Pentafluorobenzoic Acid Catalyzed 1,6-Conjugate Addition of Indoles to *p*-Quinone Methides

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A dissertation submitted for the partial

fulfilment of BS-MS degree in Science

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Dedicated

To

My Beloved God, Parents and Friends

For their love, support and encouragement

Certificate of Examination

This is to certify that the dissertation titled "***Pentafluorobenzoic Acid Catalyzed 1,6-Conjugate Addition of Indoles to p-Quinone Methides***" submitted by Mr. Arjun Chowdhury (Reg. No. MS16111) for the partial fulfilment of BS-MS degree program of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

24/5/2021

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Declaration

I worked on the thesis discussed in this dissertation at the Indian Institute of Science Education and Research Mohali's Department of Chemical Sciences under the supervision of Dr. R. Vijaya Anand. This thesis has not been applied in part or in full to any other university or institute for a degree, certificate, or fellowship. Every effort is made to indicate when other people's contributions are involved, with due acknowledgement of joint studies and discussions. This thesis is a genuine record of my original work, and the bibliography lists all of the references cited inside.

Arjun Chowdhury

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Date: 24/05/2021

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

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Notations and Abbreviations

cm	Centimeter
δ	Chemical shift
$CDCl_3$	Chloroform-D
J	Coupling constant
Cy	Cyclohexyl
Ee	Enantiomeric excess
DCE	Dichloroethane
DCM	Dichloromethane
Et_2O	Diethyl ether
DME	1,2-Dimethoxyethane
DMF	*N*, *N*'-Dimethyl formamide
DMSO	Dimethyl sulfoxide
D	Doublet
Dd	Doublet of doublet
Ddd	Doublet of doublet of doublet
Dt	Doublet of triplets
EWG	Electron withdrawing group
°C	Degree Celsius
Dr	Diastereomeric ratio
EtOAc	Ethyl acetate
equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
Hz	Hertz
H	Hour(s)
i-Pr	Isopropyl
m.p.	Melting point
mg	Milligram(s)
mL	Millilitre (s)
mmol	Millimole(s)
min	Minute(s)

m	Multiplet
NMR	Nuclear Magnetic Resonance
Q	Quartet
R_f	Retention factor
rt	Room Temperature
s	Singlet
sept	Septet
tert	Tertiary
^{t}Bu	*tert*- Butyl
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet

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Abstract

Pentafluorobenzoic acid has been utilized as a non-covalent Brønsted acid catalyst for the 1,6-conjugate addition of indoles to *para*-quinone methides. This transformation tolerant to a variety of functional groups and occurs in mild conditions. This methodology provides an easy and straightforward access to a set of unsymmetrical diarylindolylmethanes in moderate to good yields.

Chapter 1

1.1. Introduction to Quinone methides

Quinone methides (QM) are cyclohexadiene ring containing compounds with a carbonyl and an exocyclic methylene group. There are mainly two types of QM, namely *ortho*-QM and *para*-QM. These compounds exist in Zwitterionic form and are better Michael acceptors than enones due to extended conjugation, and release of ring strain upon the addition of a nucleophile. Several biologically important compounds like metabolites, terpenes and plant pigments contain QM rings (**Figure 1.1**).[1,2] Apart from this, QMs are widely used as synthons to make natural products by nucleophilic attack on the benzylic position.[3,4] Introduction of steric bulk on 2nd and 6th position such as *tert*-butyl groups increase the chances of nucleophilic attack to the benzylic position. Several natural products are known that can be synthesized by using QMs (**Figure 1.2**).[5]

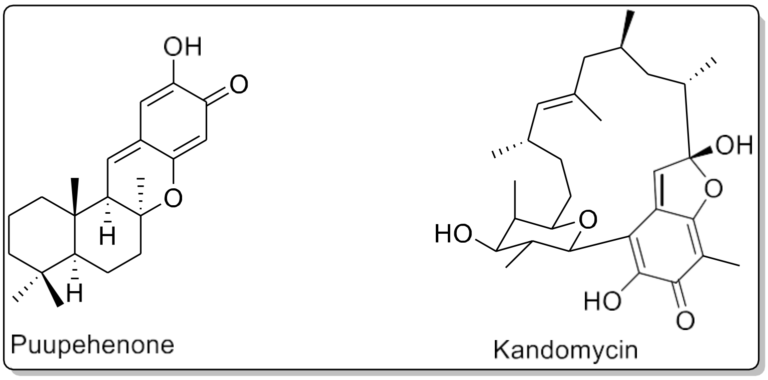


Figure 1.1: Quinone methide ring containing natural products

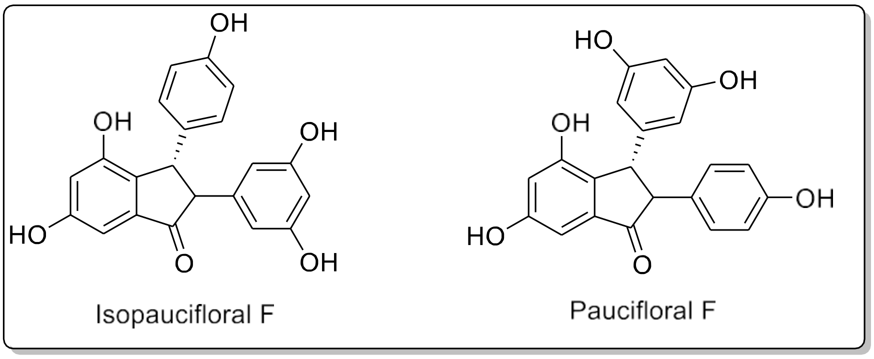


Figure 1.2: Natural products synthesized using quinone methides

1.2. Introduction to Organocatalysis and Organic Lewis Acid Catalysis

Organic Lewis acids are electron deficient or electrophilic molecules that can easily form non-covalent bonds with electron-rich functional groups and thus can facilitate reactions. There are two types of organocatalysis: Covalent and Non-Covalent.[6] Examples of covalent organocatalysts would be *N*-heterocyclic carbenes (NHCs),[7] nitrogen or phosphorous containing bases such as DABCO, piperidine or phosphines in Morita-Baylis Hillman reactions,[8,9] proline-based compounds in asymmetric aldol reactions[10] etc. These are mainly Lewis or Brønsted base or intermediate forming (like Breslow intermediate in case of NHCs) catalysts. Usually, non-covalent organocatalysts are Lewis acidic in nature. Non-benzoid carbocations like Cyclopropenium species,[11,12] Tropylium ion[13–15] or Pyridine based dications are common examples of this class. Asymmetry can also be introduced in reactions using chiral carbocations or by inducing chirality on the counteranions.

There is an enormous number of examples present, in which, organocatalysts are used to generate chirality. Primary and secondary amines and imidazolidones[16] are specifically used to induce chirality in aldol, Mannich, endo selective [4+2] and [4+3] cycloaddition reactions. NHCs are used in benzoin chemistry, Stetter and redox reactions.[7,17] Phosphoric acids are used in aza-Henry[18] and Strecker reactions[19]. Cinchona alkaloids are used in phase transfer catalysis.[20,21]

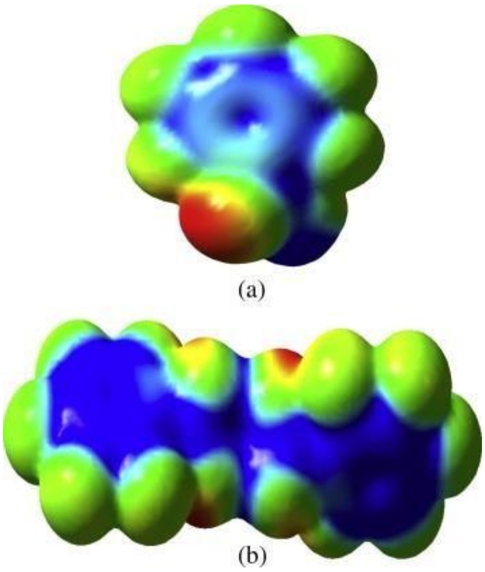
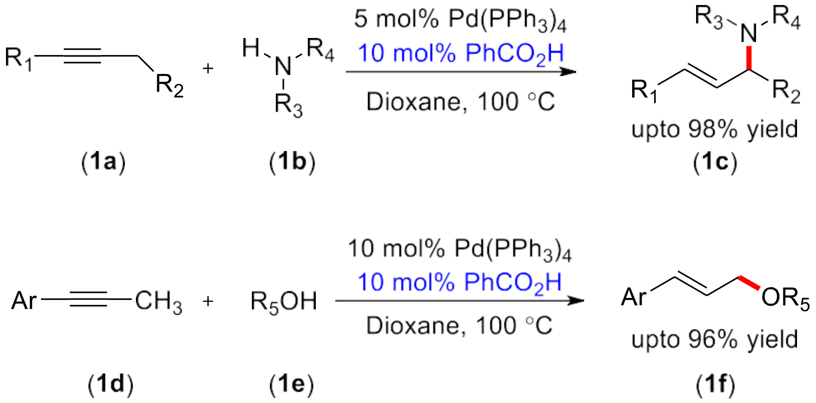


Figure 1.3: MEP for a) Monomer and b) Dimer of **A1**. Red and yellow regions are electron rich and blue regions are electron deficient.

Benzoic acids are well-known organocatalysts in Lewis acid-mediated reactions. Benzoic acids are often combined with some metal catalysts to enhance the yield or selectivity of reactions. As the aromatic core is electron deficient, due to the presence of the carboxyl group, this itself acts as a Lewis acidic moiety. In the case of pentafluorobenzoic acid (PFBA) (**A1**), the effect is further enhanced by the five fluorine atoms. **A1** usually exists in dimeric form. It's pKa is 1.6. In 2014, Kalyanaraman and co-workers conducted MEP studies[22] to show the electron density distribution of **A1**.

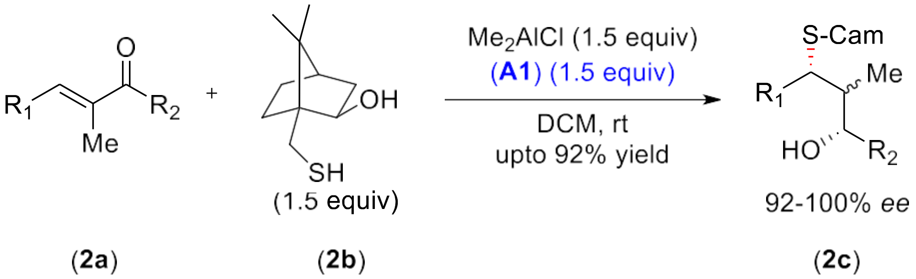
1.3. Literature Reports on Benzoic acid Catalyzed Transformations

In 1999, Yamamoto and co-workers used Pd(PPh_3)$_4$ and Benzoic acid for hydroamination of alkynes (**1a**). Later in 2001, they used a similar procedure for hydroalkoxylation of alkynes (**1d**) (**Scheme 1**).[23]



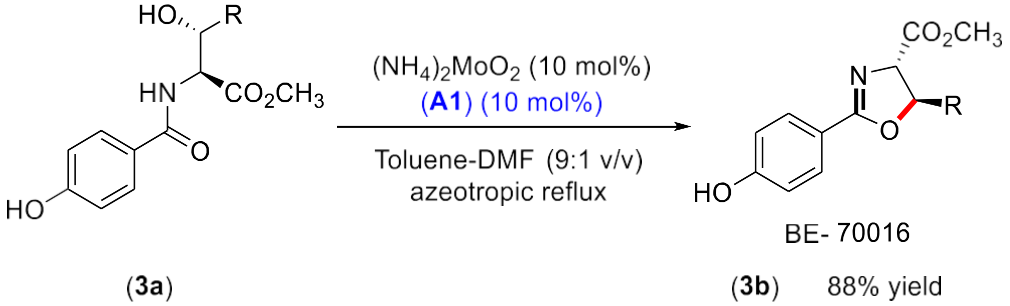
Scheme 1: Hydroamination and hydroalkoxylation of alkynes

In 2003, Node and co-workers used **A1** as an additive in asymmetric tandem Michael addition and Meerwein-Ponndorf-Varley (MPV) reduction (**Scheme 2**).[24,25] They showed that using acids especially pentafluorobenzoic acids increase the yield considerably.



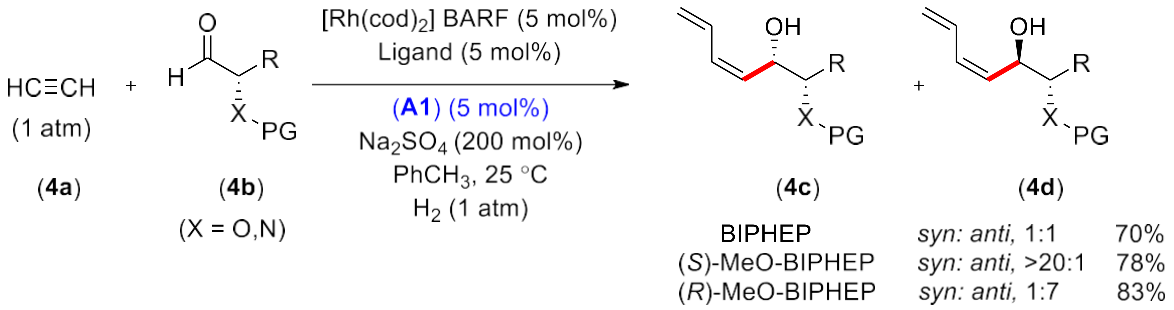
Scheme 2: Asymmetric Michael addition and MPV reduction

In 2007, Ishihara and co-workers used Molybdenum (VI) oxide and benzoic acid for dehydrative cyclization (**Scheme 3**) and reported the first-ever synthesis of antitumour agent BE-70016 (**3b**).[26]



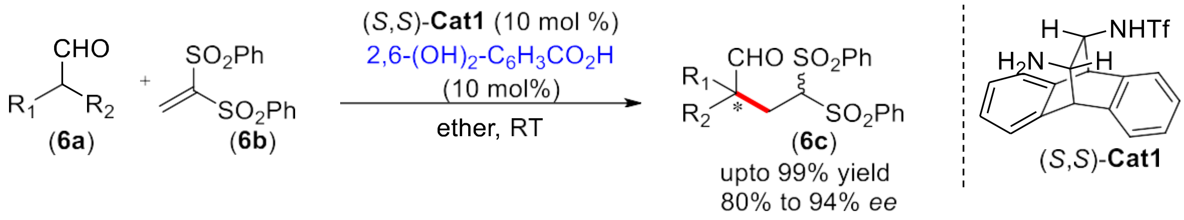
Scheme 3: Mb(VI) oxide & PFBA catalyzed dehydrative cyclization

In 2008, Krische and co-workers used **A1** as an additive in diastereoselective hydrogenative couplings (**Scheme 4**) of acetylene (**4a**) to α-chiral aldehydes (**4b**).[27]



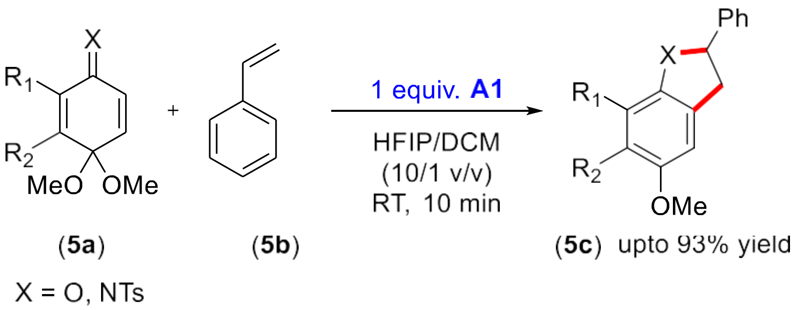
Scheme 4: Asymmetric hydrogenative coupling of acetylene to α-chiral aldehydes

In 2010, Maruoka and co-workers developed a rigid, chiral *trans*-diamine catalyst (**Cat1**) and used it for conjugate addition of heterosubstituted aldehydes (**6a**) to vinyl sulfones (**6b**) (**Scheme 6**).[28] They used bulky benzoic acids and observed a huge increase in enantioselectivity in the product. This influenced them to look for a reversal of enantioselectivity by the use of benzoic acids as well.



Scheme 5: Asymmetric addition of heterosubstituted aldehydes to vinyl sulfones

In 2011, Kita and co-workers used **A1** as an activator in [3+2] coupling of quinone monoacetals (**5a**) with alkenes (**5b**) to form cycloadducts (lactones) (**5c**) in quantitative yield (**Scheme 5**).[29,30]



Scheme 6: [3+2] coupling of quinone monoacetals with alkenes

In 2012, Keiji's group used two new diamine (**Cat2** & **Cat3**) based organocatalysts for asymmetric aldol (**Scheme 7**) and Mannich reactions (**Scheme 8**).[31] They used the Tf-amide of the diamines. Here they have shown that upon the use of benzoic acid derivatives inversion of enantioselectivity can be achieved.

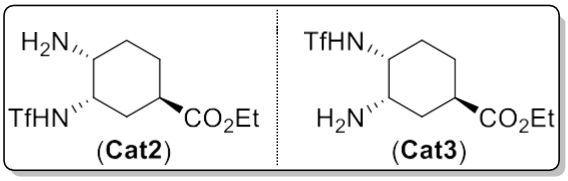
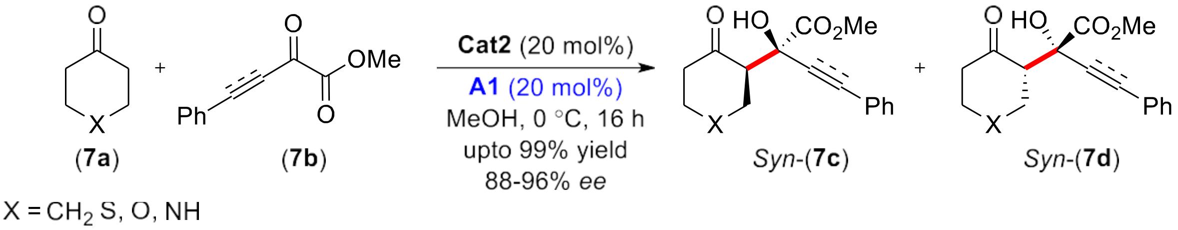


Figure 1.4: Catalysts developed by Keiji Maruoka and co-workers

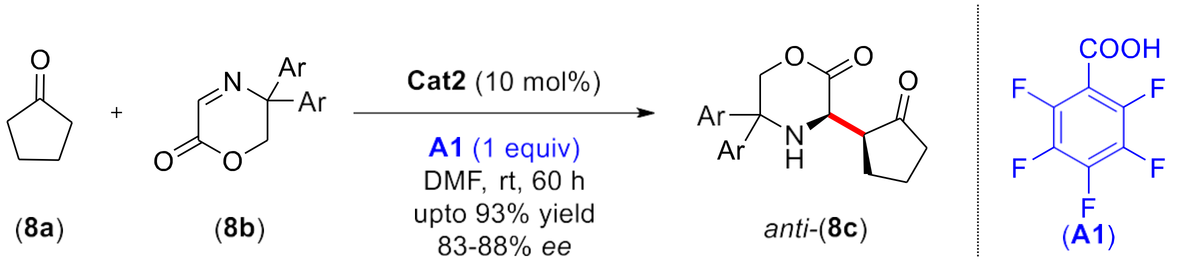
First, they checked the correlation between the acidity of benzoic acids and enantioselectivity. It was observed that the addition of acids lowered the overall enantioselectivity. But, at the same time, weaker acids lead to an increase in overall yield and where acid strength is raised, diastereoselectivity also enhances.



Scheme 7: Inversion of diastereoselectivity in aldol reaction

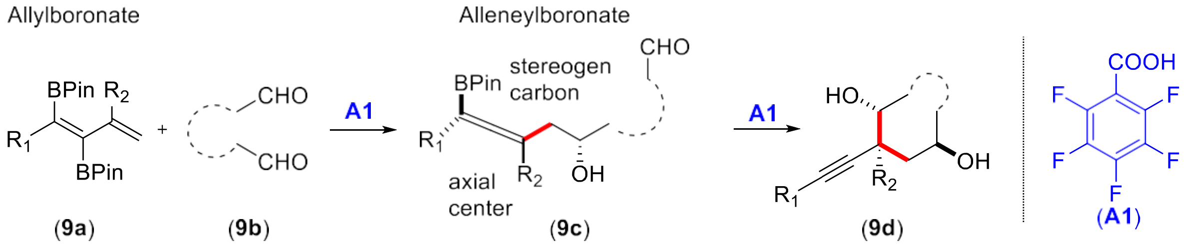
Without any additive, if **Cat2** was used, the major product was *syn*-**7c** and in case of **Cat3** it was *syn*-**7d**. Surprisingly, when 2,6-dihydroxybenzoic acid or **A1** was used, inversion of selectivity of catalyst was observed, i.e., *syn*-**7c** was the major product. The use of aqueous MeOH or acetonitrile also leads to the reversal of selectivity.

Mannich reaction with cyclic imino ester (**8b**) lead to *anti* selective products (**8c**) in presence of **Cat2**. A similar reversal was also observed when acids are used. Unlike aldol, **A1** does not reverse the selectivity, but 2,6-dinitrobenzoic acid induces the inversion. Again, in this case, the use of an aqueous environment does not cause inversion.



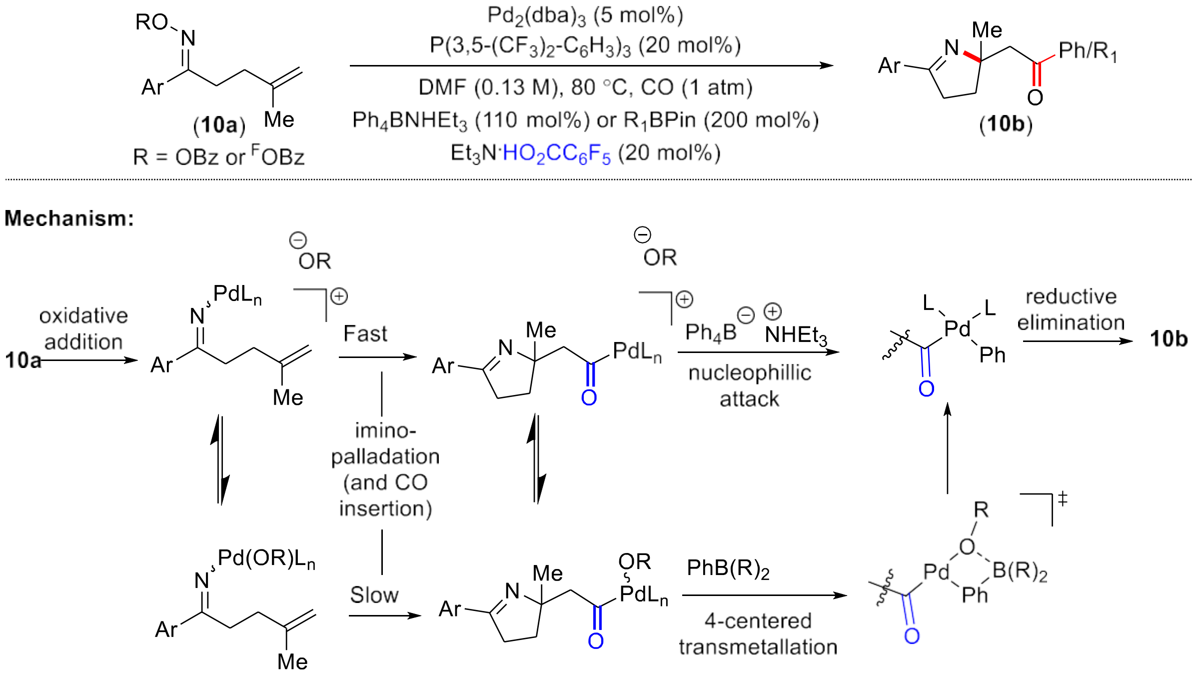
Scheme 8: Inversion of diastereoselectivity in Mannich reaction

In 2015, Szabo and co-workers synthesized chiral 1,4-diols (**9d**) by allylboration of dialdehydes followed by intramolecular allenylboration (**Scheme 9**).[32] This reaction sequence was catalyzed by **A1**. This particular reaction can also happen without adding **A1**. But the addition of **A1** decreases the reaction temperature from 80 °C to room temperature. With decreasing reaction temperature, the chances of stereoselectivity increase, this is highly useful indeed. Initially, PTSA was used, but it decomposed the allylboronate. **A1** did not show any decomposition, rather it helped in the activation of **9a** through BPin group.



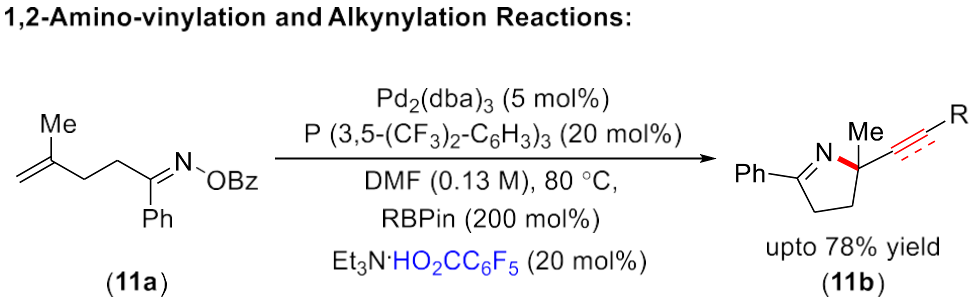
Scheme 9: PFBA catalyzed allylboration followed by allenylboration mediated 1,4-diol synthesis

In 2015, Bower and co-workers showed a palladium-catalyzed 1,2-carboamination of alkenes via an umpolung approach (**Scheme 10**).[33] They added a pentafluorobenzoate or benzoate group to the nitrogen of amine and made oxime (**10a**). Oximes are electrophilic in nature and thus pentafluorobenzoate or benzoate group induces umpolung. Initially, they screened the leaving efficiency of the OBz or ^{F}OBz group by the addition of **A1** or halides. They found that **A1** undergoes *in situ* deprotonation and forms the corresponding carboxylate and provides moderate yield. These studies show that after oxidation, the cyclization of oxime esters to bicycles requires dissociation of the leaving group from the parent molecules so that the cationic imino-Pd intermediate can form. The mechanism is shown in (**Scheme 10)**. Later they found that protic ammonium salts of **A1** undergo decarboxylation to form C_6F_5H. This accelerates the formation of the Pd (II) intermediate which in turn accelerates the formation of the C-N bond.



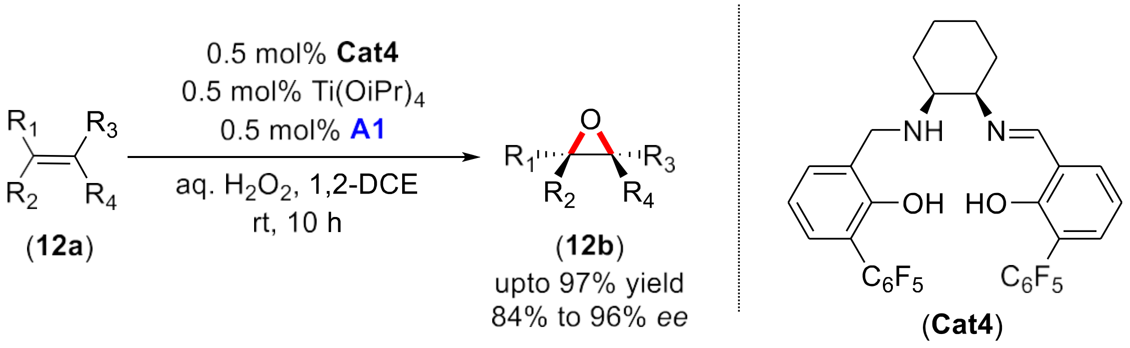
Scheme 10: Mechanism of Pd catalyzed 1,2-carboamination of alkenes

Below are the reaction conditions of 1,2- Aminoacylation, -vinylation and alkynylation. Vinylation and alkynylation also follow similar mechanistic pathways (**Scheme 11**).



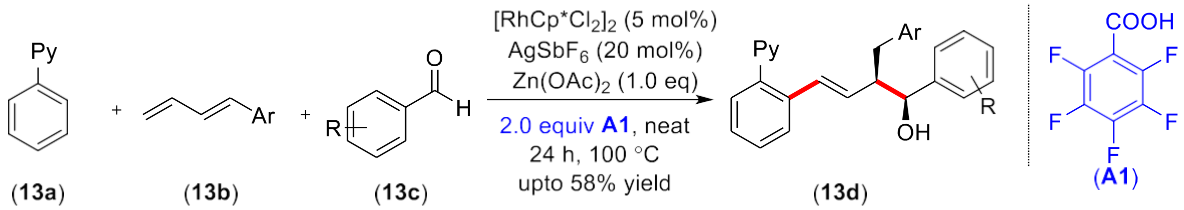
Scheme 11: Pd-catalyzed 1,2-amino-vinylation and alkynylation

In 2016, Berkessel and co-workers developed a *cis*-configured analogue of Katsuki's Ti-*trans*-DACH salalen complex (**Cat4**) and used it for asymmetric epoxidation of non-conjugated terminal alkenes (**12a**) (**Scheme 12**).[34] This reaction was compatible with many different functional groups. But, in the case of the hydroxyl group, the reaction was very slow. The catalyst is recyclable. They showed that **A1** can act as a co-catalyst and it can accelerate the reaction and also can reduce the temperature requirements to room temperature.



Scheme 12: Asymmetric epoxidation of nonconjugated terminal alkenes

In 2018, Zhao and co-workers developed Rhodium(III) catalyzed three-component C-H bond addition cascade (**Scheme 13**).[35] They used **A1** and a stoichiometric amount of $Zn(OAc)_2$ and got good results.

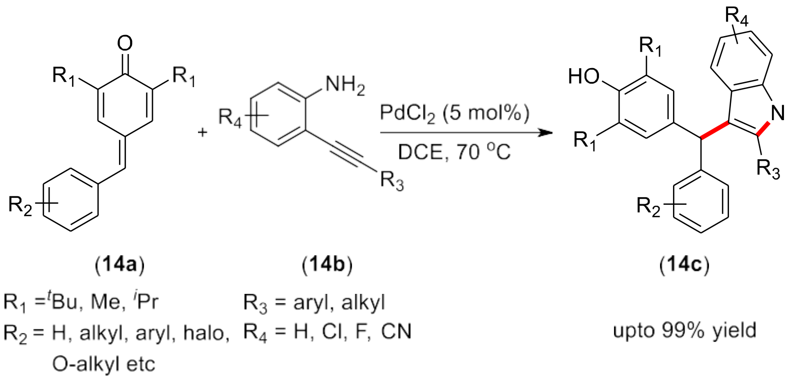


Scheme 13: Rh(III) catalyzed three-component C-H bond addition

Chapter 2

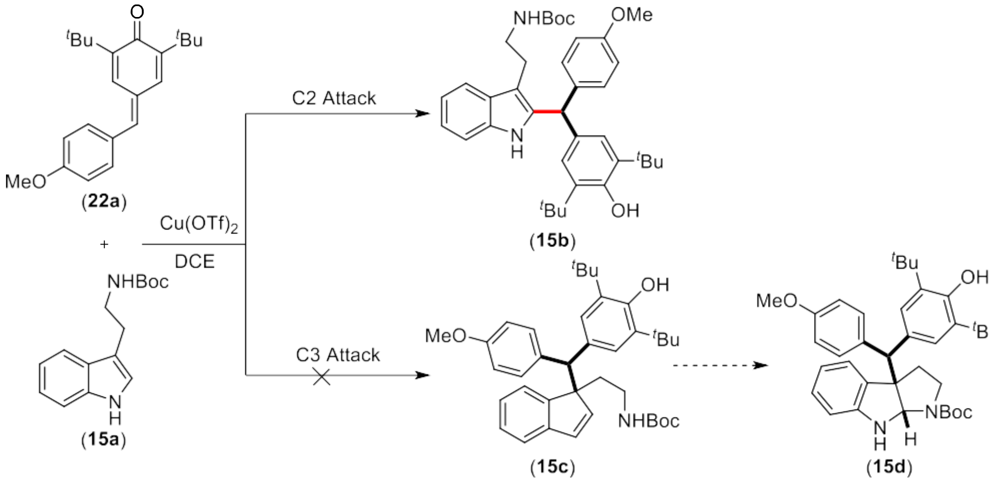
2.1. Background

In 2015, Anand's group reported a domino electrophilic cyclization that leads to diaryl(3-indolyl)methanes (**14c**) (**Scheme 14**).[36] This was catalyzed by $PdCl_2$ in DCE solvent. They used *o*-alkynylanilines (**14b**) that adds in 1,6 fashion to *p*-QMs (**14a**).



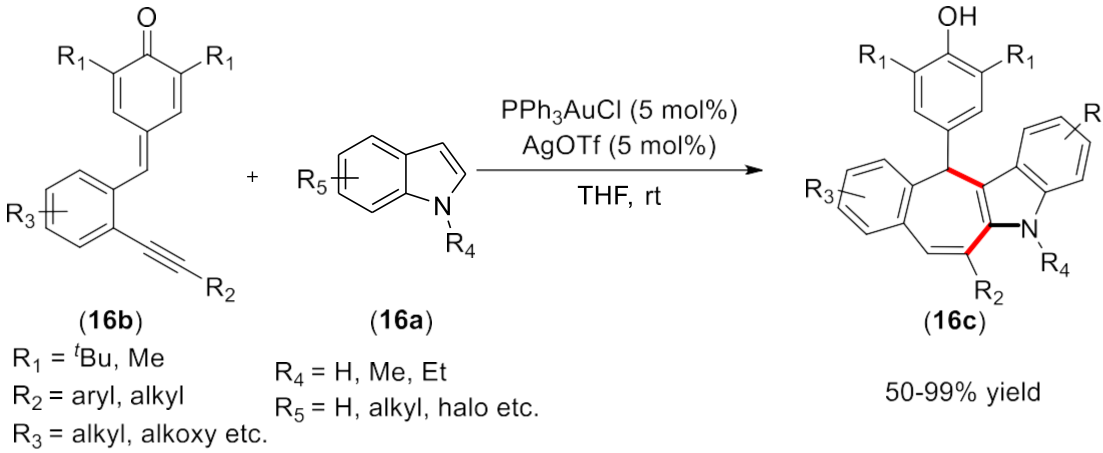
Scheme 14: $PdCl_2$ catalyzed synthesis of unsymmetrical diarylindolylmethanes

In 2016, the same reported a $Cu(OTf)_2$ catalyzed 1,6-conjugate addition of 3-substituted indoles (**15a**) to *p*-QMs (**22a**) (**Scheme 15**). This was a solvent-free approach. This lead to diaryl(2-indolyl)methanes (**15b**). Interestingly, there is no C3 attack that could have been led to further reaction of the substituting group to indole and forming another ring.

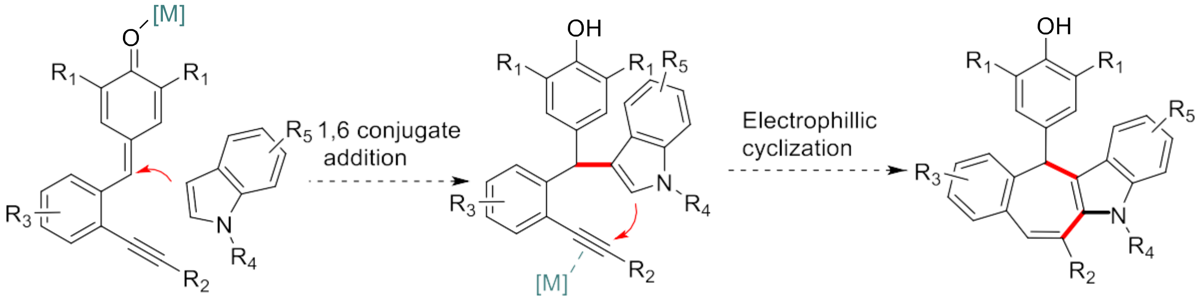


Scheme 15: Lewis acid catalyzed 1,6-conjugate addition of 3-substituted indoles to *p*-QMs

Anand's group also reported a gold and silver dual catalyzed 1,6-conjugate addition of indoles (**16a**) to 2-alkynyl *p*-QMs (**16b**) (**Scheme 16**).[37] After C3 attack, further electrophilic cyclization leads to a 7 membered ring (**16c**) (**Scheme 17**).

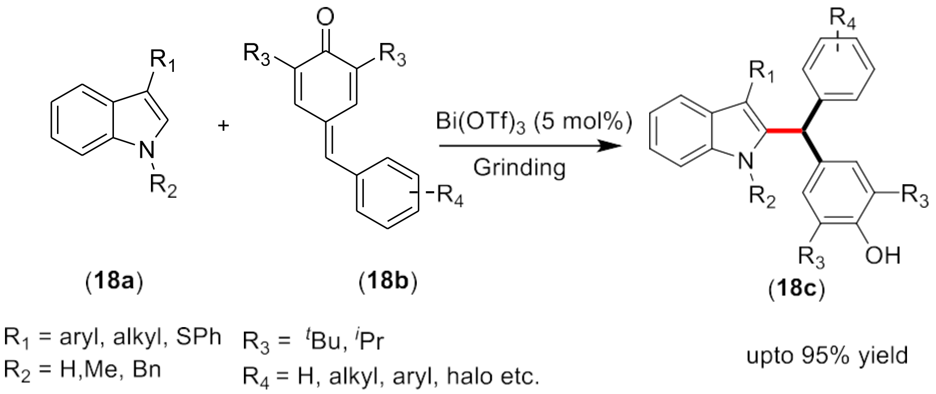


Scheme 16: Ag and Au dual catalyzed 1,6-conjugate addition of indoles to 2-alkynyl *p*-QMs



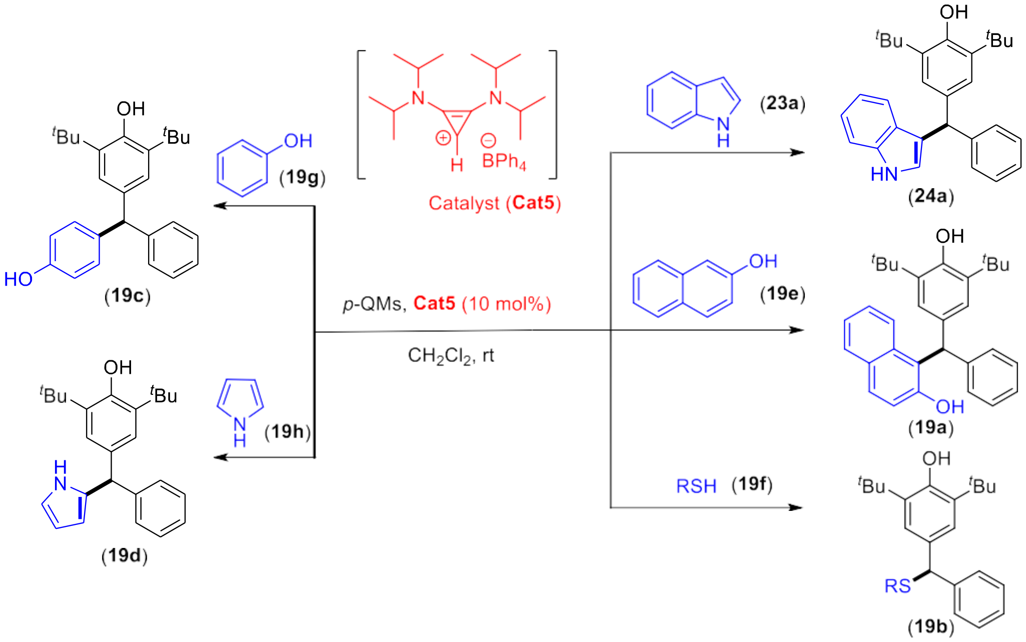
Scheme 17: Plausible mechanism of 7-membered ring formation via electrophilic cyclization

Later, Anand's group reported a Bi(OTf)3 catalyzed, solvent-free approach towards 1,6-conjugate addition of 3-substituted indoles (**18a**) to *p*-QMs (**18b**).[38] This leads to the synthesis of unsymmetrical diaryl(2-indolyl)methanes (**18c**).



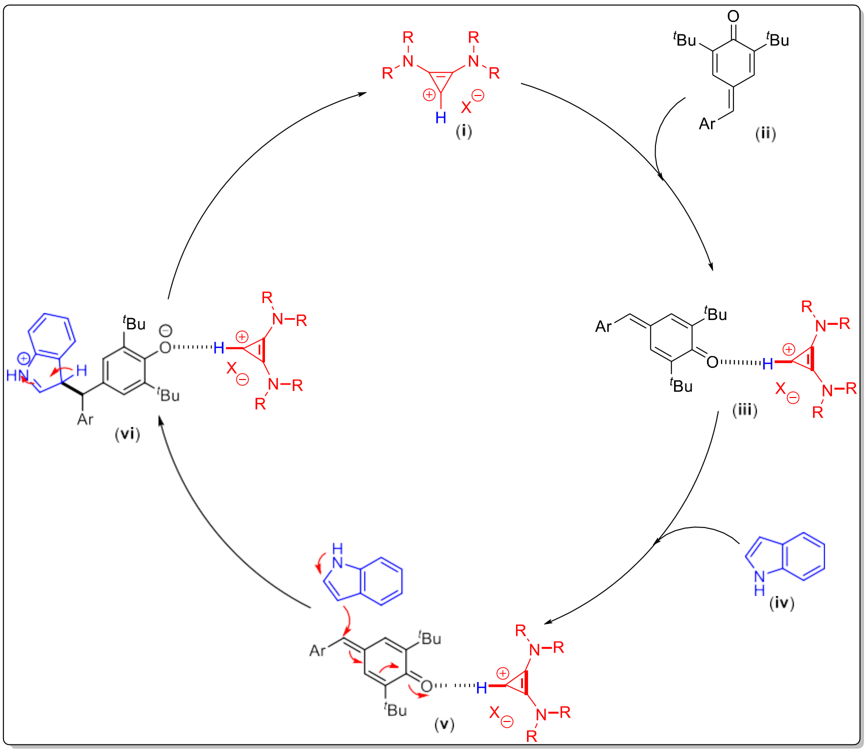
Scheme 18: Lewis acid catalyzed synthesis of unsymmetrical diaryl(2-indloyl)methane

In addition, Anand and co-workers reported a bis(amino)cyclopropenium (BAC) (**Cat5**) catalyzed 1,6-conjugate addition of nucleophiles (**23a, 19e-h**) to *p*-QMs (**Scheme 19**).[39] This catalyst acts as an H-bond donor. They used indoles, 2-naphthols, thiols, phenols and pyrroles and in all the cases they got good results.



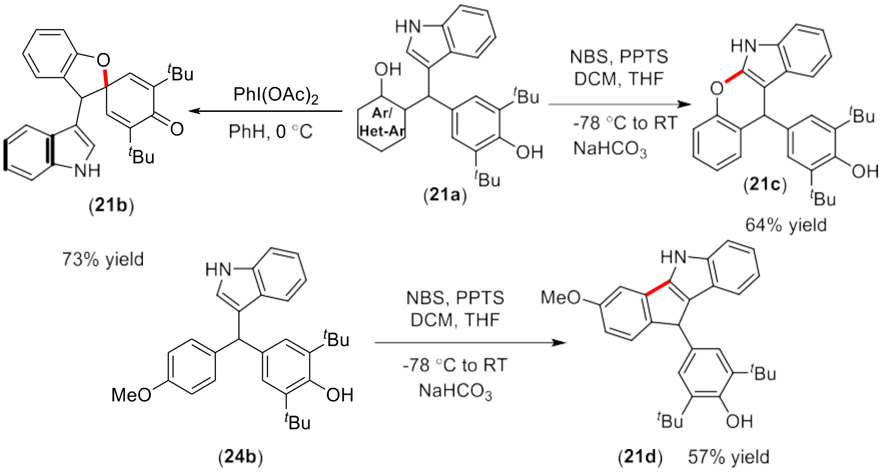
Scheme 19: BAC catalyzed 1,6-conjugate addition of nucleophiles to *p*-QMs

Initially, the catalyst (**i**) coordinates with the carbonyl group of the *p*-QM (**ii**) by H-bonding forming a complex (**iii**). Then indole (**iv**) adds in 1,6- fashion to the *p*-QM. Later, rearomatization happens through the removal of hydrogen (**vi**). And during that process, the catalyst gets detached and revives (**Scheme 20**).



Scheme 20: Plausible mechanism of BAC catalysis

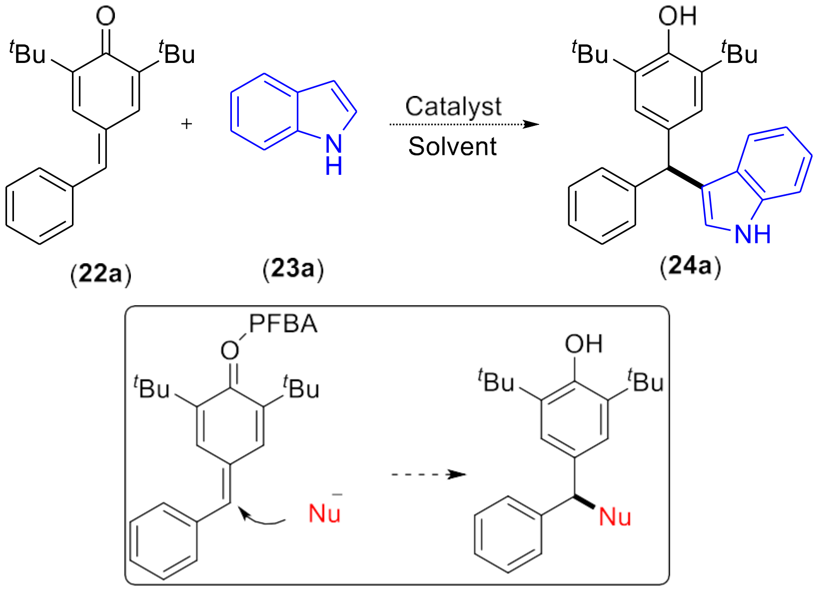
This diaryl(3-indolyl)methanes (**21a** & **24b**) can be further derivatized. As shown in **scheme 21**, **21a** can be oxidized with (diacetoxyiodo)benzene to get spirocyclic compound (**21b**). Again, this can be treated with NBS, PPTS and $NaHCO_3$ to get dihydrochromeno[2,3-b]indole (**21c**) in 64% yield. When **24b** was treated with NBS, PPTS and $NaHCO_3$, indene-fused indole (**21d**) was obtained in 57% yield.



Scheme 21: Further derivatization of diaryl(3-indolyl)methanes

2.2. Our Hypothesis

Based on the previously mentioned scientific literature reports, we hypothesized that **A1** can act as a Lewis or Brønsted acid and can coordinate with the carbonyl group of *p*-QM and activate it.



Scheme 22: Hypothesis of the present work

At this point, we anticipated that the *p*-QM moiety could be activated by the **A1** through carbonyl activation and thereby enabling the *p*-QM moiety more susceptible to nucleophilic attack at the 6th position (**Scheme 22**). Based on this hypothesis, we have developed an efficient protocol for the synthesis of unsymmetrical indolyldiarylmethanes through 1,6-conjugate addition of indoles to *p*-QMs using **A1** as a catalyst and the results are summarized in section (**Section 2.3**).

The unsymmetrical triarylmethanes are very important compounds not only in drug discovery but also in the dye industry and medicinal chemistry. These triarylmethanes have come up as essential architectural motifs, often found in many biologically active pharmaceuticals molecules (**Fig. 1.5)**. Some of their derivatives show interesting therapeutic activities such as antitumour, anticancer, anti-inflammatory activities.

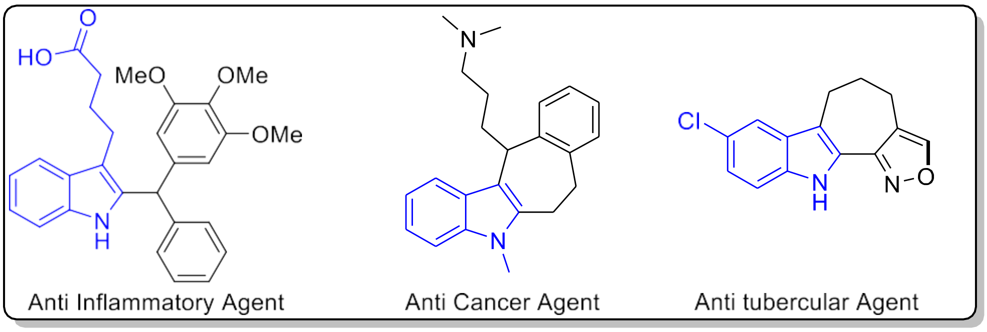
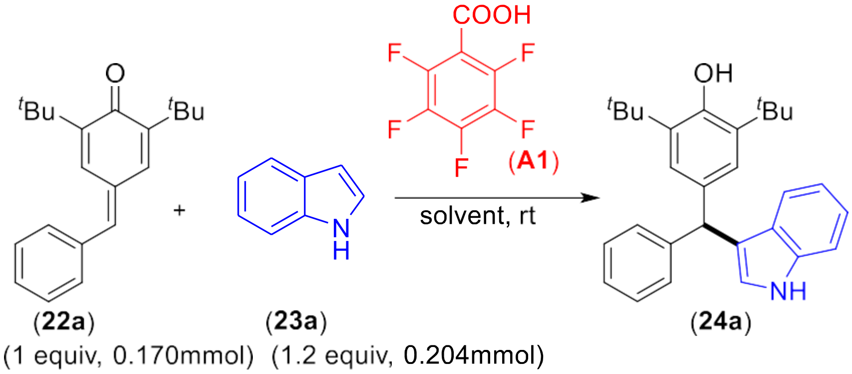


Figure 1.5: Biologically active pharmaceuticals molecules

2.3. Present Work

The results of **A1** catalyzed 1,6-conjugate addition of indoles to *p*-QMs are discussed in this section. The optimization studies have been conducted using *p*-QM (**22a**) and Indole (**23a**) using **A1** as a catalyst under various conditions and the results are summarized in Table **2.1.**



Scheme 23: Optimization of the current work

Table 2.1 Catalyst screening and optimization.

Entry	Catalyst (**A1**) (mol%)	Solvent	Time	Yield (%)
1	10	THF	24 h	NR
2	10	Toluene	5 h	Trace
3	**10**	**CH_2Cl_2**	**4 h**	**81**
4	10	MeCN	4 h	75
5	10	DMF	24 h	NR
6	10	DMSO	24 h	NR
7	10	$CHCl_3$	4 h	75
8	10	DCE	4 h	81
9	15	CH_2Cl_2	4 h	81
10	20	CH_2Cl_2	4 h	81
11	-	CH_2Cl_2	48 h	NR

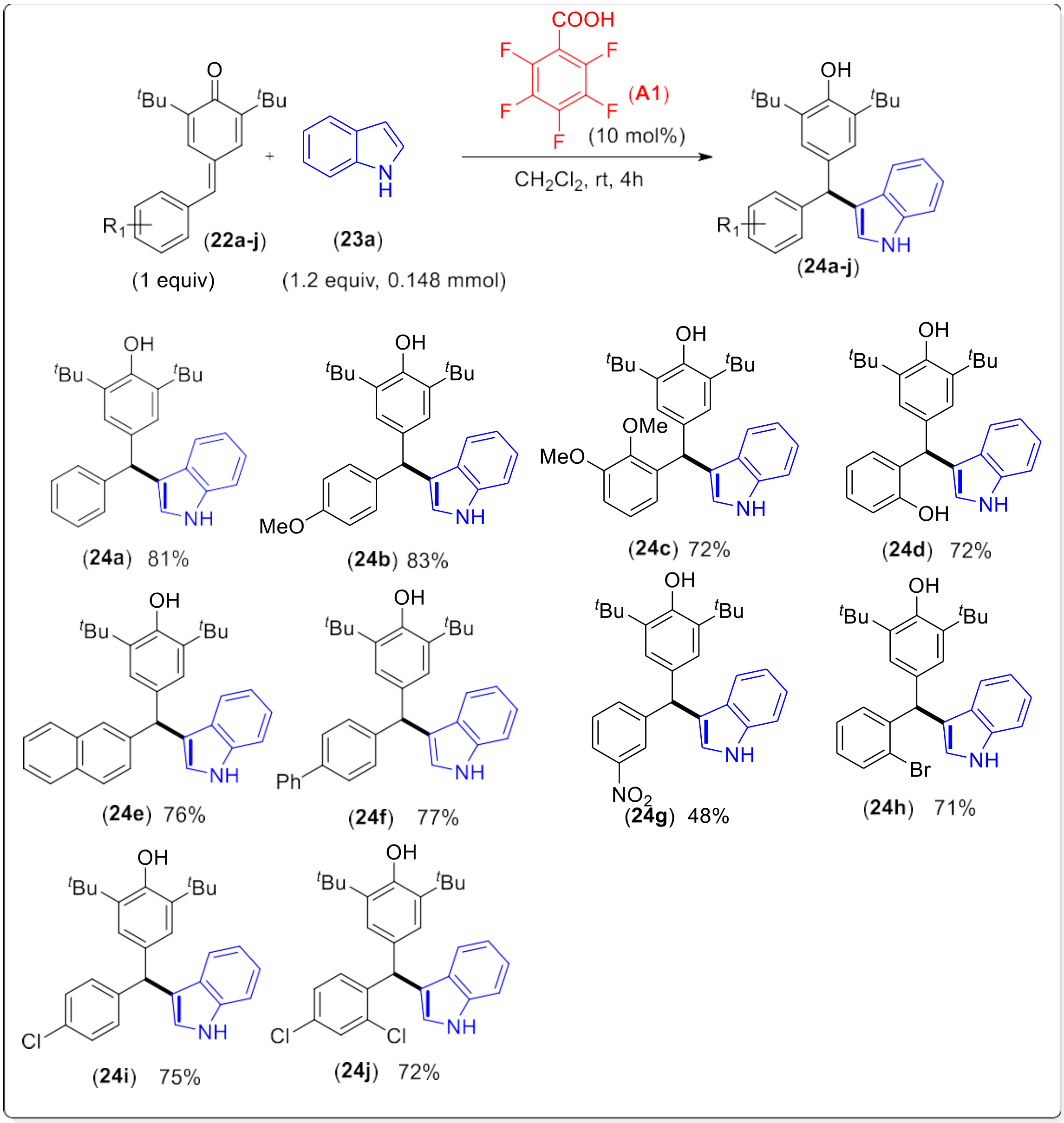
Reaction Conditions: All reactions were carried out with **22a** (0.170 mmol), **23a** (0.204 mmol) in solvent (1.5 ml). Yields reported are isolated yields.

Initially, a reaction between **22a** and **23a** were performed using 10 mol % of **A1** using THF as a solvent, and no reaction took place (Entry **1**, **Table 2.1**). Then, further optimization studies were performed using other solvents such as toluene, DCM, MeCN, DMF, DMSO etc. (Entries 2-8, **Table 2.1**). The reaction was taking place only in the case of chlorinated solvents and MeCN. In the cases of DMF and DMSO, no reaction took place even after 24 hrs. We found that the yield is highest in the case of DCM and DCE when compared to other solvents. As DCM is cheaper, we thought of using DCM as our optimized solvent for further studies. The reaction was complete within 4 h and the desired product **24a** was isolated in 81% yield (Entry 3, **Table 2.1**). When the reaction was also performed using 15 and 20 mol% of **A1** in DCM, no further improvement either in the reaction time or the chemical yield of **24a** was observed (Entries 9 & 10, **Table 2.1**). This clearly shows that 10 mol% of

A1 is good enough to push the reaction in the forward direction. The reaction did not work without the catalyst **A1**, which clearly indicates that **A1** is acting as a catalyst (Entry 11, **Table 2.1**).

It is evident from **Table 2.2** that various electron-withdrawing and electron-donating groups present on aryl ring of *p*-QMs, in all cases the desired product was obtained in moderate to good yields with low catalyst load and short time for reaction. In the case of *p*-QMs derived from *p*-methoxy benzaldehyde (**23b**) and 2,3-dimethoxy benzaldehyde (**23c**), the desired products (**24b** & **24c**) were obtained in 83 & 72% yield respectively. The *p*-QMs derived from salicylaldehyde (**22d**), 2-naphthaldehyde (**22e**) and biphenyl-4-carboxaldehyde (**22f**), the major products (**24d-f**) were obtained in moderate to good yields. Interestingly, the *p*-QMs derived from 3-Nitrobenzaldehyde (**22g**) which is an electron-poor aldehyde and other *p*-QMs (**22h-j**) derived from halo-substituted benzaldehydes also shows conversion to their respective products **24g-j** in moderate to good yields under the optimized conditions. As **22b** shows maximum yield, further studies were done by using it.

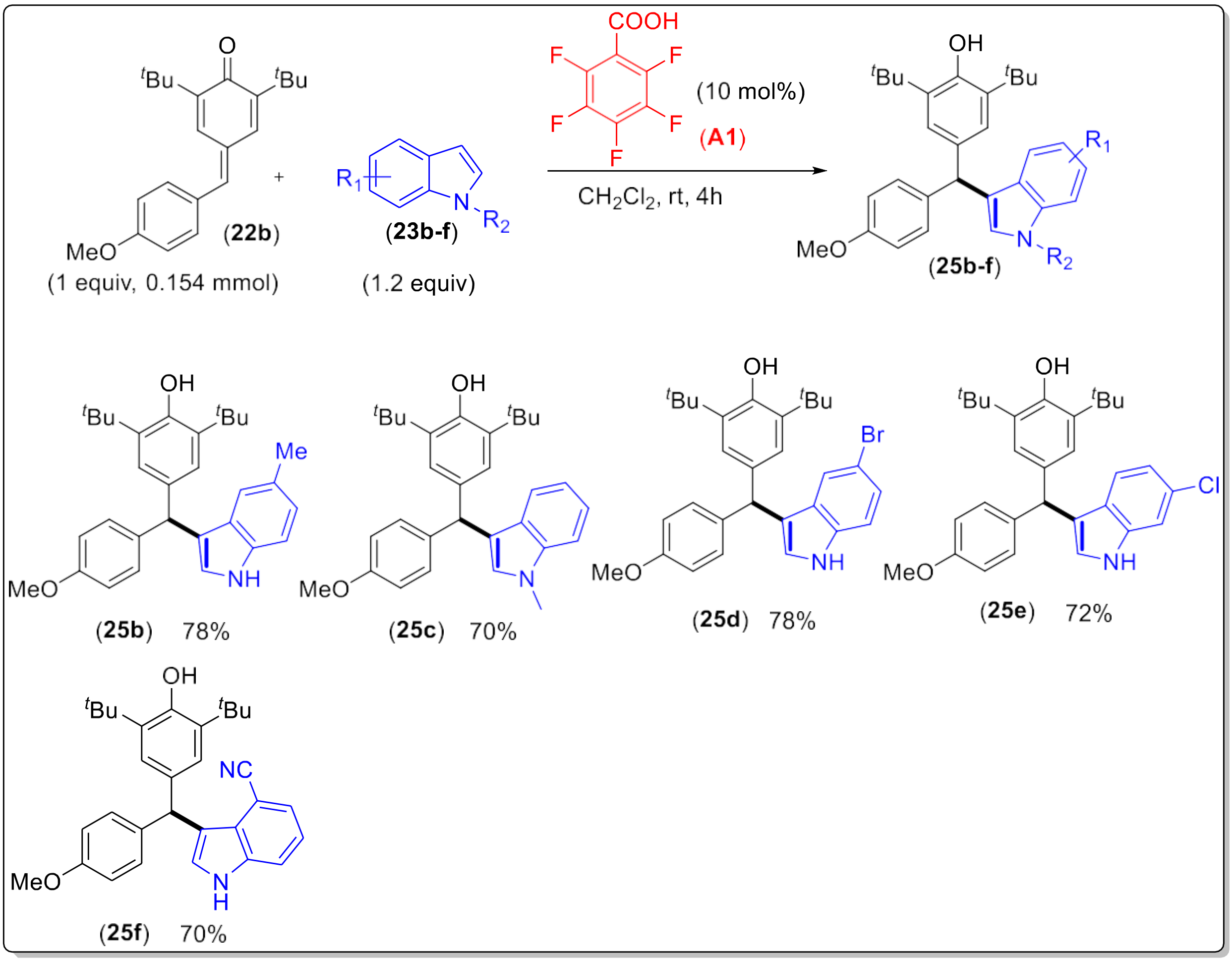
Table 2.2 Substrate scope with different *para*-quinone methides



Reactions conditions: All reactions were carried out with a 50 mg scale of **22a-j** in 1.5ml of CH_2Cl_2. Yields reported are isolated yields.

The substrate scope for this reaction was further studied using various substituted indoles and the results are summarized in **Table 2.3**. Most of the indoles, irrespective of the substituent attached to them, reacted under optimized conditions to give the products similar yields. Alkyl-substituted indoles such as 5-methyl (**23b**) or N-methylindole (**23c**) reacted with **22b** and produced the respective products **25b** and **25c** in 78 & 70% yields respectively. Halo-substituted indoles (**23d** & **23e**) also reacted with **22b** and gave the products **25d** & **25e** in good yields. Interestingly, electron-poor indole **23f** also provided the desired product **25f** in good yields.

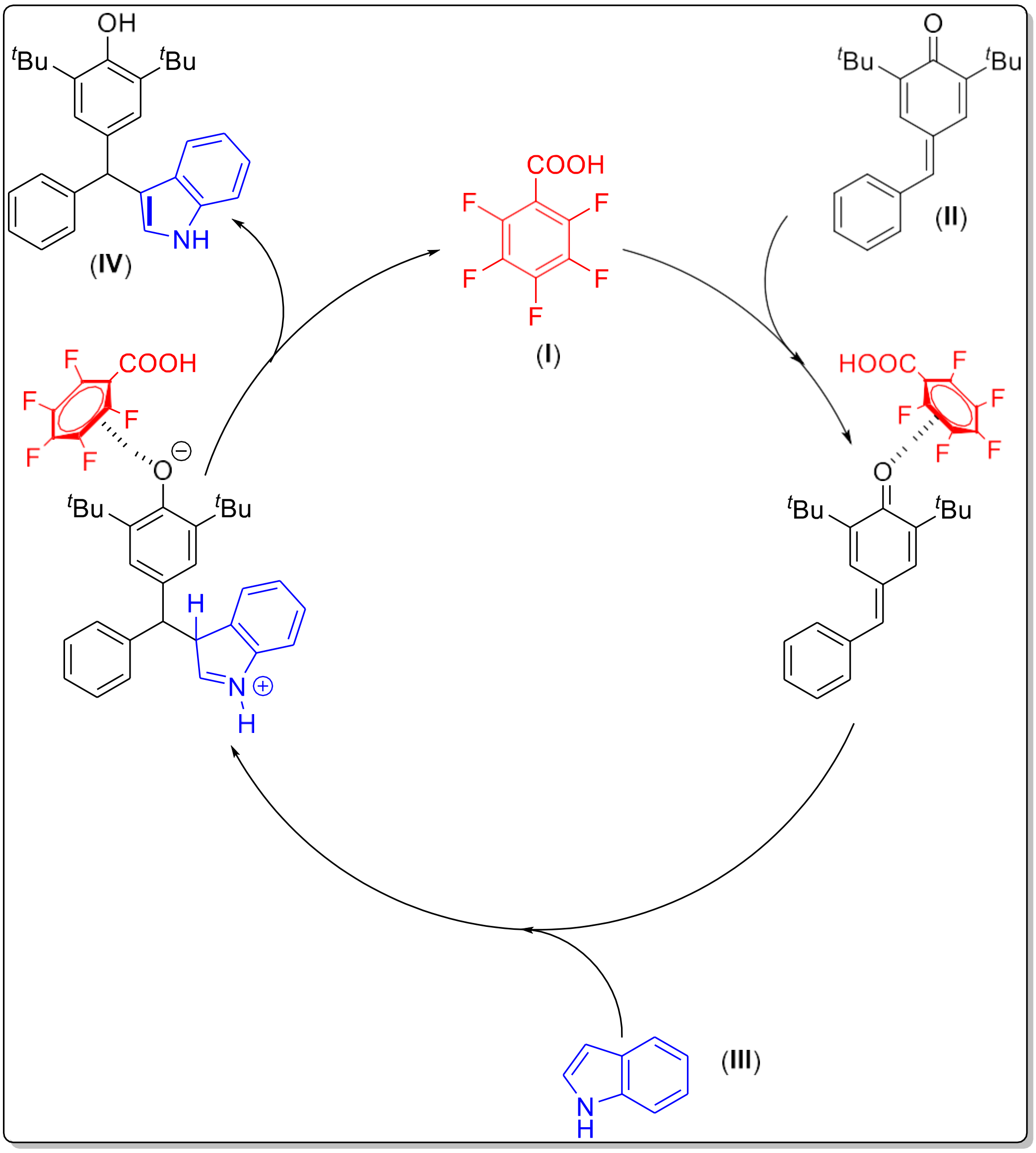
Table 2.3 Substrate scope with different Indoles



Reactions conditions: All reactions were carried out with 50 mg scale of **22b** in 1.5ml of CH_2Cl_2. Yields reported are isolated yields.

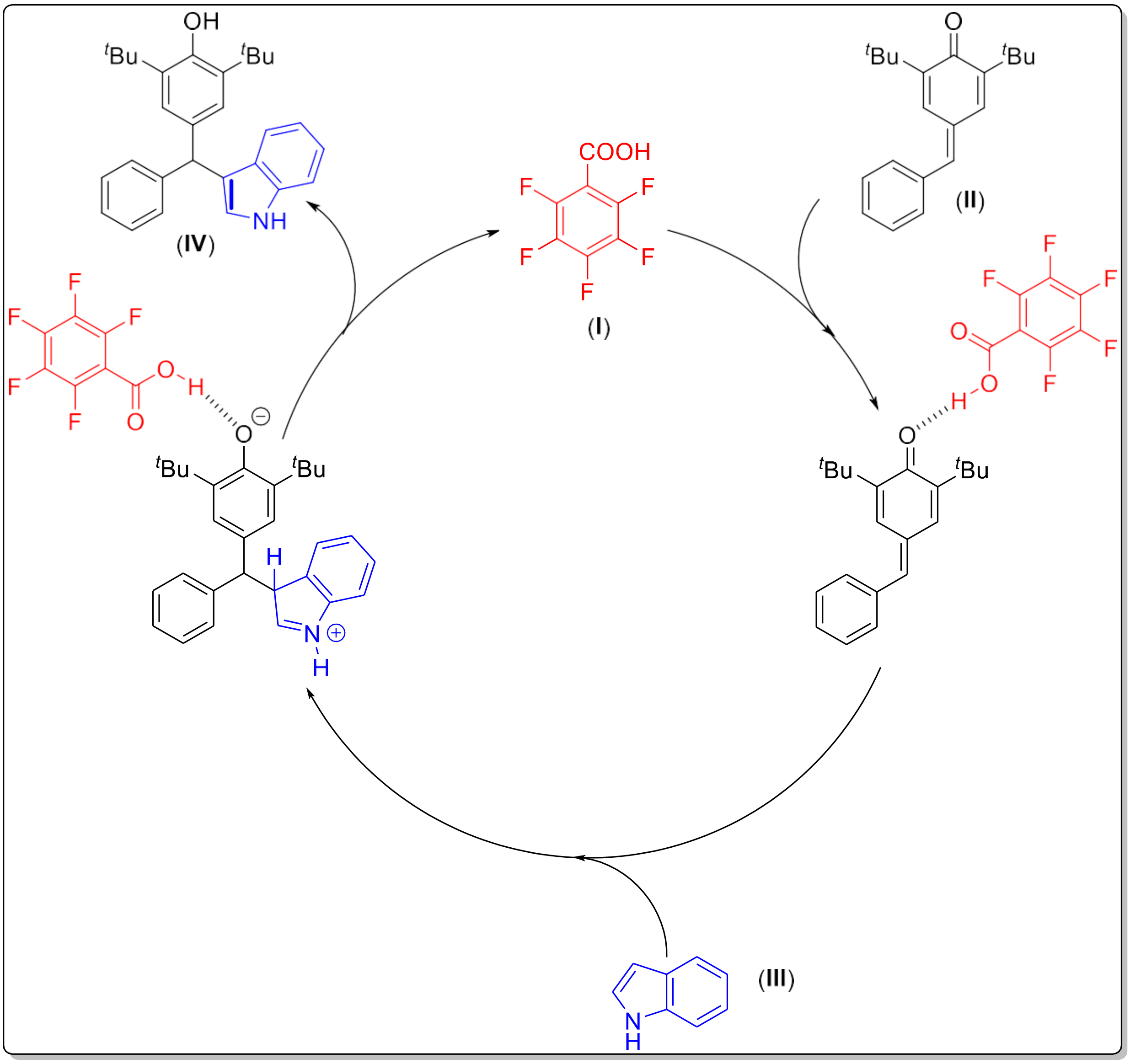
2.3. The Plausible mechanism

Based on the outcome of the reaction, we proposed a plausible mechanism for this transformation (**Scheme 24**) where PFBA acts as a Lewis acid. Initially, the PFBA (**I**) activates the carbonyl group of the *p*-QM (**II**) thereby increasing the electrophilicity of the C-6 carbon. Nucleophilic addition of indole (**III**) followed by proton transfer provided the product (**IV**).



Scheme 24: Plausible mechanism of the current work with PFBA acting as Lewis Acid

Alternatively, the PFBA (**I**) can act as a Brønsted acid as the carboxyl group is highly electron deficient due to the presence of five fluorine group attached to it (**Scheme 25**). The hydrogen of the carboxyl group easily coordinates with the carbonyl group of the *p*-QM (**II**) and activate it for further reaction. This in turn increases the electrophilicity of C-6 carbon and the reaction proceeds in a similar pathway as mentioned above.



Scheme 25: Plausible mechanism of the current work with PFBA acting as Brønsted Acid

Chapter 3

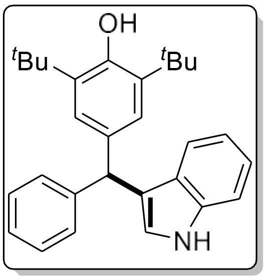
Experimental Section

All reactions were carried out under an argon atmosphere in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents, starting materials and the **A1** catalyst were purchased from commercial sources and used as such. All *p*-QMs were prepared by following a literature procedure. ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ (400 and 100 MHz respectively) on Bruker FT–NMR spectrometer at IISER Mohali. Chemical shift (δ) values are reported in ppm relatives to TMS and the coupling constants i.e., J values are reported in Hz. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ staining. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as eluent.

General procedure for the 1,6-conjugate addition of indoles to p–quinone methides:

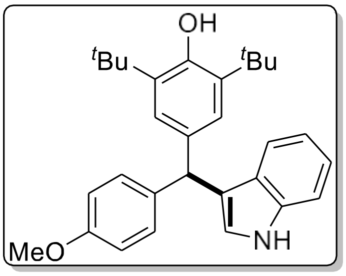
Anhydrous DCM (1.5 mL) was added to the mixture of *p*-quinone methide (**22b**) (0.154 mmol), Indole (**23a**) (0.185 mmol), catalyst (**A1**) (0.0154 mmol) under argon atmosphere and the resulting suspension was stirred at room temperature. After the reaction was complete (based on TLC analysis), the reaction mixture was concentrated under reduced pressure. The residue was then purified through a silica gel column, using EtOAc/Hexane mixture as an eluent, to get the pure product.

4-((1*H*-indol-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (24a)[39]



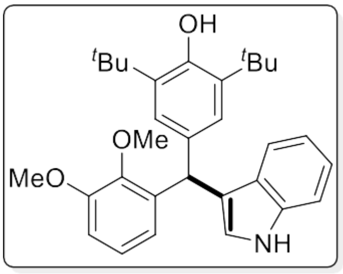
The reaction was performed at 0.1698 mmol scale of **22a**; R$_f$ = 0.5 (5% EtOAc in hexane); Yellowish white solid (56.6 mg, 81% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.26 (m, 5H), 7.26 – 7.17 (m, 2H), 7.1 (s, 2H), 7.02 (t, J= 7.48 Hz, 1H), 6.64 (d, J= 0.96 Hz, 1H), 5.62 (s, 1H), 5.11 (s, 1H), 1.41 (s, 18H).

4-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)-2,6-di-*tert*-butylphenol (24b)[39]



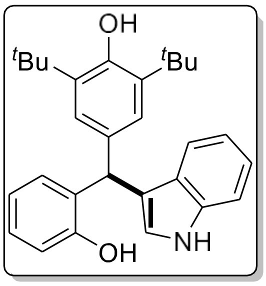
The reaction was performed at 0.1541 mmol scale of **22b**; R$_f$ = 0.3 (5% EtOAc in hexane); Yellowish white solid (56.5 mg, 83% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (s, 1H), 7.36 (d, *J* = 8.16 Hz 1H), 7.28 (d, *J* = 6.96 Hz 1H), 7.22 – 7.16 (m, 3H), 7.09 (s, 2H), 7.04 – 6.99 (m, 1H), 6.85 (d, *J* = 8.68 Hz 2H), 6.62 (s, 1H), 5.57 (s, 1H), 5.11 (s, 1H), 3.82 (s, 3H), 1.41 (s, 18H).

2,6-di-*tert*-butyl-4-((2,3-dimethoxyphenyl)(1*H*-indol-3-yl)methyl)phenol (24c)[39]



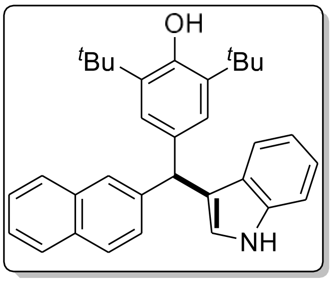
The reaction was performed at 0.1410 mmol scale of **22c**; R$_f$ =0.2 (5% EtOAc in hexane); White sticky solid (47.9 mg, 72% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (s,1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 7.28 Hz, 1H), 7.16 (t, *J* = 7.64 Hz, 1H), 7.11 (s, 1H), 7.01 (t, *J* = 7.58 Hz, 1H), 6.94 (t, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 8.08, 1H), 6.73 (d, *J* = 7.72 Hz, 1H), 6.67 (s, 1H), 6.05 (s, 1H), 5.05 (s, 1H), 3.91 (s, 3H), 3.61 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.6, 151.9, 146.7, 138.9, 136.7, 135.2, 134.4, 127.2, 125.6, 124.0, 123.4, 121.8, 121.7, 120.6, 120.1, 119.1, 110.9, 110.2, 60.4, 55.7, 41.5, 34.3, 30.4.

2,6-di-*tert*-butyl-4-((2-hydroxyphenyl)(1*H*-indol-3-yl)methyl)phenol (24d)[39]



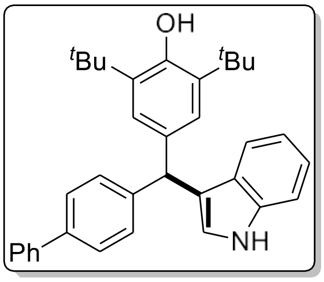
The reaction was performed at 0.1610 mmol scale of **22d**; R_f = 0.2 (5% EtOAc in hexane); brown solid (49.58 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.38 (d, *J* = 8.28 Hz, 1H), 7.34 (d, *J* = 8.32 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.14 (s, 2H), 7.08 – 7.03 (m, 2H), 6.93 – 6.85 (m, 2H), 6.72 (s, 1H), 5.73 (s, 1H), 5.22 (s, 1H), 5.18 (s, 1H), 1.41 (s, 18H).

4-((1*H*-indol-3-yl)(naphthalen-2-yl)methyl)-2,6-di-*tert*-butylphenol (24e)[39]



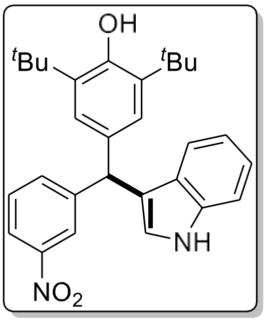
The reaction was performed at 0.1451 mmol scale of **22e**; R_f = 0.3 (5% EtOAc in hexane); Yellowish white solid (50.9 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.96 Hz, 1H), 7.91 – 7.85 (m, 2H), 7.75 (d, *J* = 8.24 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.39 – 7.33 (m, 2H), 7.27 (d, *J* = 8.92 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.10 (s, 1H), 7.00 (t, *J* = 6.64 Hz, 1H), 6.52 (s, 1H), 6.36 (s, 1H), 5.07 (s, 1H), 1.37 (s, 18H).

4-([1,1'-biphenyl]-4-yl(1*H*-indol-3-yl)methyl)-2,6-di-*tert*-butylphenol (24f)[39]



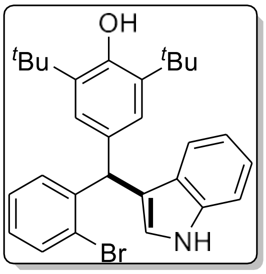
The reaction was performed at 0.1349 mmol scale of **22f**; R_f = 0.4 (5% EtOAc in hexane); Yellowish white solid (50.7 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.66 (d, *J* = 7.68 Hz, 2H), 7.57 (d, *J* = 7.84 Hz, 2H), 7.47 (t, *J* = 7.58 Hz, 2H), 7.41 – 7.33 (m, 5H), 7.22 (t, *J* = 7.64 Hz, 1H), 7.15 (s, 2H), 7.05 (t, *J* = 7.54 Hz, 1H), 6.69 (s, 1H), 5.67 (s, 1H), 5.14 (s, 1H), 1.44 (s, 18H).

4-((1*H*-indol-3-yl)(3-nitrophenyl)methyl)-2,6-di-*tert*-butylphenol (24g)[39]



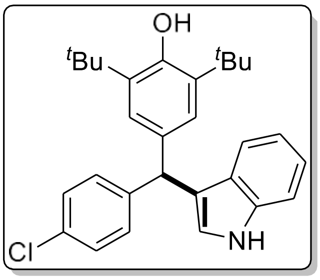
The reaction was performed at 0.1473 mmol scale of **22g**; R$_f$ = 0.3 (5% EtOAc in hexane); yellowish white solid (32.3 mg, 48% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (s, 1H), 8.13 – 8.07 (m, 2H), 7.63 (d, *J* = 7.72 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.07 (s, 2H), 7.03 (d, *J* = 7.48 Hz, 1H), 6.67 (s, 1H), 5.71 (s, 1H), 5.18 (s, 1H), 1.41 (s, 18H).

4-((2-bromophenyl)(1*H*-indol-3-yl)methyl)-2,6-di-*tert*-butylphenol (24h)[39]



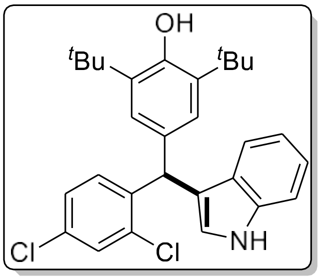
The reaction was performed at 0.1339 mmol scale of **22h**; R$_f$ = 0.3 (5% EtOAc in hexane); Yellowish white solid (46.6 mg, 71% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (s, 1H), 7.62 (d, *J* = 7.92 Hz, 1H), 7.37 (d, *J* = 8.16, 1H), 7.25 (d, *J* = 8.08 Hz 1H), 7.22 – 7.19 (m, 3H), 7.13 – 7.07 (m, 3H), 7.03 (t, *J* = 7.56 Hz, 1H), 6.63 (s, 1H), 6.03 (s, 1H), 5.14 (s, 1H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.1, 143.7, 136.7, 135.4, 132.8, 132.4, 130.6, 127.7, 127.2, 127.0, 125.8, 125.1, 124.1, 122.1, 120.0, 120.0, 119.4, 111.0, 47.8, 34.4, 30.4.

2,6-di-*tert*-butyl-4-((4-chlorophenyl)(1*H*-indol-3-yl)methyl)phenol (24i)[39]



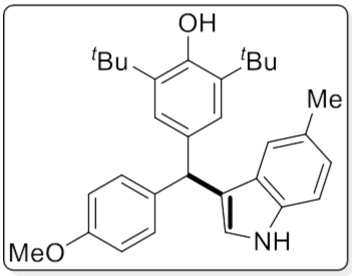
The reaction was performed at 0.1520 mmol scale of **22i**; R$_f$ = 0.4 (5% EtOAc in hexane); Yellowish white solid (50.8 mg, 75% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (s, 1H), 7.37 (d, *J* = 8.12 Hz, 1H), 7.30 –7.21 (m, 6H), 7.08 (s, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 5.59 (s, 1H), 5.14 (s, 1H) 1.41 (s, 18H).

2,6-di-*tert*-butyl-4-((2,4-dichlorophenyl)(1*H*-indol-3-yl)methyl)phenol (24j)[39]



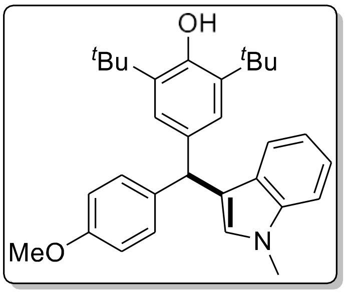
The reaction was performed at 0.1376 mmol scale of **22j**; R_f = 0.4 (5% EtOAc in hexane); Yellowish white solid (47.6 mg, 72% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.46 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.24 –7.19 (m, 2H), 7.15 – 7.09 (m, 2H), 7.07 (s, 2H), 7.04 (d, *J* = 8.24 Hz, 1H), 6.63 (s, 1H), 5.98 (s, 1H) 5.15 (s, 1H), 1.43 (s, 18H).

2,6-di-*tert*-butyl-4-((4-methoxyphenyl)(5-methyl-1*H*-indol-3-yl)methyl)phenol (25b)[39]



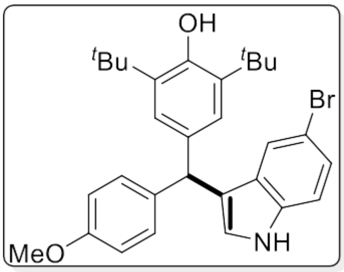
The reaction was performed at 0.1541 mmol scale of **22b**; R_f = *0.4* (5% EtOAc in hexane); Yellowish white solid (54.8 mg, 78% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.26 (d, *J* = 8.24 Hz, 1H), 7.20 (d, *J* = 8.12 Hz, 1H), 7.07 (s, 3H), 7.01 (d, *J* = 8.28 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 5.35 (s, 1H), 5.09 (s, 1H), 3.82 (s, 3H), 2.38 (s, 3H), 1.40 (s, 18H).

2,6-di-*tert*-butyl-4-((4-methoxyphenyl)(1-methyl-1*H*-indol-3-yl)methyl)phenol (25c)[39]



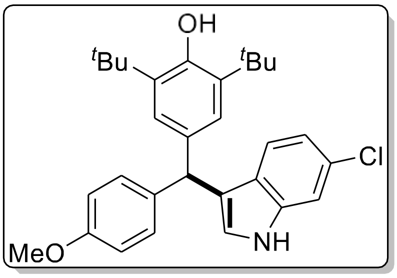
The reaction was performed at 0.1541 mmol scale of **22b**; R_f = 0.4 (5% EtOAc in hexane); Reddish orange solid (49.1 mg, 70% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.4 Hz, 1H), 7.28 (d, *J* = 6.24 Hz, 1H), 7.24-7.18 (m, 3H), 7.08 (s, 2H), 7.01 (t, *J* = 7.46 Hz, 1H), 6.85 (d, *J* = 8.68 Hz, 2H), 6.48 (s, 1H), 5.55 (s, 1H), 5.09 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 1.41 (s, 18H).

4-((5-bromo-1*H*-indol-3-yl)(4-methoxyphenyl)methyl)-2,6-di-*tert*-butylphenol (25d)[39]



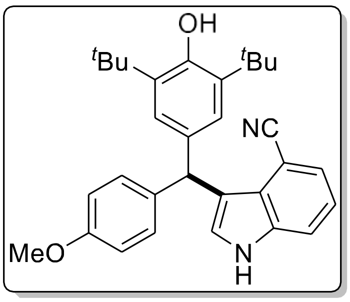
The reaction was performed at 0.1541 mmol scale of **22b**; R_f = 0.4 (5% EtOAc in hexane); Yellowish white solid (56.1 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$), *δ* 7.98 (s, 1H), 7.37 (s, 1H), 7.24 (s, 2H), 7.14 (d, J = 7.08 Hz, 2H), 7.02 (s, 2H), 6.84 (d, *J* = 7.0 Hz, 2H), 6.63 (s, 1H), 5.47 (s, 1H), 5.09 (s, 1H), 3.81 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.9, 152.1, 136.4, 135.4, 135.3, 134.3, 129.7, 128.8, 125.4, 124.9, 124.8, 122.7, 120.9, 113.6, 112.5, 112.4, 55.2, 47.7, 34.3, 30.7.

2,6-di-*tert*-butyl-4-((6-chloro-1*H*-indol-3-yl)(4-methoxyphenyl)methyl)phenol (25e)[39]

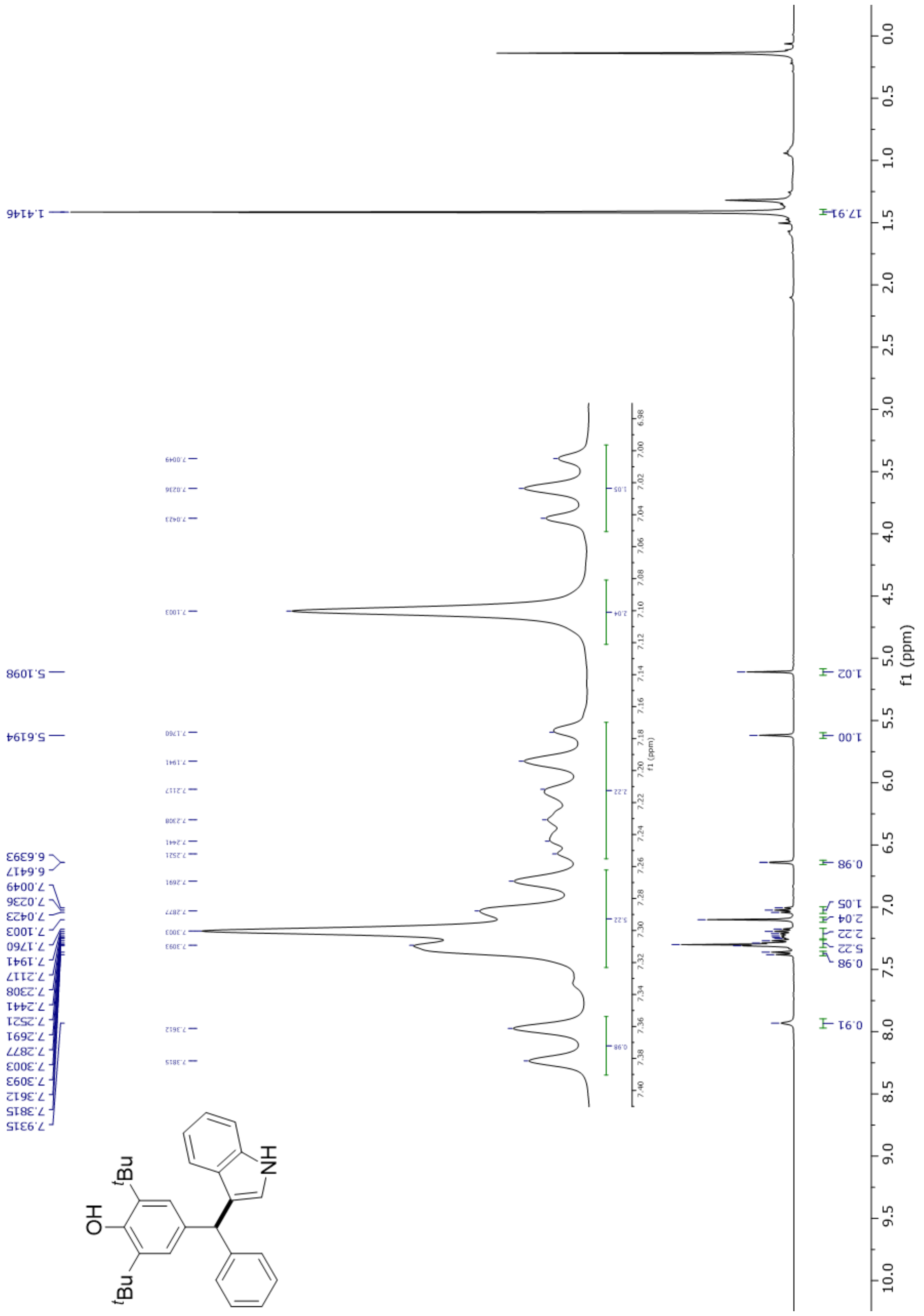


The reaction was performed at 0.1541 mmol scale of **22b**; R_f = 0.6 (5% EtOAc in hexane); Yellow white solid (52.8 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$), *δ* 7.94 (s, 1H), 7.34 (s, 1H), 7.15 (d *J* = 8.36 Hz, 2H), 7.11 (d, *J* = 8.44 Hz, 1H), 7.03 (s, 2H), 6.96 (d, *J* = 8.44 Hz, 1H), 6.84 (d, *J* = 8.36 Hz, 2H), 6.60 (s, 1H), 5.48 (s, 1H), 5.09 (s, 1H), 3.81 (s, 3H), 1.38 (s, 18H).

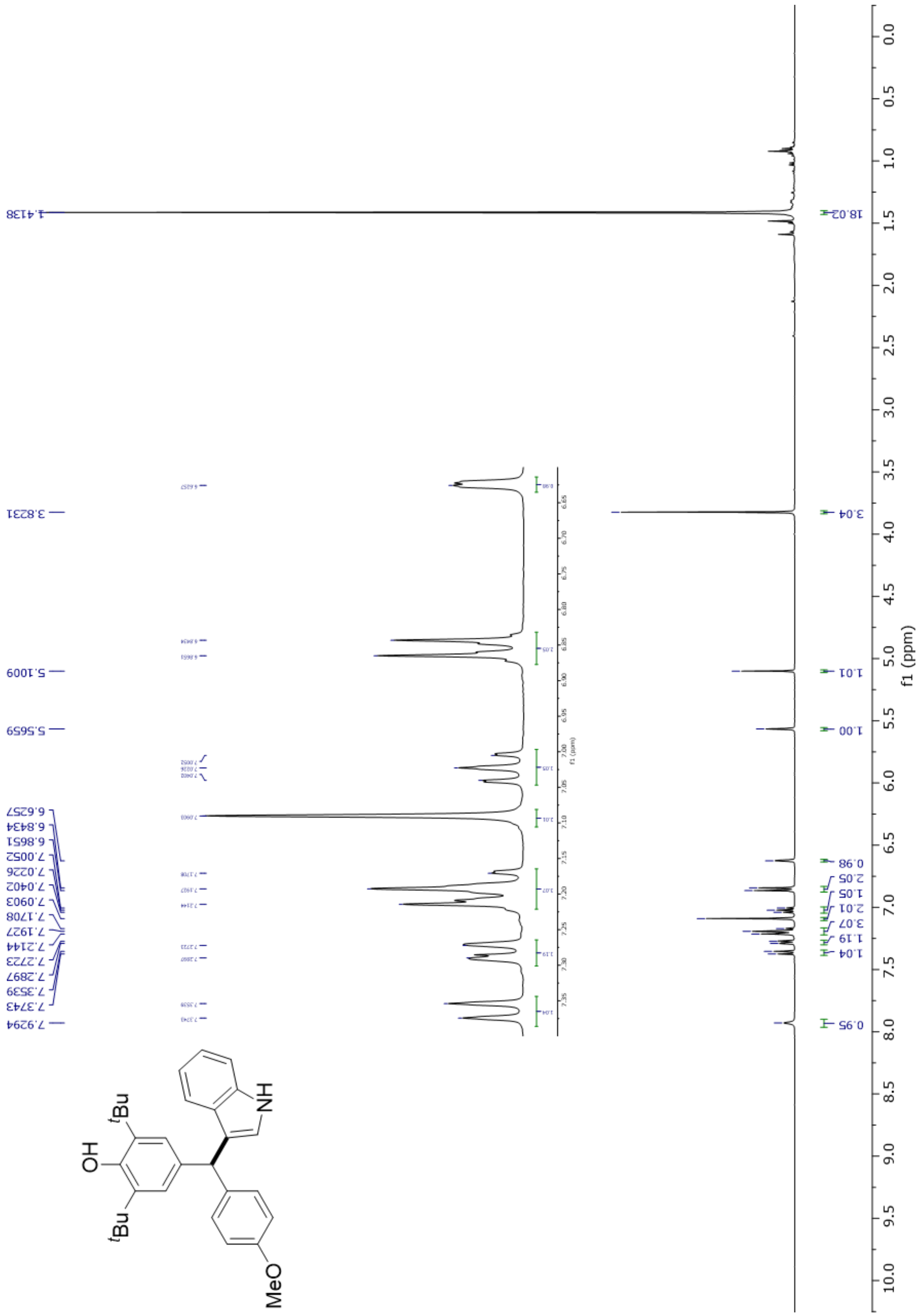
3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-1*H*-indole-4-carbonitrile (25f)[39]



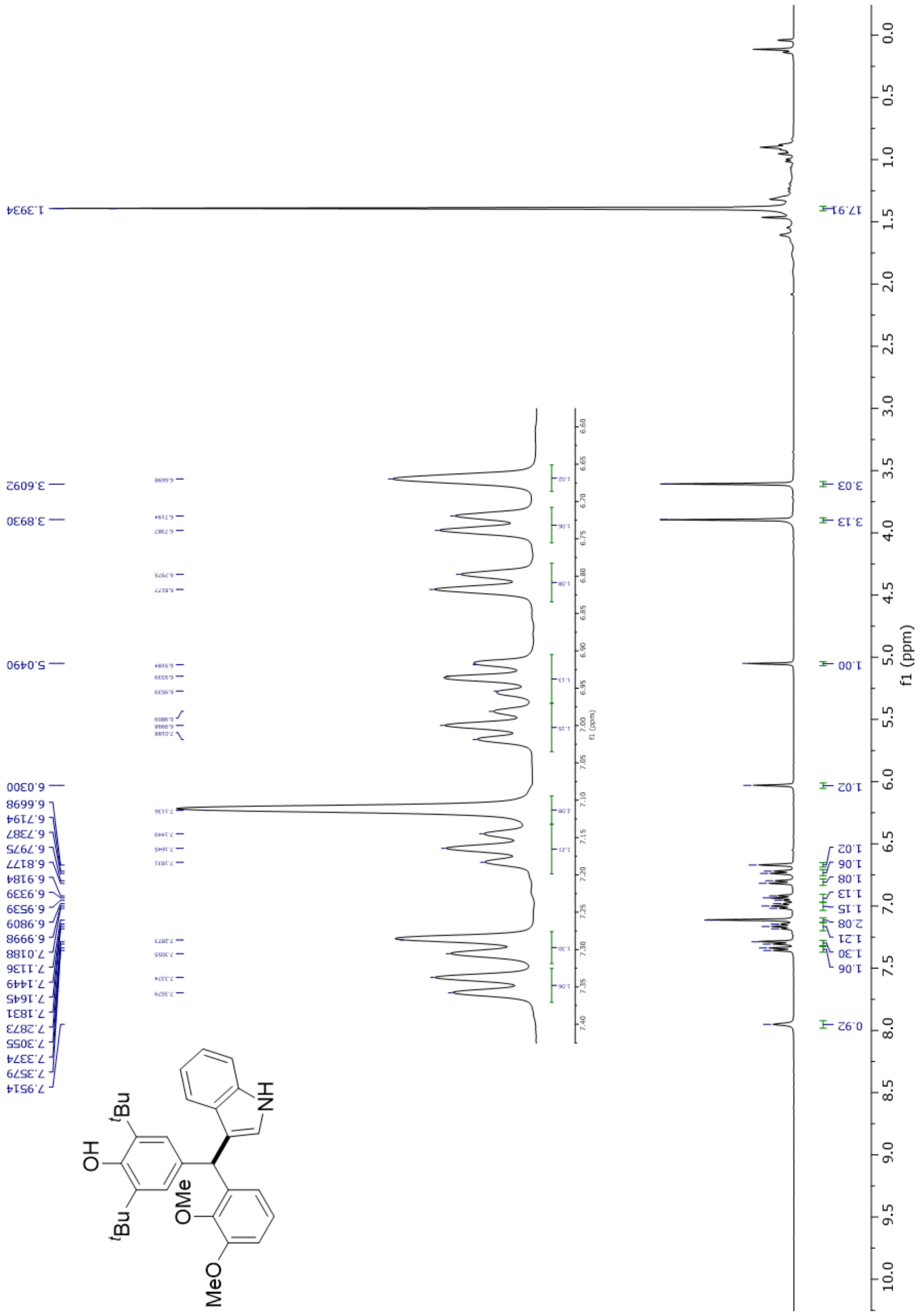
The reaction was performed at0.1541 mmol scale of **22b**; R_f = 0.3 (5% EtOAc in hexane); Yellowish white solid (50.3 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$), *δ* 8.31 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 7.36 Hz, 1H), 7.20 (t, *J* = 7.48 Hz, 1H), 7.13 (d *J* = 7.52 Hz, 2H), 7.03 (s, 2H), 6.83 (s, 1H), 6.81 (d, *J* = 7.9 Hz, 2H), 6.10 (s, 1H), 5.09 (s, 1H), 3.80 (s, 3H), 1.39 (s, 18H).



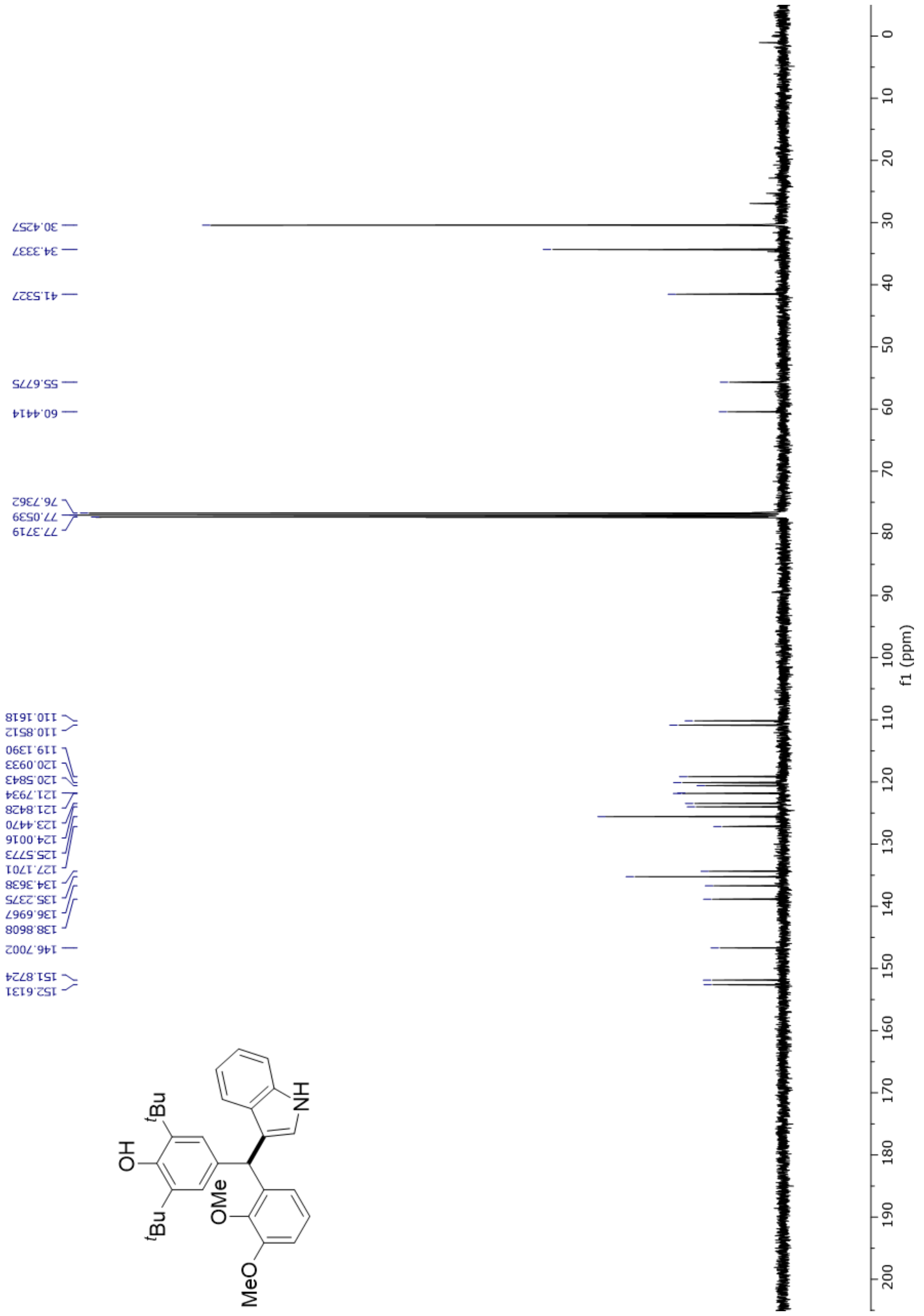
^{1}H NMR spectrum of **24a**



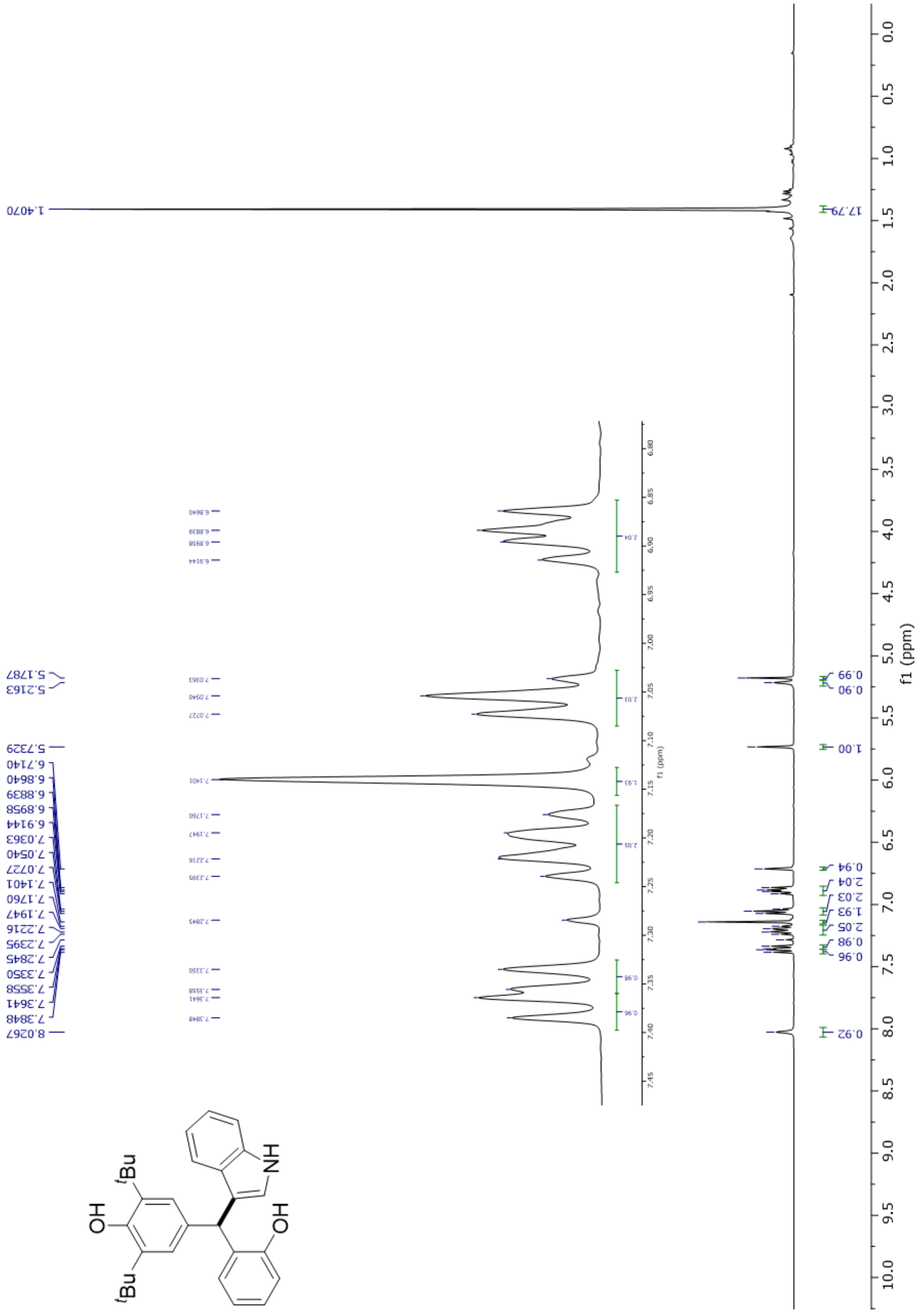
^{1}H NMR spectrum of **24b**



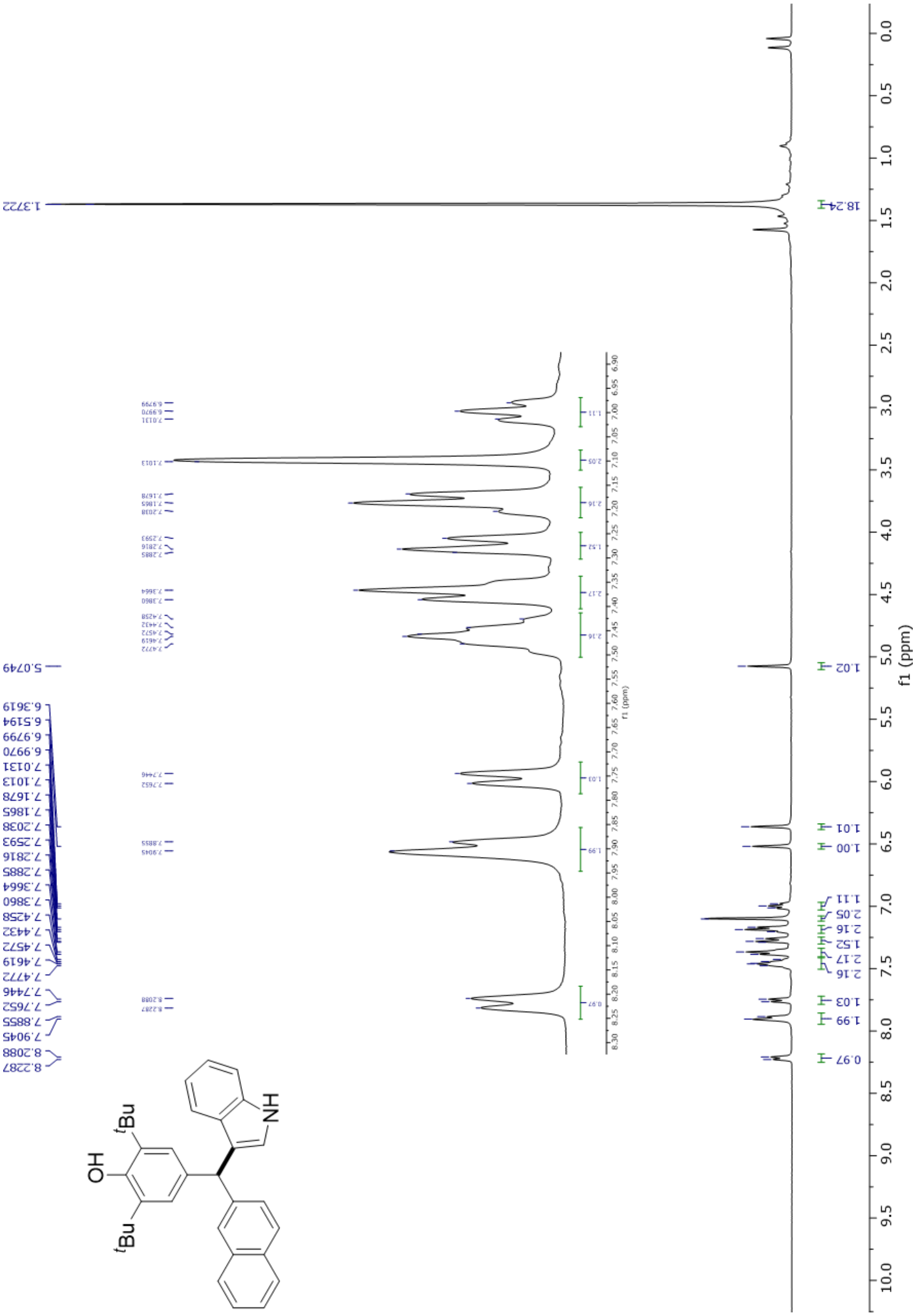
^{1}H NMR spectrum of **24c**



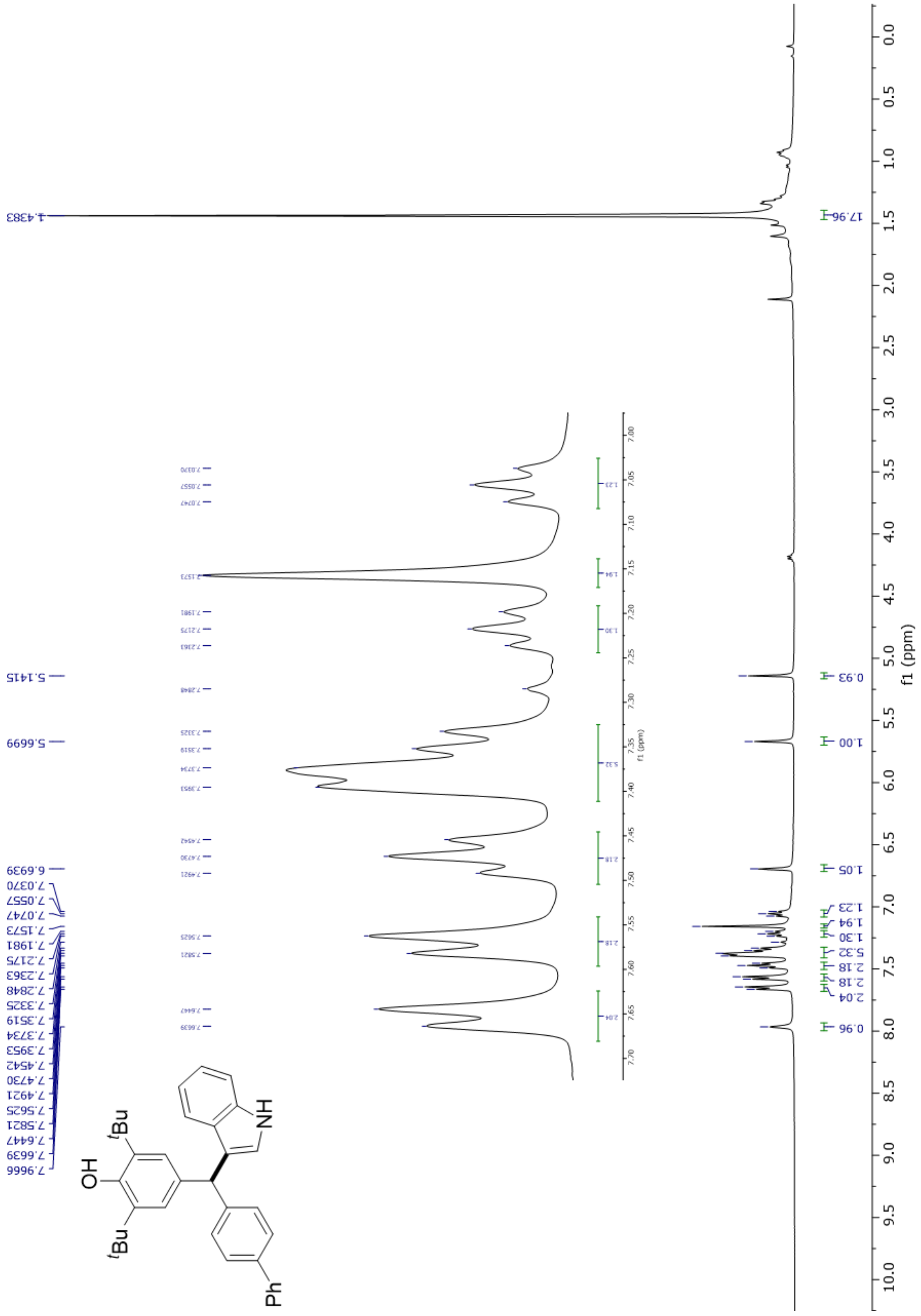
^{13}C NMR spectrum of **24c**



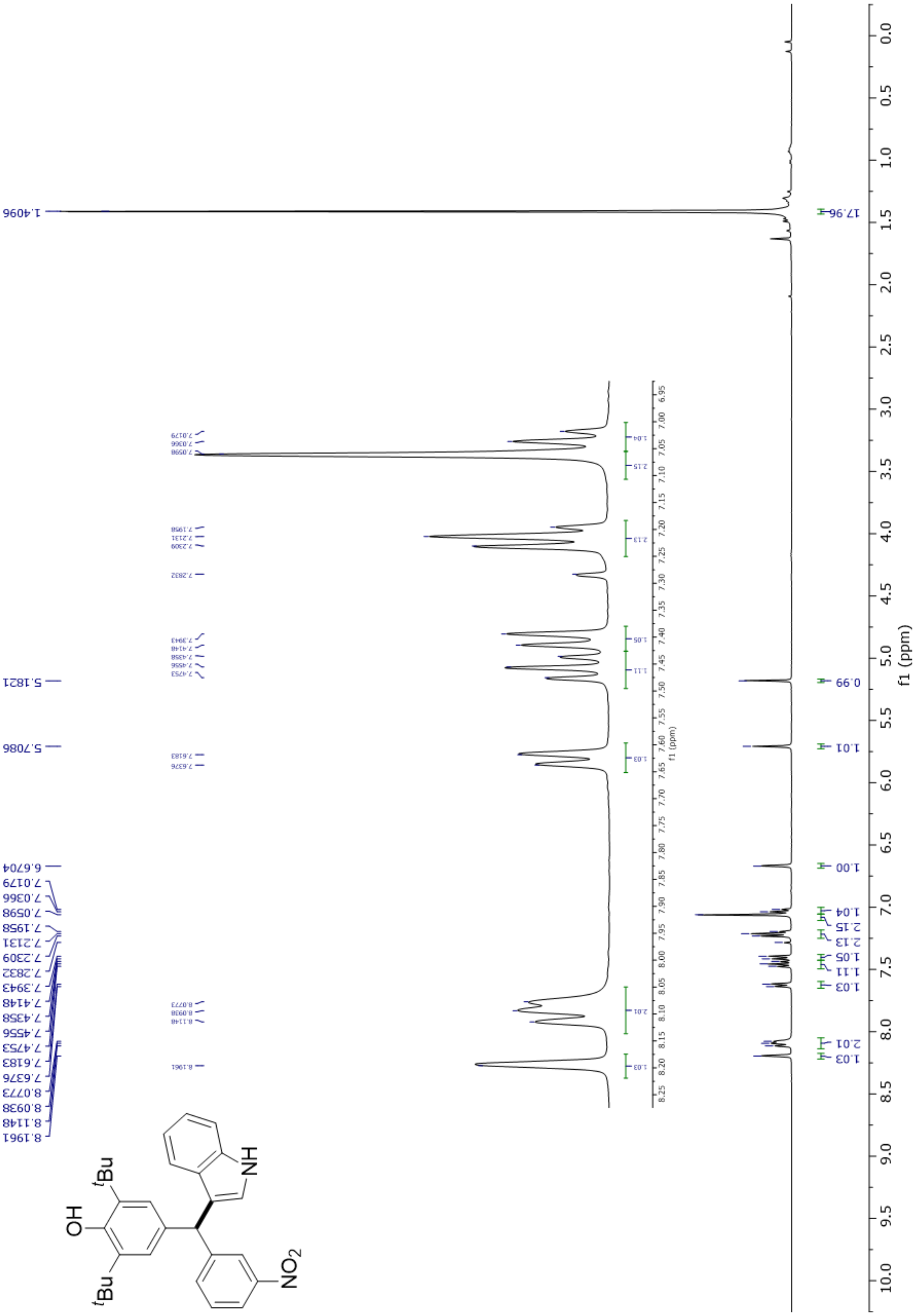
^{1}H NMR spectrum of **24d**



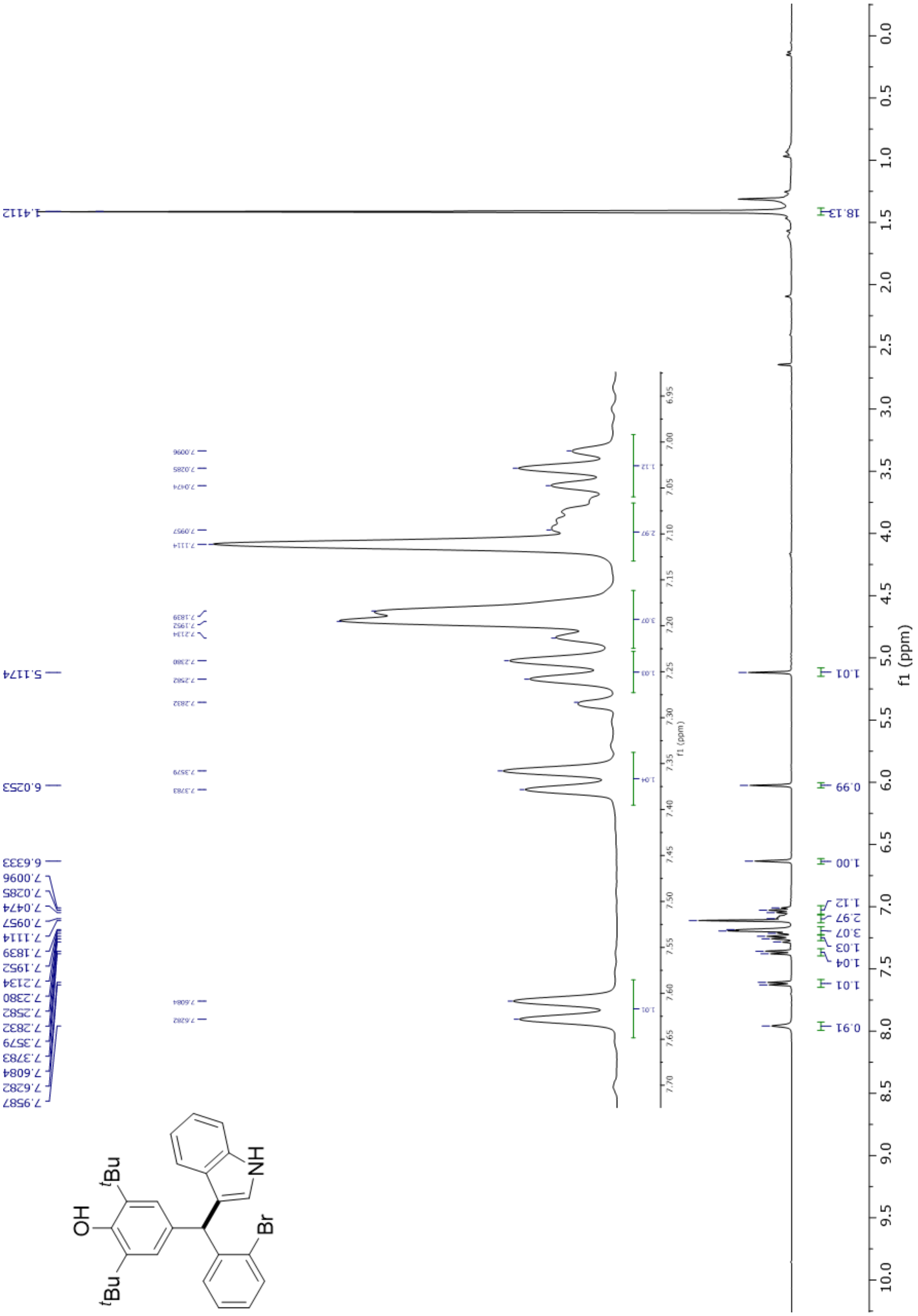
^{1}H NMR spectrum of **24e**



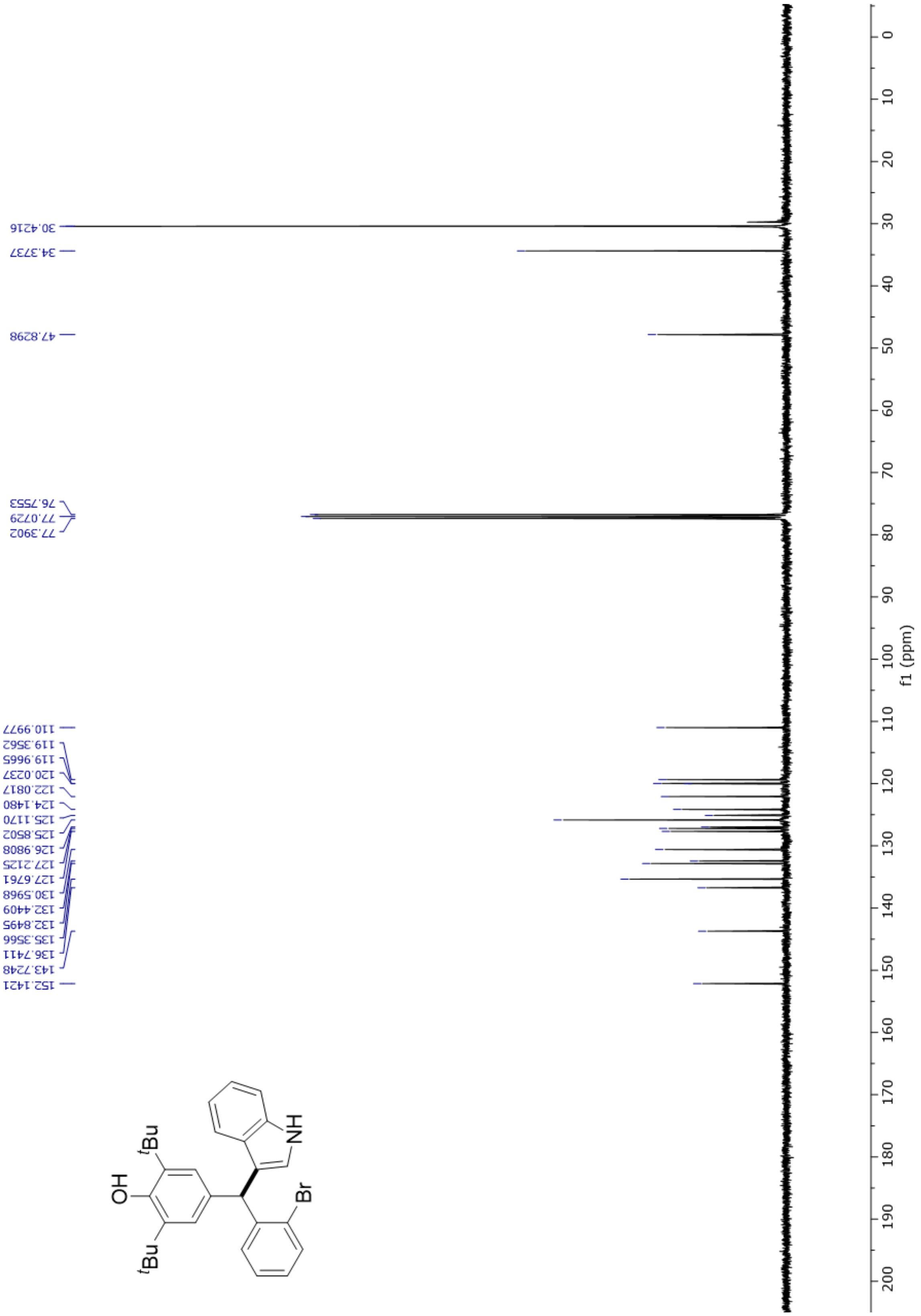
^{1}H NMR spectrum of **24f**



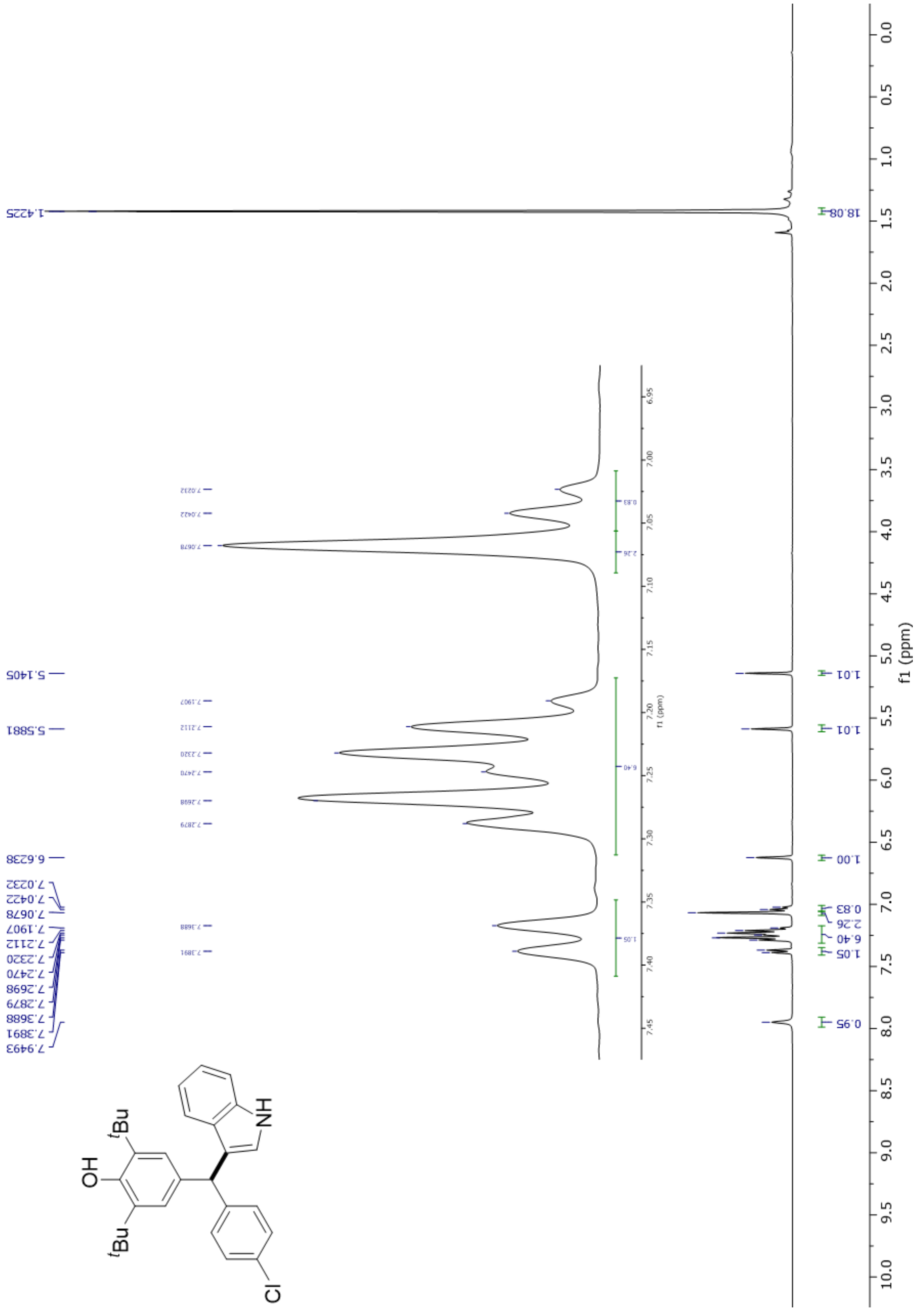
^{1}H NMR spectrum of **24g**



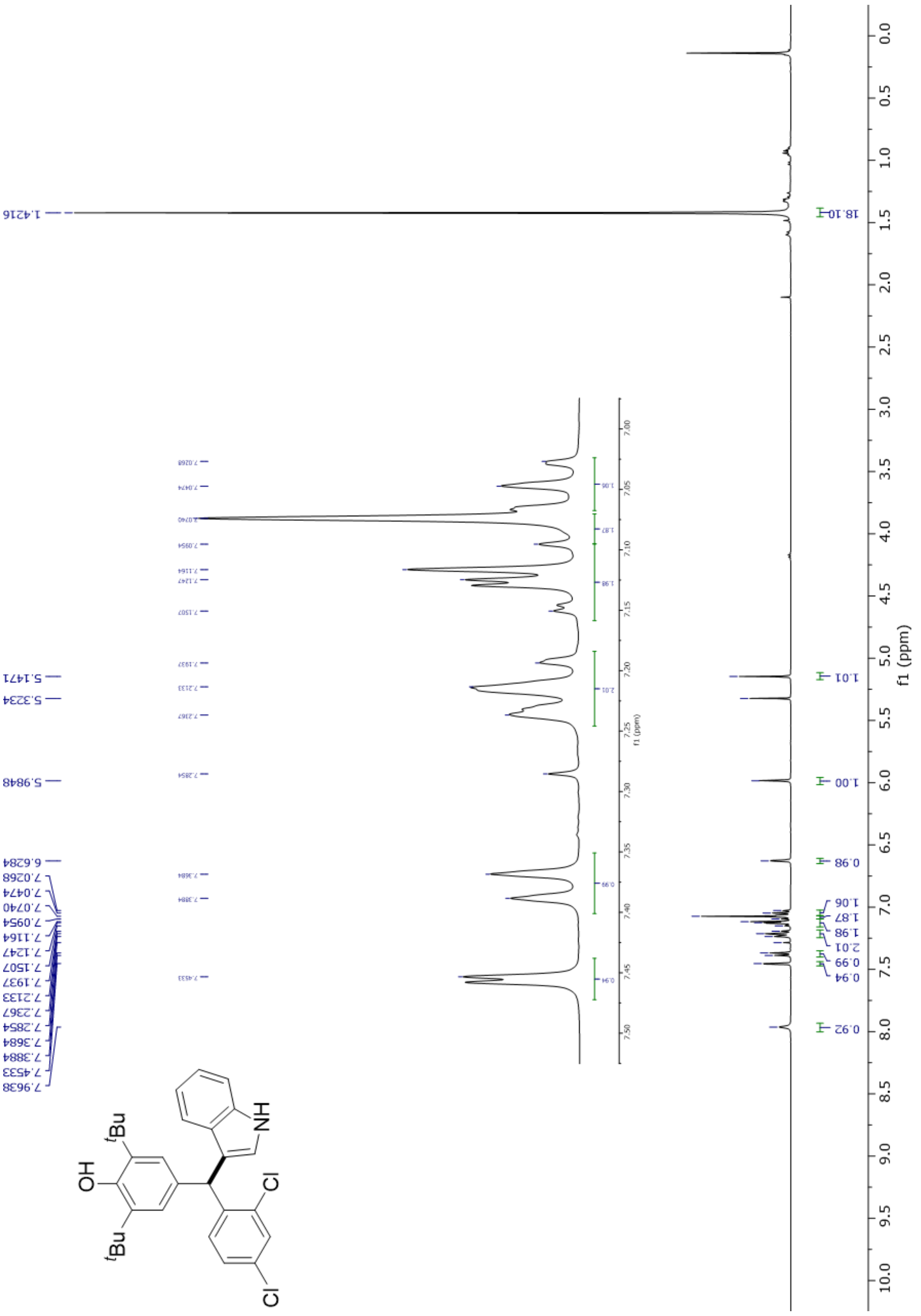
^{1}H NMR spectrum of **24h**



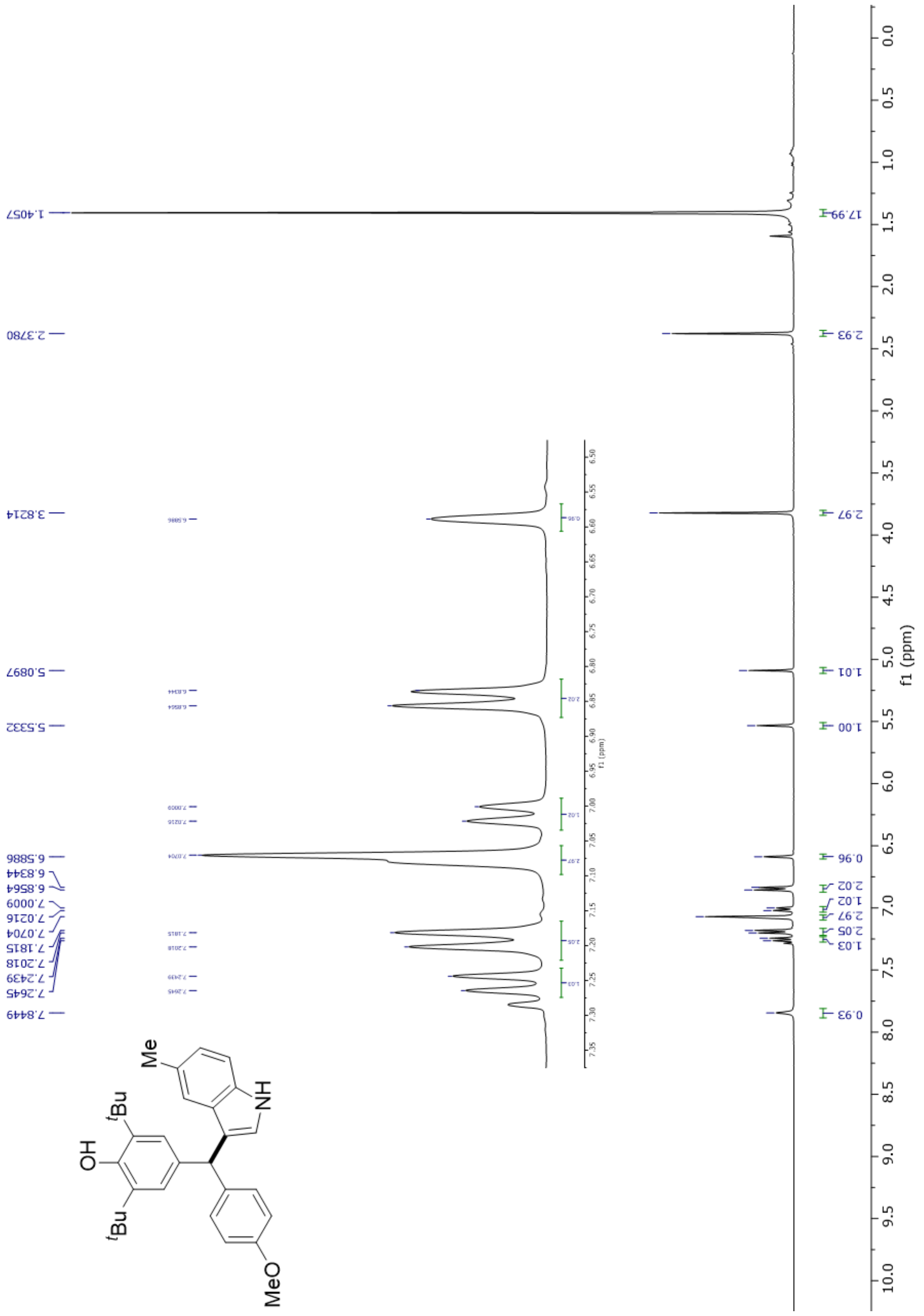
^{13}C NMR spectrum of **24h**



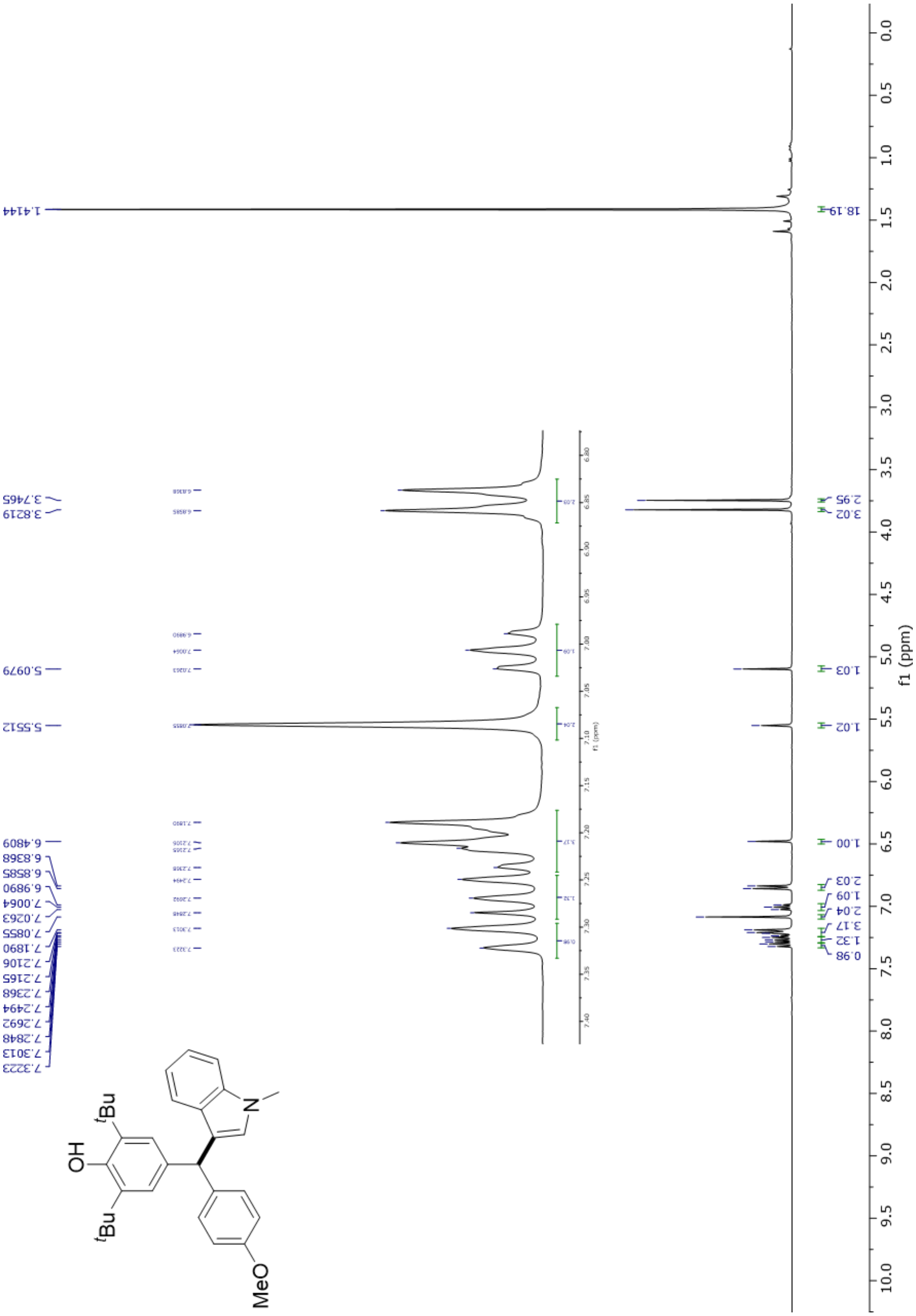
^{1}H NMR spectrum of **24i**



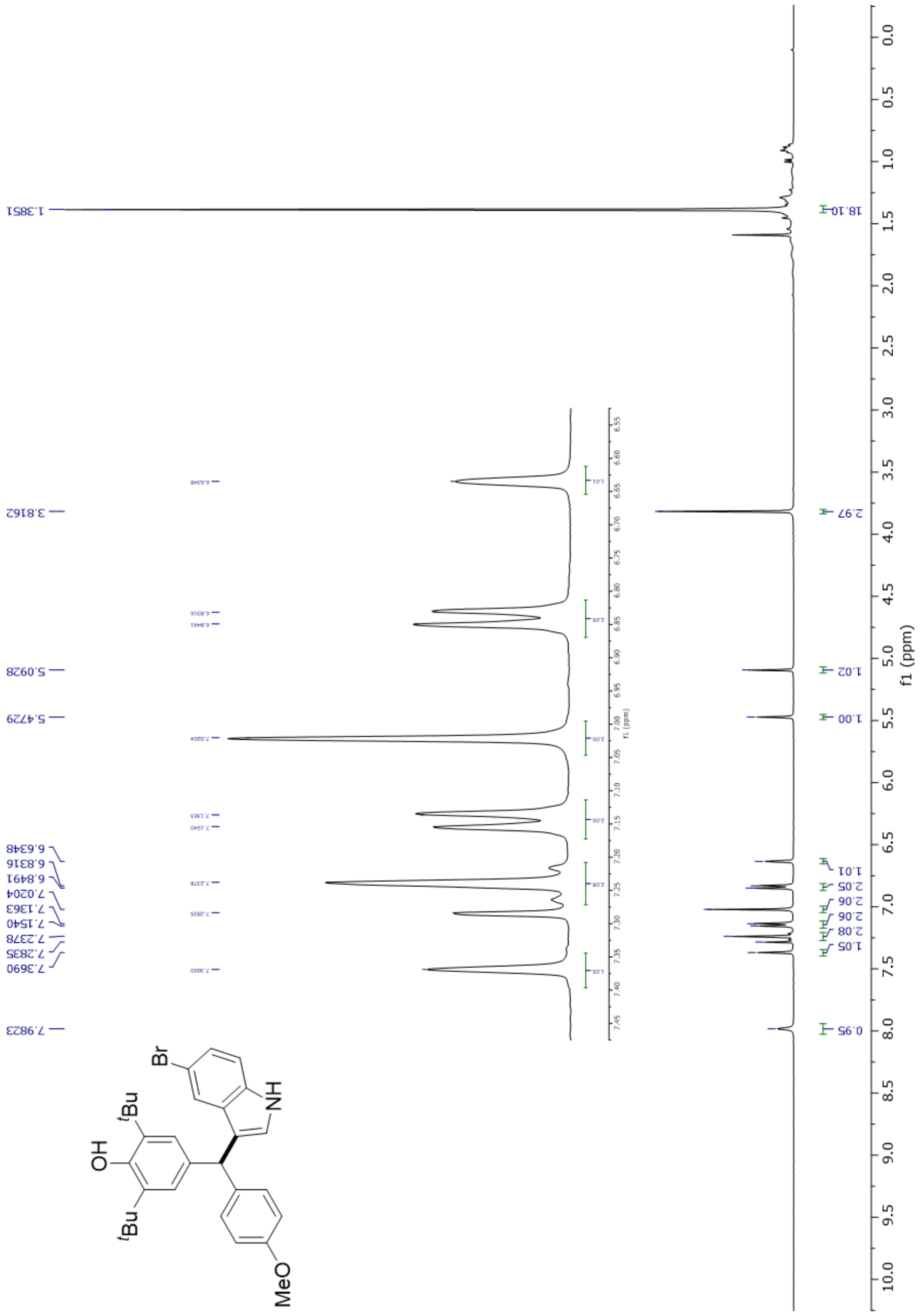
^{1}H NMR spectrum of **24j**



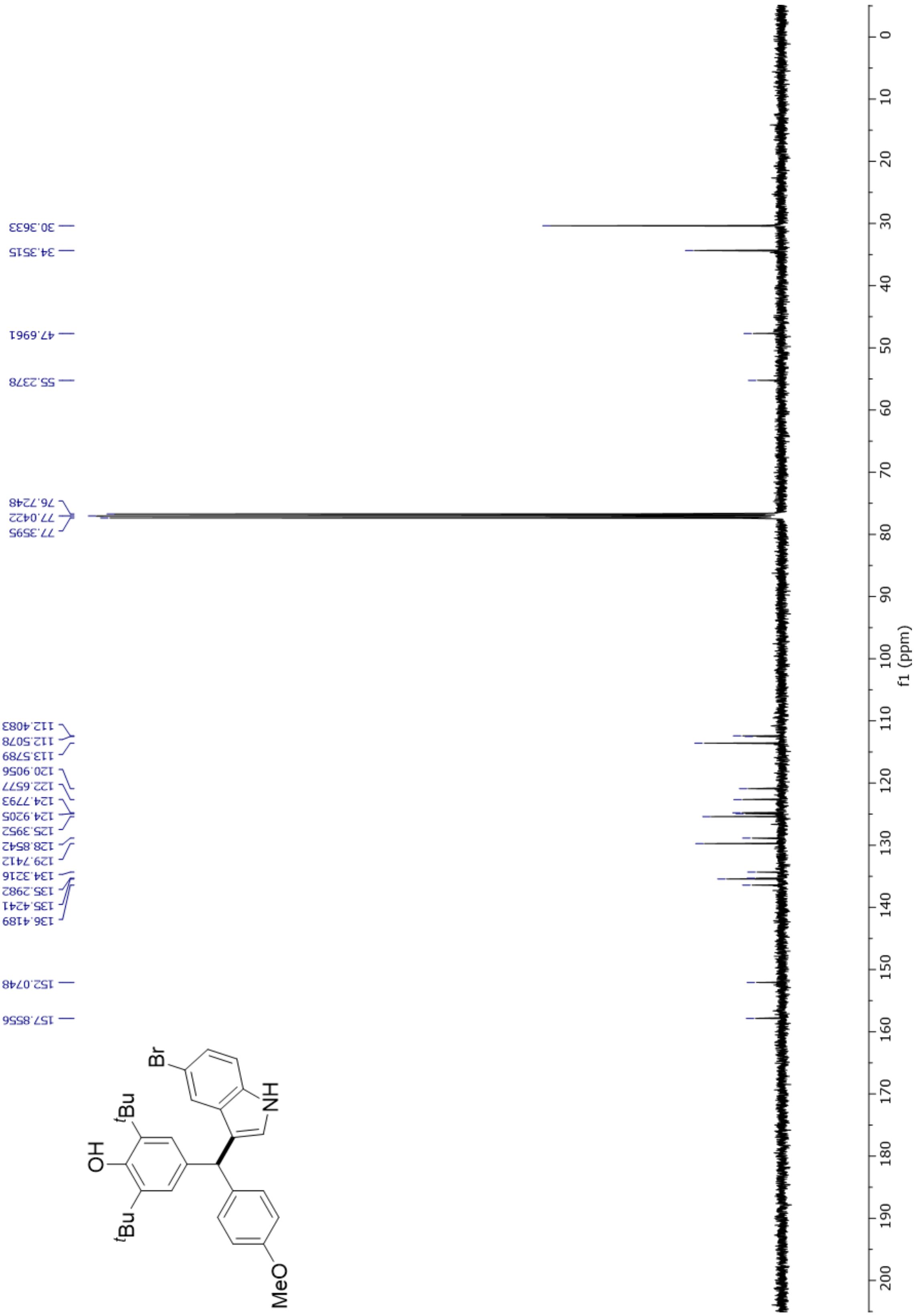
^{1}H NMR spectrum of **25b**



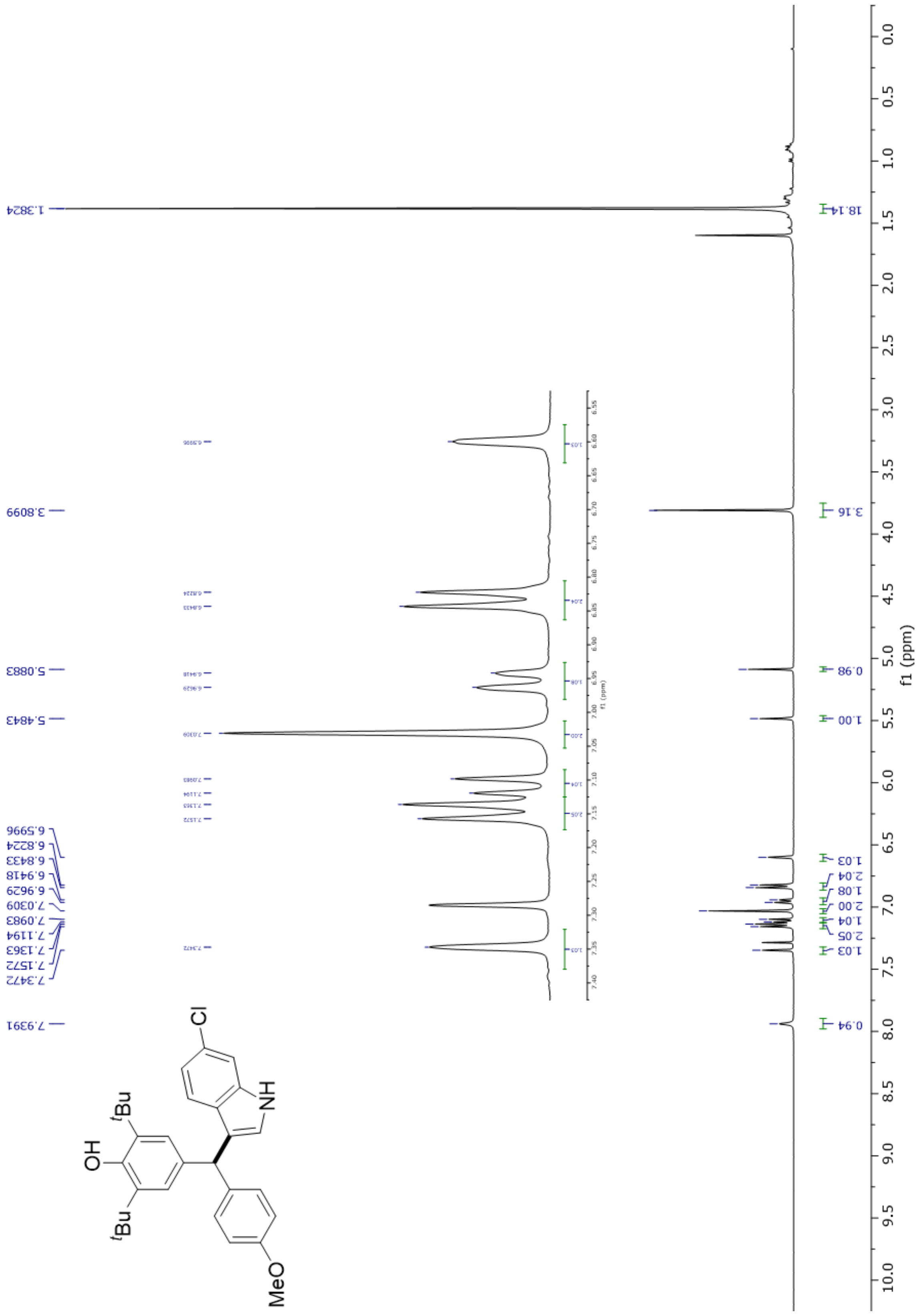
^{1}H NMR spectrum of **25c**



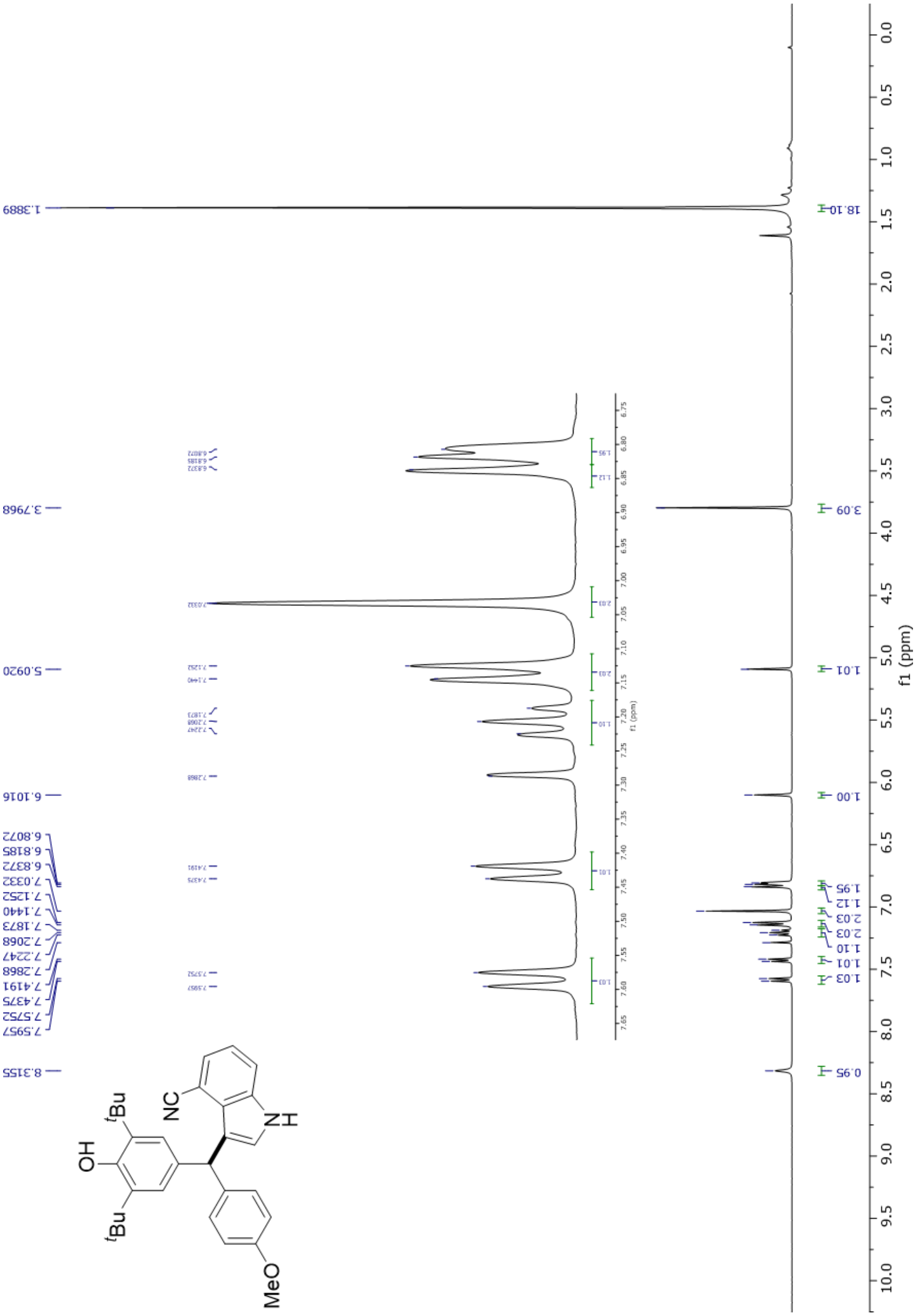
^{1}H NMR spectrum of **25d**



^{13}C NMR spectrum of **25d**



^{1}H NMR spectrum of **25e**



^{1}H NMR spectrum of **25f**

Conclusion

We have successfully established that pentafluorobenzoic acid can act as an efficient organocatalyst for the 1,6-conjugate addition of various indoles to *p*-QMs. Commercial availability of the catalyst, low amount of catalyst loading, very short time for reaction and significant yield of the respective products are the main features of this methodology. Further, this process provides us with a straightforward and cheap access to a variety of unsymmetrical diaryl(indolyl)methane and triarylmethanes in moderate to good yields.

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