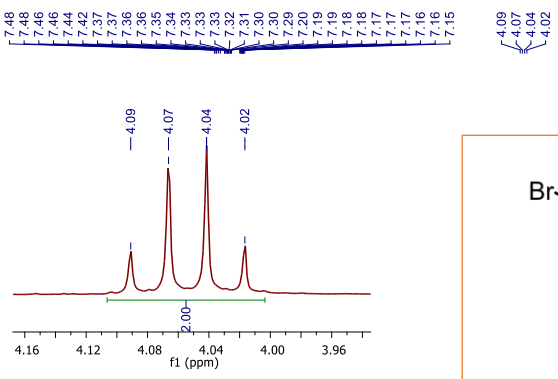

Cl
Ph
Ph
S
N
CF3
5d
1H NMR (400 MHz, CDCl3)

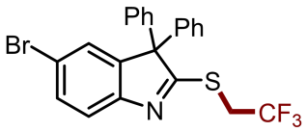

Cl
Ph
Ph
S
N
CF3
5d
13C NMR (101 MHz, CDCl3)

5d

^{19}F NMR (376 MHz, $CDCl_3$)

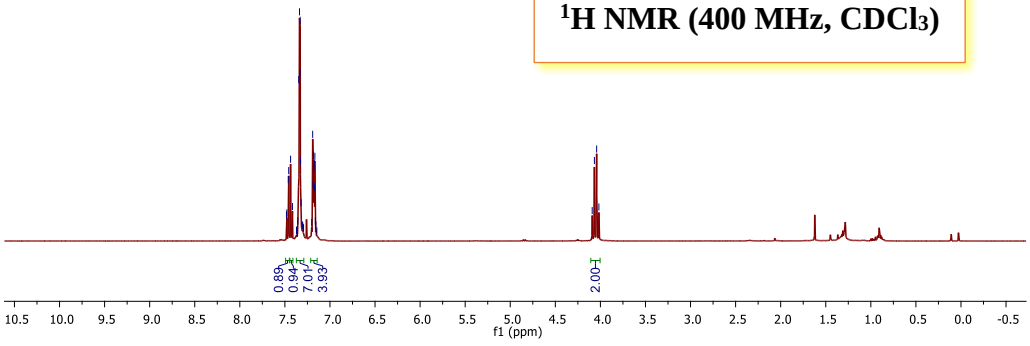


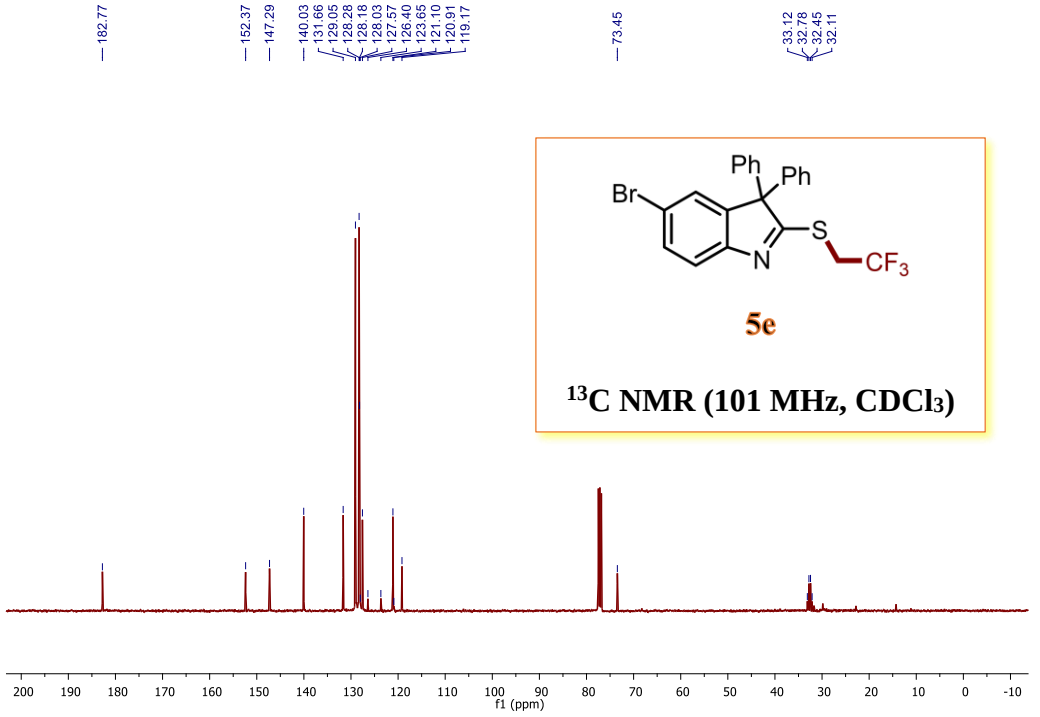


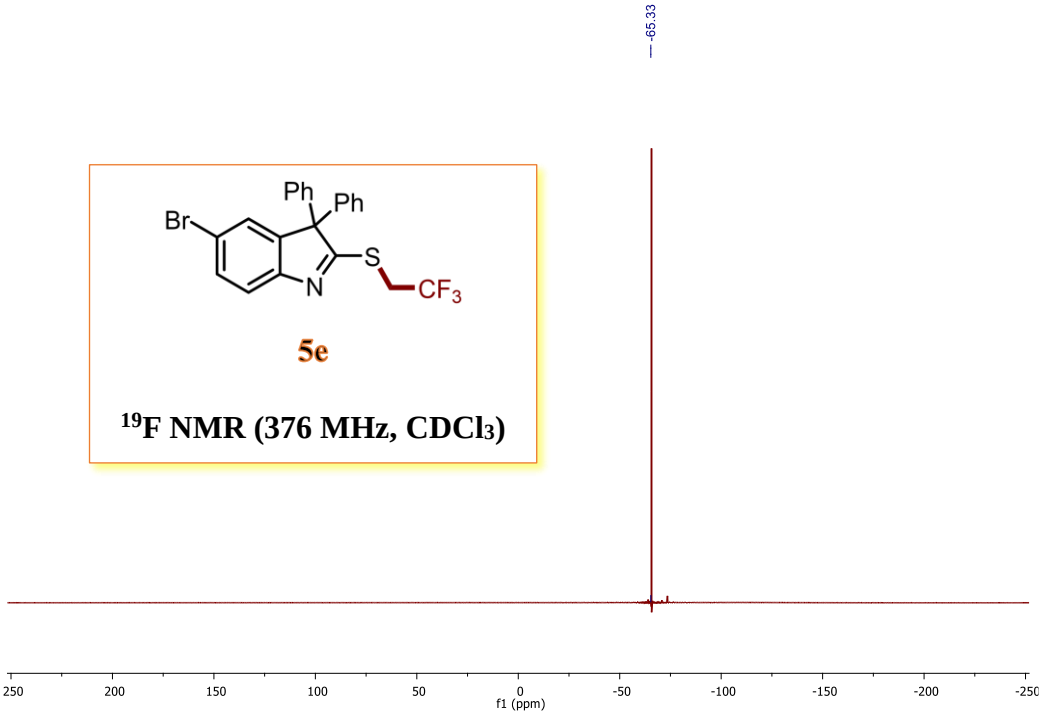


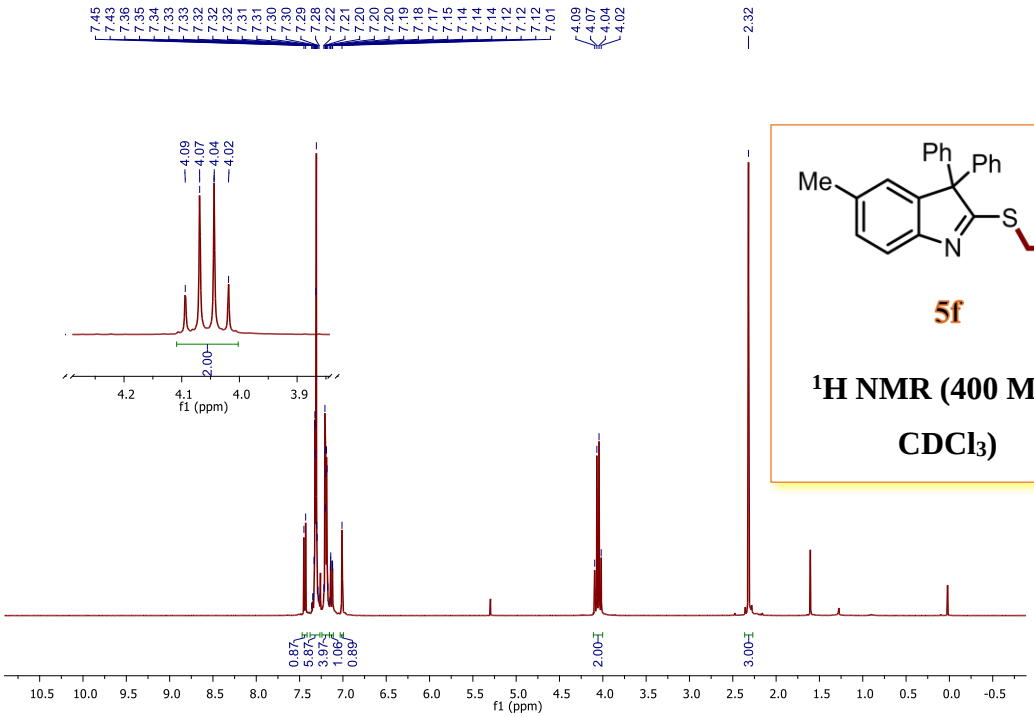
5e

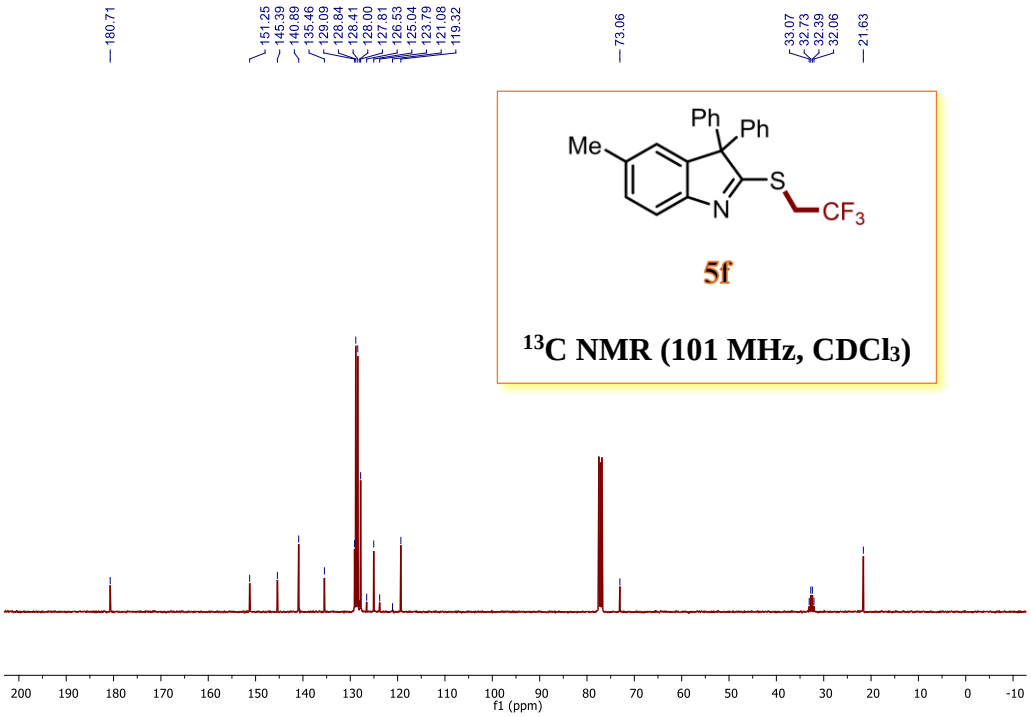
^{1}H NMR (400 MHz, $CDCl_3$)

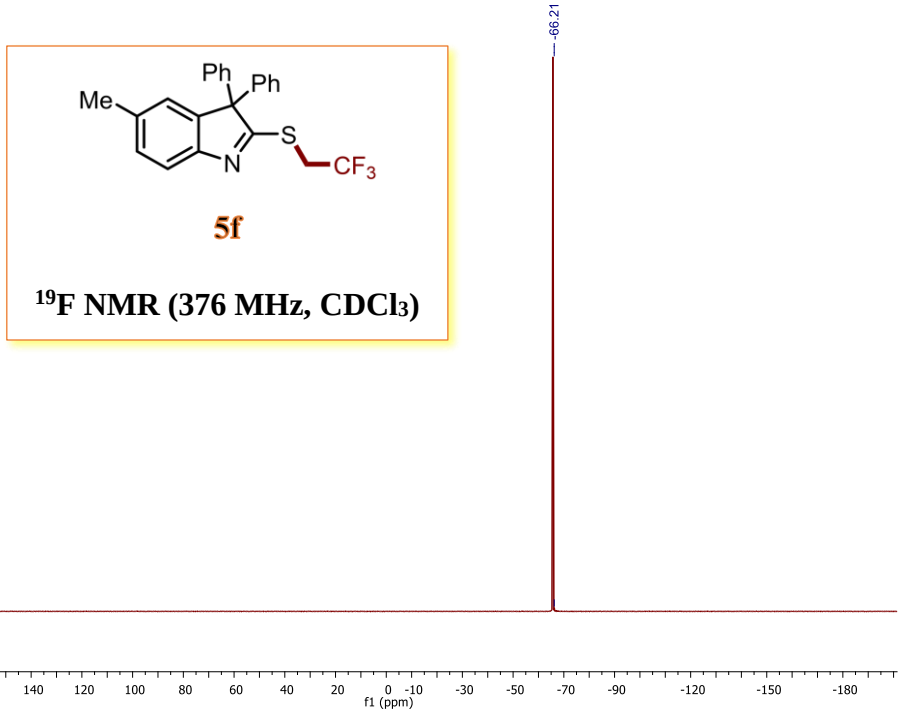


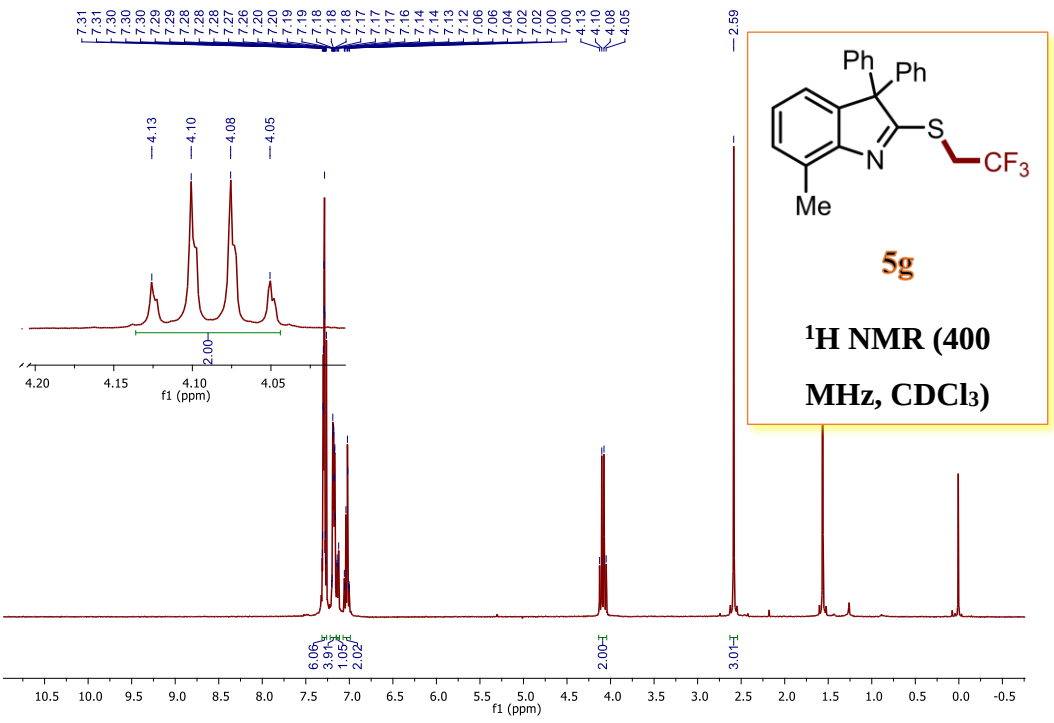

182.77
152.37
147.29
140.03
131.66
129.05
128.28
128.18
128.03
127.57
126.40
123.65
121.10
120.91
119.17
73.45
33.12
32.78
32.45
32.11
Ph
Ph
Br
S
N
CF3
5e
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

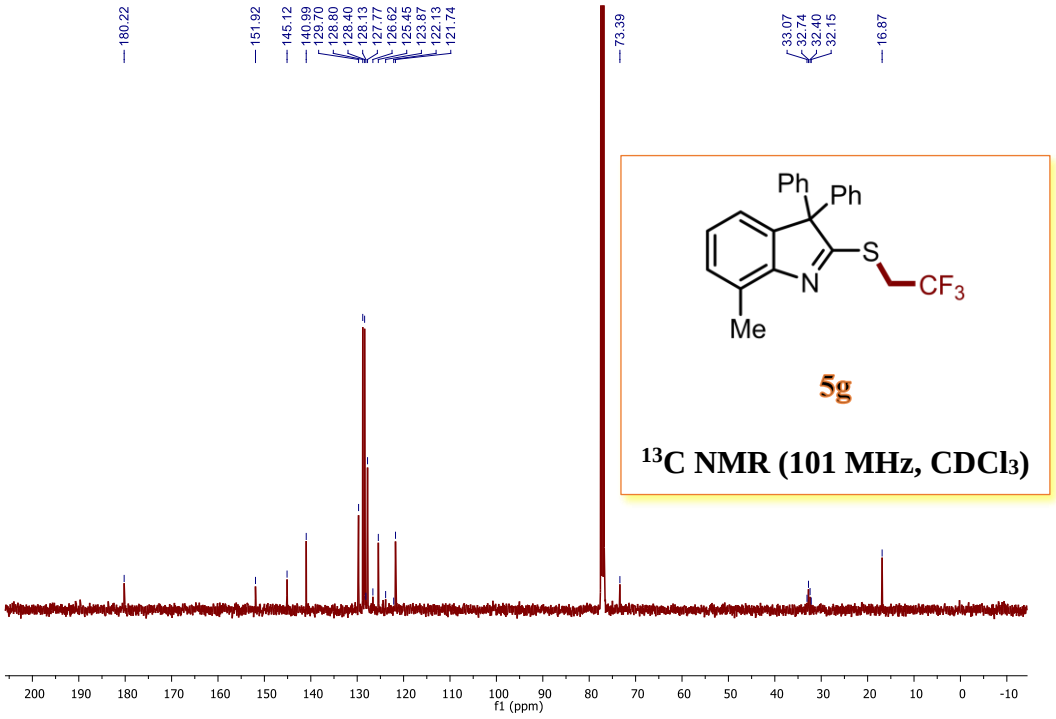

-65.33
Ph
Ph
Br
S
N
CF3
5e
19F NMR (376 MHz, CDCl3)
250 200 150 100 50 0 -50 -100 -150 -200 -250
f1 (ppm)

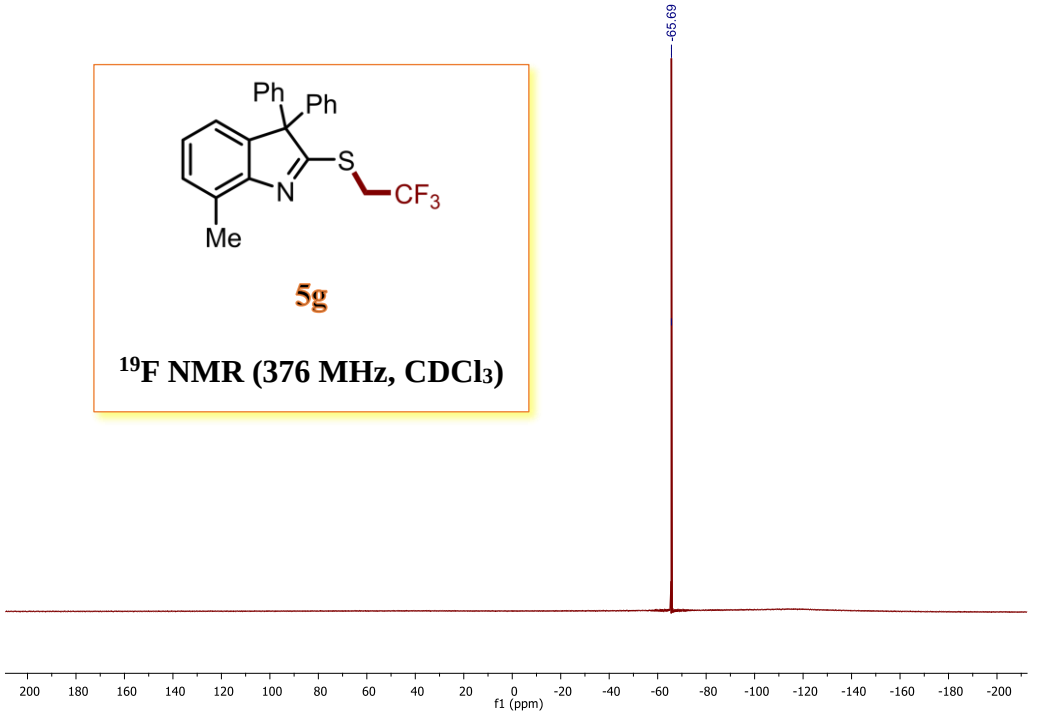

Ph
Ph
Me
S
N
CF3
5f
1H NMR (400 MHz, CDCl3)

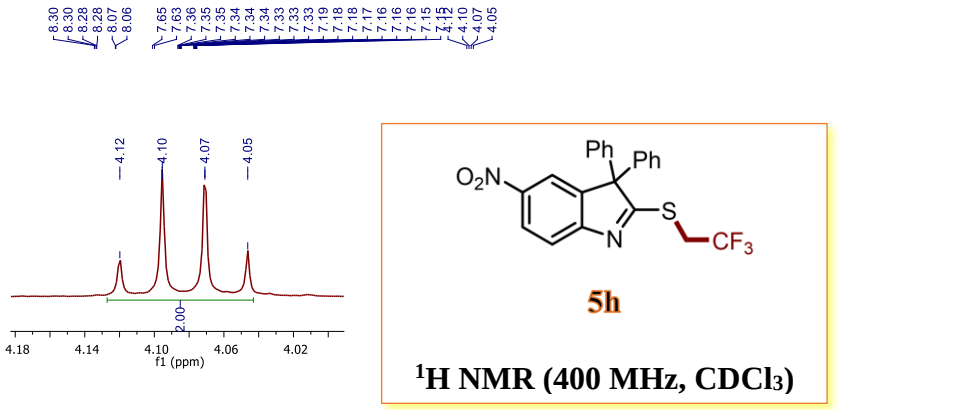

Ph
Ph
Me
S
N
CF3
5f
13C NMR (101 MHz, CDCl3)

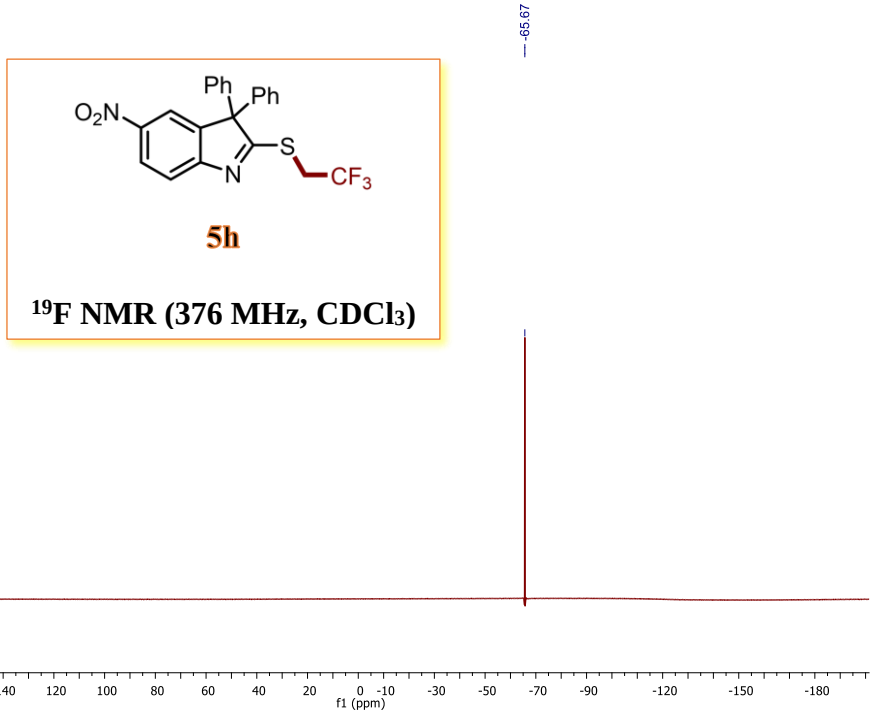

Ph
Ph
Me
S
N
CF3
5f
19F NMR (376 MHz, CDCl3)
-66.21
200 180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180
f1 (ppm)


7.31 7.31 7.30 7.30 7.30 7.29 7.29 7.28 7.28 7.28 7.27 7.26 7.20 7.20 7.19 7.19 7.18 7.18 7.18 7.17 7.17 7.17 7.16 7.16 7.14 7.14 7.13 7.12 7.06 7.06 7.04 7.02 7.02 7.00 7.00 4.13 4.10 4.08 4.05
2.59
4.13
4.10
4.08
4.05
2.00
4.20 4.15 4.10 4.05
f1 (ppm)
Ph
Ph
S
N
CF3
Me
5g
1H NMR (400 MHz, CDCl3)
6.06 3.91 1.05 2.02 2.00 3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


180.22
151.92
145.12
140.99
129.70
128.80
128.40
128.13
127.77
126.62
125.45
123.87
122.13
121.74
73.39
33.07
32.74
32.40
32.15
16.87
Ph
Ph
S
N
CF3
Me
5g
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

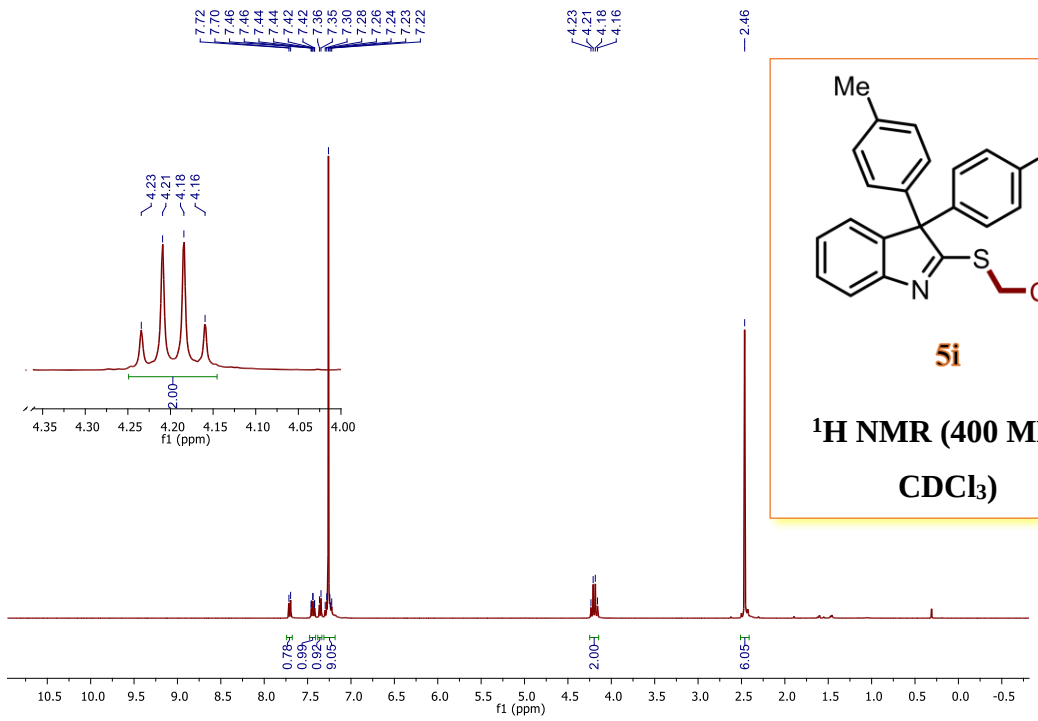

-65.69
Ph
Ph
S
N
CF3
Me
5g
19F NMR (376 MHz, CDCl3)
200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200
f1 (ppm)

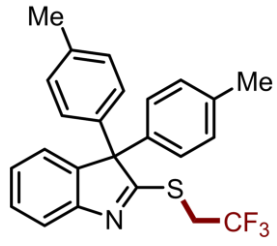

8.30
8.30
8.28
8.28
8.07
8.06
7.65
7.63
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.33
7.33
7.19
7.18
7.18
7.17
7.16
7.16
7.16
7.15
7.15
4.12
4.10
4.07
4.05
4.12
4.10
4.07
4.05
2.00
4.18
4.14
4.10
4.06
4.02
f1 (ppm)
Ph
Ph
O2N
S
N
CF3
5h
1H NMR (400 MHz, CDCl3)
0.88
0.86
0.91
5.90
3.80
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
188.79
158.25
146.44
145.62
139.34
129.31
128.59
128.18
127.71
126.23
125.43
123.48
120.94
119.98
119.89
73.62
33.36
33.03
32.69
32.38
Ph
Ph
O2N
S
N
CF3
5h
13C NMR (101 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



5h

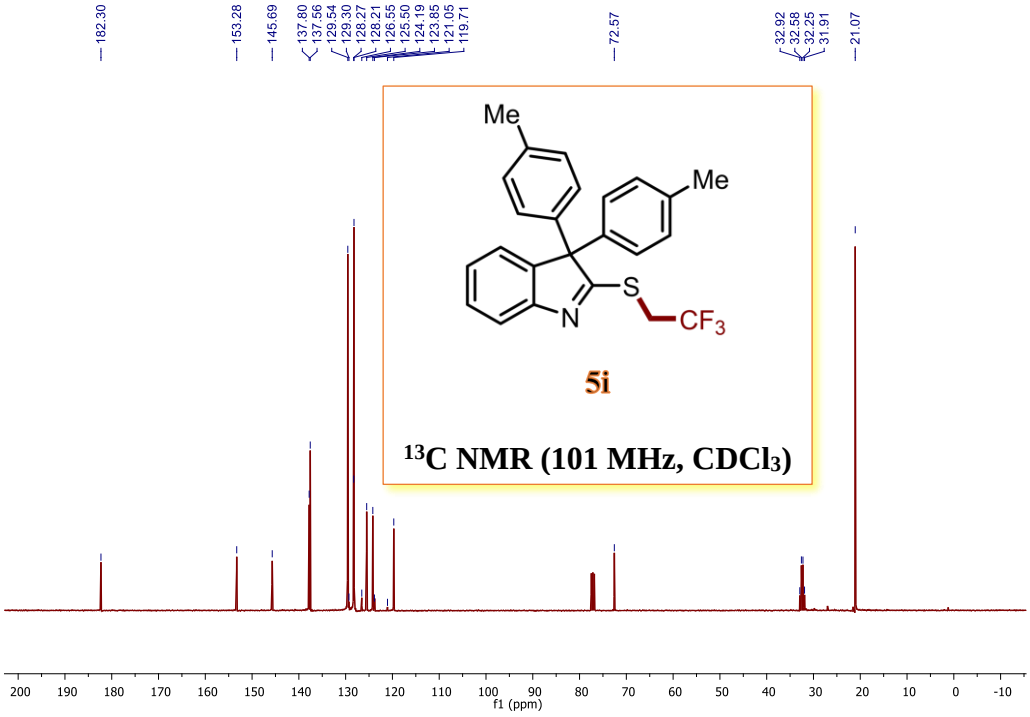
^{19}F NMR (376 MHz, $CDCl_3$)

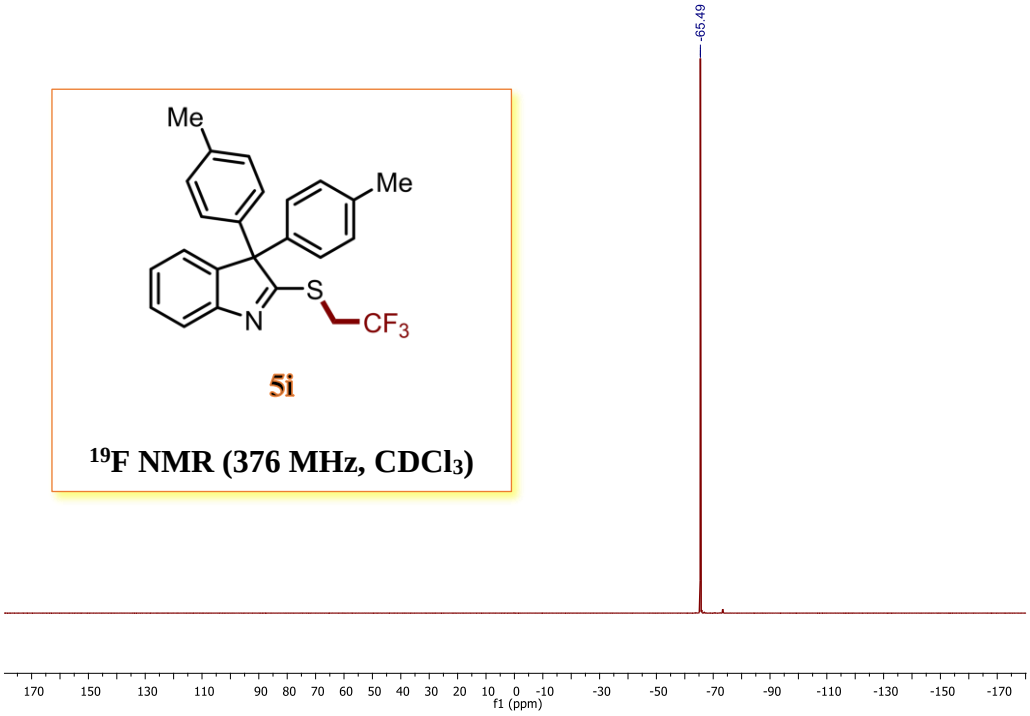


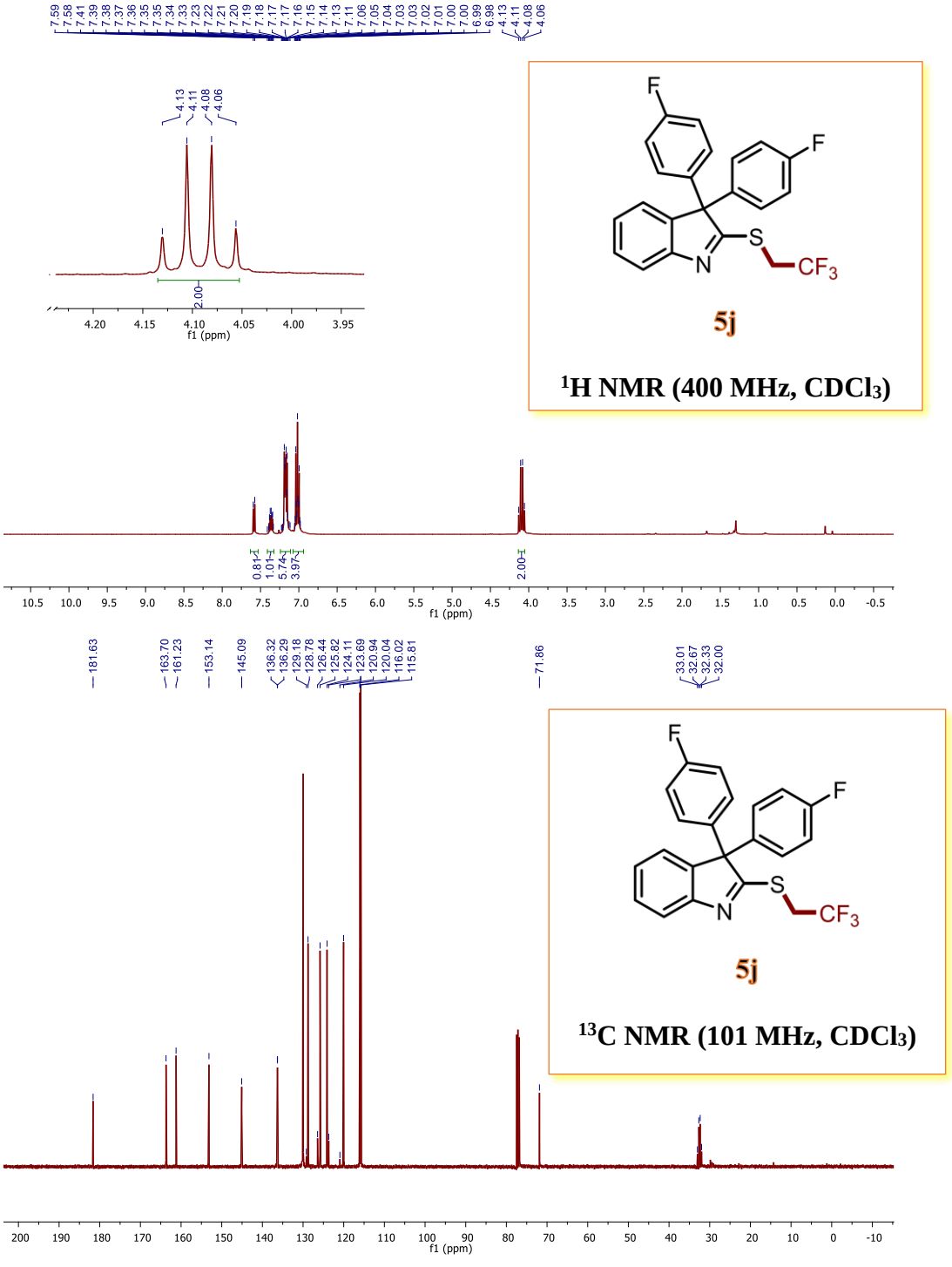


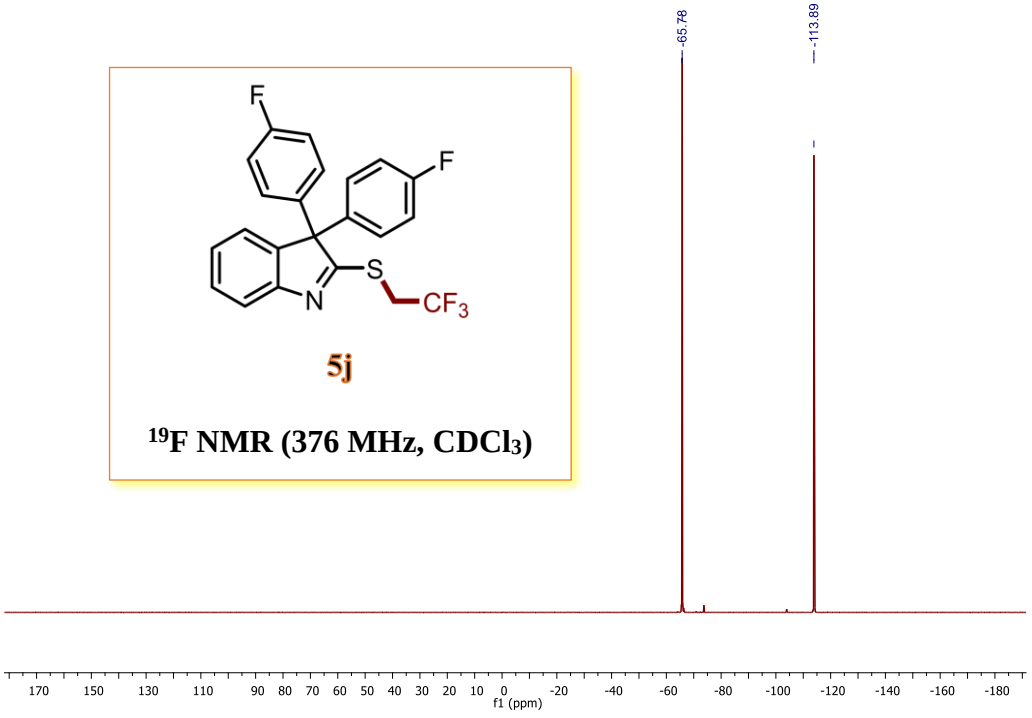
5i

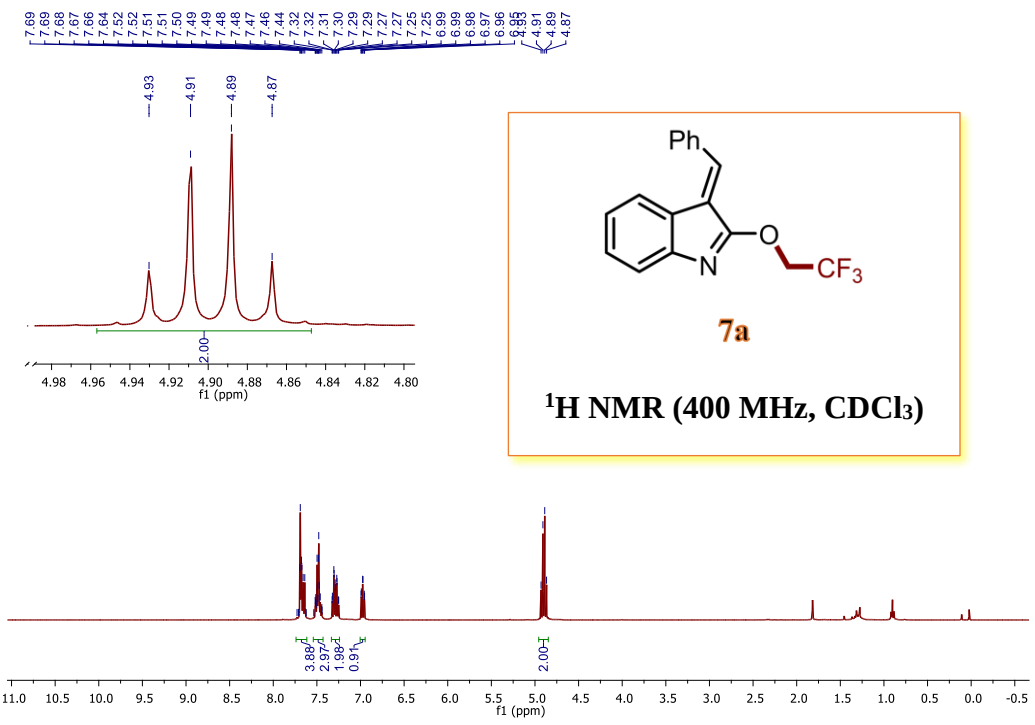
^{1}H NMR (400 MHz, $CDCl_3$)

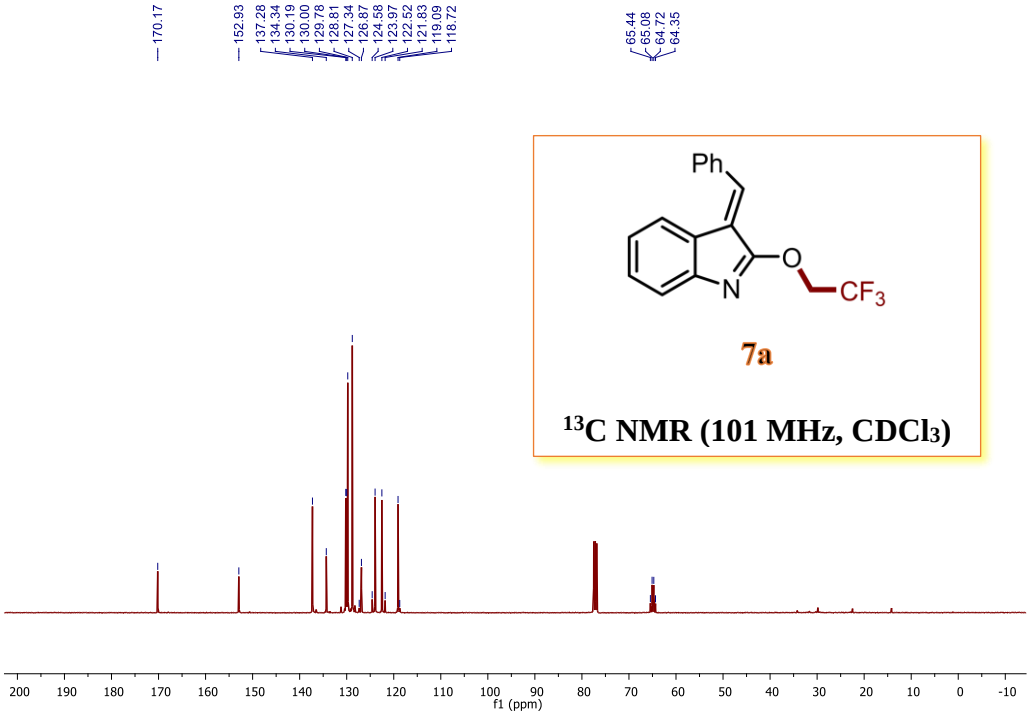

182.30
153.28
145.69
137.80
137.56
129.54
129.30
128.27
128.21
126.55
125.50
124.19
123.85
121.05
119.71
72.57
32.92
32.58
32.25
31.91
21.07
Me
Me
S
N
CF3
5i
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

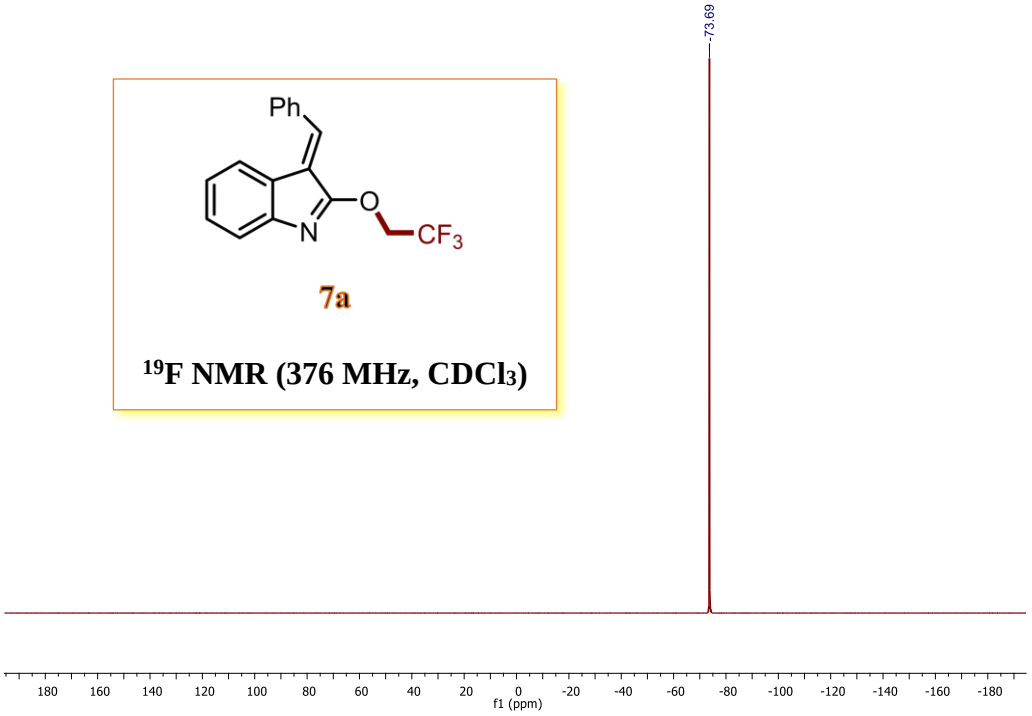

-65.49
Me
Me
S
N
CF3
5i
19F NMR (376 MHz, CDCl3)
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170
f1 (ppm)

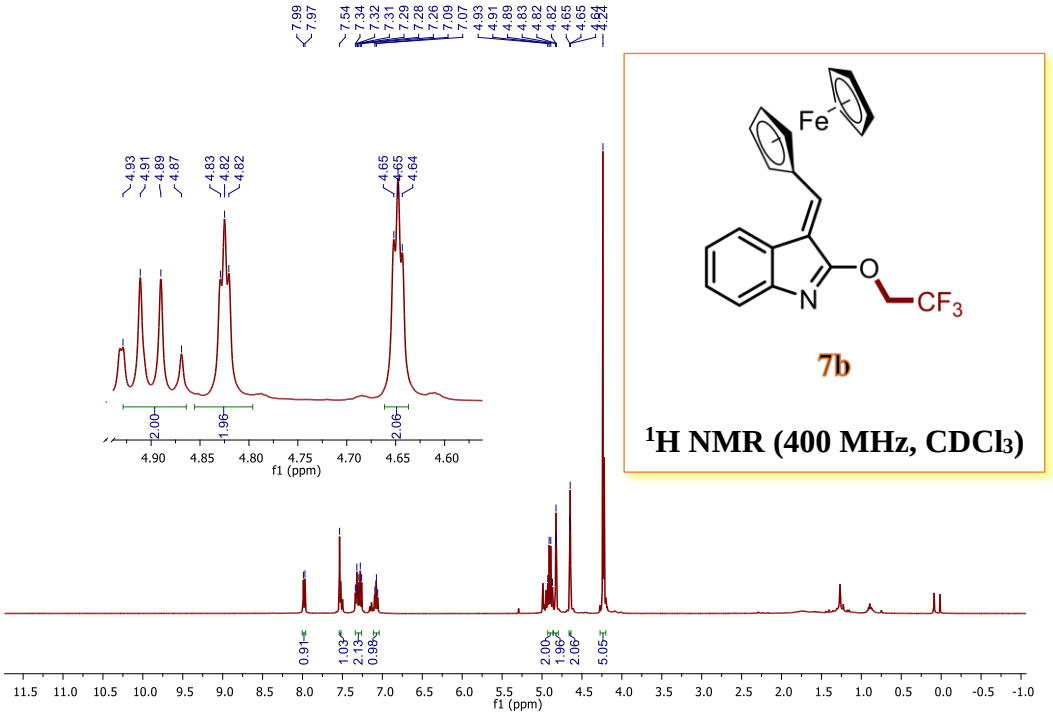

7.59 7.58 7.41 7.39 7.38 7.37 7.36 7.35 7.35 7.34 7.33 7.23 7.22 7.21 7.20 7.19 7.18 7.17 7.17 7.16 7.15 7.14 7.13 7.11 7.06 7.05 7.04 7.03 7.03 7.02 7.01 7.00 7.00 6.99 6.98 4.13 4.11 4.08 4.06
4.13 4.11 4.08 4.06
2.00
4.20 4.15 4.10 4.05 4.00 3.95
f1 (ppm)
F
F
S
N
CF3
5j
1H NMR (400 MHz, CDCl3)
0.81 1.01 5.74 3.97 2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
181.63 163.70 161.23 153.14 145.09 136.32 136.29 129.18 128.78 126.44 125.82 124.11 123.69 120.94 120.04 116.02 115.81 71.86 33.01 32.67 32.33 32.00
F
F
S
N
CF3
5j
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

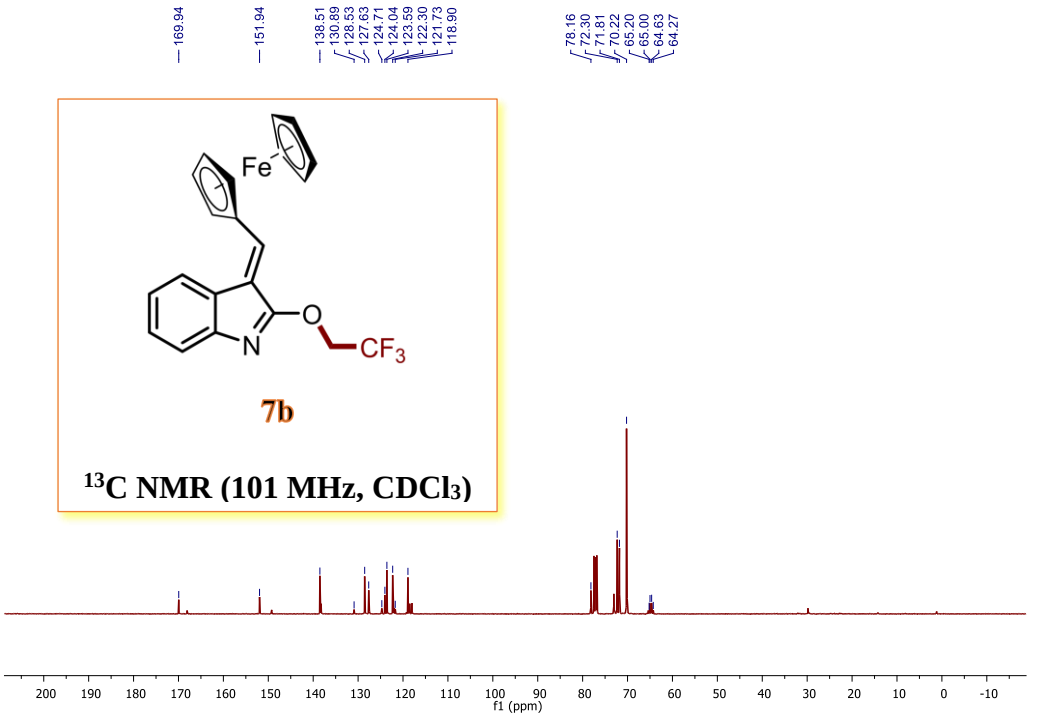

F
F
S
N
CF3
5j
19F NMR (376 MHz, CDCl3)
-65.78
-113.89
f1 (ppm)

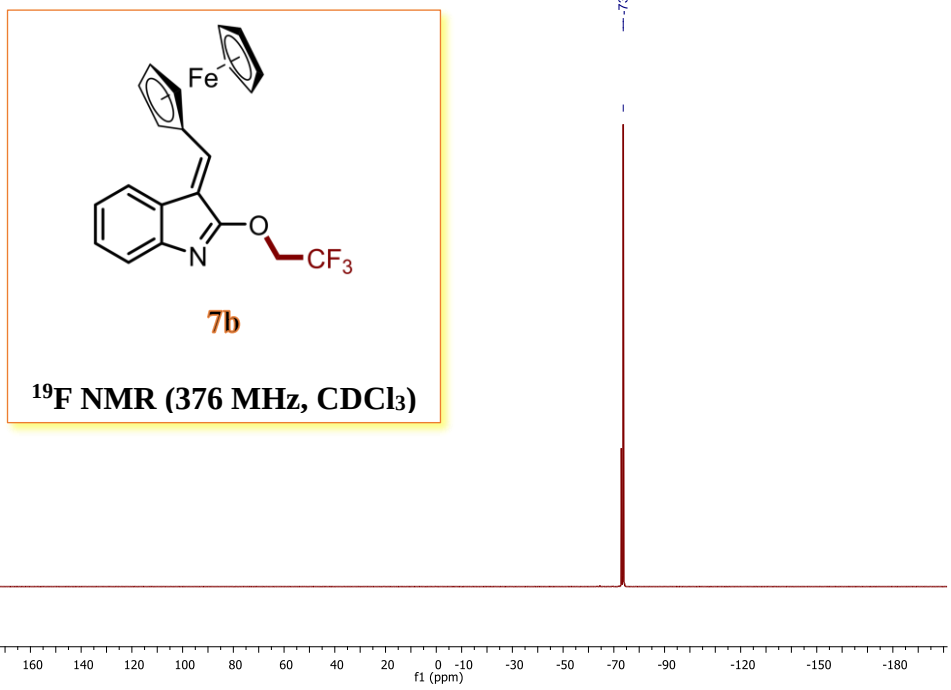

7.69
7.68
7.67
7.66
7.64
7.52
7.51
7.50
7.49
7.48
7.47
7.46
7.44
7.32
7.31
7.30
7.29
7.27
7.25
6.99
6.98
6.97
6.96
4.93
4.91
4.89
4.87
2.00
f1 (ppm)
Ph
O
N
CF3
7a
1H NMR (400 MHz, CDCl3)
3.88
2.97
1.98
0.69
2.00
f1 (ppm)

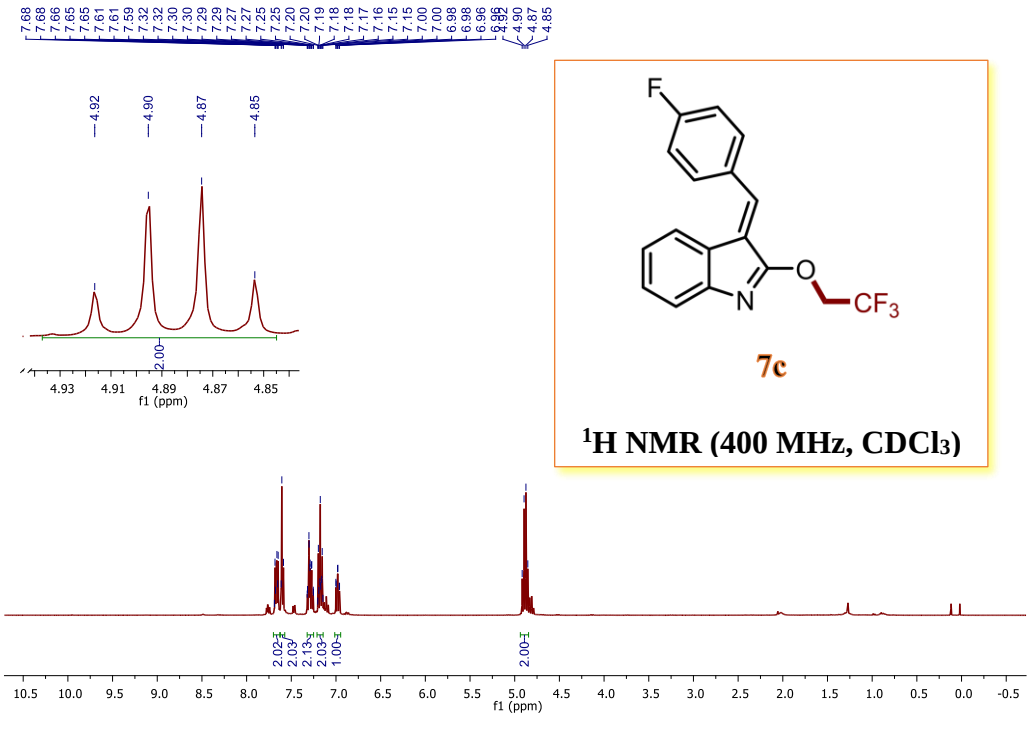

170.17
152.93
137.28
134.34
130.19
130.00
129.78
128.81
127.34
126.87
124.58
123.97
122.52
121.83
119.09
118.72
65.44
65.08
64.72
64.35
Ph
O
N
CF3
7a
13C NMR (101 MHz, CDCl3)
f1 (ppm)

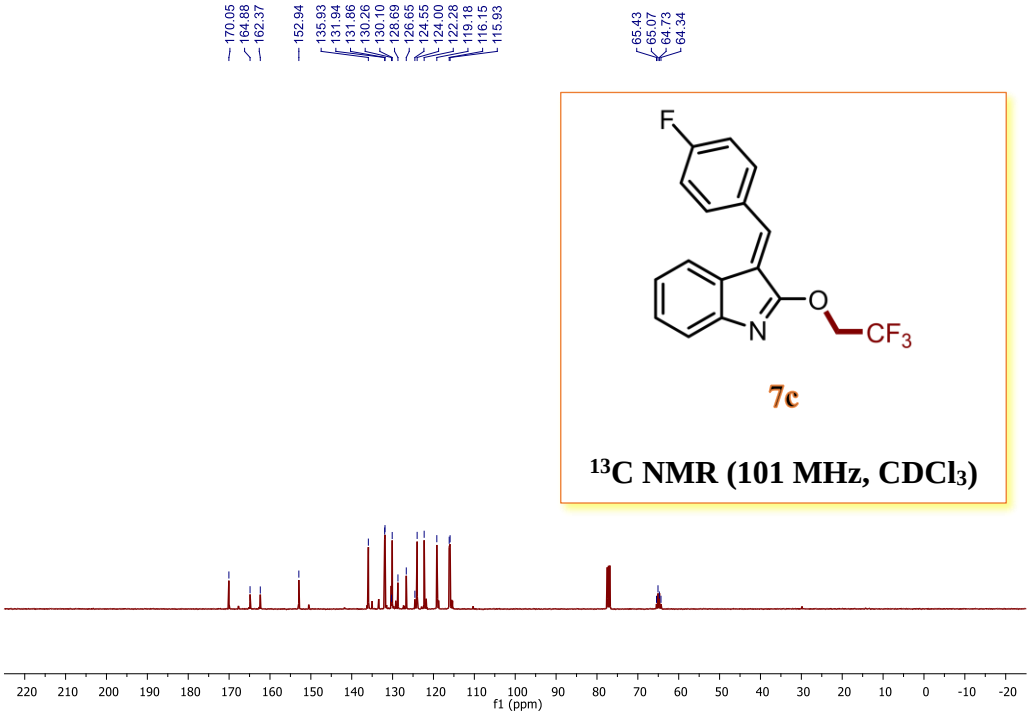

-73.69
Ph
O
N
CF3
7a
19F NMR (376 MHz, CDCl3)
f1 (ppm)

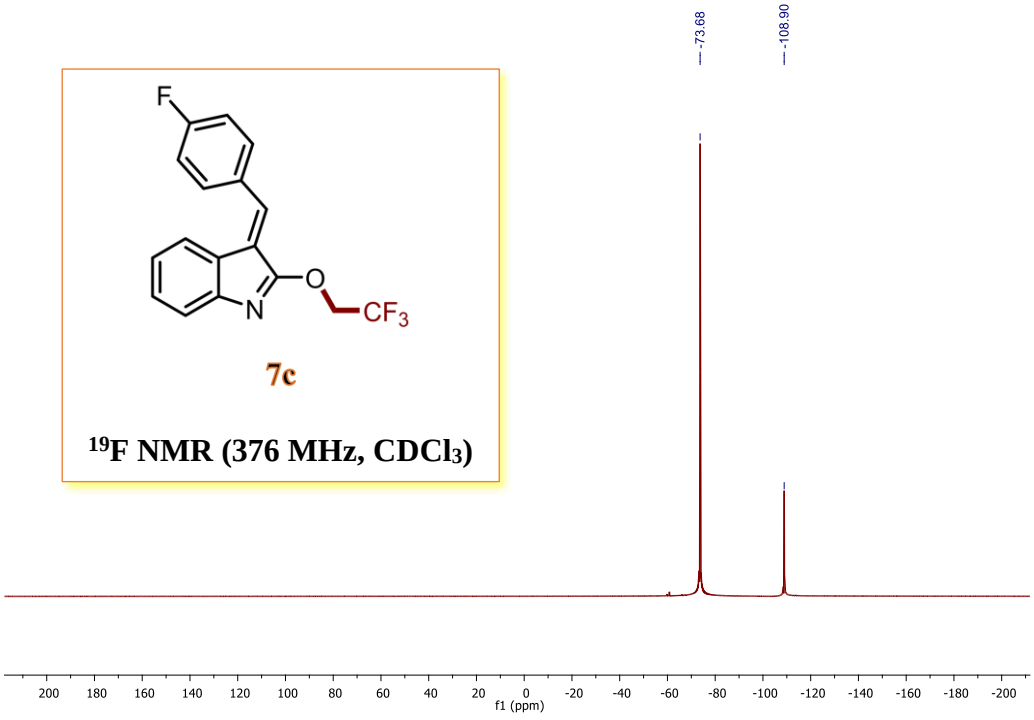

7b
^{1}H NMR (400 MHz, CDCl$_3$)

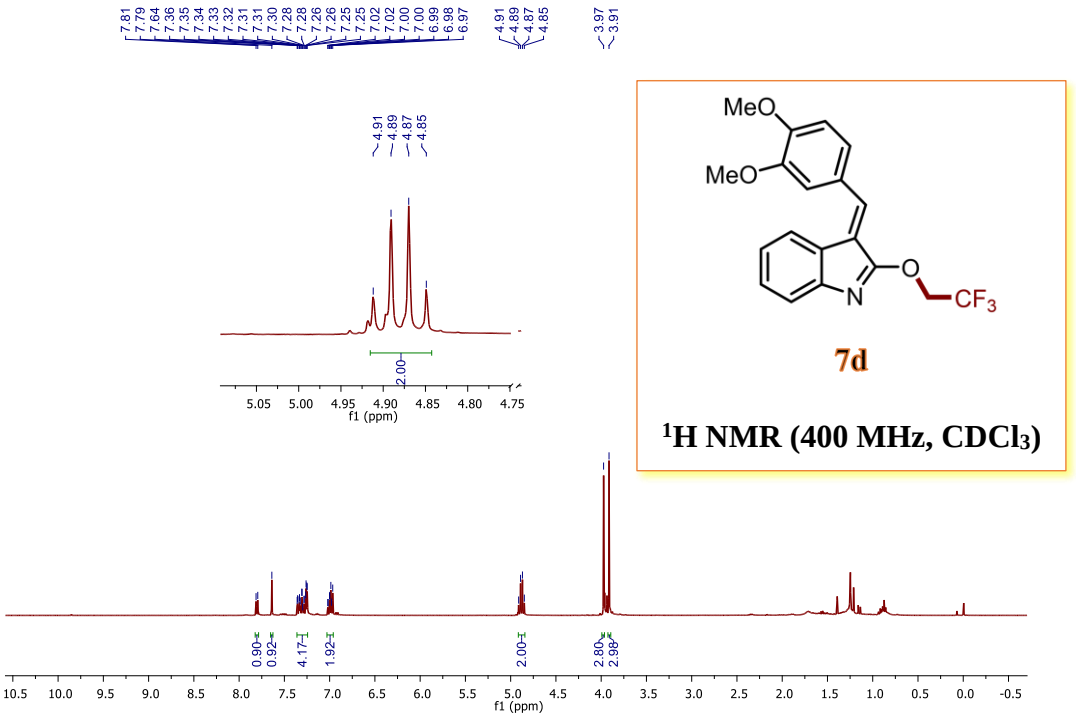

7b
^{13}C NMR (101 MHz, CDCl$_3$)

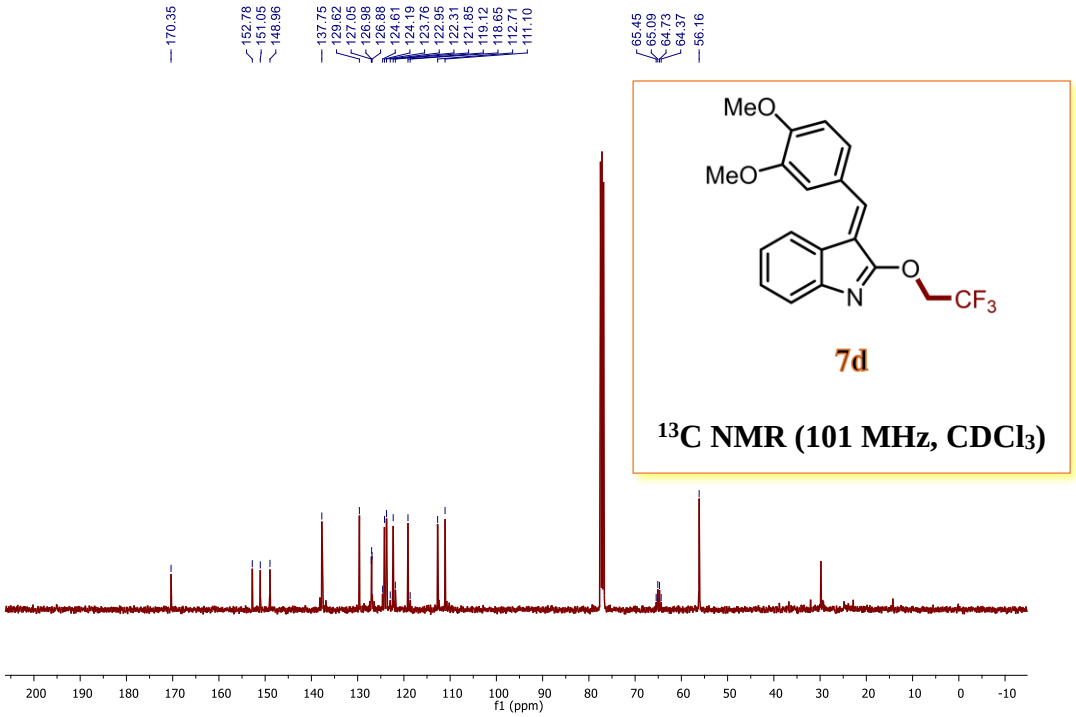

Fe
O
N
CF3
7b
19F NMR (376 MHz, CDCl3)
-73.71
200 180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180
f1 (ppm)

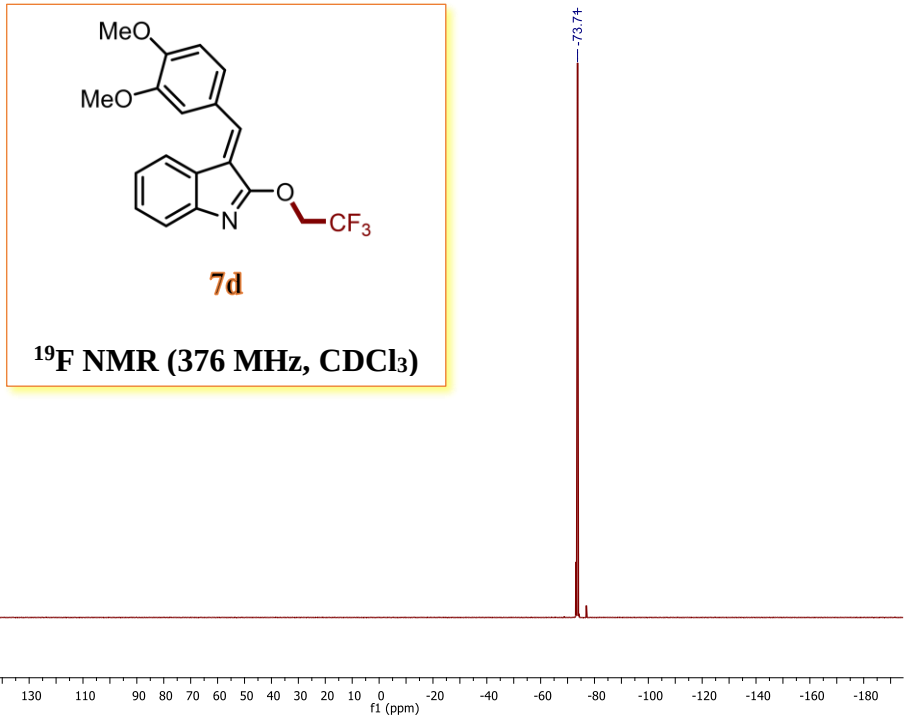

7.68 7.68 7.66 7.65 7.65 7.61 7.61 7.59 7.32 7.32 7.30 7.30 7.29 7.29 7.27 7.27 7.25 7.25 7.20 7.20 7.19 7.18 7.18 7.17 7.16 7.15 7.15 7.00 7.00 6.98 6.98 6.96 6.96 4.90 4.87 4.85
4.92 4.90 4.87 4.85
2.00
4.93 4.91 4.89 4.87 4.85
f1 (ppm)
F
O
N
CF3
7c
1H NMR (400 MHz, CDCl3)
2.02 2.03 2.13 2.03 1.00 2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

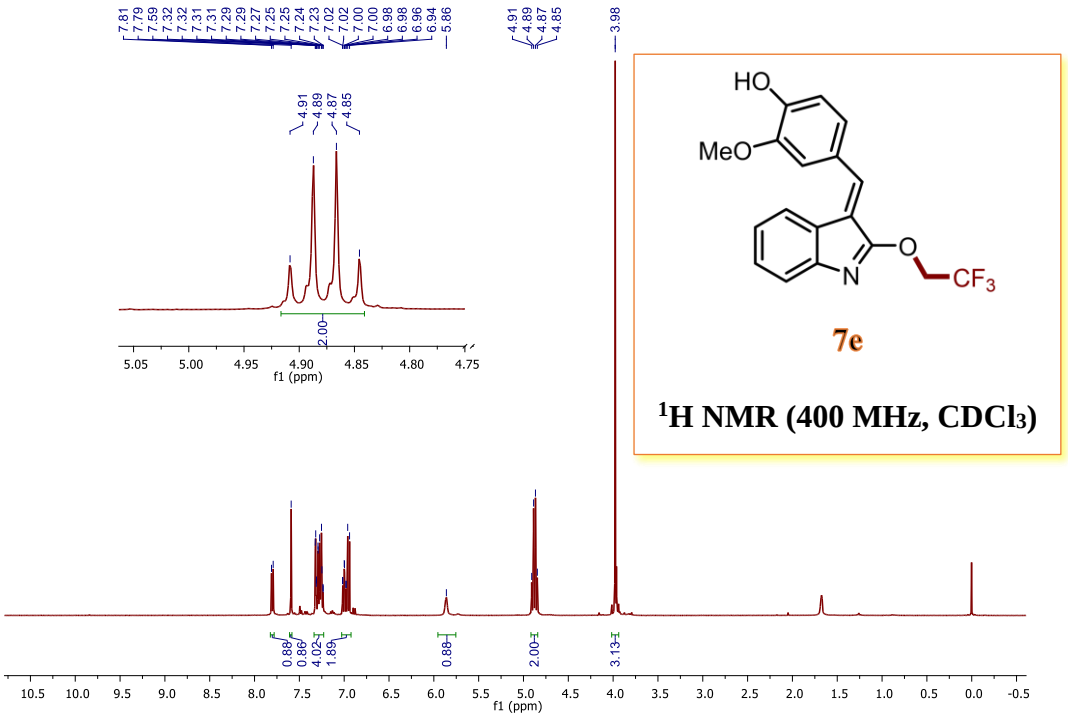

170.05
164.88
162.37
152.94
135.93
131.94
131.86
130.26
130.10
128.69
126.65
124.55
124.00
122.28
119.18
116.15
115.93
65.43
65.07
64.73
64.34
F
O
N
CF3
7c
13C NMR (101 MHz, CDCl3)
f1 (ppm)

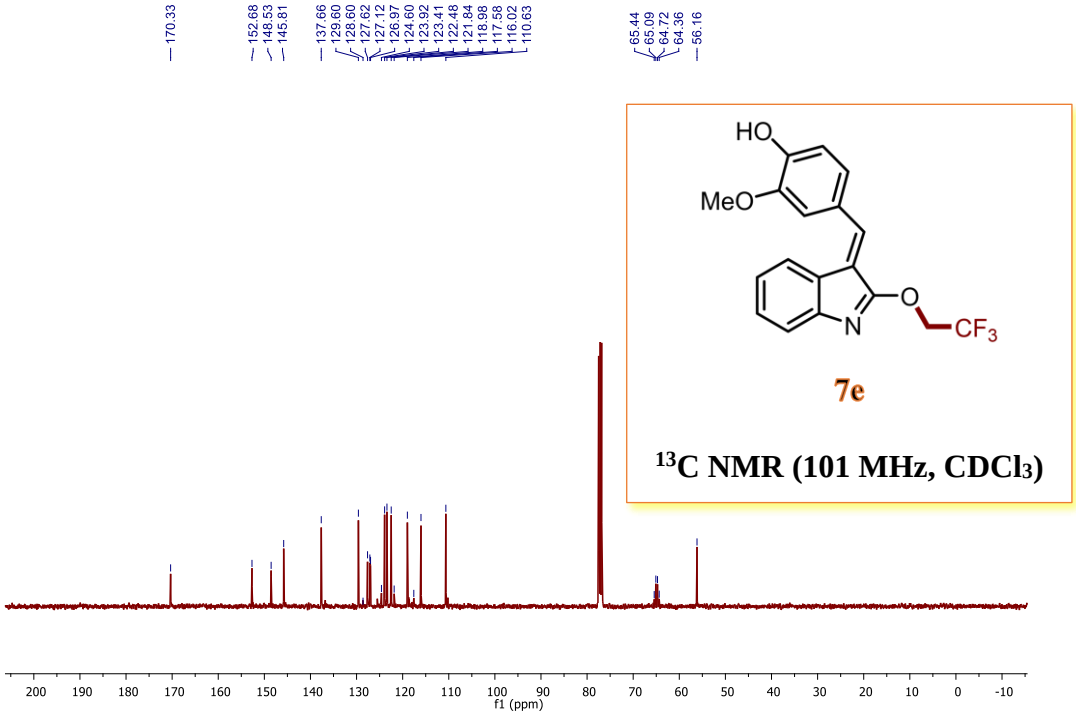

-73.68
-108.90
F
O
N
CF3
7c
19F NMR (376 MHz, CDCl3)
f1 (ppm)

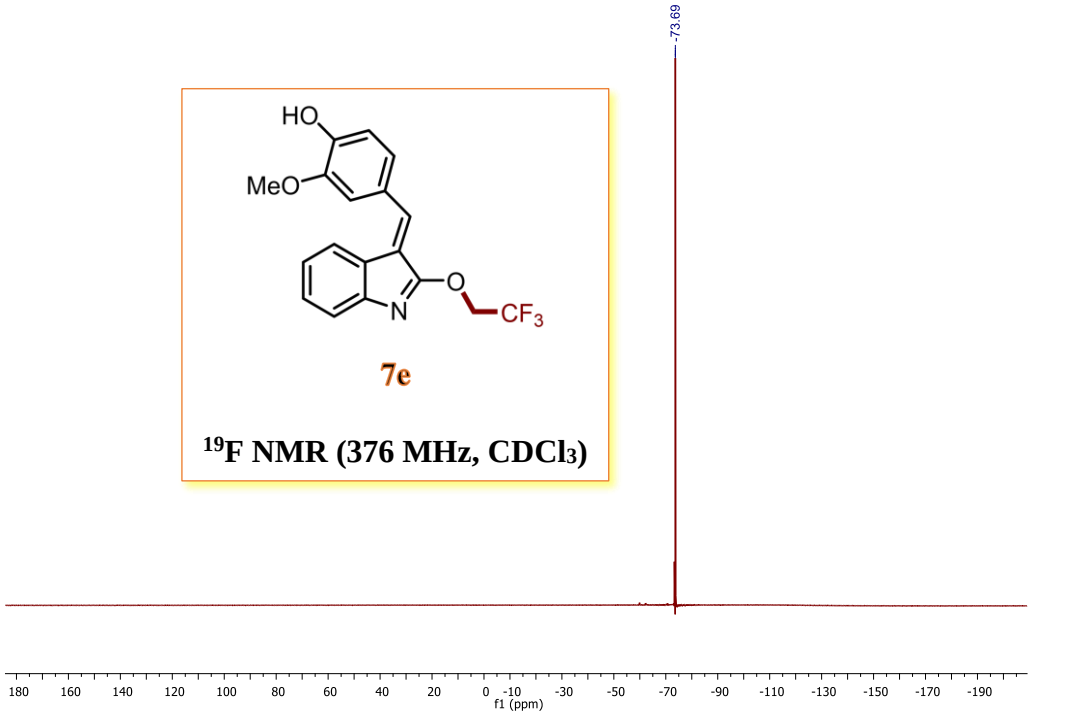

MeO
MeO
O
N
CF3
7d
1H NMR (400 MHz, CDCl3)

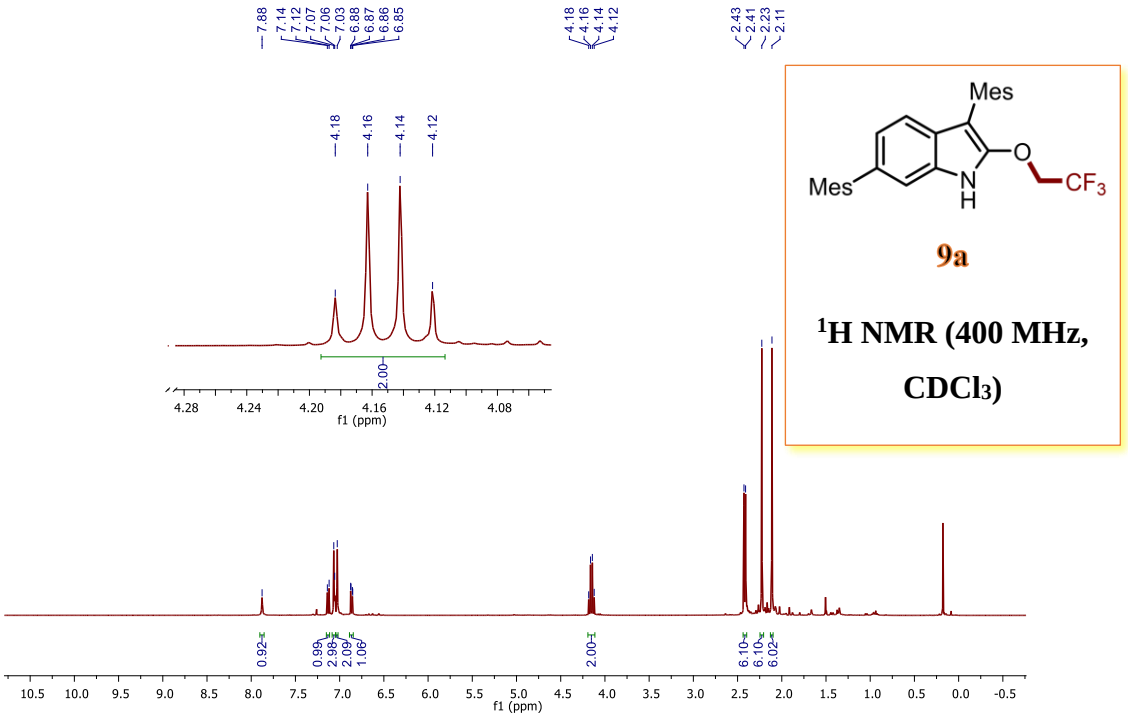

MeO
MeO
O
N
CF3
7d
13C NMR (101 MHz, CDCl3)

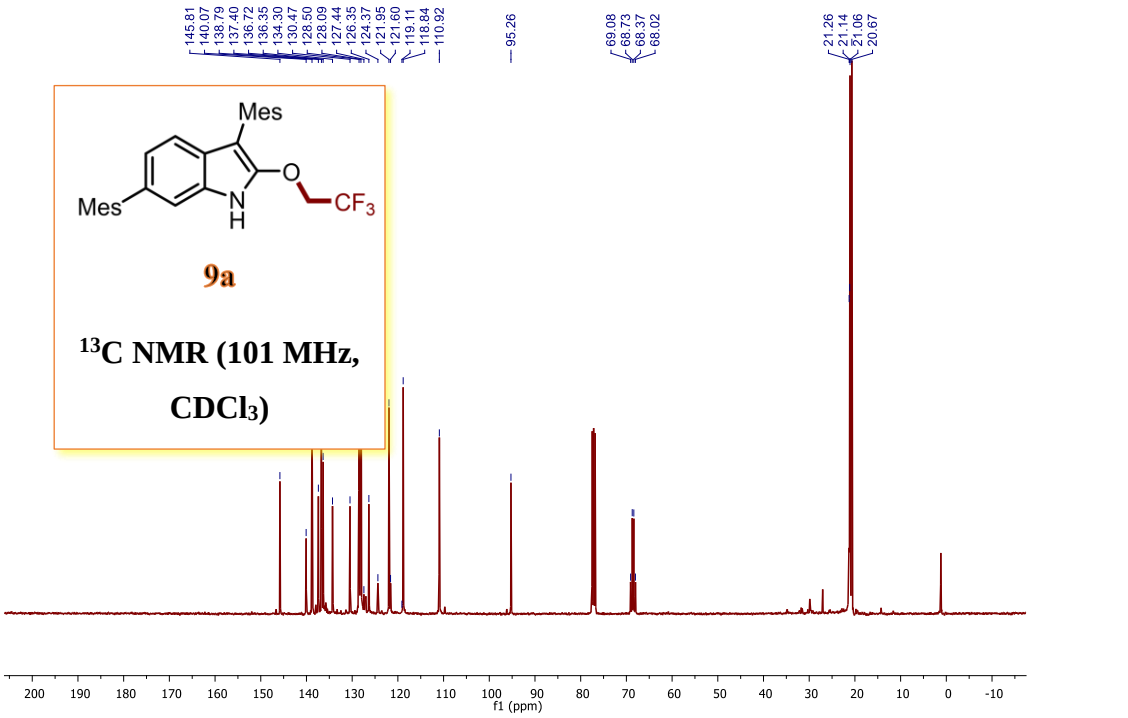

MeO
MeO
O
N
CF3
7d
19F NMR (376 MHz, CDCl3)
-73.74
f1 (ppm)


7.81
7.79
7.59
7.59
7.32
7.32
7.31
7.31
7.29
7.29
7.27
7.25
7.25
7.24
7.23
7.02
7.02
7.00
7.00
6.98
6.98
6.96
6.94
5.86
4.91
4.89
4.87
4.85
3.98
2.00
f1 (ppm)
HO
MeO
O
N
CF3
7e
1H NMR (400 MHz, CDCl3)
0.88
0.86
4.02
1.89
0.88
2.00
3.13
f1 (ppm)


170.33
152.68
148.53
145.81
137.66
129.60
128.60
127.62
127.12
126.97
124.60
123.92
123.41
122.48
121.84
118.98
117.58
116.02
110.63
65.44
65.09
64.72
64.36
56.16
HO
MeO
O
N
CF3
7e
13C NMR (101 MHz, CDCl3)
f1 (ppm)

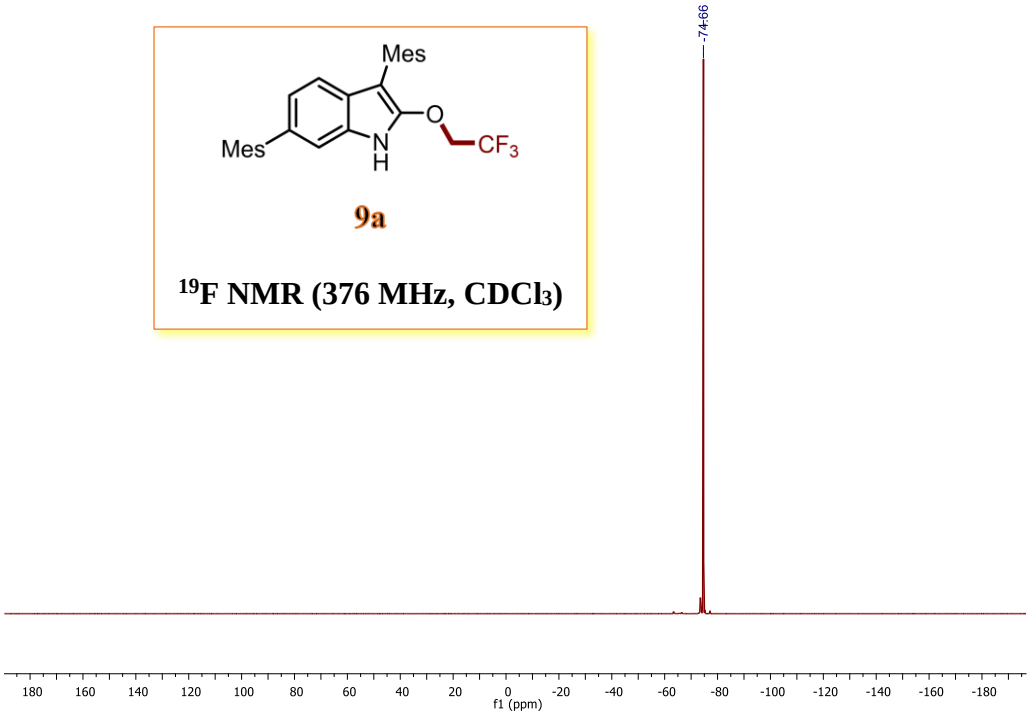

-73.69
HO
MeO
O
N
CF3
7e
19F NMR (376 MHz, CDCl3)
f1 (ppm)

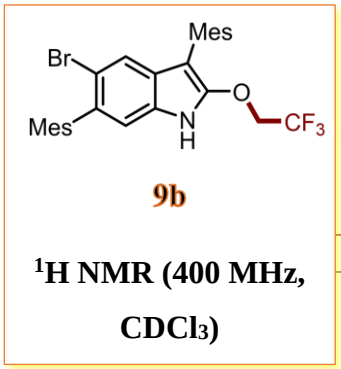

Mes
Mes
O
CF3
N
H
9a
1H NMR (400 MHz, CDCl3)


Mes
Mes
O
CF3
N
H
9a
13C NMR (101 MHz, CDCl3)

9a

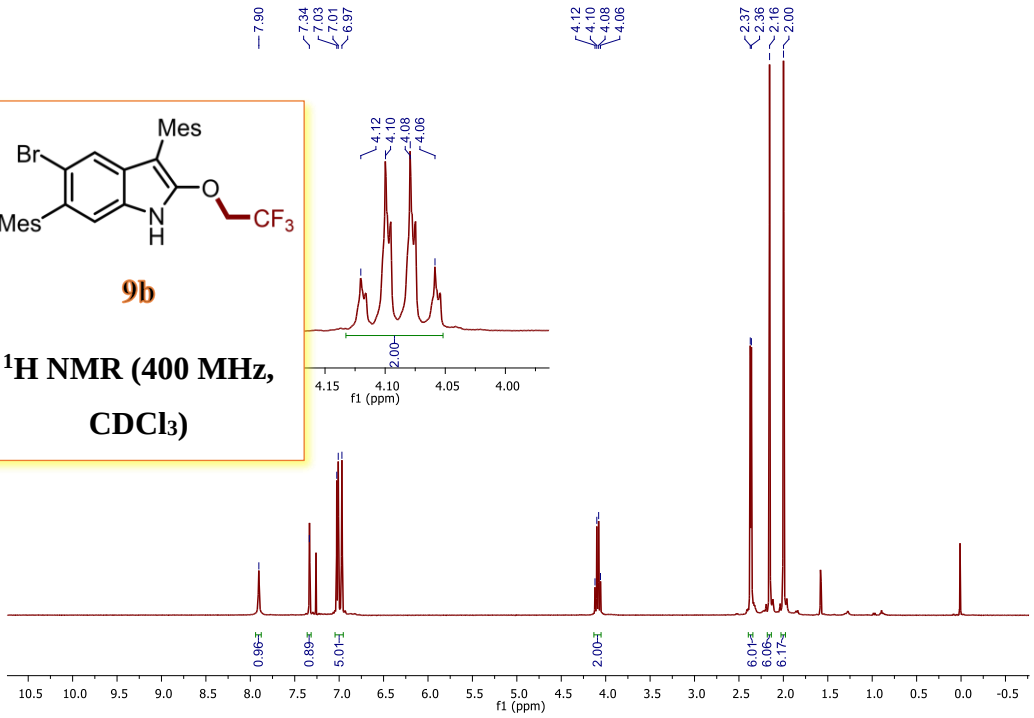
^{19}F NMR (376 MHz, $CDCl_3$)

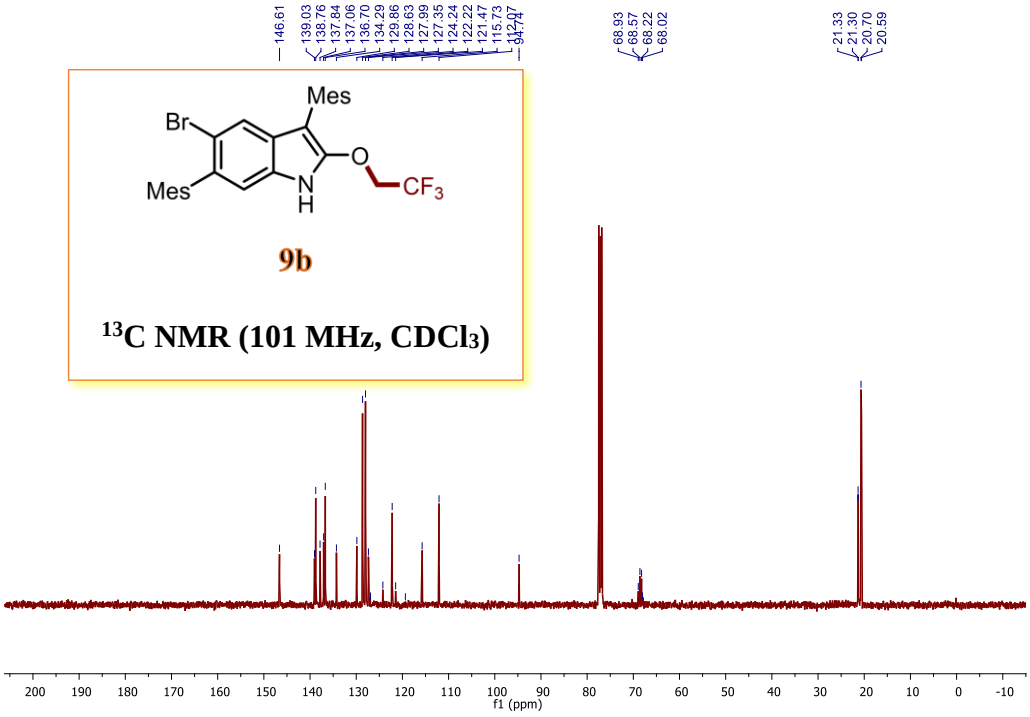


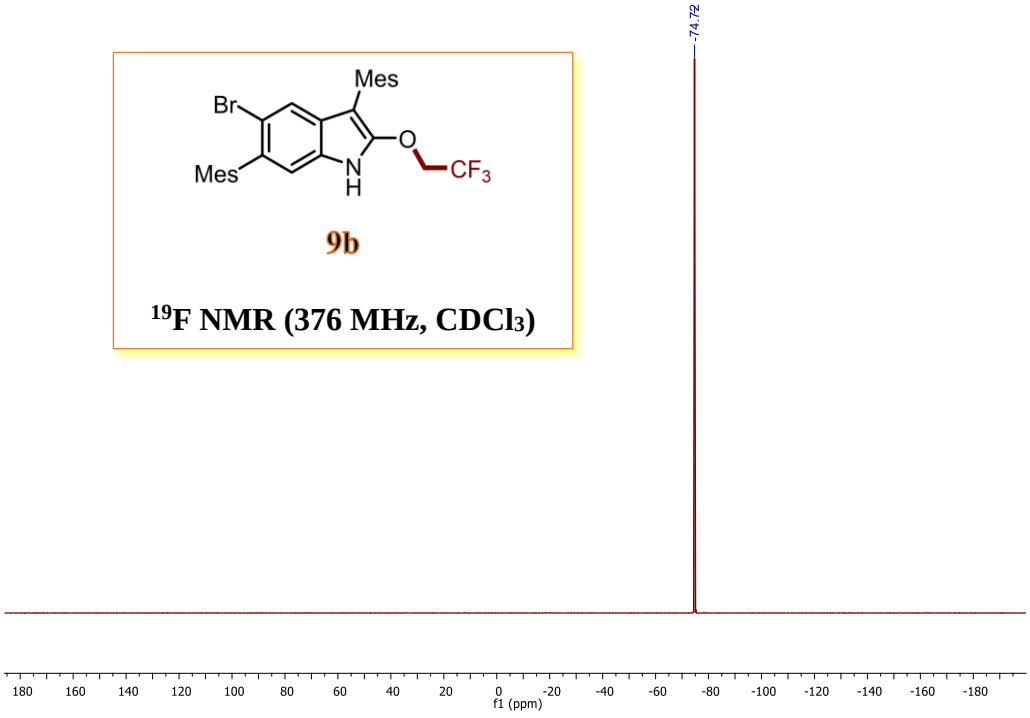


9b

^{1}H NMR (400 MHz, $CDCl_3$)




146.61
139.03
138.76
137.84
137.06
136.70
134.29
129.86
128.63
127.99
127.35
124.24
122.22
121.47
115.73
112.07
94.74
68.93
68.57
68.22
68.02
21.33
21.30
20.70
20.59
Mes
Br
Mes
O
CF3
N
H
9b
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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Br
Mes
O
CF3
N
H
9b
19F NMR (376 MHz, CDCl3)
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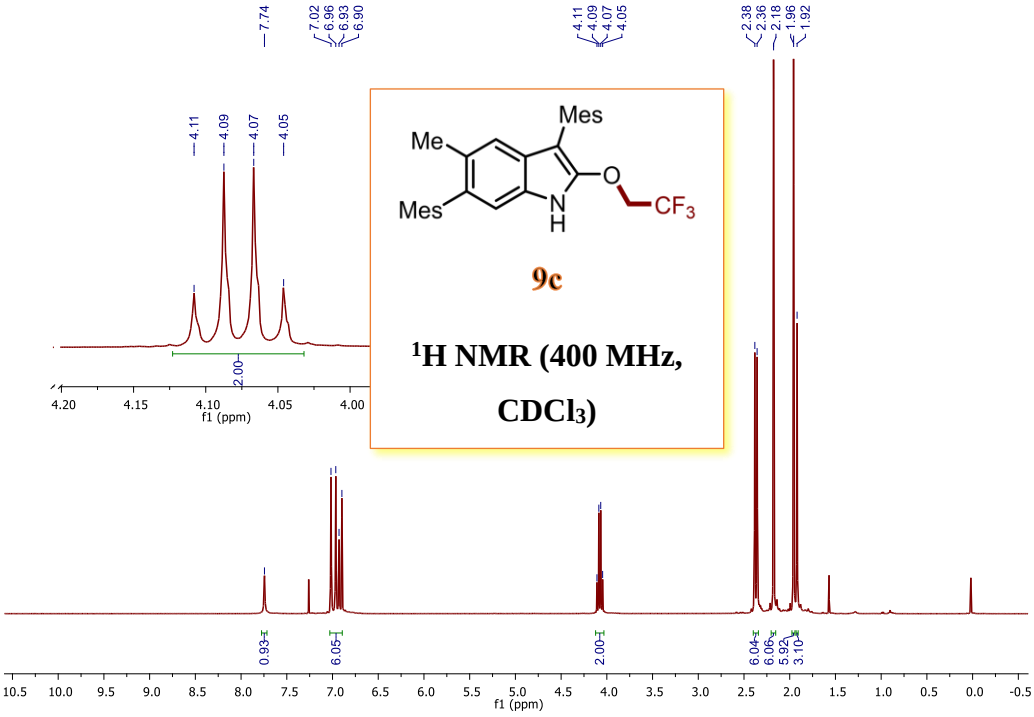
f1 (ppm)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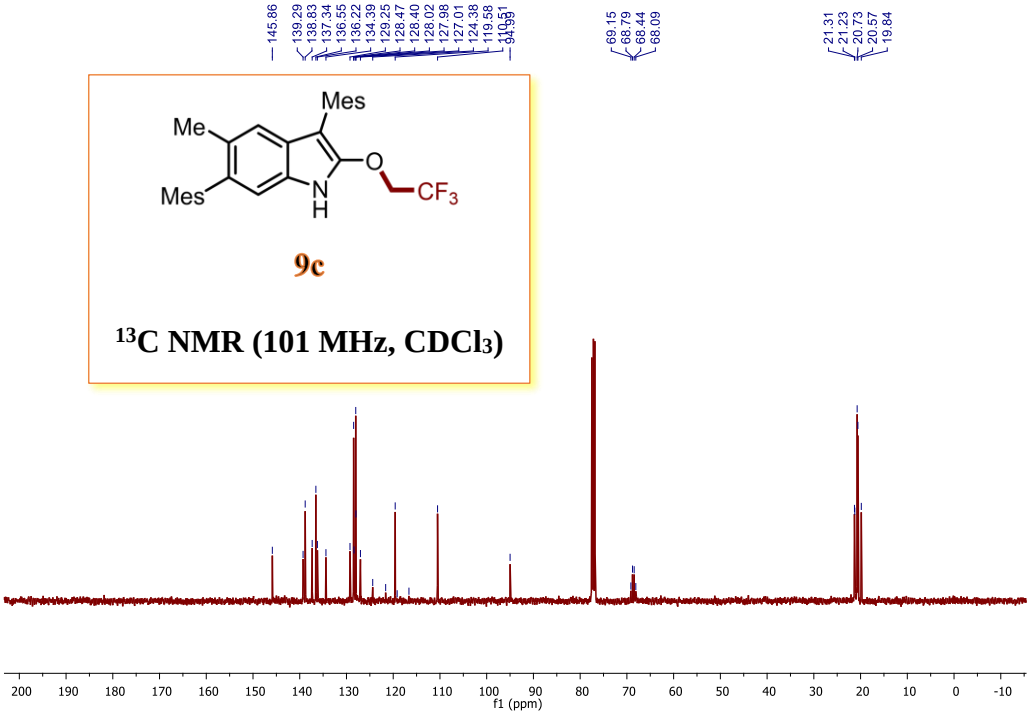
Me
Mes
O
CF3
N
H
9c
1H NMR (400 MHz, CDCl3)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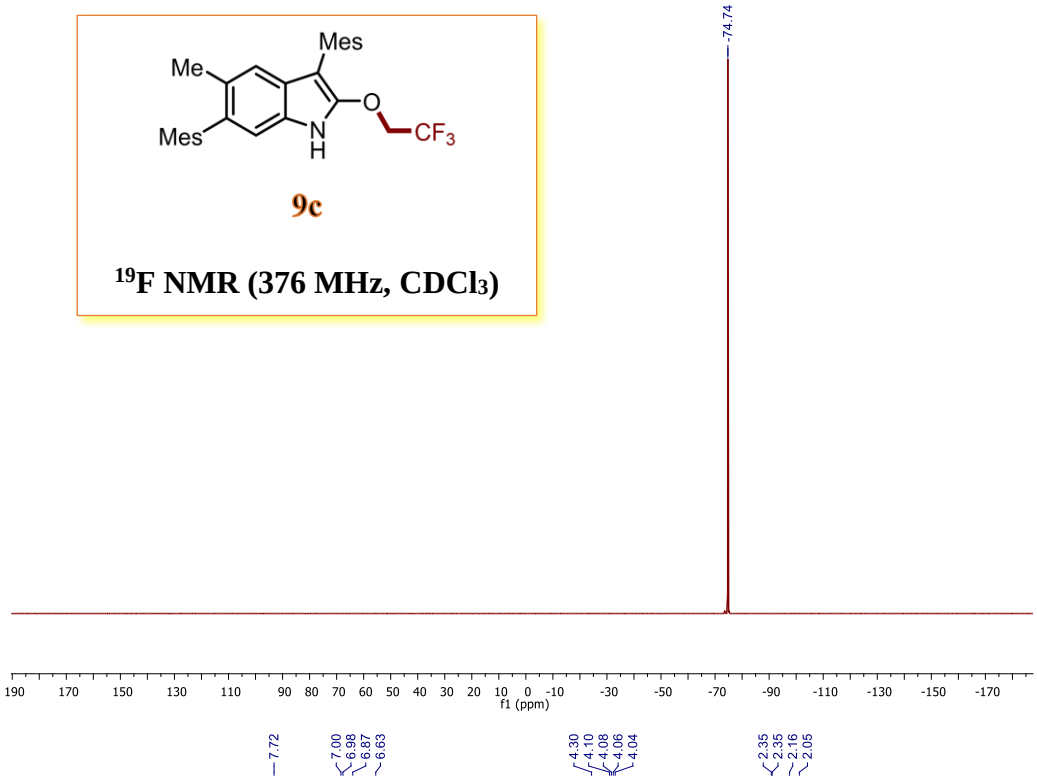
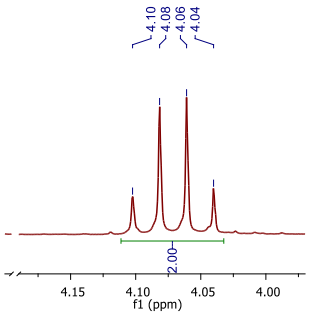
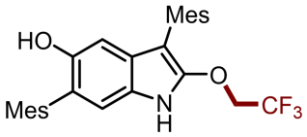
Me
Mes
O
CF3
N
H
9c
13C NMR (101 MHz, CDCl3)

9c

^{19}F NMR (376 MHz, $CDCl_3$)

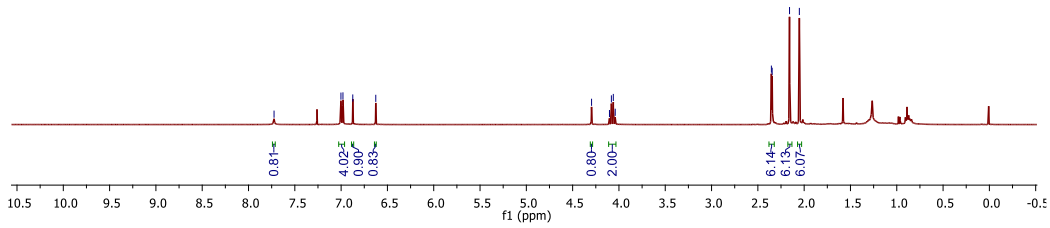


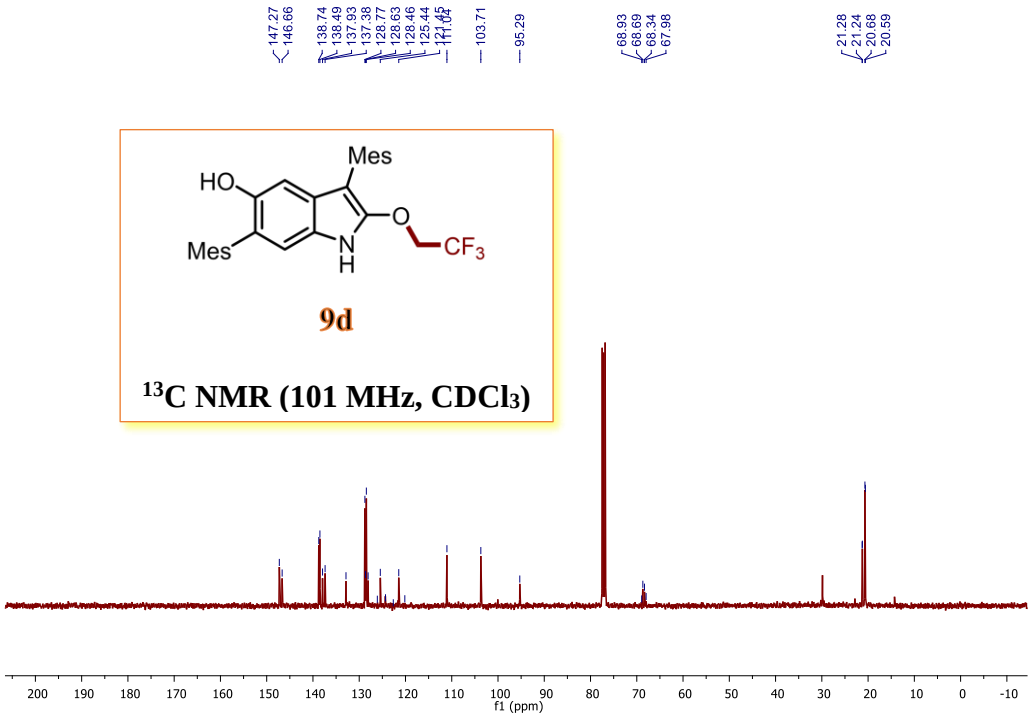




9d

^{1}H NMR (400 MHz, $CDCl_3$)

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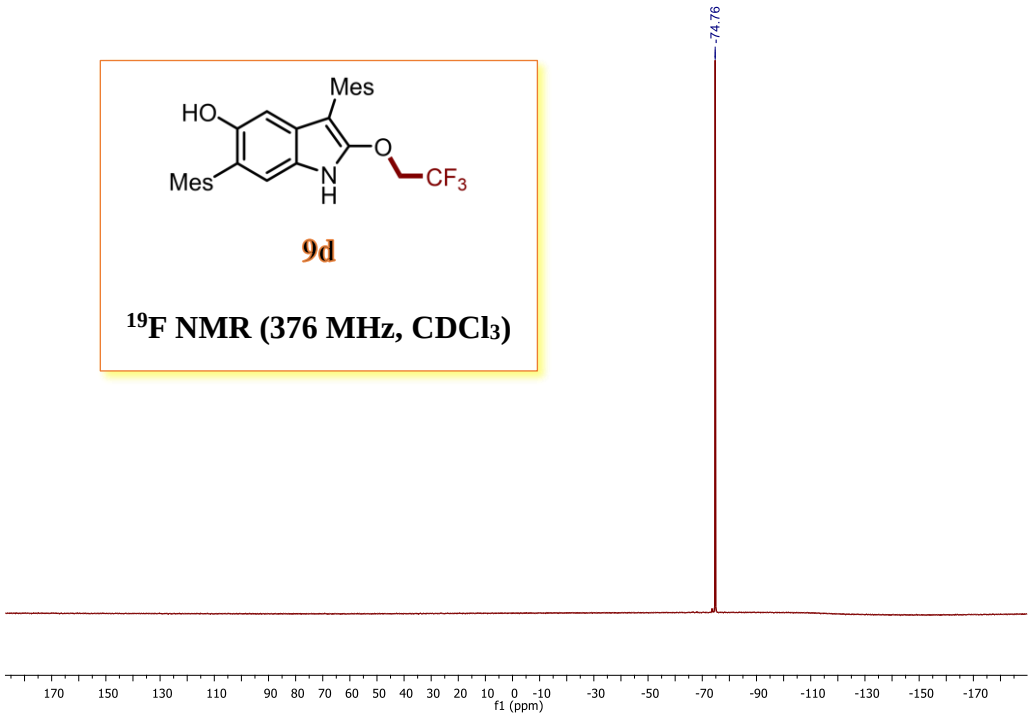
138.49
137.93
137.38
128.77
128.63
128.46
125.44
103.71
95.29
68.93
68.69
68.34
67.98
21.28
21.24
20.68
20.59
HO
Mes
Mes
O
CF3
N
H
9d
13C NMR (101 MHz, CDCl3)
f1 (ppm)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Mes
Mes
O
CF3
N
H
9d
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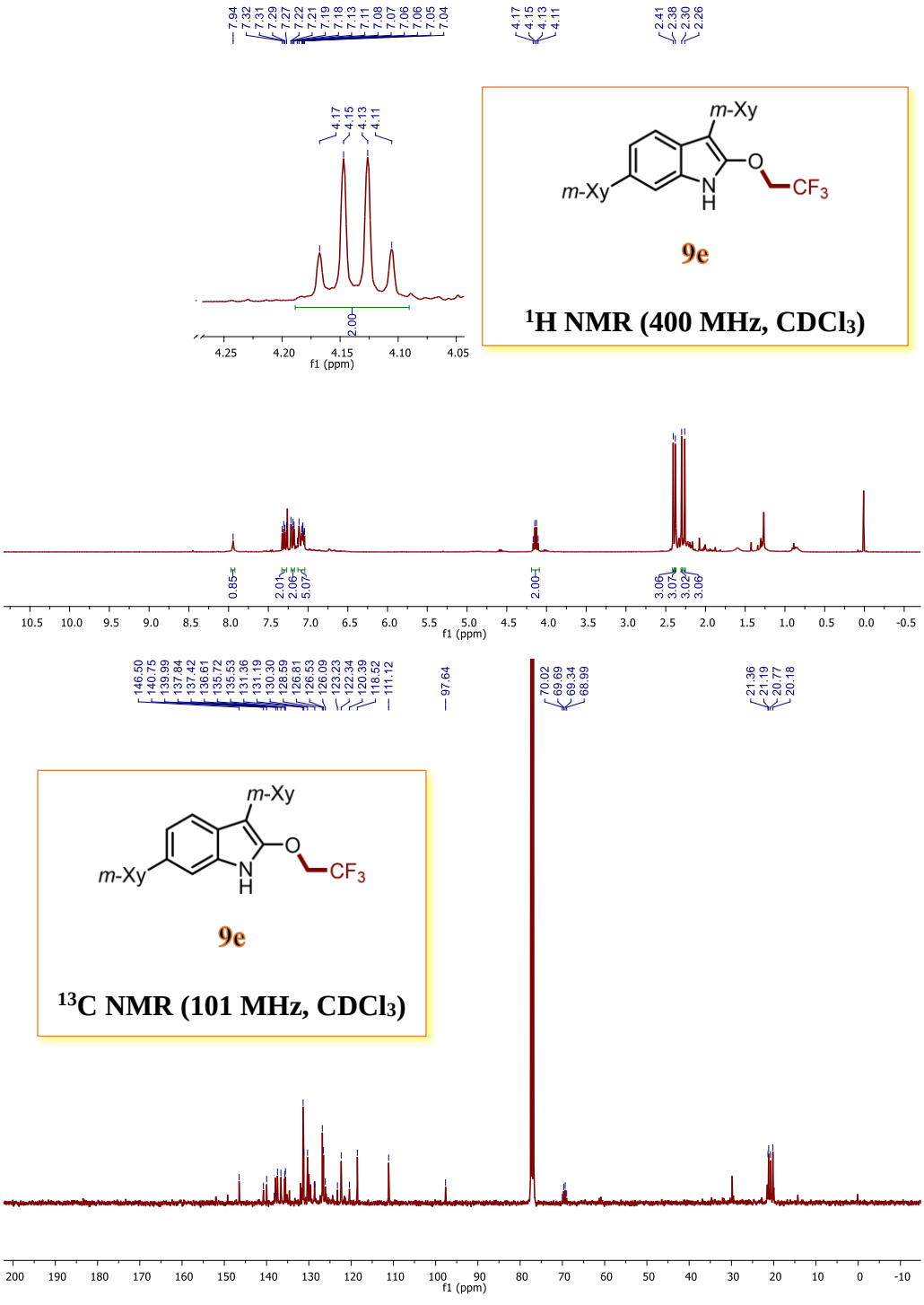
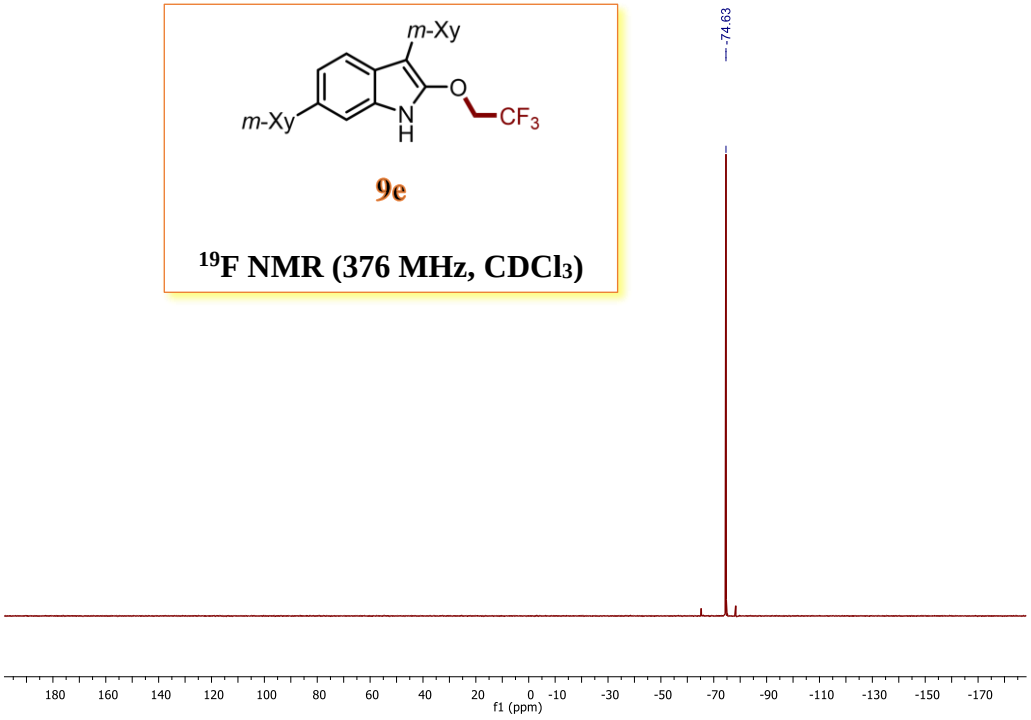
f1 (ppm)


9e
^{1}H NMR (400 MHz, CDCl$_3$)
9e
^{13}C NMR (101 MHz, CDCl$_3$)

9e

^{19}F NMR (376 MHz, $CDCl_3$)



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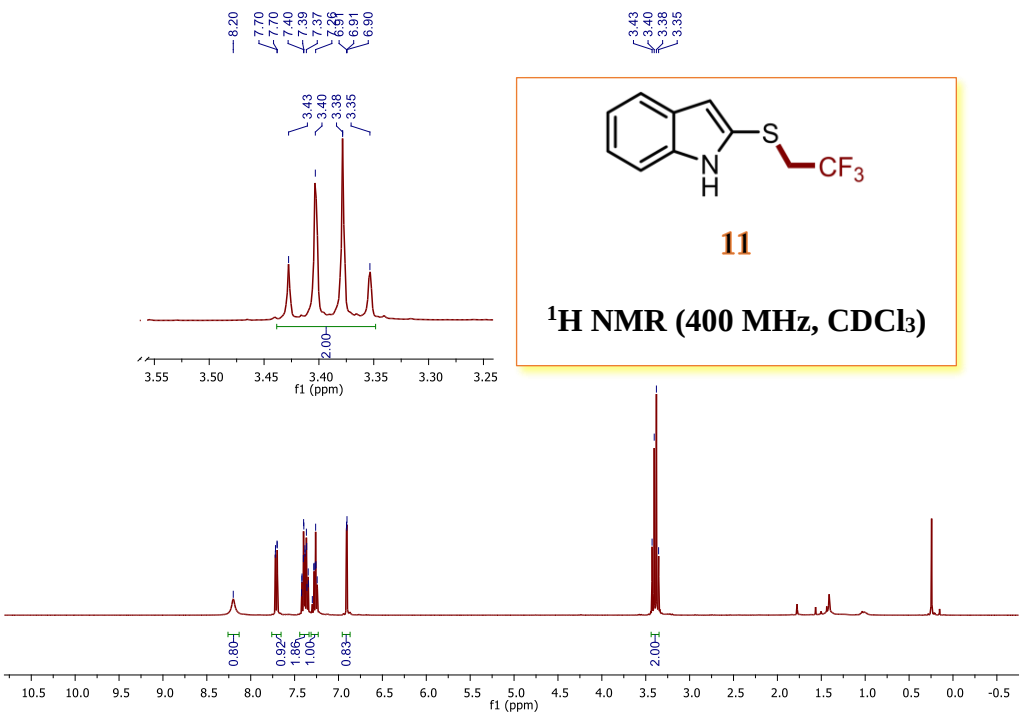

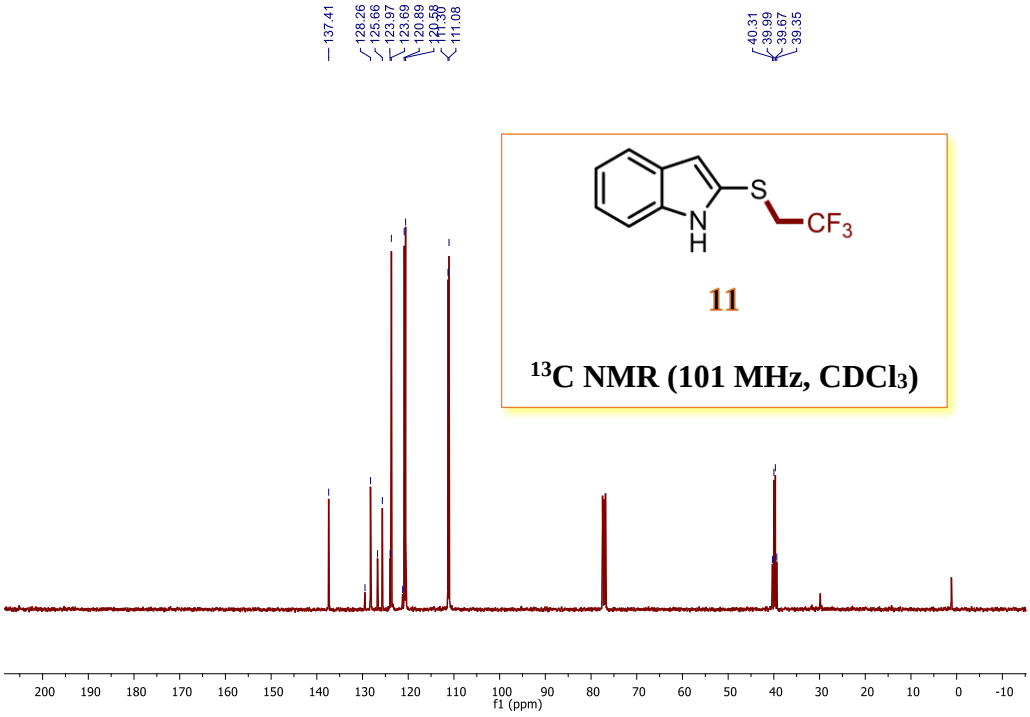
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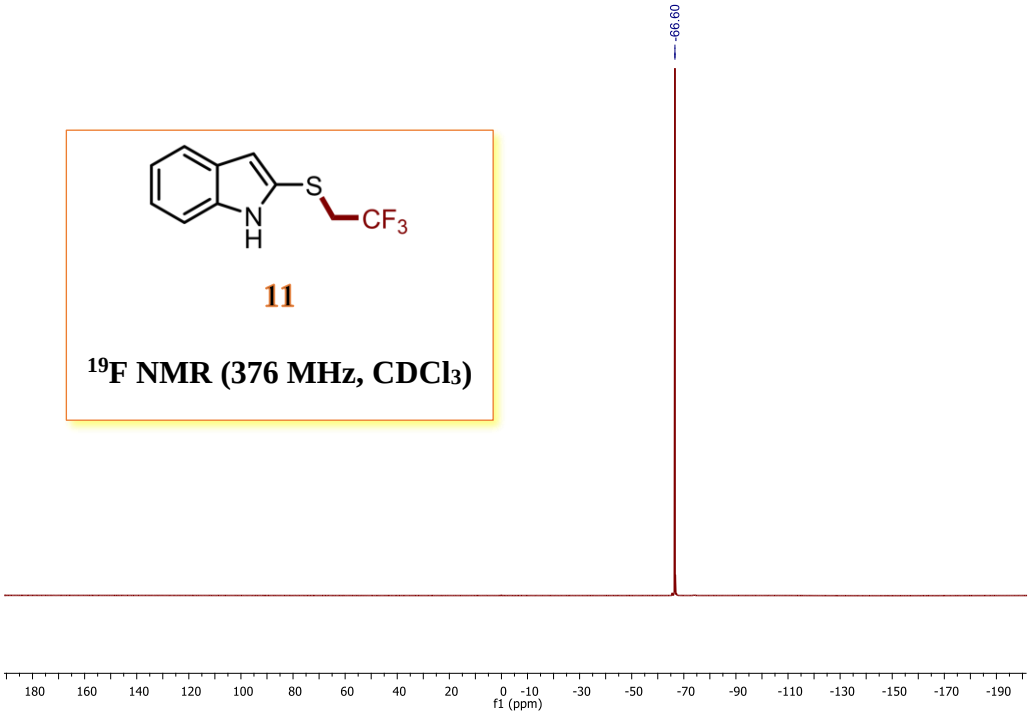
128.26
125.66
123.97
123.69
120.89
111.30
111.08
40.31
39.99
39.67
39.35
S
N
H
CF3
11
13C NMR (101 MHz, CDCl3)
f1 (ppm)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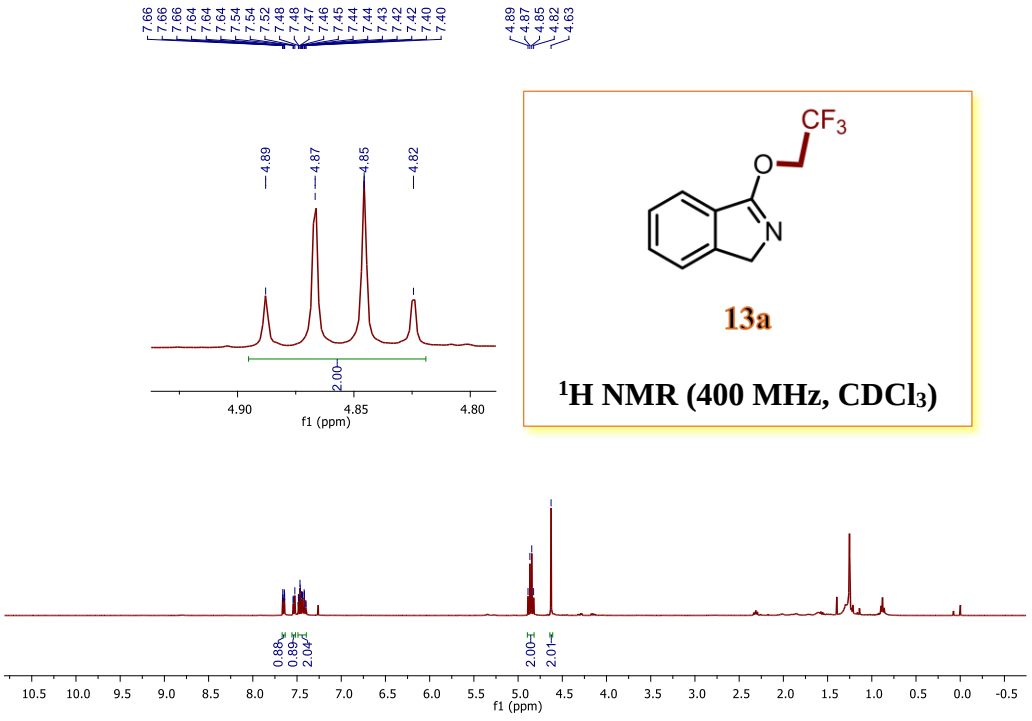
S
N
H
CF3
11
19F NMR (376 MHz, CDCl3)
f1 (ppm)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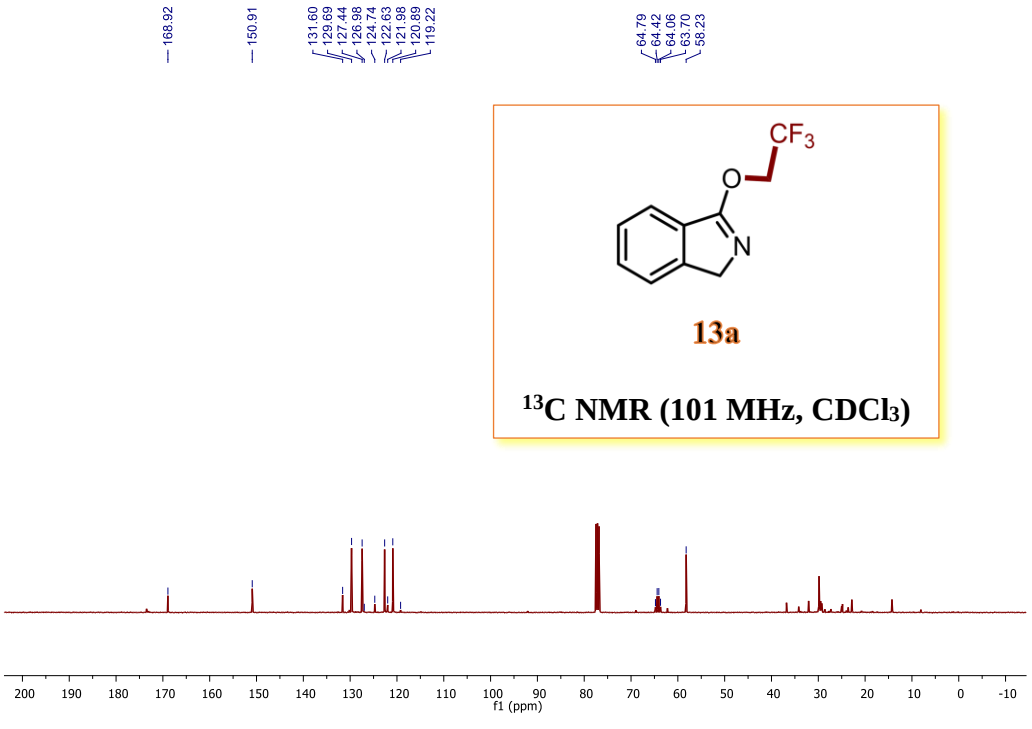
7.66
7.66
7.64
7.64
7.64
7.54
7.54
7.52
7.48
7.48
7.47
7.46
7.45
7.44
7.44
7.43
7.42
7.42
7.40
7.40
4.89
4.87
4.85
4.82
4.63
4.89
4.87
4.85
4.82
2.00
4.90
4.85
4.80
f1 (ppm)
CF3
O
N
13a
1H NMR (400 MHz, CDCl3)
0.88
0.89
2.04
2.00
2.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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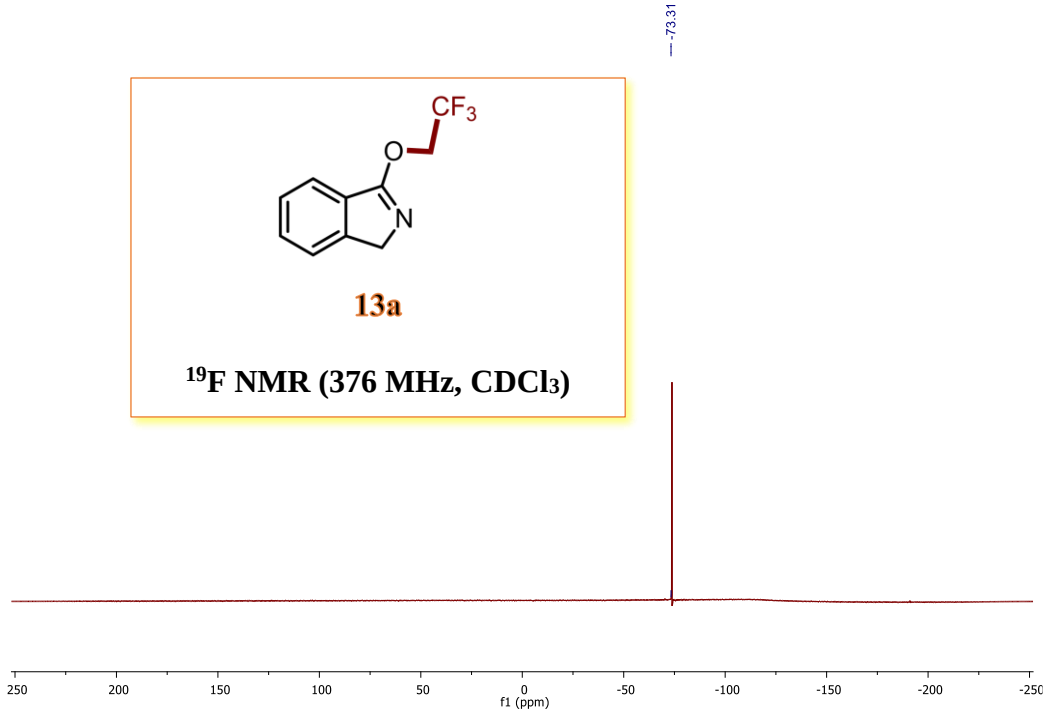
150.91
131.60
129.69
127.44
126.98
124.74
122.63
121.98
120.89
119.22
64.79
64.42
64.06
63.70
58.23
CF3
O
N
13a
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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CF3
O
N
13a
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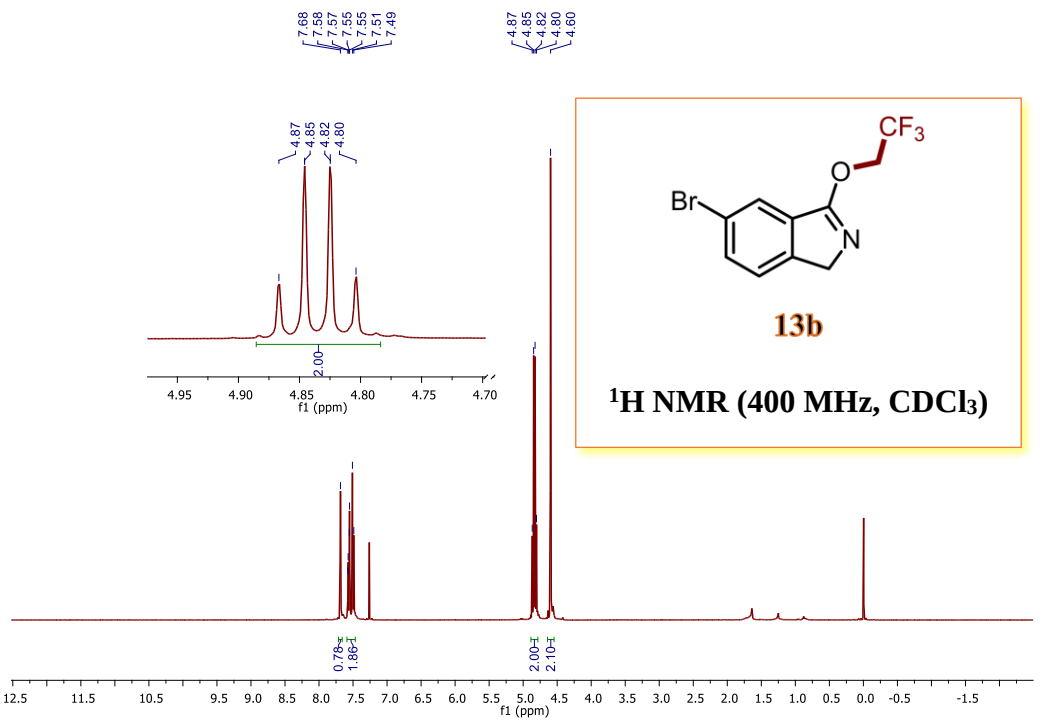
200
150
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)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7.55
7.55
7.51
7.49
4.87
4.85
4.82
4.80
4.60
4.87
4.85
4.82
4.80
2.00
4.95
4.90
4.85
4.80
4.75
4.70
f1 (ppm)
CF3
O
Br
N
13b
1H NMR (400 MHz, CDCl3)
0.78
1.86
2.00
2.10
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
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0.0
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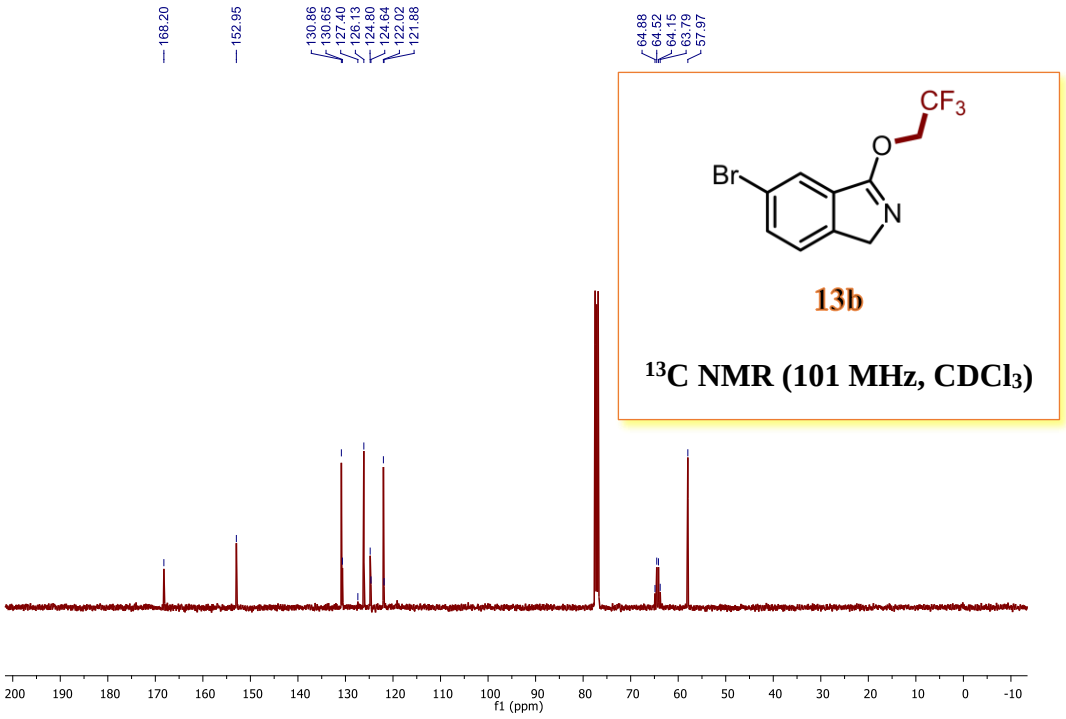
-1.5
f1 (ppm)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126.13
124.80
124.64
122.02
121.88
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63.79
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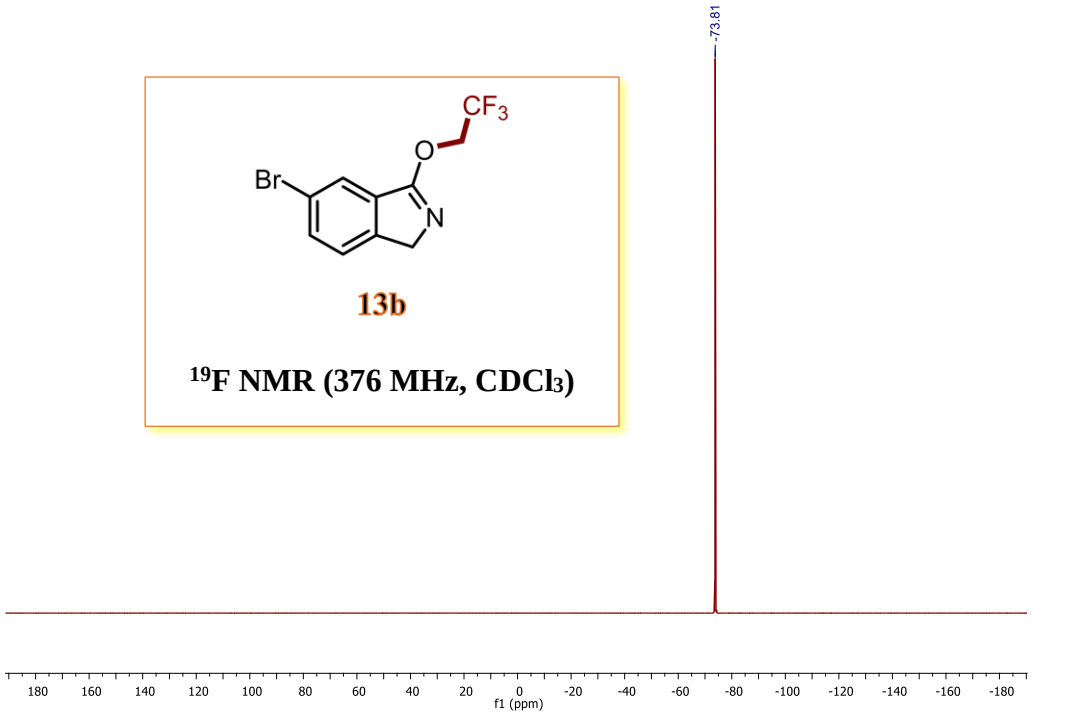
CF3
O
Br
N
13b
13C NMR (101 MHz, CDCl3)
f1 (ppm)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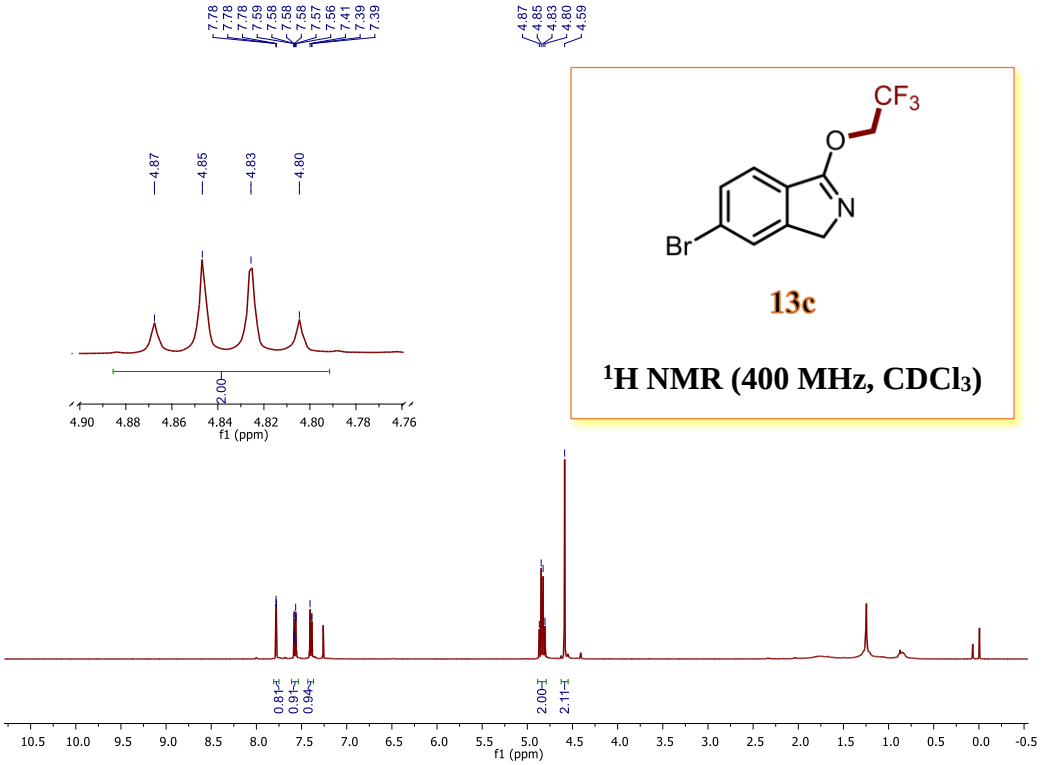
O
Br
N
13b
19F NMR (376 MHz, CDCl3)
f1 (ppm)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7.78
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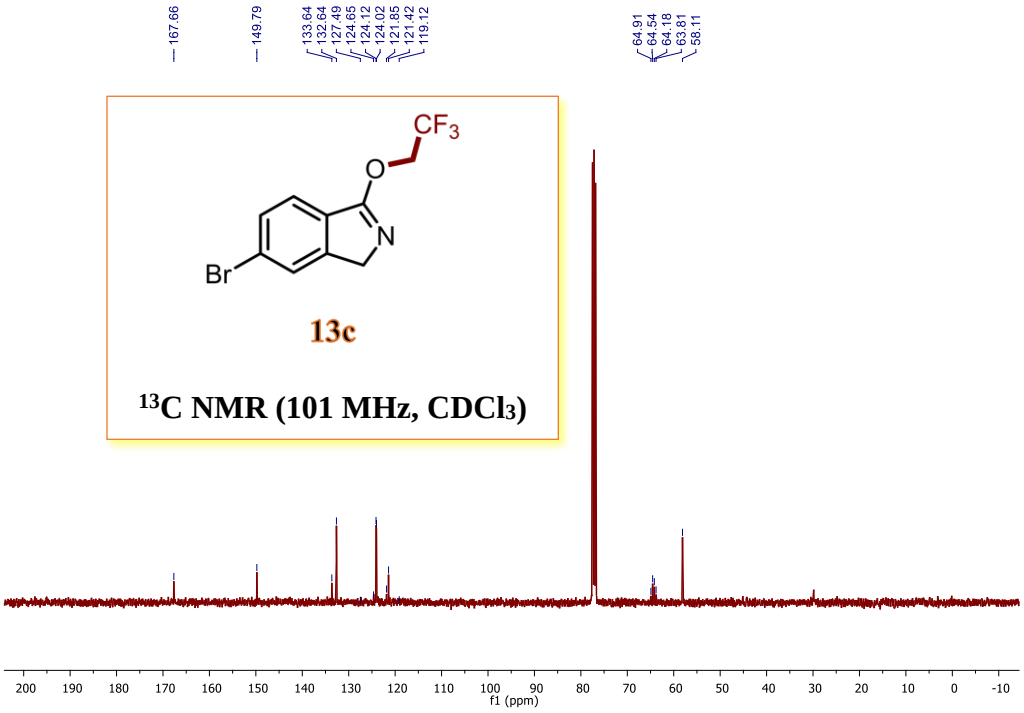
7.58
7.58
7.58
7.57
7.56
7.41
7.39
7.39
4.87
4.85
4.83
4.80
4.59
4.87
4.85
4.83
4.80
2.00
4.90 4.88 4.86 4.84 4.82 4.80 4.78 4.76
f1 (ppm)
CF3
O
N
Br
13c
1H NMR (400 MHz, CDCl3)
0.81
0.91
0.94
2.00
2.11
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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127.49
124.65
124.12
124.02
121.85
121.42
119.12
64.91
64.54
64.18
63.81
58.11
CF3
O
N
Br
13c
13C NMR (101 MHz, CDCl3)
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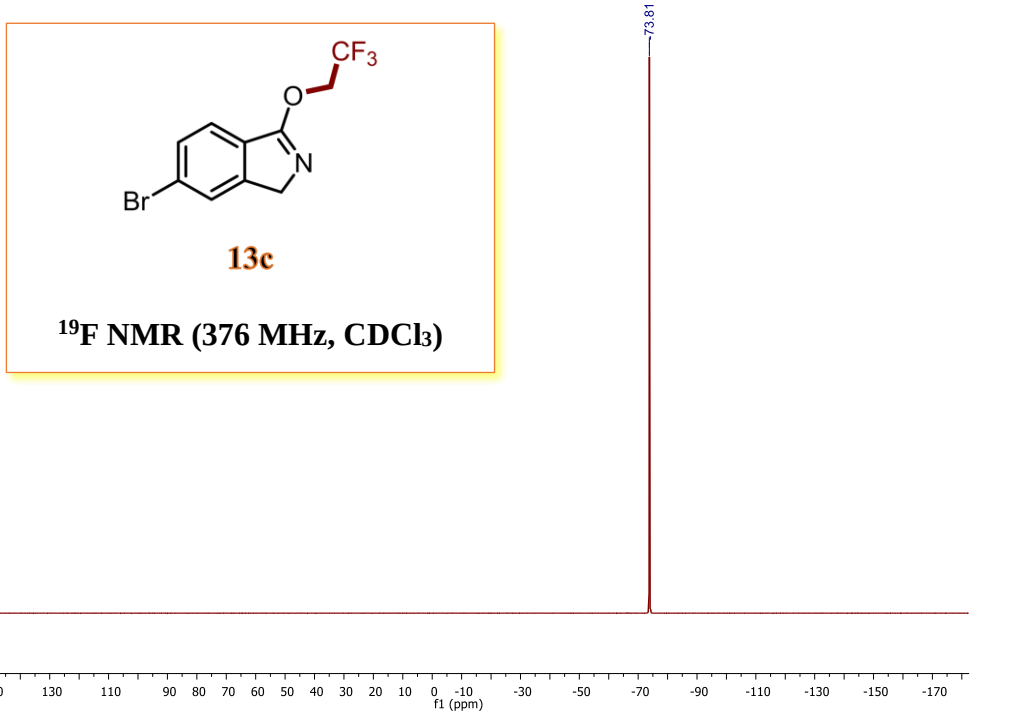
f1 (ppm)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N
Br
13c
19F NMR (376 MHz, CDCl3)
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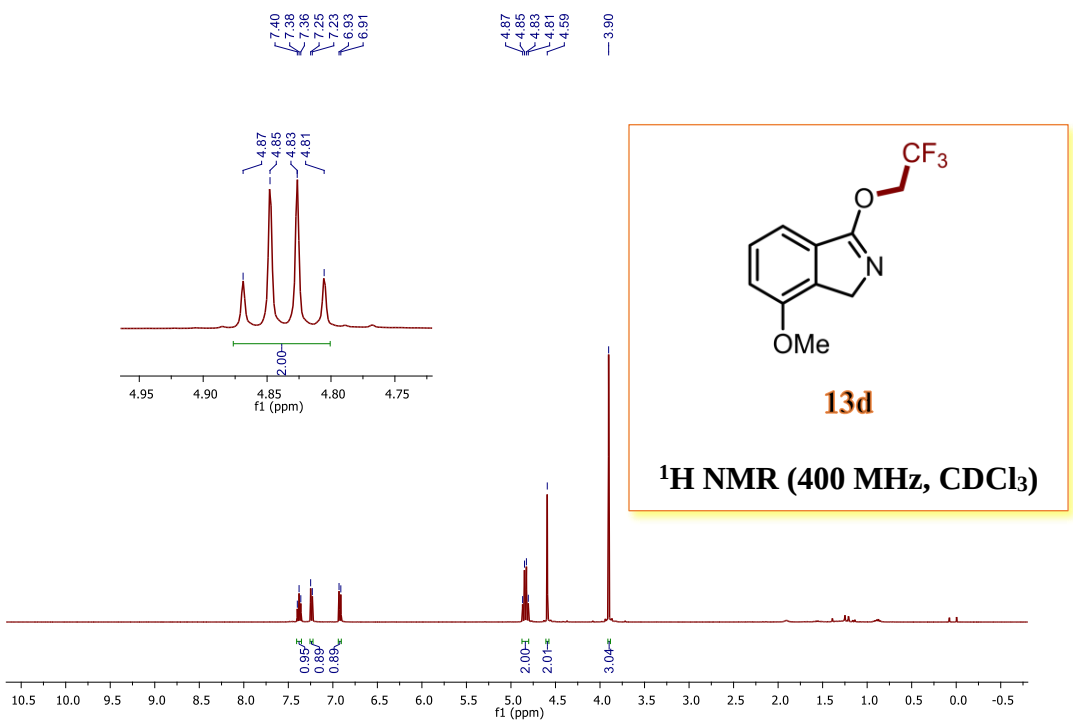
f1 (ppm)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7.38
7.36
7.25
7.23
6.93
6.91
4.87
4.85
4.83
4.81
4.59
3.90
2.00
f1 (ppm)
CF3
O
N
OMe
13d
1H NMR (400 MHz, CDCl3)
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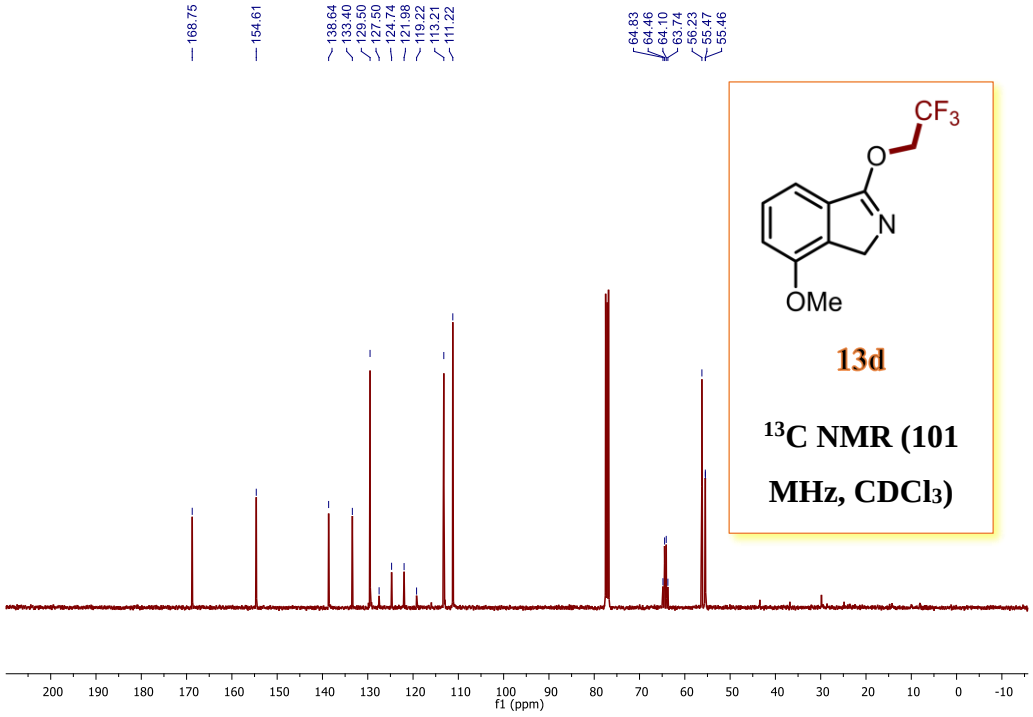
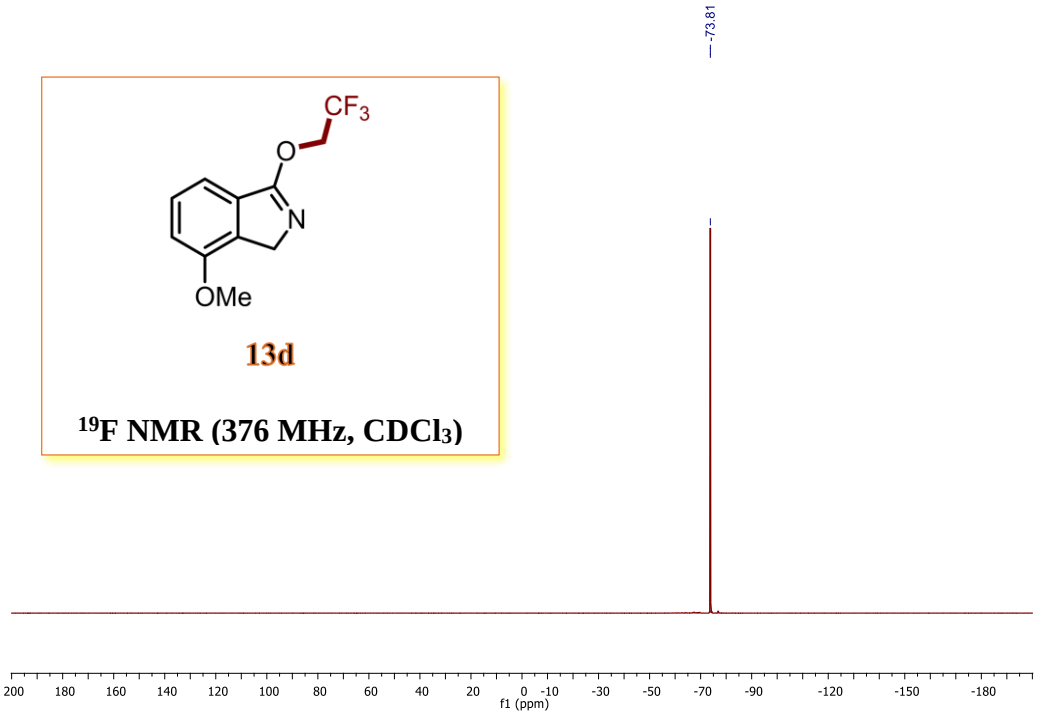
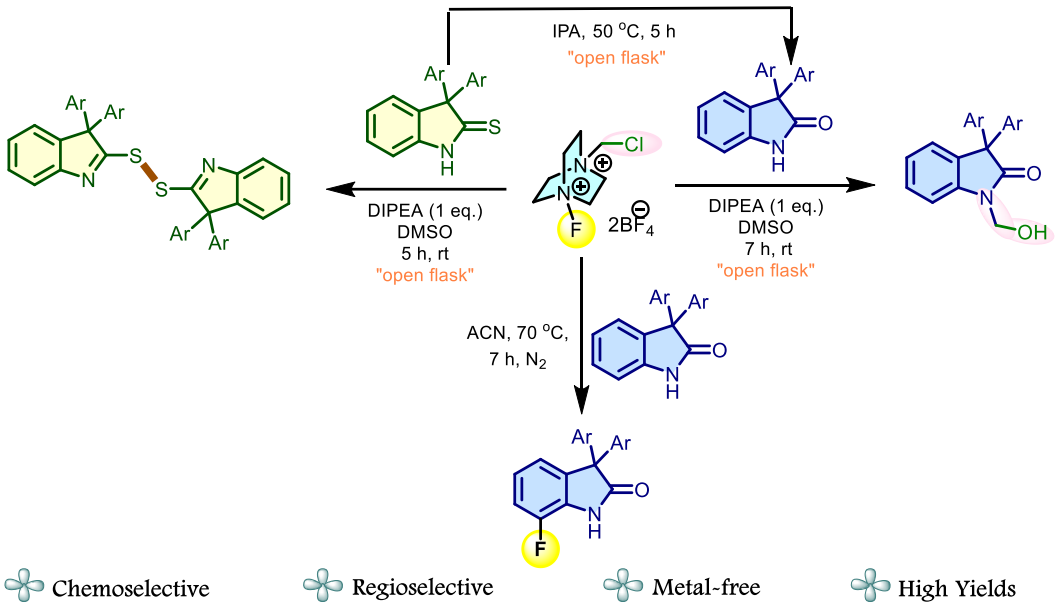
0.89
0.89
2.00
2.01
3.04
f1 (ppm)


168.75
154.61
138.64
133.40
129.50
127.50
124.74
121.98
119.22
113.21
111.22
64.83
64.46
64.10
63.74
56.23
55.47
55.46
CF3
O
N
OMe
13d
13C NMR (101 MHz, CDCl3)
f1 (ppm)


-73.81
CF3
O
N
OMe
13d
19F NMR (376 MHz, CDCl3)
f1 (ppm)

Chapter 4

Chemo- and Regioselective Reactions of Oxindoles and Thio-oxindoles with Selectfluor



4.1 Introduction

After exploring the C5-, N-, and O-center of oxindole in the previous chapters, here, I will focus on the C7 functionalization of oxindole and the formation of dithianes from thio-oxindole. The 3,3-diaryloxindole scaffolds are highly versatile and promising pharmacophoric constructs, potentially exhibiting a broad range of biological activities. Many researchers have focused on the synthesis and functionalization of 3,3-diarylated-2-oxindole derivatives, as these compounds have shown remarkable antioxidant, anticancer, mineralocorticoid receptor antagonist, and calcium-depleting translation initiation inhibitory activities, among others (Figure 4.1).[1] However, despite the significant progress made in the field, the methodologies specifically targeted toward the functionalization of 3,3-diaryloxindoles are still relatively few, inducing little access to the structural heterogeneity around this moiety.[2]

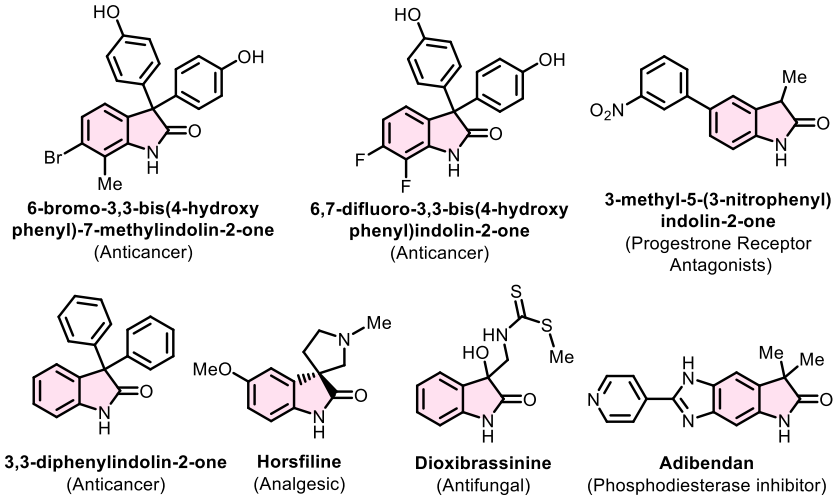


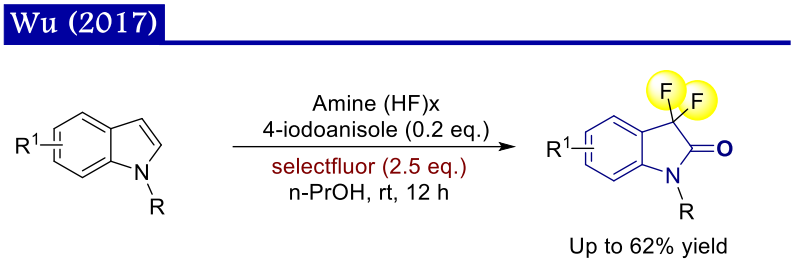
Figure 4.1. Biologically active oxindole-containing compounds.

Similarly, their sulfur analogs like thioamides, thioxindoles, and thioimidates are a group of organic compounds known to have significant biological and chemical applications. The

indole motifs bearing C2-thioether or disulfane scaffolds have potential applications as anti-cancer, anti-HIV, anti-bacterial, and anti-inflammatory agents. Despite being less investigated from synthetic perspectives, these motifs have shown promising results.[3] Due to their biological activity, these compounds are used as drugs or plant protection agents. They are also used as vulcanization and flotation agents, where they are added to the mineral slurries to improve the separation of minerals from ores. Additionally, they are utilized as additives to greases and lubricating oils to enhance their lubrication properties. These sulfur analogs are also known to be interesting and useful ligands in coordination chemistry, where they act as binding agents to metal ions in coordination complexes.[4] However, functionalization of oxindoles and thio-oxindoles presents challenges due to their bidentate nucleophilicity, containing carbonyl and N-H or thio-carbonyl and N-H groups, which can lead to side products and chemoselectivity issues. Given the importance of these motifs and the gap in technology, my project aimed to identify an efficient dimerization process capable of producing diverse disulfane-containing indolenines and converting thio-oxindole into oxindoles, N- and C7 functionalization of oxindole.

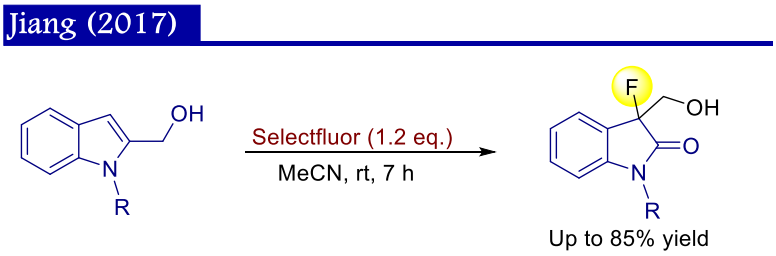
On the other hand, selectfluor (1-(Chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium ditetrafluoroborate) is a remarkable compound that has proven to be an exceptional improvement over traditional electrophilic fluorinating agents. It is a crystalline solid with remarkable stability, is non-hygroscopic and is safe to handle.[5] In the past few decades, there has been a renewed interest in the innovative chemistry of selectfluor. This compound is highly versatile and can be used under different reaction conditions to achieve a variety of unique transformations.[6] Its exceptional stability and versatility make it a valuable tool for synthetic chemists and researchers seeking to achieve complex molecular structures with ease and effectiveness, *viz*., it has been widely used for synthesizing oxindoles. For instance, in 2017, the team led by Wu successfully synthesized 3,3-difluoro-2-oxindoles from indoles by simultaneously difluorinating at the C3 position and oxidizing at the C2 position. They devised a metal-free method that exhibited high

regioselectivity. The C3 difluorination was achieved using $PhIF_2$ and $PhI(OAc)_2$ as the fluorinating agents (Scheme 4.1). They extensively examined the substrate scope, evaluated different substituents at various positions, and harnessed the good yields of the product.[7]



Scheme 4.1: Synthesis of C3 difluorinated oxindoles from indole.

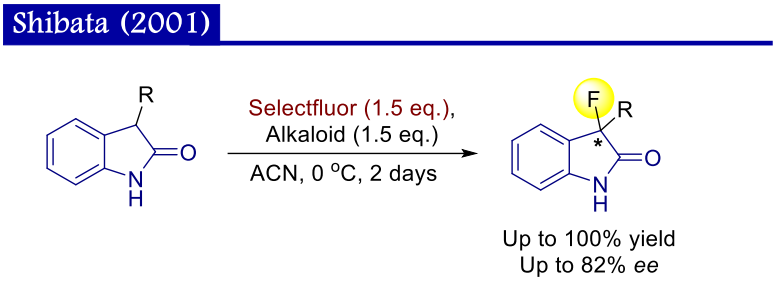
A novel and straightforward method has been devised for producing a wide range of quaternary 3-fluoro-3-hydroxymethyl-2-oxindole derivatives from their respective 2-hydroxymethylindoles (Scheme 4.2). This innovative approach enables the production of various 3-fluorooxindoles with high yields and without the need for a catalyst. Such advancements hold great promise for applications in the fields of synthesis and medicine.[8]



Scheme 4.2: Synthesis of C3 fluorinated oxindoles from 2-hydroxymethylindole.

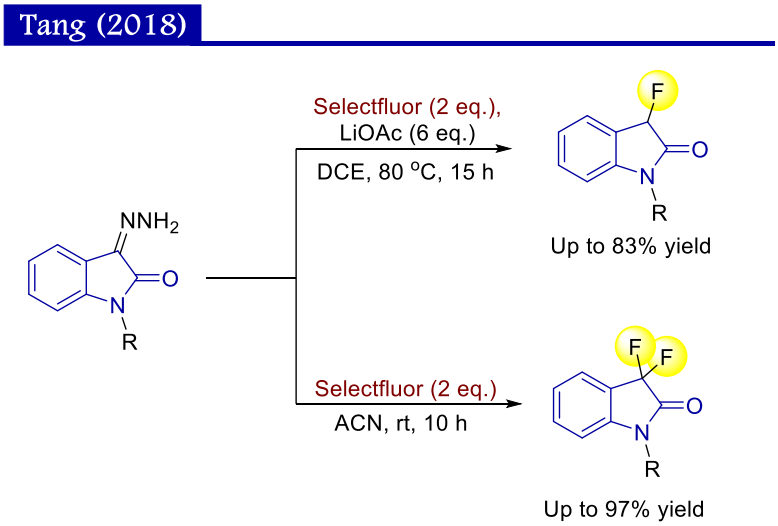
The combination of selectfluor and Cinchona alkaloids has been found to be an efficient method for fluorinating various carbonyl compounds with high enantioselectivity, resulting in the production of chiral R-fluorocarbonyls. For instance, 3-Fluorooxindoles have been prepared with up to 82% *ee* using either the $(DHQD)_2PYR$/Selectfluor or the

$(DHQ)_2AQN$/Selectfluor combination (Scheme 4.3). Furthermore, through ^1H NMR and X-ray crystallography analyses, it has been established that the mediating species for this novel reaction are N-fluoroammonium cinchona alkaloid tetrafluoroborates, which tend to have open conformations.[9]



Scheme 4.3: Synthesis of C3 fluorinated oxindoles from 2-hydroxymethylindole.

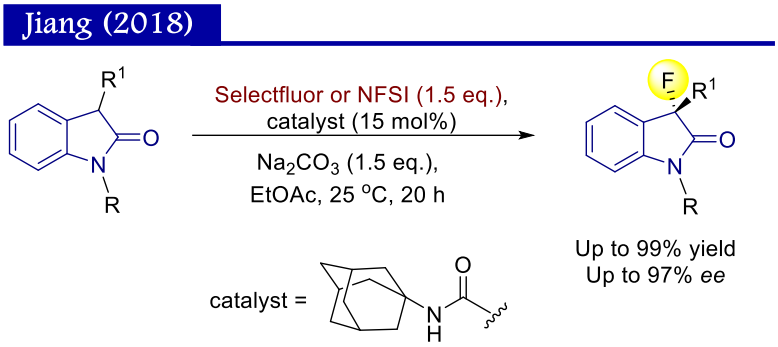
Tang *et al.* have achieved a significant breakthrough by devising an effective method for producing a wide range of C3 difluorinated and monofluorinated indolin-2-ones using selectflour (Scheme 4.4). This approach offers distinct advantages over existing methods



Scheme 4.4: Selective synthesis of C3 difluorinated and C3 monofluorinated oxindoles through solvent effect.

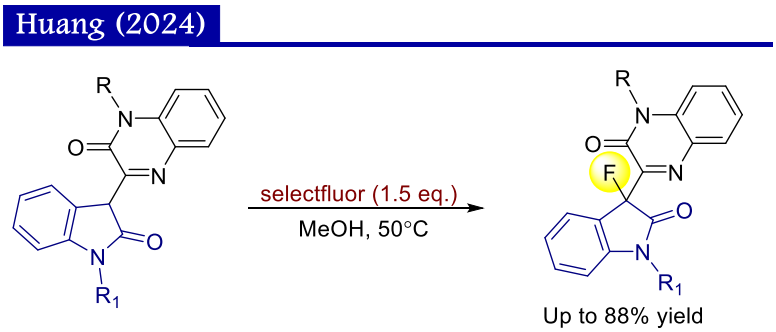
due to its exceptional selectivity and its ability to accommodate a broad range of substrates. The exceptional tolerance for functional groups makes these protocols highly relevant and promising for applications in drug discovery.[10]

Jiang and co-authors developed a highly efficient and selective method for introducing fluorine atoms into 3-substituted 2-oxindoles using a chiral urea catalyst (Scheme 4.5). This method has allowed to synthesize a wide variety of tertiary 3-oxindoles, both with and without N-protection, with high yields and enantioselectivities. The expansion of the range of tertiary 3-fluoro-2-oxindoles has significant implications for biochemists.[11]



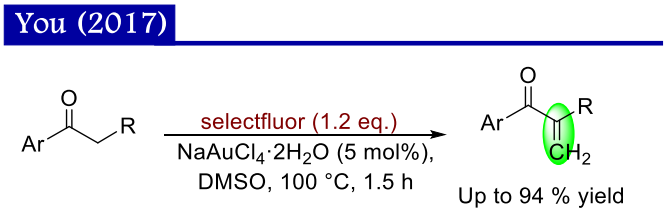
Scheme 4.5: Selective synthesis of C3 fluorination of oxindoles.

Recently, in 2024, Huang *et al.* demonstrated a protocol for the direct addition of fluorine at the C3 position of 3-heteroaryl-oxindoles using selectfluor (Scheme 4.6). This was achieved by testing different solvents and reaction temperatures to produce 3-heteroaryl-3-fluorooxindoles. In this method, selectfluor serves a dual purpose as a source of fluorine and an oxidant. This innovative protocol provides a practical and efficient approach to harnessing variations of the oxindole structure under mild conditions, with yields ranging from medium to good.[12]



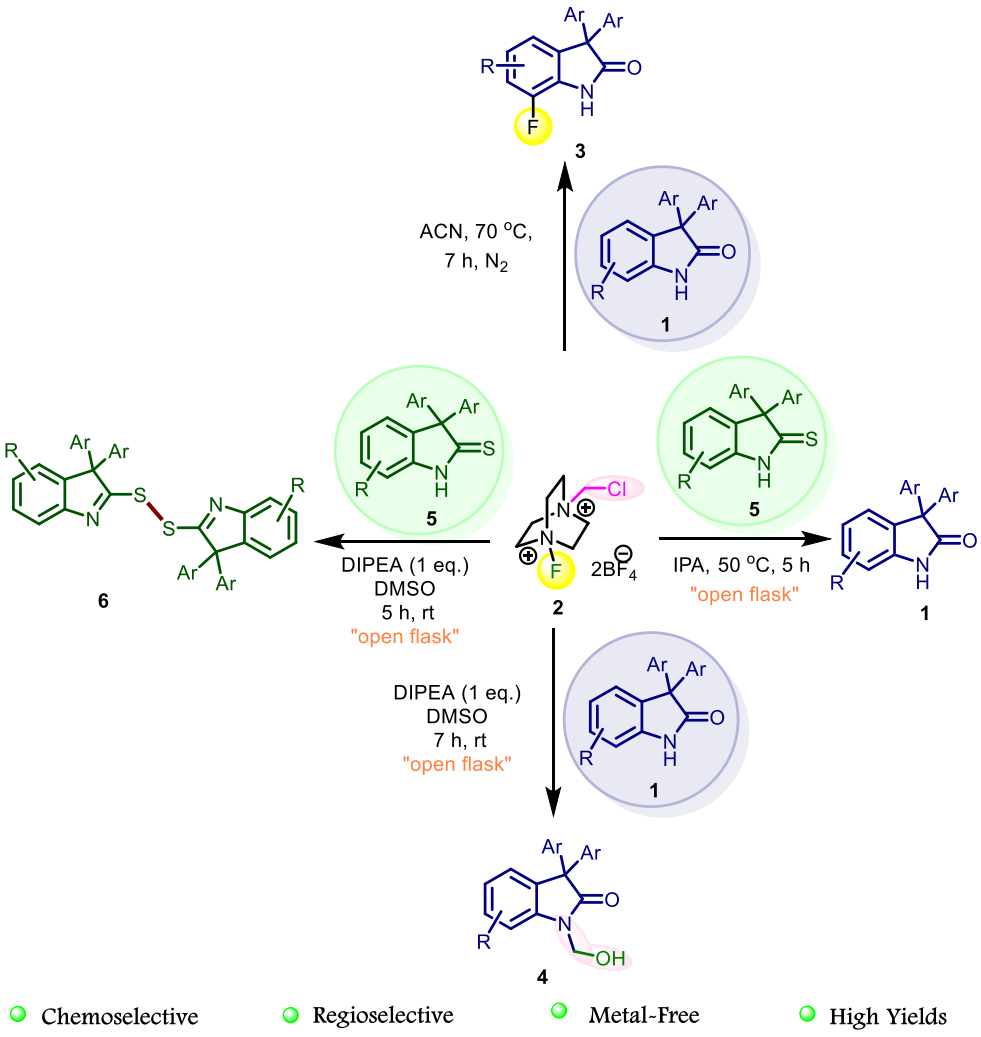
Scheme 4.6: Selective synthesis of C3 fluorination of 3-heteroaryl oxindoles.

Besides fluorination, selectfluor has also been used as a methylating reagent, but there is only one report on this application (Scheme 4.7).[13]



Scheme 4.7: Selective methylenation of ketones.

In this context, I would like to depict my latest efforts in the C7 fluorination and N-hydroxymethylation of oxindoles, the formation of disulfane-containing thioimidates, and the conversion of thio-oxindoles into oxindoles using selectfluor (Scheme 4.8). As per the literature suggestions, these types of reactivities of oxindole and thio-oxindole have not yet been reported.



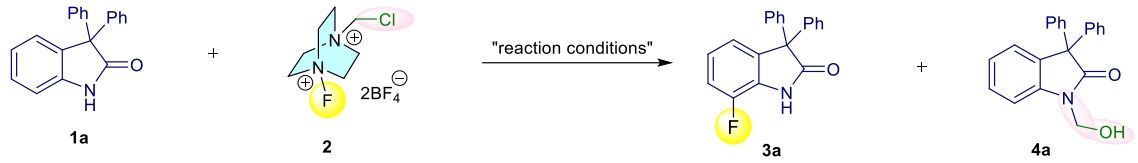
Scheme 4.8: C7 Fluorination and N-hydroxymethylation of oxindoles, formation of dithianes, and transformation of thio-oxindole into oxindole.

4.2 Results and Discussions

I started my investigation using 3,3-diphenyl indoline-2-one **1a** and selectfluor **2** as the model substrates. The reaction was performed using different bases, initially, DBU was chosen and it delivered product **4a** in 68% yield when used with DMSO as solvent at room

temperature (Table 4.1, entry 1). Further changing the bases to NEt_3, and DMAP significantly decreased the yield of **4a** (Table 4.1, entries 2-3). Later, the use of DIPEA bestowed us with a 90% yield of product **4a** (Table 4.1, entry 4). Further, our curiosity to have fluorination, made us switch from an organic base to an inorganic base like Cs_2CO_3, however, it completely shut down the reaction (Table 4.1, entry 5-6). Thereafter, I experimented with some heating conditions, and this time, I was offered a different type of product, **3a.** Then, motivated by this result I tried different inorganic bases, and in the case of Na_2CO_3, I got product **3a** with an 88% yield (Table 4.1, entries 7-9). Next, attempting the reaction in a mixture of DMSO and water (1:1) and using 1 eq. of DIPEA handed over the product **4a** in 72% yield (Table 4.1, entry 10). After that, screening of different solvents with 1 eq. of DIPEA was performed, however, no fruitful result was obtained (Table 4.1, entries 11-15). After many trials, I found out that the omission of the base in the presence of TFE solvent under reflux conditions granted us product **4a** in 70% yield (Table 4.1, entries 16,17). Under base-free conditions, I attempted the transformation with various protic and aprotic solvents, but none were effective. (Table 4.1, entries 18-20). Later on, I exploited MeOH as the solvent and surprisingly, it delivered product **4a** with an 85% yield (Table 4.1, entry 21). After optimizing the reaction conditions, I conducted the reaction in an open-to-air flask to determine how the resulting yield is affected in an open setup. Notably, the isolated yield of **4a** was almost the same as that obtained in an inert environment, however, a decrement in yield was observed in the case of **3a**. Therefore, I performed all the subsequent reactions of compound **4** in an open flask and that of **3** under a nitrogen atmosphere.

Table 4.1. Optimization of the reaction conditions[a]

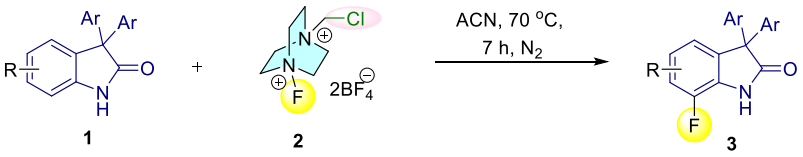


No.	Base (eq.)	Solvent	Temp. (°C)	Time (h)	3a yield[b]	4a yield[b]
1	DBU (2 eq.)	DMSO	rt	12 h	-	68%
2	NEt_3 (2 eq.)	DMSO	rt	12 h	-	45%
3	DMAP (2 eq.)	DMSO	rt	12 h	-	47%
4	**DIPEA (1 eq.)**	**DMSO**	**rt**	**7 h**	**-**	**90%**
5	Cs_2CO_3 (2 eq.)	DMSO	rt	12 h	-	-
6	Cs_2CO_3 (2 eq.)	ACN	rt	12 h	-	-
7	Cs_2CO_3 (2 eq.)	ACN	70 °C	12 h	65%	-
8	K_2CO_3 (2 eq.)	ACN	70 °C	12 h	72%	-
9	**-**	**ACN**	**70 °C**	**12 h**	**88%**	**-**
10	DIPEA (1 eq.)	DMSO:H_2O (1:1)	rt	12 h	-	72%
11	DIPEA (1 eq.)	H_2O	rt	12 h	-	-
12	DIPEA (1 eq.)	ACN	80 °C	12 h	-	-
13	DIPEA (1 eq.)	Toluene	80 °C	12 h	-	-
14	DIPEA (1 eq.)	DMF	80 °C	12 h	-	52%
15	DIPEA (1 eq.)	TFE	80 °C	12 h	-	-
16	-	TFE	50 °C	12 h	-	25%
17	-	TFE	80 °C	12 h	-	70%
18	-	HFIP	80 °C	12 h	-	20%
19	-	TfOH	70 °C	12 h	-	-

20	-	$MeNO_2$	110 °C	12 h	-	-
21	-	MeOH	50 °C	5 h	-	85%

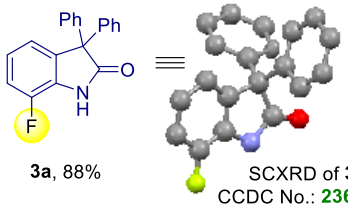
[a]Reaction conditions: **1a** (0.2 mmol, 1 eq.), **2** (0.24 mmol, 1.2 eq.), solvent (1 mL). [b]Isolated yield.

This research represents a significant leap forward in the functionalization of oxindole. While previous reports have explored C7 functionalization of indoles and indolines,[14] they have relied on directing groups at the N-centre. Gratifyingly, our optimized reaction conditions in this study mark the first instance of successful C7 functionalization of oxindole, that too, without using any directing group. I extensively investigated various indoline-2-ones to explore the breadth of this transformation, leading to promising results. (Scheme 4.9). Oxindole substituted with the -Me group at the C5 position reacted efficiently and produced **3c** in an impressive 89% yield. Further, I discovered that halides at the C5 position were incompatible with the reaction conditions as they make the C7 center electronically deficient, obstructing the formation of compounds **3d** and **3e**. Impressively, -Cl at the C4 position of oxindole was well-tolerated and handed over the product **3h** in 54% yield. Additionally, our study delved into the reactivity of both aromatic and aliphatic functionalities at the C3 position of oxindole, yielding fascinating insights. Thus, various arenes like phenyl rings with -Me, -Et, -OMe offered the respective products **3m**, **3n**, and **3o** in excellent yields. Pleasingly, less activated ring such as benzene with -Cl also behaved well in the transformation, albeit in a comparatively lower yield (**3q**). I next studied the reactivity of aliphatic functionalities and spiro-oxindoles at the C3 position. This study utilized dimethyl substituent at the C3 position as a relatively less reactive substrate to yield **3s** in 68%. Increasing the number of methyl groups leads to the enhancement of the yields of **3t** and **3u**. Yields of the products generally correlated with expected nucleophilicity trends, *viz.*, the presence of oxygens and sulfur atoms in products with aliphatic rings at the C3 position offered an increment in yields. Therefore,



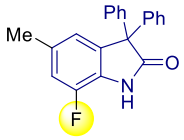
1 2 3

Scope of 3,3-disubstituted oxindoles

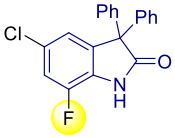


3a, 88%

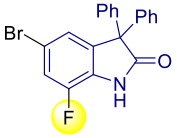
SCXRD of **3a**
CCDC No.: **2362226**



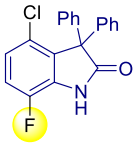
3c, 89%



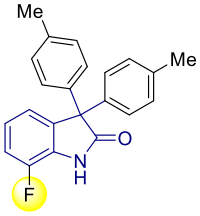
3d, 0%



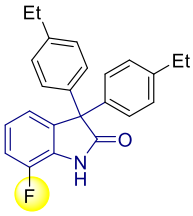
3e, 0%



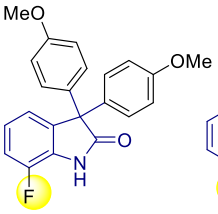
3h, 54%



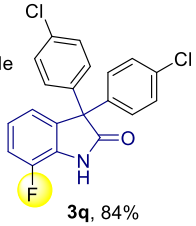
3m, 90%



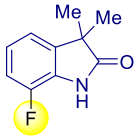
3n, 91%



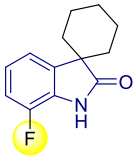
3o, 93%



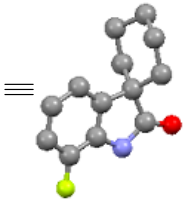
3q, 84%



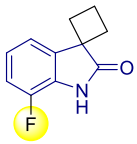
3s, 68%



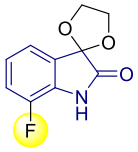
3u, 76%



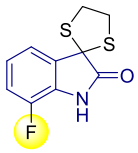
SCXRD of **3u**
CCDC No.: **2364339**



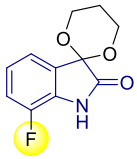
3t, 72%



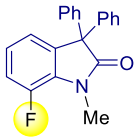
3v, 89%



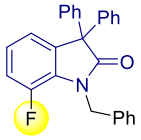
3w, 81%



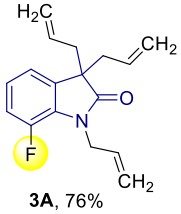
3x, 93%



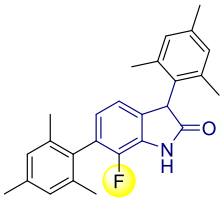
3y, 86%



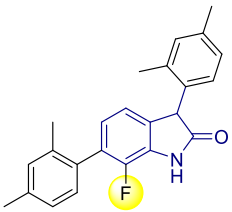
3z, 80%



3A, 76%



3B, 66%



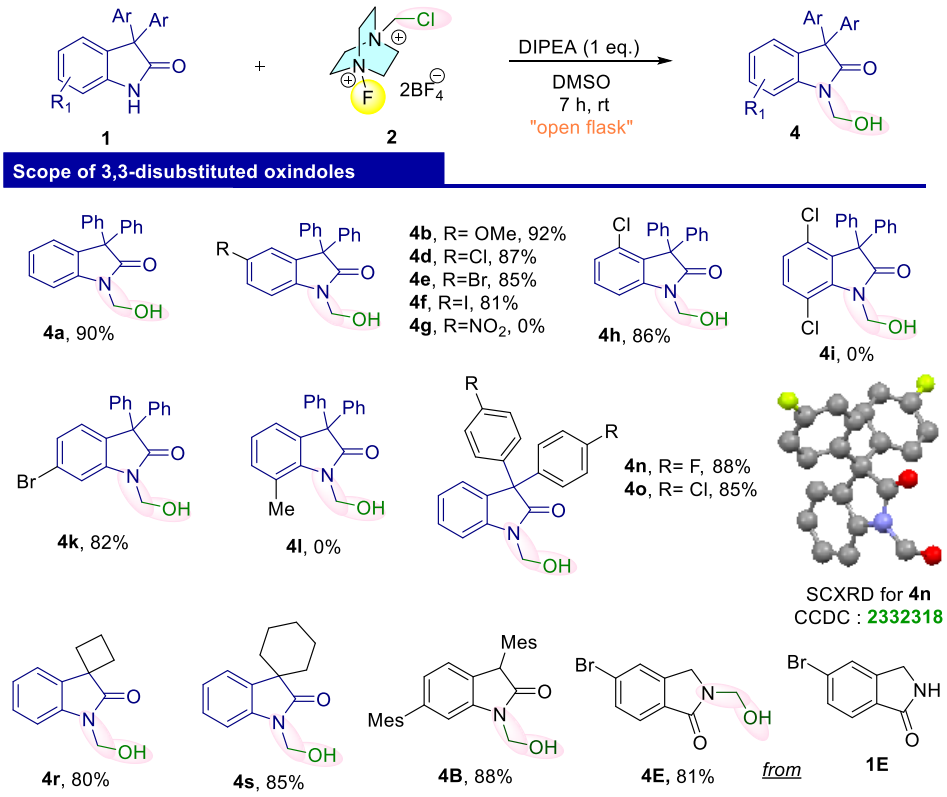
3C, 69%

Scheme 4.9: Synthesis of C7 fluorinated oxindoles.[a,b] [a]Reaction conditions: **1a** (0.2 mmol, 1 eq.), **2** (0.24 mmol, 1.2 eq.), solvent (1 mL). [b]Isolated yield.

ethers and disulfides react efficiently and result in **3v-3x** in respectable yields. Success with variation at the aromatic ring and C3 position of oxindole prompted us to explore the substitution at the N-centre of oxindole which revealed compelling findings. N-methyl decorated oxindole served as a competent nucleophile, with reaction yields (**3y**) that are comparable to C3 halogen-substituted benzene derivatives. N-benzyl and N-allyl derivatives exhibited intriguing reactivity and reacted with selectfluor to form the compounds **3z** and **3A**. Despite the superior electron donating ability of these groups in comparison to a methyl group, a decrease in yield was observed as steric effects here played a role. The reactions with C3 monosubstituted and C6 sterically substituted oxindoles were somewhat less efficient, due to increased hindrance at the C7 position. Despite these issues, the reactions delivered useful yields of the desired products **3B** and **3C**.

I have made significant progress in optimizing the testing conditions for the N-hydroxymethylation process of various oxindole derivatives with different substitutions to determine the substrate scope. Our efforts have led to the successful synthesis of 13 examples with moderate to excellent yields, which effectively showcases the broad generality of this method (Scheme 4.10). To gain insights into the reactivity of differently substituted oxindole derivatives, I performed the N-hydroxymethylation reaction on them. Our observations revealed that all the oxindole derivatives at the C5 position underwent the expected transformations **4b-4f**. However, in the presence of a -NO_2 functionality at the C5 position, the reactivity of the oxindole was arrested (**4g**), highlighting the importance of the substituent in the reaction feasibility. I also found that the C4 substituted derivative showed the transformation with an 86% yield of **4h**. However, the steric bulk at the C7 position significantly impacted the reactivity, and products **4i**, **4l** formation were not observed. The -Br group at the sixth position of oxindole produced the products **4k** in

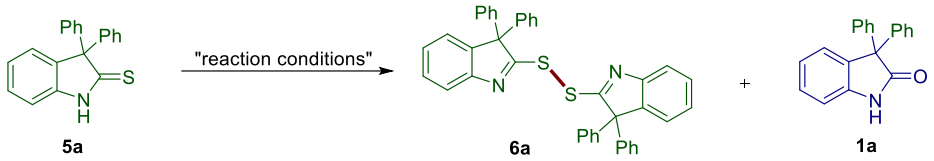
82% yield, respectively, indicating the potential of these groups in facilitating the reaction. Furthermore, I explored the variation in phenyl rings at the C3 position, which bestowed us the products **4n-4o** in excellent yields. Apart from C3 aryl derivatives, spiro oxindole derivatives also provided the desired products **4r** and **4s** in good yields, further demonstrating the versatility of this method. Thereafter, I checked the reactivity of C3 monosubstituted oxindole and it also delivered the product **4B** exclusively. However, when I exploited C3 unsubstituted oxindole, the reactivity of oxindole was arrested and no product formation was observed. Interestingly, the indoline compound produced the N-hydroxymethylated product **4E** with an 81% yield, showcasing the broad substrate scope of the approach.



Scheme 4.10: Synthesis of N-hydroxymethylated oxindoles.[a,b] [a]Reaction conditions: **1a** (0.2 mmol, 1 eq.), **2** (0.24 mmol, 1.2 eq.), solvent (1 mL). [b]Isolated yield.

Following an examination of the reactivity of oxindole with Selectfluor, the focus shifted to understanding the reactivity of thio-oxindole. The study involved the reaction of thio-oxindole **5a** with various oxidizing agents (Table 2). Initially, a reaction with 2 equivalents of TBHP resulted in a 22% yield of product **6a** and a 41% yield of product **1a** (Table 2, entry 1). The discovery that different products could be obtained by adjusting the reaction conditions led to the exploration of different oxidizing agents such as I_2, PIFA, and PIDA (Table 2, entries 2-4). The use of Selectfluor with trimethylamine in the reaction medium yielded product **6a** in a 79% yield (Table 2, entry 5). Optimization of bases such as DMAP and DIPEA led to a 94% yield of product **6a** when using DIPEA (Table 2, entries 6-7). Seeking to identify the optimal conditions for transforming thio-oxindole into oxindole, the reaction conditions were further fine-tuned. It was found that no product was obtained without the use of selectfluor (Table 2, entries 8-9). By modifying the solvents and omitting the bases while retaining the selectfluor constant, product **1a** obtained in a 71% yield using methanol (Table 2, entry 10). Further exploration using different alcohols resulted in an 87% yield of product **1a** when IPA was used as the solvent (Table 2, entries 11-14). Further, utilization of *m*CPBA and H_2O_2 delivered a mixture of both the products **6a** and **1a** (Table 2, entries 15-16).

Table 2. Optimization of the reaction conditions[a]

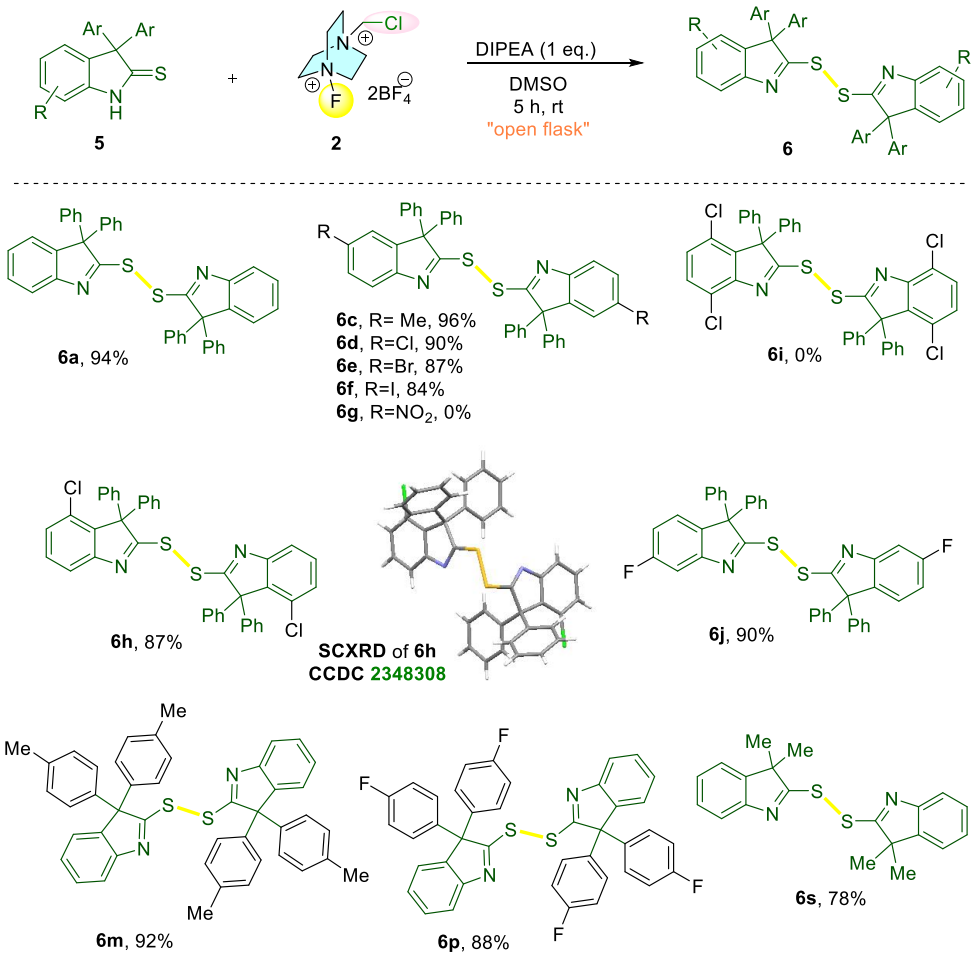


No.	Initiator (eq.)	Base (eq.)	Solvent	Temp. (°C)	Time (h)	%Yield 6a[b]	%Yield 1a[b]
1	TBHP (2 eq.)	DIPEA (1 eq.)	ACN	rt	10	22%	41%

2	I_2 (2 eq.)	DIPEA (1 eq.)	ACN	rt	10	79%	-
3	PIFA (1 eq.)	DIPEA (1 eq.)	ACN	rt	10	55%	-
4	PIDA (1 eq.)	DIPEA (1 eq.)	ACN	rt	10	63%	-
5	Selectfluor (1 eq.)	NEt_3 (1 eq.)	DMSO	rt	10	79%	-
6	Selectfluor (1 eq.)	DMAP (1eq.)	DMSO	rt	10	81%	-
7	**Selectfluor (1 eq.)**	**DIPEA (1 eq.)**	**DMSO**	**rt**	**5**	**94%**	**-**
8	-	DIPEA (1 eq.)	DMSO	rt	12	-	-
9	-	-	MeOH	50	10	-	-
10	Selectfluor (1 eq.)	-	MeOH	50	5	-	71%
11	Selectfluor (1 eq.)	-	EtOH	50	5	-	74%
12	Selectfluor (1 eq.)	-	TFE	50	5	-	52%
13	Selectfluor (1 eq.)	-	*t*BuOH	50	5	-	81%
14	**Selectfluor (1 eq.)**	**-**	**IPA**	**50**	**5**	**-**	**87%**
15	*m*CPBA (3 eq.)	DIPEA (1 eq.)	DCM	50	8	15%	42%
16	H_2O_2 (3 eq.)	DIPEA (1 eq.)	DCM	50	8	19%	49%

[a]Reaction conditions: **5a** (0.2 mmol, 1 eq.), solvent (1 mL). [b]Isolated yield.

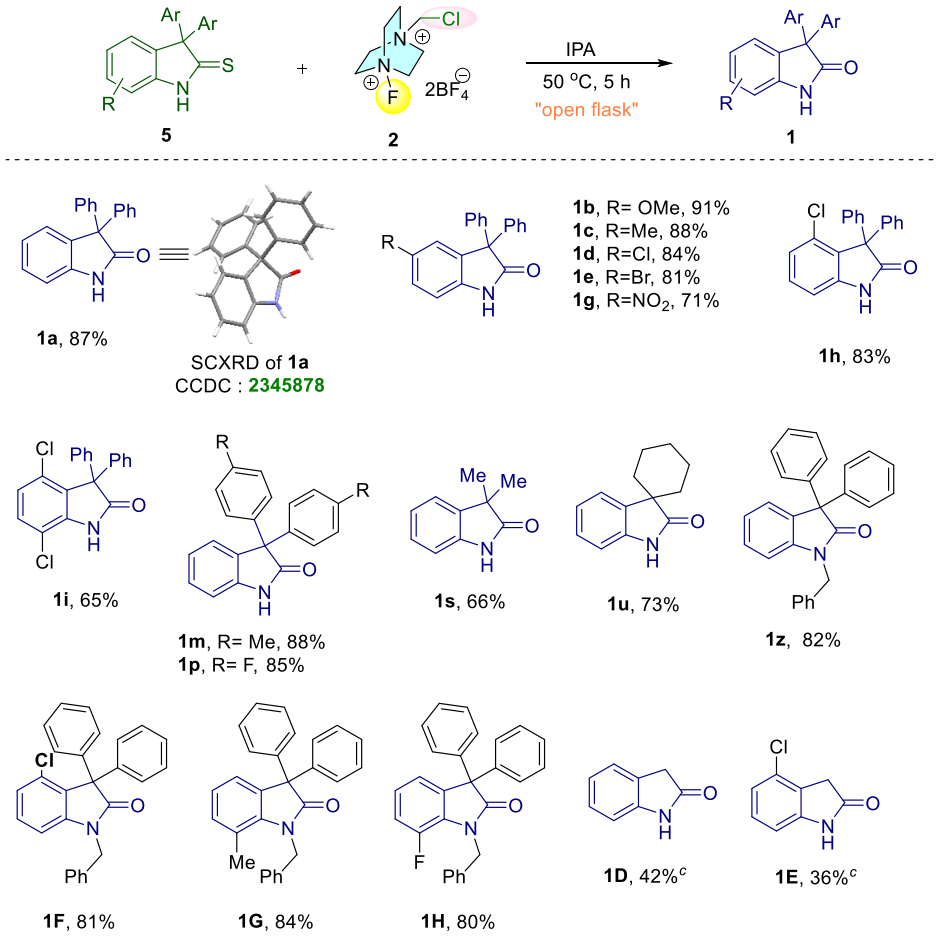
Next, I extended the applicability of the optimized reaction conditions and tested a wide range of thio-oxindoles with varying substituents on the aryl ring to explore the substrate scope of this reaction (Scheme 4.11). I observed that thio-oxindole with electron-rich substituents at the C5 position of the aryl ring, such as 5-methyl, delivered excellent yield of the desired products **6c**. I further evaluated thio-oxindole with other substituents on the aryl ring at the C5-position. Interestingly, I observed that groups such as chloro, bromo, and iodo furnished the targeted dithiane products **6d**, **6e**, and **6f** in yields ranging from 84% to 90%. However, I found that electron-deficient substituted thio-oxindole was not suitable for the transformation (**6g**). Gratifyingly, thio-oxindole with a 4-chloro substituent on the aryl ring produced the corresponding product **6h** in an 87% yield and I was able to characterize this derivative through its SCXRD data. Thio-oxindole with a fluoro substituent at the C6 position of the aryl ring produced the corresponding product **6j** in a 90% yield. However, I faced difficulties when I tested C7 substituted thio-oxindole, and no product **6i** formation was observed. I also evaluated the substrate scope by varying the C3 position of thio-oxindole. To our delight, all of the variations in the aryl group at the C3 position, like methyl and fluoro, produced the desired products **6m** and **6p** in 92% and 88% yields, respectively. Additionally, C3 methyl-substituted thio-oxindole gave the products **6s** in appreciable yield.



Scheme 4.11: Synthesis of dithianes.[a,b] [a]Reaction conditions: **5** (0.2 mmol, 1 eq.), **2** (0.2 mmol, 1 eq.), solvent (1 mL). [b]Isolated yield.

Afterward, I conducted reactions of thio-oxindole using the second optimized condition specified in Table 2, entry 14, which resulted in the production of oxindoles from thio-oxindoles. I confirmed the formation of oxindole through the single-crystal X-ray structure of **1a**. To test the versatility of this method, I performed this transformation using various substitutions on the aryl ring of thio-oxindole (as shown in Scheme 4.12). I discovered that the approach is compatible with both highly activated and less activated C5 substituted derivatives, with the 5-methoxy derivative (**1b**, Scheme 2) having the highest yield of 91%.

The electron-donating groups on the aryl ring increased the activation of the thio-oxindole ring, resulting in higher yields (**1a**, **1b**, and **1c**), while less activated substitutes like chloro, bromo, iodo, and nitro groups comparatively decreased the yield (**1d** − **1g**). Negligibly activating substitutes like 4-Cl, and 4,7-Cl also produced the respective products **1h** and **1i** in good yields. I also tried to increase the reactivity of thio-oxindole by using a more electron-releasing C3-aryl derivative, which resulted in an 88% yield of **1m**. Using less activating group in the phenyl ring at C3-position delivered us the products **1p** in good

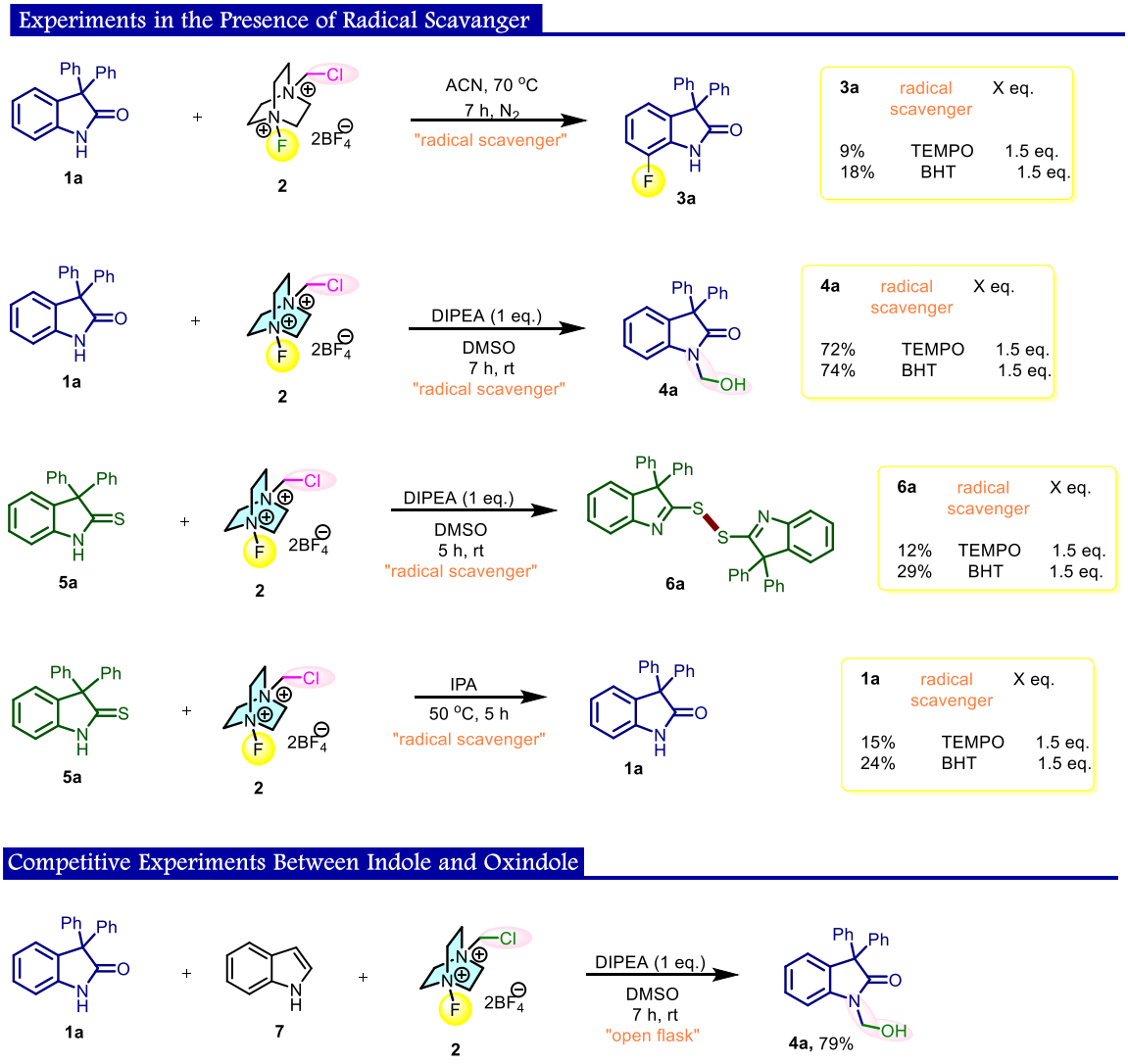


Scheme 4.12: Synthesis of oxindoles from thio-oxindoles.[a,b] [a]Reaction conditions: **5** (0.2 mmol, 1 eq.), **2** (0.2 mmol, 1 eq.), solvent (1 mL). [b]Isolated yield. [c]Reaction time = 8 h.

yield. To test whether the reaction is feasible with C3-alkyl-substituted or spiro-thio-oxindoles, I tried the standard protocol with **5s**, and **5u**, and obtained the respective products **1s**, and **1u** in appreciable yields. Even, N-protected thio-oxindoles behaved well in the reaction mixture and delivered the products **1z**, **1F**, **1G** and **1H** in respectable yields. However, when I experimented with C3-unsubstituted thioxindoles, I observed that the conversion rates were very low, as were the percentage yields (**1D** and **1E**).

To understand the underlying mechanism, I carried out reactions in the presence of radical scavengers - BHT and TEMPO. In all three reactions, only a small amount of product formation **3a, 6a,** and **1a** was observed, providing evidence that the reaction propagates radically as illustrated in scheme 4.13. However, in the case of the hydroxymethylation reaction, product **4a** was obtained in yields of 72% and 74% with TEMPO and BHT, respectively. Subsequently, I conducted a competitive experiment between indole and oxindole under the optimized conditions of hydroxymethylation. Surprisingly, product **4a** was exclusively obtained in the reaction mixture, showing no participation from the other reactant.

In our experimental findings, I have identified the reaction pathways for all the reactions under consideration. Firstly, the C7 functionalization of oxindole- this reaction pathway sheds light on the intricate steps involved in the fluorination process (Scheme 4.14). This process is initiated by the cleavage of the N-F bond in selectfluor, facilitated by the low bond dissociation energy (61-62 kcal/mol)[15] and heat, generating the corresponding radical. Subsequently, the electrophilic fluorine radical selectively reacts at the nucleophilic C-7 position of oxindole **1**, forming the radical intermediate (**int-A**). Finally, the desired fluorinated product **3** is formed through hydrogen abstraction from the C-7 position of intermediate A.



Scheme 4.13: Control Experiments.

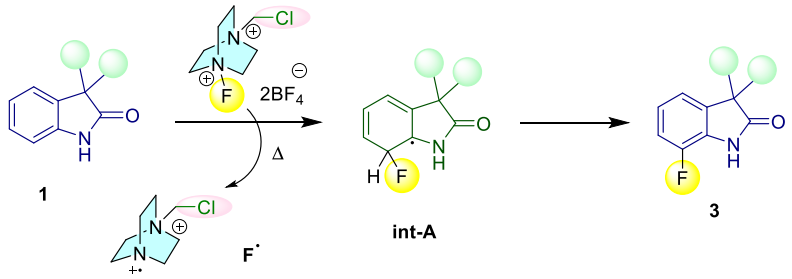
During the N-hydroxymethylation process, a simple S_N2 pathway is followed. Initially, DIPEA abstracts a proton from oxindole **1**, forming an intermediate (**int-B**). This intermediate then attacks the chlorine part of the selectfluor **2**, resulting in the formation of another intermediate (**int-C**). Subsequently, during the work-up, water attacks int-C,

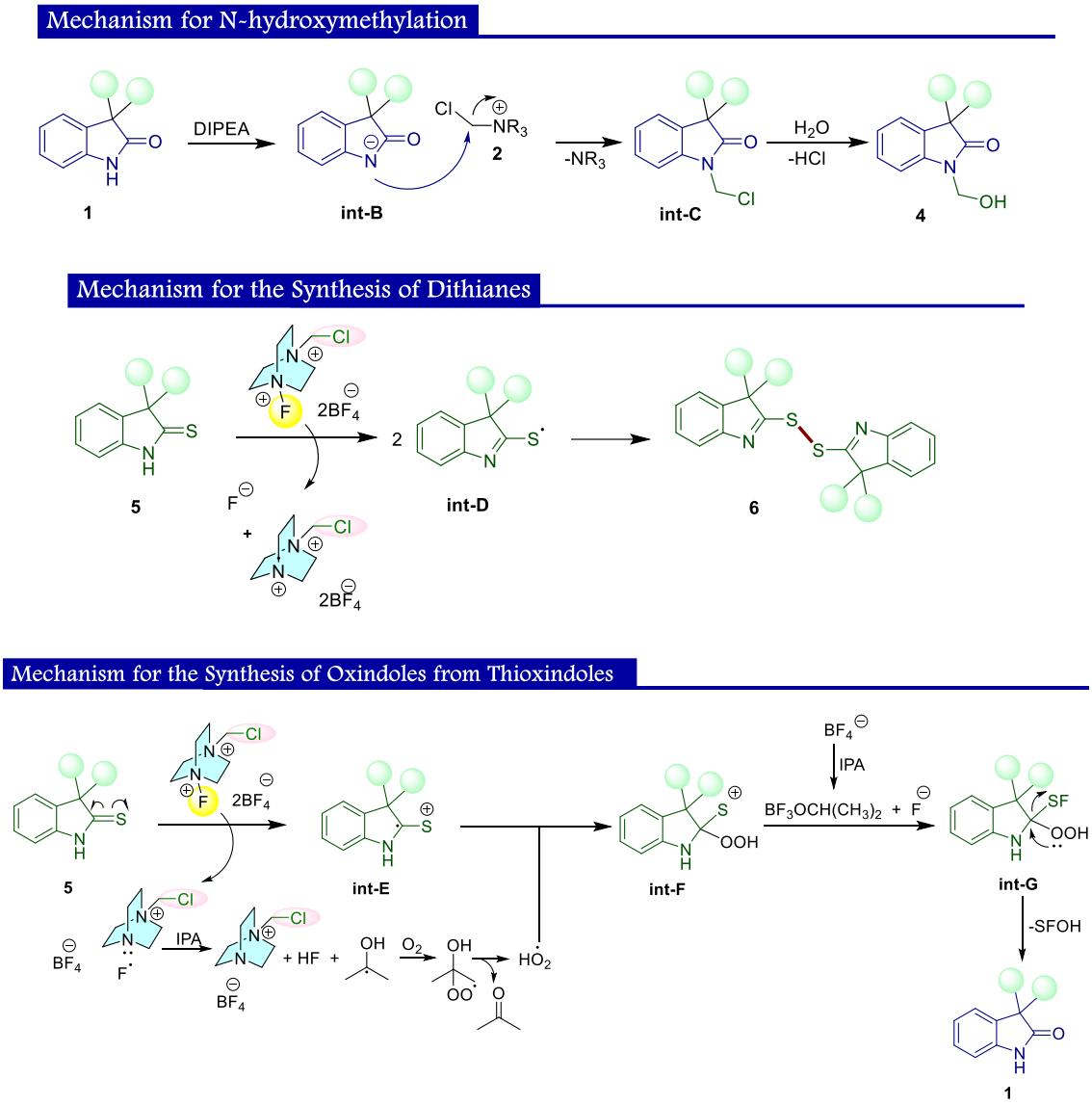
causing the elimination of the chloride ion, and ultimately leading to the formation of product **4**.

The synthesis of dithianes involves the oxidation of thio-oxindole **5** to form an intermediate (**int-D**) through single electron transfer (SET). Subsequently, this radical combines with another similar radical to yield product **6**.

The synthesis of oxindole **1** from thio-oxindoles **5** involves a series of intricate steps. It begins with a Single Electron Transfer (SET) from thio-oxindole **5**, resulting in the formation of HF in the presence of IPA. This leads to the generation of an isopropanol radical, which subsequently reacts with O_2 to form a superoxo radical. The superoxo radical then eliminates acetone and forms hydroperoxo radical. This hydroperoxo radical then attacks the radical at the tertiary carbon of intermediate (**int-E**), giving rise to intermediate (**int-F**). Subsequently, BF_4 facilitates the production of a fluoride ion, which in turn attacks **int-F**, leading to the formation of **int-G**. Finally, the elimination of SFOH yields the ultimate compound **1**.

Mechanism for the C7 Functionalization of Oxindole





Scheme 4.14: Plausible Mechanism.

4.3 Conclusions

In this project, I have achieved a breakthrough in the field of organic synthesis by successfully developing a method for directly fluorinating the C7-H position of oxindoles,

N-hydroxymethylating oxindole, forming dithianes, and transforming thio-oxindole to oxindole. This significant advancement was made possible through extensive experimentation involving the screening of various solvents, bases, and reaction temperatures. One of the key elements in this transformative process is the dual role played by selectfluor, which acts as both an oxidant and a fluorine source. This innovative protocol offers a practical and efficient approach to synthesizing oxindole analogs under mild conditions, resulting in good to excellent yields of the desired products. Importantly, our method demonstrates exceptional regioselectivity, high tolerance to functional groups, and is free of additives, making it a highly attractive option for researchers and practitioners in the fields of organic synthesis and pharmaceutical chemistry.

4.4 Experimental Section

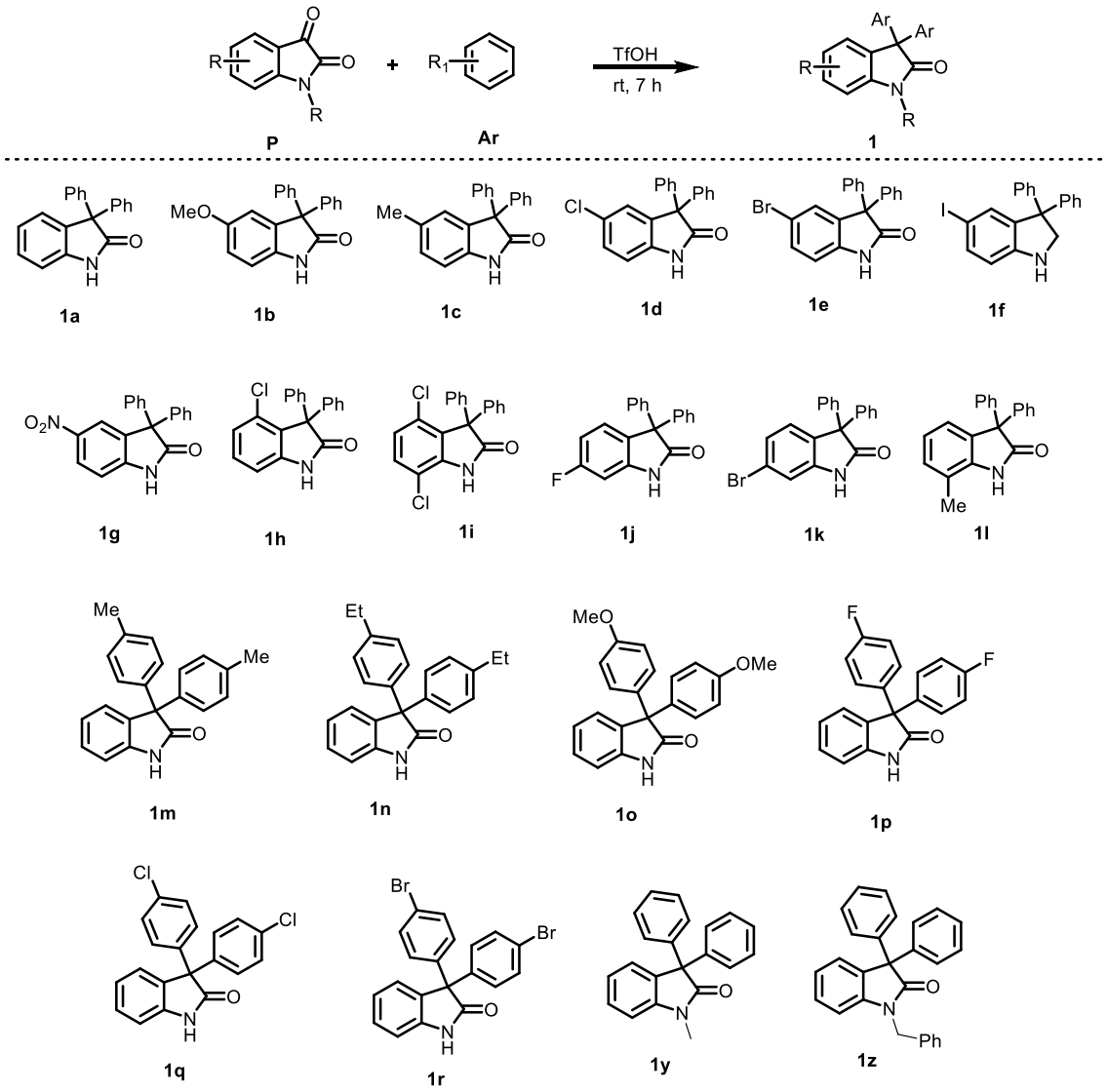
Unless otherwise noted, all reactions were performed on a Schlenk vacuum line or in a glovebox using oven-dried glassware and were stirred with teflon-coated magnetic stirring bars. All the chemicals and reagents were purchased from commercial suppliers Sigma Aldrich, GLR Innovations, BLD Pharma, Spectrochem and used without further purification. Solvents were dried and stored over molecular sieves under an argon atmosphere before use. All work-up and purification procedures were done with reagent-grade solvents in an air atmosphere. Reaction temperatures above 25 °C refer to temperatures of an aluminum heating block or a silicon oil bath, which were controlled by an electronic temperature modulator from Heidolph. Thin-layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100–200 mesh). ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded in $CDCl_3$ and d_6-DMSO, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz $\{^{1}H\}$ or 101 MHz $\{^{13}C\}$ as indicated in the individual spectrum. Chemical shifts (δ) are given in parts per million

(ppm) relative to residual solvent ($CDCl_3$, δ= 7.26 for ^1H NMR and 77.16 for ^{13}C NMR, d_6-DMSO: δ = 2.50 for ^1H NMR and δ = 39.52 for ^{13}C NMR) and coupling constants (J) in Hz. Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet, dt for doublet of triplet, and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer (XEVO G2-XS QTOF). The data collection for single crystal S-3 X-ray was performed at a 298 K on a CMOS-based Bruker D8 Venture PHOTON 100 diffractometer equipped with INCOATEC micro-focus source with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA.

4.4.1 Preparation of Starting Materials

Synthesis of 3,3 disubstituted 2-oxindole derivatives (1)[16]:

In order to synthesize 3,3 disubstituted 2-oxindoles, a solution of isatin derivatives **P** (1 eq.) was prepared in freshly distilled triflic acid. Subsequently, the respective arene (2.5 eq.) was introduced to the solution at room temperature. The reaction was closely monitored using thin-layer chromatography (TLC) until it reached completion. Once the reaction was finalized, crushed ice was added to the mixture, followed by extraction with ethyl acetate. The resultant organic layer was washed with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained compound underwent further purification *via* silica gel column chromatography using hexane and ethyl acetate (8:2) as the eluent. Ultimately, the final product was successfully obtained in good yield, and it was identified as 3,3 disubstituted 2-oxindoles, **1**.



Scheme 4.15. Synthesis of 3,3-aryl substituted oxindoles from isatins.

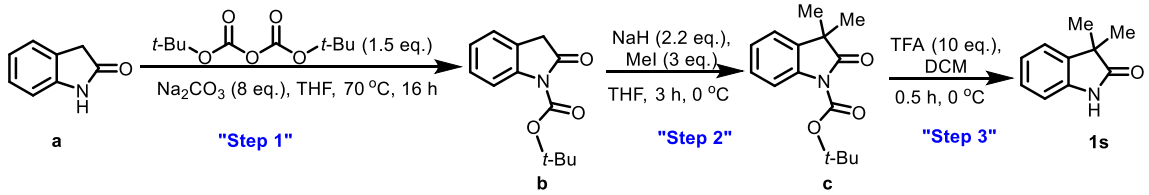
Synthesis of 3,3 dialkyl substituted 2-oxindole derivatives (1)[17]:

Step 1: To an oven-dried schlenk round-bottomed flask, indoline-2-one (1 eq.) was added and nitogen was purged. After that, freshly distilled THF was added and allowed to stir for

2 minutes. To this solution, Na_2CO_3 (8 eq.) was added and an ice bath was placed under the schlenk rbf. After cooling for 10 minutes, boc anhydride (1.5 eq.) was added dropwise and the ice bath was removed. Then the reaction mixture was placed over an oil bath and the reaction temperature was maintained up to 70 ^oC in the oil bath. Upon completion of the reaction, THF was recovered by evaporating on rota vapor and the reaction mixture was extracted with ethyl acetate. The crude mixture was purified through column chromatography using hexane and ethyl acetate as the eluent to obtain compound N-boc oxindole, **b** in 75 % yield.

Step 2: In an oven-dried schlenk round-bottomed flask, compound **b** (1 eq.) was added to freshly dried THF and nitrogen gas was purged. To this solution, methyl iodide (3 eq.) was added and the rbf was placed over an ice bath. Then, NaH (60 wt% mineral oil dispersion, 2.2 eq.) was added in three installments over a time lap of 15 minutes. After completion of reaction in 3 hours as monitored by TLC, THF was recovered by evaporating on rota vapor and cold water was added to the rbf. The product was extracted three times with DCM and the crude was further purified with column chromatography to afford N-boc 3,3-dialkyl oxindole, **c** in 65% yield.

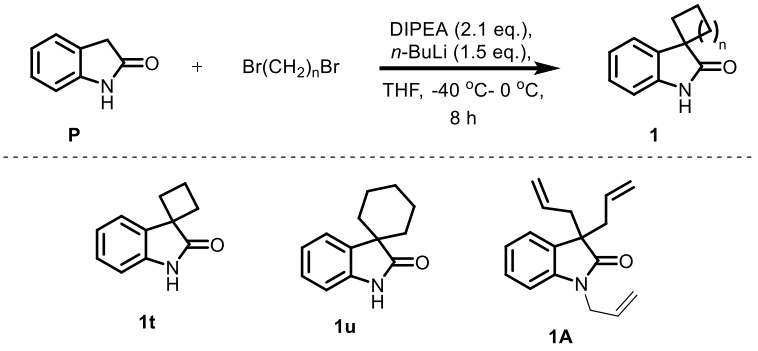
Step 3: To a solution of compound **c** (1 eq.) in DCM, TFA (10 eq.) was added dropwise while placing the rbf over ice bath and the reaction mixture was allowed to stir at room temperature for half an hour. After completion of the reaction as monitored by TLC, the solvent was collected back using rota-vapor and the crude product was purified using silica gel column chromatography to afford the final compound **1s.**



Scheme 4.16. Synthesis of 3,3 dialkyl substituted 2-oxindole derivatives from 2-oxindole.

Synthesis of spirocyclic 2-oxindole derivatives (1)[18]:

To an oven-dried schlenk round-bottomed flask, indoline-2-one was dissolved in freshly dried THF and nitrogen gas was purged. The reaction mixture was transferred to the chiller having -40 ^{o}C temperature and DIPEA (2.1 eq.) was added to the solution followed by *n*-BuLi (1.5 eq.). After that, dibromopropane or dibromopentane (3 eq.) was added slowly and allowed to stir at 0 ^{o}C for 8 hours. Upon completion of the reaction as monitored by TLC, THF was recovered back by evaporating on rota-vapor and ice was added to the reaction mixture. The crude product was extracted with ethyl acetate and purified through silica gel chromatography to afford compound **1**.

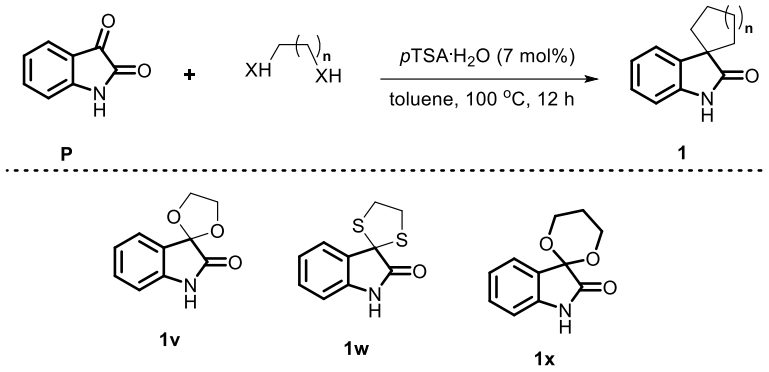


Scheme 4.17. Synthesis of spirocyclic 2-oxindole derivatives from 2-oxindole.

Synthesis of spiro-dioxolan-oxindole derivatives (1)[19]:

In a dried round-bottomed flask protected by a nitrogen atmosphere, isatin (1 eq.) in toluene was dissolved. Next, diol or dithiol (5 eq.) was added, followed by the addition of pTSA (7 mol%). The reaction mixture was then heated at 100°C for 12 hours. After verifying the

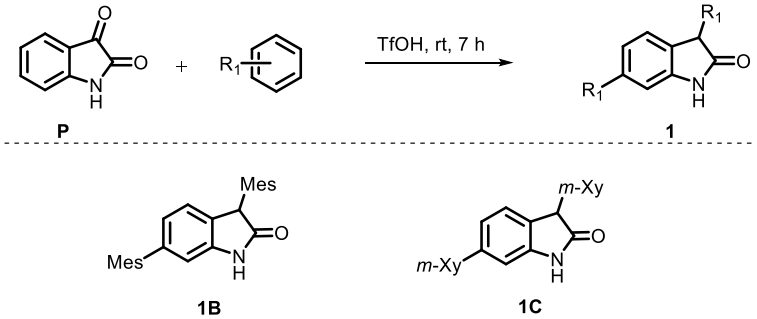
completion of the reaction using TLC, crude product was extracted with ethyl acetate and purified it through silica gel chromatography, ultimately yielding compound **1**.



Scheme 4.18. Synthesis of spiro-dioxolan-oxindole derivatives from 2-oxindole.

<u>Synthesis of 3,6-substituted indolin-2-one derivatives (1)</u>:

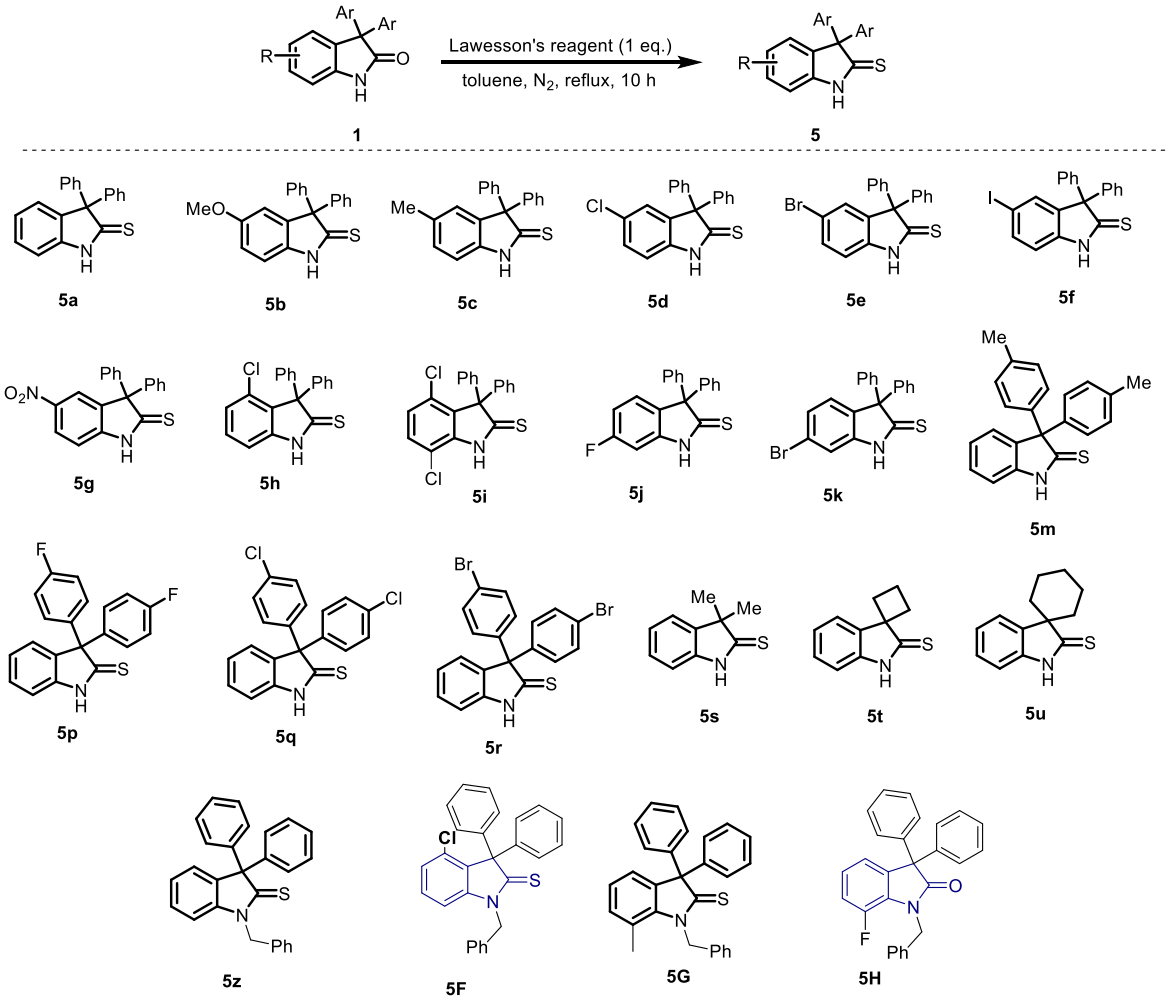
To a solution of isatin, P (1 eq.) in TfOH under an N_2 atmosphere, bulky arene was added and the resulting reaction mixture was stirred for 7 hours at ambient temperature. After analyzing the TLC, crushed ice was added to the reaction mixture and extracted with ethyl acetate. The complete organics were washed with brine once and dried over Na_2SO_4. The final product was isolated with excellent yield on purification through silica gel column chromatography.



Scheme 4.19. Synthesis of 3,6- diaryl substituted 2-oxindole derivatives from isatin.

Synthesis of 3,3-disubstituted thioindolin-2-one derivatives (5)[20]:

To a solution of 3,3-disubstituted indoline-2-one, **1** (1.5 eq.) in freshly dried THF, Lawesson's reagent (1 eq.) was added. The resulting reaction mixture was stirred under an argon atmosphere at ambient temperature for 10 hours. After completion of the reaction, THF was recovered through evaporation using rota-vapor, cold water was added to it and

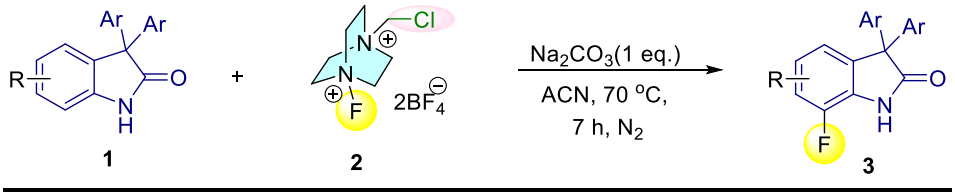


Scheme 4.20. Synthesis of thio-oxindole from 2-oxindole.

extracted with ethyl acetate. The complete organic layer was washed with brine and dried over sodium sulfate. Upon evaporation of the organic solvent under reduced pressure, a crude product was obtained which was further purified through silica gel column chromatography.

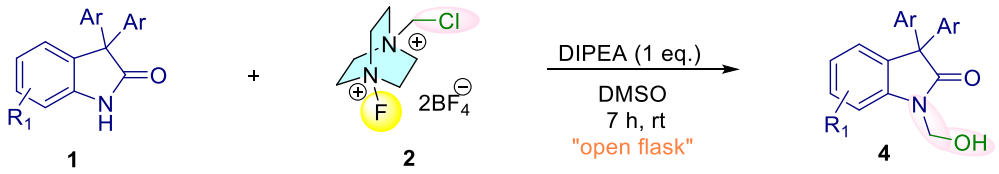
4.4.2 General Procedures

General procedure for N-hydroxymethylation of oxindoles, 3 (GP-1):



A vial containing Oxindole **1** (0.2 mmol) and selectfluor **2** (0.24 mmol) was equipped with a magnetic stir bar. Then, 1 mL of ACN and Na_2CO_3 (1 eq.) were added to the reaction mixture. The reaction was then stirred vigorously at 70 °C and monitored using TLC. After completion in 7 hours, the reaction mixture was extracted three times with ethyl acetate. The entire organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography to yield product **3**.

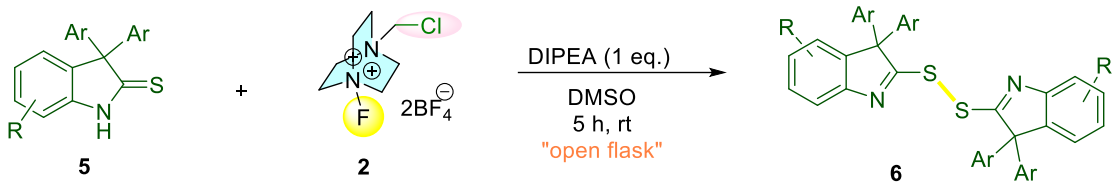
General procedure for N-hydroxymethylation of oxindoles, 4 (GP-2):



A vial containing Oxindole **1** (0.2 mmol) and selectfluor **3** (0.24 mmol) was equipped with a magnetic stir bar. Then, 1 mL of DMSO and DIPEA (1 eq.) were added to the reaction

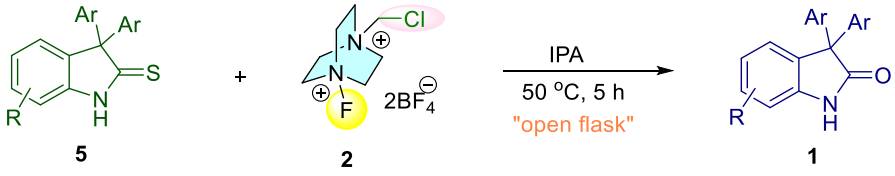
mixture. The reaction was then stirred vigorously at room temperature and monitored using TLC. After completion in 7 hours, the reaction mixture was treated with ice cold water and extracted three times with ethyl acetate. The entire organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography to yield product **4**.

General procedure for the formation of Dithianes, 6 (GP-3):



A vial containing thio-oxindole **5** (0.2 mmol) and selectfluor **2** (0.24 mmol) was set up with a magnetic stir bar. 1 mL of DMSO and DIPEA (1 eq.) were added to the reaction mixture. The reaction was stirred vigorously at room temperature and monitored using TLC. After 7 hours, the reaction was completed, and the mixture was treated with ice-cold water and extracted with DCM thrice. The organic layer was collected, dried with sodium sulfate, and evaporated under reduced pressure. Finally, the crude product was purified using silica gel chromatography to yield product **6**.

General procedure for the formation oxindole, 1 (GP-4):



A vial containing thio-oxindole **5** (0.2 mmol) and selectfluor **2** (0.24 mmol) was carefully set up with a magnetic stir bar to ensure optimal mixing. To initiate the reaction, a precise quantity of 1 mL of MeOH was added to the reaction mixture. The reaction was then

vigorously stirred at a controlled temperature of 50 °C and monitored using TLC to track the reaction progress. After 5 hours, the reaction was found to be completed, confirmed by the TLC analysis. The solvent was then removed under reduced pressure to obtain the crude product. Finally, the crude product was purified using silica gel chromatography to obtain the final product **1** with a high degree of purity.

4.4.3 Characterization data

7-fluoro-3,3-diphenylindolin-2-one (3a)

Following the general procedure (GP-1), treatment of 3,3-diphenylindolin-2-one, **1a** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-3,3-diphenylindolin-2-one, **3a** as white solid (53 mg, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.05 (s, 1H), 7.35 – 7.25 (m, 11H), 7.06 – 7.00 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.45, 148.49, 146.06, 141.24, 136.13 (d, *J* = 2.5 Hz), 128.87, 128.72, 128.49, 128.39, 127.73, 127.66, 127.53, 123.54 (d, *J* = 5.8 Hz), 122.17 (d, *J* = 3.0 Hz), 115.37 (d, *J* = 16.8 Hz), 63.34 (d, *J* = 1.6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -133.09. **HRMS:** m/z calculated for $C_{20}H_{15}FNO$ $[M+H]^+$ = 304.1138, found 304.1135.

7-fluoro-5-methyl-3,3-diphenylindolin-2-one (3c)

Following the general procedure (GP-1), treatment of 5-methyl-3,3-diphenylindolin-2-one, **1c** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-5-methyl-3,3-diphenylindolin-2-one, **3c** as white solid (56 mg, 89% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.85 (s, 1H), 7.34 – 7.29 (m, 5H), 7.28 – 7.26 (m, 4H), 7.25 (d, *J* = 1.5 Hz, 1H), 6.87 – 6.81 (m, 2H), 2.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.47, 148.14, 145.71,

141.39, 135.88, 135.86, 133.95, 133.89, 128.69, 128.51, 127.66, 124.82 (d, J = 12.6 Hz), 122.69 (d, J = 2.8 Hz), 115.83 (d, J = 16.7 Hz), 63.39 (d, J = 1.5 Hz), 21.40. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -133.91. **HRMS:** m/z calculated for $C_{21}H_{17}FNO$ $[M+H]^+$ = 318.1294, found 318.1307.

4-chloro-7-fluoro-3,3-diphenylindolin-2-one (3h)

Following the general procedure (GP-1), treatment of 4-chloro-3,3-diphenylindolin-2-one, **1h** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 4-chloro-7-fluoro-3,3-diphenylindolin-2-one, **3h** as white solid (36 mg, 54% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 – 7.42 (m, 5H), 7.40 – 7.35 (m, 6H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 7.9, 0.6 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.00, 155.20, 142.44, 135.63, 130.59, 130.08, 129.43, 128.58, 128.40, 127.08, 119.02, 74.85. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -131.02. **HRMS:** m/z calculated for $C_{20}H_{14}NOFCl$ $[M+H]^+$ = 338.0748, found 338.0759.

7-fluoro-3,3-di-*p*-tolylindolin-2-one (3m)

Following the general procedure (GP-1), treatment of 3,3-di-*p*-tolylindolin-2-one, **1m** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-3,3-di-*p*-tolylindolin-2-one, **3m** as white solid (60 mg, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.46 (s, 1H), 7.17 – 7.08 (m, 9H), 7.01 – 6.98 (m, 2H), 2.31 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.56, 138.37, 137.34 (d, *J* = 2.4 Hz), 136.60, 136.58, 136.54, 129.45, 129.34, 128.32, 123.37 (d, *J* = 1.1 Hz), 121.86, 115.15 (d, *J* = 15.1 Hz), 62.84 (d, *J* = 6.0 Hz), 23.05, 21.16. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -132.99. **HRMS:** m/z calculated for $C_{22}H_{19}NOF$ $[M+H]^+$ = 332.1451, found 332.1465

3,3-bis(4-ethylphenyl)-7-fluoroindolin-2-one (3n)

Following the general procedure (GP-1), treatment of 3,3-bis(4-ethylphenyl)-indolin-2-one, **1n** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 3,3-bis(4-ethylphenyl)-7-fluoroindolin-2-one, **3n** as white solid (65 mg, 91% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.68 (s, 1H), 7.25 – 7.10 (m, 8H), 7.06 – 6.97 (m, 3H), 2.63 (q, *J* = 7.6 Hz, 4H), 1.22 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.83, 148.56, 146.13, 143.53, 138.54, 136.68, 128.38, 128.10, 123.30 (d, *J* = 5.7 Hz), 121.89 (d, *J* = 2.7 Hz), 115.13 (d, *J* = 17.0 Hz), 62.95, 28.49, 15.48. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -132.86. **HRMS:** m/z calculated for $C_{24}H_{23}FNO$ $[M+H]^+$ = 360.1764, found 360.1780.

7-fluoro-3,3-bis(4-methoxyphenyl)indolin-2-one (3o)

Following the general procedure (GP-1), treatment of 3,3-bis(4-methoxyphenyl)indolin-2-one, **1o** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-3,3-bis(4-methoxyphenyl)indolin-2-one, **3o** as white solid (68 mg, 93% yield).m**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.67 (s, 1H), 7.21 – 7.18 (m, 4H), 7.04 – 6.99 (m, 3H), 6.87 – 6.81 (m, 4H), 3.78 (d, *J* = 0.5 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.65, 158.99, 148.55, 146.12, 136.84 (d, *J* = 2.3 Hz), 133.42, 129.55, 127.68 (d, *J* = 12.4 Hz), 126.83 (d, *J* = 8.5 Hz), 123.39 (d, *J* = 5.7 Hz), 121.84 (d, *J* = 2.8 Hz), 115.16 (d, *J* = 16.9 Hz), 113.99, 62.05 (d, *J* = 1.4 Hz), 55.37. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -132.79. **HRMS:** m/z calculated for $C_{22}H_{19}NO_3F$ $[M+H]^+$ = 364.1349, found 364.1339.

3,3-bis(4-chlorophenyl)-7-fluoroindolin-2-one (3q)

Following the general procedure (GP-1), treatment of 3,3-bis(4-chlorophenyl)-indolin-2-one, **1q** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 3,3-bis(4-chlorophenyl)-7-fluoroindolin-2-one, **3q** as white solid (62 mg, 84% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.15 (s, 1H), 7.35 – 7.26 (m, 9H), 7.05 – 7.01 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.56, 148.49, 146.06, 141.22, 136.11 (d, *J* = 2.2 Hz), 128.72, 128.62, 128.48, 127.73, 127.67, 127.58, 127.54, 123.54 (d, *J* = 5.7 Hz), 122.15 (d, *J* = 3.1 Hz), 115.38 (d, *J* = 17.0 Hz),, 63.34 (d, *J* = 1.7 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -133.02. **HRMS:** m/z calculated for $C_{20}H_{13}NOFCl_2$ $[M+H]^+$ = 372.0358, found 372.0368.

7-fluoro-3,3-dimethylindolin-2-one (3s)

Following the general procedure (GP-1), treatment of 3,3-dimethylindolin-2-one, **1s** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-3,3-dimethylindolin-2-one, **3s** as white solid (24 mg, 68% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19 (s, 1H), 7.00 - 6.97 (m, 3H), 1.41 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** 182.71, 148.39, 145.97, 139.11 (d, J = 2.7 Hz), 126.97 (d, J = 11.9 Hz), 123.30 (d, J = 5.8 Hz), 118.44 (d, J = 2.9 Hz), 114.90 (d, J = 17.2 Hz), 45.24 (d, J = 1.4 Hz), 24.49. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -133.76. **HRMS:** m/z calculated for $C_{10}H_{11}NOF$ $[M+H]^+$ = 180.0825, found 180.0833.

7'-fluorospiro[cyclobutane-1,3'-indolin]-2'-one (3t)

Following the general procedure (GP-1), treatment of spiro[cyclobutane-1,3'-indolin]-2'-one, **1t** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) 7'-fluorospiro[cyclobutane-1,3'-indolin]-2'-one, **3t** as white solid (28 mg, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 (s, 1H), 7.31 – 7.26 (m, 1H), 7.08 – 6.94 (m, 2H), 2.76 – 2.64 (m, 2H), 2.41 – 2.32 (m, 3H), 2.29 – 2.20 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.31, 148.00, 145.58, 137.59, 137.55, 127.12 (d, *J* = 11.8 Hz), 123.35 (d, *J* = 5.9 Hz), 118.48 (d, *J* = 2.7 Hz), 114.99 (d, *J* = 17.3 Hz), 48.90, 31.58, 29.86, 16.81. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -134.47. **HRMS:** m/z calculated for $C_{11}H_{11}NOF$ $[M+H]^+$ = 192.0825, found 192.0829.

7'-fluorospiro[cyclohexane-1,3'-indolin]-2'-one (3u)

Following the general procedure (GP-1), treatment of spiro[cyclohexane-1,3'-indolin]-2'-one, **1u** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7'-fluorospiro[cyclohexane-1,3'-indolin]-2'-one, **3u** as white solid (33 mg, 76% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.00 (s, 1H), 7.24 – 7.21 (m, 1H), 7.03 – 6.94 (m, 2H), 1.93 (ddd, *J* = 12.9, 6.6, 2.7 Hz, 2H), 1.89 – 1.84 (m, 2H), 1.78 – 1.69 (m, 3H), 1.66 – 1.57 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 181.87, 148.38, 145.96, 138.61 (d, *J* = 2.6 Hz), 127.26 (d, *J* = 11.8 Hz), 122.64 (d, *J* = 5.7 Hz), 120.04 (d, *J* = 3.0 Hz), 114.68 (d, *J* = 17.0 Hz), 48.59, 33.09, 25.18, 21.10. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -134.05. **HRMS:** m/z calculated for $C_{13}H_{15}NOF$ $[M+H]^+$ = 220.1138, found 220.1142

7-fluorospiro[indoline-3,2'-[1,3]dioxolan]-2-one (3v)

Following the general procedure (GP-1), treatment of spiro[indoline-3,2'-[1,3]dioxolan]-2-one, **1v** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluorospiro[indoline-3,2'-[1,3]dioxolan]-2-one, **3v** as white solid (37 mg, 89% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 (s, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.07 – 7.00 (m, 1H), 4.62 – 4.53 (m, 2H), 4.38 – 4.28 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 174.15, 148.34, 145.91, 129.13 (d, *J* = 13.2 Hz), 126.89 (d, *J* = 2.9 Hz), 124.16 (d, *J* = 5.7 Hz), 121.01 (d, *J* = 3.1 Hz), 118.86 (d, *J* = 17.0 Hz), 70.74, 66.04. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -134.56. **HRMS:** m/z calculated for $C_{10}H_9FNO_3$ $[M+H]^+$ = 210.0566, found 210.0571

7-fluorospiro[indoline-3,2'-[1,3]dithiolan]-2-one (3w)

Following the general procedure (GP-1), treatment of spiro[indoline-3,2'-[1,3]dithiolan]-2-one, **1w** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluorospiro[indoline-3,2'-[1,3]dithiolan]-2-one, **3w** as white solid (39 mg, 81% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 (s, 1H), 7.17 – 7.15 (m, 1H), 7.13 – 7.08 (m, 1H), 7.06 – 7.00 (m, 1H), 4.57 (td, *J* = 5.9, 3.8 Hz, 2H), 4.33 (td, *J* = 6.0, 3.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 174.06, 148.36, 145.92, 129.14 (d, J = 13.2 Hz), 126.94 (d, J = 3.4 Hz), 124.15 (d, J = 5.7 Hz), 121.04 (d, J = 3.4 Hz), 118.84 (d, J = 17.2 Hz), 101.97 (d, J = 4.7 Hz), 66.04. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -134.52. **HRMS:** m/z calculated for $C_{10}H_9FNOS_2$ $[M+H]^+$ = 242.0110, found 242.0118.

7-fluorospiro[indoline-3,2'-[1,3]dioxan]-2-one (3x)

Following the general procedure (GP-1), treatment of spiro[indoline-3,2'-[1,3]dioxan]-2-one, **1x** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluorospiro[indoline-3,2'-[1,3]dioxan]-2-one, **3x** as white solid (41 mg, 93% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30 (s, 1H), 7.24 – 7.22 (m, 1H), 7.09 – 6.98 (m, 2H), 4.98 (td, *J* = 12.2, 2.7 Hz, 2H), 3.98 (ddd, *J* = 12.0, 5.2, 1.6 Hz, 2H), 2.39 (qt, *J* = 12.6, 5.3 Hz, 1H), 1.70 – 1.62 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.92, 148.08, 145.65, 130.16 (d, *J* = 3.1 Hz), 127.58 (d, *J* = 13.3 Hz), 124.13 (d, *J* = 5.6 Hz), 120.07 (d, *J* = 2.9 Hz), 118.10 (d, *J* = 17.0 Hz), 93.68 (d, *J* = 3.8 Hz), 61.32, 25.31. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -134.49. **HRMS:** m/z calculated for $C_{11}H_{11}FNO_3$ $[M+H]^+$ = 224.0723, found 224.0715.

7-fluoro-1-methyl-3,3-diphenylindolin-2-one (3y)

Following the general procedure (GP-1), treatment of 1-methyl-3,3-diphenylindolin-2-one, **1y** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-1-methyl-3,3-diphenylindolin-2-one, **3y** as white solid (55 mg, 86% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.25 (m, 7H), 7.25 – 7.20 (m, 4H), 7.07 – 7.00 (m, 2H), 3.51 (d, *J* = 2.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 177.39, 149.25, 146.83, 141.63, 141.08, 135.74 (d, J = 2.5 Hz), 128.80, 128.65, 128.51, 128.40, 127.89, 127.63, 125.17 (d, J = 3.6 Hz), 124.96, 123.36 (d, J = 6.2 Hz), 122.10 (d, J = 2.8 Hz), 116.29 (d, J = 19.1 Hz), 62.88, 29.32 (d, J = 6.3 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -135.87. **HRMS:** m/z calculated for $C_{21}H_{17}FNO$ $[M+H]^+$ = 318.1294, found 318.1301

1-benzyl-7-fluoro-3,3-diphenylindolin-2-one (3z)

Following the general procedure (GP-1), treatment of 1-benzyl-3,3-diphenylindolin-2-one, **1z** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1-benzyl-7-fluoro-3,3-diphenylindolin-2-one, **3z** as white solid (63 mg, 80% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.23 (m, 15H), 7.08 – 7.04 (m, 1H), 7.04 – 6.95 (m, 2H), 5.17 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 177.46, 148.83, 146.40, 141.43 (d, *J* = 22.5 Hz), 137.00 (d, *J* = 21.6 Hz), 135.67 (d, *J* = 20.1 Hz), 129.04 (d, *J* = 7.0 Hz), 128.59, 128.43, 127.57, 127.38, 123.49 (d, *J* = 4.6 Hz), 122.03, 116.27 (d, *J* = 18.8 Hz), 62.79, 45.64. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -132.95 (d, *J* = 6.6 Hz). **HRMS:** m/z calculated for $C_{27}H_{21}FNO$ $[M+H]^+$ = 394.1607, found 394.1613

1,3,3-triallyl-7-fluoroindolin-2-one (3A)

Following the general procedure (GP-1), treatment of 1,3,3-triallyl-indolin-2-one, **1A** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,3,3-triallyl-7-fluoroindolin-2-one, **3A** as white solid (41 mg, 76% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.98 – 6.88 (m, 2H), 6.71 – 6.68 (m, 1H), 5.80 – 5.70 (m, 1H), 5.45 – 5.35 (m, 2H), 5.21 – 5.13 (m, 2H), 5.04 – 4.90 (m, 4H), 4.30 (dt, *J* = 5.1, 1.6 Hz, 2H), 2.57 (qd, *J* = 13.5, 7.3 Hz, 4H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.36, 160.40, 158.01, 138.90, 133.07 (d, *J* = 7.9 Hz), 131.93, 131.44, 119.44, 117.53, 114.11 (d, *J* = 23.6 Hz), 111.55 (d, *J* = 24.7 Hz), 109.44 (d, *J* = 8.0 Hz), 54.15, 53.31 (d, *J* = 1.2 Hz), 42.35, 41.40. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -120.91. **HRMS:** m/z calculated for $C_{17}H_{19}FNO$ $[M+H]^+$ = 272.1451, found 272.1462

7-fluoro-3,6-dimesitylindolin-2-one (3B)

Following the general procedure (GP-1), treatment of 3,6-dimesitylindolin-2-one, **1B** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 7-fluoro-3,6-dimesitylindolin-2-one, **3B** as white solid (51 mg, 66% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.32 (s, 1H), 7.04 – 6.96 (m, 3H), 6.86 – 6.71 (m, 3H), 5.20 (s, 1H), 2.58 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H), 2.04 (s, 3H), 1.85 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.64, 145.46, 143.05, 137.97, 137.60, 137.47, 137.25 (d, *J* = 2.9 Hz), 136.61, 131.81, 130.74, 130.47, 129.89, 129.25, 128.94 (d, *J* = 12.1 Hz), 128.03 (d, *J* = 14.8 Hz), 127.96, 125.03, 119.47, 48.96, 21.38, 21.19, 20.99, 20.53, 20.33, 19.16. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -136.27. **HRMS:** m/z calculated for $C_{26}H_{27}FNO$ $[M+H]^+$ = 388.2077, found 388.2081

3,6-bis(2,4-dimethylphenyl)-7-fluoroindolin-2-one (3C)

Following the general procedure (GP-1), treatment of 3,6-bis(2,4-dimethylphenyl)-indolin-2-one, **1C** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of ACN with Na_2CO_3 (1 eq.) at 70 ^oC for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 3,6-bis(2,4-dimethylphenyl)-7-fluoroindolin-2-one **3C** as white solid (50 mg, 69% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.26 (s, 1H), 7.17 – 7.03 (m, 4H), 7.00 (d, *J* = 6.7 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.81 – 6.73 (m, 1H), 4.94 (s, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 2.22 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.49, 145.53, 143.11, 137.91, 137.66, 137.08, 136.76 (d, *J* = 2.7 Hz), 136.46, 135.19 (d, *J* = 7.2 Hz), 132.32, 131.97, 131.60 (d, *J* = 24.6 Hz), 130.89, 130.35, 130.08, 129.40 (d, *J* = 13.6 Hz), 127.37, 127.21, 126.49, 125.84, 125.15, 124.58 (d, *J* = 4.5 Hz), 120.05, 115.03

(d, *J* = 17.3 Hz), 60.53, 21.22, 21.10, 19.99, 19.97. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -135.09. **HRMS:** m/z calculated for $C_{24}H_{23}FNO$ $[M+H]^+$ = 360.1764, found 360.1758

1-(hydroxymethyl)-3,3-diphenylindolin-2-one (4a)

Following the general procedure (GP-2), treatment of 3,3-diphenylindolin-2-one, **1a** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-(hydroxymethyl)-3,3-diphenylindolin-2-one **4a** as white solid (57 mg, 90% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.35 – 7.26 (m, 8H), 7.25 - 7.10 (m, 4H), 5.22 (s, 2H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 178.53, 141.56, 141.15, 132.75, 128.63, 128.59, 128.52, 127.58, 126.42, 123.58, 109.82, 64.38, 62.90. **HRMS:** m/z calculated for $C_{21}H_{187}NO_2$ $[M+H]^+$ = 316.1338, found 316.1349

1-(hydroxymethyl)-5-methoxy-3,3-diphenylindolin-2-one (4b)

Following the general procedure (GP-2), treatment of 5-methoxy-3,3-diphenylindolin-2-one, **1b** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-(hydroxymethyl)-5-methoxy-3,3-diphenylindolin-2-one **4b** as white solid (64 mg, 92% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.34 – 7.22 (m, 10H), 7.08 – 7.03 (m, 1H), 6.85 (dd, *J* = 7.3, 2.3 Hz, 2H), 5.23 (d, *J* = 7.5 Hz, 2H), 3.76 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 178.21, 156.48, 141.52, 134.61, 134.01, 128.64, 128.51, 127.58, 113.61, 112.80, 110.22, 64.46, 63.28, 55.86. **HRMS:** m/z calculated for $C_{22}H_{20}NO_3$ $[M+H]^+$ = 346.1443, found 346.1449

5-chloro-1-(hydroxymethyl)-3,3-diphenylindolin-2-one (4d)

Following the general procedure (GP-2), treatment of 5-chloro-3,3-diphenylindolin-2-one, **1d** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture

using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-chloro-1-(hydroxymethyl)-3,3-diphenylindolin-2-one **4d** as white solid (61 mg, 87% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.26 (m, 7H), 7.22 – 7.20 (m, 6H), 7.08 (d, *J* = 8.4 Hz, 1H), 5.23 (d, *J* = 3.4 Hz, 2H), 3.72 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.06, 140.87, 139.73, 134.38, 128.97, 128.81, 128.76, 128.69, 128.40, 127.88, 127.77, 126.67, 110.98, 64.43, 63.03. **HRMS:** m/z calculated for $C_{21}H_{17}NO_2Cl$ $[M+H]^+$ = 350.0948, found 350.0956

5-bromo-1-(hydroxymethyl)-3,3-diphenylindolin-2-one (4e)

Following the general procedure (GP-2), treatment of 5-bromo-3,3-diphenylindolin-2-one, **1e** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-bromo-1-(hydroxymethyl)-3,3-diphenylindolin-2-one **4e** as white solid (67 mg, 85% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 – 7.44 (m, 1H), 7.34 (t, *J* = 2.4 Hz, 1H), 7.33 – 7.27 (m, 6H), 7.24 – 7.18 (m, 4H), 7.03 (d, *J* = 8.4 Hz, 1H), 5.23 (s, 2H), 3.48 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 177.90, 140.87, 140.23, 134.75, 131.57, 129.44, 128.82, 128.41, 127.89, 116.31, 111.40, 64.45, 62.97. **HRMS:** m/z calculated for $C_{21}H_{17}NO_2Br$ $[M+H]^+$ = 394.0443, found 394.0457

1-(hydroxymethyl)-5-iodo-3,3-diphenylindolin-2-one (4f)

Following the general procedure (GP-2), treatment of 5-iodo-3,3-diphenylindolin-2-one, **1f** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-(hydroxymethyl)-5-iodo-3,3-diphenylindolin-2-one **4f** as white solid (75 mg, 85% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 – 7.64 (m, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.36 – 7.27 (m, 6H), 7.24 – 7.18 (m, 4H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.28 (d, *J* = 5.4 Hz, 2H), 3.17 (t, *J* = 7.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 177.69, 140.91, 137.50, 135.03, 128.83, 128.43, 127.89, 127.80, 111.85,

86.34, 64.48, 62.77. **HRMS:** m/z calculated for $C_{21}H_{17}INO_2$ $[M+H]^+$ = 442.0304, found 442.0311.

4-chloro-1-(hydroxymethyl)-3,3-diphenylindolin-2-one (4h)

Following the general procedure (GP-2), treatment of 4-chloro-3,3-diphenylindolin-2-one, **1h** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 4-chloro-1-(hydroxymethyl)-3,3-diphenylindolin-2-one **4h** as white solid (60 mg, 86% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 – 7.28 (m, 11H), 7.11 – 7.05 (m, 2H), 5.21 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.61, 143.15, 137.40, 132.79, 130.14, 130.04, 129.93, 129.40, 128.27, 128.23, 127.92, 127.83, 125.12, 108.45, 64.57, 63.77. **HRMS:** m/z calculated for $C_{21}H_{17}NO_2Cl$ $[M+H]^+$ = 350.0948, found 350.0951

6-bromo-1-(hydroxymethyl)-3,3-diphenylindolin-2-one (4k)

Following the general procedure (GP-2), treatment of 6-bromo-3,3-diphenylindolin-2-one, **1k** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 6-bromo-1-(hydroxymethyl)-3,3-diphenylindolin-2-one **4k** as white solid (65 mg, 82% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 (d, *J* = 1.7 Hz, 1H), 7.31 – 7.24 (m, 7H), 7.23 – 7.18 (m, 4H), 7.10 (d, *J* = 8.1 Hz, 1H), 5.23 (s, 2H), 3.57 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.20, 142.43, 140.95, 131.69, 128.77, 128.39, 127.82, 127.71, 126.50, 122.24, 113.38, 64.47, 62.66. **HRMS:** m/z calculated for $C_{21}H_{17}NO_2Br$ $[M+H]^+$ = 394.0443, found 394.0437

3,3-bis(4-fluorophenyl)-1-(hydroxymethyl)indolin-2-one (4n)

Following the general procedure (GP-2), treatment of 3,3-bis(4-fluorophenyl)indolin-2-one, **1n** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with

DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 3,3-bis(4-fluorophenyl)-1-(hydroxymethyl)indolin-2-one **4n** as white solid (62 mg, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.33 (m, 1H), 7.24 – 7.11 (m, 7H), 7.02 – 6.92 (m, 4H), 5.29 (s, 2H), 2.70 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.27, 162.29 (d, *J* = 247.3 Hz), 140.99, 137.15, 132.42, 130.15 (d, *J* = 8.0 Hz), 128.93, 126.26, 123.80, 115.63 (d, *J* = 21.4 Hz), 109.98, 64.47, 61.56. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.50. **HRMS:** m/z calculated for $C_{21}H_{16}NO_2F_2$ $[M+H]^+$ = 352.1149, found 352.1141

3,3-bis(4-chlorophenyl)-1-(hydroxymethyl)indolin-2-one (4o)

Following the general procedure (GP-2), treatment of 3,3-bis(4-chlorophenyl)indolin-2-one, **1o** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 3,3-bis(4-chlorophenyl)-1-(hydroxymethyl)indolin-2-one **4o** as white solid (65 mg, 85% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.34 (m, 1H), 7.29 – 7.24 (m, 3H), 7.20 – 7.14 (m, 4H), 5.31 (s, 2H), 3.12 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 177.68, 141.03, 139.71, 133.94, 132.24, 131.79, 129.83, 129.09, 128.55, 126.26, 123.86, 111.08, 109.99, 64.54, 61.82. **HRMS:** m/z calculated for $C_{21}H_{16}NO_2Cl_2$ $[M+H]^+$ = 384.0558, found 384.0551

1'-(hydroxymethyl)spiro[cyclobutane-1,3'-indolin]-2'-one (4r)

Following the general procedure (GP-2), treatment of spiro[cyclobutane-1,3'-indolin]-2'-one, **1r** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1'-(hydroxymethyl)spiro[cyclobutane-1,3'-indolin]-2'-one **4r** as white solid (32 mg, 80% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 7.2 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.15 – 7.11 (m, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.25 (d, *J* = 7.7 Hz, 2H), 3.66 (t, *J* = 7.9 Hz, 1H),

2.68 – 2.57 (m, 2H), 2.40 – 2.29 (m, 3H), 2.28 – 2.16 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.98, 141.01, 134.00, 128.09, 123.35, 122.67, 108.90, 64.00, 48.46, 31.43, 16.80. **HRMS:** m/z calculated for $C_{12}H_{14}NO_2$ $[M+H]^+$ = 204.1025, found 204.1036

1'-(hydroxymethyl)spiro[cyclohexane-1,3'-indolin]-2'-one (4s)

Following the general procedure (GP-2), treatment of spiro[cyclohexane-1,3'-indolin]-2'-one, **1s** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1'-(hydroxymethyl)spiro[cyclohexane-1,3'-indolin]-2'-one **4s** as white solid (39 mg, 85% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 (d, *J* = 7.4 Hz, 1H), 7.29 (m, 1H), 7.10 – 7.06 (m, 2H), 5.26 (d, *J* = 7.7 Hz, 2H), 3.17 – 3.09 (m, 1H), 1.97 – 1.89 (m, 2H), 1.87 – 1.79 (m, 2H), 1.79 – 1.71 (m, 2H), 1.71 – 1.63 (m, 2H), 1.63 – 1.55 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.35, 140.81, 135.11, 127.74, 124.23, 122.72, 109.01, 64.04, 47.71, 33.13, 29.85, 25.25, 21.20. **HRMS:** m/z calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$ = 232.1338, found 232.1347.

1-(hydroxymethyl)-3,6-dimesitylindolin-2-one (4B)

Following the general procedure (GP-2), treatment of 3,6-dimesitylindolin-2-one, **1B** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1-(hydroxymethyl)-3,6-dimesitylindolin-2-one, **4B** as white solid (70 mg, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.05 – 6.98 (m, 3H), 6.94 (s, 2H), 6.88 – 6.86 (m, 1H), 6.81 (s, 1H), 5.21 (s, 1H), 5.01 (dd, *J* = 47.1, 15.1 Hz, 2H), 2.55 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 2.06 (s, 3H), 1.98 (s, 3H), 1.70 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 176.90, 141.60, 141.42, 138.23, 138.01, 137.80, 137.15, 136.84, 136.02, 135.93, 130.61, 129.71, 129.45, 128.29, 126.41, 125.28, 123.98,

111.27, 60.43, 47.84, 41.50, 21.46, 21.17, 21.04, 20.88, 20.70, 19.45. **HRMS:** m/z calculated for $C_{27}H_{30}NO_2$ $[M+H]^+$ = 400.2277, found 400.2263.

5-bromo-2-(hydroxymethyl)isoindolin-1-one (4E)

Following the general procedure (GP-2), treatment of 5-bromo-isoindolin-1-one, **1E** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 5-bromo-2-(hydroxymethyl)isoindolin-1-one **4E** as white solid (39 mg, 81% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.57 (m, 2H), 5.12 (s, 2H), 4.53 (s, 2H), 3.81 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 168.49, 143.61, 131.76, 131.07, 127.02, 126.55, 125.40, 66.53, 48.45. **HRMS:** m/z calculated for $C_9H_9BrNO_2$ $[M+H]^+$ = 241.9817, found 241.9825

1,2-bis(3,3-diphenyl-3*H*-indol-2-yl)disulfane (6a)

Following the general procedure (GP-3), treatment of 3,3-diphenylindoline-2-thione, **5a** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(3,3-diphenyl-3*H*-indol-2-yl)disulfane **6a** as white solid (113 mg, 94% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.43 (m, 6H), 7.40 – 7.33 (m, 12H), 7.33 – 7.27 (m, 4H), 7.23 (d, *J* = 7.1 Hz, 2H), 7.18 – 7.12 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.46, 153.37, 146.13, 141.73, 140.72, 140.02, 128.91, 128.64, 128.56, 128.44, 128.38, 127.97, 127.61, 127.53, 126.58, 125.76, 124.74, 124.29, 123.05, 120.25, 110.24, 73.55. **HRMS:** m/z calculated for $C_{40}H_{29}N_2S_2$ $[M+H]^+$ = 601.1772, found 601.1784

1,2-bis(5-methyl-3,3-diphenyl-3*H*-indol-2-yl)disulfane (6c)

Following the general procedure (GP-3), treatment of 5-methyl-3,3-diphenylindoline-2-thione, **5c** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with

DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(5-methyl-3,3-diphenyl-3*H*-indol-2-yl)disulfane **6c** as white solid (121 mg, 96% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 – 7.30 (m, 11H), 7.20 – 7.01 (m, 2H), 7.01 – 6.69 (m, 11H), 6.67 – 6.47 (m, 2H), 2.30 (s, 6H), 1.76 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.18, 151.27, 146.19, 140.83, 135.55, 128.94, 128.83, 128.64, 127.83, 124.90, 119.74, 73.34, 21.63. **HRMS:** m/z calculated for $C_{42}H_{33}N_2S_2$ $[M+H]^+$ = 629.2085, found 629.2095

1,2-bis(5-chloro-3,3-diphenyl-3H-indol-2-yl)disulfane (6d)

Following the general procedure (GP-3), treatment of 5-chloro-3,3-diphenylindoline-2-thione, **5d** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(5-chloro-3,3-diphenyl-3*H*-indol-2-yl)disulfane **6d** as white solid (120 mg, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 – 7.34 (m, 22H), 7.31 – 7.29 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.90, 151.91, 147.67, 139.99, 131.53, 129.08, 128.68, 128.51, 128.28, 124.70, 121.03, 73.78. **HRMS:** m/z calculated for $C_{40}H_{27}N_2S_2Cl_2$ $[M+H]^+$ = 669.0993, found 669.1000

1,2-bis(5-bromo-3,3-diphenyl-3*H*-indol-2-yl)disulfane (6e)

Following the general procedure (GP-3), treatment of 5-bromo-3,3-diphenylindoline-2-thione, **5e** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(5-bromo-3,3-diphenyl-3*H*-indol-2-yl)disulfane **6e** as white solid (131 mg, 87% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 – 7.44 (m, 2H), 7.43 – 7.33 (m, 24H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.97, 152.34, 148.01, 139.95, 131.60, 129.09, 128.51, 128.29, 127.51, 121.49, 119.44, 73.80. **HRMS:** m/z calculated for $C_{40}H_{27}N_2S_2Br_3$ $[M+H]^+$ = 756.9982, found 756.9990

1,2-bis(5-iodo-3,3-diphenyl-3*H*-indol-2-yl)disulfane (6f)

Following the general procedure (GP-3), treatment of 5-iodo-3,3-diphenylindoline-2-thione, **5f** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(5-iodo-3,3-diphenyl-3H-indol-2-yl)disulfane **6f** as white solid (143 mg, 84% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 – 7.64 (m, 21H), 7.53 (s, 2H), 7.43 – 7.34 (m, 20H), 7.28 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.96, 153.04, 148.29, 139.96, 137.60, 133.21, 129.09, 128.92, 128.53, 128.28, 121.99, 90.51, 73.71. **HRMS:** m/z calculated for $C_{40}H_{27}N_2S_2I_2$ $[M+H]^+$ = 852.9705, found 852.9715

1,2-bis(4-chloro-3,3-diphenyl-3*H*-indol-2-yl)disulfane (6h)

Following the general procedure (GP-3), treatment of 4-chloro-3,3-diphenylindoline-2-thione, **5h** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(4-chloro-3,3-diphenyl-3*H*-indol-2-yl)disulfane **6h** as white solid (116 mg, 87% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.47 – 7.43 (m, 10H), 7.41 – 7.35 (m, 12H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.09 (dd, *J* = 8.2, 0.7 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.01, 155.23, 142.46, 135.66, 130.60, 130.07, 129.44, 128.58, 128.40, 127.07, 119.02, 74.87. **HRMS:** m/z calculated for $C_{40}H_{27}N_2S_2Cl_2$ $[M+H]^+$ = 669.0993, found 669.0989

1,2-bis(6-fluoro-3,3-diphenyl-3*H*-indol-2-yl)disulfane (6j)

Following the general procedure (GP-3), treatment of 6-fluoro-3,3-diphenylindoline-2-thione, **5j** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(6-fluoro-3,3-

diphenyl-3*H*-indol-2-yl)disulfane **6j** as white solid (115 mg, 90% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 – 7.34 (m, 20H), 7.23 – 7.20 (m, 2H), 7.17 – 7.14 (m, 2H), 6.90 – 6.83 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.68, 164.32, 161.88, 154.63 (d, *J* = 11.0 Hz), 141.71 (d, *J* = 2.6 Hz), 140.45, 129.02, 128.51, 128.17, 112.47 (d, *J* = 23.2 Hz), 107.93 (d, *J* = 24.3 Hz), 73.22. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.61. **HRMS:** m/z calculated for $C_{40}H_{27}N_2S_2F_2$ $[M+H]^+$ = 637.1584, found 637.1594.

1,2-bis(3,3-di-*p*-tolyl-3*H*-indol-2-yl)disulfane (6m)

Following the general procedure (GP-3), treatment of 3,3-di-*p*-tolylindoline-2-thione, **5m** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(3,3-di-*p*-tolyl-3*H*-indol-2-yl)disulfane **6m** as white solid (121 mg, 92% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 8H), 7.34 – 7.31 (m, 2H), 7.25 – 7.13 (m, 12H), 2.38 (s, 12H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.78, 153.36, 146.53, 137.76, 137.59, 129.54, 128.50, 128.15, 125.62, 124.09, 120.14, 72.91, 21.25. **HRMS:** m/z calculated for $C_{44}H_{37}N_2S_2$ $[M+H]^+$ = 657.2398, found 657.2401

1,2-bis(3,3-bis(4-fluorophenyl)-3*H*-indol-2-yl)disulfane (6p)

Following the general procedure (GP-3), treatment of 3,3-bis(4-fluorophenyl)indoline-2-thione, **5p** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(3,3-bis(4-fluorophenyl)-3*H*-indol-2-yl)disulfane **6p** as white solid (118 mg, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 7.7 Hz, 2H), 7.45 – 7.38 (m, 8H), 7.38 – 7.33 (m, 2H), 7.21 – 7.15 (m, 4H), 7.11 – 7.03 (m, 8H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.96, 163.85, 161.38, 153.06, 145.90, 136.23, 136.20, 130.33, 130.25, 128.76, 126.10, 124.07, 120.36,

116.08, 115.86, 72.17. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -113.79. **HRMS:** m/z calculated for $C_{40}H_{25}N_2S_2F_4$ $[M+H]^+$ = 673.1395, found 673.1402.

1,2-bis(3,3-dimethyl-3*H*-indol-2-yl)disulfane (6s)

Following the general procedure (GP-3), treatment of 3,3-dimethylindoline-2-thione, **5s** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of DMSO with DIPEA (1 eq.) at rt for 7 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 20) afforded 1,2-bis(3,3-dimethyl-3*H*-indol-2-yl)disulfane **6s** as white solid (55 mg, 78% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.77 – 7.73 (m, 1H), 7.45 – 7.32 (m, 4H), 7.23 – 7.15 (m, 2H), 6.84 – 6.80 (m, 1H), 1.56 (s, 67H), 1.53 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 175.54, 150.43, 145.37, 143.79, 139.98, 128.15, 127.88, 127.39, 124.46, 123.26, 122.19, 121.27, 110.93, 56.22, 55.62, 28.78, 25.31. **HRMS:** m/z calculated for $C_{20}H_{21}N_2S_2$ $[M+H]^+$ = 353.1146, found 353.1154

3,3-diphenylindoline-2-one (1a)

Following the general procedure (GP-4), treatment of 3,3-diphenylindoline-2-thione, **5a** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 3,3-diphenylindolin-2-one **1a** as white solid (50 mg, 87% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.05 (s, 1H), 7.32 – 7.27 (m, 10H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.27, 141.75, 140.34, 133.66, 128.62, 128.57, 128.39, 127.50, 126.39, 122.94, 110.59, 63.25. **HRMS:** m/z calculated for $C_{20}H_{16}NO$ $[M+H]^+$ = 286.1232, found 286.1241

5-methoxy-3,3-diphenylindolin-2-one (1b)

Following the general procedure (GP-4), treatment of 5-methoxy-3,3-diphenylindolin-2-thione, **5b** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using

silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-methoxy-3,3-diphenylindolin-2-one **1b** as white solid (57 mg, 91% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.77 (s, 1H), 7.34 – 7.24 (m, 10H), 7.13 – 7.06 (m, 1H), 6.57 (ddd, *J* = 10.4, 5.3, 2.8 Hz, 2H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.71, 160.15, 142.07, 141.36, 129.30, 128.60, 128.50, 128.38, 128.03, 127.41, 127.03, 125.62, 108.06, 97.41, 62.70, 55.68. **HRMS:** m/z calculated for $C_{21}H_{18}NO_2$ $[M+H]^+$ = 316.1338, found 316.1345

5-methyl-3,3-diphenylindolin-2-one (1c)

Following the general procedure (GP-4), treatment of 5-methyl-3,3-diphenylindolin-2-thione, **5c** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-methyl-3,3-diphenylindolin-2-one, **1c** as white solid (53 mg, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12 (s, 1H), 7.34 – 7.30 (m, 2H), 7.29 (d, *J* = 2.6 Hz, 6H), 7.28 – 7.26 (m, 2H), 7.03 (dd, *J* = 9.9, 1.1 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.63, 141.91, 137.62, 133.64, 132.52, 128.84, 128.61, 127.45, 127.14, 109.97, 63.15, 21.41. **HRMS:** m/z calculated for $C_{21}H_{18}NO$ $[M+H]^+$ = 300.1388, found 300.1394

5-chloro-3,3-diphenylindolin-2-one (1d)

Following the general procedure (GP-43), treatment of 5-chloro-3,3-diphenylindolin-2-thione, **5d** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-chloro-3,3-diphenylindolin-2-one, **1d** as white solid (54 mg, 84% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.47 (s, 1H), 7.35 – 7.32 (m, 2H), 7.32 – 7.27 (m, 5H), 7.26 (s, 1H), 7.25 – 7.24 (m, 2H), 7.23 – 7.21 (m, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.33, 141.09, 138.71, 135.31, 128.81, 128.55, 128.47, 128.36, 127.82, 126.84, 111.33, 63.30. **HRMS:** m/z calculated for $C_{20}H_{15}NOCl$ $[M+H]^+$ = 320.0842, found 320.0854

5-bromo-3,3-diphenylindolin-2-one (1e)

Following the general procedure (GP-4), treatment of 5-bromo-3,3-diphenylindolin-2-thione, **5e** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-bromo-3,3-diphenylindolin-2-one, **1e** as white solid (59 mg, 81% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.29 (s, 1H), 7.39 – 7.36 (m, 1H), 7.35 – 7.29 (m, 7H), 7.26 – 7.23 (m, 4H), 6.86 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 179.10, 141.06, 139.15, 135.67, 131.44, 129.60, 128.82, 128.47, 127.84, 115.67, 111.78, 63.24. **HRMS:** m/z calculated for $C_{20}H_{15}NOBr$ $[M+H]^+$ = 364.0337, found 364.0348.

5-nitro-3,3-diphenylindolin-2-one (1g)

Following the general procedure (GP-4), treatment of 5-nitro-3,3-diphenylindolin-2-thione, **5g** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 5-nitro-3,3-diphenylindolin-2-one, **1g** as white solid (47 mg, 71% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 9.45 (s, 1H), 8.22 – 8.20 (m, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 7.37 – 7.31 (m, 6H), 7.27 – 7.24 (m, 4H), 7.06 (d, *J* = 8.6 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 180.57, 146.14, 143.94, 140.18, 134.60, 129.06, 128.34, 128.27, 125.62, 122.33, 110.52, 63.20. **HRMS:** m/z calculated for $C_{20}H_{15}N_2O_3$ $[M+H]^+$ = 331.1083, found 331.1091

4-chloro-3,3-diphenylindolin-2-one (1h)

Following the general procedure (GP-4), treatment of 4-chloro-3,3-diphenylindolin-2-thione, **5h** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 4-chloro-3,3-diphenylindolin-2-one, **1h** as

white solid (53 mg, 83% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.24 (s, 1H), 7.35 – 7.26 (m, 5H), 7.24 (d, *J* = 1.3 Hz, 1H), 7.22 – 7.18 (m, 4H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.10 - 7.06 (m, 1H), 6.97 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 179.81, 140.23, 139.82, 133.84, 132.73, 129.87, 128.92, 126.14, 123.29, 110.96, 62.17. **HRMS:** m/z calculated for $C_{20}H_{15}NOCl$ $[M+H]^+$ = 320.0842, found 320.0851

4,7-dichloro-3,3-diphenylindolin-2-one (1i)

Following the general procedure (GP-4), treatment of 4,7-dichloro-3,3-diphenylindolin-2-thione, **5i** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^oC for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 4,7-dichloro-3,3-diphenylindolin-2-one, **1i** as white solid (32 mg, 65% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.44 (s, 1H), 7.33 (s, 10H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.52, 139.80, 137.04, 131.54, 131.11, 129.78, 129.36, 128.36, 128.10, 125.16, 114.13, 65.21. **HRMS:** m/z calculated for $C_{20}H_{14}NOCl_2$ $[M+H]^+$ = 354.0452, found 354.0459.

3,3-di-*p*-tolylindolin-2-one (1m)

Following the general procedure (GP-4), treatment of 3,3-di-*p*-tolylindolin-2-thione, **5m** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^oC for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 3,3-di-*p*-tolylindolin-2-one, **1m** as white solid (55 mg, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.93 (s, 1H), 7.24 – 7.16 (m, 6H), 7.11 (d, *J* = 8.3 Hz, 4H), 7.07 – 7.01 (m, 1H), 6.95 (dd, *J* = 7.4, 1.2 Hz, 1H), 2.32 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 180.61, 140.34, 138.89, 137.15, 134.09, 129.30, 128.41, 128.21, 126.24, 122.88, 110.50, 62.58, 21.17. **HRMS:** m/z calculated for $C_{22}H_{20}NO$ $[M+H]^+$ = 314.1545, found 314.1552

1-(hydroxymethyl)-3,3-diphenylindolin-2-one (1p)

Following the general procedure (GP-4), treatment of 3,3-bis(4-fluorophenyl)indolin-2-thione, **5p** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 3,3-bis(4-fluorophenyl)indolin-2-one, **1p** as white solid (55 mg, 85% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 9.10 (s, 1H), 7.28 – 7.21 (m, 5H), 7.17 (d, *J* = 6.8 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.03 – 6.96 (m, 5H). **^{13}C NMR (101 MHz, CDCl$_3$):** ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 180.15, 163.50, 161.04, 140.16, 137.31 (d, *J* = 3.0 Hz), 133.33, 130.19 (d, *J* = 8.1 Hz), 128.74, 126.21, 123.21, 115.60 (d, *J* = 21.7 Hz), 110.81, 61.89. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -114.68. **HRMS:** m/z calculated for $C_{20}H_{14}NOF_2$ $[M+H]^+$ = 322.1043, found 322.1047

3,3-dimethylindolin-2-one (1s)

Following the general procedure (GP-4), treatment of 3,3-dimethylindolin-2-thione, **5s** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 3,3-dimethylindolin-2-one, **1s** as white solid (21 mg, 66% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.77 (s, 1H), 7.22 – 7.18 (m, 2H), 7.07 – 7.01 (m, 1H), 6.95 – 6.93 (m, 1H), 1.41 (s, 6H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 184.29, 139.96, 136.41, 127.77, 122.73, 122.57, 110.03, 44.82, 24.45. **HRMS:** m/z calculated for $C_{10}H_{12}NO$ $[M+H]^+$ = 162.0919, found 162.0925

spiro[cyclobutane-1,3'-indolin]-2'-one (1u)

Following the general procedure (GP-4), treatment of spiro[cyclohexane-1,3'-indolin]-2'-thione, **5u** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded spiro[cyclohexane-1,3'-indolin]-2'-one, **1u**

as white solid (29 mg, 73% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.01 (s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.04 – 7.00 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 1.99 – 1.84 (m, 4H), 1.83 – 1.71 (m, 3H), 1.68 – 1.58 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 184.05, 140.33, 135.89, 127.50, 124.31, 121.89, 110.08, 48.25, 32.95, 25.27, 21.23. **HRMS:** m/z calculated for $C_{13}H_{16}NO$ $[M+H]^+$ = 202.1232, found 202.1241.

1-benzyl-3,3-diphenylindolin-2-one (1z)

Following the general procedure (GP-4), treatment of 1-benzyl-3,3-diphenylindolin-2-thione, **5z** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^oC for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-benzyl-3,3-diphenylindolin-2-one, **1z** as white solid (61 mg, 71% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.23 (m, 16H), 7.21 - 7.17 (m, 1H), 7.07 – 7.03 (m, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.00 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 177.76, 142.29, 142.09, 135.94, 133.04, 128.95, 128.63, 128.60, 128.34, 127.75, 127.48, 127.32, 126.22, 123.03, 109.76, 62.68, 44.20. **HRMS:** m/z calculated for $C_{27}H_{22}NO$ $[M+H]^+$ = 376.1701, found 376.1706

1-benzyl-4-chloro-3,3-diphenylindolin-2-one (1F)

Following the general procedure (GP-3), treatment of 1-benzyl-4-chloro-3,3-diphenylindolin-2-thione, **5F** (0.2 mmol, 1 eq.) and selectfluor **3** (0.24 mmol, 1.2 eq.) in 2 mL of IPA at 60 ^oC for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-benzyl-4-chloro-3,3-diphenylindolin-2-one, **1F** as white solid (61 mg, 81% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.30 (m, 12H), 7.30 – 7.25 (m, 3H), 7.20 - 7.16 (m, 1H), 6.99 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.77 (dd, *J* = 7.8, 0.8 Hz, 1H), 4.97 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.09, 144.23, 137.86, 135.60, 132.66, 130.22, 129.86, 129.46, 129.01, 128.25, 127.95, 127.81, 127.43, 124.57, 108.28, 63.58, 44.50. **HRMS:** m/z calculated for $C_{27}H_{20}NOCl$ $[M+H]^+$ = 409.1233, found 409.1241

1-benzyl-7-methyl-3,3-diphenylindolin-2-one (1G)

Following the general procedure (GP-4), treatment of 1-benzyl-7-methyl-3,3-diphenylindolin-2-thione, **5G** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ºC for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-benzyl-7-methyl-3,3-diphenylindolin-2-one, **1G** as white solid (65 mg, 84% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.30 – 7.27 (m, 8H), 7.26 – 7.21 (m, 3H), 7.14 – 7.08 (m, 5H), 6.97 (d, *J* = 1.5 Hz, 1H), 6.68 (d, *J* = 1.0 Hz, 1H), 5.26 (s, 2H), 2.25 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.74, 143.99, 142.35, 138.82, 138.76, 137.91, 133.79, 133.07, 129.45, 128.95, 128.68, 128.50, 128.40, 127.34, 127.26, 126.46, 125.80, 125.70, 119.84, 62.16, 56.25, 45.38, 19.15. **HRMS:** m/z calculated for $C_{28}H_{24}NO$ $[M+H]^+$ = 390.1858, found 390.1864

1-benzyl-7-fluoro-3,3-diphenylindolin-2-one (1H)

Following the general procedure (GP-3), treatment of 1-benzyl-7-fluoro-3,3-diphenylindolin-2-thione, **5H** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 2 mL of IPA at 60 ºC for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 1-benzyl-7-fluoro-3,3-diphenylindolin-2-one, **1H** as white solid (65 mg, 80% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.23 (m, 5H), 7.06 – 6.95 (m, 1H), 5.15 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 177.60, 148.97, 146.53, 141.63, 137.22, 135.90 (d, *J* = 2.3 Hz), 129.16 (d, *J* = 8.7 Hz), 128.69, 128.53, 127.67, 127.51, 123.59 (d, *J* = 6.3 Hz), 122.13 (d, *J* = 2.8 Hz), 116.39 (d, *J* = 19.6 Hz), 62.89, 45.77 (d, *J* = 4.6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -133.02. **HRMS:** m/z calculated for $C_{27}H_{20}NOF$ $[M+H]^+$ = 393.1529, found 393.1533

indolin-2-one (1D)

Following the general procedure (GP-4), treatment of indolin-2-thione, **5D** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ºC for 5 hours followed

by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded indolin-2-one, **1D** as off white solid (11 mg, 42% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.35 (s, 1H), 7.23 – 7.17 (m, 2H), 7.03 – 6.97 (m, 1H), 6.92 – 6.87 (m, 1H), 3.54 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 178.45, 142.77, 128.03, 125.40, 124.65, 122.42, 110.01, 36.45. **HRMS:** m/z calculated for C_8H_8NO $[M+H]^+$ = 134.0606, found 134.0613

4-chloroindolin-2-one (1E)

Following the general procedure (GP-$), treatment of 4-chloroindolin-2-thione, **5E** (0.2 mmol, 1 eq.) and selectfluor **2** (0.24 mmol, 1.2 eq.) in 1 mL of MeOH at 60 ^{o}C for 5 hours followed by column chromatography of the crude reaction mixture using silica gel in EtOAc : *n*-hexane (1 : 5) afforded 4-chloroindolin-2-one, **1E** as off white solid (12 mg, 71% yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.44 (s, 1H), 7.21 – 7.15 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.82 – 6.76 (m, 1H), 3.55 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 176.32, 176.22, 130.70, 129.59, 129.45, 128.54, 123.97, 122.66, 108.08, 35.79. **HRMS:** m/z calculated for C_8H_7NOCl $[M+H]^+$ = 168.0216, found 168.0222.

4.5 References

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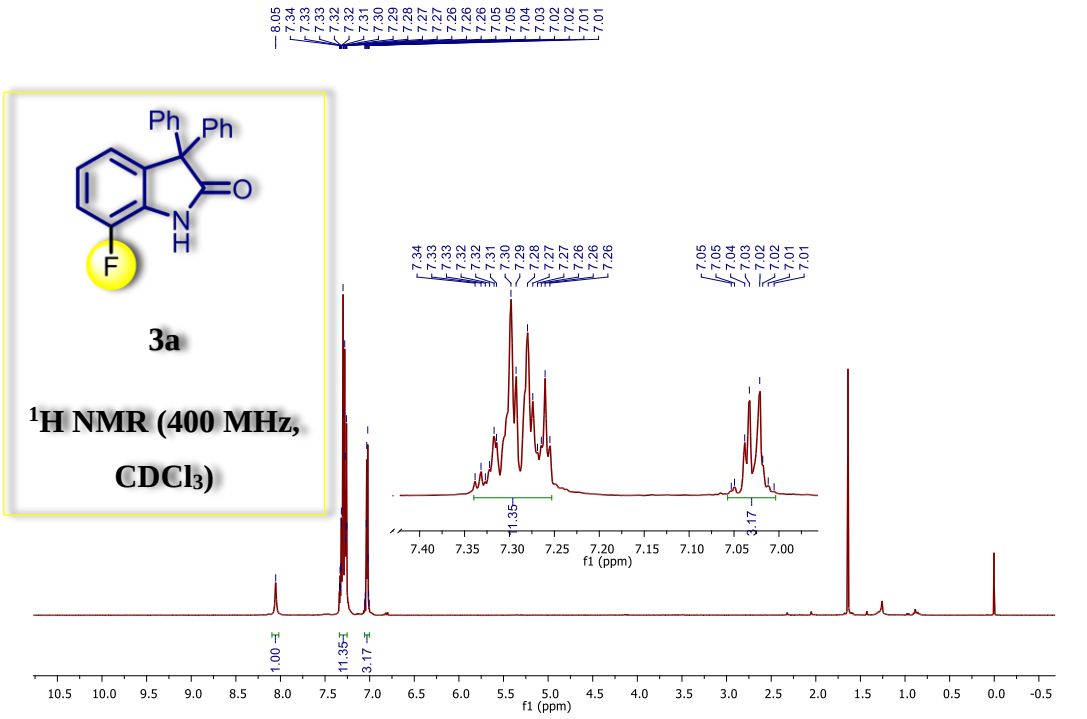
4.6 NMR spectras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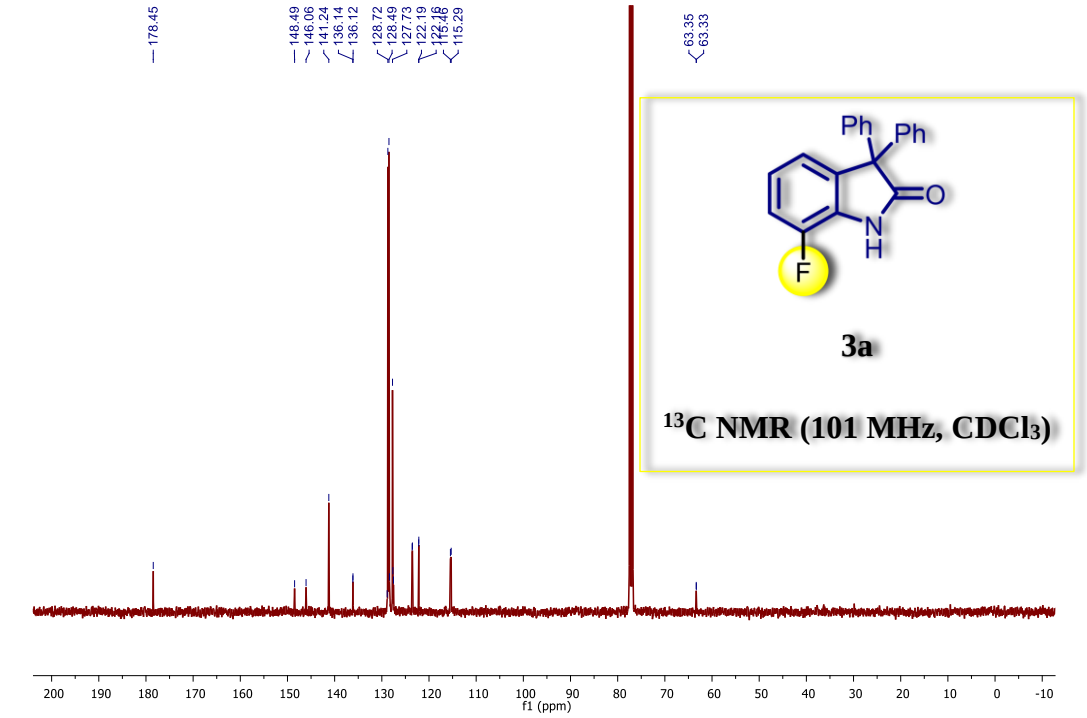
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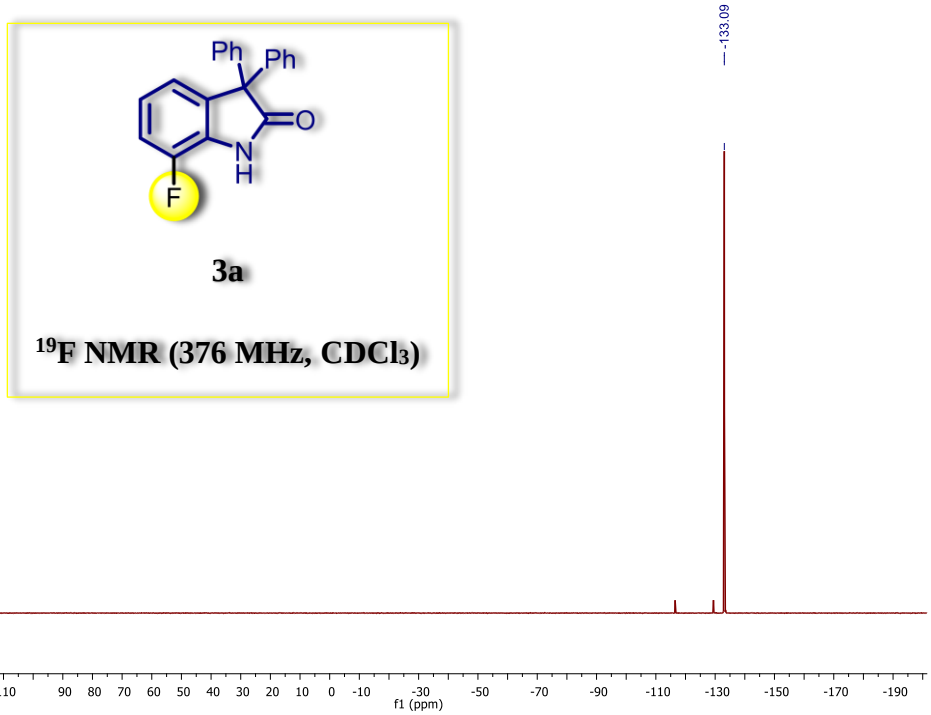
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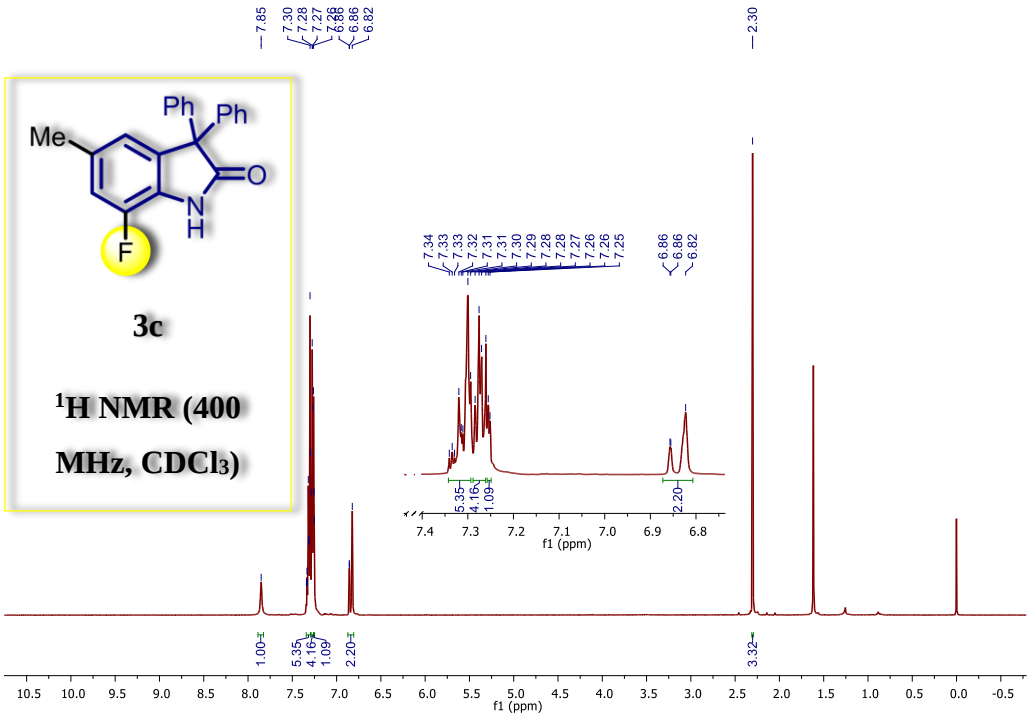
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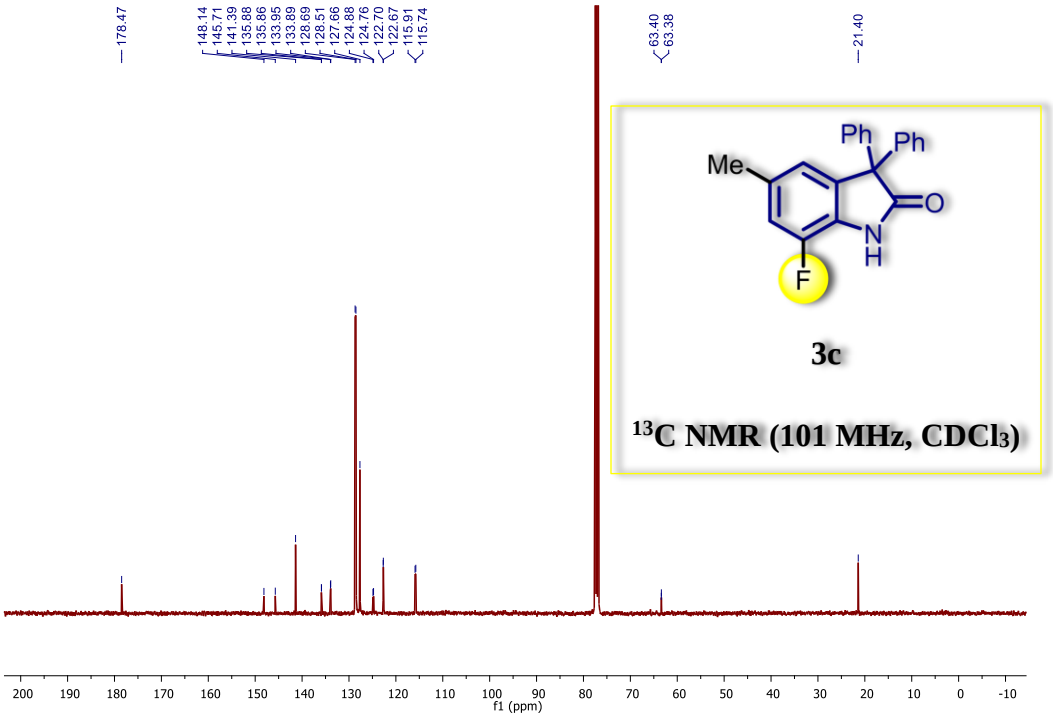
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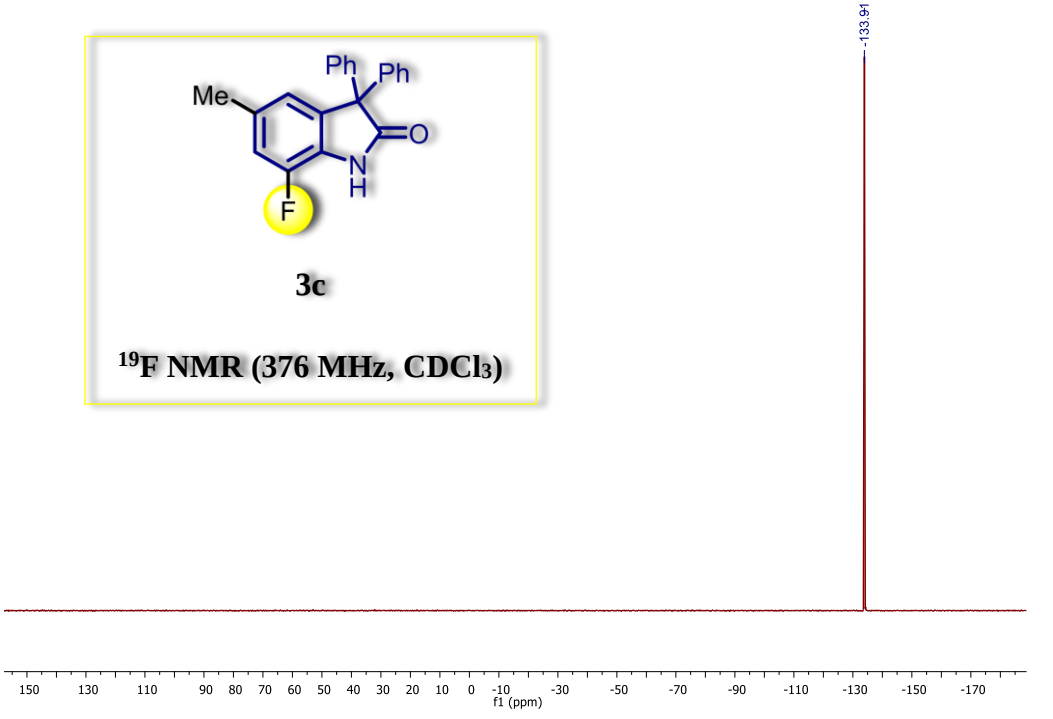
f1 (ppm)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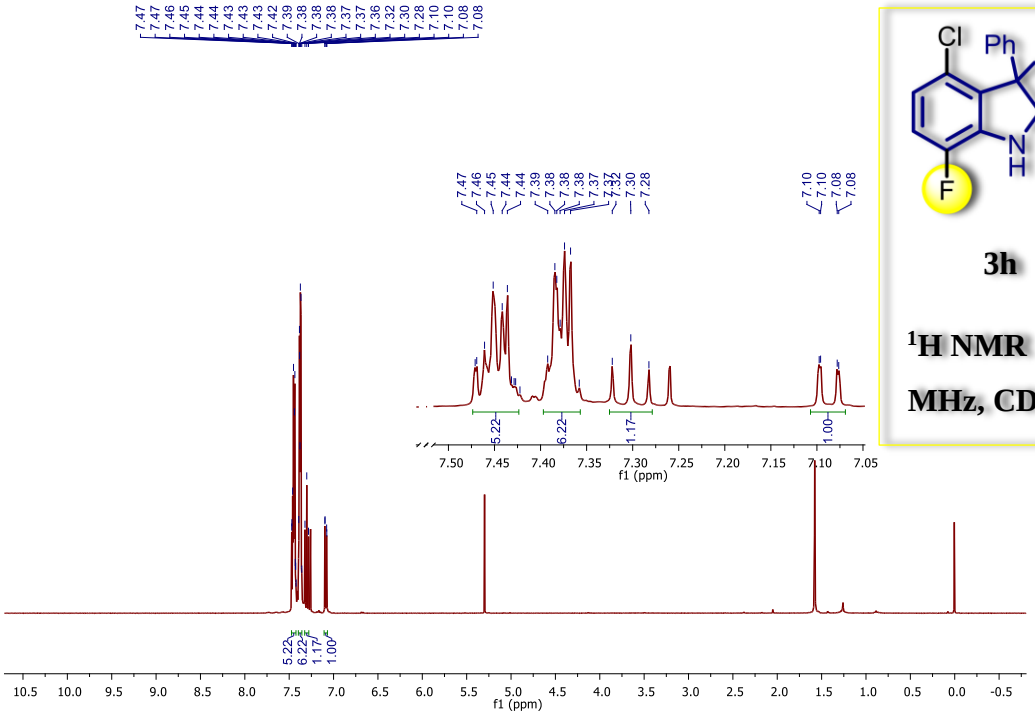

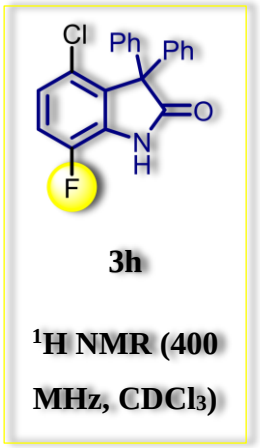

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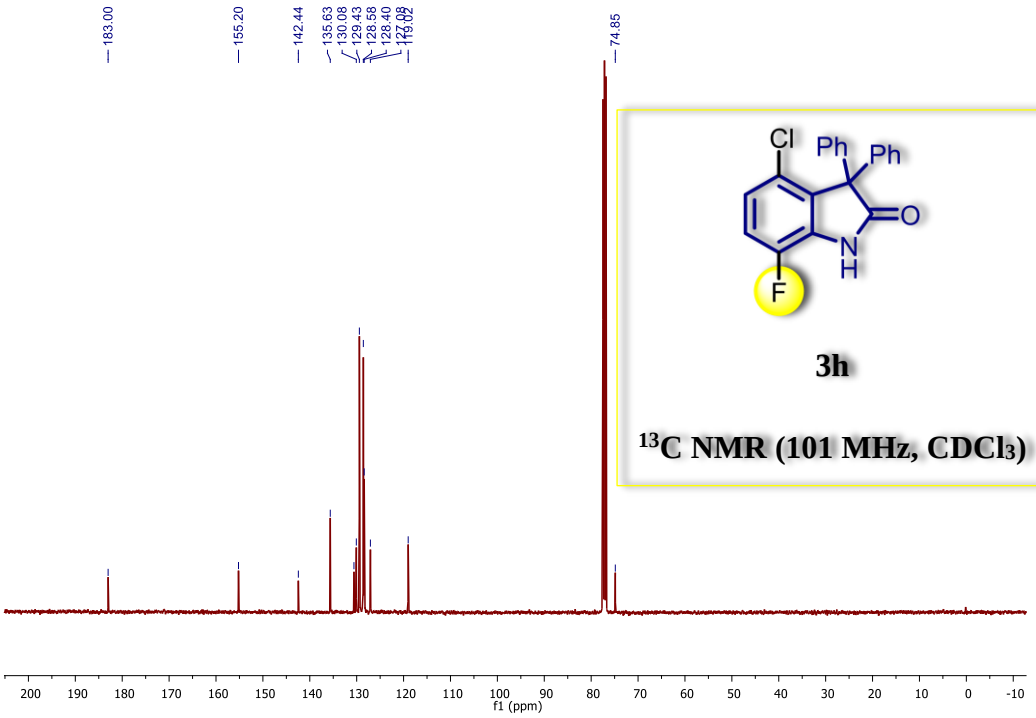

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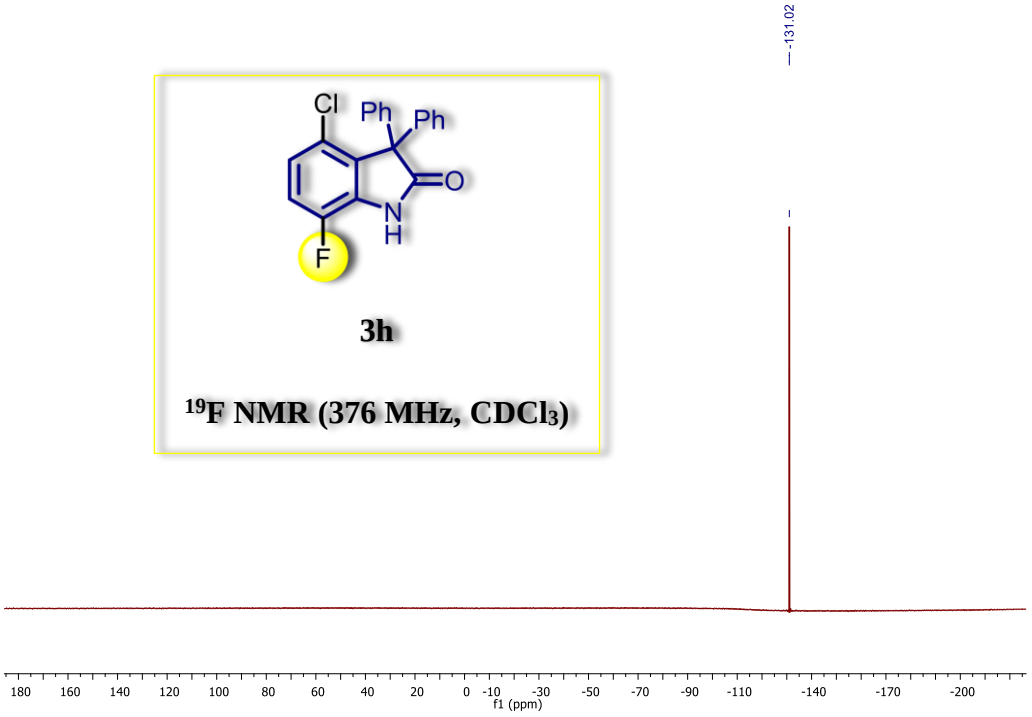
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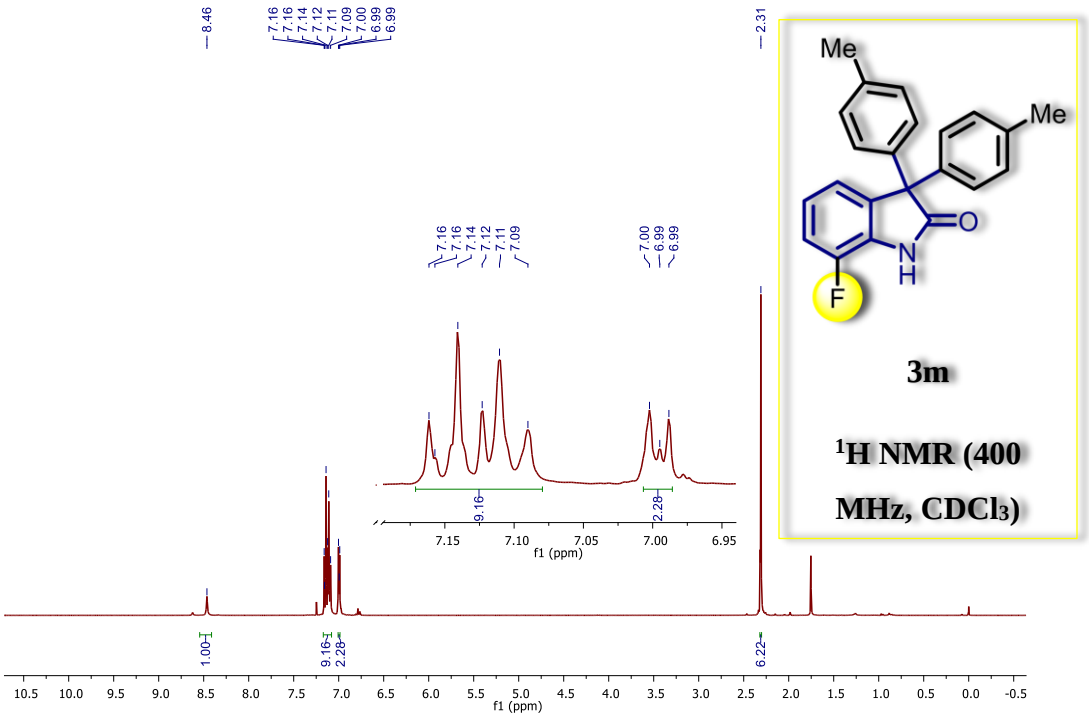
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Me
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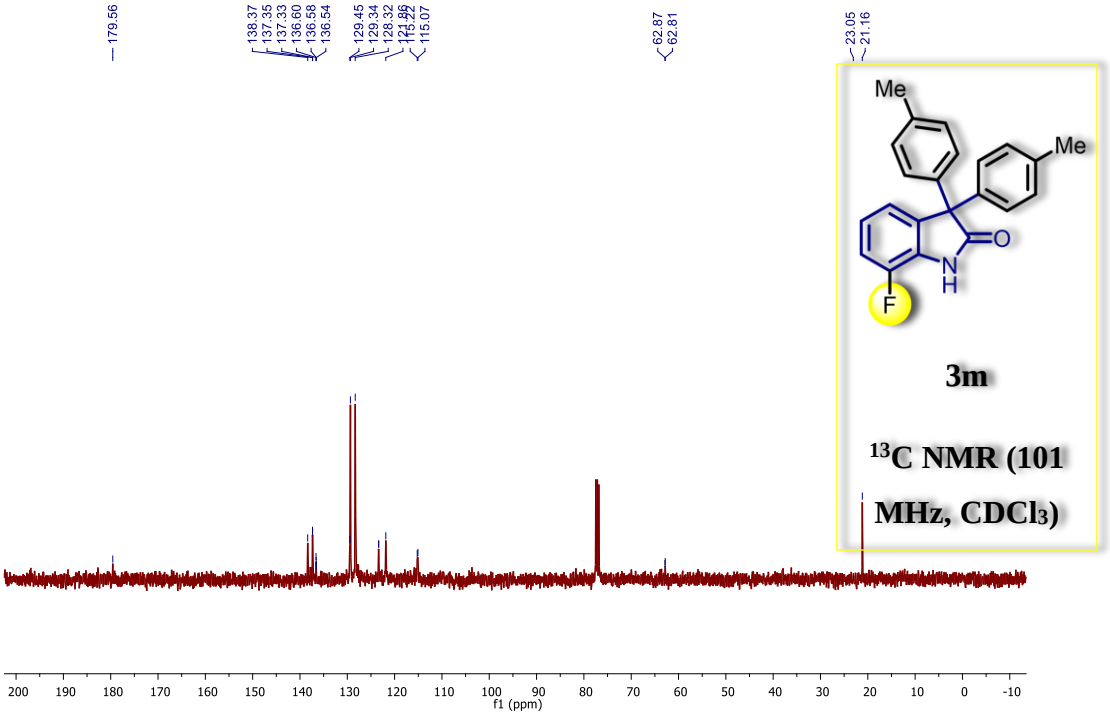
2.28
6.22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Me
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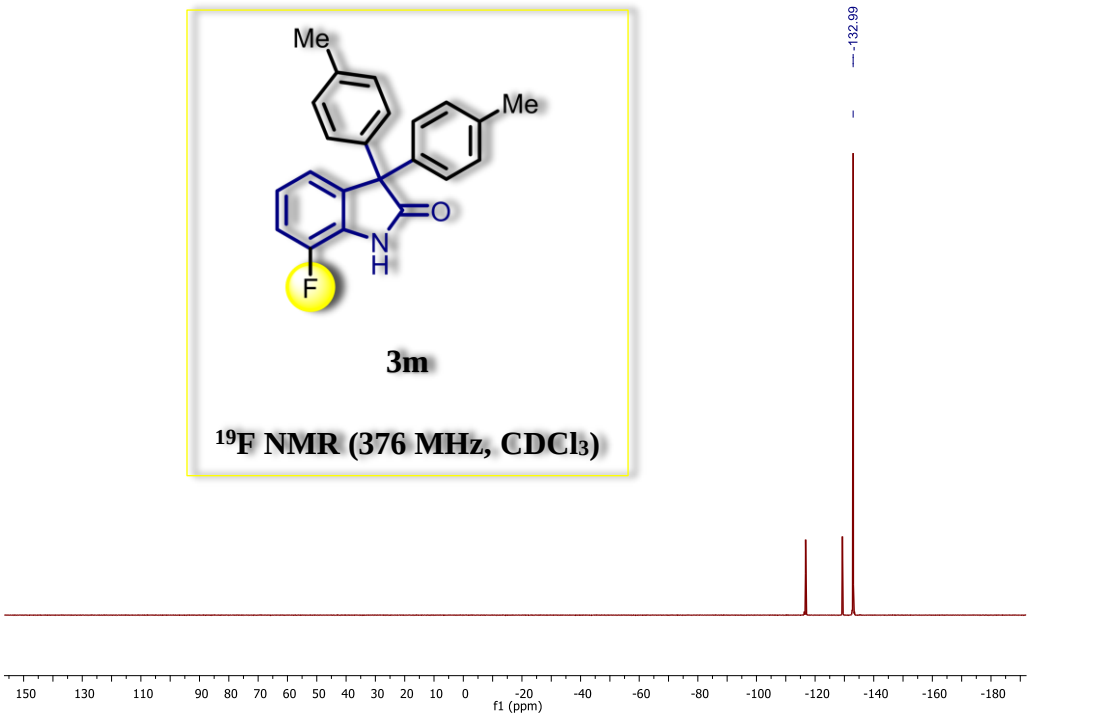
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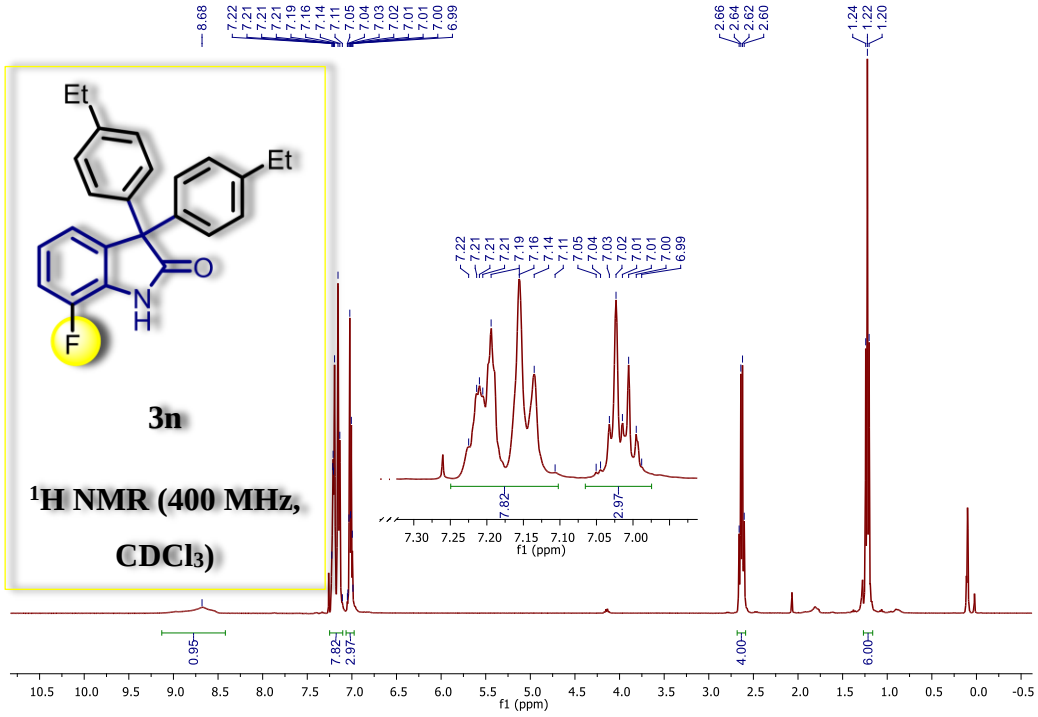
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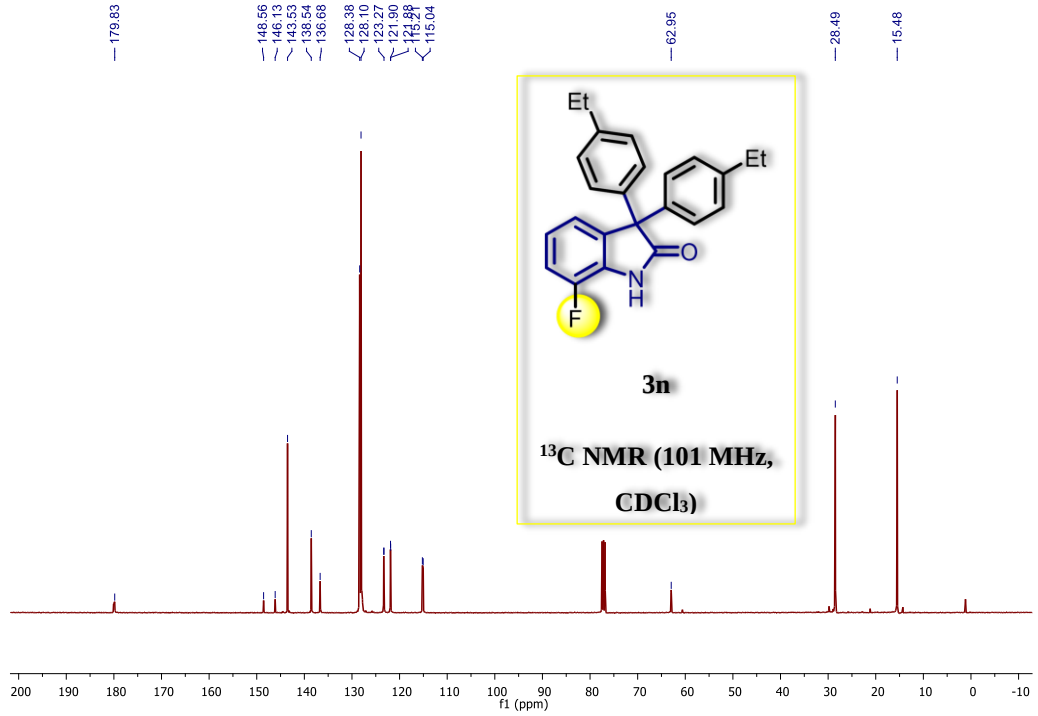
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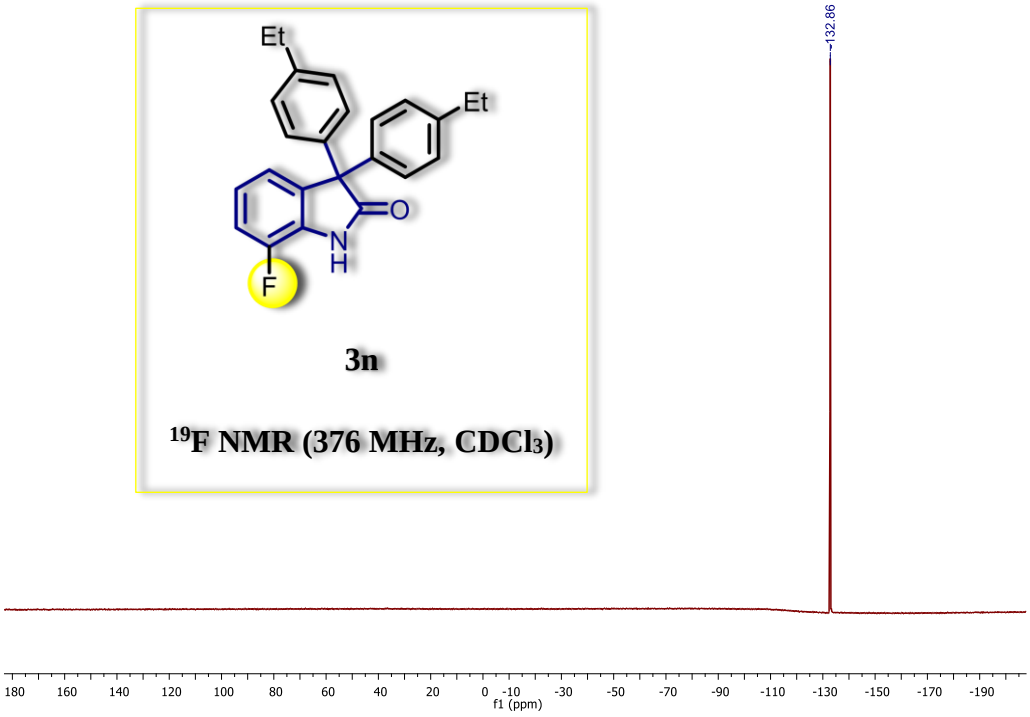
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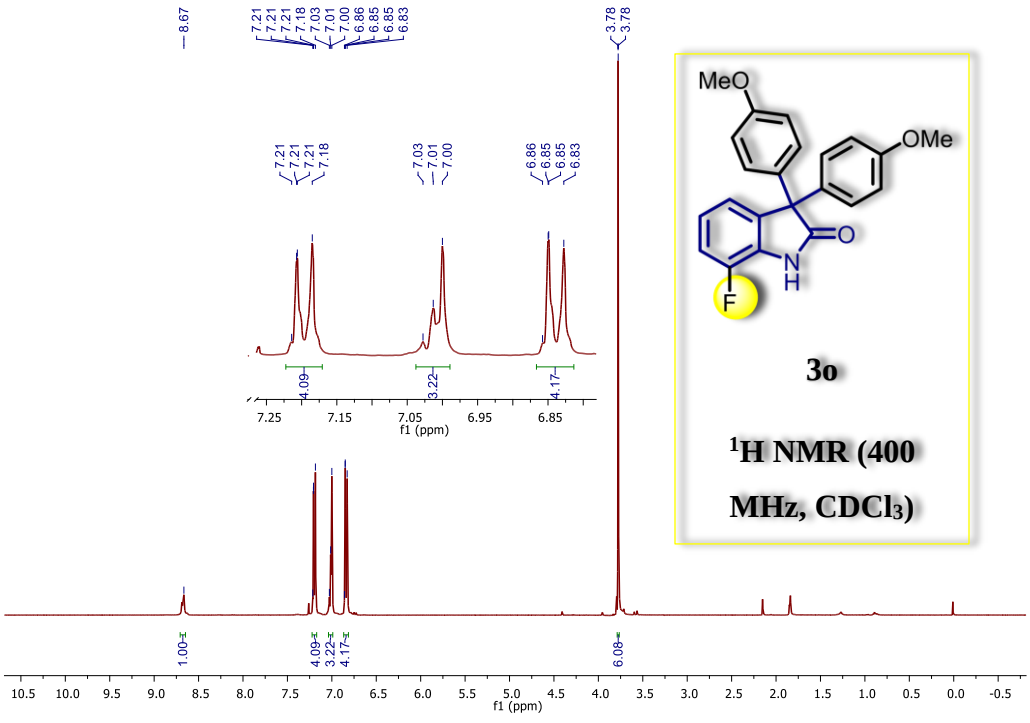
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O
N
H
F
3o
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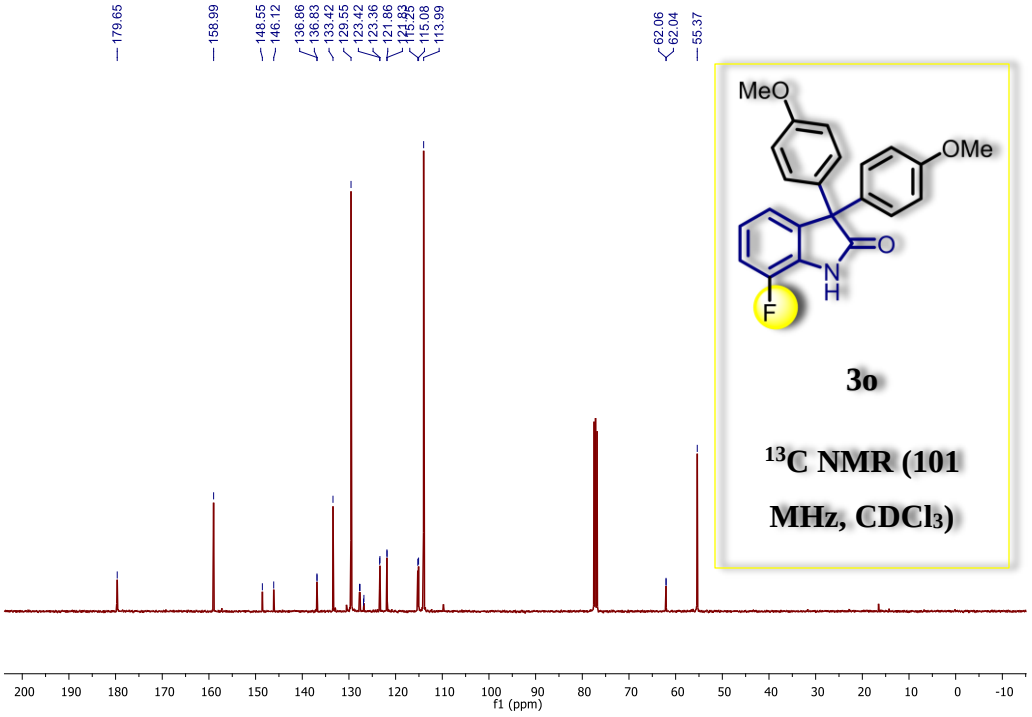
f1 (ppm)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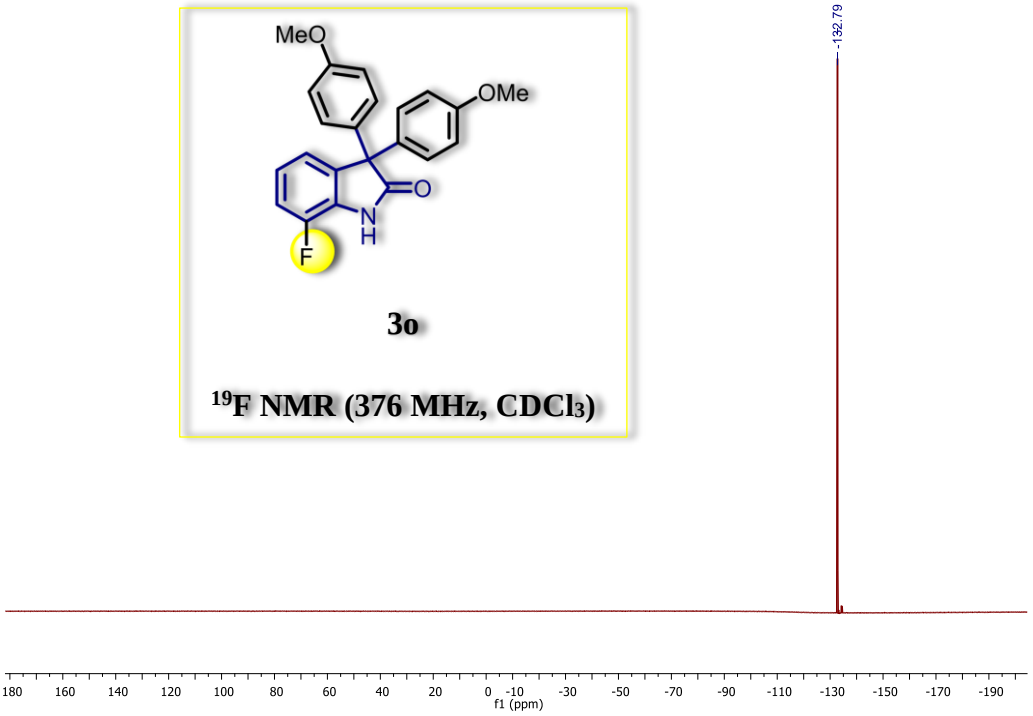
f1 (ppm)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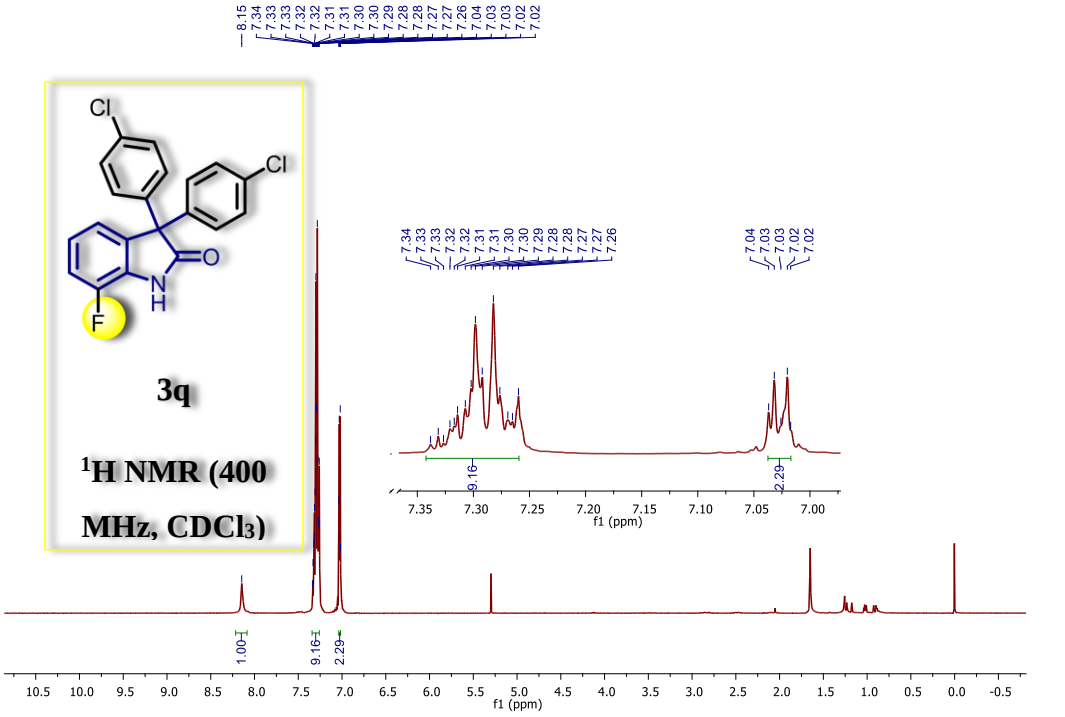
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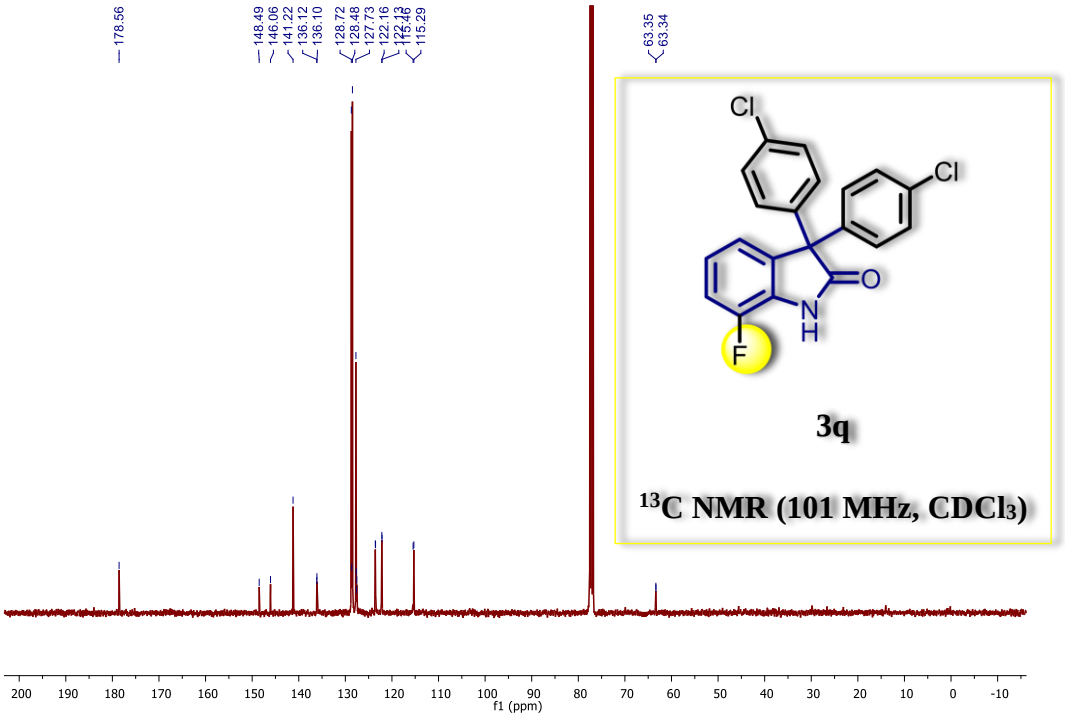
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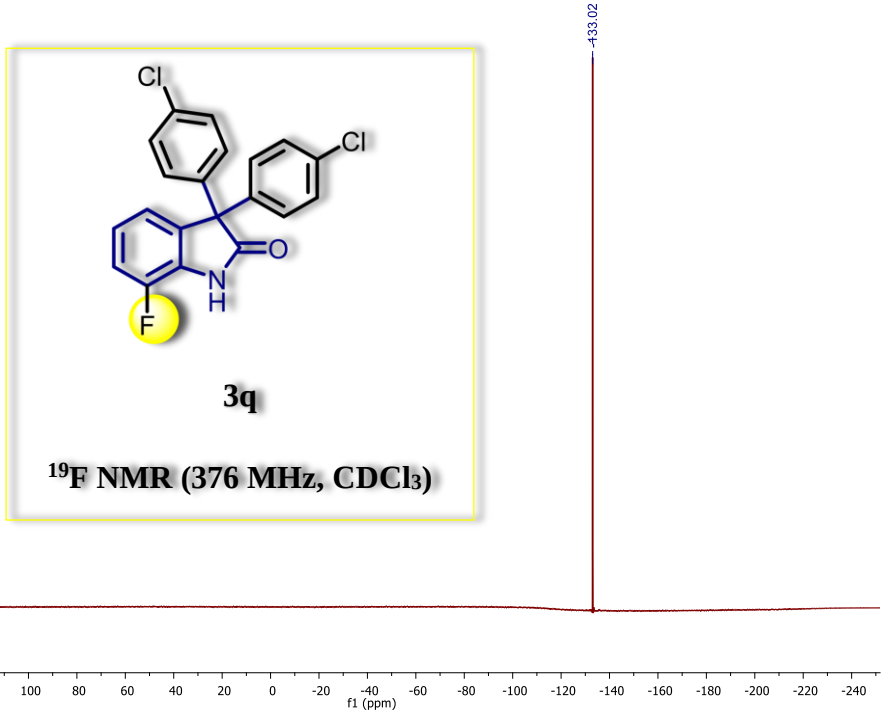
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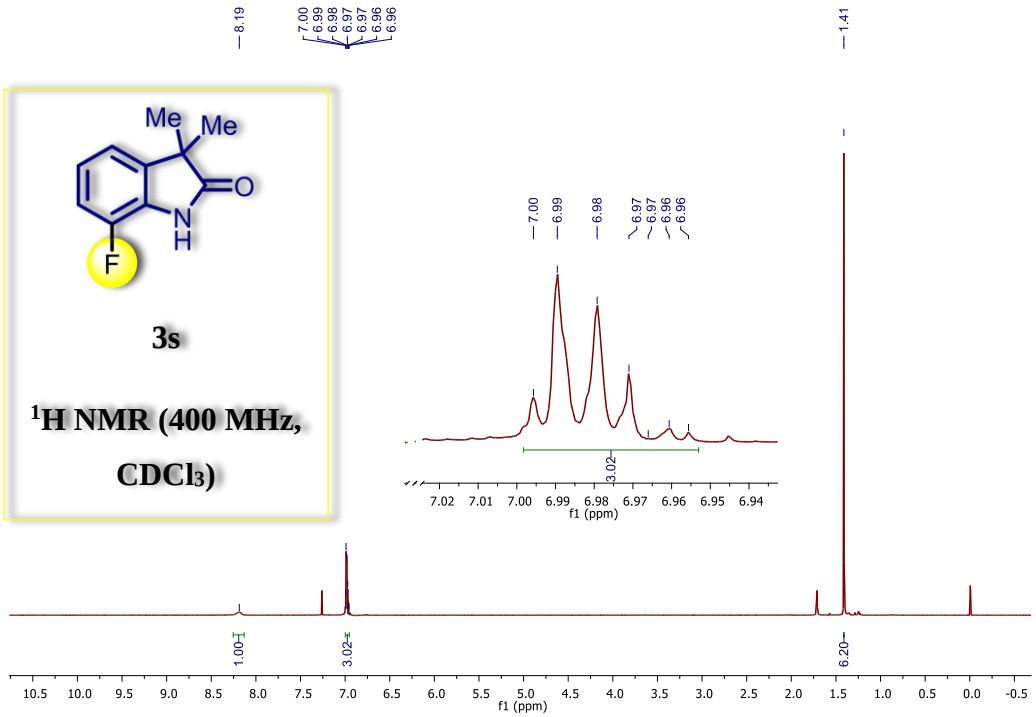
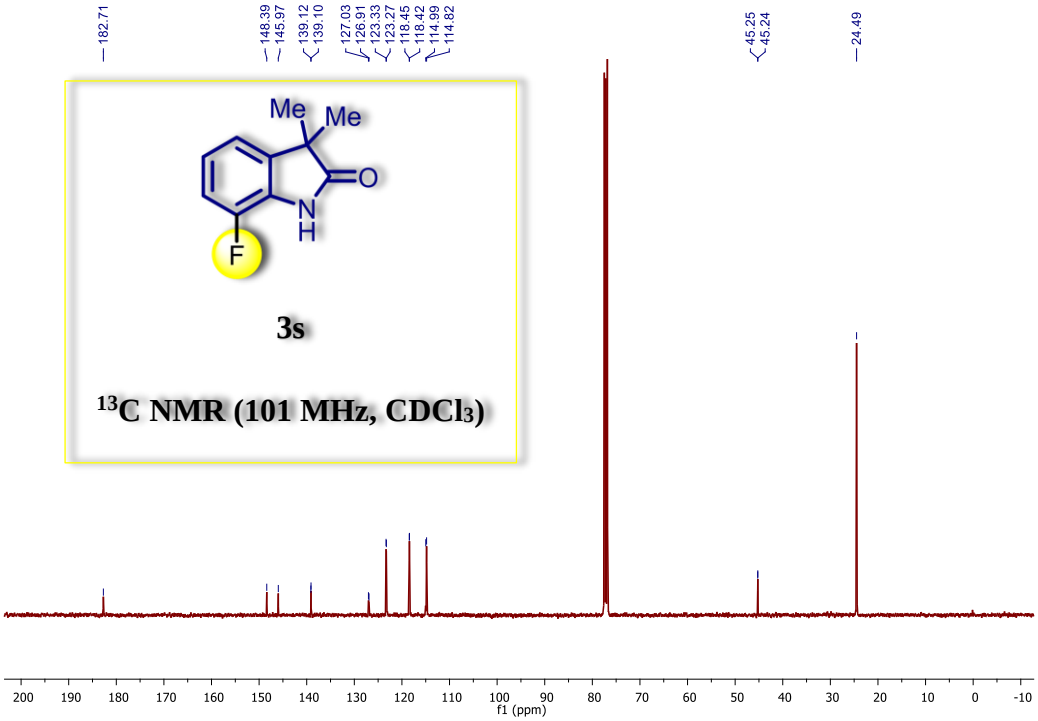
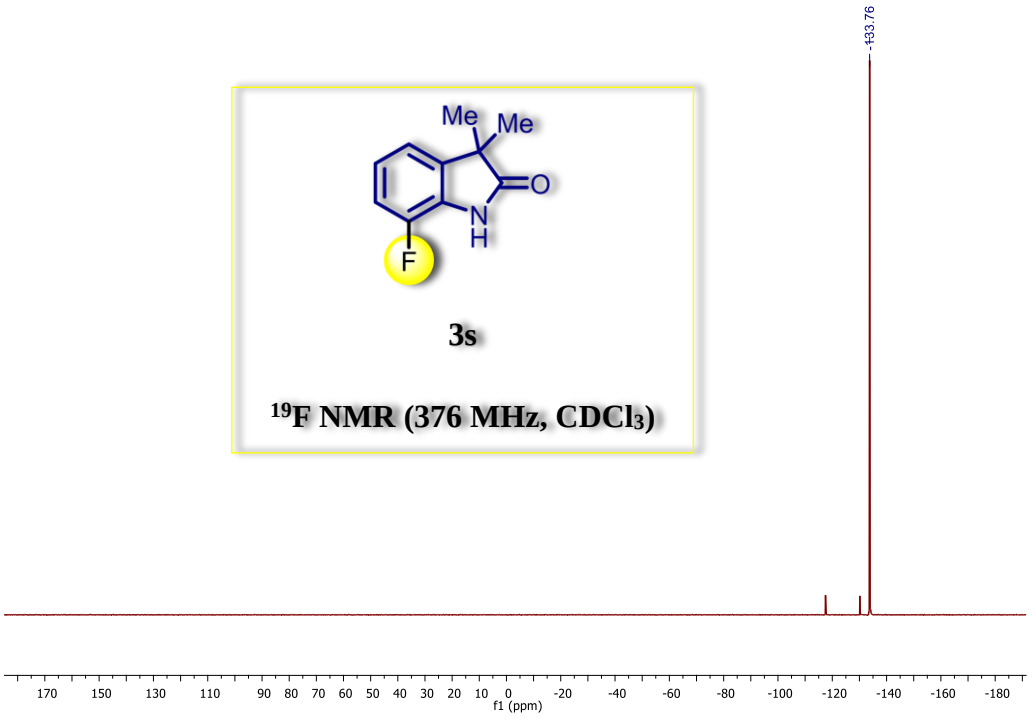
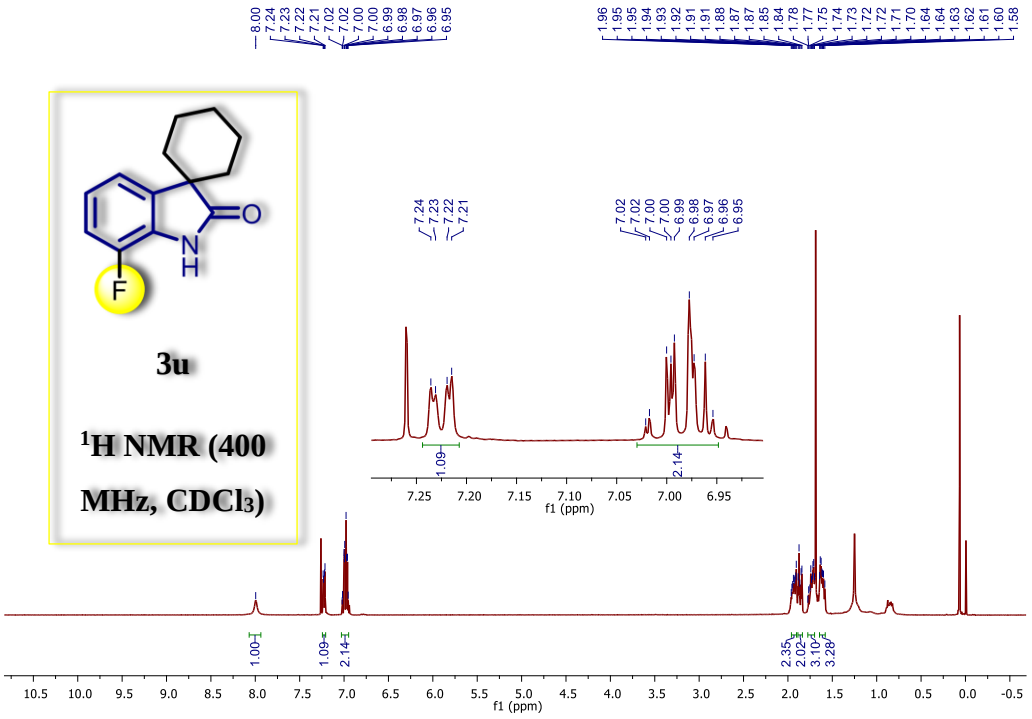
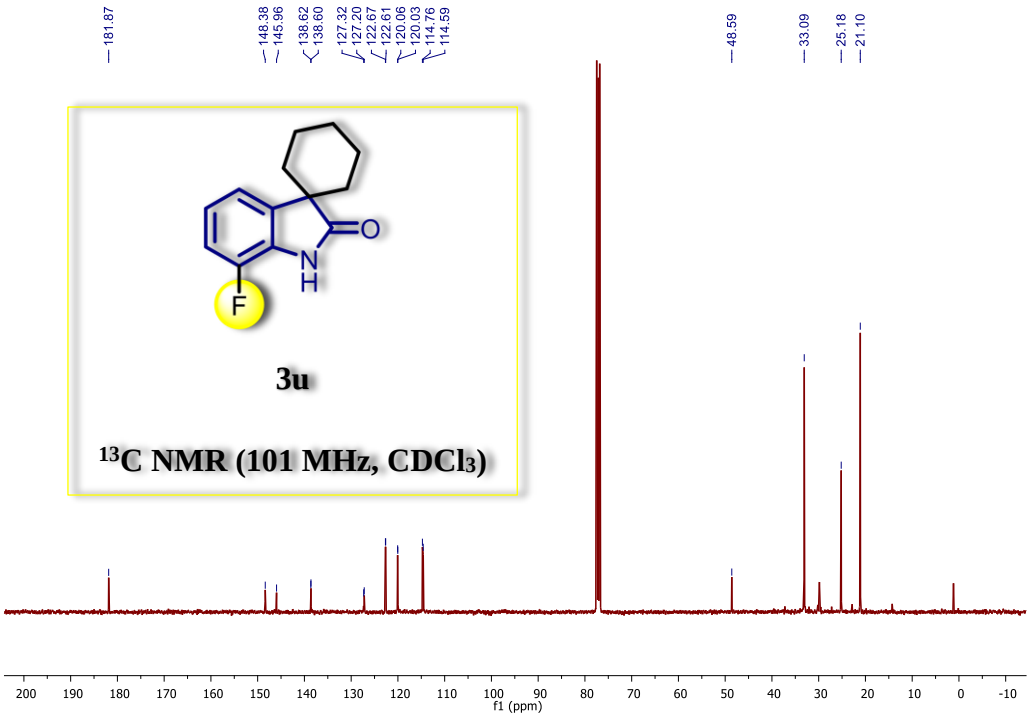
-133.02
f1 (ppm)

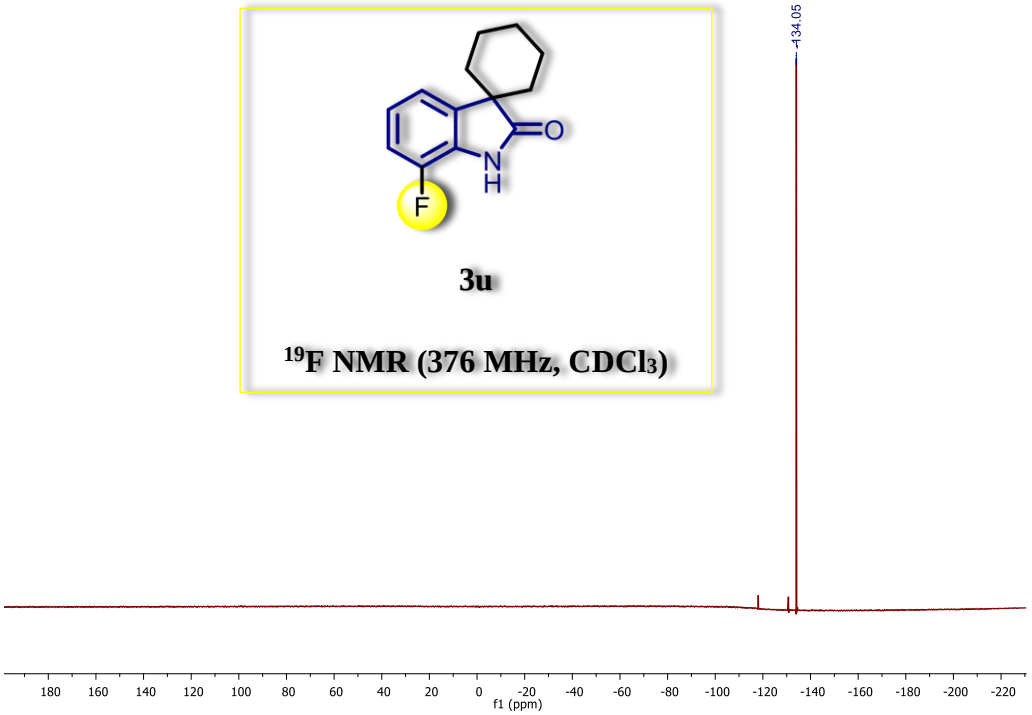

Me
Me
O
N
H
F
3s
^{1}H NMR (400 MHz, CDCl$_3$)
8.19
7.00
6.99
6.98
6.97
6.96
6.96
1.41
3.02
1.00
3.02
6.20
f1 (ppm)

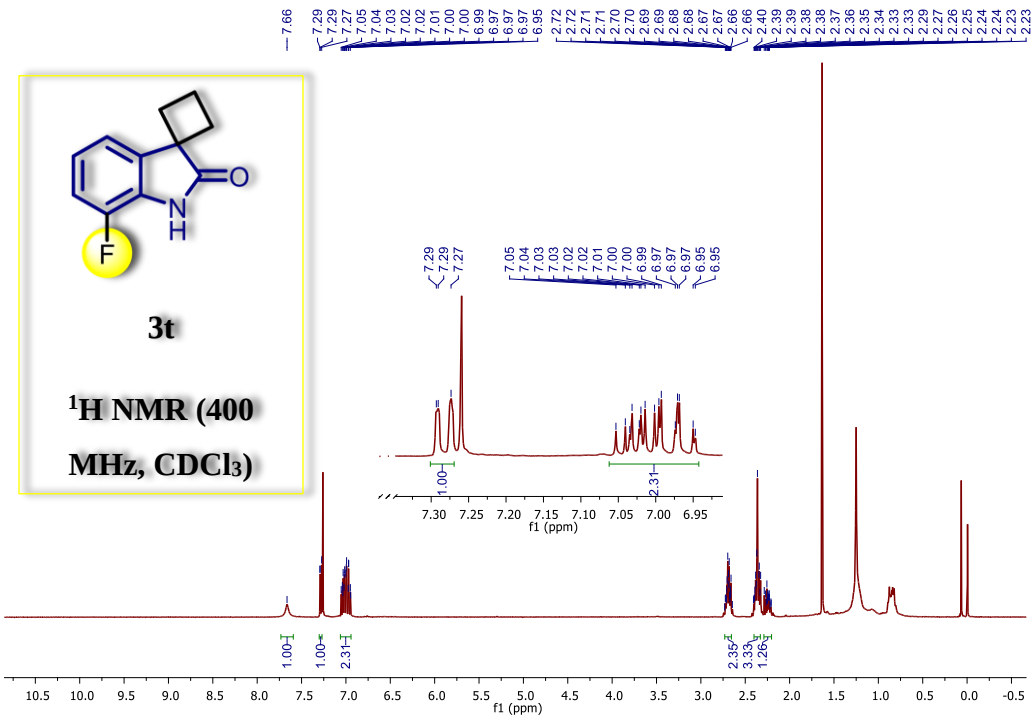

182.71
148.39
145.97
139.12
139.10
127.03
126.91
123.33
123.27
118.45
118.42
114.99
114.82
45.25
45.24
24.49
Me
Me
O
N
H
F
3s
13C NMR (101 MHz, CDCl3)
f1 (ppm)

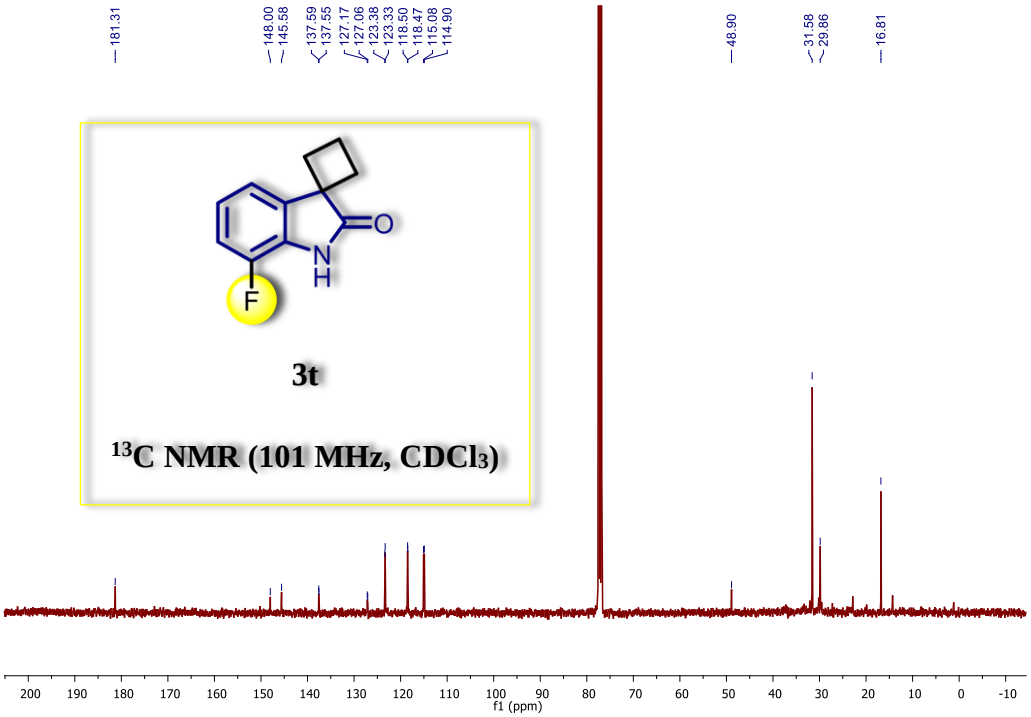

-133.76
Me
Me
O
N
H
F
3s
19F NMR (376 MHz, CDCl3)
f1 (ppm)

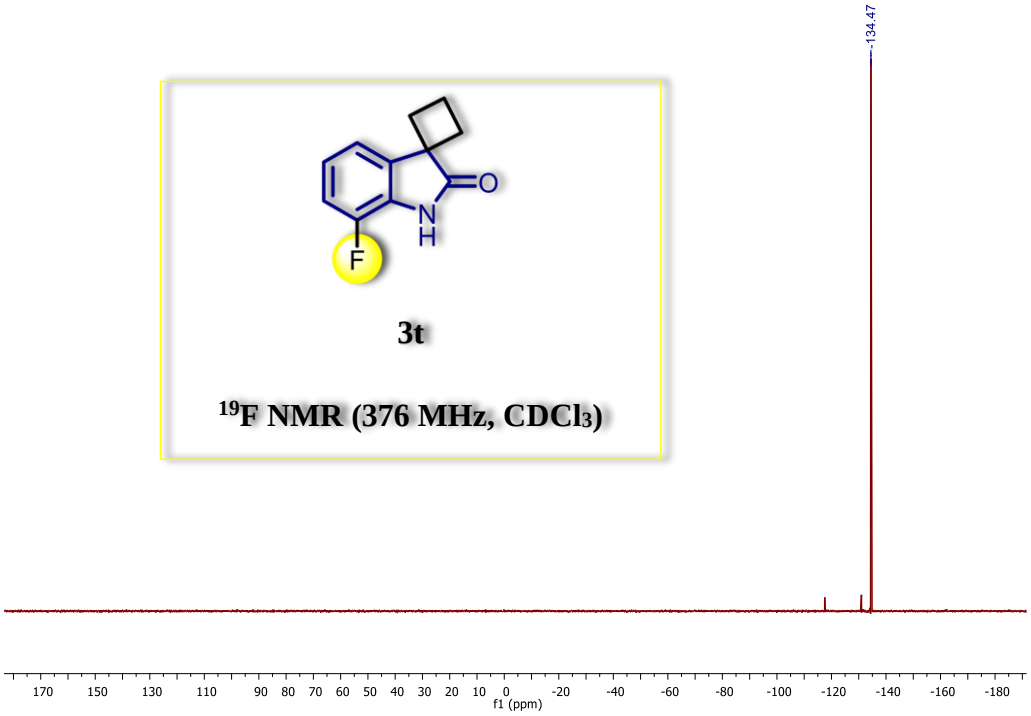

3u
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

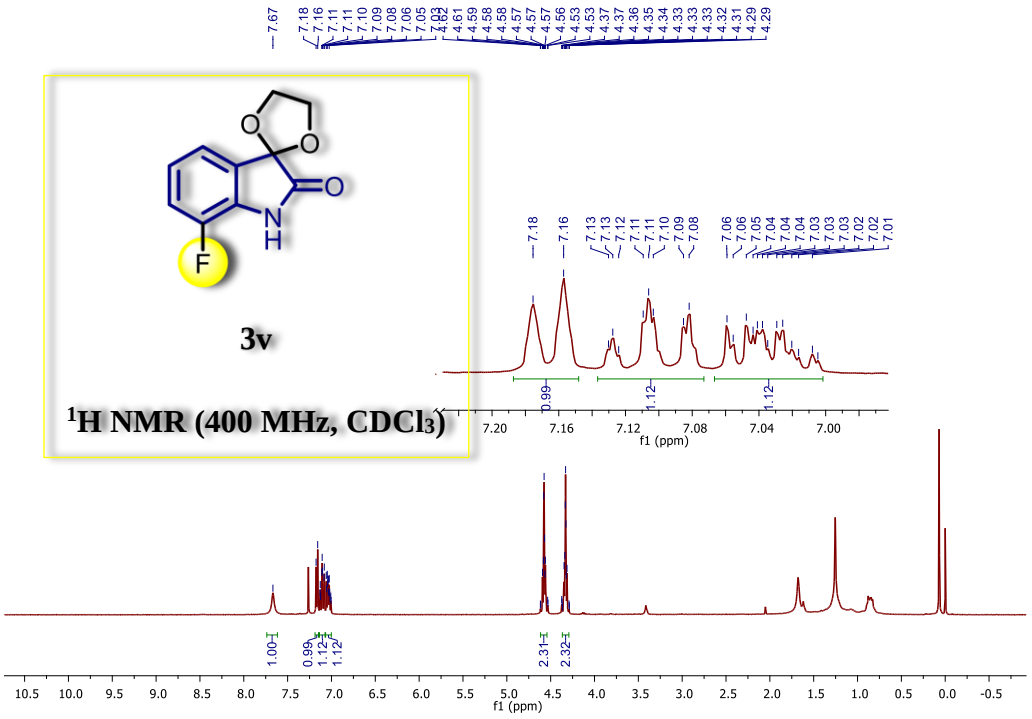

3u
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

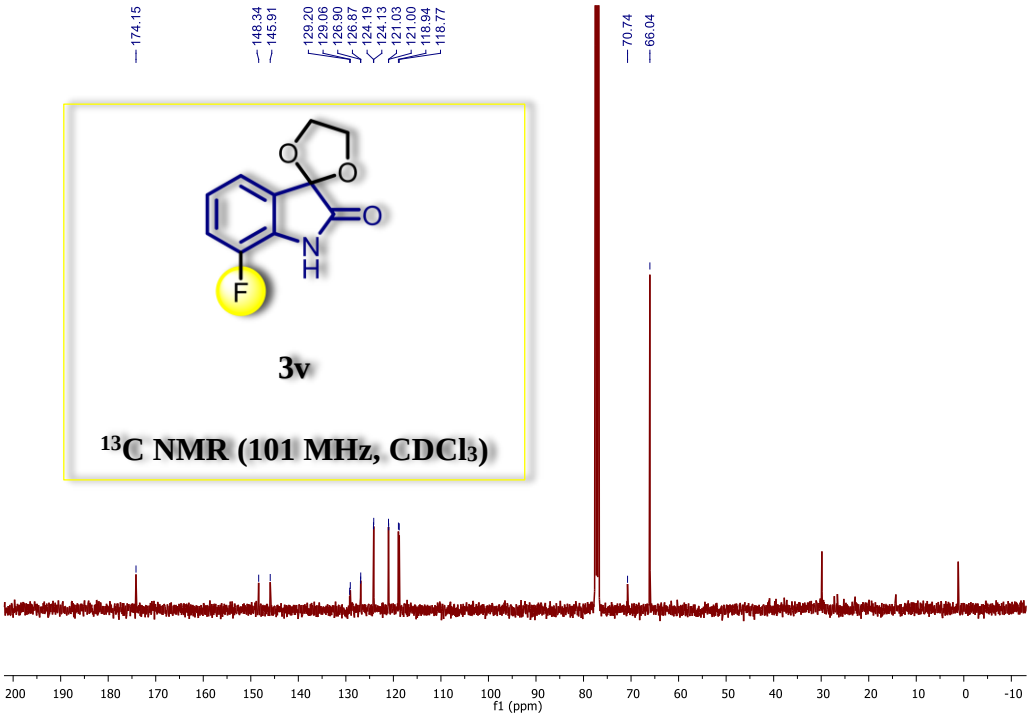

3u
19F NMR (376 MHz, CDCl3)
-134.05
f1 (ppm)

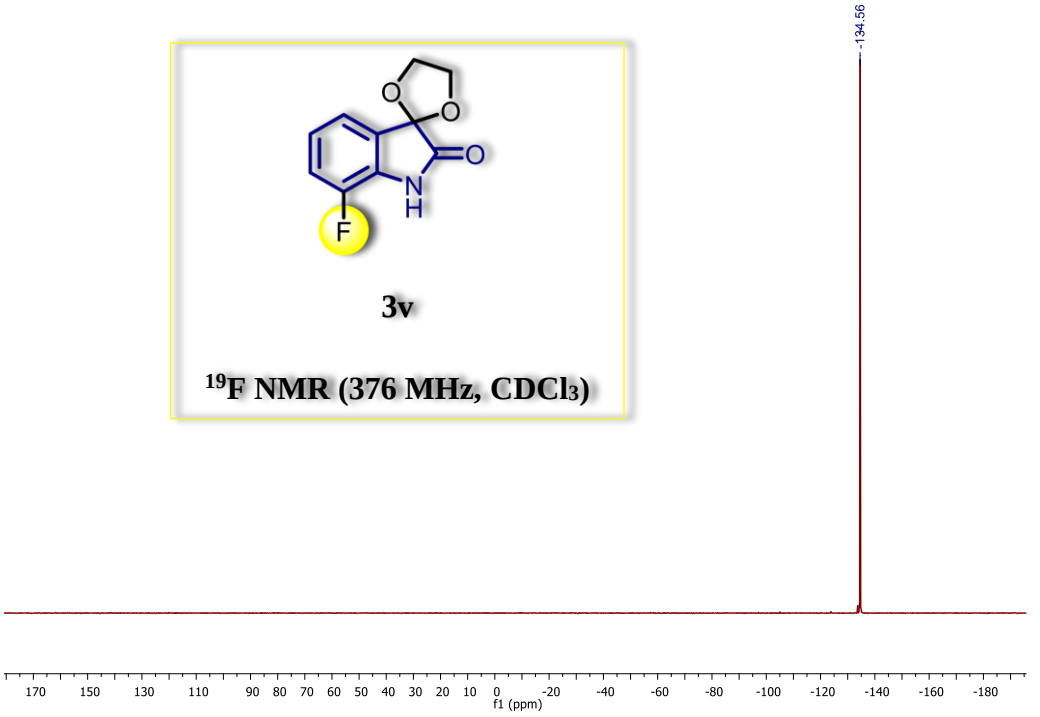

3t
1H NMR (400 MHz, CDCl3)
f1 (ppm)


181.31
148.00
145.58
137.59
137.55
127.17
127.06
123.38
123.33
118.50
118.47
115.08
114.90
48.90
31.58
29.86
16.81
O
N
H
F
3t
13C NMR (101 MHz, CDCl3)
f1 (ppm)


134.47
O
N
H
F
3t
19F NMR (376 MHz, CDCl3)
f1 (ppm)

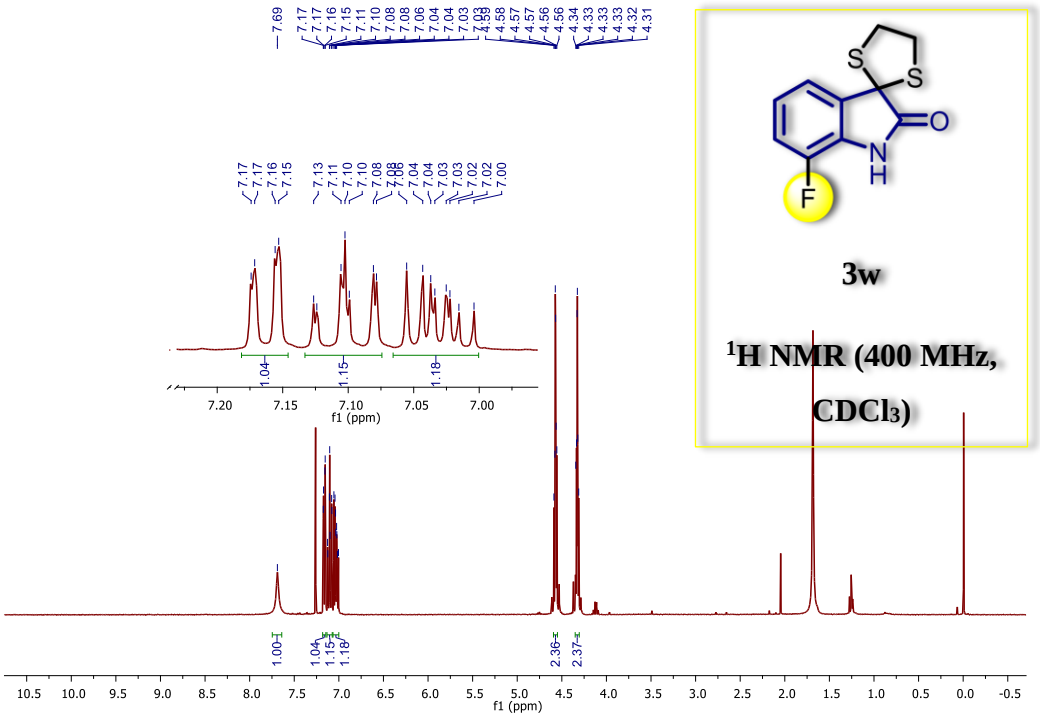

3v
^{1}H NMR (400 MHz, CDCl$_3$)


3v
^{13}C NMR (101 MHz, CDCl$_3$)



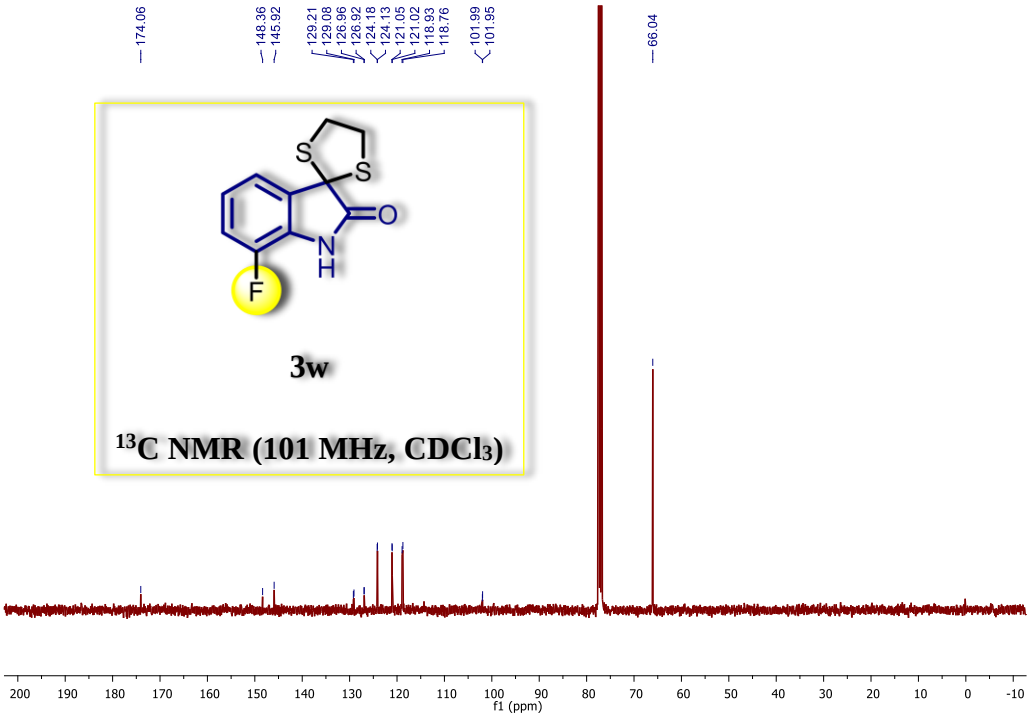
3v

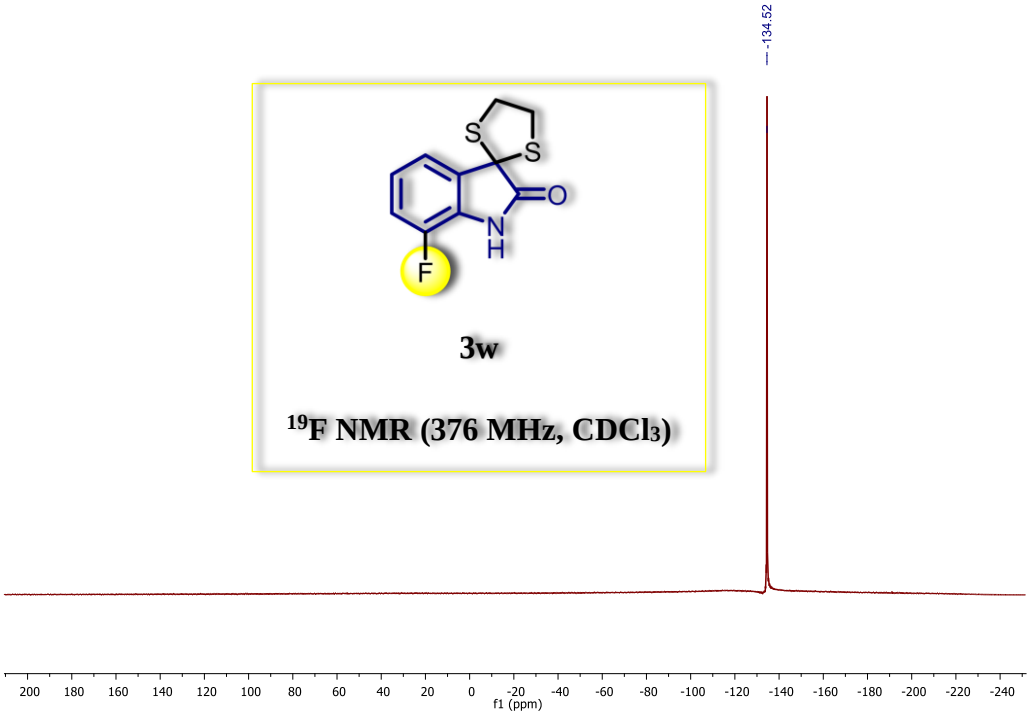
^{19}F NMR (376 MHz, $CDCl_3$)

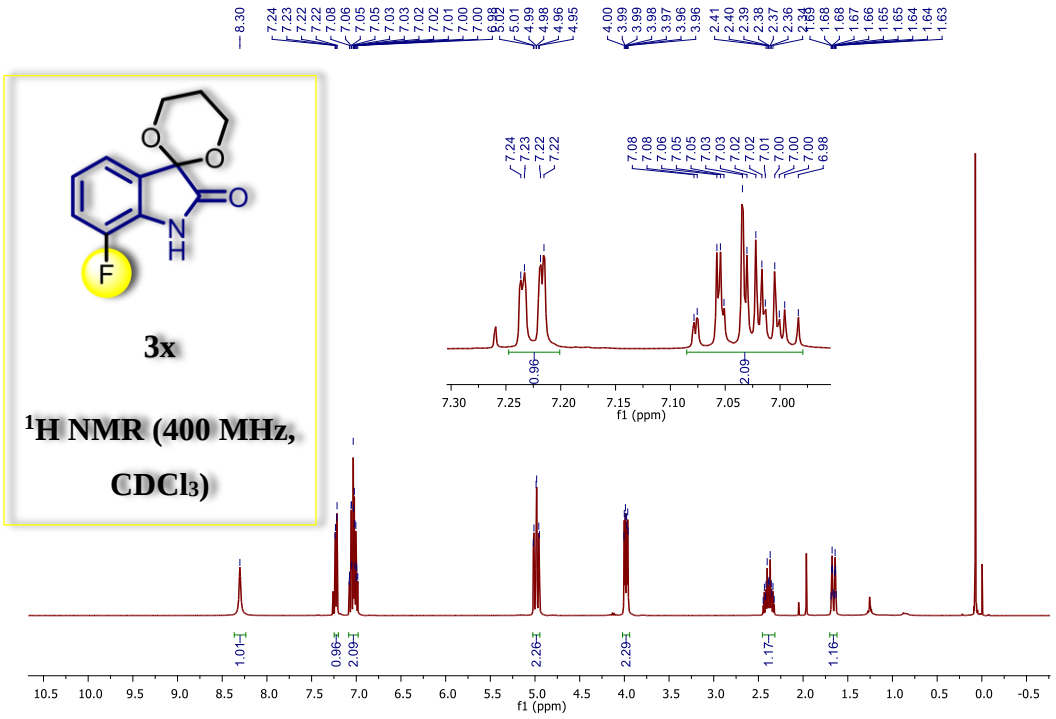


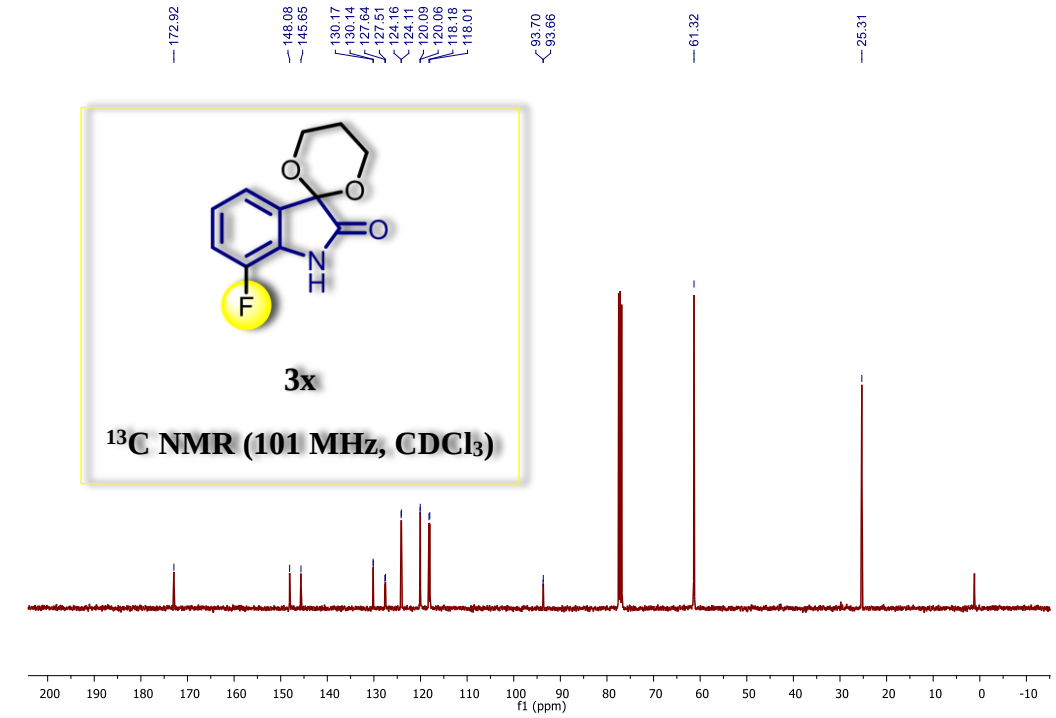
3w

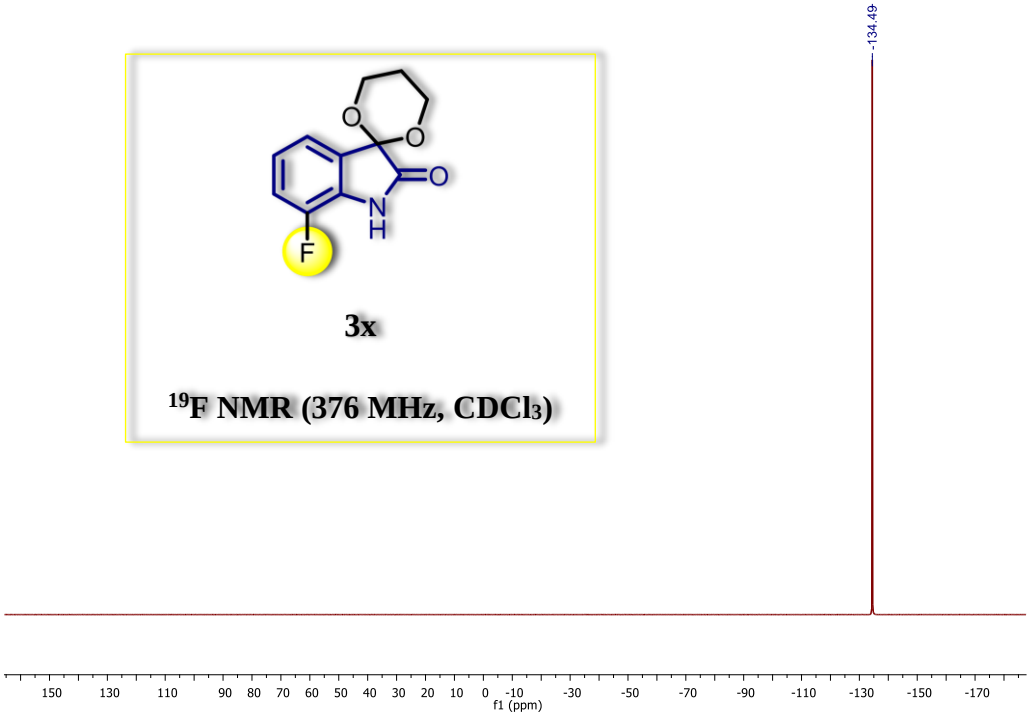
^{1}H NMR (400 MHz, $CDCl_3$)

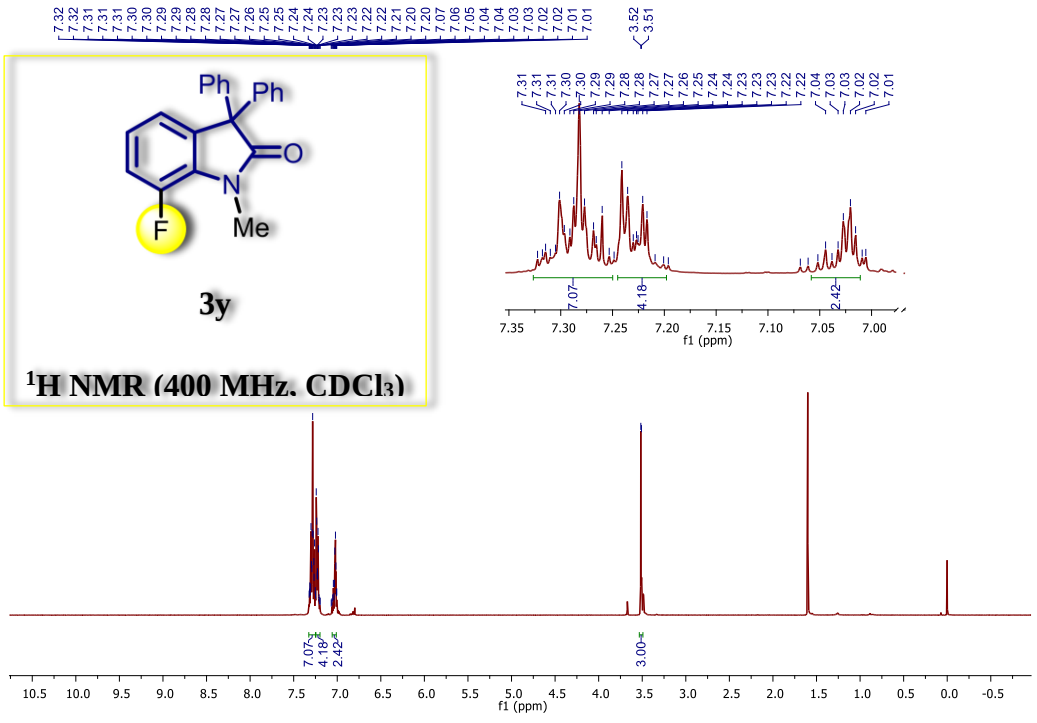

174.06
148.36
145.92
129.21
129.08
126.96
126.92
124.18
124.13
121.05
121.02
118.93
118.76
101.99
101.95
66.04
3w
13C NMR (101 MHz, CDCl3)
f1 (ppm)

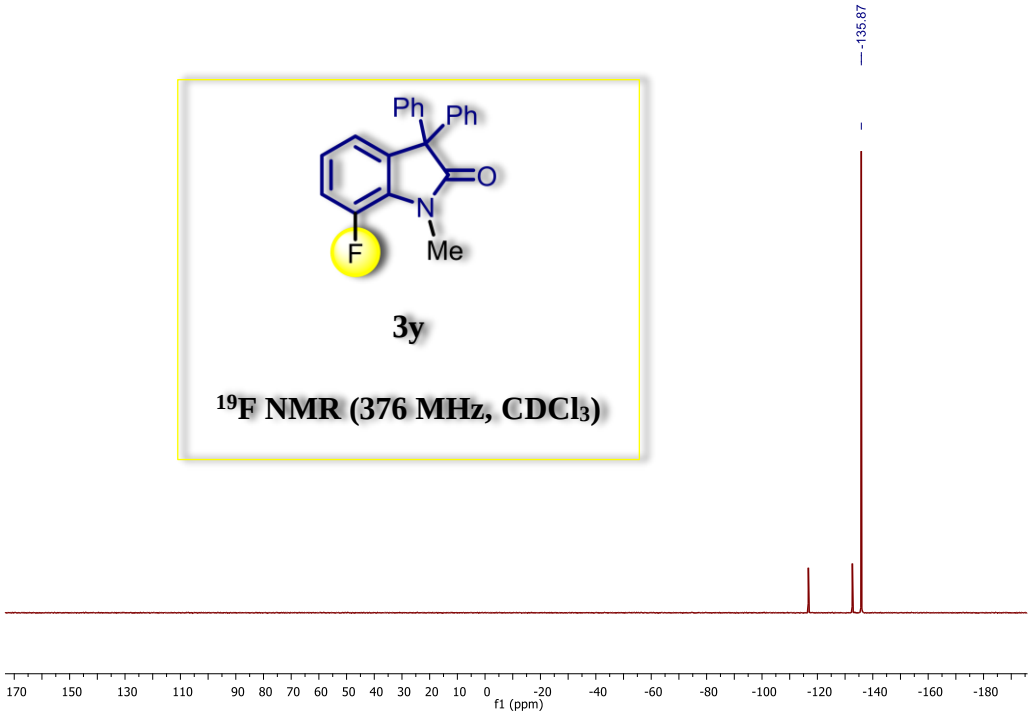

-134.52
3w
19F NMR (376 MHz, CDCl3)
f1 (ppm)

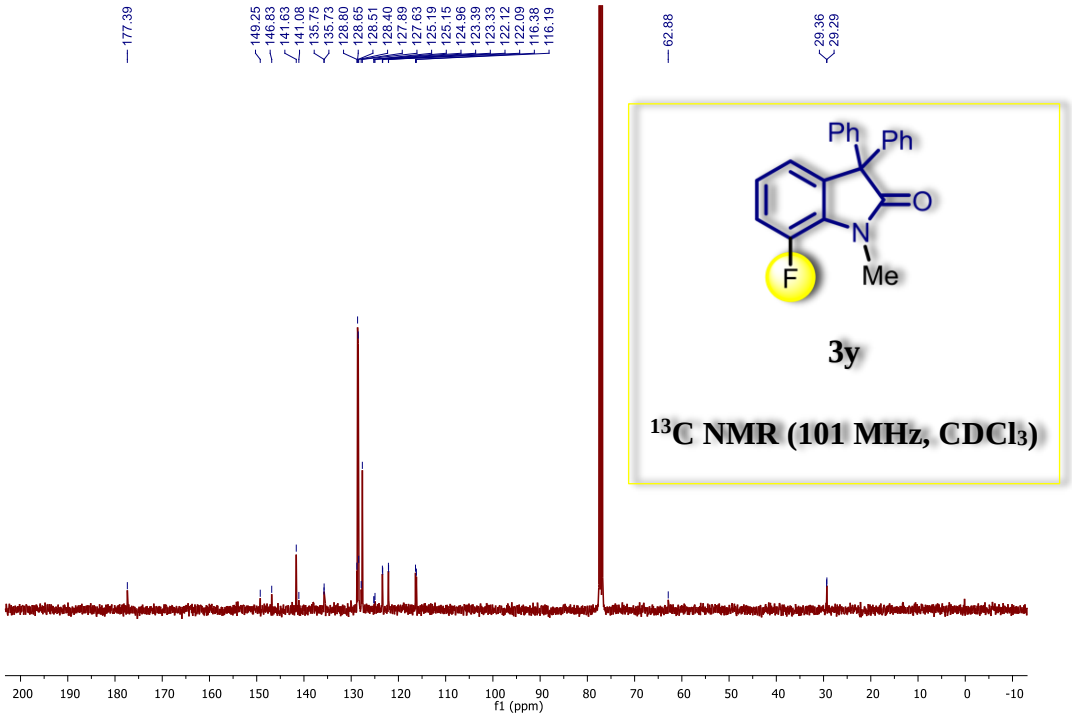

3x
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

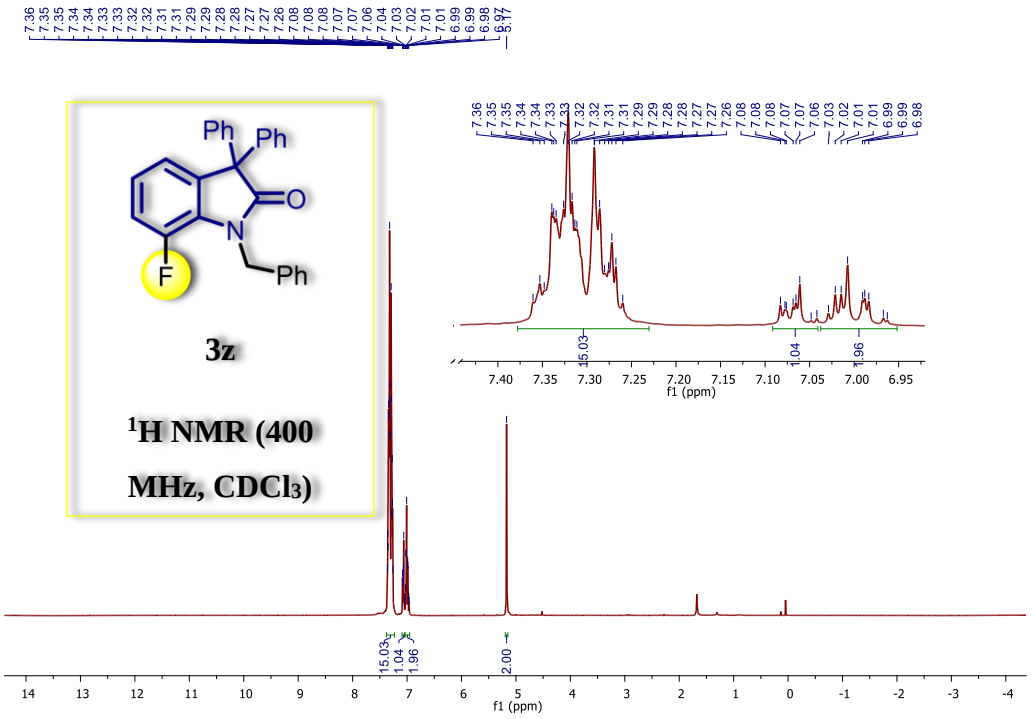

3x
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

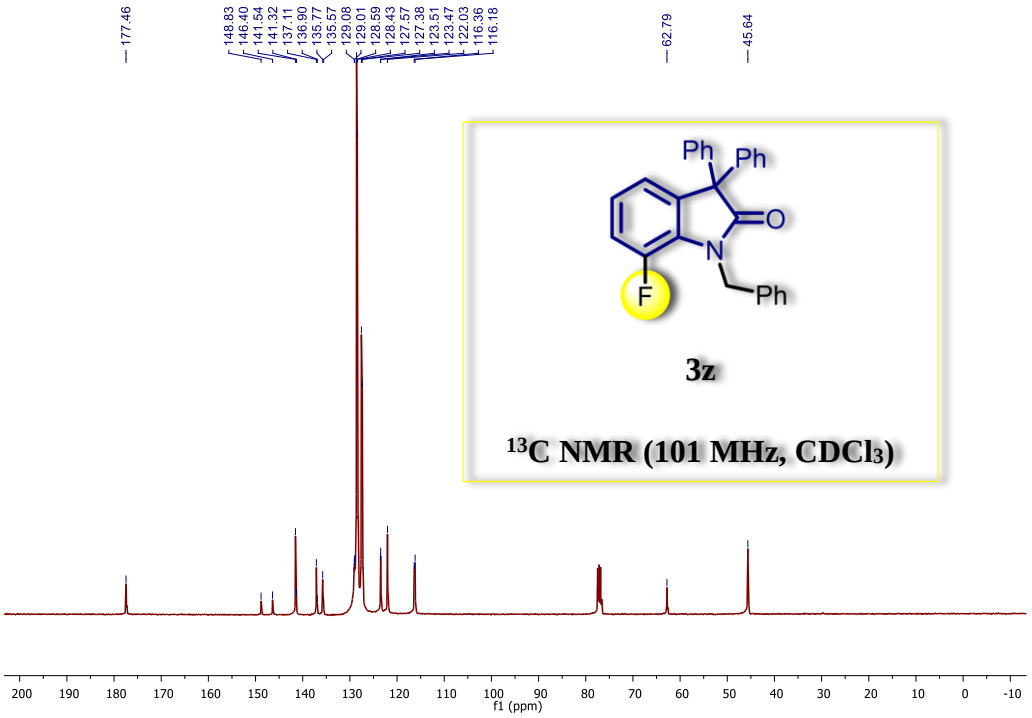

-134.49
3x
19F NMR (376 MHz, CDCl3)
f1 (ppm)

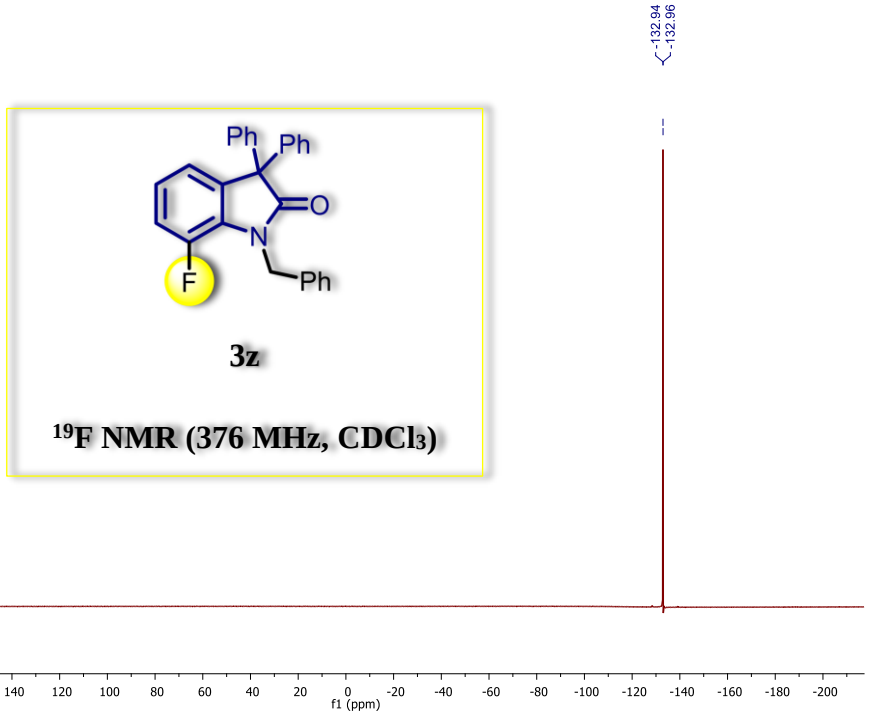

3y
1H NMR (400 MHz, CDCl3)
7.07
4.18
2.42
3.00
f1 (ppm)

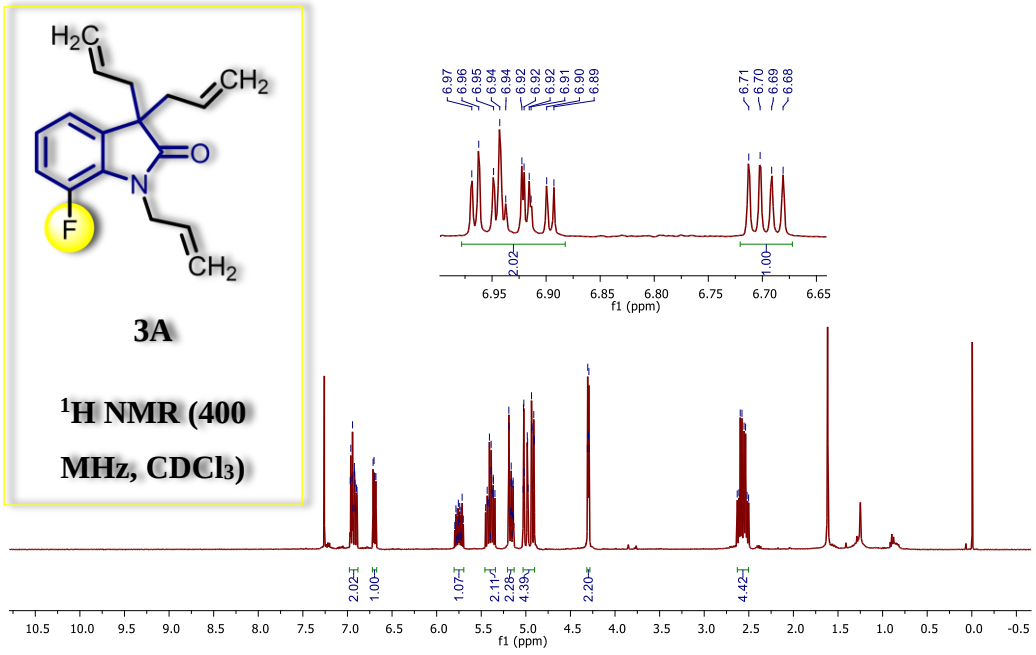

-135.87
Ph
Ph
O
N
Me
F
3y
^{19}F NMR (376 MHz, CDCl$_3$)
f1 (ppm)

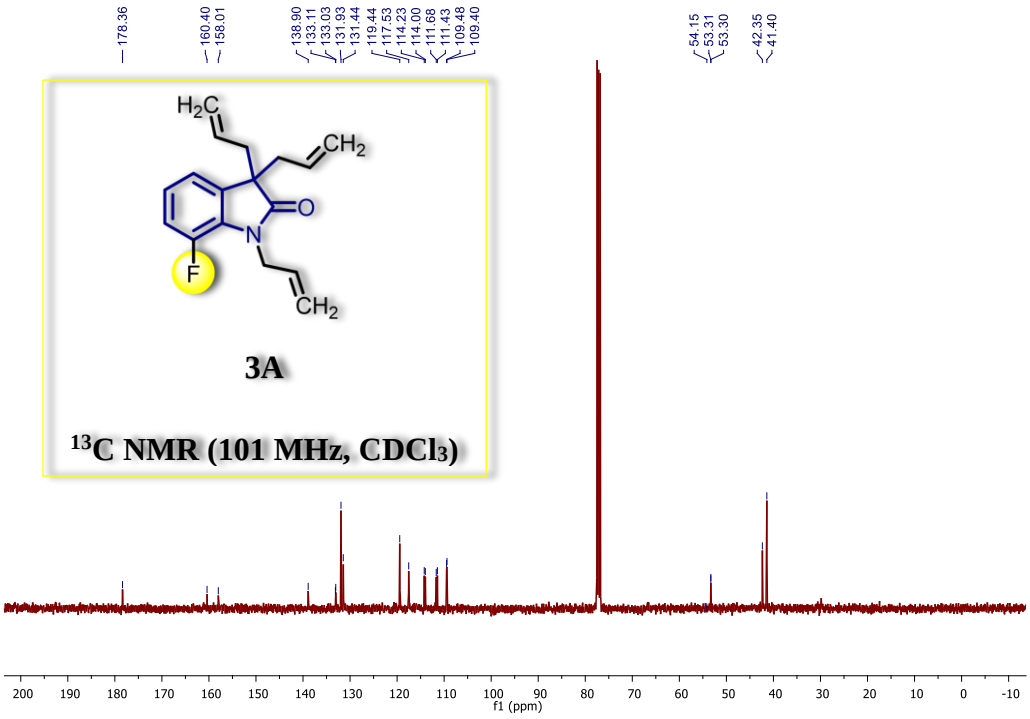

177.39
149.25
146.83
141.63
141.08
135.75
135.73
128.80
128.65
128.51
128.40
127.89
127.63
125.19
125.15
124.96
123.39
123.33
122.12
122.09
116.38
116.19
62.88
29.36
29.29
Ph
Ph
O
N
Me
F
3y
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

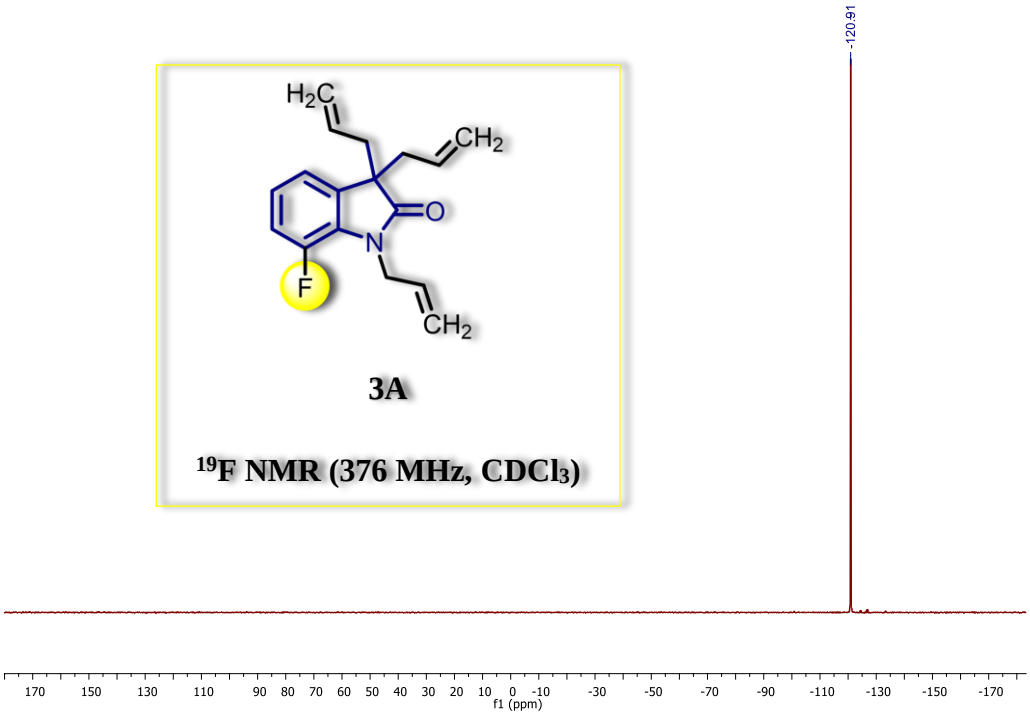

Ph
Ph
O
N
F
Ph
3z
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

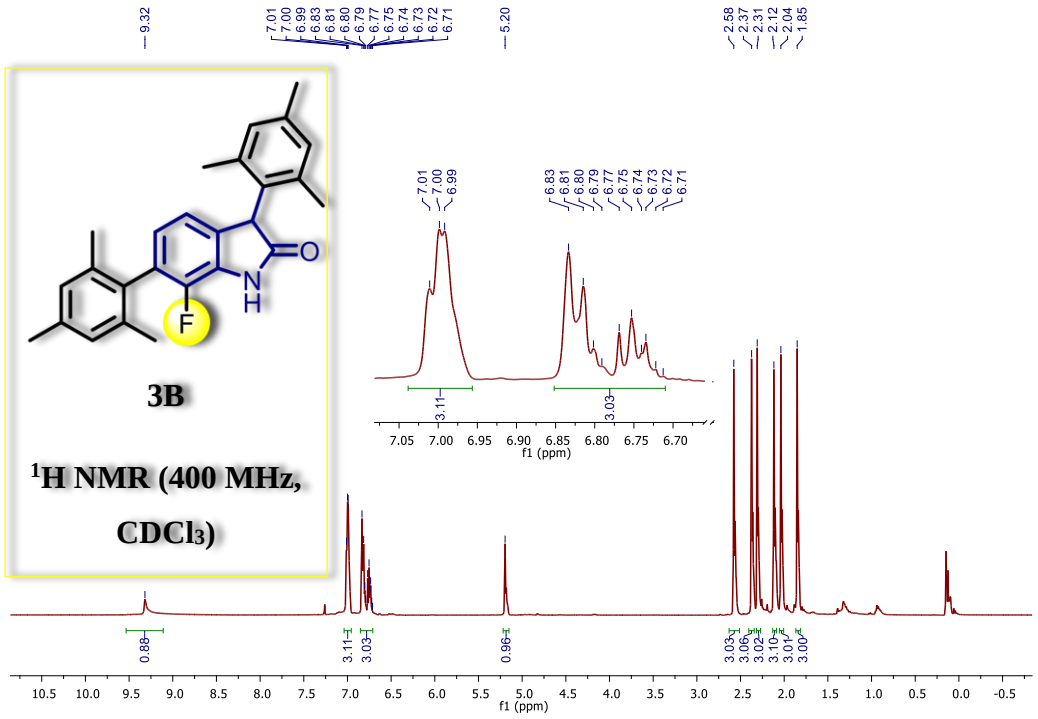

Ph
Ph
O
N
F
Ph
3z
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

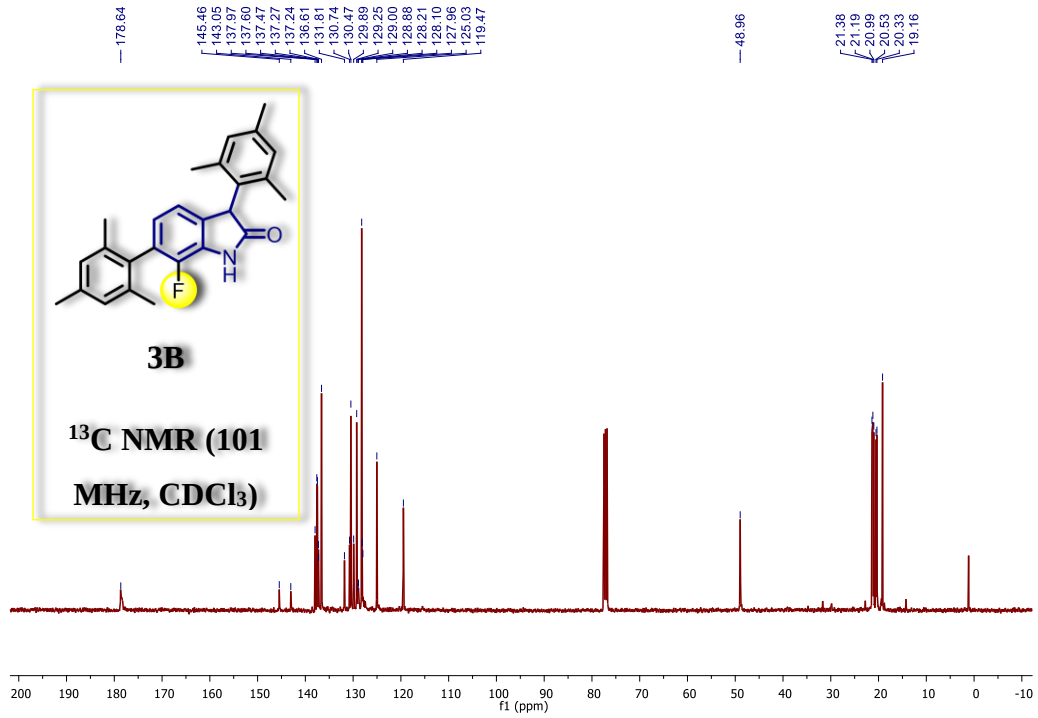

Ph
Ph
O
N
F
Ph
3z
19F NMR (376 MHz, CDCl3)
-132.94
-132.96
f1 (ppm)

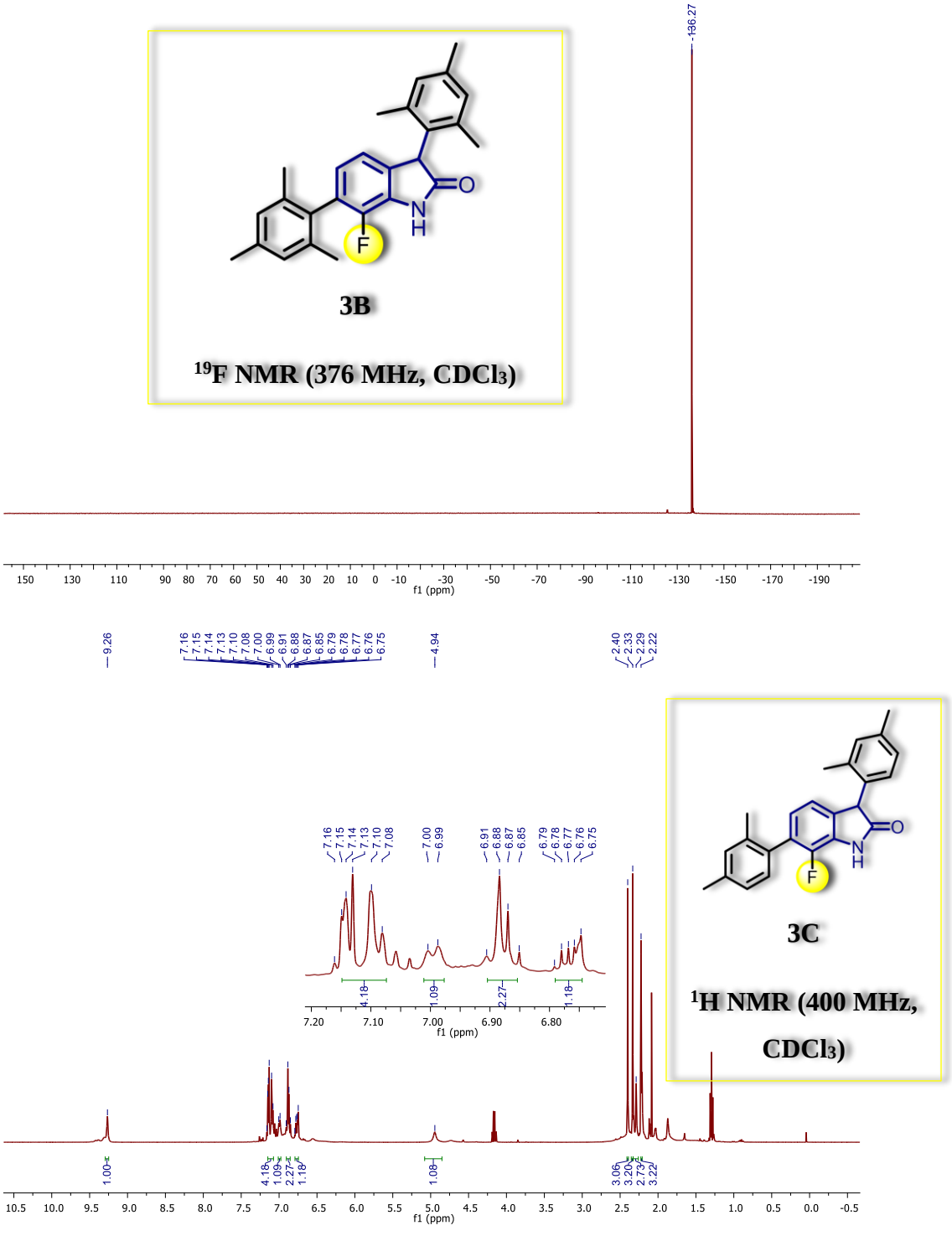

H2C
CH2
O
N
F
CH2
3A
1H NMR (400 MHz, CDCl3)
f1 (ppm)

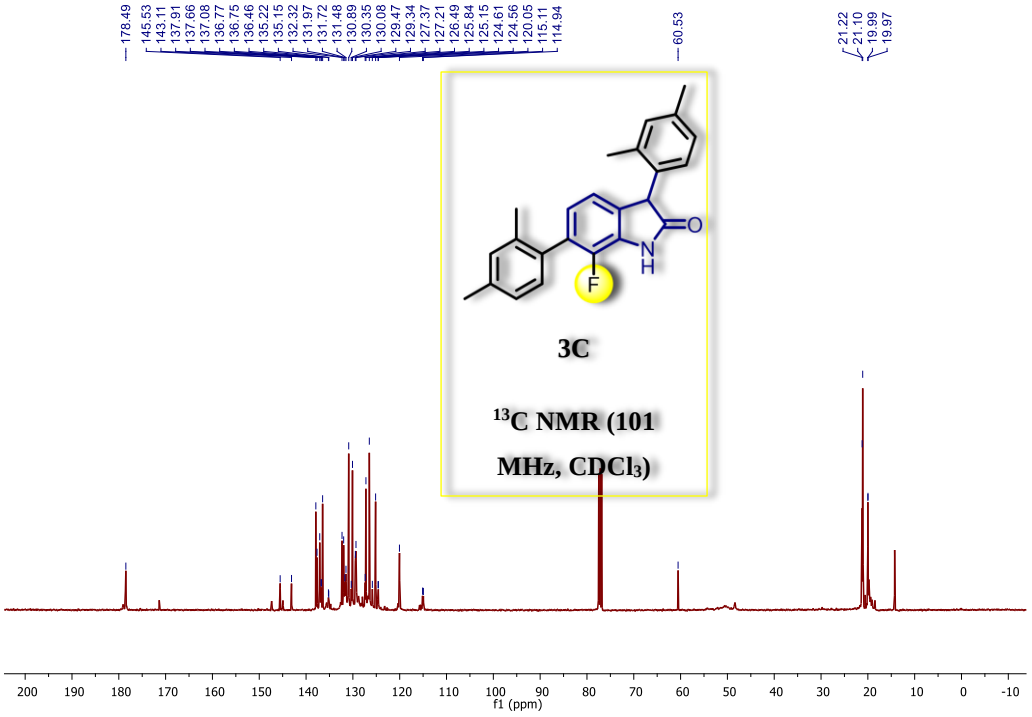

178.36
160.40
158.01
138.90
133.11
133.03
131.93
131.44
119.44
117.53
114.23
114.00
111.68
111.43
109.48
109.40
54.15
53.31
53.30
42.35
41.40
H2C
CH2
O
N
F
CH2
3A
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

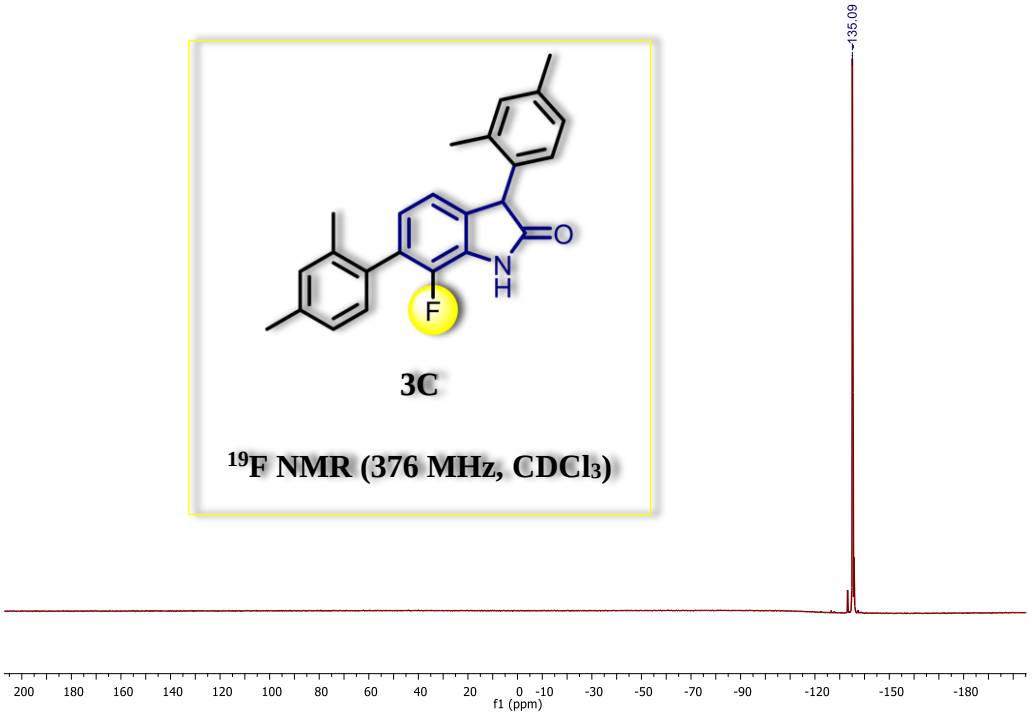

-120.91
H2C
CH2
O
N
F
CH2
3A
19F NMR (376 MHz, CDCl3)
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170
f1 (ppm)

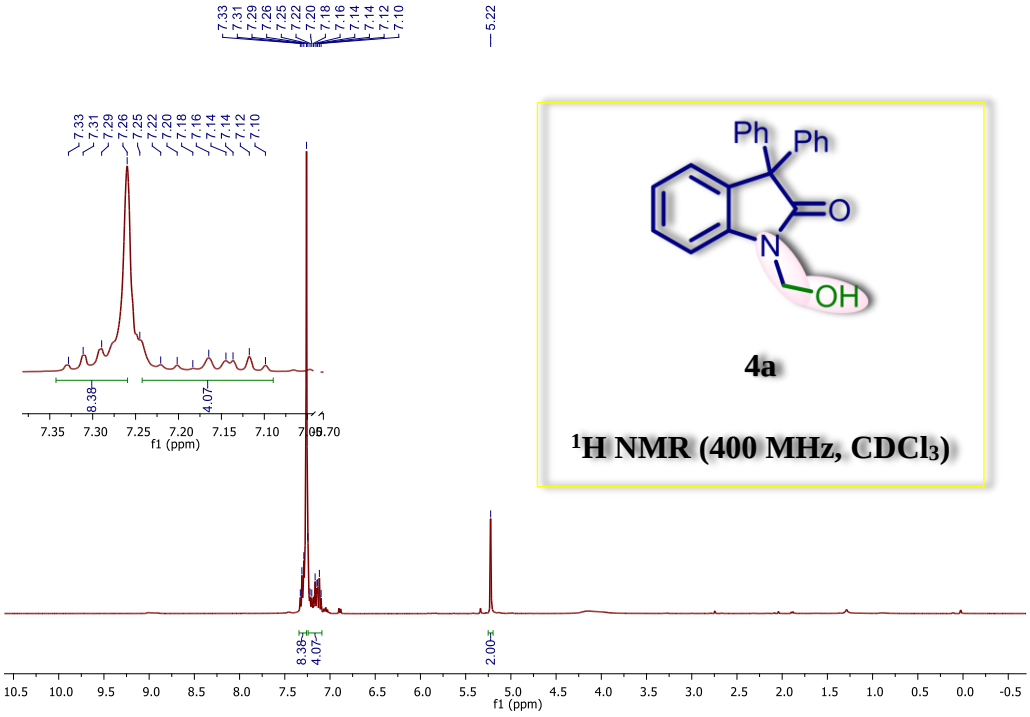

3B
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)


3B
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)


3B
19F NMR (376 MHz, CDCl3)
-136.27
f1 (ppm)
3C
1H NMR (400 MHz, CDCl3)
f1 (ppm)

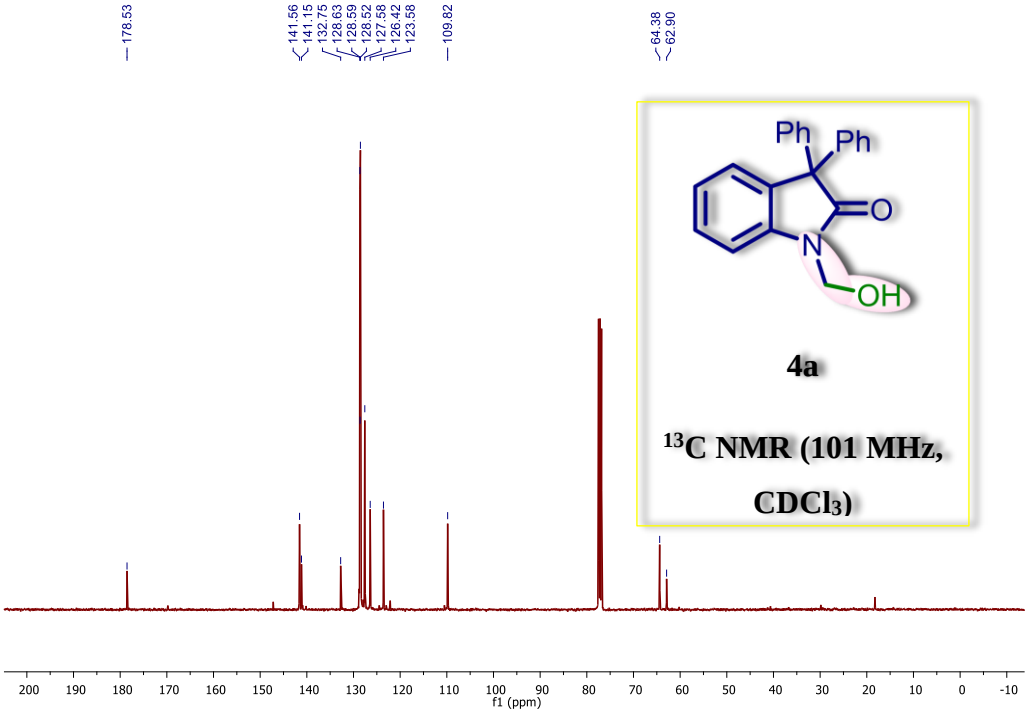

178.49
145.53
143.11
137.91
137.66
137.08
136.77
136.75
136.46
135.22
135.15
132.32
131.97
131.72
131.48
130.89
130.35
130.08
129.47
129.34
127.37
127.21
126.49
125.84
125.15
124.61
124.56
120.05
115.11
114.94
60.53
21.22
21.10
19.99
19.97
O
N
H
F
3C
13C NMR (101 MHz, CDCl3)
f1 (ppm)


-135.09
O
N
H
F
3C
19F NMR (376 MHz, CDCl3)
f1 (ppm)



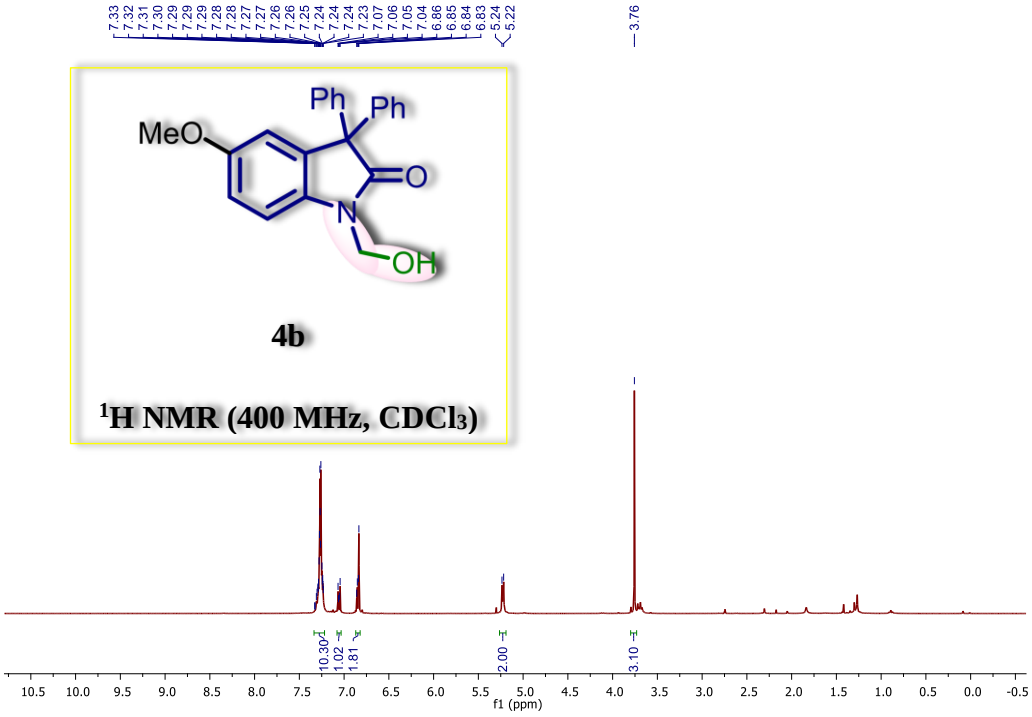
4a

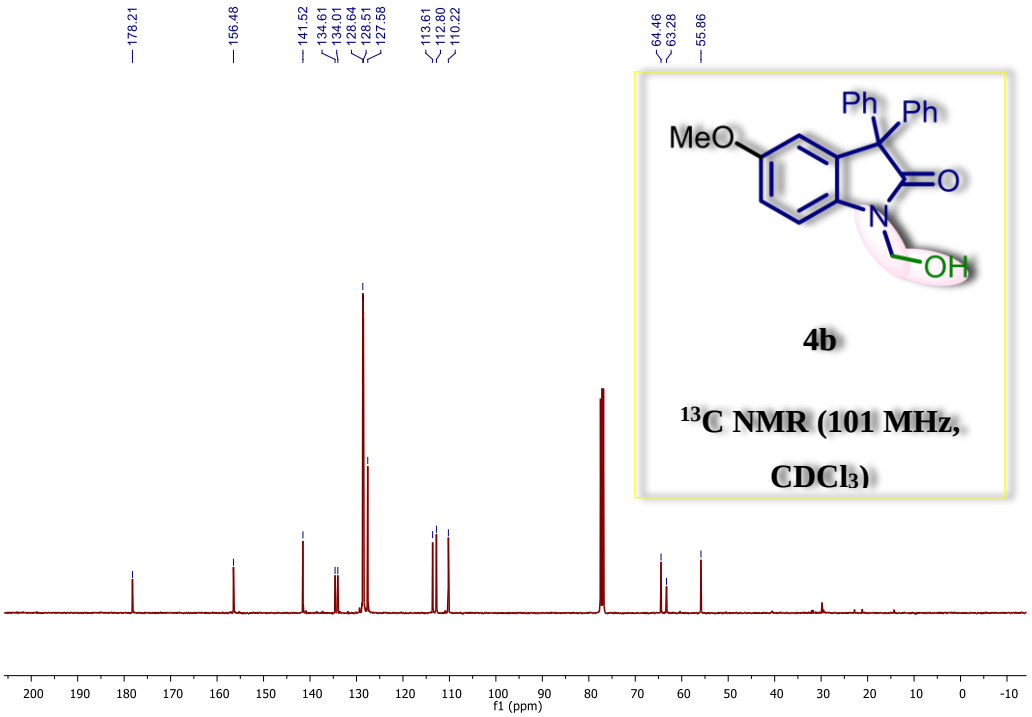
^{1}H NMR (400 MHz, $CDCl_3$)

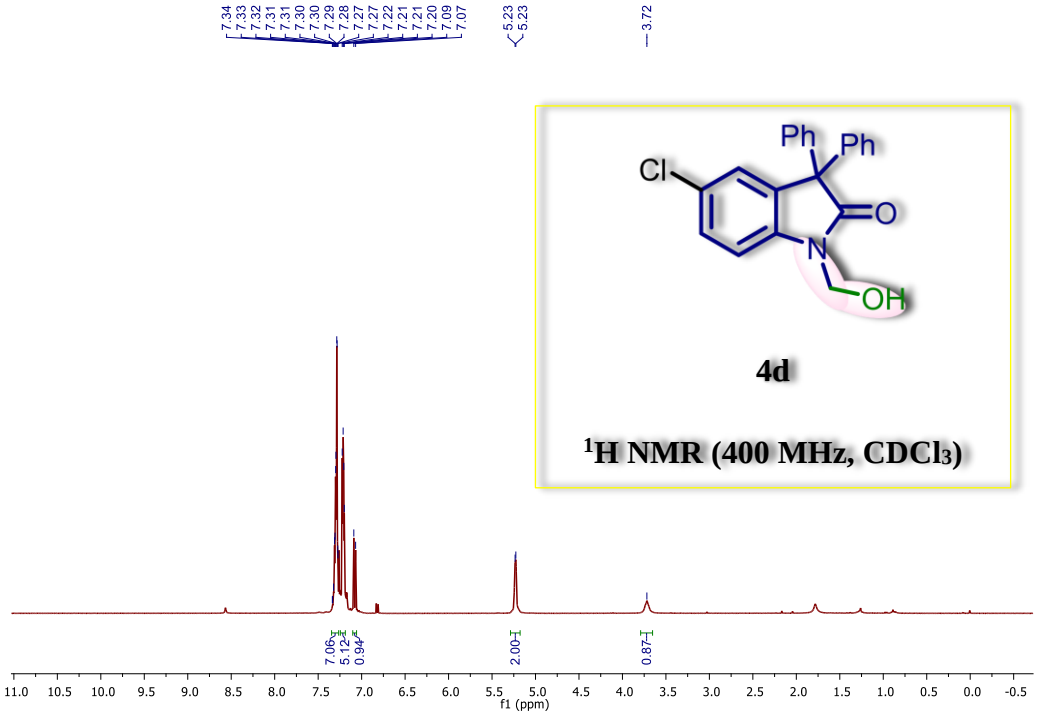


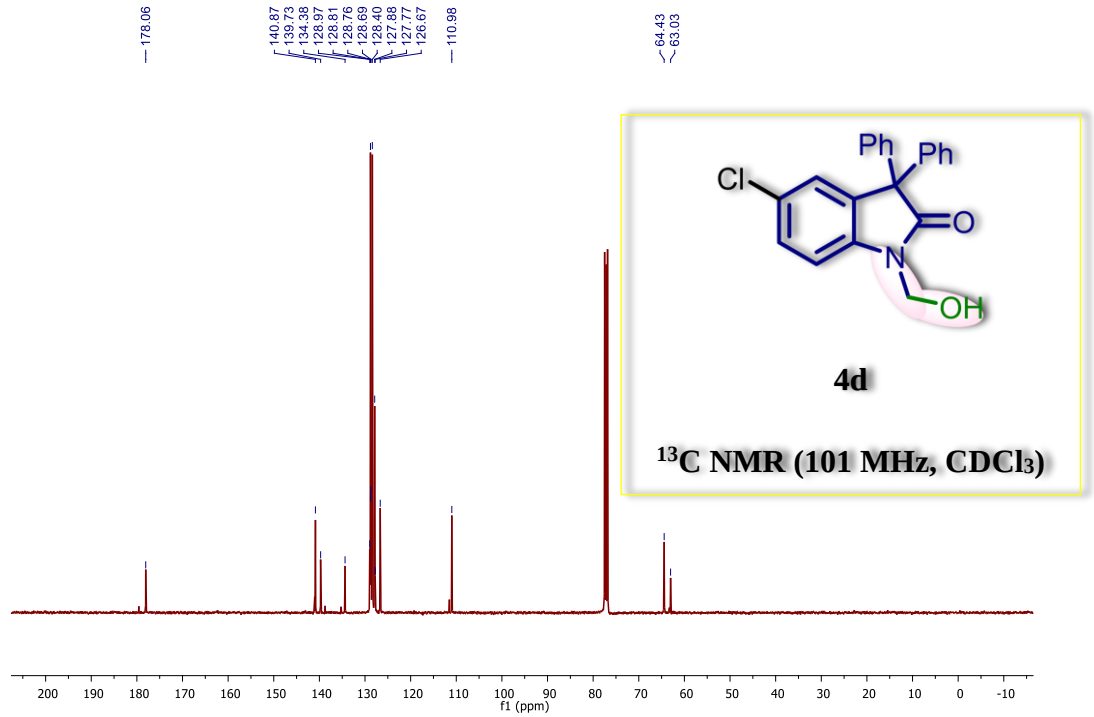
4a

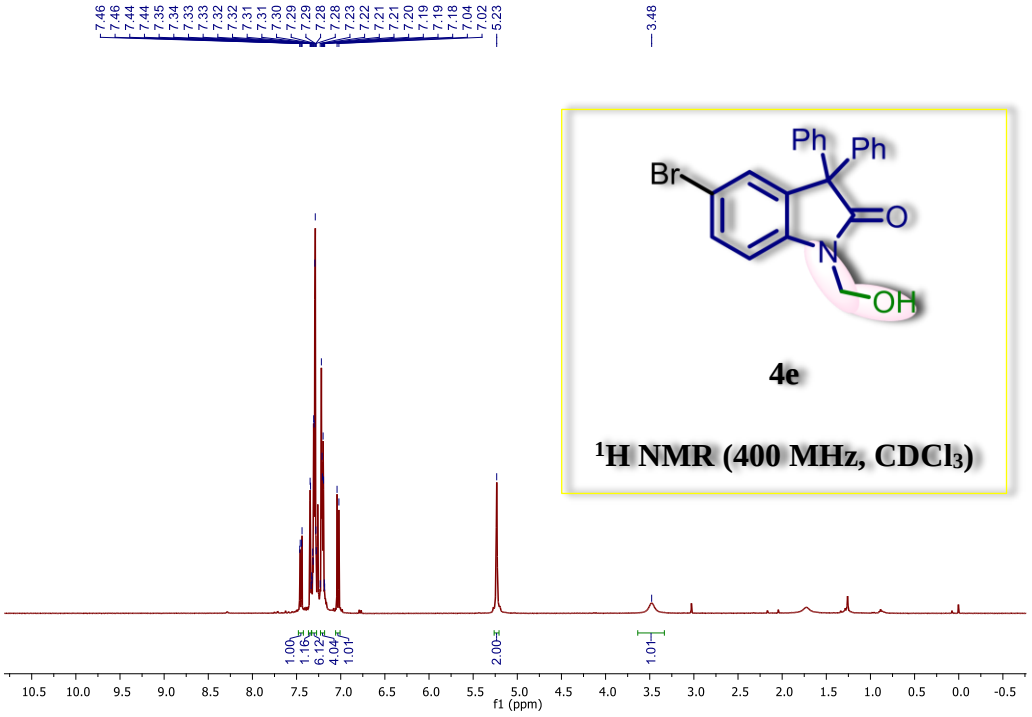
^{13}C NMR (101 MHz, $CDCl_3$)

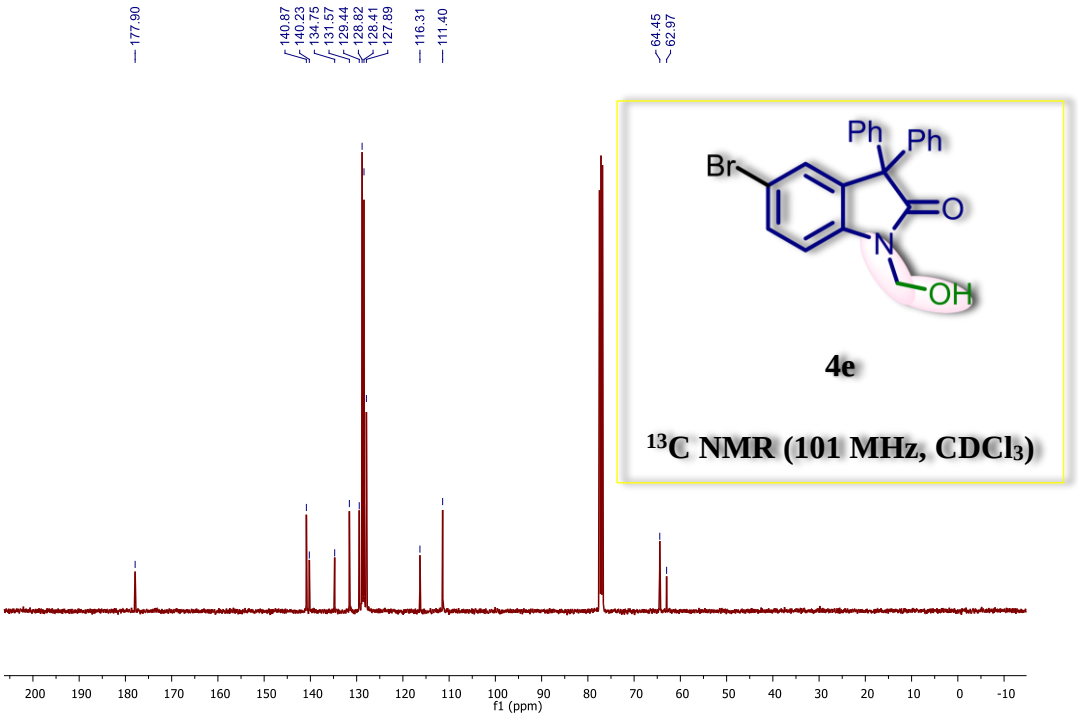

7.33
7.32
7.31
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.24
7.24
7.24
7.23
7.07
7.06
7.05
7.04
6.86
6.85
6.84
6.83
5.24
5.22
3.76
Ph
Ph
MeO
O
N
OH
4b
1H NMR (400 MHz, CDCl3)
10.30
1.02
1.81
2.00
3.10
f1 (ppm)

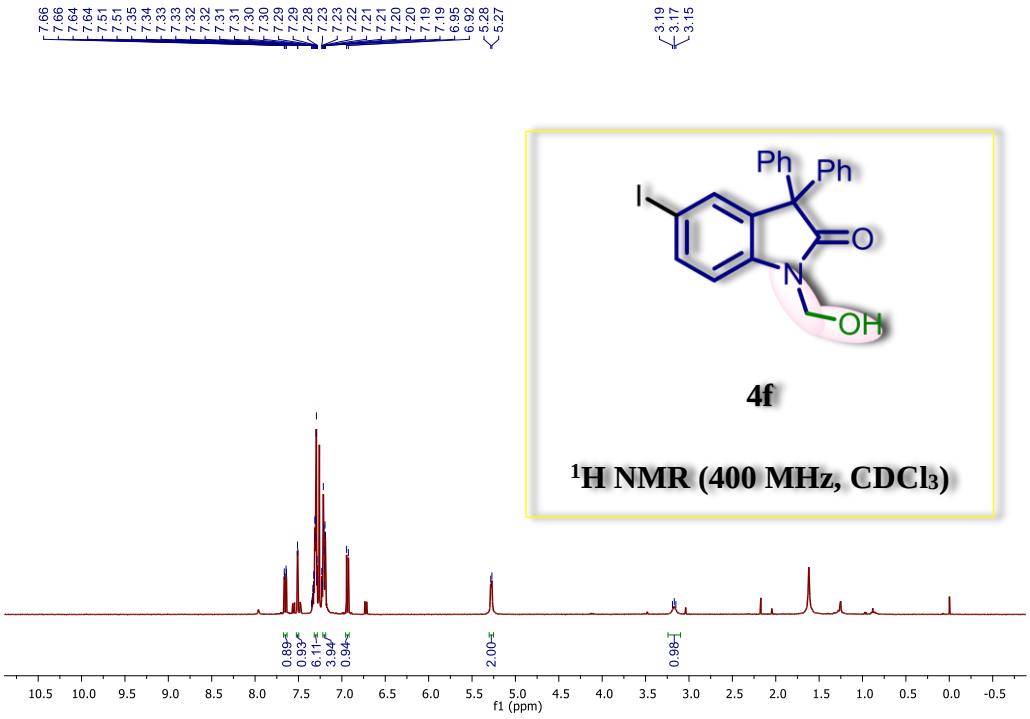

178.21
156.48
141.52
134.61
134.01
128.64
128.51
127.58
113.61
112.80
110.22
64.46
63.28
55.86
Ph
Ph
MeO
O
N
OH
4b
13C NMR (101 MHz, CDCl3)
f1 (ppm)

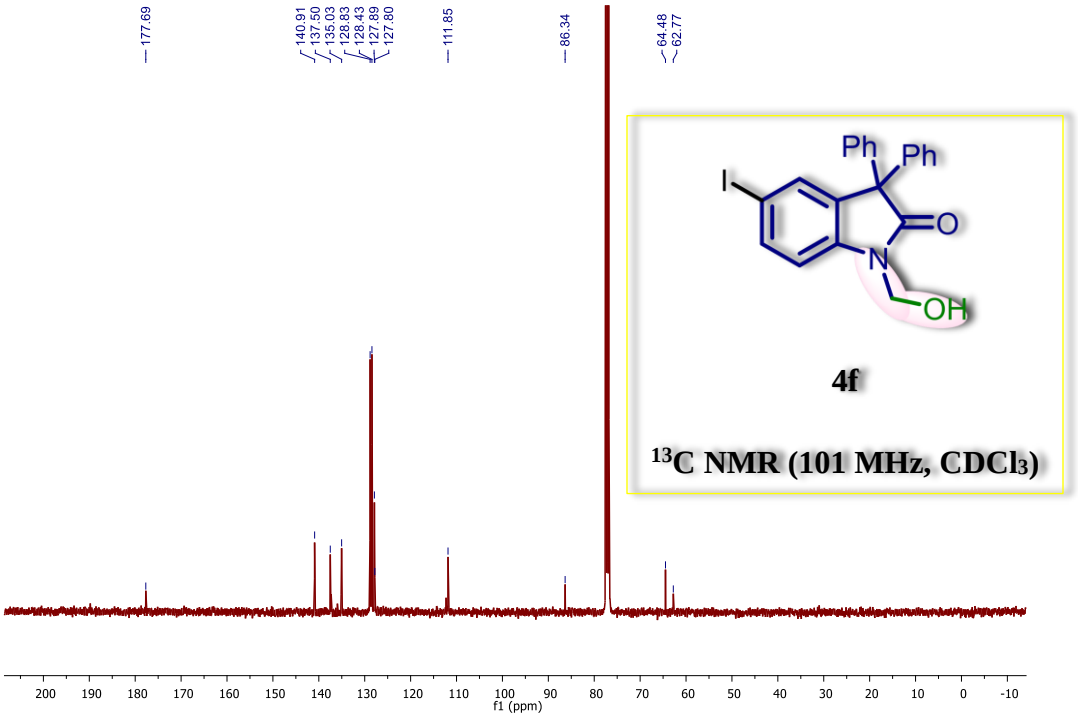

7.34
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.22
7.21
7.21
7.20
7.09
7.07
5.23
5.23
3.72
Ph
Ph
Cl
O
N
OH
4d
1H NMR (400 MHz, CDCl3)
7.06
5.12
0.94
2.00
0.87
f1 (ppm)

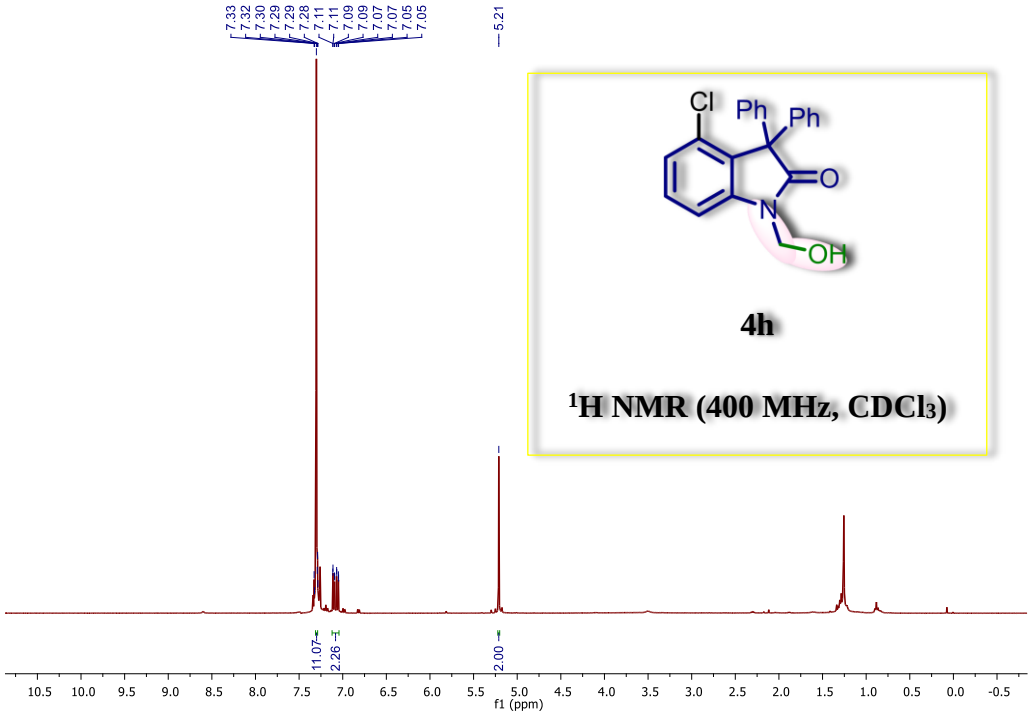

178.06
140.87
139.73
134.38
128.97
128.81
128.76
128.69
128.40
127.88
127.77
126.67
110.98
64.43
63.03
Ph
Ph
Cl
O
N
OH
4d
13C NMR (101 MHz, CDCl3)
f1 (ppm)

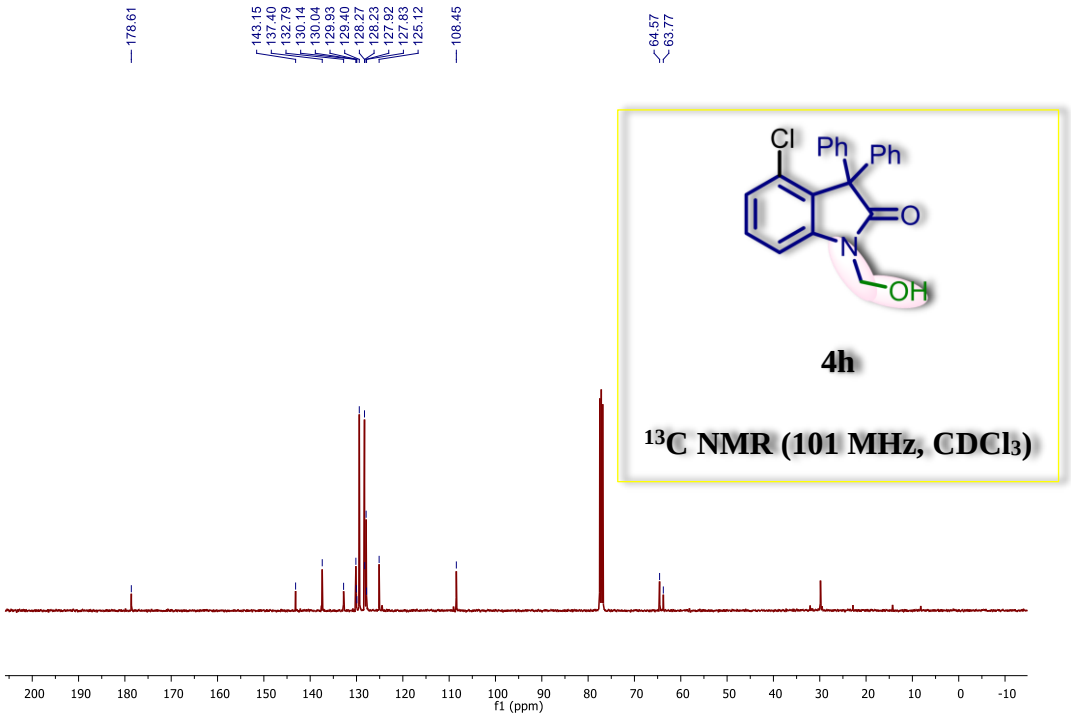

7.46
7.46
7.44
7.44
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.23
7.22
7.21
7.21
7.20
7.19
7.19
7.18
7.04
7.02
5.23
3.48
Ph
Ph
Br
O
N
OH
4e
1H NMR (400 MHz, CDCl3)
1.00
1.16
6.12
4.04
1.01
2.00
1.01
f1 (ppm)

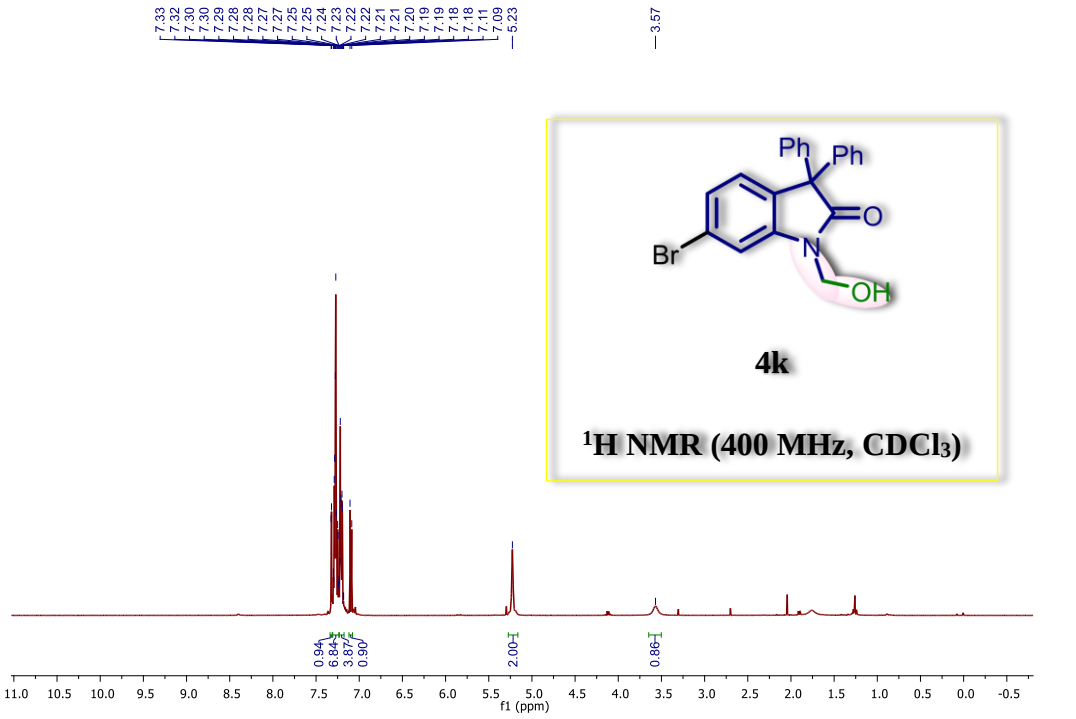

177.90
140.87
140.23
134.75
131.57
129.44
128.82
128.41
127.89
116.31
111.40
64.45
62.97
Ph
Ph
Br
O
N
OH
4e
13C NMR (101 MHz, CDCl3)
f1 (ppm)

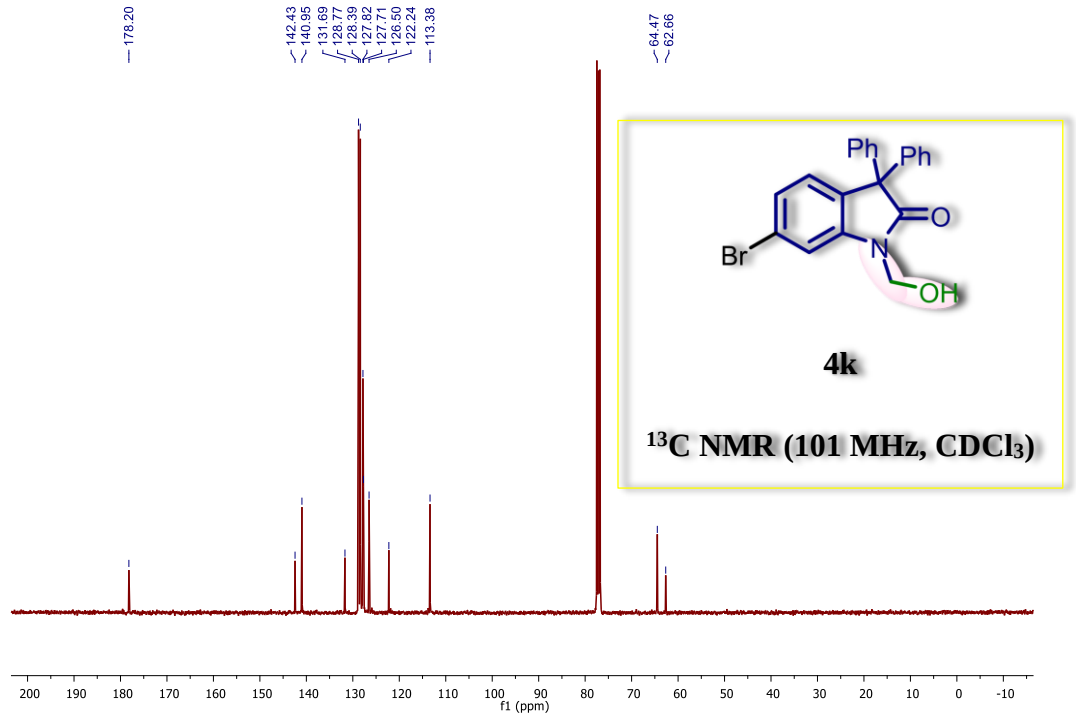

7.66
7.66
7.64
7.64
7.51
7.51
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.23
7.22
7.21
7.21
7.20
7.20
7.19
6.95
6.92
5.28
5.27
3.19
3.17
3.15
Ph
Ph
I
O
N
OH
4f
1H NMR (400 MHz, CDCl3)
0.89
0.93
6.11
3.94
0.94
2.00
0.98
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

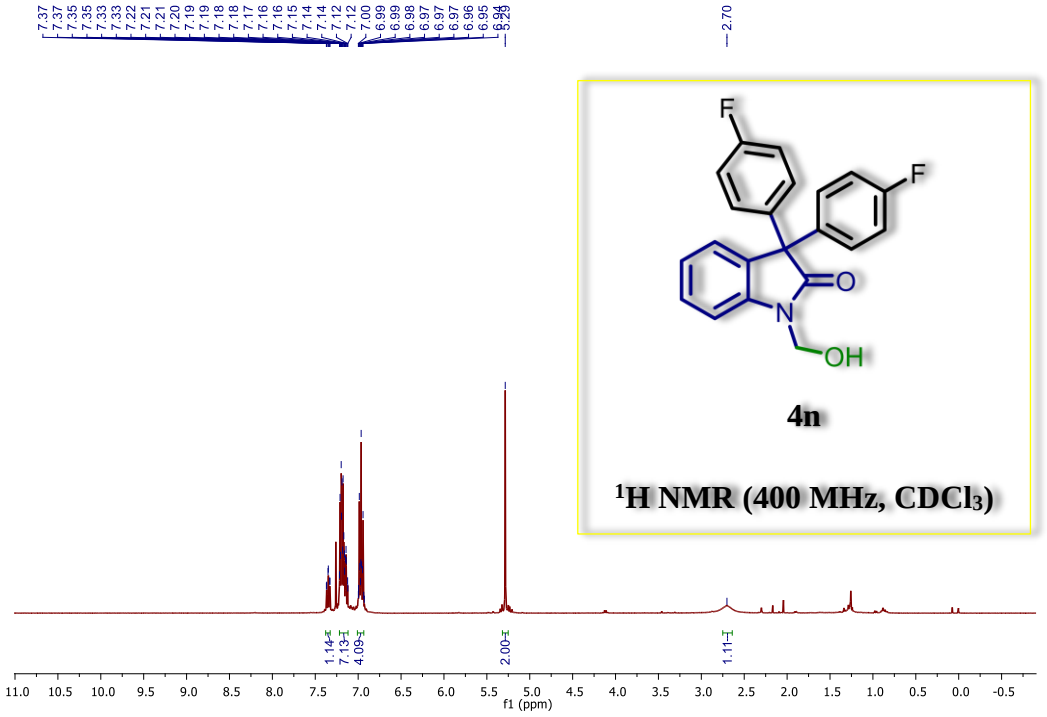

177.69
140.91
137.50
135.03
128.83
128.43
127.89
127.80
111.85
86.34
64.48
62.77
Ph
Ph
I
O
N
OH
4f
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

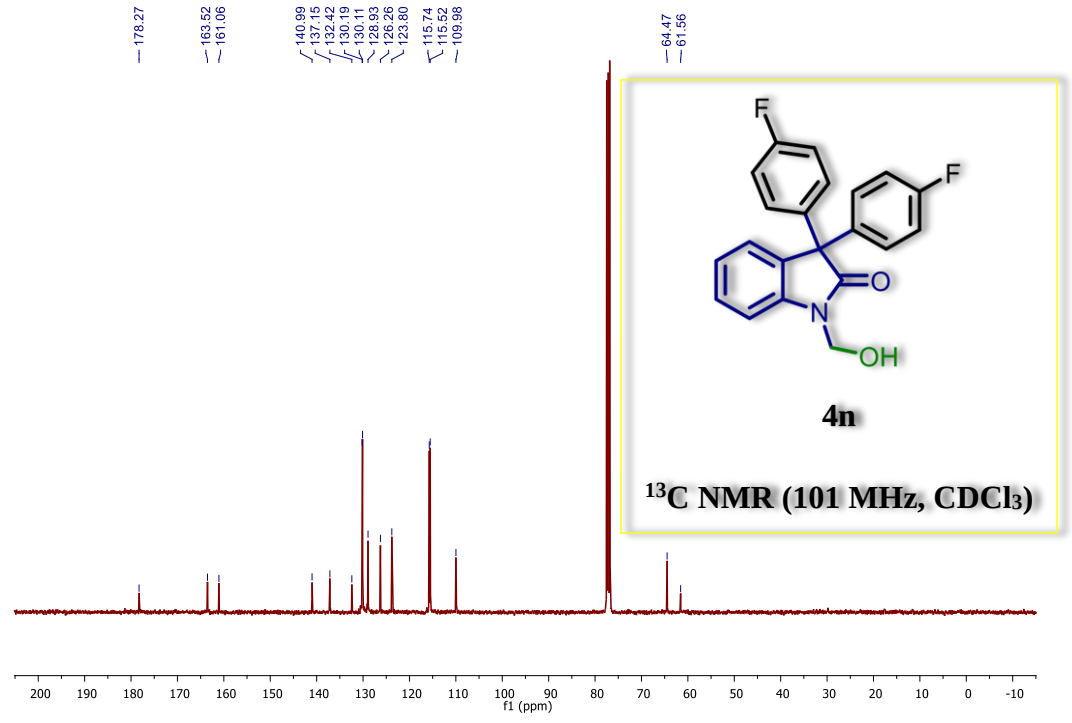

7.33
7.32
7.30
7.29
7.29
7.28
7.11
7.11
7.09
7.09
7.07
7.07
7.05
7.05
5.21
Cl
Ph
Ph
O
N
OH
4h
1H NMR (400 MHz, CDCl3)
11.07
2.26
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

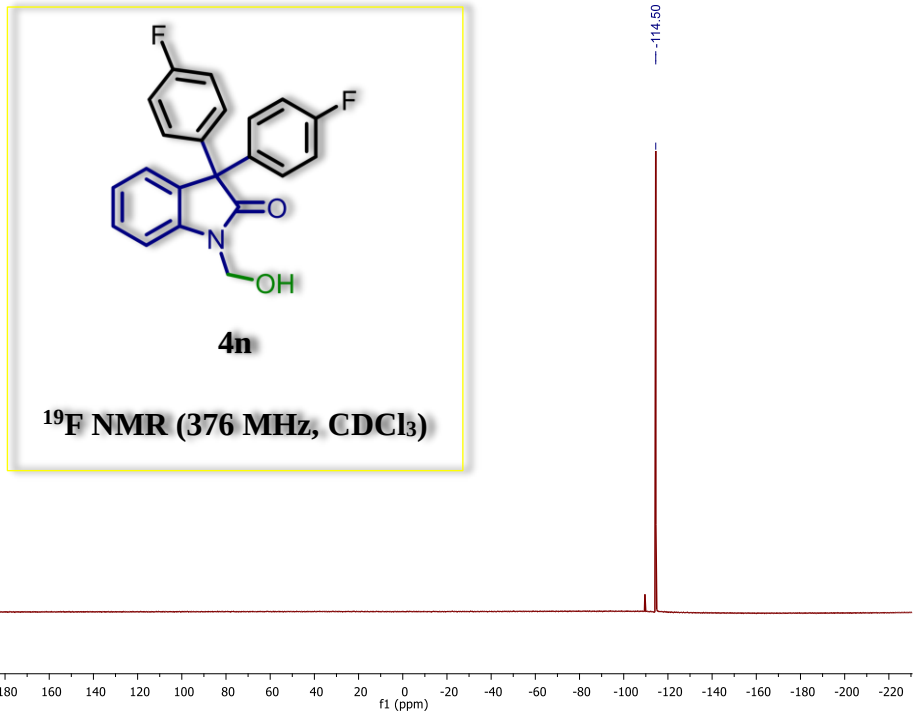

178.61
143.15
137.40
132.79
130.14
130.04
129.93
129.40
128.27
128.23
127.92
127.83
125.12
108.45
64.57
63.77
Cl
Ph
Ph
O
N
OH
4h
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

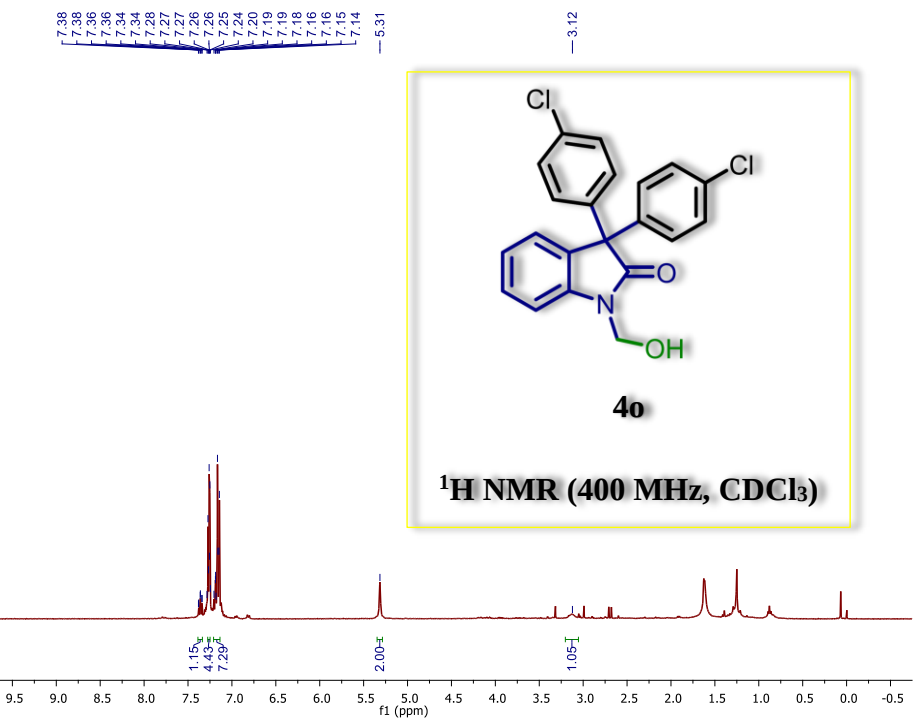

7.33
7.32
7.30
7.30
7.29
7.28
7.28
7.27
7.27
7.25
7.25
7.24
7.23
7.22
7.22
7.21
7.21
7.20
7.19
7.19
7.18
7.18
7.11
7.09
5.23
3.57
Ph
Ph
O
N
Br
OH
4k
1H NMR (400 MHz, CDCl3)
0.94
6.84
3.87
0.90
2.00
0.86
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

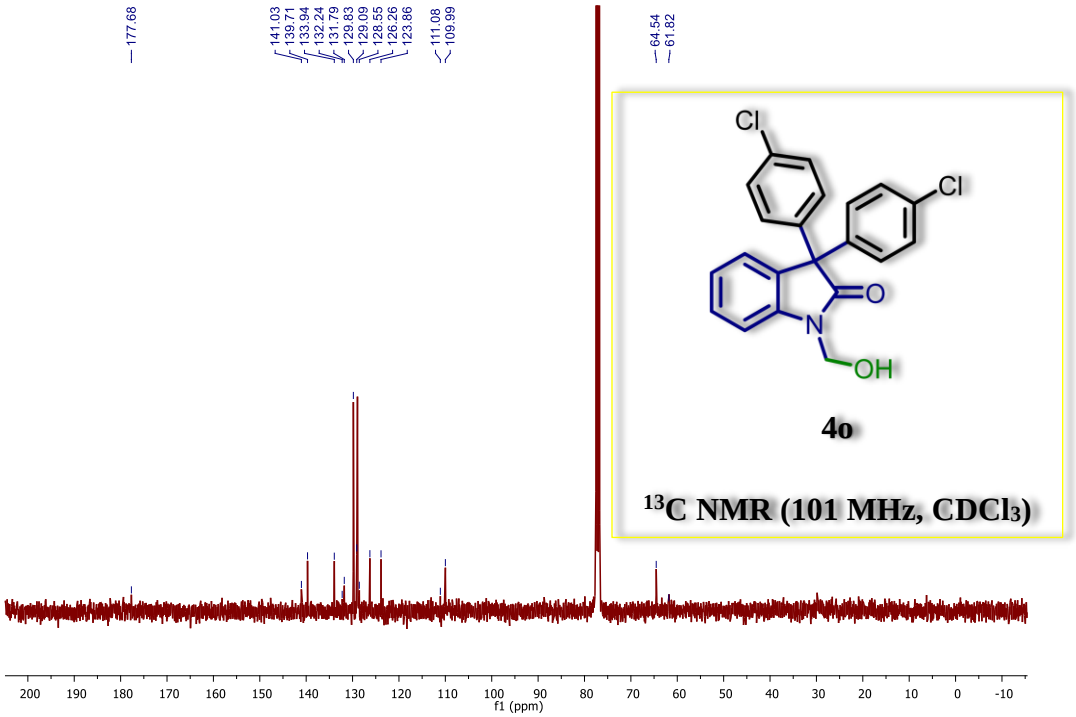

178.20
142.43
140.95
131.69
128.77
128.39
127.82
127.71
126.50
122.24
113.38
64.47
62.66
Ph
Ph
O
N
Br
OH
4k
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

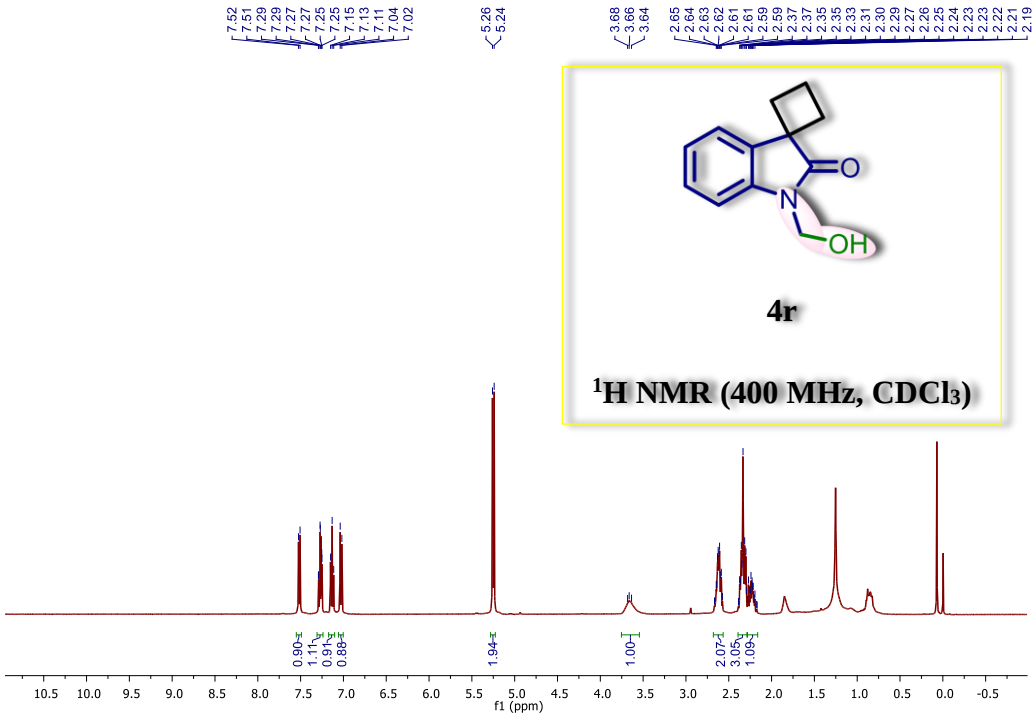

7.37
7.37
7.35
7.35
7.33
7.33
7.22
7.21
7.21
7.20
7.19
7.19
7.18
7.18
7.17
7.16
7.16
7.15
7.14
7.14
7.12
7.12
7.00
6.99
6.99
6.98
6.97
6.97
6.97
6.96
6.95
6.94
5.29
2.70
F
F
O
N
OH
4n
1H NMR (400 MHz, CDCl3)
1.14
7.13
4.09
2.00
1.11
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

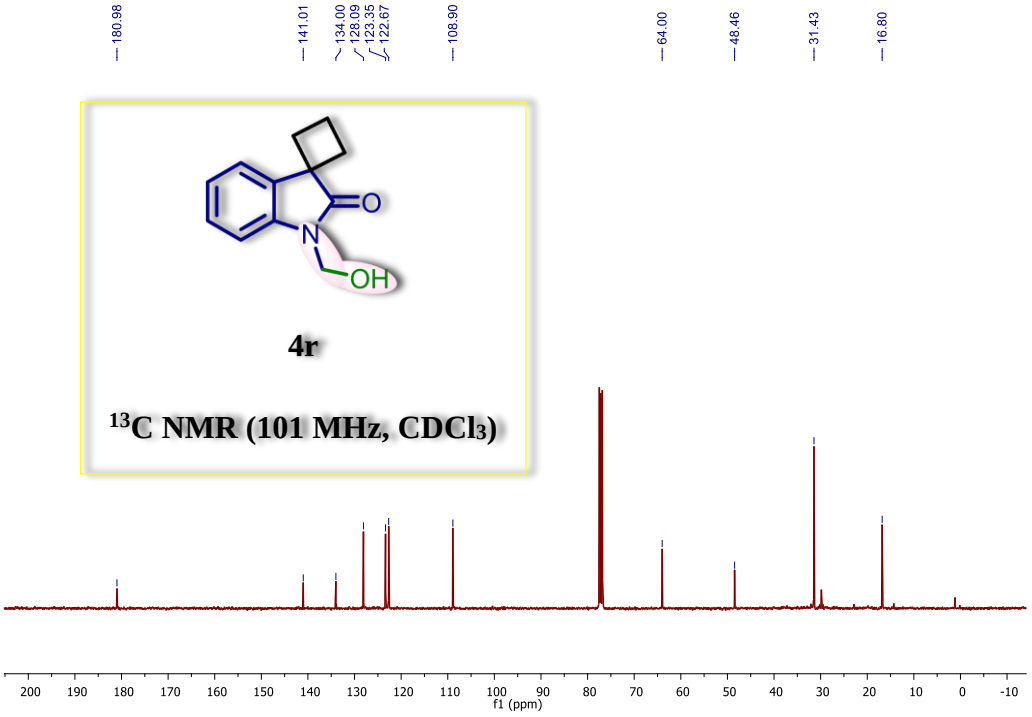

178.27
163.52
161.06
140.99
137.15
132.42
130.19
130.11
128.93
126.26
123.60
115.74
115.52
109.98
64.47
61.56
F
F
O
N
OH
4n
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

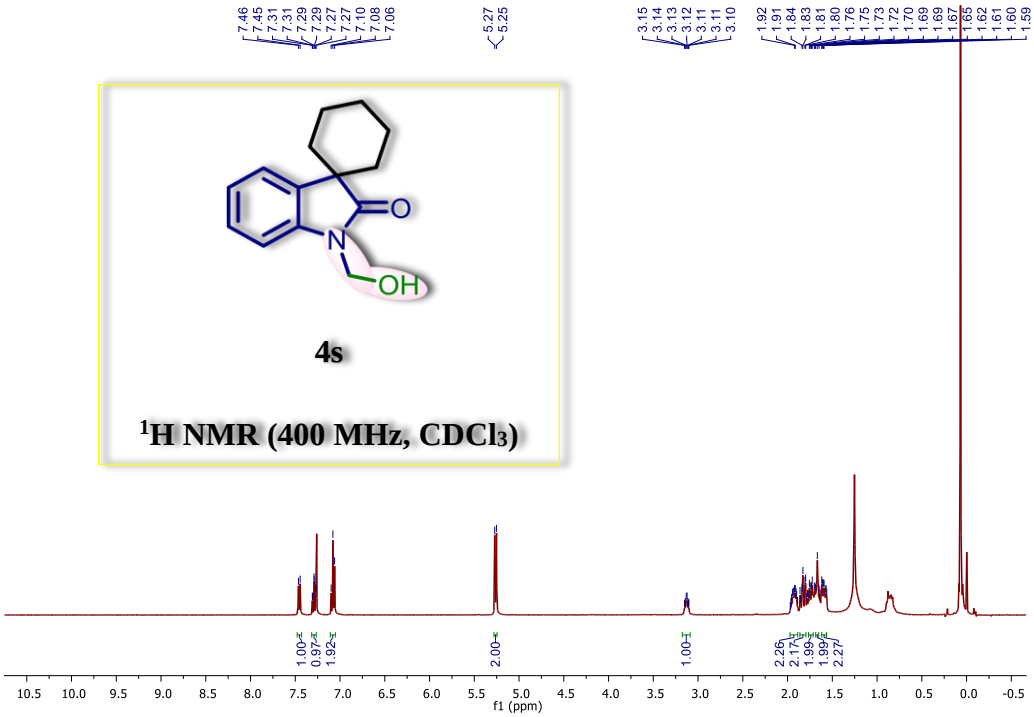

F
F
O
N
OH
4n
19F NMR (376 MHz, CDCl3)
-114.50
220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220
f1 (ppm)

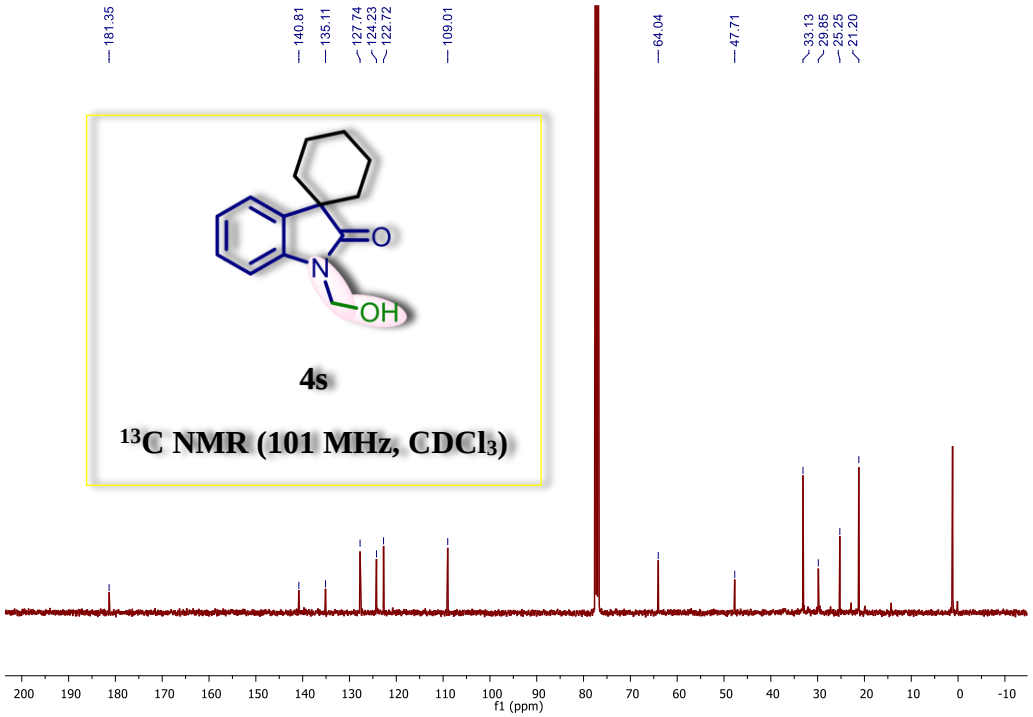

7.38
7.38
7.36
7.36
7.34
7.34
7.28
7.27
7.27
7.26
7.26
7.25
7.24
7.20
7.19
7.19
7.18
7.16
7.16
7.15
7.14
5.31
3.12
Cl
Cl
O
N
OH
4o
1H NMR (400 MHz, CDCl3)
1.15
4.43
7.29
2.00
1.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

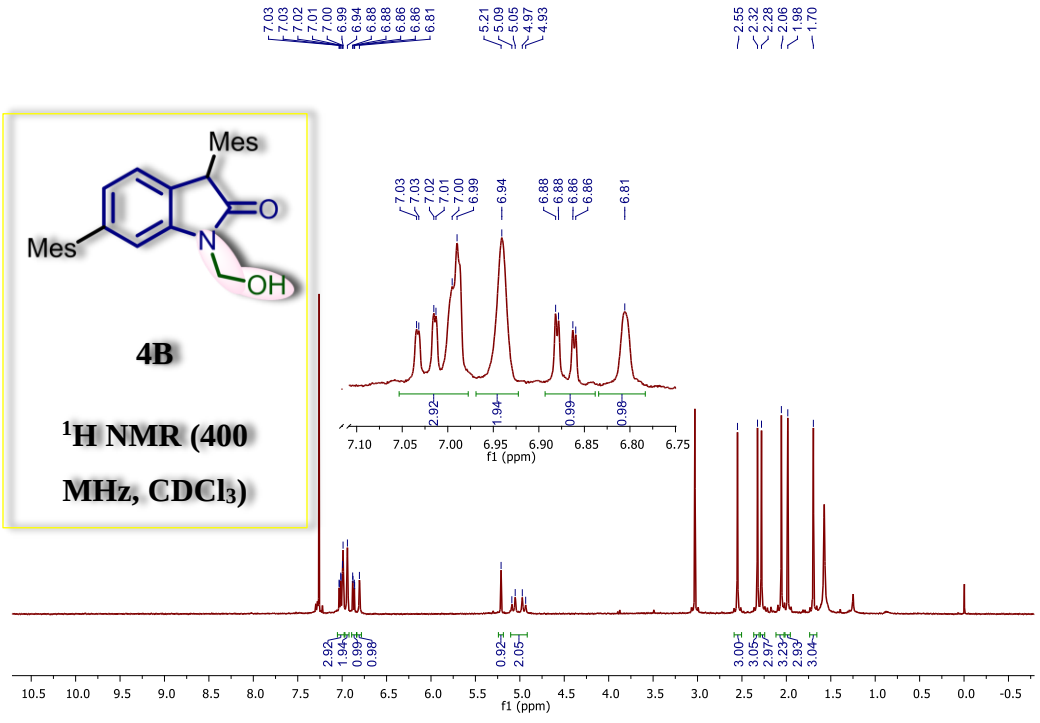

177.68
141.03
139.71
133.94
132.24
131.79
129.83
129.09
128.55
126.26
123.86
111.08
109.99
64.54
61.82
Cl
Cl
O
N
OH
4o
13C NMR (101 MHz, CDCl3)
f1 (ppm)

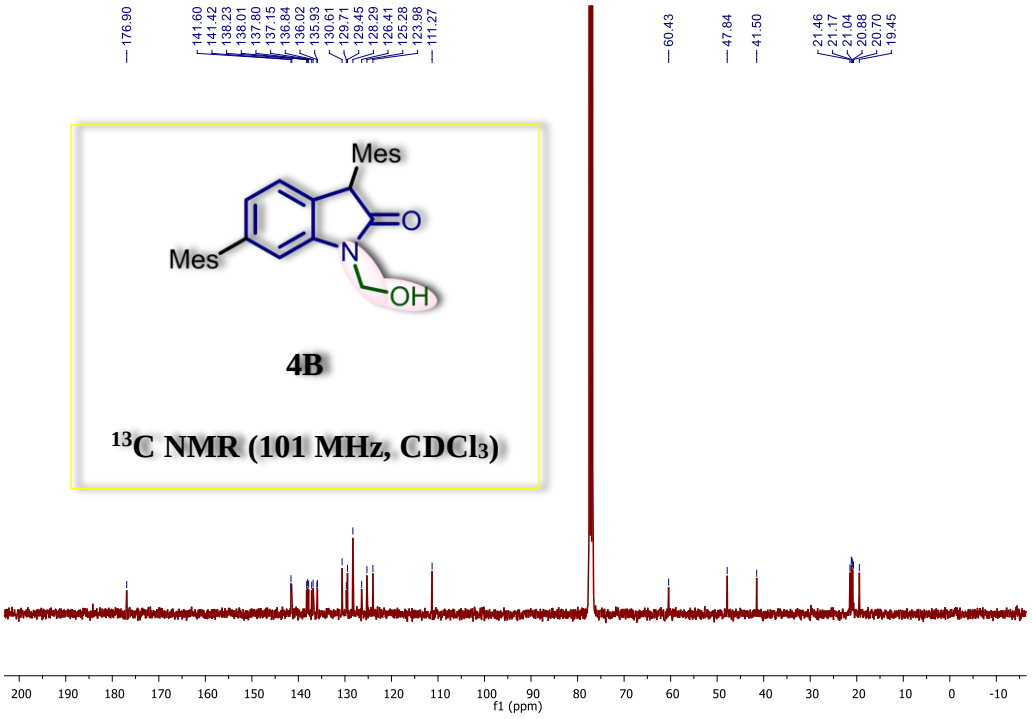

7.52
7.51
7.29
7.29
7.27
7.27
7.25
7.25
7.15
7.13
7.11
7.04
7.02
5.26
5.24
3.68
3.66
3.64
2.65
2.64
2.63
2.62
2.61
2.61
2.59
2.59
2.37
2.37
2.35
2.35
2.33
2.31
2.30
2.29
2.27
2.26
2.25
2.24
2.23
2.23
2.22
2.21
2.19
O
N
OH
4r
1H NMR (400 MHz, CDCl3)
0.90
1.11
0.91
0.88
1.94
1.00
2.07
3.05
1.09
f1 (ppm)

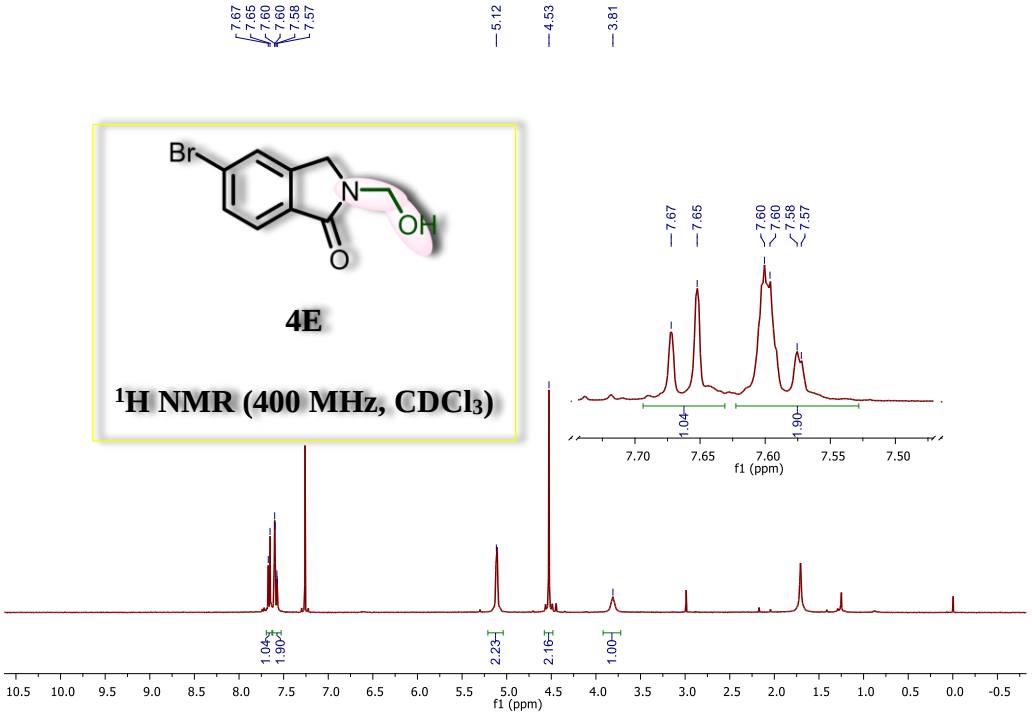

180.98
141.01
134.00
128.09
123.35
122.67
108.90
64.00
48.46
31.43
16.80
O
N
OH
4r
13C NMR (101 MHz, CDCl3)
f1 (ppm)

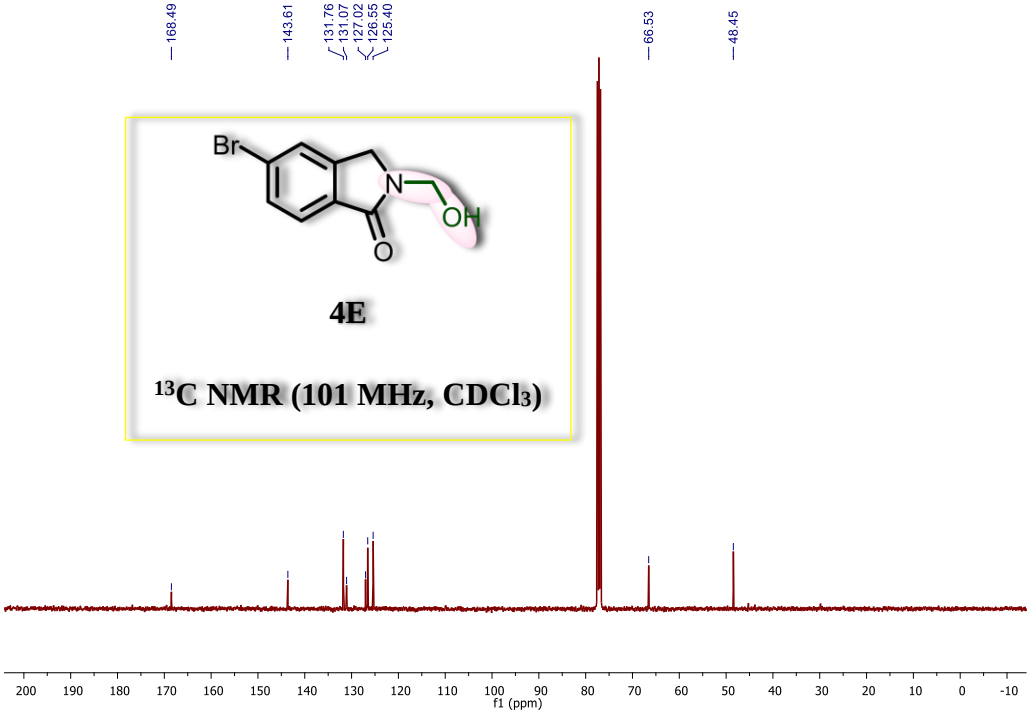

7.46
7.45
7.31
7.29
7.27
7.10
7.08
7.06
5.27
5.25
3.15
3.14
3.13
3.12
3.11
3.10
1.92
1.91
1.84
1.83
1.81
1.80
1.76
1.75
1.73
1.72
1.70
1.69
1.67
1.65
1.62
1.61
1.60
1.59
O
N
OH
4s
1H NMR (400 MHz, CDCl3)
1.00
0.97
1.92
2.00
1.00
2.26
2.17
1.99
1.99
2.27
f1 (ppm)

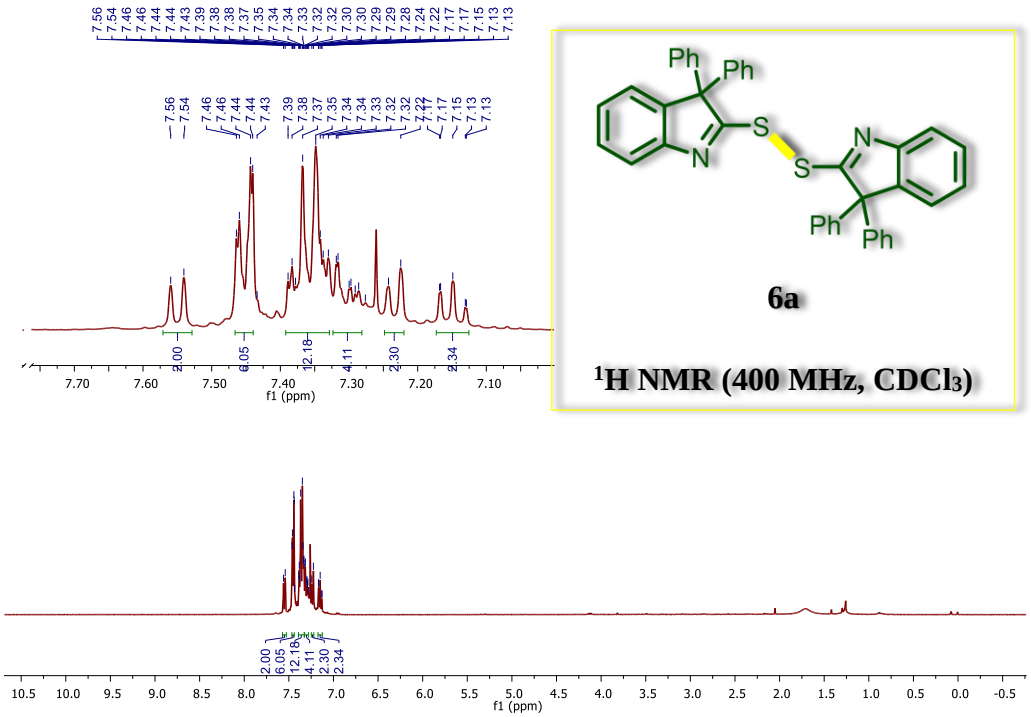

181.35
140.81
135.11
127.74
124.23
122.72
109.01
64.04
47.71
33.13
29.85
25.25
21.20
O
N
OH
4s
13C NMR (101 MHz, CDCl3)
f1 (ppm)

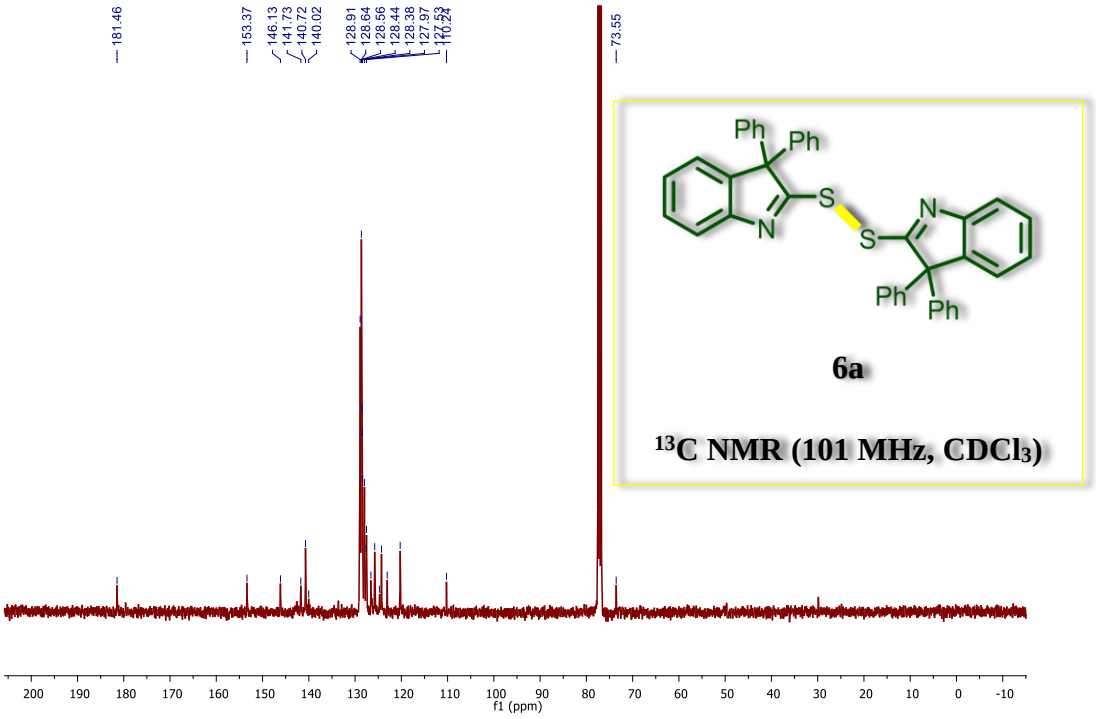

7.03
7.03
7.02
7.01
7.00
6.99
6.94
6.88
6.88
6.86
6.86
6.81
5.21
5.09
5.05
4.97
4.93
2.55
2.32
2.28
2.06
1.98
1.70
Mes
Mes
O
N
OH
4B
1H NMR (400 MHz, CDCl3)
2.92
1.94
0.99
0.98
f1 (ppm)

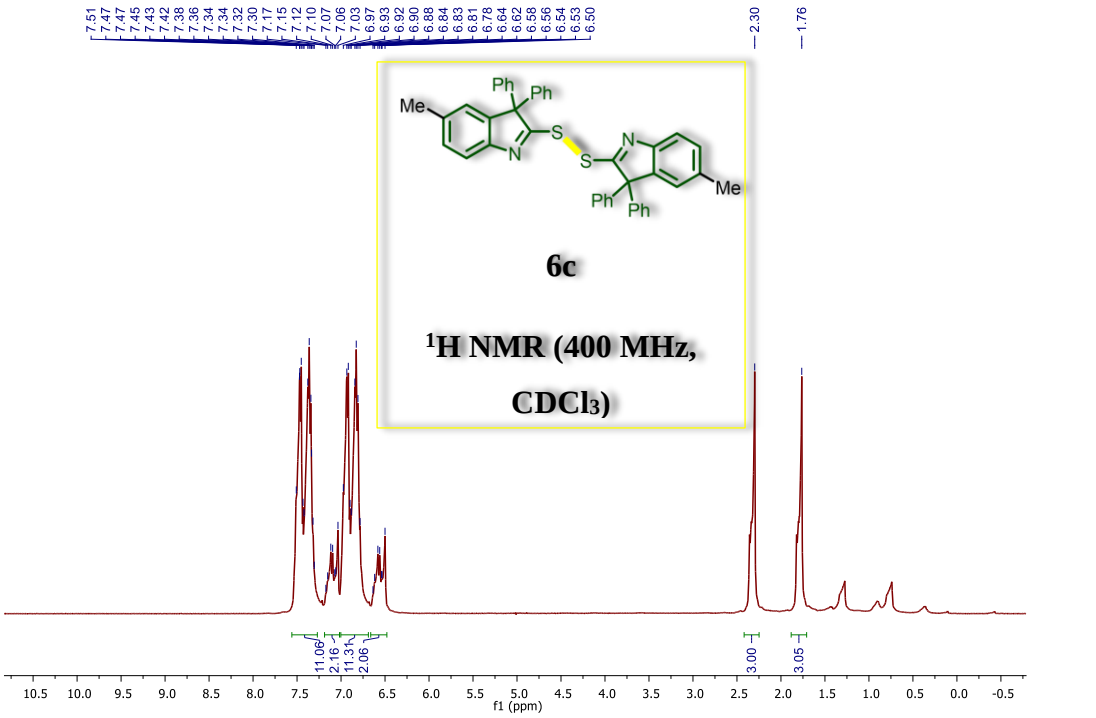

Mes
Mes
O
N
OH
4B
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

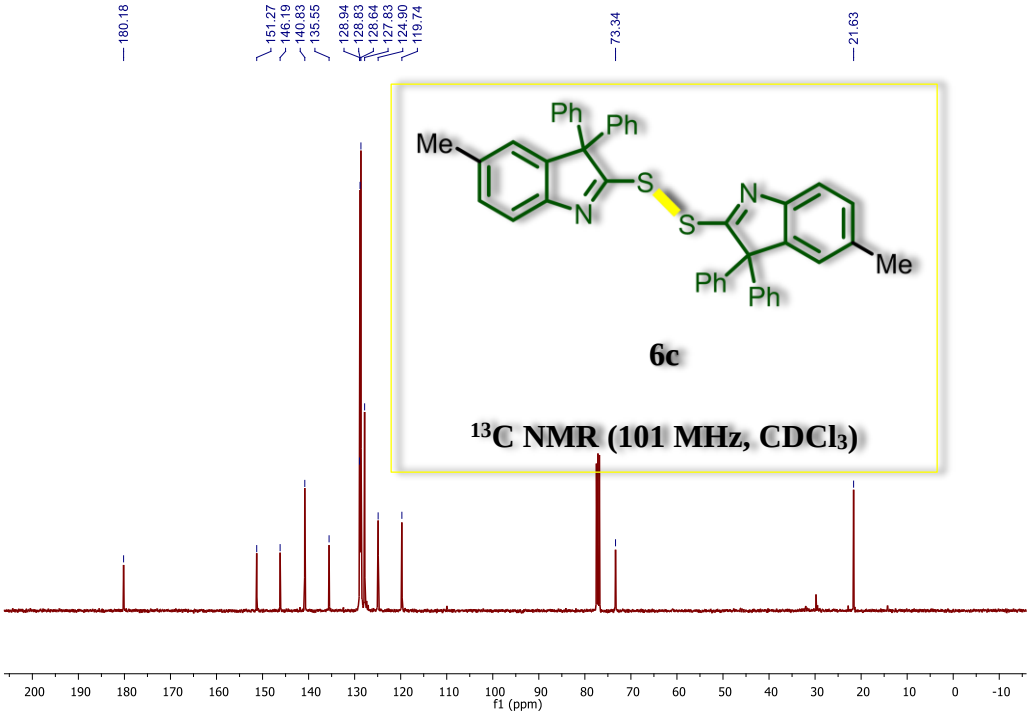

Br
N
OH
O
4E
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

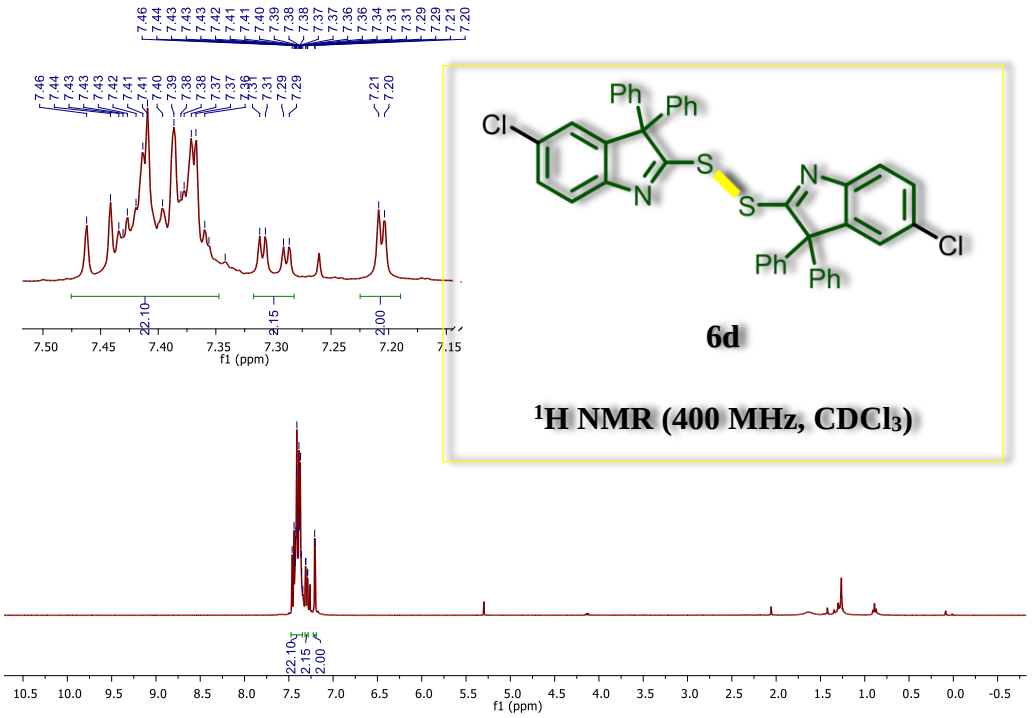

168.49
143.61
131.76
131.07
127.02
126.55
125.40
66.53
48.45
Br
N
OH
O
4E
13C NMR (101 MHz, CDCl3)
f1 (ppm)

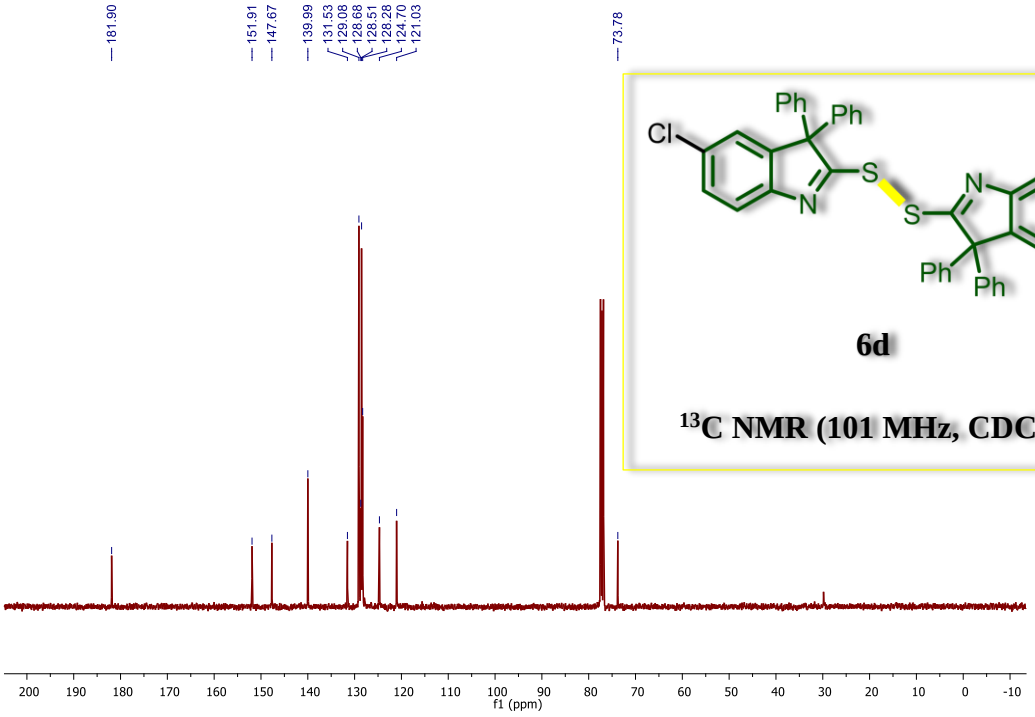

7.56
7.54
7.46
7.44
7.43
7.39
7.38
7.37
7.35
7.34
7.33
7.32
7.30
7.29
7.28
7.24
7.22
7.17
7.15
7.13
Ph
Ph
S
N
6a
1H NMR (400 MHz, CDCl3)
2.00
6.05
12.18
4.11
2.30
2.34
f1 (ppm)

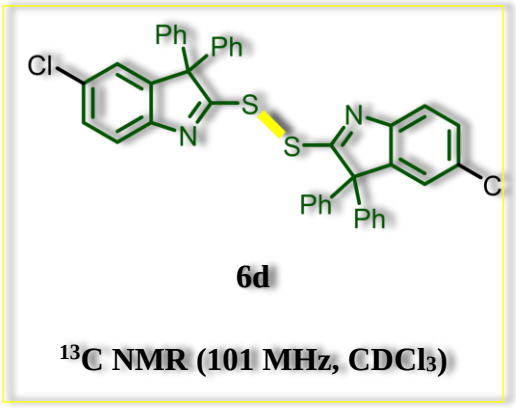

181.46
153.37
146.13
141.73
140.72
140.02
128.91
128.64
128.56
128.44
128.38
127.97
127.53
110.24
73.55
Ph
Ph
S
N
N
S
Ph
Ph
6a
13C NMR (101 MHz, CDCl3)
f1 (ppm)


7.51
7.47
7.47
7.45
7.43
7.42
7.38
7.36
7.34
7.34
7.32
7.30
7.17
7.15
7.12
7.10
7.07
7.06
7.03
6.97
6.93
6.92
6.90
6.88
6.84
6.83
6.81
6.78
6.64
6.62
6.58
6.56
6.54
6.53
6.50
2.30
1.76
Me
Ph
Ph
S
N
N
S
Ph
Ph
Me
6c
1H NMR (400 MHz, CDCl3)
11.06
2.16
11.31
2.06
3.00
3.05
f1 (ppm)


180.18
151.27
146.19
140.83
135.55
128.94
128.83
128.64
127.83
124.90
119.74
73.34
21.63
Ph
Ph
Me
S
N
S
N
Ph
Ph
Me
6c
13C NMR (101 MHz, CDCl3)
f1 (ppm)

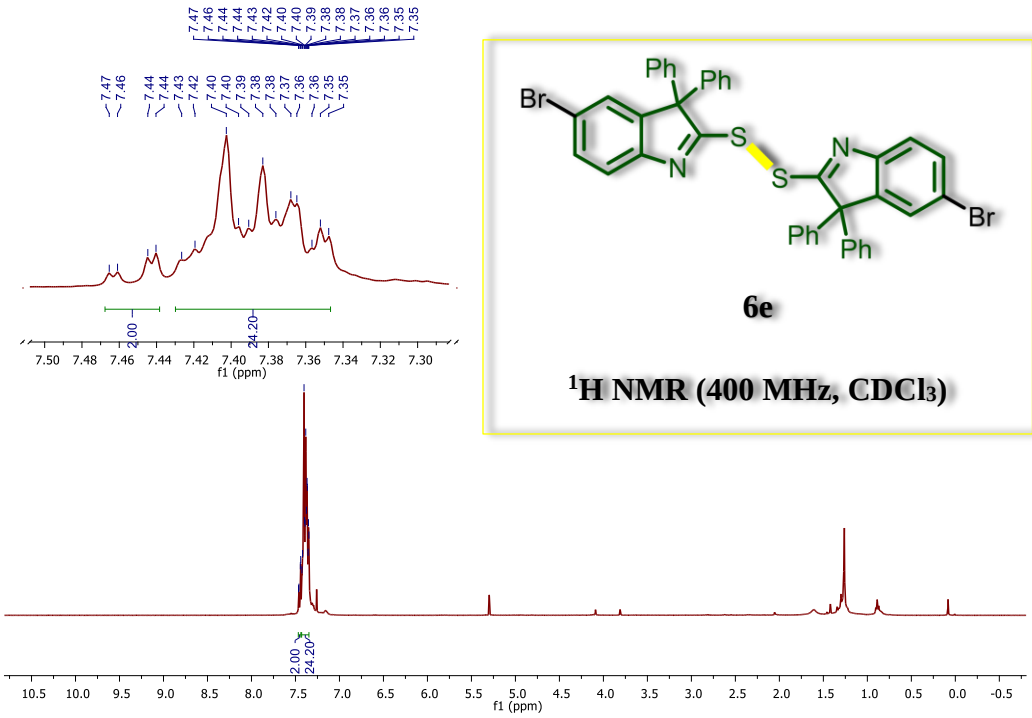

7.46
7.44
7.43
7.43
7.43
7.42
7.41
7.41
7.40
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.34
7.31
7.29
7.29
7.21
7.20
22.10
2.15
2.00
f1 (ppm)
Cl
Ph
Ph
S
N
S
N
Ph
Ph
Cl
6d
1H NMR (400 MHz, CDCl3)





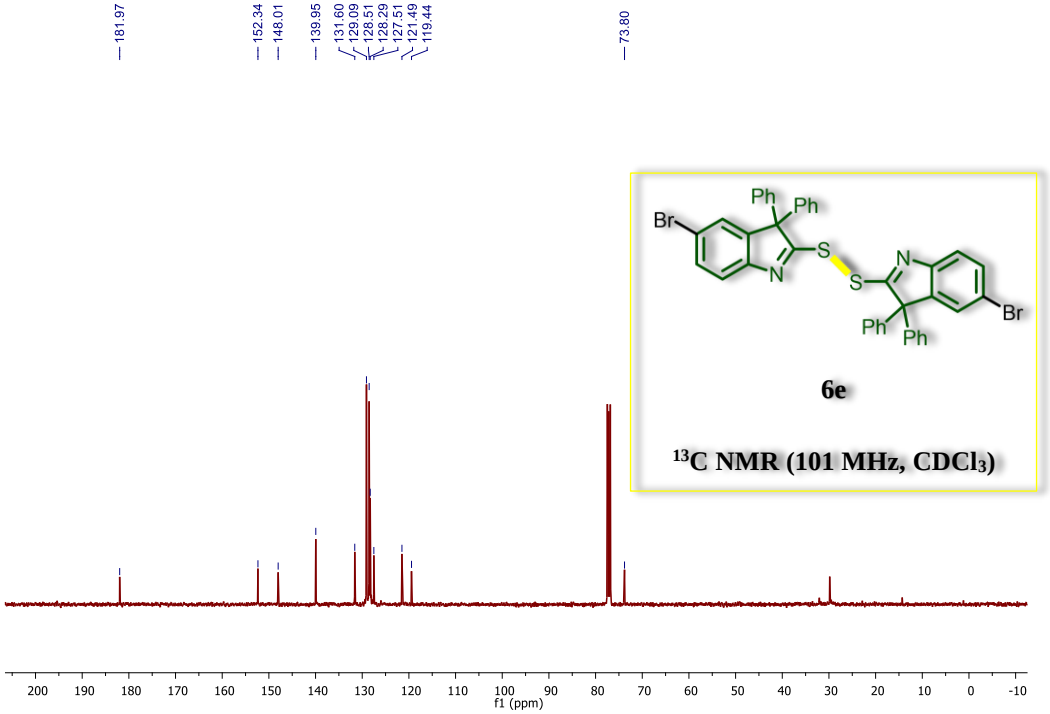
6d

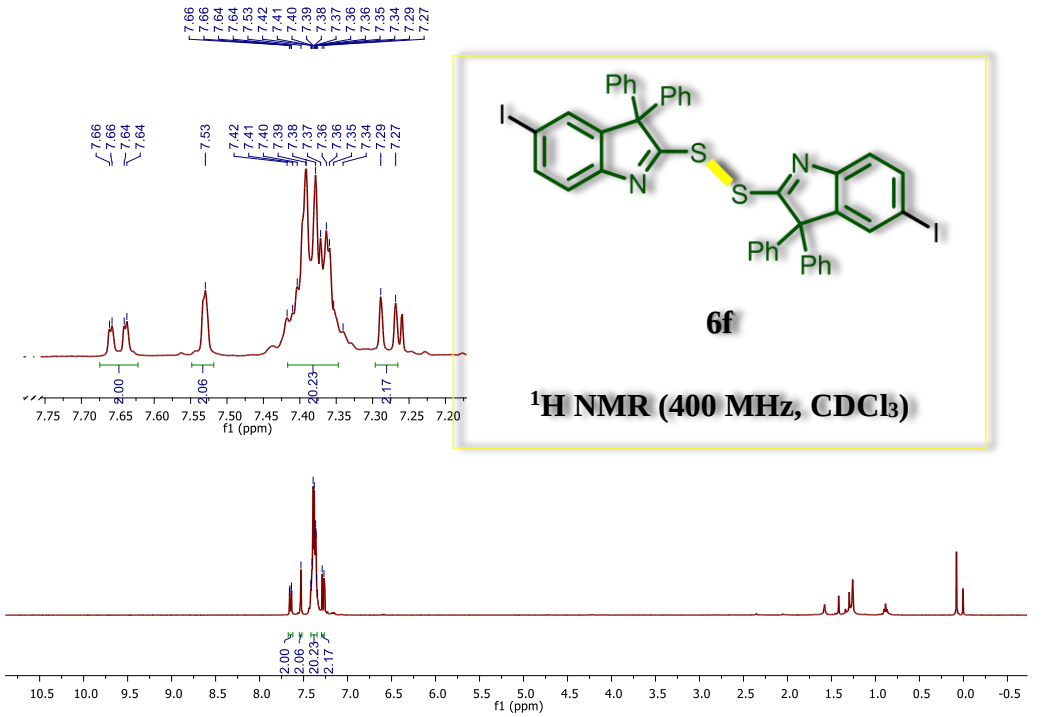
^{13}C NMR (101 MHz, $CDCl_3$)

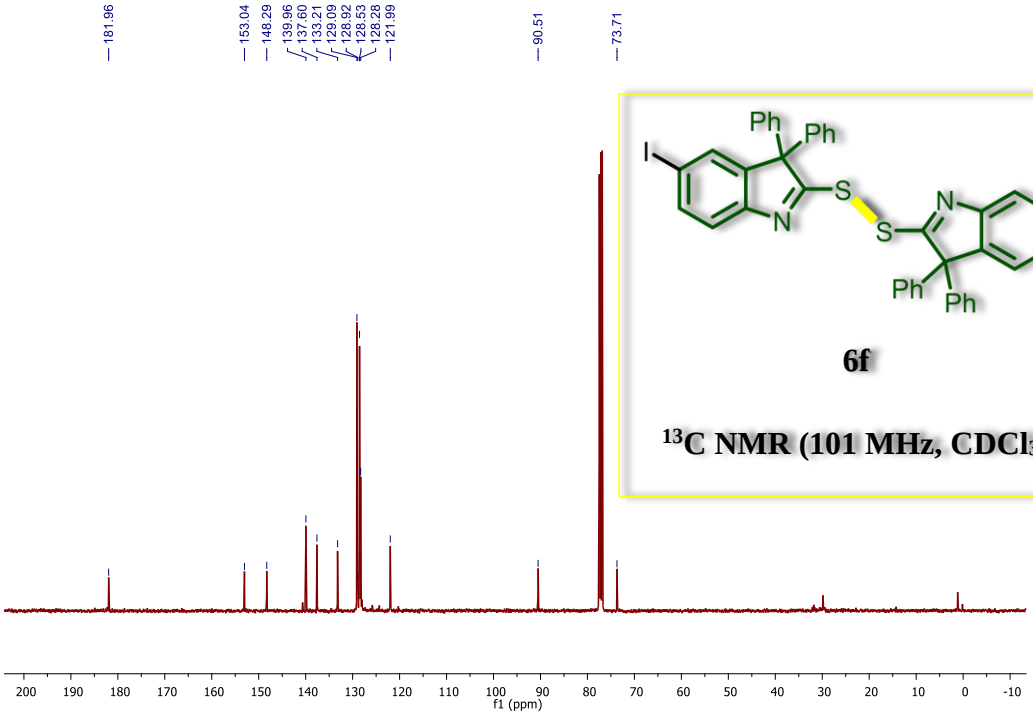


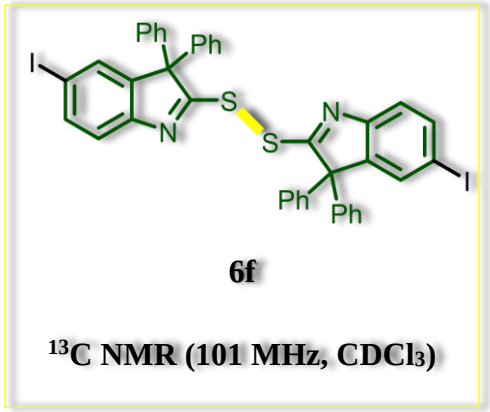
6e

^{1}H NMR (400 MHz, $CDCl_3$)


181.97
152.34
148.01
139.95
131.60
129.09
128.51
128.29
127.51
121.49
119.44
73.80
Ph
Ph
Br
S
N
S
N
Br
Ph
Ph
6e
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

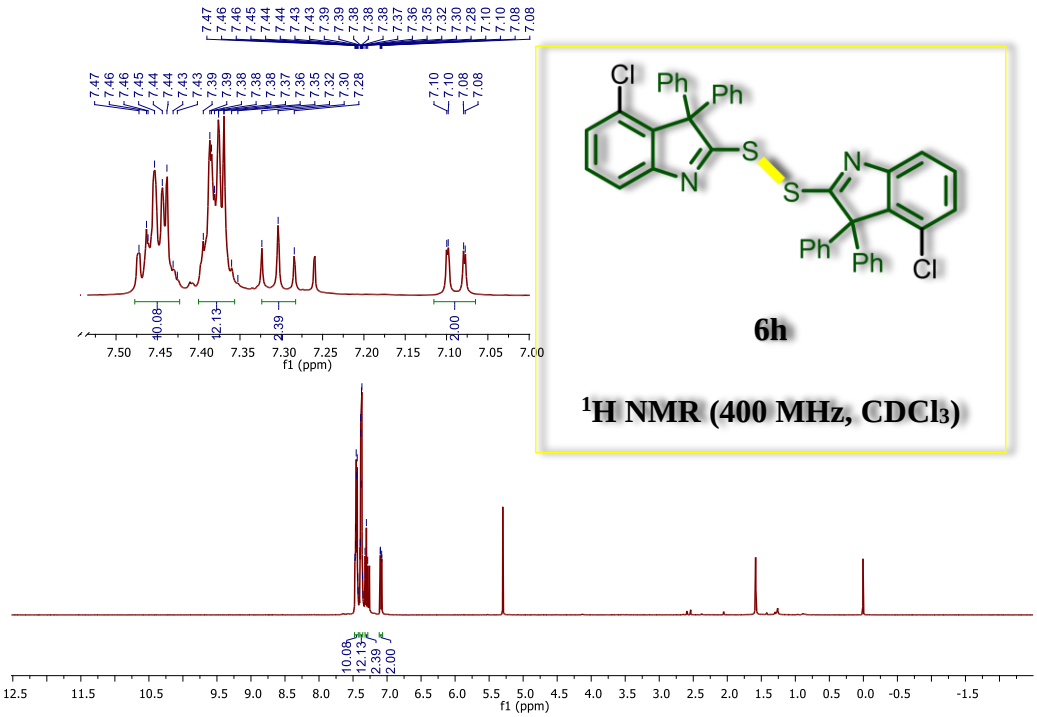

7.66
7.66
7.64
7.64
7.53
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.36
7.35
7.34
7.29
7.27
2.00
2.06
20.23
2.17
f1 (ppm)
Ph
Ph
I
S
N
S
N
I
Ph
Ph
6f
^{1}H NMR (400 MHz, CDCl$_3$)





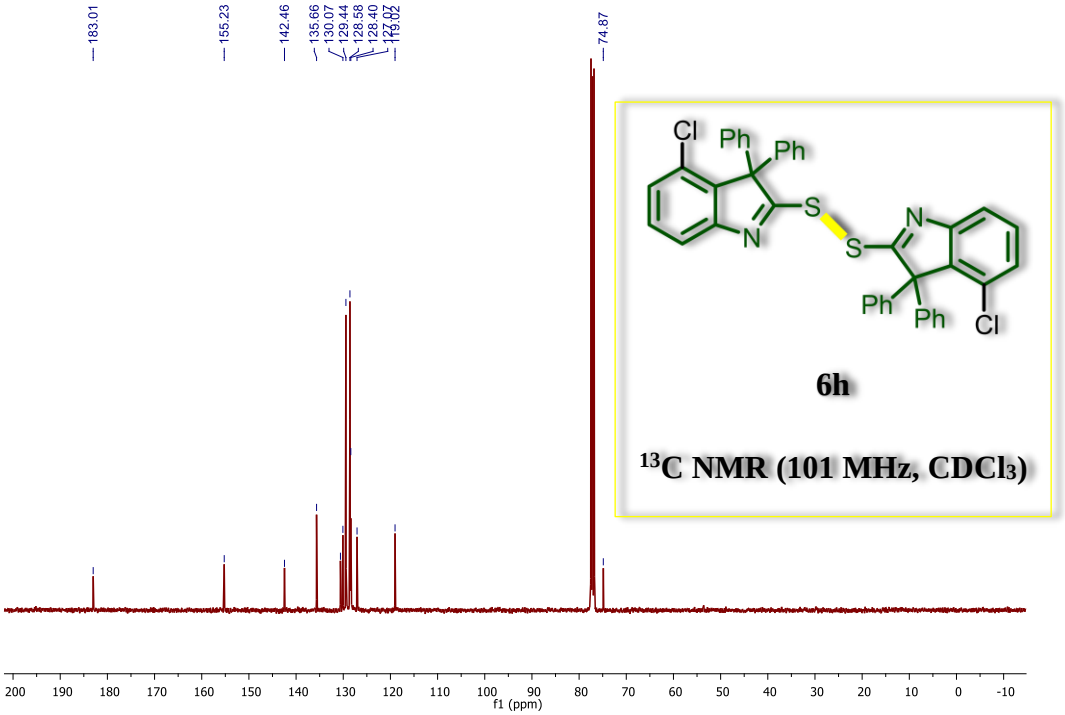
6f

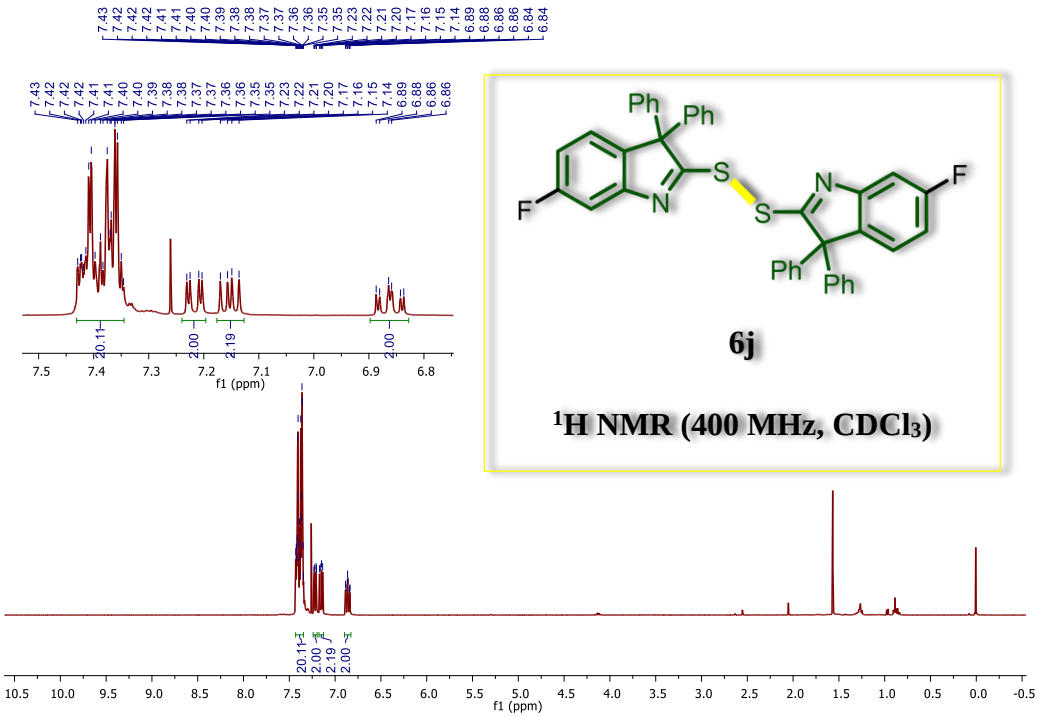
^{13}C NMR (101 MHz, $CDCl_3$)

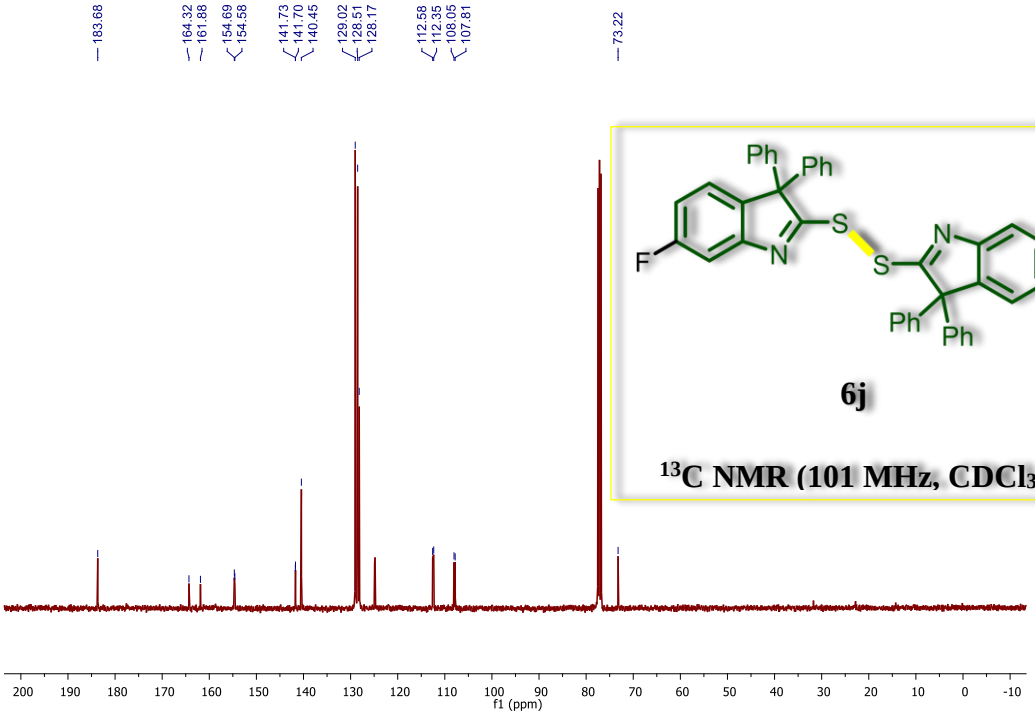


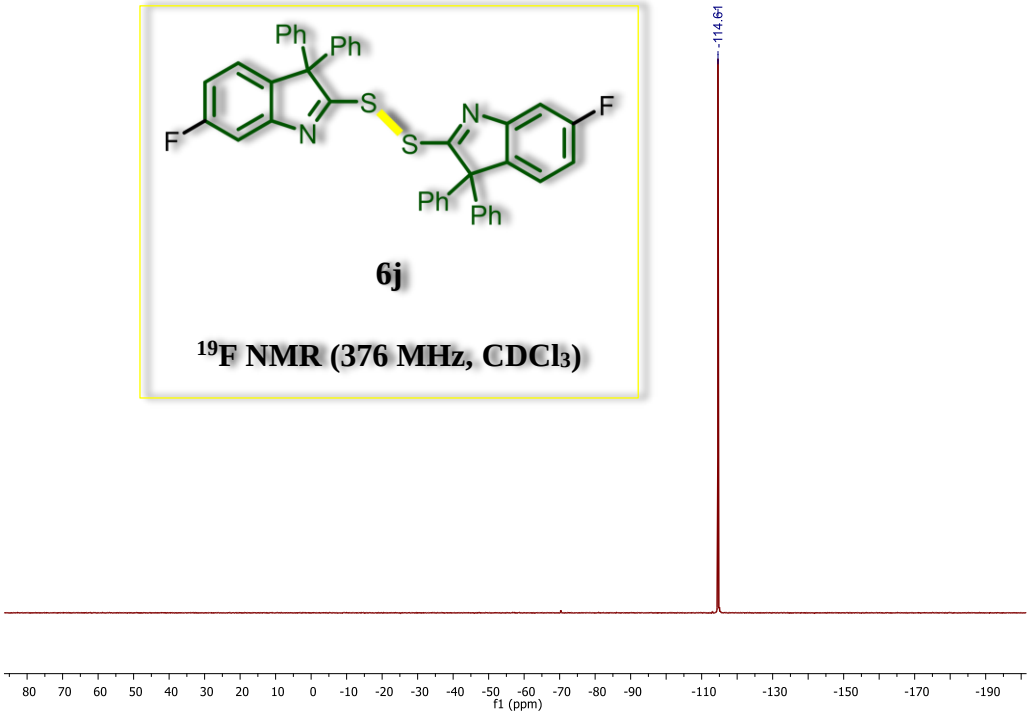
6h

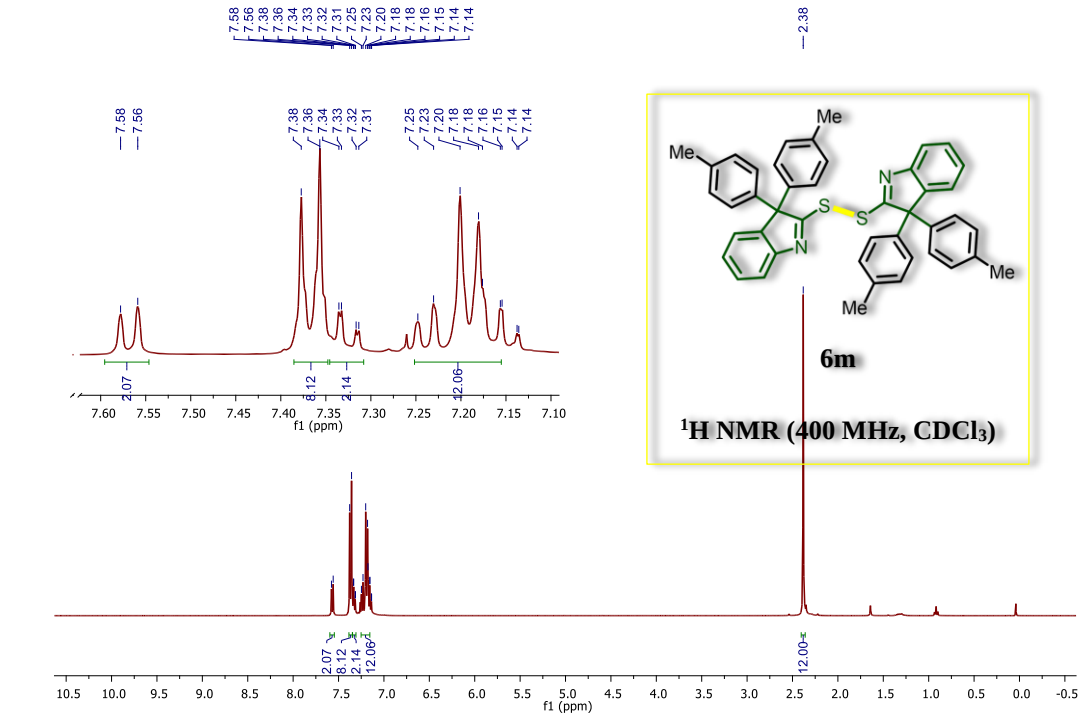
^{1}H NMR (400 MHz, $CDCl_3$)

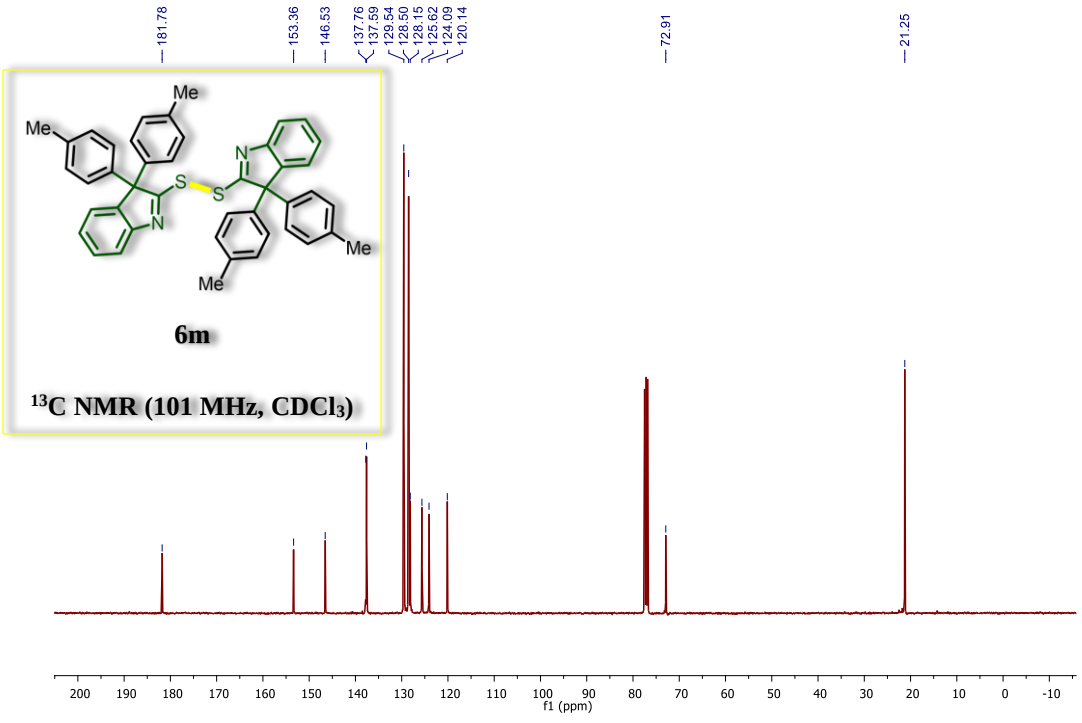

183.01
155.23
142.46
135.66
130.07
129.44
128.58
128.40
127.07
119.02
74.87
Cl
Ph
Ph
S
N
S
N
Ph
Ph
Cl
6h
13C NMR (101 MHz, CDCl3)
f1 (ppm)

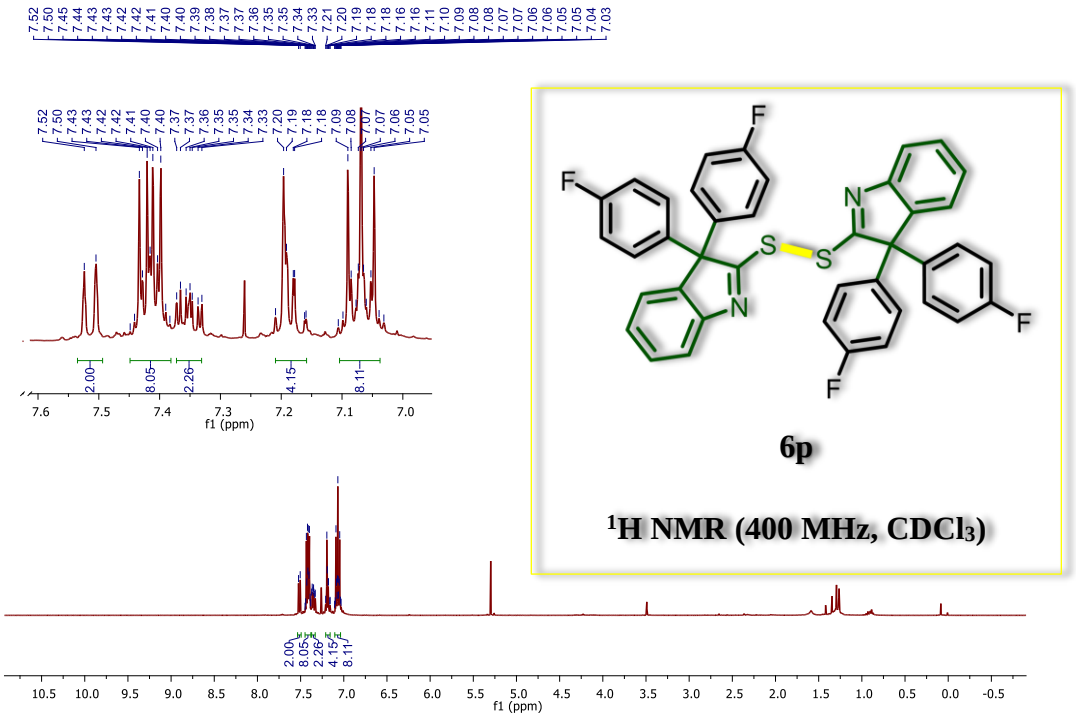

Ph
Ph
S
N
S
N
F
F
Ph
Ph
6j
1H NMR (400 MHz, CDCl3)
f1 (ppm)

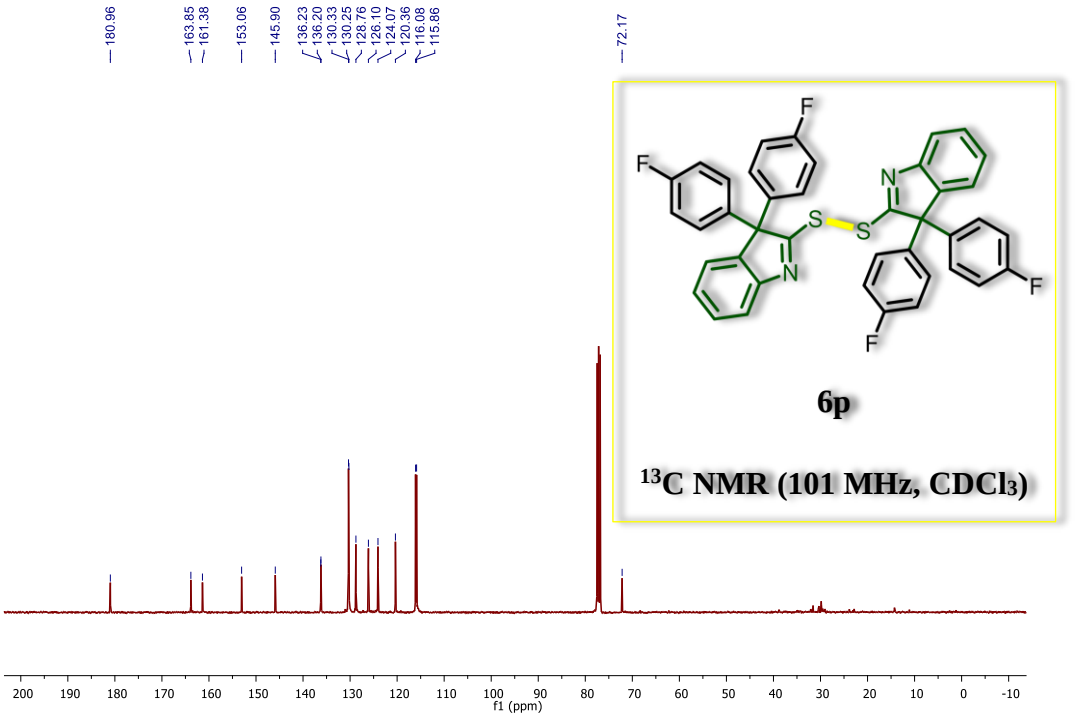

183.68
164.32
161.88
154.69
154.58
141.73
141.70
140.45
129.02
128.51
128.17
112.58
112.35
108.05
107.81
73.22
Ph
Ph
S
N
F
S
N
F
Ph
Ph
6j
13C NMR (101 MHz, CDCl3)
f1 (ppm)


-114.61
Ph
Ph
S
N
F
S
N
F
Ph
Ph
6j
19F NMR (376 MHz, CDCl3)
f1 (ppm)


6m
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

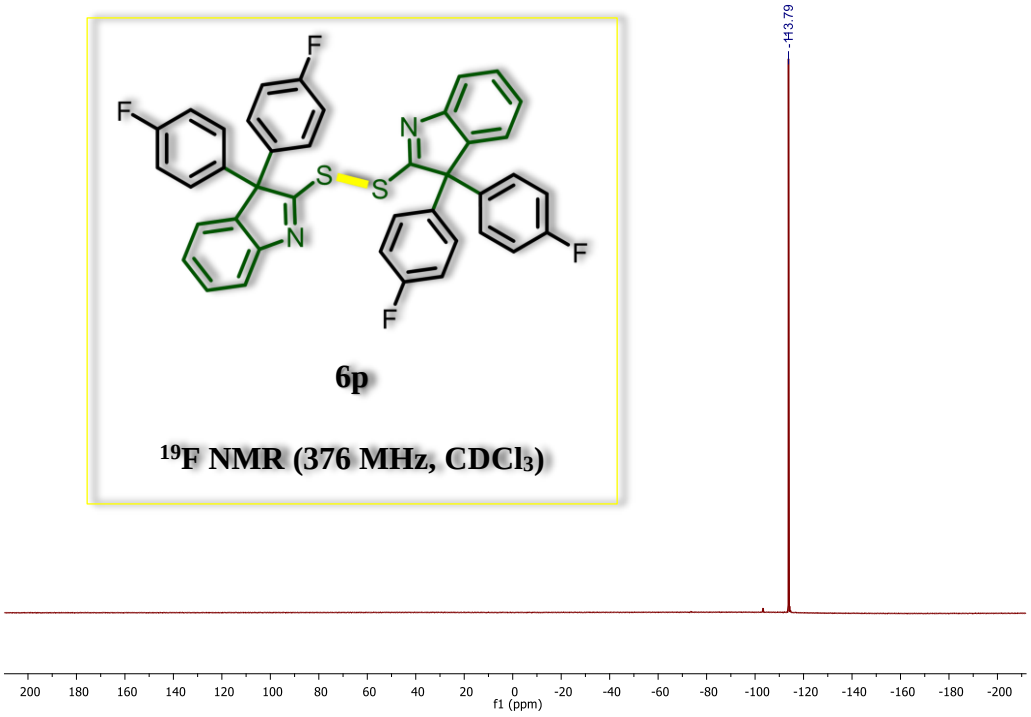

6m
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)


F
F
S
S
N
N
F
F
6p
1H NMR (400 MHz, CDCl3)


F
F
S
S
N
N
F
F
6p
13C NMR (101 MHz, CDCl3)

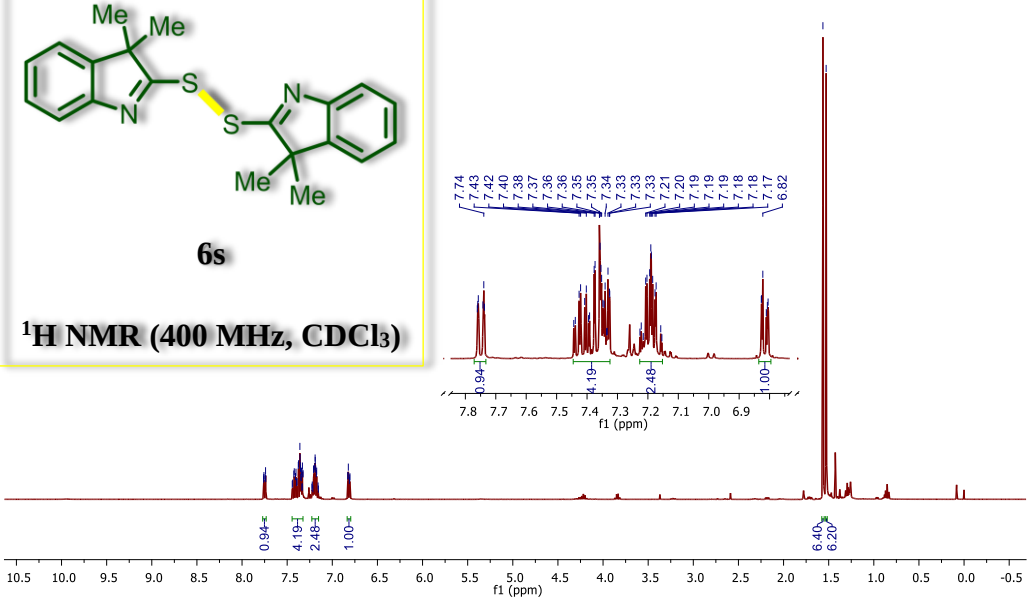
6p

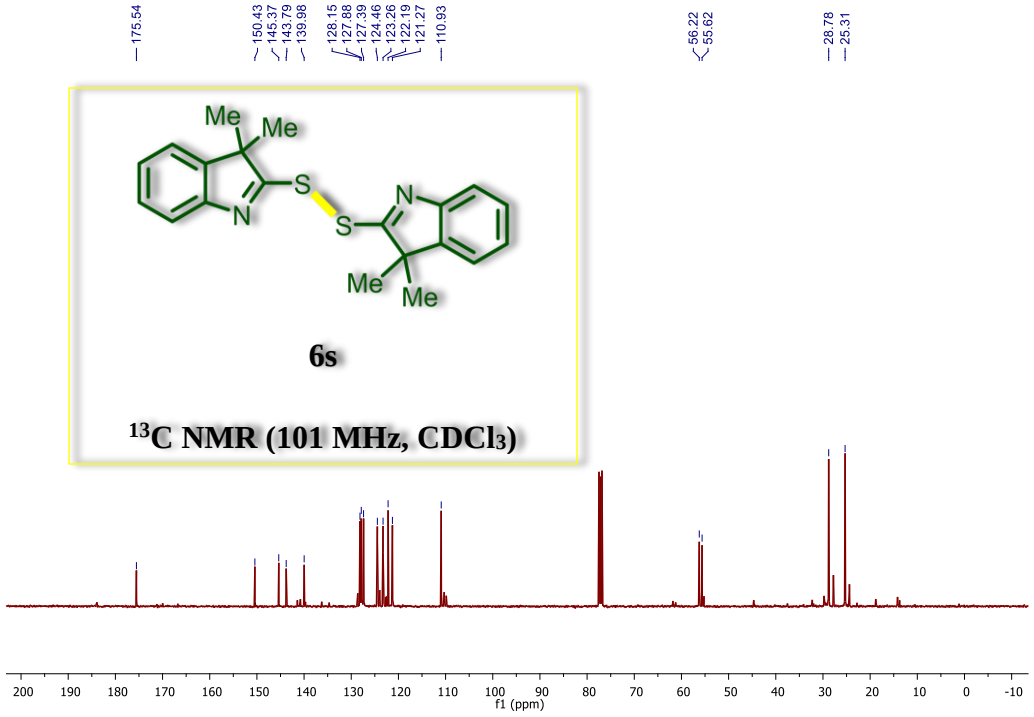
^{19}F NMR (376 MHz, $CDCl_3$)

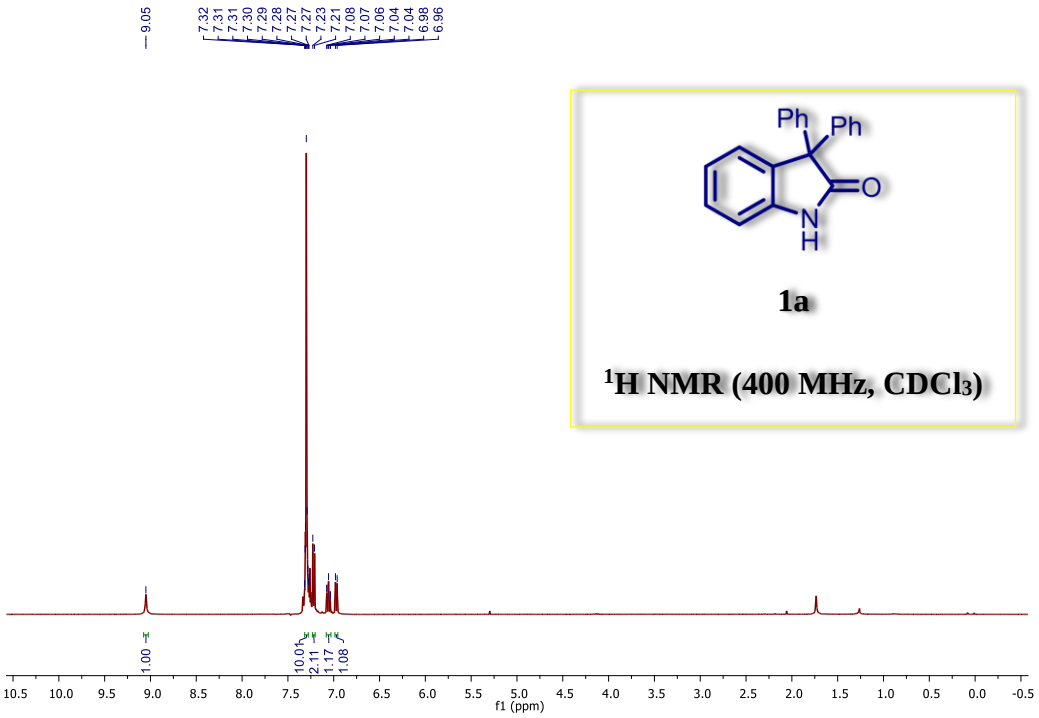


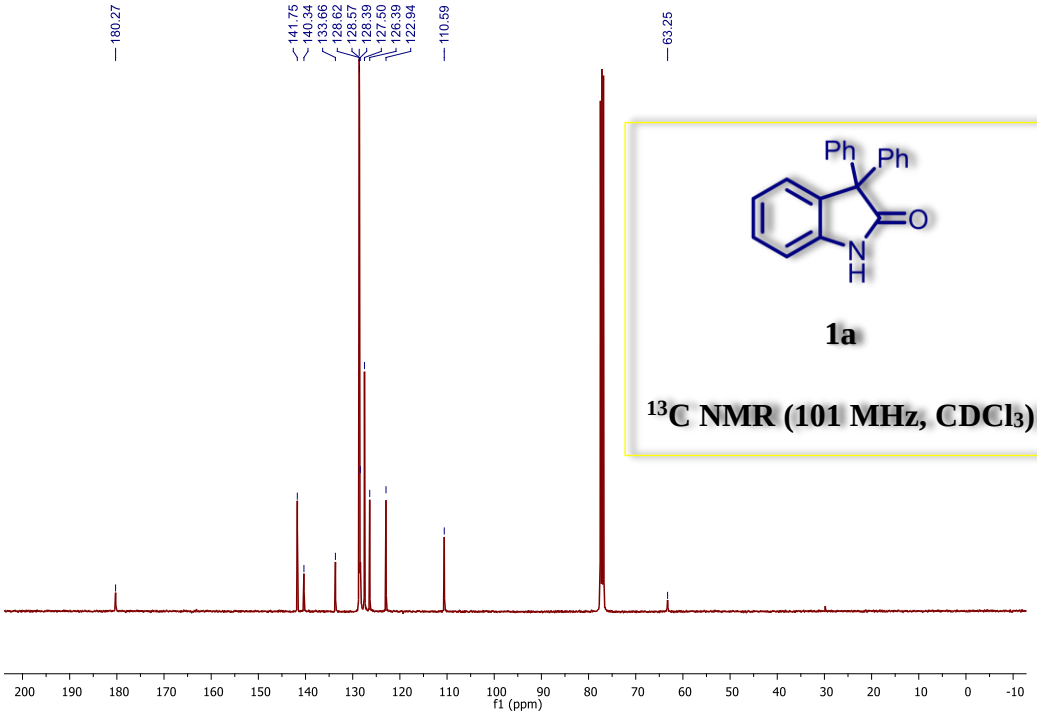
6s

^{1}H NMR (400 MHz, $CDCl_3$)



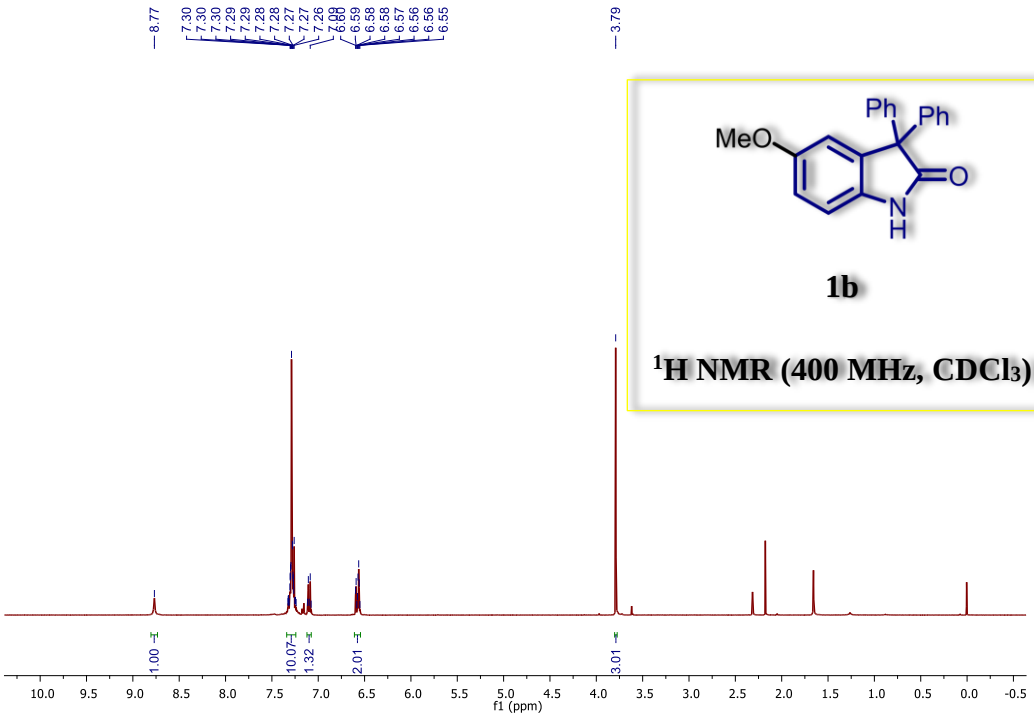

175.54
150.43
145.37
143.79
139.98
128.15
127.88
127.39
124.46
123.26
122.19
121.27
110.93
56.22
55.62
28.78
25.31
Me
Me
S
N
S
N
Me
Me
6s
13C NMR (101 MHz, CDCl3)
f1 (ppm)


9.05
7.32
7.31
7.31
7.30
7.29
7.28
7.27
7.27
7.23
7.21
7.08
7.07
7.06
7.04
7.04
6.98
6.96
Ph
Ph
O
N
H
1a
1H NMR (400 MHz, CDCl3)
1.00
10.0
2.11
1.17
1.08
f1 (ppm)



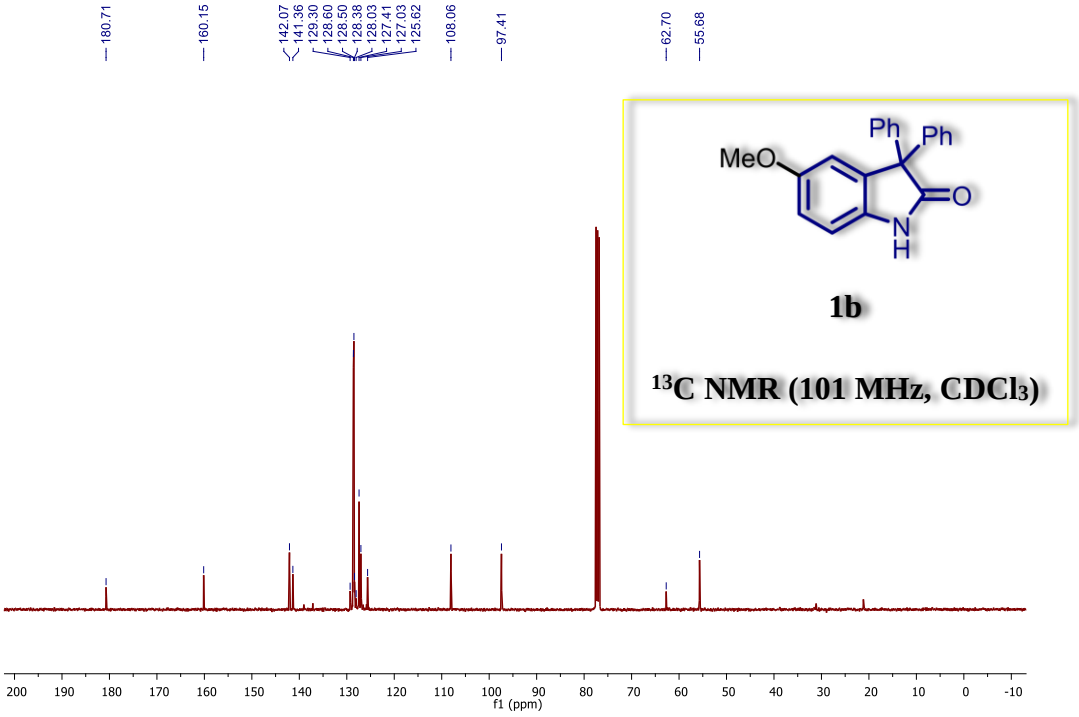
1a

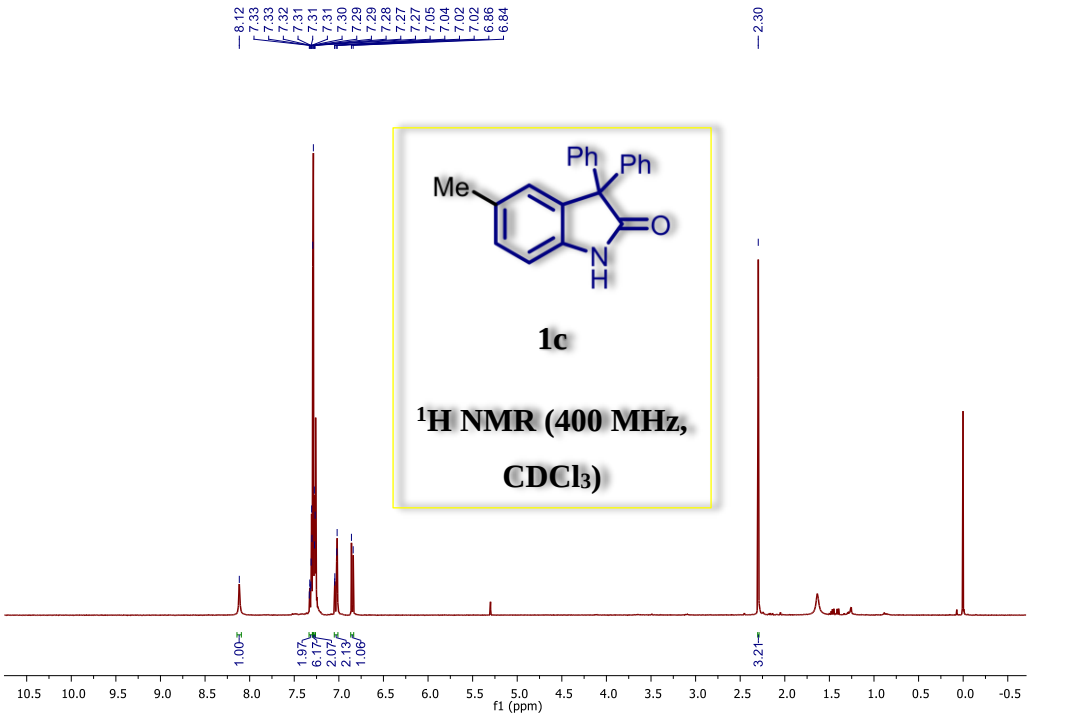
^{13}C NMR (101 MHz, $CDCl_3$)

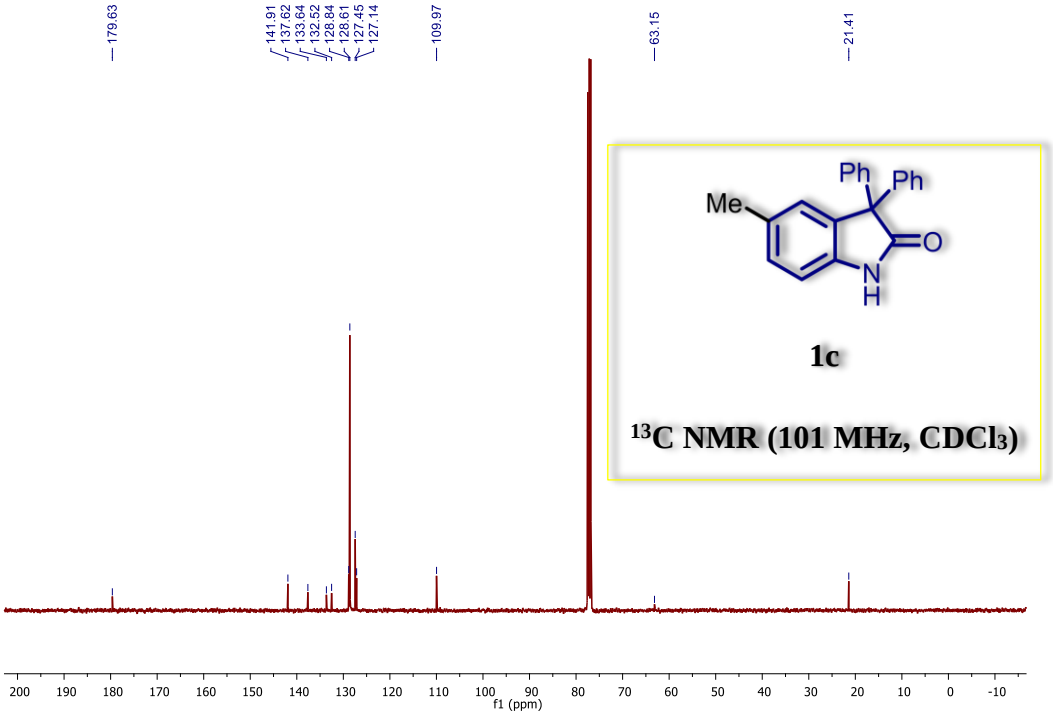


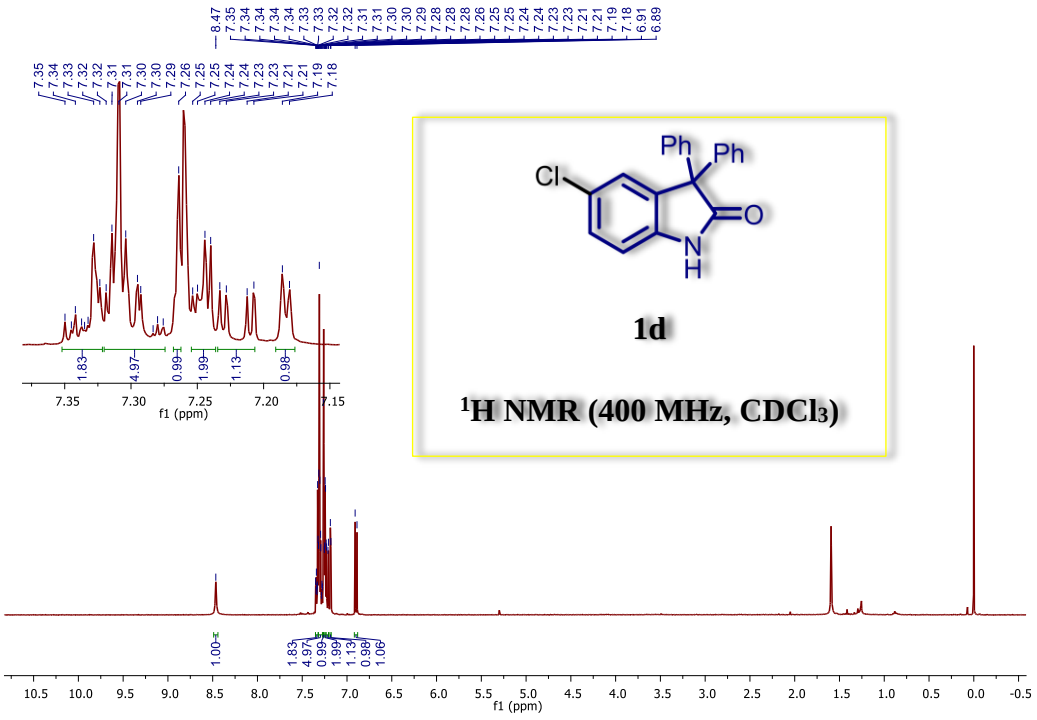
1b

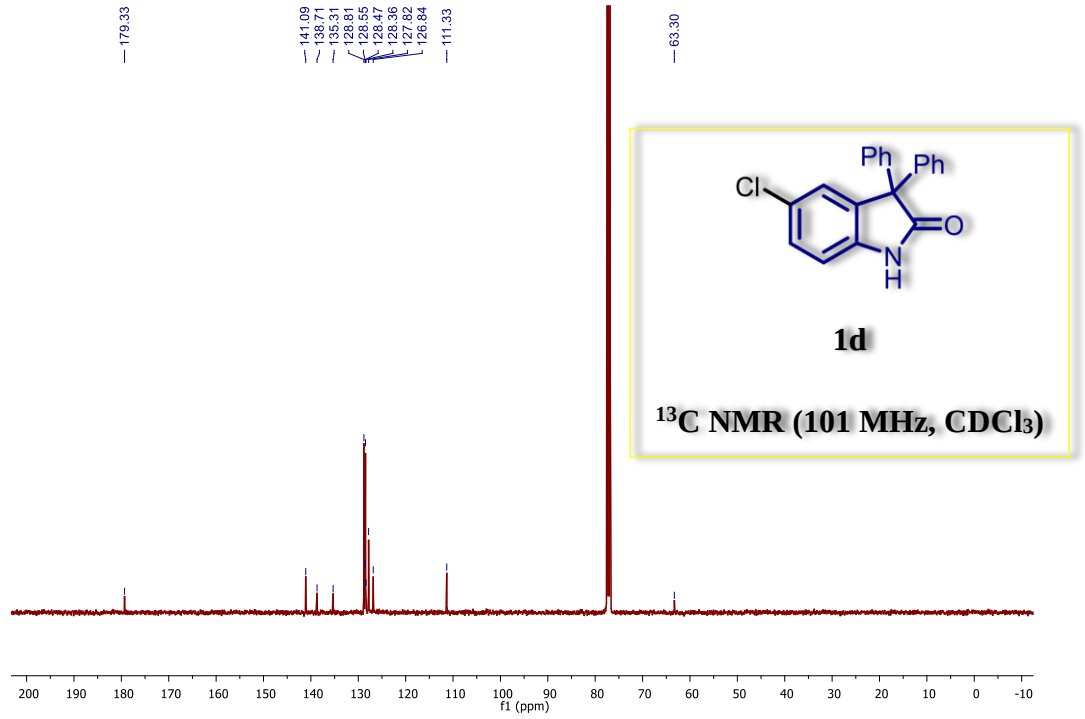
^{1}H NMR (400 MHz, $CDCl_3$)


180.71
160.15
142.07
141.36
129.30
128.60
128.50
128.38
128.03
127.41
127.03
125.62
108.06
97.41
62.70
55.68
Ph
Ph
MeO
O
N
H
1b
13C NMR (101 MHz, CDCl3)
f1 (ppm)


8.12
7.33
7.33
7.32
7.31
7.31
7.31
7.30
7.29
7.29
7.28
7.27
7.27
7.05
7.04
7.02
7.02
6.86
6.84
2.30
Ph
Ph
Me
O
N
H
1c
1H NMR (400 MHz, CDCl3)
1.00
1.97
6.17
2.07
2.13
1.06
3.21
f1 (ppm)

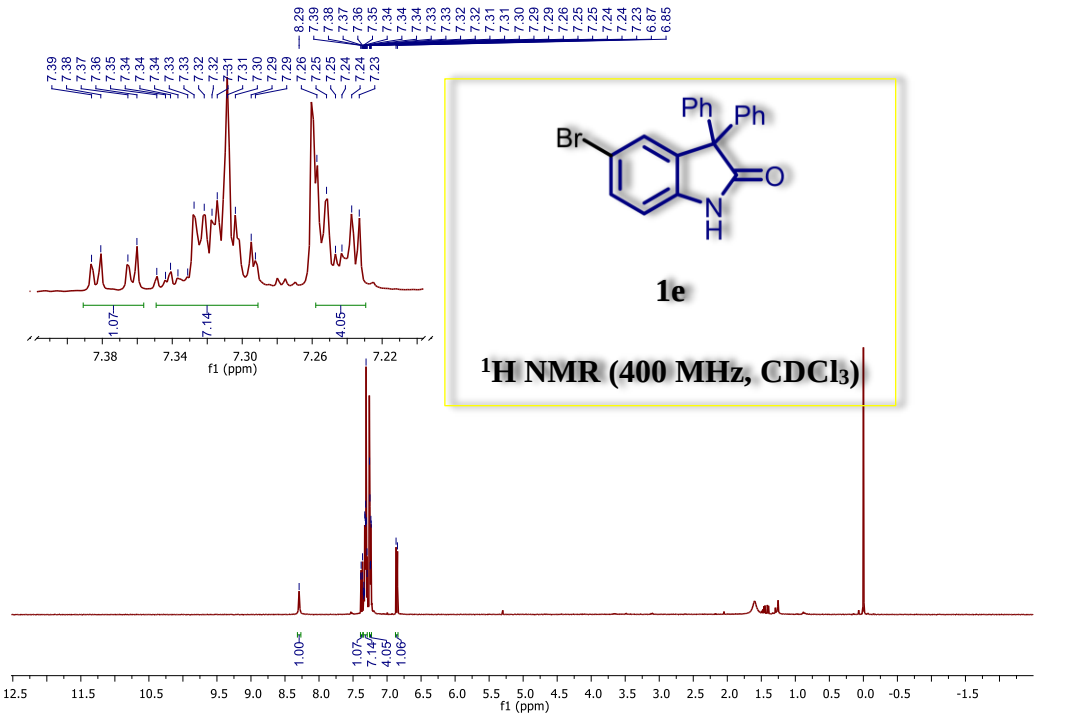

179.63
141.91
137.62
133.64
132.52
128.84
128.61
127.45
127.14
109.97
63.15
21.41
Ph
Ph
Me
O
N
H
1c
13C NMR (101 MHz, CDCl3)
f1 (ppm)


8.47
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.26
7.25
7.24
7.23
7.21
7.19
7.18
6.91
6.89
1.83
4.97
0.99
1.99
1.13
0.98
1.00
Cl
Ph
Ph
O
N
H
1d
1H NMR (400 MHz, CDCl3)
f1 (ppm)



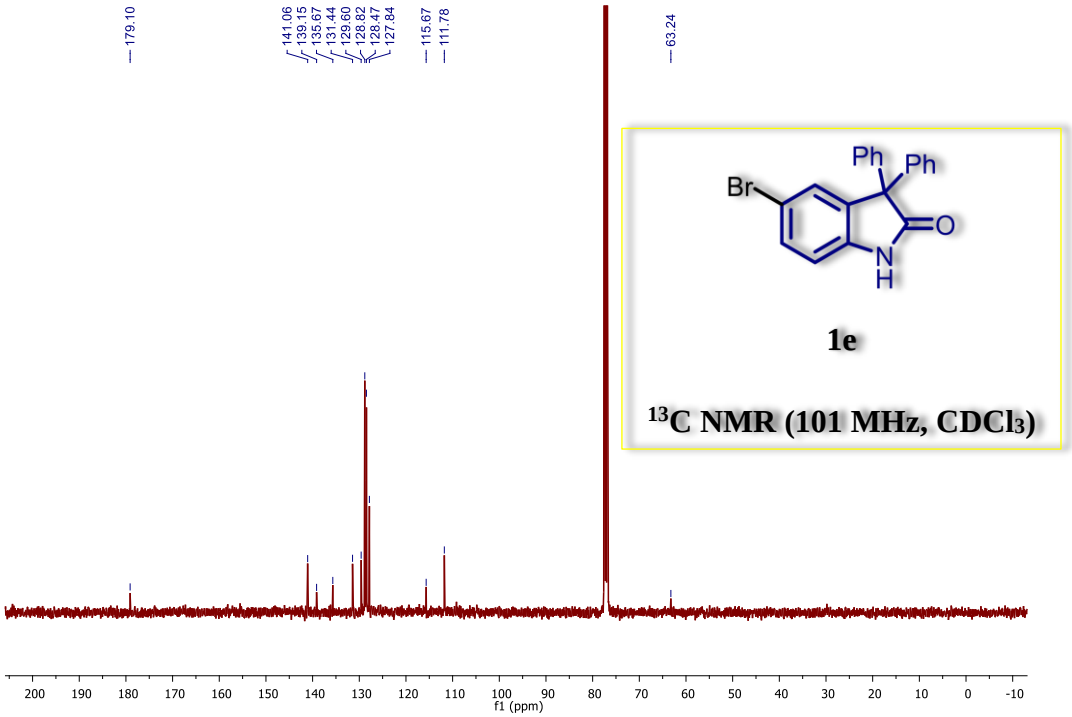
1d

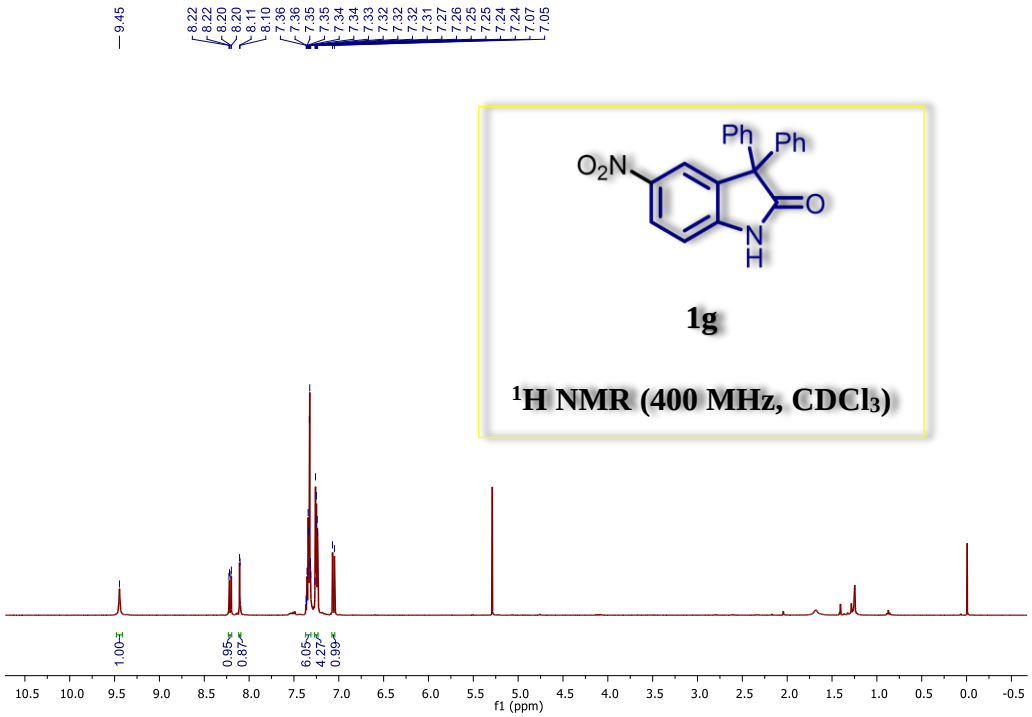
^{13}C NMR (101 MHz, $CDCl_3$)

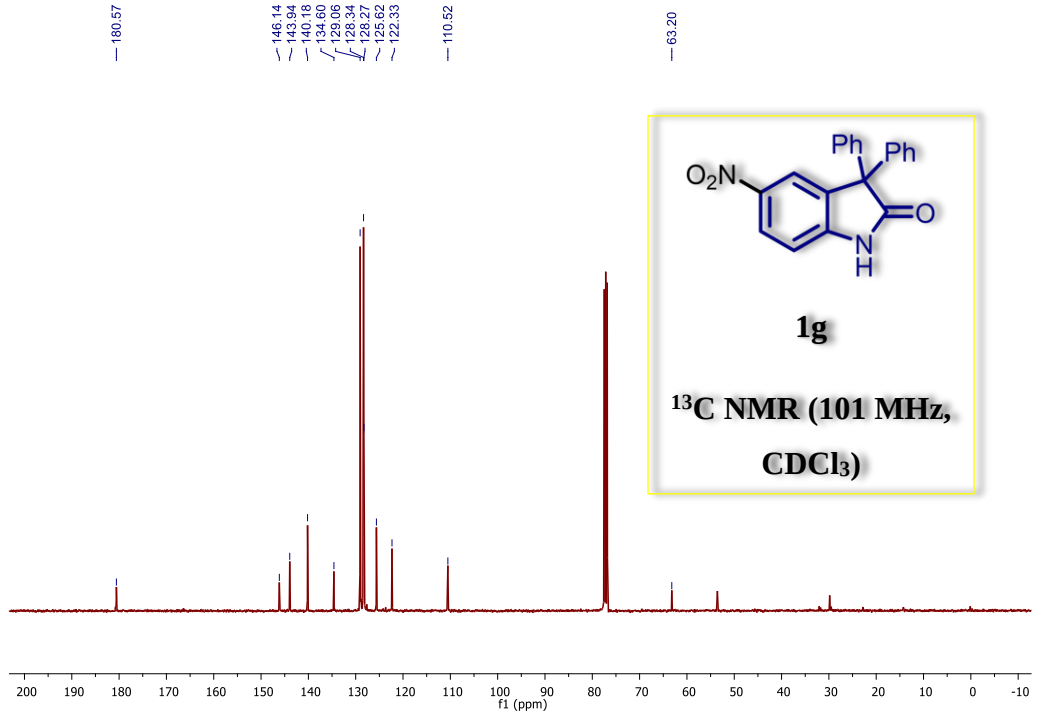


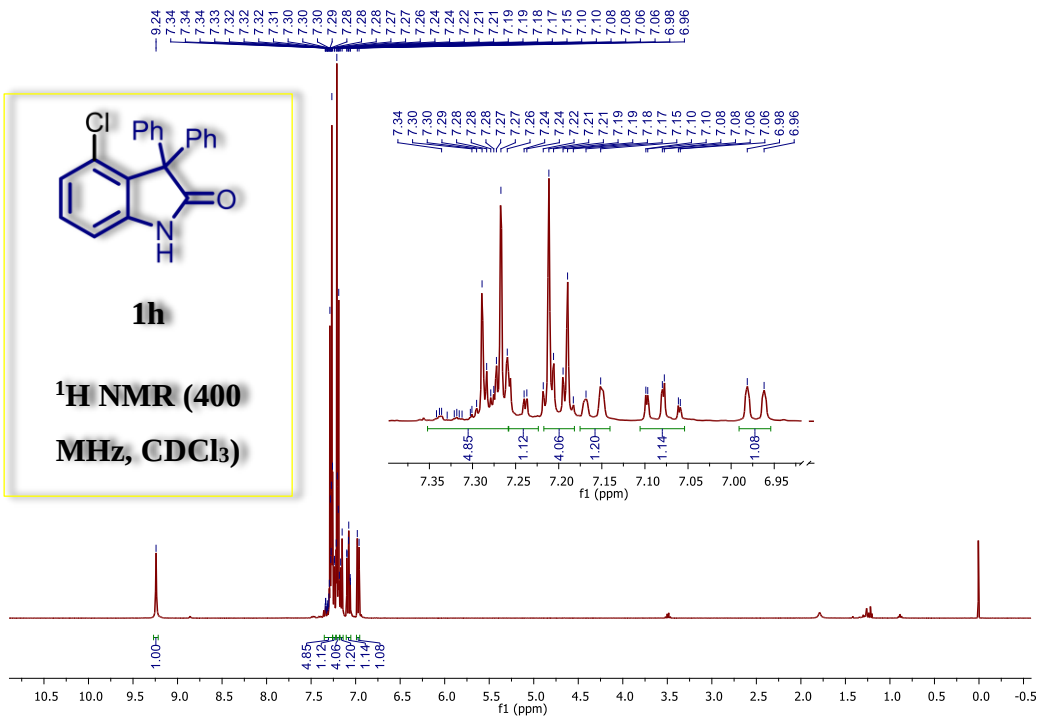
1e

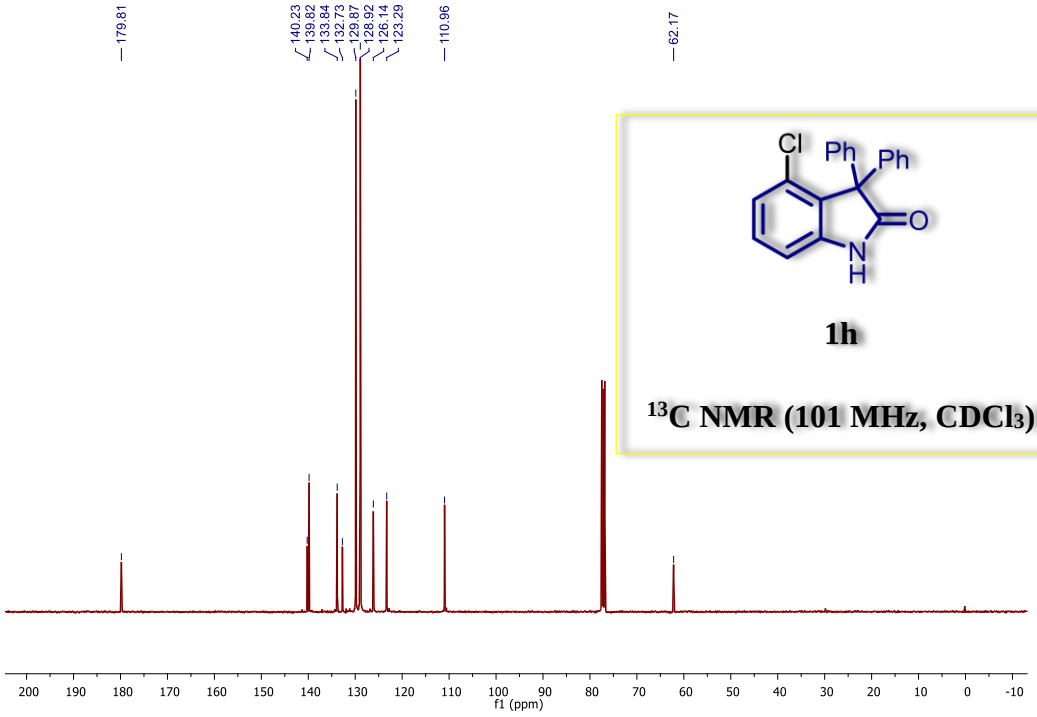
^{1}H NMR (400 MHz, $CDCl_3$)


179.10
141.06
139.15
135.67
131.44
129.60
128.82
128.47
127.84
115.67
111.78
63.24
Ph
Ph
Br
O
N
H
1e
13C NMR (101 MHz, CDCl3)
f1 (ppm)


9.45
8.22
8.22
8.20
8.20
8.11
8.10
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.27
7.26
7.25
7.25
7.24
7.24
7.07
7.05
Ph
Ph
O2N
O
N
H
1g
1H NMR (400 MHz, CDCl3)
1.00
0.95
0.87
6.05
4.27
0.99
f1 (ppm)

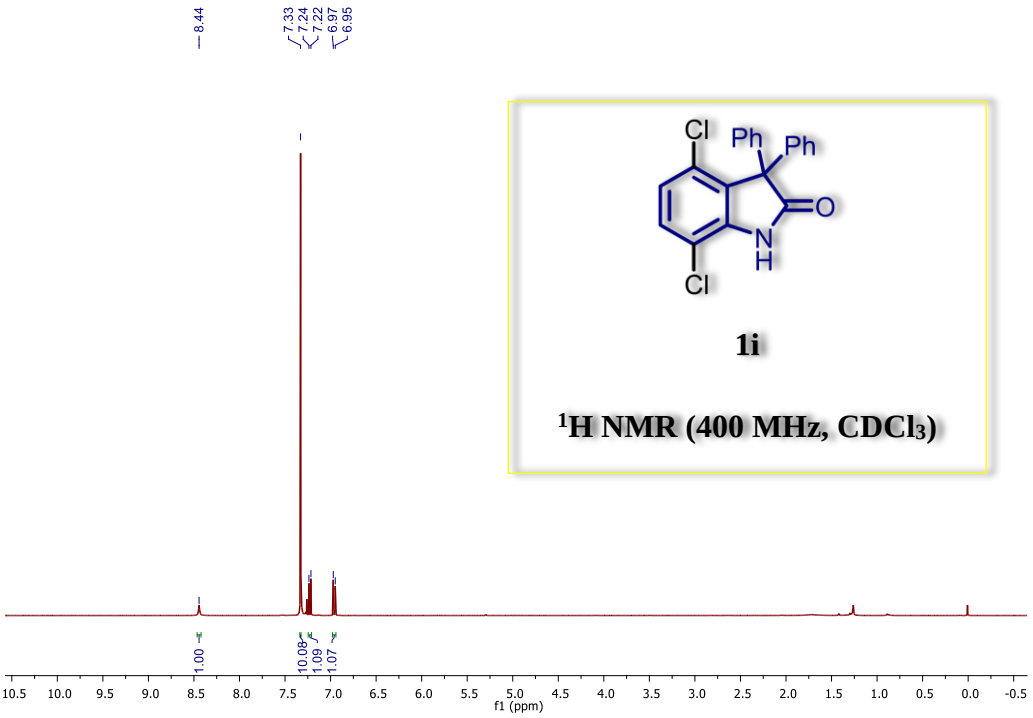

180.57
146.14
143.94
140.18
134.60
129.06
128.34
128.27
125.62
122.33
110.52
63.20
Ph
Ph
O2N
O
N
H
1g
13C NMR (101 MHz, CDCl3)
f1 (ppm)


9.24
7.34
7.30
7.29
7.28
7.27
7.26
7.24
7.22
7.21
7.19
7.18
7.17
7.15
7.10
7.08
7.06
6.98
6.96
Cl
Ph
Ph
O
N
H
1h
1H NMR (400 MHz, CDCl3)
4.85
1.12
4.06
1.20
1.14
1.08
1.00
f1 (ppm)



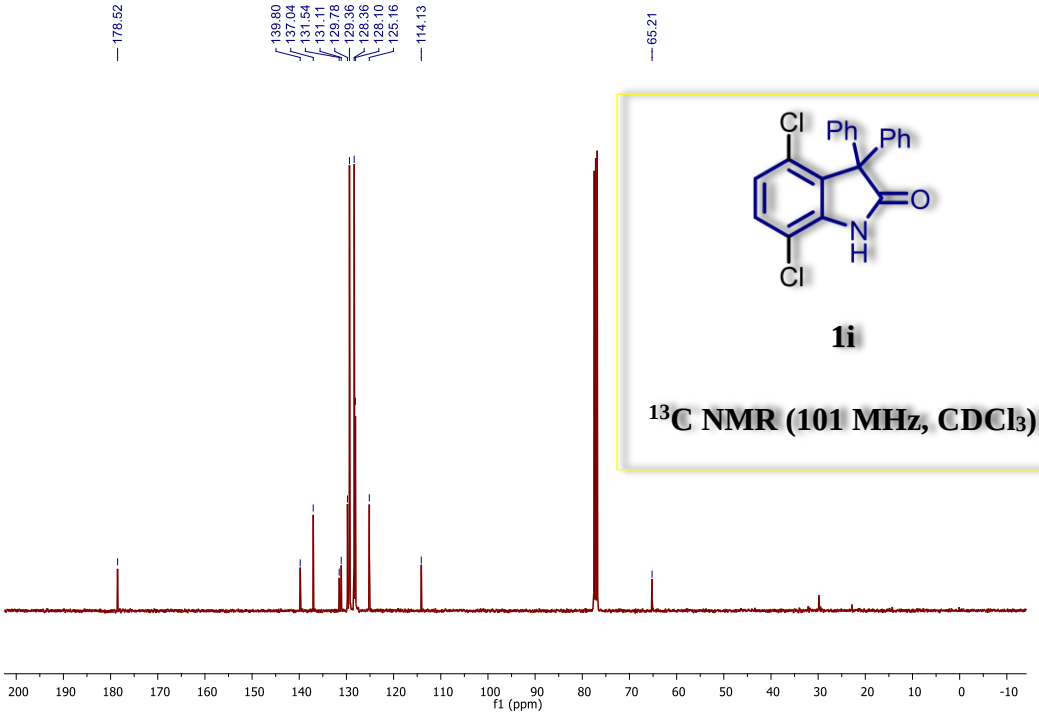
1h

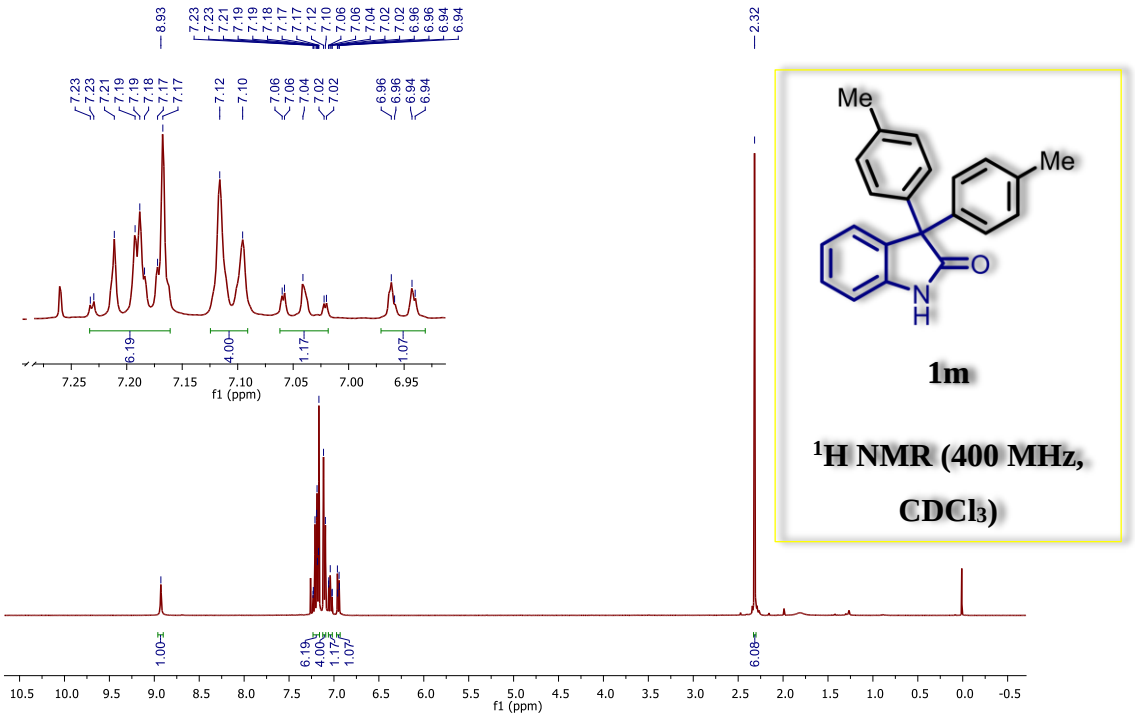
^{13}C NMR (101 MHz, $CDCl_3$)

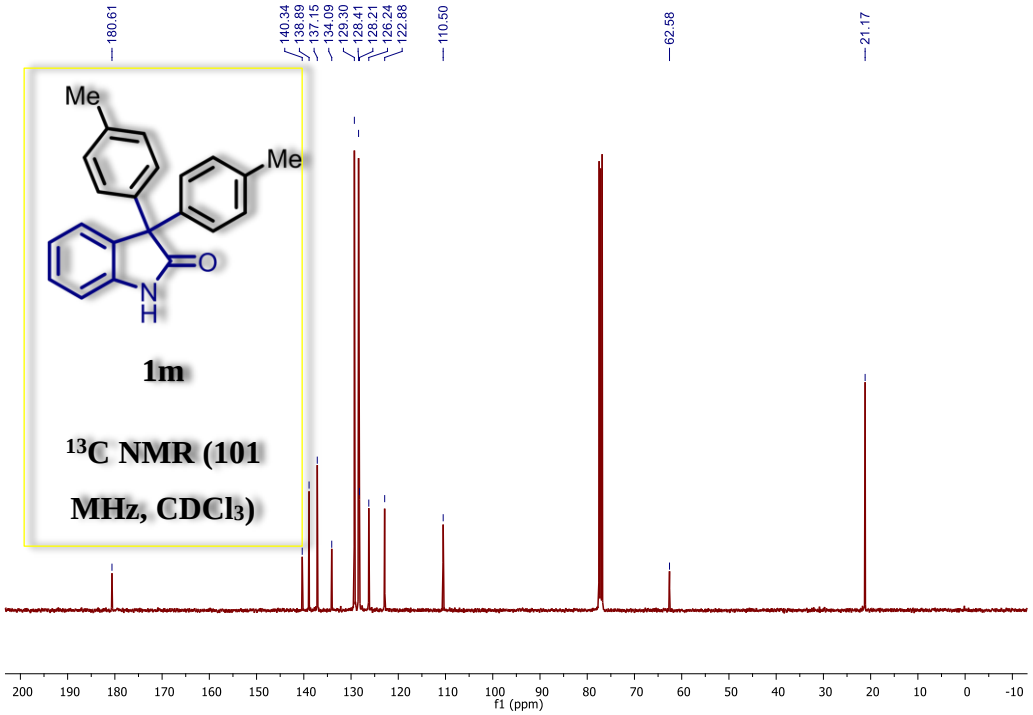


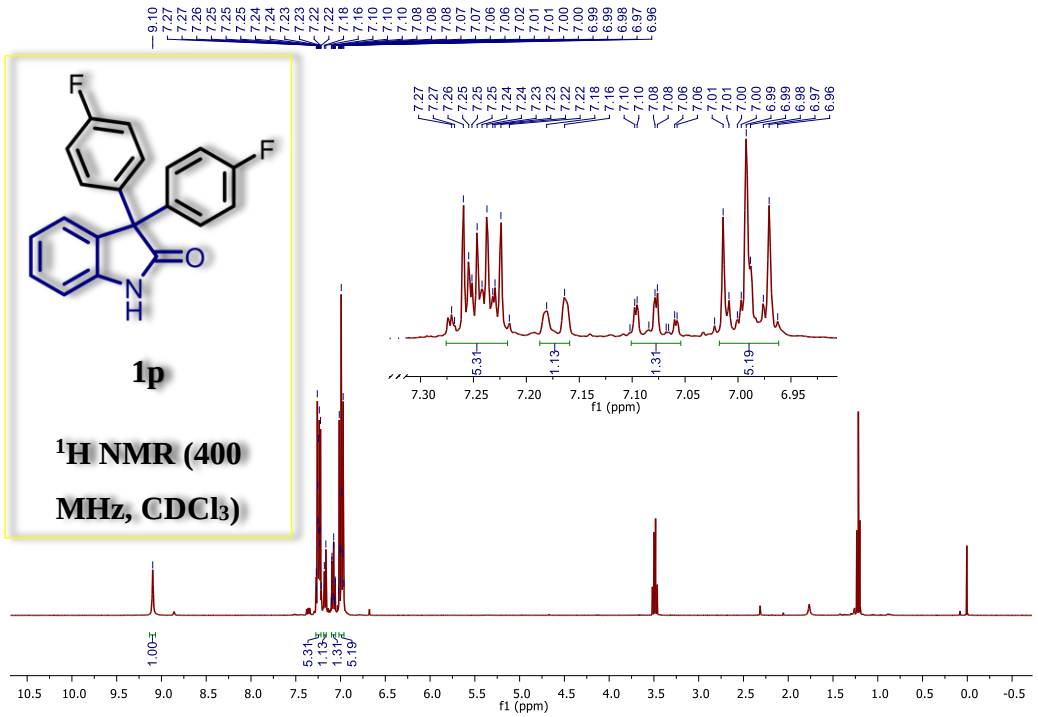
1i

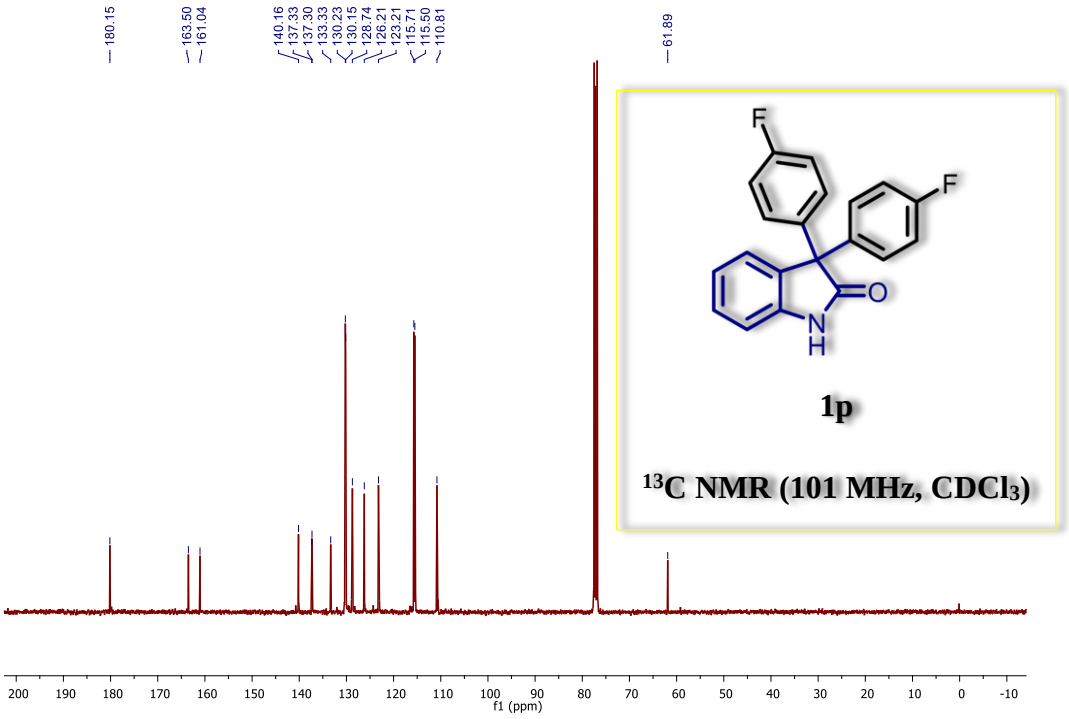
^{1}H NMR (400 MHz, $CDCl_3$)

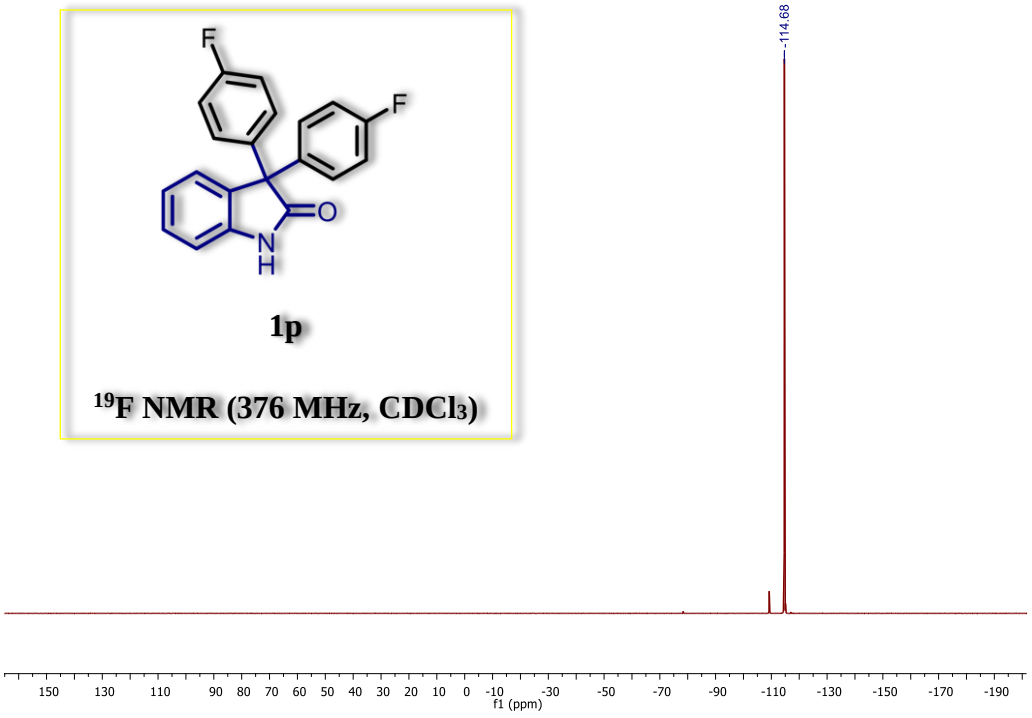

178.52
139.80
137.04
131.54
131.11
129.78
129.36
128.36
128.10
125.16
114.13
65.21
Cl
Ph
Ph
O
N
H
Cl
1i
13C NMR (101 MHz, CDCl3)
f1 (ppm)

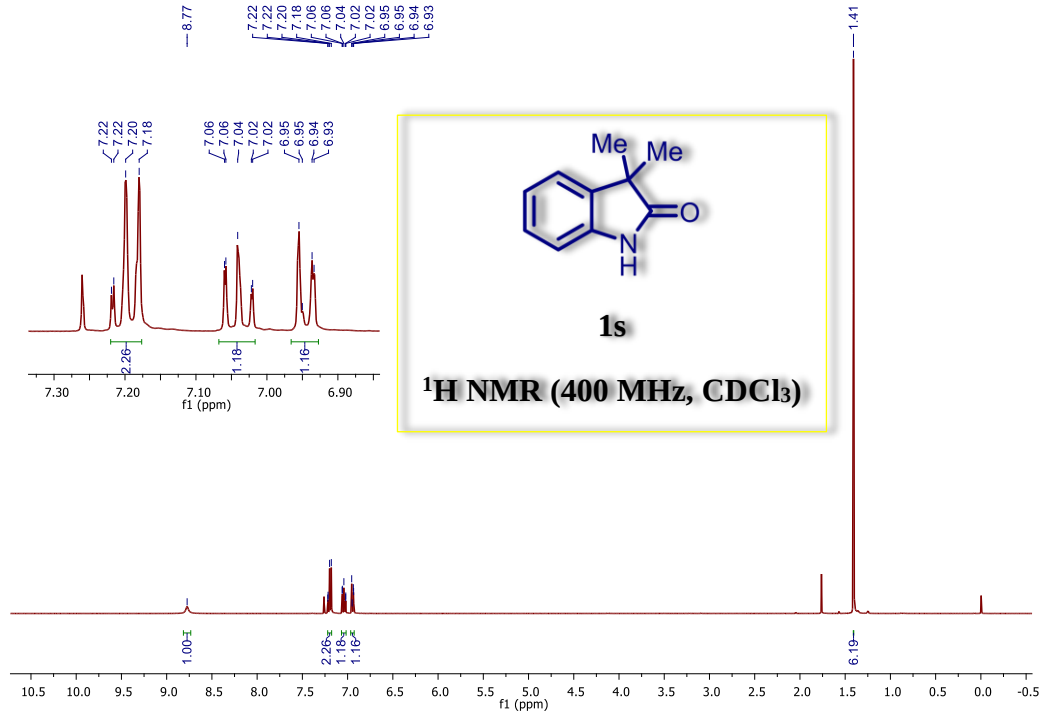

8.93
7.23
7.23
7.21
7.19
7.19
7.18
7.17
7.17
7.17
7.12
7.10
7.06
7.06
7.04
7.02
7.02
6.96
6.96
6.94
6.94
6.94
2.32
Me
Me
O
N
H
1m
1H NMR (400 MHz, CDCl3)
6.19
4.00
1.17
1.07
1.00
6.08
f1 (ppm)

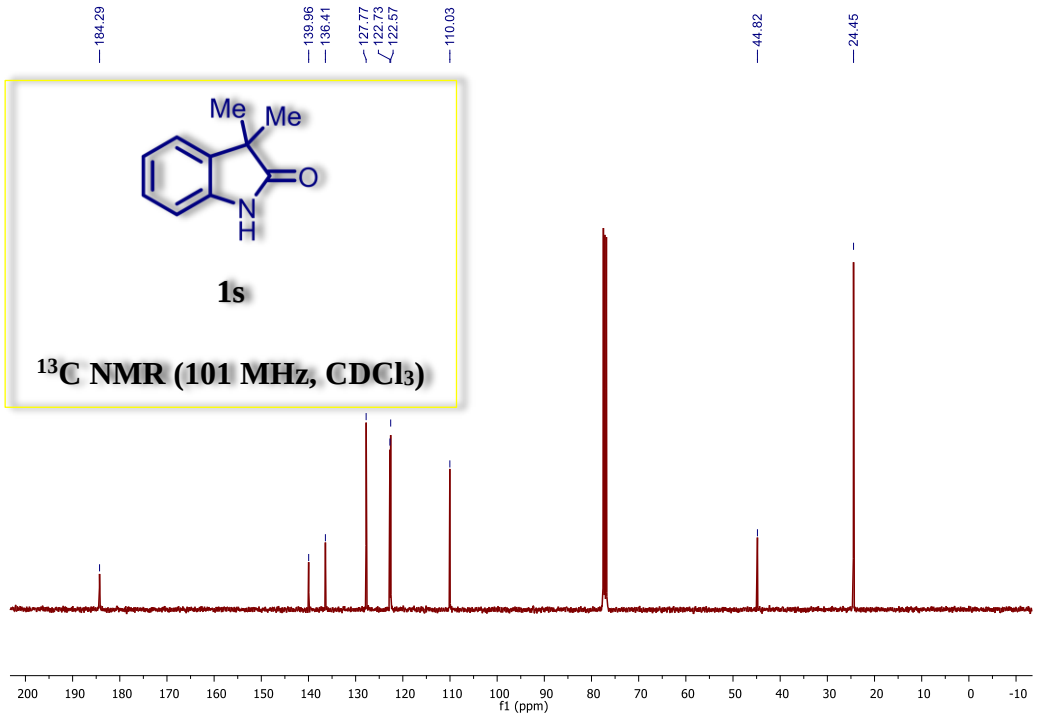

180.61
140.34
138.89
137.15
134.09
129.30
128.41
128.21
126.24
122.88
110.50
62.58
21.17
Me
Me
O
N
H
1m
13C NMR (101 MHz, CDCl3)
f1 (ppm)

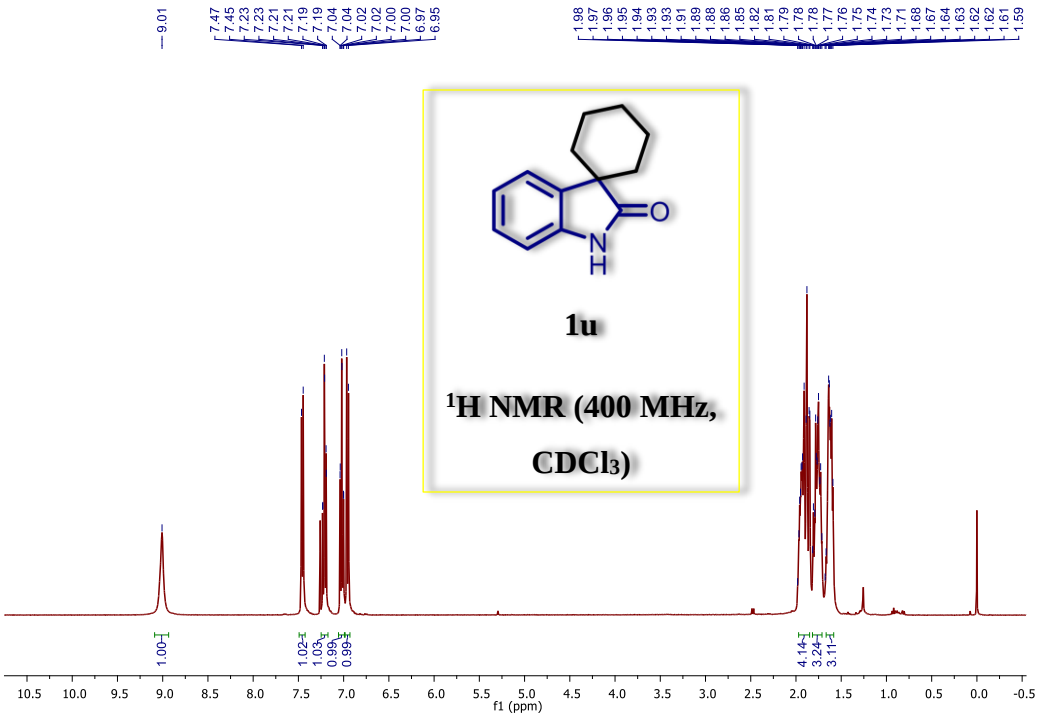

9.10
7.27
7.26
7.25
7.24
7.23
7.22
7.18
7.16
7.10
7.08
7.07
7.06
7.02
7.01
7.00
6.99
6.98
6.97
6.96
F
F
O
N
H
1p
1H NMR (400 MHz, CDCl3)
1.00
5.31
1.13
1.31
5.19
f1 (ppm)

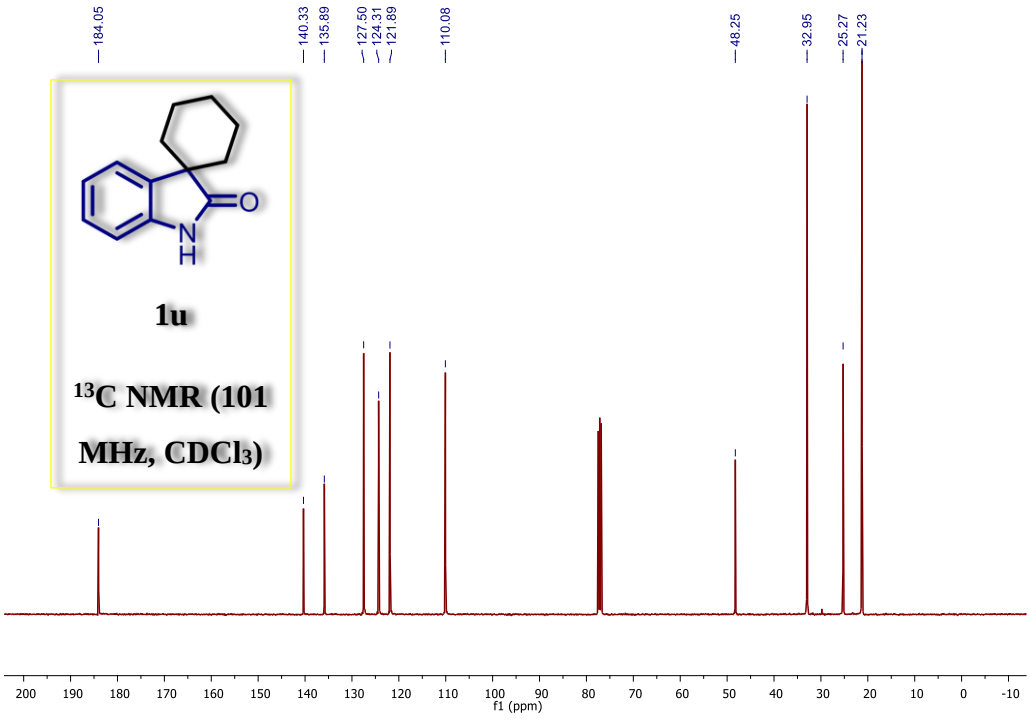

180.15
163.50
161.04
140.16
137.33
137.30
133.33
130.23
130.15
128.74
126.21
123.21
115.71
115.50
110.81
61.89
F
F
O
N
H
1p
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

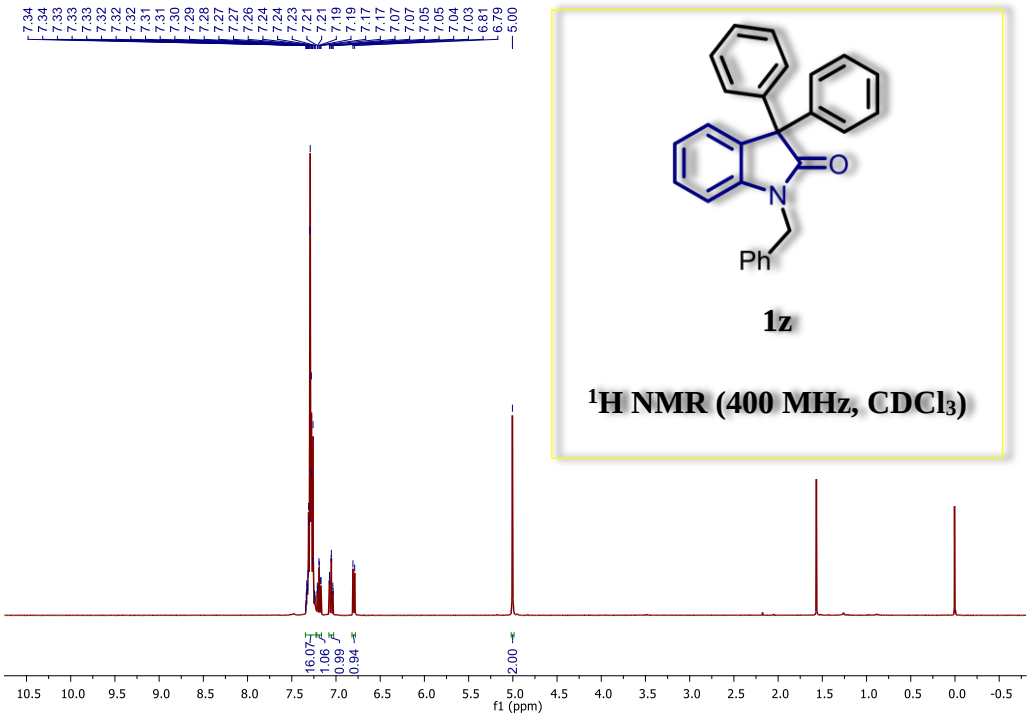

F
F
O
N
H
1p
19F NMR (376 MHz, CDCl3)
-114.68
150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

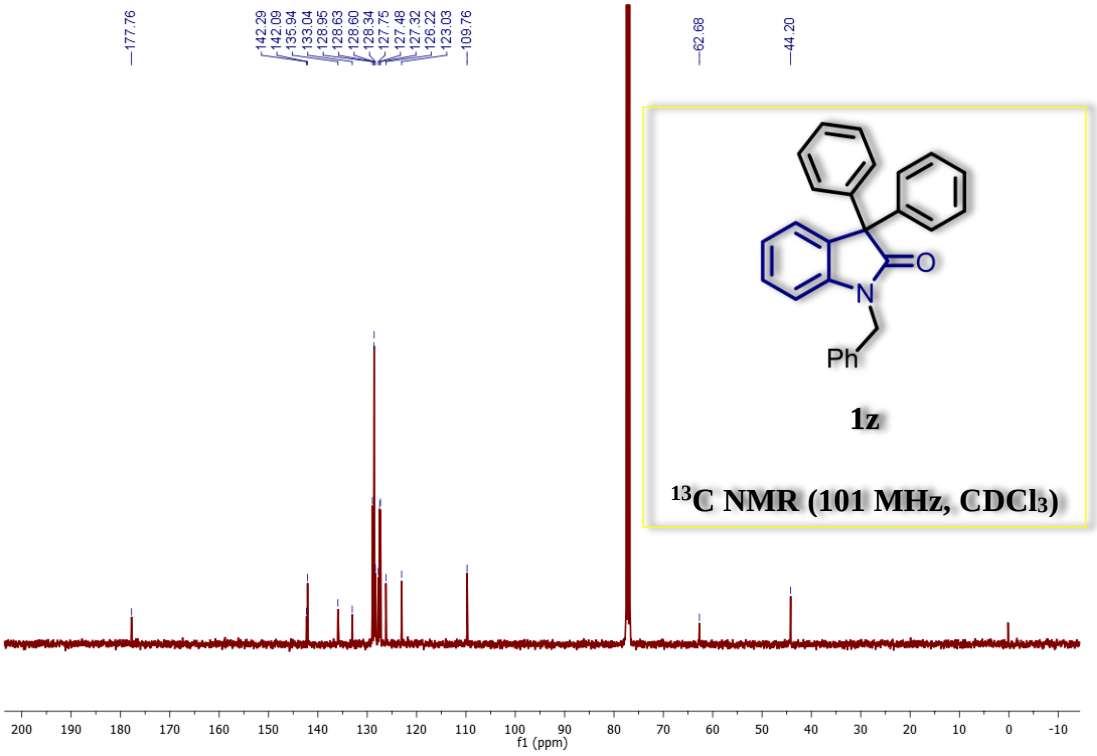

Me
Me
O
N
H
1s
^{1}H NMR (400 MHz, CDCl$_3$)

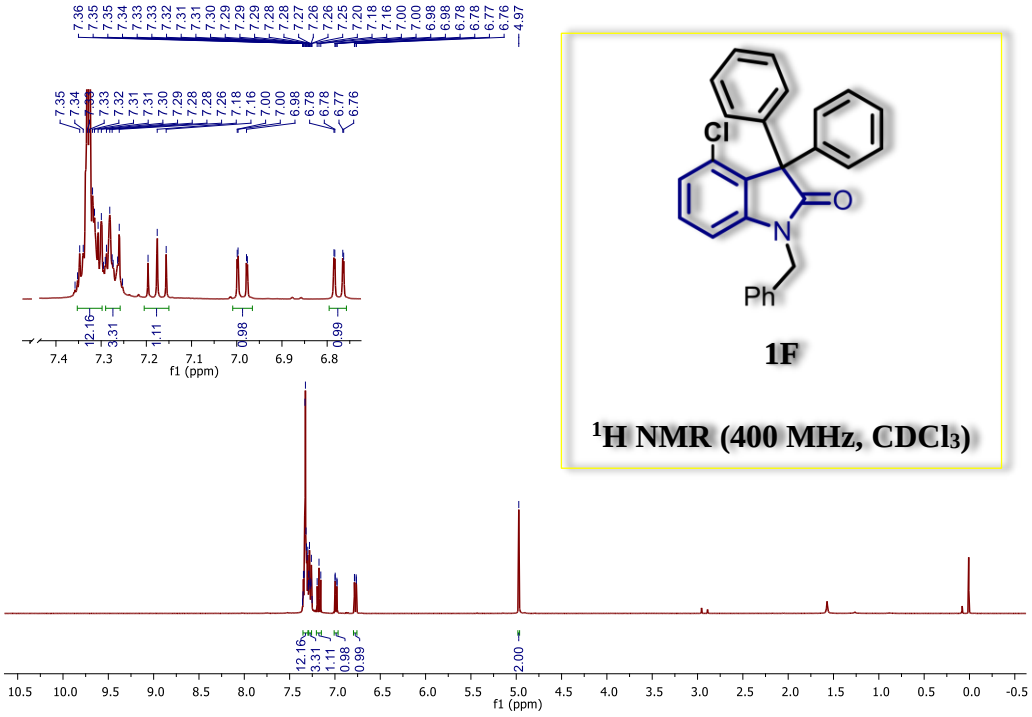

Me
Me
O
N
H
1s
^{13}C NMR (101 MHz, CDCl$_3$)

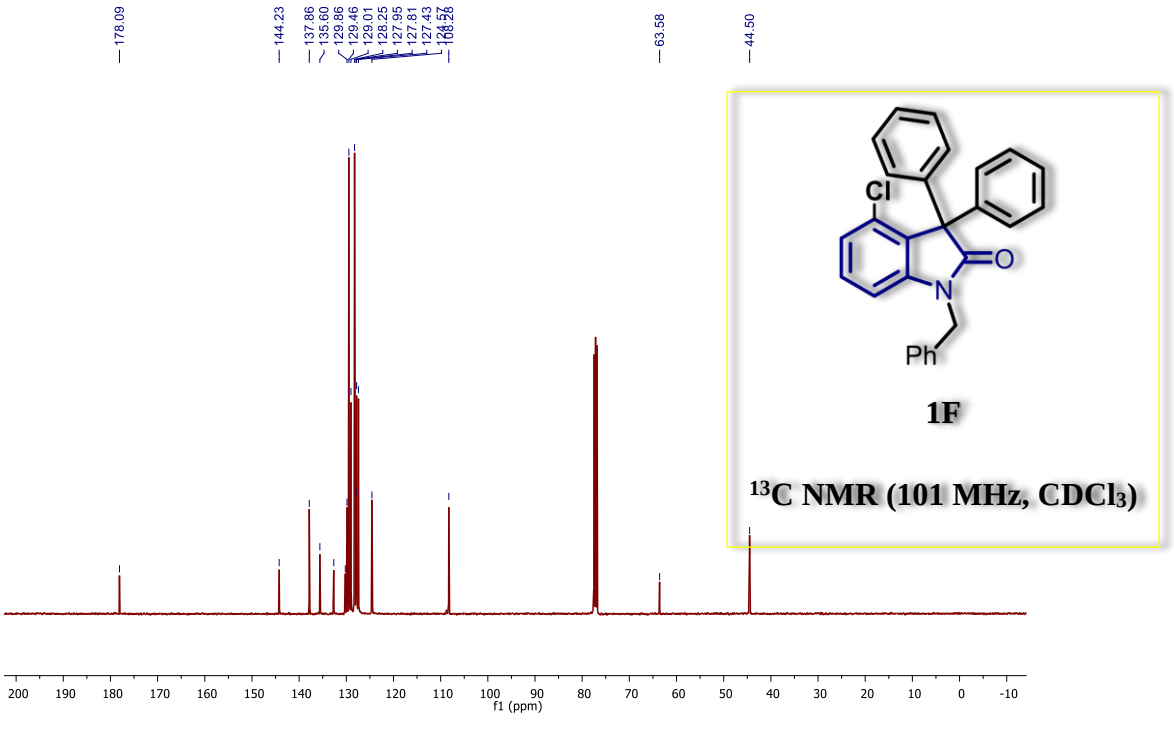

1u
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

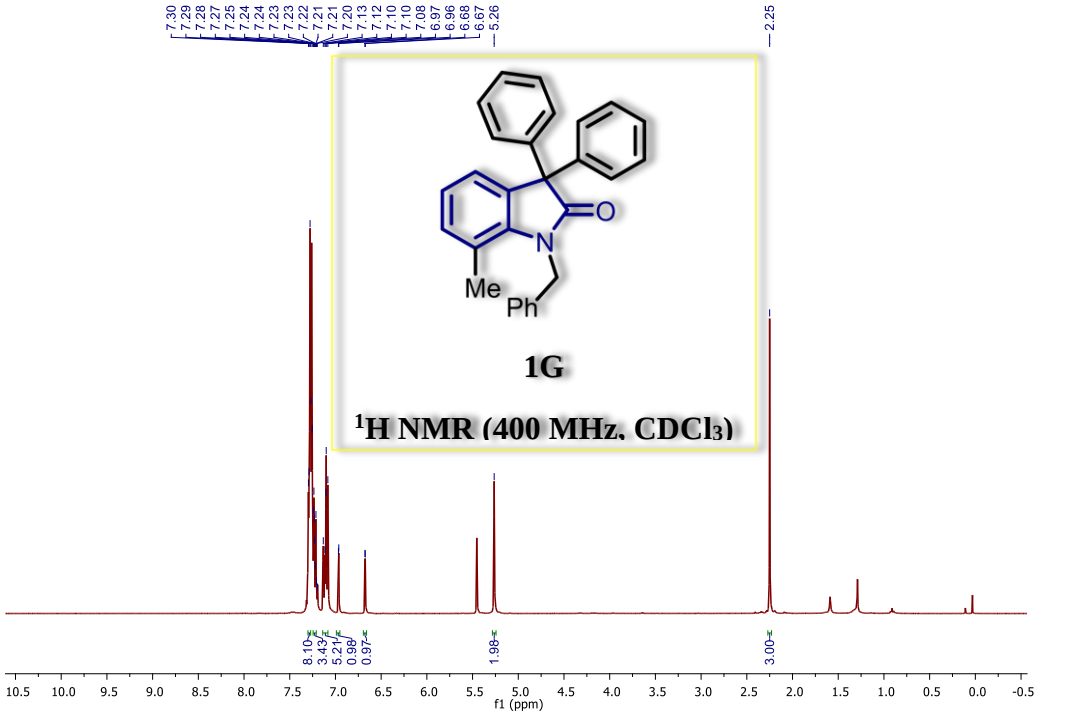

1u
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

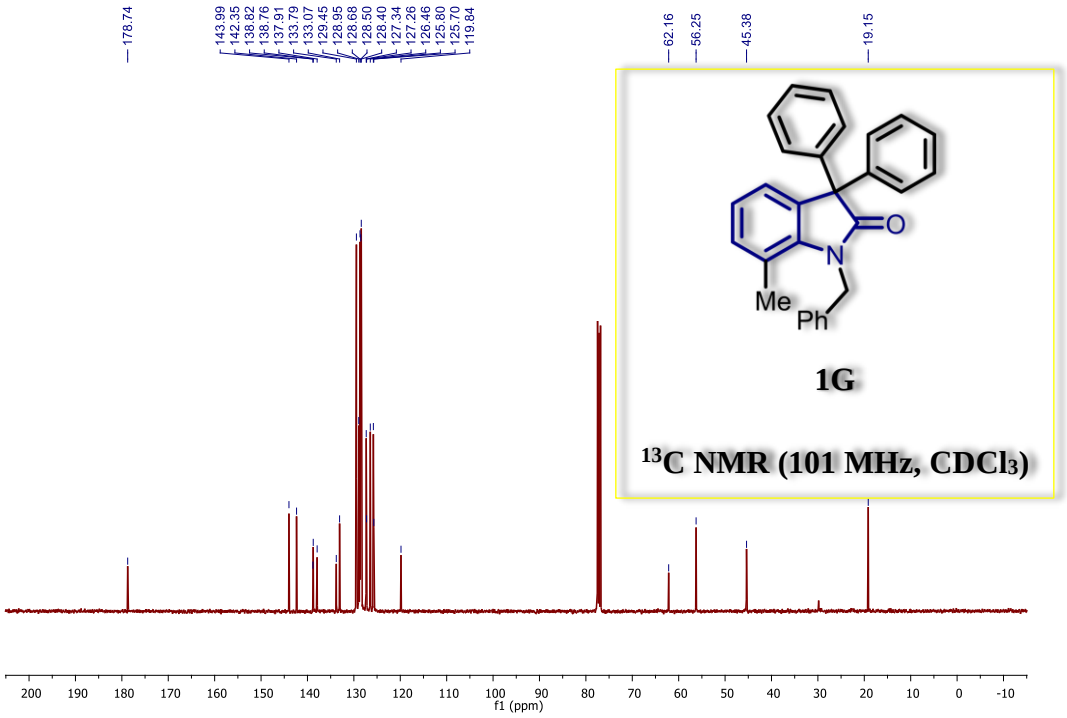

7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.29
7.28
7.27
7.27
7.26
7.24
7.24
7.23
7.21
7.21
7.19
7.19
7.17
7.17
7.07
7.05
7.05
7.04
7.03
6.81
6.79
5.00
16.07
1.06
0.99
0.94
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
O
N
Ph
1z
1H NMR (400 MHz, CDCl3)

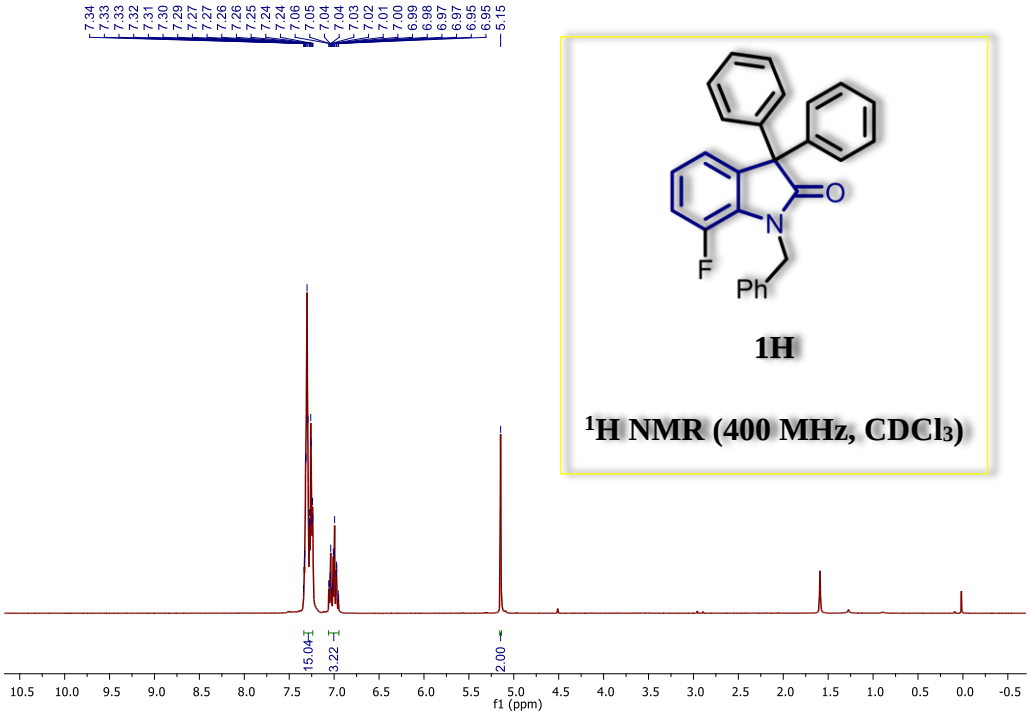

177.76
142.29
142.09
135.94
133.04
128.95
128.63
128.60
128.34
127.75
127.48
127.32
126.22
123.03
109.76
62.68
44.20
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
O
N
Ph
1z
13C NMR (101 MHz, CDCl3)

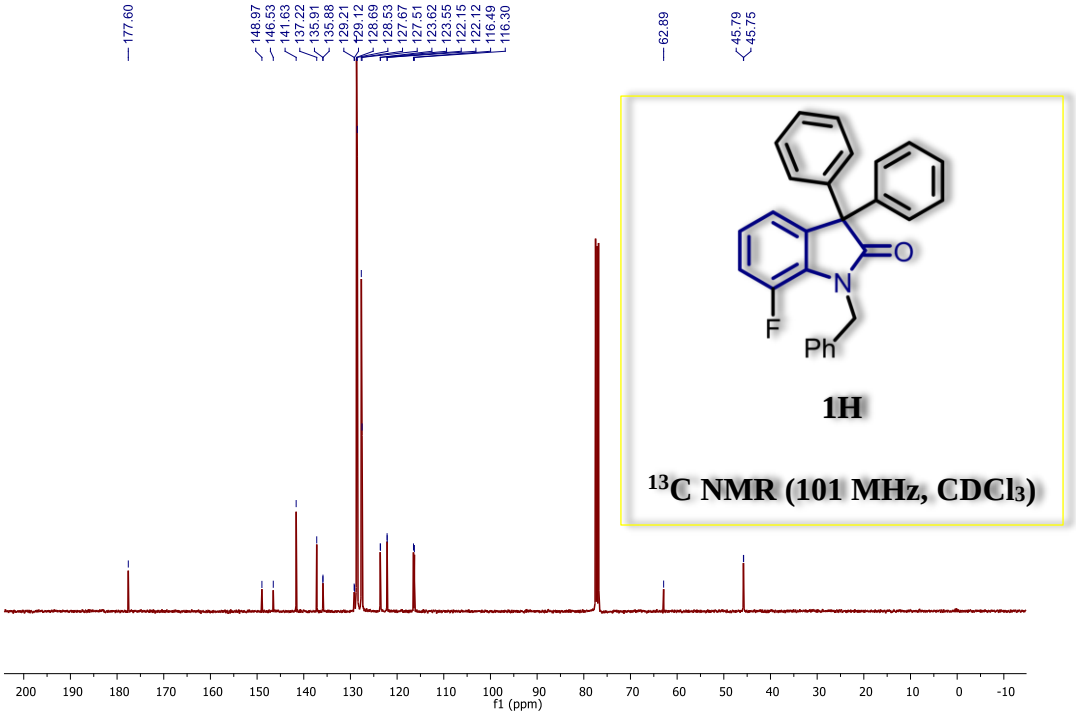

Cl
O
N
Ph
1F
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)


Cl
O
N
Ph
1F
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)


7.30
7.29
7.28
7.27
7.25
7.24
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.13
7.12
7.10
7.10
7.08
6.97
6.96
6.68
6.67
5.26
2.25
Me
Ph
1G
1H NMR (400 MHz, CDCl3)
8.10
3.43
5.21
0.99
0.97
1.98
3.00
f1 (ppm)

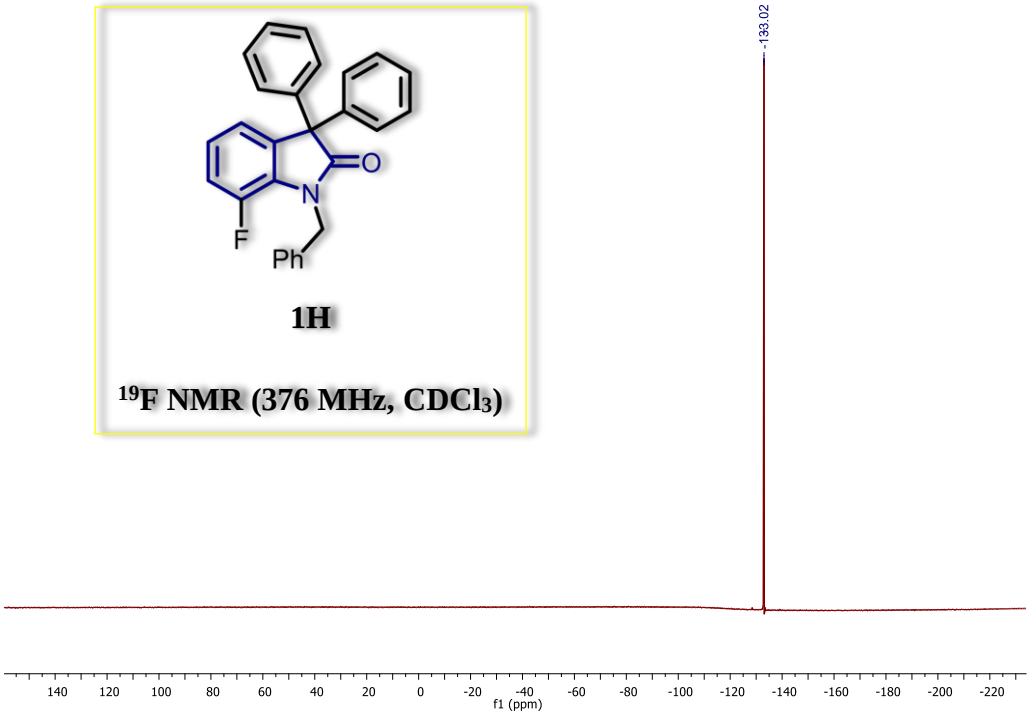

178.74
143.99
142.35
138.82
138.76
137.91
133.79
133.07
129.45
128.95
128.68
128.50
128.40
127.34
127.26
126.46
125.80
125.70
119.84
62.16
56.25
45.38
19.15
Me
Ph
1G
13C NMR (101 MHz, CDCl3)
f1 (ppm)

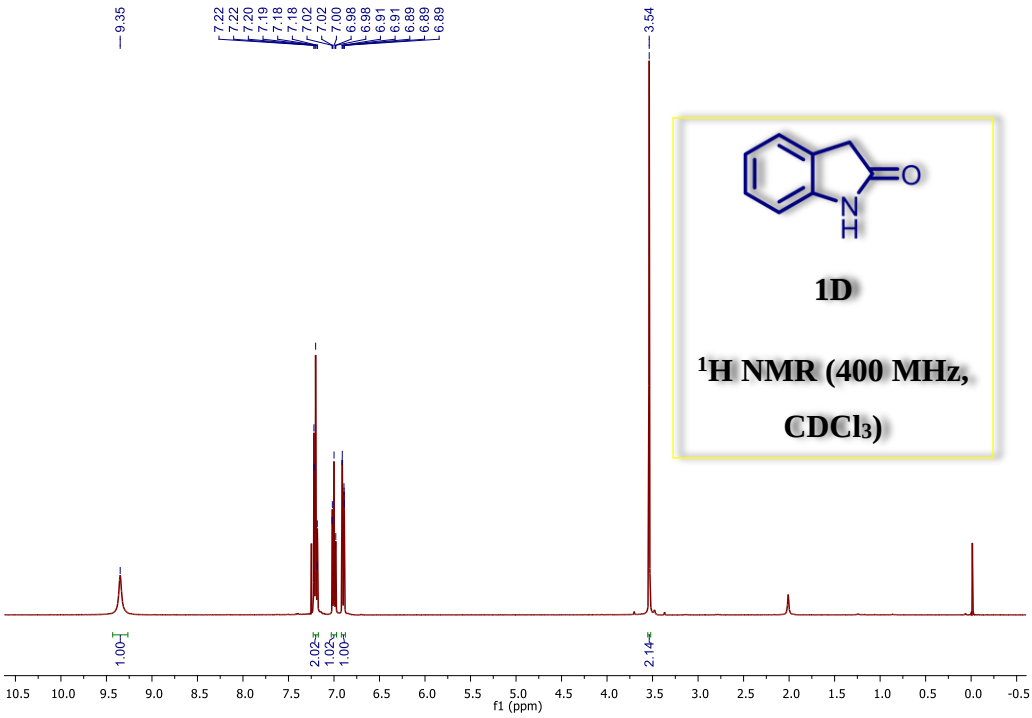

7.34
7.33
7.33
7.32
7.31
7.30
7.29
7.27
7.27
7.26
7.26
7.25
7.24
7.24
7.06
7.05
7.04
7.04
7.03
7.02
7.01
7.00
6.99
6.98
6.97
6.97
6.95
6.95
5.15
15.04
3.22
2.00
f1 (ppm)
O
N
F
Ph
1H
1H NMR (400 MHz, CDCl3)


177.60
148.97
146.53
141.63
137.22
135.91
135.88
129.21
129.12
128.69
128.53
127.67
127.51
123.62
123.55
122.15
122.12
116.49
116.30
62.89
45.79
45.75
f1 (ppm)
O
N
F
Ph
1H
13C NMR (101 MHz, CDCl3)

1H

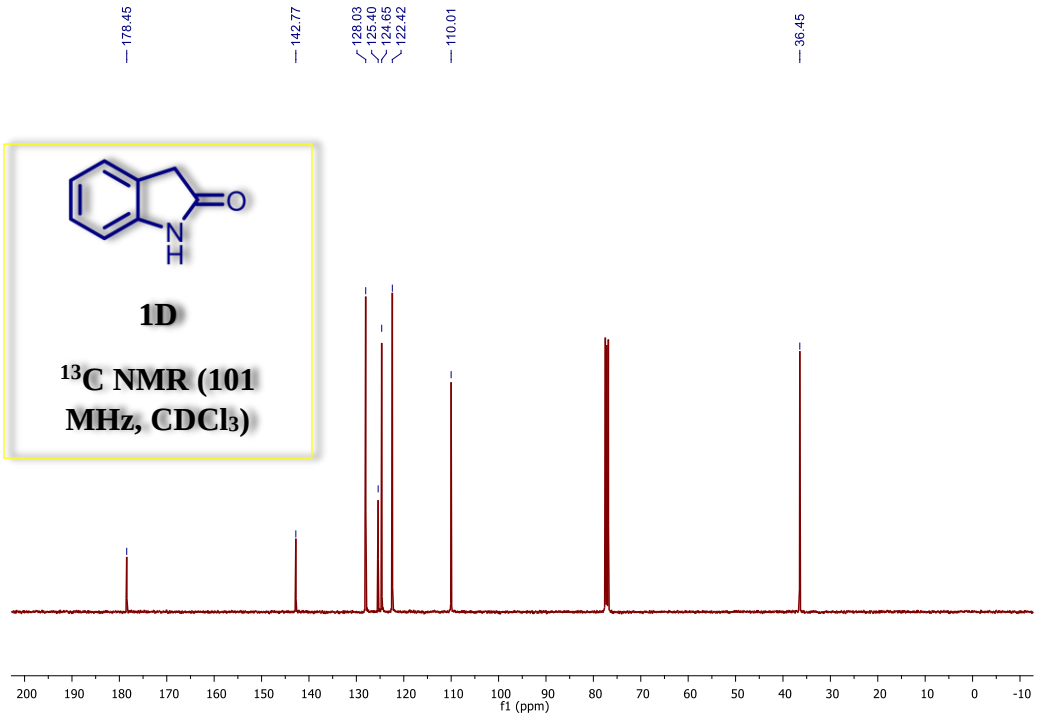
^{19}F NMR (376 MHz, $CDCl_3$)

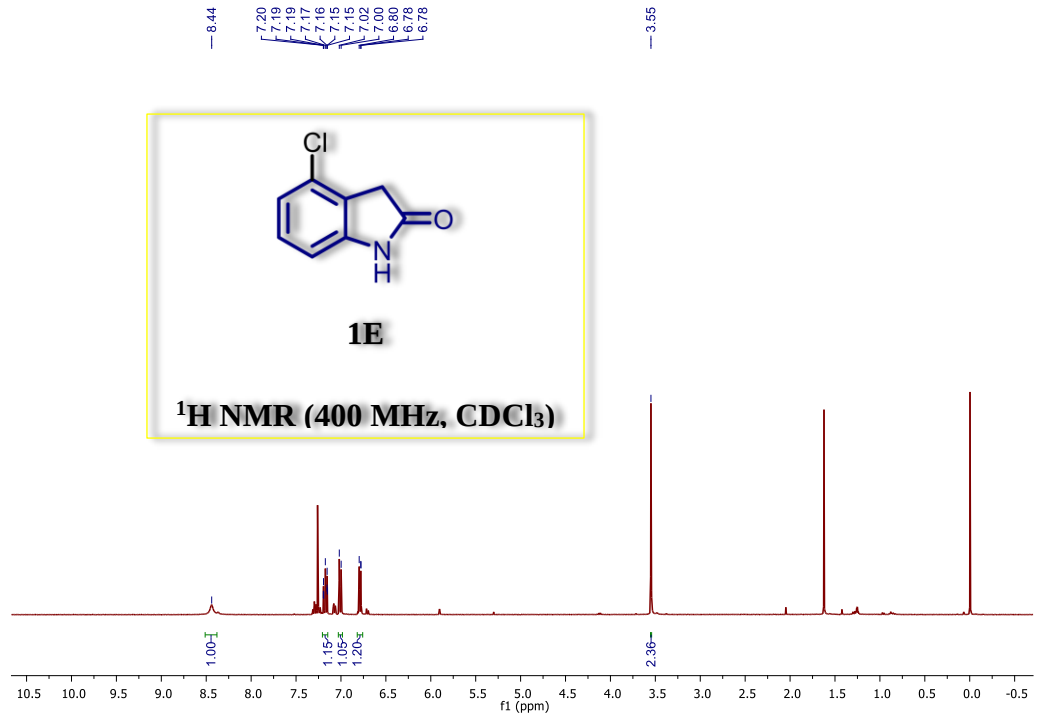


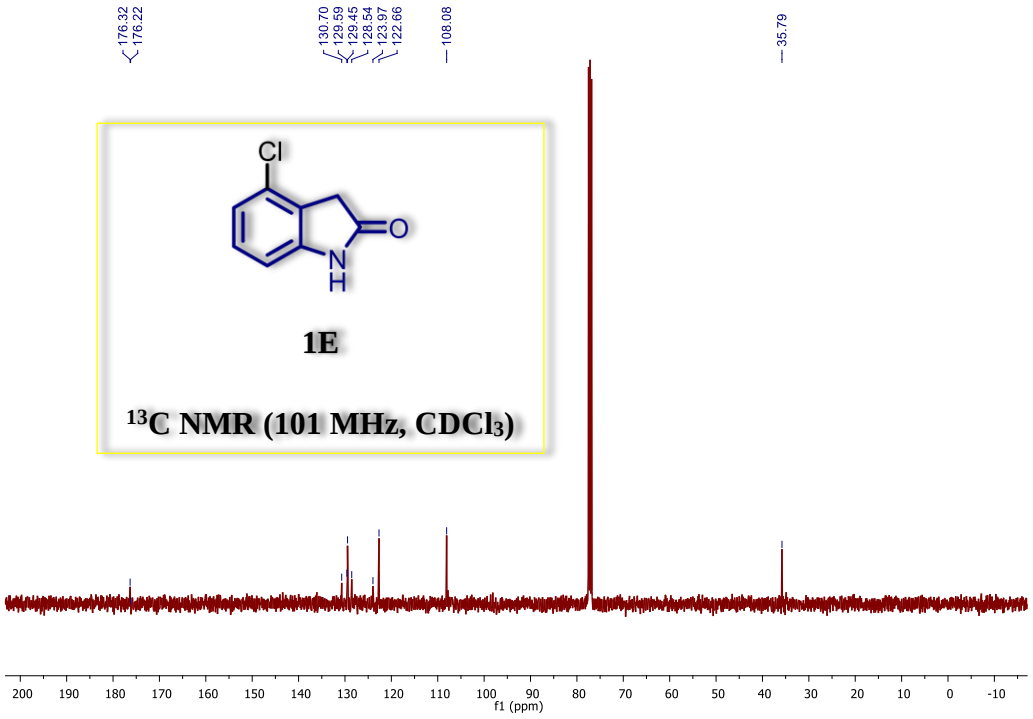


1D

^{1}H NMR (400 MHz, $CDCl_3$)

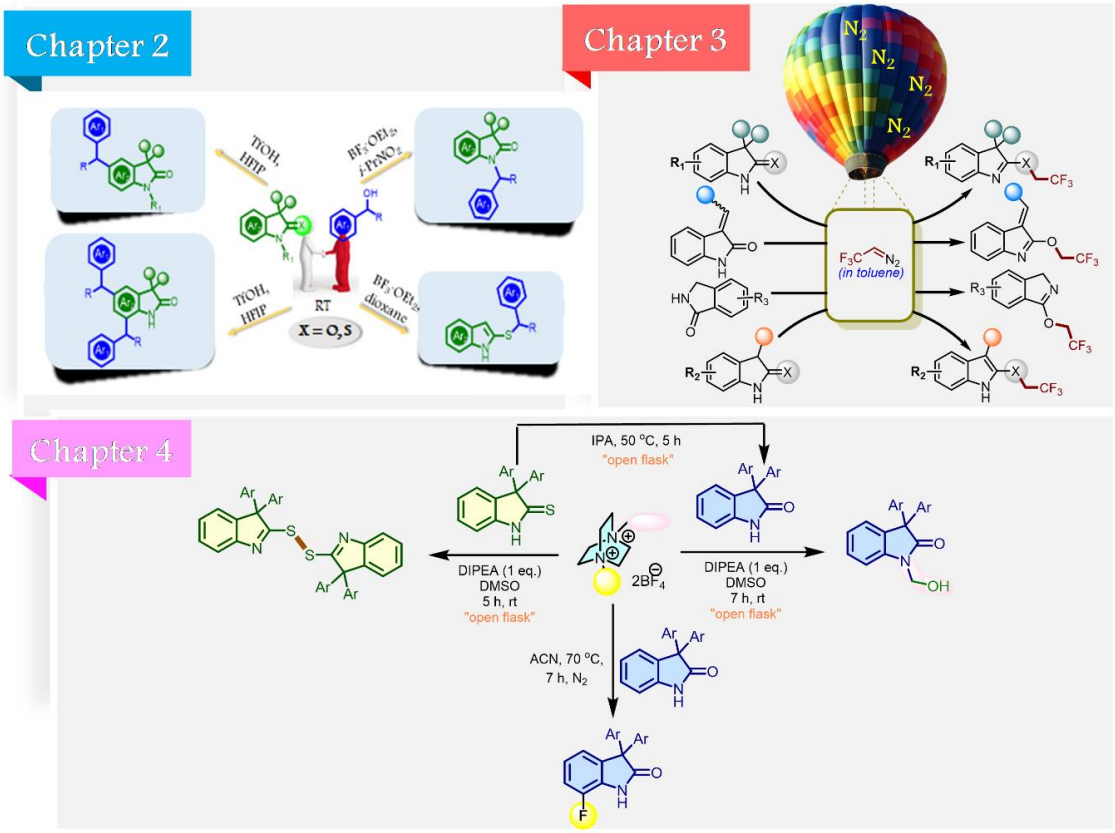

178.45
142.77
128.03
125.40
124.65
122.42
110.01
36.45
1D
13C NMR (101 MHz, CDCl3)
f1 (ppm)


8.44
7.20
7.19
7.19
7.17
7.16
7.15
7.15
7.02
7.00
6.80
6.78
6.78
3.55
1E
1H NMR (400 MHz, CDCl3)
1.00
1.15
1.05
1.20
2.36
f1 (ppm)


176.32
176.22
130.70
129.59
129.45
128.54
123.97
122.66
108.08
35.79
Cl
O
N
H
1E
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5.1 Conclusions

The thesis delves into the exploration of "Functionalization of Oxindoles and Thio-oxindoles under Metal-Free Conditions," offering a comprehensive analysis of the reactivity of these chemical compounds. This study involves meticulous experimentation and analysis to uncover the diverse reactivities associated with oxindoles and thio-oxindoles, providing profound insights that significantly contribute to the broader scientific understanding of these vital chemical species. Through the synthesis and characterization of a wide array of new derivatives, the research sheds light on the underlying mechanisms governing the reactivity of oxindoles and thio-oxindoles, emphasizing the potential



Scheme 5.1: Schematic diagram for thesis summary.

applications of these compounds in future research and development endeavors. The thesis is meticulously organized into four chapters, where each aspect is extensively discussed and explored. (Scheme 5.1).

Oxindole is a highly versatile compound that plays a pivotal role in the development and creation of novel drugs. Its remarkable ability to undergo modification by various functional groups enables the generation of sophisticated biological functions, making it an essential component in drug design and fabrication (Chapter 1). Chapter 2 delves into a detailed discussion of an innovative and practical protocol for the selective alkylation of oxindoles and thio-oxindoles using secondary alcohols. The report showcases the successful achievement of regioselectivity in C-alkylation by selectively protecting the N-centre of the amide moiety of the oxindoles. The text highlights the efficiency of the approach through gram scale experiments. Furthermore, it presents a case where one of the C5 alkylated oxindoles was subjected to further modification, undergoing a novel protocol for C-H oxygenation at the benzylic position. In Chapter 3, an innovative and efficient procedure for the selective addition of O-trifluoroethyl and S-trifluoroethyl groups to a range of compounds is detailed. This method stands out due to its ability to operate under mild reaction conditions, omitting the use of hazardous fluorinating reagents, while yielding excellent results. Notably, the treatment of chalcone-based oxindoles resulted in the production of E-selective products. The protocol exhibited exceptional compatibility with diverse functional groups, showcasing promising potential for a wide array of applications. A key feature of this method is the utilization of an environmentally benign catalyst, TfOH, which significantly enhances its sustainability compared to previous trifluoroethylation protocols. Moreover, the method involves the use of renewable and cost-effective feedstock chemicals, eliminating the need for solvents and further enhancing its eco-friendly nature. In Chapter 4, we explore a groundbreaking development in organic synthesis. We have successfully devised a method for directly introducing fluorine at the C7-H position of oxindoles, as well as N-hydroxymethylating oxindole, forming dithianes,

and converting thio-oxindole to oxindole. This achievement was made possible through thorough experimentation involving the evaluation of various solvents, bases, and reaction temperatures. A pivotal aspect of this innovative process is the versatile role of Selectfluor, serving as both an oxidant and a source of fluorine. Our novel protocol provides an effective and practical approach for synthesizing oxindole analogs under gentle conditions, yielding an impressive range of the desired products. Notably, our method exhibits exceptional regioselectivity, accommodates various functional groups, and is devoid of additives, rendering it an appealing option for researchers and practitioners in the realms of organic synthesis and pharmaceutical chemistry.

Appendix A: Chapter 2

Single Crystal X-Ray

For the determination of the X-ray crystal structure of **3ja, 4ka 5ma** and **9** single crystals were selected and mounted with paratone oil on a glass fiber using the gum. The data were collected at 293 K on a CMOS-based Bruker D8 Venture PHOTON 100 diffractometer equipped with an INCOATEC micro-focus source with graphite monochromatic Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. For the integration of diffraction profiles, SAINT program[1] was used. Adsorption correction was done by applying the SADABS program.[2] The crystal structure was solved by SIR 92[3] and refined by full-matrix least square method using SHELXL-97[4] WinGX system, Ver 1.70.01.[5] All the non-hydrogen atoms in the structure were located from the Fourier map and refined anisotropically. The hydrogen atoms were fixed by HFIX in their ideal positions and refined using a riding model with isotropic thermal parameters. The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition number are **2269433** (for **3ja**), **2359356** (for **4ka**), **2243550** (for **5ma**), **2280698** (for **9**).

Crystal structure of 3ja:

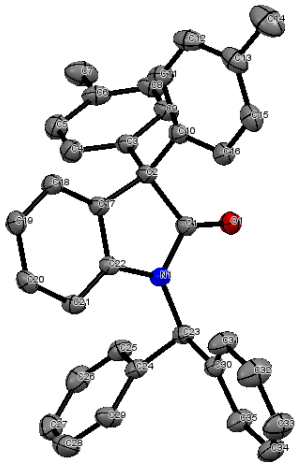


Figure S1. X-ray crystal structure of compound **3ja** with 30% probability level.

Appendix

Table 1 Crystal data and structure refinement of **3ja**

Ccdc no.	2269433
Empirical formula	$C_{35}H_{29}NO$
Formula weight	479.59
Temperature/K	298.00
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.9394(16)
b/Å	17.1857(16)
c/Å	14.6459(14)
α/°	90
β/°	106.919(4)
γ/°	90
Volume/Å^3	2634.3(5)
Z	4
ρ_{calc}g/cm^3	1.209
μ/mm^{-1}	0.072
F(000)	1016.0
Crystal size/mm^3	0.351 × 0.123 × 0.056
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.758 to 52.802
Index ranges	$-13 \leq h \leq 13$, $-21 \leq k \leq 21$, $-18 \leq l \leq 18$
Reflections collected	25819
Independent reflections	5386 [R_{int} = 0.0585, R_{sigma} = 0.0435]
Data/restraints/parameters	5386/0/337
Goodness-of-fit on F^2	1.057

Final R indexes [I>=2σ (I)]	R_1 = 0.0557, wR_2 = 0.1325
Final R indexes [all data]	R_1 = 0.0710, wR_2 = 0.1408
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.16

Crystal structure of 4ka:

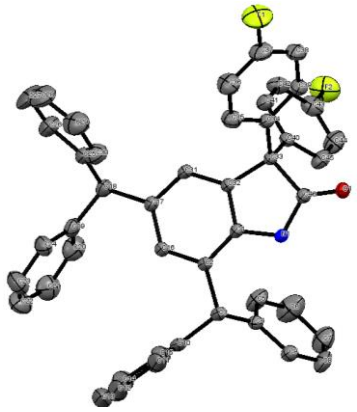


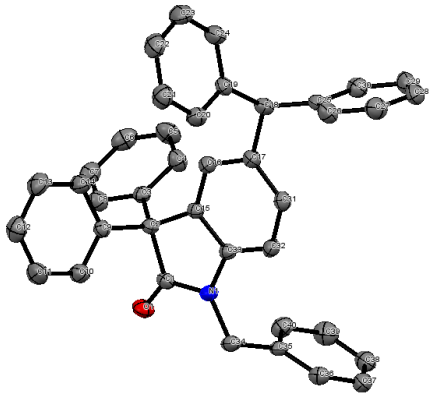
Figure S2. X-ray crystal structure of compound **4ka** with 30% probability level.

Table 2 Crystal data and structure refinement of **4ka**

Ccdc no.	2359356
Empirical formula	$C_{46}H_{33}F_2NO$
Formula weight	653.73
Temperature/K	298
Crystal system	triclinic
Space group	P-1
a/Å	10.7045(14)
b/Å	12.7465(18)
c/Å	13.725(2)
α/°	73.141(5)
β/°	75.571(5)

γ/°	76.961(5)
Volume/Å^3	1711.7(4)
Z	2
ρ_{calc}g/cm^3	1.268
μ/mm^{-1}	0.082
F(000)	684.0
Crystal size/mm^3	0.215 × 0.123 × 0.108
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.984 to 52.87
Index ranges	-13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -17 ≤ l ≤ 17
Reflections collected	23418
Independent reflections	6980 [R_{int} = 0.0669, R_{sigma} = 0.0694]
Data/restraints/parameters	6980/13/451
Goodness-of-fit on F^2	1.062
Final R indexes [I>=2σ (I)]	R_1 = 0.0796, wR_2 = 0.1723
Final R indexes [all data]	R_1 = 0.1245, wR_2 = 0.1951
Largest diff. peak/hole / e Å^{-3}	0.27/-0.22

Crystal structure of 5ma:



Appendix

Figure S3. X-ray crystal structure of compound **5ma** with 30% probability level.

Table 3 Crystal data and structure refinement of **5ma**

Ccdc no.	2243550
Empirical formula	$C_{40}H_{31}NO$
Formula weight	541.66
Temperature/K	298
Crystal system	orthorhombic
Space group	Pbcn
a/Å	39.339(2)
b/Å	8.3138(3)
c/Å	18.2789(9)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	5978.3(5)
Z	8
ρ_{calc}g/cm^3	1.204
μ/mm^{-1}	0.071
F(000)	2288.0
Crystal size/mm^3	0.245 × 0.213 × 0.123
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.456 to 51.41
Index ranges	-38 ≤ h ≤ 48, -10 ≤ k ≤ 9, -22 ≤ l ≤ 20
Reflections collected	29257
Independent reflections	5686 [R_{int} = 0.0693, R_{sigma} = 0.0549]

Data/restraints/parameters	5686/0/380
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0630, wR_2 = 0.1202
Final R indexes [all data]	R_1 = 0.0932, wR_2 = 0.1326
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.16

Crystal structure of 9:

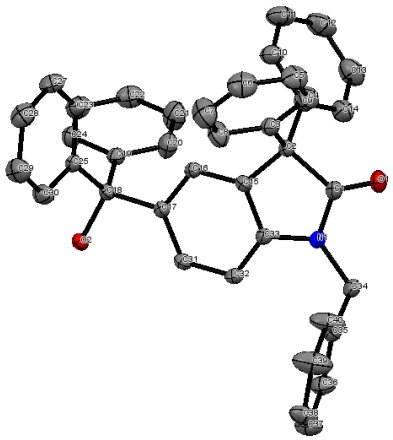


Figure S4. X-ray crystal structure of compound **9** with 30% probability level.

Table 4 Crystal data and structure refinement of **9**

Ccdc no.	2280698
Empirical formula	$C_{40}H_{31}NO_2$
Formula weight	557.66
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.0211(3)

b/Å	17.9009(5)
c/Å	16.1979(4)
α/°	90
β/°	108.8920(10)
γ/°	90
Volume/Å^3	3023.50(14)
Z	4
ρ_{calc}g/cm^3	1.225
μ/mm^{-1}	0.075
F(000)	1176.0
Crystal size/mm^3	0.28 × 0.231 × 0.125
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.52 to 52.932
Index ranges	-13 ≤ h ≤ 12, -22 ≤ k ≤ 22, -19 ≤ l ≤ 20
Reflections collected	22594
Independent reflections	6152 [R_{int} = 0.0488, R_{sigma} = 0.0401]
Data/restraints/parameters	6152/0/389
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0555, wR_2 = 0.1360
Final R indexes [all data]	R_1 = 0.0641, wR_2 = 0.1420
Largest diff. peak/hole / e Å^{-3}	0.37/-0.31

Appendix B: Chapter 3

Single Crystal X-Ray data of 3y, 5b, 5f, 7a, 9b, 13c

The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition number is **2243514** (for **3y**), **2257366** (for **5b**), **2257371** (for **5f**), **2288102** (for **7a**),

2285990 (for **9b**) and **2269435** (for **13c**). Suitable single – crystals for X-ray analysis were grown up from slow crystallization in DCM at room temperature.

Crystal structure of 3y:

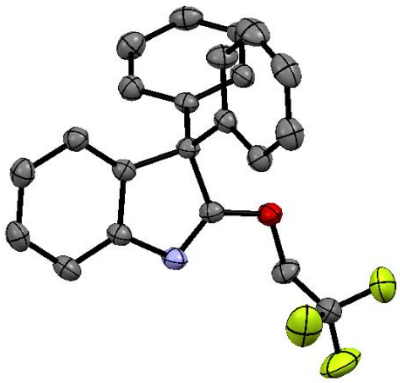


Figure S5. X-ray crystal structure of compound **3y** with 30% probability level.

Table 5 Crystal data and structure refinement of **3y**

Ccdc no.	2243514
Empirical formula	$C_{22}H_{16}F_3NO$
Formula weight	367.36
Temperature/K	298.00
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	6.8883(9)
b/Å	15.522(2)
c/Å	16.668(2)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	1782.1(4)

Z	4
$\rho_{calc}g/cm^3$	1.369
μ/mm^{-1}	0.105
F(000)	760.0
Crystal size/mm^3	0.356 × 0.256 × 0.098
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.548 to 52.812
Index ranges	$-8 \leq h \leq 8$, $-19 \leq k \leq 19$, $-20 \leq l \leq 20$
Reflections collected	11776
Independent reflections	3526 [R_{int} = 0.0469, R_{sigma} = 0.0457]
Data/restraints/parameters	3526/1/309
Goodness-of-fit on F^2	1.035
Final R indexes [I>=2σ (I)]	R_1 = 0.0387, wR_2 = 0.0883
Final R indexes [all data]	R_1 = 0.0521, wR_2 = 0.0965
Largest diff. peak/hole / e $Å^{-3}$	0.11/-0.12
Flack parameter	0.4(5)

Crystal structure of 5b:

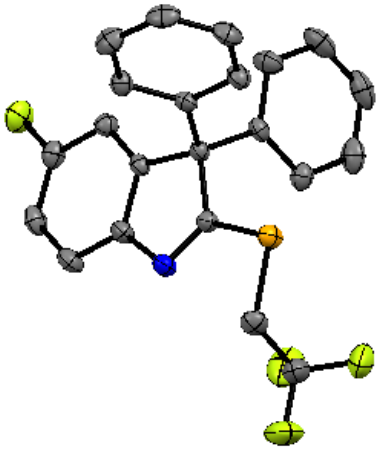


Figure S6. X-ray crystal structure of compound **5b** with 30% probability level.

Appendix

Table 6 Crystal data and structure refinement of **5b**

Ccdc no.	2257366
Empirical formula	$C_{22}H_{15}F_4NS$
Formula weight	401.41
Temperature/K	298
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	6.8631(3)
b/Å	16.0474(5)
c/Å	16.9025(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1861.56(12)
Z	4
ρ_{calc}g/cm^3	1.432
μ/mm^{-1}	0.219
F(000)	824.0
Crystal size/mm^3	0.235 × 0.123 × 0.098
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.448 to 52.834
Index ranges	$-7 \le h \le 8$, $-20 \le k \le 17$, $-21 \le l \le 20$
Reflections collected	9025
Independent reflections	3786 [R_{int} = 0.0595, R_{sigma} = 0.0601]
Data/restraints/parameters	3786/1/257
Goodness-of-fit on F^2	1.045

Final R indexes [I>=2σ (I)]	R_1 = 0.0441, wR_2 = 0.1068
Final R indexes [all data]	R_1 = 0.0496, wR_2 = 0.1112
Largest diff. peak/hole / e $Å^{-3}$	0.21/-0.25
Flack parameter	0.03(5)

Crystal structure of 5f:

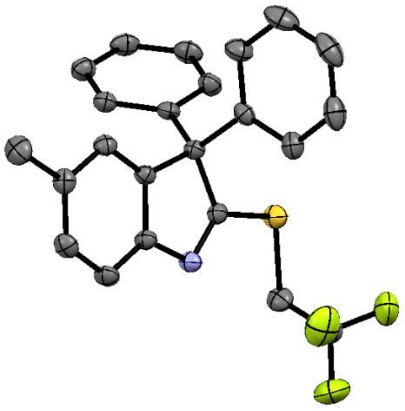


Figure S7. X-ray crystal structure of compound **5f** with 30% probability level.

Table 7 Crystal data and structure refinement of **5f**

Ccdc No.	2257371
Empirical formula	$C_{23}H_{18}F_3NS$
Formula weight	397.44
Temperature/K	298
Crystal system	orthorhombic
Space group	Pbca
a/Å	7.0705(6)
b/Å	16.8461(16)
c/Å	32.575(3)
α/°	90
β/°	90

γ/°	90
Volume/Å^3	3880.1(6)
Z	8
ρ_{calc}g/cm^3	1.361
μ/mm^{-1}	0.202
F(000)	1648.0
Crystal size/mm^3	0.235 × 0.156 × 0.123
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.444 to 52.826
Index ranges	-8 ≤ h ≤ 8, -21 ≤ k ≤ 20, -36 ≤ l ≤ 40
Reflections collected	55828
Independent reflections	3971 [R_{int} = 0.0511, R_{sigma} = 0.0206]
Data/restraints/parameters	3971/0/254
Goodness-of-fit on F^2	1.151
Final R indexes [I>=2σ (I)]	R_1 = 0.0507, wR_2 = 0.1272
Final R indexes [all data]	R_1 = 0.0553, wR_2 = 0.1296
Largest diff. peak/hole / e Å^{-3}	0.23/-0.27

Crystal structure of 7a:

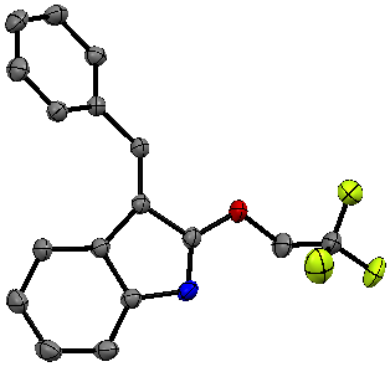


Figure S8. X-ray crystal structure of compound **7a** with 30% probability level.

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Table 8 Crystal data and structure refinement of **7a**

Ccdc no.	2288102
Empirical formula	$C_{34}H_{26}F_6N_2O_2$
Formula weight	608.57
Temperature/K	298
Crystal system	triclinic
Space group	P-1
a/Å	10.0648(8)
b/Å	11.6308(8)
c/Å	13.8611(10)
α/°	68.976(2)
β/°	87.671(3)
γ/°	69.921(2)
Volume/Å^3	1416.21(18)
Z	2
ρ_{calc}g/cm^3	1.427
μ/mm^{-1}	0.116
F(000)	628.0
Crystal size/mm^3	0.123 × 0.104 × 0.098
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.008 to 52.856
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 14$, $-17 \le l \le 17$
Reflections collected	18765
Independent reflections	5794 [R_{int} = 0.0577, R_{sigma} = 0.0585]
Data/restraints/parameters	5794/0/397
Goodness-of-fit on F^2	1.033

Final R indexes [I>=2σ (I)]	R_1 = 0.0626, wR_2 = 0.1794
Final R indexes [all data]	R_1 = 0.0737, wR_2 = 0.1917
Largest diff. peak/hole / e Å^{-3}	0.43/-0.48

Crystal structure of 9b:

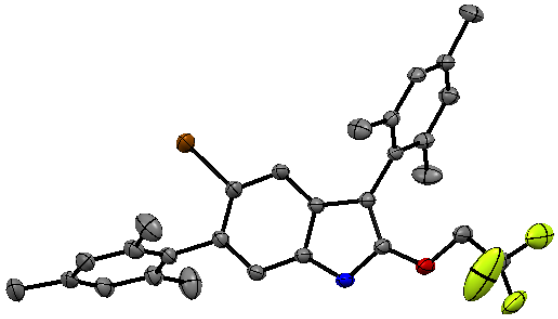

Figure S9. X-ray crystal structure of compound **9b** with 30% probability level.

Table 9 Crystal data and structure refinement of **9b**

Ccdc no.	2285990
Empirical formula	$C_{28}H_{26}BrF_3NO$
Formula weight	529.41
Temperature/K	298.00
Crystal system	triclinic
Space group	P-1
a/Å	7.9716(2)
b/Å	10.9315(3)
c/Å	15.7731(4)
α/°	75.9800(10)
β/°	78.6930(10)
γ/°	81.3380(10)
Volume/Å^3	1299.96(6)

Z	2
ρ_{calc}g/cm^3	1.353
μ/mm^{-1}	1.622
F(000)	542.0
Crystal size/mm^3	0.215 × 0.212 × 0.125
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.864 to 56.904
Index ranges	-10 ≤ h ≤ 10, -14 ≤ k ≤ 14, -21 ≤ l ≤ 21
Reflections collected	35476
Independent reflections	6457 [R_{int} = 0.0576, R_{sigma} = 0.0362]
Data/restraints/parameters	6457/0/313
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0639, wR_2 = 0.1626
Final R indexes [all data]	R_1 = 0.0766, wR_2 = 0.1725
Largest diff. peak/hole / e Å^{-3}	2.00/-1.42

Crystal structure of 13c:

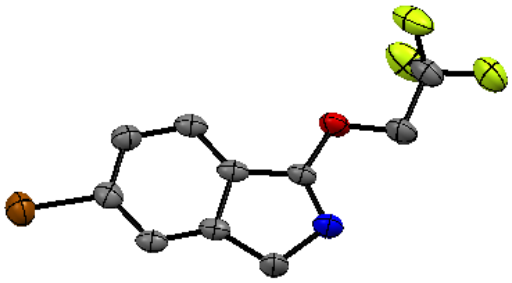

Figure S10. X-ray crystal structure of compound **13c** with 30% probability level.

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Table 10 Crystal data and structure refinement of **13c**

Ccdc no.	2269435
Empirical formula	$C_{10}H_6BrF_3NO$
Formula weight	293.07
Temperature/K	298.00
Crystal system	monoclinic
Space group	C2
a/Å	17.093(12)
b/Å	10.057(10)
c/Å	6.991(4)
α/°	90
β/°	113.89(3)
γ/°	90
Volume/Å^3	1098.8(15)
Z	4
ρ_{calc}g/cm^3	1.772
μ/mm^{-1}	3.759
F(000)	572.0
Crystal size/mm^3	0.215 × 0.123 × 0.105
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.816 to 52.984
Index ranges	$-21 \leq h \leq 21$, $-12 \leq k \leq 12$, $-8 \leq l \leq 8$
Reflections collected	5500
Independent reflections	2145 [R_{int} = 0.0522, R_{sigma} = 0.0635]
Data/restraints/parameters	2145/1/145
Goodness-of-fit on F^2	0.986

Final R indexes [I>=2σ (I)]	R_1 = 0.0421, wR_2 = 0.1070
Final R indexes [all data]	R_1 = 0.0497, wR_2 = 0.1132
Largest diff. peak/hole / e Å^{-3}	0.30/-0.24
Flack parameter	0.076(11)

Appendix C: Chapter 4

The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition number are **2362226** (for **3a**), **2364339** (for **3u**), **2332318** (for **4n**), **2348308** (for **6h**), and **2345878** (for **1a**). Suitable single crystals for X-ray analysis were grown up from slow crystallization in DCM at room temperature.

Crystal structure of 3a:

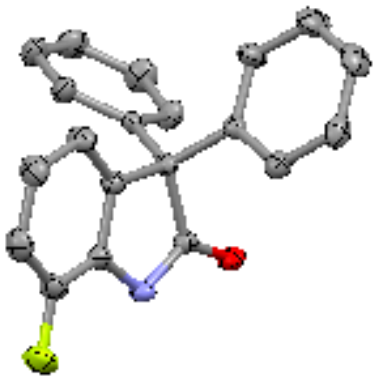

Figure S11. X-ray crystal structure of compound **3a** with 30% probability level.

Table 11 Crystal data and structure refinement of **3a**

Ccdc no.	2362226
Empirical formula	$C_{20}H_{14}FNO$
Formula weight	303.32
Temperature/K	298
Crystal system	triclinic

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Space group	P-1
a/Å	8.5589(19)
b/Å	9.347(2)
c/Å	10.566(3)
α/°	87.558(7)
β/°	86.779(7)
γ/°	64.466(6)
Volume/$Å^3$	761.4(3)
Z	2
$\rho_{calc}g/cm^3$	1.323
μ/mm^{-1}	0.090
F(000)	316.0
Crystal size/mm^3	0.245 × 0.231 × 0.123
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.862 to 52.958
Index ranges	$-10 \leq h \leq 10$, $-11 \leq k \leq 11$, $-13 \leq l \leq 13$
Reflections collected	8807
Independent reflections	3011 [R_{int} = 0.0491, R_{sigma} = 0.0476]
Data/restraints/parameters	3011/0/209
Goodness-of-fit on F^2	1.067
Final R indexes [I>=2σ (I)]	R_1 = 0.1060, wR_2 = 0.3310
Final R indexes [all data]	R_1 = 0.1129, wR_2 = 0.3371
Largest diff. peak/hole / e $Å^{-3}$	0.60/-0.35

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Crystal structure of 3u:

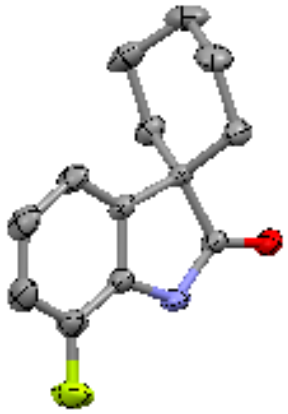

Figure S12. X-ray crystal structure of compound **3u** with 30% probability level.

Table 12 Crystal data and structure refinement of **3u**

CCDC No.	2364339
Empirical formula	$C_{13}H_{14}NOF$
Formula weight	219.25
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.0429(11)
b/Å	10.9749(8)
c/Å	11.1060(11)
α/°	90
β/°	106.733(3)
γ/°	90
Volume/Å^3	1172.27(19)
Z	4
ρ_{calc}g/cm^3	1.242

μ/mm^{-1}	0.089
F(000)	464.0
Crystal size/mm^3	0.215 × 0.156 × 0.089
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.334 to 52.766
Index ranges	$-12 \leq h \leq 11$, $-13 \leq k \leq 13$, $-10 \leq l \leq 13$
Reflections collected	9901
Independent reflections	2368 [R_{int} = 0.0441, R_{sigma} = 0.0339]
Data/restraints/parameters	2368/0/145
Goodness-of-fit on F^2	1.064
Final R indexes [I>=2σ (I)]	R_1 = 0.0601, wR_2 = 0.1618
Final R indexes [all data]	R_1 = 0.0669, wR_2 = 0.1673
Largest diff. peak/hole / e $Å^{-3}$	0.30/-0.14

Crystal structure of 4n:

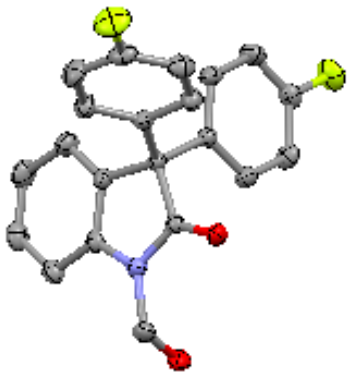

Figure S13. X-ray crystal structure of compound **4n** with 30% probability level.

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Table 13 Crystal data and structure refinement of **4n**

CCDC No.	2332318
Empirical formula	$C_{21}H_{15}F_2NO_2$
Formula weight	351.34
Temperature/K	298
Crystal system	orthorhombic
Space group	Pbca
a/Å	14.5726(10)
b/Å	12.3220(7)
c/Å	18.7806(14)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3372.3(4)
Z	8
ρ_{calc}g/cm^3	1.384
μ/mm^{-1}	0.104
F(000)	1456.0
Crystal size/mm^3	0.256 × 0.231 × 0.125
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.842 to 52.856
Index ranges	-18 ≤ h ≤ 18, -12 ≤ k ≤ 15, -23 ≤ l ≤ 23
Reflections collected	45905
Independent reflections	3454 [R_{int} = 0.0533, R_{sigma} = 0.0212]
Data/restraints/parameters	3454/0/238
Goodness-of-fit on F^2	1.078

Final R indexes [I>=2σ (I)]	R_1 = 0.0461, wR_2 = 0.1119
Final R indexes [all data]	R_1 = 0.0526, wR_2 = 0.1162
Largest diff. peak/hole / e Å^{-3}	0.22/-0.19

Crystal structure of 6h:

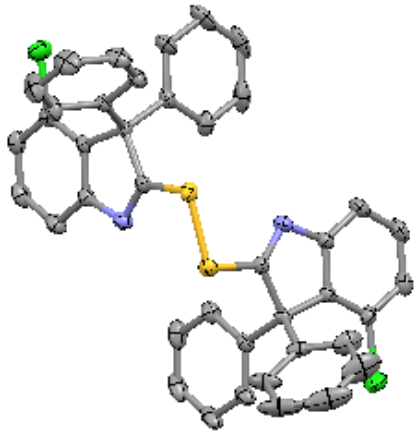

Figure S14. X-ray crystal structure of compound **6h** with 30% probability level.

Table 14 Crystal data and structure refinement of **6h**

CCDC No.	2348308
Empirical formula	$C_{40}H_{26}Cl_2N_2S_2$
Formula weight	669.65
Temperature/K	298
Crystal system	triclinic
Space group	P-1
a/Å	8.9623(6)
b/Å	13.4345(8)
c/Å	15.1300(9)
α/°	103.683(2)
β/°	98.591(2)

γ/°	90.567(2)
Volume/Å^3	1748.21(19)
Z	2
ρ_{calc}g/cm^3	1.272
μ/mm^{-1}	0.336
F(000)	692.0
Crystal size/mm^3	0.321 × 0.256 × 0.214
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.752 to 52.996
Index ranges	-11 ≤ h ≤ 11, -16 ≤ k ≤ 16, -18 ≤ l ≤ 18
Reflections collected	50379
Independent reflections	7156 [R_{int} = 0.0453, R_{sigma} = 0.0226]
Data/restraints/parameters	7156/0/415
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0420, wR_2 = 0.1120
Final R indexes [all data]	R_1 = 0.0445, wR_2 = 0.1144
Largest diff. peak/hole / e Å^{-3}	0.42/-0.44

Crystal structure of 1a:

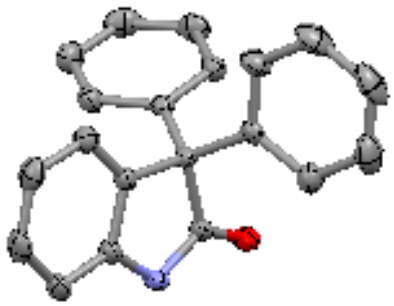

Figure S15. X-ray crystal structure of compound **1a** with 30% probability level.

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Table 15 Crystal data and structure refinement of **1a**

CCDC No.	2345878
Empirical formula	$C_{20}H_{15}NO$
Formula weight	285.33
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.7474(14)
b/Å	21.757(4)
c/Å	8.9831(14)
α/°	90
β/°	118.058(4)
γ/°	90
Volume/Å^3	1508.7(4)
Z	4
ρ_{calc}g/cm^3	1.256
μ/mm^{-1}	0.077
F(000)	600.0
Crystal size/mm^3	0.287 × 0.216 × 0.158
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.47 to 53.018
Index ranges	$-10 \leq h \leq 11$, $-27 \leq k \leq 27$, $-11 \leq l \leq 11$
Reflections collected	27361
Independent reflections	3115 [R_{int} = 0.0690, R_{sigma} = 0.0367]
Data/restraints/parameters	3115/0/199
Goodness-of-fit on F^2	1.231

Final R indexes [I>=2σ (I)]	R_1 = 0.0744, wR_2 = 0.1670
Final R indexes [all data]	R_1 = 0.0845, wR_2 = 0.1717
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.25

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3. Altomare, A.; Cascarano, G.; Giacovazzo C.; Guagliardi, A.; *J. Appl. Cryst*. **1993**, *26*, 343-350.
4. Sheldrick, G. M. SHELXL-97, Program for Crystal Structure Solution and Refinement; University of Göttingen, Göttingen, Germany, 1997.
5. Farrugia, L. J. *WINGX: A Windows Program for Crystal Structure Analysis*; University of Glasgow: Glasgow, U.K., 1988.
6. Gaussian 09, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Jr., Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J; Fox, D. J. Gaussian, Inc., Wallingford CT, 2010.

Conferences Attended

- **Research Conclave-2018:** Department of Chemistry, IIT Ropar, India
- **Activity:** Attended.

- **UK-India Interdisciplinary Workshop on Advanced Biomaterials and Biosensors [ABB] 2018:** Center for Biomedical Engineering, Indian Institute of Technology Ropar, Punjab, India
- **Activity:** Attended.

- **International Conference on Recent Advances in Chemical Sciences [RACS-2022]:** Department of Chemistry and Chemical Sciences, Central University of Jammu, J&K, India
- **Activity: Poster Presentation**

- **Contemporary Facts in Organic Chemistry [CFOS-2022]:** Department of Chemistry, IIT Roorkee, Roorkee, UK, India
- **Activity: Poster Presentation**

- **Recent Advances in Bioorganic and Medicinal Chemistry [RABMC-2022]:** Department of Chemistry, NIPER Mohali, Punjab, India
- **Activity: Poster Presentation**

- **23rd Tetrahedron Symposium-2023:** 27-30 June 2023 | Svenska Massan – The Swedish Exhibition and Congress Centre in Gothenburg, Gothenburg, Sweden.
- **Activity: Poster Presentation**

- **ChemFest-2024:** Department of Chemistry, IIT Ropar, India
- **Activity: Oral Presentation**

List of Publications

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