Catalytic Functionalization of Benzofurans and Total Synthesis of Propolisbenzofuran B

Thesis Submitted to AcSIR for the Award of

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In

Chemical Sciences

By

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December–2017

Dedicated To

My Family and

My Supervisor

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled ***"Catalytic Functionalization of Benzofurans and Total Synthesis of Propolisbenzofuran B"*** submitted by ***Mr. Kolluru Srinivas*** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy***, embodies original research work under my supervision. This work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Kolluru Srinivas
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DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

15th December, 2017
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Dr. Venu, Dr. Manoj, Dr. Chaithanya, Dr. Shiva, Dr. Janakiram, Dr. Narsimha Rao Kanna, Dr. Bogesh, Dr. Ramireddy, Dr. Bala, Dr. Rambabu, Dr. Chaithanya krishna, Dr. Shanthivardan, Innaiah, Dr. Upender Reddy, Dr. Laxmi Prasad, Dr. Deva Datta, Srikanth, Dr. Nagendra, Dr. Trinadh, Viswanath, Ramu, Dr. Naresh, Dr. Sathish Bhattu, Dr. Suresh, Dr. Seetharam sing, Dr. Sathish, Kumar raja, Dr. Kasinath, Hari, Tharun, Eswar, Dr. Nookaraju, Sagar, Prabhakar Reddy, Praveen, Dr. Sudhakar, Dr. Eshwar, and Dr. Ramesh. They have always been and will continue to be an inspiration to me. I always enjoy their company and they are my strength for many things. I am lucky to have such a big family, which I have got kind gift in NCL. I also thank my friends in IISER. RaviKiran, Kishor padala, Chenna Reddy.

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I am also thankful to UGC, New Delhi for the financial assistance in the form of fellowship.

Above all, I thank God Almighty for His enormous blessings.

Kolluru Srinivas

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
Cat.	Catalytic
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
Conc.	Concentrated
DCE	1,2-Dichloroethane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
PhMgBr	Phenyl magnesium bromide
^{n}BuLi	*n*-Butyl lithium
HRMS	High Resolution Mass Spectrometry
$LiAlH_4$	Lithium aluminium hydride
AcOH	Acetic acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
NaH	Sodiumhydride
DIBAL-H	Diisobutyl aluminium hydride
Im	Imidazole
HF.Py	Hydrogen fluoride in pyridine
CSA	Camphorsulphonic acid
Ph	Phenyl
Py	Pyridine
Ad_2CO_2H	1-Adamantanecarboxylic acid
AgOAc	Silver acetate
TBSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride

ABBREVIATIONS

DFT	Density functional theory
ln	Linear
br	Branched
PPh_3	Triphenylphosphine
rt	Room Temperature
sat.	Saturated
IBX	2-Iodoxybenzoic acid
^{t}BuOK	Potassium tertiary butoxide
TBAF	Tetra-n-butylammonium fluoride
THF	Tetrahydrofuran
NMP	N-Methyl-2-pyrrolidone

Abbreviations used for NMR spectral informations:

br	broad	s	singlet	dt	doublet of triplets
d	doublet	t	triplet	ddd	doublet of doublet of doublets
m	multiplet	q	quartet	ddt	doublet of doublet of triplets
quint	quintet	sept	septet	tt	triplet of triplets

GENERAL REMARKS

- All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. The anhydrous solvents were distilled prior to use: CH_2Cl_2 and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate.

- ^1H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL- 400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL- 100 (100 MHz) and DRX–125 MHz spectrometer.

- High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I2, and anisaldehyde in ethanol as developing agents.

- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C unless otherwise specified.

- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

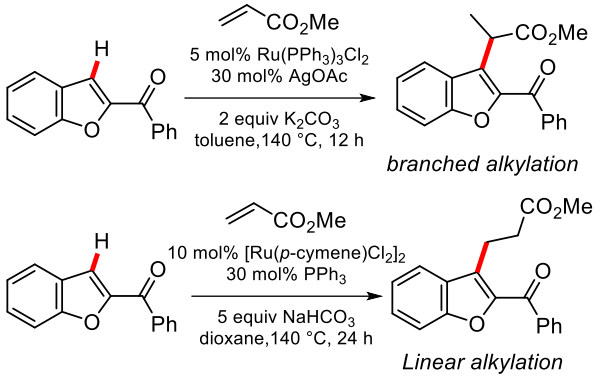
SYNOPSIS

Name of the Candidate	**Kolluru Srinivas**
AcSIR Enrolment No. & Date	**10CC11A26048; August 2011**
Faculty	**Chemical Sciences**
CSIR Lab Affiliated With	**Division of Organic Chemistry, CSIR-NCL, Pune**
Title of the Thesis	**Catalytic Functionalization of Benzofurans and Total Synthesis of Propolisbenzofuran B**
Research Supervisor	**Dr. C. V. Ramana**

Benzofurans are important structural motifs of natural products and pharmaceutical drugs. Methods to functionalize the benzofurans are very important in pharmaceutical industry which helps in development of new drugs. The thesis describes methodologies developed for the catalytic functionalization of benzofurans and total synthesis of natural product "Propolisbenzofuran B". The work embodied in this thesis has been divided into two chapters as described below.

Chapter 1: Catalytic Functionalization of Benzofurans

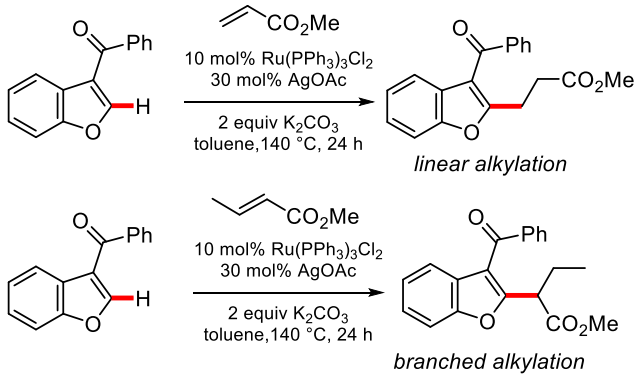
C–H activation is an important strategy for the functionalization of unactivated C–H bonds replacing traditional crosscouppling reactions. However reports on C–H activation strategy for functionalization of heterocyclic compounds like benzofurans are limited.[1] Benzofuran drugs like budiodarone, amiodarone, benzbromarone and dronedarone contain the aroylbenzofuran moiety, which acts as antiarrhythmic, uricosuric and antitubulin agents.[2] Budiodarone, especially, is an antiarrhythmic drug that is presently in clinical trials. The ready availability of a carbonyl in these important class of drugs and the recent interest on the directed C–H activation and functionalization, we have devised a project aiming the synthesis of functionalized 2-aroyl benzofurans. In this direction, 2-aroylbenzofuran on reaction with acrylates in the presence of $Ru(PPh_3)_3Cl_2$ catalyst at 140 °C in toluene results in branched alkylation as major product. Tuning the catalyst to $[Ru(p\text{-cymene})Cl_2]_2$ and optimizing the reaction conditions which includes $NaHCO_3$ as a base, PPh_3 as additive in 1,4-dioxane solvent at 140 °C results in linear alkylation as major product.[3]



Scheme 1: *[Ru]–catalysed branched vs linear selective alkylation of 2-aroylbenzofurans.*

The complementary alkylation was due to steric *vs* electronic effects of the active catalyst participating in the reaction which is different in both cases.

To check whether, electronic nature of carbon center influence the polarity of Ru–C, which in turn effects the mode of alkylation we moved from 2-aroylbenzofuran to 3-aroylbenzofuran. Thus 3-aroylbenzofuran on reaction with acrylate in presence of $Ru(PPh_3)_3Cl_2$ catalyst under previously optimized branched conditions, surprisingly instead of expected branched alkylation, resulted in linear alkylation.[4] However the reaction of methylcrotonate under similar conditions resulted in branched alkylation. The optimization reaction in DMF solvent resulted in benzofuran rearrangement product.

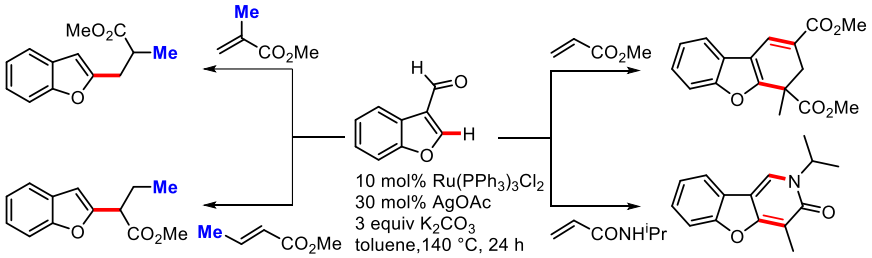


Scheme 2: *[Ru]–catalysed branched vs linear selective alkylation of 3-aroylbenzofurans.*

In case of 3-aroylbenzofurans, the nucleophilicity of carbon center influenced the polarity of Ru–C bond to be more polar resulting in linear alkylation with acrylates however in case of methylcrotonates due to the steric effect of methyl group dominates the polarity of Ru–C bond resulting branched alkylation. Further DFT calculations have been carried out which reveal that

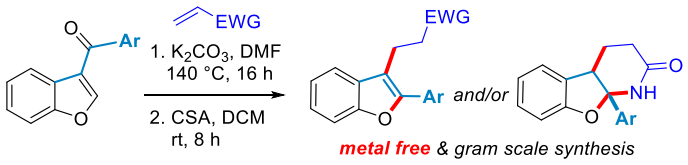
the charge distribution on the Ru–C bond decides the mode of selectivity which corroborates well with the experimental findings.

To further gain insights in to factors affecting the mode of alkylation, the aroyl group was replaced with weak directing aldehyde functional group. Thus benzofuran-3-carbaldehyde on reaction with acrylamide in presence of $Ru(PPh_3)_3Cl_2$ catalyst results in the formation of pyridones derivatives which is formed by C–H activation, Aldehyde-amide condensation and electron redistribution in one pot. By replacing acrylamide with methylacrylate, it results in the formation of dihydrodibenzofuran derivatives which is formed involving series of reactions like branched C–H activation, baylis hillman reaction, michaeladdition followed by dehydration in one pot. Employing methylcrotonate results in branched alkylation and deformylation, whereas methylmethacrylate results in linear alkylation and deformylation in one pot resulting product formation.



Scheme 3: *[Ru]–catalysed C–H activation of benzofuran-3-carbaldehyde*

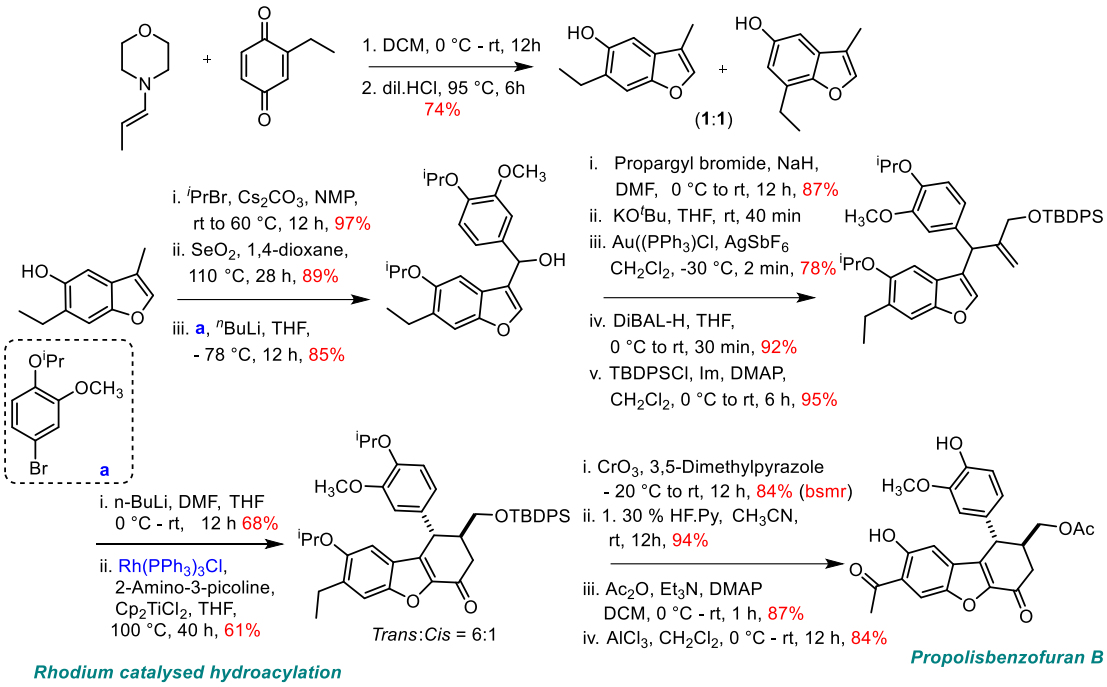
During our optimization studies in dealing with the alkylation of 3-aroylbenzofuran with acrylate in DMF solvent, we noticed benzofuran rearranged product resulting from the opening of O-C(2) bond of 3-aroylbenzofurans and subsequent Michael addition of intermediate 1,3-dicarbonylcompounds with the acrylate present followed by deformylation and acid catalyzed dehydrative cyclization. Control experiments revealed that this benzofuran ring transformation reaction is happening in the presence of K_2CO_3 alone and there is no need of any Ru or Ag complexes. This reactions has been generalized by employing a wide range of acrylates and acrylamides. In case of simple acrylamide the formation of tricyclic aminal derivatives has been noticed.



Scheme 4: *Metal-free benzofuran-ring transformation*

Chapter 2: Total Synthesis of Propolisbenzofuran B

Propolisbenzofuran B was isolated from the methanol extracts of Brazilian propolis.[5] The compound exhibit cytotoxicity to murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells. The first total synthesis was reported in 2014 by Thomson group.[6] The key strategy employed by us in the total synthesis include base catalyzed [1,3] O→C rearrangement and rhodium catalyzed hydroacylation reaction. Further to demonstrate the flexibility of total synthesis various analogues have been synthesized.



Scheme 5: *Total synthesis of propolisbenzofuran B*

References:

1. (a) J. Zhao, H. Fang, C. Xie, J. Han, G. Li, Y. Pan, *Asian J. Org. Chem*, **2013**, 3245. (b) T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett*, **2011**, *13*, 706**.** (c) M. Lonita, J. Roger, H. Doucet, *ChemSusChem* **2010**, *3*, 367. (d) A. Carrer, D. Brinet, J. Florent, P. Rousselle, E. Bertounesque, *J. Org. Chem.* **2012**, *77*, 1316.
2. (a) P. Druzgala, P. G. Milner, Int. publ. WO 01/29018 A2. **2001**. (b) P. Druzgala, P. G. Milner, U. S. Pat. Appl. Publ. US 2002/0193428 A1. **2002**. (c) P. Druzgala, U. S. Pat. Appl. Publ. US 6,710,070 B2. **2004**. (d) P. Druzgala, J. J. Tien, A. Cooper, C. Becker, Int. publ. WO 2007/011835 A2. **2007**.
3. Y. Kommagalla, K. Srinivas, C. V. Ramana, *Chem. –Eur. J.* **2014**, *20*, 7884.

4. K. Srinivas, Y. Dangat, Y. Kommagalla, K. Vanka and C. V. Ramana, *Chem. –Eur. J.* **2017**, *23*, 7570.
5. A. H. Banskota, Y. Tezuka, K. Midorikawa, K. Matsushige, S. Kadota, *J. Nat. Prod.*, **2000,** *63,* `1277.
6. B. T. Jones, C. T. Avetta, R. J. Thomson, *Chem. Sci.*, **2014**, *5*, 1794.

CHAPTER I

Catalytic Functionalization of Benzofurans

1.1 Introduction:

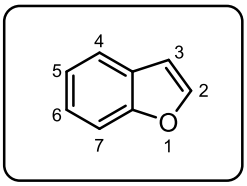
Heterocyclic compounds, "those containing at least one atom other than carbon atom, most frequently nitrogen, oxygen or sulfur," form the major class of organic compounds. Out of six million compounds recorded in the chemical abstract, more than half of them are heterocyclic in nature. Despite the multidimensional progress of organic chemistry since the 1800s, the prominence of heterocycles in organic synthesis started only at the end of the World War II, which is evident from the fact that more than 70% of the drugs marketed today contain at least one heterocyclic unit in their core. Indeed, most of the primary metabolites that are required for basic metabolic processes in the living organisms are either heterocyclic in nature or contain at least one heteroatom.

Compounds with nitrogen containing heterocyclic units dominate the primary as well secondary metabolite families. Indeed, the key building blocks in the molecules of life, DNA and RNA, which form the bits of genetic algorithm, are N-heterocylcic compounds. Next come the oxygen containing heterocycles, the family which is not as diverse as the N-heterocyclic family, but takes the major share in terms of the volume. This is expected, considering the fact that approximately 46% of earth's crust is oxygen. Carbohydrates, which dominate the O-heterocyclic compounds, are another important member of the biomolecules. Carbohydrates are the main structural components of the body (cellulose, chitin, and heparin) and are essential for the storage of energy (e.g. starch and glycogen). Importantly, at the cell surface, the glycol-conjugates derived from the peptides and oligosaccharides play an important role in cell-cell and cell-pathogen recognition/adhesion. Coming to the other elements, sulphur-containing heterocyclic compounds comes next with a reasonable presence in the molecules of natural origin and in the drugs marketed today and are showing increasing dominance in functional materials.

The above brief introduction is qualitative in nature and has been placed to reveal that synthesis and manipulation of heterocyclic units is an important aspect in organic synthesis, in general, and in medicinal chemistry, in particular. Considering the fact that the work presented in this thesis will be dealing mainly with the benzofuran nucleus, the following discussion will be restricted mainly to the synthesis and functionalization of benzofurans. However, as the major portion of this thesis deals with the functionalization

of the heterocyclic carbons of the benzofuran nucleus *via* C–H bond activation, similar chemistry that has been documented with simple aryl/heteroaryl rings will be discussed in detail.

Benzofuran is an important oxygen atom containing bicyclic heterocyclic compound in which the benzene and furan rings are fused together. It is a colorless, sweet-smelling liquid and is usually extracted from coal tar. Benzofurans have been known to exist in nature since the 19th century and, till date, several investigations have been carried out to understand its chemical and biological properties. The benzofuran structural core is an integral part of several complex natural products that are known to exhibit a diverse range of biological activities. Benzofurans are the precious scaffolds that form the intrinsic part of several pharmaceutical drugs and functional materials.



1.2. Significance of benzofurans in natural products:

Benzofuran represents an important scaffold present in a variety of complex natural products that are known to exhibit a diverse range of biological activities, such as antibacterial,[1] antimicrobial,[2] anti-inflammatory,[3] antitumor,[4] and antidiabetic[5]. In general, the 2-substituted benzofuran derivatives exhibit excellent biological properties in comparison to the other derivatives. Machicendiol is a natural product isolated from the leaves of machilus glaucescens and contains the benzofuran structural core, which is used for the treatment of asthma, ulcers and rheumatism.[6] Ailanthoidol and XH-14 are of the benzofuran family of natural products isolated from the stem woods of zanthoxylum ailanthoidos and exhibit antiviral, antioxidant and antifungal properties.[7] Ribisin A-D are the important benzofuran derivatives isolated form the fruiting bodies of Phellinus Ribis and are known to promote nerve growth in PC12 cells.[8] Liphagal isolated from sponge Aka Coralliphaga is known to inhibit the PI3kα cycle[9] and a another structurally similar natural product Frondosin B isolated from the sponge Dysidea Frondosa prevents the binding of

IL-8 to its receptors, in turn preventing a chronic inflammatory disorder.[10] Apart from this, several other natural products such as Malibatols A, Egonol, Coumestan, Machaeriol, Cicerfuran, Eupomatenoid, Moracin O, Furoventalene, Khellin, Lanceolatin B, Corsifuran C, Vignafuran, Glycyrol, Kynapcin-24, Laetirobin, Diptoindonesin G, Coumestrol, Propolisbenzofuran B, Daphnodorin A, Anastatin B, Diptoindonesin G etc. contain a benzofuran structural core and exhibit interesting biological activities.

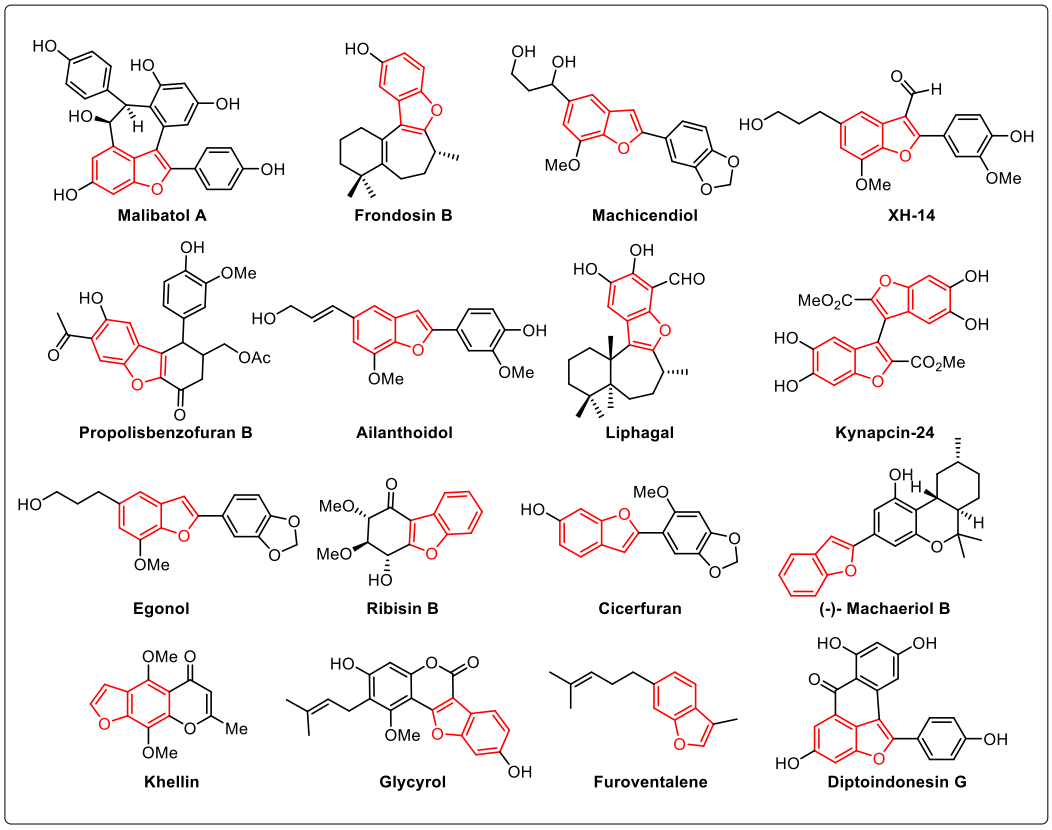


Figure F1.1: *Natural products containing the benzofuran structural core*

1.3 Significance of benzofurans in pharmaceuticals:

Benzofurans are vital heterocyclic compounds present in a variety of pharmaceutical drugs. A few marketed medications, for example, Amiodarone, Budiodarone, Benzbromarone and Dronedarone contain the benzofuran basic unit. Inspired by the presence of the benzofuran core in a variety of natural products and pharmaceutical drugs, chemists have synthesized several benzofuran derivatives having the potential to become pharmaceutical drugs. Amiodarone is an important benzofuran drug that came into the market in 1961 as antiarrhythmic medication.[11] But soon, in 1967, it was pulled out of the

market due to its adverse side effects, which include liver damage, vision problems, thyroid problems and lung toxicity.

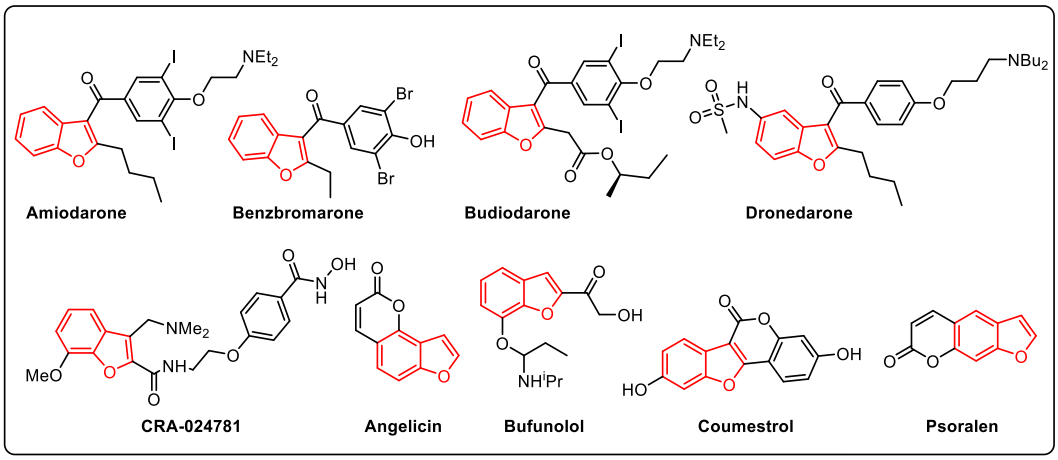


Figure F1.2: *Pharmaceutical drugs containing benzofuran structural core*

The structurally modified Amiodarone, called as Budiodarone,[12] is in clinical trials and differs from the Amiodarone at the C2 position of benzofuran, where the *n*-butyl chain was replaced with the *sec*-butyl acetate. Budiodarone has lesser side effects than the Amiodarone due to its shorter half-life in the body and gets metabolized faster, generally in 7 hours compared to 35–68 days, and has a fast action of drug with lesser side effects. Benzbromarone is a disubstituted benzofuran drug which acts as a uricosuric agent.[13] In 1981, it was in clinical trials and in 2008 it was declared as a more effective uricosuric agent than the allopurinol for the treatment of gout. In 2009, the FDA approved Dronedarone as a class III antiarrhythmic drug. It is structurally similar and much more effective than Amiodarone.[14] The toxicity of Amiodarone is due to its high iodine content, which causes damage to thyroid, liver and other organs whereas Dronedarone does not contain any iodine moiety in its structure, thus reducing the damage to thyroid and other organs. Befunolol has been used in glaucoma treatment, Angelicin acts as an antiviral agent, Coumestrol shows estrogrenic activity and contains the benzofuran core as an integral part of a complex structure.

1.4 Significance of benzofurans in functional materials:

The fascinating benzofuran structure has attracted the attention of material chemists. As a result it has become a vital substrate in material science. For instance, thieno[2,3-

f]benzofuran based conjugated polymers (TBFPS-BT) show excellent performance in organic solar cells with high fill factor.[15] Derivatives of aminobenzofuran fused to a rhodamine dye (AFR2) act as fluorescent dyes which show excellent applications in biological systems.[16] An asymmetric carbazole-dibenzofuran hydrid host material (CzDBF) is known to function as organic light emitting diodes.[17] Furthermore, benzofuran derivatives are known to act as antioxidant agents.[18] Several benzofuran compounds are known to show photovoltaic applications. In general, benzodifurans are known to play a prominent role in semiconductors due to their symmetry and extended π–conjugation, which facilitates the electron delocalization, in turn influencing the charge mobility.

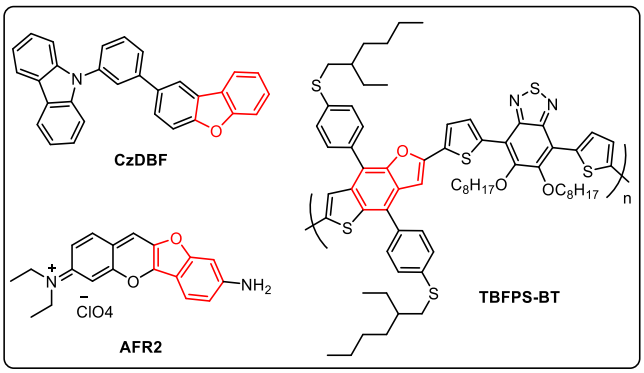


Figure F1.3: *Functional materials containing benzofuran structural core*

1.5 Synthetic strategies for benzofuran synthesis:

The significance of benzofurans for biological systems/material science has attracted the attention of chemists. They have explored the methods for the synthesis of benzofuran derivatives. The methods developed for benzofuran synthesis can be broadly classified into two groups. The first group pertains to strategies involving the construction of furan ring of benzofuran and the second to techniques developed for the annulation of the carbocyclic ring to a furan ring. However, strategies for the construction of the furan ring have been investigated extensively, while the construction of carbocyclic rings has been rarely explored. The methods available for the construction of the furan ring of benzofuran can be broadly classified in to four types.

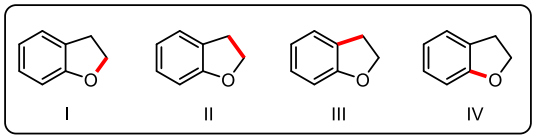
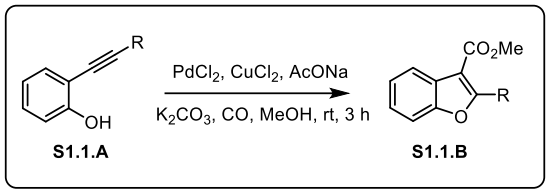


Figure F1.4: *Strategies for construction of furan ring*

1.6 Benzofuran Synthesis *via* O–C2 Bond Construction (Type-1):

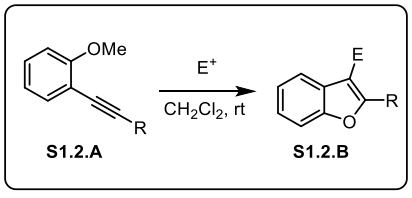
A substantial number of literature reports demonstrate benzofuran synthesis by the construction of the O-C2 bond. Some of them are illustrated in the following section.

Sakamoto *et al*. have reported a general method for the synthesis of 2,3-disubstituted benzofuran derivatives. O-alkynyl phenol (**S1.1.A**) in the presence of palladium catalyst catalyzed and base in methanol undergoes cyclization followed by carbonylation resulting in the formation of benzofuran-3-carboxylates (Scheme S1.1).



Scheme S1.1: *Sakamoto's approach for benzofuran synthesis*
(Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812)

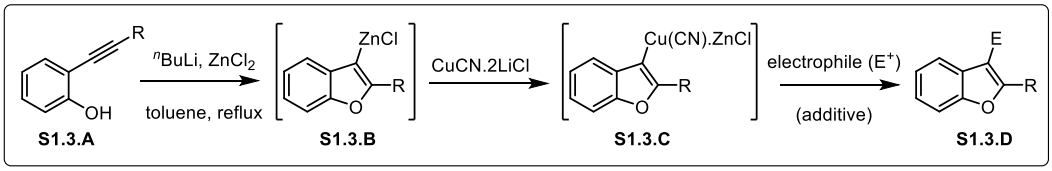
Larock and coworkers have developed an attractive strategy for the synthesis of a variety of 2,3-disubstituted benzofurans. In this method, *o*-iodoanisoles undergo cross-coupling with terminal alkynes in the presence of Pd/Cu catalysts resulting in 2-methoxy alkyne, which then undergoes electrophilic cyclization with I_2, *p*-$NO_2C_6H_4SCl$ or PhSeCl, resulting in 2,3-disubstituted benzofuran derivatives in excellent yields. The significance of this reaction is that the 3-iodobenzofuran formed in the reaction is a useful substrate in several cross couppling reactions (Scheme S1.2).



Scheme S1.2: *Larock's approach for 2,3-disubstituted benzofuran synthesis*
(Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292–10296)

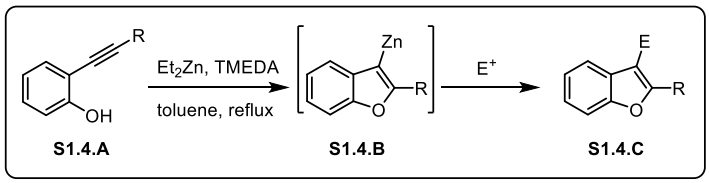
Nakamura and coworkers have reported a general method for synthesizing a variety of 2,3-disubstituted benzofurans from 2-alkynylphenol. Substrate **S1.3.A** on reaction with ^{n}BuLi followed by $ZnCl_2$ results in the intermediate 3-zincobenzofuran, which on reaction with CuCN.2LiCl undergoes transmetallation to a cuprate intermediate, which on reaction

with various electrophiles in the presence of additives results in 2,3-disubstituted benzofurans in excellent yields (Scheme S1.3).



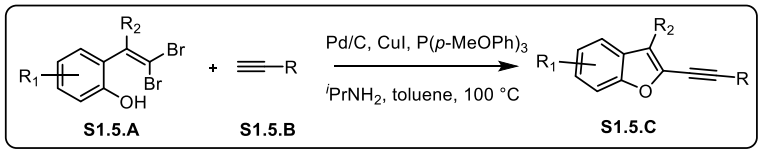
Scheme S1.3: Nakamura's approach for synthesis of 2,3-disubstituted benzofuran
(Nakamura, M.; Llies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *13*, 2803–2805)

In another report, Nakamura and coworkers have reported a simple method for the synthesis of 3-zincobenzofurans and have demonstrated their utility for the synthesis of various 2,3-disubstituted benzofuran derivatives. 2-Alkynyl phenol, on reaction with Et_2Zn in the presence of TMEDA in refluxing toluene undergoes cyclization and results in the formation of a reactive intermediate, 3-zincobenzofuran. This intermediate, on reaction with electrophiles in the presence of 10 mol% $[Pd_2(dba)_3].CHCl_3$ and 40 mol% of $^tBu_3P$ undergoes a coupling reaction, resulting in 2,3-disubstituted benzofurans (Scheme S1.4).



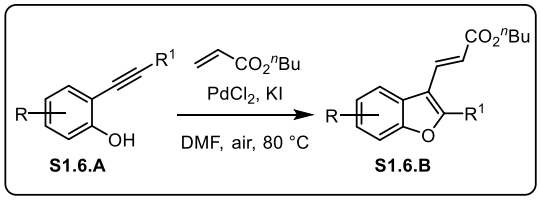
Scheme S1.4: Nakamura approach for benzofuran synthesis
(Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 944–947)

Lauten and coworkers have developed an efficient method for the synthesis of 2-alkynyl benzofurans starting from simple gemdibromovinyl substrates. The reaction works in the presence of a CuI and Pd/C dual catalytic system, where CuI is utilized for Ullman coupling and Pd/C for Sonogashira coupling. Heating a mixture of substrate (**S1.5.A**), Pd/C, CuI, P(*p*-MeOPh)$_3$ and $^iPr_2NH$ in toluene at 100 °C for 48 h results in the formation of 2-alkynylbenzofuran derivatives in excellent yields (Scheme S1.5).



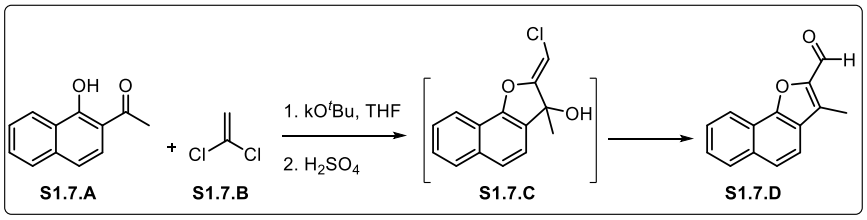
Scheme S1.5: *Lauten's 2-alkynyl benzofuran synthesis*
(Nagamochi, M.; Fang, Y.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955–2958)

Aurrecoechea and coworkers have developed an efficient strategy for the synthesis of 3-alkenylbenzofurans. In this method, 2-alkynylphenols undergo oxypalladation resulting in an intermediate which then undergoes Heck-type coupling with olefins containing electron withdrawing groups such as esters, nitriles, amides and sulfones (Scheme S1.6).



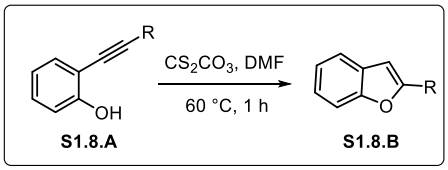
Scheme S1.6: *Aurrecoechea's synthesis of 3-alkenylbenzofurans*
(Martinez, C.; Alvarez, R.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083–1086)

Recently, Marko and coworkers have revealed an acid-base catalyzed synthesis of benzofurans starting from 2-hydroxy acetophenones, which took place in two steps. In the first step, 2-hydroxy acetophenone, on reaction with 1,1-dichloroethylene in the presence of K^{t}OBu, resulted in the formation of chloromethylene furan. This intermediate underwent an acid-catalyzed rearrangement to provide a 2-formybenzofuran derivative in excellent yields (Scheme S1.7).



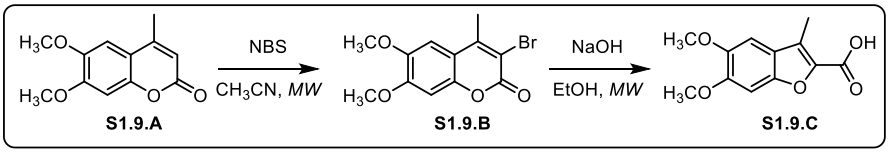
Scheme S1.7: *Marko's acid-base catalyzed benzofuran synthesis*
(Schevenels, F.; Marko, I. *Org. Lett.* **2012**, *14*, 1298–1301)

Wang and coworkers reported a base-catalyzed alkynol cycloisomerization approach for the synthesis of 2-substituted benzofurans. The *ortho*-alkynyl phenol was heated in the presence of Cs_2CO_3 at 60 °C in DMF for 1 h to obtain 2-substituted benzofurans in good yields. (Scheme S1.8).



Scheme S1.8: *Wang's base catalyzed alkynol cycloisomerization*
(Damera, K.; Ke, B.; Wang, K.; Dai, C.; Wang, L.; Wang, B. *RSC Adv.* **2012**, *2*, 9403–9405)

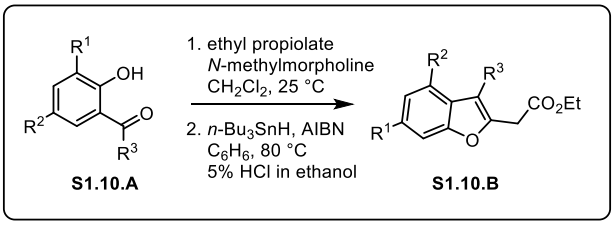
Marriott *et al.* reported an interesting approach for the synthesis of benzofuran-3-carboxylic acid from 3-halocoumarins *via* the Perkin rearrangement reaction (coumarin-benzofuran ring contraction) under microwave conditions. The coumarin derivative **S1.9.A** on treatment with NBS under microwave irradiation results in the formation of 3-bromocoumarin (**S1.9.B**). The resulting 3-bromocoumarin again on exposure to the microwave irradiation in the presence of NaOH in EtOH, rearranges to the corresponding benzofuran-2-carboxylic acid. In the presence of base, the coumarin ring opens up, resulting in the formation of a phenoxide anion which then attacks the vinyl halide resulting in the formation of a product on the elimination of halogen (Scheme S1.9).



Scheme S1.9: *Marriott's microwave approach for benzofuran synthesis*
(Marriott, K. C.; Bartee, R.; Morrison, A. Z.; Stewart, L.; Wesby, J. *Tetrahedron. Lett.* **2012**, *53*, 3319–3321)

1.7 Strategies involving the construction of the C2-C3 bond of thefuran ring in benzofuran (Type-2):

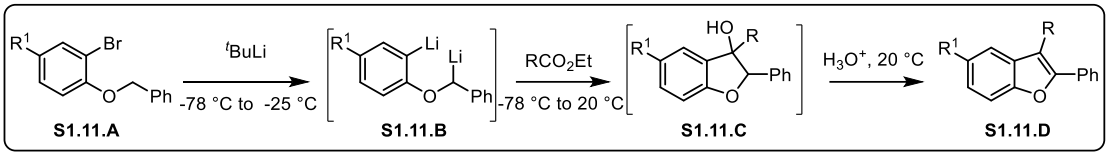
Recently, Tae and coworkers reported a two-step sequence for the synthesis of 2,3-disubstituted benzofurans starting with simple *o*-acyl phenols. In this approach, **S1.10.A**, on reaction with ethyl propiolate in the presence of *N*-methylmorpholine in CH_2Cl_2 results in *β*-aryloxy acrylates, which on treatment with $^{n}Bu_3SnH$ in the presence of a catalytic amount AIBN in benzene at 80 °C followed by treatment with 5% HCl in ethanol furnishes 2,3-disubstituted benzofurans in excellent yields (Scheme S1.10).



Scheme S1.10: *Tae's approach for benzofuran synthesis*
(Kim, K.; Tae, J. *Synlett* **2005**, 387–390)

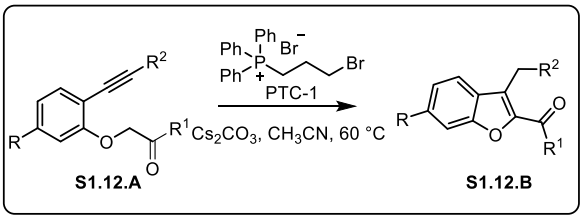
Recently, a metal free approach for the synthesis of 2,3-disubstituted benzofurans has been reported by Sanz and co-workers. Benzyl 2-halophenylethers (**S1.11.A**) in the

presence of ^{t}BuLi in THF at –78 °C undergo lithium halogen exchange and simultaneous lithiation at the benzylic methylene unit. The resulting dianion, on reaction with carboxylic esters, affords the 3-hydroxy-2,3-dihydrobenzofurans. Treating this product with acid facilitates dehydration and results in the formation of 2,3-disubstituted benzofurans. This method suffers from the use of pyrophoric compounds and difficulty in handling ^{t}BuLi, and therefore cannot be practiced in large scales. However one can appreciate this method, as it does not involve any metal catalyst, while many literature reports show the synthesis of similar benzofurans employing metal catalysts (Scheme S1.11).



Scheme S1.11: *Sanz' multistep approach for benzofuran synthesis*
(Sanz, R.; Miguel, D.; Martinez, A.; Perez, A. *J. Org. Chem.* **2006**, *71*, 4024–4027)

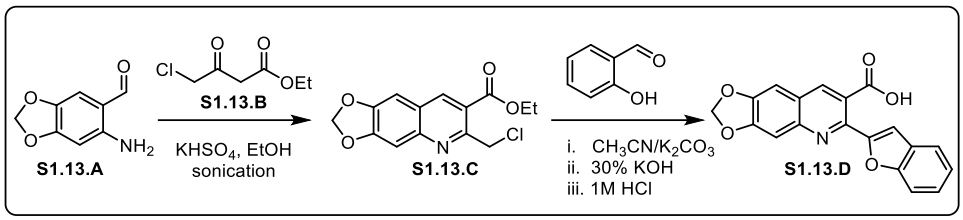
Liang and coworkers reported a phase transfer catalyst mediated synthesis of benzofuran derivatives. In this approach, treatment of *o*-(1-alkynylphenoxy)-1-phenylethanone **S1.12.A** with Cs_2CO_3 in CH_3CN in the presence of PCT-1 at 60 °C resulted in the formation of benzofuran derivatives in good yields. A wide range of substrates with various functional groups showed tolerance in the present reaction. Further, the reaction is ecofriendly and can be practiced at industrial scales (Scheme S1.12).



Scheme S1.12: *Liang's approach for 2-acylbenzofurans*
(Hu, J.; Wu, L.; Wang, X.; Hu, Y.; Niu, Y.; Liu, X.; Yang, S.; Liang, Y.
Adv. Synth. Catal. **2012**, *352*, 351–356)

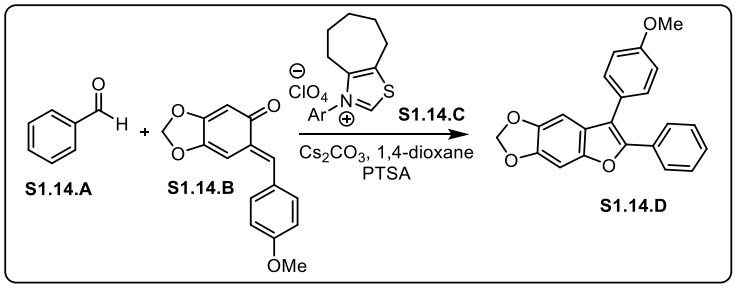
Gao's group reported an attractive metal free approach for benzofuran synthesis. In this approach, the product **S1.13.C** was synthesized using the Friedlander condensation reaction, which on further reaction with salicylaldehyde transformed to ether in refluxing acetonitrile followed by ester hydrolysis and intramolecular cyclization, resulting in the

incorporation of the benzofuran unit at the 2-position of the quinolone nucleus in excellent yields (Scheme S1.13).



Scheme S1.13: *Gao's 2-(2'-qunioliny)benzofuran synthesis*
(Gao, W. T.; Liu, J.; Jiang, Y.; Li, Y. *Beilstein J. Org. Chem.* **2011**, *7*, 210–217)

Recently, Yao and co-workers have developed an NHC based approach for the synthesis of 2,3-disubstituted benzofurans. In this method, *o*-quinone methides (**S1.14.B**), on reaction with aldehydes in the presence of the NHC catalyst (**S1.14.C**) triggers the formation of 2,3-disubstituted benzofurans in excellent yields. The key note of this reaction is that mild reaction conditions were employed with a broad substrate scope (Scheme S1.14).

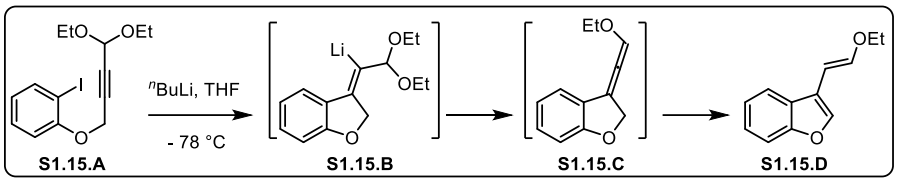


Scheme S1.14: *Yao's NHC based approach for benzofuran synthesis*
(Xie, Y.; Yu, C.; Que, Y.; Li, T.; Wang, Y.; Lu, Y.; Wang, W.; Shen, S.; Yao, C. *Org. Biomol. Chem.* **2016**, *14*, 6463–6469)

1.8 Strategies involving the construction of the Ar–C3 bond of benzofuran (Type 3):

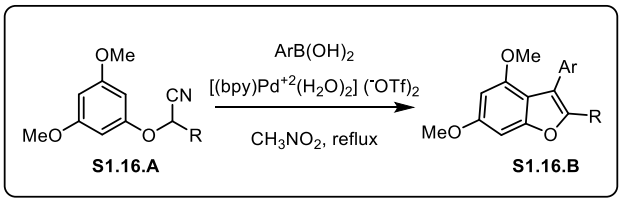
Maddaluno and coworkers have described an efficient approach for the synthesis of 3-vinyl benzofurans. The substrate **S1.15.A** in the presence of ^{n}BuLi undergoes lithium-halogen exchange, resulting in an aryl anion that undergoes a 5-*exo* dig cyclization to form an intermediate **S1.15.B** which, upon elimination of lithium ethoxide, results in the formation of an exocyclic allene. This exocyclic allene is then isomerised to 3-vinyl benzofuran. The product in this reaction contains a 1,3 diene system which can undergo

[4+2] cycloaddition with acrylates resulting in the formation of tricyclic structures (Scheme S1.15).



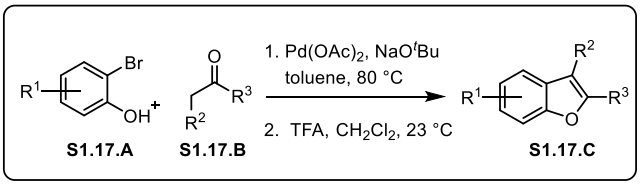
Scheme S1.15: *Maddaluno's 3-vinyl benzofuran synthesis*
(Start, F. L.; Maddaluno J. *Org. Lett.* **2002**, *4*, 2791–2793)

Lu's group reported an interesting method for the synthesis of benzofurans employing phenoxyacetonitriles as starting precursors. In this process, a cationic palladium complex was employed which mediated the addition of an aryl boronic acid to nitriles resulting in arylketones. Further, these ketones underwent C–H activation or a Friedel-Crafts reaction that triggered the formation of 3-arylbenzofurans in excellent yields (Scheme S1.16).



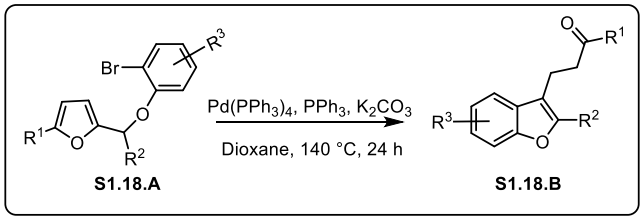
Scheme S1.16: *Lu approach for synthesis of 3-arylbenzofurans*
(Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987–5990)

Recently, Burch and coworkers have reported a simple, efficient technique for the synthesis of 2,3-disubstituted benzofurans. In this process, 2-bromophenol on reaction with ketones and with the aid of a palladium catalyst undergoes enolate arylation, resulting in an intermediate which, upon on reaction with TFA, undergo dehydrative cyclization, resulting in 2,3-disubstituted benzofurans. A variety of 2-bromophenols containing EDG as well as EWG showed compatibility in this reaction. Further, this methodology was applied in the total synthesis of Eupomatenoid natural products (Scheme S1.17).



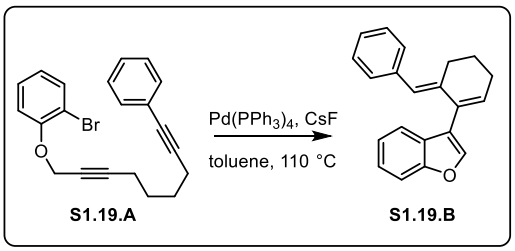
Scheme S1.17: *Burch's synthesis of benzofuran from o-bromophenols*
(Eidamshaus, C.; Burch, J. D. *Org. Lett.* **2008**, *10*, 4211–4214)

Yin *et al* developed an innovative approach for benzofurans synthesis based on furan ring transformation to the benzofuran ring. When treated with the *o*-arylated hydroxymethylfuran **S1.18.A**, palladium catalyst, it undergoes dearomatizing intramolecular arylation on the furan ring forming an allylic palladium complex which, up on furan ring opening and *β*–hydride elimination, results in the formation of the benzofuran derivative **S1.18.B**. The reaction was explored using large number of substrates containing substituents on the aryl ring to give the corresponding 2,3-substituted benzofurans in excellent yields. (Scheme S1.18).



Scheme S1.18: Yin *approach for furan transformation to benzofuran*
(Yin, B.; Cai, C.; Zeng, G.; Zhang, R.; Li, X.; Jiang, H. *Org. Lett.* **2012**, *14*, 1098–1101)

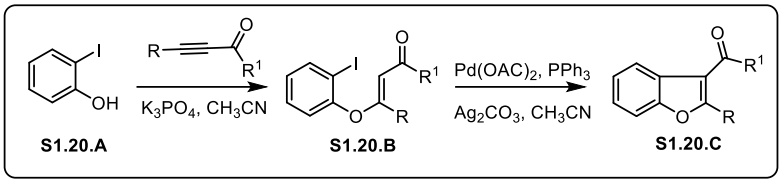
Recently, Werz and coworkers have reported an approach for the synthesis of highly functionalized benzofuran derivatives starting with a diynyl substituted bromoarene. The substrate **S1.19.A** on heating in the presence of $Pd(PPh_3)_4$, CsF in toluene at 110 °C results in the formation of a benzofuran nucleus (Scheme S1.19).



Scheme S1.19: Werz's *domino-approach for benzofuran synthesis*
(Leibeling, M.; Pawliczek, M.; Kratzert, D.; Stalke, D.; Werz, D. B. *Org. Lett.* **2012**, *14*, 346–349)

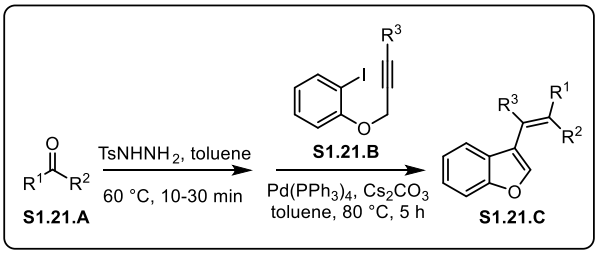
Zhang *et al.* reported an efficient approach for benzofuran synthesis using Heck coupling. Iodopenol, on conjugate addition with activated alkynes, results in an intermediate **S1.20.B** which undergoes intramolecular Heck coupling in the presence of

$Pd(OAc)_2$ resulting in 2-substituted-3-functionalised benzofurans. This approach was used in the context of total synthesis of the natural product Daphnodorin B (Scheme S1.20).



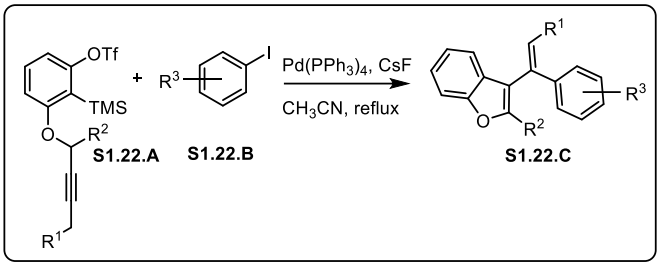
Scheme S1.20: *Zhang's approach for 3-acylbenzofurans synthesis*
(Yuan, H.; Bi, K.; Yue, R.; Ye, J.; Shen, Y.; Shan, L.; Jin, H.; Sun, Q.; Zhang, W. *Org. Lett.* **2013**, *15*, 4742–4745)

Wang and coworkers reported a novel approach for the synthesis of 3-vinylbenzofurans. The reaction includes palladium catalyzed cyclization on to an alkyne **S1.21.B**, generating a C–C single bond and palladium carbene migratory insertion generating a C=C double bond in one catalytic cycle, resulting in the synthesis of 3-vinylbenzofuran. Further, the reaction showed tolerance to various functional groups, indicating practical applicability of the reaction (Scheme S1.21).



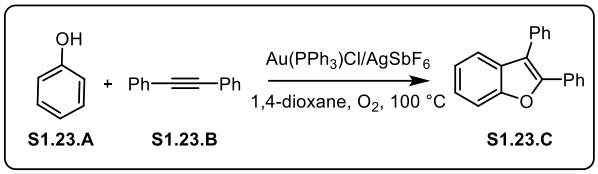
Scheme S1.21: *Wang's approach for synthesis of 3-vinylbenzofuran*
(Liu, Z.; Xia, Y.; Zhou, S.; Wang, L.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 5032–5035)

Shengming *et al.* developed an attractive approach for the synthesis of 2,3-disubstituted benzofurans containing a trisubstituted alkene functionality. In this approach, alkynyl substituted benzyne **S1.22.A** in the presence of a palladium catalyst undergoes the ene reaction, resulting in an exocyclic allene intermediate, which, on reaction with arylhalide, results in a benzofuran derivative with an alkene functionality. The importance of this approach is that the heterocycles synthesized have potential applicability in biological systems and pharmaceuticals (Scheme S1.22).



Scheme S1.22: *Ma's approach for benzofuran synthesis*
(Yuan, W.; Ma, S. *Org. Lett.* **2014**, *16*, 193–195)

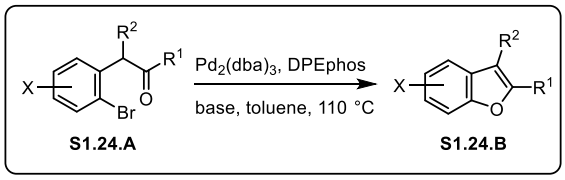
Guo *et al.* revealed a gold catalyzed approach for the synthesis of 2,3-disubstituted benzofurans. In this process, phenols, on reaction with disubstituted alkynes (**S1.23.A**) in the presence of the $Au(PPh_3)Cl$ catalyst and molecular oxygen trigger the formation of 2,3-disubstituted benzofurans in excellent yields. In this method, both C–C and C–O bonds are formed in one catalytic cycle (Scheme S1.23).



Scheme S1.23: *Guo's approach for benzofuran synthesis*
(Liao, J.; Guo, P.; Chen, Q. *Catal. Commun.* **2016**, *77*, 22–25)

1.9 Strategies involving the construction of the Ar–O bond of benzofuran (Type-4):

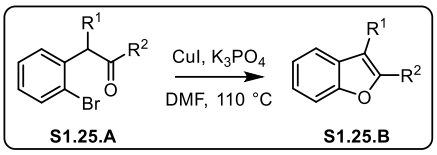
Willis and coworkers have developed an efficient strategy of benzofurans synthesis using the intramolecular *o*-arylation of enolates. Ketones **S1.24.A** in the presence of the $Pd_2(dba)_3$ catalyst, DPEphos ligand in toluene at 110 °C resulted in benzofuran derivatives. By employing this strategy, the synthesis of large number of benzofuran derivatives in excellent yields has been achieved.



Scheme S1.24: *Willis's intramolecular o-arylation approach*
(Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755–4757)

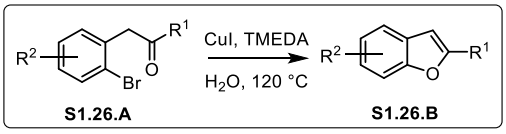
On similar lines, Chen's group revealed a copper catalyzed ring closure of 2-haloaromatic ketones as a method for the synthesis of diverse benzofuran derivatives.

Heating **S1.25.A** in the presence of CuI, K_3PO_4 in DMF at 110 °C resulted in the formation of the benzofuran nucleus (Scheme S1.25).



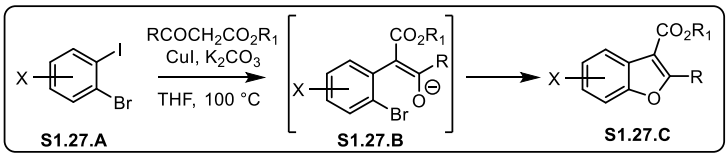
Scheme S1.25: *Chen's intramolecular o-arylation approach*
(Chen, C.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964–6967)

Dominguez and co-workers reported a copper-TMEDA complex mediated conversion of ketone derivatives to the corresponding benzofuran products. The ketone **S1.26.A** on heating in the presence of the copper-TMEDA complex at 120 °C in water resulted in the 2-substituted benzofuran **S1.26.B**. The current approach is environmental friendly as water is used as the solvent. Moreover, after extraction of the product, the left over water solution containing the copper complex can be reused for the reaction, making this process unique in benzofuran synthesis (Scheme S1.26).



Scheme S1.26: *Dominguez's intramolecular o-arylation*
(Carril, M.; Sanmartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, 8, 1467–1470)

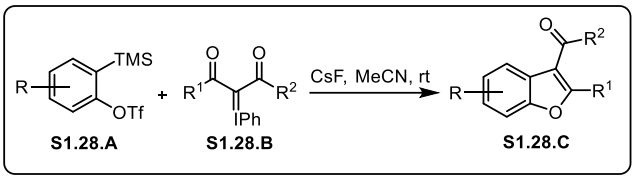
Ma's group reported the reaction 1-bromo-2-iodobenzenes β–keto esters in THF at 100 °C, which resulted in benzofuran-3-carboxylate derivatives *via* simultaneous formation an intermolecular C–C bond and an intramolecular C–O bond. This reaction showed tolerance to a variety of functional groups such as nitro, fluro, chloro, carboxylate, ketone, vinyl *etc.* during benzofuran synthesis (Scheme S1.27).



Scheme S1.27: *Ma approach for benzofuran synthesis*
(Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337–5341)

Li and coworkers revealed an aryne-based approach for benzofuran synthesis. In this method, *o*-silyl triflate **S1.28.A**, when treated with CsF, generates aryne, which then

undergoes cycloaddition with iodonium ylides **S1.28.B** resulting in the synthesis of 3-aroylbenzofuran derivatives. The reaction was performed at room temperature and was applied to a variety of substrates resulting in 2-substituted-3-aroylbenzofurans in excellent yields (Scheme S1.28).



Scheme S1.28: *Li approach for benzofuran synthesis*
(Huang, X.; Liu, Y.; Liang, Y.; Pi, S.; Wang, F.; Li, J. *Org. Lett.* **2008**, *10*, 1525–1528)

1.10 C–H activation:

The formation of the C–C bond plays a vital role in organic chemistry. Since the Wohler synthesis of urea in 1828, chemists have started developing methods for the construction of C–C and the C–heteroatom bond. In early part of the 19th century, the chemists mostly relayed on the alkali metals for the construction of C–C bonds. In 1855, a notable contribution came from Wurtz, when homodimerization of alkyl halides in the presence of sodium metal was achieved.[19] Following this, in 1862, Fittig extended it to the dimerization reaction to arylhalides under similar conditions.[20] In the latter part of the 19th century, chemists realized the role of transition metals for the construction of C–C bonds. In 1869, Glaser reported the dimerization of copper phenylacetylide to diphenyldiacetylene, which was highly appreciated by the scientific community.[21] Further, this reaction was employed for the synthesis of indigo by Baeyer in 1882.[22] The 20th century witnessed notable innovative contributions for the construction of C–C bonds. In 1901, Ullmann reported the dimerization of 2-bromo and 2-chloro nitrobenzenes in the presence of metallic copper.[23] Following this, in 1914, Bennett and Turner observed the dimerization of phenyl magnesium bromide in the presence of chromium chloride.[24] Till then, the chemistry of homodimerization was explored well but the earliest report of cross coupling chemistry came into existence with the report of Kharasch in 1941, where he revealed the coupling of vinyl halides with aryl magnesium halide in the presence of cobalt dichloride.[25] After this report, several groups developed strategies for cross couppling chemistry for the construction of the C–C bond. Till the mid 1970's chemists mainly

focused on acetylene coupling by the use of a copper catalyst and major drawback of most of these reactions was the use of a stoichiometric amount of metal salts, performing reactions at elevated temperatures and the formation of side products (homocoupled products). A revolution in cross coupling chemistry came with the reports of the independent research of Mizoroki (1971)[26] and Heck (1972)[27] where the cross coupling of aryl, styryl, benzyl halides with alkenes was carried out by employing catalytic amounts of the palladium catalyst without any homodimerized side products. This work opened up the future of palladium for the formation of C–C bonds. In 1975, a notable contribution came from Sonogashira whereby using a palladium catalyst, the coupling of $C(SP^2)$–C(SP) was carried out successfully.[28] The advantage of this reaction compared to many other reports is the feasibility of the reaction at room temperature. The latter part of the 20th century witnessed several cross couppling reactions which laid the foundation for modern organic chemistry. Some of the notable coupling reactions around this time include the Kumada coupling (1972, Grignard reagent),[29] Negishi coupling (1977, organozinc reagent),[30] Stille coupling (1978, organotin reagent),[31] Suzuki coupling (1979, organoboron reagent),[32] and Hiyama coupling (1988, organosilicon reagent).[33] These discoveries changed the face of modern organic chemistry. The major disadvantage with these coupling reactions is the use of prefunctionalised coupling partners which generally include toxic metals such as tin, zinc and boron reagents which are environmental hazards. Towards the end of the 20th and in beginning of the 21st century, chemists started looking towards developing efficient, economic, environmental friendly methods for the construction of C–C bonds by activating the C–H bond, which led to the discovery of C–H activation and C–H functionalization.

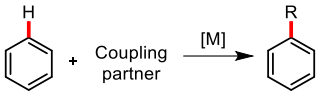
Over the last few decades, C–H activation has become an attractive strategy for the construction of C–C and C–heteroatoms bonds with the involvement of C–H bonds for the functionalization of organic molecules in the synthesis of pharmaceutical drugs. Initial approaches in C–H activation focused on developing methods for simple hydrocarbons but recently C–H activation has obtained a status where it is involved in the synthesis of complex organic molecules. The salient features of C–H activation include avoiding the prefunctionalized starting materials which shortens the synthetic route and makes it environmental friendly. The reaction having high atom economy has wide synthetic

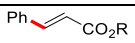
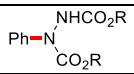
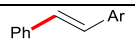
applicability. However some of the challenges associated with C–H activation include the low reactivity of the C–H bond, which forces the chemist to employ harsh reaction conditions, which sometimes may result in the formation of side products, lowering the yield of the required product. The other important aspect is that C–H bonds are ubiquitous in organic molecules and so the selective functionalization of a particular C–H bond is really a difficult task. Despite all these drawbacks, C–H activation remains an important strategy for the construction of the C–C bond in modern chemistry for the synthesis of various valued functional materials. Several transition metal complexes of palladium, rhodium, ruthenium, iridium, iron etc. have efficiently catalyzed the C–H activation. Initially, a stoichiometric amount of the metal catalyst is employed by chemists for the C–H activation process. In 1986, pioneering works of Lewis and Murai where *otho*-C–H activation of phenol or acetophenone with olefins or vinylsilanes respective was achieved by using catalytic amounts of ruthenium complexes showed the way towards the development of efficient, effective, cost limited catalytic methods for C–H activation.[34] Based on the mode of reaction, the C–H activation process can be broadly classified into two categories. The first is direct C–H activation and the second is chelation assisted C–H activation.

1.11 Direct C–H activation

Direct C–H activation refers to a reaction that occurs without employing any proximal chelating groups. Direct C–H activation has broad synthetic applications since it eliminates the introduction of a directing group and its removal after the reaction, which shortens the synthetic route and makes it more efficient, economic and environmentally friendly. Considering the fact that our work will be dealing mainly with directed C–H activation, only some of the latest and representative reports on the direct C–H functionalization reaction have been compiled in the following table.

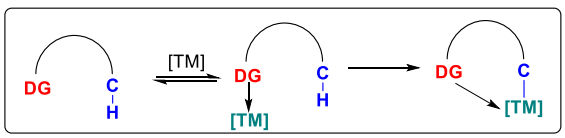
Table T1.1: *Literature reports on direct C–H Functionalization of arene*



S. No.	Coupling partner	Metal Catalyst	Product	Reference
1.	Et_3SiH	Rh	Ph–$SiEt_3$	*Organometallics* **1998**, *17*, 1455.
2.	$B_2(pin)_2$	Ir	Ph–Bpin	*J. Am. Chem. Soc.* **2002**, *124*, 390.
3.	$[Si(F_2)sBu]_2$	Ir	Ph–SiF_2sBu	*Angew. Chem. Int. Ed.* **2003**, *42*, 5346.
4.	H_2CO_2	Pd	Ph–CO_2H	*Tetrahedron Lett.* **2005**, *46*, 959.
5.	$HSi(OSiMe_3)_2Me$	Pt	Ph–$Si(OSiMe_3)_2Me$	*Chem. Lett.* **2007**, *36*, 910.
6.	IPh=NNs	Au	Ph–NHNS	*J. Am. Chem. Soc.* **2007**, *129*, 12058.
7.		Pd		*J. Am. Chem. Soc.* **2009**, *131*, 5072.
8.		Au		*J. Am. Chem. Soc.* **2010**, *132*, 1512.
9.	Ar-NH_2	Cu	Ph–NHAr	*Adv. Synth. Catal.* **2010**, *352*, 1301.
10.	NBS	Au	Ph–Br	*Angew. Chem. Int. Ed.* **2010**, *49*, 2028.
11.	$PhI(OAc)_2$	Pd	Ph–OAc	*Angew. Chem. Int. Ed.* **2011**, *50*, 9409.
12.	$RO_2C–N=N–CO_2R$	Au		*Org. Lett.* **2011**, *13*, 1872.
13.	O_2(air)	Cu	Ph–OH	*Angew. Chem. Int. Ed.* **2012**, *51*, 4666.
14.		Rh		*Org. Lett.* **2011**, *13*, 6346.

1.12 Chelation assisted C–H Activation:

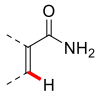
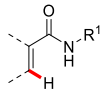
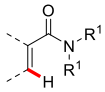
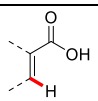
The direct functionalization of desired C–H bonds is a well desired transformation. In heterocyclic molecules, at least one C–H bond will have different reactivity compared to other C–H bonds due to electronic bias induced by the ring-heteroatom. In case of simple arenes, where all C–H bonds are supposed to have the same reactivity, selective functionalization of one of the C–H bonds over others will be extremely difficult and some special strategies/techniques will be required. Chelation assisted C–H activation is a method in which the reaction occurs in the presence of a directing group or a chelating group. In this approach, the metal first coordinates with the chelating group and then it activates the proximal C–H bond by forming metallacycle (Scheme S1.41**)**.

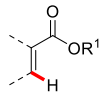
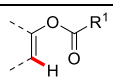


Scheme S1.29: *Representation of Chelation assisted C–H Activation*

Over a few decades, chelation assisted C–H activation has gained importance in synthetic organic chemistry for complex molecules synthesis. The advantage in using the directing group is due to its coordinating ability, thus bringing the transition metal in close proximity of the C–H bond, thus enhancing reaction rates and, importantly, the regioselectivity. Functional groups such as amides, acids, ketones, aldehydes, cyanides, hydroxyl groups, esters, amines and imines serve as efficient directing/chelating groups in C–H activations. The reports showing the usage of these directing groups in C–H arylation, alkenylation, alkylation and hydroxylation are formulated in the following table.

Table T1.2: *Chelating/Directing groups employed in C–H activation*

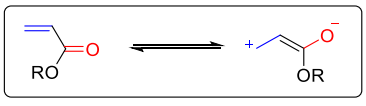
S. No.	Directing Group	C–H Functionalization	[Metal]	Reference
1.		Arylation	Pd	*Org. Chem.* **2012**, *77*, 3341.
2.		Arylation/Annulation	Pd	*Angew. Chem. Int. Ed.* **2011**, *50*, 1380.
		Alkoxylation	Pd	*Chem. – Eur. J.* **2013**, *19*, 11184.
		Olefination	Rh	*J. Org. Chem.* **2010**, *75*, 476.
		Alkylation/ Annulation	Rh	*J. Am. Chem. Soc.* **2013**, *135*, 5364.
		Allenylation	Rh	*J. Am. Chem. Soc.* **2013**, *135*, 18284.
		Alkynylation	Rh	*Angew. Chem. Int. Ed.* **2014**, *53*, 2722.
		Amination	Rh	*Org. Lett.* **2012**, *14*, 656.
		Hydroxyamination	Rh	*Chem. Commun.* **2014**, *50*, 4420.
3.		Arylation	Rh	*Angew. Chem. Int. Ed.* **2012**, *51*, 2247.
		Allylation	Rh	*Angew. Chem., Int. Ed.* **2013**, *52*, 5386.
		Alkynylation	Rh	*Chem. Commun.* **2014**, *50*, 4459.
		Acylation	Rh	*Chem. Commun.* **2013**, *49*, 1654.
		Halogenation	Rh	*J. Am. Chem. Soc.* **2012**, *134*, 8298.
		Hydroxylation	Ru	*Org. Lett.* **2012**, *14*, 4210.
4.		Arylation	Pd	*Org. Lett.* **2011**, *13*, 1286.
		Alkoxylation	Pd	*J. Org. Chem.* **2012**, *77*, 8362.
		Halogenation	Pd	*J. Org. Chem.* **2013**, *78*, 2786.
5.		Olefination	Rh	*J. Org. Chem.* **2011**, *76*, 3024.
		Arylation	Pd	*J. Am. Chem. Soc.* **2007**, *129*, 3510.
		Alkylation	Pd	*J. Am. Chem. Soc.* **2007**, *129*, 3510.
		Acylation	Rh	*Angew. Chem. Int. Ed.* **2013**, *52*, 6704
		Carboxylation	Pd	*J. Am. Chem. Soc.* **2008**, *130*, 14082.
		Hydroxylation	Pd	*J. Am. Chem. Soc.* **2009**, *131*, 14654
		Amination	Rh	*Chem. – Eur. J.* **2014**, *20*, 4474.
		Halogenation	Pd	*Org. Lett.* **2010**, *12*, 3140.
6.		Alkylation	Ru	*Org. Lett.* **2010**, *12*, 3038.
		Olefination	Ru	*Chem. Lett.* **1995**, 681.
		Arylation	Ru	*J. Am. Chem. Soc.* **2003**, *125*, 1689.
		Amidation	Pd	*J. Am. Chem. Soc.* **2011**, *133*, 1466.
		Hydroxylation	Ir	*Angew. Chem. Int. Ed.* **2014**, *53*, 2203.
		Alkylation/Annulation	Rh	*Org. Lett.* **2013**, *15*, 1476.
		Olefination/Annulation	Rh	*Org. Lett.* **2007**, *9*, 2203.
7.		Alkylation	Ru	*J. Am. Chem. Soc.* **1995**, *117*, 5371.

		Olefination	Ru	*Angew. Chem. Int. Ed.* **2009**, *48*, 5752.
		Borylation	Ir	*Eur. J. Org. Chem.* **2012**, 417.
		Hydroxylation	Ru	*Org. Lett.* **2012**, *14*, 2874.
		Halogenation	Pd	*Angew. Chem. Int. Ed.* **2013**, *52*, 4440.
		Amination	Ir	*Angew. Chem. Int. Ed.* **2014**, *53*, 2203.
8.		Arylation	Pd	*Org. Biomol. Chem.* **2009**, *7*, 4853.
		Olefination	Rh	*Org. Lett.* **2011**, *13*, 3235.
		Halogenation	Pd	*J. Org. Chem.* **2012**, *77*, 5600.
9.		Olefination	Ru	*J. Am. Chem. Soc.* **1986**, *108*, 2728.
		Arylation	Rh	*Angew. Chem. Int. Ed.* **2003**, *42*, 112.
10.		Alkenylation	Ru	*Org. Lett.* **2012**, *14*, 1134.
		Halogenation	Pd	*J. Am. Chem. Soc.* **2017**, *139*, 888.
		Hydroxylation	Ru	*Angew.Chem. Int. Ed.* **2014**, *53*, 11285.
		Amidation	Ir	*J. Org. Chem.* **2017**, *82*, 4497.

Despite a large amount of work that has been carried out during the last decade, this method has its own disadvantages, such as exclusive functionalization of *ortho* C–H bonds (with respect to the directing group), requiring additional steps to install and the removal/modification of a directing group. However, on several occasions, the directing heteroatom adds to the unsaturated units of the incoming electrophiles, thus leading to the annulation of heterocyclic rings. This is an important aspect especially when the resulting heterocyclic unit is part of any natural product scaffolds or in the marketed drugs. Currently, there is great deal of interest on developing traceless directing groups and the designer directing groups that can mediate selective functionalization of *meta* C–H bonds over the *ortho* C–H bonds. In the context of the focus of the next chapter that dealt mainly with the use of conjugated esters as electrophiles in the ruthenium-catalyzed C–H activation, a brief compilation of various reports wherein the conjugated olefins are used as electrophiles will be presented, with particular emphasis on hydroarylation of acrylates which is the main topic of interest.

1.13 Conjugated Olefins in C–H activation:

Acrylates contain a vinyl group in conjugation with a carboxylate group. Because of the withdrawing effect of carbonyl, the *β*–carbon becomes electrophilic and these compounds undergo nucleophilic additions. Acrylates are commonly used coupling partners in C–H activation.



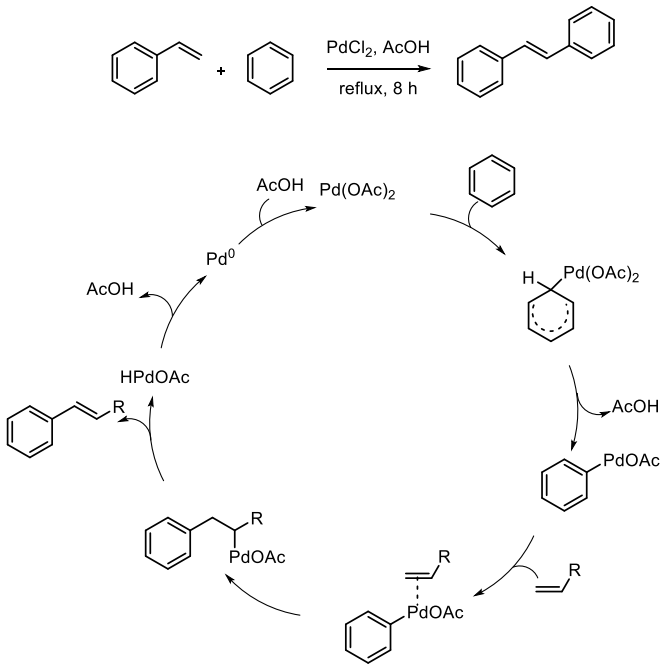
Scheme S1.30: *Resonance in acrylates*

Acrylates can undergo two types of reactions in C–H activation

1. Alkenylation (Cross dehydrogenative coupling)
2. Alkylation (Hydroarylation)

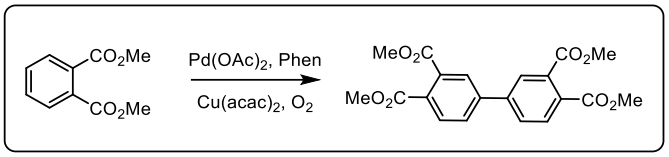
1.14: Cross dehydrogenative coupling (alkenylation) with acrylates in C–H activation

The Pd-catalyzed alkenylation of benzene with styrene documented by Fujiwara and Moritani in 1967 (Scheme S1.31), a year earlier to the Heck coupling reaction, is one of the classical examples for the cross dehydrogenative coupling *via* C–H activation. As the Fujiwara-Moritani type direct coupling reactions avoid the pre-functionalized starting compounds and thus reduce the generation of salt wastes, they have emerged as powerful alternatives to Heck type couplings.



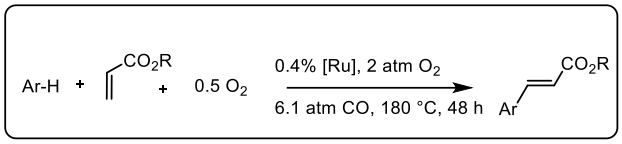
Scheme S1.31: Fujiwara-Moritani reaction and mechanism
(Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122)

The Pd-catalyzed direct homo-coupling of dimethyl phthalate leading to a biaryl species, developed by Ube Industries, is one of the early industrial applications of the Fujiwara-Moritani reaction (Scheme S1.32).



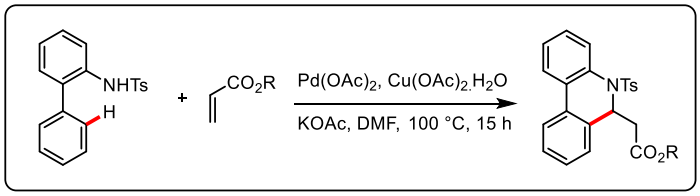
Scheme S1.32: *Synthesis of dimethyl phthalate*
(Shiotani, A.; Itatni, H.; Inagaki, T.; *J. Mol. Catal.* **1986**, *34*, 57–66)

Founded upon these, palladium complexes have been extensively studied in the direct cross dehydrogenative coupling reactions. The first example of the direct oxidative coupling of acrylate was presented by Milstein in 2001 using ruthenium (II or III) catalysts (Scheme S1.33).



Scheme S1.33: *Milstein approach for acrylate coupling*
(Weissman, H.; Song, X.; Milstein, D.; *J. Am. Chem. Soc.* **2001**, *123*, 337–338)

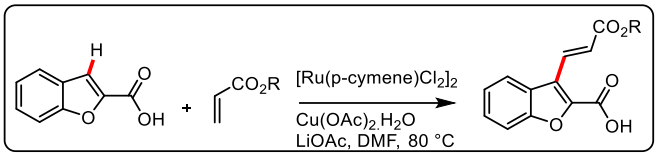
However, as mentioned earlier – the major drawbacks of the direct coupling reactions is the positional selectivity especially when there are several C–H bonds having similar reactivity. In 1998, Miura and co-workers reported one of the early examples on the directed cross dehydrogenative coupling of 2-phenylanilines with acrylates (Scheme S1.34) employing Pd-catalysis.



Scheme S1.34: *Miura approach for acrylate coupling*
(Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M.
J. Org. Chem. **1998**, *63*, 5211–5215)

Later, the van Leeuwen (2002) and the Lipshutz (2010) groups have documented milder reaction conditions for ortho-alkenylations of anilides with acrylates. These early successes on the Pd-catalyzed directed cross-dehydrogenative coupling of acrylates has led to the exploration of various other metal-complexes with a variety of directing groups. Coming to the use of acrylates as electrophiles in Ru-catalyzed cross-dehydrogenative couplings,

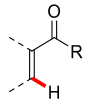
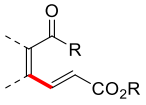
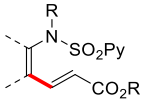
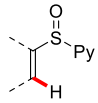
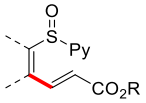
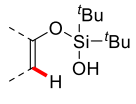
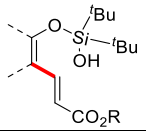
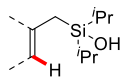
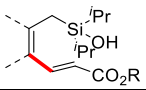
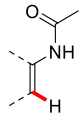
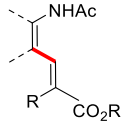
Satoh and Miura have documented the first report only recently in 2011, employing heteroarylcarboxylic acids (Scheme S1.35).

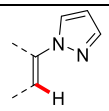
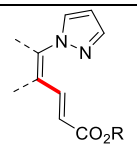
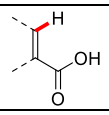
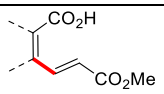
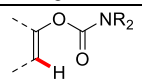
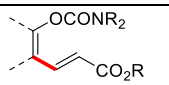
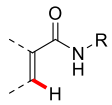
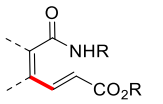
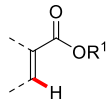
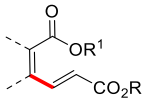
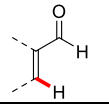
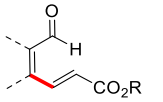
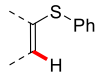
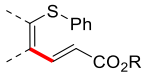
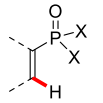
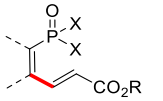
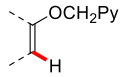
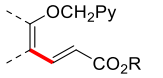
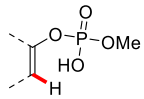
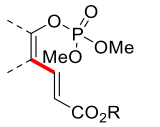
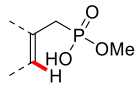
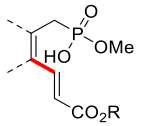
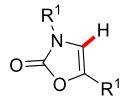
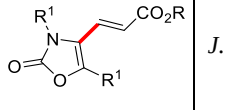
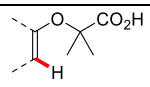
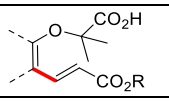


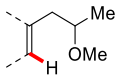
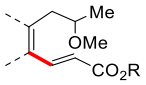
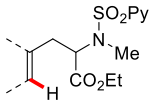
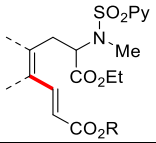
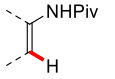
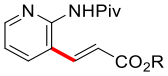
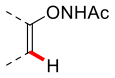
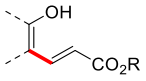
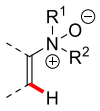
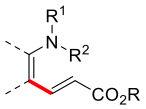
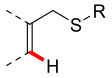
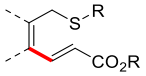
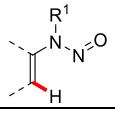
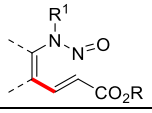
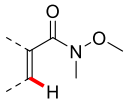
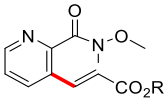
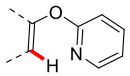
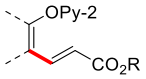
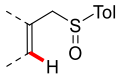
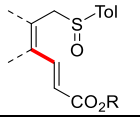
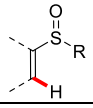
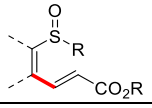
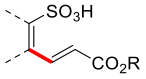
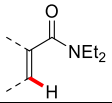
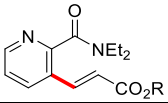
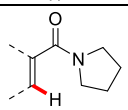
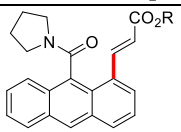
Scheme S1.35: *Miura approach for coupling of acrylate with heterocycle*
(Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M.
Org. Lett. **2011**, *13*, 706–708)

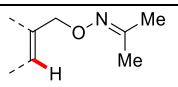
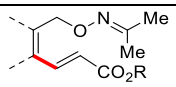
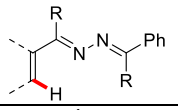
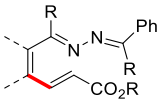
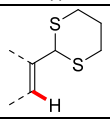
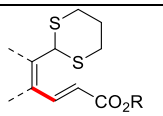
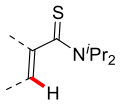
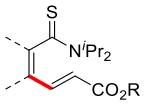
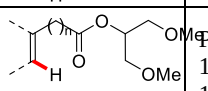
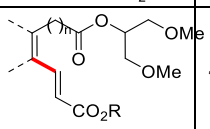
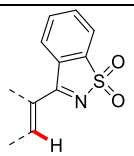
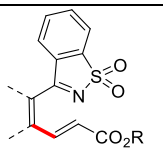
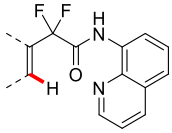
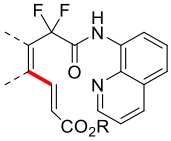
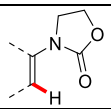
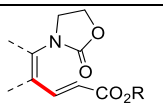
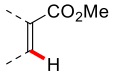
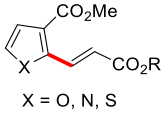
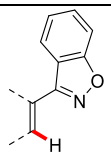
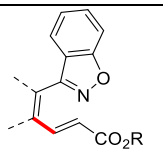
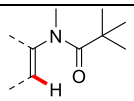
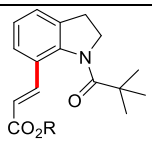
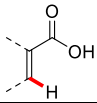
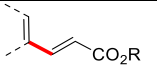
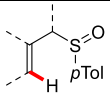
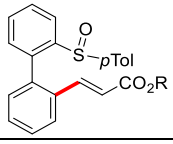
Since this early report on Ru-catalyzed cross-dehydrogenative coupling by Miura and Sato, many groups have explored this, employing a variety of weakly bonding functional groups (FG) as directing groups on a variety of arene and heterocycle derivatives. From 2011 onwards, there are more than 300 papers that have appeared on this topic and the contributions by the groups of Ackermann, Dixneuf and Jeganmohan are notable in this regard. As this topic has been covered extensively, some important findings have been mentioned in the Table T1.3 given below.

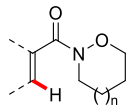
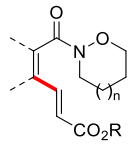
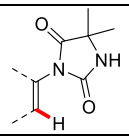
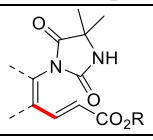
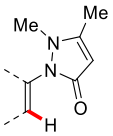
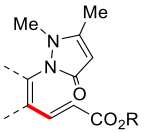
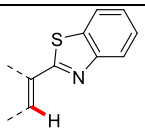
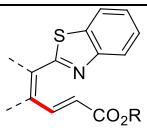
Table T1.3: *Dehydrogenative coupling reactions of acrylates in presence of various directing groups*

S. No.	Directing Group	Reaction conditions	product	Reference
1.		$[RuCl_2(P\text{-cymene})]_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ DCE, 110 °C, 12 h		*Org. Lett.* **2011**, *13*, 6144.
2.		$Pd(OAc)_2$, $[F^+]$ DCE, 110 °C, 12 h		*Angew. Chem. Int. Ed.* **2011**, *50*, 10927.
3.		$Pd(OAc)_2$, $Ag(OAc)_2$ CH_3CN, 80 °C, 12 h		*J. Org. Chem.* **2011**, *76*, 4987.
4.		$Pd(OAc)_2$ Boc-Val-OH Li_2CO_3, AgOAc DCE, 100 °C, 24 h		*J. Am. Chem. Soc.* **2011**, *133*, 12406.
5.		$Pd(OAc)_2$, AgOAc KH_2PO_4, $CHCl_3$ 100 °C, 16 h		*Chem. Eur. J.* **2011**, *17*, 14371.
6.		[a]$Pd(OAc)_2$, $Cu(OAc)_2$ TsOH, AcOH, $PhCO_3{}^tBu$, rt		[a]*J. Org. Chem.* **2011**, *76*, 8022. [b]*Chem. commun.* **2012**, *48*, 4350.

		[b]$Pd(OAc)_2$, TFA/CH_2Cl_2 $K_2S_2O_8$, 20 °C		
7.		[a][Ru(OAc)$_2$(*p*-cymene)] $Cu(OAc)_2.H_2O$ AcOH, 100 °C, 5 h, air [b][{$RuCl_2$(*P*-cymene)}$_2$] $Cu(OAc)_2.H_2O$ DMF, 100 °C, 4 h		[a]*Green Chem.* **2011**, *13*, 3075. [b]*Chem. Lett.* **2011**, *40*, 1165.
8.		[$RuCl_2$(*P*-cymene)]$_2$ $Cu(OAc)_2.H_2O$ LiOAc, DMF, 80 °C, 6 h		*Org. Lett.* **2011**, *13*, 706.
9.		[a][$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ DCE, 110 °C, 24 h		*Chem. commun.* **2012**, *48*, 11343. *Eur. J. Org. Chem.* **2013**, 1150.
10.		[a][$RuCl_2$(*P*-cymene)]$_2$ $Cu(OAc)_2.H_2O$, KPF_6 H_2O, 100 °C, 20 h [b][$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, AcOH DCE, rt, 24 h		[a]*Org. Lett.* **2012**, *14*, 728. [b]*ACS Catal.* **2016**, *6*, 230.
11.		[a]$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ DCE, 100 °C, 16 h, air [b]$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ THF, 100 °C, 12 h		[a]*Org. Lett.* **2012**, *14*, 4110. [b]*Chem. commun.* **2012**, *48*, 7140.
12.		$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ DCE, 100 °C, 16 h, air		*Org. Lett.* **2012**, *14*, 1134.
13.		$Pd(OAc)_2$ AgOTFA DCE, 100 °C, 12 h		*Org. Lett.* **2012**, *14*, 2164.
14.		$RhCp^*(CH_3CN)_3(SbF_6)_2$ $Cu(OAc)_2$, DCE 130 °C, 24 h, air		*Org. Lett.* **2013**, *15*, 4504.
15.		$Pd(OAc)_2$ Boc-Val-OH $KHCO_3$, *t*-AmylOH O_2, 90 °C, 20 h		*Chem. commun.* **2013**, *49*, 662.
16.		i) $Pd(OAc)_2$, AgOAc 1,4-dioxane 110 °C, 20 h ii)TMS-CHN2, CH3OH rt, 30 min		*Chem. commun.* **2013**, *49*, 4682.
17.		i) $Pd(OAc)_2$, AgOAc 1,4-dioxane, 110 °C, 20 h ii)TMS-CHN_2, CH_3OH rt, 30 min		*Org. Lett.* **2013**, *15*, 1910.
18.		$Pd(OAc)_2$, $Cu(OAc)_2$ DMF/NMP (2:1) 100 °C, 8–16h, air		*J. Org. Chem.* **2013**, *78*, 10894.
19.		$Pd(OAc)_2$, Boc-Val-OH $KHCO_3$, ^{t}AmylOH O_2, 90 °C, 24 h		*J. Am. Chem. Soc.* **2013**, *135*, 7567.

20.		$Pd(OAc)_2$, Ac-Gly-OH Ag_2CO_3, HFIP, 80 °C, 24h		*Angew. Chem. Int. Ed.* **2013**, *52*, 1245.
21.		$Pd(OAc)_2$, $[F^+]$ AcOH, 110 °C, 18 h		*Org. Lett.* **2013**, *15*, 4504.
22.		$[Cp^*RhCl_2]_2$ $AgSbF_6$, $Cu(OAc)_2$ DCE, 120 °C, 24 h		*Org. Lett.* **2013**, *15*, 3460.
23.		$[Cp^*RhCl_2]_2$, CsOAc EtOH, 50 °C, 8 h		*Org. Lett.* **2013**, *13*, 3366.
24.		$[Cp^*RhCl_2]_2$, $AgSbF_6$ CuOPiv, PivOH MeOH, rt, 24 h, N_2		*Angew. Chem. Int. Ed.* **2013**, *52*, 12970.
25.		$[Cp^*Rh(MeCN)_3][SbF_6]_2$ $Cu(OAc)_2$, AgOAc MeOH, 120 °C, 24 h		*Chem. Eur. J.* **2013**, *19*, 11898.
26.		$[Cp^*RhCl_2]_2$ $AgSbF_6$, AgOAc MeOH, 60 °C, 12 h		*J. Am. Chem. Soc.* **2013**, *135*, 468.
27.		$[Cp^*RhCl_2]_2$ $AgSbF_6$, $Cu(OAc)_2$ DCE, 120 °C, 1 h		*Adv. Synth. Catal.* **2013**, *355*, 1724.
28.		[a] $[RuCl_2(P\text{-cymene})]_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ *t*AmOH, 120 °C, 16 h, air [b] $Pd(OAc)_2$ $MeNO_2$-DMPU (20:1) O_2, 100 °C [c] $[Cp^*RhCl_2]_2$ $AgSbF_6$, $Cu(OAc)_2$ MeOH, 110 °C, 15 h		[a] *Chem. Eur. J.* **2013**, *19*, 13925. [b] *J. Org. Chem.* **2014**, *79*, 1521. [c] *Eur. J. Org. Chem.* **2015**, 4782.
29.		$Pd(OAc)_2$ Selectfluor TFA, DCE, 100 °C, 24 h		*Org. Lett.* **2014**, *16*, 46.
30.		$[Cp^*Rh(MeCN)_2][SbF_6]_2$ Ag_2CO_3, PhCl 120 °C, 6 h		*Org. Lett.* **2014**, *16*, 1188.
31.		$RuCl_2(P\text{-cymene})]_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ DMA, 120 °C, 16 h		*Chem. Eur. J.* **2014**, *20*, 15251.
32.		$[Cp^*RhCl_2]_2$ $AgSbF_6$, $Cu(OAc)_2$ DCE, 120 °C, 24 h		*Adv. Synth. Catal.* **2014**, *356*, 1038.
33.		$[Cp^*Rh(MeCN)_3][SbF_6]_2$ $Cu(OAc)_2.H_2O$ DCE, 110 °C, 12 h		*Org. Lett.* **2014**, *16*, 4224.

34.		$Pd(OAc)_2$, Ac-Val-OH AgOAc, 1,4-dioxane 90 °C, 12 h		*Org. Lett.* **2015**, *17*, *1802*.
35.		$[Cp^*RhCl_2]_2$, $Cu(OAc)_2$ MeCN, 40 °C, 12 h		*J. Org. Chem.* **2015**, *80*, 10457.
36.		$[Cp^*Rh(MeCN)_3][SbF_6]_2$ $Cu(OAc)_2.H_2O$ THF, 60 °C, 24 h		*Org. Lett.* **2015**, *17*, 704.
37.		$[Cp^*Rh(MeCN)_3][SbF_6]_2$ $Cu(OAc)_2.H_2O$ 1,4-dioxane, 120 °C, 24 h		*Chem. Lett.* **2015**, *44*, 1104.
38.		$Pd(OAc)_2$, Ag_2CO_3 1,10-phenanthroline 1-AdOH, HFIP 100 °C, 24 h		*J. Org. Chem.* **2015**, *80*, 7896.
39.		$RuCl_2(P\text{-cymene})]_2$ $AgSbF_6$, AgOAc DCE, 100 °C, 24 h		*Eur. J. Org. Chem.* **2016**, 4013.
40.		$Pd(OAc)_2$ BQ, TFA DCE, 140 °C, 6 h		*Eur. J. Org. Chem.* **2016**, 5529.
41.		$RuCl_2(P\text{-cymene})]_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ 2-MeTHF, 120 °C, 18 h		[b]*ACS Catal.* **2016**, *6*, 5520.
42.		$RuCl_2(P\text{-cymene})]_2$ $Cu(OAc)_2.H_2O$ 100 °C, 24 h	 X = O, N, S	*Adv. Synth. Catal.* **2016**, *358*, 4129.
43.		$[Cp^*RhCl_2]_2$ $Cu(OAc)_2$ NaOAC, DCE 90°C, 24 h		*J. Org. Chem.* **2016**, *81*, 12169.
44.		$RuCl_2(P\text{-cymene})]_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ THF, 100 °C, 20 h, air		*Org. Chem. Front.* **2016**, *3*, 1271.
45.		$[Ru(O_2CMes)_2(p\text{-}$ Cymene) PhMe, 100 °C, 24 h, N_2		*Angew. Chem. Int. Ed.* **2016**, *55*, 6929.
46.		$Pd(OAc)_2$ AgOAc DCE, 80 °C, 6 h		*Chem. Eur. J.* **2016**, *22*, 1735.

47.		$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ DCE, 100 °C, 16 h, air		*Chem. Eur. J.* **2016**, *22*, 16986.
48.		$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ 2-MeTHF, 100 °C, 18 h, air		*J. Org. Chem.* **2016**, *81*, 10081.
49.		$RuCl_2$(*P*-cymene)]$_2$ $AgSbF_6$, $Cu(OAc)_2.H_2O$ 1,4-ioxane, 100 °C, 4 h		*Adv. Synth. Catal.* **2017**, *359*, 966.
50.		$RuCl_2$(*P*-cymene)]$_2$ $Cu(OAc)_2.H_2O$ H_2O, KPF_6 SDBS, 80 °C, 24 h		*Tetrahedron* **2017**, *73*, 594.

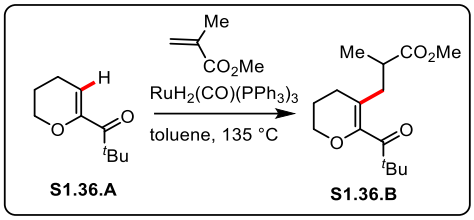
From the selected examples provided in the above table, it is evident that the cross dehydrogenative coupling of acrylates has seen extensive efforts by employing various metal catalysts and diverse directing groups. In most of the cases, the products have been obtained in high regioselectivity with excellent diastereoselectivity. In almost all the cases, the products are obtained in high yields and in many cases, the reaction has been explored in gram scale, making it a vital process at the industrial level. Further, in some cases, the reaction has been applied in the context of the total synthesis of natural products. However, the alkylation reactions of acrylates are still in premature level. Following are a few examples that have appeared before our group disclosed early reports on the Ru-catalyzed alkylation with acrylates.

1.15: Alkylation of acrylates in C–H activation:

The carbonyl-directed ortho-alkylaton of acetophenones with vinylsilanes reported by Miura and Chatani is a trendsetter in the history of C–H functionalization. However, the alkylation reaction with acrylates in C–H activation is less explored compared to alkenylation reactions.

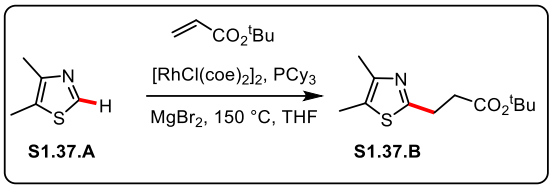
Murai and Chatani developed an efficient method of C–H alkylation of dihydopyran derivatives using ruthenium catalysis. In this approach, substrate **S1.36.A** on reaction with methylmethacrylate in the presence of the $RuH_2(CO)(PPh_3)_3$ catalyst results in the C–H alkylation product in 30% yield, whereas by employing other coupling partners, the

reaction resulted in excellent yields of alkylation products. As a result, it was concluded that acrylates are not good coupling partners in C–H alkylation reaction (Scheme S1.36).



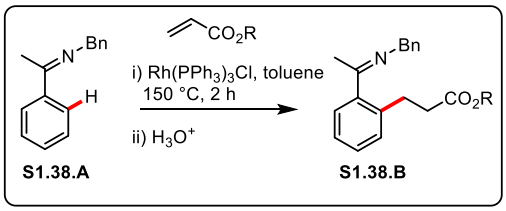
Scheme S1.36: *Murai approach for alkylation of dihydopyran derivatives*
(Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679–680)

Ellman and coworkers reported the rhodium catalyzed C–H alkylation of 4,5-dimethylthiazole. In this approach, substrate **S1.37.A** on reaction with terbutylacrylate in the presence of $[RhCl(coe)_2]_2$ at 150 °C in THF results in the formation of the alkylation product in 93% yield (Scheme S1.37).



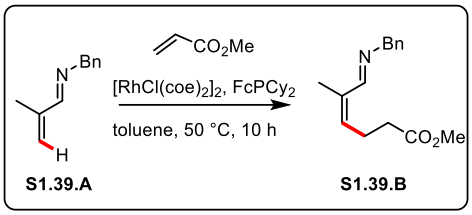
Scheme S1.37: *Ellman approach for alkylation of 4,5-dimethylthiazole*
(Tan. K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*, **2002**, *124*, 13964)

Jun and coworkers have reported the rhodium catalyzed *ortho* C–H alkylation of the imines of aromatic ketones. In this method, substituted imines **S1.38.A** on reaction with acrylate in the presence of Wilkinson's catalyst at 150 °C for 2 h undrgo *ortho*-alkylation, subsequent hydrolysis produces *ortho* functionalized aromatic ketones with excellent yields. A wide range of acrylates were employed in the current transformation, resulting in the corresponding *ortho* functionalized ketones (Scheme S1.38).



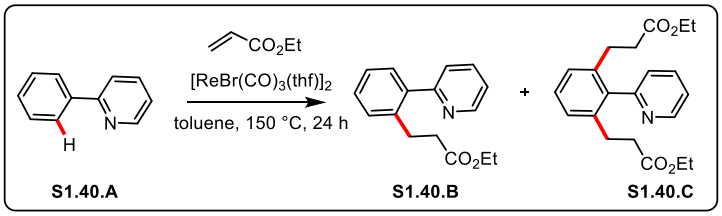
Scheme S1.38: *Jun approach for alkylation of imines*
(Lim, S.; Ahn, J.; Jun, C. *Org. Lett.* **2004**, *6*, 4687–4690)

Ellman *et al.* reported the alkylation of α, β-unsaturated imines with acrylates using the rhodium catalyst. In this approach, substrate **S1.39.A**, on reaction with methyl acrylate or ethyl acrylate in the presence of the active catalyst obtained by the reaction of $[RhCl(coe)_2]_2$ catalyst with (dicyclo-hexylphosphinyl)ferrocene ligand in toluene at 50 °C for 10 h gave the alkylation product **S1.39.B** in excellent yield (Scheme S1.39).



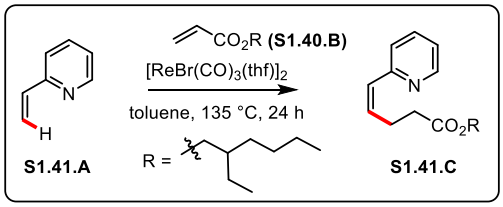
Scheme S1.39: *Ellman approach for alkylation of* α, β-unsaturated imines
(Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2006**, *128*, 5604)

Takai *et al.* reported the alkylation of 2-phenylpyridine catalyzed by a rhenium catalyst. In this report, substituted 2-phenylpyridines **S1.40.A** on reaction with ethyl acrylate in presence of $[ReBr(CO)_3(thf)]_2$ catalyst in toluene at 150 °C for 24 h gave the monoalkylated **S1.40.B** as the major product along with minor amounts of the dialkylation product **S1.40.B**. In this approach, even the $Re_2(CO)_{10}$ catalyst effectively catalyzed the alkylation reaction (Scheme S1.40).



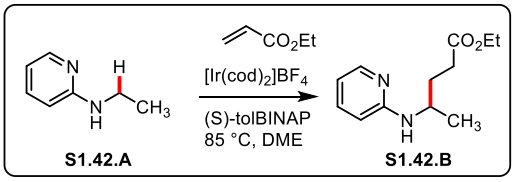
Scheme S1.40: *Takai approach for alkylation of 2-phenylpyridine*
(Kuninobu, Y.; Nishina, Y.; Okaguchi, K.; Shouho, M.; Takai, K.
Bull. Chem.Soc.Jpn. **2008**, *81*, 1393–1401)

Takai and coworkers reported the rhenium catalyzed alkylation of olefins with acrylates. In this method, substituted olefin substrates **S1.41.A**, on reaction with acrylate **S1.41.B** in the presence of $[ReBr(CO)_3(thf)]_2$ catalyst in toluene at 135 °C for 24 h results in formation of alkylation products (Scheme S1.41).



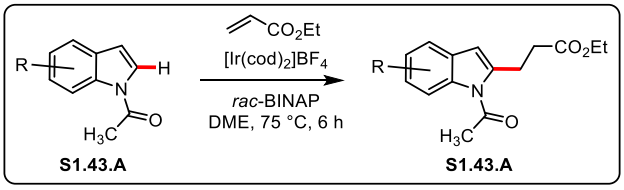
Scheme S1.41: *Takai approach for alkylation of olefins*
(Kuninobu, Y.; Fujii, Y.; Matsuki, T.; Nishina, Y.; Takai, K. *Org. Lett*. **2009**, *11*, 2711–2714)

Shibata and coworkers reported a unique approach for iridium catalyzed enantioselective sp^3 C–H activation of 2-(alkylamino) pyridines. In this method, (**S1.42.A**), on reaction with ethyl or terbutyl acrylate in the presence of the $[Ir(cod)_2]BF_4$ catalyst, (S)-tolBINAP ligand in DME at 85 °C underwent enantioselective sp^3 C–H alkylation with 99% and 89% *ee* in case of ethyl and terbutylacrylate respectively (Scheme S1.42).



Scheme S1.42: *Takai approach for alkylation of 2-(alkylamino) pyridines*
(Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. *Tetrahedron*, **2012**, *68*, 9009–9015)

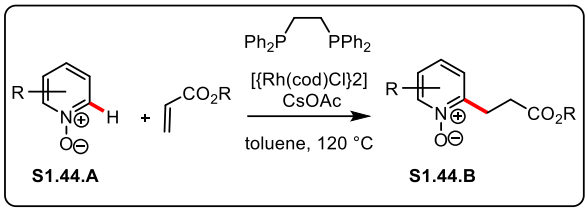
Shibata *et al* reported the iridium catalyzed linear alkylation of *N*-acetylindole with acrylate. In this approach, the substituted *N*-acetylindole derivatives (**S1.43.A**) react with ethyl acrylate in the presence of the $[Ir(cod)_2]BF_4$ catalyst, *rac*-BINAP ligand in DME at 75 °C for 6 h resulting in the formation of the linear alkylation product (**S1.43.A**) in excellent yields. However, by using *N*-benzoylindole, the branched alkylation products were predominantly formed (Scheme S1.43).



Scheme S1.43: *Takai approach for alkylation of N-Acetylindole*
(Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474–17477)

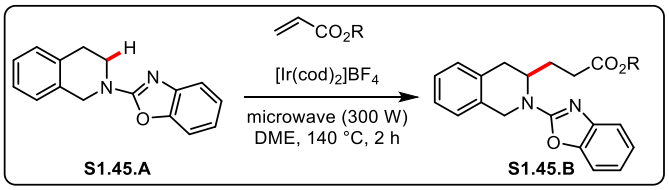
Chang *et al.* revealed a novel method for the alkylation of pyridine *N*-oxides with acrylates using the rhodium catalyst. In this method, a base co-catalyst is vital for product

formation. A larger number of substrates, including electron donating and electron withdrawing pyridine *N*-oxides showed compatibility in the reaction, resulting in alkylation products in excellent yields (Scheme S1.44).



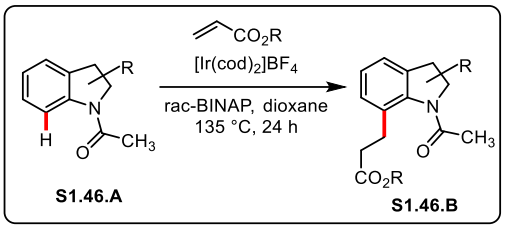
Scheme S1.44: *Chang approach for alkylation of pyridine N-oxides*
(Ryu, J.; Cho, S. H.; Chang, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3677–3681)

Opatz and coworkers reported microwave assisted iridium catalyzed sp^3 C–H activation of secondary amines using the benzoxazole moiety as a removable directing group. In this approach, the substrate **S1.45.A**, on reaction with various acrylates in the presence of the $[Ir(cod)_2]BF_4$ under microwave irradiation at 300 W in DME at 140 °C for 2 h resulted in alkylation product (Scheme S1.45).



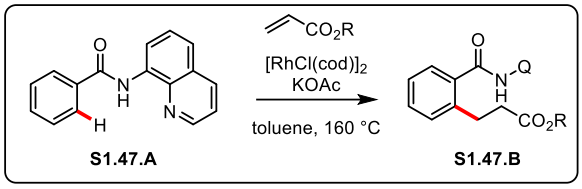
Scheme S1.45: *Opatz approach for alkylation of secondary amines*
(Lahm, G.; Opatz, T. *Org. Lett*. **2014**, *16*, 4201–4203)

Shibata *et al.* reported the C–7 alkylation of indolines catalyzed by the iridium catalyst. In this method, substituted indolines **S1.46.A**, on reaction with acrylates in the presence of $[Ir(cod)_2]BF_4$, *rac*-BINAP in1,4-dioxane at 135 °C for 24 h resulted in C–7 alkylation with excellent yields (Scheme S1.46).



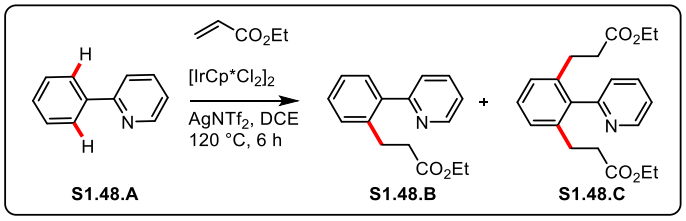
Scheme S1.46: *Shibata approach for alkylation of indolines*
(Pan, S.; Ryu, N.; Shibata, T. *Adv. Synth. Catal*. **2014**, *356*, 929–933)

Chatani and coworkers developed an attractive strategy for the alkylation of aromatic amides containing the 8-aminoquinoline (8-AQ) moiety using acrylates as coupling partners. In this process, substrate **S1.47.A** on reaction with acrylate in the presence of $[RhCl(cod)]_2$ in toluene at 160 °C resulted in *ortho*-alkylation products in good yields (Scheme S1.47).



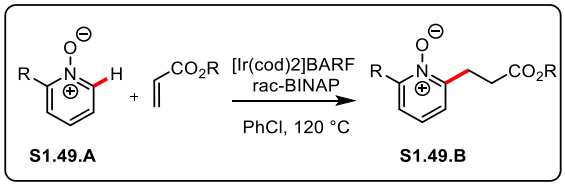
Scheme S1.47: *Chatani's 8AQ-directed alkylation of aromatic amide*
(Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148–5151)

Chang and coworkers reported a iridium catalyzed C–H alkylation of 2-phenyl pyridine. In this method, $[IrCp^*Cl_2]_2$ in the presence of $AgNTf_2$ formed the active catalyst, which then catalyzed the alkylation of substituted 2-phenylpyridine with ethyl acrylate in DCE at 120 °C in excellent yields (Scheme S1.48).



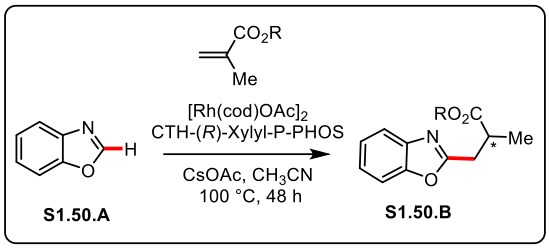
Scheme S1.48: *Cheng approach for alkylation of 2-phenyl pyridine*
(Kim, J.; Park, S.; Baik, M.; Chang, S. *J. Am. Chem. Soc*. **2015**, *137*, 13448–13451)

Shibata's group revealed an approach for the C–6 alkylation of 2-substituted pyridine *N*-oxides with acrylates. Heating a mixture of substrate **S1.49.A** and acrylate in the presence of the iridium catalyst and the BINAP ligand in chlorobenzene at 120 °C resulted in the formation of C–6 alkylation of pyridine *N*-oxides in excellent yields (Scheme S1.49).



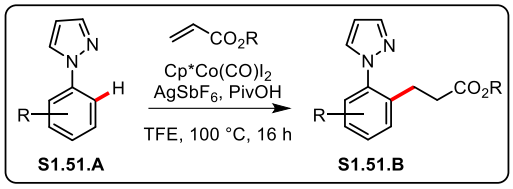
Scheme S1.49: *Shibata approach for alkylation of pyridine N-oxides*
(Shibata, T.; Takano, H. *Org. Chem. Front.* **2015**, *2*, 383–387)

Rovis and coworkers reported the rhodium catalyzed enantioselective C–H activation of benzoxazoles using metha acrylates as coupling partners. In this approach, substituted benzoxazoles, on reaction with metha acrylates, in the presence of $[Rh(cod)OAc]_2$ and the chiral CTH-(*R*)-Xylyl-P-PHOS ligand in CH_3CN at 100 °C for 48 h gave C–2 alkylation with excellent yields and *ee* (Scheme S1.50).



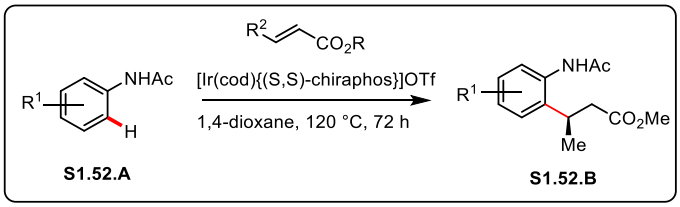
Scheme S1.50: *Rovis' approach for enantioselective alkylation of benzoxazoles*
(Filloux, C. M.; Rovis, T. *J. Am. Chem. Soc*. **2015**, *137*, 508–517)

Sundararaju and coworkers reported the cobalt catalyzed alkylation of N-phenyl imidazoles with acrylates as coupling partners. In this approach, substituted *N*-phenylimidazoles, on reaction with acrylates in the presence of $Cp^*Co(CO)I_2$, $AgSbF_6$ and PivOH in TFE at 100 °C for 16 h formed monoalkylation products in excellent yields (Scheme S1.51).



Scheme S1.51: *Pyrazole directed alkylation of N-phenyl imidazoles*
(Barsu, N.; Emayavaramban, B.; Sundararaju, B. *Eur. J. Org. Chem.* **2017**, 4370–4374)

Shibata and coworkers reported an efficient method of enantioselective alkylation of acetanilides using β substituted α,β-unsaturated esters. In this approach, the substrate **S1.52.A** on reaction with methyl crotonate in the presence of chiral iridium catalyst renders alkylation products with high *ee*. The significance of this reaction is a variety of chiral δ aminoacids derivatives with an excellent *ee* have been synthesized using commercially available staring materials (Scheme S1.52).



Scheme S1.52: *Shibata approach for alkylation of acetanilides*
(Shibata, T.; Michino, M.; Kurita, H.; Tahara, Y.; Kanyiva, K. S. *Chem. Eur. J.* **2017**, *23*, 88–91)

From the reports described above on C–H activation, it is evident that a lot of work on the alkenylation reaction [**Fujiwara-Moritani reaction**] of acrylates using various directing groups has been documented. Extensive research by employing various metal catalysts has been reported. In most of the cases, the products were obtained in high regioselectivity with excellent diastereoselectivity. In almost all the cases, the products were obtained in high yields and in many cases, the reaction was explored in gram scale, making them vital processes at industrial level. Further, in some cases, the reaction was applied in the context of the total synthesis of natural products. However, the alkylation reactions of acrylates [**Murai Reaction**] are still at an early stage. Even though the Murai report on the *ortho*-alkylation of aromatic ketones employing vinylsilanes dates back to in 1993, after that, sufficient scientific reports on alkylation did not exist till date. Only a few research publications, which have been described above, show the alkylation reaction with acrylates. These reports suffer from several disadvantages, such as the lack of substrate scope, notwithstanding sensitive functional groups, the feasibility of the reaction in only milligram scale etc. The use of various directing groups with different transition metal catalyst has not been explored for the alkylation with acrylates, compared to the alkenylation reaction. Thus, we have taken up this challenge in the context of synthesizing functionalized 2/3-aroyl-2-(benzofuran-2/3-yl)acetate and 2/3-aroyl-3-(benzofuran-2/3-yl)propanoate derivatives – the scaffolds that are found in various natural products and marketed drugs. As one could notice, the realization of all these four scaffolds requires the possibility of carrying out selective linear and branched alkylation with acrylates. In the next part of this section is provided a comprehensive investigation that has been carried out in this pursuit and that reveals some fundamentally important aspects of the C–H activation.

1.16 Results and discussion:

Benzofuran is an important structural motif with widespread occurrence in natural products and in pharmaceutically important drugs. For instance, 2-aroylbenzofuran-3-yl-propionate derivatives are reported to possess anti-inflamatory activity and drugs like budiodarone, amiodarone, benzbromarone, and dronedarone contain the 3-aroylbenzofuran moiety which acts as antiarrhythmic, uricosuric, and antitubulin agents.[35] Budiodarone, especially, is an antiarrhythmic drug which is presently in clinical trials. The reported methods for the synthesis of these drug molecules include classical acid/base catalyzed condensations and Friedel-Crafts alkylation/aroylation both of which involve harsh reaction conditions and are generally multistep in nature. Therefore an alternative approaches for the synthesis of these drug molecules is much demanding and has been neglected so far by the scientific community.

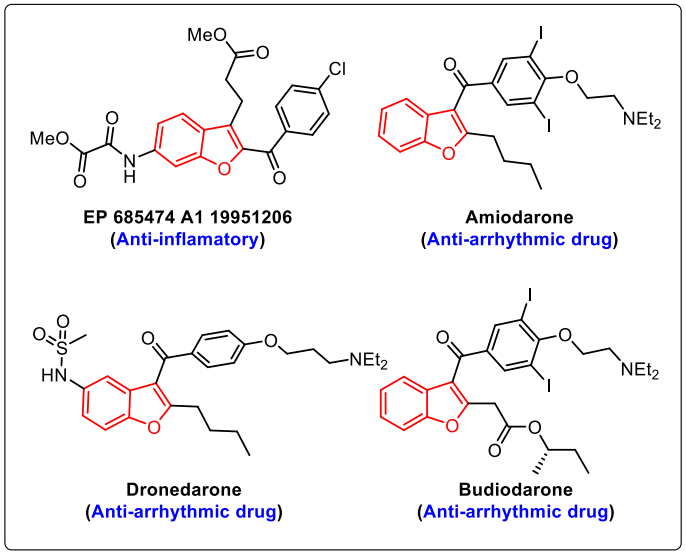


Figure F1.5: *Pharmaceutical drugs containing 2-/3-aroylbenzofuran moieties*

A close examination of the benzofuran moiety in pharmaceutical drugs and drug candidates has revealed four different types of benzofuran scaffolds. Type-1 and Type-2 moieties contain the 2-aroylbenzofuran moiety and functionalization can be achieved at the C3 position. Type-3 and Type-4 molecules contain the 3-aroylbenzofuran moiety and functionalization can be achieved at the C2 position. While Type-1 and Type-2 represent some investigational drug candidates, the Type-3 and type-4 structural motifs closely resemble the amiodarone and budiodarone drug molecules. Thus, developing a one-step

strategy for the functionalization of these molecules should provide an easy access to a large number of benzofuran derivatives for biological activity studies. The C2/C3-aroyl moiety present in this class of molecules provides a ready handle for the diversification at C3/C2 *via* carbonyl directed C–H functionalization. Quite surprisingly, there are no reports in this direction so far. The following are the few literature reports that reveal the functionalization of benzofurans using the C–H activation strategy.

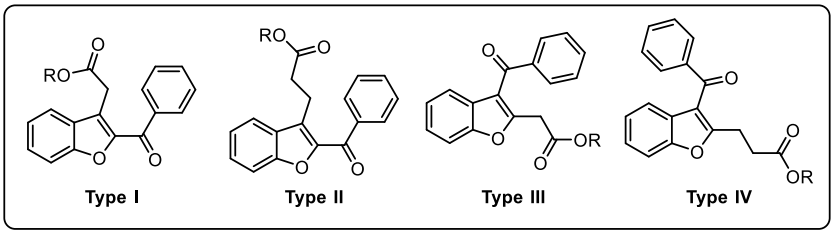
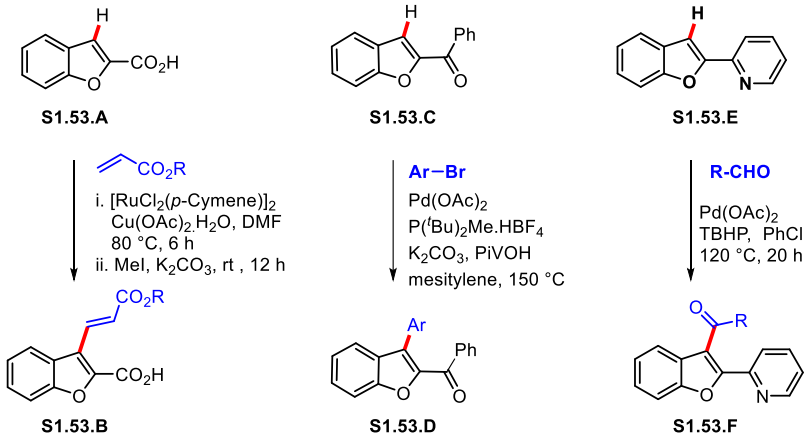


Figure F1.6: *Representative benzofuran Scaffolds*

1.17 Literature survey of C–H activation on benzofurans:

Miura *et al.* reported the *ortho*-C–H alkenyltaion of the benzofuran-2-carboxylic acid using acrylates as coupling partners employing $[RuCl_2(p\text{-cymene})]_2$ as a catalyst, and $Cu(OAc)_2.H_2O$ as oxidant leading to the alkenylated products in good yields (Scheme S1.53).[36] On the other hand, Bertounesque and co-workers reported the Pd-catalyzed C3 arylation of 2-aroylbenzofurans using arylhalides as coupling partners (Scheme S1.53).[37] Yi's group reported a pyridine-directed Pd-catalyzed C3 acylation of benzofuran by cross dehydrogenative coupling with aldehydes (Scheme S1.53).[38]

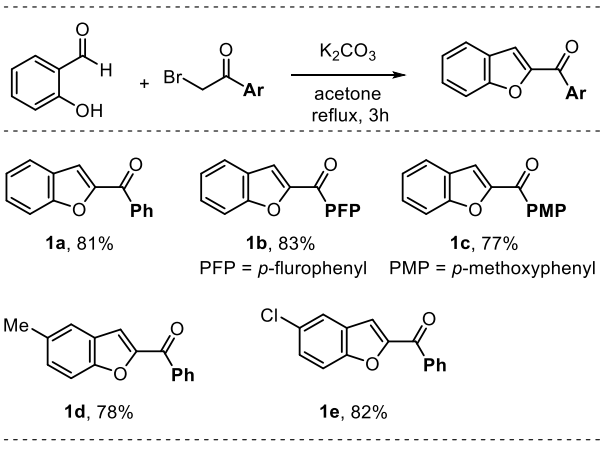


Scheme S1.53: *Literature reported "directed C–H functionalizations" on the benzofuran ring*

From the above reports, it is evident that alkenylation, acylation, arylation reactions on benzofuran has been explored well by the scientific community. But many of the benzofuran drugs, as shown in Figure F1.5, contain the alkyl group either at the C2 or the C3 position, even though the alkylation reaction on benzofuran has not been explored till date. This has inspired us to investigate the possibility of the carbonyl directed C3 alkylation of 2-aroylbenzofurans using the α,β-unsaturated carbonyl compounds. Needless to say, alkylation with acrylates is still a big challenge with any known metal catalyst, because many endeavours end up with only alkenylation as the sole product and very few reports deal with alkylation employing rhodium and rhenium catalysts. Towards this end, we started our journey with the synthesis of simple 2-aroylbenzofuran.

1.18 Present work:

Five representative 2-aroylbenzofurans **1a** – **1e**, have been synthesized according to the reported procedures.[39] The employed method involves refluxing a mixture of salicylaldehyde and 2-bromoacetophenone in acetone in the presence of K_2CO_3 (Scheme S1.54).

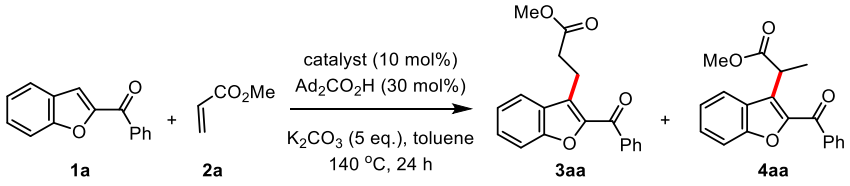


Scheme S1.54: *Synthesis of 2-aroylbenzofurans*

Initially, the simple 2-benzoylbenzofuran **1a** has been selected as the model substrate for examining the ruthenium catalyzed C3 functionalization with methyl acrylate. From the literature reports, it is evident that employing oxidants such as $Cu(OAc)_2$ facilitates dehydrogenative coupling, resulting in alkenylation products. We therefore thought of avoiding the use of such oxidants in our reaction. Furthermore, in general,

cationic ruthenium complexes are mostly employed, which results in dehydrogenative coupling products. We hypothesized that by employing neutral ruthenium complexes there may be a change for the alkylation over the alkenylation. With this hypothesis, our initial studies began with investigation of the optimal ruthenium catalyst for the desired transformation by employing conditions commonly encountered in ruthenium catalyzed directed C–H activation and screened various commercial ruthenium catalyst. Initial conditions employed are borrowed from the reports of Ackermann's group and involve heating a mixture of 2-aroylbenzofuran (**1a**, 1 equiv) with methyl acrylate (**2a**, 3 equiv) in the presence of the Ru(II) catalyst (10 mol%), adamantane-1-carboxylic acid (30 mol%) and K_2CO_3 (5 equiv) in toluene at 140 °C for 24 h in a screw capped pressure. As shown in Table T1.4, the formation of two products, with varying proportions depending upon the catalyst, was observed. On careful analysis of the NMR of products formed in the reaction revealed that along with the linear alkylation product **3aa** that we had aimed for, there is the formation of the branched alkylation product **4aa**. The structures of these two products have been established with the help of NMR data.

Table T1.4: *Catalyst screening for C3-functionalization of 2-benzoylbenzofuran with methyl acrylate*



S.No	Catalyst	Yield (%)[a] (**3aa**/**4aa**)
1	**[Ru(*p*-cymene)Cl$_2$]$_2$**	**23 (72/28)**
2	$Ru_3(CO)_{12}$	31(17/83)
3	$RuCl_3.H_2O$	nd
4	RuO_2	No reaction
5	$(PPh_3)_3Ru(CO)H_2$	73 (11/83)
6	**Ru(PPh$_3$)$_3$Cl$_2$**	**82 (6/94)**

[a]isolated yield; nd = not determined (complex reaction mixture)

For example, in the ^{1}H NMR spectrum of the linear alkylated product **3aa**, the characteristic benzofuran C3–H proton seems to have disappeared. The (CH_2) units of propionates resonated at δ 2.81 and 3.44 ppm as triplets with a coupling constant J = 7.8 Hz. The methoxy protons (OCH_3) of the propionate appeared at δ 3.63 ppm. The C2'–H and C6'–H were seen to resonate at δ 8.10–8.13 ppm as a multiplet. In ^{13}C NMR, the

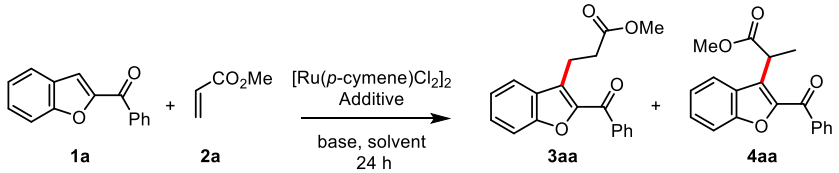
carbons of the (CH_2) unit of propionate resonate at δ 20.2, 33.7 ppm and the methoxy carbon of propionate appears at δ 51.8 ppm. In the HRMS, the exact mass calculated for the linear product was $C_{19}H_{16}O_4Na$ $[M+Na]^+$: 331.0941, and it was found to be 331.0938. Thus, from ^1H, ^{13}C and the HRMS spectrum, the formation of the linear alkylation product **3aa** was confirmed. In the ^1H NMR spectrum of the branched alkylation product **4aa**, the characteristic benzofuran C3–H proton disappeared. The terminal methyl group of propionate appeared at δ 1.67 ppm as a doublet with J = 7.2 Hz and (CH) resonated at δ 4.96 ppm as a quartet with J = 7.2 Hz. In ^{13}C NMR spectrum, the terminal methyl carbon appeared at δ 16.8 ppm and the corresponding (CH) carbon appeared at δ 35.9 ppm. In the HRMS, the exact mass calculated for the branched product was $C_{19}H_{16}O_4Na$ $[M+Na]^+$: 331.0941, and it was found to be 331.0938.

After confirming the structures of the linear and branched alkylation products by spectroscopic techniques, we move forward to optimize the reaction conditions. The ratio of linear *vs* branched products seems to be catalyst dependent. Among the various ruthenium complexes screened, the best branched selectivity was obtained by employing the $Ru_3(CO)_{12}$, $RuH_2(CO)(PPh_3)_3$ and $Ru(PPh_3)_3Cl_2$ catalysts and the best linear selectivity was achieved by employing the $[RuCl_2(p\text{-cymene})]_2$ catalyst (Table T1.4, entry 1). The use of $RuCl_3$ resulted in the formation of a complex reaction mixture (Table T1.4, entry 3) and with RuO_2 the starting 2-aroylbenzofuran was recovered completely (Table T1.4, entry 4). The optimization of these initial findings towards the branched-selective alkylation has been carried out initially in our group, where it has been found that a recipe comprising of benzofuran (1 equiv), acrylate (3 equiv), $Ru(PPh_3)_3Cl_2$ (5 mol%), K_2CO_3 (3 equiv), AgOAc (30 mol%) in toluene as a solvent and heating at 140 °C for 12 h gave the best yields with the highest branched selectivity. The scope of this reaction has been explored by one of the group members.

Coming to the current work, considering the better linear selectivity obtained when $[RuCl_2(p\text{-cymene})]_2$ was used as catalyst, further optimization studies have been carried out by employing the same. As shown in (Table T1.5, entry 1), the initial conditions employing $[RuCl_2(p\text{-cymene})]_2$ as a catalyst and Ag(OAc) as the additive and K_2CO_3 as the base in toluene at 140 °C resulted in a product mixture of **3aa** and **4aa** in a 3:1 ratio in 21% yield. In search of improving the yield/selectivity of the linear alkylation product, the

same catalyst has been employed and various other additives were screened. When $AgSbF_6$ was employed as additive in DCE solvent at 100 °C, using the conditions developed by Jeganmohan and Ackermann's groups independently, there was no formation of any product and benzofuran **1a** (Table T1.5, entry 2) was recovered. This prompted us to look at various other possibilities that have been documented in the Ru-catalyzed C–H functionalization reactions. In this context, we came across the findings of Darses and Genet on the use of additional phosphine for the high linear selectivity in alkylations with styrenes.[40]

Table T1.5: *Optimization of reaction conditions using [Ru(p-cymene)Cl$_2$]$_2$ complex*[a]



entry	additive	solvent	base	temp	yield% (3/4)[b]
1.	Ag(OAc)	toluene	K_2CO_3	140 °C	21(3/1)[c]
2.	$AgSbF_6$	DCE	-	100 °C	nd
3.	PPh_3	DMSO	$NaHCO_3$	160 °C	28[c]
4.	PPh_3	DMF	$NaHCO_3$	160 °C	45[c]
5.	PPh_3	dioxane	$NaHCO_3$	140 °C	73 (89/11)[d]
6.	PPh_3	dioxane	CH_3CO_2Na	140 °C	nd
7.	Ad_2.PBz[f]	dioxane	$NaHCO_3$	140 °C	60(94/6)[e]

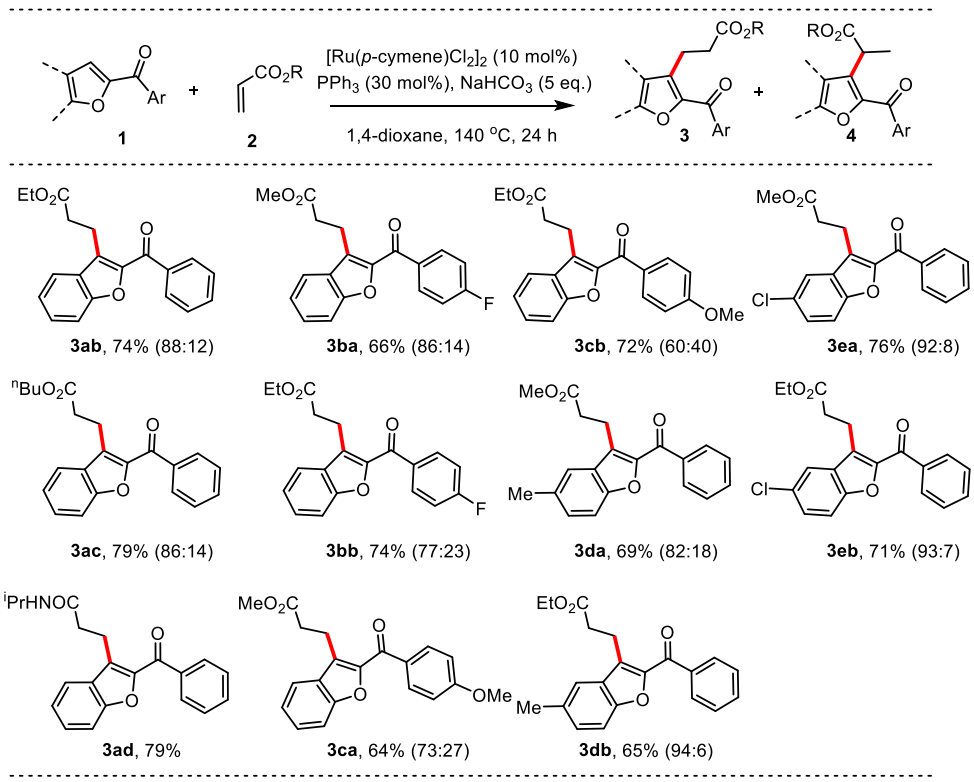
[a]**Reaction conditions: 1a** (1 equiv), **2a** (3 equiv), catalyst (10 mol%), Additive (30 mol%), Base (5 equiv). [b]isolated yield after chromatographic purification. [c]intractable compounds increased in the reaction mixture. [d]clean reaction. [e]recovered unreacted starting material. [f]Di(1-adamantyl)benzylphosphine. nd = not determined (complex reaction mixture).

This prompted us to examine PPh_3 as an additive in our further optimization studies. To this end, the addition of 30 mol% PPh_3[41] and the use of $NaHCO_3$ as base (5 equiv) in DMSO solvent at 160 °C results in exclusive formation of the linear product **3aa** in 28% yield (Table T1.5, entry 3). Replacing the solvent with DMF increased the yield to 45% (Table T1.5, entry 4). However 1,4-dioxane was identified as the best solvent for the current transformation resulting in the linear alkylation in 73% yield with good selectivity of 89:11 (Table T1.5, entry 5). The idea of varying the base for a better yield was not fruitful when replacing $NaHCO_3$ with CH_3CO_2Na, which resulted in a complex reaction mixture (Table T1.5, entry 6). The idea of increasing the sterics around the phosphine ligand for better selectivity was successful when Ad_2.PBz was employed as ligand, which

increased the selectivity to 94:6 but unfortunately it resulted in 24% recovery of the starting benzofuran **1a** (Table T1.5, entry 7).

1.19 Exploring the scope of acrylates and benzofurans:

After having the optimised conditions in hand, we moved further to explore the scope of the acrylate in the present transformation. Thus, benzofuran **1a** on reaction with methyl, ethyl and butyl acrylates under optimised conditions resulted in linear alkylation products as major products along with minor amounts of branched alkylation products. However, the reaction with isopropyl acrylamide (**1d**) resulted in exclusive formation of the linear product in 79% yield (Scheme S1.55). After exploring the scope of the acrylate in the present transformation, we moved forward to investigate the benzofuran scope. Thus benzofurans **1b**–**1e** containing electron donating and electron withdrawing groups on the aroyl phenyl ring and benzofuran ring were considered. In all the cases, the reaction proceeded smoothly, resulting in linear alkylation products as the major products.



Scheme S1.55: *Acrylate & benzofuran scope in linear alkylations*

The ratio of linear to branched products formed in the reaction was mainly affected by the groups/substituents present on the starting benzofurans. For instance, the best linear selectivity was observed with the substrate **1e** (with chlorine at the C5 position of the benzofuran ring). On the other hand, the presence of the electron donating group on the phenyl ring (substrate **1c**) reduced the selectivity (**3cb**/**4cb** = 60: 40). This indicates a competing steric *vs* electronic influence on the branched *vs* linear selectivity.

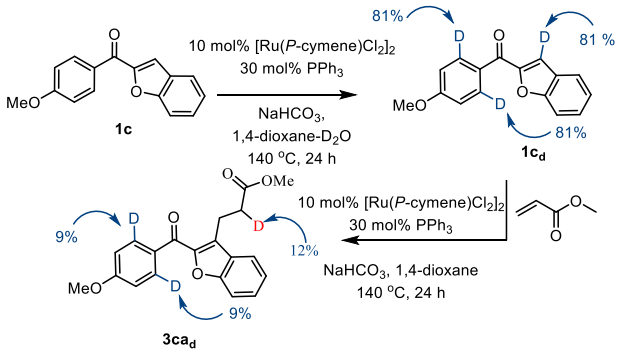
1.20 Mechanism:

After successful completion of the linear alkylation on 2-aroylbenzofurans with acrylates using the $[RuCl_2(p\text{-cymene})]_2$ catalyst, we moved ahead to understand the mechanism of the reaction. We also observed the complementary branched alkylation using the $Ru(PPh_3)_3Cl_2$ catalyst. This opposite course of alkylation reveals that the active catalyst involved in both the processes is different with respect to their electronic and steric preferences. In general, ruthenium catalyzed C–H activation occurs through two different mechanistic pathways. In the first case, the reaction starts with the Ru(0) species (Murai type) which undergoes the oxidative addition mechanism for initiation of the catalytic cycle, whereas in second case, the reaction starts with the Ru (II) species, which undergoes the deprotonation pathway for initiation of the catalytic cycle.

Considering these issues, the deuterium labelling experiments have been carried out for further understanding. The reactions were carried out in the presence of D_2O and without acrylate. As shown in **Table T1.6**, deuterium incorporation was observed at the C3 position of benzofuran and also at the C2'/C6' position of the pendant aryl ring. The magnitude of the deuterium incorporation seems to depend upon the presence and/or absence of the additives and base. Maximum deuterium incorporation (81% at C3 and 81% at C2'/C6') was observed when PPh_3 was used as an additive, $NaHCO_3$ was used as the base along with the ruthenium complex and only 10% deuteration at C3 was observed in the absence of additive and base which indicates that additive, base and catalyst are important for the alkylation reaction. This observation reveals that the path of the reaction involves deprotonation pathway with a Ru (II) species intermediate as proposed by Dixneuf and others for the [Ru]-catalyzed directed arylations.[42] Quite interestingly, when **1c$_d$** was subjected for alkylation with methyl acrylate, the incorporation of deuterium at the

α-position of the propionate unit was observed. However, the percentage of deuterium incorporation was quite nominal (12%). This observed partial deuterium retention in the resulting alkyl group appears to rule out the possibility of an intermediate [Ru]–H species in the current catalytic cycle, which has been generally proposed in case of the ruthenium-catalysed hydroarylation of olefins.

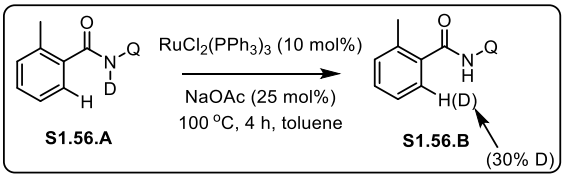
Table T1.6: *Deuterium labelling experiments*



entry	additive	% of deuterium labelling[a]	
		C3 (%)	C2'+C6' (%)
1	PPh_3 (30 mol%)	57	28
2	$NaHCO_3$ (3 equiv)	55	23
3	no additive and base	10	--
4	PPh_3 (30 mol%) $NaHCO_3$ (3 equiv)	81	81

([a]the amount of deuterium incorporation was calculated by ^{1}H NMR spectroscopy)

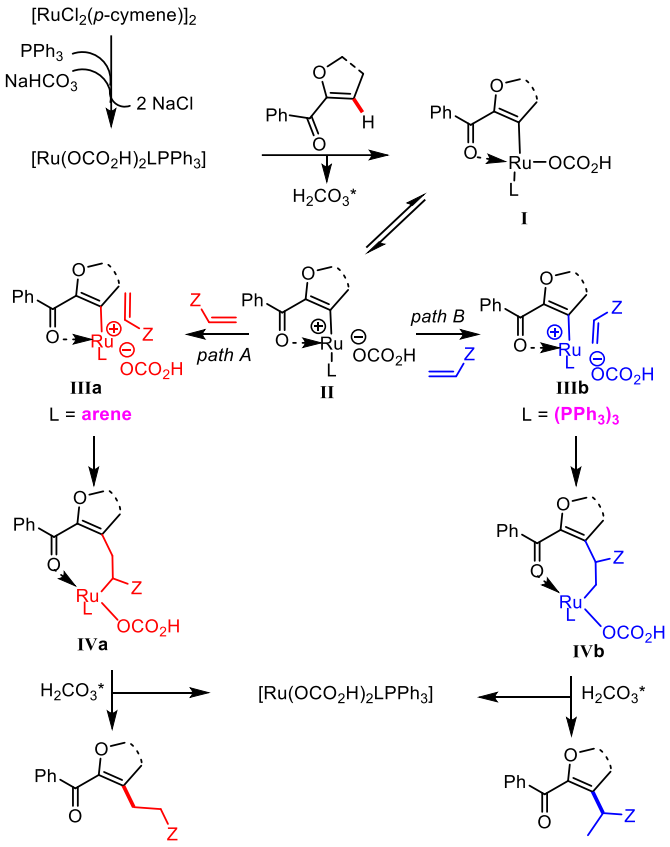
In 2013, Chatani and co-workers revealed a similar observation for the ruthenium catalysed *ortho*-alkylation of aromatic amides containing the bidentate 8-aminoquinoline ligand based directing group with α,β-unsaturated ketones and concluded that the involvement of [Ru]–H species (Murai mechanism) in the reaction cycle is yet to be clarified.[43] When the reaction was carried using substrate **S1.56.A**, it resulted in 30% D at *ortho* position, which indicates that the mechanism proceeds through N–H cleavage.



Scheme S1.56: *Chatani's approach for deuteration studies*

1.21 Proposed mechanism:

After obtaining some clues from the deuterium labelling experiments and based upon earlier insights, we propose that there exist two complementary mechanistic pathways for the branched *vs* linear selective alkylation with acrylates which differ mainly with regard to the nature of the intermediate ruthenacycle involved and its reactivity with the acrylate. $[RuCl_2(p\text{-cymene})]_2$ in presence of PPh_3 results in dimer breaking to form $[RuCl_2(p\text{-cymene})PPh_3]$ which, upon reaction with $NaHCO_3$, results in the formation of the active Ru(II) species $[Ru(OCO_2H)_2(p\text{-cymene})PPh_3]$. The coordination of this active Ru(II) species with the carbonyl group and the subsequent bicarbonate-mediated deprotonation results in the formation of ruthenacycle **I** releasing H_2CO_3. The easy dissociation of the HCO_2O–Ru (II) bond in complex **I** results in the cationic intermediate **II**. Here, there exist two possible pathways for the olefin coordination and insertion into the Ru–C bond. In case of the $[RuCl_2(p\text{-cymene})]_2$ catalyst (path a), where L = arene, which is much less electron donating than the three PPh_3 ligands, the Ru–C bond is more polar (**IIIb**). Therefore the electrophilic β-carbon of acrylate will be oriented close to the nucleophilic Ru–C carbon atom while the α-carbon will be close to the metal centre and will get inserted, resulting in the intermediate (**IVa**) which is a linear product precursor (Scheme S1.57). On the other hand, in case of the $Ru(PPh_3)_3Cl_2$ catalyst (path b), where L_3 = $(PPh_3)_3$ the Ru–C bond appears to be less polar, but it does not alone decide the orientation of the olefin for its insertion into the Ru–C bond. The large steric effect of L_3 = $(PPh_3)_3$ with respect to L_3 = arene likely influences the insertion of the alkene into the Ru–C bond, taking the functional group far from the PPh_3 ligands. As a result, the sterically less demanding β-carbon of acrylate will be close to the metal centre and gets inserted, resulting in intermediate (**IVb**), which is a branched product precursor (Scheme S1.57). Finally, protodemetallation by the released carbonic acid results in the linear and/or branched products and regenerates the active Ru(II) species for continuing the catalytic cycle.



Scheme S1.57: *Proposed catalytic cycle for the hydroarylation*

To conclude, we could successfully accomplish the synthesis of the projected Type 1 and Type 2 of 2-aroylbenzofuran derivatives by developing a complementary catalyst dependent linear *vs* branched selective alkylation of 2-aroylbenzofurans with acrylates. As mentioned above, our next concern will be the synthesis of Type 3 and Type 4 derivatives that contain 3-aroylbenzofurans having either acetic or propionic acid substituents at the C2 position. However, in case of the intermediate ruthenacycle formed from the 3-aroylbenzofurans, the Ru–C bond is expected to be more polar due to the conjugation of carbonyl with the ring heteroatom and that is going to decide the nucleophilicity of the carbon centre involved in formation of Ru–C bond. As one can see from the Figure F1.7, in case of 3-aroylbenzofurans, due to the conjugation of the heteroatom with the carbonyl, the Ru–C bond in the intermediate ruthenacycle appears to be polar. If this is sufficient enough to override the steric factors of the bulky PPh_3 then it should result in the linear alkylation. On the other hand, if polarity of the Ru–C bond does not override the steric

effects, it should result in branched alkylation. Thus, there is a competition between the steric and the electronic effects in deciding the mode of alkylation in 3-aroylbenzofurans.

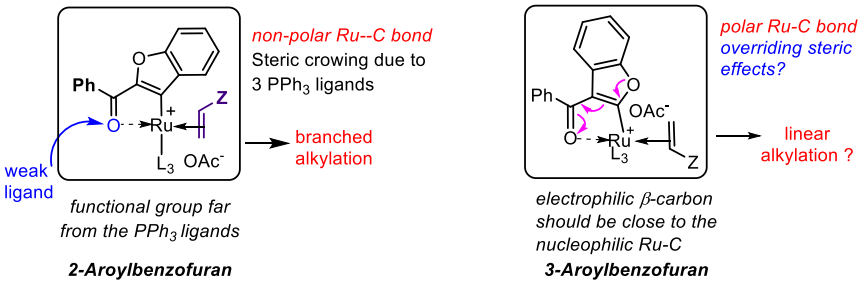
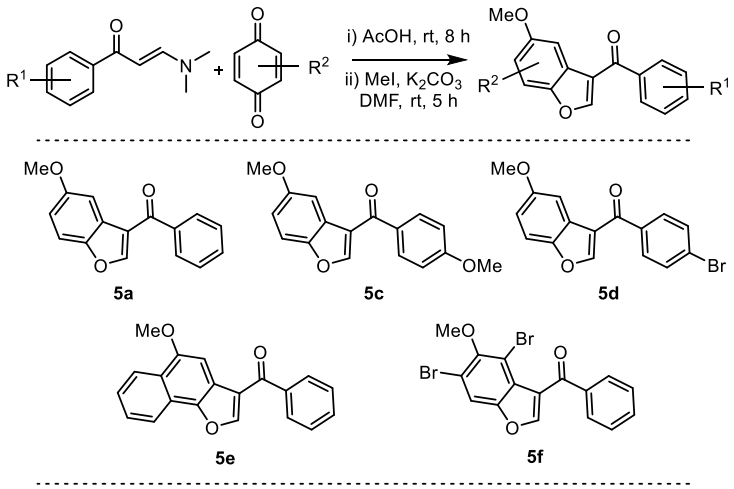


Figure F1.7: *Intermediate ruthenacycle in 2-/3-Aroylbenzofurans*

Thus, the C2–H functionalization of 3-aroylbenzofurans with acrylates is going to be a testing ground to understand how the subtle competition between steric and electronic effects will determine the regioselectivity of the alkylation with acrylates.

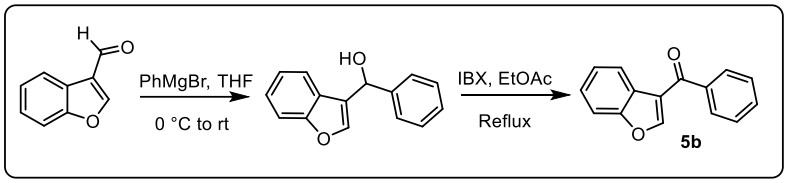
1.22 Ruthenium catalyzed C–H activation of 3-aroylbenzofurans:

To start in this direction, the synthesis of some easily accessible 3-aroylbenzofurans has been carried out by using literature reported methods.[44] Thus, the reaction of *p*-quinone's with 3-(dimethylamino)-1-arylprop-2-en-1-one in presence of acetic acid at room temperature resulted in the formation of 5-hydroxybenzofuran derivatives which on methylation in the presence of methyliodide and K_2CO_3 resulted in 3-aroylbenzofuran derivatives **5a**, **5c** – **5f** (Scheme S1.58).



Scheme S1.58: *Synthesis of substituted 3-Aroylbenzofurans*

The simple unsubstituted benzofuran **5b** was synthesized by the Grignard addition of phenyl magnesium bromide on to 3-formylbenzofuran resulting in an alcohol which on IBX oxidation in refluxing ethyl acetate gave 3-aroylbenzofuran **5b** in excellent yield.



Scheme S1.59: *Synthesis of simple 3-Aroylbenzofurans*

After having the requisite 3-aroylbenzofurans **5a** – **5f** in hand, we proceeded to examine their C2–H functionalization with acrylates under earlier established conditions for the linear or branched selective alkylation of 2-aroylbenzofurans. Thus, the reaction of 3-aroylbenzofuran **5a** (1 equiv) with *tert*-butyl acrylate **2e** (3 equiv) in the presence of $Ru(PPh_3)_3Cl_2$ (A, 10 mol%), AgOAc (30 mol%) and K_2CO_3 (5 equiv) at 140 °C for 24 h gave exclusively one product **6ae** in 84% yield (Table T1.7, entry 1) resulting from the linear selective alkylation with acrylate. The constitution of the resulting product **6ae** was established with the help of ^1H and ^{13}C NMR spectra data analysis. In the ^1H NMR spectrum of **6ae**, the characteristic benzofuran C2–H disappeared. The (CH_2) units of propionate unit resonated at δ 2.66 and 3.13 ppm as triplets with a coupling constant J = 7.5 Hz. The *tert*-butyl protons of propionate appeared at δ 1.39 ppm. In the ^{13}C NMR spectrum of compound **6ae**, the characteristic benzofuran C2 carbon appeared at 164.1 ppm. The carbons of the (CH_2) unit of propionate resonate at δ 24.2, 33.3 ppm. Further, the terbutyl carbons of propionate appear at δ 28.0, 80.73 ppm. In the HRMS, the exact mass calculated for the linear product was $C_{23}H_{24}O_5Na$ $[M+Na]^+$: 403.1516 and it was found to be 403.1517. Thus, from ^1H, ^{13}C and HRMS spectra, the formation of the linear alkylation product **6aa** was confirmed.

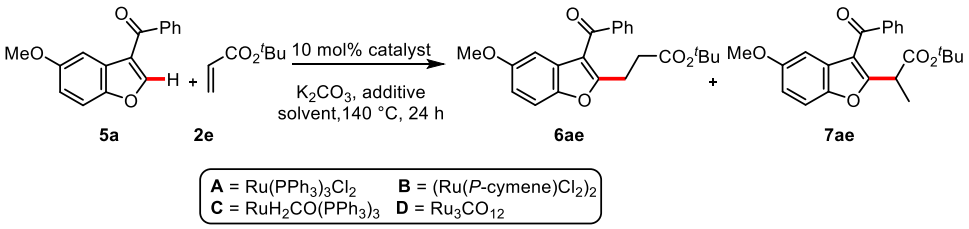
The exclusive formation of the linear product from the alkylation of 3-aroylbenzofuran **5a** is quite remarkable, as under similar conditions, with the same catalyst, the corresponding 2-aroylbenzofuran gave the branched alkylation as the major event. This reversal of selectivity indicates that the magnitude of the polarity of the Ru–C

bond in the ruthenacycle intermediate is sufficiently strong to override the steric effects created by the ligands around the ruthenium centre.

After having this initial result, we next proceeded to understand the course of the reaction with other ruthenium catalysts. Thus, the reaction of benzofuran (**5a**) and terbutylacrylate (**2e**) in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (B, 10 mol%) catalyst and PPh_3 (30 mol%) additive and $NaHCO_3$ (5 mmol) as base at 140 °C in dioxane also resulted in the linear product **6ae** in 72% yield (Table T1.7, entry 2). By employing $RuH_2CO(PPh_3)_3$ (**C,** 10 mol%), the linear product **6ae** was obtained in 60% yield (Table T1.7, entry 3). Interestingly, when Ru_3CO_{12} was employed as the catalyst (complex **D**), under similar conditions, the reaction of **5a** with acrylate **2e** resulted in a mixture of the linear product **6ae** and the branched product **7ae** in 1:1.4 ratio with 81% yield (Table T1.7, entry 4). The branched product was characterised by ^1H, ^{13}C NMR, and HRMS spectra. The structure of the branched product **7ae** was established with the help of spectral data analysis. For example, in the ^1H NMR spectrum of compound **7ae**, the characteristic terminal methyl protons of acrylate were seen as doublet at δ 1.54 with J = 7.3 Hz. The α protons of the acrylate appeared as a quartet at δ 4.12 with a coupling constant J = 7.3 Hz. In the ^{13}C NMR spectrum of compound **7ae**, the terminal methyl carbon resonated at δ 15.2 ppm as a quartet. In the HRMS, the exact mass calculated for the branched product was $C_{23}H_{24}O_5Na$ $[M+Na]^+$: 403.1516 and it was found to be 403.1517. Thus, from the catalyst screening, it was concluded that $Ru(PPh_3)_3Cl_2$ is the best catalyst for the present transformation and further optimization experiments were carried out by employing catalyst **A**. Next, various additives were screened for better linear selectivity. Thus the reaction with $AdCO_2H$, CCl_3CO_2H and $Cu(OAc)_2$ resulted in an exclusive linear alkylation product **6ae** in 49%, 57%, 73% yields respectively (Table T1.7, entry 7). However, by employing $PivCO_2H$, the linear (**6ae**) and the branched products (**7ae**) were obtained in a 6.7:1 ratio (Table T1.7, entry 8–10). Nonetheless, the initial result obtained with the AgOAc additive is far superior to any of these additives.[45] As a part of understanding solvent compatibility, the reaction was screened in various polar solvents such as DMSO, DMF and NMP, and they were found to not be suitable for the present transformation. However, in case of DMF, we noticed the formation of a new product that seemed to be resulting from the opening of the benzofuran ring followed by Michael addition with

acrylate and subsequent deformylation. The details of this reaction will be discussed in the later part of this section.

Table T1.7: *Optimization of reaction conditions*[a]



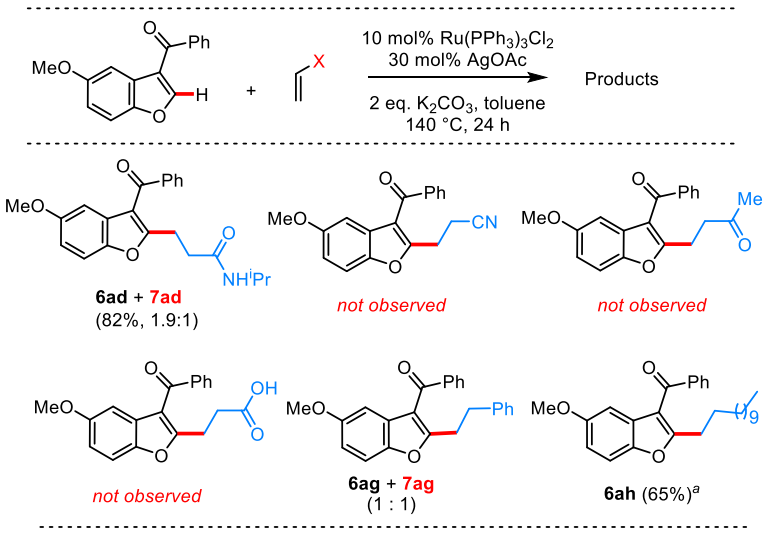
S. No	catalyst/additive	solvent	yield(6:7)[b]
1.	[**A**]/Ag(OAc)	toluene	84 (20:1)
2.	[**B**]/PPh_3 [c]	dioxane	72(20:1)
3.	[**C**]/Ag(OAc)	toluene	60 (20:1)
4.	[**D**]/Ag(OAc)	toluene	81 (1:1.4)
5.	[**A**]/Ag(OAc)	Toluene (100 °C)	no reaction
6.	[**A**]/Ag(OAc)	Toluene (120 °C)	87(20:1) [d]
7.	[**A**]/pivalic acid	toluene	84 (6.7:1)
8.	[**A**]/$AdCO_2H$	toluene	49 (20:1)
9.	[**A**]/$Cu(OAc)_2$	toluene	57
10.	[**A**]/CCl_3CO_2H	toluene	73 (20:1) [e]
11.	[**A**]/Ag(OAc)	dioxane	57 (20:1) [e]
12.	[**A**]/Ag(OAc)	DCE	71 (20:1) [e]

[a] **Reaction conditions: 5a** (1 equiv), **2e** (3 equiv), K_2CO_3 (5 equiv) unless mentioned, Additive (30 mol%). [b] isolated yields. [c] $NaHCO_3$ was used as base. [d] 2 equiv of K_2CO_3 used. [e] % of yield based on recovery of starting material

In case of the 1,4-dioxane solvent, the reaction resulted in the product **6ae** in 57% yield based on the recovered starting benzofuran (Table T1.7, entry 11). The scenario is the same with the 1,2-dichloroethane (DCE) solvent where the linear product **6ae** was obtained in 71% yield based on the recovered starting material. This confirms that toluene is the best solvent for the present transformation. Variable temperature experiments employing optimized conditions revealed that the alkylation was facile even at 120 °C in the presence of 2 equiv of K_2CO_3 (Table T1.7, entry 6). However, at 100 °C, the starting material was recovered completely (Table T1.7, entry 5).

1.23 Scope of olefins & directing group:

After having the optimised conditions in hand, we moved ahead to explore the scope of conjugated olefins in the present reaction. Thus, the reaction of 3-aroylbenzofuran (**5a**) with isopropyl acrylamide **2d** leads to a mixture of linear **6ad** and branched **7ad** alkylation products in 1.9:1 ratio. The experiments conducted with the acrylonitrile, acrylic acid, acryl aldehyde and methylvinyl ketone are not fruitful in the present transformation and resulted in the recovery of the starting benzofuran **5a**. The reaction with styrene resulted in a 1:1 mixture of linear and branched products. However, characterizing the products proved difficult due to contamination by impurities resulting from the self-condensation of styrene.[46] The reaction with dodec-1-ene was found to be sluggish resulting in the linear product **6ah** in 65% yield with respect to the 70% recovered starting material (scheme S1.60).[47]

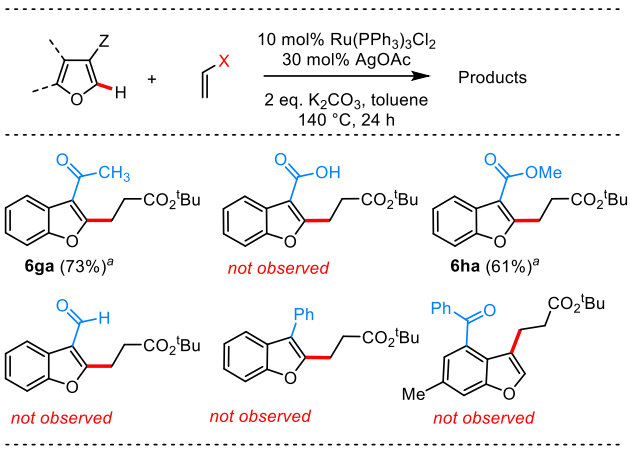


[a]Yields based on the recovered starting material

Scheme S1.60: *Olefin scope in the Ru-catalyzed alkylation of 3-aroylbenzofurans*

After exploring the olefin scope, we moved ahead to check the feasibility of different directing groups in the present transformation. The reaction of 3-acetylbenzofuran with acrylate **2e** under the previously optimized conditions was found be sluggish and gave mainly the linear alkylation product **6ga** in 73% yield with respect to the 28% recovered starting material. The reaction of the benzofuran-3-carboxylic acid with terbutylacrylate **2e** was not successful, resulting in decomposition of the starting material. When ester was employed as a directing group, the reaction was incomplete, resulting in the linear product

6ha in 61% yield with respect to 58% of the starting material recovered. The benzofuran-3-carbaldehyde on reaction with acrylate **2e** under optimised reaction conditions gave a complex reaction mixture. As expected, 3-phenylbenzofuran was found to be intact when employed as a substrate for alkylation with **2e**. This indicates that the reaction proceedes through chelation/directing group assisted C–H activation. The reaction of the regioisomeric substrate 4-aroylbenzofuran[48] with terbutyl acrylate (**2e**) under optimised reaction conditions did not result in any alkylation product and the intact starting material was recovered (Scheme S1.61).

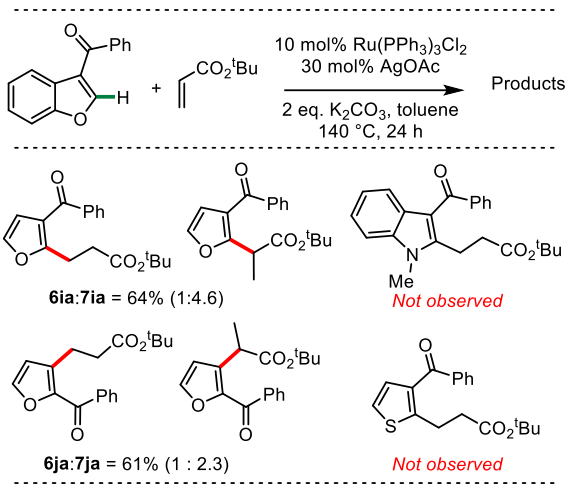


[a]Yields based on the recovered starting material

Scheme S1.61: *Scope of directing group*

1.24 Scope of heterocycles:

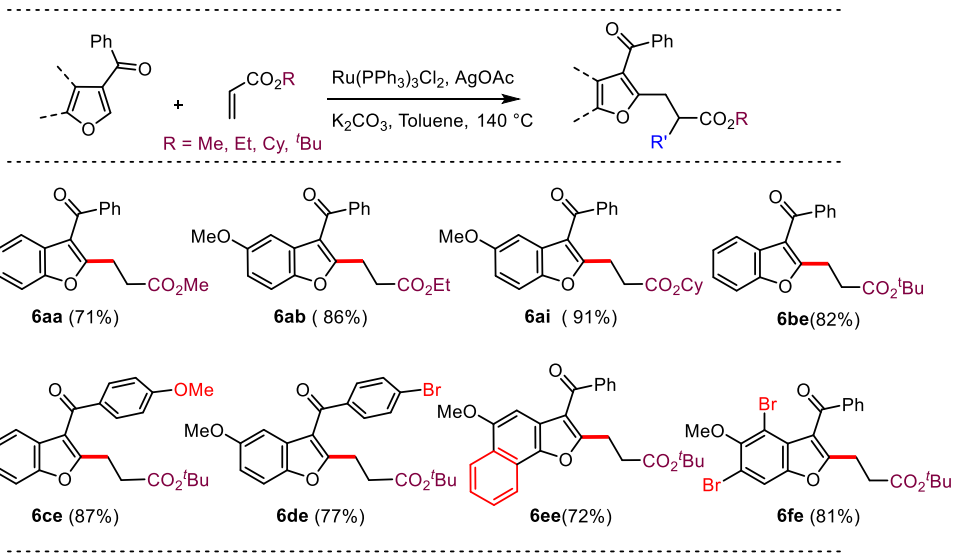
Next, we examined the scope of other heterocyclic moieties in the present transformation. Thus, the reaction of 3-aroylfuran **1i**[49] with acrylate **2e** under optimised reaction conditions resulted in the formation of linear and branched products in a 1:4.6 ratio. Similarly, the regioisomeric substrate 2-aroylfuran **1j**[49] gave a mixture of linear and branched products in a 1:2.3 ratio. However, the reaction with 3-aroylindole[50] was not successful and resulted in the recovery of the starting indole. Similarly the reaction with 3-aroylthiophene[51] was also not fruitful, resulting in the recovery of the starting materials (scheme S1.62).



Scheme S1.62: *Scope of heterocycles*

1.25 Scope of 3-aroylbenzofurans:

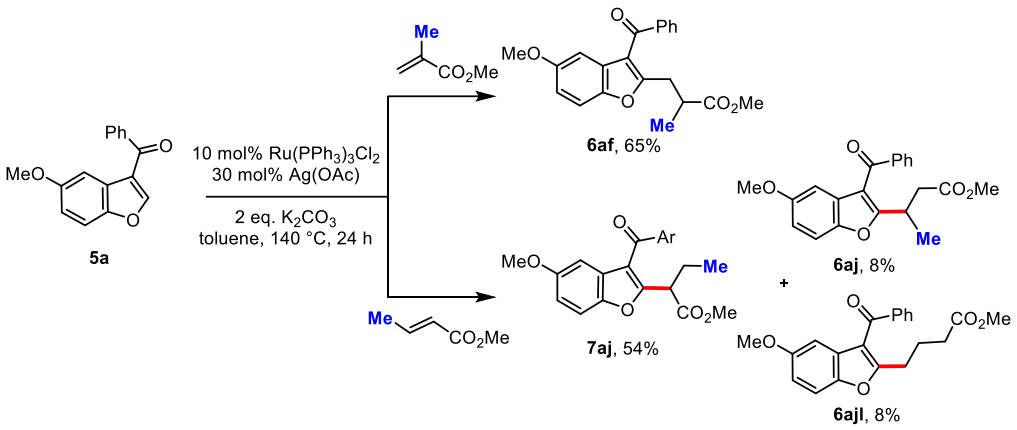
After extensive investigations on the compatibility of various other conjugated olefins, directing groups and other heterocycles in the current transformation, we next moved forward to examine the substrate scope in the present transformation. Thus by employing variously substituted benzofurans (**5b**–**5f**) and methyl, ethyl, cyclohexyl, terbutyl acrylates as shown in the scheme S1.63, under optimized reaction conditions, all the reactions proceeded smoothly, resulting in linear alkylated products in good to excellent yields. In all the cases <5% of the branched products were formed, and were difficult to isolate and characterize.



Scheme S1.63: *Acrylates and benzofurans scope*

1.26 Exploring the methacrylate/crotonate:

After having established the scope of the current reaction with simple acrylates employing variously substituted benzofurans, we next examined the compatibility of sterically demanding methyl methacrylate (**2f**) and methyl crotonate (**2j**) employing benzofuran **5a** under the optimized conditions. The results are interesting. In case of methacrylate **2f**, exclusive formation of linear alkylation product **6af** (65% yield) was seen. On the other hand, methyl crotonate gave mainly the branched alkylation product **7aj** along with minor amounts of an inseparable mixture of 1,4 and 1,5 linear addition products (16%). The structure of branched product **7aj** was established with the help of spectral data analysis. In the ^{1}H NMR spectrum of compound **7aj**, the protons of the *β*–methyl group of crotonate appeared as a triplet at δ 0.89 ppm with a coupling constant J = 7.5 Hz. The –CH_2– unit gave two separate multiplets at δ 2.02–2.11 and 2.14–2.22 ppm, each integrating for 1H. The –CH– proton resonated at δ 4.11 ppm as "dd" with J = 6.4, 8.8 Hz. In the ^{13}C NMR spectrum of compound **7aj**, the terminal *β*–methyl carbon appeared at δ 11.9 ppm. Futhermore, the –CH_2– & –CH– carbons appeared at δ 23.7 & 46.0 ppm respectively. The –OCH_3 carbon appeared at δ 55.8 ppm. In the HRMS, the exact mass calculated for the branched product was $C_{21}H_{20}O_5Na$ $[M+Na]^+$: 375.1203, and it was found to be 375.1203. Thus ^{1}H, ^{13}C and the HRMS spectrum confirmed the structure of product **7aj** as the branched alkylation product.

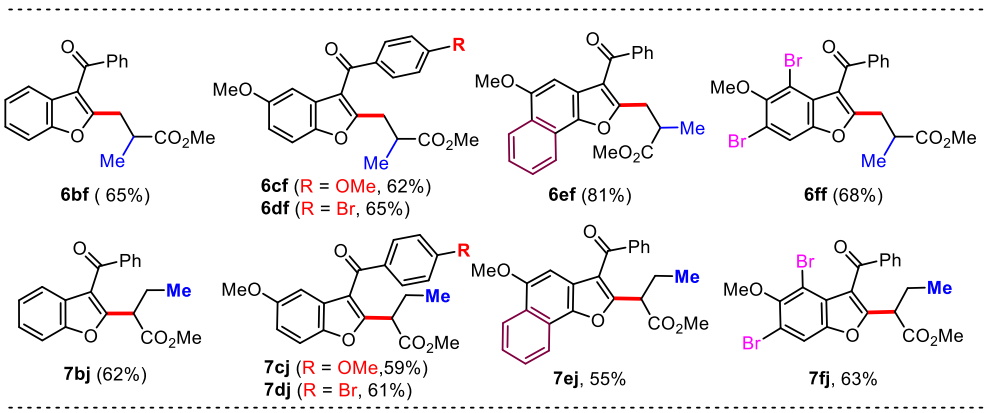


Scheme S1.64: *Complementary linear and branched alkylation of **5a** with methacrylate and crotonate*

The formation of a branched product from the alkylation of **5a** with methyl crotonate is quite surprising, as under similar conditions with methyl acrylate and with

methyl methacrylate, linear alkylation was the major event. In all the cases, the sterics around the ruthenium centre due to bulky phosphine ligands is the same, but the sterics associated with the methyl crotonate due to the presence of an extra *β*–methyl group compared to the methyl acrylate dominated the role of polarity of the Ru–C bond of the intermediate ruthenacycle leading to branched alkylation. This indicates that the sterics associated with the incoming coupling partner also plays a prominent role in deciding the regioselectivity of alkylation.

After having this complementary linear *vs* branched alkylation with methyl methacrylate and methyl crotonate, the scope of these reactions has been explored employing other avalable benzofurans **6b**–**6f**. In all the cases, formation of linear products with methyl methacrylate and branched products with methyl crotonate was observed. In case of benzofuran **5a** with methyl crotonate**,** along with the branched product **7aj**, the separated separable 1,4 addition product **6aj** and the 1,5 addition product **6ajl** were obtained in 10% and 6% yield respectively.



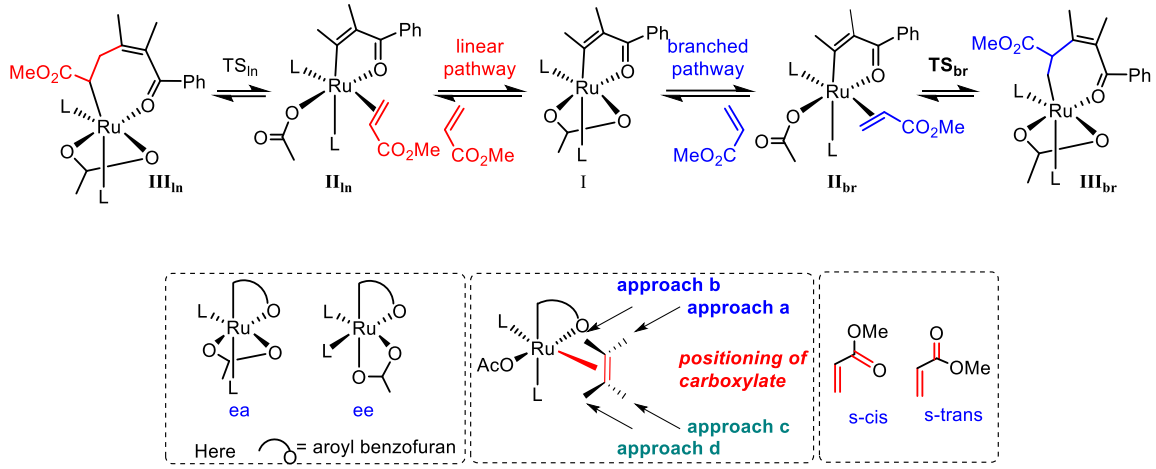
Scheme S1.65: *Generalization of reactions with methyl methacrylate/crotonate*

1.27 DFT Calculations:

From the above results, it is evident that the alkylation 3-aroyl benzofurans with acrylates results in linear alkylation while branched alkylation was noticed with 2-aroylbenzofurans under similar conditions. Furthermore, the alkylation of both 2-/3-aroylbenzofurans with methyl crotonates resulted in the branched alkylation products. This revealed interplay between steric *vs* electronic factors that leads to the observed regioselectivity of alkylation. This possess a theoretical problem of much interest and we

proceeded further to carry density functional theory (DFT) investigations to get some insights into the mechanism. Keeping the computational expense of the calculations in mind, a model system with two triphenyl phosphine groups, instead of three, was employed and was found to be in good agreement with the experiments.

We have focused mainly on two important steps occurring during the catalysis: (i) coordination of the methyl acrylate to the ruthenium centre and (ii) the migratory insertion of the methyl acrylate into the Ru–C bond. We have considered 16 possibilities for the coordination of the acrylate at the ruthenium centre by considering: i. two different possible conformations *ee* and *ea* of the intermediate ruthenacycle [in octahedral complexes, the positioning of the PPh_3 ligands in equatorial-equatorial or equatorial-axial fashion]; ii. the relative orientation of the acrylate's carboxylate with respect to Ru···O=C; that broadly decides the linear *vs* branched alkylation, denoted as branched (br) and linear (ln) and finally, iii. two different *s-cis* or *s-trans* conformers of the methyl acrylate.



Scheme S1.66: *Coordination of the acrylate at the ruthenium centre and the possible conformations of the ruthenium catalyst/acrylate*

For 2-/3-aroylbenzofuran alkylations, the energies of these sixteen transition states, energy barriers and the energy of inserted complexes has been calculated. In general, with both 2-/3-aroylbenzofurans, the insertion transition states [8] with the *ee* coordination mode of the PPh_3 ligands were found to be higher in energy. The energies of the corresponding inserted complexes have been excluded. Table T1.8 saliently describes the minimum energy transition states noticed in case of 2-aroylbenzofurans.

Table T1.8: *The free energy values for the two important steps shown in Scheme S1.66 at the PBE/TZVP level of theory. The values are with respect to the ee conformer of the 2-aroylbenzofuran. All energy values are in kcal/mol.*

approach	I	II_{br}/ II_{ln}	TS_{br}/TS_{ln}	III_{br}/III_{ln}
ee				
$a_{s\text{-}cis}$	0.0	10.1	36.4	–
$a_{s\text{-}trans}$		18.5	37.8	–
$b_{s\text{-}cis}$		21.0	44.9	–
$b_{s\text{-}trans}$		25.5	44.1	–
$c_{s\text{-}cis}$		11.6	33.7	–
$c_{s\text{-}trans}$		12.4	35.2	–
$d_{s\text{-}cis}$		18.6	39.1	–
$d_{s\text{-}trans}$		14.7	40.6	–
ea				
$a_{s\text{-}cis}$	6.0	6.8	**22.6**	11.6
$a_{s\text{-}trans}$		7.9	**22.7**	
$b_{s\text{-}cis}$		14.6	27.9	9.2
$b_{s\text{-}trans}$		17.8	28.0	
$c_{s\text{-}cis}$		13.8	**23.6**	5.2
$c_{s\text{-}trans}$		13.9	24.8	
$d_{s\text{-}cis}$		11.4	23.9	8.6
$d_{s\text{-}trans}$		13.3	24.7	

It was observed that approaches $a_{s\text{-}cis}$ [22.6 kcal/mol barrier] and $a_{s\text{-}trans}$ [22.7 kcal/mol barrier] leading to the pro-branched complexes (III_{br}) have lower energy barriers in comparison to the other pathways. The other two pro-branched approaches $b_{s\text{-}cis}$ and $b_{s\text{-}trans}$ are comparatively higher in energy [~4.5 kcal/mol]. The lowest energy barrier for the formation of the pro-linear complex (III_{ln}) is 23.6 kcal/mol, through the $c_{s\text{-}cis}$ approach, which is 1.0 kcal/mol higher in energy in comparison to the lowest energy barrier forming the pro-branched complex.

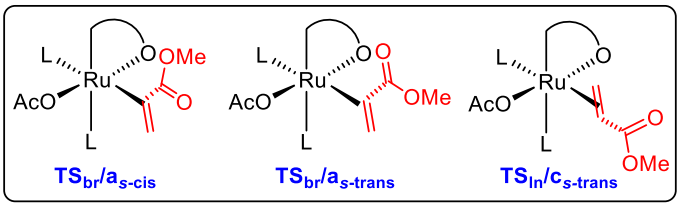


Figure F1.8: Various *approaches of acrylate to the Ru–C bond in 2-aroylbenzofurans*

Therefore, given the multiple means by which the pro-branched complex III_{br} would be formed, it would be expected to be the major product formed by a significant margin: about 90%. This prediction of a high percentage for the major product corroborates well with the experimental findings.

In case of 3-aroylbenzofuran, the lowest difference between the transition states leading to the formation of pro-branched and pro-linear complexes is 0.8 kcal/mol ($TS_{ln}/c_{s\text{-}cis}$ [27.1 kcal/mol barrier]), which suggests that the transition states leading to the formation of pro-linear complexes will be 3.7 times more populated than the corresponding transition states leading to formation of pro-branched complexes. Furthermore, there are two more transition states: $TS_{ln}/c_{s\text{-}trans}$ [27.5 kcal/mol barrier] and $TS_{ln}/d_{s\text{-}cis}$ [27.4 kcal/mol barrier] that have barriers lower than $TS_{br}/a_{s\text{-}trans}$, [27.9 kcal/mol barrier] by 0.4 kcal/mol and 0.5 kcal/mol respectively. This suggests that the transition state $TS_{ln}/c_{s\text{-}trans}$ will be 1.9 times and $TS_{ln}/d_{s\text{-}cis}$ will be 2.3 times more populated than the transition state $TS_{br}/a_{s\text{-}trans}$, leading to formation of pro-branched complexes. This suggests that the probability of formation of the pro-linear complex would be significantly higher: to a selectivity of ~88% for the linear isomer.

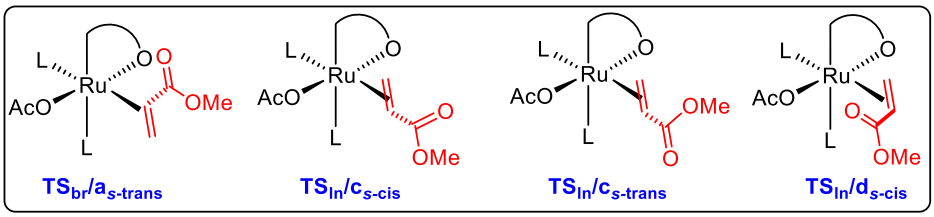


Figure F1.9: Various *approaches of acrylate to the Ru–C bond in 3-aroylbenzofurans*

Table T1.9: *The free energy values for the two important steps shown in Scheme S1.66 at the PBE/TZVP level of theory. The values are with respect to the IV ee conformer of 3-aroyl benzofuran. All energy values are in kcal/mol.*

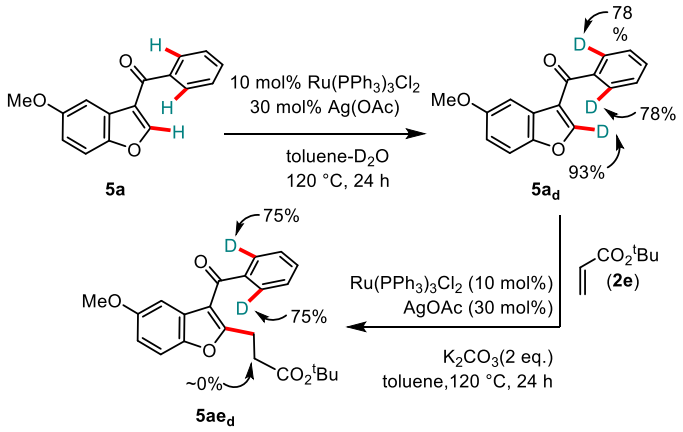
approach	IV	V_{br}/ V_{ln}	TS_{br}/TS_{ln}	Vl_{br}/Vl_{ln}
ee				
$\mathbf{a}_{s\text{-}cis}$	0.0	7.9	43.2	–
$\mathbf{a}_{s\text{-}trans}$		16.9	42.3	–
$\mathbf{b}_{s\text{-}cis}$		23.7	43.6	–
$\mathbf{b}_{s\text{-}trans}$		10.4	46.6	–
$\mathbf{c}_{s\text{-}cis}$		9.7	37.1	–
$\mathbf{c}_{s\text{-}trans}$		10.5	39.2	–
$\mathbf{d}_{s\text{-}cis}$		16.7	44.7	–
$\mathbf{d}_{s\text{-}trans}$		13.4	45.7	–
ea				
$\mathbf{a}_{s\text{-}cis}$	10.0	11.2	28.2	16.8
$\mathbf{a}_{s\text{-}trans}$		12.5	**27.9**	
$\mathbf{b}_{s\text{-}cis}$		22.9	41.4	15.0
$\mathbf{b}_{s\text{-}trans}$		19.4	34.0	
$\mathbf{c}_{s\text{-}cis}$		17.7	**27.1**	09.9
$\mathbf{c}_{s\text{-}trans}$		17.6	**27.5**	
$\mathbf{d}_{s\text{-}cis}$		15.3	**27.4**	12.6
$\mathbf{d}_{s\text{-}trans}$		15.9	27.9	

Thus, DFT calculation on 2-/3-aroylbenzofurans reveal that the charge distribution across the Ru–C bond during insertion of acrylate, as well as the donating ability of the directing group plays a prominent role in deciding the mode of alkylation.

1.28 Mechanism:

To get insights into the mechanism, deuterium labelling experiments have been carried out. Initially, when benzofuran **5a** was heated in the presence of D_2O, catalyst and additive in toluene at 140 °C for 24 h, the deuterated benofuran $\mathbf{5a_d}$ with 93% deuteration at C2 and 78% deuteration at C2' and C6'on the aroyl phenyl ring was obtained. The amount of deuterium incorporation depends on the presence or absence of additive, which is shown in the Table T1.10. The deuterated benzofuran $\mathbf{5a_d}$, on reaction with acrylate **2e** under optimised reaction conditions, results in $\mathbf{5ae_d}$ where deuterium was not observed at any of the methylene groups of the propanoate unit. This ruled out the involvement of the Ru–H species in the catalytic cycle.

Table T1.10: *Deuterium labelling experiment*

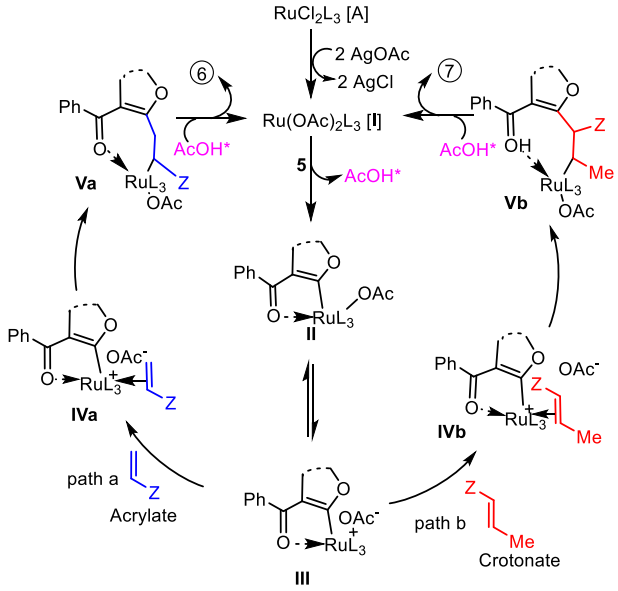


S. NO.	additive and or base	% of deuterium labelling	
		C2(%)	C2'+C6'(%)
1.	AgOAc (30 mol%)	93	78
2.	K_2CO_3 (2 equiv)	18	0
3.	AgOAc (30 mol%) K_2CO_3 (2 equiv)	14	0
4.	no additive and base	90	0

(the amount of deuterium incorporation was calculated by ^{1}HNMR spectroscopy)

Coming to the mechanism of the reaction, under similar conditions, branched alkylation was observed with 2-aroylbenzofuran and linear alkylation was observed with 3-aroylbenzofurans, which indicates that the magnitude of polarity of the Ru–C bond of the ruthenacycle intermediates derived from these substrates is comparatively different. It was revealed by us that in presence of a strong directing group, the Ru–C bond in the intermediate ruthenacycle will be polar and the orientation of olefin with respect to this nucleophilic Ru–C carbon will be decided by electronic factors.[52] The linear selectivity observed in case of 3-aroylbenzofurans with acrylates suggests that the polarity of the intermediate Ru–C bond was also influenced by the relative nucleophilicity of the carbon centre involved. However, the observed branched selectivity with the same 3-aroylbenzofuran when methyl crotonate was employed, indicates that the magnitude of this electronic effect on the Ru–C bond is not sufficiently strong and thus the steric factors override the selectivity towards the branched alkylation. Based upon this and the earlier inputs from the other groups, we have extended the following tentative mechanistic cycle for the current catalytic reaction (Scheme S1.67). The catalytic cycle starts with the

generation of the active ruthenium catalyst (**I**) by the reaction of $Ru(PPh_3)_3Cl_2$ and Ag(OAc).[53] Then, coordination to the carbonyl group of benzofuran and subsequent acetate mediated deprotonation results in the formation of a five membered ruthenacycle **II**, releasing AcOH.[54] In case of the coordination of acrylate to this complex, the electrophilic β-carbon of olefin prefers to approach the nucleophilic carbon atom of Ru–C. However, when crotonate is employed, as mentioned above, the sterically less demanding α-carbon of the olefin approaches the carbon atom of the Ru–C bond. Insertion of the olefin into the metallacycle **IV** generates the intermediates **V**. Finally, protodemetallation by the released AcOH gives the linear or branched alkylated product generating the active ruthenium catalyst to continue the catalytic cycle.



Scheme S1.67: *Mechanism of [Ru]-catalyzed linear vs branched selective alkylation with acrylate/crotonate*

1.29 Alkylation of 3-formylbenzofurans with acrylates:

As described above, with the $Ru(PPh_3)_3Cl_2$ catalyst, the alkylation of 2-aroylbenzofurans resulted in exclusive branched alkylation and 3-aroylbenzofurans gave linear alkylation products. This complementary alkylation was explained based up on the proposal founded upon steric factors associated with the ligands around the ruthenium centre and electronic factors associated with the directing carbonyl group, *inter alia*, the polarity of the Ru–C bond of the intermediate ruthenacycle. Due to the suitably conjugated

ring oxygen, the carbonyl of 3-aroylbenzofurans coordinates much more strongly than that of the 2-aroylbenzofurans carbonyl and hence, increased polarization of the Ru–C bond favour linear alkylation. This explanation has been supported by DFT calculations that reveal that the charge distribution across the Ru–C bond of the intermediate ruthenacycle is an important determining factor for the orientation of the incoming acrylate with respect to the Ru–C bond in the ruthenacycle which, in turn, affects the mode of alkylation. However, with methyl crotonate, the same 3-aroylbenzofuran gave mainly branched alkylation.

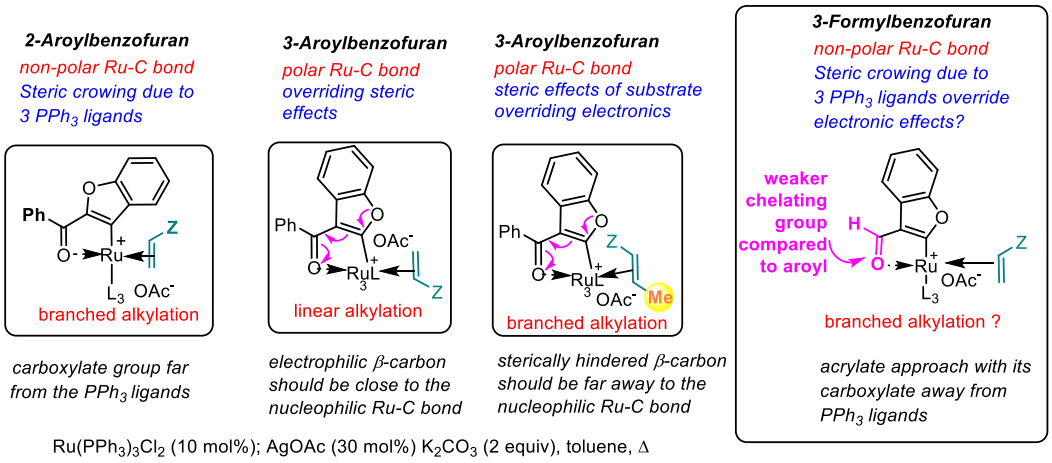
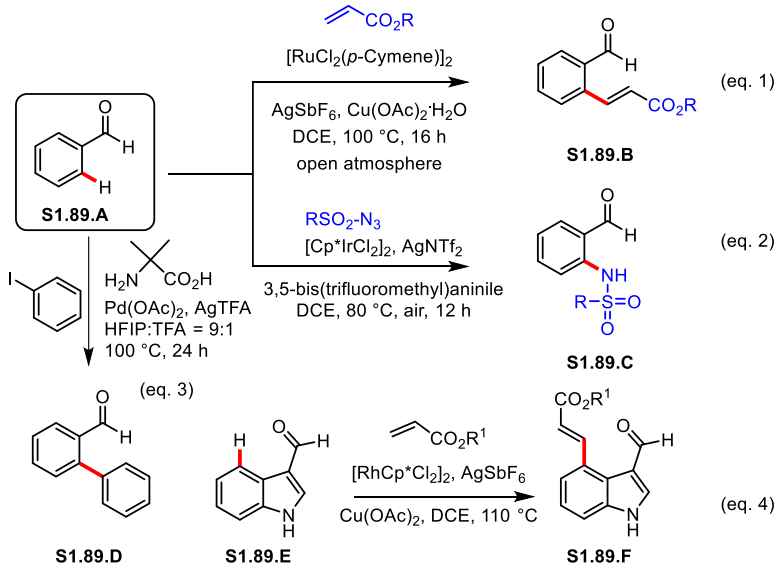


Figure F1.10: *Interplay between the steric and electronic effects in the alkylation of 2-/3-aroylbenzofurans with acrylates and proposal of branched alkylation of 3-formylbenzofuran*

This is an important aspect, because it reveals that the electronic effects associated with the ring-oxygen induced polarization of Ru–C bond are subside when sterically demanding methyl crotonate is employed as the incoming electrophile. This prompted us to look at the alkylation of 3-formylbenzofuran with acrylates. This will be an interesting substrate to be employed considering the fact that the formyl functionality will be a weaker chelating/directing group when compared to the aroyl carbonyl group and thus there will be reduced charge distribution across the Ru–C bond. In other words, is it possible to counteract the electronic perturbance caused by the ring oxygen atom so that the selectivity can be switched from linear to branched alkylation. However, when we looked at the literature on the aldehyde directed C–H activation, the reports are scarce.

In 2012, Jeganmohan's group reported the cross dehydrogenative coupling of various (hetero)aromatic aldehydes with acrylates using the $[Ru(p\text{-Cymene})Cl_2]_2$ catalyst in presence of the $AgSbF_6$ additive and $Cu(OAc)_2.H_2O$.[55a] Later, Gang and coworkers

reported the $[Cp^*IrCl_2]_2$ catalysed C–H amidation of benzaldehydes using organic azides as coupling partners. In this process, 3,5-di(trifluoromethyl)aniline was used as promoter to form the aldimine intermediate, which then undergo C–H amidation.[55b] Jia and coworkers reported the rhodium catalysed C–H functionalization at the C4 position of indoles with acrylates using aldehyde as a chelating/directing group. Furthermore, the methodology has been applied for the total synthesis of natural products (–)-Agroclavine and (–)-Elymoclavine (Scheme S1.91).[55c] Quan Yu and coworkers reported the palladium catalysed arylation, chlorination and the bromination of benzaldehydes using the transient directing group strategy. The transient directing group forms the imine linkage with the aldehyde functionality resulting in an intermediate which then undergoes C–H functionalization (Scheme S1.92).[55d]

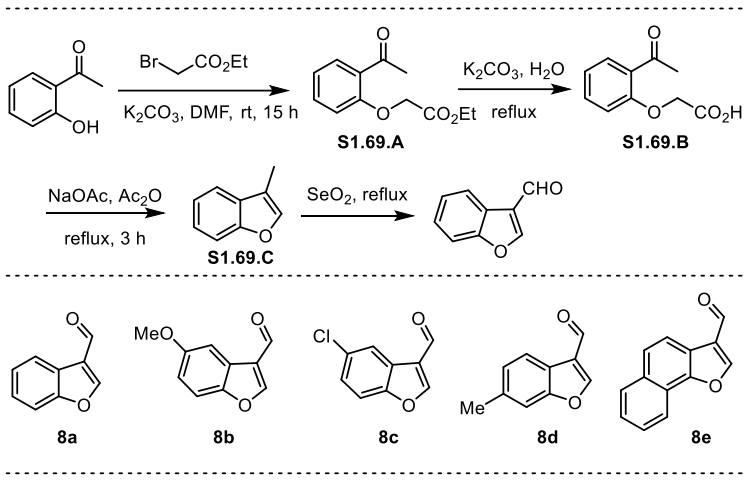


Scheme S1.68: *Selected examples of aldehyde directed C–H functionalizations*

To this end, we realized that the proposal of conducting the alkylation of 3-formylbenzofurans is a challenging one to execute. Indeed, as mentioned in the previous section, the attempted alkylation of 3-formylbenzofuran [under the standardized conditions [at 140 °C] in the process of understanding the compatibility of various directing groups] led to a complex mixture. This indicated that tweaking the reaction conditions is warranted for a successful realization of the current proposal.

1.30 Synthesis of 3-formylbenzofurans:

Having realised this, we moved forward for the synthesis of the required 3-formylbenzofurans according to the literature reported procedures.[56] Various commercially available 2-hydroxyacetophenones were subjected for *O*-alkylation with ethyl bromoacetate in DMF. The base-mediated hydrolysis of the resulting 2-aryloxyacetates gave the corresponding acids, which upon heating with NaOAc in presence of Ac_2O, underwent dehydrative ring closure followed by decarboxylation resulting in 3-methylbenzofurans. Subsequent oxidation of the methyl groups with SeO_2 resulted in the formation of the required 3-formylbenzofurans (Scheme S1.69).

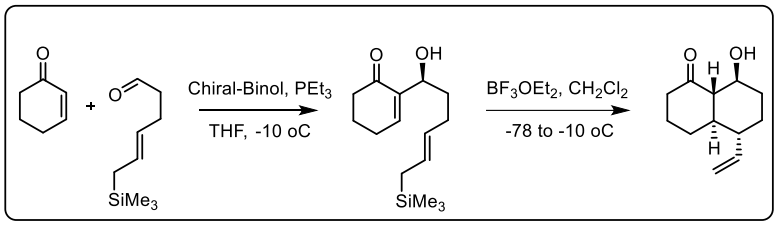


Scheme S1.69: *Synthesis of 3-Formylbenzofurans*

After having the requisite substituted 3-formylbenzofuran **8a**–**8e** in hand, we moved ahead towards the alkylation reaction following the conditions that have been established in case of 2-/3-aroylbenzofurans. The employed conditions involve the heating of **8a** in the presence of methyl acrylate (**2a,** 5 equiv), $Ru(PPh_3)_3Cl_2$ (10 mol%), AgOAc (30 mol%), K_2CO_3 (5 equiv) in toluene solvent at 120 °C for 12 h (as in the case of 2-aroylbenzofurans) or at 140 °C for 24 h (used in the case of 3-aroylbenzofurans). Under both the conditions, the decomposition of the starting compound was observed. Considering the fact that 3-aroyl derivatives needed higher temperatures and longer times in comparison to the 2-aroyl derivatives for successful alkylation and that the formyl group is a much weaker donor than the aroyl group, we examined the same reaction at 160 °C employing the same amount of catalyst/additive/base. Working up the reaction after 24 h

led to isolation of a product in moderate yields and prolonging the reaction time to 36 h improved the yield up to 62%. Initial LC-MS of this new compound revealed that two molecules of methyl acrylate are inserted and the analysis of its ^{1}H, ^{13}C NMR revealed the annulation of a tri-substituted cyclohexene ring to the benzofuran ring. For example, in the ^{1}H NMR spectrum of **9aa**, both the benzofuran C2–H and the aldehyde–H disappeared. One methyl group appeared as a singlet at δ 1.68 ppm, indicating that it is attached to a quaternary carbon. There are two methoxy groups (OCH_3) at δ 3.66, 3.82 ppm revealing the incorporation of two units of acrylate. Out of two $–CH_2–$ protons, one of the protons appeared as "dd" at δ 2.75 with a coupling constant J = 2.1, 17.4 Hz and the other proton appeared as a doublet at δ 3.55 with a coupling constant J = 17.2 Hz. This indicated the presence of a quaternary carbon adjacent to the methylene unit. Further, there is one olefinic proton that appeared as a doublet at δ 7.70 with a coupling constant J = 2.1 Hz, suggesting that this proton has a through-bond (allylic) coupling with one of the $–CH_2–$ protons and that this is the beta-carbon of the olefin that is conjugated with a carboxylate. In the ^{13}C NMR spectrum of compound **9aa**, the methyl carbon resonated at δ 21.9 ppm and the $–CH_2–$ carbon at δ 36.4 ppm. The $–OCH_3$ carbons of two carboxylates appeared at δ 51.9 and 52.8 ppm. In the HRMS, the exact mass calculated for $C_{17}H_{16}O_5Na$ $[M+Na]^+$ was 323.0890 and it was found to be 323.0891. Thus, from the ^{1}H, ^{13}C and HRMS spectra of the product **9aa**, we speculated its structure as shown in Table T1.11 with a net annulation of cyclohexene that was confirmed by its single crystal *X*-ray diffractions studies. The product formation of **9aa** from 3-formylbenzofuran **8a** involves a series of reactions in one pot – i. C–H activation and branched alkylation with one molecule of methyl acrylate, ii. The Morita-Baylis-Hillman reaction (MBH reaction) of C3-aldehyde with the second molecule of methyl acrylate, iii. Intramolecular Michael addition of enolate and iv. dehydration. The observed initial branched alkylation with acrylate thus validated our proposal of the non-polar nature of the Ru–C bond of the ruthenacycle intermediate due to the weaker donating ability of the formyl group. The subsequent MBH reaction, though not planned one, is expected considering the well-known use of Ru–C complexes for this transformation.[57] The ready formation of the enolate is expected under mild conditions, since the corresponding carbon is positioned between the heteroaryl and the carboxylate groups. The subsequent intramolecular Michael addition should facile, as it

leads to a 6-membered ring. Overall, our attempted alkylation of 3-formylbenzofuran with excess acrylate led to the identification of a novel post-alkylation process that has never been documented in the well-explored MBH reaction chemistry. There are several reports where the MBH products resulting from the prefunctionalized aldehydes that bear internal reactive functional groups, have been subjected for cyclization in a subsequent separate step. This includes the intramolecular addition of suitably positioned heteroatoms, the use of ring closing metathesis and Diels-Alder cycloaddition. One notable report that was documented recently was the construction of the clerodane decalin core by combining the MBH reaction with the Lewis acid promoted intramolecular addition of a suitably positioned allyl silane.

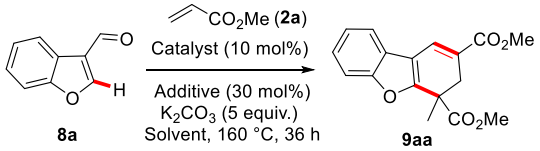


Scheme S1.70: *Ring-annulation via MBH-reaction followed by Lewis-acid mediated intramolecular allylation*

Having identified this interesting domino-process, next, various other ruthenium catalysts were screened for their compatibility for the current transformation. As shown in Table T1.11, under the standard conditions, the reaction employing $[Ru(p\text{-Cymene})Cl_2]_2$ resulted in the formation of a complex mixture (Table T1.11, entry 2). On the other hand, the reaction with $Ru_3(CO)_{12}$ was sluggish, resulting in the product **9aa** in 8% yield along with high amounts of intractable compounds in the mixture (Table T1.11, entry 3). When the $RuCOH_2(PPh_3)_3$ catalyst was employed, the product **9aa** was obtained in 34% yield (Table T1.11, entry 4). However, the reaction with $RuCl_3$ was not fruitful, resulting in the recovery of the starting benzofuran **8a** (Table T1.11, entry 5). Thus, among various ruthenium catalysts screened, $Ru(PPh_3)_2Cl_2$ was found to be best for the current transformation. Next, we examined the various additives such as $Cu(OAC)_2$, $PivCO_2H$ and $AdCO_2H$ under standard conditions employing the $Ru(PPh_3)_2Cl_2$ catalyst. As shown in Table T1.11, in all the cases, the requisite product **9aa** was isolated in poor to moderate yields (Table T1.11, entries 6–8). Coming to the various polar solvents such as DMSO, DMF, NMP and H_2O screened, in all the cases, formation of an intractable complex

mixture was observed (Table T1.11, entries 9–12). A similar observation was made when 1,2-dichloroethane was used as the solvent and **9aa** could be isolated in 5% yield (Table T1.11, entry 13) from the complex mixture obtained. Interestingly, when 1,4-dioxane was used as the solvent, the product **9aa** was obtained in 42% yield (Table T1.11, entry 14).

Table T1.11: *Optimization of reaction conditions*[a]



entry	catalyst	solvent	additive	yield (9aa)
1.	[A]	Toluene	AgOAc	62%
2.	[B]	Toluene	AgOAc	Complex mixture
3.	[C]	Toluene	AgOAc	8%
4.	[D]	Toluene	AgOAc	34%
5.	[E]	Toluene	AgOAc	No reaction
6.	[A]	Toluene	$Cu(OAC)_2$	21%
7.	[A]	Toluene	$PivCO_2H$	43%
8.	[A]	Toluene	$AdCO_2H$	37%
9.	[A]	DMF	AgOAc	Complex mixture
10.	[A]	NMP	AgOAc	Complex mixture
11.	[A]	DMSO	AgOAc	Decomposed
12.	[A]	H_2O[b]	AgOAc	Decomposed
13.	[A]	1,2-DCE[b]	AgOAc	5%
14.	[A]	1,4-Dioxane	AgOAc	42%

[a] Reaction conditions: **8a** (1 equiv), **2a** (5 equiv), K_2CO_3 (5 equiv), toluene (3 ml). [b]Reaction carried out at 140 °C

1.31 Acrylate and benzofuran scope:

Having the optimized reaction conditions in hand, we next examined the compatibility of methyl methacrylate and methyl crotonate in the current transformation. As shown in the Scheme S1.71, the reaction of 3-formylbenzofuran **8a** with methyl methacrylate (**2f**) under the optimized conditions led to the formation of **10aa** in 63% yield. The analysis of the spectral data of compound **10aa** revealed a C2-linear alkylation followed by the C3-deformylation. For example, in the ^1H NMR spectrum of compound **10aa**, the characteristic aldehyde proton disappeared and in its place, benzofuran C3–H

appeared as a singlet at δ 6.52 ppm. In addition, the appearance of two separate doublet of doublets at δ 2.95 ppm (J = 7.3, 14.7 Hz) and at δ 3.28 ppm (J = 6.7, 14.7 Hz) revealed the presence of a methylene group. The α-CH_3 of methacrylate appeared as a doublet at δ 1.33 ppm with a coupling constant J = 7.3 Hz that was coupled with a sextet at δ 3.06 ppm (J = 7.0 Hz) which was found to be H–C-CO_2Me. In the ^{13}C NMR spectrum of compound **10aa**, the methyl carbon of acrylate appeared at δ 16.9 ppm. The –CH_2– and –OCH_3 carbon of acrylate resonated at δ 32.2, 51.8 ppm respectively. The α carbon of acrylate appeared at δ 38.4 ppm. There is no aldehyde carbon and in its place the benzofuran C3 carbon appeared at δ 103.5 ppm. In the HRMS, the exact mass calculated for $C_{13}H_{14}O_3Na$ $[M+Na]^+$ was 241.0835 and it was found to be 241.0835, thus confirming the proposed constitution.

Under similar conditions, the reaction of 3-formylbenzofuran **8a** with methyl crotonate **2j** gave mainly **11aa** (52% yield) resulting from the branched alkylation. The constitution of **11aa** was established with the help of spectral data analysis. For example, in the ^{1}H NMR spectrum compound **11aa**, the terminal methyl protons of crotonate appeared as triplet at δ 0.98 ppm with a coupling constant J = 7.4 Hz and its adjacent –CH_2– protons appeared as two separate multiplets at δ 2.00–2.08 and 2.09–2.18 ppm. The α proton of acrylate appeared as a triplet at δ 3.75 with J = 7.6 Hz and the characteristic aldehyde proton disappeared and in its place the benzofuran C3-H proton appeared as a singlet at δ 6.59 ppm. In ^{13}C NMR, the benzofuran C3 carbon resonates at δ 103.9 ppm, the terminal methyl and its adjacent –CH_2– carbons resonate at δ 11.9 and 24.2 ppm respectively. In the HRMS, the exact mass calculated for $C_{13}H_{14}O_3Na$ $[M+Na]^+$ was 241.0835 and it was found to be 241.0835.

To summarize, under similar conditions, 3-formylbenzofuran underwent branched alkylation with both methyl acrylate and methyl crotonate and linear alkylation with methyl methacrylate. In addition, with simple methyl acrylate, the C3-aldehyde group proceeded for an MBH reaction and deformylation occurred when crotonate and methacrylate were employed. The complementary branched *vs* linear alkylation are as expected considering the competing steric effects associated either with the metal center or with the incoming electrophiles, which essentially operate when the Ru–C bond of the

intermediate ruthenacycle is not sufficiently polar. The ready deformylation noticed with both methyl methacrylate and methyl crotonate indicates that their participation in the subsequent MBH reaction is prohibited due to the presence of a methyl group either at the alpha or the beta position to the carboxylate. This is an important observation that reveals that the proposed sequence of reactions in the cascade process that occurs during the cycloannulation on 3-formylbenzofuran with acrylate is indeed valid.

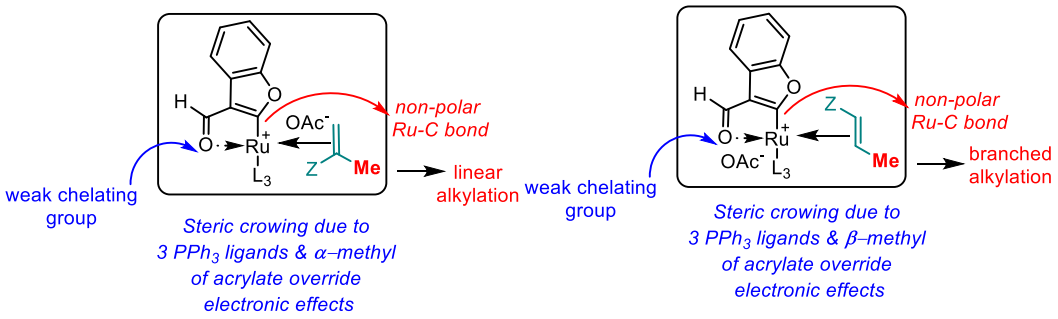
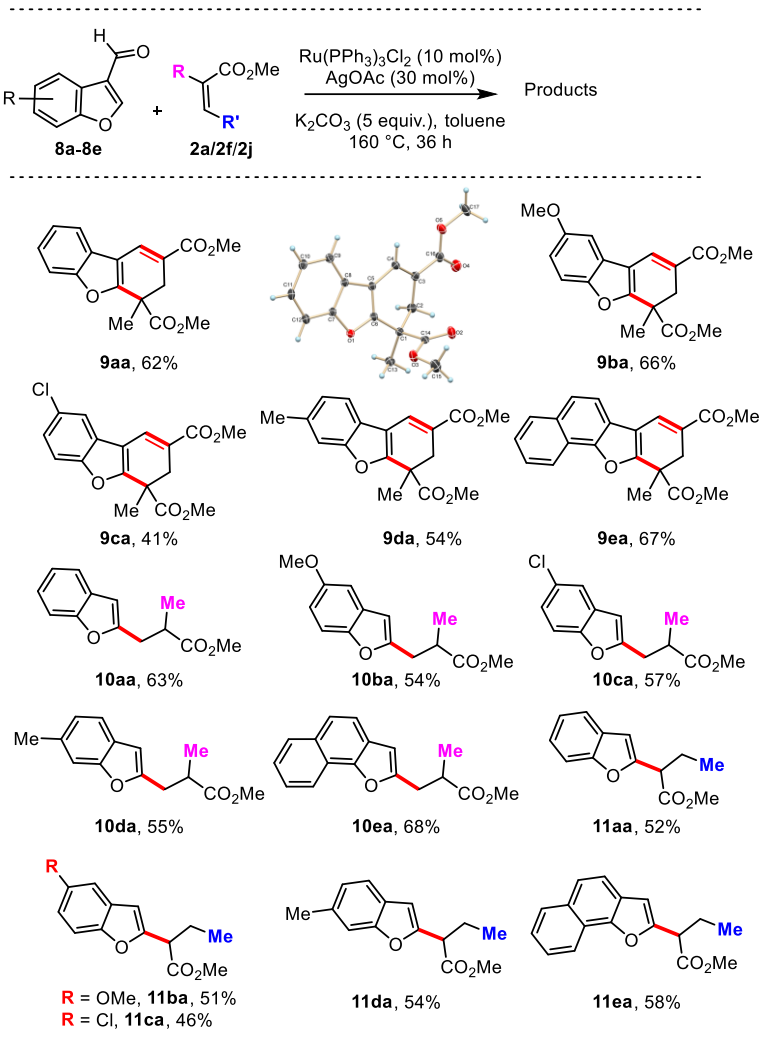


Figure F1.11: *Intermediate ruthenacycle in 3-formylbenzofurans*

After having these interesting results, we next proceeded for examining the scope of these reactions with the other substituted 3-formylbenzofurans. Thus, the reaction of substituted 3-formylbenzofurans **8b**–**8e** with methyl acrylate (**2a**) under optimized reaction conditions proceeded smoothly, resulting in the dihydrodibenzofurans **9ba**–**9ea** in good yields. Similarly, the reaction of these benzofurans **8b**–**8e** with methyl methacrylate (**2f**) under optimized reaction conditions resulted in the deformylated linear alkylated products **10ba**–**10ea** and with methyl crotonate (**2j**) gave the deformylated branched alkylation products **11ba**–**11fe** in moderate yields. In general, it was found that the reaction with substrates containing electron donating groups produced high yields compared to substrates containing electron withdrawing groups.

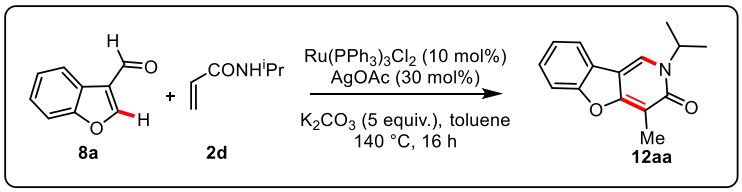


Scheme S1.71: *Scope of 3-formylbenzofurans with acrylates* ***2a/2f/2j***

1.32 Initial attempts by employing acrylamide:

On one hand, the above results are supportive of our hypothesis of the weak donating ability of a formyl group over an aroyl carbonyl group. On the other hand, as mentioned above, the C3-aldehyde group is prone to deformylation under current conditions, although it, can be trapped, as was noticed in case of the simple methyl acrylate. This suggested the possibility of trapping it intramolecularly with an internal nucleophile carried by the alkylating agent. As shown below, we hypothesized the possibility of a pyridin-2-one ring annulation employing simple acryl amide *via* branched alkylation, followed by intramolecular aldehyde-amide condensation.

With this hypothesis in mind, we have carried out the alkylation reaction of 3-formylbenzofuran (**8a**) employing three different acrylamides **2d**, **2w**, **2x** in the presence of $Ru(PPh_3)_2Cl_2$ (10 mol%), AgOAc (30 mol%), K_2CO_3 (5 equiv) at 160 °C for 36 h in toluene. The formation of a complex mixture was noticed with simple acrylamide (**2x**) and N,N-dimethyl acrylamide (**2w**). On the other hand, with N-isopropyl acrylamide (**2d**), the reaction resulted in the formation of a new product (with the expected molecular weight) which was observed to be fluorescent. The usual workup after 36 h, followed by purification, led to the isolation of **12aa** in 45% yield. Later, a simple screening of temperature and reaction duration led to the identification of the optimized conditions that involve heating the reaction for 16 h at 140 °C, giving the desired **12aa** in 75% yield. The spectral data analysis of **12aa** has indeed revealed that it was what we designed\desired. For example, in the ^{1}H NMR spectrum of compound **12aa**, the characteristic aldehyde proton disappeared and a singlet appeared at δ 7.86 ppm instead. A methyl group appeared as a singlet at δ 2.33 indicating that it is pendant on the (hetero)aryl ring. The *N*-isopropyl protons appeared as doublet at δ 1.47 ppm with J = 6.8 Hz and a septet at δ 5.51 ppm with a coupling constant J = 6.8 Hz. In the ^{13}C NMR spectrum of compound **12aa**, the quaternary methyl group appeared at δ 9.6 ppm. The isopropyl carbons of acrylamide appeared at δ 22.5 and 47.2 ppm. The characteristic olefinic carbon appeared at δ 127.4 ppm. In the HRMS, the exact mass calculated for $C_{15}H_{16}O_2N$ $[M+H]^+$ was 242.1176 and it was found to be 242.1175. Thus, the spectral data of **12aa** was indicative of a pyridine-2-one ring presence. As mentioned earlier, the pyridine ring annulation involves a series of reactions in one pot: C–H activation and branched alkylation with acryl amide, aldehyde-amide condensation followed by dehydration.

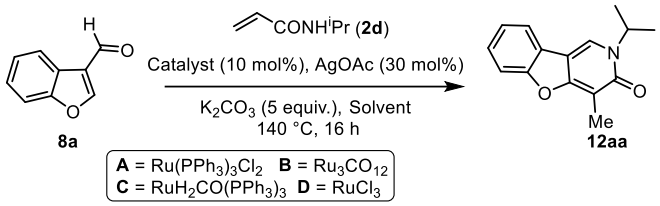


Scheme S1.72: *Reaction of 3-formylbenzofurans with isopropyl acrylamide*

1.33 Optimization of reaction conditions:

For the sake of completion and out of curiosity, we have examined the compatibility of various ruthenium catalysts for the current transformation and have also screened the compatibility of different solvents with the current catalyst. As shown in Table T1.12, $Ru(PPh_3)_2Cl_2$ was found to be the best catalyst for the current transformation when compared with the other ruthenium complexes and toluene also turned out to be the best solvent.

Table T1.12: *Optimization of the reaction conditions*[a]



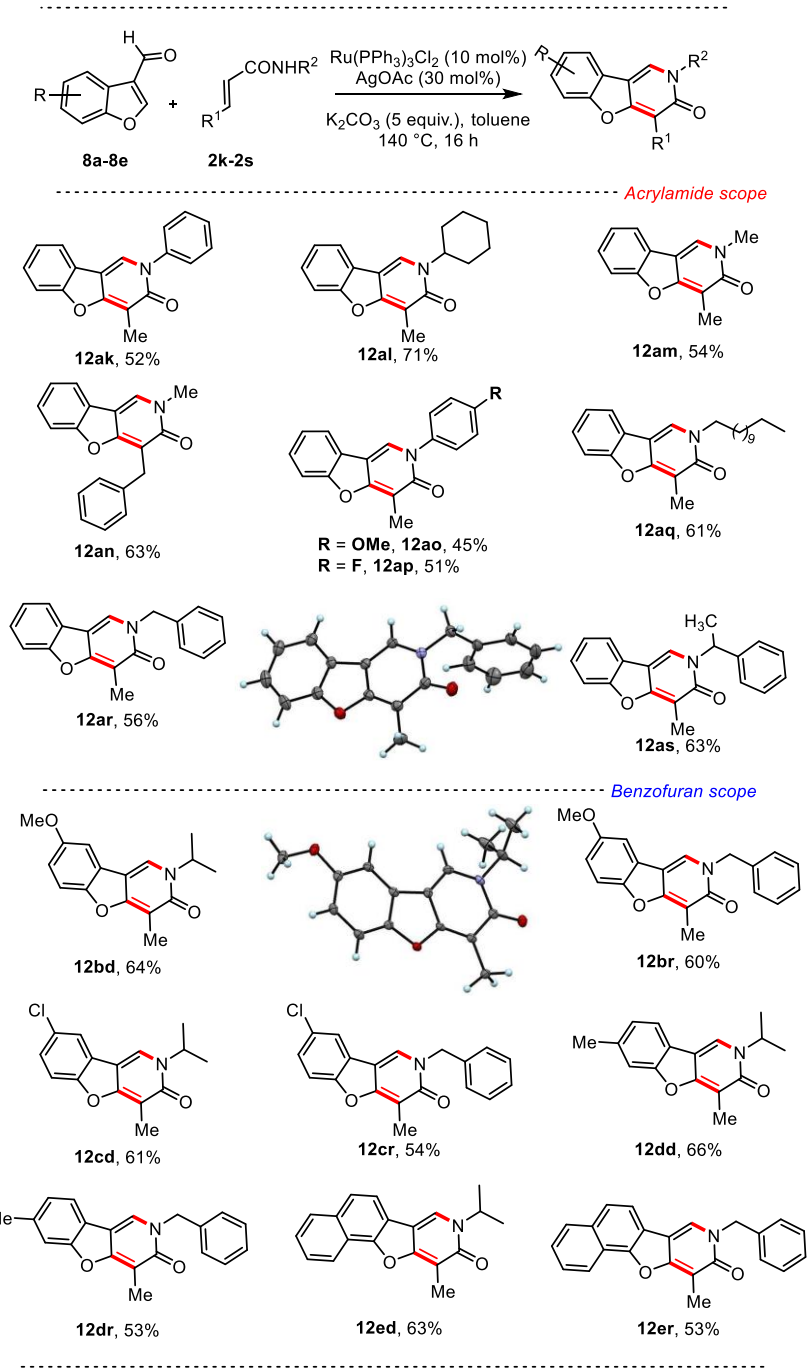
entry	catalyst	solvent	yield (12aa)
1.	[A]	toluene	75%
2.	[B]	toluene	56%
3.	[C]	toluene	40%
4.	[D]	toluene	Complex mixture
5.	–	toluene	No reaction
6.	[A]	toluene	No reaction[b]
7.	[A]	DMF	Decomposed
8.	[A]	DMSO	Decomposed
9.	[A]	H_2O	Decomposed
10.	[A]	NMP	Complex mixture
11.	[A]	1,4-dioxane	61%

[a] Reaction conditions: 8a (1 equiv), 2d (3 equiv), K_2CO_3 (5 equiv), toluene (3ml). [b]Reaction in absence of K_2CO_3.

1.34 Scope of acrylamide & benzofuran:

After optimizing the reaction conditions, we moved ahead to explore the scope of acrylamide and benzofuran in the current transformation. Initially, the scope of acrylamides has been explored by employing 3-formyl benzofuran (**8a**) and *N*-phenyl, *N*-cyclohexyl, *N*-methyl acrylamides **2k**–**2m**. In all the case, under optimized conditions, the reactions proceeded smoothly resulting in the corresponding pyridine-2-one derivatives **12ak**–**12am** in good yields. The *N*-methyl cinnamamide (**2n**) also showed compatibility in

the current transformation resulting in **12an** in 63% yield. The use of the acrylamide containing electron donating group (**2o**) or electron withdrawing group (**2p**) does not show much effect on the yield of the product **12ao** and **12ap**. Similarly, the reactions with other acrylamides **2q**, **2r**, **2s** proceeded smoothly and provided the corresponding tricyclic pyrdin-2-ones in excellent yields.

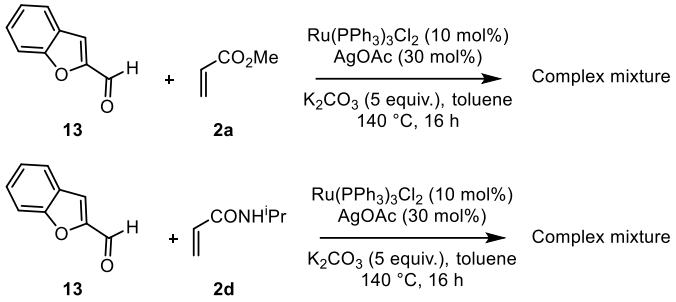


Scheme S1.73: *Scope of acrylamides and 3-formylbenzofurans*

Next, we have examined the benzofuran scope by conducting the alkylation of substituted 3-formylbenzofurans **8b**–**8e** with isopropyl acrylamide (**2d**) and benzyl acrylamide (**2r**). In all the cases, the reactions proceeded smoothly and gave the corresponding substituted pyridine-2-one derivatives **12bd**–**12er** in good yields. The 3-formylbenzofurans containing both electron donating and electron withdrawing groups showed compatibility in the current transformation.

1.35 Feasibility of 2-formylbenzofurans:

After having studied the alkylation 3-formylbenzofuran with various electrophiles wherein we could conclude that overriding electronic effects induced by the ring oxygen atom that favour a linear alkylation with acrylate could be counteracted by replacing an aryl carbonyl with a weaker formyl group as a directing group, we were next interested to understand what the outcome of the alkylation of regioisomeric 2-formylbenzofurans. However, when 2-formylbenzofuran (**13**) was subjected to the alkylation reaction with methyl acrylate (**2a**) and isopropyl acrylamide (**2d**) under optimized reaction conditions, the formation of complex reaction mixture was observed.

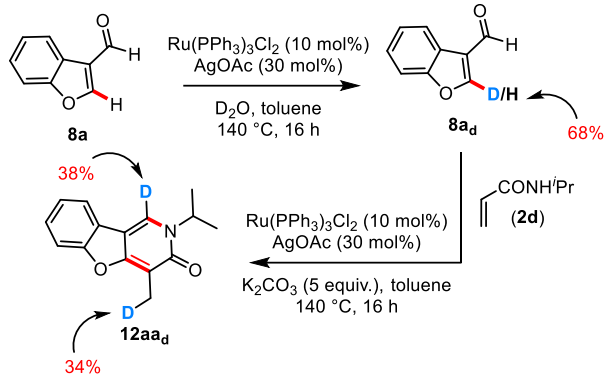


Scheme S1.74: *Exploration of 2-Formylbenzofurans*

1.36 Mechanism:

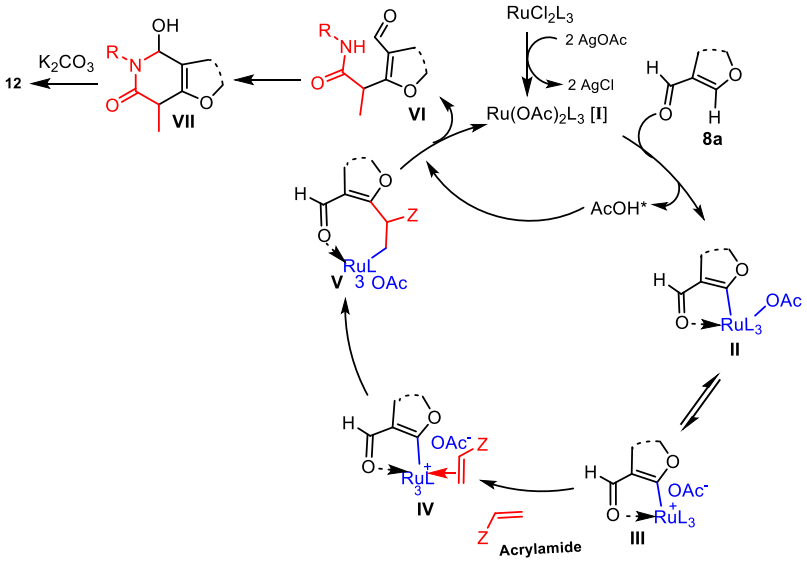
To get insights into the mechanism of the reaction, deuteration studies were carried out. Benzofuran (**8a**) on reaction with D_2O in the presence of $Ru(PPh_3)_2Cl_2$ catalyst (10 mol%), AgOAc additive (30 mol%) in toluene at 140 °C for 16 h results in the deuterated benzofuran $\mathbf{8a_d}$ with 48% deuterium incorporation at the C2 position and 39% deuteration of aldehyde proton. The reaction of deuterated benzofuran $\mathbf{8a_d}$ with *N*-isopropyl acrylamide (**2d**) under optimized reaction conditions gave $\mathbf{12aa_d}$ with (34%) deuterium

labelling of terminal methyl group and 38% deuterium incorporation at internal olefin. This ruled out the involvement of a Ru–H species in current catalytic cycle.



Scheme S1.75: *Deuterium labelling experiment*

Based upon the previous studies, we proposed the following mechanism for the current transformation. The catalytic cycle starts with the formation of the active $Ru(OAc)_2L_3$ (**I**) species by the reaction of $Ru(PPh_3)_3Cl_2$ with AgOAc. The coordination of the $Ru(OAc)_2L_3$ catalyst to the carbonyl and deprotonation of the adjacent C2–H results in the formation of the five membered ruthenacycle **II**.



Scheme S1.76: *proposed mechanistic cycle*

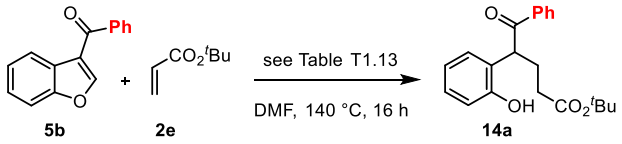
The easy dissociation of the Ru–OAc bond in the ruthenacycle results in the formation of the ionic complex **III**. Now, the coordination of acrylamide with complex (**III**) occurs in

such a way that the amide functionality of acrylamide is oriented away from the sterically hindered PPh_3 ligands around the ruthenium center and gets inserted into the Ru–C bond, leading to the inserted complex **V**. Finally, protodemetallation by the released AcOH results in formation of intermediate **VI** generating the active ruthenium (II) catalyst, continuing the catalytic cycle. The intermediate **VI** is converted to the final product **12** by aldehyde-amide condensation followed by dehydration.

1.37 Base Catalysed Benzofuran Rearrangement in the Presence of Acrylates

During our initial studies on alkylation of 3-aroylbenzofurans with acrylates, we observed the formation of a new product **14a** when the reaction was performed in polar solvents like DMSO, DMF and NMP, with the better yields obtained in DMF. Simple control experiments replacing the catalyst and/or additive and base led us to the realization to identify that simply heating the 3-aroylbenzofuran and acrylate in the presence of 5 equiv base can result in the formation of this product.

Table T1.13: *Control experiments*

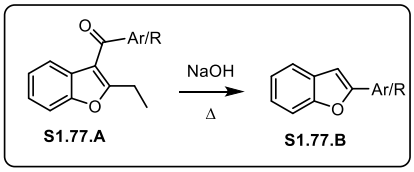


entry	$Ru(PPh_3)_2Cl_2$	AgOAc	K_2CO_3	Crude yield
1.	10 mol%	30 mol%	5 equiv.	65%
2.	---	30 mol%	5 equiv.	76%
3.	---	---	5 equiv.	83%
4.	---	---	---	No reaction

This product has been characterised as *tert*-butyl 5-oxo-4,5-diphenylpentanoate with the help of spectral data analysis. For example, in the ^1H NMR spectrum of compound **14a**, the *tert*-butyl protons of acrylate appeared as a singlet at δ 1.43 ppm. The two CH_2 units of acrylate resonated as mutiplets at δ 2.12–2.29 and 2.36–2.44 ppm, which indicated the attachment of the CH_2 beta to the carboxylate to a stereogenic center. Further, the characteristic benzofuran C2–H proton disappeared and a triplet was observed at δ 4.94 ppm with a coupling constant J = 7.0 Hz. In the ^{13}C NMR, there are only six carbons seen

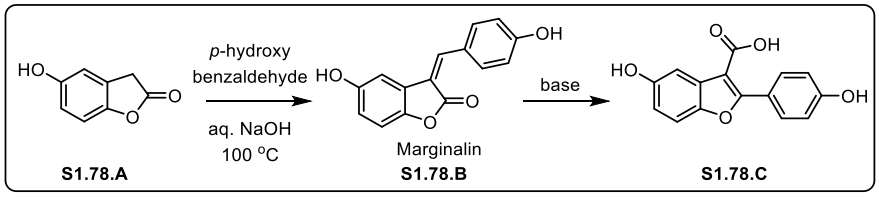
in the aromatic region. The two CH_2 carbons of the propanoate resonated at δ 27.0, 32.7 ppm as triplets. Further, a doublet appeared at δ 47.1 ppm. The ester and keto carbonyls were found to resonate at δ 174.1, 201.6 ppm respectively and the *tert*-butyl carbons of the carboxylate appeared at δ 28.0, 81.3 ppm. In the HRMS, the exact mass calculated for $C_{21}H_{24}O_4Na$ $[M+Na]^+$ was 363.1567 and it was found to be 363.1562. Thus, from the ^1H, ^{13}C & HRMS spectra, was confirmed to be the product.

The formation of product **14a** could be explained by considering the facile opening of the O1–C2 bond of benzofurans bearing an electron withdrawing group such as a carbonyl at the C3 under basic conditions, leading to a 1,3-dicarbonyl compound. In general, these intermediates undergo decarbonylation under the same conditions. For example, in 1960, Royer and his co-workers described the alkali mediated ring opening of the O1–C2 bond in 2-ethyl-3-aroylbenzofurans followed by dealkanoylation [losing C2] and subsequent dehydrative ring closure resulting in a new benzofuran derivative wherein the substituent attached to carbonyl becomes the C2 substituent (Scheme S1.77).[58]



Scheme S1.77: *Rearrangement of 3-aroylbenzofurans.*

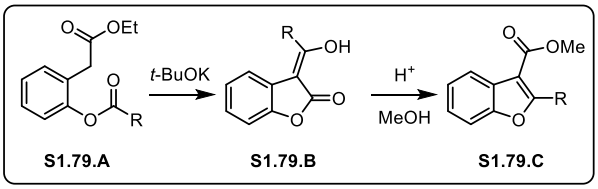
In 1991, Barbier reported the base mediated rearrangement of the natural product marginalin. In this approach, lactone **S1.78.A** on reaction with *p*-hydroxybenzaldehyde in the presence of NaOH, results in the natural product marginalin **S1.78.B** which, in the basic medium, got rearranged to the 2-arylbenzofuran-3-carboxylic acid derivative (Scheme S1.78).[59]



Scheme S1.78: Base catalysed *rearrangement of marginalin*

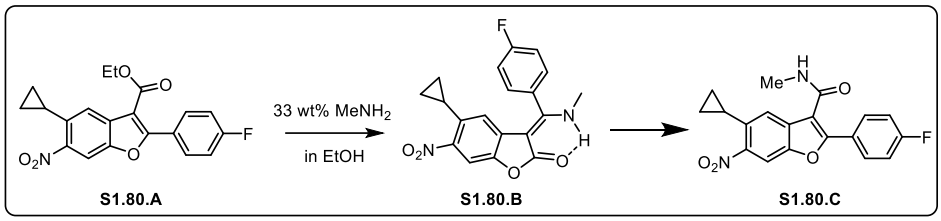
In 2015, Chi and co-workers developed an attractive strategy for the synthesis of 2-substituted methylbenzofuran-3-carboxylate. In this process, substrate **S1.79.B** in the

acidic medium got rearranged to 2-substituted methylbenzofuran-3-carboxylate derivatives. The reaction was performed on a large number of substrates, resulting in 2-alkyl or 2-aryl benzofuran-3-carboxylate which otherwise are prepared by cross-coupling chemistry. Furthermore in many cases, the products were obtained in pure form avoiding column chromatography (Scheme S1.79).[60]



Scheme S1.79: *Chi approach for benzofuran synthesis*

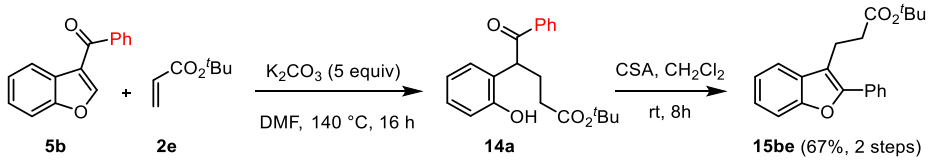
In a seminal paper, Xie and co-workers have identified such an opening and ring transformation during the amidation of the 2-arylbenzofuran-3-carboxylate intermediate used in the synthesis of the HCV polymerase inhibitor GSK852A (Scheme S1.80).[61]



Scheme S1.80: *Xie approach for amidation of benzofuran*

From the above mentioned examples, it was clear that benzofurans bearing an electron withdrawing group such as a carbonyl at the C3, undergo opening of the O1–C2 bond under basic conditions, leading to the formation of a 1,3-dicarbonyl compound. Under the same conditions, the decarbonylation of these 1,3-dicarbonyl compounds is facile. Subsequently, the acid treatment of the resulting products leads to the formation of C2-substituted benzofurans *via* dehydrative cyclization. Overall, this two-step, coined as – "benzofuran ring transformation" results in the preparation of C2-substituted benzofurans, wherein the C3-carbonyl carbon of the starting benzofuran becomes the C2 of the newly formed benzofuran ring and the substituent attached to carbonyl becomes the C2 substituent. Coming to the present case, since excess acrylate is present, the Michael addition of the enolate of the intermediate 1,3-dicarbonyl is expected prior to deformylation [loss of C2] that results in the formation of product **14a**. Considering, the

above reports on benzofuran ring transformation, when the crude **14a** was treated with camphor sulphonic acid (CSA) in dichloromethane, the known 2,3-disubstituted benzofuran **15be** was obtained in 67% overall yield.



Scheme S1.81: *Base-mediated benzofuran ring transformation in the presence of acrylate*

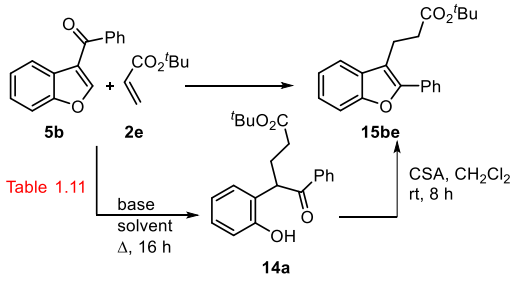
1.38 Optimization of reaction conditions:

With this preliminary information on this new approach for the synthesis of 2,3-disubstituted benzofurans, we next proceeded for screening other bases and solvents, and optimising the reaction conditions. In all the cases, where there was a product formation, the reaction was subjected to a simple aqueous work up and the resulting crude was treated with 1 equiv of CSA in dichloromethane to obtain the corresponding 2,3-disubstituted benzofuran. As shown in the Table T1.14, in non-polar solvents such as toluene, 1,2-dichloroethane and also in 1,4-dioxane or in water, there was no reaction and the starting benzofuran was recovered. The reaction in polar solvents like DMSO, NMP and DMF was successful, leading to the formation of product **14a** which, upon treatment with CSA, gave the intended product **15be** in 65%, 57% and 69% yields respectively (Table T1.14, entries 6–8). Considering the better yields obtained in DMF solvent, further optimization/control experiments were conducted in the same solvent. As a part of the optimization, when the same reaction was carried out at 100 °C, **15be** was isolated in 46% yield based on 44% recovered starting material. Even the reaction at 120 °C under similar conditions was incomplete, resulting in 28% recovery of the starting benzofuran **5b** (Table T1.14, entries 9, 10). The reaction was feasible even when reducing the K_2CO_3 from 5 to 2 equiv, resulting in the product **15be** in 73% yield after CSA cyclization (Table T1.14, entry 11).

After solvent optimization, we moved ahead to explore the compatibility of other bases in the current transformation. The reaction of benzofuran **5b** with terbutyl acrylate (**2e**) in the presence of Cs_2CO_3 or K^{t}OBu in DMF solvent at 140 °C resulted in the final product **15be** in 63% and 52% yields respectively (Table T1.14, entries 13, 14). The

reaction with CsOAc was sluggish and 46% of the starting material was recovered (Table T1.14, entry 15) along with the isolation of **15be** in 61% yield. However, NaOAc and $NaHCO_3$ were not compatable for the current transformation (Table T1.14, entry 16, 17). The scope of Lewis acids for the cyclization step was then examined by screening the reaction with PTSA, $ZnCl_2$, HCl and $Cu(OTf)_2$, with the reaction being fruitful in all the cases, resulting in the final product **15be** in 52%, 68%, 70% and 71% yields respectively. The initial results obtained by using CSA were better than the other Lewis acids screened and for further experiments, we proceeded by employing the same.

Table T1.14: *Optimization of reaction conditions*



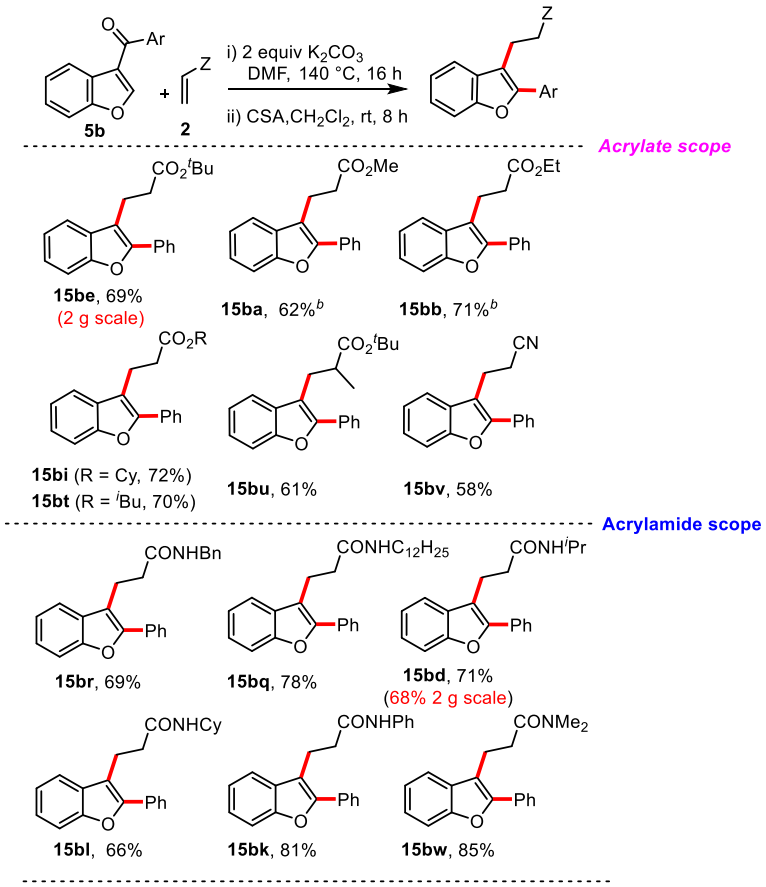
entry	base	solvent	temp.	yield[b]
1.	K_2CO_3	1,2-DCE	rt	--
2.	K_2CO_3	1,2-DCE	110 °C	--
3.	K_2CO_3	H_2O	110 °C	--
4.	K_2CO_3	toluene	140 °C	--
5.	K_2CO_3	1,4-dioxane	140 °C	--
6.	K_2CO_3	DMSO	140 °C	65%
7.	K_2CO_3	NMP	140 °C	57%
8.	K_2CO_3	DMF	140 °C	69%
9.	K_2CO_3	DMF	100 °C	46%[c]
10.	K_2CO_3	DMF	120 °C	67%[d]
11.	**K_2CO_3**	**DMF**	140 °C	**73%**[e]
12.	—	DMF	140 °C	--
13.	Cs_2CO_3	DMF	140 °C	63%
14.	K^{t}OBu	DMF	140 °C	52%
15.	CsOAc	DMF	140 °C	61%[f]
16.	NaOAc	DMF	140 °C	--
17.	$NaHCO_3$	DMF	140 °C	--

[a]Reaction conditions: i) **5b** (0.22 mmol), **2e** (0.44 mmol), base (1.1 mmol), DMF (3 mL), Δ, 16 h. ii) CSA (0.22 mmol), CH_2Cl_2 (10 mL). [b]Isolated yields after CSA reaction. [c]Reaction at 100 °C and Yield based on 44% recovered S.M. [d]Reaction at

120 °C and yield based on 28% recovered **5b**. [e]Reaction with (0.44 mmol) of K_2CO_3. [f]Yield based on 46% recovered **5b**.

1.39 Exploring the acrylate & acrylamide scope:

After having optimised conditions in hand, we moved forward to explore the scope of acrylate, acrylamide, acrylonitrile in the current transformation. All the reactions were performed using standard optimised conditions by employing 2 equiv. K_2CO_3 and DMF as a solvent at 140 ºC for 16 h. The crude products that resulted after the aqueous workups were directly subjected for the cyclization with CSA to get the desired disubstituted benzofuran.



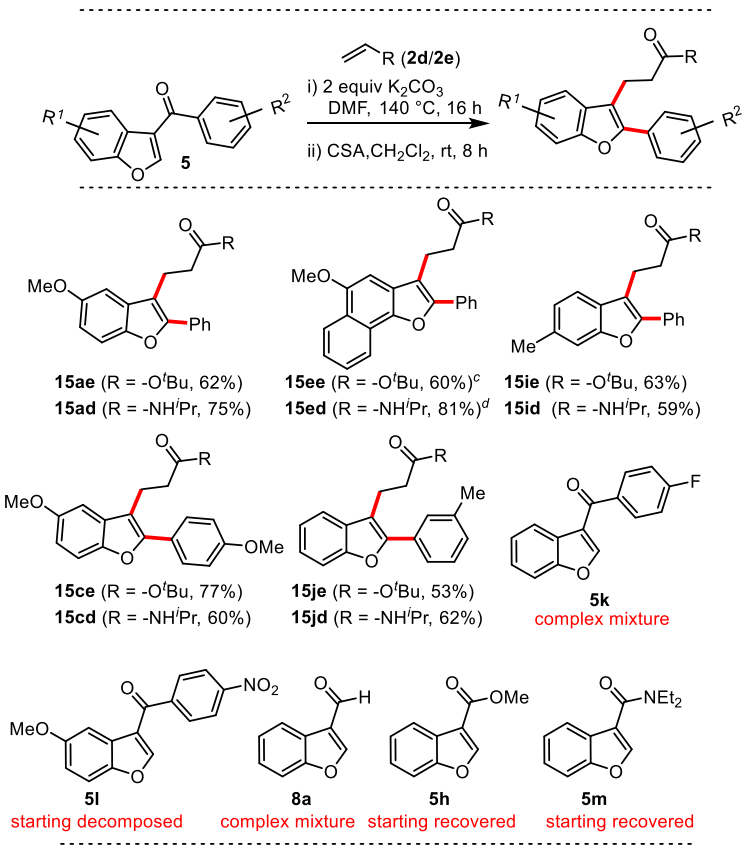
Scheme S1.82: *Scope of acrylate/acrylamide*[a]

[a]Reaction conditions: i) **5b** (1 equiv), **2** (2 equiv), DMF (3 mL). ii) CSA (1 equiv for acrylate and 3 equiv for acrylamide), CH_2Cl_2 (10 mL). [b]For **15ba**, **15bb** – the corresponding acid were obtained in 30% and 32% respectively and the combined yields were given.

For the reaction with methyl-, ethyl acrylates, nearly 33% of the ester hydrolysed product was observed along with the desired products **15ba**, **15bb**. In all the other cases, the reactions proceeded smoothly, resulting in the disubstituted benzofurans as the sole product in excellent yields. Both *tert*-butyl methacrylate (**2u**) and acrylonitrile (**2v**) also showed compatibility in the present reaction, resulting in the products **15bu** and **15bv** respectively in good yields. A wide range of acrylamides such as *N*-benzyl, *N*-dodecyl, *N*-isopropyl, *N*-cyclohexyl and N-phenyl acrylamides have been screened in the current transformation, which proceeded smoothly, resulting in the corresponding 2,3-disubstituted benzofuran in excellent yields. Even the *N*,*N*-dimethyl acrylamide (**2w**) worked well resulting in **15bw** in 85% yield.

1.40 Benzofuran scope:

The generality of this methodology has been further examined by employing benzofurans having substituents either on benzofuran or on the aroyl phenyl ring. The reaction of benzofurans **5a**, **5c**, **5i**, **5j** with *tert*-butyl acrylate **2e** and *iso*-propyl acrylamide **2d** under optimised reaction conditions proceeded smoothly, resulting in the corresponding 2,3-disubstituted benzofurans in good yields. However, in case of benzofuran **5e**, the reactions with both **2e** and **2d** were sluggish and the starting material was recovered along with the required product. Prolonged heating during the first step was found to be of no use in this case. The benzofurans containing an electron withdrawing group *para* to the carbonyl, such as fluoro in case of **5k** and nitro in **5l** on reaction with *tert*-butyl acrylate **2e** resulted in either a complex mixture or the decomposition of the starting aroylbenzofuran indicating that they were unsuccessful. This is anticipated, considering the earlier Royer's report on similar 3-aroylbenzofurans which undergo oxidative dearylation under the base-mediated ring transformation conditions, leading to the corresponding benzofuran-3-carboxylic acid. We moved ahead to check the feasibility of other benzofurans in the current transformation by replacing the aroyl group with aldehyde, ester or the amide functionality. Thus, benzofuran 3-carbaldehyde **8a** on reaction with terbutyl acrylate **2e** was not fruitful, resulting in a complex reaction mixture, while the reaction of benzofurans **5h** and **5m** with acrylate **2e** resulted in the recovery of the starting material.



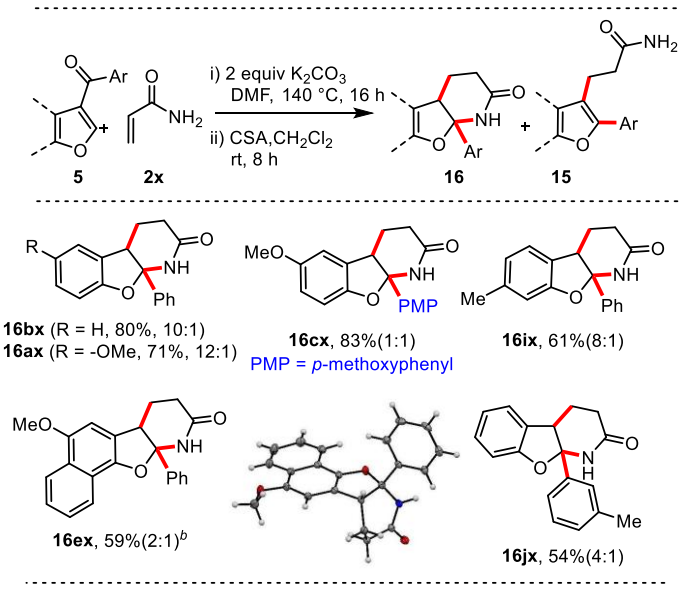
Scheme S1.83: *Scope of benzofurans*[a]

[a]Reaction conditions: i) **5** (1 equiv), **2d**/**2e** (2 equiv), DMF (3 mL). ii) CSA (1 equiv for acrylate and 3 equiv for acrylamide), CH_2Cl_2 (10 mL). [b]Yield based on 28% recovered starting material. [c]Yield based on 24% recovered starting material.

1.41 Exploring the reaction with simple acrylamide:

Next, we examined the compatibility of the simple acrylamide under these conditions. The reaction of benzofuran **5a** with simple acrylamide **2x** under standard conditions following the usual two-step sequence results in an inseparable mixture of the cyclized product **16ax** and the disubstitued benzofuran **15ax** in a 12:1 ratio with 71% yield.[62] Similarly, the benzofuran **5j** also gave inseparable mixtures of cyclised and uncyclized products. However, the reaction with benzofurans **5a**, **5c**, **5i** resulted in separable mixtures of cyclized and uncyclized derivatives in varying proportions. In case of benzofuran **5e**, the reaction was sluggish, resulting in recovery of the starting material along with a separable

mixture of **16ex** and **15ex**. As observed with the acrylates, the reaction of benzofuran **5k** with acrylamide **2x** also led to a complex mixture.

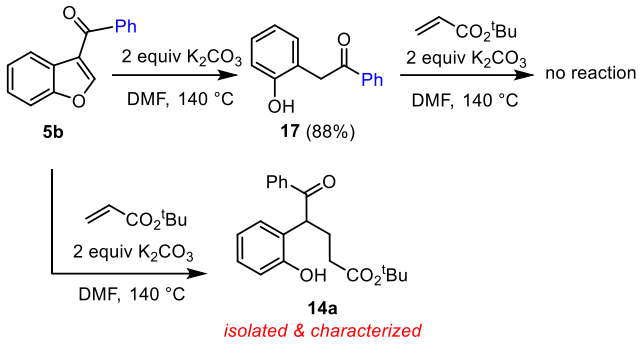


Scheme S1.84: *Reactions with simple acrylamide and substrate scope*[a]

[a]Reaction conditions: i) **5** (1 equiv), **2x** (2 equiv), DMF (3 mL). ii) CSA (3 equiv), CH_2Cl_2 (10 mL). Isolated yields after CSA reaction. [b]Yield based on 48% recovered S.M. The ratio in the parenthesis is that of **16**:**15**.

1.42 Mechanistic studies:

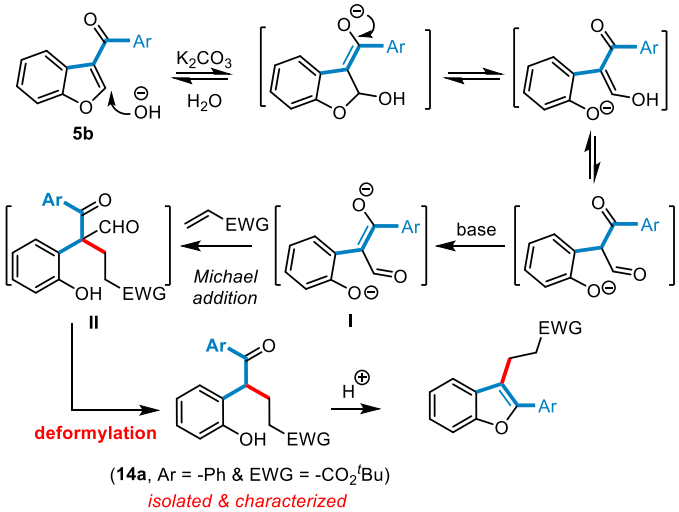
After having established the proposed hypothesis, we moved ahead to carry out control experiments to establish the mechanism of the reaction. At first, benzofuran **5b** was heated alone with 2 equiv of K_2CO_3 in DMF at 140 °C for 16 h, which resulted in the formation of the known deformylated product **17** in 88% yield.[63] This confirmed that K_2CO_3 is sufficiently basic enough to open the benzofuran ring and to perform deformylation under the current reaction conditions. To know the occurrence of Michael addition prior to or after deformylation, the ketone **17** was subjected to the current reaction in the presence of acrylate under standard optimised conditions. This did not result in product formation and the starting ketone was recovered completely. These results suggested that Michael addition with acrylates precedes over the deformylation event.



Scheme S1.85: *Control experiments*

1.43 Proposed mechanism:

With this available information, we propose the following mechanism. It is known that in the presence of base, benzofuran **5b** having an electron withdrawing group at C3 undergoes a ring opening to form the enolate intermediate **I.** This intermediate **I** undergoes Michael addition with a conjugated olefin resulting in the intermediate **II** which, on subsequent deformylation, results in the isolable ketone intermediate **14a**. This intermediate **14a** undergoes a dehydrative cyclization when treated with CSA giving the required disubstituted benzofuran **15be**.



Scheme S1.86: *Proposed mechanistic cycle*

Conclusion:

In this chapter, we have developed several methods for the functionalization of 2-/3-aroylbenzofurans, which are the key scaffolds present in many bioactive molecules. The work has been initiated mainly to examine the carbonyl directed Ru-catalyzed C–H

activation and functionalization of 2-/3-aroylbenzofurans employing various conjugated olefins as the alkylating agents. This has been carried out in order to understand the interplay between electronic (associated with the coordinating ability of the carbonyl group) and steric factors (resulting either from steric crowding around the Ru-center or from the sterically demanding electrophiles such as acrylates bearing methyl groups on either of the olefin carbons).

In the first part, we have presented the catalyst-dependent linear *vs* branched alkylation of 2-aroylbenzofurans with acrylates. This has been attributed mainly to the nature of the intermediate ruthenacycle involved and its reactivity with the acrylate. In case of the linear alkylation observed with $[RuCl_2(p\text{-cymene})]_2$ having the less electron donating arene ligand (when compared to the three PPh_3 ligands in the other Ru-complex employed), the Ru–C bond is more polar and the electrophilic β-carbon of acrylate will be oriented close to the nucleophilic Ru–C carbon atom and the α-carbon will be close to the metal centre, which leads to a linear alkylation product. On the other hand, in case of the $Ru(PPh_3)_3Cl_2$ catalyst the Ru–C bond appears to be less polar (because of the presence of strongly electron donating phosphine ligands). The orientation of the acrylate with respect to the Ru–C bond will be decided mainly by the steric crowding around the metal center. The large steric effect due to the presence of three PPh_3 ligands (with respect to the arene in the former case), likely influences the insertion of the alkene into the Ru–C bond, taking the functional group far from the PPh_3 ligands. As a result, the sterically less demanding β-carbon of acrylate will be close to the metal centre, which ultimately leads to the branched alkylation product.

In the next part, we have executed the carbonyl directed Ru-catalyzed C–H activation of 3-aroylbenzofurans and functionalization with acrylates. This has been planned to understand how a subtle variation in the donating ability of the carbonyl group will influence the regioselectivity of alkylation. As expected, with $Ru(PPh_3)_3Cl_2$ catalyst, a linear alkylation was observed with 3-aroylbenzofurans with simple acrylate. In case of 2-aroyl benzofurans, with the same catalyst, an exclusive branched alkylation was noticed. This complementary reactivity has been attributed to stronger donating ability of the same aroyl carbonyl [leading to a more polar Ru–C bond] due to the conjugation of the

benzofuran ring oxygen. This has been verified with the help of DFT calculations. Subsequent experiments with methyl crotonate (which resulted in complimentary branched alkylation) revealed yet another interesting observation – the magnitude of this electronic effect on Ru–C bond is not sufficiently strong enough and thus the steric factors associated with the incoming electrophile override the selectivity towards the branched alkylation.

To further probe in the direction of understating the role of electronic factors associated with the directing carbonyl group *inter alia* polarity of the Ru–C bond of the intermediate ruthenacycle, we have examined the alkylation of 3-formylbenzofuran. This has been planned to counteract the electronic perturbation caused by the ring oxygen atom so as the selectivity can be switched from linear to branched alkylation (the formyl group is a weaker coordinating group when compared to the corresponding aroyl carbonyl). Interestingly, with simple methylacrylate, branched alkylation was the major event. However, the intermediate alkylation products further participated in a cascade reaction process that comprises of – MBH reaction of the acrylate with the formyl group, intramolecular Michael addition followed by dehydration leading to the annulation of the densely functionalized dihydrodibenzofuran skeleon. However, with methacrylate and crotonates, the C3-formyl group underwent decarbonylation after alkylation. Later, we have developed another cascade process to annulate a pyridine-2-one ring employing *N*-substituted acrylamides.

In the final part, analysis of one of the side reaction that was observed during the alkylation of 3-aroylbenzofurans with acrylate, has led to the development of a simple, metal free, base catalysed method for the synthesis of 2,3-disubstituted benzofurans. This involves the intermediates that are base-mediated ring opened [O1–C2] products of 3-aroylbenzofurans with Michael acceptors prior to the decarbonylation. A large number of acrylates, acrylamides and acrylonitriles have shown feasibility in the current transformations. The method is executed in gram scale making this process practical.

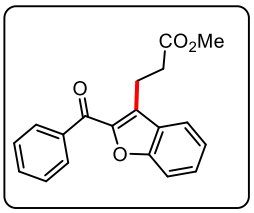
Ruthenium catalyzed C–H activation of 2-aroylbenzofurans:

General Experimental procedure:

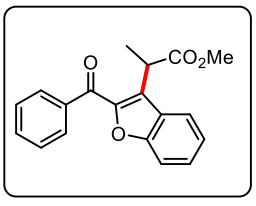
2-aroylbenzo[b]furan (0.1 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous dioxane (2 mL), which was then evacuated and back filled with argon. To the reaction vessel alkene (acrylate) (0.3 mmol), $NaHCO_3$ (0.5 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.01 mmol) and PPh_3 (0.03 mmol) were added. The solution was then stirred at 140 °C (bath temperature) for 24 h. The reaction mixture was cooled to room temperature. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/AcOEt) to give analytically pure.

Experimental Data:

Methyl 3-(2-benzoylbenzofuran-3-yl)propanoate (3aa): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil; ratio of linear to the branched product is 86:14; 87 mg, 63%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.81 (t, J = 7.8 Hz, 2H), 3.44 (t, J = 7.8 Hz, 2H), 3.63 (s, 3H), 7.35 (ddd, J = 1.4, 6.8, 8.2 Hz, 1H), 7.47–7.55 (m, 4H), 7.59–7.64 (m, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.10–8.13 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.1 (t), 33.6 (t), 51.7 (q), 112.3 (d), 121.6 (d), 123.5 (d), 128.1 (s), 128.3 (d, 3C), 129.6 (s), 129.8 (d, 2C), 132.7 (d), 137.5 (s), 148.4 (s), 154.3 (s), 173.3 (s), 185.5 (s) ppm; IR (neat): ν 3020, 2400, 1731, 1644, 1438, 1215, 1045, 850, 758, 669 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{16}O_4Na$ (M^++Na): 331.0941; found: 331.0938.

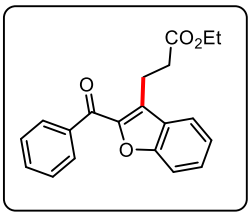


Methyl 2-(2-benzoylbenzofuran-3-yl)propanoate (4aa): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 14 mg, 10%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.67 (d, J = 7.2 Hz, 3H), 3.68 (s, 3H), 4.96 (q, J = 7.2 Hz, 1H), 7.32 (ddd, J = 1.4, 6.8, 8.1 Hz, 1H), 7.45−7.68 (m, 5H), 7.75 (d, J = 8.0 Hz, 1H), 8.10–8.16 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 16.8 (q),

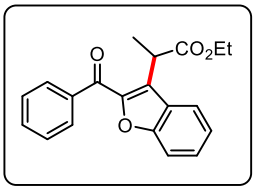


35.9 (d), 52.2 (q), 112.5 (d), 122.2 (d), 123.7 (d), 126.7 (s), 128.1 (d), 128.3 (d, 2C), 128.8 (s), 129.9 (d, 2C), 132.9 (d), 137.3 (s), 147.7 (s), 154.3 (s), 173.7 (s), 185.9 (s) ppm; IR(neat): *v* 3020, 2400, 1735, 1645, 1563, 1261, 1215, 1059, 877, 757, 669 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{16}O_4Na$ (M^++Na): 331.0941; found: 331.0938.

Ethyl 3-(2-benzoylbenzofuran-3-yl)propanoate (3ab): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil; ratio of linear to the branched product is 88:12; 94 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.1 Hz, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 3.44 (t, *J* = 7.6 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 7.32–7.36 (m, 1H), 7.47–7.54 (m, 4H), 7.59–7.63 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 1H) 8.11 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 20.1 (t), 33.9 (t), 60.5 (t), 112.3 (d), 121.7 (d), 123.5 (d), 128.2 (s), 128.3 (d, 3C), 129.7 (s), 129.8 (d, 2C), 132.7 (d), 137.5 (s), 148.4 (s), 154.3 (s), 172.8 (s), 185.5 (s) ppm; IR(neat): *v* 2960, 2934, 2874, 1735, 1654, 1599, 1465, 1261, 1175, 973, 876, 751 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{18}O_4Na$ (M^++Na): 345.1097; found: 345.1095.

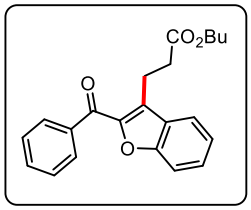


Ethyl 2-(2-benzoylbenzofuran-3-yl)propanoate (4ab): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 13 mg, 9%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.67 (d, *J* = 7.3 Hz, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.91 (q, *J* = 7.3 Hz, 1H), 7.32 (ddd, *J* = 1.4, 6.8, 8.1 Hz, 1H), 7.44−7.67 (m, 5H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.09–8.14 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1 (q), 16.9 (q), 36.1 (d), 61.0 (t), 112.4 (d), 122.3 (d), 123.5 (d), 126.7 (s), 128.0 (d), 128.3 (d, 2C), 129.0 (s), 129.9 (d, 2C), 132.9 (d), 137.4 (s), 147.7 (s), 154.3 (s), 173.2 (s), 185.8 (s) ppm; IR(neat): *v* 3278, 3061, 2984, 1908, 1732, 1645, 1599, 1448, 1300, 1200, 1093, 876, 752, 680 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{18}O_4Na$ (M^++Na): 345.1097; found: 345.1095.

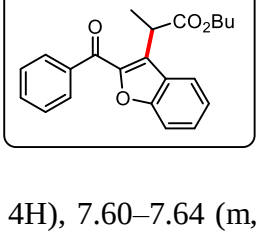


Butyl 3-(2-benzoylbenzofuran-3-yl)propanoate (3ac): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil; and ratio of linear to the branched product is 86:14; 107 mg, 68%; **^{1}H NMR**

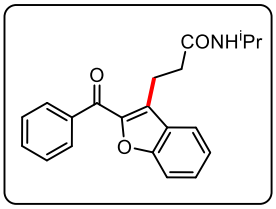
(400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.26–1.33 (m, 2H), 1.50–1.57 (m, 2H), 2.81 (t, J = 7.6 Hz, 2H), 3.45 (t, J = 7.6 Hz, 2H), 4.03 (t, J = 6.7 Hz, 2H), 7.34–7.37 (m, 1H), 7.49–7.56 (m, 4H), 7.61–7.65 (m, 1H), 7.80 (d, J = 7.7 Hz, 1H), 8.12 (d, J = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7 (q), 19.0 (t), 20.1 (t), 30.5 (t), 33.8 (t), 64.5 (t), 112.3 (d), 121.7 (d), 123.5 (d), 128.2 (s), 128.3 (d, 3C), 129.8 (s), 129.8 (d, 2C), 132.8 (d), 137.5 (s), 148.4 (s), 154.3 (s), 173.0 (s), 185.5 (s) ppm; IR(neat): v 3059, 2960, 2935, 2874, 1735, 1654, 1560, 1449, 1355, 1263, 1175, 876, 751, 725 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{22}O_4Na$ (M^++Na): 373.1410; found: 373.1410.



Butyl 2-(2-benzoylbenzofuran-3-yl)propanoate (4ac): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 17 mg, 11%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.77 (t, J = 7.3 Hz, 3H), 1.10−1.30 (m, 2H), 1.43−1.54 (m, 2H), 1.66 (d, J = 6.9 Hz, 3H), 4.09 (t, J = 6.6 Hz, 2H), 4.90 (q, J=7.3 Hz, 1H), 7.31 (td, J = 0.9, 7.6 Hz, 1H), 7.46–7.56 (m, 4H), 7.60–7.64 (m, 1H), 7.77 (d, J = 7.8 Hz, 1H), 8.07–8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.5 (q), 16.8 (q), 18.9 (t), 30.5 (t), 36.1 (d), 64.9 (t), 112.4 (d), 122.4 (d), 123.6 (d), 126.8 (s), 128.1 (d), 128.3 (d, 2C), 129.0 (s), 129.9 (d, 2C), 132.9 (d), 137.4 (s), 147.7 (s), 154.4 (s), 173.3 (s), 185.9 (s) ppm; IR(neat): v 3393, 2959, 1735, 1647, 1448, 1300, 1260, 876, 751, 724 cm^{-1}; **HRMS** (ESI) calcd for $C_{22}H_{23}O_4$ (M^++H): 351.1591; found: 351.1589.

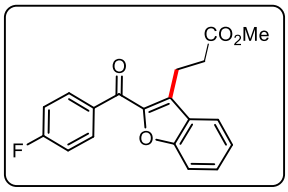


3-(2-benzoylbenzofuran-3-yl)-N-isopropylpropanamide (**3ad**): Isolated by column chromatography (pet.ether/AcOEt = 7:3, R_f = 0.4). The title compound was determined as colourless solid; 119 mg, 79%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.04 (d, J = 6.6 Hz, 6H), 2. 66 (t, J = 7.4 Hz, 2H), 3.45 (t, J = 7.4 Hz, 2H), 3.98–4.04 (m, 1H), 5.87 (br. s., 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.48–7.56 (m, 4H), 7.62–7.65 (m, 1H), 7.83 (d, J = 7.9 Hz, 1H), 8.13 (d, J = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0 (t), 22.6 (q, 2C), 36.6 (t), 41.3 (d), 112.2 (d), 122.1 (d), 123.7 (d), 128.1 (s), 128.4 (d, 2C), 128.5 (d), 129.9 (d, 2C), 130.7 (s), 132.9 (d), 137.4 (s), 148.2 (s), 154.4 (s), 171.0 (s), 185.9 (s) ppm;

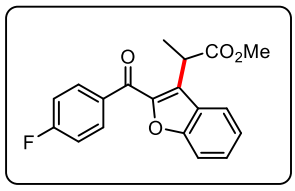


IR(neat): *v* 3250, 2960, 2845, 2874, 1736, 1653, 1560, 1401, 1322, 1263, 1205, 921, 610 cm^{-1}.

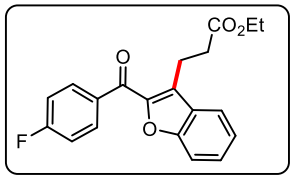
Methyl 3-(2-(4-fluorobenzoyl)benzofuran-3-yl)propanoate (3ba): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil and ratio of linear to the branched product is 86:14; 77 mg, 57%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.82 (t, *J* = 7.5 Hz, 2H), 3.45 (t, *J* = 7.5 Hz, 2H), 3.64 (s, 3H), 7.19−7.23 (m, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.49−7.53 (m, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 8.19−8.22 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.1 (t), 33.6 (t), 51.7 (q), 112.3 (d), 115.5 (d, *J* = 21.6 Hz, 2C), 121.7 (d), 123.6 (d), 128.1 (s), 128.4 (d), 130.0 (s, 2C), 132.6 (d, *J* = 9.3 Hz, 2C), 148.2 (s), 154.2 (s), 173.2 (s, 2C), 183.7 (s) ppm; IR(neat): *v* 2951, 1736, 1642, 1598, 1559, 1437, 1290, 1233, 1158, 1047, 878, 849, 748 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{15}O_4FNa$ (M^++Na): 349.0847; found: 349.0843.



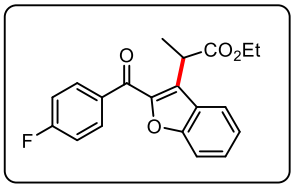
Methyl 2-(2-(4-fluorobenzoyl)benzofuran-3-yl)propanoate (4ba): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 12 mg, 9%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.67 (d, *J* = 7.2 Hz, 3H), 3.68 (s, 3H), 4.95 (q, *J* = 7.2 Hz, 1H), 7.15−7.26 (m, 2H), 7.29−7.37 (m, 1H), 7.46−7.54 (m, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 8.15−8.25 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 16.8 (q), 35.9 (d), 52.2 (q), 112.4 (d), 115.5 (d, *J* = 21.6 Hz, 2C), 122.3 (d), 123.7 (d), 126.7 (s), 128.2 (d), 129.2 (s), 132.7 (d, *J* = 9.1 Hz, 2C), 133.5 (s, *J* = 2.9 Hz), 147.5 (s), 154.3 (s), 165.1 (s, *J* = 255.1 Hz), 173.6 (s), 184.0 (s) ppm; IR(neat): *v* 3459, 2989, 1910, 1739, 1646, 1599, 1304, 1232, 1059, 879, 749 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{15}O_4FNa$ (M^++Na): 349.0847; found: 349.0843.



Ethyl 3-(2-(4-fluorobenzoyl)benzofuran-3-yl)propanoate (3bb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil and ratio of linear to the branched product is 77:23; 81 mg, 57%; **^{1}H NMR** (400 MHz,

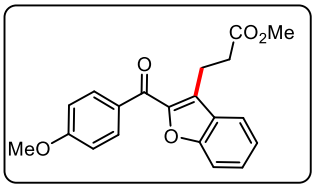


$CDCl_3$): δ 1.19 (t, J = 7.3 Hz, 3H), 2.80 (t, J = 7.6 Hz, 2H), 3.45 (t, J = 7.6 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 7.19–7.23 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.51 (ddd, J = 1.3, 8.3, 15.2 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 8.18–8.22 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 20.1 (t), 33.8 (t), 60.5 (t), 112.2 (d), 115.5 (d, J = 21.6 Hz, 2C), 121.7 (d), 123.6 (d), 128.2 (s), 128.4 (d), 130.1 (s), 132.6 (d, J = 9.3 Hz, 2C), 133.7 (s), 148.2 (s), 154.2 (s), 165.5 (s, J = 255.1 Hz), 172.8 (s), 183.7 (s) ppm; IR(neat): ν 3069, 2982, 1909, 1735, 1645, 1598, 1506, 1446, 1347, 1266, 1099, 954, 878, 750, 625 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{17}O_4FNa$ (M^++Na): 363.1003; found: 363.1003.



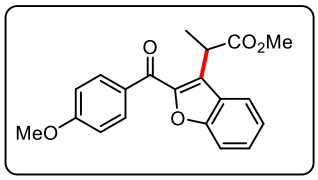
Ethyl 2-(2-(4-fluorobenzoyl)benzofuran-3-yl)propanoate (4bb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 24 mg, 17%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.67 (d, J = 7.2 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.91 (q, J = 7.2 Hz, 1H), 7.15–7.26 (m, 2H), 7.32 (ddd, J = 1.4, 6.8, 8.1 Hz, 1H), 7.50 (ddd, J = 1.3, 8.3, 15.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 8.14–8.24 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1 (q), 16.8 (q), 36.1 (d), 61.0 (t), 112.4 (d), 115.5 (d, J = 21.6 Hz, 2C), 122.4 (d), 123.6 (d), 126.7 (s), 128.2 (d), 129.3 (s), 132.7 (d, J = 9.1 Hz, 2C), 133.7 (s), 147.5 (s), 154.3 (s), 165.1 (s, J = 255.1 Hz), 173.1 (s), 184.1 (s) ppm; IR(neat): ν 3444, 3069, 2982, 1909, 1735, 1645, 1598, 1446, 1347, 1234, 1159, 1046, 878, 750 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{17}O_4FNa$ (M^++Na): 363.1003; found: 363.1002.

Methyl 3-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate (3ca): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless solid and the ratio of linear to branch product is 73:27; 63 mg, 47%; mp: 78–79 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.82 (t, J = 7.7 Hz, 2H), 3.45 (t, J = 7.7 Hz, 2H), 3.65 (s, 3H), 3.92 (s, 3H), 7.03 (d, J = 8.8 Hz, 2H), 7.34–7.38 (m, 1H), 7.48–7.52 (m, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.1 (t), 33.7 (t), 51.6 (q), 55.5 (q), 112.2 (d), 113.7 (d, 2C), 121.5 (d), 123.4 (d), 128.0 (d), 128.2 (s), 128.9 (s), 130.2 (s), 132.3 (d, 2C), 148.8 (s), 154.1 (s), 163.4 (s), 173.3 (s), 183.8 (s) ppm; IR(neat): ν 3019, 2400, 1732, 1635,

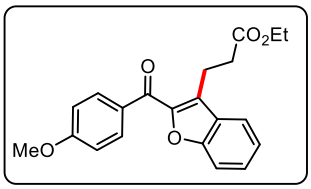


1600, 1421, 1259, 1215, 1121, 1032, 928, 845, 757, 669 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{18}O_5Na$ (M^++Na): 361.1046; found: 361.1046.

Methyl 2-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate (4ca): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 23 mg, 17%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65 (d, J = 7.3 Hz, 3H), 3.66 (s, 3H), 3.91 (s, 3H), 4.93 (q, J = 7.2 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 7.31 (dt, J = 0.9, 7.8 Hz, 1H), 7.47 (dt, J = 1.4, 8.7 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9 (q), 35.9 (d), 52.2 (q), 55.5 (q), 112.4 (d), 113.7 (d, 2C), 122.2 (d), 123.6 (d), 126.8 (s), 127.8 (d), 128.2 (s), 130.1 (s), 132.5 (d, 2C), 148.1 (s), 154.2 (s), 163.6 (s), 173.9 (s), 184.2 (s) ppm; IR(neat): ν 3453, 2953, 1954, 1736, 1643, 1600, 1437, 1364, 1258, 1170, 1027, 989, 878, 754 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{19}O_5$ (M^++H): 339.1227; found: 339.1226.

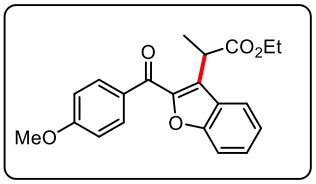


Ethyl 3-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate (3cb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil and ratio of linear to branch product is (60:40); 60 mg, 43%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H), 2.79 (t, J = 7.6 Hz, 2H), 3.42 (t, J = 7.6 Hz, 2H), 3.90 (s, 3H), 4.08 (q, J = 7.2 Hz, 2H), 7.00 - 7.03 (m, 2H), 7.33 (ddd, J = 0.9, 6.8, 7.8 Hz, 1H), 7.48 (ddd , J = 1.4, 7.3, 8.7 Hz, 1H), 7.53–7.56 (m, 1H), 7.79 (dd, J = 1.1, 7.8 Hz, 1H), 8.17–8.20 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 20.1 (t), 33.9 (t), 55.5 (q), 60.5 (t), 112.2 (d), 113.7 (d, 2C), 121.6 (d), 123.4 (d), 128.0 (d), 128.3 (s), 129.0 (s), 130.3 (s), 132.3 (d, 2C), 148.8 (s), 154.1 (s), 163.4 (s), 172.9 (s), 183.8 (s) ppm; IR(neat): ν 3020, 2982, 2928, 2855, 1731, 1636, 1600, 1510, 1446, 1372, 1295, 1259, 1166, 1030, 878, 755, 667 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{20}O_5Na$ (M^++Na): 375.1203; found: 375.1201.

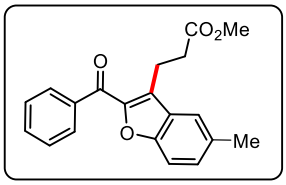


Ethyl 2-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate (4cb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 40 mg, 29%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 3H), 1.66

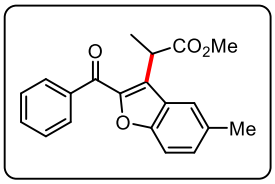
(d, *J* = 7.2 Hz, 3H), 3.92 (s, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.89 (q, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 1.3, 6.8 Hz, 1H), 7.47 (dt, *J* = 1.1, 8.3 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 14.1 (q), 16.9 (q), 36.1 (d), 55.5 (q), 61.0 (t), 112.4 (d), 113.7 (d, 2C), 122.3 (d), 123.5 (d), 126.8 (s), 127.8 (d), 128.3 (s), 130.2 (s), 132.5 (d, 2C), 148.1 (s), 154.2 (s), 163.5 (s), 173.4 (s), 184.2 (s) ppm; IR(neat): *ν* 3070, 2981, 1732, 1638, 1600, 1572, 1456, 1298, 1258, 1167, 1029, 878, 749 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{21}O_5$ (M^++H): 353.1384; found: 353.1382.



Methyl 3-(2-benzoyl-5-methylbenzofuran-3-yl)propanoate (3da): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless solid and ratio of linear to branch product is 82:18; 78 mg, 57%; mp 71–72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.48 (s, 3H), 2.79 (t, *J* = 7.9 Hz, 2H), 3.41 (t, *J* = 7.9 Hz, 2H), 3.65 (s, 3H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.50–7.53 (m, 3H), 7.58–7.62 (m, 1H), 8.10 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 20.1 (t), 21.4 (q), 33.6 (t), 51.7 (q), 111.9 (d), 121.0 (d), 128.2 (s), 128.3 (d, 2C), 129.4 (s), 129.8 (d, 2C), 129.9 (d), 132.7 (d), 133.2 (s), 137.6 (s), 148.6 (s), 152.8 (s), 173.3 (s), 185.5 (s) ppm; IR(neat): *ν* 2997, 2954, 2850, 1736, 1659, 1599, 1437, 1319, 1271, , 911, 857, 722 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{18}O_4Na$ (M^++Na): 345.1097; found: 345.1094.

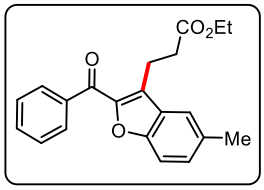


Methyl 2-(2-benzoyl-5-methylbenzofuran-3-yl)propanoate (4da): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless solid; 16 mg, 12%; mp 114-115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.65 (d, *J* = 7.3 Hz, 3H), 2.46 (s, 3H), 3.67 (s, 3H), 4.93 (q, *J* = 7.3 Hz, 1H), 7.29 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.50–7.54 (m, 3H), 7.61 (tt, *J* = 1.4, 7.3 Hz, 1H), 8.09–8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 16.8 (q), 21.5 (q), 35.9 (d), 52.2 (q), 112.0 (d), 121.6 (d), 126.8 (s), 128.3 (d,2C), 128.6 (s), 129.8 (d), 130.0 (d, 2C), 132.8 (d), 133.4 (s), 137.4 (s), 147.9 (s), 152.9 (s), 173.8 (s), 185.9 (s) ppm; IR(neat): *ν* 2949,

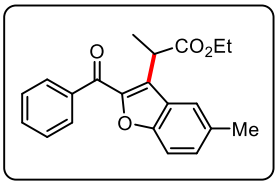


1739, 1645, 1563, 1448, 1300, 1206, 1057, 905, 804, 720 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{19}O_4$ (M^++H): 323.1278; found: 323.1276.

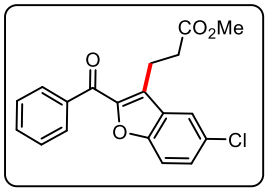
Ethyl 3-(2-benzoyl-5-methylbenzofuran-3-yl)propanoate (3db): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil and ratio of linear to branch product is 94:6; 97 mg, 68%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 3H), 2.48 (s, 3H), 2.77 (t, J = 7.5 Hz, 2H), 3.41 (t, J = 7.5 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 7.30 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.50–7.53 (m, 3H), 7.58–7.62 (m, 1H), 8.10 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2 (q), 20.1 (t), 21.4 (q), 33.9 (t), 60.5 (t), 111.9 (d), 121.1 (d), 128.3 (d, 2C), 128.3 (s), 129.5 (s), 129.8 (d, 2C), 129.9 (d), 132.6 (d), 133.2 (s), 137.7 (s), 148.6 (s), 152.9 (s), 172.9 (s), 185.5 (s).ppm; IR(neat): ν 2982, 2936, 2874, 1945, 1732, 1655, 1563, 1447, 1370, 1263, 1182,1035, 977, 861, 757 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{20}O_4Na$ (M^++Na): 359.1254; found: 359.1251.



Ethyl 2-(2-benzoyl-5-methylbenzofuran-3-yl)propanoate (4db): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 16 mg, 11%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.15 (t, J = 7.3 Hz, 3H), 1.64 (d, J = 7.0 Hz, 3H), 2.46 (s, 3H), 4.15 (q, J = 7.3 Hz, 2H), 4.88 (q, J = 7.0 Hz, 1H), 7.29 (dd, J = 1.5, 8.5 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.50−7.53 (m, 3H), 7.61 (tt, J = 1.2, 7.3 Hz, 1H), 8.08–8.11 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.1 (q), 16.8 (q), 21.4 (q), 36.1 (d), 61.0 (t), 112.0 (d), 121.8 (d), 126.8 (s), 128.3 (d, 2C), 128.8 (s), 129.7 (d), 129.9 (d, 2C), 132.8 (d), 133.2 (s), 137.5 (s), 147.9 (s), 152.9 (s), 173.3 (s), 185.9 (s) ppm; IR(neat): ν 2981, 1945, 1743, 1648, 1447, 1373, 1259, 1180,1027, 856, 722, 696 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{21}O_4$ (M^++H): 337.1434; found: 337.1430.

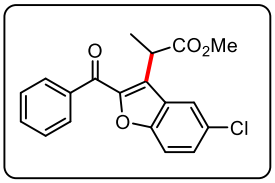


Methyl 3-(2-benzoyl-5-chlorobenzofuran-3-yl)propanoate (3ea): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless solid and ratio of linear to branch product is 92:8; 93 mg, 70%; mp: 82–83 °C; **^{1}H NMR** (400

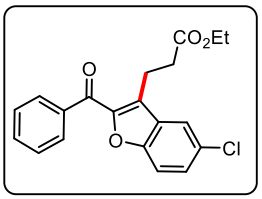


MHz, $CDCl_3$): δ 2.79 (t, J = 7.6 Hz, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.64 (s, 3H), 7.42–7.54 (m, 4H), 7.59–7.66 (tt, J = 1.4, 3.7 Hz, 1H), 7.75 (d, J = 2.3 Hz, 1H), 8.07–8.10 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0 (t), 33.5 (t), 51.7 (q), 113.4 (d), 121.1 (d), 128.4 (d, 2C), 128.6 (d), 128.8 (s), 129.3 (s), 129.5 (s), 129.8 (d, 2C), 133.0 (d), 137.1 (s), 149.4 (s), 152.5 (s), 173.0 (s), 185.3 (s) ppm; IR(neat): ν 3022, 2953, 2926, 2854, 1735, 1647, 1557, 1448, 1282, 1216, 1062, 808, 758, 694 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{15}ClO_4Na$ (M^++Na): 365.0551; found: 365.0551

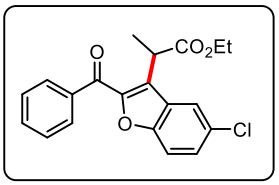
Methyl 2-(2-benzoyl-5-chlorobenzofuran-3-yl)propanoate (4ea): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless solid; 8 mg, 6%; mp: 90–91 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.65 (d, J = 7.3 Hz, 3H), 3.69 (s, 3H), 4.89 (q, J = 7.3 Hz, 1H), 7.43 (dd, J = 2.1, 8.9 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.51–7.54 (m, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 8.07–8.08 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 16.9 (q), 35.8 (d), 52.4 (q), 113.6 (d), 121.8 (d), 128.0 (s, 2C), 128.4 (d, 2C), 128.5 (d), 129.4 (s), 129.9 (d, 2C), 133.2 (d), 137.1 (s), 148.8 (s), 152.7 (s), 173.4 (s), 185.7 (s) ppm; IR(neat): ν 2953, 1956, 1735, 1653, 1437, 1369, 1257, 1199, 1173, 988, 857, 757 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{16}O_4Cl$ (M^++H): 343.0732; found: 343.0733.



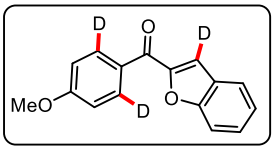
Ethyl 3-(2-benzoyl-5-chlorobenzofuran-3-yl)propanoate (3eb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.4). The title compound was determined as colourless oil and ratio of linear to branch product is 93:7; 92 mg, 66%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3H), 2.80 (t, J = 7.5 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 7.44–7.56 (m, 4H), 7.62–7.66 (m, 1H), 7.77 (d, J = 1.7 Hz, 1H), 8.09–8.11 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 20.0 (t), 33.8 (t), 60.6 (t), 113.4 (d), 121.2 (d), 128.4 (d, 2C), 128.6 (d), 128.9 (s), 129.3 (s), 129.6 (s), 129.8 (d, 2C), 133.0 (d), 137.2 (s), 149.5 (s), 152.5 (s), 172.6 (s), 185.3 (s) ppm; IR(neat): ν 2983, 2938, 2908, 1732, 1655, 1598, 1560, 1447, 1370, 1263, 1181, 1035, 977, 860, 727 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{17}ClO_4Na$ (M^++Na): 379.0708; found: 379.0709.



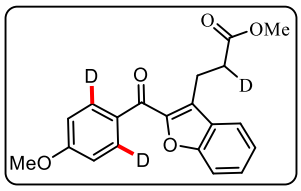
Ethyl 2-(2-benzoyl-5-chlorobenzofuran-3-yl)propanoate (4eb): Isolated by column chromatography (pet.ether/AcOEt = 9:1, R_f = 0.5). The title compound was determined as colourless oil; 7 mg, 5%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, J = 7.1 Hz, 3H), 1.64 (d, J = 7.3 Hz, 3H), 4.16 (q, J = 7.1 Hz, 2H), 4.84 (q, J = 7.3 Hz, 1H), 7.43–7.46 (m, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.55 ((t, J = 7.8 Hz, 2H),) 7.61−7.65 (m, 1H), 7.74 (d, J = 1.8 Hz, 1H), 8.05–8.09 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 16.9 (q), 36.1 (d), 61.2 (t), 113.6 (d), 122.0 (d), 128.0 (s), 128.2 (s), 128.4 (d, 3C), 129.3 (s), 129.9 (d, 2C), 133.1 (d), 137.1 (s), 148.8 (s), 152.7 (s), 172.9 (s), 185.7 (s) ppm; IR(neat): v 3036, 2928, 1733, 1650, 1598, 1557, 1447, 1295, 1197, 1068, 961, 806, 723, 694 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{18}O_4Cl$ (M^++H): 357.0888; found: 357.0887.



(benzofuran-2-yl-3-d)(4-methoxyphenyl-2,6-d2)methanone ($1c_d$) :**^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.01–7.05 (m, 2H), 7.31–7.36 (m, 1H), 7.47–7.52 (m, 1H), 7.54 (s, 0.19H (81% D)), 7.65 (d, J = 8.2 Hz, 1H), 7.72–7.76 (m, 1H), 8.11–8.13 (m, 0.37H (81% D)) ppm.



Methyl 3-(2-(4-methoxybenzoyl)benzofuran-3-yl)propanoate ($3ca_d$): The experiment was performed according to general procedure B and product was isolated by column chromatography (pet ether/AcOEt = 9:1, R_f = 0.5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.82 (t, J = 7.7 Hz, 1.88H), 3.44 (t, J = 7.7 Hz, 2H), 3.65 (s, 3H), 3.92 (s, 3H), 7.03 (d, J = 8.9 Hz, 2H), 7.32–7.39 (m, 1H), 7.45–7.59 (m, 2H), 7.78 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1.8H) ppm. **HRMS** (ESI) calcd for $C_{20}H_{16}{}^2H_3O_5$ (M^++H): 342.1411; found: 342.1415.



Ruthenium catalyzed C–H activation of 3-aroylbenzofurans:

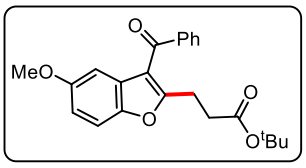
General Experimental procedure:

3-Aroylbenzo[b]furan (0.1 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous toluene, which was then evacuated and back filled with argon. To the reaction vessel alkene (acrylate) (0.3 mmol), K_2CO_3 (0.2 mmol), $Ru(PPh_3)_3Cl_2$ (0.010 mmol) and AgOAc (0.03 mmol) were added. The solution was then stirred at 120 ^oC (bath

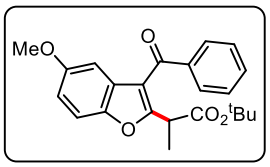
temperature) for 24 h. The reaction mixture was cooled to room temperature and filtered through Celite pad. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/ethyl acetate) to give analytically pure products.

Experimental Data:

***tert*-Butyl 3-(3-benzoyl-5-methoxybenzofuran-2-yl)propanoate** (**6ae**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as white solid; 131 mg, 87%; mp 61–62 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.66 (t, J = 7.5 Hz, 2H), 3.13 (t, J = 7.5 Hz, 2H), 3.69 (s, 3H), 6.83 (d, J = 2.3 Hz, 1H), 6.87 (dd, J = 2.3, 8.9 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 24.2 (t), 28.0 (q, 3C), 33.3 (t), 55.7 (q), 80.7 (s), 103.9 (d), 111.5 (d), 113.3 (d), 117.1 (s), 127.3 (s), 128.5 (d, 2C), 129.1 (d, 2C), 132.7 (d), 139.2 (s), 148.6 (s), 156.4 (s), 164.1 (s), 171.1 (s), 191.8 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{24}O_5Na$: 403.1516 $[M+Na]^+$; found: 403.1517.

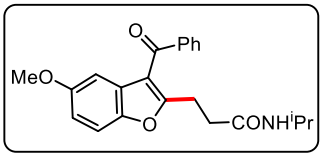


***t*ert-Butyl (S)-2-(3-benzoyl-5-methoxybenzofuran-2-yl)propanoate** (**7ae**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 122 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.54 (d, J = 7.3 Hz, 3H), 3.69 (s, 3H), 4.12 (q, J = 7.3 Hz, 1H), 6.81 (d, J = 2.6 Hz, 1H), 6.89 (dd, J = 2.6, 8.9 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.60 (tt, J = 1.3, 7.0 Hz, 1H), 7.85 (dd, J = 1.2, 8.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 15.2 (q), 27.9 (q, 3C), 40.1 (d), 55.7 (q), 81.7 (s), 104.0 (d), 111.8 (d), 113.6 (d), 117.3 (s), 127.2 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.8 (d), 139.0 (s), 148.8 (s), 156.5 (s), 162.5 (s), 170.1 (s), 191.6 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{24}O_5Na$: 403.1516 $[M+Na]^+$; found: 403.1517.

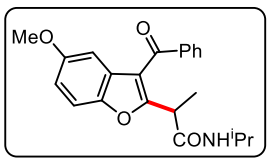


3-(3-Benzoyl-5-methoxybenzofuran-2-yl)-N-isopropylpropanamide (**6ad**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.2); The title compound was determined as colourless solid; The ratio of linear to the branched product

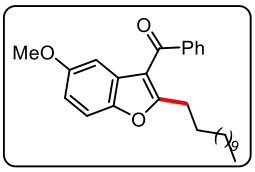
was 1.9:1; 78 mg, 66%; mp 97–98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.07 (d, J = 6.6 Hz, 6H), 2.63 (t, J = 7.5 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H), 3.67 (s, 3H), 4.03 (sex, J = 6.6 Hz, 1H), 5.86 (brd, J = 6.9 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 6.86 (dd, J = 2.6, 8.9 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.82 (d, J = 7.8Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.6 (q, 2C), 24.4 (t), 34.6 (t), 41.4 (d), 55.7 (q), 104.0 (d), 111.6 (d), 113.3 (d), 117.2 (s), 127.1 (s), 128.5 (d, 2C), 129.2 (d, 2C), 133.0 (d), 138.9 (s), 148.7 (s), 156.4 (s), 164.5 (s), 169.9 (s), 192.1 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{24}O_4N$: 366.1700 $[M+H]^+$; found: 366.1694.



2-(3-Benzoyl-5-methoxybenzofuran-2-yl)-N-isopropylpropanamide (**7ad**): Isolated by column chromatography (petroleum ether/ethyl acetate = 8:2, R_f = 0.5); The title compound was determined as white solid; 40 mg, 34%; mp 77–79 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.01 (d, J = 6.7 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H), 1.60 (d, J = 7.0 Hz, 3H), 3.61 (s, 3H), 3.99 (dq, J = 6.7, 13.4 Hz, 1H), 4.16 (d, J = 7.0 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 2.4, 8.9 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.5 (q), 22.4 (q), 22.7 (q), 39.6 (d), 41.7 (d), 55.7 (q), 104.2 (d), 112.3 (d), 113.3 (d), 117.0 (s), 126.5 (s), 128.6 (d, 2C), 129.7 (d, 2C), 133.6 (d), 138.1 (s), 148.7 (s), 156.3 (s), 164.6 (s), 168.6 (s), 192.6 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{23}O_4NNa$: 388.1519 $[M+Na]^+$; found: 388.1519.

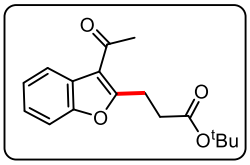


(2-Dodecyl-5-methoxybenzofuran-3-yl)(phenyl)methanone (**6ah**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as colourless oil; 109 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91 (t, J = 7.1 Hz, 3H), 1.24–1.28 (m, 18H), 1.75 (quint, J = 7.4 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 3.75 (s, 3H), 6.89–6.91 (m, 2H), 7.38 (d, J = 8.6 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.83 (d, J = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 28.0 (t), 28.4 (t), 29.2 (t, 2C), 29.3 (t), 29.4 (t), 29.6 (t, 2C), 29.7 (t), 31.9 (t), 55.8 (q), 104.0 (d), 111.4 (d), 113.0 (d), 116.8 (s), 127.6 (s), 128.4 (d, 2C), 129.0 (d, 2C), 132.5 (d), 139.5 (s),

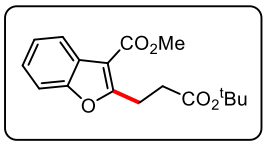


148.6 (s), 156.5 (s), 166.5 (s), 192.2 (s) ppm; **HRMS** (ESI) calcd for $C_{28}H_{37}O_3$: 421.2737 $[M+H]^+$; found: 421.2736.

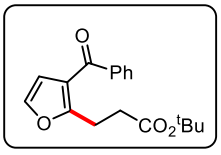
***tert*-Butyl 3-(3-acetylbenzofuran-2-yl)propanoate** (**6ga**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as colourless oil; 132 mg, 73%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.66 (s, 3H), 2.73 (t, J = 7.6 Hz, 2H), 3.44 (t, J = 7.5 Hz, 2H), 7.29–7.32 (m, 2H), 7.43–7.45 (m, 1H), 7.89–7.91 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.5 (t), 28.0 (q, 3C), 31.3 (q), 32.8 (t), 80.8 (s), 111.2 (d), 117.4 (s), 121.3 (d), 124.0 (d), 124.5 (d), 125.8 (s), 153.6 (s), 164.4 (s), 171.3 (s), 194.2 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{20}O_4Na$: 311.1254 $[M+Na]^+$; found: 311.1252.



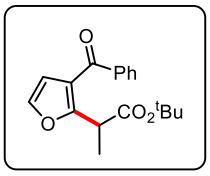
Methyl 2-(3-(tert-butoxy)-3-oxopropyl)benzofuran-3-carboxylate (**6ha**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as colourless oil; 106 mg, 61%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.71 (t, J = 7.6 Hz, 2H), 3.47 (t, J = 7.6 Hz, 2H), 3.94 (s, 3H), 7.27–7.31 (m, 2H), 7.40–7.43 (m, 1H), 7.94–7.98 (m, 1H); **^{13}C NMR** (125 MHz, CDCl3) δ 23.9 (t), 28.0 (q, 3C), 33.1 (t), 51.5 (q), 80.7 (s), 108.9 (s), 110.9 (d), 121.9 (d), 123.9 (d), 124.5 (d), 126.0 (s), 153.6 (s), 164.6 (s), 165.2 (s), 171.3 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{20}O_5Na$: 327.1203 $[M+Na]^+$; found: 327.1198.



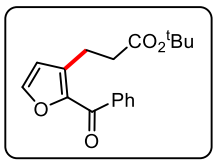
***tert*-Butyl 3-(3-benzoylfuran-2-yl)propanoate** (**6ia**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Colourless oil; The ratio of linear to branched product is 1:4.6; 19 mg, 11%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.63 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 6.57 (b s, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.42–7.57 (m, 3H), 7.79 (d, J = 6.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.8 (t), 28.0 (q, 3C), 33.3 (t), 80.5 (s), 111.9 (d), 120.4 (s), 128.4 (d, 2C), 129.0 (d, 2C), 132.3 (d), 139.0 (s), 140.4 (d), 161.3 (s), 171.5 (s), 191.1 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{21}O_4$: 301.1434 $[M+H]^+$; found: 301.1430.



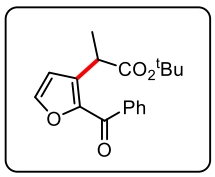
***tert*-Butyl 2-(3-benzoylfuran-2-yl)propanoate** (**7ia**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Colourless oil; 93 mg, 53%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.52 (d, J = 7.4 Hz, 3H), 4.32 (q, J = 7.4 Hz, 1H), 6.59 (d, J = 1.4 Hz, 1H), 7.36 (d, J = 1.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.0 (q), 27.9 (q, 3C), 39.8 (d), 81.3 (s), 111.9 (d), 120.7 (s), 128.4 (d, 2C), 129.0 (d, 2C), 132.3 (d), 138.8 (s), 140.8 (d), 159.7 (s), 170.9 (s), 190.9 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{21}O_4$: 301.1434 $[M+H]^+$; found: 301.1429.



***tert*-Butyl 3-(2-benzoylfuran-3-yl)propanoate** (**6ja**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Colourless oil; The ratio of linear to branched product is 1:2.3; 37 mg, 18%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.65 (t, J = 7.6 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 6.25 (d, J = 2.9 Hz, 1H), 7.11 (d, J = 3.1 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 24.0 (t), 28.0 (q, 3C), 33.3 (t), 80.9 (s), 108.6 (d), 122.4 (d), 128.4 (d, 2C), 129.1 (d, 2C), 132.3 (d), 137.6 (s), 151.1 (s), 160.7 (s), 171.2 (s), 182.2 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{21}O_4$: 301.1434 $[M+H]^+$; found: 301.1426.

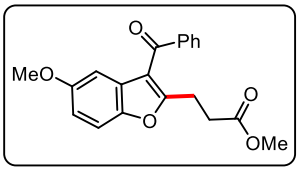


***tert*-Butyl 2-(2-benzoylfuran-3-yl)propanoate** (**7ja**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Colourless oil; 75 mg, 43%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.47 (d, J = 7.2 Hz, 3H), 4.50 (q, J = 7.2 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.51 (d, J = 1.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.99 (d, J = 7.7 Hz, 2H); **^{13}C NMR** (125 MHz, CDCl3): δ 18.1 (q), 28.0 (q, 3C), 37.6 (d), 80.8 (s), 112.9 (d), 128.2 (d, 2C), 129.6 (d, 2C), 132.3 (d), 136.2 (s), 137.7 (s), 144.7 (d), 147.9 (s), 173.1 (s), 183.7 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{21}O_4$: 301.1434 $[M+H]^+$; found: 301.1427.

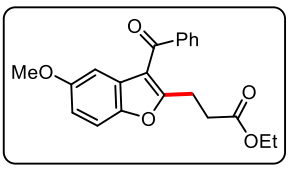


Methyl 3-(3-benzoyl-5-methoxybenzofuran-2-yl)propanoate (**6aa**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as brown oil; 95 mg, 71%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.78 (t, J = 7.5 Hz,

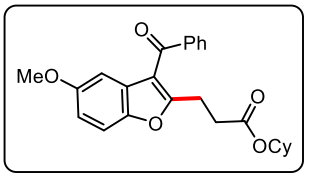
2H), 3.19 (t, *J* = 7.4 Hz, 2H), 3.64 (s, 3H), 3.69 (s, 3H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.9 (t), 31.9 (t), 51.9 (q), 55.8 (q), 104.0 (d), 111.5 (d), 113.4 (d), 117.3 (s), 127.3 (s), 128.5 (d, 2C), 129.1 (d, 2C), 132.8 (d), 139.1 (s), 148.7 (s), 156.5 (s), 163.5 (s), 172.3 (s), 191.8 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}O_5Na$: 361.1046 $[M+Na]^+$; found: 361.1048.



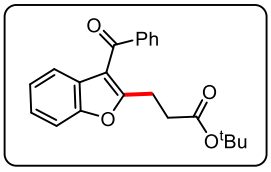
Ethyl 3-(3-benzoyl-5-methoxybenzofuran-2-yl)propanoate (**6ab**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as light yellow oil; 120 mg, 86%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.1 Hz, 3H), 2.75 (t, *J* = 7.5 Hz, 2H), 3.19 (t, *J* = 7.3 Hz, 2H), 3.69 (s, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.44–7.52 (m, 2H), 7.56–7.64 (m, 1H), 7.79–7.84 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1 (q), 24.0 (t), 32.1 (t), 55.7 (q), 60.7 (t), 103.9 (d), 111.5 (d), 113.3 (d), 117.3 (s), 127.3 (s), 128.5 (d, 2C), 129.1 (d, 2C), 132.8 (d), 139.1 (s), 148.6 (s), 156.5 (s), 163.7 (s), 171.9 (s), 191.8 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}O_5Na$: 375.1203 $[M+Na]^+$; found: 375.1204.



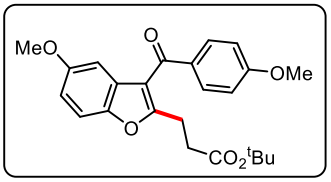
Cyclohexyl 3-(3-benzoyl-5-methoxybenzofuran-2-yl)propanoate (**6ai**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as yellow oil; 147 mg, 91%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32–1.37 (m, 4H), 1.48–1.52 (m, 1H), 1.64–1.67 (m, 3H), 1.76–1.79 (m, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 3.17 (t, *J* = 7.4 Hz, 2H), 3.69 (s, 3H), 4.70–4.75 (m, 1H), 6.82 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 2.6,8.9 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.80–7.82 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6 (t, 2C), 24.1 (t), 25.3 (t), 31.5 (t, 2C), 32.4 (t), 55.7 (q), 72.9 (d), 104.0 (d), 111.5 (d), 113.3 (d), 117.2 (s), 127.3 (s), 128.5 (d, 2C), 129.1 (d, 2C), 132.7 (d), 139.2 (s), 148.6 (s), 156.5 (s), 163.9 (s), 171.3 (s), 191.8 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}O_5Na$: 429.1672 $[M+Na]^+$; found: 429.1674.



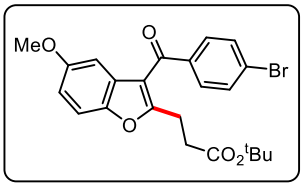
***tert*-Butyl 3-(3-benzoylbenzofuran-2-yl)propanoate (6be)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 130 mg, 82%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.70 (t, J = 7.6 Hz, 2H), 3.20 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.28–7.33 (m, 2H), 7.45–7.50 (m, 3H), 7.60 (t, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.0 (t), 28.0 (q, 3C), 33.4 (t), 80.7 (s), 111.0 (d), 117.0 (s), 121.4 (d), 123.6 (d), 124.5 (d), 126.7 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.8 (d), 139.2 (s), 153.6 (s), 163.5 (s), 171.1 (s), 191.7 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{22}O_4Na$: 373.1410 $[M+Na]^+$; found: 373.1411.



***tert*-Butyl 3-(5-methoxy-3-(4-methoxybenzoyl)benzofuran-2-yl)propanoate (6ce)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as brown solid; 127 mg, 87%; mp 84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.67 (t, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 3.72 (s, 3H), 3.88 (s, 3H), 6.85–6.87 (m, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 9.5 Hz, 1H), 7.84 (d, J = 8.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.1 (t), 28.0 (q, 3C), 33.4 (t), 55.5 (q), 55.8 (q), 80.7 (s), 103.9 (d), 111.4 (d), 113.1 (d), 113.7 (d, 2C), 117.3 (s), 127.6 (s), 131.6 (s), 131.7 (d, 2C), 148.6 (s), 156.4 (s), 163.0 (s), 163.5 (s), 171.2 (s), 190.3 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{27}O_6$: 411.1802 $[M+H]^+$; found: 411.1804.

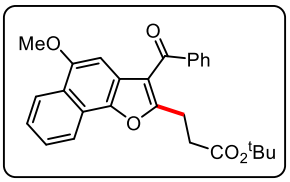


***tert*-Butyl 3-(3-(4-bromobenzoyl)-5-methoxybenzofuran-2-yl)propanoate (6de)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as white solid; 107mg, 77%; mp 115–116 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.67 (t, J = 7.5 Hz, 2H), 3.13 (t, J = 7.5 Hz, 2H), 3.72 (s, 3H), 6.81 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 2.4, 8.9 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 24.2 (t), 28.0 (q, 3C), 33.2 (t), 55.8 (q), 80.8 (s), 104.0 (d), 111.6 (d), 113.2 (d), 116.8 (s), 127.1 (s), 127.8 (s), 130.7 (d, 2C), 131.8 (d, 2C), 137.8 (s), 148.6 (s), 156.6 (s),

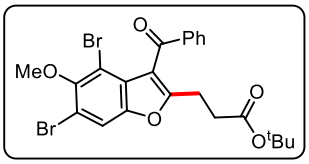


164.3 (s), 171.0 (s), 190.5 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{23}O_5BrNa$: 481.0621 $[M+Na]^+$; found: 481.0618.

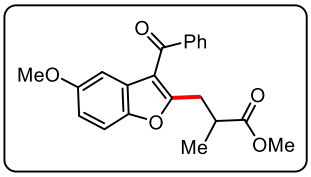
***tert*-Butyl 3-(3-benzoyl-5-methoxynaphtho[1,2-b]furan-2-yl)propanoate** (**6ee**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as yellow solid; 102 mg, 72%; mp 109–111 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.75 (t, J = 7.6 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 3.84 (s, 3H), 6.74 (s, 1H), 7.48–7.52 (m, 3H), 7.61 (t, J = 7.6 Hz, 2H), 7.84–7.87 (m, 2H), 8.20 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 24.3 (t), 28.0 (q, 3C), 33.6 (t), 55.7 (q), 80.7 (s), 96.9 (d), 118.3 (s), 119.6 (d), 121.1 (s), 122.0 (s), 123.1 (d), 123.9 (s), 124.9 (d), 127.2 (d), 128.5 (d, 2C), 129.2 (d, 2C), 132.8 (d), 139.3 (s), 144.1 (s), 152.6 (s), 162.0 (s), 171.2 (s), 192.1 (s) ppm; **HRMS** (ESI) calcd for $C_{27}H_{26}O_5Na$: 453.1672 $[M+Na]^+$; found: 453.1669.



***tert*-Butyl 3-(3-benzoyl-4,6-dibromo-5-methoxybenzofuran-2-yl)propanoate** (**6fe**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 107 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.60 (t, J = 7.5 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 3.82 (s, 3H), 7.45 (t, J = 7.8 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.66 (s, 1H), 7.84 (d, J = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.1 (t), 28.0 (q, 3C), 33.1 (t), 60.9 (q), 81.0 (s), 108.7 (s), 114.1 (s), 114.8 (d), 117.9 (s), 128.3 (s), 128.7 (d, 2C), 129.7 (d, 2C), 133.8 (d), 138.7 (s), 150.0 (s), 150.8 (s), 159.8 (s), 170.8 (s), 191.2 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{22}O_5Br^{81}BrNa$: 560.9706 $[M+Na]^+$; found: 560.9704.

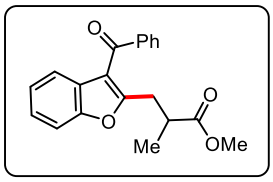


Methyl 3-(3-benzoyl-5-methoxybenzofuran-2-yl)-2-methylpropanoate (**6af**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as light yellow oil, 97 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.17 (d, J = 6.7 Hz, 3H), 2.99–3.05 (m, 2H), 3.25–3.30 (m, 1H), 3.62 (s, 3H), 3.68 (s, 3H), 6.74 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 2.5, 8.8 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz,

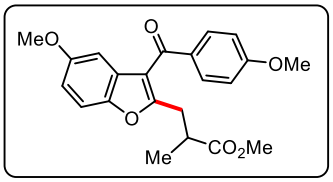


$CDCl_3$): δ 16.9 (q), 31.8 (t), 38.5 (d), 51.9 (q), 55.8 (q), 104.0 (d), 111.6 (d), 113.4 (d), 118.0 (s), 127.3 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.8 (d), 139.0 (s), 148.7 (s), 156.4 (s), 162.9 (s), 175.4 (s), 191.8 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}O_5Na$: 375.1203 $[M+Na]^+$; found: 375.1205.

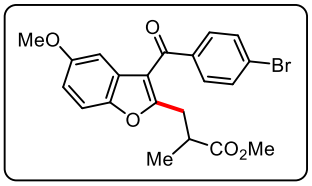
Methyl 3-(3-benzoylbenzofuran-2-yl)-2-methylpropanoate (**6bf**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil, 94 mg, 65%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.22 (d, J = 6.9 Hz, 3H), 3.06 (q, J = 6.9 Hz, 1H), 3.12 (dd, J = 7.3, 14.4 Hz, 1H), 3.35 (dd, J = 6.7, 14.4 Hz, 1H), 3.64 (s, 3H), 7.18 (t, J = 7.5 Hz, 1H), 7.27–7.31 (m, 2H), 7.50 (t, J = 8.2 Hz, 3H), 7.62 (t, J = 7.4 Hz, 1H), 7.83 (d, J = 7.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 16.9 (q), 31.7 (t), 38.5 (d), 51.9 (q), 111.1 (d), 117.9 (s), 121.4 (d), 123.6 (d), 124.6 (d), 126.6 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.9 (d), 139.0 (s), 153.7 (s), 162.2 (s), 175.4 (s), 191.7 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}O_4Na$: 345.1097 $[M+Na]^+$; found: 345.1092.



Methyl 3-(5-methoxy-3-(4-methoxybenzoyl)benzofuran-2-yl)-2-methylpropanoate (**6cf**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as colourless oil, 84 mg, 62%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.17 (d, J = 6.7 Hz, 3H), 2.99–3.05 (m, 2H), 3.25–3.32 (m, 1H), 3.61 (s, 3H), 3.71 (s, 3H), 3.89 (s, 3H), 6.80 (d, J = 2.1 Hz 1H), 6.87 (dd, J = 2.4, 8.9 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 7.34 (d, J = 8.9 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 16.9 (q), 31.7 (t), 38.5 (d), 51.9 (q), 55.5 (q), 55.9 (q), 104.0 (d), 111.5 (d), 113.2 (d), 113.7 (d, 2C), 118.2 (s), 127.5 (s), 131.5 (s), 131.8 (d, 2C), 148.7 (s), 156.4 (s), 161.8 (s), 163.6 (s), 175.5 (s), 190.2 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{23}O_6$: 383.1489 $[M+H]^+$; found: 383.1487.

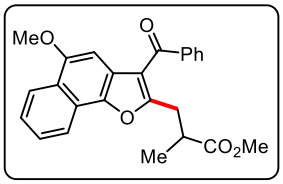


Methyl 3-(3-(4-bromobenzoyl)-5-methoxybenzofuran-2-yl)-2-methylpropanoate (**6df**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as yellow oil; 85 mg, 65%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.18 (d,

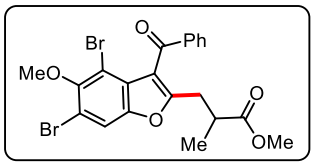


J = 6.7 Hz, 3H), 2.99–3.05 (m, 2H), 3.25–3.30 (m, 1H), 3.61 (s, 3H), 3.70 (s, 3H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 2.3, 9.0 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 16.9 (q), 31.8 (t), 38.4 (d), 51.9 (q), 55.8 (q), 103.9 (d), 111.7 (d), 113.3 (d), 117.6 (s), 127.0 (s), 127.9 (s), 130.8 (d, 2C), 131.8 (d, 2C), 137.6 (s), 148.7 (s), 156.5 (s), 163.1 (s), 175.3 (s), 190.4 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{19}BrNaO_5$: 453.0308 $[M+Na]^+$; found: 453.0308.

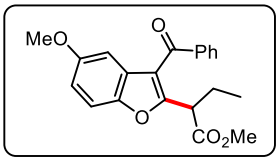
Methyl 3-(3-benzoyl-5-methoxynaphtho[1,2-b]furan-2-yl)-2-methylpropanoate (**6ef**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as Brown oil; 108 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.21 (d, *J* = 7.0 Hz, 3H), 3.05–3.15 (m, 2H), 3.36 (dd, *J* = 6.9, 14.5 Hz, 1H), 3.64 (s, 3H), 3.81 (s, 3H), 6.66 (s, 1H), 7.50 (t, *J* = 7.6 Hz, 3H), 7.62 (t, *J* = 7.3 Hz, 2H), 7.86 (d, *J* = 7.3 Hz, 2H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (125 MHz, CDCl3): δ 16.9 (q), 32.0 (t), 38.8 (d), 51.9 (q), 55.7 (q), 96.8 (d), 119.2 (s), 119.6 (d), 121.2 (s), 121.8 (s), 123.1 (d), 124.0 (s), 125.0 (d), 127.3 (d), 128.5 (d, 2C), 129.3 (d, 2C), 132.8 (d), 139.1 (s), 144.2 (s), 152.6 (s), 160.7 (s), 175.5 (s), 192.0 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{23}O_5$: 403.1540 $[M+H]^+$; found: 403.1537.



Methyl 3-(3-benzoyl-4,6-dibromo-5-methoxybenzofuran-2-yl)-2-methylpropanoate (**6ff**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as light yellow oil, 85 mg, 68%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.15 (d, *J* = 6.9 Hz, 3H), 2.77–2.83 (m, 1H), 2.92–2.97 (m, 1H), 3.06–3.12 (m, 1H), 3.58 (s, 3H), 3.82 (s, 3H), 7.45(t, *J* = 7.7 Hz, 2H), 7.59 (tt, *J* = 1.3, 7.2 Hz, 1H), 7.68 (s, 1H), 7.83 (dd, *J* = 1.4, 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9 (q), 31.0 (t), 38.2 (d), 51.9 (q), 60.9 (q), 108.7 (s), 114.2 (s), 114.9 (d), 119.0 (s), 128.2 (s), 128.7 (d, 2C), 129.6 (d, 2C), 133.8 (d), 138.7 (s), 150.1 (s), 150.8 (s), 158.8 (s), 175.0 (s), 191.0 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{19}O_5Br^{81}Br$: 510.9573 $[M+H]^+$; found: 510.9569.

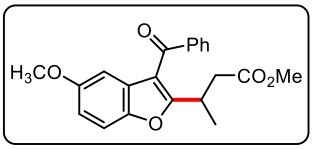


Methyl 2-(3-benzoyl-5-methoxybenzofuran-2-yl)butanoate (**7aj**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was

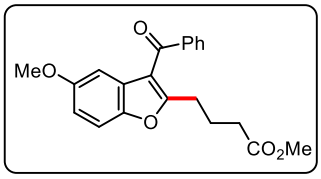


determined as light brown oil, 75 mg, 54%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 3H), 2.02–2.11 (m, 1H), 2.14–2.22 (m, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 4.11 (dd, J = 6.4, 8.8 Hz, 1H), 6.75 (d, J = 2.1 Hz, 1H), 6.90 (dd, J = 2.4, 9.2 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.83 (d, J = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 11.9 (q), 23.7 (t), 46.0 (d), 52.4 (q), 55.8 (q), 104.0 (d), 112.0 (d), 113.8 (d), 118.9 (s), 126.9 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.9 (d), 138.9 (s), 148.9 (s), 156.5 (s), 160.6 (s), 171.0 (s), 191.6 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}O_5Na$: 375.1203 $[M+Na]^+$; found: 375.1203.

Methyl-3-(3-benzoyl-5-methoxybenzofuran-2-yl)butanoate (**6aj**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.3); The title compound was determined as light yellow oil; 11 mg, 8%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.38 (d, J = 7.0 Hz, 3H), 2.62 (dd, J = 7.0, 15.9 Hz, 1H), 2.83 (dd, J = 7.9, 15.9 Hz, 1H), 3.56 (s, 3H), 3.68 (s, 3H), 3.69–3.75 (m, 1H), 6.76–6.80 (m, 1H), 6.87 (dd, J = 2.7, 8.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.58–7.61 (m, 1H), 7.82–7.84 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 19.0 (q), 29.8 (d), 39.4 (t), 51.7 (q), 55.8 (q), 104.0 (d), 111.6 (d), 113.3 (d), 116.4 (s), 127.4 (s), 128.5 (d, 2C), 129.2 (d, 2C), 132.8 (d), 139.2 (s), 148.6 (s), 156.4 (s), 166.8 (s), 171.7 (s), 191.9 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}O_5Na$: 375.1203 $[M+Na]^+$; found: 375.1200.

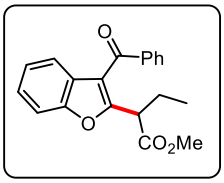


Methyl 4-(3-benzoyl-5-methoxybenzofuran-2-yl)butanoate (**6ajl**)**:** Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); The title compound was determined as light yellow oil; 11 mg, 8%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.08 (quin, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 2.91 (t, J = 7.3 Hz, 2H), 3.61 (s, 3H), 3.69 (s, 3H), 6.80 (d, J = 2.2 Hz, 1H), 6.87 (dd, J = 2.4, 8.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.2 (t), 27.6 (t), 33.2 (t), 51.6 (q), 55.8 (q), 104.0 (d), 111.5 (d), 113.3 (d), 117.4 (s), 127.3 (s), 128.5 (d, 2C), 129.1 (d, 2C), 132.7 (d), 139.2 (s), 148.7 (s),

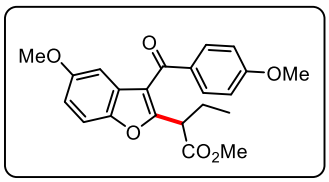


156.5 (s), 164.9 (s), 173.3 (s), 191.9 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}O_5Na$: 375.1203 $[M+Na]^+$; found: 375.1198.

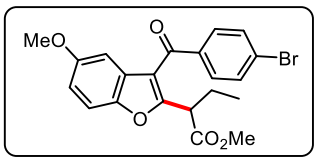
Methyl 2-(3-benzoylbenzofuran-2-yl)butanoate (**7bj**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 89 mg, 62%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.91 (t, J = 7.4 Hz, 3H), 2.06–2.14 (m, 1H), 2.17–2.24 (m, 1H), 3.69 (s, 3H), 4.19 (dd, J = 6.3, 9.0 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 6.1 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.53 (d, J = 8.3 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.83 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, CDCl3) δ11.9 (q), 23.7 (t), 45.8 (d), 52.4 (q), 111.5 (d), 118.7 (s), 121.6 (d), 123.7 (d), 124.9 (d), 126.3 (s), 128.5 (d, 2C), 129.2 (d, 2C), 133.0 (d), 138.9 (s), 153.9 (s), 160.0 (s), 171.1 (s), 191.5 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{19}O_4$: 323.1278 $[M+H]^+$; found: 323.1276.



Methyl 2-(5-methoxy-3-(4-methoxybenzoyl)benzofuran-2-yl)butanoate (**7cj**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as white solid; 80 mg, 59%; M. P. 82–84 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 3H), 2.00–2.11 (m, 1H), 2.12–2.23 (m, 1H), 3.68 (s, 3H), 3.71 (s, 3H), 3.89 (s, 3H), 4.10 (dd, J = 6.4, 8.9 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.90 (dd, J = 2.8, 9.0 Hz, 1H), 6.94–6.96 (m, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.85–7.88 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 11.9 (q), 23.8 (t), 45.9 (d), 52.4 (q), 55.5 (q), 55.9 (q), 104.0 (d), 111.9 (d), 113.6 (d), 113.7 (d, 2C), 119.1 (s), 127.2 (s), 131.4 (s), 131.8 (d, 2C), 148.9 (s), 156.4 (s), 159.6 (s), 163.7 (s), 171.2 (s), 190.0 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{22}O_6Na$: 405.1309 $[M+Na]^+$; found: 405.1305.

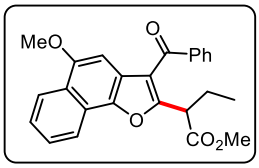


Methyl 2-(3-benzoyl-5-methoxybenzofuran-2-yl)butanoate (**7dj**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 79 mg, 61%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 3H), 2.01–2.12 (m, 1H), 2.14–2.24 (m, 1H), 3.68 (s, 3H), 3.71 (s, 3H), 4.10 (dd, J = 6.2, 8.9 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.7, 9.0 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.63

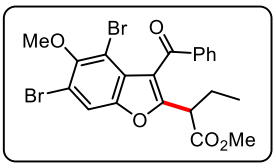


(d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, CDCl3): *δ* 11.9 (q), 23.7 (t), 46.0 (d), 52.5 (q), 55.9 (q), 104.0 (d), 112.1 (d), 113.7 (d), 118.6 (s), 126.7 (s), 128.1 (s), 130.8 (d, 2C), 131.9 (d, 2C), 137.5 (s), 148.9 (s), 156.6 (s), 160.8 (s), 170.9 (s), 190.4 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{20}BrO_5$: 431.0489 $[M+H]^+$; found: 431.0487.

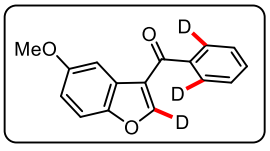
Methyl 2-(3-benzoyl-5-methoxynaphtho[1,2-b]furan-2-yl)butanoate (7ej): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as brown liquid; 73 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.93 (t, *J* = 7.6 Hz, 3H), 2.14–2.20 (m, 1H), 2.22–2.29 (m, 1H), 3.69 (s, 3H), 3.81 (s, 3H), 4.15 (dd, *J* = 6.4, 8.7 Hz, 1H), 6.64 (s, 1H), 7.48–7.53 (m, 3H), 7.63 (t, *J* = 7.3 Hz, 2H), 7.87–7.90 (m, 2H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 12.0 (q), 23.9 (t), 46.0 (d), 52.4 (q), 55.7 (q), 96.7 (d), 119.9 (d), 120.1 (s), 121.2 (s), 121.6 (s), 123.0 (d), 124.2 (s), 125.2 (d), 127.3 (d), 128.5 (d, 2C), 129.3 (d, 2C), 133.0 (d), 139.0 (s), 144.6 (s), 152.6 (s), 158.5 (s), 171.2 (s), 191.9 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{23}O_5$: 403.1540 $[M+H]^+$; found: 403.1534.



Methyl 2-(3-benzoyl-4,6-dibromo-5-methoxybenzofuran-2-yl)butanoate (**7fj)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 78 mg, 63%; **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 0.88 (t, *J* = 7.3 Hz, 3H), 2.01–2.05 (m, 1H), 2.10–2.15 (m, 1H), 3.58 (s, 3H), 3.67–3.70 (m, 1H), 3.82 (s, 3H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.74 (s, 1H), 7.85 (d, *J* = 7.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 11.9 (q), 23.3 (t), 45.8 (d), 52.4 (q), 61.0 (q), 108.9 (s), 114.7 (s), 115.3 (d), 120.0 (s), 128.0 (s), 128.7 (d, 2C), 129.7 (d, 2C), 133.9 (d), 138.6 (s), 150.2 (s), 151.0 (s), 156.4 (s), 170.4 (s), 191.0 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{18}O_5Br^{81}BrNa$: 532.9393 $[M+Na]^+$; found: 532.9388.

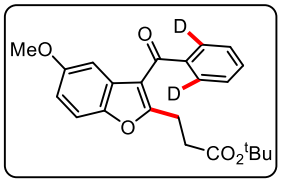


(5-Methoxybenzofuran-3-yl-2-d)(phenyl-2,6-d2)methanone (**5a$_d$)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.6); The title compound was determined as white solid; 91 mg, 90%; mp 79–81 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): *δ* 3.89 (s, 3H), 7.00 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.44 (dd, *J* = 0.4, 9.0 Hz, 1H), 7.48–7.54 (m, 2H), 7.57–7.65 (m, 1H),



7.73 (d, *J* = 2.6 Hz, 1H), 7.85–7.90 (m, 0.47H, (22%)), 8.04 (s, 0.07H, (7%)) ppm; **HRMS** (ESI) calcd for $C_{16}H_{10}{}^{2}H_3O_3$: 256.1048 $[M+H]^+$; found: 256.1047.

***tert*-Butyl 3-(3-(benzoyl-2,6-d2)-5-methoxybenzofuran-2-yl)propanoate** (**5ae$_d$**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); The title compound was determined as colourless oil; 121 mg, 81%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.66 (t, *J* = 7.3 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 6.82–6.89 (m, 2H), 7.33 (dd, *J* = 0.9, 8.6 Hz, 1H), 7.45–7.52 (m, 2H), 7.56–7.63 (m, 1H), 7.78–7.83 (m, 0.5H (25%)) ppm; **HRMS** (ESI) calcd for $C_{23}H_{23}{}^{2}H_2O_5$: 383.1822 $[M+H]^+$; found: 383.1818.



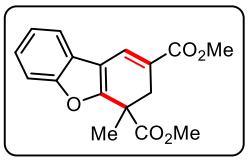
Alkylation of 3-formylbenzofurans with acrylates:

General Experimental procedure A:

3-Formylbenzo[b]furan (1 equiv) was placed in a screw cap pressure tube and dissolved in anhydrous toluene, which was then evacuated and back filled with argon. To the reaction vessel acrylate (5 equiv), K_2CO_3 (5 equiv), $Ru(PPh_3)_3Cl_2$ (10 mol%) and AgOAc (30 mol%) were added. The solution was then stirred at 160 ^{o}C for acrylate (bath temperature) for 36 h. The reaction mixture was cooled to room temperature and filtered through Celite pad. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/ethyl acetate) to give analytically pure products.

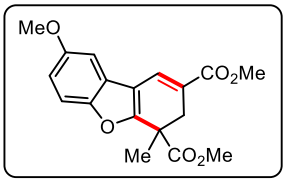
Experimental Data:

Dimethyl 4-methyl-3,4-dihydrodibenzo[*b,d*]furan-2,4-dicarboxylate (**9aa**): Purified by column chromatography (petroleum ether/ethyl acetate = 18:2, R_f = 0.5); colourless solid; 128 mg, 62%; mp 132–134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.68 (s, 3H), 2.75 (dd, *J* = 2.1, 17.4, Hz, 1H), 3.55 (d, *J* = 17.2 Hz, 1H), 3.66 (s, 3H), 3.82 (s, 3H), 7.27–7.32 (m, 2H), 7.51 (dd, *J* = 2.6, 6.3 Hz, 1H), 7.58–7.60 (m, 1H), 7.70 (br. d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.9 (q) 36.4 (t) 44.1 (s) 51.9 (q) 52.8 (q) 111.9 (d) 113.7 (s) 119.0 (d) 123.1 (s) 123.6 (d)

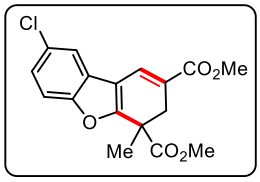


124.6 (d) 125.1 (s) 128.4 (d) 155.6 (s) 158.2 (s) 167.0 (s) 173.7 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{16}O_5Na$: 323.0890 $[M+Na]^+$; found: 323.0891.

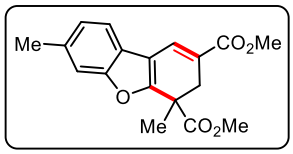
Dimethyl 8-methoxy-4-methyl-3,4-dihydrodibenzo[*b*,*d*]furan-2,4-dicarboxylate (**9ba**): Purified by column chromatography (petroleum ether/ethyl acetate = 18:2, R_f = 0.5); brown solid; 124 mg, 66%; mp 138–140 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.66 (s, 3H), 2.73 (dd, *J* = 2.2, 17.4 Hz, 1H), 3.54 (d, *J* = 17.4 Hz, 1H), 3.66 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 6.89 (dd, *J* = 2.5, 9.0, Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.9 (q), 36.4 (t), 44.2 (s), 51.9 (q), 52.8 (q), 55.9 (q), 101.7 (d), 112.4 (d), 113.1 (d), 113.9 (s), 122.8 (s), 125.7 (s), 128.4 (d), 150.6 (s), 156.6 (s), 159.0 (s), 167.0 (s), 173.6 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{18}O_6Na$: 353.0996 $[M+Na]^+$; found: 353.0994.



Dimethyl 8-chloro-4-methyl-3,4-dihydrodibenzo[*b*,*d*]furan-2,4-dicarboxylate (**9ca**): Purified by column chromatography (petroleum ether/ethyl acetate = 18:2, R_f = 0.5); Light brown solid; 76 mg, 41%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.67 (s, 3H), 2.74 (dd, *J* = 2.3, 17.5 Hz, 1H), 3.56 (d, *J* = 17.5 Hz, 1H), 3.67 (s, 3H), 3.82 (s, 3H), 7.25–7.27 (m, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.9 (q), 36.4 (t), 44.2 (s), 52.0 (q), 52.9 (q), 112.9 (d), 113.4 (s), 118.9 (d), 123.7 (s), 124.8 (d), 126.5 (s), 127.6 (d), 129.4 (s), 154.0 (s), 159.5 (s), 166.8 (s), 173.4 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{15}O_5ClNa$: 357.0500 $[M+Na]^+$; found: 357.0497.

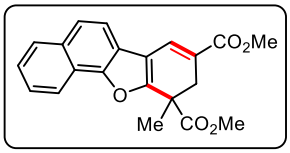


Dimethyl 4,7-dimethyl-3,4-dihydrodibenzo[b,d]furan-2,4-dicarboxylate (**9da**): Purified by column chromatography (petroleum ether/ethyl acetate = 18:2, R_f = 0.5); colourless solid; 106 mg, 54%; mp 117–119 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.66 (s, 3H), 2.47 (s, 3H), 2.73 (dd, *J* = 2.3, 17.4 Hz, 1H), 3.54 (dd, *J* = 0.7, 17.4 Hz, 1H), 3.65 (s, 3H), 3.81 (s, 3H), 7.11 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.31 (br. s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.68 (dd, *J* = 0.8, 2.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.7 (q), 21.9 (q), 36.4 (t), 44.1 (s), 51.9 (q), 52.8 (q), 112.1 (d), 113.6 (s), 118.5 (d), 122.6 (s), 122.8 (s), 124.9 (d), 128.6 (d), 135.0 (s), 156.1

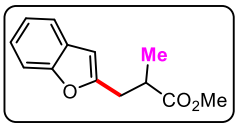


(s), 157.6 (s), 167.0 (s), 173.8 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{18}O_5Na$: 337.1046 $[M+Na]^+$; found: 337.1044.

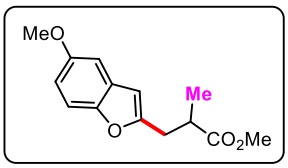
Dimethyl 10-methyl-9,10-dihydronaphtho[1,2-b]benzofuran-8,10-dicarboxylate (**9ea**): Purified by column chromatography (petroleum ether/ethyl acetate = 18:2, R_f = 0.5); brown solid; 119 mg, 67%; mp 148–150 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.77 (s, 3H), 2.79 (dd, J = 2.3, 17.4 Hz, 1H), 3.60 (d, J = 17.4 Hz, 1H), 3.67 (s, 3H), 3.84 (s, 3H), 7.49 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 22.1 (q), 36.6 (t), 44.2 (s), 51.9 (q), 52.8 (q), 114.8 (s), 117.4 (d), 120.0 (d), 120.7 (s), 121.4 (s), 123.4 (s), 124.3 (d), 125.3 (d), 126.6 (d), 128.4 (d), 128.6 (d), 131.5 (s), 151.2 (s), 157.2 (s), 167.0 (s), 173.8 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{18}O_5Na$: 373.1046 $[M+Na]^+$; found: 373.1046.



Methyl 3-(benzofuran-2-yl)-2-methylpropanoate (**10aa**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 94 mg, 63%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (d, J = 7.3 Hz, 3H), 2.95 (dd, J = 7.3, 14.7 Hz, 1H), 3.06 (sxt, J = 7.0 Hz, 1H), 3.28 (dd, J = 6.7, 14.7, Hz, 1H), 3.78 (s, 3H), 6.52 (s, 1H), 7.25–7.34 (m, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.9 (q), 32.3 (t), 38.4 (d), 51.8 (q), 103.5 (d), 110.8 (d), 120.4 (d), 122.5 (d), 123.4 (d), 128.7 (s), 154.7 (s), 156.3 (s), 175.9 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{14}O_3Na$: 241.0835 $[M+Na]^+$; found: 241.0835.

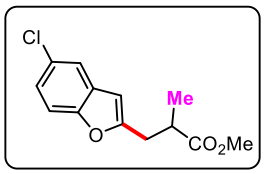


Methyl 3-(5-methoxybenzofuran-2-yl)-2-methylpropanoate (**10ba**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 76 mg, 54%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 2.82 (dd, J = 7.4, 14.7 Hz, 1H), 2.94 (sxt, J = 7.0 Hz, 1H), 3.15 (dd, J = 6.8, 14.7 Hz, 1H), 3.67 (s, 3H), 3.81 (s, 3H), 6.36 (s, 1H), 6.81 (dd, J = 2.4, 8.9 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.9 (q), 32.3 (t), 38.4 (d), 51.8 (q), 55.9 (q), 103.1

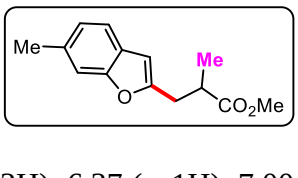


(d), 103.7 (d), 111.2 (d), 111.8 (d), 129.2 (s), 149.7 (s), 155.8 (s), 157.2 (s), 175.9 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{16}O_4Na$: 271.0941 $[M+Na]^+$; found: 271.0940.

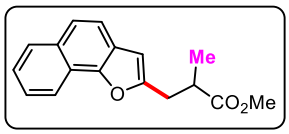
Methyl 3-(5-chlorobenzofuran-2-yl)-2-methylpropanoate (**10ca**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 80 mg, 57%; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 2.84 (dd, J = 7.0, 14.7 Hz, 1H), 2.94 (sxt, J = 6.9 Hz, 1H), 3.17 (dd, J = 6.9, 14.7 Hz, 1H), 3.68 (s, 3H), 6.37 (s, 1H), 7.16 (dd, J = 1.8, 8.6 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.43 (br. s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.0 (q), 32.2 (t), 38.3 (d), 51.9 (q), 103.2 (d), 111.7 (d), 120.0 (d), 123.6 (d), 128.1 (s), 130.0 (s), 153.1 (s), 158.0 (s), 175.7 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{13}O_3ClNa$: 275.0445 $[M+Na]^+$; found: 275.0442.



Methyl 2-methyl-3-(6-methylbenzofuran-2-yl)propanoate (**10da**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 80 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 2.44 (s, 3H), 2.83 (dd, J = 7.4, 14.7 Hz, 1H), 2.94 (sxt, J = 7.0 Hz, 1H), 3.16 (dd, J = 6.7, 14.7 Hz, 1H), 3.68 (s, 3H), 6.37 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.21 (br. s, 1H), 7.34 (d, J = 7.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.9 (q), 21.6 (q), 32.3 (t), 38.4 (d), 51.8 (q), 103.3 (d), 111.1 (d), 119.8 (d), 123.8 (d), 126.1 (s), 133.6 (s), 155.2 (s), 155.6 (s), 176.0 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{16}O_3Na$: 255.0992 $[M+Na]^+$; found: 255.0991.

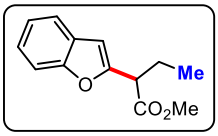


Methyl 2-methyl-3-(naphtho[1,2-*b*]furan-2-yl)propanoate (**10ea**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 93 mg, 68%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.29 (d, J = 6.8 Hz, 3H), 2.99 (dd, J = 7.4, 14.4 Hz, 1H), 3.04 (sxt, J = 7.0 Hz, 1H), 3.30 (dd, J = 6.3, 14.4 Hz, 1H), 3.71 (s, 3H), 6.57 (s, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.55–7.58 (m, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 16.9 (q), 32.4 (t), 38.7 (d), 51.8 (q), 104.6 (d), 119.4 (d), 119.7 (d), 121.2 (s), 123.1 (d), 124.1 (s), 124.6 (d), 126.1 (d), 128.3 (d), 131.0

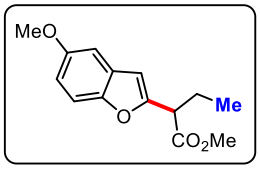


(s), 150.0 (s), 155.5 (s), 176.0 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{16}O_3Na$: 291.0992 $[M+Na]^+$; found: 291.0991.

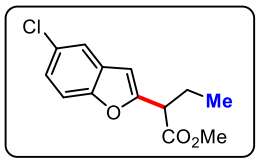
Methyl 2-(benzofuran-2-yl)butanoate (**11aa**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 78 mg, 52%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H), 2.00–2.08 (m, 1H), 2.09–2.18 (m, 1H), 3.72 (s, 3H), 3.75 (t, J = 7.6 Hz, 1H), 6.59 (s, 1H), 7.19 (br. t, J = 7.4 Hz, 1H), 7.22–7.25 (m, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.51 (br. d, J = 7.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 11.9 (q), 24.2 (t), 47.3 (d), 52.3 (q), 103.9 (d), 111.1 (d), 120.7 (d), 122.7 (d), 123.9 (d), 128.4 (s), 154.7 (s), 155.1 (s), 172.0 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{14}O_3Na$: 241.0835 $[M+Na]^+$; found: 241.0835.



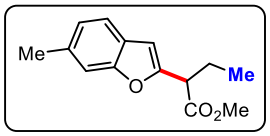
Methyl 2-(5-methoxybenzofuran-2-yl)butanoate (**11ba**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 72 mg, 51%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.96–2.06 (m, 1H), 2.08–2.15 (m, 1H), 3.70–3.73 (m, 4H), 3.82 (s, 3H), 6.53 (s, 1H), 6.84 (dd, J = 2.4, 8.9 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 11.9 (q), 24.1 (t), 47.3 (d), 52.3 (q), 55.9 (q), 103.3 (d), 104.0 (d), 111.5 (d), 112.4 (d), 128.9 (s), 149.7 (s), 155.8 (s), 155.9 (s), 172.0 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{16}O_4Na$: 271.0941 $[M+Na]^+$; found: 271.0941.



Methyl 2-(5-chlorobenzofuran-2-yl)butanoate (**11ca**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 64 mg, 46%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.98–2.06 (m, 1H), 2.08–2.18 (m, 1H), 3.72–3.75 (m, 4H), 6.54 (s, 1H), 7.19 (dd, J = 1.9, 8.7 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 1.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 11.9 (q), 24.1 (t), 47.2 (d), 52.4 (q), 103.6 (d), 112.1 (d), 120.3 (d), 124.1 (d), 128.3 (s), 129.7 (s), 153.1 (s), 156.7 (s), 171.7 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{13}O_3ClNa$: 275.0445 $[M+Na]^+$; found: 275.0442.

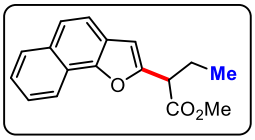


Methyl 2-(6-methylbenzofuran-2-yl)butanoate (**11da**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 79 mg,



54%; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.94–2.20 (m, 2H), 2.44 (s, 3H), 3.68–3.76 (m, 4H), 6.53 (s, 1H), 7.02 (dd, J = 0.8, 7.9 Hz, 1H), 7.25 (br. s, 1H (peak merged with chloroform peak)), 7.38 (d, J = 7.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 11.9 (q), 21.6 (q), 24.1 (t), 47.3 (d), 52.2 (q), 103.6 (d), 111.4 (d), 120.1 (d), 124.0 (d), 125.8 (s), 134.0 (s), 154.3 (s), 155.1 (s), 172.1 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{16}O_3Na$: 255.0992 $[M+Na]^+$; found: 255.0992.

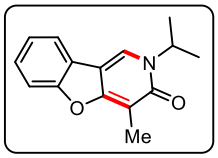
Methyl 2-(naphtho[1,2-b]furan-2-yl)butanoate (**11ea**): Purified by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 79 mg, 58%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3H), 2.06–2.25 (m, 2H), 3.74 (s, 3H), 3.87 (t, J = 7.5 Hz, 1H), 6.73 (s, 1 H), 7.46 (t, J = 7.4 Hz, 1H), 7.54–7.64 (m, 3H), 7.90 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 12.0 (q), 24.5 (t), 47.4 (d), 52.3 (q), 104.9 (d), 119.5 (d), 120.0 (d), 121.2 (s), 123.3 (d), 123.9 (s), 124.9 (d), 126.2 (d), 128.3 (d), 131.2 (s), 150.1 (s), 154.3 (s), 172.2 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{16}O_3Na$: 291.0992 $[M+Na]^+$; found: 291.0992.



General Experimental procedure B:

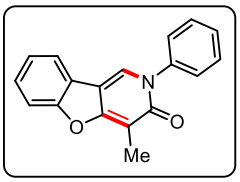
3-Formylbenzo[b]furan (1 equiv) was placed in a screw cap pressure tube and dissolved in anhydrous toluene, which was then evacuated and back filled with argon. To the reaction vessel acrylamide (3 equiv), K_2CO_3 (5 equiv), $Ru(PPh_3)_3Cl_2$ (10 mol%) and AgOAc (30 mol%) were added. The solution was then stirred at 140 ^oC for acrylate (bath temperature) for 16 h. The reaction mixture was cooled to room temperature and filtered through Celite pad. The solvent were evaporated and the crude products were purified by column chromatography (pet ether/ethyl acetate) to give analytically pure products.

2-Isopropyl-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12aa**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 124 mg, 75%; mp 124–127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.47 (d, J = 6.8 Hz, 6H), 2.33 (s, 3H), 5.51 (hept, J = 6.8 Hz, 1H), 7.28 (d, J = 6.8 Hz, 1H), 7.35–7.43 (m, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.86 (s, 1H);

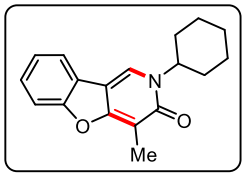


^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6 (q), 22.5 (q, 2C), 47.2 (d), 106.1 (s), 110.0 (s), 111.4 (d), 119.7 (d), 122.3 (d), 122.5 (s), 123.4 (d), 127.4 (d), 157.1 (s), 161.3 (s), 162.9 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{16}O_2N$: 242.1176 $[M+H]^+$; found: 242.1175.

4-Methyl-2-phenylbenzofuro[3,2-c]pyridin-3(2H)-one (**12ak**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 98 mg, 52%; mp 186–188 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.27–7.29 (m, 1H), 7.38–7.48 (m, 5H), 7.52–7.55 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.88 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.4 (q), 107.1 (s), 110.3 (s), 111.5 (d), 120.0 (d), 122.2 (s), 123.6 (d), 127.0 (d, 2C), 127.1 (d), 127.8 (d), 128.5 (d), 129.3 (d, 2C), 141.7 (s), 157.4 (s), 162.2 (s), 163.3 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{13}O_2NNa$: 298.0838 $[M+Na]^+$; found: 298.0835.

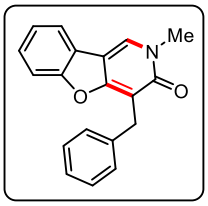


2-Cyclohexyl-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12al**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 136 mg, 71%;**^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27–1.31 (m, 1H), 1.52–1.63 (m, 4H), 1.80–1.83 (m, 1H), 1.94–2.03 (m, 4H), 2.31 (s, 3H), 5.05–5.15 (m, 1H), 7.24–7.28 (m, 1H), 7.34–7.37 (m, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.6 (q), 25.5 (t), 25.9 (t, 2C), 33.2 (t, 2C), 54.9 (d), 106.0 (s), 109.7 (s), 111.3 (d), 119.6 (d), 122.5 (s), 123.1 (d), 123.4 (d), 127.3 (d), 157.1 (s), 161.3 (s), 162.9 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{20}O_2N$: 282.1489 $[M+H]^+$; found: 282.1488.

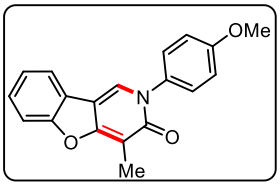


2,4-Dimethylbenzofuro[3,2-c]pyridin-3(2H)-one (**12am**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 79 mg, 54%; mp 218–220 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.71 (s, 3H), 7.23 (dd, J = 1.2, 7.4 Hz, 1H), 7.33–7.37 (m, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 9.4 (q), 38.8 (q), 106.5 (s), 109.9 (s), 111.5 (d), 119.8 (d), 122.2 (s), 123.5 (d), 127.3 (d), 127.5 (d), 157.1 (s), 162.1 (s), 163.7 (s) ppm; **HRMS** (ESI) calcd for $C_{13}H_{12}O_2N$: 214.0863 $[M+H]^+$; found: 214.0862.

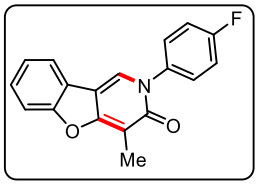
4-Benzyl-2-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12an**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 125 mg, 63%; mp 171–174 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 4.15 (s, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.27–7.28 (m, 3H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 30.0 (t), 38.8 (q), 110.0 (s), 111.6 (d), 119.7 (d), 122.1 (s), 123.6 (d), 126.1 (d), 127.5 (d), 128.3 (d, 2C), 128.9 (d, 2C), 140.0 (s), 157.1 (s), 162.1 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{16}O_2N$: 290.1176 $[M+H]^+$; found: 290.1175.



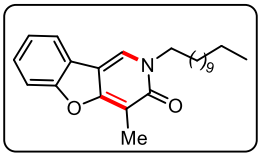
2-(4-Methoxyphenyl)-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12ao**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 95 mg, 45%; mp 208–210 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.86 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.23 (dd, *J* = 1.0, 7.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.35–7.39 (m, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.84 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ9.5 (q), 55.6 (q), 107.0 (s), 110.2 (s), 111.5 (d), 114.5 (d, 2C), 119.9 (d), 122.2 (s), 123.6 (d), 127.5 (d), 127.7 (d), 128.1 (d, 2C), 134.6 (s), 157.4 (s), 159.4 (s), 162.2 (s), 163.6 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{15}O_3NNa$: 328.0944 $[M+Na]^+$; found: 328.0938.



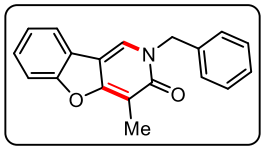
2-(4-Fluorophenyl)-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12ap**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 102 mg, 51%; mp 220–223 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.31 (s, 3H), 7.19 (t, *J* = 8.5 Hz, 2H), 7.24–7.26 (m, 1H (peak merged with chloroform peak)), 7.37–7.43 (m, 4H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ9.4 (q), 107.2 (s), 110.6 (s), 111.6 (d), 116.1 (d), 116.3 (d), 120.0 (d), 122.0 (s), 123.7 (d), 127.0 (d), 128.0 (d), 128.8 (d), 128.9 (d), 137.6 (s), 157.4 (s), 161.3 (s), 162.3 (s), 163.4 (s); **HRMS** (ESI) calcd for $C_{18}H_{13}O_2NF$: 294.0925 $[M+H]^+$; found: 294.0923.



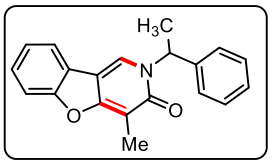
2-Dodecyl-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12aq**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 154 mg, 61%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.25–1.31 (m, 14H), 1.33–1.41 (m, 4H), 1.82 (quint, J = 7.2 Hz, 2H), 2.31 (s, 3H), 4.10 (t, J = 7.5 Hz, 2H), 7.23–7.27 (m, 1H), 7.34–7.37 (m, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ9.4 (q), 14.1 (q), 22.6 (t), 26.7 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.5 (t), 29.6 (t, 2C), 29.7 (t), 31.9 (t), 51.1 (t), 106.6 (s), 109.7 (s), 111.4 (d), 119.7 (d), 122.3 (s), 123.4 (d), 126.7 (d), 127.4 (d), 157.1 (s), 161.8 (s), 163.1 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{34}O_2N$: 368.2584 $[M+H]^+$; found: 368.2581.



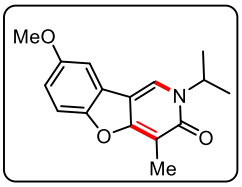
2-Benzyl-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12ar**): Purified by column chromatography (petroleum ether/ethyl acetate 15:5, R_f = 0.5); Colourless solid; 111 mg, 56%; mp 156–158 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 5.32 (s, 2H), 7.21 (td, J = 1.0, 7.4 Hz, 1H), 7.28–7.31(m, 1H), 7.32–7.35 (m, 5H), 7.38 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 9.5 (q), 52.9 (t), 106.8 (s), 110.3 (s), 111.4 (d), 119.9 (d), 122.1 (s), 123.4 (d), 126.4 (d), 127.6 (d), 128.0 (d), 128.1 (d, 2C), 128.9 (d, 2C), 136.7 (s), 157.2 (s), 161.9 (s), 163.3 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{16}O_2N$: 290.1176 $[M+H]^+$; found: 290.1172.



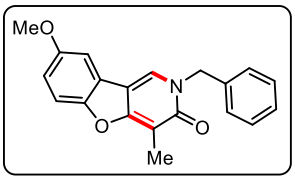
4-Methyl-2-(1-phenylethyl)benzofuro[3,2-c]pyridin-3(2H)-one (**12as**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Brown liquid; 131 mg, 63%; mp 156–158 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.79 (d, J = 7.1 Hz, 3H), 2.33 (s, 3H), 6.66 (q, J = 7.1 Hz, 1H), 7.17 (td, J = 1.1, 7.5 Hz, 1H), 7.31 (td, J = 1.2, 8.2 Hz, 2H), 7.35–7.37 (m, 5H), 7.52 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 9.7 (q), 19.5 (q), 53.4 (d), 106.1 (s), 110.2 (s), 111.3 (d), 119.9 (d), 122.3 (s), 123.3 (d), 123.8 (d), 127.4 (d, 2C), 127.5 (d), 128.0 (d), 128.9 (d, 2C), 140.6 (s), 157.1 (s), 161.4 (s), 163.1 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}O_2N$: 304.1332 $[M+H]^+$; found: 304.1332.



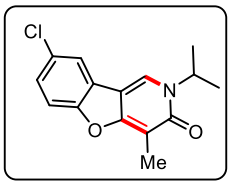
2-Isopropyl-8-methoxy-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12bd**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 99 mg, 64%; mp 120–123 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (d, J = 6.8 Hz, 6H), 2.28 (s, 3H), 3.86 (s, 3H), 5.48 (hept, J = 6.8 Hz, 1H), 6.90 (dd, J = 2.6, 8.9 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 8.9 Hz, 1H), 7.80 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 9.6 (q), 22.5 (q, 2C), 47.3 (d), 56.0 (q), 104.1 (d), 106.1 (s), 110.5 (s), 111.8 (d), 114.1 (d), 122.4 (d), 123.1 (s), 128.2 (s), 151.7 (s), 156.3 (s), 162.0 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{18}O_3N$: 272.1281 $[M+H]^+$; found: 272.1280.



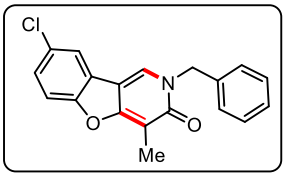
2-Benzyl-8-methoxy-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12br**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 109 mg, 60%; mp 218–221 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.81 (s, 3H), 5.31 (s, 2H), 6.88 (br. d., J = 8.9 Hz, 1H), 7.05 (br. s., 1H), 7.26 (d, J = 8.9 Hz, 1H), 7.29–7.33 (m, 5H), 7.76 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.5 (q), 52.9 (t), 56.0 (q), 104.2 (d), 110.7 (s), 111.8 (d), 114.4 (d), 122.7 (s), 126.4 (d), 128.0 (d), 128.1 (d, 2C), 128.9 (d, 2C), 136.7 (s), 151.7 (s), 156.3 (s), 162.5 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}O_3N$: 320.1281 $[M+H]^+$; found: 320.1279.



8-Chloro-2-isopropyl-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12cd**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 93 mg, 61%; mp 178–180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (d, J = 6.8 Hz, 6H), 2.28 (s, 3H), 5.46 (hept, J = 6.8 Hz, 1H), 7.27–7.32 (m, 2H), 7.63 (br. s., 1H), 7.82 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.6 (q), 22.5 (q, 2C), 47.4 (d), 106.4 (s), 109.1 (s), 112.3 (d), 119.7 (d), 123.1 (d), 124.1 (s), 127.2 (d), 128.9 (s), 155.5 (s), 161.6 (s), 162.9 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{14}O_2NClNa$: 298.0605 $[M+Na]^+$; found: 298.0602.

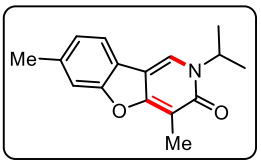


2-Benzyl-8-chloro-4-methylbenzofuro[3,2-c]pyridin-3(2H)-one (**12cr**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 162 mg,

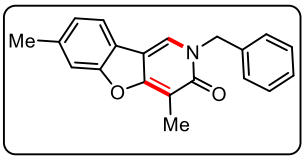


54%; mp 212–214 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.31 (s, 2H), 7.28–7.35 (m, 7H), 7.52 (br. s., 1H), 7.77 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.5 (q), 53.0 (t), 107.0 (s), 109.3 (s), 112.3 (d), 119.9 (d), 123.8 (s), 127.0 (d), 127.5 (d), 128.2 (d, 2C), 128.9 (s), 129.0 (d, 2C), 136.4 (s), 155.6 (s), 162.1 (s), 163.2 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{15}O_2NCl$: 324.0786 $[M+H]^+$; found: 324.0784.

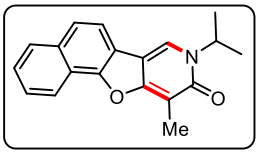
2-Isopropyl-4,7-dimethylbenzofuro[3,2-c]pyridin-3(2H)-one (**12dd**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 105 mg, 66%; mp 189–193 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42 (d, J = 6.8 Hz, 6H), 2.28 (s, 3H), 2.45 (s, 3H), 5.47 (hept, J = 6.8 Hz, 1H), 7.05 (br. d, J = 7.8 Hz, 1H), 7.19 (br. s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.76 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.6 (q), 21.8 (q), 22.4 (q, 2C), 47.1 (d), 106.1 (s), 110.2 (s), 111.8 (d), 119.2 (d), 119.7 (s), 121.7 (d), 124.4 (d), 138.0 (s), 157.5 (s), 161.5 (s), 162.8 (s) ppm; **HRMS** (ESI) calcd for $C_{16}H_{18}O_2N$: 256.1332 $[M+H]^+$; found: 256.1331.



2-Benzyl-4,7-dimethylbenzofuro[3,2-c]pyridin-3(2H)-one (**12dr**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); Colourless solid; 100 mg, 53%; mp 139–141 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.44 (s, 3H), 5.31 (s, 2H), 7.02 (br. d, J = 7.8 Hz, 1H), 7.18 (br. s, 1H), 7.27–7.33 (m, 5H), 7.43 (d, J = 7.8 Hz, 1H), 7.71 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.5 (q), 21.9 (q), 52.9 (t), 106.8 (s), 110.5 (s), 111.9 (d), 119.4 (s), 119.5 (d), 124.5 (d), 125.7 (d), 128.0 (d), 128.1 (d, 2C), 128.9 (d, 2C), 136.8 (s), 138.3 (s), 157.6 (s), 162.1 (s), 163.2 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}O_2N$: 304.1332 $[M+H]^+$; found: 304.1331.

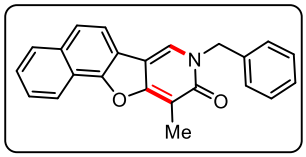


8-Isopropyl-10-methylnaphtho[2',1':4,5]furo[3,2-c]pyridin-9(8H)-one (**12ed**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); brown solid; 94 mg, 63%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48 (d, J = 6.7 Hz, 6H), 2.41 (s, 3H), 5.53 (hept, J = 6.7 Hz, 1H), 7.52–7.55 (m, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.71–7.75 (m, 2H), 7.87 (s, 1H), 7.93 (d, J = 8.3 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.8 (q), 22.5 (q, 2C),



47.4 (d), 106.6 (s), 111.2 (s), 117.3 (d), 120.8 (d), 120.9 (s), 121.7 (d), 124.0 (d), 126.3 (d), 126.8 (d), 128.4 (d), 133.1 (s), 152.9 (s), 161.4 (s), 162.7 (s); **HRMS** (ESI) calcd for $C_{19}H_{18}O_2N$: 292.1332 $[M+H]^+$; found: 292.1331.

8-Benzyl-10-methylnaphtho[2',1':4,5]furo[3,2-c]pyridin-9(8H)-one (**12er**): Purified by column chromatography (petroleum ether/ethyl acetate = 15:5, R_f = 0.5); brown solid; 109 mg, 53%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.36 (s, 2H), 7.32 (dd, *J* = 4.2, 8.1 Hz, 1H), 7.36–7.37 (m, 3H), 7.51–7.55 (m, 1H), 7.59–7.63 (m, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ9.7 (q), 53.0 (t), 107.3 (s), 111.4 (s), 117.0 (s), 117.4 (d), 120.8 (d), 124.0 (d), 125.7 (d), 126.4 (d), 126.8 (d), 128.0 (d), 128.2 (d, 2C), 128.4 (d), 128.9 (d, 2C), 133.2 (s), 136.8 (s), 153.0 (s), 162.0 (s), 163.1 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{18}O_2N$: 340.1332 $[M+H]^+$; found: 340.1331.



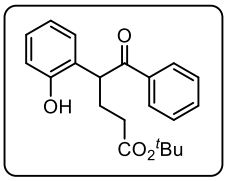
Base Catalysed Benzofuran Rearrangement in the Presence of Acrylates

General Experimental procedure:

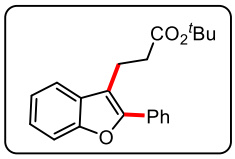
3-Aroylbenzo[b]furan (0.1 mmol) was placed in a screw cap pressure tube and dissolved in anhydrous DMF, which was then evacuated and back filled with argon. To the reaction vessel alkene (acrylate/acrylamide) (0.3 mmol), K_2CO_3 (0.2 mmol) were added. The solution was then stirred at 140 ^oC (bath temperature) for 16 h. The reaction mixture was cooled to room temperature and compound extracted using ethylacetate, dried over Na_2SO_4 and concentrated. The crude reaction mixture, without column chromatography, was dissolved in DCM (10 ml). To this camphorsulphonic acid (0.3 mmol for acrylamide/0.1 mmol for acrylate) was added and stirred for 8 h at room temperature. After completion of reaction, as indicated by TLC, the reaction mixture was subjected to aqueous workup using DCM solvent, then dried over Na_2SO_4 and concentrated. The crude products were purified by column chromatography (pet ether/ethyl acetate) to give analytically pure products.

Experimental Data:

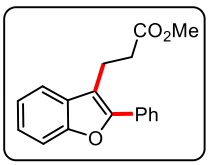
***tert*-Butyl 4-(2-hydroxyphenyl)-5-oxo-5-phenylpentanoate** (**14a**): Isolated by column chromatography (petroleum ether/ethyl acetate = 8:2, R_f = 0.3); Pale yellow liquid; 82%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.12–2.29 (m, 3H), 2.36–2.44 (m, 1H), 4.94 (t, *J* = 7.0 Hz, 1H), 6.78 (dt, *J* = 0.9, 7.4 Hz, 1H), 6.93–6.98 (m, 2H), 7.09–7.13 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.99–8.01 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.0 (t), 28.0 (q, 3C), 32.7 (t), 47.1 (d), 81.3 (s), 117.9 (d), 120.9 (d), 124.8 (s), 128.6 (d, 2C), 128.8 (d, 2C), 128.9 (d), 129.2 (d), 133.5 (d), 136.0 (s), 154.4 (s), 174.1 (s), 201.6 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{24}O_4Na$: 363.1567 $[M+Na]^+$; found: 363.1562.



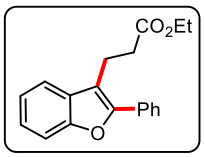
***tert*-Butyl 3-(2-phenylbenzofuran-3-yl)propanoate** (**15be**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Brown liquid; 53 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.63–2.67 (m, 2H), 3.23–3.26 (m, 2H), 7.24–7.27 (m, 1H (chloroform peak merged)), 7.30 (td, *J* = 1.4, 8.0 Hz, 1H), 7.38 (tt, *J* = 1.2, 7.4 Hz, 1H), 7.47–7.50 (m, 3H), 7.60 (dd, *J* = 1.1, 7.4 Hz, 1H), 7.80 (dd, *J* = 1.3, 8.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.0 (t), 28.0 (q, 3C), 35.3 (t), 80.6 (s), 111.1(d), 114.5 (s), 119.6 (d), 122.5 (d), 124.4 (d), 126.9 (d, 2C), 128.3 (d), 128.7 (d, 2C), 130.0 (s), 131.0 (s), 151.0 (s), 153.9 (s), 172.1 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{22}O_3Na$: 345.1461 $[M+Na]^+$; found: 345.1461.



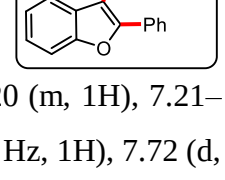
Methyl 3-(2-phenylbenzofuran-3-yl)propanoate (**15ba**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Pale yellow liquid; 20 mg, 62%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.72–2.76 (m, 2H), 3.26–3.30 (m, 2H), 3.66 (s, 3H), 7.25 (td, *J* = 1.1, 7.3 Hz, 1H), 7.30 (td, *J* = 1.3, 7.5 Hz, 1H), 7.36–7.40 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 3H), 7.57 (dd, *J* = 1.1, 7.2 Hz, 1H), 7.77–7.80 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.8 (t), 33.8 (t), 51.8 (q), 111.1 (d), 114.2 (s), 119.3 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.4 (d), 128.8 (d, 2C), 129.8 (s), 130.9 (s), 151.1 (s), 153.9 (s), 173.2 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{16}O_3Na$: 303.0992 $[M+Na]^+$; found: 303.0985.



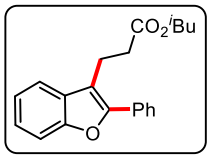
Ethyl 3-(2-phenylbenzofuran-3-yl)propanoate (**15bb**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Pale yellow liquid; 26 mg, 71%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (t, J = 7.1 Hz, 3H), 2.67 (t, J = 8.2 Hz, 2H), 3.23 (t, J = 8.2 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 7.18–7.22 (m, 1H), 7.23–7.27 (m, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 19.8 (t), 34.1 (t), 60.6 (t), 111.1 (d), 114.3 (s), 119.4 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.3 (d), 128.8 (d, 2C), 129.9 (s), 130.9 (s), 151.1 (s), 153.9 (s), 172.8 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{19}O_3$: 295.1329 $[M+H]^+$; found: 295.1325.



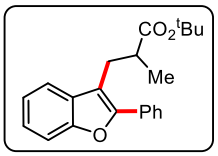
Cyclohexyl 3-(2-phenylbenzofuran-3-yl)propanoate (**15bi**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); White solid; 56 mg, 72%; mp 65–66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18–1.33 (m, 5H), 1.43–1.47 (m, 1H), 1.59–1.64 (m, 2H), 1.70–1.73 (m, 2H), 2.65 (t, J = 8.2 Hz, 2H), 3.20 (t, J = 8.2 Hz, 2H), 4.68 (m, 1H), 7.16–7.20 (m, 1H), 7.21–7.25 (m, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.39–7.43 (m, 3H), 7.52 (d, J = 7.4 Hz, 1H), 7.72 (d, J = 7.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0 (t), 23.7 (t, 2C), 25.3 (t), 31.5 (t, 2C), 34.5 (t), 72.9 (d), 111.1 (d), 114.4 (s), 119.5 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.3 (d), 128.8 (d, 2C), 129.9 (s), 131.0 (s), 151.1 (s), 153.9 (s), 172.3 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{24}O_3Na$: 371.1618 $[M+Na]^+$; found: 371.1611.



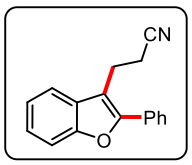
Isobutyl 3-(2-phenylbenzofuran-3-yl)propanoate (**15bt**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Pale yellow liquid; 51 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.81 (d, J = 6.7 Hz, 6H), 1.81 (sep, J = 6.7 Hz, 1H), 2.68 (t, J = 8.1 Hz, 2H), 3.22 (t, J = 8.2 Hz, 2H), 3.78 (d, J = 6.7 Hz, 2H), 7.17–7.20 (m, 1H), 7.22–7.25 (m, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 3H), 7.51 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.9 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 19.0 (q, 2C), 19.9 (t), 27.6 (d), 34.1 (t), 70.8 (t), 111.1 (d), 114.3 (s), 119.4 (d), 122.5 (d), 124.5 (d), 126.9 (d, 2C), 128.3 (d), 128.8 (d, 2C), 129.9 (s), 130.9 (s), 151.1 (s), 153.9 (s), 172.9 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{22}O_3Na$: 345.1461 $[M+Na]^+$; found: 345.1457.



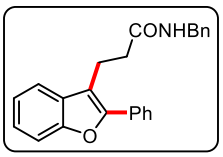
***tert*-Butyl 2-methyl-3-(2-phenylbenzofuran-3-yl)propanoate** (**15bu**): Isolated by column chromatography (petroleum ether/ethyl acetate = 19:1, R_f = 0.5); Pale yellow liquid; 46 mg, 61%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.08 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H), 2.76–2.83 (m, 1H), 2.91 (dd, J = 8.9, 14.4 Hz, 1H), 3.26 (dd, J = 6.3, 14.4 Hz, 1H), 7.16–7.18 (m, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 16.9 (q), 27.9 (q, 3C), 28.3 (t), 40.5 (d), 80.3 (s), 111.0 (d), 113.8 (s), 120.0 (d), 122.4 (d), 124.4 (d), 126.9 (d, 2C), 128.2 (d), 128.7 (d, 2C), 130.4 (s), 131.1 (s), 151.5 (s), 153.8 (s), 175.4 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{24}O_3Na$: 359.1618 $[M+Na]^+$; found: 359.1614.



3-(2-Phenylbenzofuran-3-yl)propanenitrile (**15bv**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.3); Brown liquid; 32 mg, 58%; **^{1}H NMR** (400 MHz, $CDCl_3$): 2.74 (t, J = 7.4 Hz, 2H), 3.32 (t, J = 7.5 Hz, 2H), 7.29 (td, J = 1.1, 7.4 Hz, 1H), 7.34 (td, J = 1.4, 7.3 Hz, 1H), 7.42 (tt, J = 1.4, 7.4 Hz, 1H), 7.48–7.57 (m, 4H), 7.74 (dd, J = 1.4, 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): 17.4 (t), 20.8 (t), 111.4 (d), 112.1 (s), 118.9 (d), 119.0 (s), 122.9 (d), 124.9 (d), 127.1 (d, 2C), 128.9 (d), 129.0 (d, 2C), 129.1 (s), 130.3 (s), 152.2 (s), 154.0 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{13}ONNa$: 270.0889 $[M+Na]^+$; found: 270.0888.

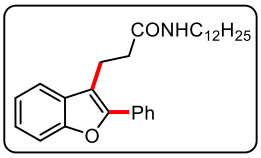


N-Benzyl-3-(2-phenylbenzofuran-3-yl)propanamide (**15br**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); White solid; 55 mg, 69%; mp 149–151 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.56 (t, J = 7.5 Hz, 2H), 3.29 (t, J = 7.6 Hz, 2H), 4.28 (d, J = 5.6 Hz, 2H), 5.52 (br. s., 1H), 7.00–7.01 (m, 2H), 7.16–7.20 (m, 4H), 7.24 (dt, J = 1.2, 8.1 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.41 (dd, J = 7.6, 14.2 Hz, 3H), 7.54 (d, J = 7.36 Hz, 1H), 7.73 (d, J = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3 (t), 36.3 (t), 43.7 (t), 111.1 (d), 114.5 (s), 119.6 (d), 122.6 (d), 124.5 (d), 126.8 (d, 2C), 127.5 (d), 127.7 (d, 2C), 128.4 (d), 128.6 (d, 2C), 128.8 (d, 2C), 130.0 (s), 130.9 (s), 137.9 (s), 151.1 (s), 153.9 (s), 171.7 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{21}O_2NNa$: 378.1465 $[M+Na]^+$; found: 378.1458.

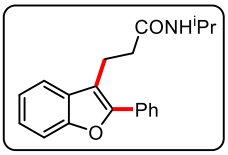


***N*-Dodecyl-3-(2-phenylbenzofuran-3-yl)propanamide** (**15bq**) : Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.3); Grey solid; 76 mg, 78%;

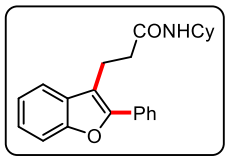
mp 105–106 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, J = 6.7 Hz, 3H), 1.29–1.35 (m, 20H), 2.61 (t, J = 7.6 Hz, 2H), 3.17 (q, J = 6.6 Hz, 2H), 3.36 (t, J = 7.6 Hz, 2H), 5.38 (t, J = 6.2 Hz, 1H), 7.24–7.35 (m, 2H), 7.37–7.46 (m, 1H), 7.49–7.57 (m, 3H), 7.62–7.66 (m, 1H), 7.84–7.88 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.1 (q), 20.4 (t), 22.7 (t), 26.8 (t), 29.2 (t), 29.3 (t, 2C), 29.5 (t), 29.6 (t, 3C), 31.9 (t), 36.3 (t), 39.6 (t), 111.1 (d), 114.6 (s), 119.6 (d), 122.5 (d), 124.5 (d), 126.8 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.0 (s), 130.9 (s), 151.0 (s), 153.8 (s), 171.8 (s) ppm; **HRMS** (ESI) calcd for $C_{29}H_{40}O_2N$: 434.3054 $[M+H]^+$; found: 434.3052.



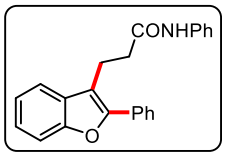
N-Isopropyl-3-(2-phenylbenzofuran-3-yl)propanamide (**15bd**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); White solid; 49 mg, 71%; mp 132–134 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.97 (d, J = 6.6 Hz, 6H), 2.54 (t, J = 7.6 Hz, 2H), 3.30 (t, J = 7.6 Hz, 2H), 3.95–4.02 (m, 1H), 5.10 (d, J = 6.5 Hz, 1H), 7.24 (td, J = 1.0, 7.4 Hz, 1H), 7.29 (td, J = 1.3, 7.8 Hz, 1H), 7.37 (tt, J = 1.2, 7.4 Hz, 1H), 7.46–7.51 (m, 3H), 7.60 (d, J = 7.6 Hz, 1H), 7.80–7.82 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): 20.3 (q, 2C), 22.6 (t), 36.4 (d), 41.4 (t), 111.1 (d), 114.7 (s), 119.6 (d), 122.5 (d), 124.5 (d), 126.8 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.0 (s), 130.9 (s), 151.0 (s), 153.8 (s), 170.9 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{22}O_2N$: 308.1645 $[M+H]^+$; found: 308.1640.



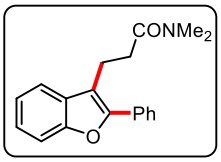
N-Cyclohexyl-3-(2-phenylbenzofuran-3-yl)propanamide (**15bl**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); White solid; 52 mg, 66%; mp 183–185°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.80–0.89 (m, 2H), 0.98–1.04 (m, 1H), 1.16–1.26 (m, 3H), 1.46–1.50 (m, 1H), 1.52–1.56 (m, 1H), 1.65 (dd, J = 3.0, 12.4 Hz, 2H), 2.48 (t, J = 7.6 Hz, 2H), 3.24 (t, J = 7.6 Hz, 2H), 3.61 (m, 1H), 5.08 (d, J = 7.2 Hz, 1H), 7.13–7.23 (m, 1H), 7.21–7.25 (m, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.40–7.43 (m, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.4 (t), 24.7 (t, 2C), 25.4 (t), 32.9 (t, 2C), 36.5 (t), 48.2 (d), 111.1 (d), 114.7 (s), 119.6 (d), 122.5 (d), 124.5 (d), 126.8 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.0 (s), 131.0 (s), 151.0 (s), 153.9 (s), 170.9 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{26}O_2N$: 348.1958 $[M+H]^+$; found: 348.1955.



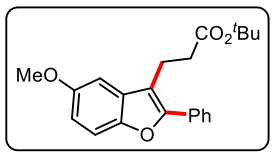
N-Phenyl-3-(2-phenylbenzofuran-3-yl)propanamide (**15bk**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Pale white solid; 62 mg, 81%; mp 153–155 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.73 (t, J = 7.7 Hz, 2H), 3.37 (t, J = 7.8 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 7.20–7.31 (m, 5H), 7.37 (d, J = 7.5 Hz, 3H), 7.47 (dd, J = 7.6, 14.4 Hz, 3H), 7.58 (d, J = 7.6 Hz,1H), 7.79 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.0 (t), 37.0 (t), 111.1 (d), 114.4 (s), 119.5 (d), 120.0 (d, 2C), 122.6 (d), 124.4 (d), 124.6 (d), 126.8 (d, 2C), 128.4 (d), 128.8 (d, 2C), 128.9 (d, 2C), 129.8 (s), 130.8 (s), 137.5 (s), 151.1 (s), 153.9 (s), 170.2 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{20}O_2N$: 342.1489 $[M+H]^+$; found: 342.1477.



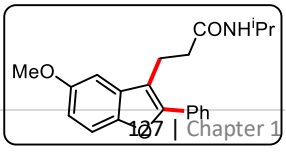
N,N-Dimethyl-3-(2-phenylbenzofuran-3-yl)propanamide (**15bw**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.2); Yellow solid; 56 mg, 85%; mp 64–65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.62–2.66 (m, 2H), 2.80 (s, 3H), 2.87 (s, 3H), 3.22–3.26 (m, 2H), 7.16 (td, J = 0.9, 7.3 Hz, 1H), 7.23 (td, J = 1.3, 7.3 Hz, 1H), 7.29 (tt, J = 1.2, 7.4 Hz, 1H), 7.38–7.43 (m, 3H), 7.49–7.51 (m, 1H), 7.73–7.74 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 19.9 (t), 32.9 (t), 35.4 (q), 37.1 (q), 111.1 (d), 115.0 (s), 119.4 (d), 122.5 (d), 124.5 (d), 126.7 (d, 2C), 128.2 (d), 128.8 (d, 2C), 130.1 (s), 131.0 (s), 150.9 (s), 153.9 (s), 172.1 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{20}O_2N$: 294.1489 $[M+H]^+$; found: 294.1487.



***tert*-Butyl 3-(5-methoxy-2-phenylbenzofuran-3-yl)propanoate** (**15ae**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Pale yellow liquid; 43 mg, 62%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.63 (t, J = 8.2 Hz, 2H), 3.20 (t, J = 8.2 Hz, 2H), 3.88 (s, 3H), 6.89 (dd, J = 2.2, 8.8 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 7.35–7.38 (m, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0 (t), 28.0 (q), 28.1 (q, 2C), 35.2 (t), 56.0 (q), 80.6 (s), 102.2 (d), 111.5 (d), 113.0 (d), 114.6 (s), 126.8 (d, 2C), 128.2 (d), 128.7 (d, 2C), 130.5 (s), 131.1 (s), 148.9 (s), 151.9 (s), 155.8 (s), 172.2 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{25}O_4$: 353.1747 $[M+H]^+$; found: 353.1745.

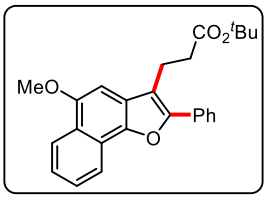


N-Isopropyl-3-(5-methoxy-2-phenylbenzofuran-3-yl)propanamide (**15ad**): Isolated by

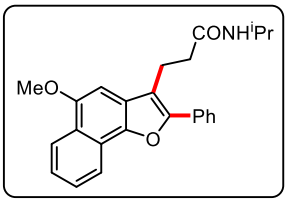


column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); White solid; 50 mg, 75%; mp 193–194 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (d, J = 6.6 Hz, 6H), 2.52 (t, J = 7.6 Hz, 2H), 3.26 (t, J = 7.7 Hz, 2H), 3.87 (s, 3H), 3.94–4.05 (m, 1H), 5.12 (d, J = 6.5 Hz, 1H), 6.89 (dd, J = 2.5, 8.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 7.34–7.37 (m, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3 (t), 22.6 (q, 2C), 36.4 (t), 41.4 (d), 56.1 (q), 102.1 (d), 111.5 (d), 113.2 (d), 114.9 (s), 126.7 (d, 2C), 128.3 (d), 128.8 (d, 2C), 130.5 (s), 131.0 (s), 148.8 (s), 151.8 (s), 155.9 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{24}O_3N$: 338.1751 $[M+H]^+$; found: 338.1745.

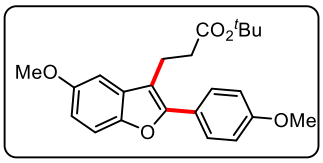
***tert*-Butyl 3-(5-methoxy-2-phenylnaphtho[1,2-b]furan-3-yl)propanoate** (**15ee**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Light brown solid; 29 mg, 60%; mp 124–126 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.67 (t, J = 7.7 Hz, 2 H), 3.29 (t, J = 7.7 Hz, 2H), 4.07 (s, 3H), 6.94 (s, 1H), 7.37 (t, J = 6.7 Hz, 1H), 7.46–7.51 (m, 3H), 7.60 (t, J = 7.1 Hz, 1H), 7.85 (d, J = 7.3 Hz, 2H), 8.30 (t, J = 9.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.1 (t), 28.1 (q, 3C), 35.5 (t), 56.0 (q), 80.6 (s), 95.3 (d), 116.1 (s), 119.8 (d), 121.6 (s), 123.1 (d), 124.2 (s), 124.5 (d), 124.7 (s), 126.5 (d, 2C), 126.9 (d), 127.8 (d), 128.8 (d, 2C), 131.4 (s), 144.4 (s), 150.5 (s), 152.1 (s), 172.3 (s) ppm; **HRMS** (ESI) calcd for $C_{26}H_{27}O_4$: 403.1904 $[M+H]^+$; found: 403.1900.



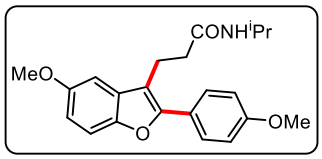
N-Isopropyl-3-(5-methoxy-2-phenylnaphtho[1,2-b]furan-3-yl)propanamide (**15ed**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.5); Brown solid; 40 mg, 81%; mp 190–192 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.6 Hz, 6H), 2.56 (t, J = 7.5 Hz, 2H), 3.35 (t, J = 7.5 Hz, 2H), 3.96–4.03 (m, 1H), 4.06 (s, 3H), 5.13 (d, J = 7.0 Hz, 1H), 6.96 (s, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.46–7.52 (m, 3H), 7.60 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.8 Hz, 2H), 8.29 (t, J = 9.1 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.5 (t), 22.6 (q, 2C), 36.7 (t), 41.4 (d), 56.0 (q), 95.4 (d), 116.4 (s), 119.9 (d), 121.6 (s), 123.2 (d), 124.3 (s), 124.6 (d), 124.8 (s), 126.4 (d, 2C), 126.9 (d), 127.9 (d), 128.9 (d, 2C), 131.4 (s), 144.3 (s), 150.4 (s), 152.2 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{26}O_3N$: 388.1907 $[M+H]^+$; found: 388.1905.



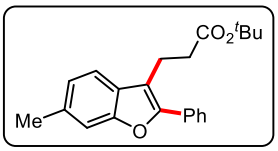
***tert*-Butyl 3-(5-methoxy-2-(4-methoxyphenyl)benzofuran-3-yl)propanoate (15ce)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.4); Brown liquid; 46 mg, 77%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.60 (t, J = 8.0 Hz, 2H), 3.16 (t, J = 8.0 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 7.00 (dd, J = 3.0, 5.9 Hz, 3H), 7.34 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0 (t), 28.0 (q, 3C), 35.2 (t), 55.3 (q), 56.0 (q), 80.6 (s), 102.1 (d), 111.3 (d), 112.4 (d), 113.2 (s), 114.2 (d, 2C), 123.8 (s), 128.3 (d, 2C), 130.7 (s), 148.7 (s), 152.1 (s), 155.8 (s), 159.6 (s), 172.3 (s) ppm; **HRMS** (ESI) calcd for $C_{23}H_{27}O_5$: 383.1853 $[M+H]^+$; found: 383.1847.



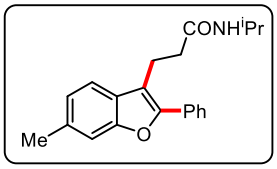
N-Isopropyl-3-(5-methoxy-2-(4-methoxyphenyl)benzofuran-3yl)propanamide(15cd): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.4); Light brown solid; 45 mg, 60%; mp 136–137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (d, J = 6.5 Hz, 6H), 2.50 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 7.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.94–4.03 (m, 1H), 5.12 (d, J = 6.6 Hz, 1H), 6.86 (dd, J = 0.6, 8.7 Hz, 1H), 6.99 (d, J = 8.4 Hz, 3H), 7.34 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.3 (t), 22.6 (q, 2C), 36.3 (t), 41.4 (d), 55.3 (q), 56.0 (q), 102.0 (d), 111.3 (d), 112.5 (d), 113.3 (s), 114.3 (d, 2C), 123.7 (s), 128.2 (d, 2C), 130.7 (s), 148.6 (s), 152.0 (s), 155.8 (s), 159.6 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{26}O_4N$: 368.1856 $[M+H]^+$; found: 368.1854.



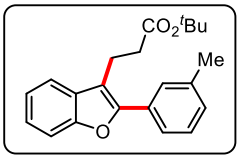
***tert*-Butyl 3-(6-methyl-2-phenylbenzofuran-3-yl)propanoate (15ie)**: Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Pale yellow liquid; 45 mg, 63%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.49 (s, 3H), 2.62–2.66 (m, 2H), 3.20–3.24 (m, 2H), 7.08 (d, J = 7.7 Hz, 1H), 7.30 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.46–7.49 (m, 3H), 7.78 (d, J = 7.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.0 (t), 21.7 (q), 28.0 (q, 3C), 35.3 (t), 80.6 (s), 111.3 (d), 114.4 (s), 119.1 (d), 123.8 (d), 126.7 (d, 2C), 127.5 (s), 128.0 (d), 128.7 (d, 2C), 131.2 (s), 134.7 (s), 150.4 (s), 154.3 (s), 172.2 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{24}O_3Na$: 359.1618 $[M+Na]^+$; found: 359.1614.



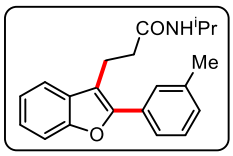
N-Isopropyl-3-(6-methyl-2-phenylbenzofuran-3-yl)propanamide (**15id**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.5); White solid; 40 mg, 59%; mp 164–165 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (d, J = 6.5 Hz, 6H), 2.47 (s, 3H), 2.52 (t, J = 7.8 Hz, 2H), 3.27 (t, J = 7.8 Hz, 2H), 3.94–4.02 (m, 1H), 5.18 (br. d, J = 6.8 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.33–7.36 (m, 1H), 7.44–7.49 (m, 3H), 7.77–7.79 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.4 (t), 21.7 (q), 22.6 (q, 2C), 36.4 (t), 41.4 (d), 111.3 (d), 114.6 (s), 119.1 (d), 123.9 (d), 126.6 (d, 2C), 127.5 (s), 128.1 (d), 128.8 (d, 2C), 131.1 (s), 134.8 (s), 150.4 (s), 154.3 (s), 171.1 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{24}O_2N$: 322.1802 $[M+H]^+$; found: 322.1802.



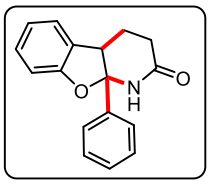
***tert*-Butyl 3-(2-(m-tolyl)benzofuran-3-yl)propanoate** (**15je**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Pale yellow liquid; 38 mg, 53%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.44 (s, 3H), 2.63–2.67 (m, 2H), 3.22–3.26 (m, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.25 (ddd, J = 1.1, 6.6, 7.5 Hz, 1H), 7.30 (td, J = 1.5, 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.58–7.62 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0 (t), 21.6 (q), 28.0 (q, 3C), 35.3 (t), 80.6 (s), 111.0 (d), 114.4 (s), 119.5 (d), 122.4 (d), 124.1 (d), 124.3 (d), 127.6 (d), 128.6 (d), 129.1 (d), 130.0 (s), 130.9 (s), 138.4 (s), 151.2 (s), 153.9 (s), 172.2 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{24}O_3Na$: 359.1618 $[M+Na]^+$; found: 359.1614.



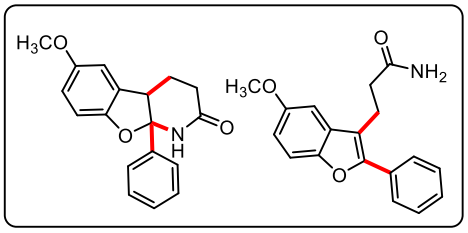
N-Isopropyl-3-(2-(m-tolyl)benzofuran-3-yl)propanamide (**15jd**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.5); White solid; 42 mg, 62%; mp 125–126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (d, J = 6.6 Hz, 6H), 2.43 (s, 3H), 2.53 (t, J = 7.7 Hz, 2H), 3.29 (t, J = 7.7 Hz, 2H), 3.94–4.03 (m, 1H), 5.17 (d, J = 6.9 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.23 (td, J = 7.4, 0.9 Hz, 1H), 7.28 (td, J = 7.4, 1.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.58–7.63 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3 (t), 21.6 (q), 22.6 (q, 2C), 36.4 (t), 41.3 (d), 111.0 (d), 114.6 (s), 119.6 (d), 122.5 (d), 123.9 (d), 124.4 (d), 127.4 (d), 128.7 (d), 129.1 (d), 130.0 (s), 130.8 (s), 138.5 (s), 151.1 (s), 153.8 (s), 171.0 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{24}O_2N$: 322.1802 $[M+H]^+$; found: 322.1801.



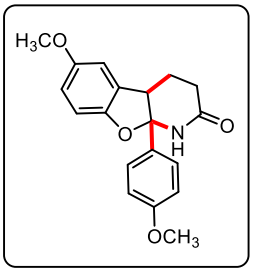
9a-Phenyl-3,4,4a,9a-tetrahydrobenzofuro[2,3-b]pyridin-2(1H)-one (**16bx**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.4); Brown gummy liquid; 48 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.18–2.33 (m, 4H), 3.68 (br. s., 1H), 6.35 (br. s., 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.29–7.35 (m, 3H), 7.49 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 22.5 (t), 27.3 (t), 47.7 (d), 98.7 (s), 110.2 (d), 121.8 (d), 123.8 (d), 125.1 (d, 2C), 126.6 (s), 128.8 (d, 2C), 129.0 (d), 129.3 (d), 142.2 (s), 158.0 (s), 173.1 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{16}O_2N$: 266.1176 $[M+H]^+$; found: 266.1172.



Inseparable mixture of 6-methoxy-9a-phenyl-3,4,4a,9a-tetrahydrobenzofuro[2,3-b]pyridin-2(1H)-one (**16ax**) **and 3-(5-methoxy-2-phenylbenzofuran-3-yl)propanamide** (**15ax**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.4); Brown solid; 42 mg, 71%; mp 103–106 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.19–2.27 (m, 2H), 2.29–2.42 (m, 2H), 2.68–2.71 (m, 0.16H), 3.18–3.21 (m, 0.16H), 3.71 (t, J = 4.5 Hz, 1H), 3.77 (s, 3H), 3.84 (s, 0.23H), 6.45 (br. s., 1H), 6.67 (d, J = 2.1 Hz, 1H), 6.76 (dd, J = 2.3, 8.7 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 6.88 (dd, J = 2.4, 8.8 Hz, 0.08H), 6.99 (d, J = 2.2 Hz, 0.09H), 7.35–7.41 (m, 3H), 7.45 (d, J = 7.7 Hz, 0.14H), 7.55 (d, J = 7.4 Hz, 2H), 7.73 (d, J = 7.8 Hz, 0.17H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 19.7 (t), 22.2 (t), 27.3 (t), 33.7 (t), 48.1 (d), 56.0 (q), 98.9 (s), 101.8 (d), 110.0 (d), 110.3 (d), 111.5 (d), 113.2 (d), 113.9 (d), 114.5 (s), 125.1 (d, 2C), 126.7 (d, 2C) 127.6 (s), 128.2 (d), 128.7 (d, 2C), 128.8 (d, 2C), 128.9 (d), 142.2 (s), 148.8 (s), 151.9 (s), 152.0 (s), 155.1 (s), 155.8 (s), 173.0 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{17}O_3NNa$: 318.1101 $[M+Na]^+$; found: 318.1095.

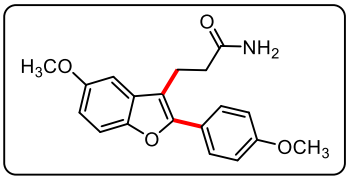


6-Methoxy-9a-(4-methoxyphenyl)-3,4,4a,9a-tetrahydrobenzofuro[2,3-b]pyridin-2(1H)-one (**16cx**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); White solid; 23 mg, 40%; mp 163–166 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.19–2.22 (m, 2H), 2.29–2.37 (m, 2H), 3.68 (t, J = 4.2 Hz,

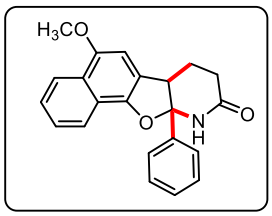


1H), 3.77 (s, 3H), 3.81 (s, 3H), 6.19 (s, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): 22.1 (t), 27.3 (t), 48.2 (d), 55.4 (q), 56.0 (q), 99.0 (s), 110.1 (d), 110.4 (d), 113.9 (d), 114.0 (d, 2C), 126.5 (d, 2C), 127.7 (s), 134.3 (s), 152.0 (s), 155.1 (s), 160.0 (s), 172.8 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{20}O_4N$: 326.1387 $[M+H]^+$; found: 326.1386.

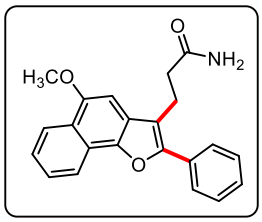
3-(5-methoxy-2-(4-methoxyphenyl)benzofuran-3-yl)propanamide (**15cx**): Isolated by column chromatography (petroleum ether/ethyl acetate = 1:1, R_f = 0.3); Pale white solid; 25 mg, 43%; mp 164–165 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 2.61 (dd, *J* = 6.6, 9.2 Hz, 2H), 3.23 (dd, *J* = 6.5, 9.3 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 5.40 (br. s., 2H), 6.86 (dd, *J* = 2.6, 8.8 Hz, 1H), 6.99–7.00 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): 19.9 (t), 35.1 (t), 55.3 (q), 56.0 (q), 101.9 (d), 111.4 (d), 112.5 (d), 113.0 (s), 114.3 (d, 2C), 123.6 (s), 128.2 (d, 2C), 130.6 (s), 148.7 (s), 152.1 (s), 155.8 (s), 159.6 (s), 174.4 (s) ppm; **HRMS** (ESI) calcd for $C_{19}H_{19}O_4NNa$: 348.1206 $[M+Na]^+$; found: 348.1203.



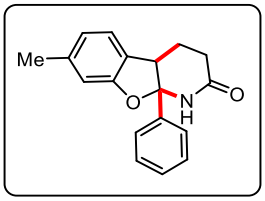
5-Methoxy-10a-phenyl-7,8,10,10a-tetrahydronaphtho[2',1':4,5]furo[2,3-b]pyridin-9(6bH)-one (**16ex**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); Brown solid; 23 mg, 39%; Decomposed at 235 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 2.28–2.34 (m, 3H), 2.38–2.42 (m, 1H), 3.91 (br. S, 1H), 3.96 (s, 3H), 6.36 (s, 1H), 6.57 (s, 1H), 7.36–7.42 (m, 3H), 7.48–7.56 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): 23.1 (t), 27.6 (t), 49.4 (d), 56.0 (q), 98.8 (s), 99.3 (d), 118.0 (s), 120.8 (s), 121.3 (d), 122.7 (d), 125.1 (d, 2C), 125.7 (d), 126.1 (s), 126.6 (d), 128.9 (d, 2C), 128.9 (d), 142.7 (s), 147.2 (s), 151.4 (s), 173.6 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{19}O_3NNa$: 368.1257 $[M+Na]^+$; found: 368.1255.



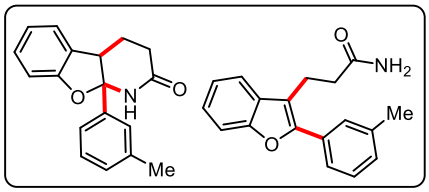
3-(5-methoxy-2-phenylnaphtho[1,2-b]furan-3-yl)propanamide (**15ex**): Isolated by column chromatography (petroleum ether/ethyl acetate = 1:1, R_f = 0.3); Brown solid; Decomposed at 173 °C; 11 mg, 20%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.66 (t, J = 7.7 Hz, 2H), 3.37 (t, J = 7.7 Hz, 2H), 4.06 (s, 3H), 5.36 (br. s., 2H), 6.95 (s, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.8 Hz, 3H), 7.60 (t, J = 7.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 2H), 8.28 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.1 (t), 35.5 (t), 56.0 (q), 95.2 (d), 116.0 (s), 119.8 (d), 121.6 (s), 123.1 (d), 124.3 (s), 124.7 (d), 126.4 (d, 2C), 127.0 (d), 127.9 (d), 128.9 (d, 2C), 128.9 (s), 131.4 (s), 144.4 (s), 150.5 (s), 152.2 (s), 174.3 (s) ppm; **HRMS** (ESI) calcd for $C_{22}H_{20}O_3N$: 346.1438 $[M+H]^+$; found: 346.1433.



7-Methyl-9a-phenyl-3,4,4a,9a-tetrahydrobenzofuro[2,3-b]pyridin-2(1H)-one (**16ix**): Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); Brown gummy liquid; 36 mg, 61%; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.19–2.24 (m, 2H), 2.25–2.33 (m, 2H), 2.35 (s, 3H), 3.70 (br. s, 1H), 6.31 (br. s., 1H), 6.75 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.35–7.41 (m, 3H), 7.55 (d, J = 7.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.6 (q), 22.6 (t), 27.3 (t), 47.5 (d), 98.9 (s), 110.9 (d), 122.5 (d), 123.4 (d), 123.5 (s), 125.1 (d, 2C), 128.8 (d, 2C), 128.9 (d), 139.6 (s), 142.3 (s), 158.3 (s), 173.1 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{18}O_2N$: 280.1332 $[M+H]^+$; found: 280.1330.

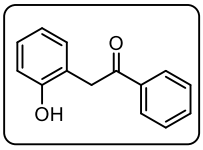


Inseparable mixture of 9a-(*m*-Tolyl)-3,4,4a,9a-tetrahydrobenzofuro[2,3-b]pyridin-2(1H)-one (**16jx**) **& 3-(2-(*m*-Tolyl)benzofuran-3-yl)propanamide** (**15jx**)**:** Isolated by column chromatography (petroleum ether/ethyl acetate = 6:4, R_f = 0.3); Yield 54%; Brown gummy liquid; 32 mg, 54%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.18–2.27 (m, 4H), 2.30 (s, 3H), 2.35 (s, 0.75H), 2.67 (t, J = 8.2 Hz, 0.45H), 3.18 (t, J = 7.9 Hz, 0.45H), 3.68 (br. s., 1H), 6.52 (br. s., 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.92 (t, J = 7.3 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1.35H), 7.16–7.24 (m, 3.11H), 7.29 (d, J = 8.4 Hz, 2.44H), 7.42 (d, J = 8.0 Hz, 0.31H), 7.48–7.53 (m, 0.83H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.7 (t), 21.5 (q), 21.6 (q), 22.3 (t), 27.3 (t), 33.8 (t), 47.7 (d), 98.8 (s), 110.3 (d), 111.1 (d), 114.1 (s), 119.4 (d), 121.8 (d), 122.2 (d),

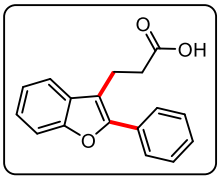


122.5 (d), 123.8 (d), 124.0 (d), 124.4 (d), 125.8 (d), 126.6 (s), 127.6 (d), 128.7 (d), 128.8 (d), 129.2 (d), 129.3 (d), 129.7 (d), 129.9 (s), 130.8 (s), 138.5 (s), 138.7 (s), 142.1 (s), 151.4 (s), 153.9 (s), 158.1 (s), 173.4 (s), 176.6 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{18}O_2N$: 280.1332 $[M+H]^+$; found: 380.1330.

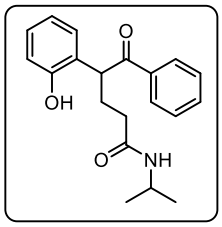
2-(2-Hydroxyphenyl)-1-phenylethan-1-one (**17**): Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Light yellow solid; 42 mg, 88%; mp 107–108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.28 (s, 2H), 6.87 (td, *J* = 1.2, 7.4 Hz, 1H), 6.95 (dd, *J* = 1.2, 8.6 Hz, 1H), 7.15–7.18 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.61 (tt, *J* = 1.2, 7.3 Hz, 1H), 7.69 (s, 1H), 8.08–8.10 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.1 (t), 117.7 (d), 120.8 (d), 121.0 (s), 128.8 (d, 2C), 129.1 (d, 3C), 131.0 (d), 134.1 (d), 135.8 (s), 155.6 (s), 201.2 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{12}O_2Na$: 235.0730 $[M+Na]^+$; found: 235.0728.



3-(2-Phenylbenzofuran-3-yl)propanoic acid (**15$_a$**): Isolated by column chromatography (petroleum ether/ethyl acetate = 8:2, R_f = 0.3); Light brown solid; mp 104–105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): 2.83 (t, *J* = 8.3 Hz, 2H), 3.33 (t, *J* = 8.0 Hz, 2H), 7.29–7.31 (m, 1H), 7.33–7.36 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.51–7.55 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): 19.6 (t), 33.7 (t), 111.2 (d), 113.9 (s), 119.3 (d), 122.6 (d), 124.6 (d), 126.9 (d, 2C), 128.4 (d), 128.8 (d, 2C), 129.8 (s), 130.9 (s), 151.3 (s), 153.9 (s), 178.3 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{14}O_3Na$: 289.0835 $[M+Na]^+$; found: 289.0833.



4-(2-Hydroxyphenyl)-N-isopropyl-5-oxo-5-phenylpentanamide (**14b**): Isolated by column chromatography (petroleum ether/ethyl acetate = 7:3, R_f = 0.3); Yield 85%; Light brown solid; 62 mg, 85%; mp 164–165 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 2.07–2.11 (m, 1H), 2.14–2.21 (m, 2H), 2.27–2.34 (m, 1H), 4.05–4.14 (m, 1H), 5.10 (dd, *J* = 5.7, 8.5 Hz, 1H), 5.62 (d, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 7.07–7.11 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 9.70 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.5 (q, 2C), 28.5 (t), 33.1 (t), 41.9 (d), 45.3 (d),



118.5 (d), 120.7 (d), 125.6 (s), 127.8 (d), 128.5 (d, 2C), 128.8 (d, 3C), 133.1 (d), 135.8 (s), 154.7 (s), 173.5 (s), 200.3 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{23}O_3NNa$: 348.1570 $[M+Na]^+$; found: 348.1564.

1. Rao, G. K.; Venugopala, K. N.; Pai, P. N. S. *j. pharmacol. Taxicol.* **2007**, *2*, 481–488.
2. Koca, M.; Servi, S.; Kirilmis, C.; Ahmedzade, M.; Kazaz, C.; Ozbek, B.; Otuk, G. *Eur. J. Med. Chem.* **2005**, *40*, 1351–1358.
3. Dawood, K. M.; Abdel-Gawad, H.; Rageb, E. A.; Ellithey, M.; Mohamed, H. A. *Bioorg. Med. Chem*, **2006**, *14*, 3672–3680.
4. Pieters, L.; Dyck, S. V.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemiere, G. *J. Med. Chem.* **1999**, *42*, 5475–5481.
5. Tsujihara, K.; Hongu, M.; Saito, K.; Kawanishi, H.; Kuriyama, K.; Matsumoto, M.; Oku, A.; Ueta, K.; Tsuda, M.; Saito, A. *J. Med. Chem.* **1999**, *42*, 5311–5324.
6. (a) Talapatra, B.; Ray, T.; Talapatra, S. K. *Indian J. Chem*, **1976**, *14b*, 613–614. (b) Schneiders, G. E.; Stevenson, R. *J. Org. Chem*, **1979**, *44*, 4710–4711. (c) More, K. R.; Mali, R. S. *synth. Commun.* **2017**, *47*, 788–792.
7. Lin, S. Y.; Chen, C. L.; Lee, Y. J. *J. Org. Chem*, **2003**, *68*, 2968–2971.
8. Liu, Y.; Kubo, M.; Fukuyama, Y.; *J. Nat. Prod.* **2012**, *75*, 2152–2157.
9. Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Soest, R. V.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321–324.
10. Vanheyst, M. D.; Wright, D. L.; *Eur. J. Org. Chem.* **2015**, 1387–1401.
11. (a) Druzgala, P.; Milner, P. G. Int. publ. WO 2001/29018 A2. **2001**. (b) Druzgala, P.; Milner, P. G. U. S. Pat. Appl. Publ. US 2002/0193428 A1. **2002**. (c) Druzgala, P. U. S. Pat. Appl. Publ. US 6,710,070 B2. **2004**. (d) Druzgala, P.; Tien, J. J.; Cooper, A.; Becker, C. Int. publ. WO 2007/011835 A2. **2007**.
12. Druzgala, P. Int. publ. WO 2014/143625 A1. **2014**.
13. Yamamato, T.; Moriwaki, Y.; Takahashi, S.; Tsutsumi, Z.; Yamakita, J.; Higashino, K. *Metabolism* **1997**, *46*, 1473–1476.
14. Hivarekar, R. R.; Deshmukh, S. S.; Tripathy, N. K. *Org. Process. Res. Dev.* **2012**, *16*, 677–681.
15. He, D.; Qiu, L.; Yuan, J.; Zhang, Z.; Li, Y.; Zou, Y. *Polymer* **2017**, *114*, 348–354.
16. Niu, G.; Liu, W.; Wu, J.; Zhou, B.; Chen, J.; Zhang, H.; Ge, J.; Wang, Y.; Xu, H.; Wang, P. *J. Org. Chem*. **2015**, *80*, 3170–3175.

17. Lee, C. W.; Yook, K. S.; Lee, J. Y. *Org. Electron.* **2013**, *14*, 1009–1014.
18. Rindhe, S. S.; Rode, M. A.; Karale, B. K. *Indian J. Pharm. Sci.* **2010**, *72*, 231–235.
19. (a) Wurtz, A. *Ann. Chim, Phys.* **1855**, *44*, 275–312. (b) Wurtz, A. *Ann. Chim, Phys.* **1855**, *96*, 364–375.
20. Fittig, R. *Justus Liebigs Ann. Chem.* **1862**, *121*, 361–365.
21. Glaser, C.; *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424.
22. Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1882**, **15**, 50–56.
23. Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.***1901**, *34*, 2174–2185.
24. Bennett, G. M.; Turner, E. E. *J. Chem. Soc. Trans.* **1914**, *105*, 1057–1062.
25. Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 504–507.
26. (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505–1508. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581–584.
27. (a) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.***1974**, *96*, 1133–1136. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.
28. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
29. Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.***1972**, *94*, 9268–9269.
30. (a) Negishi, E.; King, A. O., Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821–1823. (b) King, A. O., Okukado, N.; Negishi, E. *J. Chem. Soc. Chem. Commun.* **1977**, 683–684.
31. Milstein, D.; Stille, J. k. *J. Am. Chem. Soc.***1978**, *100*, 3636–3638.
32. Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866–867.
33. (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.
34. Lewis, L. N.; smith, J. F.; *J. Am. Chem. Soc.***1986**, *108*, 2728–2735.
35. (a) Druzgala, P.; Milner, P. G. Int. publ. WO 01/29018 A2. **2001**. (b) Druzgala, P.; Milner, P. G. U. S. Pat. Appl. Publ. US 2002/0193428 A1. **2002**. (c) Druzgala, P. U. S. Pat. Appl. Publ. US 6,710,070 B2. **2004**. (d) Druzgala, P.; Tien, J. J.; Cooper, A.; Becker, C. Int. publ. WO 2007/011835 A2. **2007**.
36. Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708.

37. Carrer, A.; Brinet, D.; Florent, J.; Rousselle, P. Bertounesque, E. *J. Org. Chem.* **2012**, *77*, 1316–1327.
38. Zhao, J.; Fang, H.; Xie, C.; Han, J.; Li, G.; Pan, Y. *Asian J. Org. Chem*. **2013**, *2*, 1044–1047.
39. Bachelet, J. P.; Demerseman, P.; Royer, R.; Cavier, R.; Lemoine, J. *Eur. J. Med. Chem*. **1982**, *17*, 323−325.
40. Simon, M. O.; Genet, J. P.; and Darses, S. *J. Org. Chem.* **2010**, *75*, 208–210.
41. Martinez, R.; Simon, M.; Chevalier, R.; Pautigny, C.; Genet, J.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887–7895.
42. (a) Flegeau, E. F.; Bruneau, C.; Dixneuf P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170. (b) Lafrance M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.
43. Rouquet, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201–2208.
44. (a) Antczak, C.; Shum, D.; Bassit, B.; Frattini, M. G.; Li, Y. M.; de Stanchina, E.; Scheinberg, D. A.; Djaballah, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4528–4532. (b) Gong, W. C.; Liu, Y.; Zhang, J.; Jiao, Y. D.; Xue, J. J.; Li, Y. *Chem. Asian J.* **2013**, *8*, 546–551.
45. (a) Patrick, S. R.; Boogaerts, I. I. F.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Beilstein J. Org. Chem.* **2011**; 892–896. (b) Truong, T.; Daugulis, O. *Chem. Sci.* **2013**, *4*, 531–535.
46. (a) Cherian, A. E.; Domski, G. J.; Rose, J. M.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett.* **2005**, *7*, 5135-5137. (b) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19-22. (c) Rueping, M.; Bootwicha, T.; Sugiono, E. *Adv. Synth. Catal* **2010**, *352*, 2961-2965. (d) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6410-6413. (e) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 4451-4454. (f) Pan, S. G.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474-17477. (g) Lee, P. S.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 1240-1244.
47. (a) Wang, B.; Lee, C. W.; Cai, T. X.; Park, S. E. *Bull. Korean Chem. Soc.* **2001**, *22*, 1056-1058. (b) Yadav, G. D.; Doshi, N. S. *Org. Process Res. Dev.* **2002**, *6*, 263-272. (c) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem. Int. Ed.* **2013**,

52, 3977-3980. (d) Aslam, W.; Siddiqui, M. A. B.; Jermy, B. R.; Aitani, A.; Cejka, J.; Al-Khattaf, S. *Catal. Today* **2014**, *227*, 187-197.

48. Asao, N.; Aikawa, H. *J. Org. Chem.* 2**006**, *71*, 5249–5253.
49. a) Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, *64*, 5974–5981. b) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* 2**011**, *13*, 2372–2375.
50. (a) Lanke, V.; Bettadapur, K. R.; Prabhu, K. R. *Org. Lett.* **2016**, *18*, 5496–5499. b) Wong, M. Y.; Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 442–445. c) Wang, L.; Wolfram, R.; Lygin, A. V.; Ackermann, L. *Org. Lett.* **2012**, *14*, 728–731.
51. (a) Iitsuka, T.; Schaal, P.; Hirano, K.; Satoh, T.; Bolm, C.; Miura M. *J. Org. Chem.* **2013**, *78*, 7216–7222. b) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T. *Org. Lett.* **2011**, 13, 706–708. c) Padala, K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134–1137.
52. Kommagalla, Y.; mullapudi, V. B.; Francis, F.; Ramana, C. V. *Catal. Sci. Technol.,* **2015**, 5, 114–117.
53. (a) Robinson, S. D.; Uttley, M. F. *J. Chem. Soc. Dalton Trans.* **1973**, 1912–1920. (b) Moore, D. S.; Robinson, S. D. *Inorg. Chem.* **1979**, *18*, 2307–2309. (c) Jardine, F. H. *Progress in Inorg. Chem.* **1983**, *31*, 265–370.
54. (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (b) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749–823. (c) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170. (d) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886–896. (e) Fabre, I.; von Wolff, N.; Le Duc, G.; Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *Chem. Eur. J.* **2013**, *19*, 7595–7604.
55. (a) Padala, K.; Jeganmohan, M. *Org. Lett.* **2012**, 14, 1134–1137. (b) Mu, D.; Wang, X.; Chen, G.; He, G. *J. Org. Chem.* **2017**, *82*, 4497–4503. (c) Lv, J.; Wang, B.; Yuan, K.; Wang, Y.; Jia, Y. *Org. Lett.* **2017**, 19, 3664–3667. (d) Liu, X.; Park, H.; Hu, J.; Hu, Y.; Zhang, Q.; Wang, B.; Sun, B.; yeung, K.; Zhang, F.; Yu, J. *J. Am. Chem. Soc.* **2017**, *139*, 888–896.

56. Ando, K.; Kawamura, Y.; Akai, Y.; Kunitomo, J.; Yokomizo, T.; Yamashita, M.; Ohta, S.; Ohishi, T.; Ohishi, Y. *Org. Biomol. Chem.* **2008**, *6*, 296–307

57. (a) Sato, S.; Matsuda, I.; Izumi, Y. *Chem. Lett.* **1985**, 1875–1878. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S.; *Tetrahedron*, **1996**, *52*, 8001–8062. (c) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741–6743.

58. (a) Bisagni, E.; Royer, R. *C. R. Acad. Sci.* **1960**, *250*, 3339–3341. (b) Takagi, K.; Hubertha, M.; Royer, R. *C. R. Acad. Sc.* **1965**, *260*, 5302–5305. (c) Astoin, J.; Demerseman, P.; Riveron, A.; Royer, R. *J. Heterocycl. Chem.* **1977**, *14*, 867–869. (d) Astoin, J.; Demerseman, P.; Royer, R. *C. R. Acad. Sc.* **1977**, *284*, 249–251. (e) Guillaumel, J.; Boccara, N.; Demerseman, P.; Royer, R.; Bideau, J. P.; Cotrait, M.; Platzer, N. *J. Heterocycl. Chem.* **1990**, *27*, 605–614.

59. (a) Barbier, M. *Liebigs Ann. Chem.* **1991**, 393–416. (b) Barbier, M. *Org. Prep. Proced. Int.* **1991**, *23*, 676–679. (c) Barbier, M. *Syn. Commun.* **1991**, *21*, 2317–2327.

60. Kang, B.; Lee, M. H.; Kim, M.; Hwang, J.; Kim, H. B.; Chi, D. Y. *J. Org. Chem.* **2015**, *80*, 8254–8261.

61. Bowman, R. K.; Bullock, K. M.; Copley, R. C. B.; Deschamps, N. M.; McClure, M. S.; Powers, J. D.; Wolters, A. M.; Wu, L.; Xie, S. *J. Org. Chem.* **2015**, *80*, 9610–9619.

62. (a) Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3775–3782. (b) Jana, S.; Rainier, J. D. *Org. Lett.* **2013**, *15*, 4426–4429.

63. (a) Ledoussal, B.; Gorgues, A.; Lecoq, A. *J. Chem. Soc. Chem. Commun.* **1986**, 171–172. (b) Ledoussal, B.; Gorgues, A.; Lecoq, A. *Tetrahedron* **1987**, *43*, 5841–5852. (c) Katritzky, A. R.; Zhang, Z. X.; Lan, X. F.; Lang, H. Y. *J. Org. Chem.* **1994**, *59*, 1900–1903. (d) Lattanzi, A.; Senatore, A.; Massa, A.; Scettri, A. *J. Org. Chem.* **2003**, *68*, 3691–3694. (e) Do, Y. S.; Sun, R.; Kim, H. J.; Yeo, J. E.; Bae, S. H.; Koo, S. *J. Org. Chem.* **2009**, *74*, 917–920. (f) Ruan, L. B.; Shi, M.; Li, N. A.; Ding, X.; Yang, F.; Tang, J. *Org. Lett.* **2014**, *16*, 733–735.

CHAPTER II

Total Synthesis of Propolisbenzofuran B

2.1 Introduction:

Nature is amazing and inspirational and exploring it is a continuous challenge. The process of understanding, mimicking and competing with nature has paved the path for scientific development since the beginning of mankind. This is also true for chemists. Chemists have always been fascinated to explore and understand natural phenomena at the molecular level. For synthetic chemists, it was nature's molecules aiding the treatment of the human ailments that have inspired the unraveling of their molecular structures and the possibility of their synthesis in the lab. These are natural products and the program that aims to synthesize them was total synthesis and the complementary area that tries to understand how they are synthesized inside the cells is biosynthesis. The molecular complexity of these natural products manifest nature's creativity and the diverse biological activities displayed by these natural products demonstrate its foresight for the wellbeing of all living organisms. Till date, a large number of natural products have been isolated and characterized, yet, there are millions and millions of natural products that present a challenge to chemists to unravel their existence.

Until recently, selected plants and herbs were employed for the treatment of human illnesses. For instance, mandrake plant extracts were used for acute pain relief, endive plant roots for the treatment of gall bladder disorders, turmeric for blood clotting, raw garlic for circulatory disorders etc. Even today, such methods are practiced in Ayurveda medicines, which occupy a unique place in Indian traditional medicine. In the olden days, crude plant extracts obtained following defined indigenous undisclosed protocols were used to treat disorders without knowing the nature of the components of the extracts. The natural product chemistry was revolutionized with the discovery of an opiate drug called morphine by the German chemist Sertürner in the year 1806. Since then, the terminology of natural products was determined by identifying the active component from the crude extracts used in the traditional medicine and the elucidation of their structures. This had sparked the association of natural products with the progress of organic chemistry, with the efforts of our early chemists to decipher the plant extracts that are used in traditional medicine. Seminally, the accidental synthesis of urea (discovered in 1799) in 1828 by Wöhler and his popular statement "*synthesizing urea without thereby needing to have*

kidneys, or anyhow, an animal, be it human or dog" has laid the foundations for organic synthesis, in general and total synthesis, in particular. With time, millions of complex natural products have been identified and indeed these natural products have played a major role in sophistication of organic synthesis on one hand and the advancement of modern drug discovery – almost one third of current drugs are natural products or their derivatives (or mimics) – on the other.

The important biological activities and the fascinating architectures of natural products has attracted the attention of organic chemists ever since the continuous story of organic synthesis got its start and is continuing to have profound influence on the development of modern synthetic tools and on understanding the mechanism of molecular synthesis. Especially due to their availability in insufficiently small quantities, the synthesis of these natural products has always been considered as an important exercise for establishing their structures in general and for the development of new drug candidates in particular. The unprecedented molecular scaffolds that are often displayed by the newly isolated natural products have always challenged the synthetic chemist to develop new synthetic methods and innovative strategic concepts. Indeed, this has created the foundations of the work that has been embodied in this part of the thesis that deals with the total synthesis of Propolisbenzofuran B that was isolated by Kadota and co-workers from the honeybee propolis resin that displayed the unprecedented dihydrodibenzofuran scaffold with promising anticancer activity.

2.2 Isolation and structural elucidation of Propolisbenzofuran B:

Propolis is a resinous substance collected by honeybees from plants. In ancient days, it was extensively used in traditional medicines. It has a wide range of biological properties such as anticancer, anti-inflammatory, antifungal, antibacterial and antioxidant. It is widely used in food and health drinks to prevent diseases such as heart diseases, diabetes, inflammation and cancer. The importance of propolis in traditional medicine and its extensive use in food and health drinks attracted the attention of chemists with regard to the identification of the active components of this resinous substance. Further, it was observed that propolis collected from temperate zones differs in the constituents to that of tropical zones due to the difference in vegetation but exhibits similar biological activities.

In 2000, the group led by Kadota reported the isolation and structure elucidation of two novel benzofuran derivatives and named them as Propolisbenzofuran A and Propolisbenzofuran B.[1] Both Propolisbenzofurans A and B exhibit cytotoxicity towards murine colon 26-L5 carcinoma cells with ED_{50} 12.4 and 13.7 μg/ml respectively and also towards human HT-1080 fibrosarcomacells with ED_{50} 13.9 and 43.2 μg/ml respectively. The structures of both compounds are quite similar with Propolisbenzofuran B having one carbon atom less than Propolisbenzofuran A. Propolisbenzofuran B is a tricyclic structure with two continuous stereocentres having *trans* stereochemistry. This has been elucidated with the help of extensive NMR studies. For example, in the ^{1}H NMR spectrum of Propolisbenzofuran B, the hydroxyl proton signal appeared at δ 11.81 ppm. The aromatic ring protons resonate at δ 6.13 and 8.21 ppm as singlets indicating their *para* positioning. The acetoxy methyl and acetyl methyl groups resonated at δ 2.03 and 2.75 ppm as singlets. The other aromatic protons appeared at δ 7.02 (d, J = 2.0 Hz), 6.89 (d, J = 8.0 Hz), 6.87 (dd, J = 2.0, 8.0 Hz) ppm indicates the presence of another 1,3,4 trisubstituted aromatic ring. Further, two vicinal methines (-CH-) appeared at δ 2.94 (m) and 4.33 (d, J = 9.9 Hz) and two methylenes (-CH_2-) at δ 2.86 (m, 2H), 4.05 (m, 2H) and a methoxy at δ 3.73 ppm. In the ^{13}C NMR spectrum, two quaternary carbon signals at δ 151.7 and 135.0 ppm indicate the presence of tetrasubstituted olefin. The keto carbonyl at δ 187.5 has HMBC correlation with methylene protons which indicates the presence of carbonyl at C-10. Further, the H-13 proton showed HMBC correlation with C3 and C2 that established the connection between them. Based on the coupling constant of proton H-C13 (J = 9.9 Hz), an equatorial disposition of the aryl ring at C13 with the CH_2OAc at C12 was inferred. The methyl protons at δ 2.71 (C9) and the aromatic proton at δ 6.92 (C7) showed HMBC correlation with a keto carbonyl at δ 204.5 and a quaternary aromatic carbon at δ 116.3 ppm which indicates the presence of the methyl ketone group attached to a 1,2,4,5-tetrasubstituted aryl ring. Thus, from the connectivity established from the ^{1}H and ^{13}C NMR spectra, the following structure has been proposed for Propolisbenzofuran B. The proposed tricyclic structure of Propolisbenzofuran B is a unique one when the substitution pattern is considered and importantly, this scaffold has been rarely explored in drug discovery. This has prompted us to develop simple strategies for constructing this tricyclic core having a substitution pattern that the natural product displayed on its cyclohexane

core, with a keen interest of developing and deploying catalytic methods at multiple stages. In the following sections, the salient features of the first total synthesis of Propolisbenzofuran B that appeared recently will be described first. Next, we will present various methods that have been documented for the construction of the dihydrodibenzofuran core and also the details of the intramolecular olefin hydroacylation reaction that we have chosen as a key skeletal construct as well as a comprehensive compilation of the reports on the same.

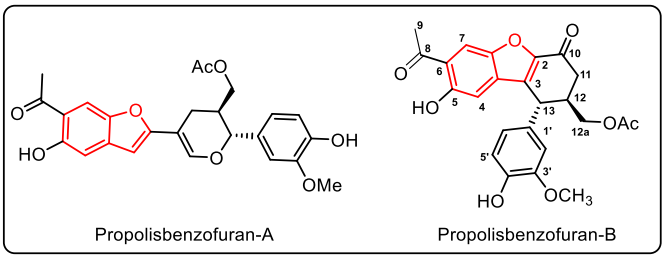
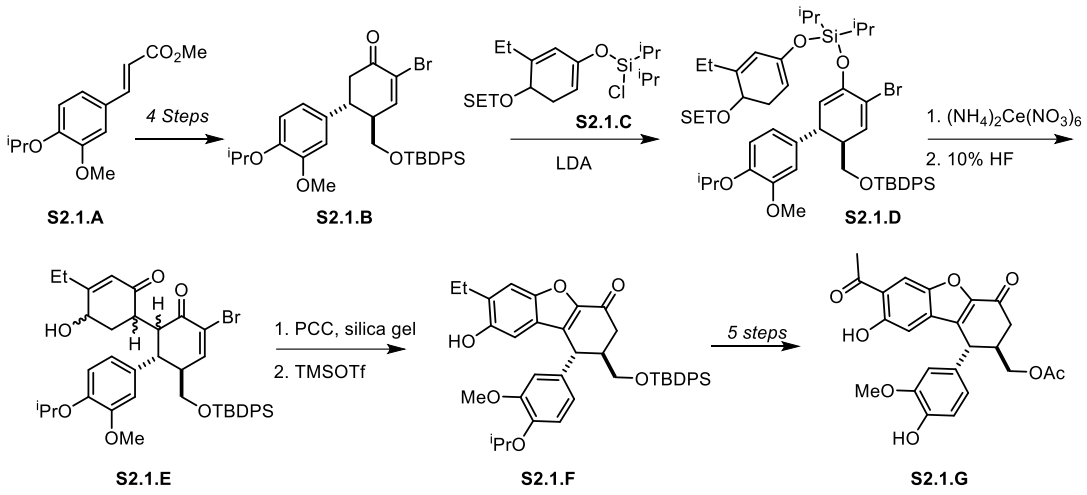


Figure F2.1: *Structures of Propolisbenzofurans A and B*

2.3: First total synthesis of Propolisbenzofuran B:

In 2014, Regan J. Thomson's group from North Western University reported the first total synthesis of Propolisbenzofuran B. The documented synthesis is highly convergent and features the annulation of a benzofuran ring on a prefunctionalized cyclohexenone *via* a silicon-tether controlled oxidative ketone–ketone cross-coupling and a novel benzofuran-generating cascade reaction. As shown in Scheme S2.1, the synthesis commenced with cheap and commercially available vanillin that was subjected to *O*-isopropyl protection followed by the Horner-Wadsworth-Emmons reaction using diethyl phosphonoacetate, which results in the formation of compound **S2.1.A**. The compound **S2.1.A** was then subjected to a four step chemical transformations to arrive at the key enone intermediate **S2.1.B**. This compound, in the presence of LDA, generates lithium enolate, which then reacts with chloroenolsilane **S2.1.C** resulting in a silyl bis-enol ether **S2.1.D**. The compound **S2.1.D** undergoes an intramolecular (silicon–tether controlled) oxidative ketone-ketone cross coupling in the presence of ceric ammonium nitrate (CAN) resulting in 1,4-diketone **S2.1.E**. This intermediate was subjected for a cascade process that generates the benzofuran structural core, thus completing the synthesis of the core structure of the natural product **S2.1.F**. From this advanced intermediate, in another five

steps comprising of a couple of protection and deprotection events, benzylic CH_2-oxidation to install the acyl group and final hydrolysis of isopropyl ethers complete the total synthesis of the natural product in 17 steps (Scheme S2.1).[2]



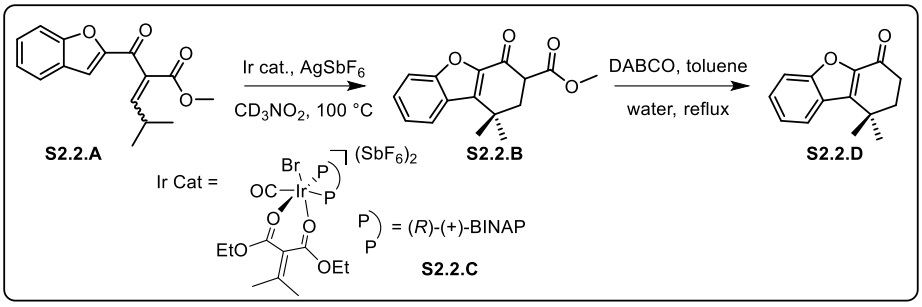
Scheme S2.1: *Thomson approach for total synthesis of propolisbenzofuran B*

Coming to Thomson's approach, one of the concerns is the installation of the benzofuran core and the complexity of the strategy that has been employed. In addition, there are several drawbacks, such as prolonged heating in several cases in the synthetic sequence. For example, the Diels-Alder reaction requires heating at 90 °C for 3 days. Even the *O*-isopropylation reactions (for the synthesis of the starting substrate **S2.1A** and for conversion of **S2.1E** to **S2.1F**) have been carried out at reflux for 4 days. In addition, on several instances, the reagents/substrates employed and the chemistry involved are more sophisticated/require special handling. As we have presented in the main introduction, benzofuran is one of the simplest cores to be constructed. This has prompted us to focus mainly on the annulation of the cyclohexanone core to a benzofuran ring in our retrosynthetic design. In the following section, we will describe some of the methods that have been documented for this purpose.

2.4 Literature reported strategies for the synthesis of 2,3-dihydrodibenzo[b,d]furan-4(1H)-one core:

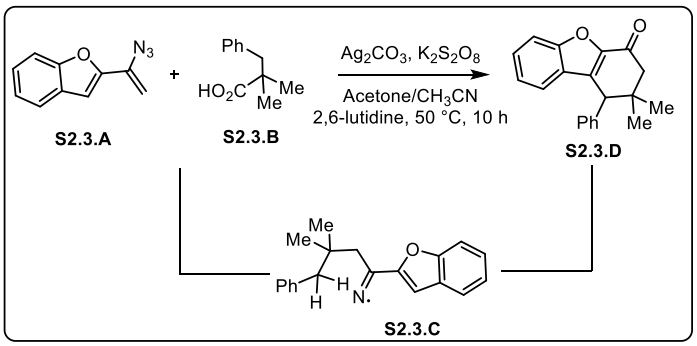
Eisenberg *et al.* reported a novel strategy for the construction of a 1,1-dimethyl-2,3-dihydrodibenzo[b,d]furan-4(1H)-one core. The 2-substituted benzofuryl enones **S2.2.A** in

presence of iridium catalyst **S2.2.C** undergoes 1,2-H shift followed by Friedal-Crafts alkylation resulting in **S2.2.B** which upon decarboxylation leads to the benzofuran fused cyclohexanone ring systems (Scheme S2.2).



Scheme S2.2: *Eisenberg approach for construction of cyclohexanone ring*.
(Vaidya, T.; Manbeck, G. F.; Chen, S.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc*. **2011**, *133*, 3300–3303)

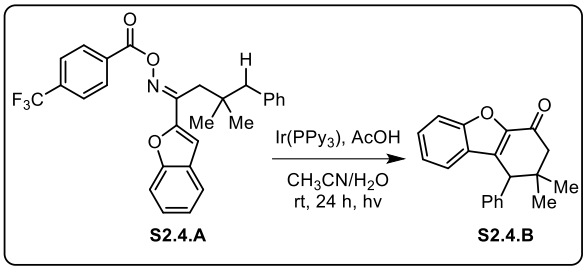
Recently, Nevado and coworkers revealed a unique approach for the synthesis of the benzofuran conjugated cyclohexanone ring system by using the radical mediated stereoselective C–H functionalization strategy. In this approach, aliphatic acids **S2.3.B** in the presence of Ag_2CO_3 and $K_2S_2O_8$ undergo decarboxylation generating radicals, which then undergo radical mediated SP^3 C–H activation with vinyl azides **S2.3.A**. The intermediate **S2.3.C** undergo a 1,5-H shift, radical mediated SP^2 C–H functionalization followed by imine hydrolysis, arriving at the target product (Scheme S2.3).



Scheme S2.3: *Nevado's approach for construction of cyclohexanone ring.*
(Shu, W.; Lorente, A.; Bengoa, E. G.; Nevado, C. *Nat. Commun.* **2017**, *8*, 13832)

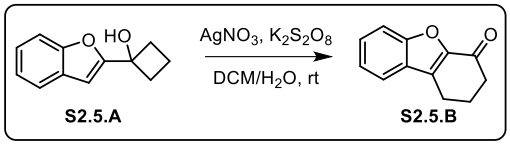
In another report, the same group documented a visible light mediated C(SP^2)–H functionalization strategy for the synthesis of benzofuran fused cyclohexanone ring systems. Exposure of a suitably functionalized benzofuranyl oxime **S2.4.A** to visible light in the presence of Ir(III) catalyst results in N–O cleavage to form the iminyl radical, which then undergoes 1,5-H shift followed by homolytic aromatic substitution (SP^2 C–H

functionalization) and imine hydrolysis in the presence of H_2O/AcOH to give the desired product (Scheme S2.4).



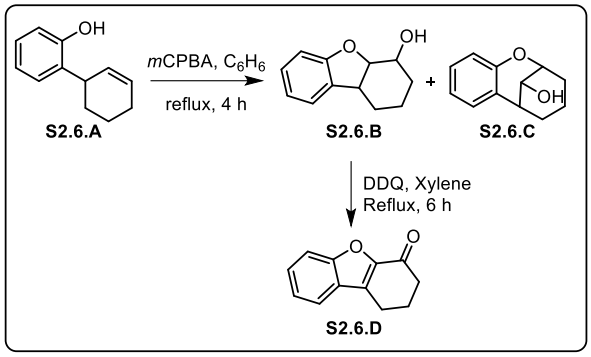
Scheme S2.4: *Light mediated synthesis of cyclohexanone ring*
(Shu, W.; Nevado, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 1881–1884)

Zhu and coworkers reported a simple and efficient method for the construction of the 2,3-dihydrodibenzo[b,d]furan-4(1H)-one core employing an intramolecular radical addition to the benzofuran ring. The benzofuranlycyclobutanol **S2.5.A** when treated with $AgNO_3$ and oxone, initially forms a cyclobutoxy radical, which then undergoes ring opening followed by intramolecular radical addition to arrive at the desired target (Scheme S2.5).



Scheme S2.5: *Zhu approach for construction of the cyclohexanone ring*
(Yu, J.; Zhao, H.; Liang, S.; Bao, X.; Zhu, C. *Org. Biomol. Chem.* **2015**, *13*, 7924–7927)

Majumdar and coworkers reported a simple and practical approach for the synthesis of the 2,3-dihydrodibenzo[*b*,*d*]furan-4(1H)-one structural core using the expoxidation/oxidation reactions. The 2-cyclohexenyl phenol **S2.6.A** on reaction with *m*-chloroperoxybenzoic acid results in formation of hexahydrodibenzofurans **S2.6.B** along with the endocyclic product **S2.6.C**. Further, the product **S2.6.B** on reaction with DDQ in refluxing xylene for 6 h results in the desired cyclohexanone annulated benzofuran derivative (Scheme S2.6).

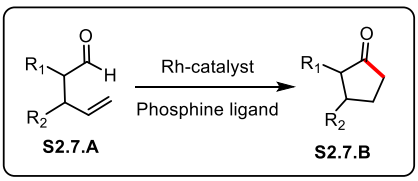


Scheme S2.6: *Majumdar approach for construction of cyclohexanone ring*
(Majumdar, K. C.; Chatterjee, P.; Kundu, A. K. *Synth. Commun.* **1996**, *26*, 3331–3344)

2.5 Intramolecular Olefin Hydroacylation

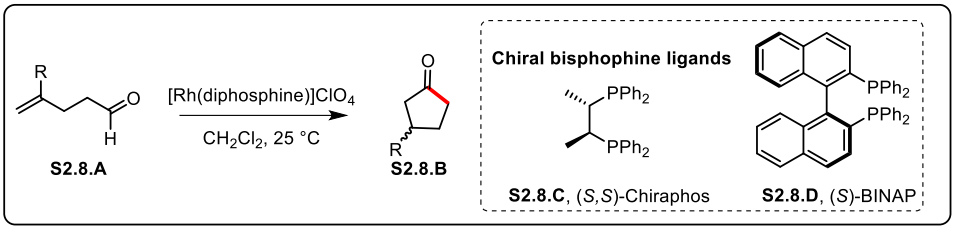
The hydroacylation reaction involves the addition of an acyl group and a hydrogen atom across the C–C multiple bonds. In 1972, Nakamura and coworkers revealed the first report on intramolecular olefin hydroacylation by employing pent-4-enal systems in the presence of Wilkinson's catalyst resulting in the synthesis of cyclopentanone derivatives.[3] Following Nakamura's report, immense contributions from various groups culminated in the deployment of various other transition metal complexes such as iridium, ruthenium, cobalt, nickle and even NHC catalysts for both intramolecular as well as intermolecular hydroacylation reactions. Indeed, asymmetric hydroacylation has been well explored in the context of synthesis of natural products and pharmaceutically important building blocks. In the following section selected literature reports on intramolecular hydroacylation will be discussed.

Larock and coworkers revealed the rhodium (I) catalyzed intramolecular hydroacylation of unsaturated aldehydes resulting in the cyclopentanone derivatives. The reaction was explored using 3 different types of rhodium catalysts that were synthesized by employing tri-*p*-tolylphosphine, tri-*p*-anisylphosphine or tris(*p*-dimethylaminophenyl) phosphine ligands with chlorobis(cyclooctene)rhodium (I) in ethylene-saturated methylene chloride (Scheme S2.7).



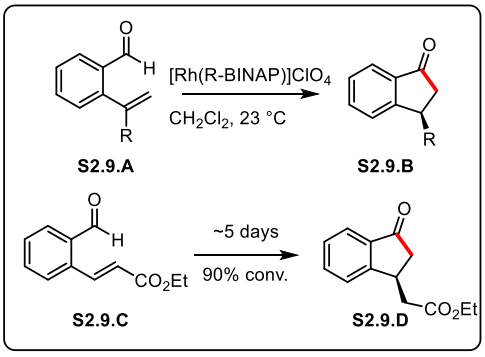
Scheme S2.7: *Larock approach for intramolecular hydroacylation*
(Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190–197)

Bosnich and coworkers have extensively worked on the asymmetric intramolecular olefin hydroacylations to prepare the chiral 3-substituted cyclopentanones starting with 4 substituted 4-pentenals and employing rhodium catalysts in presence of C2-symmetric bisphosphine ligands such as (*S*,*S*)-Chiraphos (**S2.8.C**) or (*S*)-BINAP (**S2.8.D**). Later the same group has reported hydroacylation reaction using [Rh(*S*,*S*-Me-duphos)(acetone)$_2$]PF$_6$ catalyst (Scheme S2.8).



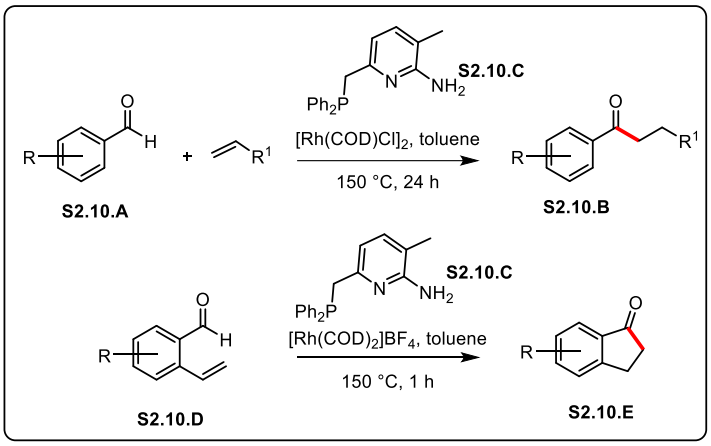
Scheme S2.8: *Bosnich approach for Asymmetric hydroacylation*
(Barnhart, R. W.; Wang, X. Q.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821–1830. Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Chem. Commun.* **1997**, 589–590)

Andrew and coworkers revealed the hydroacylation of 2-vinylbenzaldehydes in the presence of the chiral rhodium catalyst [Rh(R-BINAP)]ClO$_4$ resulting in the formation of 3-substituted indanones **S2.9.B** with excellent yields and ee. However, it was observed that *β*–substituted 2-vinyl benzoaldehydes were not a suitable substrates in the current transformation where the ethyl (*E*)-3-(2-formylphenyl), **S2.9.C** acrylate took 5 days for 90% conversion of the starting material to the desired product (Scheme S2.9).



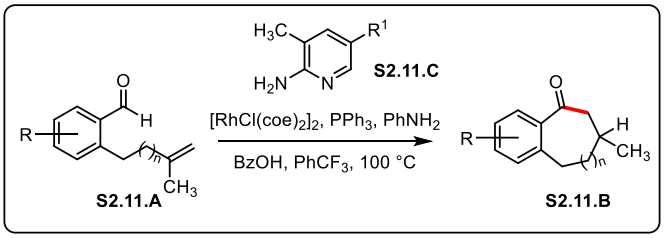
Scheme S2.9: *Asymmetric hydroacylation for chiral indanones*
(Kundu, K.; McCullagh, J. V.; Morehead, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 16042–16043)

Breit and coworkers reported a novel approach for the inter and intramolecular hydroacylation reaction catalyzed by rhodium in the presence of bifunctional P,N ligands. The substituted aldehyde **S2.10.A** on reaction with olefin in the presence of the $[Rh(COD)Cl]_2$ catalyst and bifunctional P,N ligands **S2.10.C** in toluene at 150 °C results in the formation of the intermolecular hydracylation product. Similarly, the substrate **S2.10.D** in the presence of $[Rh(COD)_2]BF_4$ under similar conditions results in the intramolecular hydroacylation product **S2.10.E** in excellent yields (Scheme S2.10).



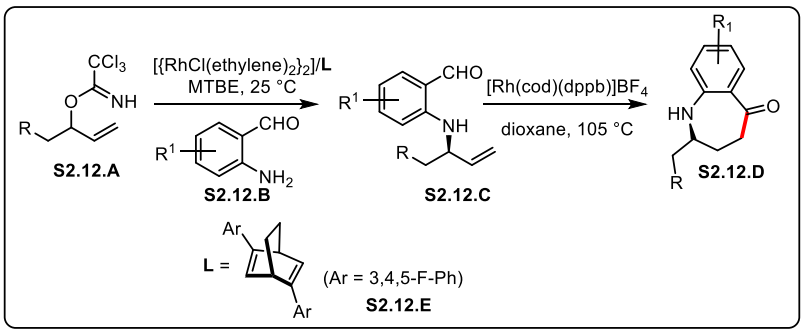
Scheme S2.10: *P,N-Ligands in Rh-catalyzed inter & intramolecular hydroacylation*
(Vautravers, N. R.; Regent, D. D.; Breit, B. *Chem. Commun.* **2011**, *47*, 6635–6637)

Douglas and coworkers employed intramolecular hydroacylation for the construction of six and seven membered rings. The suitably C2-functionalized benzaldehydes **S2.11.A** undergo an intramolecular reaction in the presence of $[RhCl(coe)_2]_2$ catalyst and the additive 2-amino-3-picoline derivative **S2.11.C**, PPh_3, aniline and benzoic acid in trifluorotoluene at 100 °C giving the corresponding six or seven membered rings in excellent yields (Scheme S2.11).



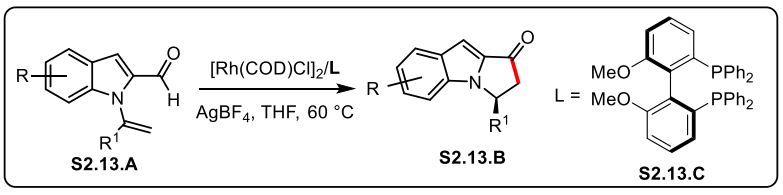
Scheme S2.11: *Douglas approach for intramolecular hydroacylation*
(Beletskiy, E. V.; Sudheer, C.; Douglas, C. J. *J. Org. Chem.* **2012**, *77*, 5884–5893)

Nguyen and coworkers reported the synthesis of seven membered nitrogen heterocycles in high enantiomeric excess by using the intramolecular hydroacylation reaction. In this approach, the substituted 2-aminobenzaldehydes **S2.12.B** on reaction with allylic trichloroacetimidates **S2.12.A** in the presence of [{RhCl(ethylene)$_2$}$_2$] catalyst and the chiral ligand **S2.12.E** in MTBE at rt results in asymmetric allylation of the amine to give **S2.12.C**, which then undergoes intramolecular hydroacylation in the presence of the [Rh(cod)(dppb)]BF_4 catalyst resulting in the formation of 2-alkyl-dihydrobenzoazepin-5-ones with excellent yields and *ee* (Scheme S2.12).



Scheme S2.12: *Nguyen approach for synthesis of 7-membered ring heterocycles*
(Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 3688–3692)

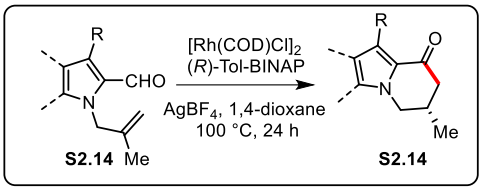
Stanley and co-workers reported the asymmetric hydroacylation reaction of *N*-vinylindole-2-carbaldehyde resulting in the formation of tricyclic heterocycles with excellent yield and *ee*. In this protocol, the active chiral Rh-catalyst has been generated *in situ* by the reaction of [Rh(COD)Cl]$_2$ catalyst with the chiral biphenyl ligand **S2.13.C**. The reaction was explored by employing a wide range of substrates by placing aryl or alky substituents on the olefin or on the indole moiety at different positions (Scheme S2.13).



Scheme S2.13: *Stanley approach for hydroacylation on N-Vinylindole derivatives*
(Ghosh, A.; Stanley, L. M. *Chem. Commun.* **2014**, *50*, 2765–2768)

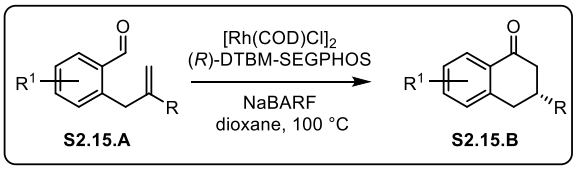
A similar approach has been documented by Stanley and coworkers wherein the asymmetric intramolecular hydroacylation of *N*-allylindole-2-carbaldehyde **S2.14.A** and *N*-allylpyrrole-2-carbaldehyde **S2.14.C** have been explored with the [Rh(COD)Cl]$_2$ catalyst

and (*R*)-Tol-BINAP as ligand. This methodology has been applied for the asymmetric synthesis of the nonsteroidal aromatase inhibitor MR20492 (Scheme S2.14).



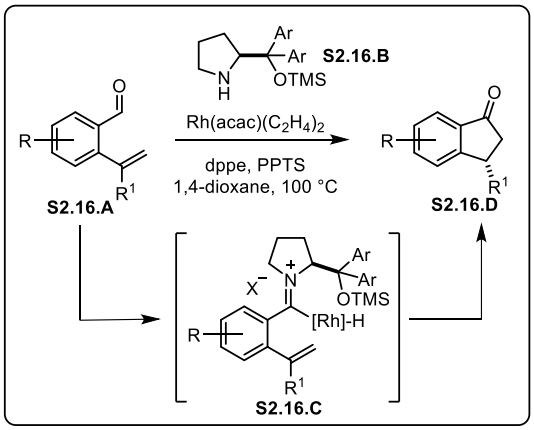
Scheme S2.14: *Stanley approach for hydroacylation on N-allylindole and Pyrrole derivatives*
(Du, X. W.; Ghosh, A.; Stanley, L. M. *Org. Lett.* **2014**, *16*, 4036–4039)

Later, this has been extended for the asymmetric hydroacylation to *O*-allylbenzaldehydes employing $[Rh(COD)Cl]_2$, (*R*)-DTBM-SEGPHOS and NaBARF. Interestingly, in this case, the endo selective products are formed exclusively, unlike the exoproducts with NHC catalysis. The *in situ* generation of the active catalyst in the present reaction avoids the side reactions such as alkene isomerization and the ene reaction and results in exclusive formation of the hydroacylation products with excellent yields and ee (Scheme S2.15).



Scheme S2.15: *Stanley approach of endo selective hydroacylation*
(Johnson, K. F.; Schmidt, A. C.; Stanley, L. M. *Org. Lett.* **2015**, *17*, 4654–4657)

Recently, Coltart's group has introduced a novel approach in the area of Rh-catalyzed hydroacylations – the use of prolione based chiral aminol along with the Rh-catalyst. As shown in the Scheme 2, vinyl benzaldehyde **S2.16.A** undergoes asymmetric iminium ion catalysis with the chiral secondary amine catalyst **S2.16.B** followed by insertion of rhodium into the iminium C–H bond, resulting in the intermediate **S2.16.C**, which then leads to the product. The significance of this reaction is in its use of a simple chiral secondary amine for asymmetric induction, unlike the use of chiral phosphine ligands in other reports (Scheme S2.16).



Scheme S2.16: *Chiral amines in the Rh-catalyzed asymmetric hydroacylation*
(Rastelli, E. J.; Truong, N. T.; Coltart, D. M. *Org. Lett.* **2016**, *18*, 5588–5591)

The reports mentioned above are some representative examples of the Rh-catalyzed hydroacylation reactions that involve the construction/annulation of a cycloalkanone ring. In general, the reactions with the mono-/disubstituted terminal olefins are facile when compared to the internal olefins. Coming to its relevance in the context of Proplisbenzofuran B, as one could notice, the acetoxymethyl group is rightly positioned with the carbon β to the carbonyl, which indicates the ready disconnection of the connecting bond with intramolecular olefin hydroacylation as the key transform. However, reports on the intramolecular hydroacylation of substrates that bear an existing stereogenic center next to the olefin are scarce. Thus, one of the problems with the current proposition will be the diastereoselectivity during the intramolecular hydroacylation. In the next part, will be describe the examination of the suitability of this intramolecular hydroacylation approach for constructing the central core of Propolisbenzofuran B, employing model substrate and then extending this to accomplish the total synthesis of this natural product.

2.6 Results and Discussion:

In 2000, Kadota and co-workers reported the isolation of two natural products propolisbenzofurans A and B from the bioactivity guided fractionation of the methanol extracts of Brazilian propolis.[1] Propolisbenzofuran A possesses a unique 2,3,5-trisubstituted dihydropyran core, whereas propolisbenzofuran B is characterized by a 1-aryl-2,3-dihydrodibenzo[b,d]furan-4(1H)-one tricyclic skeleton. Both these natural products exhibited moderate cytotoxicity to murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells. Thus, the unique tricyclic core present in propolisbenzofurana and the unexplored origin of their biological activity warrants efficient methods for the construction of these central cores. Considering this fact, propolisbenzofuran B has been selected as a target to develop an efficient strategy for the construction of its central tricyclic core and complete the total synthesis. In 2014, Thomson's group reported the first total synthesis of Propolisbenzofuran B employing a cascade reaction comprising of cyclocondensation of a dihydrobenzoquinone with a pendant cyclohexenone to construct the central benzofuran ring.[2]

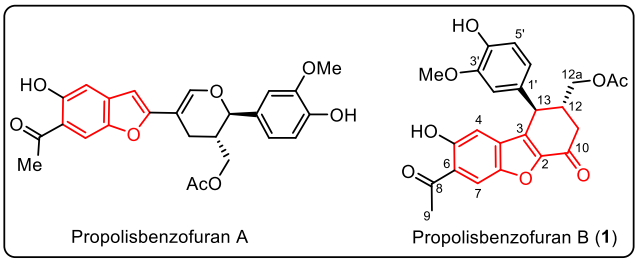
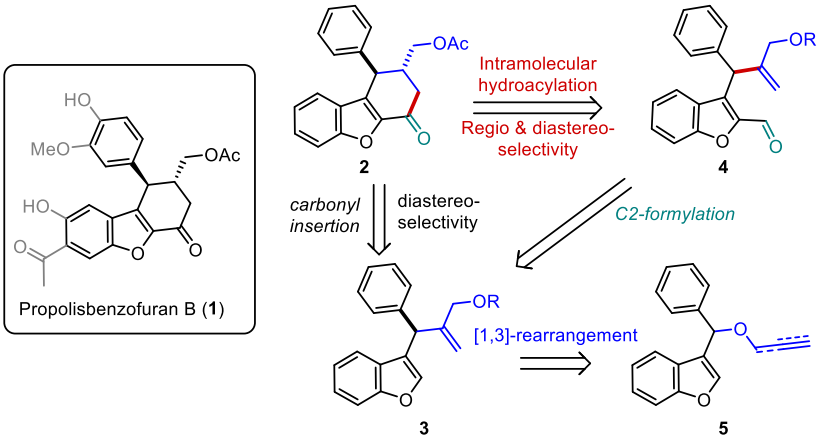


Figure F2.1: Structure of Propolisbenzofuran A/B

2.7 Retrosynthetic strategy:

Our initial concern was developing a simple approach for the central tricyclic core of Propolisbenzofuran B. In this regard, we have opted to forge a cyclohexanone skeleton to a benzofuran ring. This complements Thomson's approach, wherein a benzofuran ring has been annulated to cyclohexanone. As shown in Scheme S2.17, to construct the central cyclohexanone core, we thought of employing either carbonyl insertion or an intramolecular alkene hydroacylation reaction as the key skeletal constructs.[3] However, the

use of either of carbonyl insertion and/or hydroacylation reactions is going to be a key issue also as there are both regio and diastereoselectivity issues that need to be addressed.[4] In this context, we have first selected the model substrate **2** as an interim target to examine our strategy. The requisite starting material for the carbonyl insertion reaction was identified as compound **3**. If the carbonyl insertion was problematic, the C2-formylation of **3** will provide the key substrate **4** to examine the intramolecular hydroacylation reaction. To install the key prop-2-en-1-ol unit in **3**, we decided to employ the gold(I)-catalyzed [1,3] O→C rearrangement of the corresponding allenyl ether,[5] which, in turn, was planned from the propargylic ether **5**.

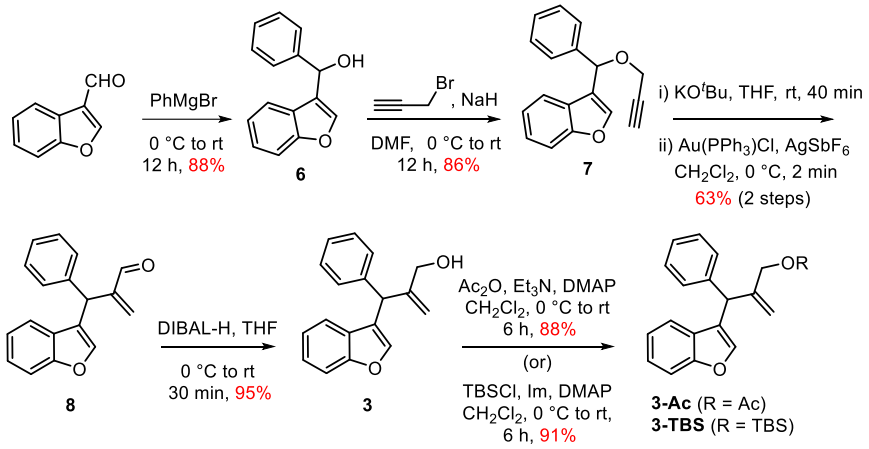


Scheme S2.17: *Design of retrosynthetic strategy*

2.8 Model study:

Our model studies to construct the central core of propolisbenzofuran B started with easily accessible benzofuran-3-carbaldehyde and its Grignard reaction with phenylmagnesium bromide in THF to obtain the alcohol **6** in 88% yield. The propargylation of the resulting alcohol **6** using proprgyl bromide in the presence of NaH in DMF gave the propargyl ether **7** in 86% yield. The next task was the isomerization of propargyl ether **7** to the corresponding allenyl ether. The product **7** on reaction with KO^{t}Bu in THF at room temperature results in the formation of the intermediate allene which, after aqueous workup without chromatographic purification was subjected to the key gold(I)-catalyzed [1,3] O→C rearrangement reaction employing the $Au(PPh_3)Cl/AgSbF_6$ catalyst combination in CH_2Cl_2 at 0 °C.[5] The rearrangement was instantaneous and provided the

corresponding acryl aldehyde **8** derivative in less than 2 min with 63% yield over two steps. The product **8** was characterized with the help of ^{1}H, ^{13}C NMR and HRMS spectra. In the ^{1}H NMR spectrum of compound **8**, the characteristic aldehyde proton was seen to resonate at δ 9.73 ppm and two olefinic protons, one as doublet at δ 6.20 with J = 1.1 Hz and the other one as singlet at δ 6.32 ppm. In the ^{13}C NMR spectrum, the terminal olefin carbon appeared at δ 136.3 ppm whereas the aldehyde carbonyl resonate at δ 192.95 ppm. In the HRMS, the exact mass calculated was $C_{18}H_{14}O_2Na$ $[M+Na]^+$ was 285.0886 and it was found to be 285.0882. The aldehyde functionality in compound **8** was then reduced with DIBAL-H to obtain alcohol **3** which, upon acetylation using acetic anhydride, Et_3N, DMAP in CH_2Cl_2 at 0 °C gave the acetate **3-Ac** in 88% yield. On the other hand, the alcohol **3** was treated with TBSCl and imidazole in CH_2Cl_2 to obtain the TBS ether **3-TBS** in 91% yield (Scheme S2.18).

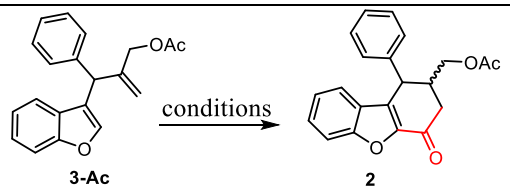


Scheme S2.18: *Synthesis of Acetate intermediate* **3**

The acetate intermediate **3-Ac** has been prepared mainly to explore the possibility of insertion of the carbonyl group between benzofuran C2 and the terminal olefin using carbon monoxide or paraformaldehyde.[6] If successful, this direct carbonylation insertion is expected to avoid the additional step of introducing the formyl group on the **3-TBS** using pyrophoric reagents such as ^{n}BuLi. With this aim, the reaction of benzofuran **3-Ac** with paraformaldehyde in the presence of $[Rh(dppb)(COD)]BF_4$ in DMF at 120 °C was examined first. This led only to the recovery of the starting material (Table T2.1, entry 1). Switching to Wilkinson's catalyst and performing the reaction under similar conditions at 150 °C was also not successful (Table T2.1, entry 2).[7] Examined next was the reaction of

benzofuran **3-Ac** with carbon monoxide gas at 150 psi in the presence of Ru_3CO_{12} catalyst in toluene at 150 °C for 10 h. Regrettably, under these conditions also, the recovery of the starting benzofuran (Table T2.1, entry 3) was observed.[8]

Table T2.1: *Attempted conditions for carbonyl insertion*

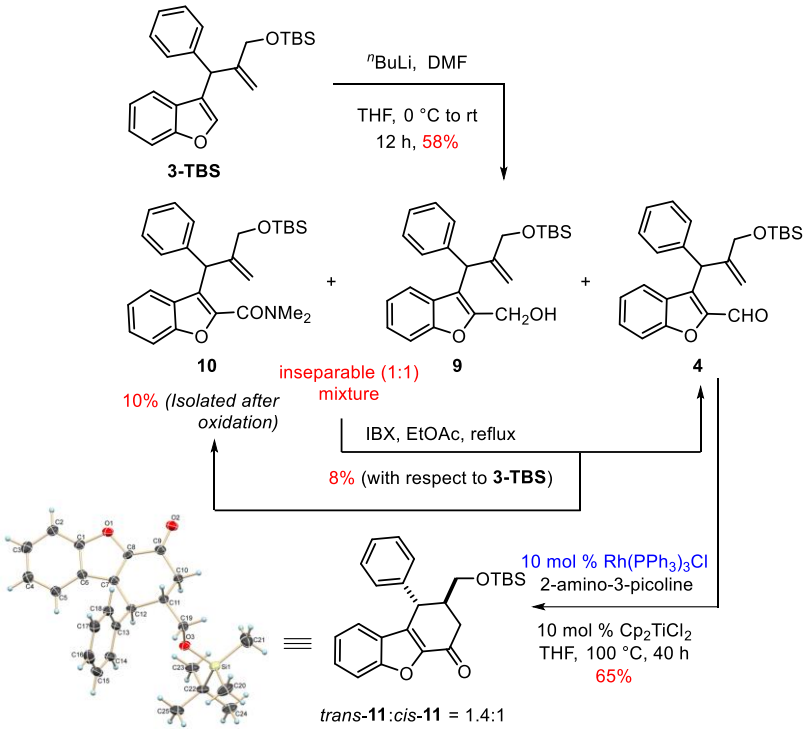


entry	Reaction conditions	Result
1.	$(CH_2O)n$, $[Rh(dppb)(COD)]BF_4$ DMF, 120 °C, 24 h	No reaction
2.	$(CH_2O)n$, $Rh(PPh_3)_3Cl$ DMF, 150 °C, 24 h	No reaction
3.	CO gas (150 Psi), Ru_3CO_{12} Toluene,150 °C, 10 h	No reaction

After failed attempts at carbonyl insertion, we then turned our attention to introducing the formyl group first and going for the intramolecular olefin hydroacylation next. Accordingly, the C2 fromylation of compound **3-TBS** has been attempted by employing ^{n}BuLi and DMF at -78 °C in THF. Even after 12 h, the starting material was found to be intact. Carrying out the reaction at -40 °C was also not fruitful and resulted in the recovery of the starting benzofuran **3-TBS**. Gratifyingly, when the reaction was conducted at 0 °C, the required 2-formylbenzofuran **4** was obtained in 58% yield along with an inseparable mixture of compounds **9** and **10** in a 1:1 ratio. The structure of compound **4** was confirmed by ^{1}HNMR spectrum, in which the aldehyde proton appeared at δ 9.75 ppm. The inseparable mixture of alcohol **9** and amide **10** was then treated with IBX in refluxing EtOAc, where the alcohol got oxidized to aldehyde **4**, leaving the amide **10** intact (Scheme S2.19)

Our next concern was the key hydroacylation reaction. Initially, we resorted to the conditions reported by Jun and coworkers for the intermolecular hydroacylation of benzaldehyde that was claimed to be a highly active system. The employed conditions involve the heating of aldehyde **4** in the presence of aniline, benzoic acid, 2-amino-3-picoline and Wilkinson's catalyst in toluene at 130 °C for 24 h. However, under these

conditions, the aldehyde **4** was found to be unstable and the reaction resulted in the formation of a complex mixture.[9]



Scheme S2.19: *Exploring the key hydroacylation reaction*

Next, we examined another set of conditions reported by the same group for the hydroacylation of furan and indole heterocycles, wherein it had been suggested that addition of Cp_2TiCl_2 improves the yields.[10] Accordingly, the aldehyde **4** was heated with Wilkinson's catalyst in the presence of 2-amino-3-picoline and Cp_2TiCl_2 in THF at 100 °C with a continuous monitoring of the reaction progress with TLC. After 40 h, the complete consumption of the starting aldehyde was noticed and TLC indicated the formation of a new spot. This has been isolated in 65% yield and the ^{1}H NMR of it revealed the presence of two isomers in a 1.4:1 ratio. The isomers were separated by preparative HPLC and were characterized with the help of spectral data analysis. These compounds were found to be the *cis* and *trans* isomers having a cyclohexanone core. This indicated that the intramolecular hydroacylation reaction proceeded mainly *via* the 6-*endo*-trig mode resulting in a six membered ring. In the ^{1}H NMR spectrum of *trans*-**11**, the benzylic proton resonates at δ 4.50 ppm as a doublet with characteristic large coupling constant J = 9.5 Hz.

The methine proton appeared as mutiplet at δ 2.59–2.66 ppm. The methylene protons attached to the OTBS group appeared at δ 3.50 (dd, J = 3.1, 10.3 Hz, 1H), 3.56 (dd, J = 3.9, 10.3 Hz, 1 H) and the methylene protons in the cyclohexanone ring resonates at δ 2.80 (dd, J = 4.0, 16.8 Hz, 1H), 3.00 (dd, J = 12.0, 16.8 Hz, 1H) ppm. In ^{13}C NMR spectrum of compound *trans*-**11**, the benzylic carbon and the methine carbon were seen to resonate at δ 47.8 and 41.9 ppm respectively. The methylene carbon resonated at δ 41.3 and 62.8 ppm. The carbonyl peak appeared at δ 188.4 ppm. In the HRMS, the exact mass calculated was $C_{25}H_{31}O_3Si$ $[M+H]^+$: 407.2037 and it was found to be 407.2035. Similarly, the *cis*-**11** was fully characterized with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of the *cis* isomer, the benzylic proton appeared at δ 4.76 ppm as a doublet with a coupling constant J = 5.1 Hz. The methine proton appeared as mutiplet at δ 2.91–2.98 ppm. The methylene protons attached to the OTBS group appeared at δ 3.33 (dd, J = 8.2, 10.2 Hz, 1H), 3.36 (dd, J = 6.2, 10.2 Hz, 1H) and the methylene protons in the cyclohexanone ring resonate at δ 2.54 (dd, J = 5.6, 17.2 Hz, 1H), 2.59 (dd, J = 11.5, 17.2 Hz, 1H) ppm. In the ^{13}C NMR spectrum of *cis*-**11**, the benzylic and the methine carbons were seen at δ 43.2 and 39.7 ppm respectively. The methylene carbons resonated at δ 37.1 and 63.6 ppm and the carbonyl peak at δ 187.7 ppm. In the HRMS, the exact mass calculated was $C_{25}H_{31}O_3Si$ $[M+H]^+$: 407.2037 and it was found to be 407.2035.

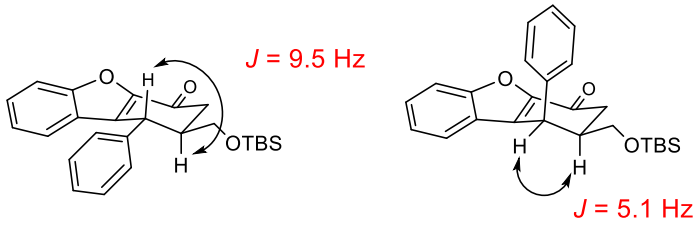
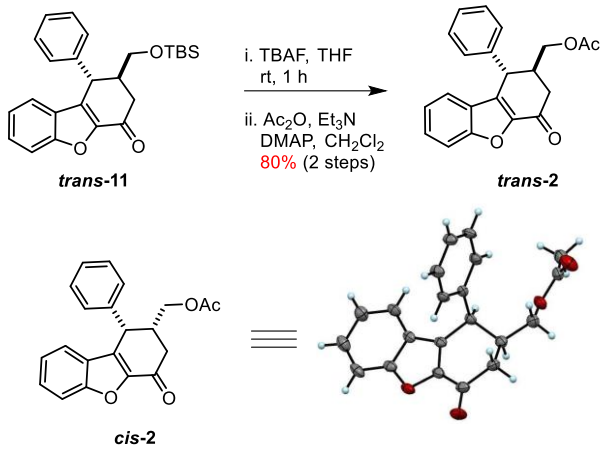


Figure F2.2: *Coupling constants for Trans and Cis isomers of* ***11***

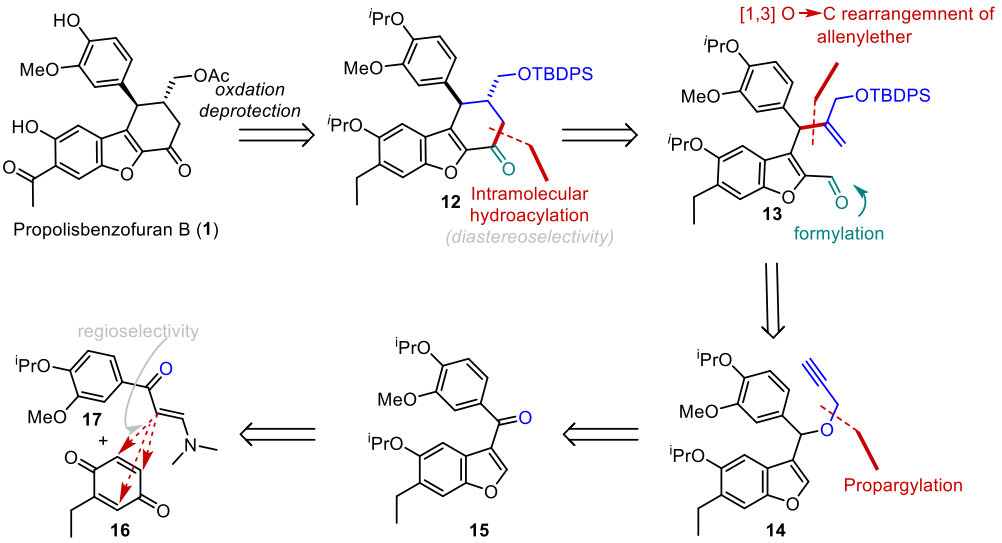
After confirming the structure of the *trans* and the *cis* isomers, we moved ahead to complete the synthesis of the model substrate. In this regard, both the cis- and trans-isomers have been subjected for –OTBS deprotection with TBAF in THF followed by acetylation of the resulting free –OH employing acetic anhydride, Et_3N, DMAP in CH_2Cl_2 to obtain *cis* and *trans* acetates ***cis*-2** and ***trans*-2** in 72% and 75% yields respectively over two steps. A comparison of the spectral data of the cyclohexanone region of the natural product with both the isomers available has been carried out to confirm the assigned

structures. Finally, the structure of ***cis*-2** has been further established with the help of single crystal X-ray diffraction studies.



Scheme S2.20: *Completion of model studies*

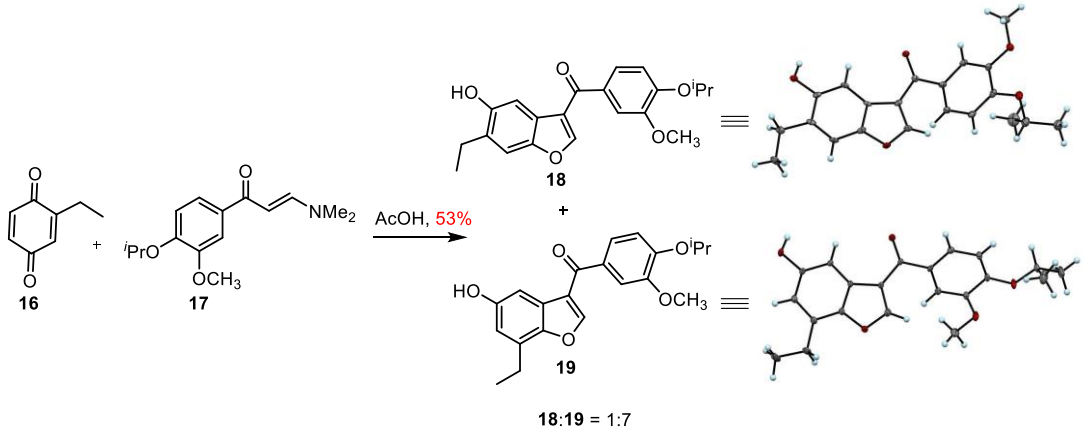
After completion of model studies where the key reactions – gold catalyzed [1,3] O→C rearrangement and rhodium catalyzed intramolecular hydroacylation have been explored successfully for the construction of the core structure of the natural product, we moved ahead to attempt the total synthesis of the natural product. The key retrosynthetic disconnections are provided in Scheme S2.21.



Scheme S2.21: *Design of retrosynthetic strategy*

In the previous total synthesis, direct introduction of the C6-acyl group was found to be problem at the final stages and this has been overcome by proceeding with a C6-ethyl group as a surrogate for the C6-acyl group. Keeping this in mind, compound **13** has been identified as the key intermediate for the hydroacylation reaction. The propargylic ether **14**, which is the key precursor for the gold(I)-catalyzed [1,3] O→C rearrangement,[5] was planned from ketone **15**. The synthesis of ketone **15** is a straightforward proposition considering the well-established methods that are available for the synthesis of 3-aroylbenzofurans, involving the condensation of a 2-ethyl-1,4-benzoquinone **16**[11] with a suitable enaminone such as **17**.[12]

At the outset, starting with the benzoquinone **16**, we realized that synthesis of the intended benzofuran intermediate **18** is associated with several challenges - mainly, the regioselectivity during the initial Michael addition. In this context, initially we examined the condensation of benzoquinone **16** with the 3-(dimethylamino)-1-arylprop-2-en-1-one **17**.[12] This reaction led to the isolation of a mixture of two regioisomers **18** and **19** in a 1:7 ratio Scheme S2.22.

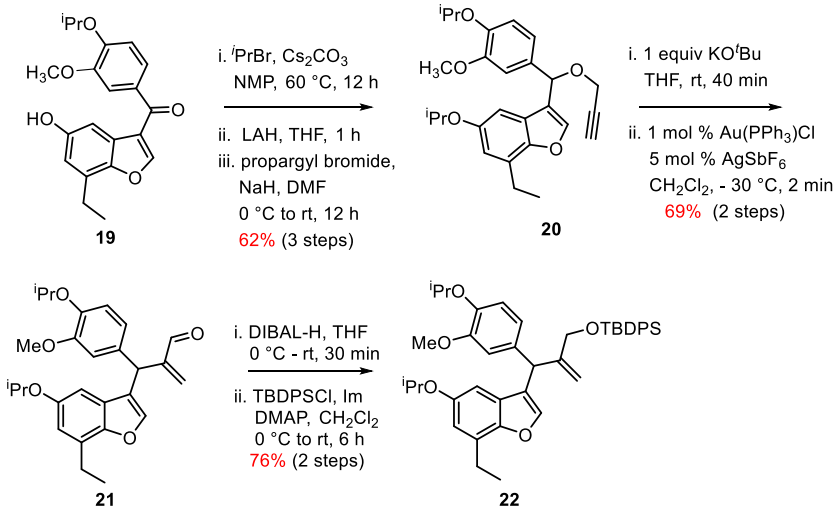


Scheme S2.22: *Synthesis of keto benzofuran 18*

The constitution of these two isomers has been established with the help of NMR spectral data and single crystal X-ray diffraction studies. For example, in the ^{1}H NMR spectrum of compound **18**, the Ar–H_2 of the aryl ring that is part of the benzofuran core were seen to resonate as singlets at δ 7.33, 8.06, 8.10 ppm whereas the same Ar–H_2 of compound **19** gave two doublets, one at δ 6.83 with a coupling constant J = 1.9 Hz and the other one merged in the mutiplet at δ 7.50–7.52 ppm. An examination of their NMR

spectra and the single crystal X-ray of the minor isomer **18** revealed that it was the desired 5-hydroxy-6-ethyl-3-aroylbenzofuran. Varying the reaction conditions such as solvent and/or temperature had no substantial effect on the outcome of the reaction.

The undesired regioisomer **19** differs from the required isomer in the positioning of the ethyl group at C7 instead of C6. Considering its ease of synthesis, it has been advanced quickly to the corresponding hydroacylation precursor **23** to check the outcome of diastereoselectivity in hydroacylation reaction. As shown in Scheme S2.23, the protection of the Ar–OH in compound **19** as isopropyl ether followed by carbonyl reduction with LAH and the propargylation of the resulting crude alcohol gave alkyne **20** in 62% yield over three steps. The isomerization of propargyl ether **20** to the corresponding allenyl ether followed by gold(I)-catalyzed [1,3] O→C rearrangement gave aldehyde **21** in 69% yield (Scheme S2.23).

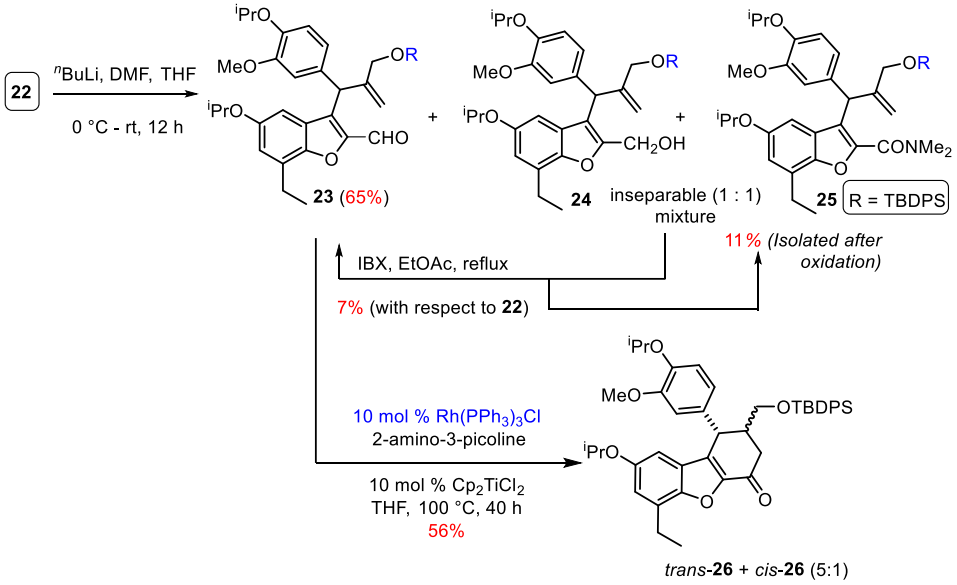


Scheme S2.23: *Synthesis of compopund 22*

The aldehyde **21** was characterized by ^{1}H, ^{13}C and HRMS spectra. In the ^{1}H NMR spectrum, the characteristic aldehyde proton resonates at δ 9.69 ppm. The terminal olefin protons appeared as singlets at δ 6.16, 6.26 ppm. The benzylic proton appeared as singlet at δ 5.29 ppm. In the ^{13}C spectrum, the aldehyde, olefin, benzylic carbons seen to resonate at δ 193.2, 136.1 and 39.1 ppm respectively. In HRMS spectrum, the exact mass calculated was $C_{27}H_{32}O_5Na$ $[M+Na]^+$: 459.2142 and it was found to be 459.2141. The aldehyde **21** was reduced with DIBAL-H and the resulting crude alcohol was subjected for TBDPS

protection to obtain the key benzofuran intermediate **22** in 76% yield over 2 steps (Scheme S2.23).

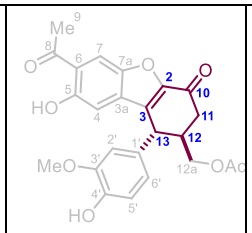
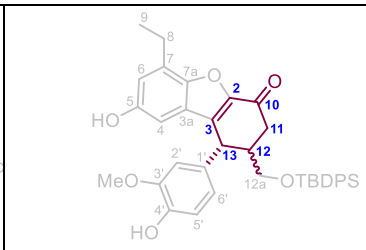
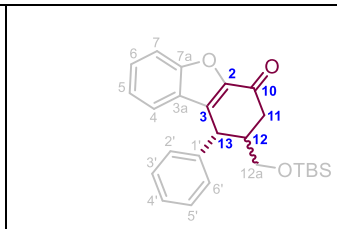
The formylation of compound **22** using ^{n}BuLi and DMF in THF at room temperature gave the requisite aldehyde **23** in 65% yield, along with a 1:1 mixture of reduced alcohol **24** and amide **25**. After having the aldehyde **23** in hand, the stage was set for the key hydroacylation reaction. The Rh-catalyzed intramolecular hydroacylation of compound **23** employing the established conditions resulted in the formation of a 5:1 regiomeric mixture **26**, with the requisite *trans*-**26** as the major one, which was determined after separating the isomers by preparative HPLC and carrying out the spectral data analysis.



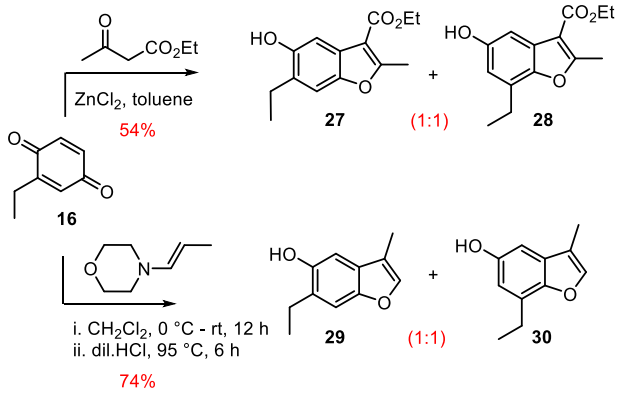
Scheme S2.24: *Completing the synthesis of regioisomers*

Table T2.2 provides the compilation of the chemical shifts and coupling constants of the cyclohexanone core of these two isomers along with the previously synthesized model compounds and the natural product.

Table T2.2: *Comparison of ^{1}H, ^{13}C NMR chemical shifts and coupling constants of the cyclohexanone core of natural product in acetone-d_6, regioisomers (trans-**26** & cis-**26**) in $CDCl_3$ and model compound (trans-**11** & cis-**11**) in $CDCl_3$*

										
	trans		***trans***		***cis***		***trans***		***cis***	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
2	–	151.7	–	154.1	–	154.6	–	156.4	–	156.4
3	–	135.0	–	133.2	–	133.5	–	136.1	–	136.2
13	4.33 (d, *J* = 9.9 Hz	44.9	4.50 (d, *J* = 10.1 Hz	47.8	4.66 (d, *J* = 5.0 Hz	43.2	4.50 (d, J = 9.5 Hz, 1H)	47.8	4.76 (d, J = 5.1 Hz, 1H)	43.2
12	2.94, m	43.1	2.60–2.64, m	42.0	2.87–2.93, m	39.5	2.59–2.66, m	41.9	2.91–2.98, m	39.7
11	2.86 (m, 2H)	42.3	2.82 (dd, *J* = 3.4, 16.8 Hz, 1H), 3.09 (dd, *J* = 12.3, 16.6 Hz, 1H)	41.7	2.41(dd, *J* = 4.0, 17.2 Hz, 1H), 2.52 (dd, *J* = 13.0, 17.1 Hz, 1H)	37.1	2.80 (dd, *J* = 4.0, 16.8 Hz, 1H), 3.00 (dd, *J* = 12.0, 16.8 Hz, 1H)	41.3	2.54 (dd, *J* = 5.6, 17.2 Hz, 1H), 2.59 (dd, *J* = 11.5, 17.2 Hz, 1H)	37.1
10	–	187.5	–	188.2	–	187.6	–	188.4	–	187.7

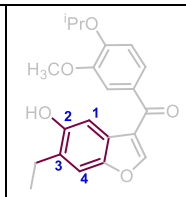
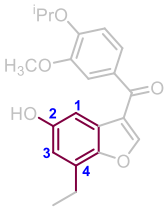
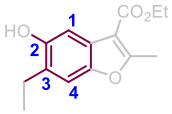
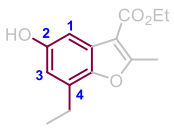
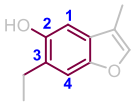
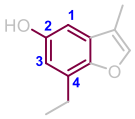
Having a promising result on the regioselectivity of hydroacylation with a regiomeric substrate, the next concern was synthesizing a suitable 6-ethylbenzofuran substrate. In this context, the condensation of benzoquinone **16** with ethyl acetoacetate[13] has been attempted, employing $ZnCl_2$ as the catalyst. This reaction resulted in the formation of two regioisomeric benzofurans in equal proportions. Both the regiomers **27** and **28** were separated and characterized with the help of NMR spectral data analysis.



Scheme S2.25: *Synthesis of starting benzofurans*

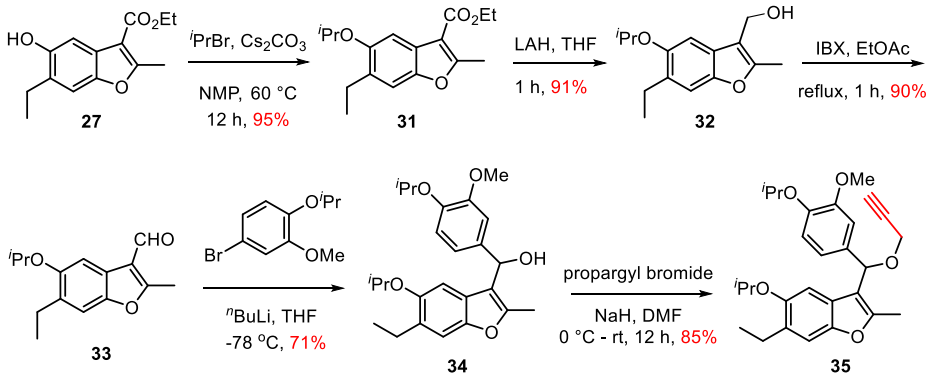
In case of the desired benzofuran **27**, the characteristic singlets of Ar–H_2 of the aryl ring of benzofuran core appeared at δ 7.18 and 7.40 ppm. On the other hand, the same protons appeared as doublets at δ 6.65 and at δ 7.29 with a coupling constant J = 2.2 Hz in case of the undesired regioisomers **28**. Similarly, the reaction of benzoquinone **16** with the (4-(prop-1-en-1-yl)morpholine[14] produced the desired benzofuran **29** along with the undesired isomer **30** in a 1:1 ratio (Scheme S2.25). In the table given below, provided are the characteristic coupling constants and chemical shifts of the three pairs of the benzofurans that have been synthesized which provides a simple logic to deduce the regiomeric constitution

Table T2.3: *Comparison of ^1H NMR chemical shifts and coupling constants of the 3 pairs of benzofuran regioisomeric substrates.*

						
1-H	8.06 (s)	merged with m at 7.50–7.52	7.40 (s)	7.29(d, J = 2.2 Hz, 1H)	7.22 (s)	6.78(d, J = 2.2 Hz, 1H)
2-H	–	–	–	–		–
3-H	–	6.83(d, J = 1.9 Hz, 1H)	–	6.65(d, J = 2.2 Hz, 1H)		6.69(d, J = 2.2 Hz, 1H)
4-H	7.33(s)	–	7.18 (s)	–	6.86 (s)	–

Despite having regioselectivity issues, with easy access to the two intermediates **27** and **29**, we proceeded further to examine the proposed approach for the synthesis of propolisbenzofuran B. Initially, the carboxylate **27** was selected as a starting material in which the free phenolic-OH was protected as its isopropyl ether by treating it with isopropyl bromide and Cs_2CO_3 at 60 ºC in *N*-methylpyrrolidin-2-one, resulting in compound **31** with 95% isolated yield. The compound **31** was then subjected to ester reduction using LAH and the resulting alcohol **32** was oxidized with IBX in refluxing EtOAc to obtain aldehyde **33**. The 4-bromo-1-isopropoxy-2-methoxybenzene was then added to the aldehyde **33** in the presence of ^{n}BuLi, which resulted in the formation of alcohol **34** in 71% yield. The alcohol **34** was then subjected to the propargylation using propargyl bromide and sodium hydride in DMF to generate alkyne **35** in 85% yield.

Having the alkyne **35** in hand, the next step was its isomerization to allene and the subsequent gold catalysed [1,3] O→C rearrangement (Scheme S2.26).

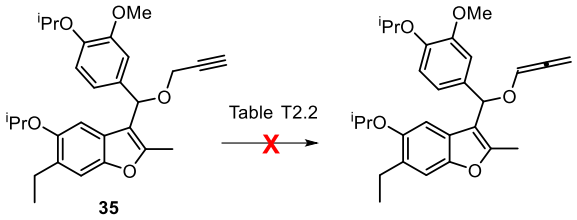


Scheme S2.26: *Synthesis of alkyne 35*

Surprisingly, when the alkyne **35** was subjected for the KO^{t}Bu mediated isomerization under previously optimized conditions,[15] there was no formation of allene and the starting alkyne **35** was recovered (Table T2.2, entry1). Heating the reaction mixture at 60 °C for 1 h resulted in the formation of a complex mixture (Table T2.2, entry2). Screening the reaction in various solvents such as toluene, DMF and DMSO in the presence of KO^{t}Bu was not fruitful, resulting in either recovery of the starting alkyne or formation of a complex mixture (Table T2.2, entries 3–5). Replacing the KO^{t}Bu with other bases such as KOH and NaOMe in DMSO at room temperature or at 60 °C failed to deliver the required allene (Table T2.2, entries 6–9)[16]. Even screening the reaction with LDA[17] or a mixture of bases (NaH and KO^{t}Bu)[18] in one pot at room temperature or at 50 °C was not successful in generating the allene (Table T2.2, entries 10–13). Having synthesized a wide-range of allenes during our method development and the success with the two model substrates mentioned above, we have taken this step of allene synthesis for granted and this failure is completely unanticipated. Probably, this methyl group may be deprotonated rather than the propargyl ether. Under forcing conditions, this would then lead to the potential fragmentation of the benzylic C–O bond. Though the reasons are not obvious, at this stage, it become apparent that the intended shortcut route that aimed to avoid the C2-formylation event is not viable and we needed to go ahead with the originally established sequence with model substrates that comprise of C2-formylation. This has

forced us to go back to the ready available benzofuran precursor **29** that needs a major make-up before arriving at the key hydroacylation substrate.

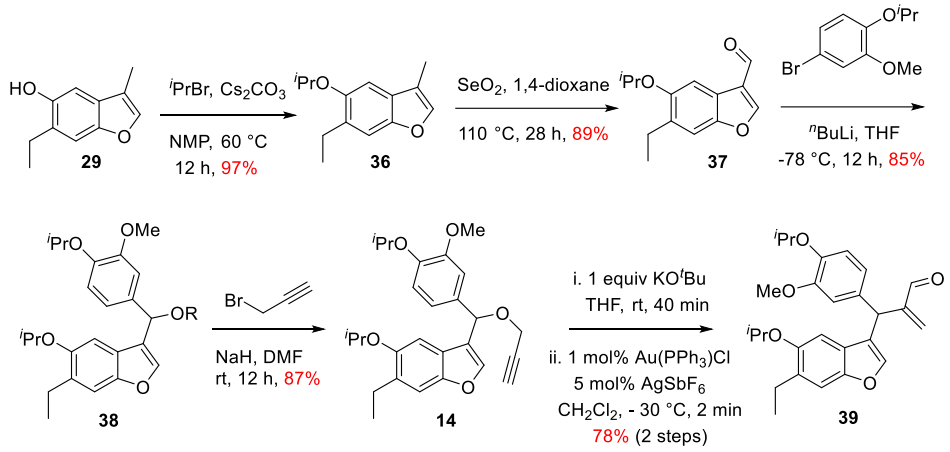
Table T2.3: *Attempted conditions for conversion of alkyne **35** to the corresponding allene*:



entry.	*Base*	*Solvent*	*Temp.*(°C)	*Result*
1.	KO^{t}Bu	THF	rt	No reaction
2.	KO^{t}Bu	THF	60	Complex mixture
3.	KO^{t}Bu	Toluene	rt	No reaction
4.	KO^{t}Bu	DMF	rt	No reaction
5.	KO^{t}Bu	DMSO	rt	Complex mixture
6.	KOH	DMSO	rt	No reaction
7.	KOH	DMSO	60	No reaction
8.	NaOMe	DMSO	rt	No reaction
9.	NaOMe	DMSO	60	No reaction
10.	LDA	THF	rt	No reaction
11.	LDA	THF	50	No reaction
12.	NaH, KO^{t}Bu	THF	rt	No reaction
13.	NaH, KO^{t}Bu	THF	50	No reaction

The next approach for propolisbenzofuran B commenced with benzofuran **29**. The benzofuran **29** was subjected for phenolic *O*-isopropylation to obtain compound **36** in 97% yield. Compound **36** was then subjected for the SeO_2 mediated benzylic oxidation, which resulted in the formation of aldehyde **37** in 89% yield. In ^{1}H NMR spectrum of compound **37**, the aldehyde proton appeared at δ 10.09 ppm. Next, the aldehyde, **37** was subjected to the addition of 4-bromo-1-isopropoxy-2-methoxybenzene to obtain the alcohol **38** in 85% yield. The alcohol was then propargylated using propargyl bromide in DMF at room temperature, which resulted in the formation of propargyl ether **14** in 87% yield. In ^{1}H NMR spectrum, the alkyne proton appeared as a triplet at δ 2.49 with coupling constant J = 2.1 Hz and the propargyl protons resonated at δ 4.13 (dd, J = 2.1, 15.9 Hz, 1H) and 4.23 (dd, J = 2.1, 15.9 Hz, 1H) ppm. To our delight, the alkyne **14** on reaction with KO^{t}Bu in THF at room temperature was isomerised to allene, which, after aqueous workup was

subjected to the gold(I)-catalyzed [1,3] O→C rearrangement to obtain the aldehyde **39** in 78% yield over two steps (Scheme S2.27). The aldehyde **39** was characterized by ^{1}H, ^{13}C and HRMS spectra.

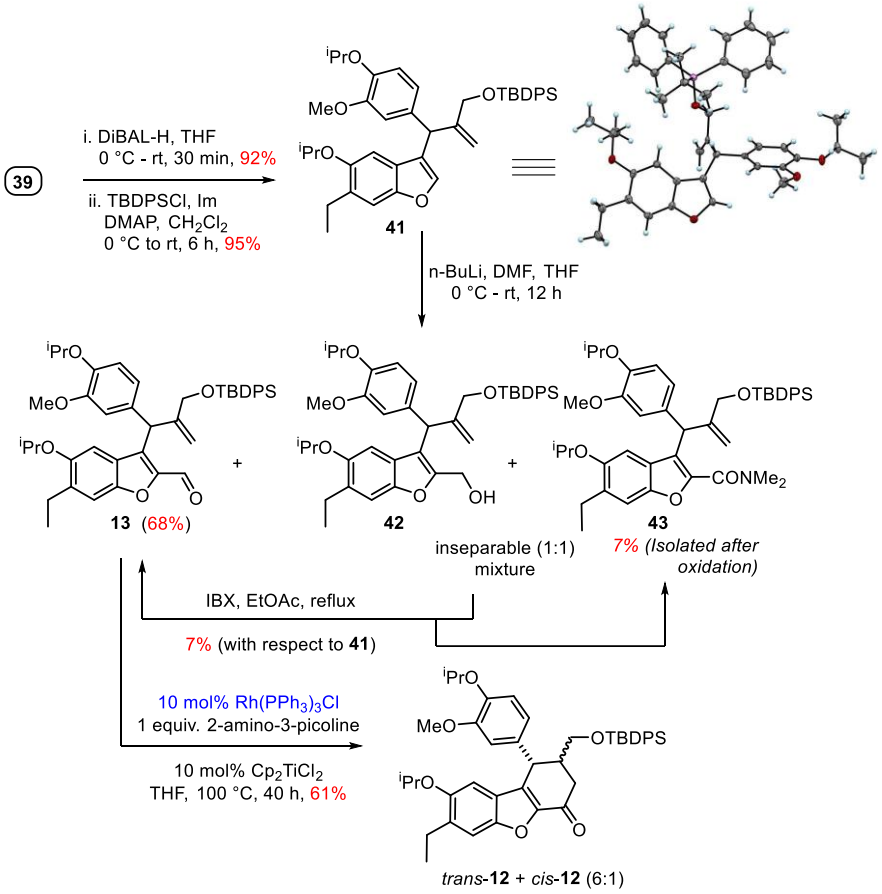


Scheme S2.27: *Synthesis of key intermediate by gold-catalyzed [1,3] O→C rearrangement*

In the ^{1}H NMR spectrum of aldehyde **39**, the characteristic aldehyde proton resonated at δ 9.70 ppm and the olefin protons appeared as singlets at δ 6.17 and 6.26 ppm. The benzylic proton appeared as a singlet at δ 5.31 ppm. In the ^{13}C NMR spectrum, the benzylic and the olefin carbons resonated at δ 39.1, 136.1 ppm respectively and the aldehyde carbon appeared at δ 193.2 ppm. In the HRMS, the exact mass calculated was $C_{27}H_{33}O_5Si$ $[M+H]^+$: 437.2323 and it was found to be 437.2325. Thus, the structure of the product was confirmed by spectroscopic techniques.

The aldehyde **39** was then reduced using DIBAL-H and the resulting alcohol **40** in (92% yield) was subjected for TBDPS protection to obtain the benzofuran **41** in 95% yield. Next, the C2-formylation of benzofuran **41** was carried out employing DMF and ^{n}BuLi to obtain the key hydroacylation precursor **13** (68%) and a mixture of reduced alcohol **42** and amide **43** (1:1 ratio). The oxidation of this mixture with IBX in refluxing EtOAc led to the isolation of another 7% aldehyde **13** (with respect to the starting **41**) and 7% of amide **43** was recovered. In the ^{1}H NMR spectrum of aldehyde **13**, the characteristic aldehyde proton resonated at δ 9.66 ppm. With the aldehyde **13** in hand, the stage was set for another key reaction – rhodium catalyzed intramolecular olefin hydroacylation. The aldehyde **13** on reaction with Wilkinson's catalyst in the presence of 2-amino-3-picoline and Cp_2TiCl_2 in THF at 100 °C for 40 h resulted in the formation of a diastereomeric mixture, *trans*-**12** and

cis-**12** in a 6:1 ratio. Both the isomers were separated by preparative HPLC. The spectral data of *trans*-**12** is comparable with the data reported by Thomson's group[2] (Scheme S2.28).

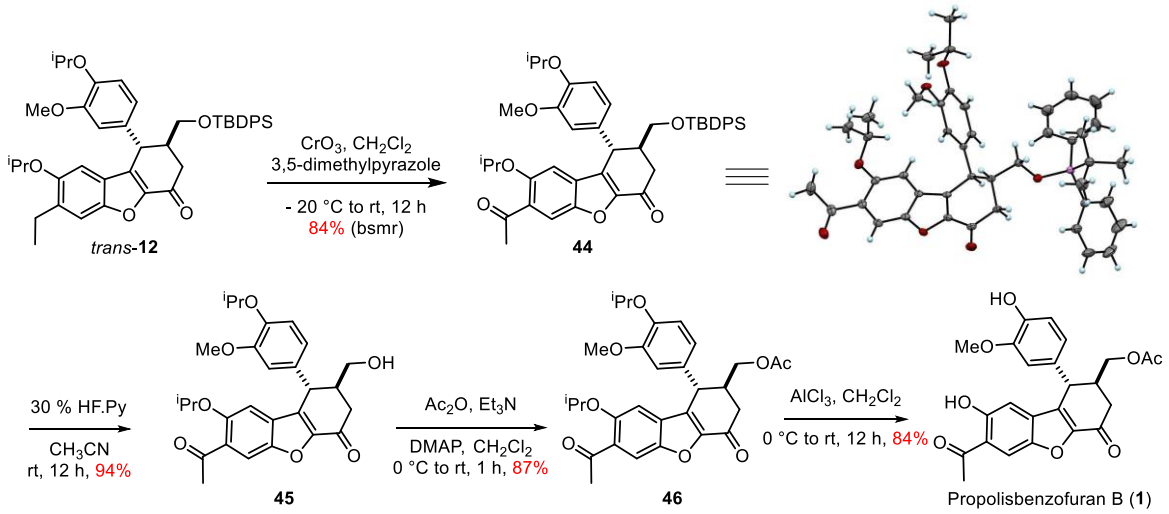


Scheme S2.28: *Exploring the key intramolecular hydroacylation*

In the ^{1}H NMR spectrum of the *trans*-**12**, the benzylic proton resonates at δ 4.46 ppm as a doublet with coupling constant J = 10.0 Hz. The methine proton appeared as mutiplet at δ 2.57–2.60 ppm. The methylene protons attached to OTBS group appeared at δ 3.52 (dd, J = 2.8, 10.5 Hz, 1H), 3.64 (dd, J = 3.8, 10.5 Hz, 1H) ppm and the methylene protons in the cyclohexanone ring resonated at δ 2.77 (dd, J = 3.9, 16.7 Hz, 1H), 3.07 (dd, J = 12.3, 16.7 Hz, 1 H) ppm. In the ^{13}C NMR spectra, the benzylic carbon and the methine carbons were seen to resonate at δ 47.7 and 42.1 ppm respectively. The methylene carbons resonated at δ 41.6 and 63.7 ppm and the carbonyl peak appeared at δ 187.9 ppm. In the HRMS, the exact mass calculated was $C_{44}H_{53}O_6Si$ $[M+H]^+$: 705.3606 and it was found to be 705.3604. Similarly, in case of the *cis*-**12**, the benzylic proton appeared at δ 4.64 ppm as

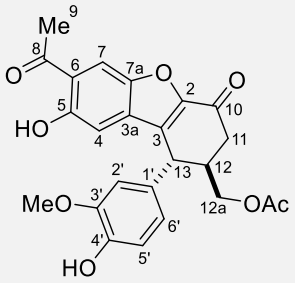
doublet with coupling constant J = 5.0 Hz. The methine proton appeared as mutiplet at δ 2.85–2.92 ppm. The methylene protons attached to OTBS group appeared at δ 3.37 (dd, J = 5.7, 10.4 Hz, 1H), 3.49 (dd, J = 8.9, 10.4 Hz, 1H) and the methylene protons in cyclohexanone ring resonates at δ 2.40 (dd, J = 4.2, 17.2 Hz, 1H), 2.49 (dd, J = 12.7, 17.2 Hz, 1H) ppm. In ^{13}C NMR, the benzylic carbon and the methine carbon were seen at δ 43.3 and 39.6 ppm respectively. The methylene carbon resonates at δ 37.1 and 64.7 ppm. The carbonyl peak appeared at δ 187.2 ppm. In the HRMS, the exact mass calculated was $C_{44}H_{53}O_6Si$ $[M+H]^+$: 705.3606 and it was found to be 705.3602.

The intermediate *trans*-**12** was converted to the natural product following the sequence reported by Thomson's group.[2] Thus, *trans*-**12,** on reaction with CrO_3 resulted in ethyl oxidation, forming ketone **44** in 84% yield based on the starting material recovered (27% conversion). The ketone **44** was then subjected for the TBDPS deprotection and the resulting alcohol **45** was subjected for acetylation to give compound **46** in 87% yield. Finally, compound **46** on isopropyl deprotection gave the propolisbenzofuran B (**1**) in 84% yield (Scheme S2.29). The spectral data of synthetic **1** is in full agreement with the data reported by isolation and synthetic groups.[1, 2]



Scheme S2.29: *Completion of total synthesis*

Table SI2. *Comparison of ^{13}C (recorded in d_6-acetone) and ^{1}H NMR (recorded in d_6-acetone) Chemical Shifts and Coupling Constants of Natural & Synthetic Samples of Propolisbenzofuran B*



Propolisbenzofuran B

C(n)	Natural Product *(100 MHz)*	Thomson's Sample *(125 MHz)*	This paper *(125 MHz)*
2	151.7	151.8	151.9 (s)
3	135.0	135.1	135.1 (s)
3a	134.0	134.1	134.2 (s)
4	110.0	110.0	110.1 (d)
5	158.2	158.2	158.3 (s)
6	120.5	120.6	120.6 (s)
7	115.5	115.6	115.6 (d)
7a	149.5	149.6	149.7 (s)
8	205.8	205.0	206.0 (s)
9	27.3	27.4	27.4 (q)
10	187.5	187.6	187.6 (s)
11	42.3	42.4	42.4 (t)
12	44.9	44.9	45.0 (d)
12a	65.2	65.2	65.3 (t)
13	43.1	43.1	43.2 (d)
1'	131.1	131.7	131.7 (s)
2'	112.9	112.9	113.0 (d)
3'	148.9	148.9	149.0 (s)
4'	147.2	147.2	147.3 (s)
5'	116.1	116.1	116.2 (d)
6'	122.5	122.5	122.6 (d)
OMe	56.3	56.3	56.4 (q)
OAc	20.6 170.8	20.7 (not given)	20.7 (q) 171.0 (s)

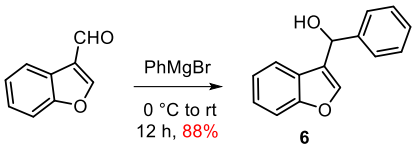
C(n)–H	Natural Product (*400 MHz*)	Thomson's Sample (*500 MHz*)	This paper (*700 MHz*)
4	6.13 s	6.14 (s)	6.14 (s, 1H)
7	8.21 s	8.24 (s, 1H)	8.21 (s, 1H)
9	2.75 s	2.76 (s, 3H)	2.76 (s, 3H)
11	2.86 (m, 2H)	2.81 (m, 2H)	2.82 (dd, *J* = 4.4, 16.3 Hz, 1H) 2.87 (dd, *J* = 11.9, 16.3 Hz, 1H)
12	2.94 m	2.96 m	2.92–2.97 (m, 1H)
12a	4.05 (m, 2H)	4.05 (t, *J* = 4.5 Hz, 2H)	4.04 (dd, *J* = 5.7, 11.3 Hz, 1H) 4.07 (dd, *J* = 3.6, 11.3 Hz, 1H)
13	4.33 (d, *J* = 9.9 Hz)	4.35 (d, *J* = 9.9 Hz, 2H)	4.34 (d, *J* = 10.0 Hz, 1H)
2'	7.02 (d, *J* = 2.0 Hz)	7.03 br. s	7.03 (br. s, 1H)
5'	6.89 (d, *J* = 8.0 Hz)	6.88 (d, *J* = 1.7 Hz, 2H)	6.89 (d, *J* = 8.1 Hz, 1H)
6'	6.87 (dd, *J* = 8.0, 2.0 Hz)	6.88 (d, *J* = 1.7 Hz, 2H)	6.87 (dd, *J* = 1.6, 8.1 Hz, 1H)
OMe	3.73 s	3.75 (s)	3.76 (s, 3H)
OAc	2.03 s	2.04 (s)	2.04 (s, 3H)
C(4')–OH	8.01 b s	7.75 s	7.69 (s, 1H)
C(5)–OH	11.81 s	11.82 (s, 1H)	11.81 (s, 1H)

To conclude, the total synthesis of propolisbenzofuran B was accomplished. The adopted approach is highly modular and is characterized by the use of easily accessible building blocks and simple reagents. The gold catalyzed [1,3] O→C rearrangement and the

Rh-catalyzed intramolecular olefin hydroacylation have been aptly applied to construct the central cyclohexanone core with the requisite functional groups.

***Experimental Data*:**

Benzofuran-3-yl(phenyl)methanol (**6**):

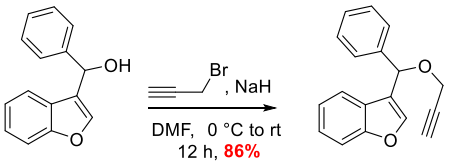


6

At 0 °C, a solution of benzofuran-3-carbaldehyde (6.0 g, 41.05 mmol) in dry THF (40 ml) was added PhMgBr (49.62 ml, 49.26 mmol, 1 M solution in THF) and stirred for 12 h at room temperature. After completion of reaction as indicated by TLC, the reaction was quenched by adding saturated ammonium chloride solution and extracted using ethyl acetate (3x50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→15% ethyl acetate in petroleum ether) to afford **6** (8.10 g, 88%) as a yellow solid.

R_f = 0.5 (15% ethyl acetate in petroleum ether); mp 59–61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.38 (br. s., 1H), 5.90 (s, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.22–7.28 (m, 3H), 7.32–7.37 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 69.5 (d), 111.5 (d), 120.6 (d), 122.6 (d), 123.7 (s), 124.5 (d), 126.1 (s), 126.6 (d, 2C), 128.0 (d), 128.6 (d, 2C), 142.0 (s), 142.4 (d), 155.7 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{12}O_2Na$: 247.0730 $[M+Na]^+$; found: 247.0726.

3-(Phenyl(prop-2-yn-1-yloxy)methyl)benzofuran (**7**)**:**



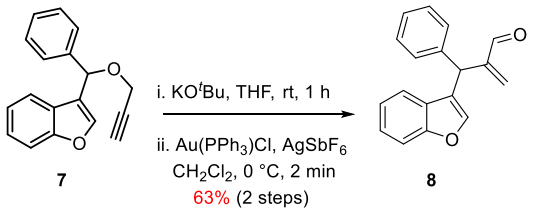
6 **7**

At 0 °C, a solution of **6** (6.20 g, 27.64 mmol) in dry DMF (30 mL) was treated with NaH (1.65 g, 41.46 mmol, 60% dispersion in mineral oil) and stirred for 20 min. To this propargyl bromide (3.13 mL, 33.17 mmol, 80 wt. % in toluene) was added dropwise and allowed to stirr for 12 h at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was cooled to 0 °C and treated with sat. NaCl. The reaction

mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (3X50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford **7** (6.23 g, 86%) as yellow oil.

R_f = 0.5 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.53 (t, J = 2.3 Hz, 1H), 4.16 (dd, J = 2.3, 15.9 Hz, 1H), 4.26 (dd, J = 2.3, 15.9 Hz, 1H), 5.95 (s, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.33–7.43 (m, 4H), 7.47–7.52 (m, 3H), 7.58 (d, J = 7.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.4 (t), 74.5 (d), 74.9 (d), 79.6 (s), 111.5 (d), 120.8 (d), 121.4 (s), 122.7 (d), 124.5 (d), 126.3 (s), 127.4 (d, 2C), 128.2 (d), 128.5 (d, 2C), 139.1 (s), 143.2 (d), 155.7 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{14}O_2Na$: 285.0886 $[M+Na]^+$; found: 285.0883.

2-(Benzofuran-3-yl(phenyl)methyl)acrylaldehyde (8):



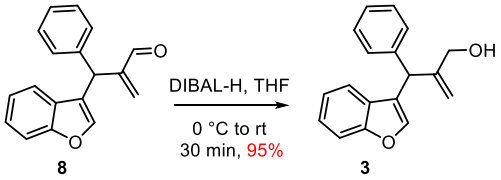
A solution of **7** (1.50 g, 5.71 mmol) in dry THF (20 mL) was treated with KO^{t}Bu (642 mg, 5.71 mmol) at room temperature and stirred for 1 h. After completion of reaction as indicated by TLC, the reaction mixture cooled to 0 °C and quenched by adding water. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude allene was directly used for the next step.

The crude allene was dissolved in dry CH_2Cl_2 (20 ml) and cooled to 0 ºC. To this, added a premixed solution of $Au(PPh_3)Cl$ (28 mg, 0.057 mmol) and $AgSbF_6$ (72 mg, 0.28 mmol) in dichloromethane (5 mL) and stirred for 2 min and the reaction was quenched by adding water. The contents were partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted using CH_2Cl_2 (2x50 mL). The combined organic layer was washed with brine solution, dried (Na_2SO_4) and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0→5% ethyl acetate in petroleum ether) to afford **8** (945 mg, 63% over 2 steps) as a yellow solid.

R_f = 0.3 (5% ethyl acetate in petroleum ether); Mp 92–94 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.48 (s, 1H), 6.20 (d, J = 1.1 Hz, 1H), 6.32 (s, 1H), 7.11 (d, J = 1.1 Hz, 1H), 7.18–7.21 (m, 1H), 7.29–7.33 (m, 5H), 7.35–7.38 (m, 2H), 7.50 (d, J = 8.1 Hz, 1H), 9.73 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 39.5 (d), 111.6 (d), 120.2 (d), 121.7 (s), 122.5 (d), 124.5 (d), 127.0 (s), 127.1 (d), 128.5 (d, 2C), 128.6 (d, 2C), 136.3 (t), 139.5 (s), 143.7 (d), 150.5 (s), 155.8 (s), 192.9 (d) ppm; **HRMS** (ESI) calcd for $C_{18}H_{14}O_2Na$: 285.0886 $[M+Na]^+$; found: 285.0882.

2-(Benzofuran-3-yl(phenyl)methyl)prop-2-en-1-ol (3):

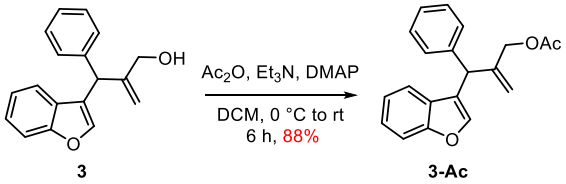


At 0 °C, a solution of **8** (2.41 g, 9.18 mmol) in of dry THF (20 mL) was treated with a 25% solution of DIBAL-H in toluene (6.79 mL, 11.94 mmol) dropwise over 5 min. The reaction mixture was slowly brought to room temperature and stirred for 30 min. After completion of reaction as indicated by TLC, the reaction mixture was cooled to 0 °C and excess of DIBAL-H was quenched by adding methanol dropwise followed by saturated solution of sodium potassium tartarate. The reaction mixture was portioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (3x50 mL). The combined organic layers was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→20% ethyl acetate in petroleum ether) to afford **3** (2.31 g, 95%) as a yellow oil.

R_f = 0.5 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.11 (s, 2H), 4.80 (s, 1H), 4.87 (s, 1H), 5.29 (s, 1H), 7.03 (s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.18–7.26 (m, 6H), 7.34 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ 44.4 (d), 65.6 (t), 111.5 (d), 113.7 (t), 120.5 (d), 122.3 (s), 122.4 (d), 124.3 (d), 127.0 (d), 127.5 (s), 128.6 (d, 4C), 140.3 (s), 143.6 (d), 148.9 (s), 155.7 (s) ppm; **HRMS** (ESI) calcd for $C_{18}H_{16}O_2Na$: 287.1043 $[M+Na]^+$; found: 287.1038.

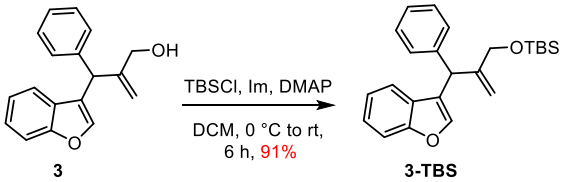
2-(Benzofuran-3-yl(phenyl)methyl)allyl acetate (**3-Ac**)**:**



At 0 °C, a solution of **3** (230 mg, 0.87 mmol) and DMAP (10.6 mg, 0.087 mmol) in CH_2Cl_2 (5 ml) was treated with Et_3N (363 µl, 2.61 mmol) followed by Ac_2O (164 µl, 1.74 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h. After completion of reaction as indicated by TLC, it was quenched by adding sat. NH_4Cl. The reaction mixture was portioned between water (10 mL) and dichloromethane (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (5→10% ethyl acetate in petroleum ether) to afford **3-Ac** (234 mg, 88%) as a brown oil.

R_f = 0.5 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 4.65 (s, 2H), 4.92 (s, 1H), 4.97 (s, 1H), 5.40 (s, 1H), 7.12 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.28–7.39 (m, 6H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.8 (q), 45.0 (d), 66.5 (t), 111.5 (d), 116.3 (t), 120.5 (d), 122.1 (s), 122.4 (d), 124.3 (d), 127.1 (d), 127.4 (s), 128.6 (d, 4C), 139.7 (s), 143.8 (d), 143.9 (s), 155.7 (s), 170.6 (s) ppm; **HRMS** (ESI) calcd for $C_{20}H_{18}O_3Na$: 329.1148 $[M+Na]^+$; found: 329.1145.

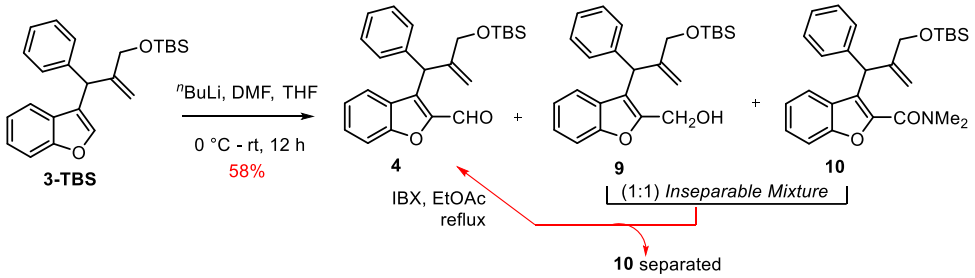
((2-(Benzofuran-3-yl(phenyl)methyl)allyl)oxy)(tert-butyl)dimethylsilane (**3-TBS**):



At 0 °C, to a stirred solution of **3** (1.80 g, 6.80 mmol) in dry CH_2Cl_2 (15 mL) imidazole (1.39 g, 20.42 mmol) and DMAP (83 mg, 0.68 mmol) was added TBSCl (1.53 g, 10.21 mmol) and stirred for 6 h at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane (50 mL) and was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→3% ethyl acetate in petroleum ether) to afford **3-TBS** (2.34 g, 91%) as a yellow oil

R_f = 0.5 (5% Ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.92 (s, 9H), 4.17 (s, 2H), 4.81 (s, 1H), 4.92 (s, 1H), 5.36 (s, 1H), 7.08 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.25–7.35 (m, 6H), 7.45 (dd, J = 3.3, 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ –5.4 (q, 2C), 18.3 (s), 25.9 (q, 3C), 43.9 (d), 65.6 (t), 111.4 (d), 112.9 (t), 120.6 (d), 122.3 (d), 122.7 (s), 124.2 (d), 126.8 (d), 127.7 (s), 128.5 (d, 2C), 128.7 (d, 2C), 140.5 (s), 143.6 (d), 148.6 (s), 155.7 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{31}O_2Si$: 379.2088 $[M+H]^+$; found: 379.2080.

Formylation at C2 of benzofuran 3-TBS:

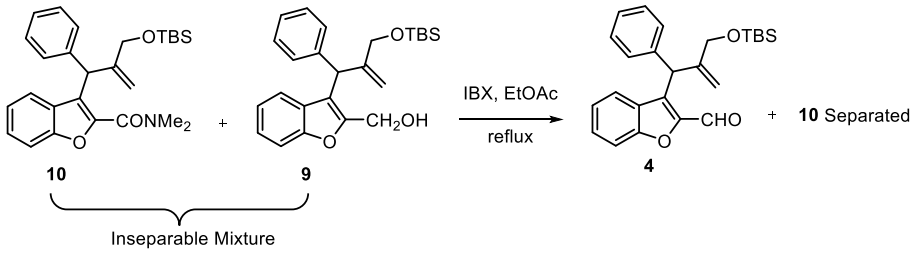


At 0 °C, a solution of **3-TBS** (300 mg, 0.79 mmol) in dry THF (10 mL) was treated with ^{n}BuLi (0.99 mL, 1.58 mmol, 1.6 M in *n*-hexane) and stirred for 30 min at the same temperature. To this, anhydrous DMF (0.37 mL, 4.75 mmol) was added and the reaction mixture was slowly brought to room temperature and stirred for 12 h. The reaction mixture quenched by adding saturated ammonium chloride solution and was portioned between water (50 mL) and ethyl acetate (mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine solution, was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3→20% ethyl acetate in

petroleum ether) to afford **4** (187 mg, 58%) as a yellow solid and an inseparable mixture of **9** & **10** (74 mg, 1:1 ratio) as a brown oil.

3-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-phenylallyl)benzofuran-2-carbaldehyde (4): R_f = 0.5 (5% ethyl acetate in petroleum ether); Mp 88–89 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.90 (s, 9H), 4.22 (d, J = 6.5 Hz, 2H), 4.86 (s, 1H), 5.49 (s, 1H), 5.71 (s, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.29 (dd, J = 4.0, 8.4 Hz, 1H), 7.35 (d, J = 4.2 Hz, 4H), 7.49 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H),7.62 (d, J = 8.0 Hz, 1H), 9.75 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ –5.5 (q), –5.6 (q), 18.2 (s), 25.8 (q, 3C), 43.5 (d), 65.7 (t), 112.6 (d), 114.6 (t), 123.6 (d), 123.7 (d), 127.3 (d), 127.7 (s), 128.7 (d, 2C), 128.9 (d, 2C), 129.0 (d), 132.5 (s), 139.4 (s), 148.4 (s), 148.5 (s), 155.3 (s), 180.4 (d) ppm; **HRMS** (ESI) calcd for $C_{25}H_{30}O_3SiNa$: 429.1856 $[M+Na]^+$; found: 429.1854.

3-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-phenylallyl)-N,N-dimethylbenzofuran-2-amine (10):

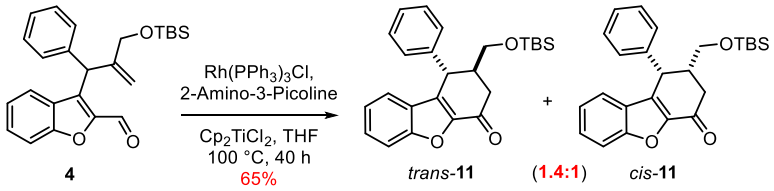


To the mixture of **9**/**10** (74 mg) in 10 mL of EtOAc was added IBX (51 mg) and refluxed for 6 h. After completion of reaction, the contents were filtered using celite pad and concentrated under reduced pressure. Purification by silica gel column chromatography (3→20% ethyl acetate in petroleum ether) gave **4** (26 mg, 8% With respect to **3-TBS**) as a yellow solid and unreacted **10** (36 mg, 10% With respect to **3-TBS**) as a yellow oil.

R_f = 0.3 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.90 (s, 9H), 2.98 (s, 3H), 3.02 (s, 3H), 4.18 (d, J = 4.2 Hz, 2H), 4.95 (s, 1H), 5.43 (s, 1H), 5.47 (s, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 7.28–7.32 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ –5.5 (q, 2C), 18.3 (s), 25.9 (q, 3C), 35.3 (q), 38.3 (q), 43.7 (d), 65.6 (t), 111.6 (d), 112.8 (t), 122.5 (d), 122.8 (s), 122.9 (d), 125.5 (d), 126.6

(d), 127.8 (s), 128.2 (d, 2C), 129.1 (d, 2C), 140.2 (s), 145.4 (s), 148.6 (s), 153.7 (s), 162.1 (s) ppm; **HRMS** (ESI) calcd for $C_{27}H_{36}O_3NSi$: 450.2459 $[M+H]^+$; found: 450.2456.

Rhodium catalyzed intramolecular hydroacylation:



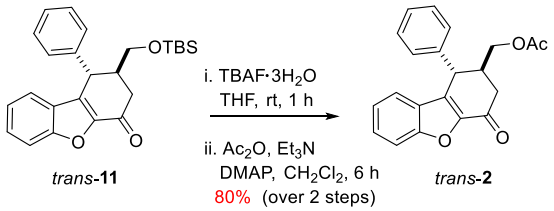
An oven dried screw cap pressure tube was charged with a solution of aldehyde **4** (62 mg, 0.15 mmol), 2-amino-3-picoline (16.5 mg, 0.15 mmol) in dry THF (3 mL) was purged with argon gas for 5 min prior to adding Cp_2TiCl_2 (3.8 mg, 0.015 mmol) and $Rh(PPh_3)_3Cl$ (14.1 mg, 0.015 mmol). The solution was again purged with argon gas for another 5 min, capped and heated at 100 °C for 40 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→10% ethyl acetate in petroleum ether) to afford a mixture of *trans*-**11** and *cis*-**11** (40 mg, 65%). Both the compounds obtained as colorless solids after HPLC purification.

(±)-**2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-phenyl-2,3-dihydrodibenzo[b,d]furan-4(1H)-one** (*cis*-**11**): R_f = 0.5 (10% ethyl acetate in petroleum ether); Mp 98–100 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.95 (s, 9H), 2.54 (dd, J = 5.6, 17.2 Hz, 1H), 2.59 (dd, J = 11.5, 17.2 Hz, 1H), 2.91–2.98 (m, 1 H), 3.33 (dd, J = 8.2, 10.2 Hz, 1H), 3.36 (dd, J = 6.2, 10.2 Hz, 1H), 4.76 (d, J = 5.1 Hz, 1H), 7.21–7.25 (m, 3H), 7.28–7.33 (m, 3H), 7.41 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ –5.4 (q), –5.5 (q), 18.2 (s), 25.9 (q, 3C), 37.1 (t), 39.7 (d), 43.2 (d), 63.6 (t), 112.8 (d), 122.2 (d), 123.7 (d), 125.7 (s), 127.5 (d), 128.5 (d, 2C), 129.2 (d), 129.3 (d, 2C), 135.7 (s), 136.2 (s), 148.2 (s), 156.4 (s), 187.7 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{31}O_3Si$: 407.2037 $[M+H]^+$; found: 407.2035.

(±)-**2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-phenyl-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (*trans*-11):** Isolated by column chromatography (petroleum ether/ethyl acetate = 9:1, R_f = 0.5); Mp 88–90 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H),

0.94 (s, 9H), 2.59–2.66 (m, 1H), 2.80 (dd, *J* = 4.0, 16.8 Hz, 1H), 3.00 (dd, *J* = 12.0, 16.8 Hz, 1H), 3.50 (dd, *J* = 3.1, 10.3 Hz, 1H), 3.56 (dd, *J* = 3.9, 10.3 Hz, 1 H), 4.50 (d, *J* = 9.5 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 7.28–7.29 (m, 2H), 7.38–7.43 (m, 4H), 7.57 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ –5.5 (q), –5.6 (q), 18.2 (s), 25.8 (q, 3C), 41.3 (t), 41.9 (d), 47.8 (d), 62.8 (t), 112.7 (d), 123.0 (d), 123.4 (d), 126.2 (s), 127.6 (d), 128.7 (d), 128.8 (d, 2C), 128.9 (d, 2C), 136.2 (s), 140.2 (s), 147.5 (s), 156.4 (s), 188.4 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{31}O_3Si$: 407.2037 $[M+H]^+$; found: 407.2035.

4-Oxo-1-phenyl-1,2,3,4-tetrahydrodibenzo[b,d]furan-2-yl)methyl acetate (*trans*-2) :



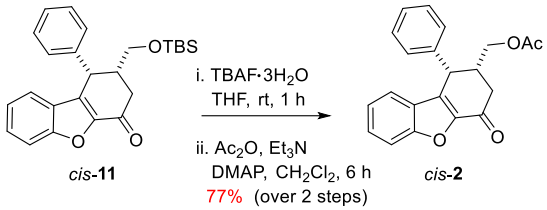
To a solution of *trans*-**11** (30 mg, 0.07 mmol) in THF (5 ml) was added TBAF (23 mg, 0.07 mmol) and stirred for 1 h. After completion of reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate (100 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude alcohol was directly used for the next step.

The crude alcohol was dissolved in dry CH_2Cl_2 (20 ml) and cooled to 0 ºC. To this, was added DMAP (1 mg, 0.007 mmol), Et_3N (31 µl, 0.22 mmol) followed by Ac_2O (14 µl, 0.15 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h. After completion of reaction as indicated by TLC, it was quenched by adding sat. NH_4Cl. The reaction mixture was portioned between water (10 mL) and dichloromethane (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (5→10% ethyl acetate in petroleum ether) to afford *trans*-**2** (20 mg, 80% over 2 steps) colorless solid.

R_f = 0.5 (10% ethyl acetate in petroleum ether); Mp 135–137 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.80–2.85 (m, 1H), 2.86–2.89 (m, 1H), 2.93 (dd, *J* = 2.4, 14.4 Hz,

1H), 4.04 (dd, *J* = 5.2, 11.4 Hz, 1H), 4.09 (dd, *J* = 3.5, 11.4 Hz, 1H), 4.35 (d, *J* = 9.4 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 7.05 (td, *J* = 0.7, 8.0 Hz, 1H), 7.26–7.28 (m, 2H), 7.38–7.45 (m, 4H), 7.59 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.7 (q), 41.1 (t), 43.1 (d), 44.4 (d), 64.8 (t), 112.8 (d), 122.9 (d), 123.6 (d), 125.9 (s), 128.0 (d), 128.6 (d, 2C), 129.0 (d), 129.1 (d, 2C), 135.5 (s), 139.3 (s), 147.3 (s), 156.4 (s), 170.7 (s), 186.8 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{18}O_4Na$: 357.1097 $[M+Na]^+$; found: 357.1091.

4-Oxo-1-phenyl-1,2,3,4-tetrahydrodibenzo[b,d]furan-2-yl)methyl acetate (*cis*-2):



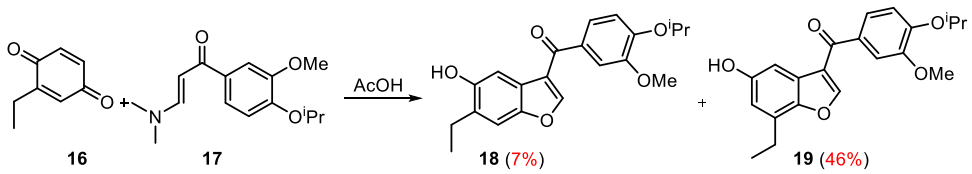
To a solution of *cis*-**11** (26 mg, 0.06 mmol) in THF (5 ml) was added TBAF (20 mg, 0.06 mmol) and stirred for 1 h. After completion of reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate (100 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude alcohol was directly used for the next step.

The crude alcohol was dissolved in dry CH_2Cl_2 (20 ml) and cooled to 0 ºC. To this, was added DMAP (1 mg, 0.007 mmol), Et_3N (25 µl, 0.18 mmol) followed by Ac_2O (14 µl, 0.15 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h. After completion of reaction as indicated by TLC, it was quenched by adding sat. NH_4Cl. The reaction mixture was portioned between water (10 mL) and dichloromethane (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (5→10% ethyl acetate in petroleum ether) to afford *cis*-**2** (19 mg, 77% over 2 steps) as colorless solid.

R_f = 0.5 (10% ethyl acetate in petroleum ether); Mp 148–150 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.61 (dd, *J* = 4.7, 17.2 Hz, 1H), 2.67 (dd, *J* = 12.5, 17.2 Hz, 1H), 3.06–3.13 (m, 1H), 3.84 (d, *J* = 7.2 Hz, 2H), 4.66 (d, *J* = 5.2 Hz, 1H), 7.15 (dd, *J* = 1.7, 8.1 Hz, 2H), 7.19–7.22 (m, 1H), 7.27–7.32 (m, 3H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.46 (ddd, *J* =

1.2, 7.2, 8.5 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.8 (q), 37.1 (t), 39.4 (d), 40.3 (d), 65.0 (t), 113.0 (d), 122.1 (d), 123.9 (d), 125.4 (s), 128.0 (d), 128.9 (d, 2C), 129.0 (d, 2C), 129.4 (d), 135.1 (s), 135.6 (s), 147.9 (s), 156.5 (s), 170.6 (s), 186.7 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{18}O_4Na$: 357.1097 $[M+Na]^+$; found: 357.1090.

Condensation of benzoquinone 16 and enaminone 17:



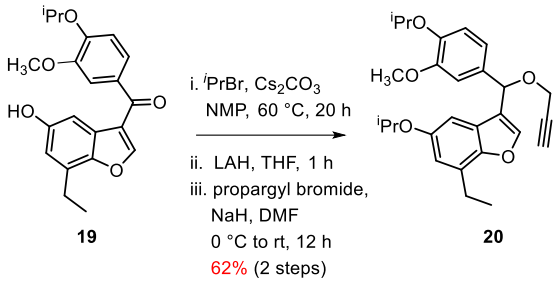
To a solution of ethyl-1,4-benzoquinone (269 mg, 1.97 mmol) in 5 mL of AcOH was added **17** (520 mg, 1.97 mmol) at room temperature and stirred for 12 h. The precipitate formed after 12 h was filtered and washed with water. The product was then purified by silica gel column chromatography (5→10% ethyl acetate in petroleum ether) to afford **18** (46 mg, 7%) and **19** (324 mg, 46%) as colorless solids.

(6-Ethyl-5-hydroxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methanone (**18**): R_f = 0.5 (10% ethyl acetate in petroleum ether); Mp 199–200 °C ; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.5 Hz, 3H), 1.44 (d, *J* = 6.1 Hz, 6H), 2.78 (q, *J* = 7.5 Hz, 2H), 4.01 (s, 3H), 4.69 (hept, *J* = 6.1 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 7.33 (s, 1H), 7.52 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 8.06 (s, 1H), 8.10 (s, 1H), 8.12 (br. s., 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (q), 21.9 (q, 2C), 23.8 (t), 56.0 (q), 71.3 (d), 106.8 (d), 111.0 (d), 112.0 (d), 112.9 (d), 120.8 (s), 123.5 (s), 123.6 (d), 130.5 (s), 131.4 (s), 150.3 (s), 150.5 (s), 151.8 (s), 152.1 (d), 152.6 (s), 190.6 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{23}O_5$: 355.1540 $[M+H]^+$; found: 355.1537.

(7-Ethyl-5-hydroxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl) methanone (**19**)**:** R_f = 0.4 (10% ethyl acetate in petroleum ether); Mp 184–185 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.5 Hz, 3H), 1.43 (d, *J* = 6.1 Hz, 6H), 2.90 (q, *J* = 7.6 Hz, 2H), 3.97 (s, 3H), 4.68 (hept, *J* = 6.1 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 7.50–7.52 (m, 2H), 7.88 (br. s., 1H), 7.93 (br. s., 1H), 8.08 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (q), 22.0 (q, 2C), 22.7 (t), 56.2 (q), 71.3 (d), 104.7 (d), 112.1 (d), 113.0 (d), 114.2 (d), 121.1 (s), 123.4 (d), 125.6 (s), 128.8 (s), 131.5 (s), 149.1 (s), 150.1 (s), 151.8 (s),

152.5 (d), 154.5 (s), 190.6 (s) ppm; **HRMS** (ESI) calcd for $C_{21}H_{23}O_5$: 355.1540 $[M+H]^+$; found: 355.1538.

7-Ethyl-5-isopropoxy-3-((4-isopropoxy-3-methoxyphenyl)(prop-2-yn-1-yloxy)methyl)benzofuran (**20**):



To a solution of **19** (2.9 g, 8.18 mmol) in NMP (20 mL) was added Cs_2CO_3 (5.33 g, 16.36 mmol) at room temperature and stirred for 15 min. To this, 2-bromopropane (1.15 mL, 12.27 mmol) was added and stirred at 60 °C for 20 h. After completion of reaction as indicated by TLC, the reaction was quenched with water and extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude compound was directly used for the next step.

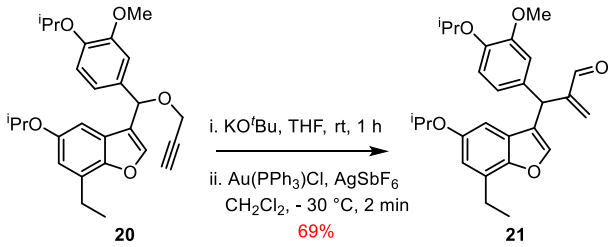
At 0 °C, a solution of crude isopropyl ether (3.24 g, 8.18 mmol) in dry THF (15 mL) was added LAH (467 mg, 12.27 mmol) and stirred for 1 h. The excess LAH was quenched by adding ethyl acetate followed by sat. Na_2SO_4. The contents were then diluted with ethyl acetate (100 mL) and filtered through Celite pad. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude alcohol was directly used for the next step.

At 0 °C, a solution of crude alcohol (3.25 g, 8.16 mmol) in dry DMF (15 mL) was treated with NaH (489 mg, 12.24 mmol, 60% dispersion in mineral oil) and stirred at same temperature for 20 min. To this propargyl bromide (0.74 mL, 9.79 mmol, 80 wt. % in toluene) was added dropwise and the contents allowed to stir at room temperature for 12 h. After completion of reaction as indicated by TLC, the reaction was cooled to 0 °C and quenched by adding cold water. The contents were partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was

extracted using ethyl acetate (2x50 mL). The combined organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→10% ethyl acetate in petroleum ether) to afford **20** (2.21 g, 62% over 3 steps) as a brown liquid.

R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.27–1.30 (m, 9H), 1.36 (d, *J* = 6.0 Hz, 6H), 2.49 (t, *J* = 2.3 Hz, 1H), 2.83 (q, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 4.12 (dd, *J* = 2.3, 16.0 Hz, 1H), 4.23 (dd, *J* = 2.3, 16.0 Hz, 1 H), 4.44 (hept, *J* = 6.1 Hz, 1H), 4.52 (hept, *J* = 6.1 Hz, 1H), 5.79 (s, 1H), 6.70 (br. d, *J* = 2.1 Hz, 1H), 6.86–6.87 (m, 2H), 6.96 (d, *J* = 1.7, 8.2 Hz, 1H), 7.01 (br. d, *J* = 1.7 Hz, 1H), 7.32 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.9 (q), 22.1 (q, 4C), 22.8 (t), 55.3 (t), 56.0 (q), 70.6 (d), 71.4 (d), 74.5 (d), 74.6 (d), 79.9 (s), 103.2 (d), 111.1 (d), 114.7 (d), 115.2 (d), 120.1 (d), 121.7 (s), 126.4 (s), 128.7 (s), 131.9 (s), 143.4 (d), 147.3 (s), 149.4 (s), 150.5 (s), 154.0 (s) ppm; **HRMS** (ESI) calcd for $C_{27}H_{33}O_5$: 437.2323 $[M+H]^+$; found: 437.2326.

2-((7-Ethyl-5-isopropoxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methyl)acrylaldehyde (21):



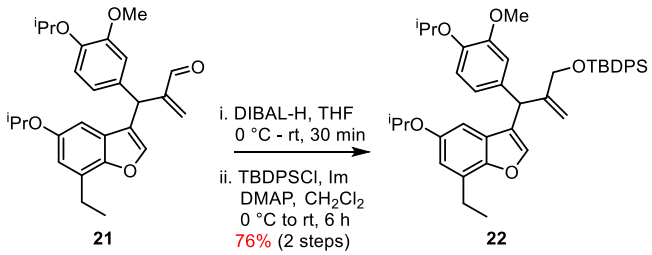
A solution of **20** (1.3 g, 2.97 mmol) in dry THF (15 mL) was treated with KO^{t}Bu (334 mg, 2.97 mmol) at room temperature and stirred for 1 h. After completion of reaction as indicated by TLC, the reaction mixture cooled to 0 °C and quenched by adding water. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude allene was directly used for the next step.

The crude allene was dissolved in dry CH_2Cl_2 (15 ml) and cooled to –30 ºC. To this, added a premixed solution of $Au(PPh_3)Cl$ (15 mg, 0.029 mmol) and $AgSbF_6$ (51 mg, 0.148 mmol) in dichloromethane (10 mL) and stirred for 2 min and the reaction was quenched by

adding water. The contents were partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted using CH_2Cl_2 (2x50 mL). The combined organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→10% ethyl acetate in petroleum ether) to afford **21** (897 mg, 69% over 2 steps) as a brown oil.

R*f* = 0.3 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.26–1.31 (m, 9H), 1.34 (d, *J* = 6.1 Hz, 6H), 2.84 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 3H), 4.40 (hept, *J* = 6.1 Hz, 1H), 4.48 (hept, *J* = 6.1 Hz, 1 H), 5.29 (s, 1H), 6.16 (s, 1H), 6.26 (s, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.71–6.73 (m, 2H), 6.77 (d, *J* = 1.9 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H) , 9.69 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.9 (q), 22.0 (q, 2C), 22.1 (q, 2C), 22.8 (t), 39.2 (d), 56.0 (q), 70.9 (d), 71.3 (d), 103.3 (d), 112.6 (d), 114.4 (d), 115.5 (d), 120.3 (d), 122.1 (s), 127.0 (s), 128.7 (s), 132.3 (s), 136.1 (t), 144.0 (d), 146.3 (s), 149.4 (s), 150.4 (s), 150.6 (s), 153.8 (s), 193.2 (d) ppm; **HRMS** (ESI) calcd for $C_{27}H_{32}O_5Na$: 459.2142 $[M+Na]^+$; found: 459.2141.

***tert*-Butyl((2-((7-ethyl-5-isopropoxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methyl)allyl)oxy)diphenylsilane (22):**



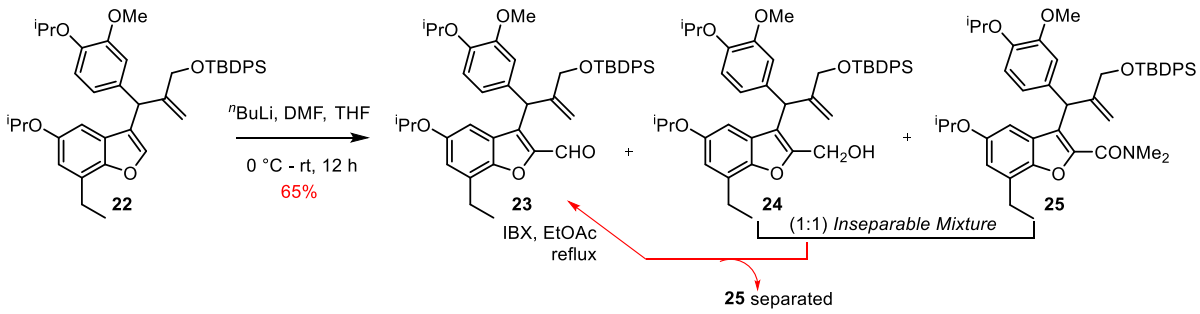
At 0 °C, a solution of **21** (872 mg, 1.99 mmol) in of dry THF (10 mL) was treated with a 25% solution of DIBAL-H in toluene (1.47 mL, 2.59 mmol) dropwise over 5 min. The reaction mixture was slowly brought to room temperature and stirred for 30 min. After completion of reaction as indicated by TLC, the reaction mixture was cooled to 0 °C and excess of DIBAL-H was quenched by adding methanol dropwise followed by saturated solution of sodium potassium tartarate. The reaction mixture was portioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer

was extracted using ethyl acetate (3x50 mL). The combined organic layers was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude alcohol was directly used for the next step.

At 0 °C, to a stirred solution of crude alcohol (876 mg, 1.99 mmol) in dry CH_2Cl_2 (10 mL) imidazole (204 mg, 2.99 mmol) and DMAP (24 mg, 0.19 mmol) was added TBDPSCl (0.52 mL, 2.99 mmol) and stirred for 6 h at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→3% ethyl acetate in petroleum ether) to afford **22** (1.02 g, 76%) as a brown oil.

R_f = 0.5 (5% Ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.26 (d, J = 6.1 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.32 (t, J = 7.5 Hz, 3H), 1.37 (d, J = 6.1 Hz, 6H), 2.86 (q, J = 7.5 Hz, 2H), 3.77 (s, 3H), 4.21 (s, 2H), 4.42 (hept, J = 6.1 Hz, 1H), 4.50 (hept, J = 6.1 Hz, 1H), 4.85 (s, 1H), 4.87 (s, 1H), 5.40 (s, 1H), 6.72–6.75 (m, 3H), 6.80–6.83 (m, 2H), 6.96 (s, 1H), 7.32–7.35 (m, 4H), 7.38–7.42 (m, 2H), 7.61–7.66 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0 (q), 19.3 (s), 22.0 (q, 2C), 22.1 (q, 2C), 22.8 (t), 26.8 (q, 3C), 43.6 (d), 55.9 (q), 66.3 (t), 70.7 (d), 71.3 (d), 103.6 (d), 112.6 (d), 113.1 (t), 114.3 (d), 115.6 (d), 120.6 (d), 123.0 (s), 127.6 (d, 4C), 128.5 (s), 129.6 (d, 2C), 133.4 (s, 2C), 135.5 (d, 4C), 143.9 (d), 146.0 (s), 148.3 (s, 2C), 149.3 (s), 150.2 (s), 153.7 (s, 2C) ppm; **HRMS** (ESI) calcd for $C_{43}H_{52}O_5SiNa$: 699.3476 $[M+Na]^+$; found: 699.3472.

3-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1-(4-isopropoxy-3-methoxyphenyl)allyl)-7-ethyl-5-isopropoxybenzofuran-2-carbaldehyde (23):

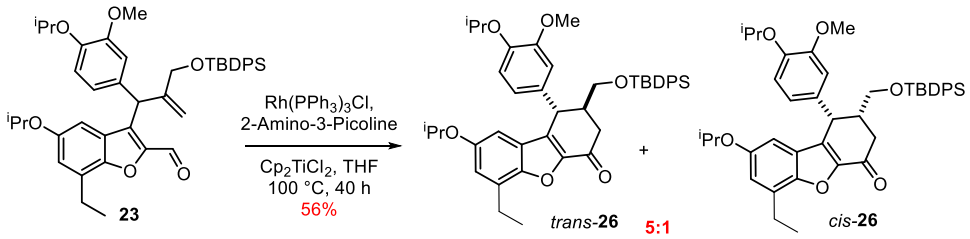


At 0 °C, a solution of **22** (208 mg, 0.30 mmol) in dry THF (10 mL) was treated with ^{n}BuLi (0.38 mL, 0.61 mmol, 1.6 M in *n*-hexane) and stirred for 30 min at the same temperature.

To this, anhydrous DMF (0.14 mL, 1.84 mmol) was added and the reaction mixture was slowly brought to room temperature and stirred for 12 h. The reaction mixture quenched by adding saturated ammonium chloride solution and was portioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine solution, was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3→20% ethyl acetate in petroleum ether) to afford **23** (141 mg, 65%) as a yellow oil and an inseparable mixture of **24** & **25** (52 mg, 1:1 ratio) as a brown oil.

R_f = 0.5 (5% ethyl acetate in petroleum ether; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (s, 9H), 1.16 (d, *J* = 6.1 Hz, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.26 (t, *J* =7.7 Hz, 3H), 1.29 (d, *J* = 6.3 Hz, 6H), 2.84 (q, *J* = 7.6 Hz, 2H), 3.66 (s, 3H), 4.12–4.19 (m, 2H), 4.22–4.26 (m, 1H), 4.42 (hept, *J* = 6.1 Hz, 1H), 4.81 (s, 1H), 5.45 (s, 1H), 5.53 (s, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.70–6.74 (m, 3H), 6.83 (d, *J* = 2.6 Hz, 1H), 7.19–7.23 (m, 2H), 7.26–7.33 (m, 4H), 7.45–7.47 (m, 2H), 7.52–7.54 (m, 2H), 9.60 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7 (q), 19.2 (s), 21.7 (q), 21.9 (q), 22.0 (q, 2C), 22.5 (t), 26.7 (q, 3C), 43.1 (d), 55.9 (q), 66.2 (t), 70.4 (d), 71.2 (d), 103.7 (d), 112.9 (d), 114.4 (t), 115.0 (s), 115.1 (d), 119.8 (d), 120.8 (d), 127.6 (d, 2C), 127.7 (d, 2C), 129.7 (d, 2C), 130.0 (s), 132.0 (s), 132.9 (s), 132.9 (s), 133.1 (s), 135.4 (d, 4C), 146.4 (s), 148.4 (s), 148.6 (s), 149.4 (s), 150.3 (s), 154.3 (s), 180.4 (d) ppm; **HRMS** (ESI) calcd for $C_{44}H_{52}O_6SiNa$: 727.3425 $[M+Na]^+$; found: 727.3422.

Rhodium catalyzed intramolecular hydroacylation:



An oven dried screw cap pressure tube was charged with a solution of aldehyde **23** (190 mg, 0.26 mmol), 2-amino-3-picoline (29 mg, 0.26 mmol) in dry THF (3 mL) was purged with argon gas for 5 min prior to adding Cp_2TiCl_2 (6.7 mg, 0.026 mmol) and $Rh(PPh_3)_3Cl$ (24.9 mg, 0.026 mmol). The solution was again purged with argon gas for another 5 min,

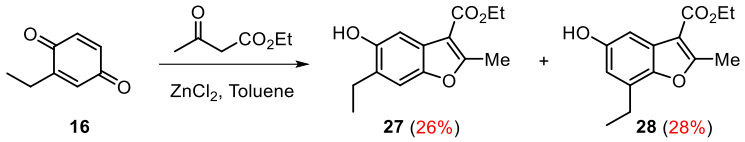
capped and heated at 100 °C for 40 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford a mixture of *trans*-**26** and *cis*-**26** (106 mg, 56%). Both the compounds obtained as colorless solids after HPLC purification.

(±)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-6-ethyl-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (*trans*-**26**): R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.10 (s, 12H), 1.22 (d, *J* = 5.9 Hz, 3H), 1.33 (t, *J* = 7.6 Hz, 3H), 1.40 (br. d, *J* = 5.6 Hz, 6H), 2.60–2.65 (m, 1H), 2.81 (dd, *J* = 3.3, 16.7 Hz, 1H), 2.88–2.98 (m, 2H), 3.09 (dd, *J* = 12.3, 16.6 Hz, 1H), 3.54 (dd, *J* = 2.4, 10.4 Hz, 1H), 3.67 (dd, *J* = 3.9, 10.4 Hz, 1H), 3.70 (s, 3H), 4.07–4.17 (m, 1H), 4.49–4.56 (m, 2H), 5.86 (br. s, 1H), 6.76–6.77 (m, 2H), 6.84–6.86 (m, 2H), 7.33–7.38 (m, 4H), 7.41–7.43 (m, 2H), 7.59–7.62 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.9 (q), 19.4 (s), 21.5 (q), 21.9 (q), 22.1 (q, 2C), 22.6 (t), 26.9 (q, 3C), 41.7 (t), 42.0 (d), 47.8 (d), 56.0 (q), 63.8 (t), 70.2 (d), 71.5 (d), 103.4 (d), 112.5 (d), 115.8 (d), 119.7 (d), 121.2 (d), 126.2 (s), 127.7 (d, 2C), 127.8 (d, 2C), 129.7 (d), 129.7 (s), 129.8 (d), 130.2 (s), 132.9 (s), 132.9 (s), 133.2 (s), 135.5 (d, 4C), 146.7 (s), 147.5 (s), 150.6 (s, 2C), 154.1 (s), 188.2 (s) ppm; **HRMS** (ESI) calcd for $C_{44}H_{52}O_6SiNa$: 727.3425 $[M+Na]^+$; found: 727.3426.

(±)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-6-ethyl-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (*cis*-**26**): R_f = 0.5 (10% ethyl acetate in petroleum ether); Mp 48–50 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.33–1.36 (m, 9H), 2.42 (dd, *J* = 4.0 17.2 Hz, 1H), 2.52 (dd, *J* = 13.0, 17.2 Hz, 1H), 2.87–3.02 (m, 3H), 3.38 (dd, *J* = 5.6, 10.4 Hz, 1H), 3.50 (dd, *J* = 8.9, 10.3 Hz, 1H), 3.68 (s, 3H), 4.42–4.49 (m, 2H), 4.67 (d, *J* = 5.0 Hz, 1H), 6.61–6.63 (m, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 7.34–7.39 (m, 4H), 7.41–7.45 (m, 2H), 7.61–7.63 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (q), 19.2 (s), 21.9 (q, 2C), 22.0 (q), 22.1 (q), 22.7 (t), 26.9 (q, 3C), 37.1 (t), 39.5 (d), 43.2 (d), 56.0 (q), 64.6 (t), 70.7 (d), 71.3 (d), 103.7 (d), 113.4 (d), 115.3 (d), 119.4 (d), 121.4 (d), 125.8 (s), 127.7 (d, 2C), 127.8 (d, 2C), 128.3 (s), 129.8 (d), 129.9 (d), 130.4 (s), 133.1 (s), 133.5 (s), 135.4 (d, 2C), 135.5 (d, 2C), 136.8 (s), 146.7 (s), 148.4

(s), 150.2 (s), 150.3 (s), 154.6 (s), 187.6 (s) ppm; **HRMS** (ESI) calcd for $C_{44}H_{52}O_6SiNa$: 727.3425 $[M+Na]^+$; found: 727.3424.

Condensation of benzoquinone 16 and EAA:

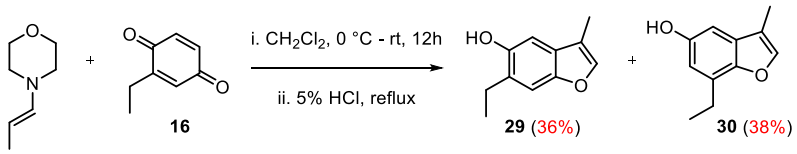


To a solution of ethyl acetoacetate (4.22 g, 32.4 mmol) and ethyl-1,4-benzoquinone, **16** (4.41 g, 32.4 mmol) in dry toluene (50 mL) was added $ZnCl_2$ (5.35 g, 39 mmol) at room temperature. The solution was heated at 70 °C for 15 min. Dean-Stark apparatus was assembled and the solution was further heated at 140 °C for 12 h. After completion of reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate and filtered through Celite pad. The filtrate was treated with brine solution and the organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→15% ethyl acetate in petroleum ether) to afford **27** (2.22 g, 26%) and **28** (2.28 g, 28%) as colorless solids.

Ethyl 6-ethyl-5-hydroxy-2-methylbenzofuran-3-carboxylate (**27**)**:** R_f = 0.5 (15% ethyl acetate in petroleum ether); Mp 148–149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.5 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H), 2.69–2.75 (m, 5H), 4.38 (q, J = 7.1 Hz, 2H), 5.49 (br. s., 1H), 7.18 (s, 1H), 7.40 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 14.4 (q), 14.6 (q), 23.5 (t), 60.4 (t), 106.4 (d), 108.7 (s), 110.4 (d), 124.7 (s), 128.1 (s), 148.7 (s), 150.7 (s), 163.4 (s), 164.9 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{17}O_4$: 249.1121 $[M+H]^+$; found: 249.1121.

Ethyl 7-ethyl-5-hydroxy-2-methylbenzofuran-3-carboxylate (**28**)**:** R_f = 0.4 (15% ethyl acetate in petroleum ether); Mp 139–140 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.29 (t, J = 7.6 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H), 2.73 (s, 3H), 2.83 (q, J = 7.6 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 6.65 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0 (q), 14.4 (q), 14.7 (q), 22.6 (t), 60.3 (t), 104.2 (d), 109.0 (s), 112.1 (d), 126.7 (s), 128.1 (s), 147.1 (s), 152.7 (s), 163.9 (s), 164.9 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{17}O_4$: 249.1121 $[M+H]^+$; found: 249.1120.

Condensation of benzoquinone 16 and 4-(prop-1-en-1-yl)morpholine:

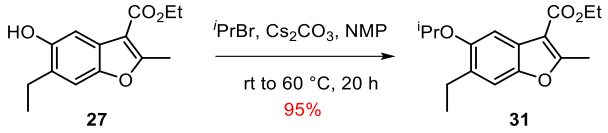


At 0 °C, a solution of ethyl-1,4-benzoquinone (1.07 g, 7.86 mmol) in dry CH_2Cl_2 (25 mL) was treated with 4-(prop-1-en-1-yl)morpholine (1.0 g, 7.86 mmol) dropwise and then stirred at room temperature for 12 h. After completion of reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF (10 mL) and treated with 5% HCl (25 mL) and the contents refluxed until TLC showed complete consumption of starting material. The reaction mixture was cooled and extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford compound **29** (500 mg, 36%) and **30** (526 mg, 38%) as colorless solids.

6-Ethyl-3-methylbenzofuran-5-ol (**29**)**:** R_f = 0.5 (5% ethyl acetate in petroleum ether); Mp 104–105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.5 Hz, 3H), 2.16 (s, 3H), 2.72 (q, J = 7.5 Hz, 2H), 4.75 (br. s., 1H), 6.86 (s, 1H), 7.22 (s, 1H), 7.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 7.9 (q), 14.2 (q), 23.5 (t), 104.2 (d), 111.0 (d), 115.2 (s), 127.4 (s), 127.7 (s), 141.5 (d), 149.3 (s), 150.5 (s) ppm; **HRMS** (ESI) calcd for $C_{11}H_{13}O_2$: 177.0910 $[M+H]^+$; found: 177.0911.

7-Ethyl-3-methylbenzofuran-5-ol (**30**)**:** R_f = 0.4 (5% ethyl acetate in petroleum ether); Mp 74–75 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.6 Hz, 3H), 2.14 (s, 3H), 2.85 (q, J = 7.6 Hz, 2H), 5.89 (br. s., 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 7.37 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 7.8 (q), 13.9 (q), 22.7 (t), 102.0 (d), 112.1 (d), 115.6 (s), 128.6 (s), 129.3 (s), 141.9 (d), 148.8 (s), 151.1 (s) ppm; **HRMS** (ESI) calcd for $C_{11}H_{13}O_2$: 177.0910 $[M+H]^+$; found: 177.0910.

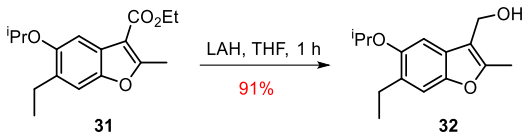
Ethyl 6-ethyl-5-isopropoxy-2-methylbenzofuran-3-carboxylate (**31**):



To a solution of **27** (1.0 g, 4.02 mmol) in NMP (15 Ml) was added Cs_2CO_3 (2.62 g, 8.05 mmol) at room temperature and stirred for 15 min. To this, 2-bromopropane (0.6 mL, 6.04 mmol) was added and stirred at 60 °C for 20 h. After completion of reaction as indicated by TLC, the reaction was quenched with water and extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3% ethyl acetate in petroleum ether) to afford **31** (1.10 g, 95%) as a colorless solid.

R_f = 0.5 (5% ethyl acetate in petroleum ether); Mp: 54–55 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.4 Hz, 3H), 1.36 (d, J = 6.0 Hz, 6H), 1.43 (t, J = 7.1 Hz, 3H), 2.68 (q, J = 7.1 Hz, 2H), 2.71 (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 4.58 (hept, J = 6.0 Hz, 1H), 7.19 (s, 1H), 7.40 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (q), 14.4 (q), 14.5 (q), 22.1 (q, 2C), 23.8 (t), 60.0 (t), 70.6 (d), 105.1 (d), 108.9 (s), 110.5 (d), 124.3 (s), 131.6 (s), 148.4 (s), 152.8 (s), 163.0 (s), 164.7 (s) ppm; **HRMS** (ESI) calcd for $C_{17}H_{23}O_4$: 291.1591 $[M+H]^+$; found: 291.1589.

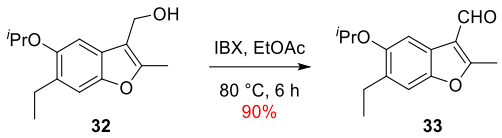
(6-Ethyl-5-isopropoxy-2-methylbenzofuran-3-yl)methanol (**32**):



At 0 °C, a solution of **31** (1.0 g, 3.44 mmol) in dry THF (25 mL) was added LAH (261 mg, 6.88 mmol) and stirred for 1 h. The excess LAH was quenched by adding ethyl acetate followed by sat. Na_2SO_4. The contents were then diluted with ethyl acetate (100 mL) and filtered through Celite pad. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10→20% ethyl acetate in petroleum ether) to afford **32** (778 mg, 91%) as a yellow oil.

R_f = 0.5 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.4 Hz, 3H), 1.34 (d, J = 6.0 Hz, 6H), 2.41 (s, 3H), 2.69 (q, J = 7.4 Hz, 2H), 4.55 (hept, J = 6.0, 1H), 4.71 (s, 2H), 7.01 (s, 1H), 7.17 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.1 (q), 14.5 (q), 22.2 (q, 2C), 23.9 (t), 55.7 (t), 70.8 (d), 103.0 (d), 110.6 (d), 114.2 (s), 126.2 (s), 131.1 (s), 148.8 (s), 152.0 (s), 152.3 (s) ppm; **HRMS** (ESI) calcd for $C_{15}H_{20}O_3Na$: 271.1305 $[M+Na]^+$; found: 271.1303.

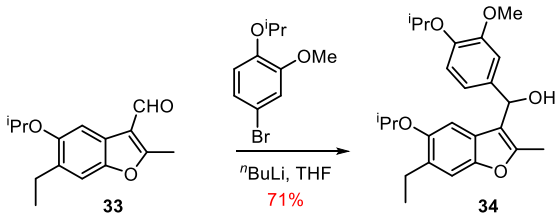
6-Ethyl-5-isopropoxy-2-methylbenzofuran-3-carbaldehyde (**33**):



To a solution of **32** (992 mg, 3.99 mmol) in ethyl acetate (30 mL) was added IBX (1.68 g, 5.99 mmol) and the contents refluxed at 80 °C for 6 h. After completion of reaction as indicated by TLC, the reaction mixture was filtered through Celite and the Celite pad was washed ethyl acetate (50 mL). The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford **33** (885 mg, 90%) as a pale brown oil.

R_f = 0.5 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.4 Hz, 3H), 1.35 (d, J = 6.0 Hz, 6H), 2.67–2.72 (m, 5H), 4.64 (hept, J = 6.0 Hz, 1H), 7.20 (s, 1H), 7.53 (s, 1H), 10.15 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.9 (q), 14.2 (q), 22.1 (q, 2C), 23.9 (t), 70.4 (d), 104.6 (d), 110.5 (d), 118.1 (s), 122.5 (s), 132.4 (s), 148.5 (s), 153.3 (s), 166.5 (s), 184.9 (d) ppm; **HRMS** (ESI) calcd for $C_{15}H_{19}O_3$: 247.1329 $[M+H]^+$; found: 247.1328.

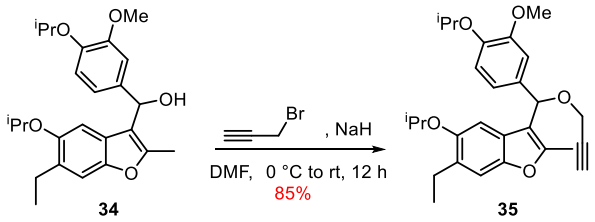
(6-Ethyl-5-isopropoxy-2-methylbenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methanol (**34**):



At –78 °C, a solution of 4-bromo-1-isopropoxy-2-methoxybenzene (552 mg, 2.25 mmol) in dry THF (15 mL) was treated with ^{n}BuLi (1.1 mL, 1.80 mmol, 1.6 M solution in *n*-hexane) dropwise over 10 min and stirred for 30 min at same temperature. To this, a solution of aldehyde **52** (222 mg, 0.90 mmol) in THF (5 mL) was added dropwise. The resulting mixture was allowed to stir at –78 °C for 12 h. After completion of reaction as indicated by TLC, the reaction was quenched by adding saturated ammonium chloride solution and extracted using ethyl acetate (3x50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→15% ethyl acetate in petroleum ether) to afford **34** (264 mg, 71%) as a yellow oil.

R_f = 0.4 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.5 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 3H), 2.41 (s, 3H), 2.64 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.31 (Hept, *J* = 6.0 Hz, 1H), 4.48 (hept, *J* = 6.0 Hz, 1H), 5.96 (s, 1H), 6.70 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.90 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.06 (d, *J* = 1.7 Hz, 1H), 7.14 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.6 (q), 14.4 (q), 21.9 (q), 22.0 (q, 2C), 22.2 (q), 23.8 (t), 55.9 (q), 68.7 (d), 70.5 (d), 71.5 (d), 104.2 (d), 110.2 (d), 110.4 (d), 115.6 (d), 116.8 (s), 118.3 (d), 125.2 (s), 130.7 (s), 135.6 (s), 146.5 (s), 148.8 (s), 150.4 (s), 151.5 (s), 151.7 (s) ppm; **HRMS** (ESI) calcd for $C_{25}H_{32}O_5Na$: 435.2142 $[M+Na]^+$; found: 435.2141.

6-Ethyl-5-isopropoxy-3-((4-isopropoxy-3-methoxyphenyl)(prop-2-yn-1-yloxy)methyl)-2-methylbenzofuran (**35**):

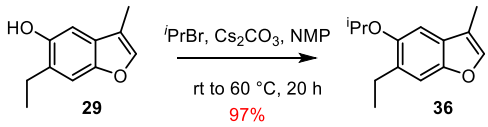


At 0 °C, a solution of **34** (420 mg, 1.01 mmol) in dry DMF (10 mL) was treated with NaH (61 mg, 1.52 mmol, 60% dispersion in mineral oil) and stirred for 20 min. To this propargyl bromide (0.13 mL, 1.22 mmol, 80 wt. % in toluene) was added dropwise and allowed to stirr for 12 h at room temperature. After completion of reaction as indicated by

TLC, the reaction mixture was cooled to 0 °C and treated with sat. NaCl. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (3X50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford **35** (388 mg, 85%) as yellow oil.

R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17–1.22 (m, 6H), 1.27 (d, J = 6.0 Hz, 3H), 1.33 (d, J = 6.0 Hz, 6H), 2.42 (s, 3H), 2.46 (t, J = 2.4 Hz, 1H), 2.66 (q, J = 7.4 Hz, 2H), 3.81 (s, 3H), 4.09 (dd, J = 2.1, 15.9 Hz, 1H), 4.24 (dd, J = 2.1, 15.9 Hz, 1H), 4.36 (hept, J = 6.0 Hz, 1H), 4.47 (Hept, J = 6.0 Hz, 1H), 5.85 (s, 1 H), 6.80–6.82 (m, 2H), 6.88 (br. dd, J = 1.8, 8.2 Hz, 1H), 7.04 (br. d, J = 1.8 Hz, 1H), 7.16 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.6 (q), 14.4 (q), 21.9 (q), 22.0 (q, 2C), 22.2 (q), 23.8 (t), 55.2 (t), 55.9 (q), 70.4 (d), 71.4 (d), 73.9 (d), 74.5 (d), 79.9 (s), 104.4 (d), 110.4 (d), 111.0 (d), 113.3 (s), 115.5 (d), 119.3 (d), 125.5 (s), 130.7 (s), 133.3 (s), 146.7 (s), 148.9 (s), 150.4 (s), 151.6 (s), 153.1 (s) ppm; **HRMS** (ESI) calcd for $C_{28}H_{34}O_5Na$: 473.2298 $[M+Na]^+$; found: 473.2297.

6-Ethyl-5-isopropoxy-3-methylbenzofuran (**36**):

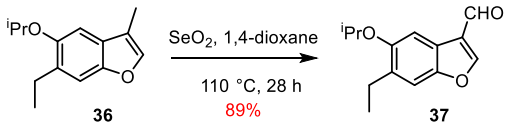


A solution of **29** (1.1 g, 6.24 mmol) in NMP (25 mL) was treated Cs_2CO_3 (4.06 g, 12.48 mmol) at room temperature and stirred for 15 min. To this 2-bromopropane (0.9 mL, 9.36 mmol) was added and stirred at 60 °C for 20 h. After completion of reaction as indicated by TLC, the reaction was quenched with water and extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→3% ethyl acetate in petroleum ether) to afford **36** (1.32 g, 97%) as a brown oil.

R_f = 0.5 (3% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.5 Hz, 3H), 1.39 (d, J = 6.0 Hz, 6H), 2.22 (s, 3H), 2.75 (q, J = 7.5 Hz, 2H), 4.58 (hept, J =

6.0 Hz, 1H), 6.94 (s, 1H), 7.26 (s, 1H), 7.33 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 8.0 (q), 14.5 (q), 22.2 (q, 2C), 23.9 (t), 70.8 (d), 103.1 (d), 111.1 (d), 115.4 (s), 126.8 (s), 131.7 (s), 141.1 (d), 150.1 (s), 151.8 (s) ppm; **HRMS** (ESI) calcd for $C_{14}H_{19}O_2$: 219.1380 $[M+H]^+$; found: 219.1380.

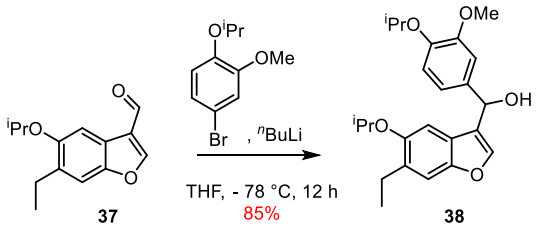
6-Ethyl-5-isopropoxybenzofuran-3-carbaldehyde (**37**):



To a solution of **36** (1.20 g, 5.49 mmol) in 1,4-dioxane (25 mL) was added SeO_2 (1.21 g, 10.9 mmol) and refluxed for 28 h. The contents of the reaction then filtered through Celite pad and the Celite pad was washed using ethyl acetate (50 mL). The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford **37** (1.13 g, 89%) as a brown liquid.

R_f = 0.4 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.5 Hz, 3H), 1.36 (d, J = 6.0 Hz, 6H), 2.71 (q, J = 7.5 Hz, 2H), 4.65 (hept, J = 6.0 Hz, 1H), 7.30 (s, 1H), 7.56 (s, 1H), 8.14 (s, 1H), 10.09 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0 (q), 22.0 (q, 2C), 24.0 (t), 70.3 (d), 104.7 (d), 111.2 (d), 120.8 (s), 123.8 (s), 133.8 (s), 150.7 (s), 153.6 (s), 155.2 (d), 184.9 (d) ppm; **HRMS** (ESI) calcd for $C_{14}H_{17}O_3$: 233.1172 $[M+H]^+$; found: 233.1172.

(6-Ethyl-5-isopropoxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methanol (**38**):

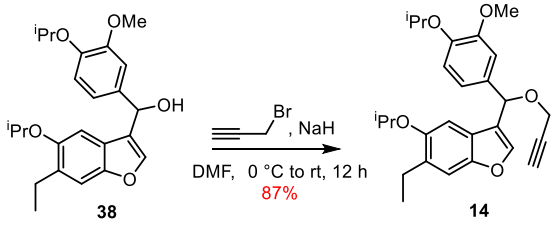


At –78 °C, a solution of 4-bromo-1-isopropoxy-2-methoxybenzene (1.61 g, 6.58 mmol) in dry THF (20 mL) was treated with ^{n}BuLi (3.3 mL, 5.26 mmol, 1.6 M solution in *n*-

hexane) dropwise over 10 min and stirred for 30 min at same temperature. To this, a solution of aldehyde **37** (612 mg, 2.63 mmol) in THF (5 mL) was added dropwise over 10 min. The resulting mixture was allowed to stir at –78 °C for 12 h. After completion of reaction as indicated by TLC, the reaction was quenched by adding saturated ammonium chloride solution and extracted with ethyl acetate (3x100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→15% ethyl acetate in petroleum ether) to afford **38** (892 mg, 85%) as a brown liquid.

R_f = 0.4 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.5 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 6H), 2.67 (q, *J* = 7.5 Hz, 2H), 3.80 (s, 3H), 4.38 (hept, *J* = 6.0 Hz, 1H), 4.51 (hept, *J* = 6.0 Hz, 1H), 5.92 (br. s., 1H), 6.78 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.95 (br. d, *J* = 8.1 Hz, 1H), 7.02 (br. s, 1H), 7.23 (s, 1H), 7.37 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (q), 22.0 (q, 4C), 23.9 (t), 55.9 (q), 69.5 (d), 70.5 (d), 71.4 (d), 103.9 (d), 110.5 (d), 111.2 (d), 115.4 (d), 118.9 (d), 123.7 (s), 124.0 (s), 132.1 (s), 135.2 (s), 142.1 (d), 147.0 (s), 150.4 (s), 150.6 (s), 151.8 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{31}O_5$: 399.2166 $[M+H]^+$; found: 399.2166.

6-Ethyl-5-isopropoxy-3-((4-isopropoxy-3-methoxyphenyl)(prop-2-yn-1-yloxy)methyl)benzofuran (**14**):

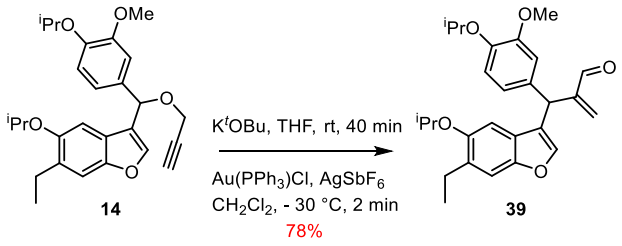


At 0 °C, a solution of alcohol **38** (510 mg, 1.27 mmol) in dry DMF (10 mL) was treated with NaH (77 mg, 1.91 mmol, 60% dispersion in mineral oil) and stirred at same temperature for 20 min. To this propargyl bromide (0.17 mL, 1.53 mmol, 80 wt. % in toluene) was added dropwise and the contents allowed to stir at room temperature for 12 h. After completion of reaction as indicated by TLC, the reaction was cooled to 0 °C and quenched by adding cold water. The contents were partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was

extracted using ethyl acetate (2x50 mL). The combined organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→10% ethyl acetate in petroleum ether) to afford **14** (486 mg, 87%) as a brown liquid.

R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.5 Hz, 3H), 1.30 (d, J = 6.0 Hz, 6H), 1.36 (d, J = 6.0 Hz, 6H), 2.49 (t, J = 2.1 Hz, 1H), 2.68 (q, J = 7.5 Hz, 2H), 3.82 (s, 3H), 4.13 (dd, J = 2.1, 15.9 Hz, 1H), 4.23 (dd, J = 2.1, 15.9 Hz, 1H), 4.43 (hept, J = 6.0 Hz, 1H), 4.52 (hept, J = 6.0 Hz, 1H), 5.80 (s, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.95–6.98 (m, 2H), 7.01 (br. s, 1H), 7.23 (s, 1H), 7.29 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (q), 22.0 (q, 4C), 23.9 (t), 55.3 (t), 55.9 (q), 70.4 (d), 71.3 (d), 74.5 (d, 2C), 80.0 (s), 104.0 (d), 111.0 (d), 111.2 (d), 115.1 (d), 120.1 (d), 121.3 (s), 124.3 (s), 131.9 (s), 132.0 (s), 142.9 (d), 147.2 (s), 150.4 (s), 150.5 (s), 151.9 (s) ppm; **HRMS** (ESI) calcd for $C_{27}H_{32}O_5Na$: 459.2142 $[M+Na]^+$; found: 459.2134.

2-((6-Ethyl-5-isopropoxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methyl)acrylaldehyde (**39**):



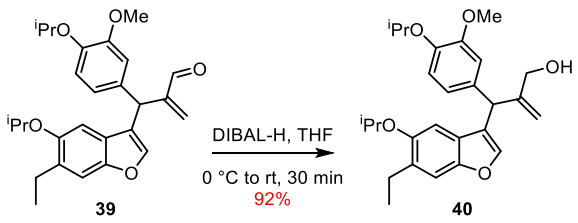
A solution of **14** (558 mg, 1.27 mmol) in dry THF (10 mL) was treated with KO^{t}Bu (143 mg, 1.27 mmol) at room temperature and stirred for 1 h. After completion of reaction as indicated by TLC, the reaction mixture cooled to 0 °C and quenched by adding water. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude allene was directly used for the next step.

The crude allene was dissolved in dry CH_2Cl_2 (10 ml) and cooled to –30 °C. To this, added a premixed solution of $Au(PPh_3)Cl$ (6.3 mg, 0.012 mmol) and $AgSbF_6$ (21.96 mg, 0.06 mmol) in dichloromethane (2 mL) and stirred for 2 min and the reaction was quenched by

adding water. The contents were partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted using CH_2Cl_2 (2x50 mL). The combined organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→10% ethyl acetate in petroleum ether) to afford **39** (435 mg, 78% over 2 steps) as a yellow liquid.

R_f = 0.3 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.5 Hz, 3H), 1.25 (d, J = 6.0 Hz, 3H), 1.28 (d, J = 6.0 Hz, 3H), 1.35 (d, J = 6.0 Hz, 6H), 2.68 (q, J = 7.5 Hz, 2H), 3.78 (s, 3H), 4.37 (hept, J = 6.0 Hz, 1H), 4.48 (hept, J = 6.0 Hz, 1H), 5.31 (s, 1H), 6.17 (s, 1H), 6.26 (s, 1H), 6.59 (s, 1H), 6.72 (br. dd, J = 1.8, 8.1 Hz, 1H), 6.78 (br. d, J = 1.8 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.98 (s, 1H), 7.23 (s, 1H), 9.70 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (q), 21.9 (q), 22.0 (q), 22.1 (q, 2C), 23.9 (t), 39.1 (d), 55.9 (q), 70.6 (d), 71.3 (d), 103.7 (d), 111.3 (d), 112.6 (d), 115.4 (d), 120.3 (d), 121.8 (s), 124.8 (s), 132.2 (s), 132.4 (s), 136.1 (t), 143.4 (d), 146.3 (s), 150.3 (s), 150.6 (s), 150.7 (s), 151.7 (s), 193.2 (d) ppm; **HRMS** (ESI) calcd for $C_{27}H_{33}O_5$: 437.2323 $[M+H]^+$; found: 437.2325.

2-((6-Ethyl-5-isopropoxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methyl)prop-2-en-1-ol (**40**):

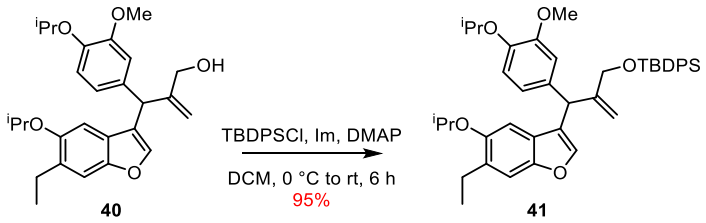


At 0 °C, a solution of **39** (900 mg, 2.06 mmol) in dry THF (15 mL) was treated with a 25% solution of DIBAL-H in toluene (0.94 mL, 2.68 mmol) dropwise over 5 min. The reaction mixture was slowly brought to room temperature and stirred for 30 min. After completion of reaction as indicated by TLC, the reaction mixture was cooled to 0 °C and excess of DIBAL-H was quenched by adding methanol dropwise followed by saturated solution of sodium potassium tartarate. The reaction mixture was portioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was

extracted using ethyl acetate (3x50 mL). The combined organic layers was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5→20% ethyl acetate in petroleum ether) to afford **40** (832 mg, 92%) as a brown liquid.

R_f = 0.4 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.5 Hz, 3H), 1.28 (d, J = 6.1 Hz, 3H), 1.30 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.0 Hz, 6H), 2.69 (q, J = 7.5 Hz, 2H), 3.78 (s, 3H), 4.18 (s, 2H), 4.41 (hept, J = 6.1 Hz, 1H), 4.49 (hept, J = 6.1 Hz, 1H), 4.81 (s, 1H), 4.90 (s, 1H), 5.33 (s, 1H), 6.76–6.84 (m, 4H), 7.03 (s, 1H), 7.23 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3 (q), 22.0 (q), 22.1 (q, 3C), 23.8 (t), 44.2 (d), 55.9 (q), 65.5 (t), 70.6 (d), 71.4 (d), 104.2 (d), 111.2 (d), 112.6 (d), 113.2 (t), 115.6 (d), 120.6 (d), 122.3 (s), 125.4 (s), 131.9 (s), 133.3 (s), 143.2 (d), 146.2 (s), 149.1 (s), 150.3 (s), 150.5 (s), 151.6 (s) ppm; **HRMS** (ESI) calcd for $C_{27}H_{35}O_5$: 439.2479 $[M+H]^+$; found: 439.2483.

***tert*-Butyl((2-((6-ethyl-5-isopropoxybenzofuran-3-yl)(4-isopropoxy-3-methoxyphenyl)methyl)allyl) oxy)diphenylsilane** (**41**):

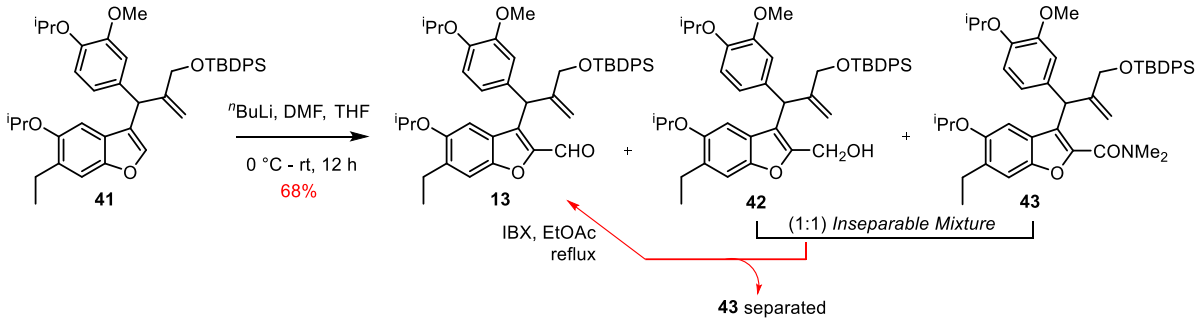


At 0 °C, to a stirred solution of **40** (725 mg, 1.65 mmol) in dry CH_2Cl_2 (15 mL), imidazole (169 mg, 2.47 mmol) and DMAP (20 mg, 0.16 mmol) was added TBDPSCl (0.42 mL, 1.65 mmol) and stirred for 6 h at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane (50 mL) and was washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→3% ethyl acetate in petroleum ether) to afford **41** (1.06 g, 95%) as a yellow solid.

R_f = 0.5 (5% Ethyl acetate in petroleum ether); Mp: 124–125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.22 (t, J = 7.4 Hz, 3H), 1.24 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.38 (d, J = 6.0 Hz, 6H), 2.71 (q, J = 7.4 Hz, 2H), 3.76 (s, 3H), 4.21 (s, 2H), 4.40

(hept, *J* = 6.0 Hz, 1H), 4.51 (hept, *J* = 6.0 Hz, 1H), 4.86 (s, 1H), 4.92 (s, 1H), 5.39 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.80–6.83 (m, 3H), 6.93 (s, 1H), 7.24 (s, 1H), 7.33 (dd, *J* = 7.0, 13.9 Hz, 4H), 7.38–7.41 (m, 2H), 7.64 (dd, *J* = 7.2, 13.9 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4 (q), 19.3 (s), 22.0 (q), 22.1 (q, 3C), 23.9 (t), 26.8 (q, 3C), 43.5 (d), 55.9 (q), 66.3 (t), 70.5 (d), 71.3 (d), 104.2 (d), 111.1 (d), 112.7 (d), 113.1 (t), 115.6 (d), 120.6 (d), 122.6 (s), 125.5 (s), 127.6 (d, 4C), 129.6 (d, 2C), 131.8 (s), 133.4 (s), 133.5 (s, 2C), 135.5 (d, 4C), 143.4 (d), 146.0 (s), 148.4 (s), 150.2 (s), 150.5 (s), 151.6 (s) ppm; **HRMS** (ESI) calcd for $C_{43}H_{52}O_5SiNa$: 699.3476 $[M+Na]^+$; found: 699.3474.

Formylation at C2 of benzofuran 13:

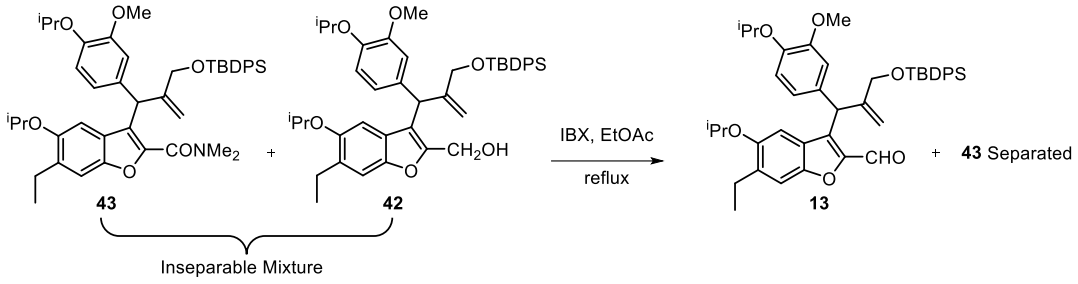


At 0 °C, a solution of **41** (500 mg, 0.73 mmol) in dry THF (10 mL) was treated with ^{n}BuLi (0.92 mL, 1.47 mmol, 1.6 M in *n*-hexane) and stirred for 30 min at the same temperature. To this, anhydrous DMF (0.34 mL, 4.43 mmol) was added and the reaction mixture was slowly brought to room temperature and stirred for 12 h. The reaction mixture quenched by adding saturated ammonium chloride solution and was portioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (3x50 mL). The combined organic layer was washed with brine solution, was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3→20% ethyl acetate in petroleum ether) to afford **13** (354 mg, 68%) as a yellow oil and an inseparable mixture of **42** & **43** (88 mg, 1:1 ratio) as a brown liquid.

3-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1-(4-isopropoxy-3-methoxyphenyl)allyl)-6-ethyl-5-isopropoxybenzofuran-2-carbaldehyde (**13**): R_f = 0.5 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.20 (d, *J* = 2.6 Hz, 3H), 1.21 (d, *J* = 4.1 Hz, 3H),1.25 (d, *J* = 6.0 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 6H), 2.68 (dq, *J* =

1.4, 7.4 Hz, 2H), 3.72 (s, 3H), 4.20–4.28 (m, 3H), 4.48 (hept, *J* = 6.0 Hz, 1H), 4.88 (s, 1H), 5.51 (s, 1H), 5.59 (s, 1H), 6.71 (s, 1H), 6.77–6.79 (m, 3H), 7.27–7.33 (m, 5H), 7.35–7.41 (m, 2H), 7.52 (dd, *J* = 1.3, 8.1 Hz, 2H), 7.58 (dd, *J* = 1.3, 8.1 Hz, 2H), 9.66 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9 (q), 19.2 (s), 21.7 (q), 21.9 (q), 22.1 (q, 2C), 24.4 (t), 26.8 (q, 3C), 43.1 (d), 56.0 (q), 66.3 (t), 70.1 (d), 71.3 (d), 104.4 (d), 112.1 (d), 113.1 (d), 114.3 (t), 115.3 (d), 120.9 (d), 125.7 (s), 127.6 (d, 2C), 127.7 (d, 2C), 129.7 (d, 2C), 132.1 (s), 132.9 (s), 133.0 (s), 133.2 (s), 135.4 (d, 4C), 138.2 (s), 146.5 (s), 148.3 (s), 148.7 (s), 150.5 (s), 150.7 (s), 152.5 (s), 179.8 (d) ppm; **HRMS** (ESI) calcd for $C_{44}H_{53}O_6Si$: 705.3606 $[M+H]^+$; found: 705.3604.

3-(2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-(4-isopropoxy-3-methoxyphenyl)allyl)-6-ethyl-5-isopropoxy-N,N-dimethylbenzofuran-2-carboxamide (**43**):

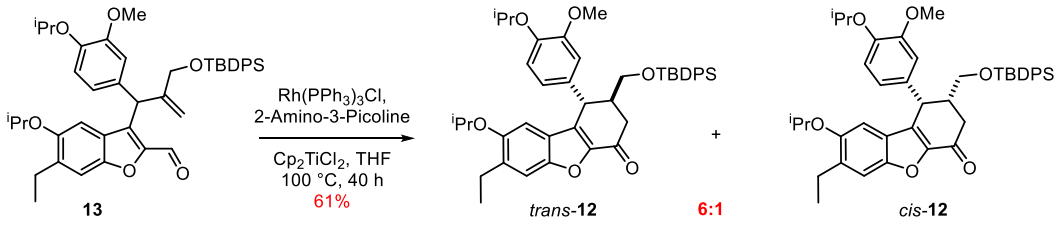


The oxidation of mixture of **42/43** (88 mg) using IBX (26 mg) in 20 mL of EtOAc followed by usual workup and purification by silica gel column chromatography (3→20% ethyl acetate in petroleum ether) gave **13** (36 mg, 7% With respect to **41**) as a yellow oil and unreacted **43** (38 mg, 7% With respect to **41**) as a brown liquid.

R_f = 0.3 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.25–1.28 (m, 6H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.37 (dd, *J* = 1.7, 6.0 Hz, 6H), 2.69–2.77 (m, 2H), 3.00 (br. s., 6H), 3.76 (s, 3H), 4.27 (s, 2H), 4.33 (hept, *J* = 6.0 Hz, 1H), 4.48 (hept, *J* = 6.1 Hz, 1H), 5.03 (s, 1H), 5.43 (s, 1H), 5.61 (s, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 1.6, 8.2 Hz, 1H), 6.88 (s, 1H), 6.93 (d, *J* = 1.6 Hz, 1H), 7.26–7.29 (m, 3H), 7.34–7.44 (m, 4H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1 (q), 19.2 (s), 21.8 (q), 22.0 (q), 22.1 (q, 2C), 24.0 (t), 26.7 (q, 3C), 38.2 (q), 38.3 (q), 43.3 (d), 55.8 (q), 66.1 (t), 70.2 (d), 71.3 (d), 105.0 (d), 111.1 (d), 112.4 (t), 113.4 (d), 115.3 (d), 120.8 (d), 123.6 (s), 125.7 (s), 127.5 (d, 2C), 127.6 (d, 2C), 129.5

(d, 2C), 133.2 (s), 133.3 (s), 133.5 (s), 133.6 (s), 135.4 (d, 4C), 144.8 (s), 145.8 (s), 148.6 (s), 148.8 (s), 150.1 (s), 151.8 (s), 162.2 (s) ppm; **HRMS** (ESI) calcd for $C_{46}H_{58}NO_6Si$: 748.4028 $[M+H]^+$; found: 748.4022.

Rhodium catalyzed intramolecular hydroacylation:



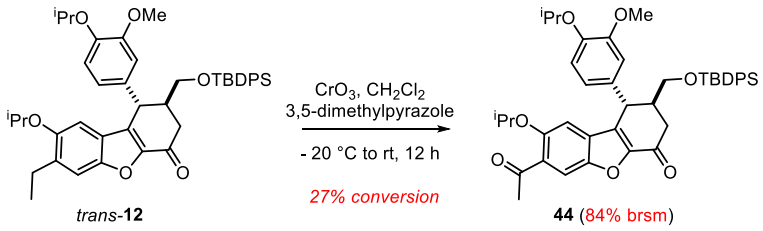
An oven dried screw cap pressure tube was charged with a solution of aldehyde **13** (110 mg, 0.15 mmol), 2-amino-3-picoline (17 mg, 0.15 mmol) in dry THF (3 mL) was purged with argon gas for 5 min prior to adding Cp_2TiCl_2 (4 mg, 0.01 mmol) and $Rh(PPh_3)_3Cl$ (14 mg, 0.01 mmol). The solution was again purged with argon gas for another 5 min, capped and heated at 100 °C for 40 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1→5% ethyl acetate in petroleum ether) to afford a mixture of *trans*-**12** and *cis*-**12** (67 mg, 61%). Both the compounds obtained as colorless solids after HPLC purification.

(±)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-7-ethyl-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (*trans*-**12**): R_f = 0.5 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.04 (d, J = 6.0 Hz, 3H), 1.07 (s, 9H), 1.16 (t, J = 7.4 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H), 1.37 (d, J = 6.0 Hz, 3H), 1.38 (d, J = 6.0 Hz, 3H), 2.57–2.60 (m, 1H), 2.64 (dq, J = 1.8, 7.4 Hz, 2H), 2.77 (dd, J = 3.9, 16.7 Hz, 1H), 3.07 (dd, J = 12.3, 16.7 Hz, 1 H), 3.52 (dd, J = 2.8, 10.5 Hz, 1H), 3.64 (dd, J = 3.8, 10.5 Hz, 1H), 3.68 (s, 3H), 4.00 (hept, J = 6.0 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 4.50 (hept, J = 6.0 Hz, 1H), 5.90 (s, 1H), 6.74–6.76 (m, 2H), 6.83 (d, J = 8.5 Hz, 1H), 7.28 (s, 1H), 7.33 (ddd, J = 3.9, 7.3, 11.3 Hz, 4H), 7.38–7.41 (m, 2H), 7.57–7.59 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.9 (q), 19.4 (s), 21.4 (q), 22.0 (q), 22.1 (q, 2C), 24.4 (t), 26.9 (q, 3C), 41.6 (t), 42.1 (d), 47.7 (d), 56.0 (q), 63.8 (t), 69.9 (d), 71.5 (d), 104.1 (d), 112.2 (d), 112.6 (d), 115.7 (d), 121.2 (d), 124.1 (s), 127.7 (d, 2C), 127.8 (d, 2C), 129.7 (d),

129.8 (d), 132.9 (s, 2C), 133.3 (s), 135.5 (d, 4C), 136.9 (s), 137.8 (s), 146.7 (s), 147.1 (s), 150.6 (s), 151.5 (s), 152.3 (s), 187.9 (s) ppm; **HRMS** (ESI) calcd for $C_{44}H_{53}O_6Si$: 705.3606 $[M+H]^+$; found: 705.3604.

(±)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-7-ethyl-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (*cis*-**12**): R_f = 0.5 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.19 (d, J = 7.4 Hz, 3H), 1.22 (d, J = 5.8 Hz, 3H), 1.30–1.34 (m, 9H), 2.40 (dd, J = 4.2, 17.2 Hz, 1H), 2.49 (dd, J = 12.7, 17.2 Hz, 1H), 2.69 (q, J = 7.4 Hz, 2H), 2.85–2.92(m, 1H), 3.37 (dd, J = 5.7, 10.4 Hz, 1H), 3.49 (dd, J = 8.9, 10.4 Hz, 1H), 3.66 (s, 3H), 4.42 (hept, J = 6.0 Hz, 1H), 4.45 (hept, J = 6.0 Hz, 1H), 4.64 (d, J = 5.0 Hz, 1H), 6.61 (dd, J = 1.8, 8.3 Hz, 1H), 6.65 (s, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 7.32–7.37 (m, 5H), 7.39–7.43 (m, 2H), 7.60 (dd, J = 1.5, 6.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (q), 19.2 (s), 21.9 (q, 2C), 22.1 (q, 2C), 24.5 (t), 26.9 (q, 3C), 37.1 (t), 39.6 (d), 43.3 (d), 56.1 (q), 64.7 (t), 70.5 (d), 71.3 (d), 103.6 (d), 112.5 (d), 113.3 (d), 115.4 (d), 121.4 (d), 123.6 (s), 127.7 (d, 2C), 127.8 (d, 2C), 128.4 (s), 129.8 (d), 129.9 (d), 133.1 (s), 133.5 (s), 135.4 (d, 2C), 135.5 (d, 2C), 136.5 (s), 138.5 (s), 146.7 (s), 148.0 (s), 150.2 (s), 151.6 (s), 152.8 (s), 187.2 (s) ppm; **HRMS** (ESI) calcd for $C_{44}H_{53}O_6Si$: 705.3606 $[M+H]^+$; found: 705.3602.

7-acetyl-2-(((tert-butyldiphenylsilyl)oxy)methyl)-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (**44**):

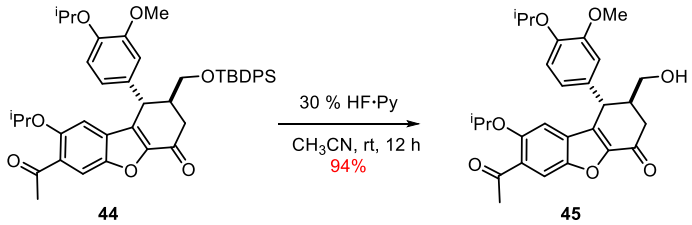


At –25 °C, to a stirred solution of CrO_3 (74 mg, 0.73 mmol) in CH_2Cl_2 (5 mL) and 3,5-dimethylpyrazole (71 mg, 0.73 mmol) was added a solution of *trans*-**12** (26 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) was added. The reaction mixture was warmed to –10 °C and allowed to stir for overnight. The reaction mixture was concentrated under reduced pressure and residue was purified by column chromatography (10→20% ethyl acetate in

petroleum ether) to afford **44** (6 mg, 23%) as a colourless solid and starting material *trans*-**12** (19 mg, 73%) recovered.

R_f = 0.5 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07–1.08 (m, 12H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 2.57 (s, 3H), 2.59–2.66 (m, 1H), 2.80 (dd, *J* = 3.6, 16.8 Hz, 1H), 3.10 (dd, *J* = 12.6, 16.8 Hz, 1H), 3.52 (dd, *J* = 2.5, 10.5 Hz, 1H), 3.65 (dd, *J* = 3.8, 10.5 Hz, 1H), 3.68 (s, 3H), 4.09 (hept, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 10.1 Hz, 1H), 4.51 (hept, *J* = 6.0 Hz, 1H), 6.00 (s, 1H), 6.74–6.76 (m, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 7.32–7.35 (m, 4H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.58 (dd, *J* = 3.6, 6.7 Hz, 4H), 7.80 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 19.4 (s), 21.2 (q), 21.9 (q), 22.1 (q), 22.1 (q), 26.9 (q, 3C), 31.8 (q), 41.9 (t), 42.0 (d), 47.7 (d), 56.0 (q), 63.6 (t), 70.9 (d), 71.5 (d), 105.6 (d), 112.4 (d), 113.9 (d), 115.6 (d), 121.2 (d), 127.7 (d, 2C), 127.8 (d, 2C), 129.8 (d), 129.8 (s), 129.9 (d), 131.4 (s), 132.4 (s), 132.8 (s), 133.2 (s), 135.5 (d, 2C), 135.5 (d, 2C), 135.6 (s), 146.9 (s), 149.4 (s), 150.4 (s), 150.7 (s), 153.0 (s), 188.3 (s), 199.9 (s) ppm; **HRMS** (ESI) calcd for $C_{44}H_{51}O_7Si$: 719.3399 $[M+H]^+$; found: 719.3386.

7-Acetyl-2-(hydroxymethyl)-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-2,3-dihydrodibenzo[b,d]furan-4(1H)-one (**45**):

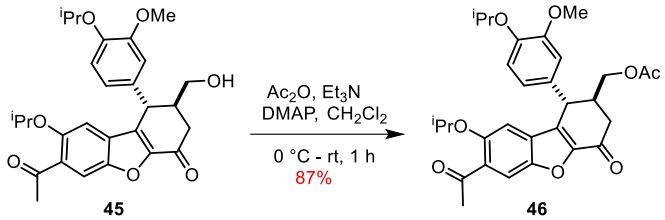


To a solution of **44** (16 mg, 0.02 mmol) in CH_3CN (5 ml) was added 70% HF in pyridine (0.45 ml) and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched with $NaHCO_3$. The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (25→50% ethyl acetate in petroleum ether) to afford **45** (10 mg, 94%) as a colorless solid.

R_f = 0.5 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.0 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.38 (d, *J* = 6.0 Hz, 6H), 2.56 (s, 3H), 2.60–2.69

(m, 1H), 2.86 (dd, *J* = 4.3, 16.7 Hz, 1H), 2.93 (dd, *J* = 12.2, 16.7 Hz, 1H), 3.64 (d, *J* = 3.8 Hz, 2H), 3.76 (s, 3H), 4.09 (hept, *J* = 6.0 Hz, 1H), 4.32 (d, *J* = 10.2 Hz, 1H), 4.52 (hept, *J* = 6.0 Hz, 1H), 5.99 (s, 1H), 6.76 (d, *J* = 1.7 Hz, 1H), 6.83 (dd, *J* = 1.7, 8.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.79 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.2 (q), 21.9 (q), 22.0 (q), 22.1 (q), 31.8 (q), 41.4 (t), 42.1 (d), 47.2 (d), 56.2 (q), 63.0 (t), 70.9 (d), 71.4 (d), 105.6 (d), 112.3 (d), 114.0 (d), 115.4 (d), 121.1 (d), 129.7 (s), 131.5 (s), 132.3 (s), 135.4 (s), 147.1 (s), 149.4 (s), 150.3 (s), 150.8 (s), 153.0 (s), 187.8 (s), 199.9 (s) ppm; **HRMS** (ESI) calcd for $C_{28}H_{33}O_7$: 481.2221 $[M+H]^+$; found: 481.2216.

7-acetyl-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[b,d]furan-2-yl)methyl acetate (**46**):

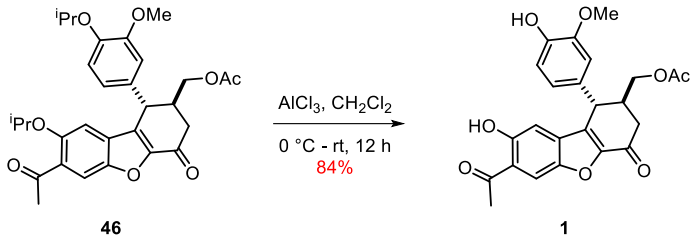


At 0 °C, a solution of **45** (19 mg, 0.03 mmol) and DMAP (0.88 mg, 0.007 mmol) in CH_2Cl_2 (5 ml) was treated pyridine (6.5 µl) followed by Ac_2O (13.7 µl, 0.14 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. After completion of reaction as indicated by TLC, it was quenched by adding sat. NH_4Cl. The reaction mixture was between water (10 mL) and dichloromethane (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). Combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (5→15% ethyl acetate in petroleum ether) to afford **46** (18 mg, 87 %) as yellow solid.

R_f = 0.5 (15% ethyl acetate in petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 2.06 (s, 3H), 2.56 (s, 3H), 2.77 (br. dd, *J* = 12.4, 14.9 Hz, 1H), 2.82–2.85 (m, 1H), 2.91 (br. dd, *J* = 2.1, 14.9 Hz, 1H), 3.75 (s, 3H), 4.03–4.10 (m, 3H), 4.18 (d, *J* = 10.0 Hz, 1H), 4.52 (hept, *J* = 6.0 Hz, 1H), 5.97 (s, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 6.79 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 7.80 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 20.8 (q), 21.2

(q), 21.9 (q), 22.0 (q), 22.1 (q), 31.8 (q), 41.6 (t), 43.0 (d), 44.2 (d), 56.2 (q), 64.8 (t), 70.9 (d), 71.4 (d), 105.5 (d), 112.2 (d), 114.0 (d), 115.4 (d), 121.2 (d), 129.4 (s), 131.5 (s), 131.6 (s), 135.0 (s), 147.3 (s), 149.3 (s), 150.3 (s), 150.9 (s), 153.0 (s), 170.7 (s), 186.8 (s), 199.8 (s) ppm; **HRMS** (ESI) calcd for $C_{30}H_{35}O_8$: 523.2326 $[M+H]^+$; found: 523.2327.

7-acetyl-8-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[b,d]furan-2-yl)methyl acetate (**1**):



46 **1**

At 0 °C, a solution of **46** (14 mg, 0.02 mmol) in CH_2Cl_2 (5 ml) was treated with $AlCl_3$ (10.7 mg, 0.08 mmol) and stirred for 10 min. The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated NH_4Cl and partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was etracted using CH_2Cl_2 (2x10 ml). The combined organic layer was washed using brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (15→40% ethyl acetate in petroleum ether) to afford **1** (9.8 mg, 84%) as yellow solid.

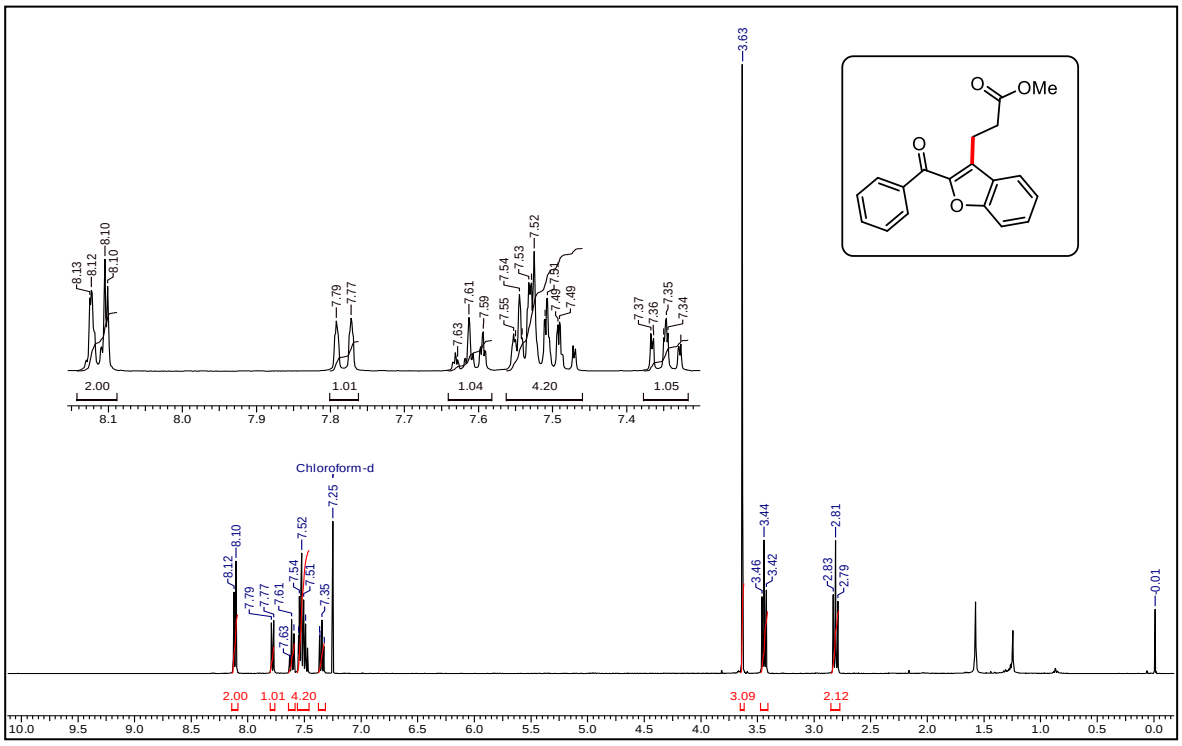
R_f = 0.5 (40% ethyl acetate in petroleum ether); Mp 198–199 °C; **^{1}H NMR** (700 MHz, d_6-Acetone): δ 2.04 (s, 3H), 2.76 (s, 3H), 2.82 (dd, J = 4.4, 16.3 Hz, 1H), 2.87 (dd, J = 11.9, 16.3 Hz, 1H), 2.92–2.97 (m, 1H), 3.76 (s, 3H), 4.04 (dd, J = 5.7, 11.3 Hz, 1H), 4.07 (dd, J = 3.6, 11.3 Hz, 1H), 4.34 (d, J = 10.0 Hz, 1H), 6.14 (s, 1H), 6.87 (dd, J = 1.6, 8.1 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 7.03 (br. s, 1H), 7.69 (s, 1H), 8.21 (s, 1H), 11.81 (s, 1H); **^{13}C NMR** (125 MHz, d_6-Acetone): δ 20.7 (q), 27.4 (q), 42.4 (t), 43.2 (d), 45.0 (d), 56.4 (q), 65.3 (t), 110.1 (d), 113.0 (d), 115.6 (d), 116.2 (d), 120.6 (s), 122.6 (d), 131.7 (s), 134.2 (s), 135.1 (s), 147.3 (s), 149.0 (s), 149.7 (s), 151.9 (s), 158.3 (s), 171.0 (s), 187.6 (s), 206.0 (s) ppm; **HRMS** (ESI) calcd for $C_{24}H_{23}O_8$: 439.1387 $[M+H]^+$; found: 439.1382.

1. Banskota, A. H.; Tezuka, Y.; Midorikawa, K.; Matsushige, K.; Kadota, S. *J. Nat. Prod.* **2000**, *63*, 1277–1279.
2. Jones, B. T.; Avetta, C. T.; Thomson, R. J. *Chem. Sci.* **2014**, *5*, 1794–1798.
3. (a) Jun, C. H.; Jo, E. A.; Park, J. W. *Eur. J. Org. Chem.* **2007**, 1869–1881. (b)Ghosh, A.; Johnson, K. F.; Vickerman, K. L.; Walker, J. A.; Stanley, L. M. *Org. Chem. Front.* **2016**, *3*, 639–644.
4. (a) Sakai, K.; Ishiguro, Y.; Funakoshi, K.; Ueno, K.; Suemune, H. *Tetrahedron Lett.* **1984**, *25*, 961–964. (b) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349–6352. (c) Taura, Y.; Tanaka, M.; Wu, X. M.; Funakoshi, K.; Sakai, K., *Tetrahedron* ***1991***, *47*, 4879–4888. (d) Barnhart, R. W.; Bosnich, B., *Organometallics* **1995,** *14*, 4343–4348. (e) Lu, H.; Lin, J. B.; Liu, J. Y.; Xu, P. F. *Chem. Eur. J.* **2014**, *20*, 11659–11663. (f) Wu, X. S.; Chen, Z. W.; Bai, Y. B.; Dong, V. M. *J. Am. Chem. Soc.* **2016**, *138*, 12013–12016. (g) Ghosh, A.; Walker, J. A.; Ellern, A.; Stanley, L. M. *Acs Catal.* **2016**, *6*, 2673–2680. (h) Yang, J. F.; Rerat, A.; Lim, Y. J.; Gosmini, C.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 2449–2453.
5. Kona, C. N.; Ramana, C. V. *Chem. Commun.* **2014**, *50*, 2152–2154.
6. Tang, Z.; Mandal, S.; Paul, N. D.; Lutz, M.; Li, P.; Vlugt, J. I. V.; Bruin, B. *Org. Chem. Front.* **2015**, *2*, 1561–1577.
7. Matsui, Y.; Orchin, M. J. Organometal. Chem.**1983**, *246*, 57–60.
8. Moore, E. J.; Pretzer, W. R.; Connell, T. J. O.; Johnel, H.; Bounty, L. L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888–5890.
9. Jun, C. H.; Lee, D. Y.; Lee, H.; Hong, J. B. Angew. Chem. Int. Ed. **2000**, *39*, 3070–3072.
10. Jun, C. H.; Lee, D. Y.; Hong, J. B. Tetrahedron Lett. **1997**, *38*, 6673–6676.
11. (a) Errazuriz, B.; Tapia, R.; Valderrama, J. A. *Tetrahedron Lett.* **1985**, *26*, 819–822. (b) Love, B. E.; Duffy, B. C.; Simmons, A. L. *Tetrahedron Lett.* **2014**, *55*, 1994–1997.
12. (a) Abbas, A. A. *J. Heterocyclic Chem.* **2009**, *46*, 340–346. (b) Antczak, C.; Shum, D.; Bassit, B.; Frattini, M. G.; Li, Y. M.; de Stanchina, E.; Scheinberg, D. A.; Djaballah, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4528–4532. (c) Gamal–Eldeen,

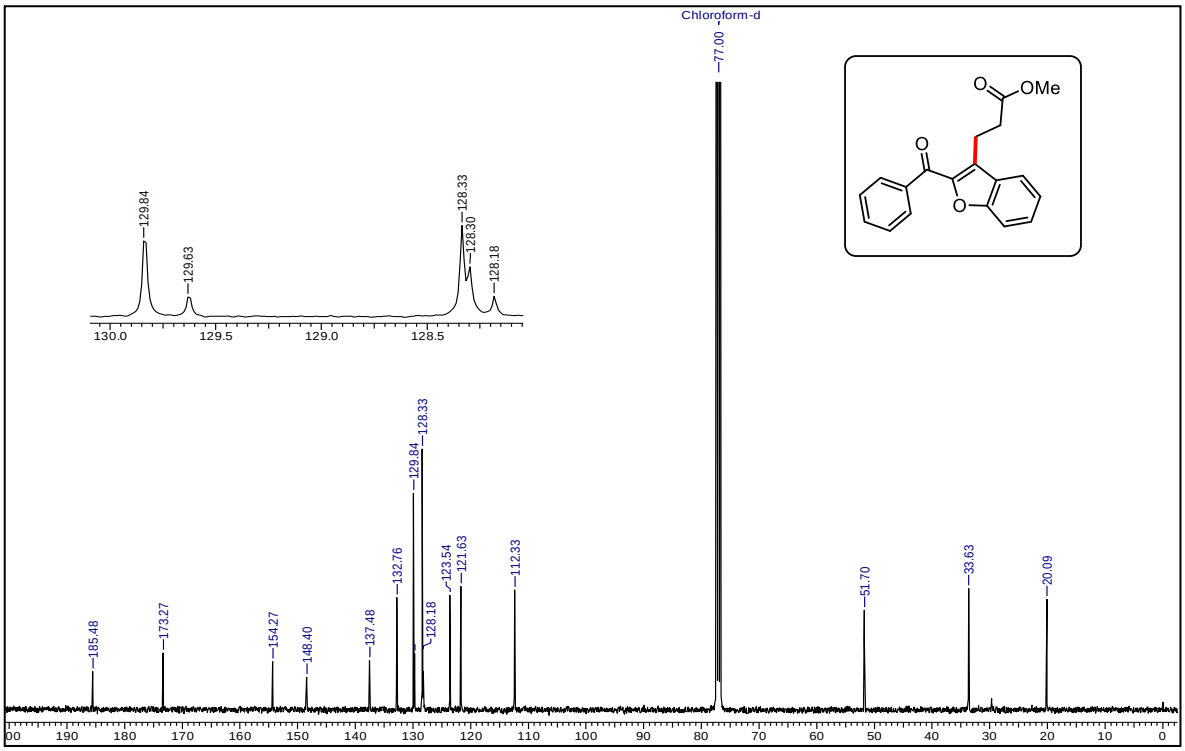
A. M.; Hamdy, N. A.; Abdel–Aziz, H. A.; El–Hussieny, E. A.; Fakhr, I. M. I. *Eur. J. Med. Chem.* **2014**, *77*, 323–333. (d) Aiken, S.; Allsopp, B.; Booth, K.; Gabbutt, C. D.; Heron, B. M.; Rice, C. R. *Tetrahedron* **2014**, *70*, 9352–9358.

13. (a) Giza, C. A.; Hinman, R. L., J. Org. Chem. **1964**, *29*, 1453–1461. (b) Mudiganti, N. V. S.; Claessens, S.; De Kimpe, N. Tetrahedron **2009**, *65*, 1716–1723. (c) Mothe, S. R.; Susanti, D.; Chan, P. W. H. Tetrahedron Lett. **2010**, *51*, 2136–2140. (d) Yadav, P.; Singh, P.; Tewari, A. K. Bioorg. Med. Chem. Lett. **2014**, *24*, 2251–2255.
14. (a) Zhang, Y. H.; Guo, Y. H.; Li, Z. L.; Xie, Z. X. Org. Lett. **2016**, *18*, 4578–4581. (b) Bian, J. L.; Deng, B.; Xu, L. L.; Xu, X. L.; Wang, N.; Hu, T. H.; Yao, Z. Y.; Du, J. Y.; Yang, L.; Lei, Y. H.; Li, X.; Sun, H. P.; Zhang, X. J.; You, Q. D. Eur. J. Med. Chem. **2014**, *82*, 56–67. (c) Chen, Y.; Chen, S. P.; Lu, X.; Cheng, H.; Oua, Y. Y.; Cheng, H. M.; Zhou, G. C. Bioorg. Med. Chem. Lett. **2009**, *19*, 1851–1854. (d) Lee, J.; Tang, J.; Snyder, J. K. Tetrahedron Lett. **1987**, *28*, 3427–3430.
15. (a) Gazzola, S.; Beccalli, E. M.; Bernasconi, A.; Borelli, T.; Broggini, G.; Mazza, A. Eur. J. Org. Chem. **2016**, 4534–4544. (b) Zhu, Y. Y.; Yin, T. T.; Li, X. L.; Su, M.; Xue, Y. X.; Yu, Z. P.; Liu, N.; Yin, J.; Wu, Z. Q. Macromolecules **2014**, *47*, 7021–7029. (c) Trost, B. M.; Me, J. J. Am. Chem. Soc. **2008**, *130*, 6231–6242. (e) Mochizuki, K.; Tomita, I. Macromolecules **2006**, *39*, 6336–6340. (f) Flogell, O.; Reissig, H. U. Eur. J. Org. Chem. **2004**, 2797–2804. (g) Mereyala, H. B.; Gurrala, S. R.; Mohan, S. K. Tetrahedron **1999**, *55*, 11331–11342. (h) Moghaddam, F. M.; Emami, R. Syn. Commun. **1997**, *27*, 4073–4077.
16. Buchner, K. M.; Woerpel, K. A. Organometallics **2010**, *29*, 1661–1669.
17. Sleeman, M. J.; Meehan, G. V. Tetrahedron Lett. **1989**, *30*, 3345–3348.
18. Ocello, R.; De Nisi, A.; Jia, M. Q.; Yang, Q. Q.; Monari, M.; Giacinto, P.; Bottoni, A.; Miscione, G. P.; Bandini, M., Chem. Eur. J. **2015**, *21*, 18445–18453.

SPECTRA OF SELECTED COMPOUNDS



^{1}H NMR Spectrum of 3aa in $CDCl_3$



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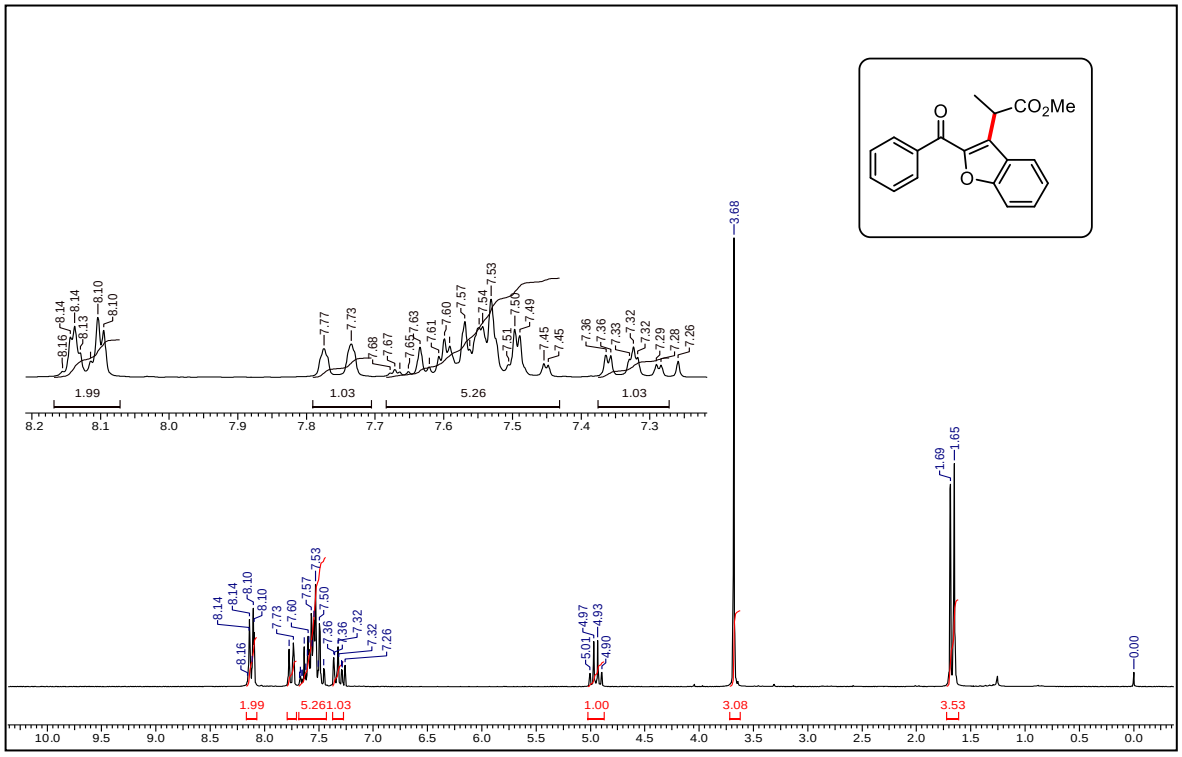

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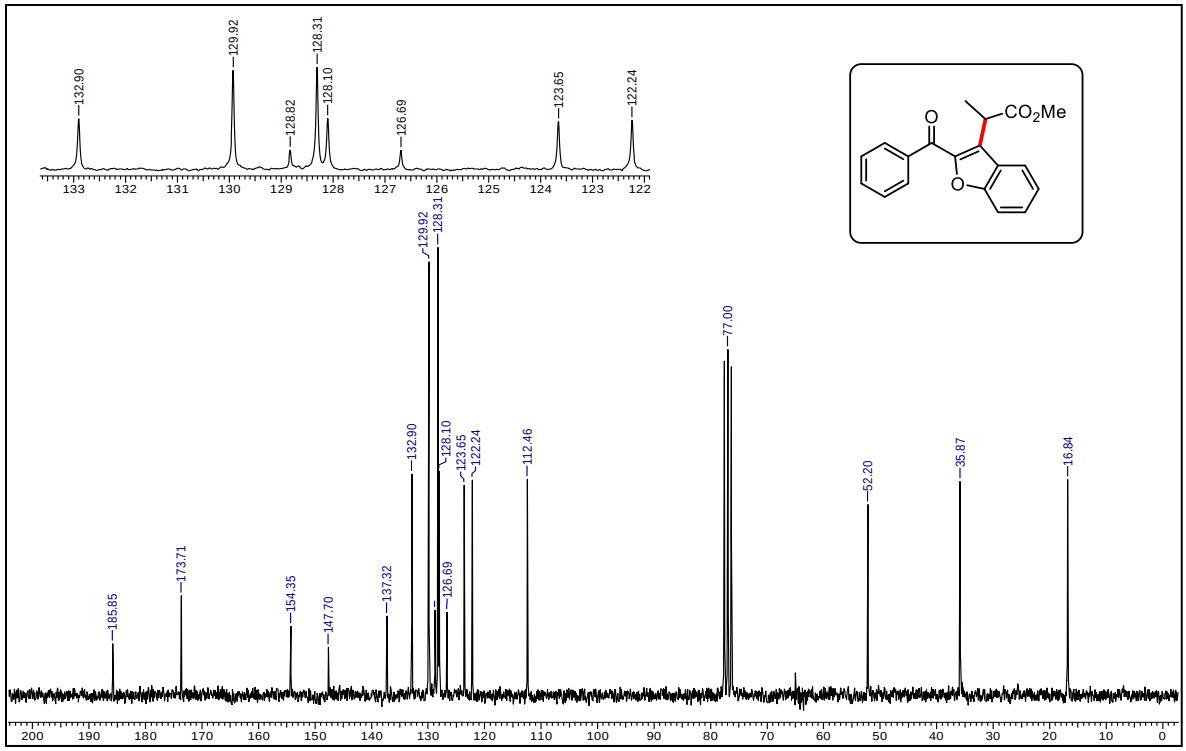

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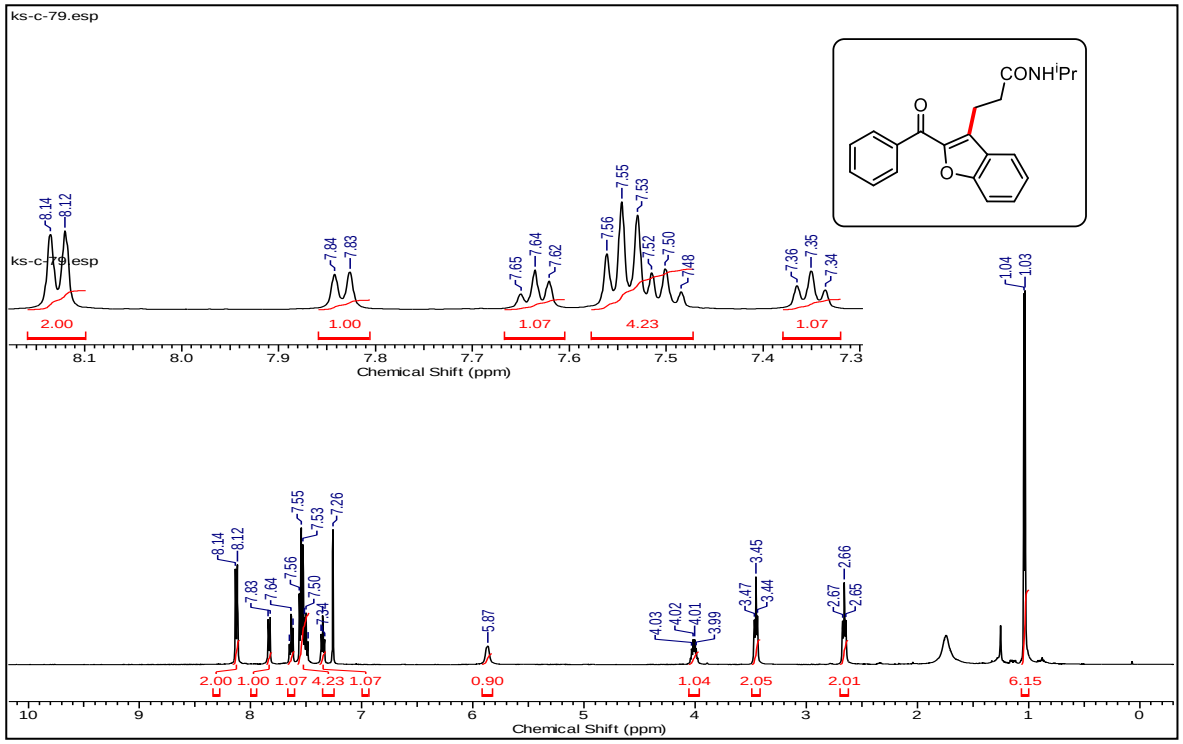

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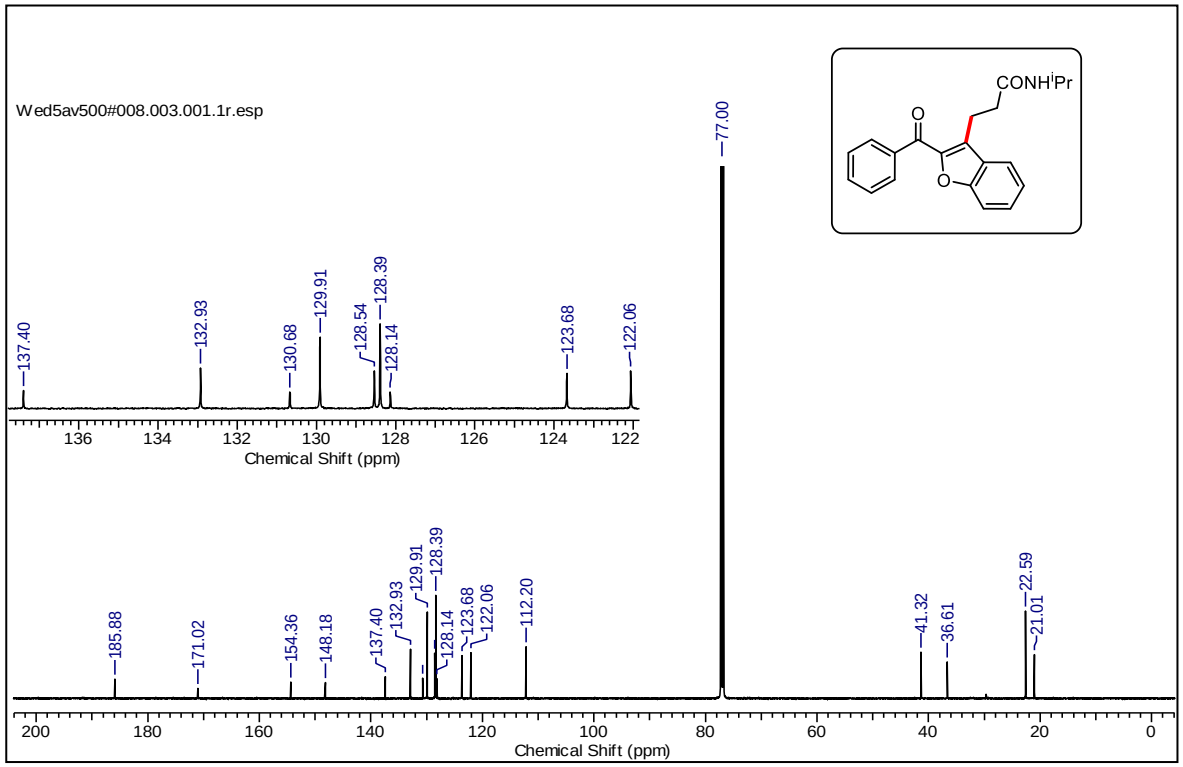

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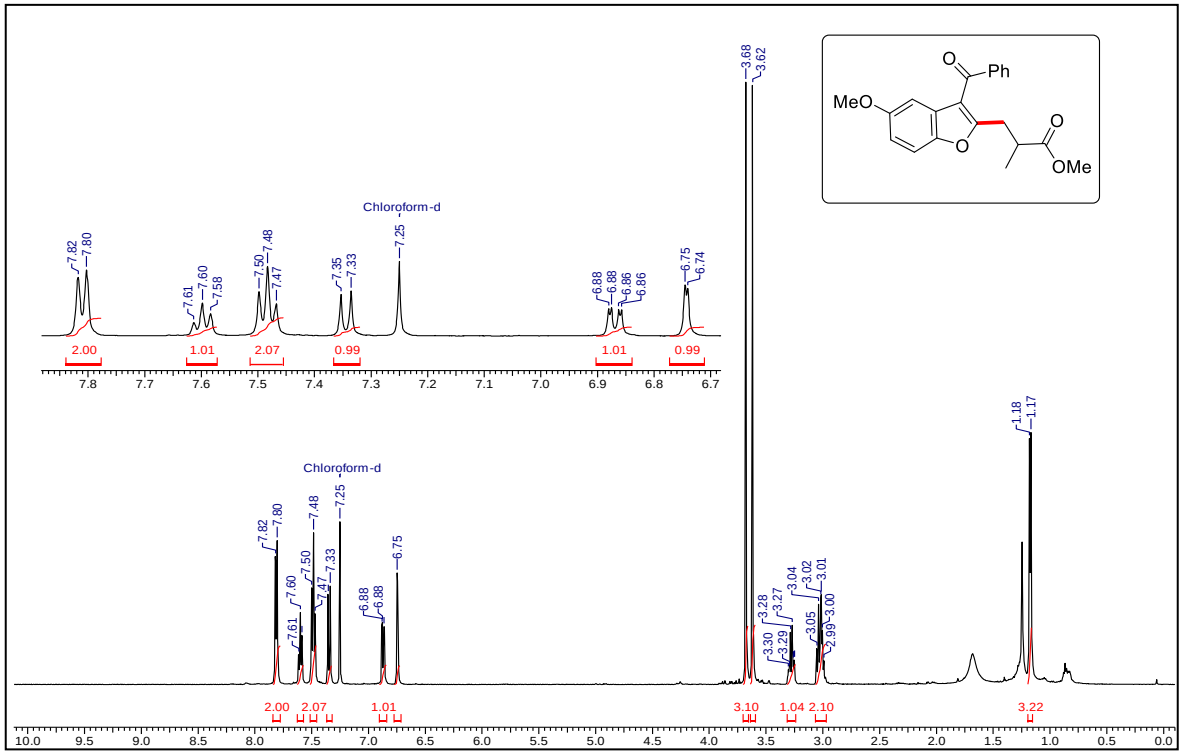

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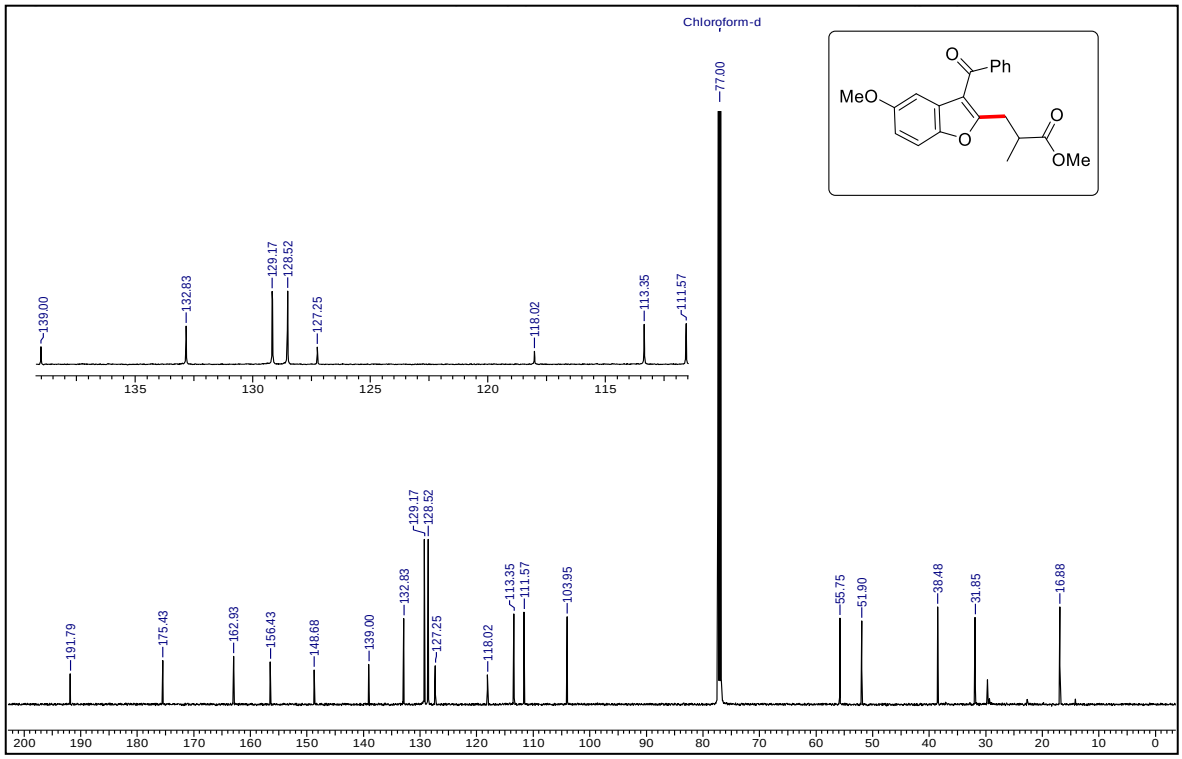

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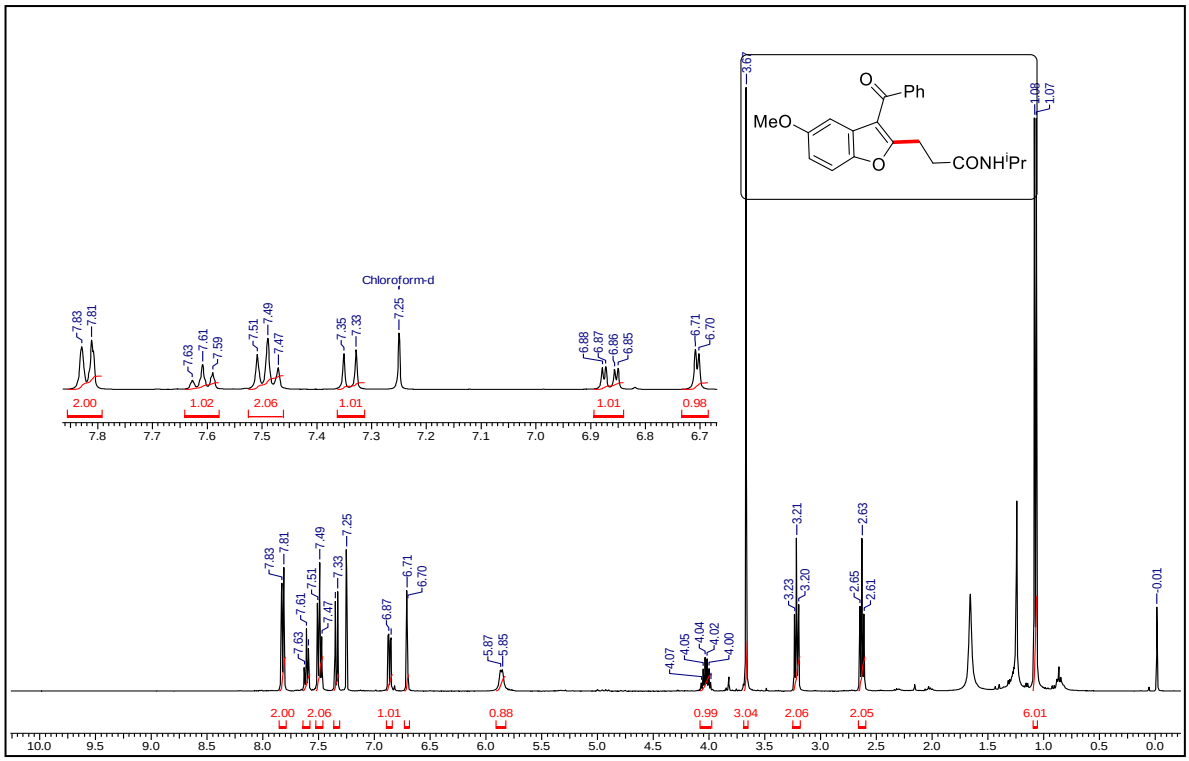

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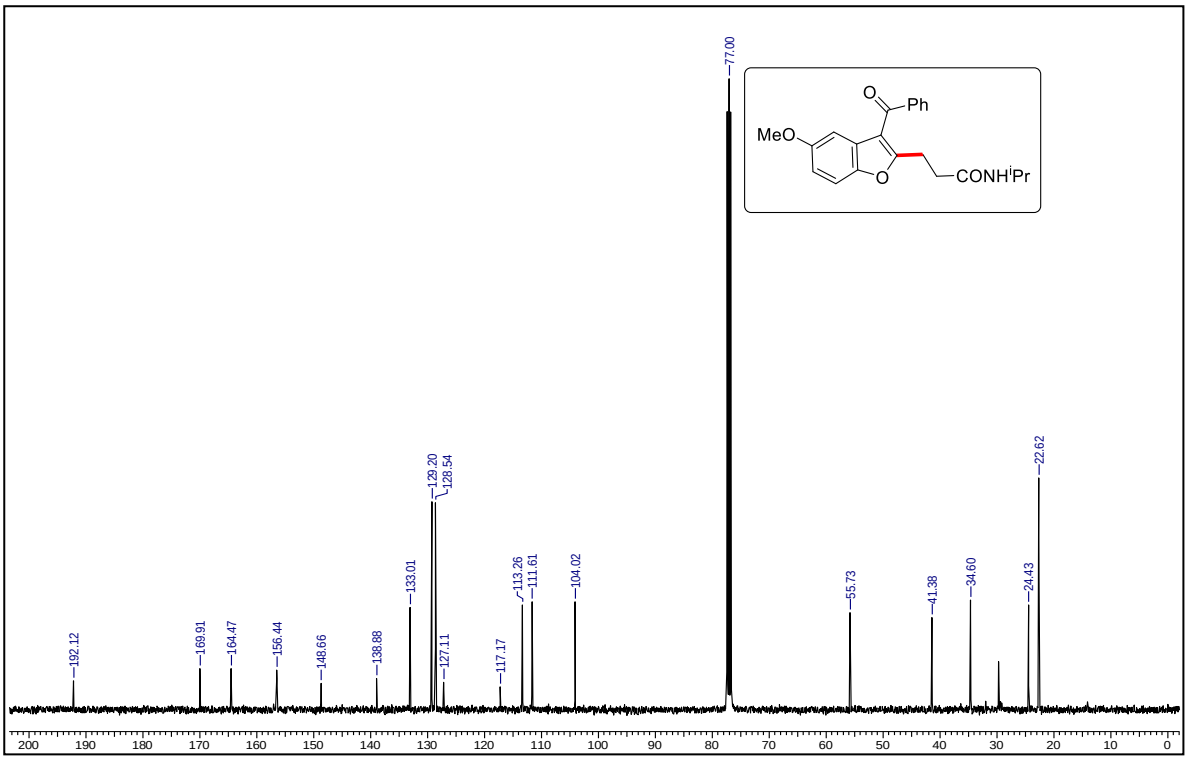

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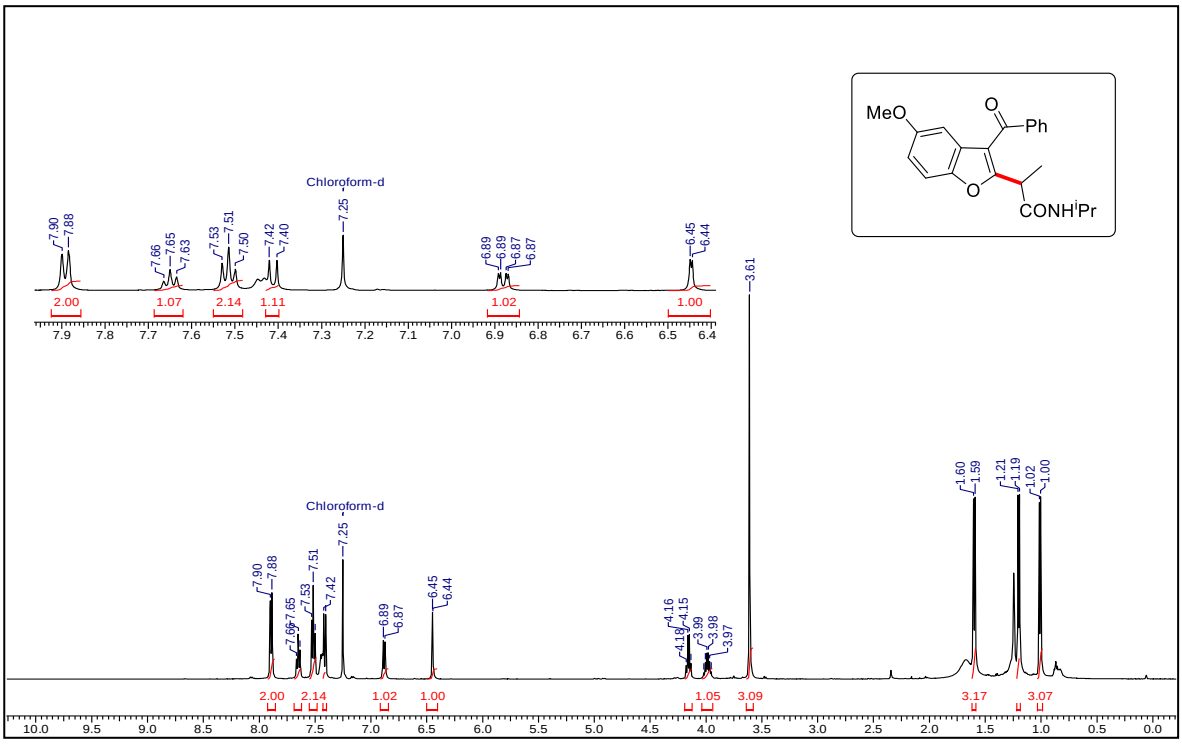

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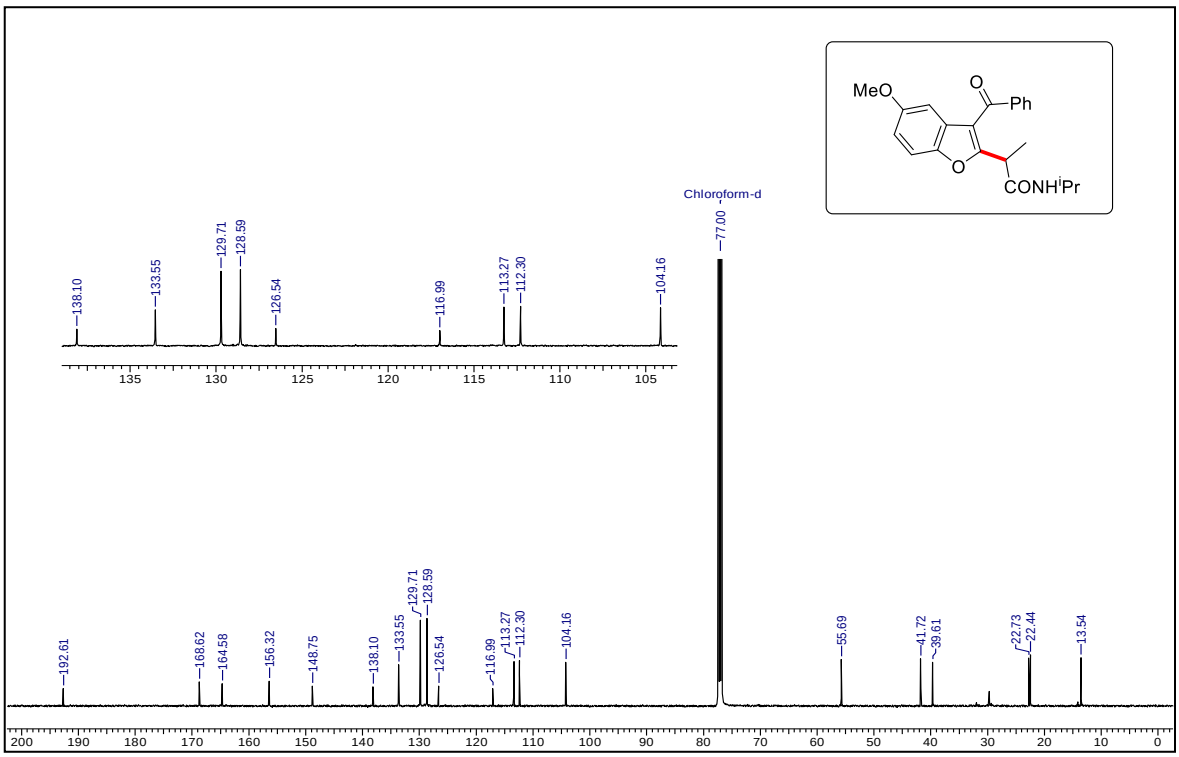

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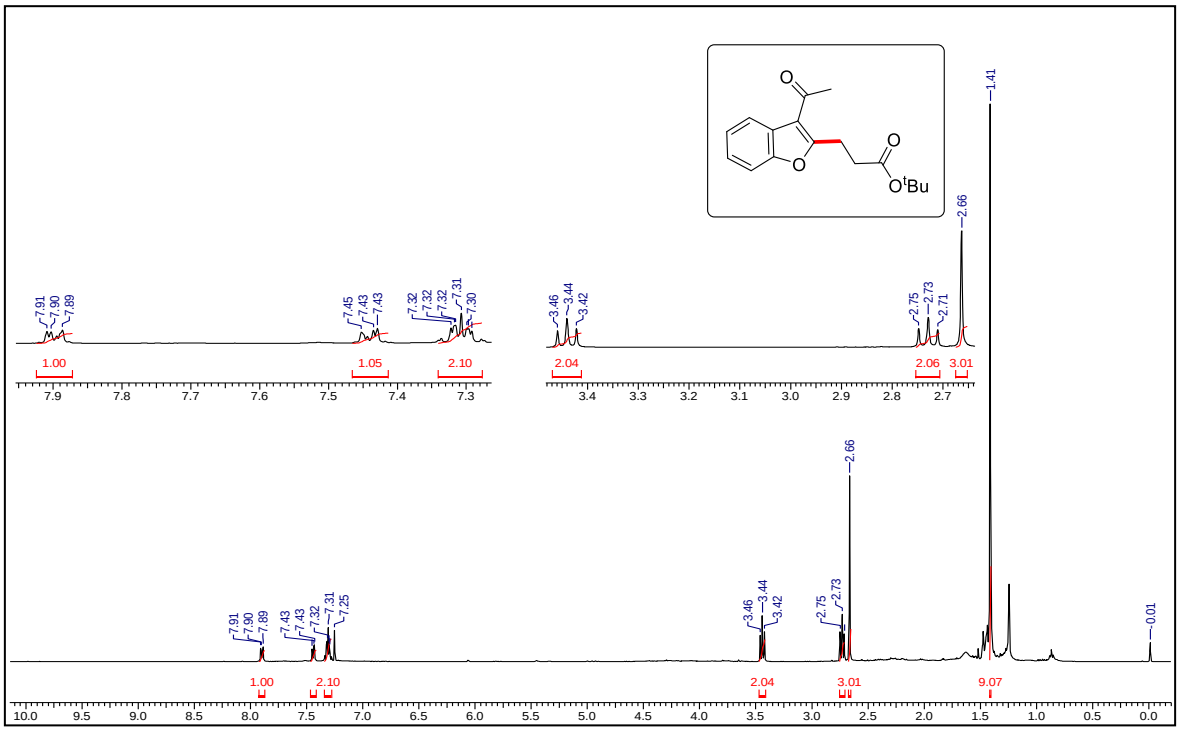

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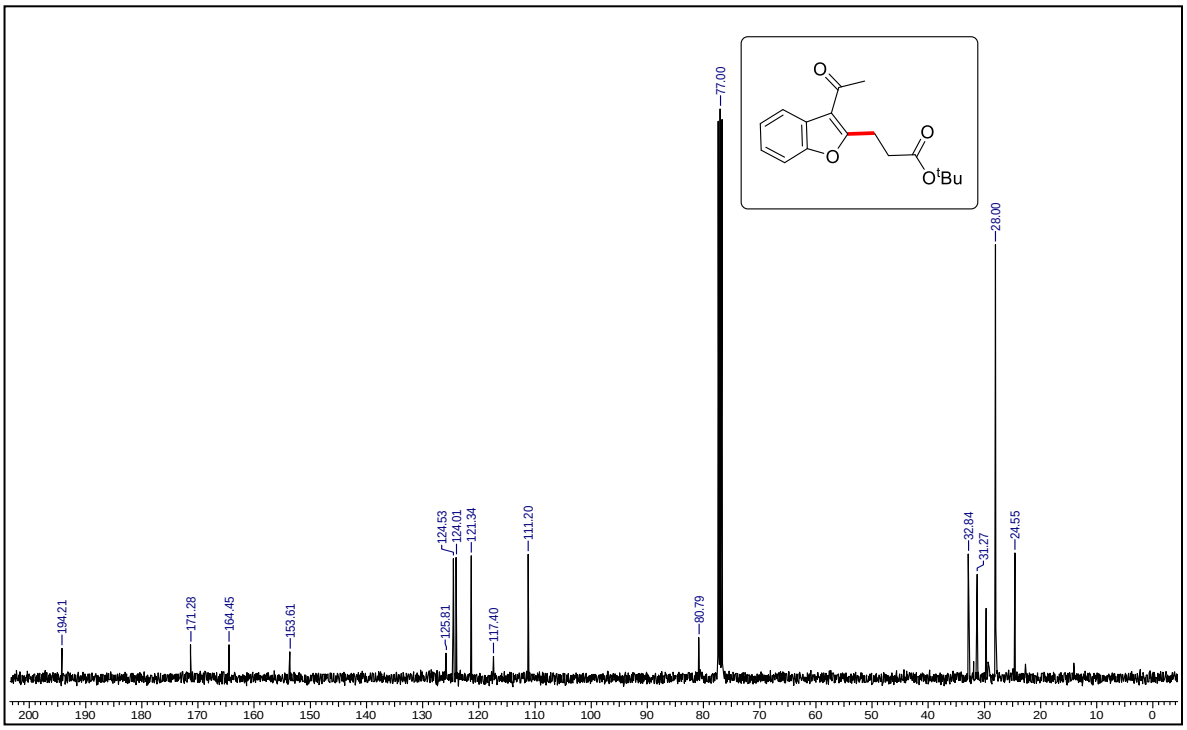

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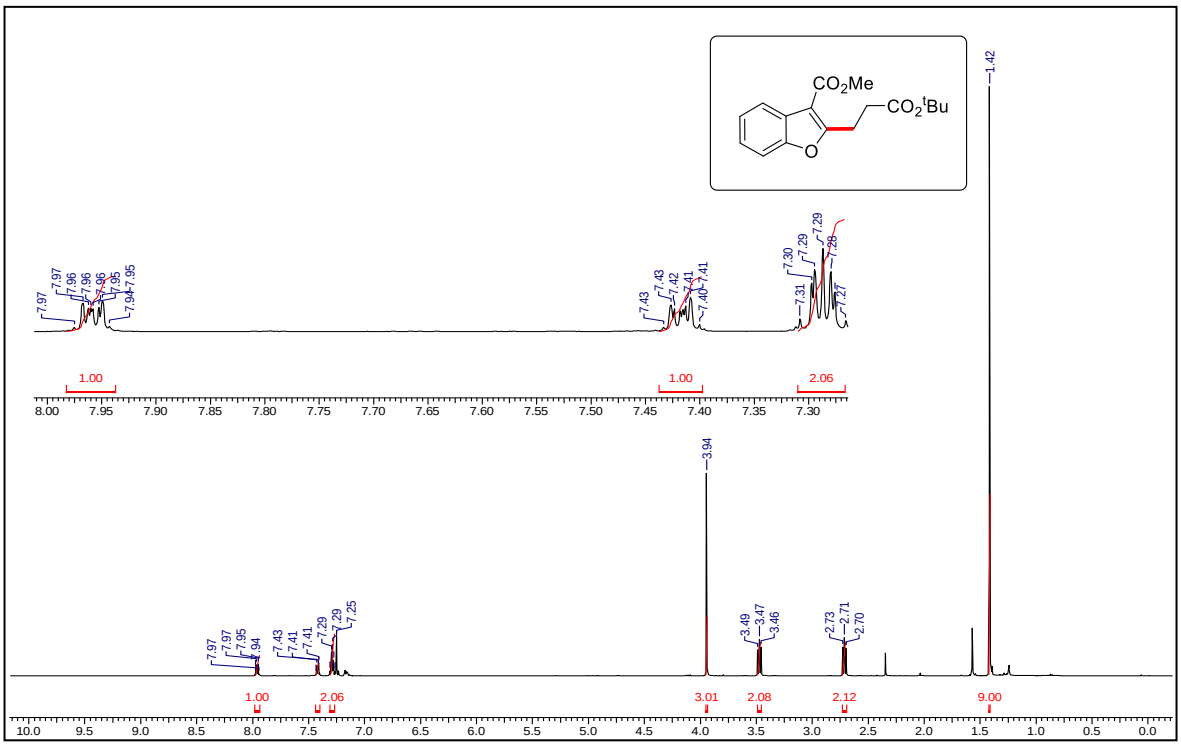

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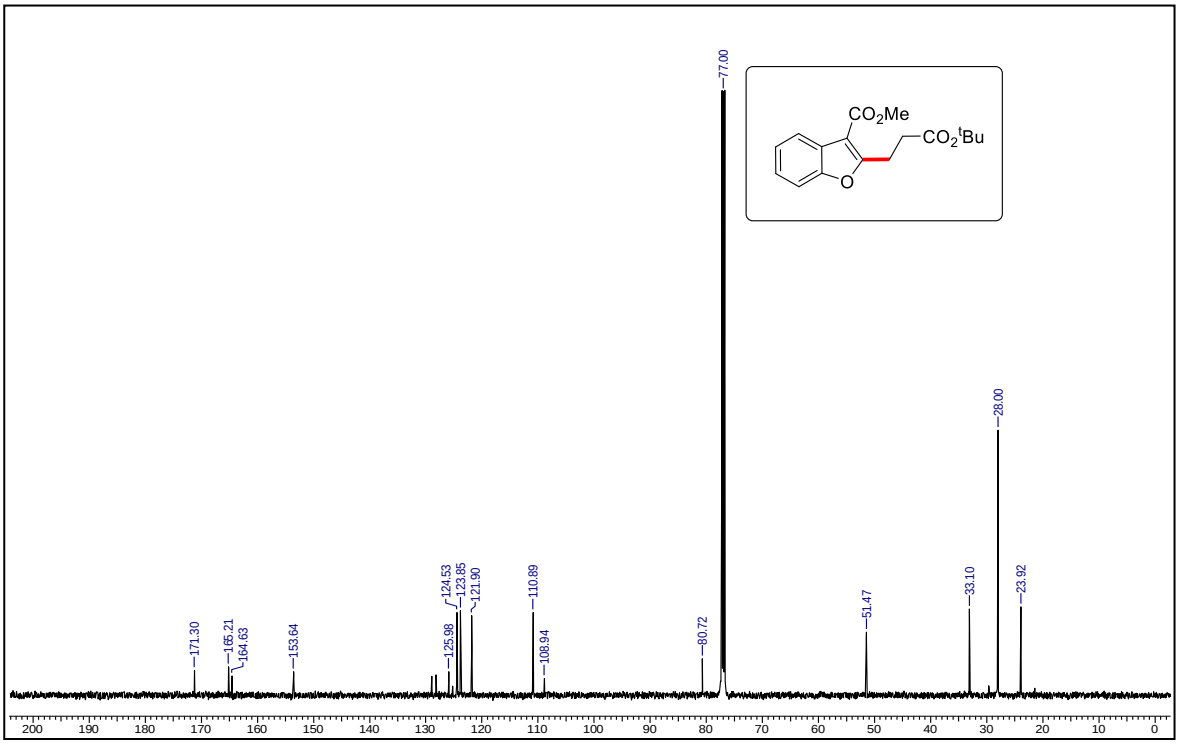
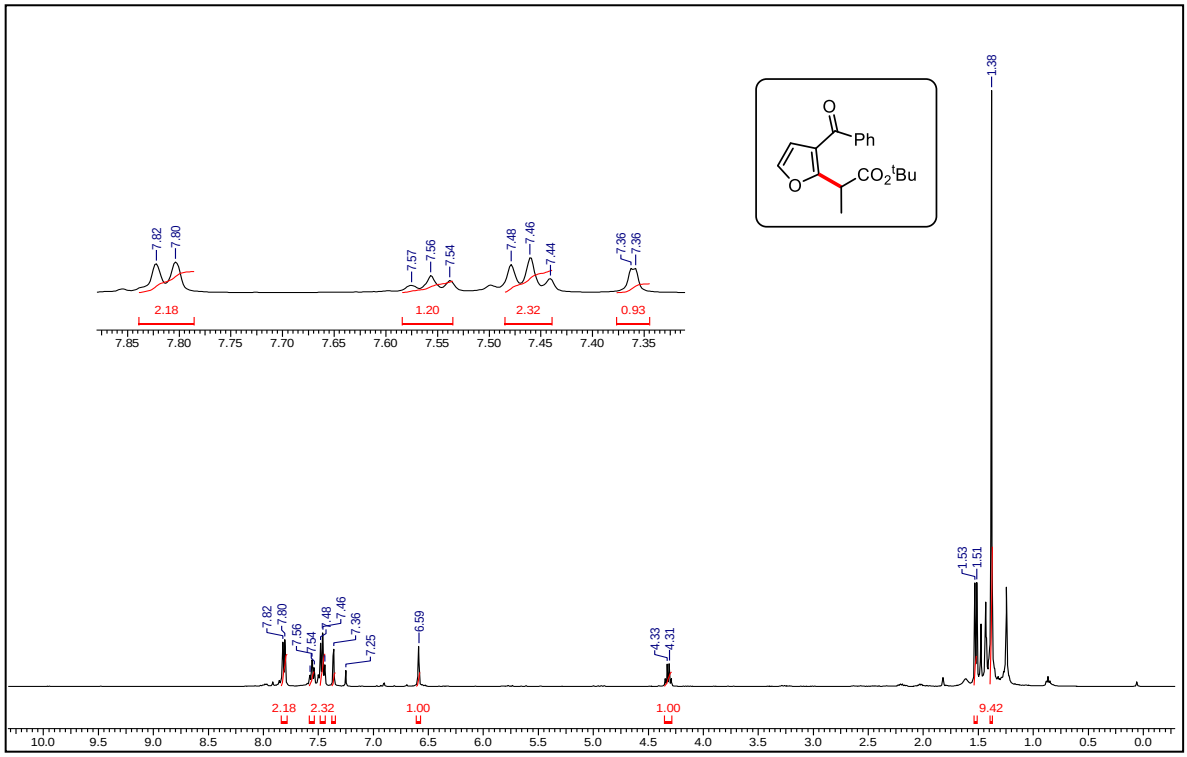
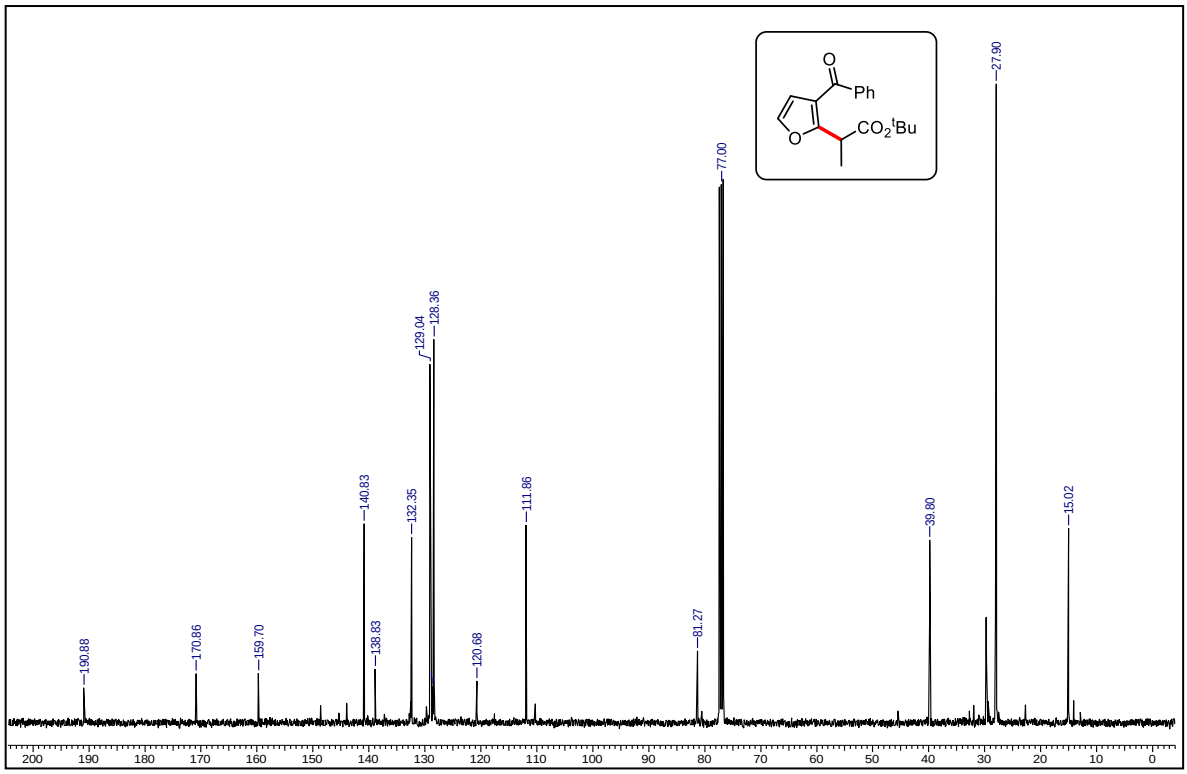


^{13}C NMR Spectrum of 6ha in $CDCl_3$



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



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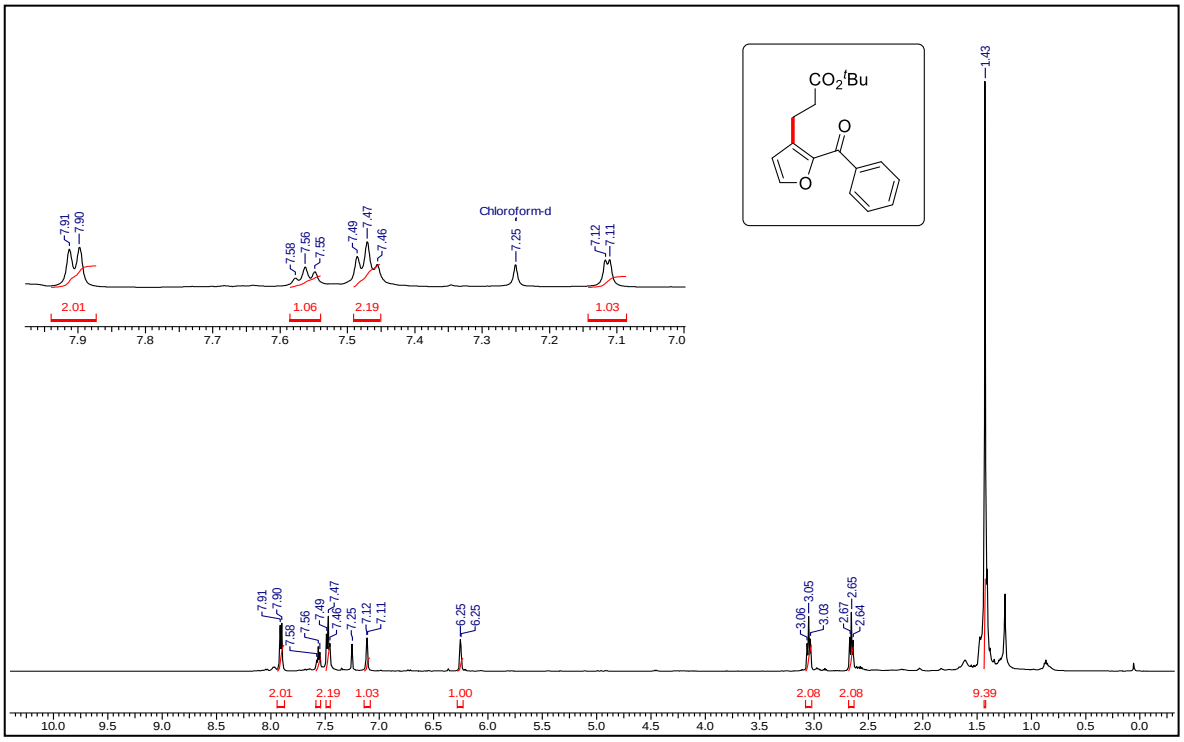

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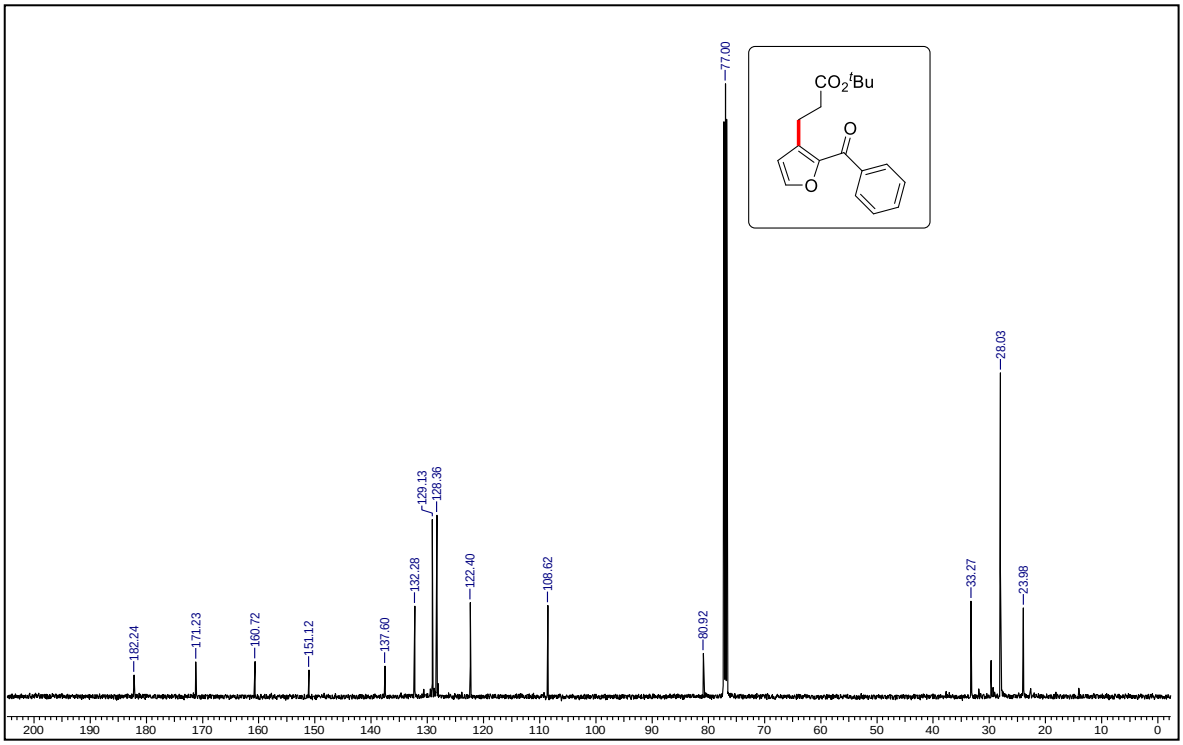
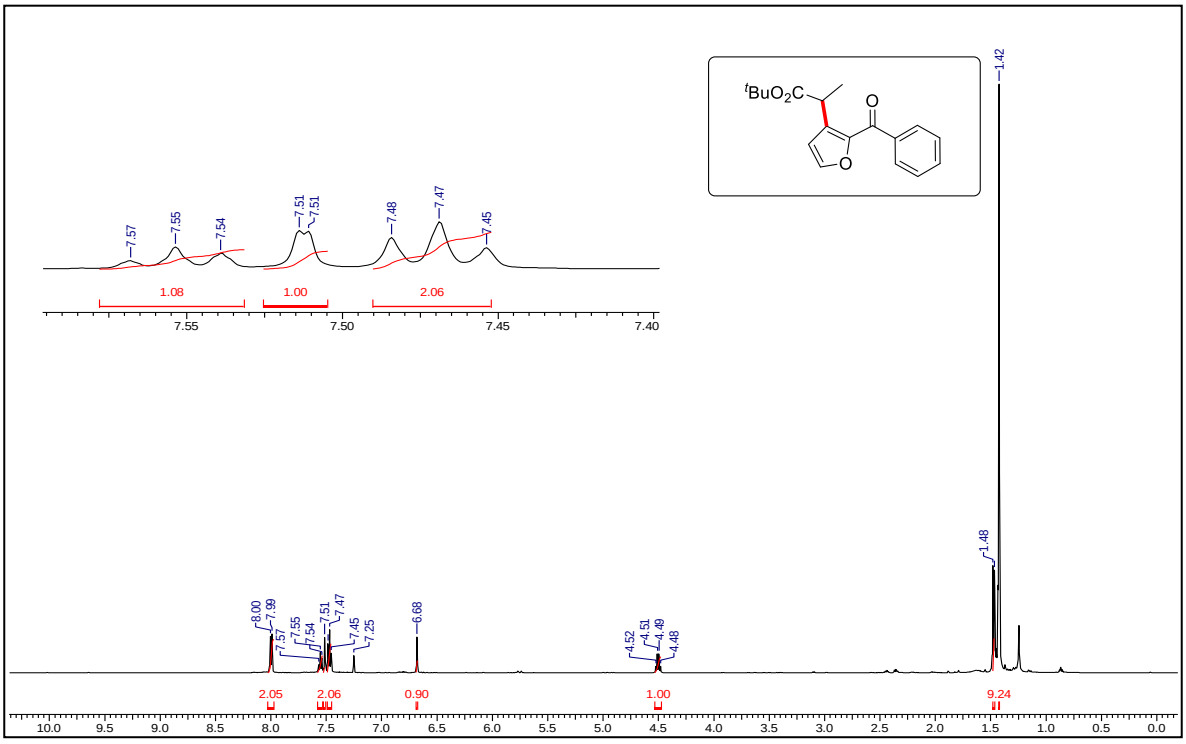
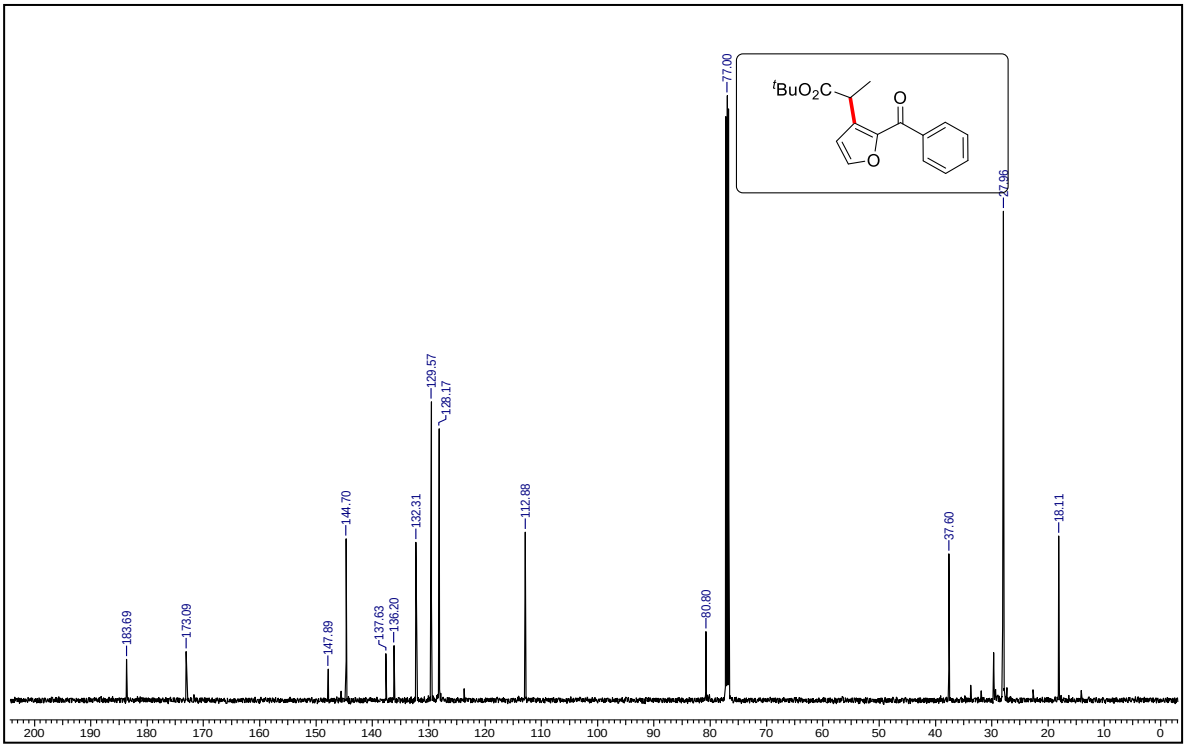


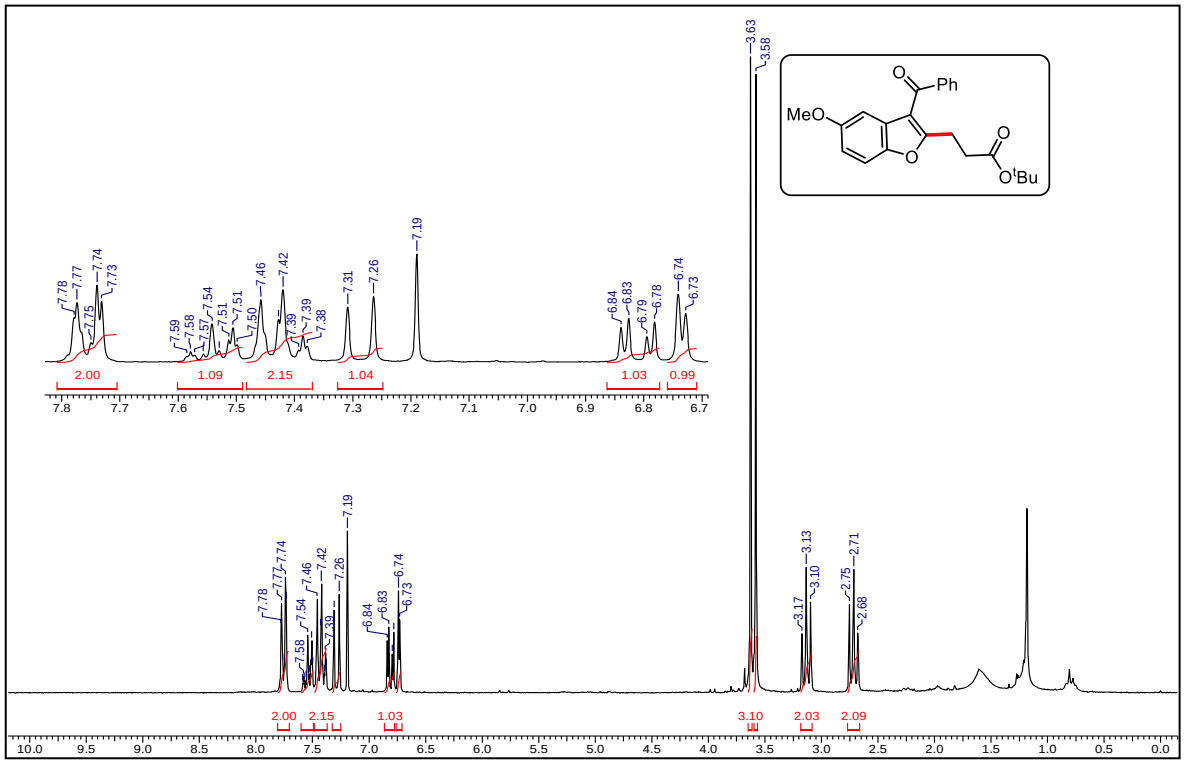
^{13}C NMR Spectrum of 6ja in $CDCl_3$



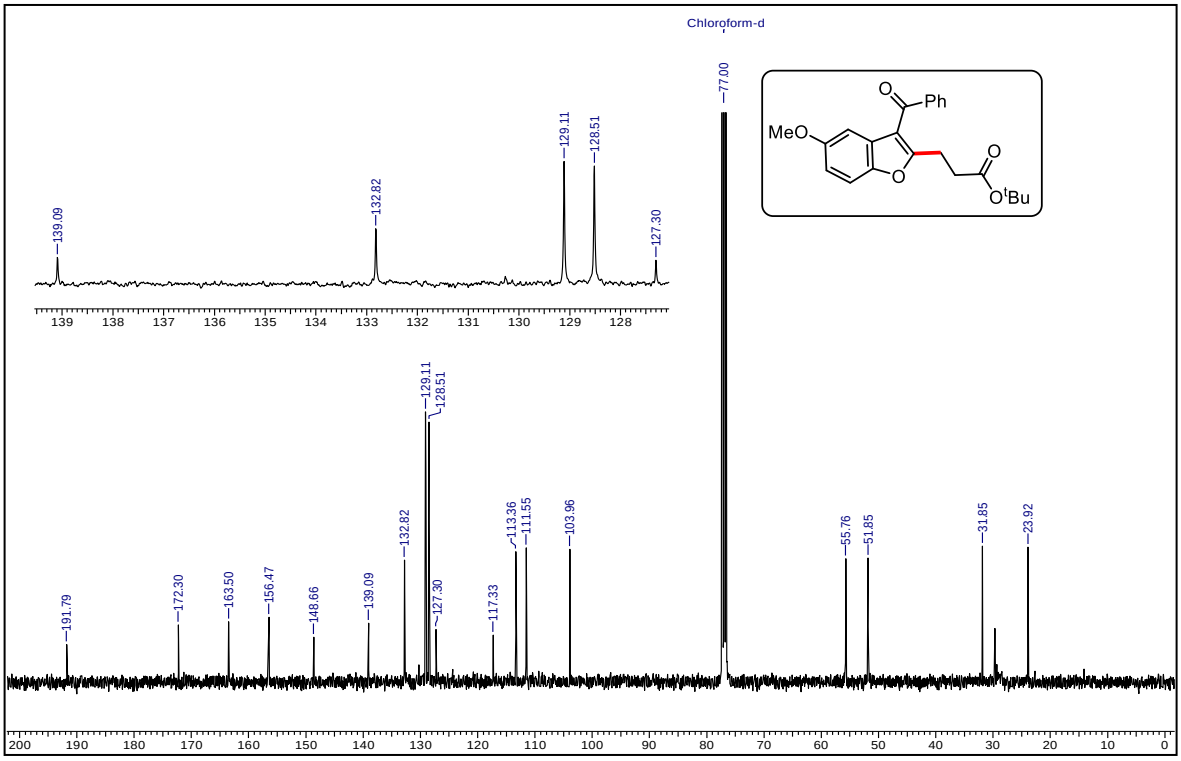
^{1}H NMR Spectrum of 7ja in $CDCl_3$



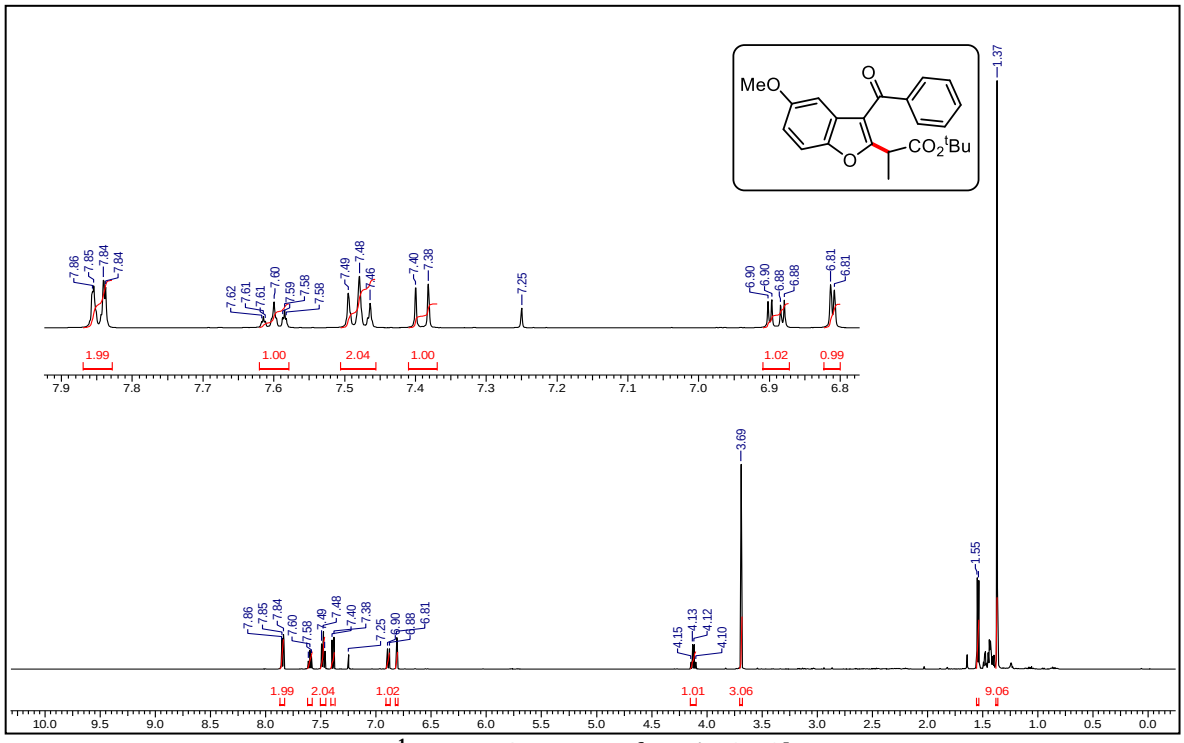
^{13}C NMR Spectrum of 7ja in $CDCl_3$



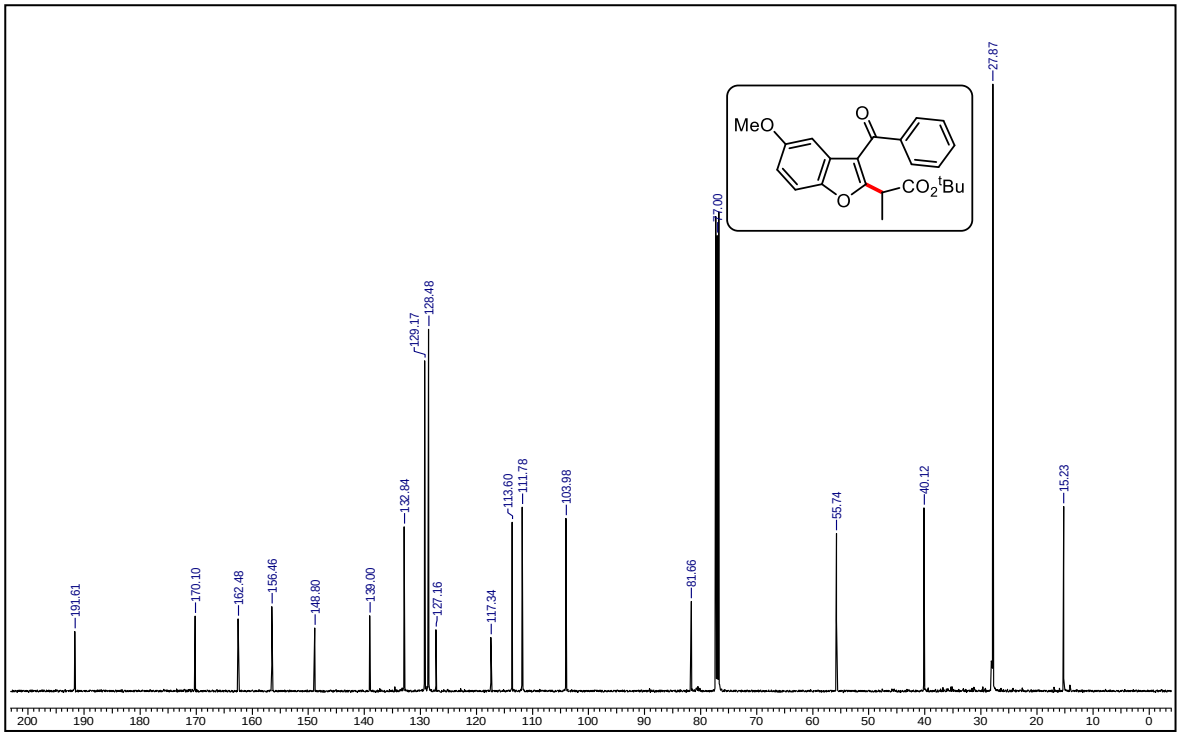
^{1}H NMR Spectrum of 6ae in $CDCl_3$



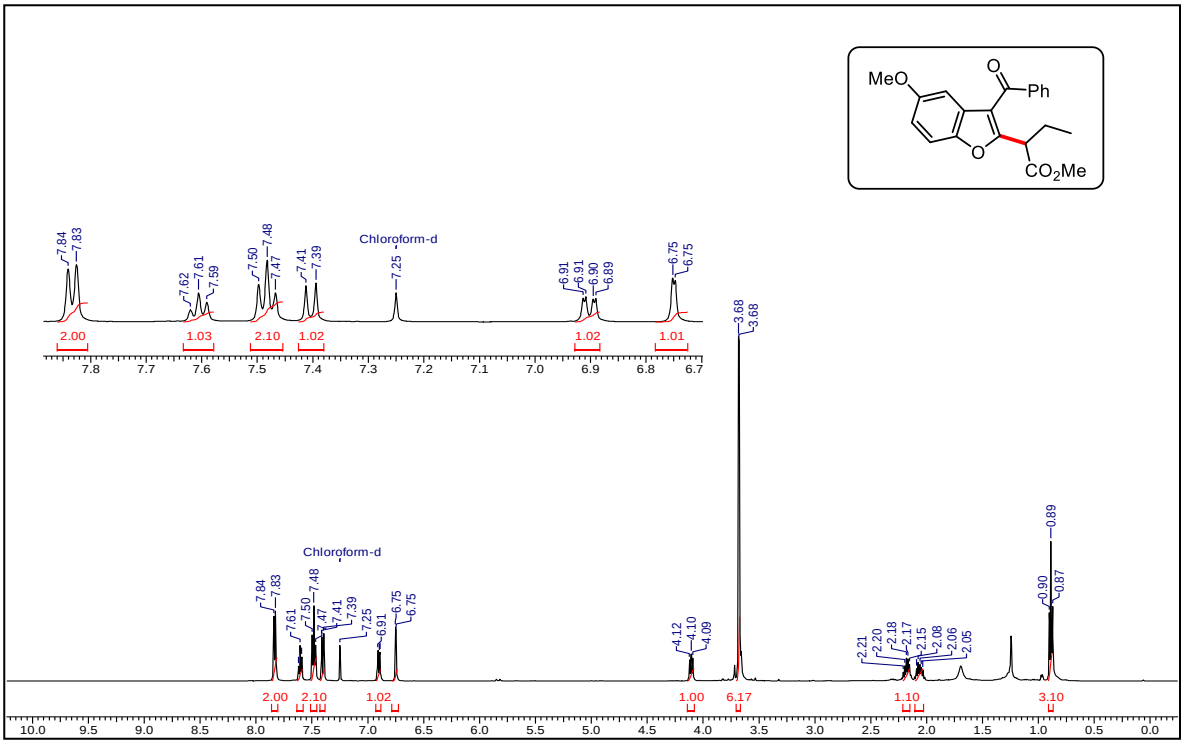
^{13}C NMR Spectrum of 6ae in $CDCl_3$



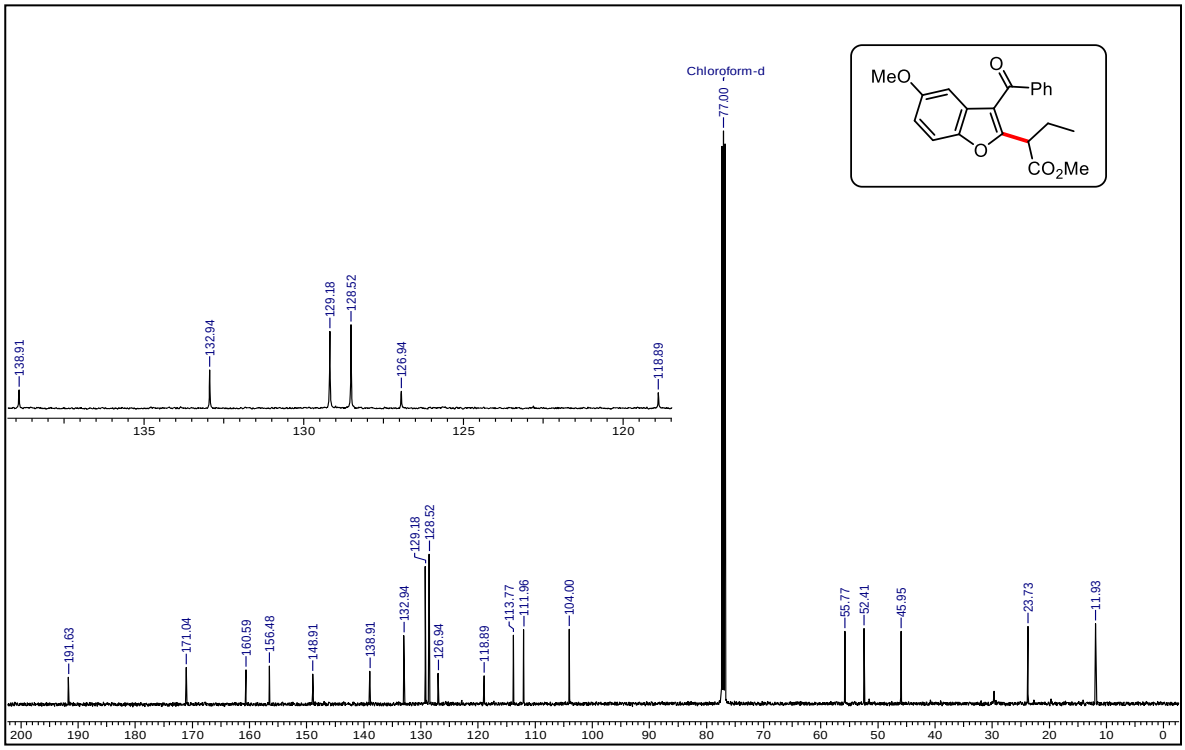
^{1}H NMR Spectrum of 7ae in $CDCl_3$



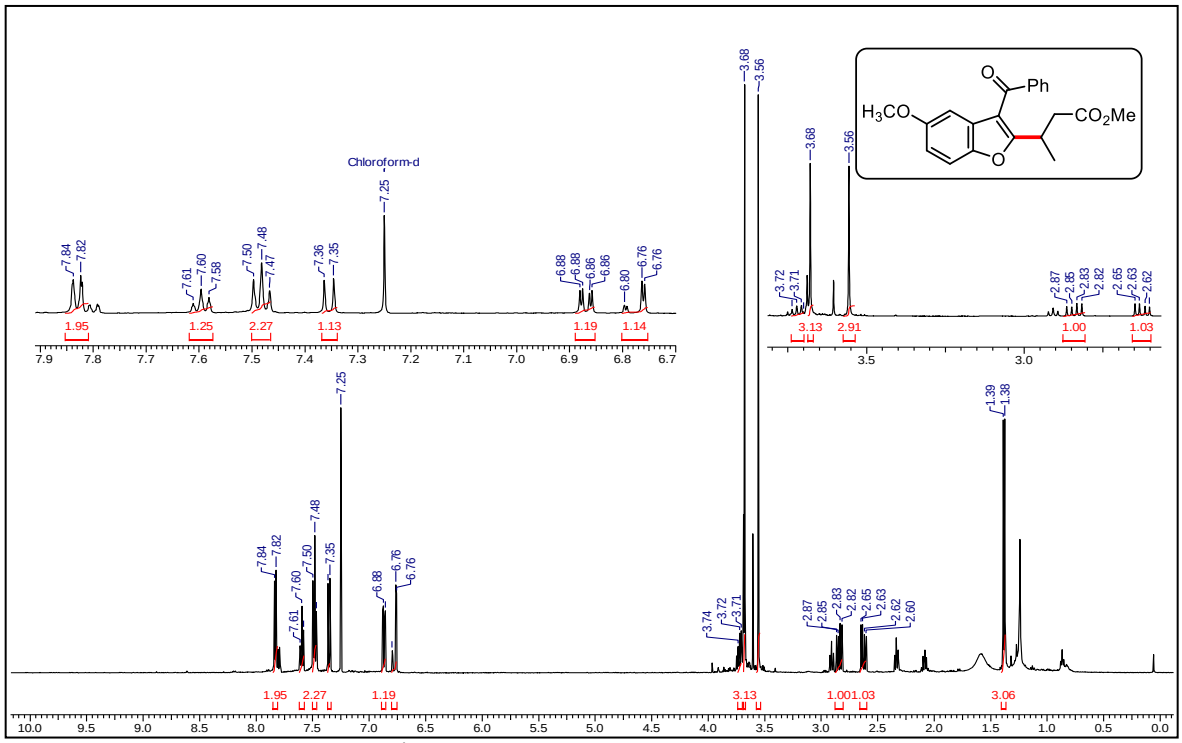
^{13}C NMR Spectrum of 7ae in $CDCl_3$



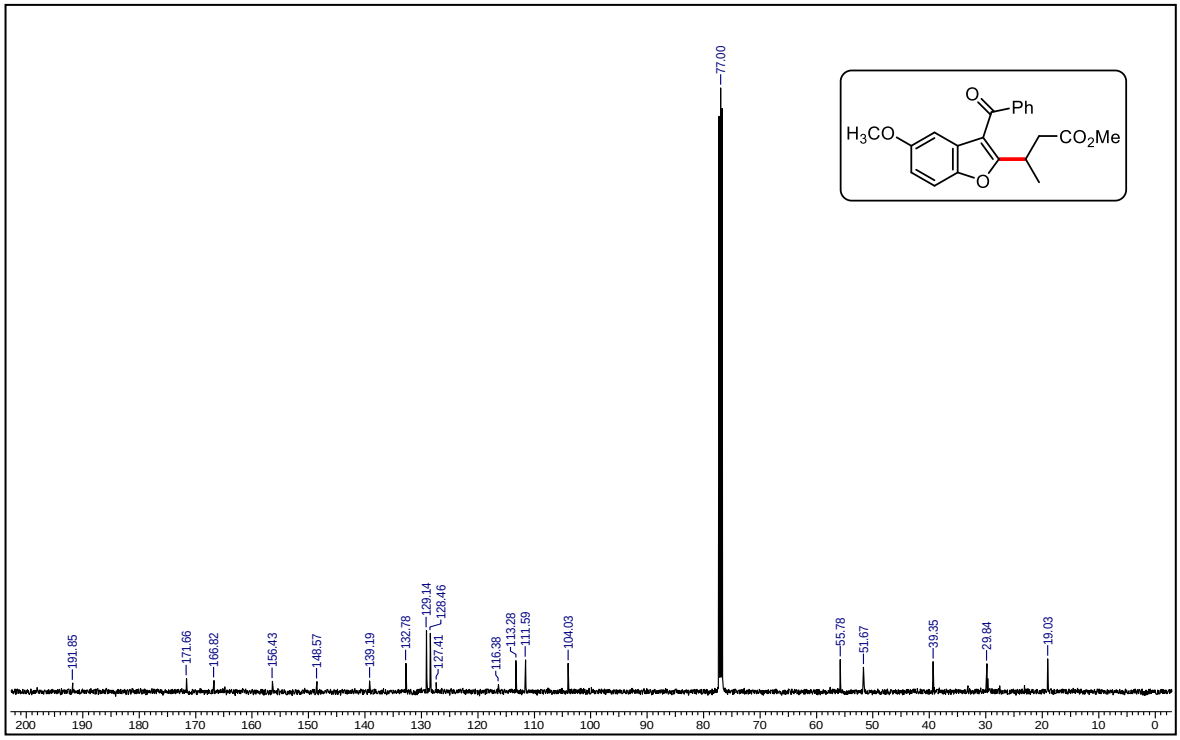
^{1}H NMR Spectrum of 7aj in $CDCl_3$



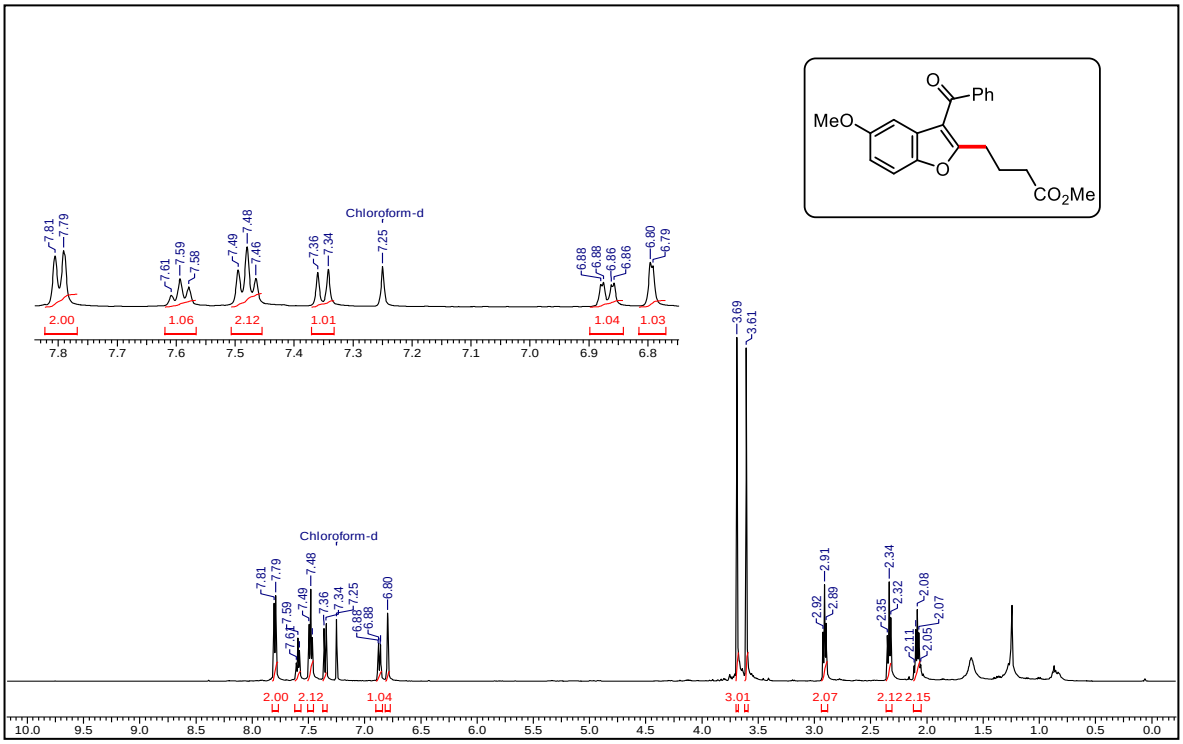
^{13}C NMR Spectrum of 7aj in $CDCl_3$



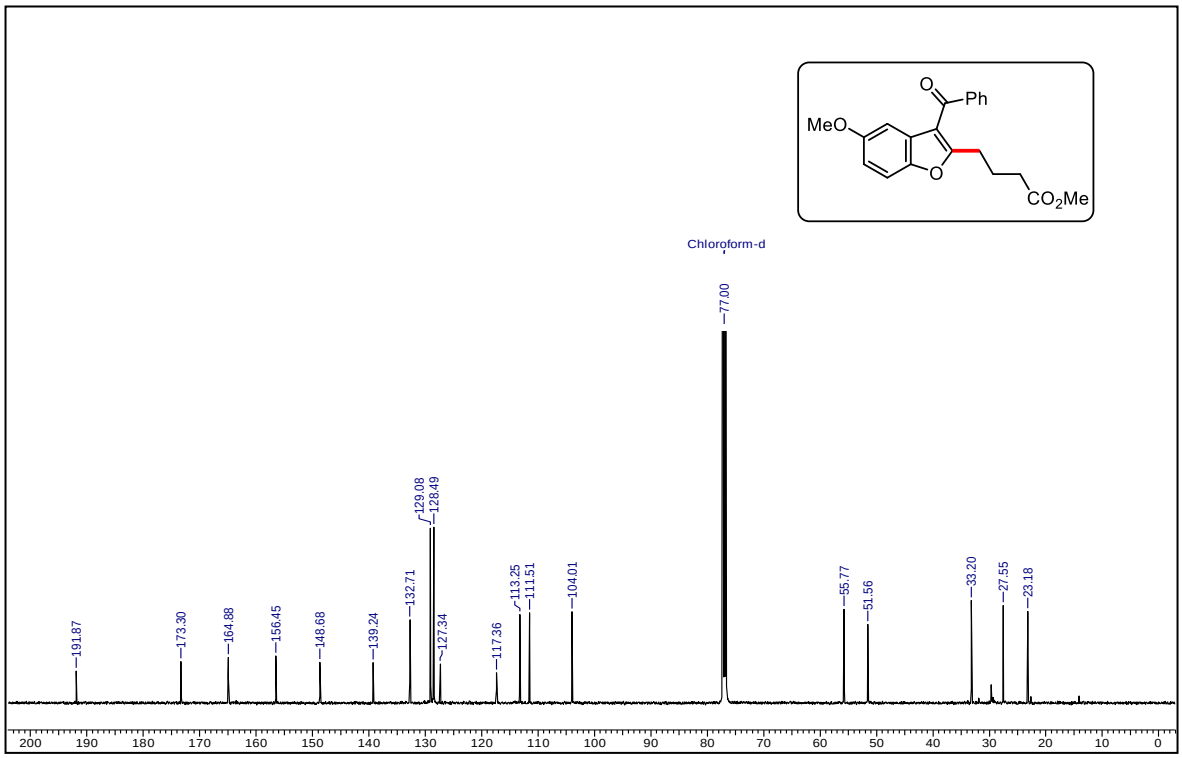
^{1}H NMR Spectrum of 6aj in $CDCl_3$



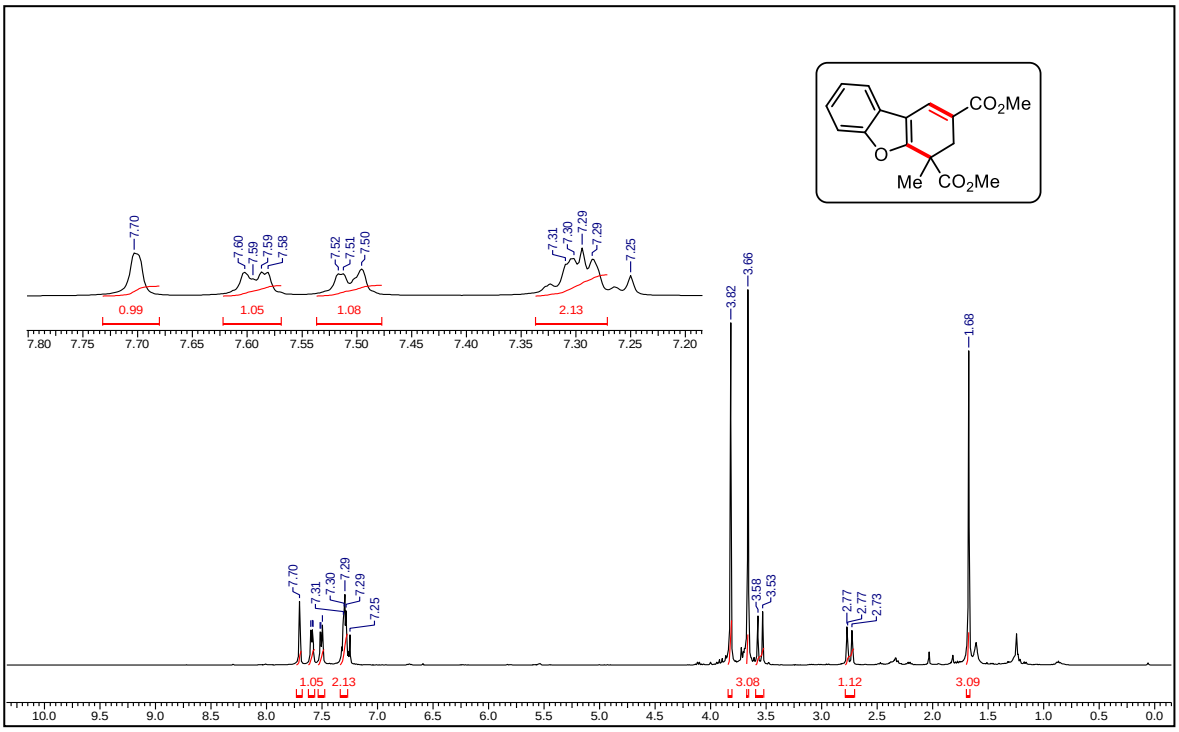
^{13}C NMR Spectrum of 6aj in $CDCl_3$



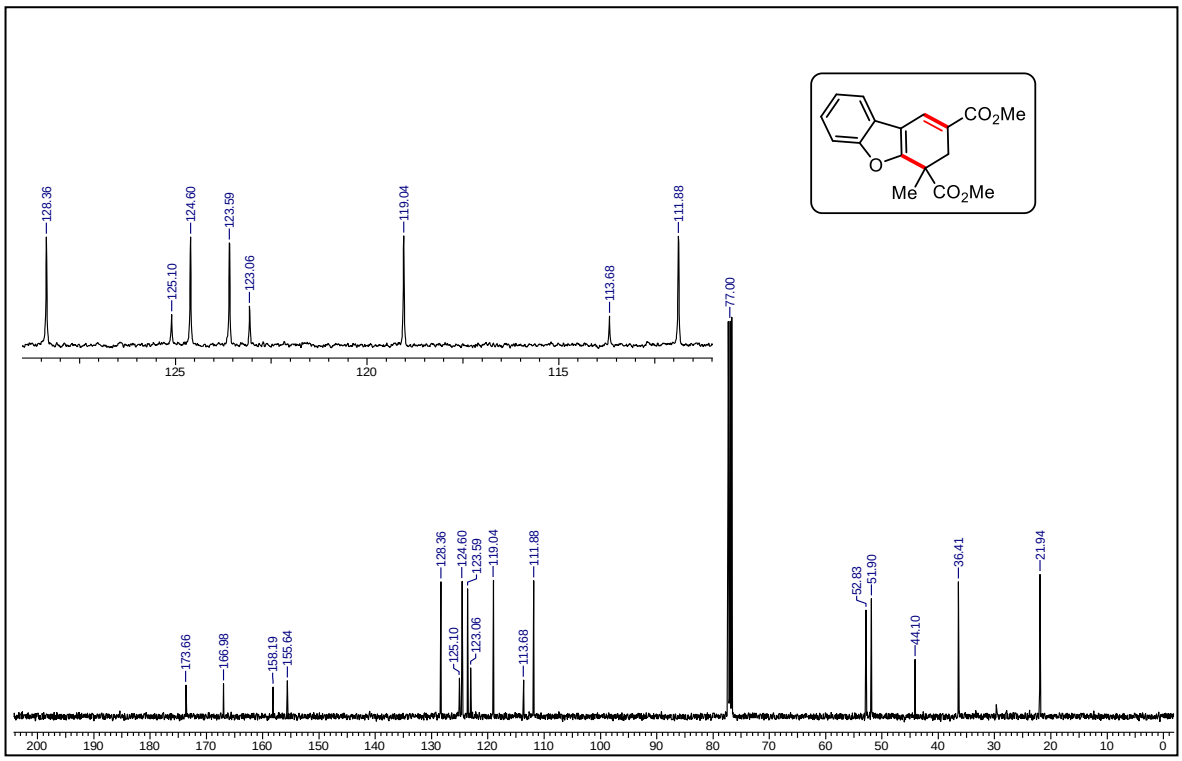
^{1}H NMR Spectrum of 6ajl in $CDCl_3$



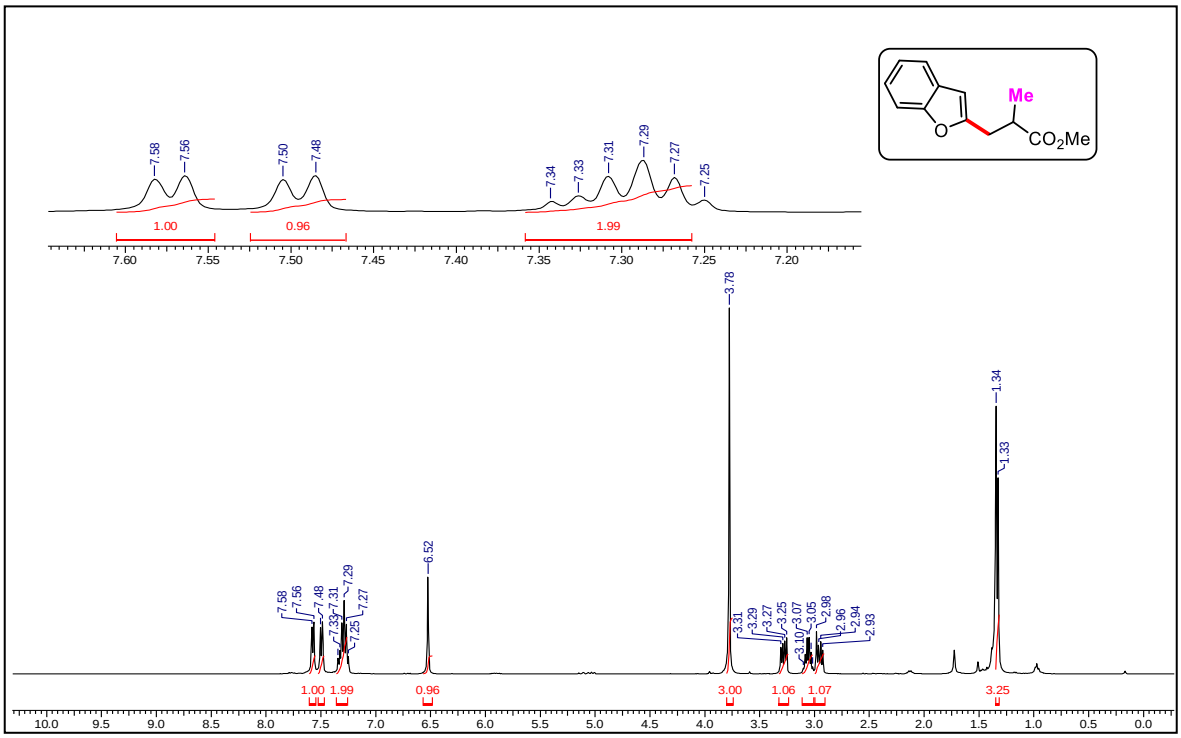
^{13}C NMR Spectrum of 6ajl in $CDCl_3$



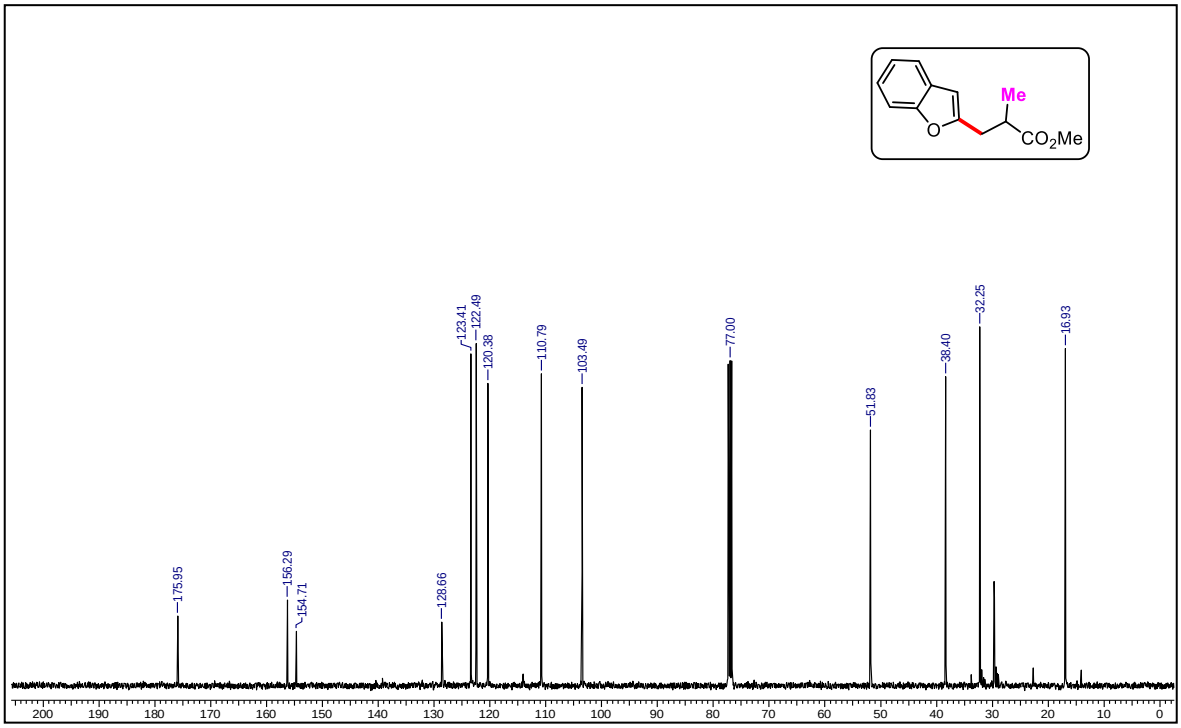
^{1}H NMR Spectrum of 9aa in $CDCl_3$



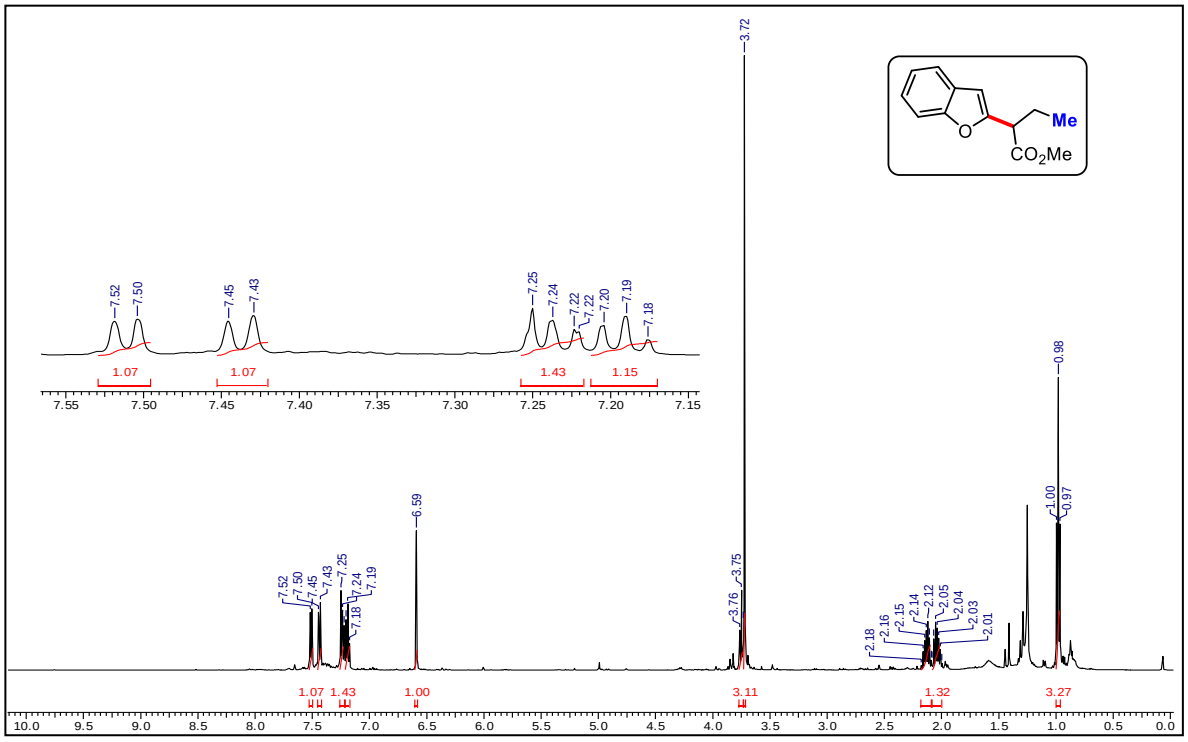
^{13}C NMR Spectrum of 9aa in $CDCl_3$



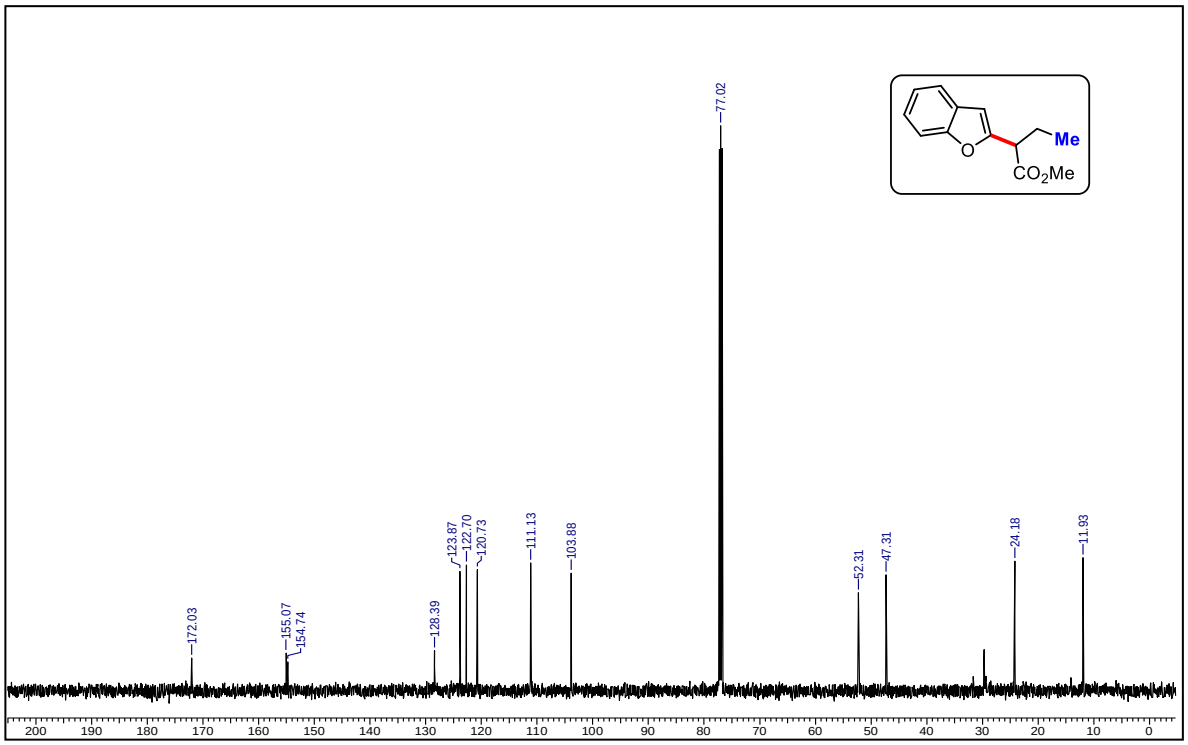
^{1}H NMR Spectrum of 10aa in $CDCl_3$



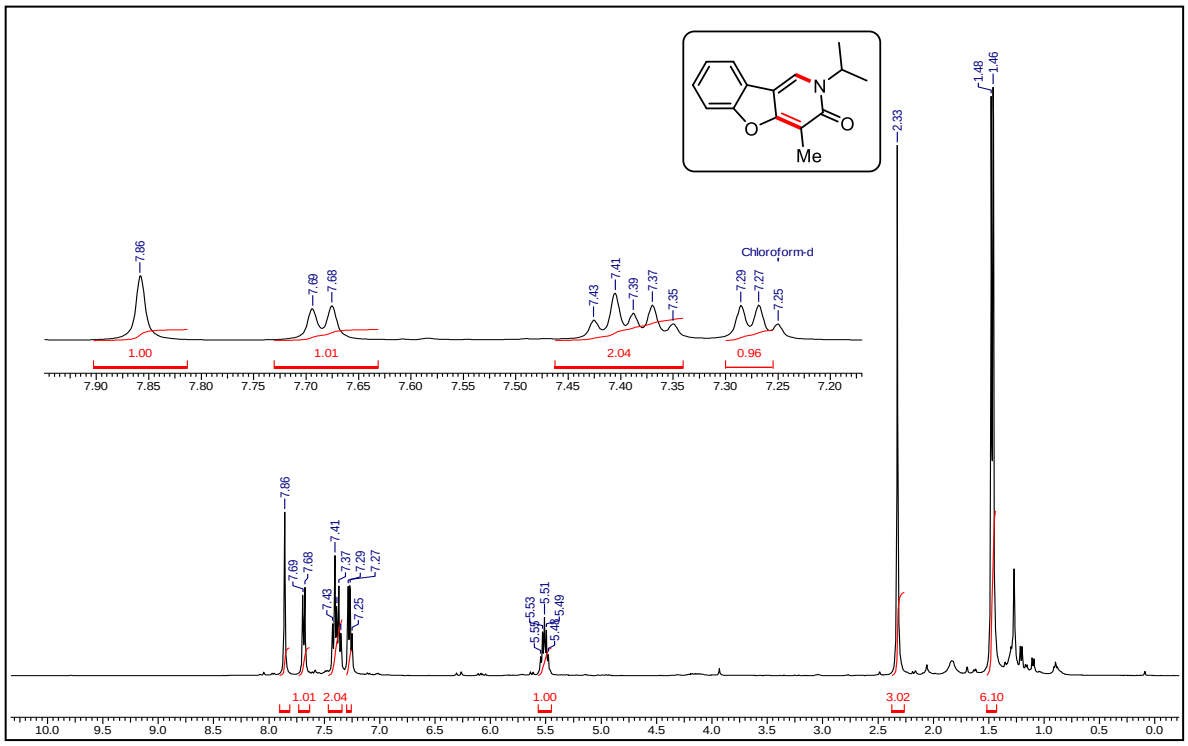
^{13}C NMR Spectrum of 10aa in $CDCl_3$



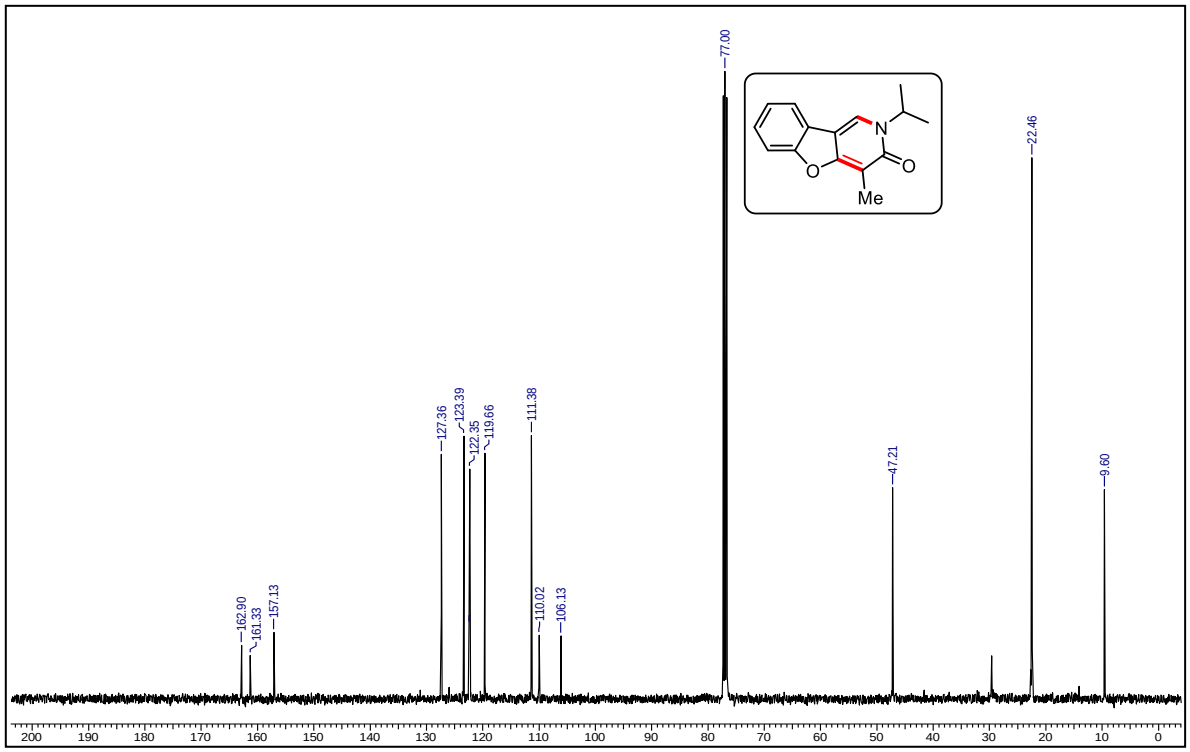
^{1}H NMR Spectrum of 11aa in $CDCl_3$



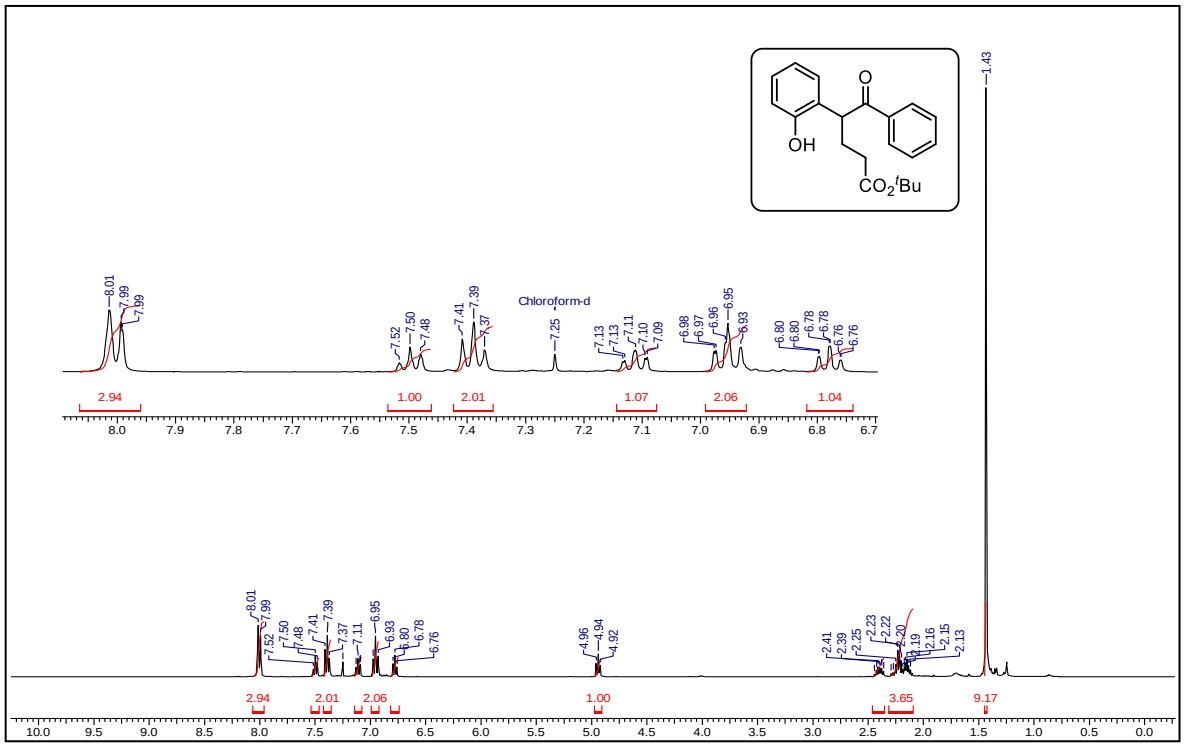
^{13}C NMR Spectrum of 11aa in $CDCl_3$



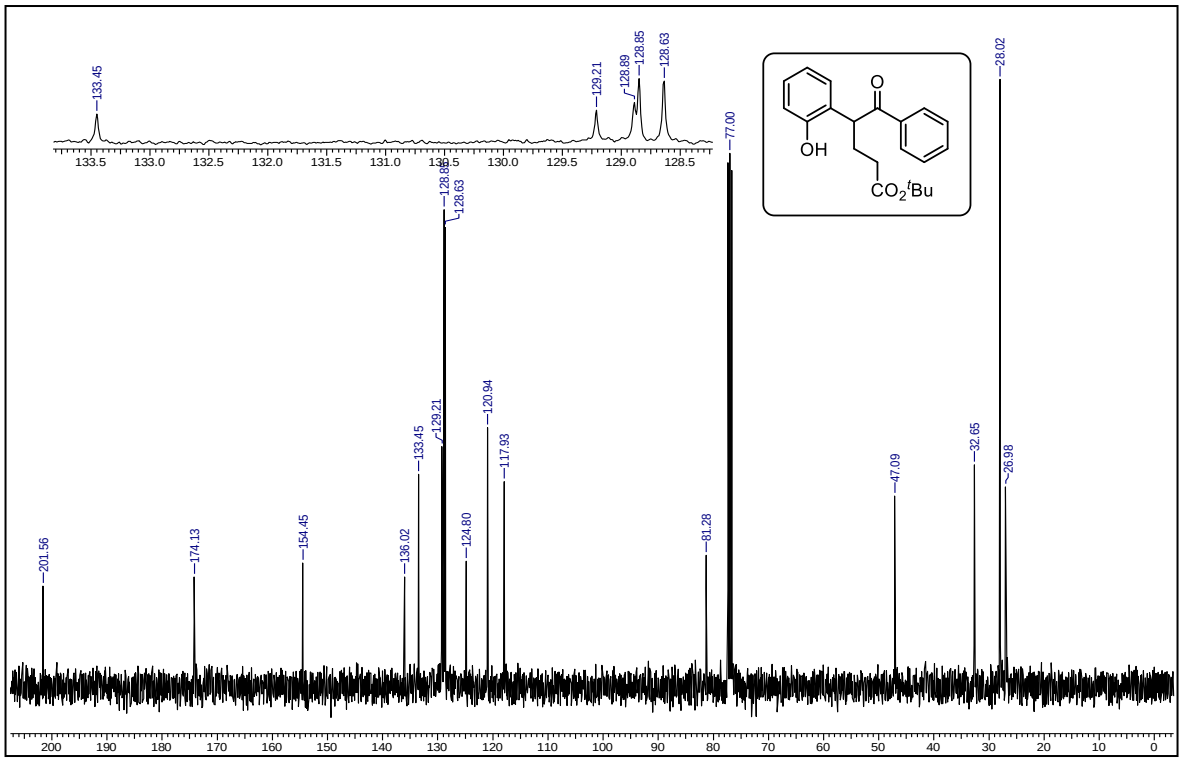
^{1}H NMR Spectrum of 12aa in $CDCl_3$



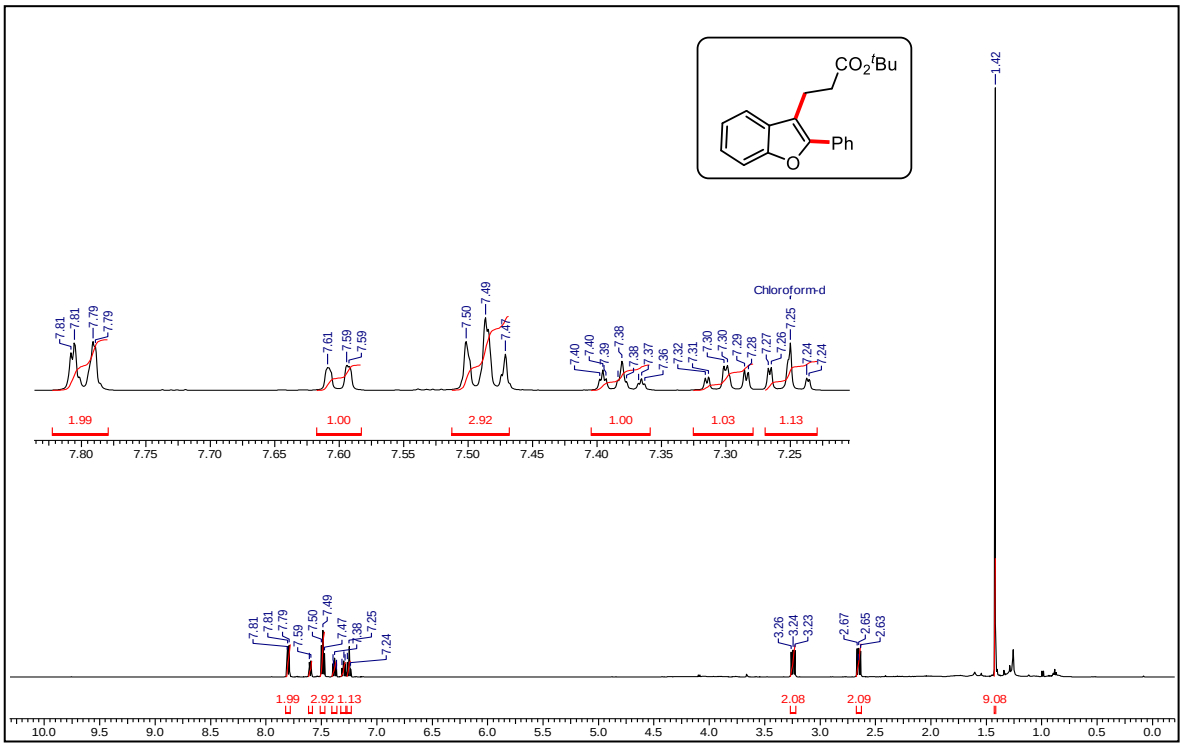
^{13}C NMR Spectrum of 12aa in $CDCl_3$



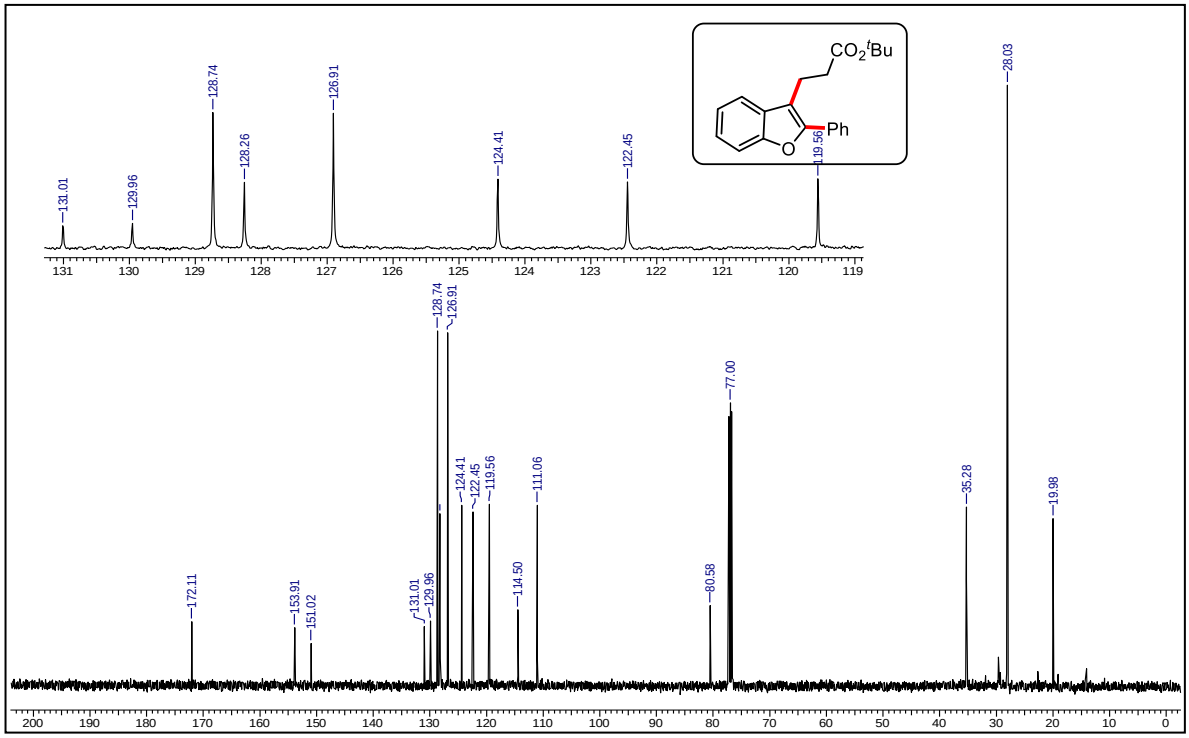
^{1}H NMR Spectrum of 14a in $CDCl_3$



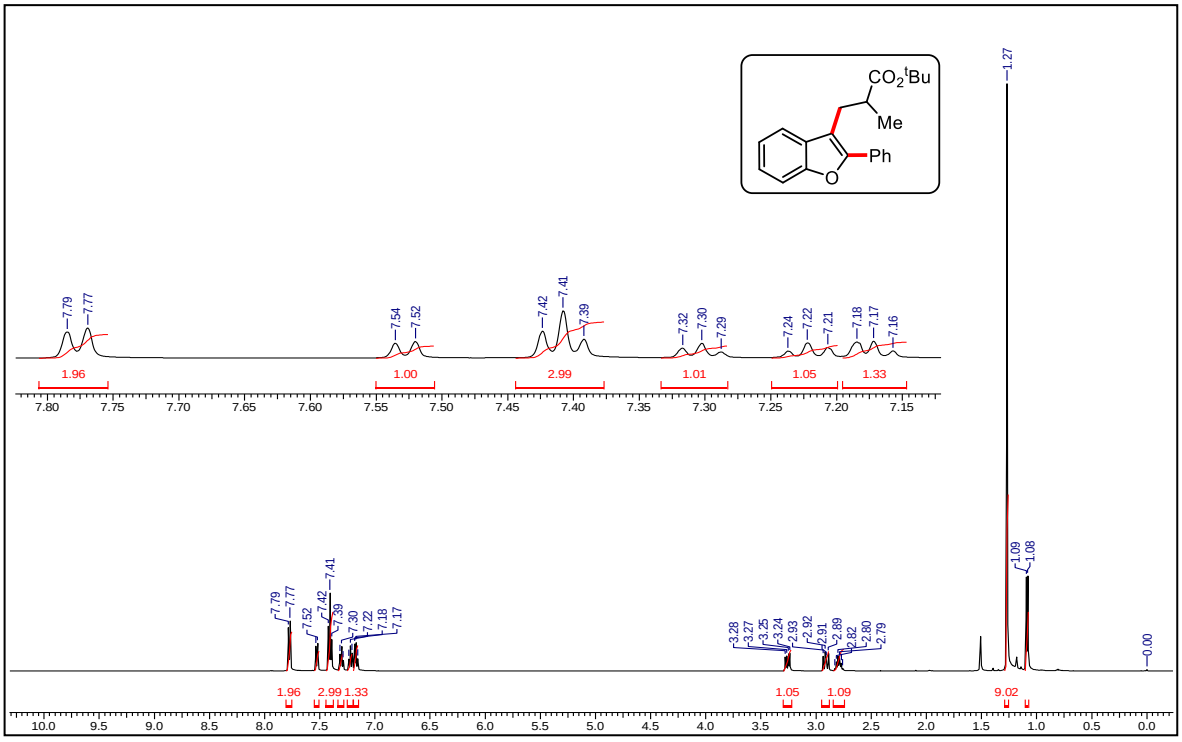
^{13}C NMR Spectrum of 14a in $CDCl_3$



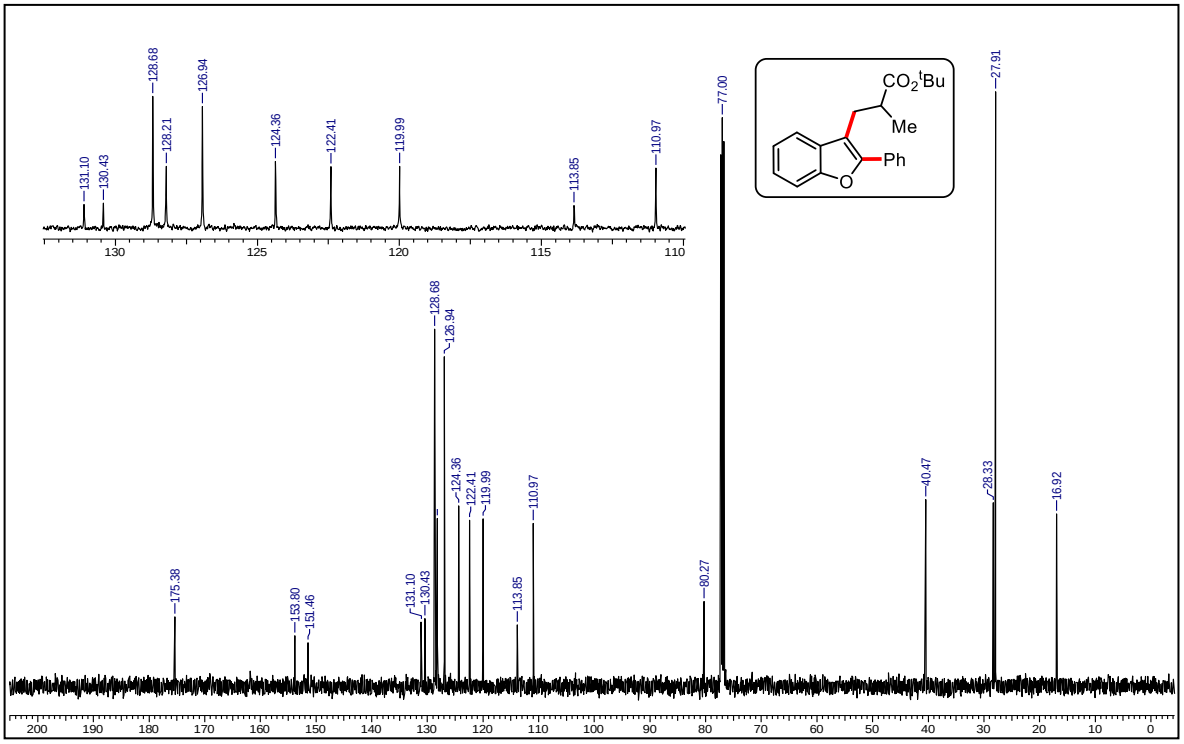
^{1}H NMR Spectrum of 15be in $CDCl_3$



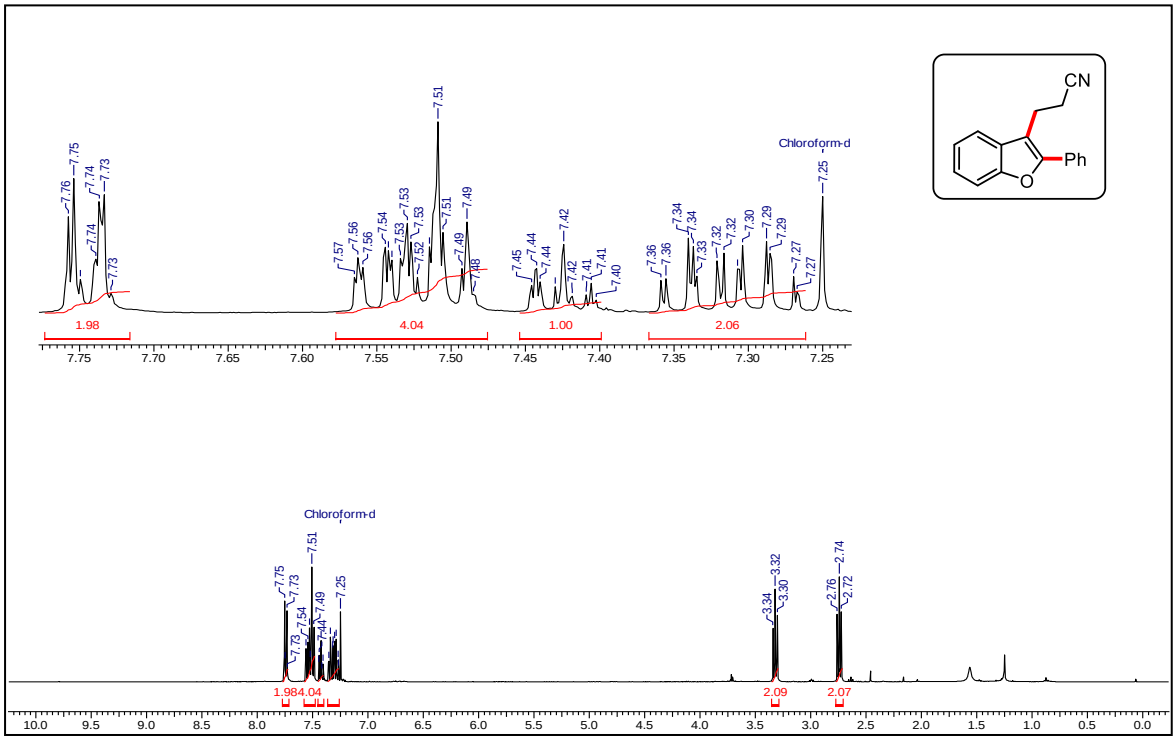
^{13}C NMR Spectrum of 15be in $CDCl_3$



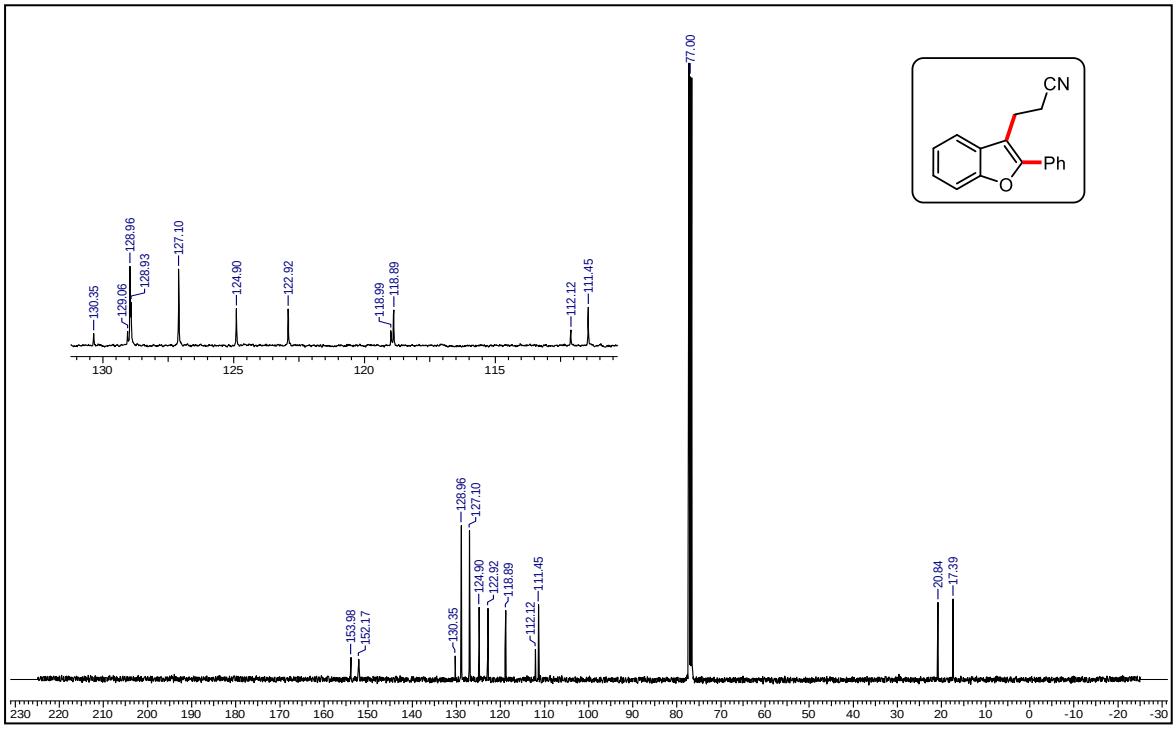
^{1}H NMR Spectrum of 15bu in $CDCl_3$



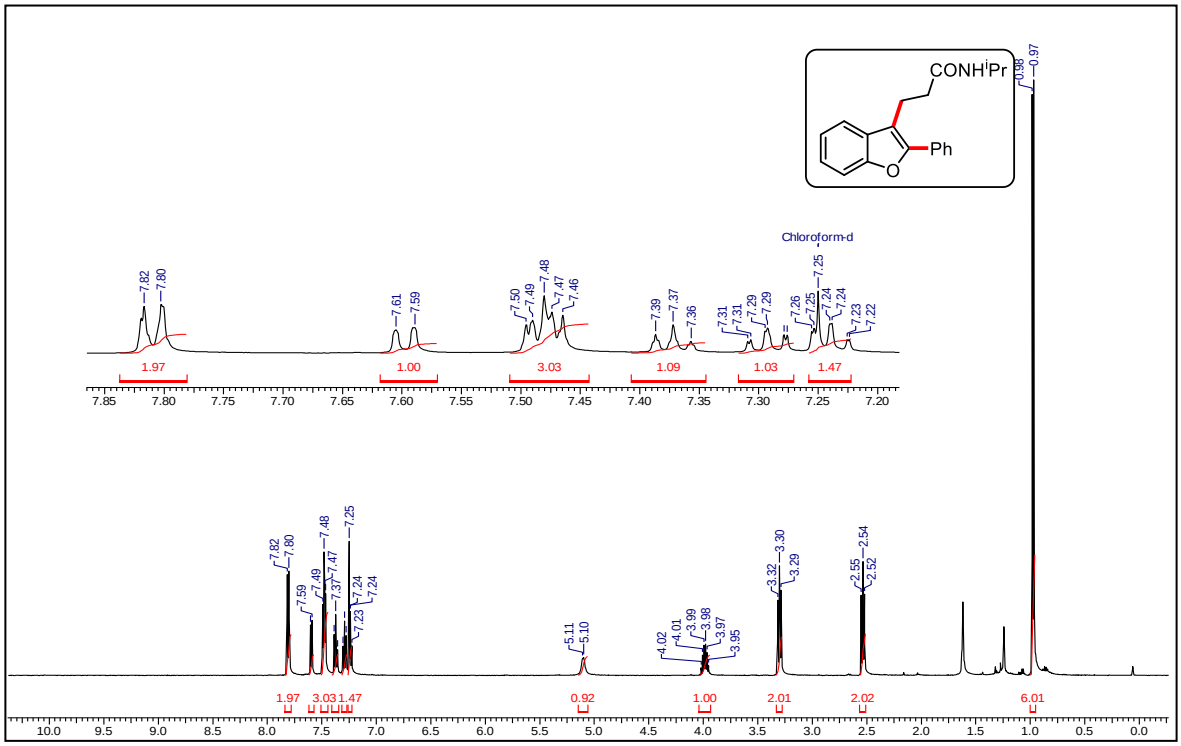
^{13}C NMR Spectrum of 15bu in $CDCl_3$



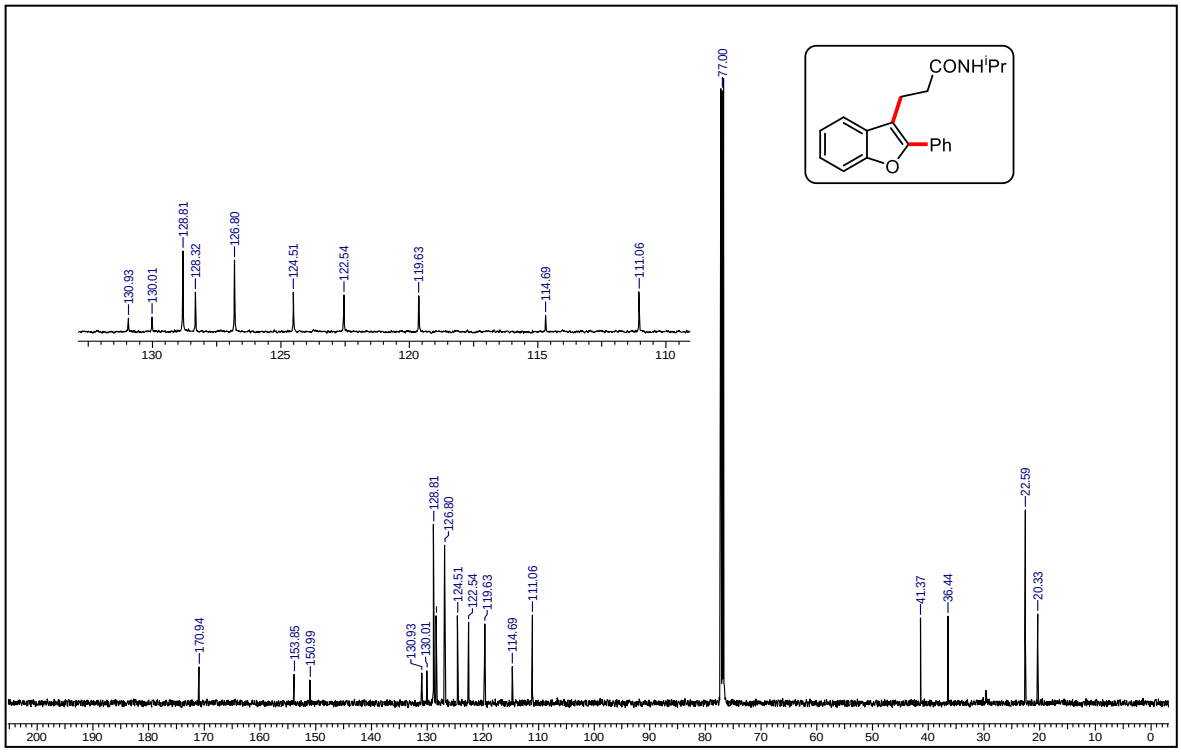
^{1}H NMR Spectrum of 15bv in $CDCl_3$



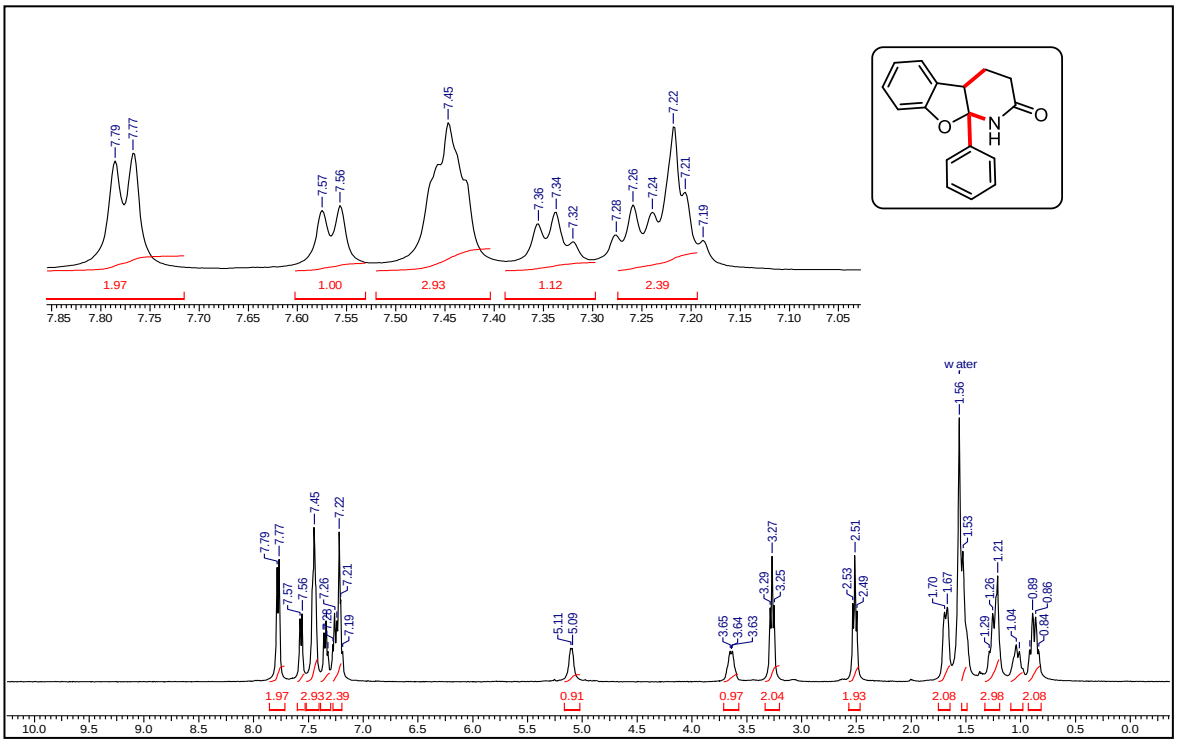
^{13}C NMR Spectrum of 15bv in $CDCl_3$



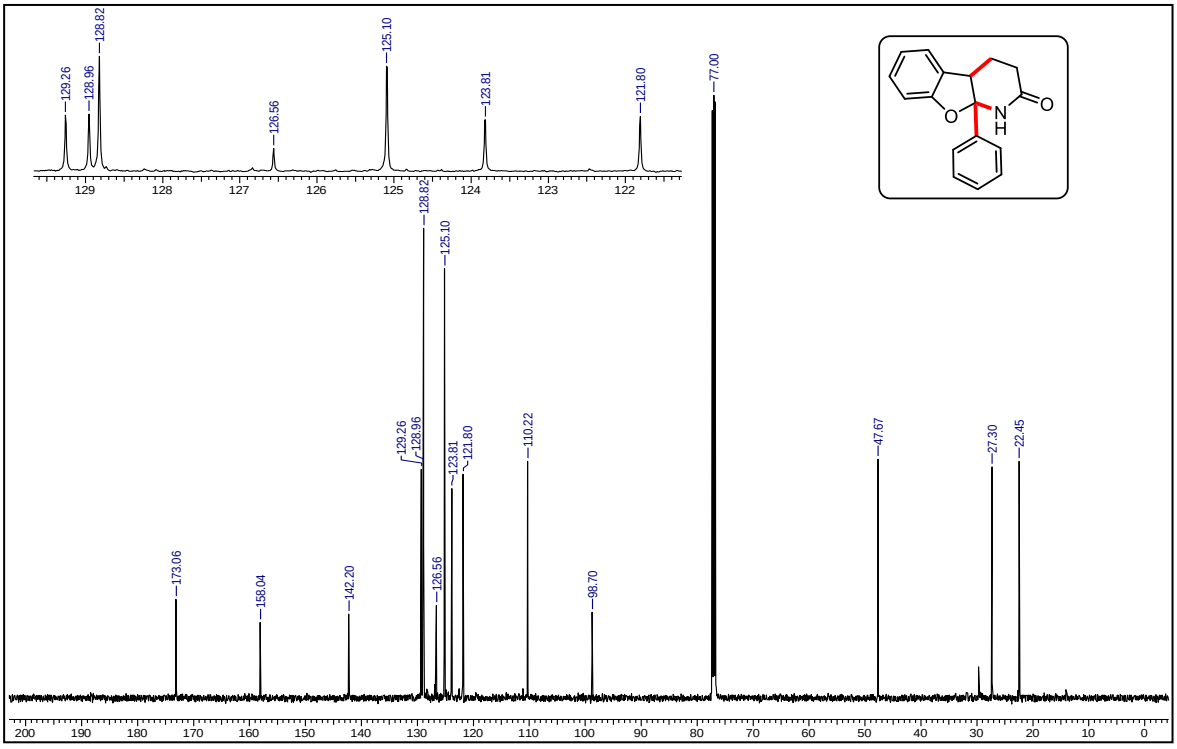
^{1}H NMR Spectrum of 15bd in $CDCl_3$



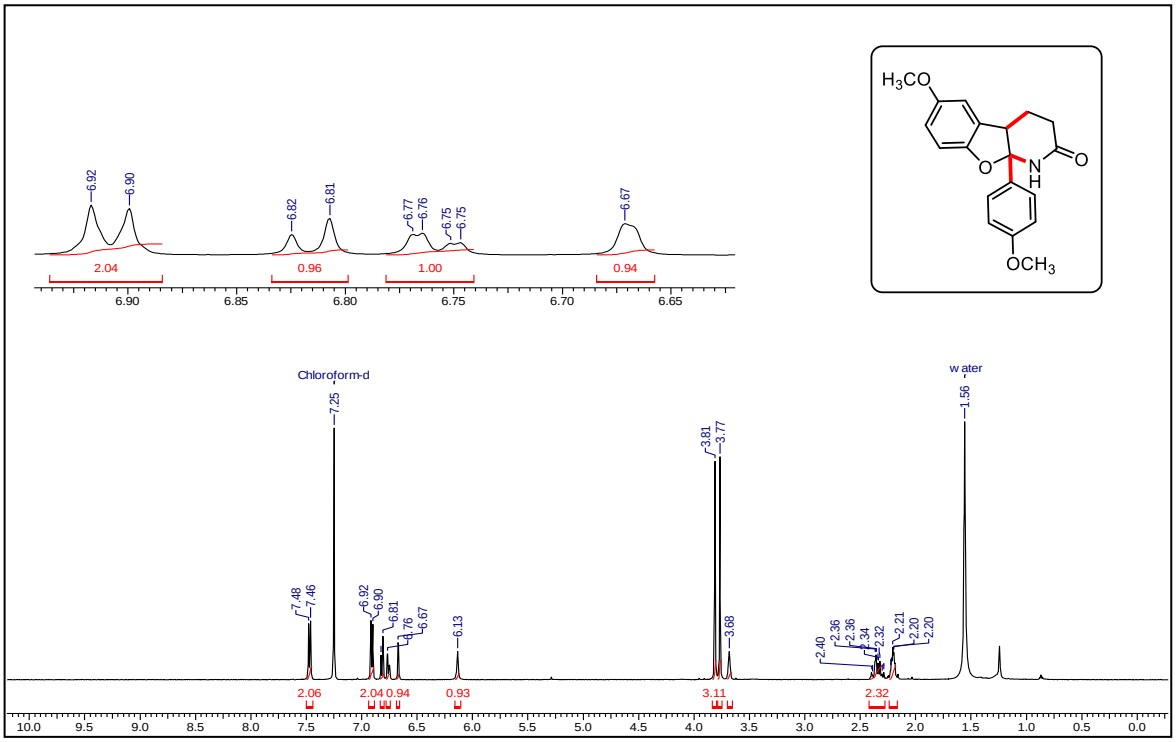
^{13}C NMR Spectrum of 15bd in $CDCl_3$



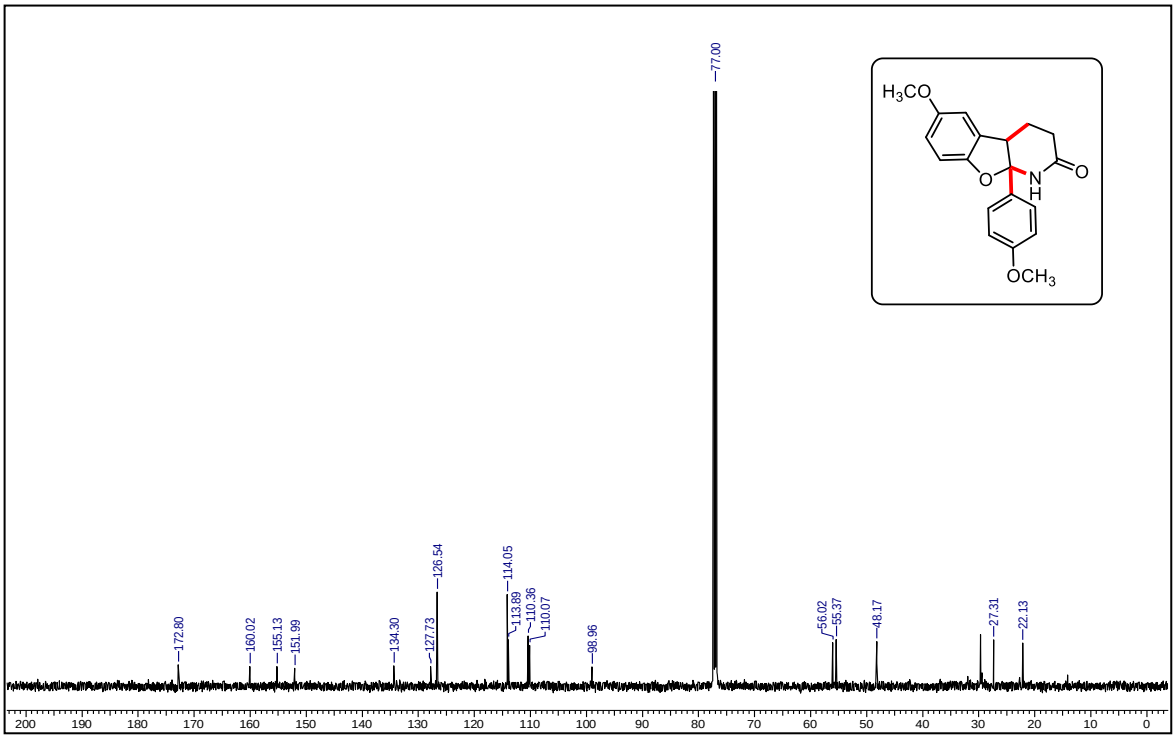
^{1}H NMR Spectrum of 16bx in $CDCl_3$



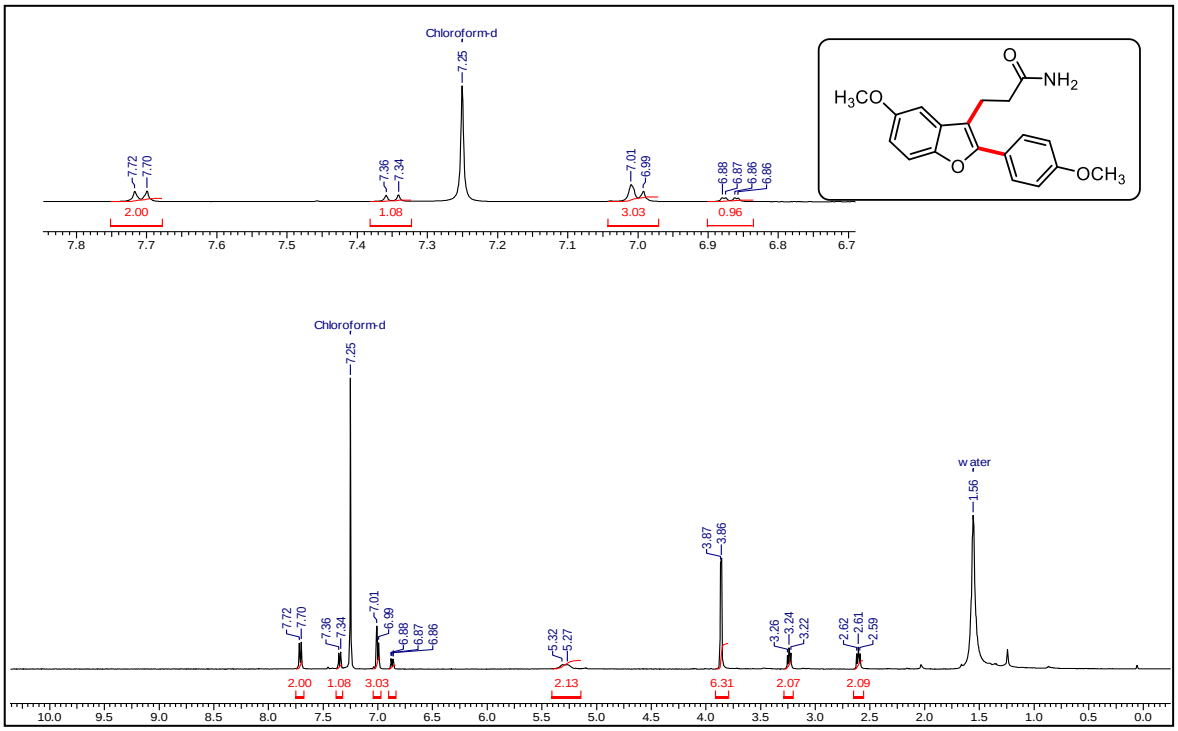
^{13}C NMR Spectrum of 16bx in $CDCl_3$



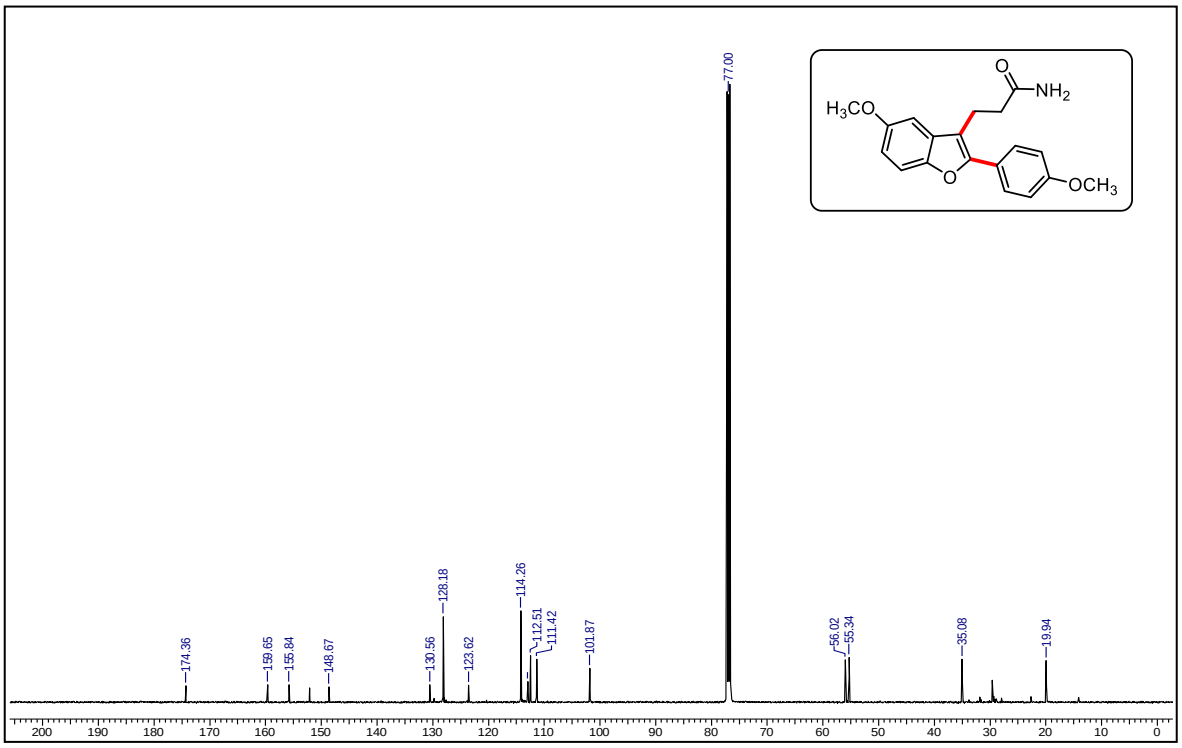
^{1}H NMR Spectrum of 16cx in $CDCl_3$



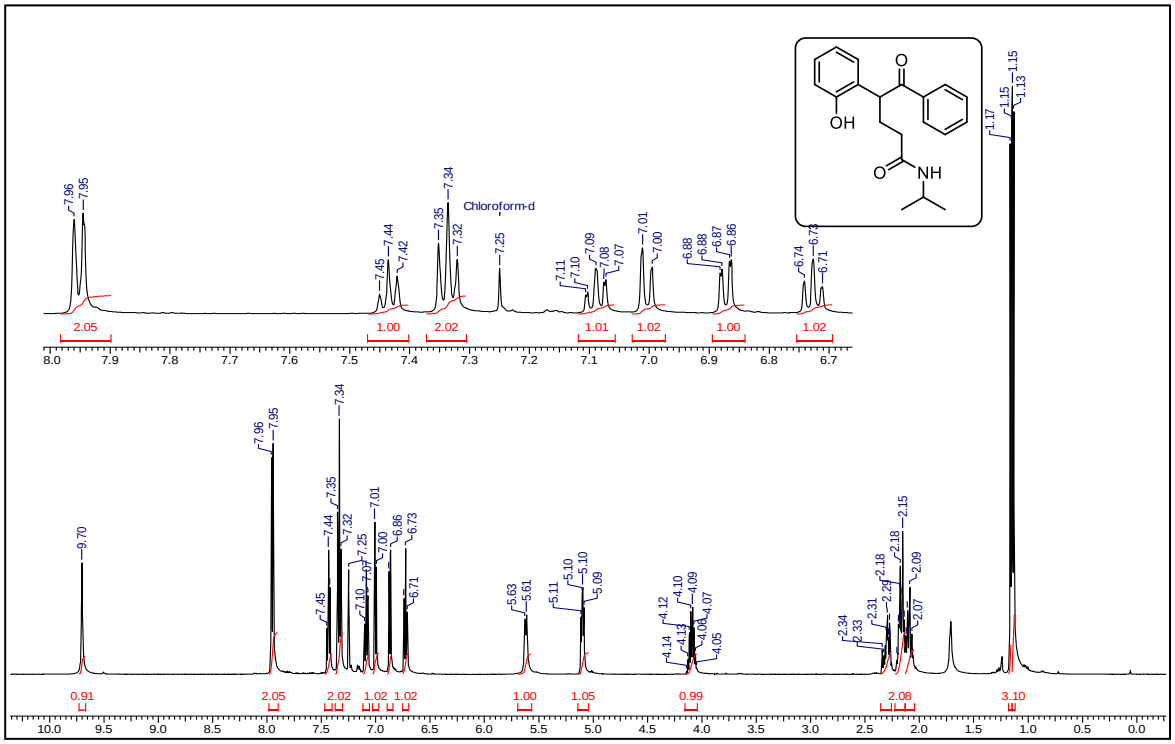
^{13}C NMR Spectrum of 16cx in $CDCl_3$



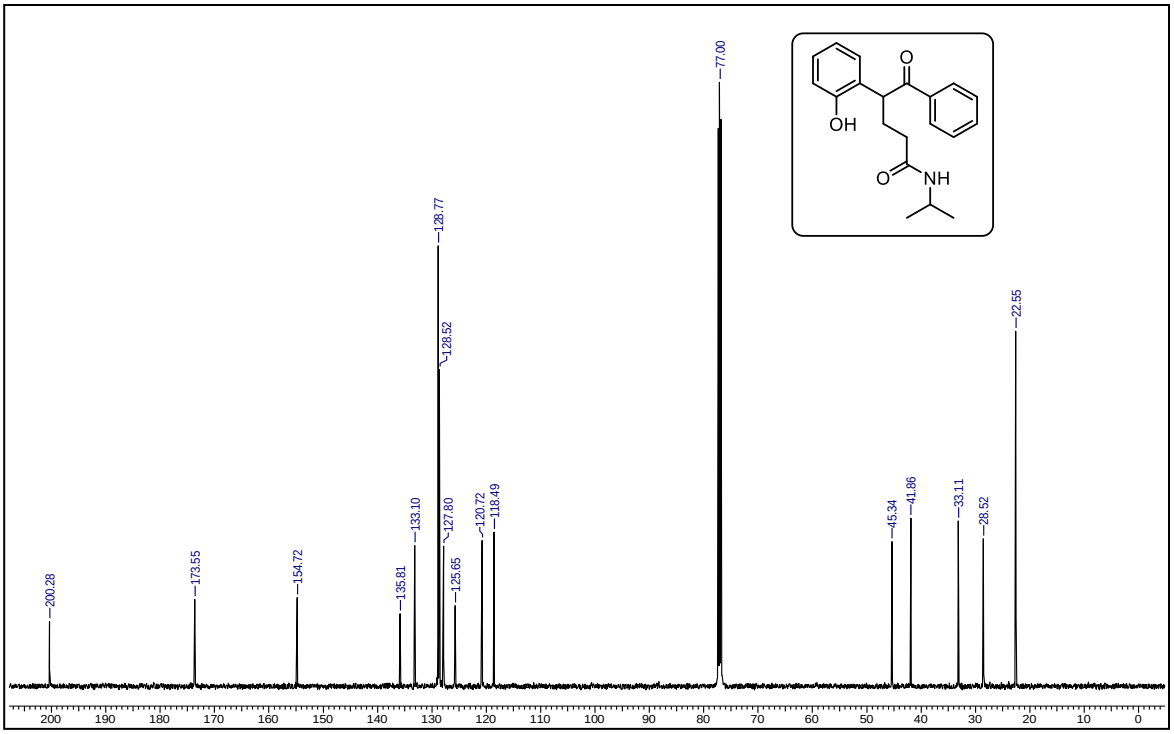
^{1}H NMR Spectrum of 15cx in $CDCl_3$



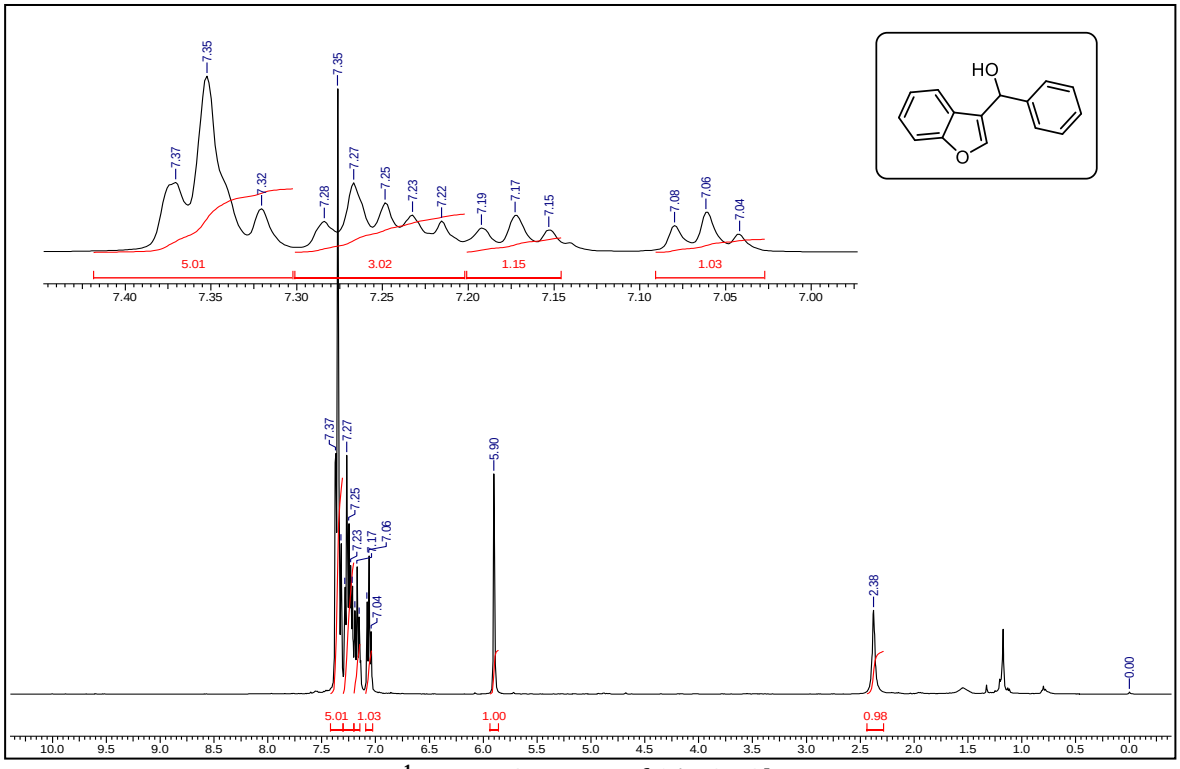
^{13}C NMR Spectrum of 15cx in $CDCl_3$



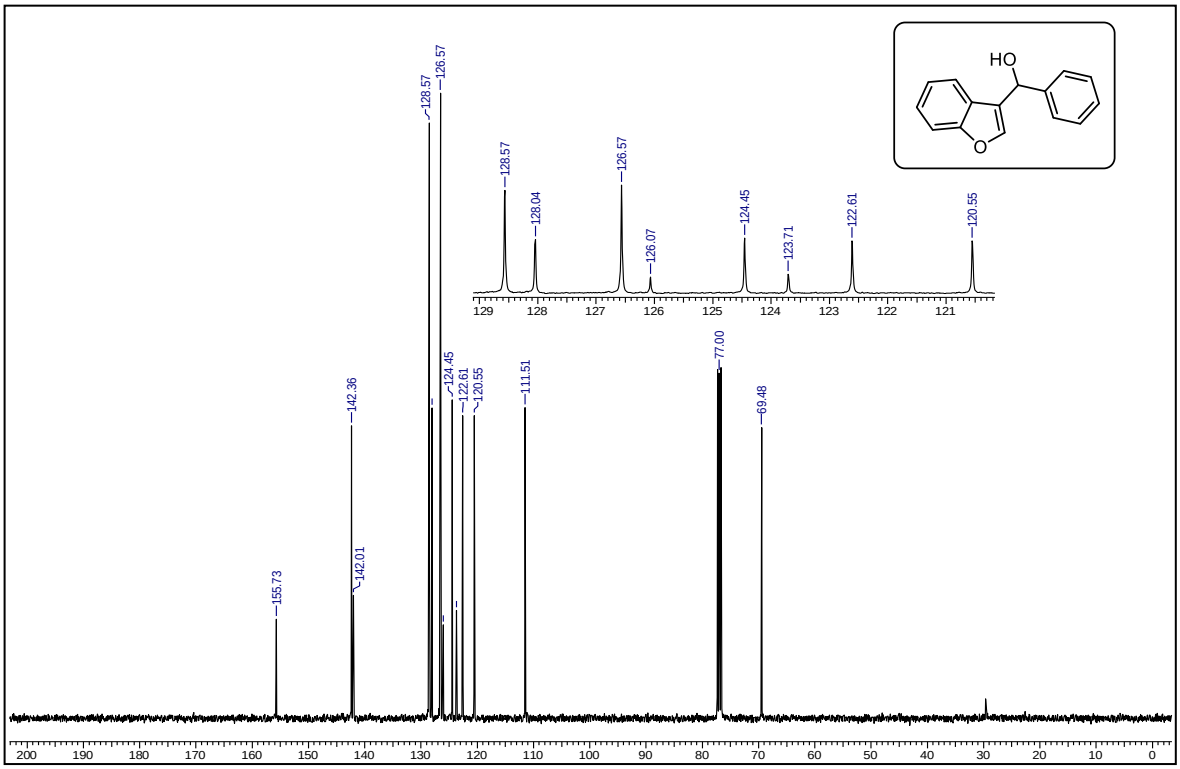
^{1}H NMR Spectrum of 14b in $CDCl_3$



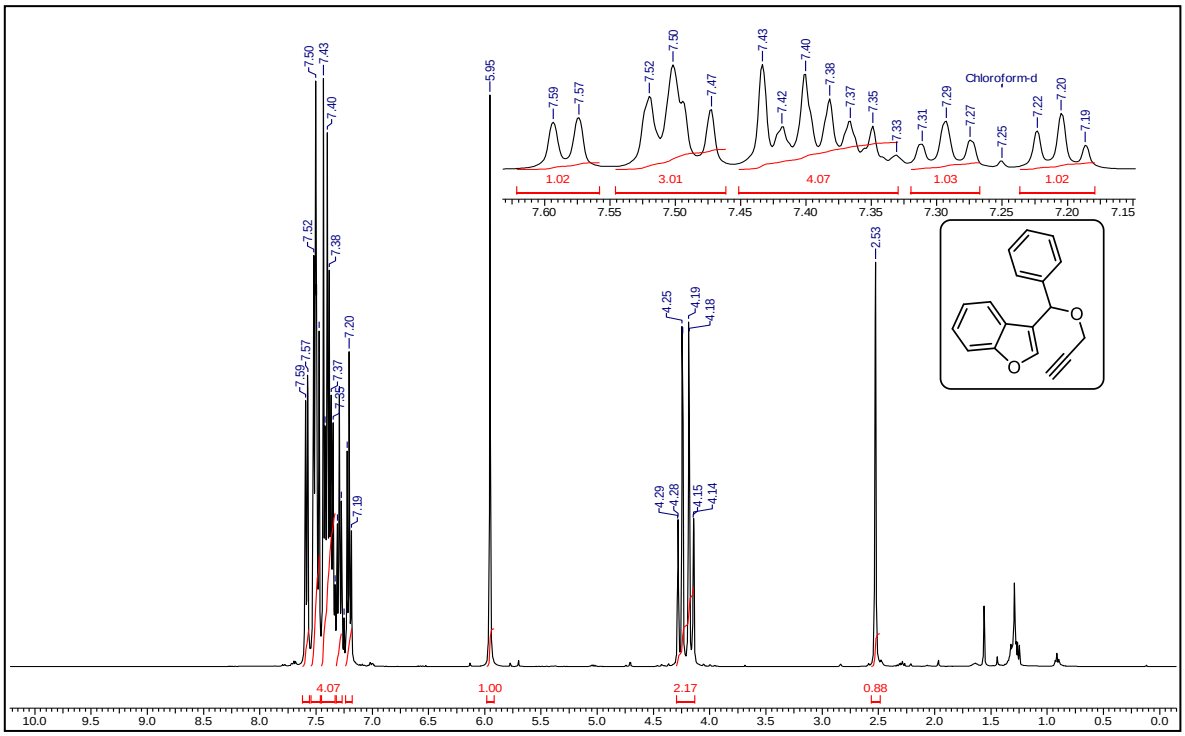
^{13}C NMR Spectrum of 14b in $CDCl_3$



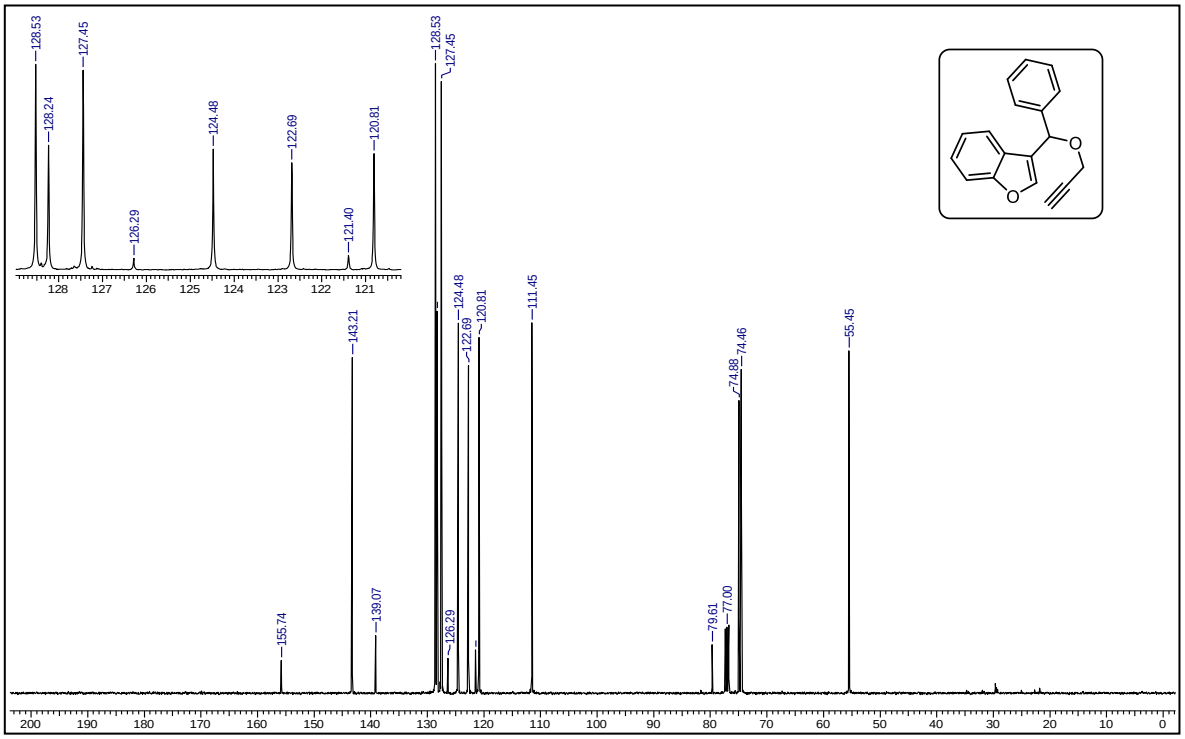
^{1}H NMR Spectrum of 6 in $CDCl_3$



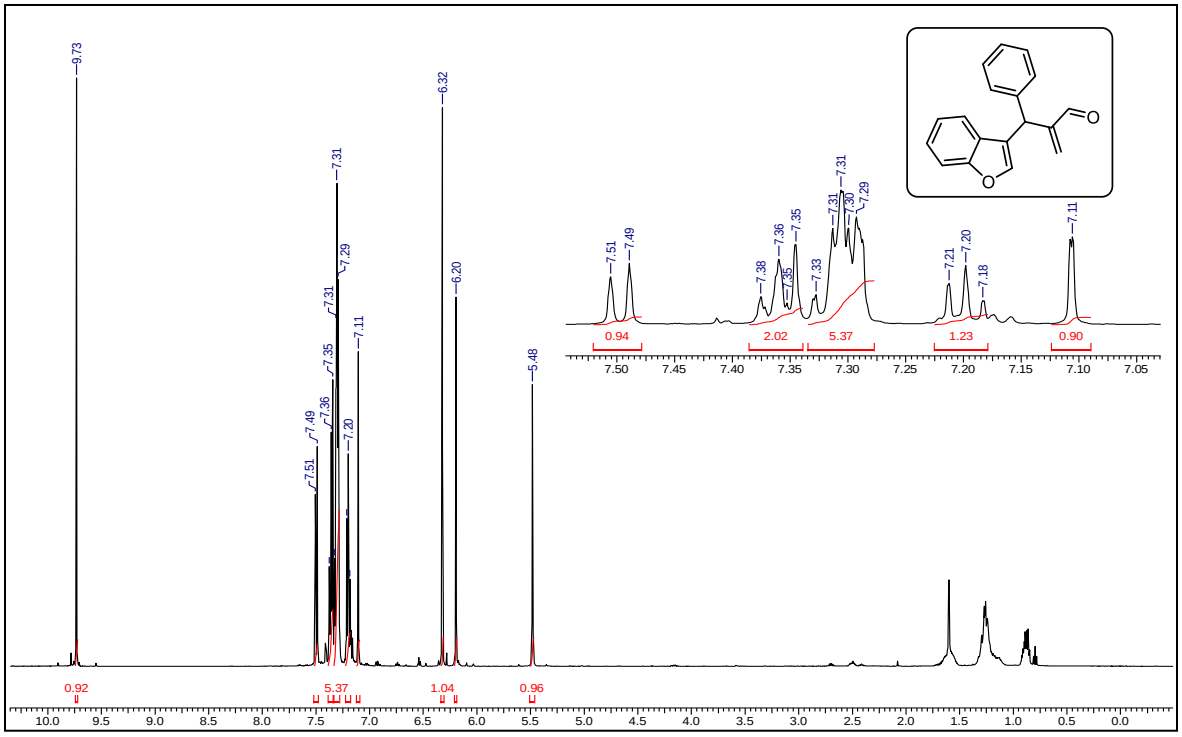
^{13}C NMR Spectrum of 6 in $CDCl_3$



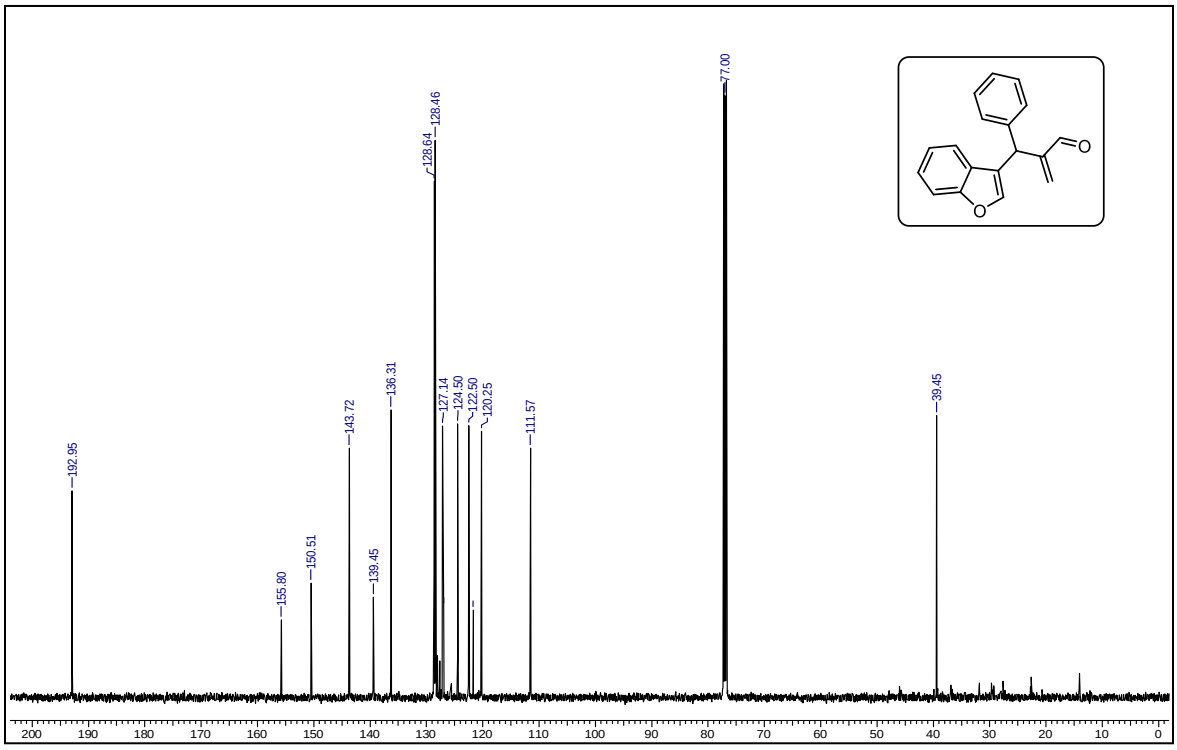
^{1}H NMR Spectrum of 7 in $CDCl_3$



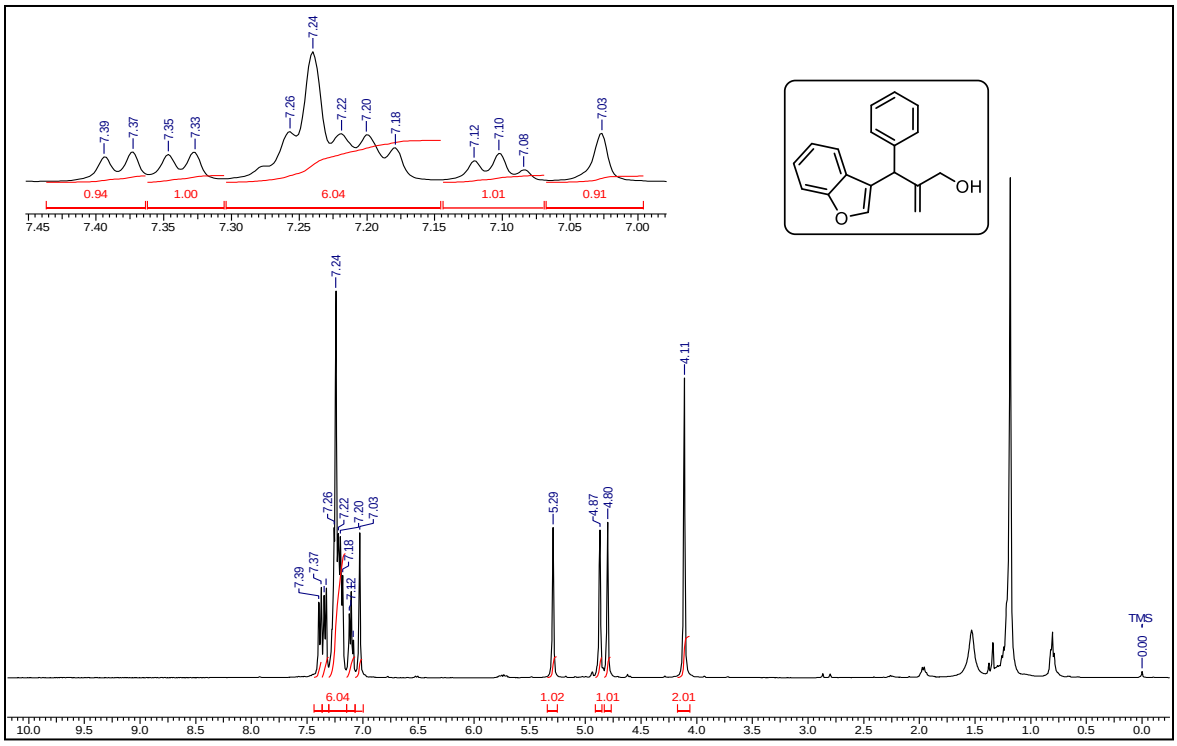
^{13}C NMR Spectrum of 7 in $CDCl_3$



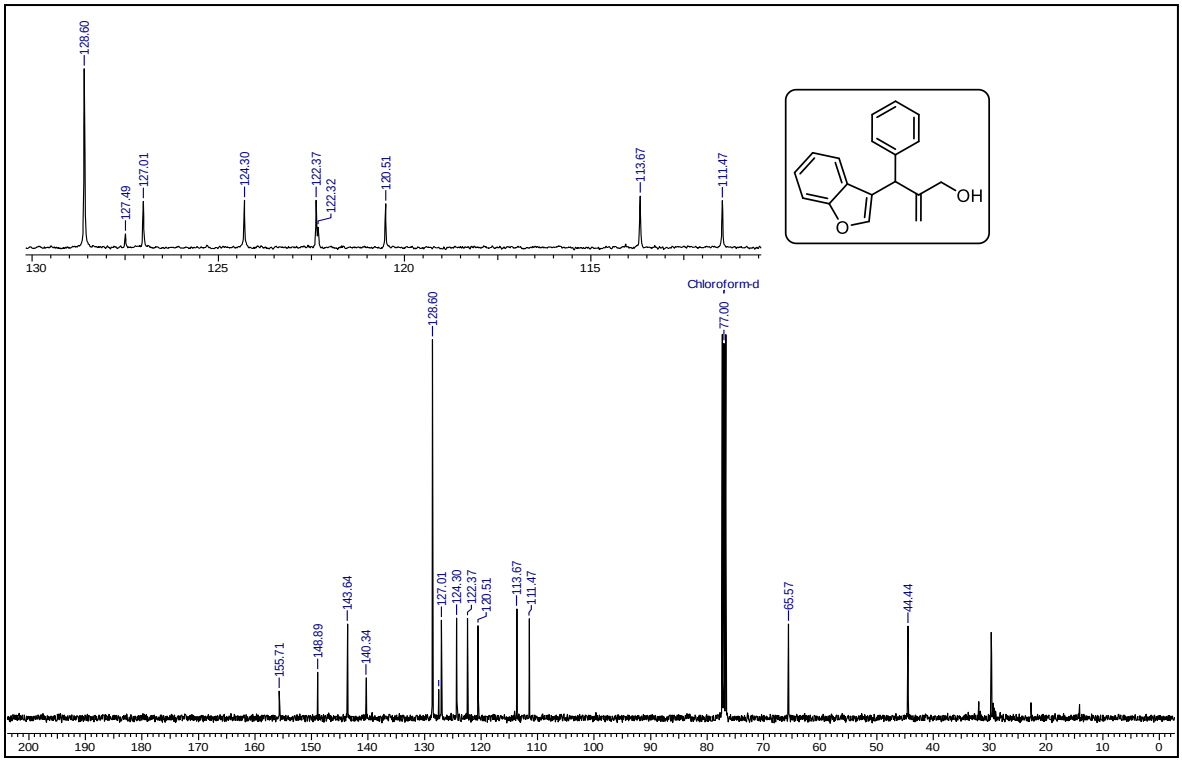
^{1}H NMR Spectrum of 8 in $CDCl_3$



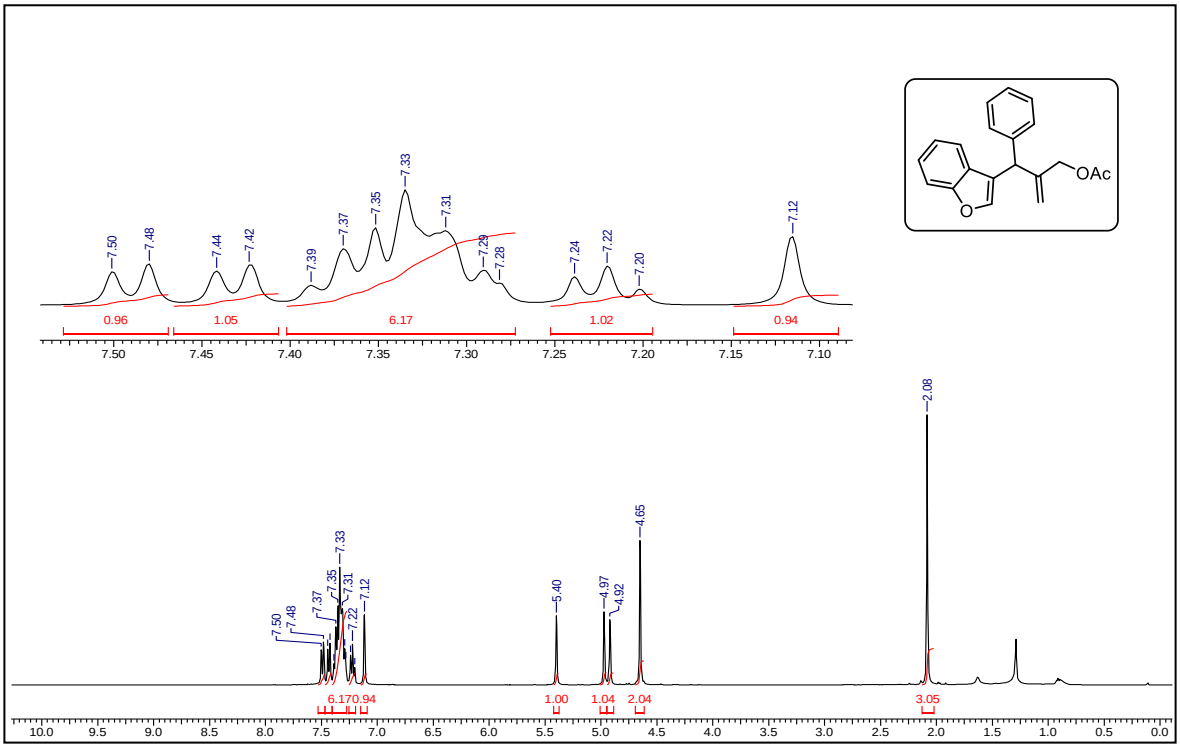
^{13}C NMR Spectrum of 8 in $CDCl_3$



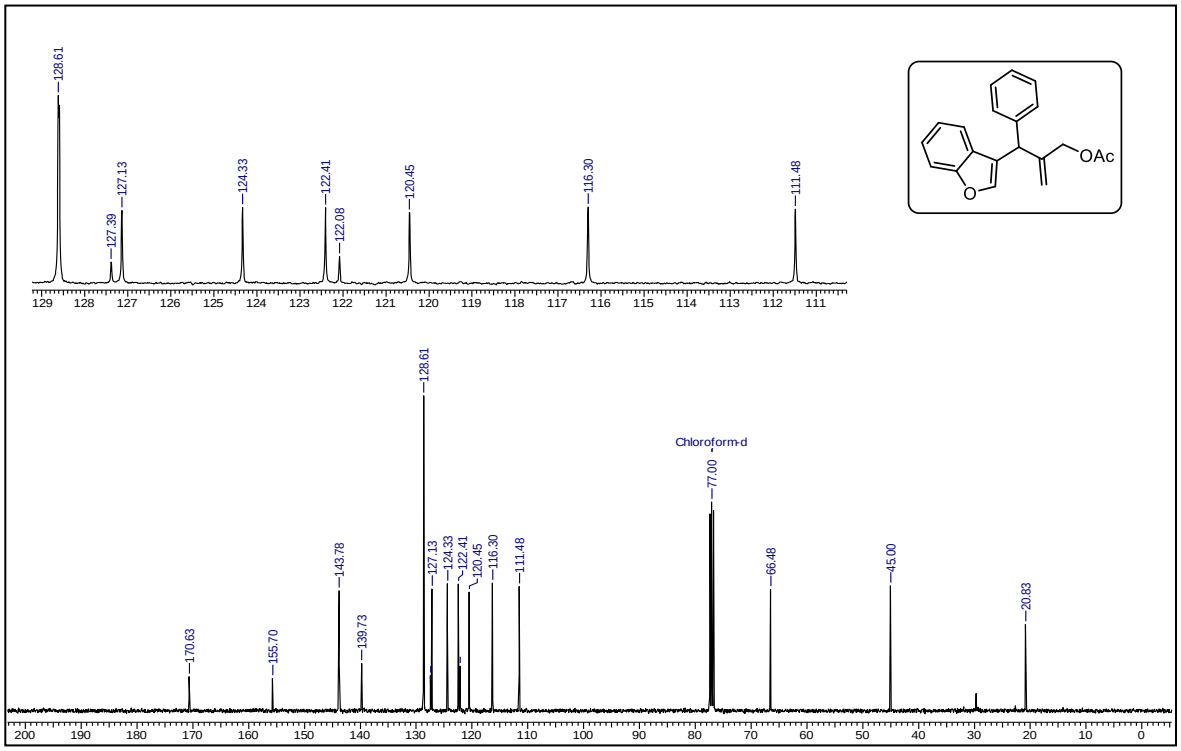
^{1}H NMR Spectrum of 3 in $CDCl_3$



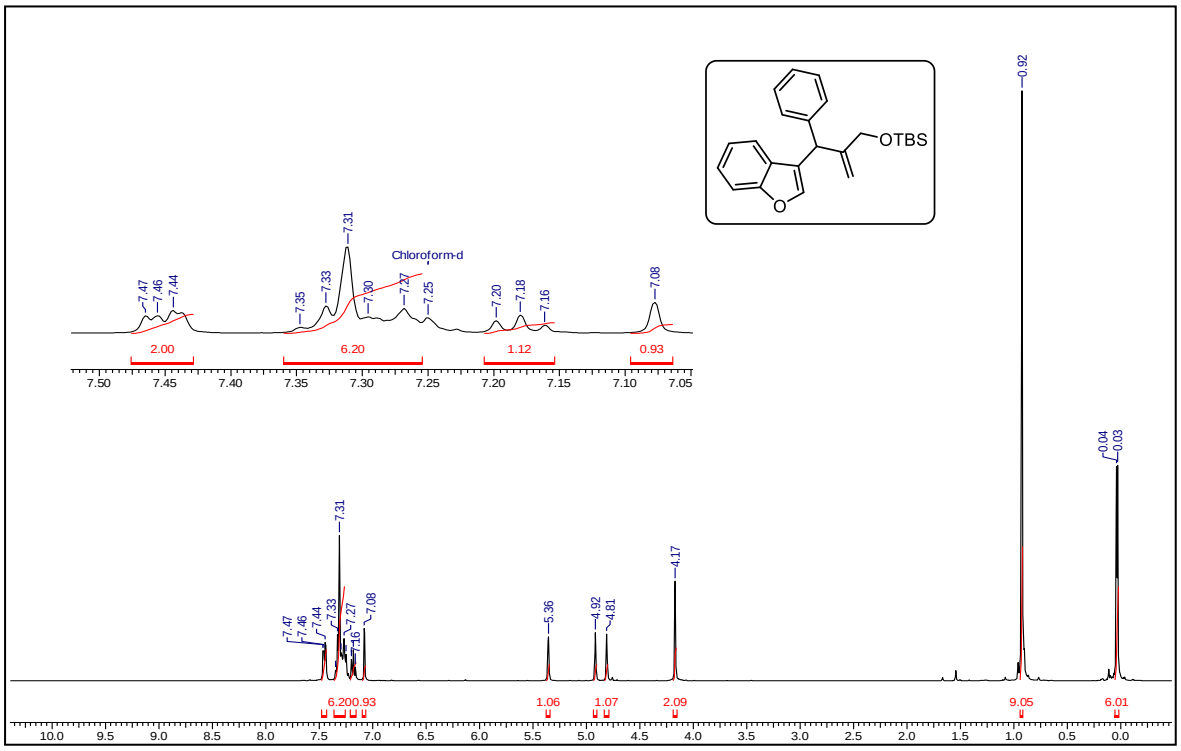
^{13}C NMR Spectrum of 3 in $CDCl_3$



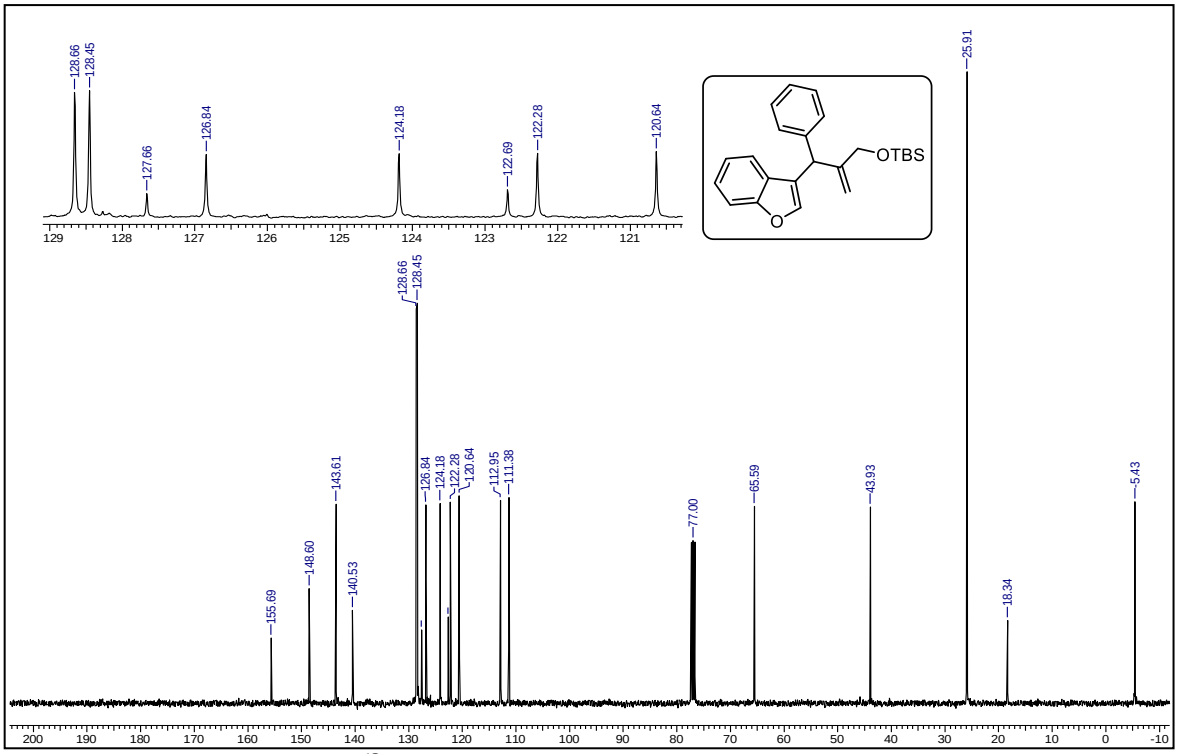
^{1}H NMR Spectrum of 3-Ac in $CDCl_3$



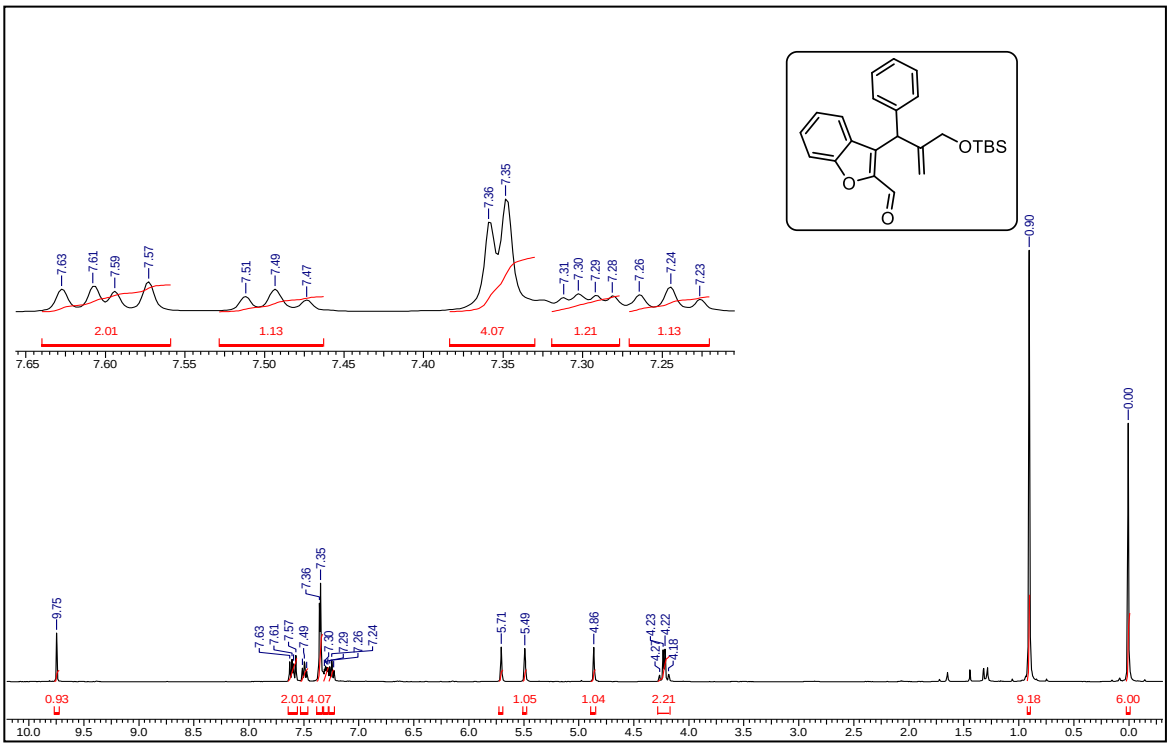
^{13}C NMR Spectrum of 3-Ac in $CDCl_3$



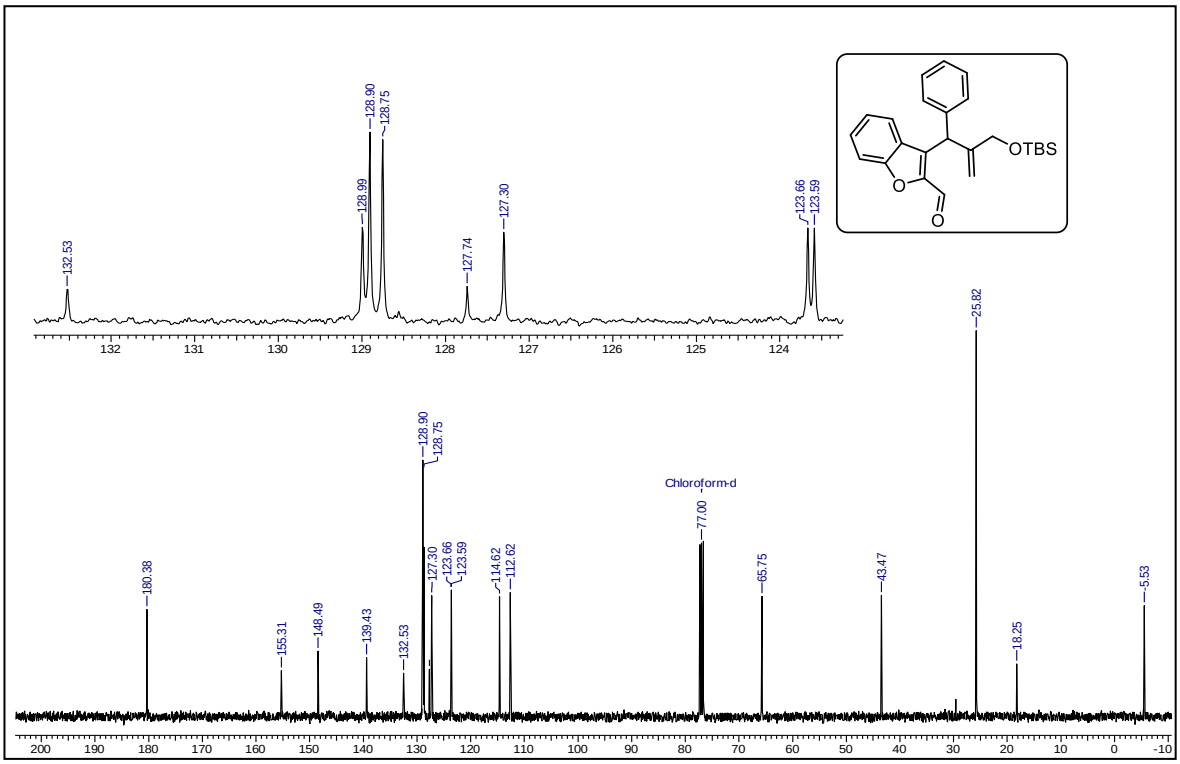
^{1}H NMR Spectrum of 3-TBS in $CDCl_3$



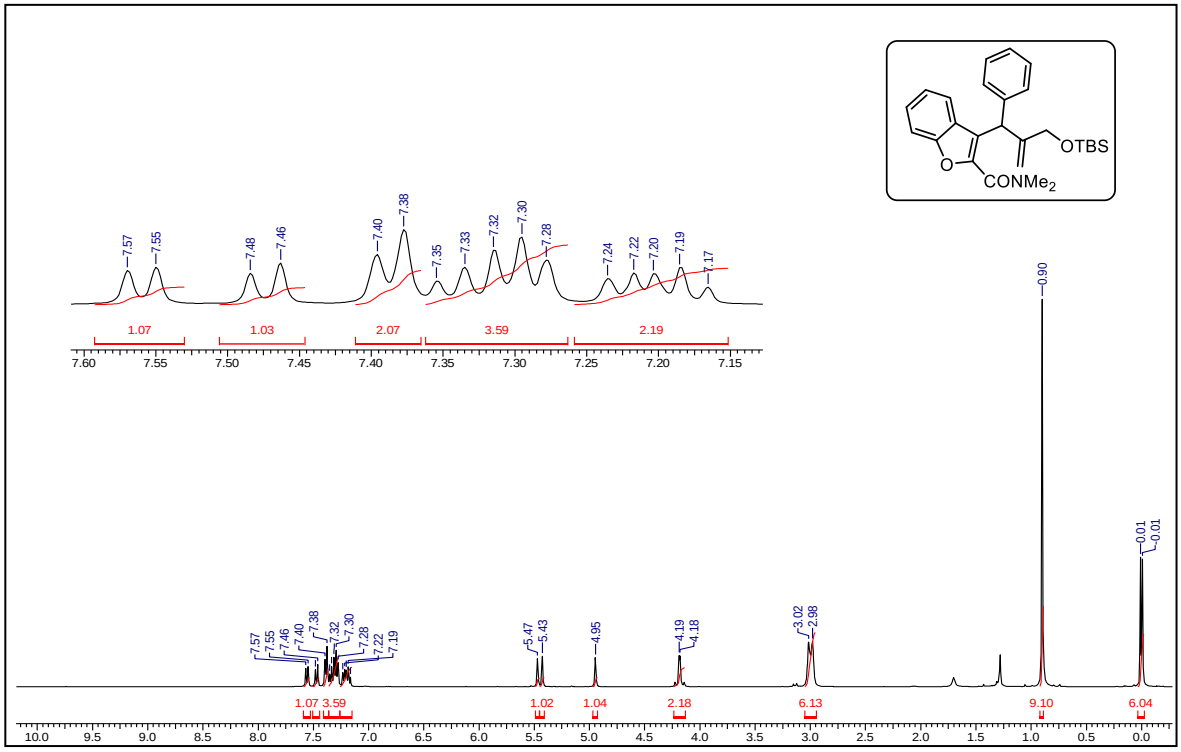
^{13}C NMR Spectrum of 3-TBS in $CDCl_3$



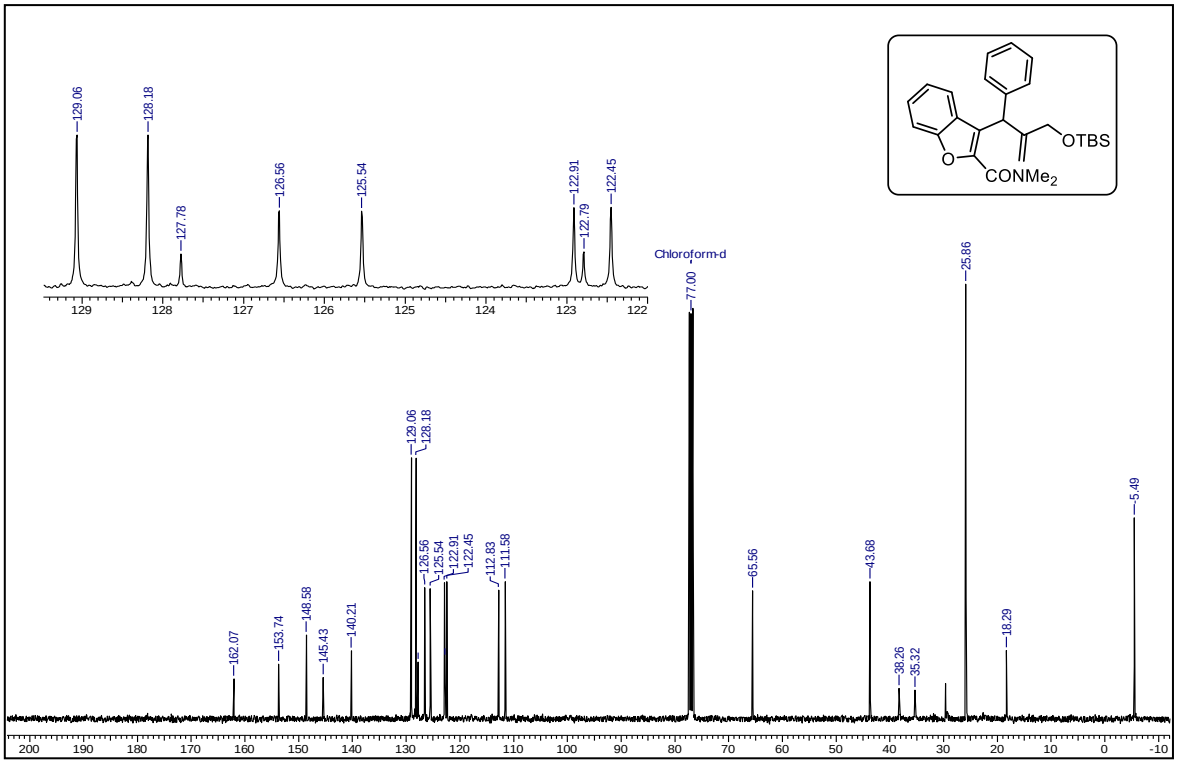
^{1}H NMR Spectrum of 4 in $CDCl_3$



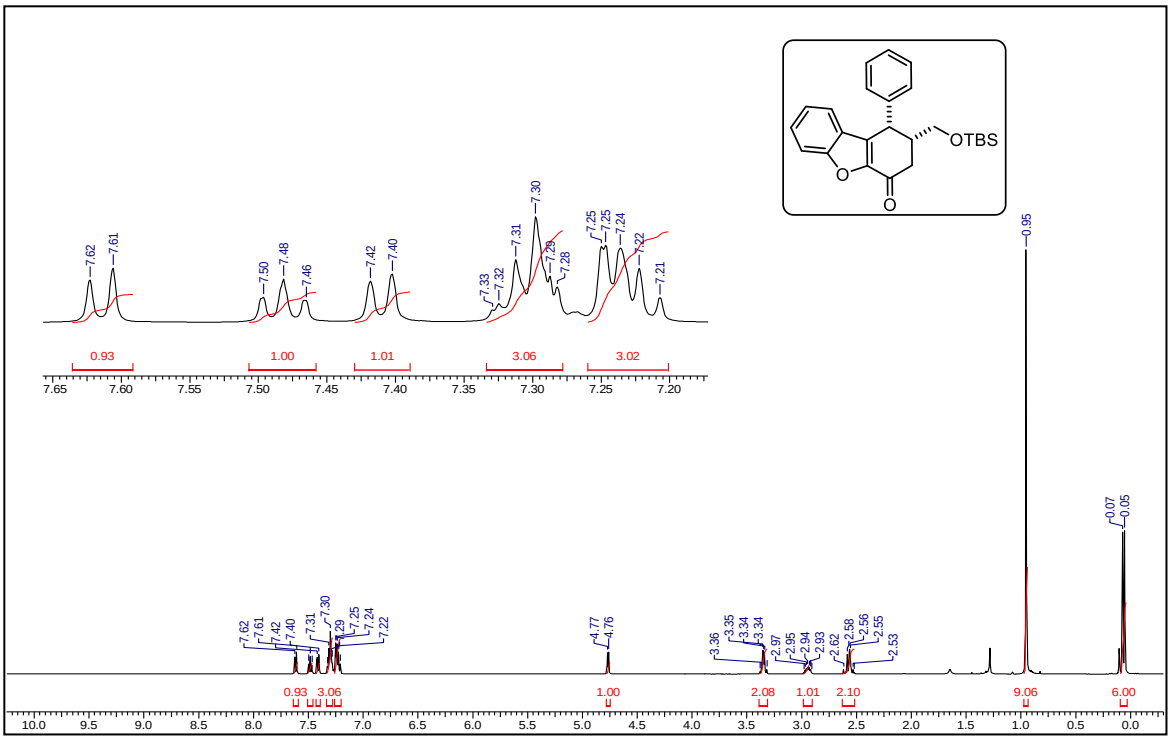
^{13}C NMR Spectrum of 4 in $CDCl_3$



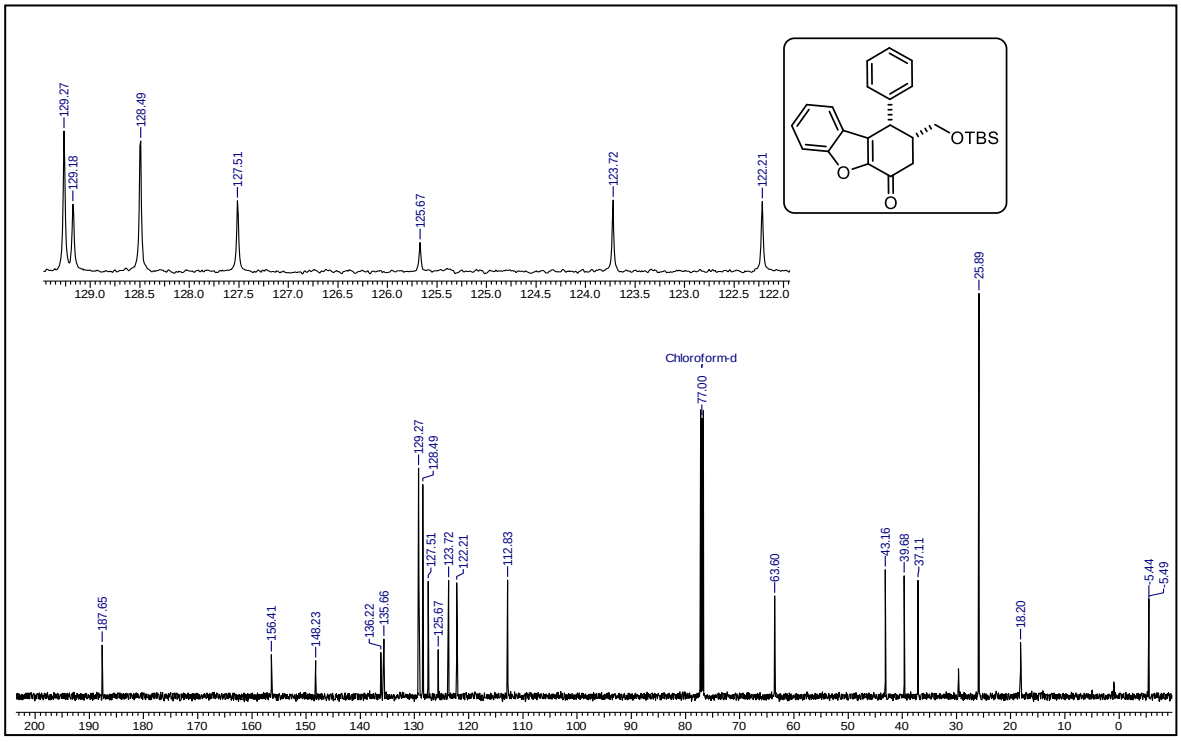
^{1}H NMR Spectrum of 10 in $CDCl_3$



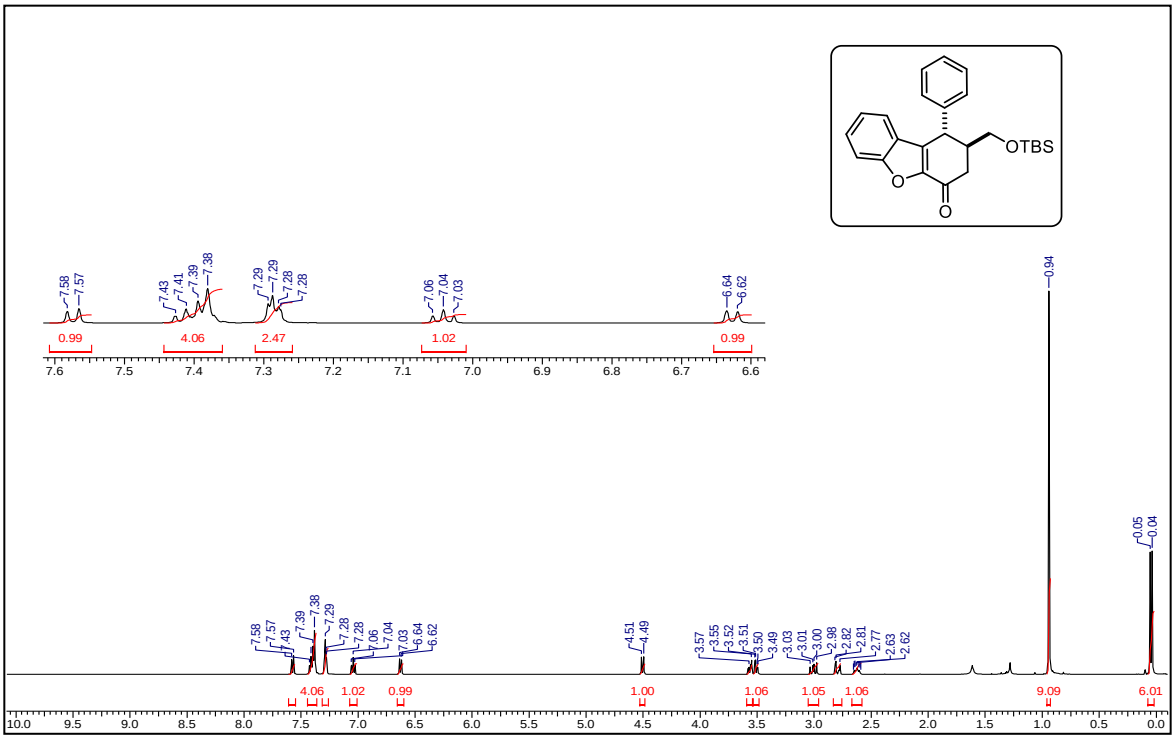
^{13}C NMR Spectrum of 10 in $CDCl_3$



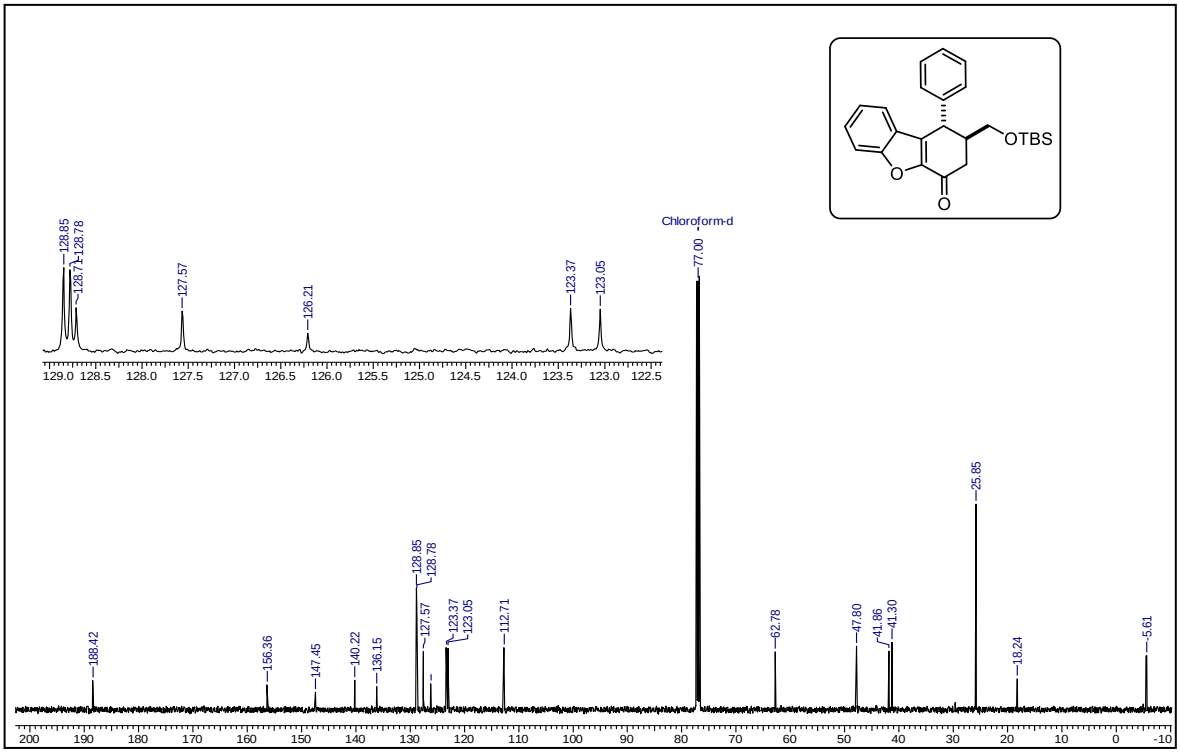
^{1}H NMR Spectrum of *cis*-11 in $CDCl_3$



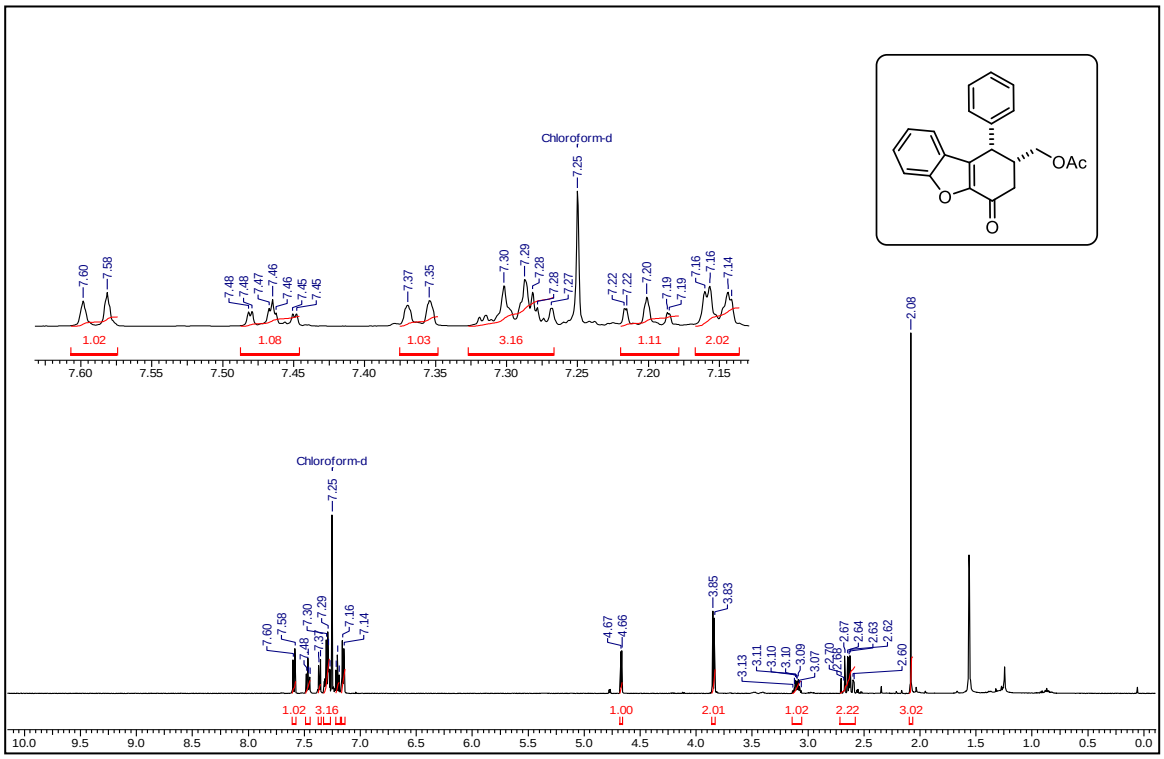
^{13}C NMR Spectrum of *cis*-11 in $CDCl_3$



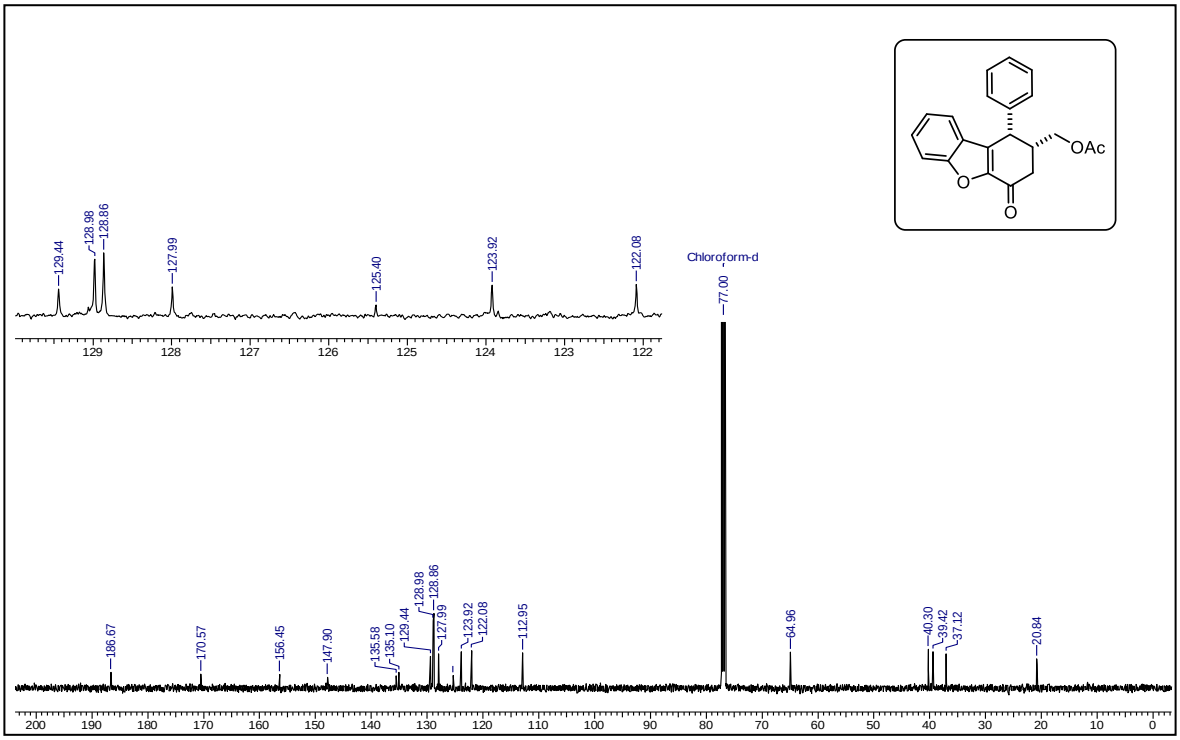
^{1}H NMR Spectrum of *trans*-11 in $CDCl_3$



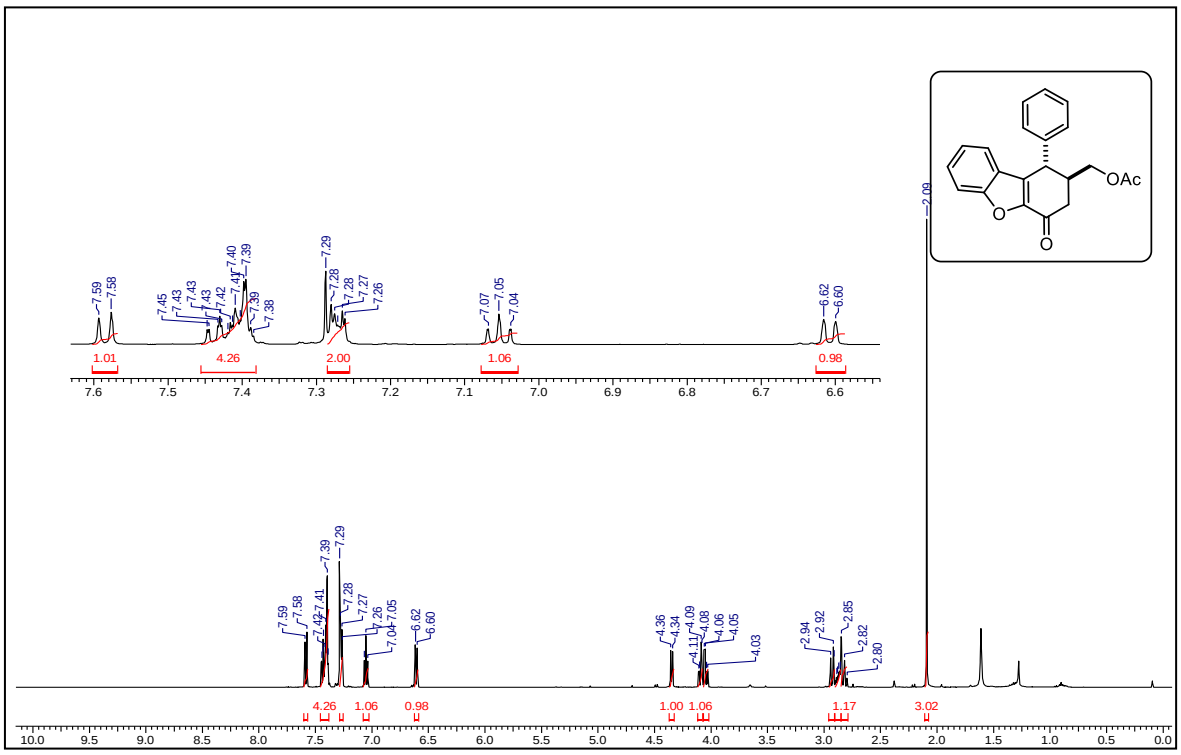
^{13}C NMR Spectrum of *trans*-11 in $CDCl_3$



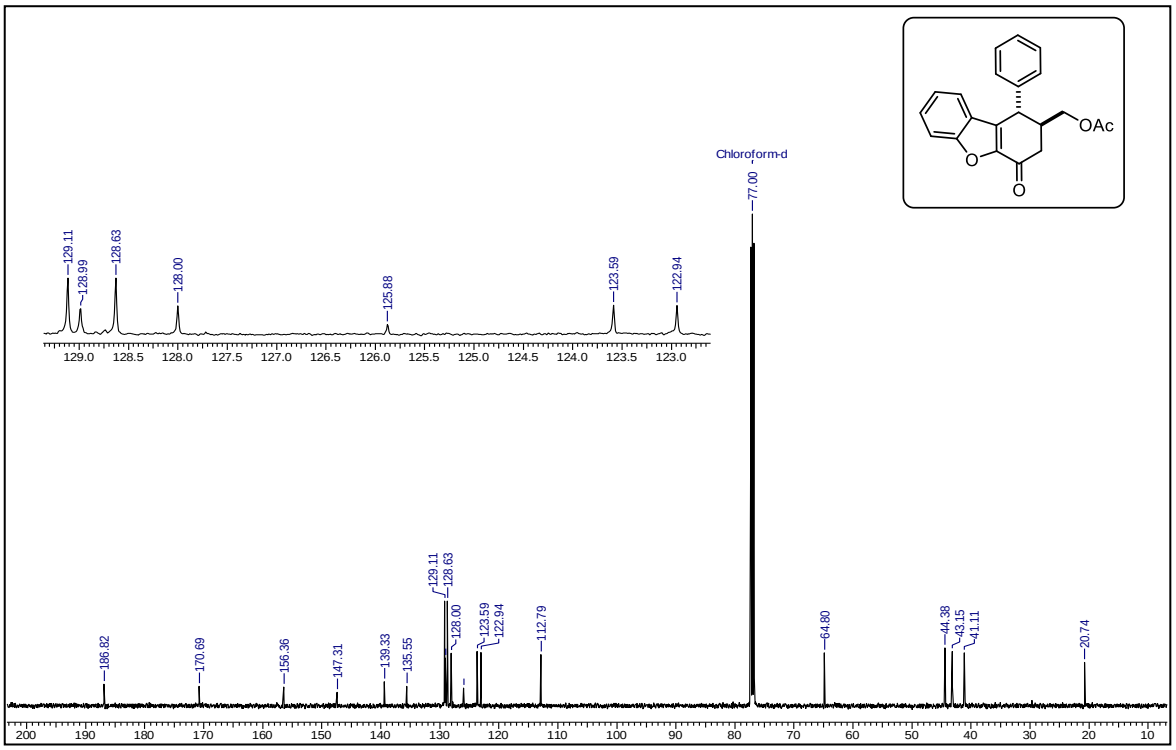
^{1}H NMR Spectrum of *cis*-2 in $CDCl_3$



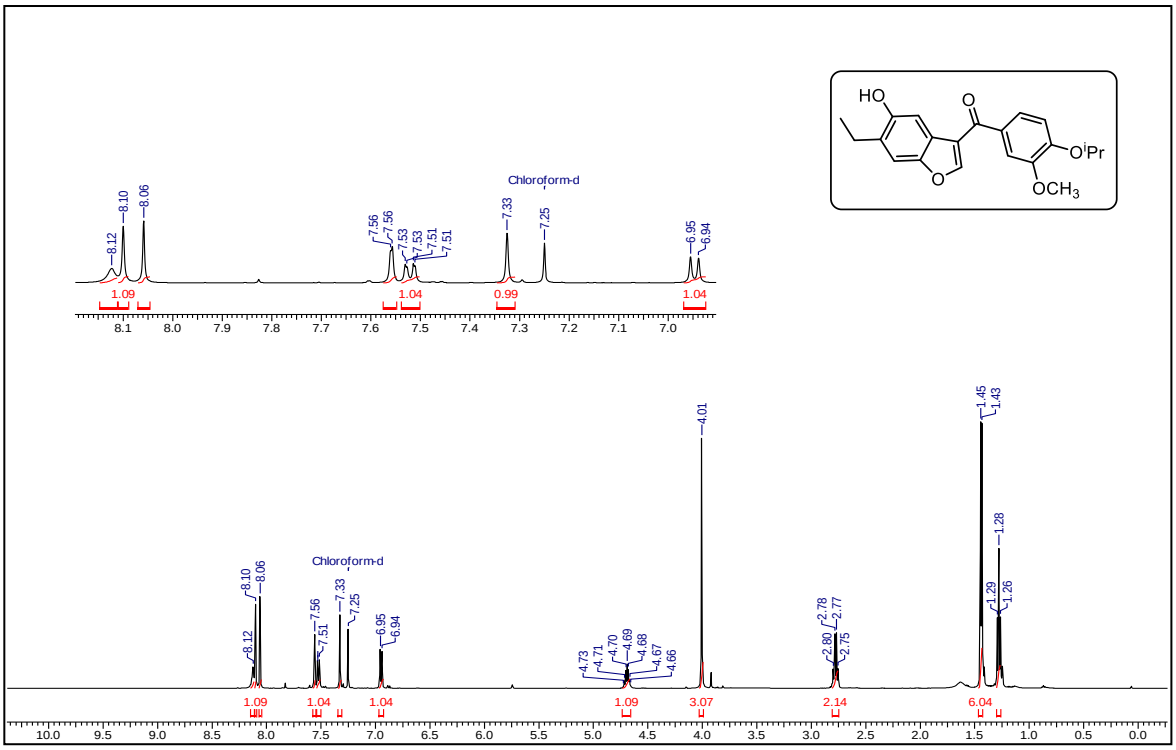
^{13}C NMR Spectrum of *cis*-2 in $CDCl_3$



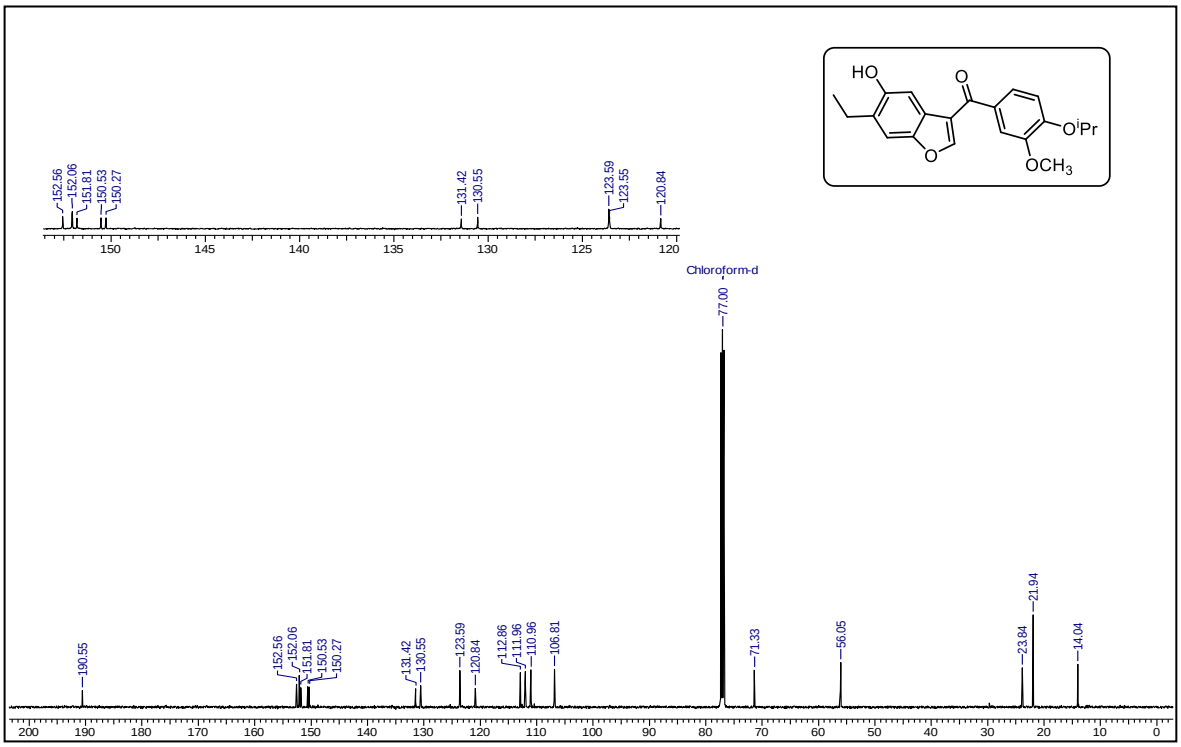
^{1}H NMR Spectrum of *trans*-2 in $CDCl_3$



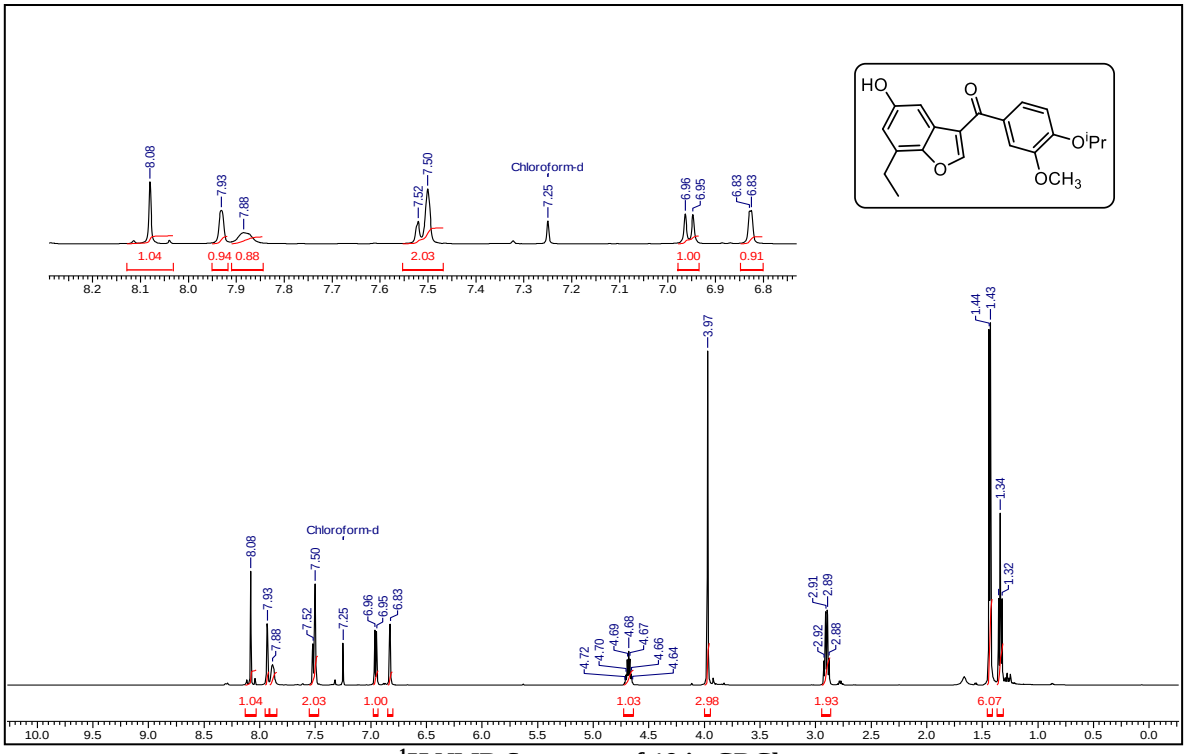
^{13}C NMR Spectrum of *trans*-2 in $CDCl_3$



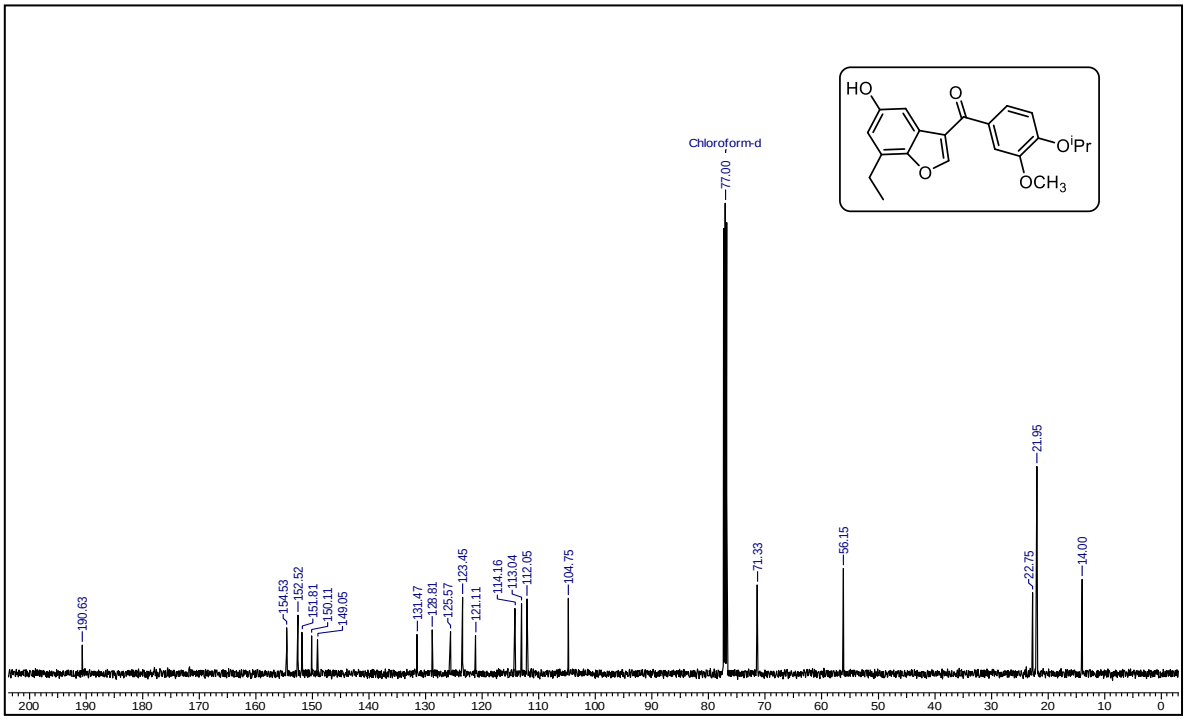
^{1}H NMR Spectrum of 18 in $CDCl_3$



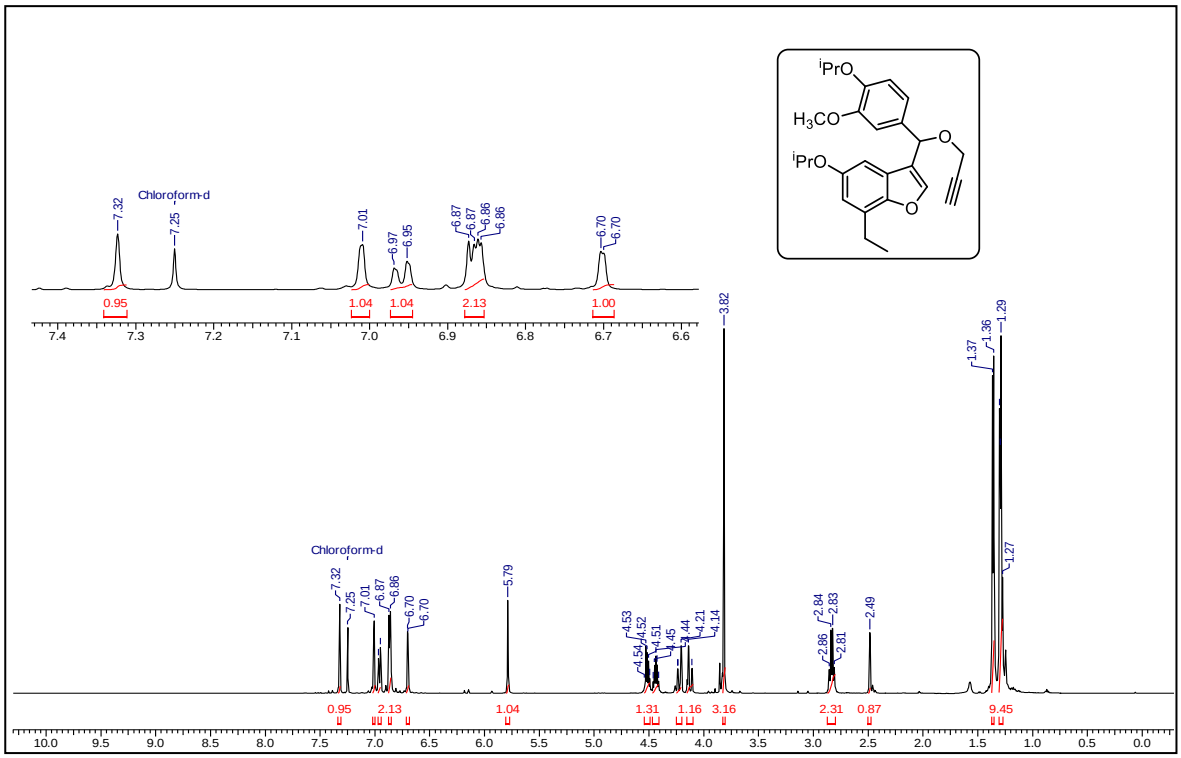
^{13}C NMR Spectrum of 18 in $CDCl_3$



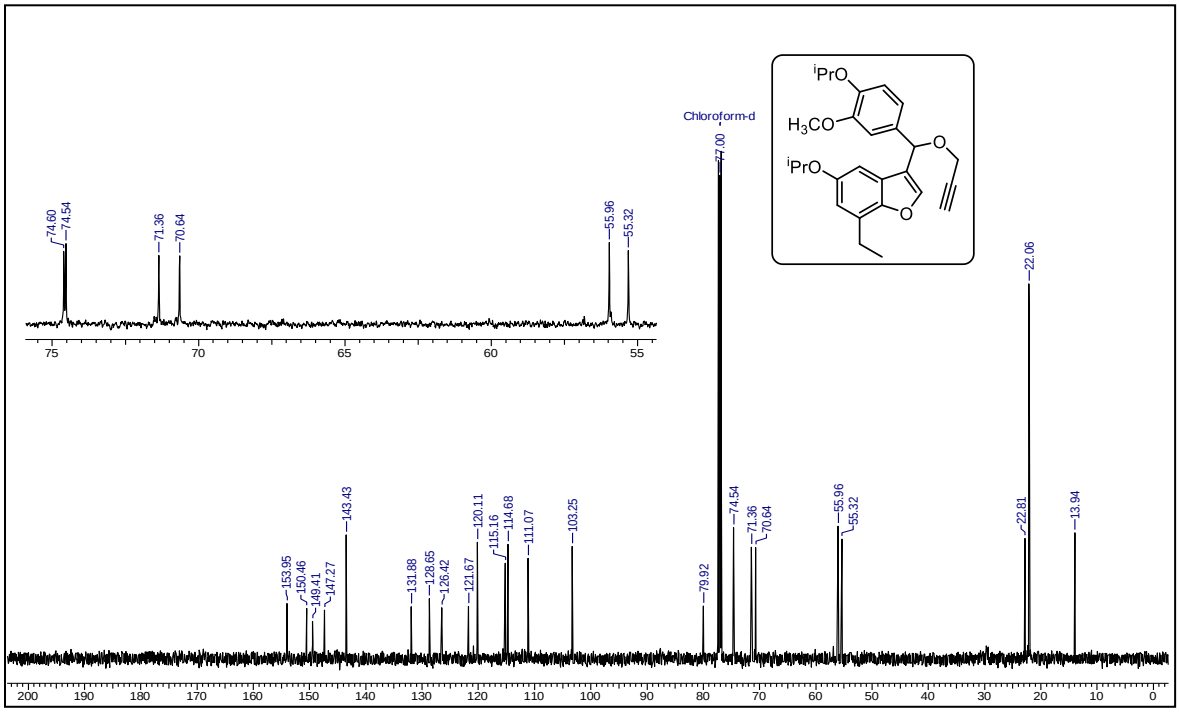
^{1}H NMR Spectrum of 19 in $CDCl_3$



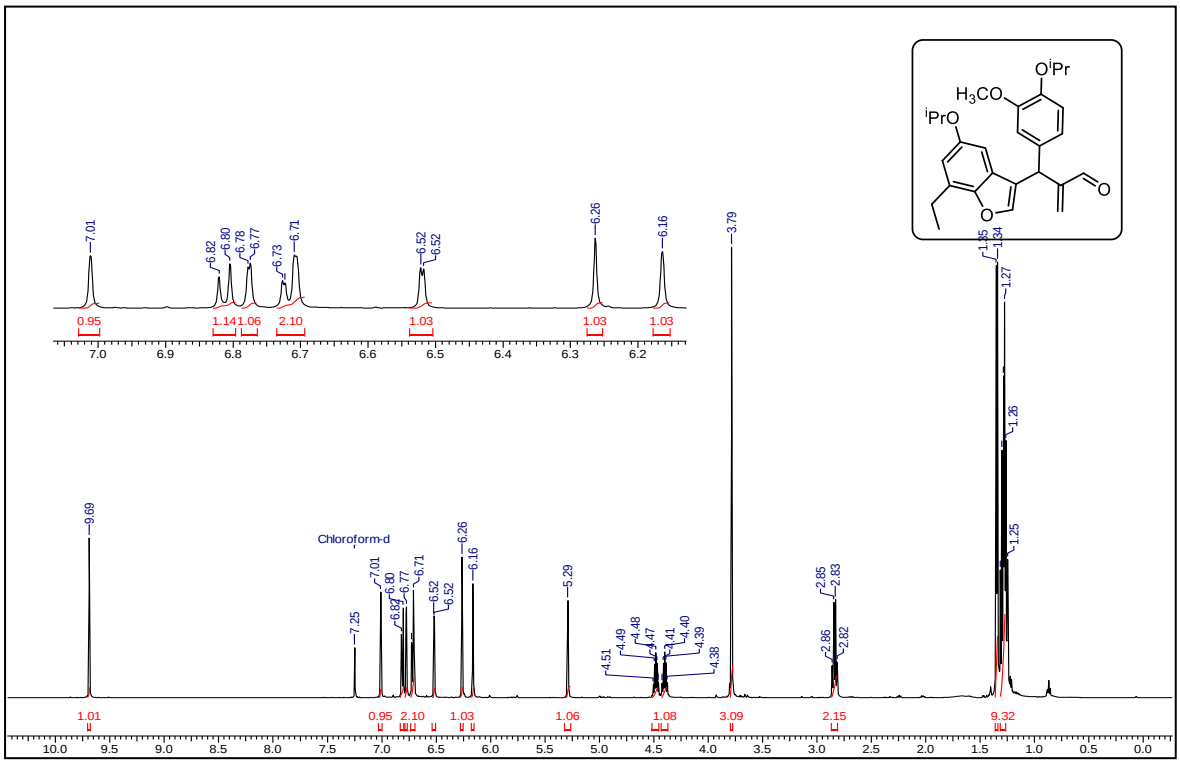
^{13}C NMR Spectrum of 19 in $CDCl_3$



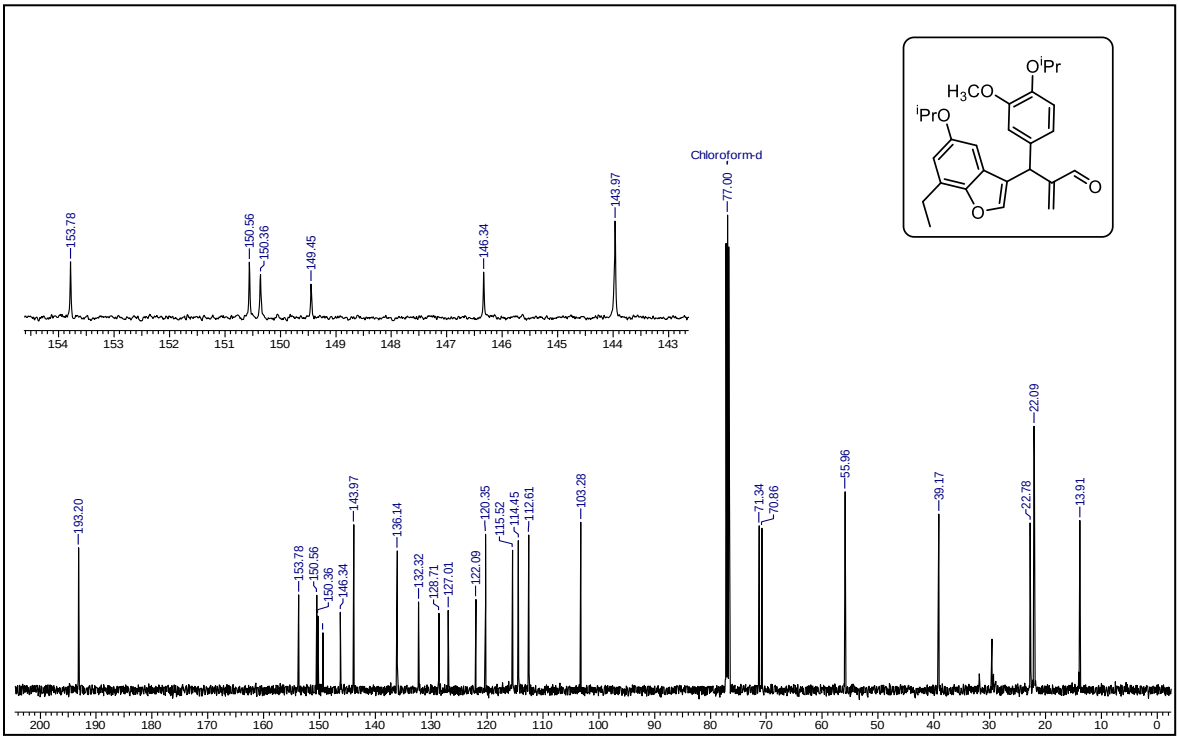
^{1}H NMR Spectrum of 20 in $CDCl_3$



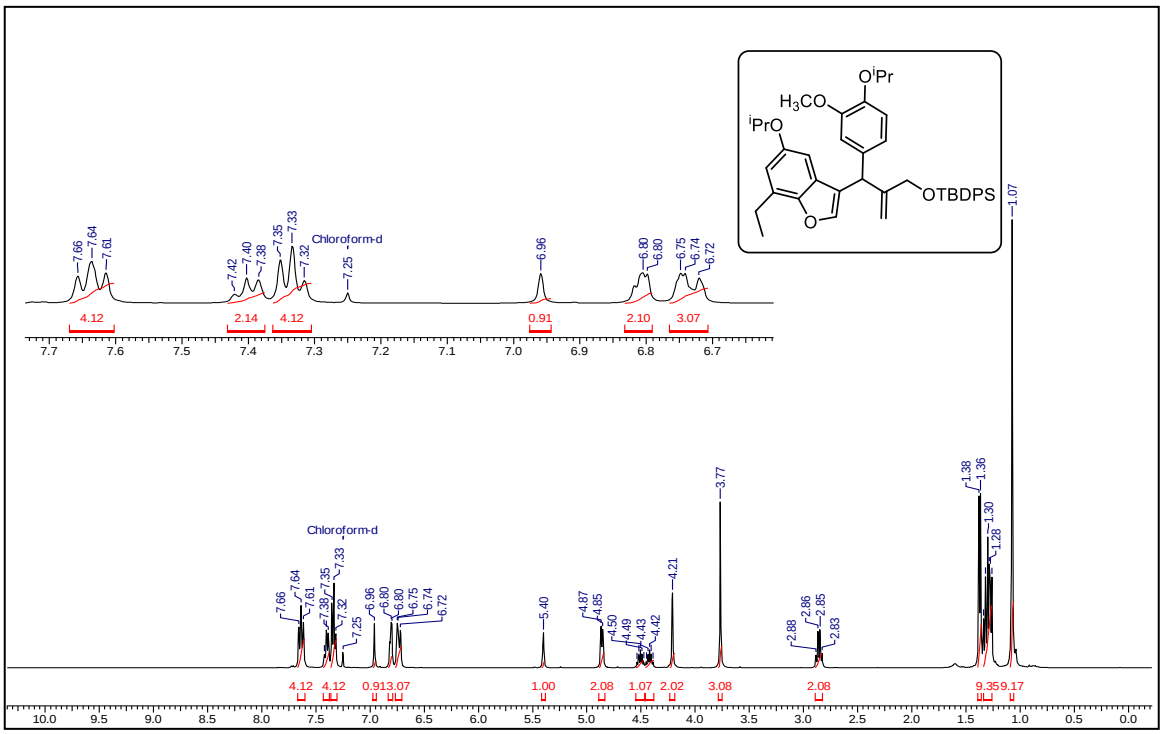
^{13}C NMR Spectrum of 20 in $CDCl_3$



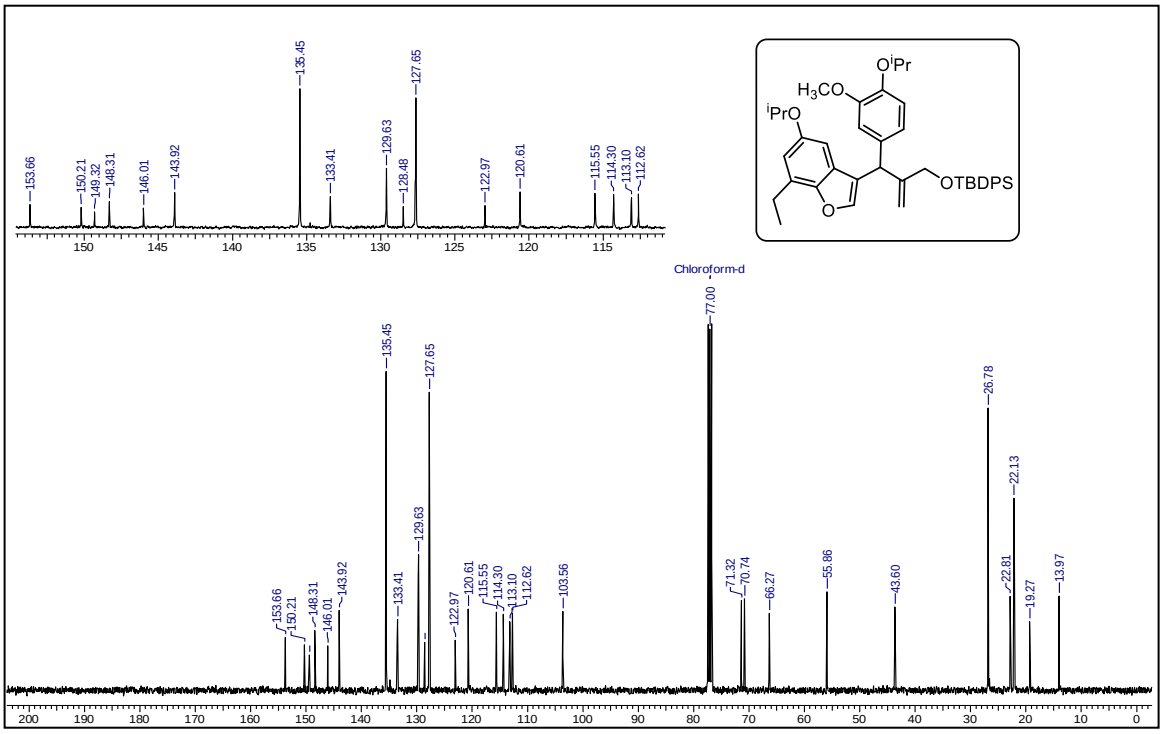
^{1}H NMR Spectrum of 21 in $CDCl_3$



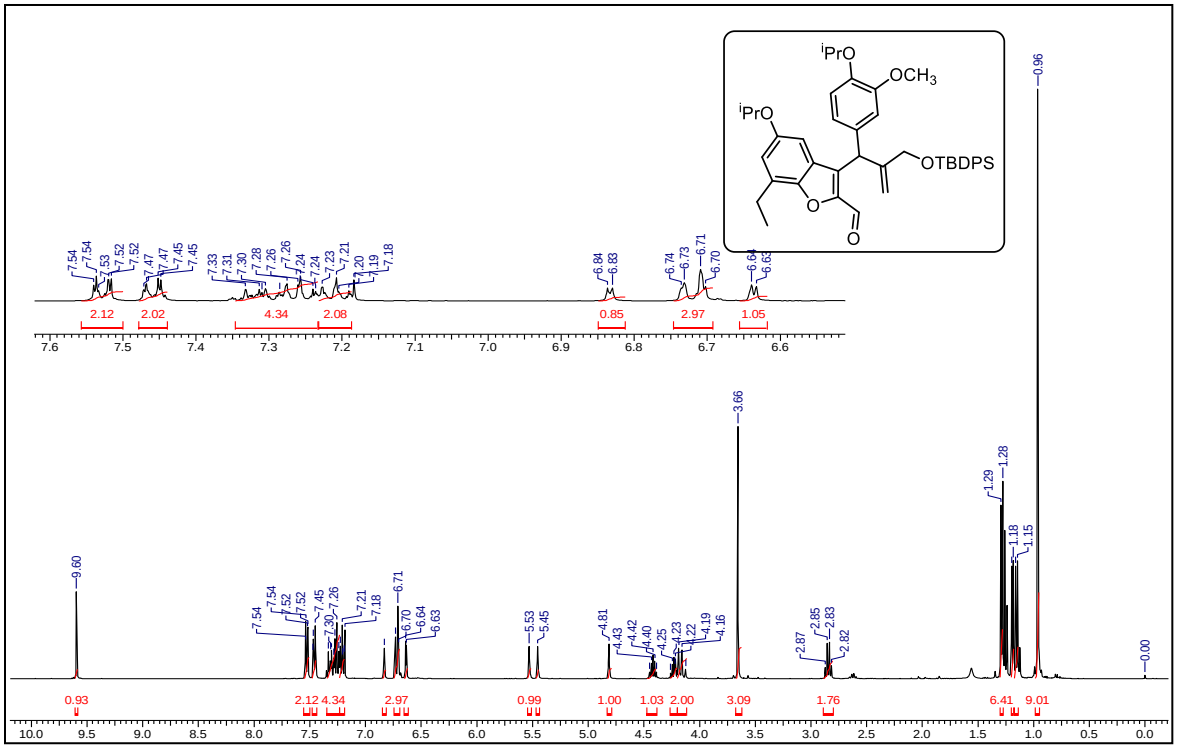
^{13}C NMR Spectrum of 21 in $CDCl_3$



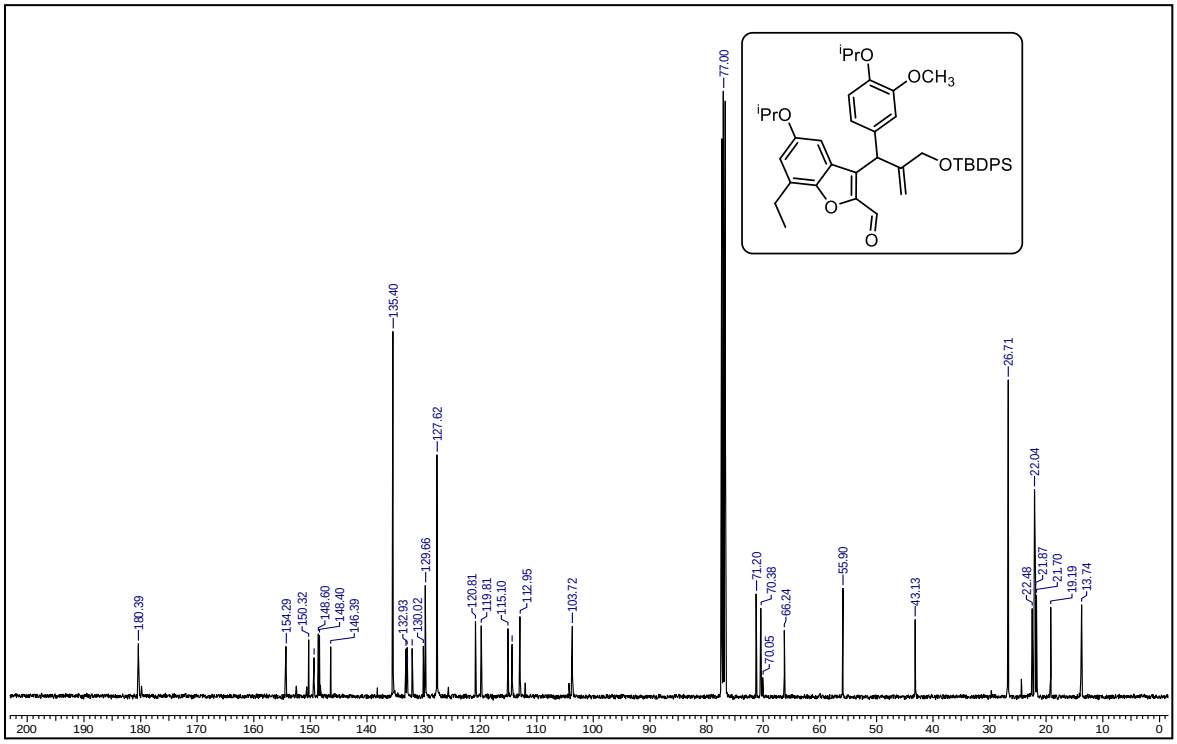
^{1}H NMR Spectrum of 22 in $CDCl_3$



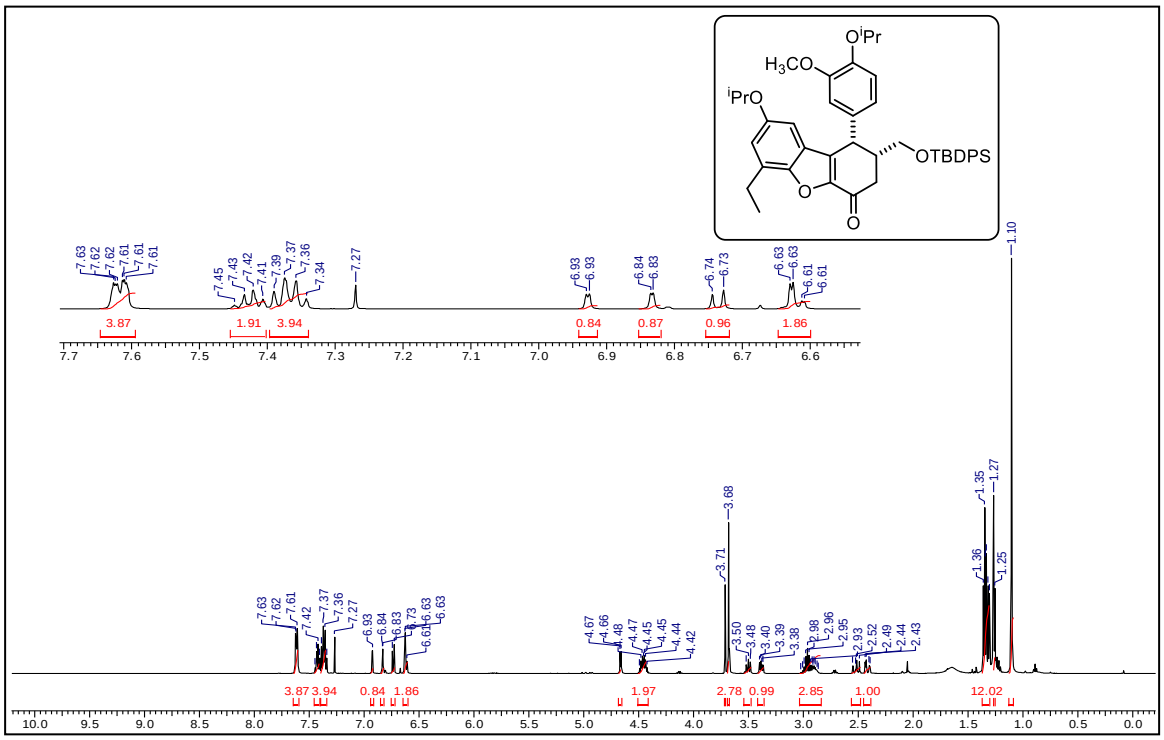
^{13}C NMR Spectrum of 22 in $CDCl_3$



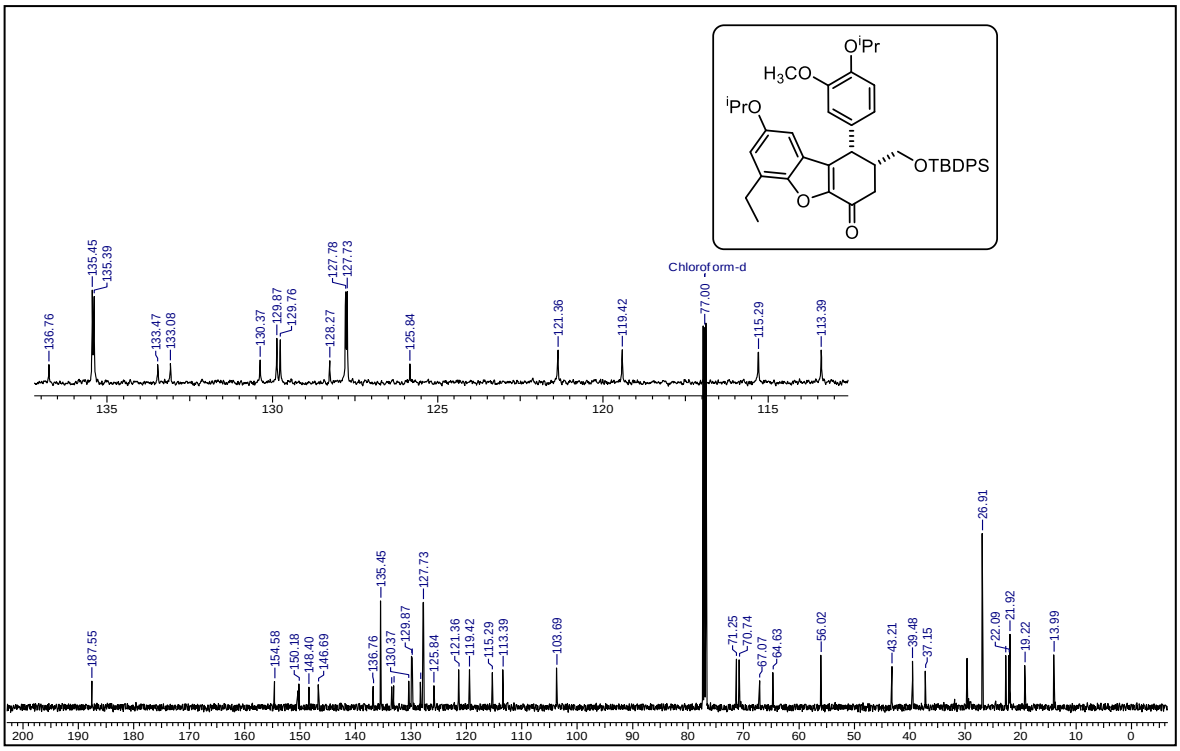
^{1}H NMR Spectrum of 23 in $CDCl_3$



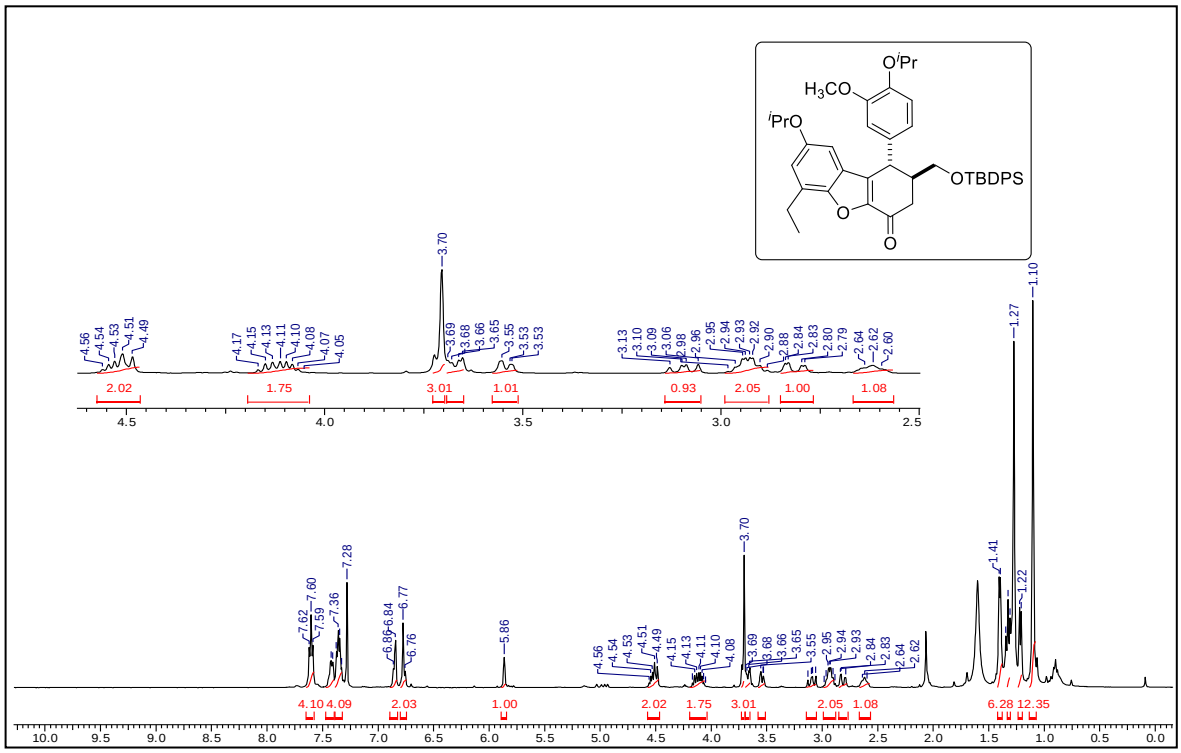
^{13}C NMR Spectrum of 23 in $CDCl_3$



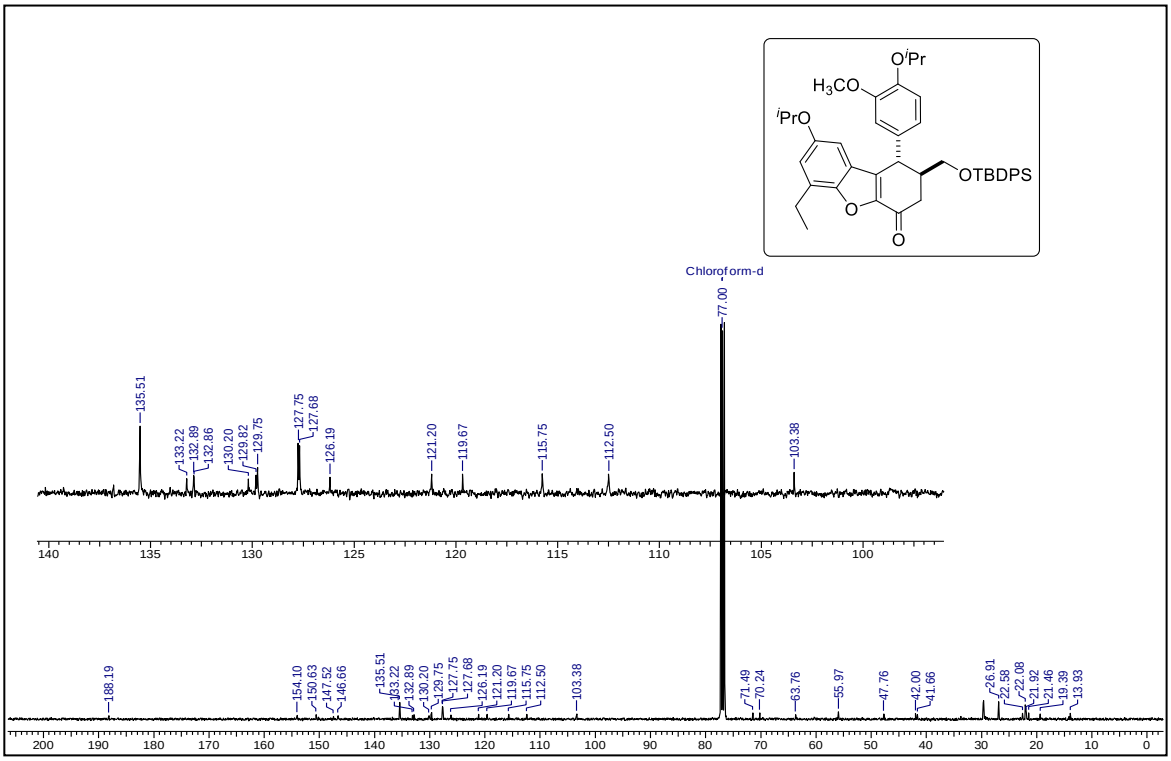
^{1}H NMR Spectrum of *cis*-26 in $CDCl_3$



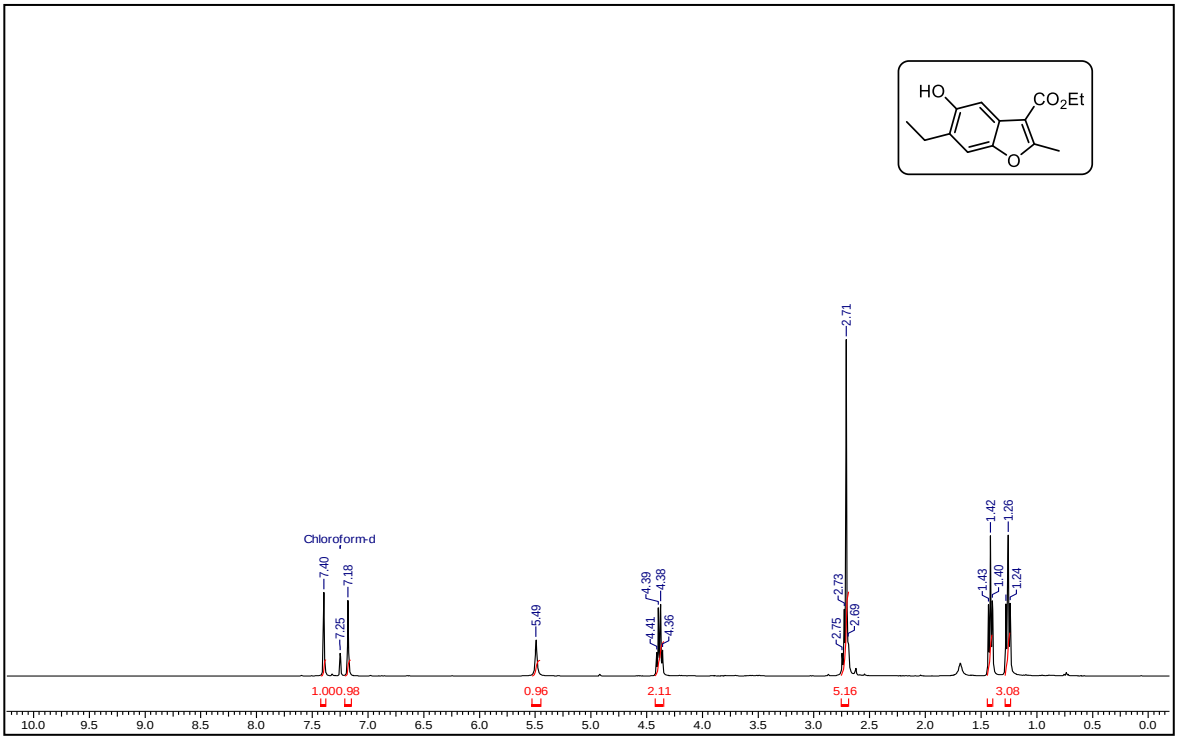
^{13}C NMR Spectrum of *cis*-26 in $CDCl_3$



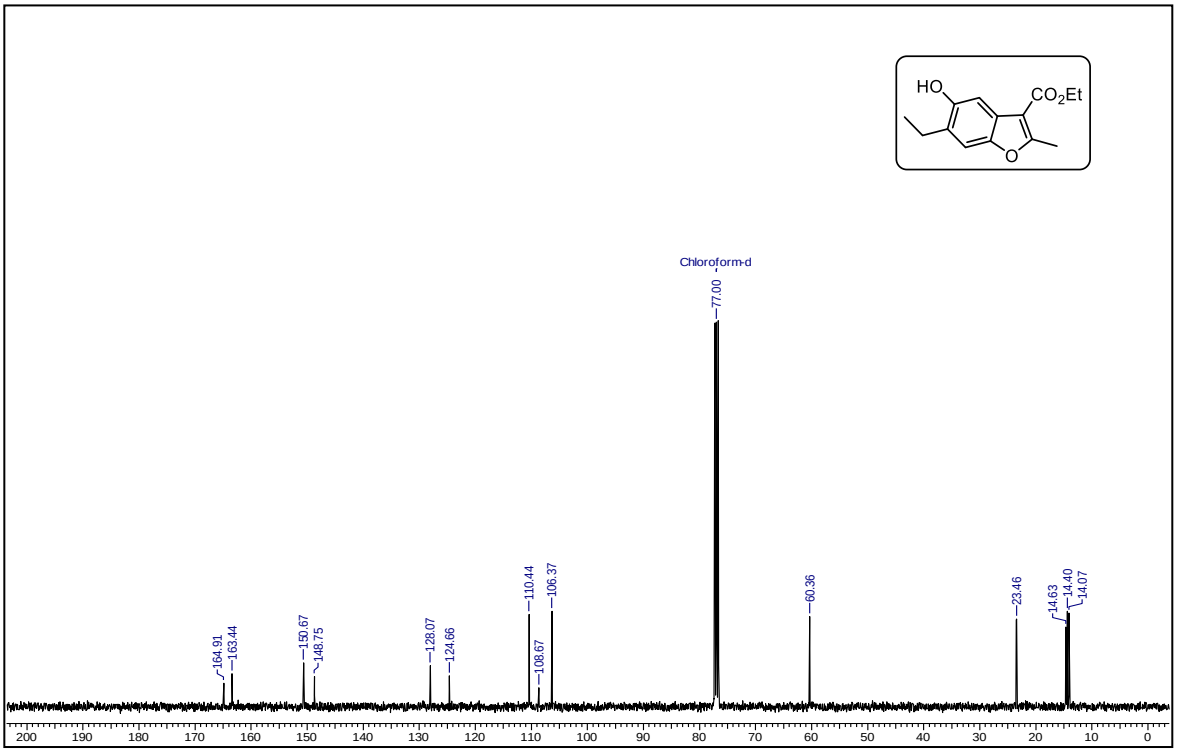
^{1}H NMR Spectrum of *trans*-26 in $CDCl_3$



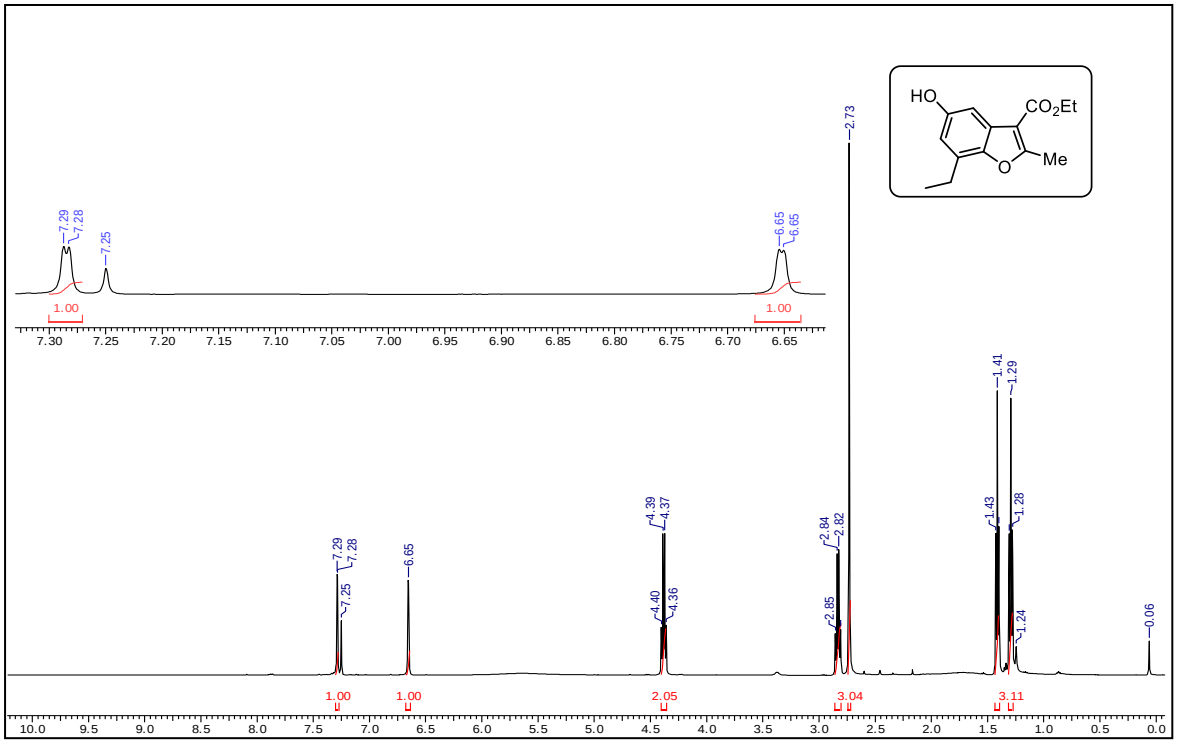
^{13}C NMR Spectrum of *trans*-26 in $CDCl_3$



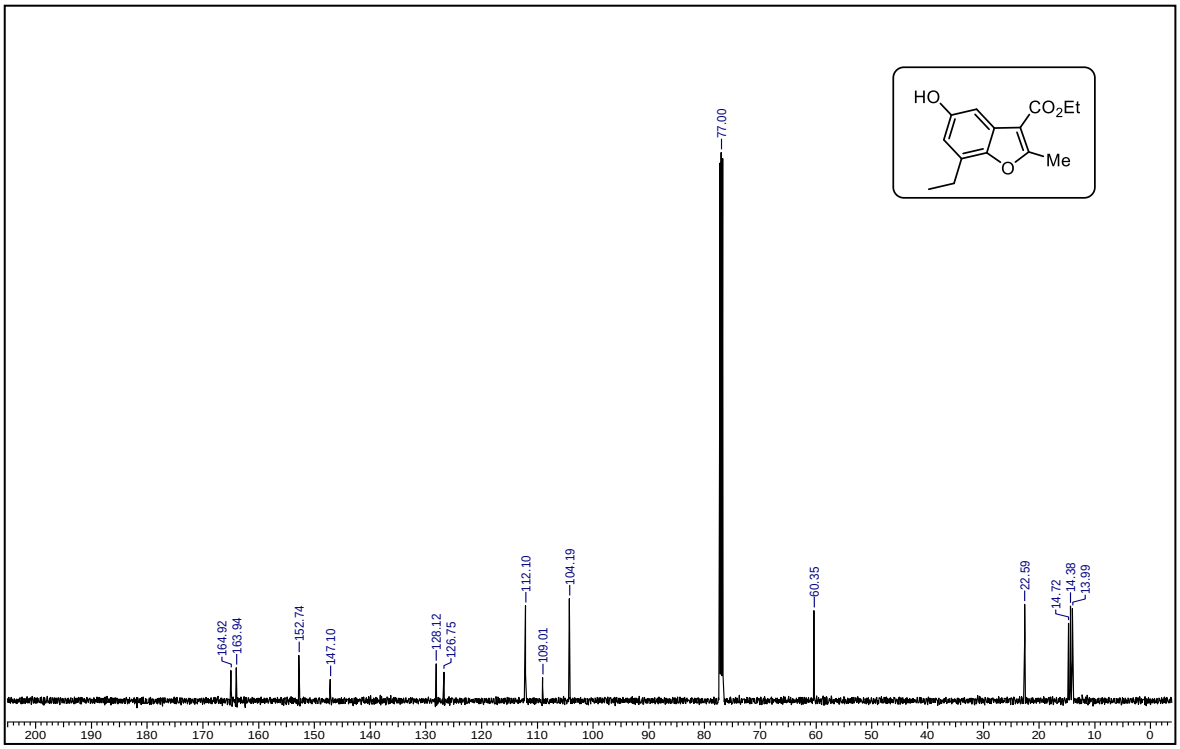
^{1}H NMR Spectrum of 27 in $CDCl_3$



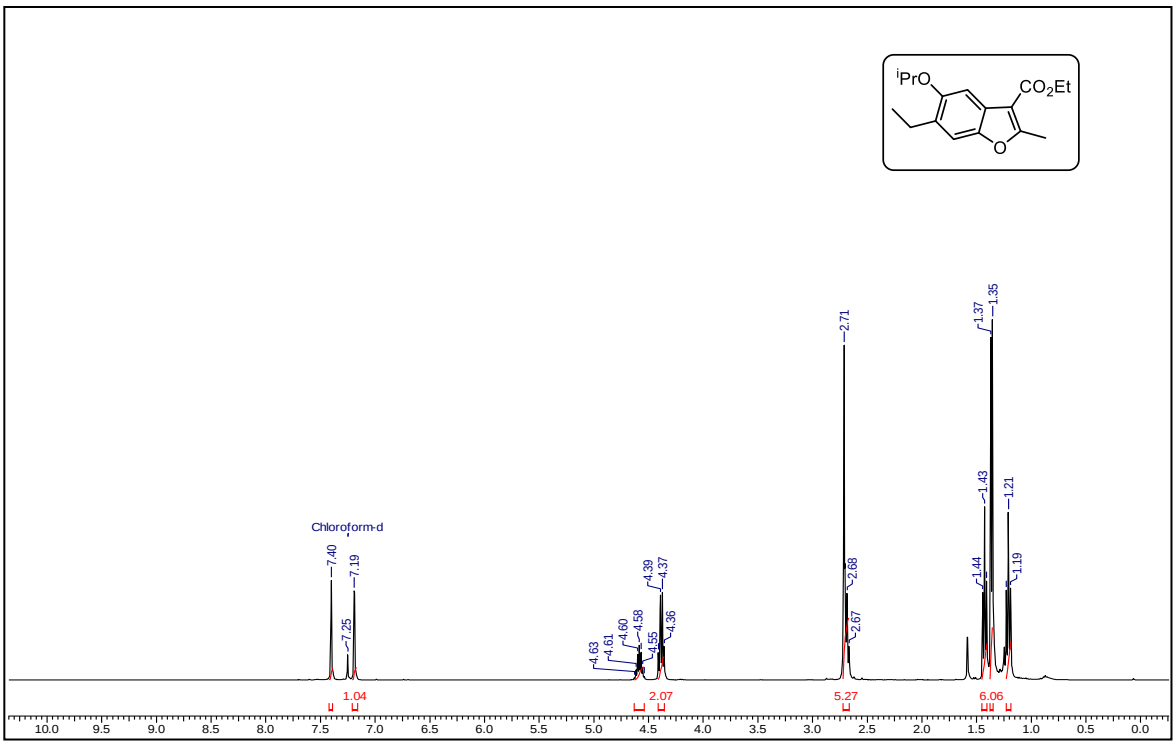
^{13}C NMR Spectrum of 27 in $CDCl_3$



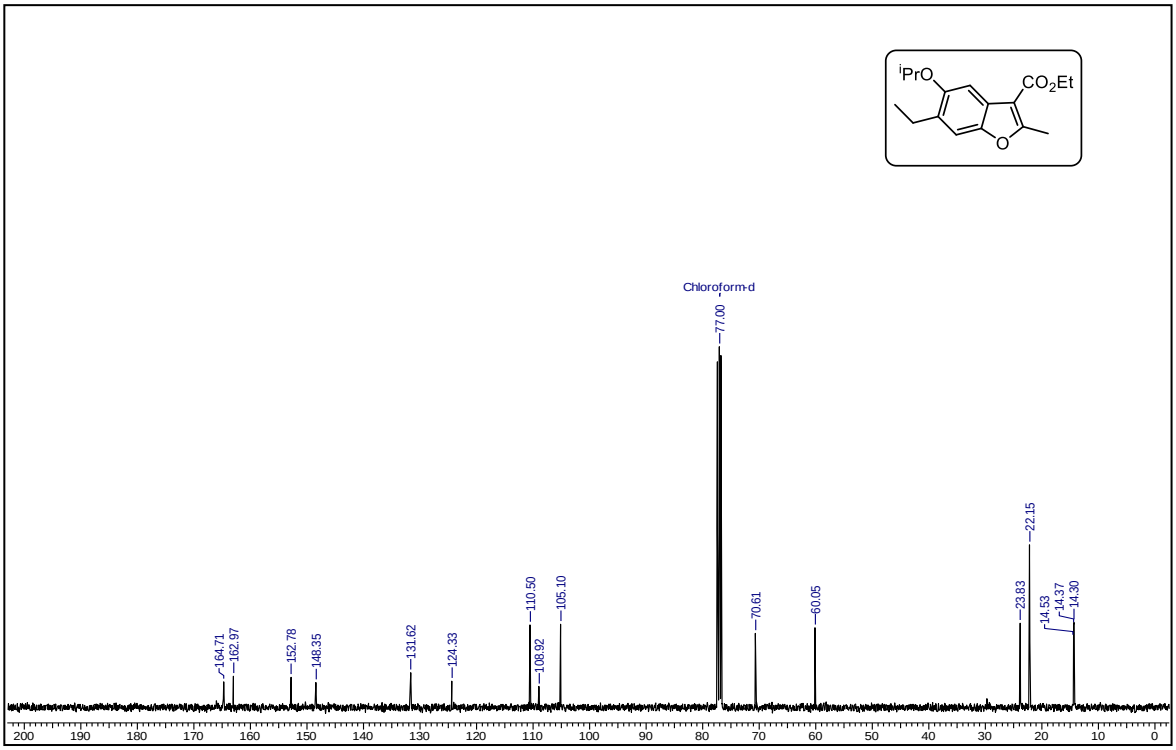
^{1}H NMR Spectrum of 28 in $CDCl_3$



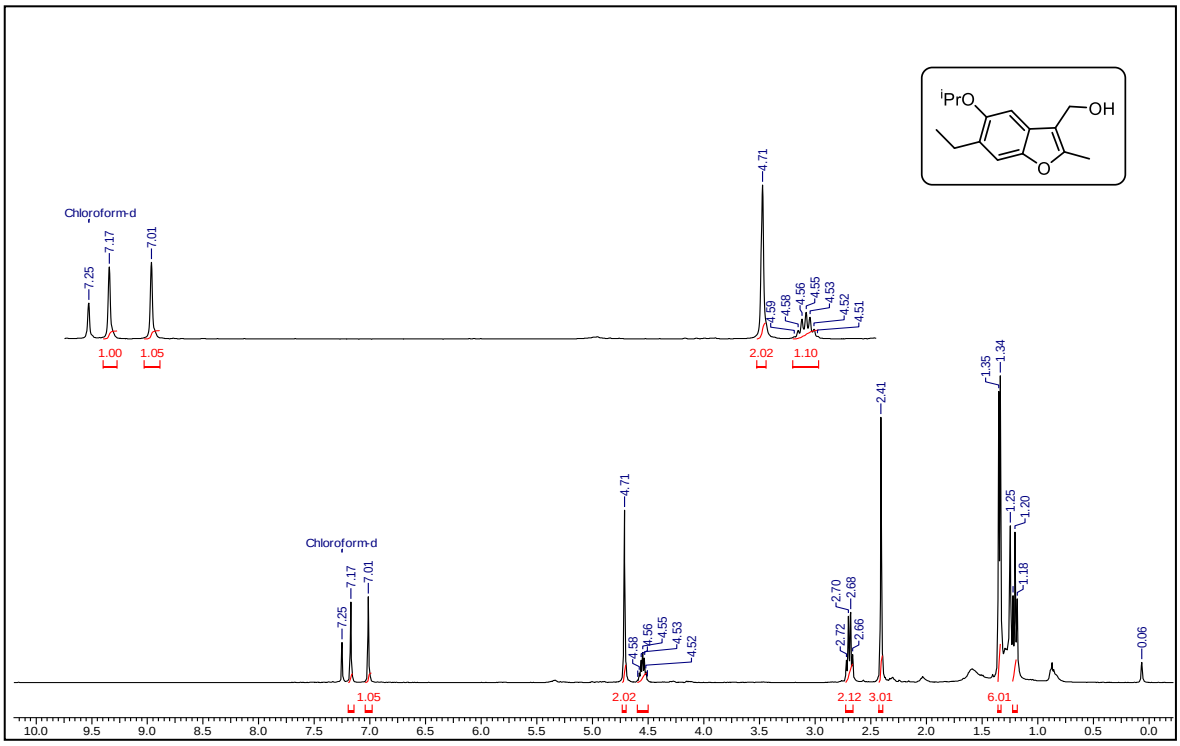
^{13}C NMR Spectrum of 28 in $CDCl_3$



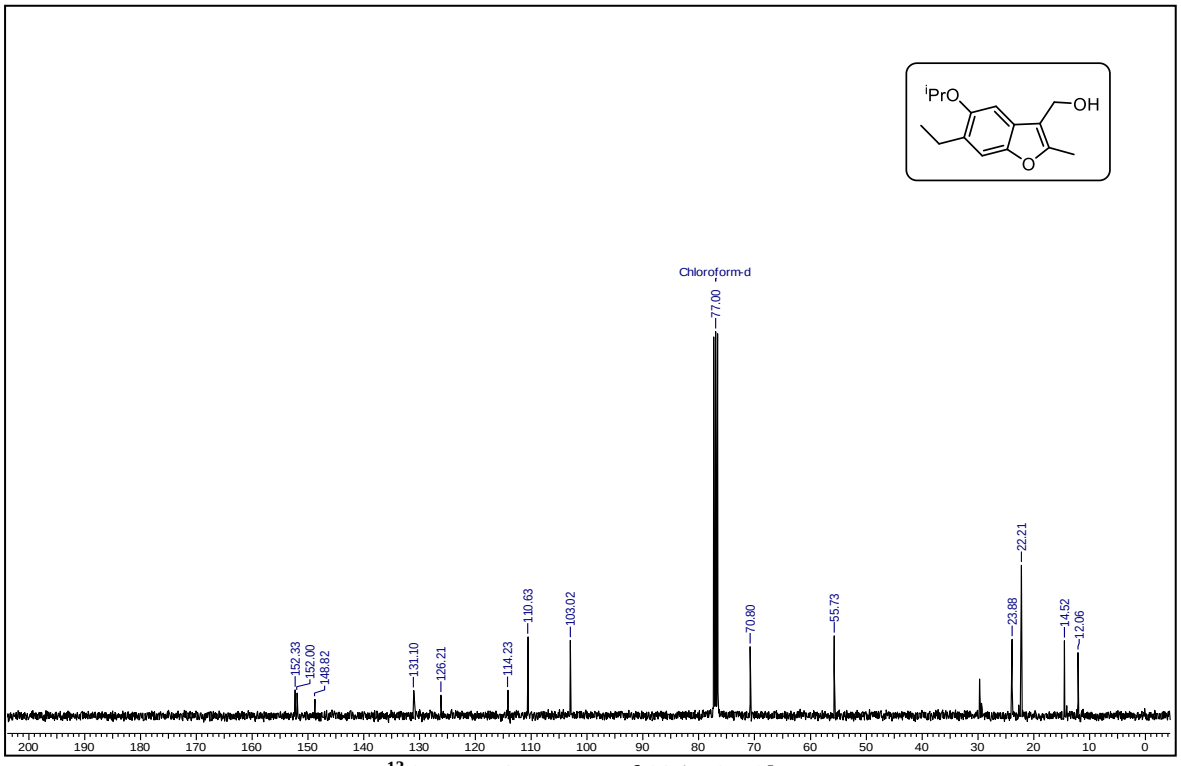
^{1}H NMR Spectrum of 31 in $CDCl_3$



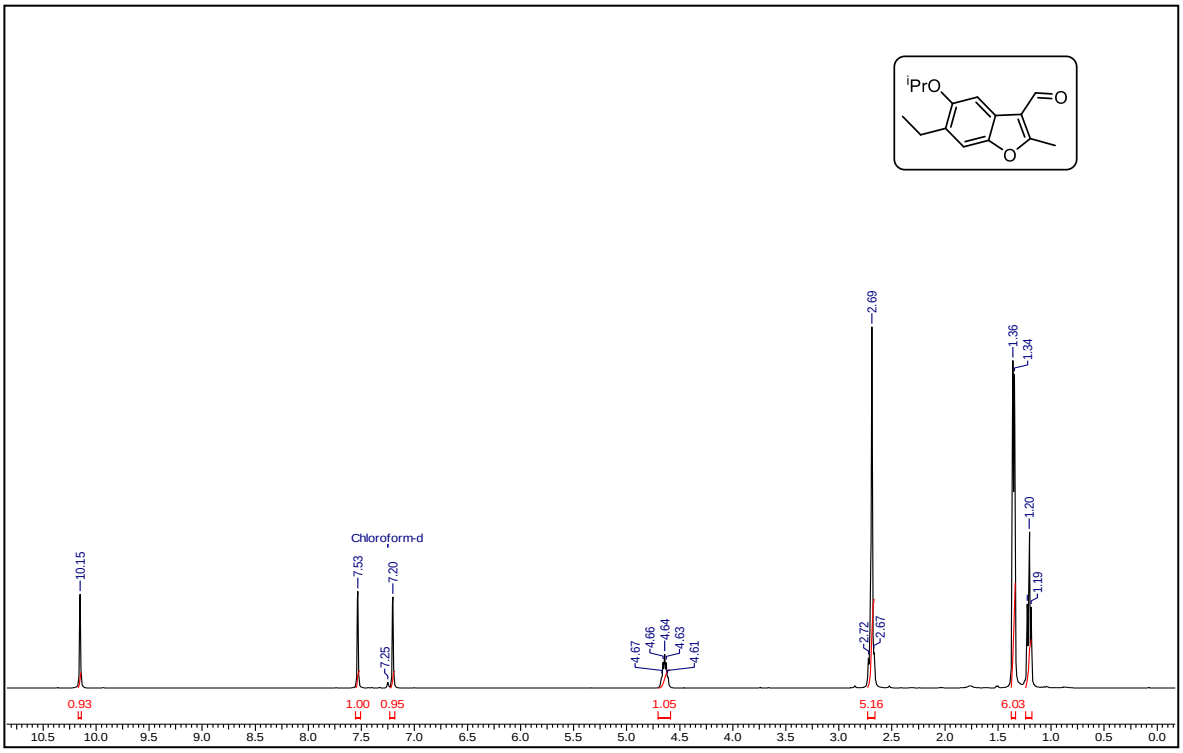
^{13}C NMR Spectrum of 31 in $CDCl_3$



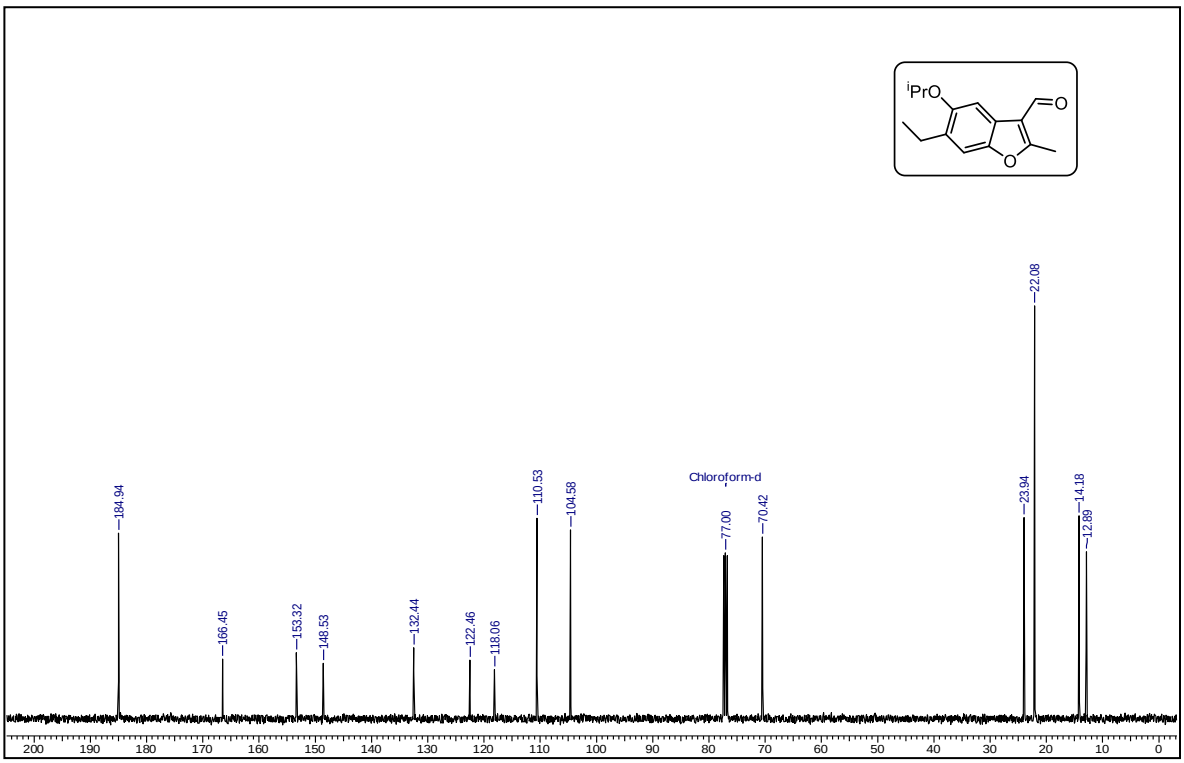
^{1}H NMR Spectrum of 32 in $CDCl_3$



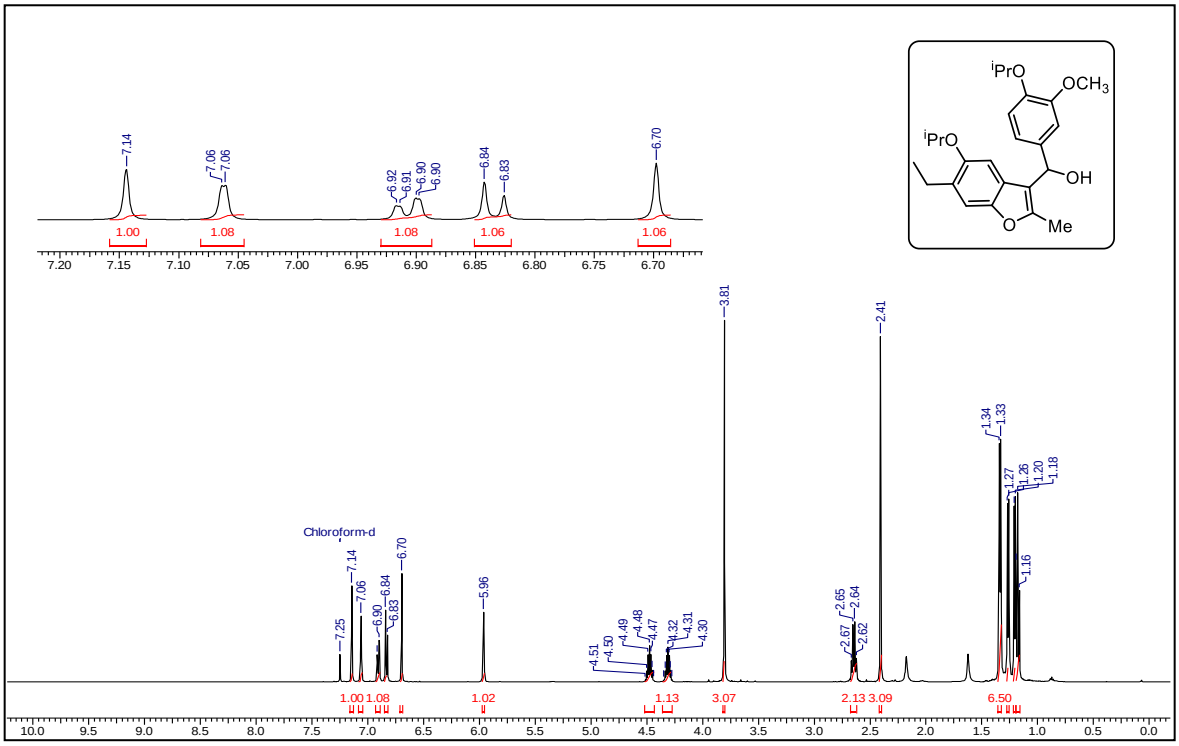
^{13}C NMR Spectrum of 32 in $CDCl_3$



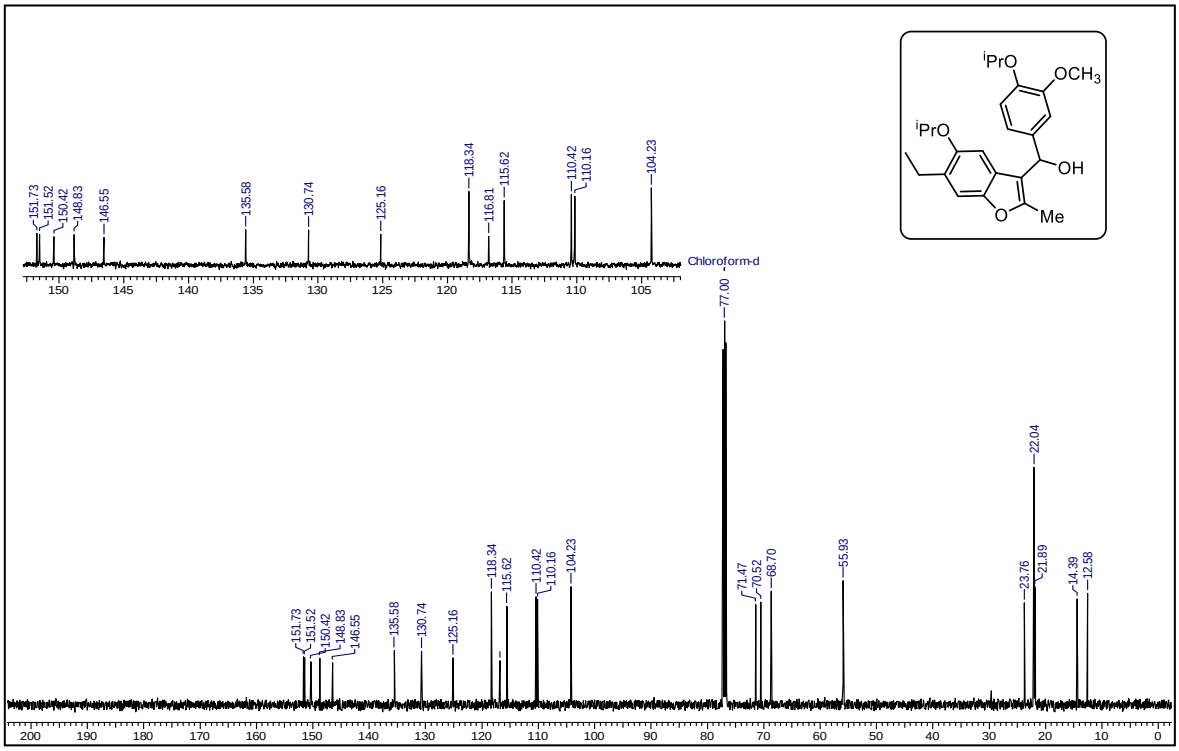
^{1}H NMR Spectrum of 33 in $CDCl_3$



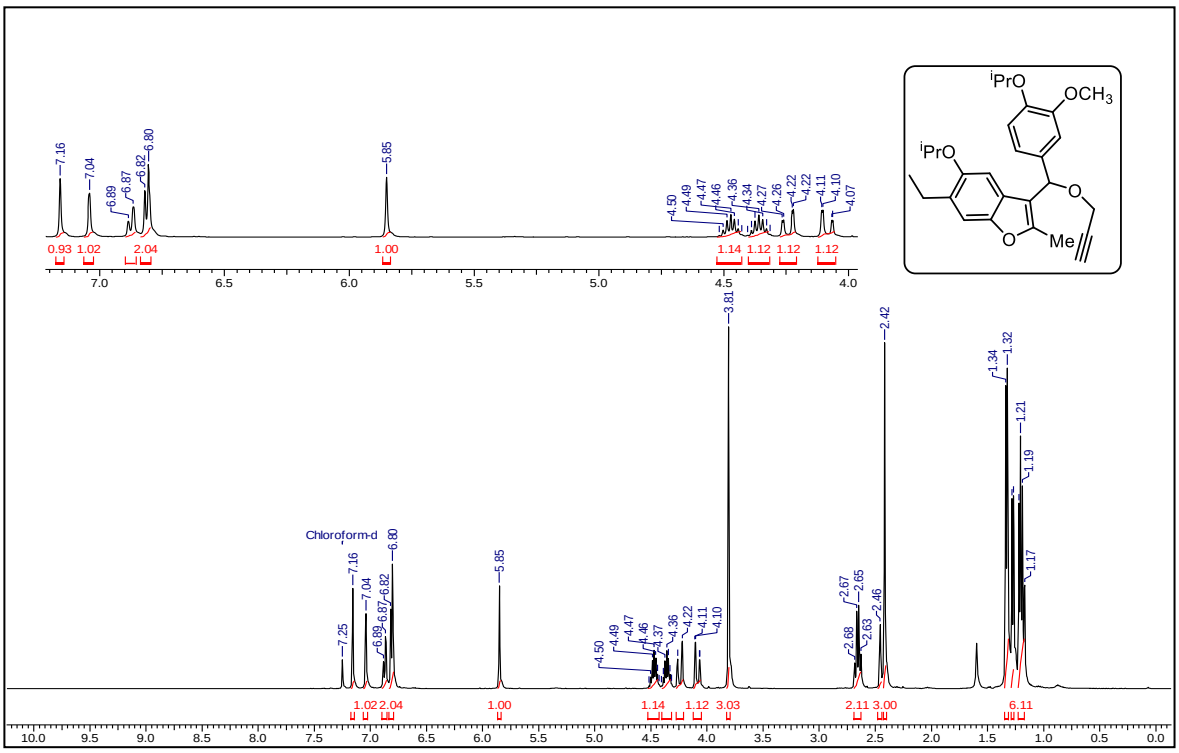
^{13}C NMR Spectrum of 33 in $CDCl_3$



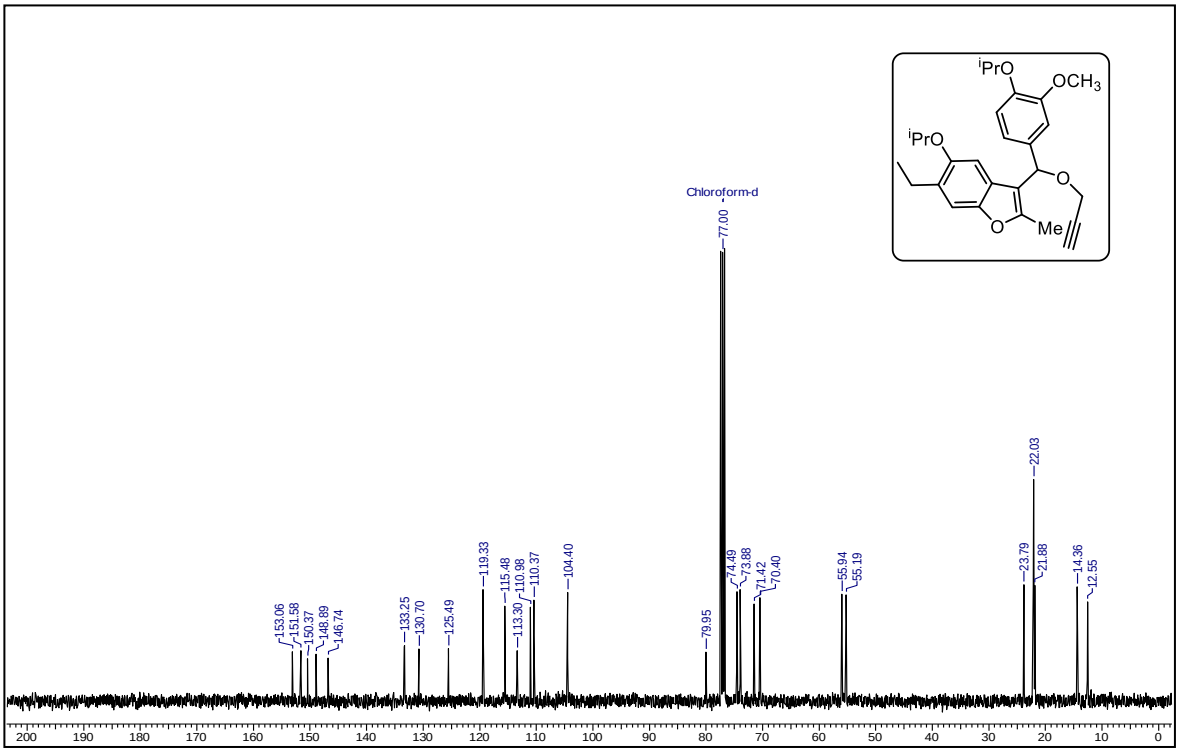
^{1}H NMR Spectrum of 34 in $CDCl_3$



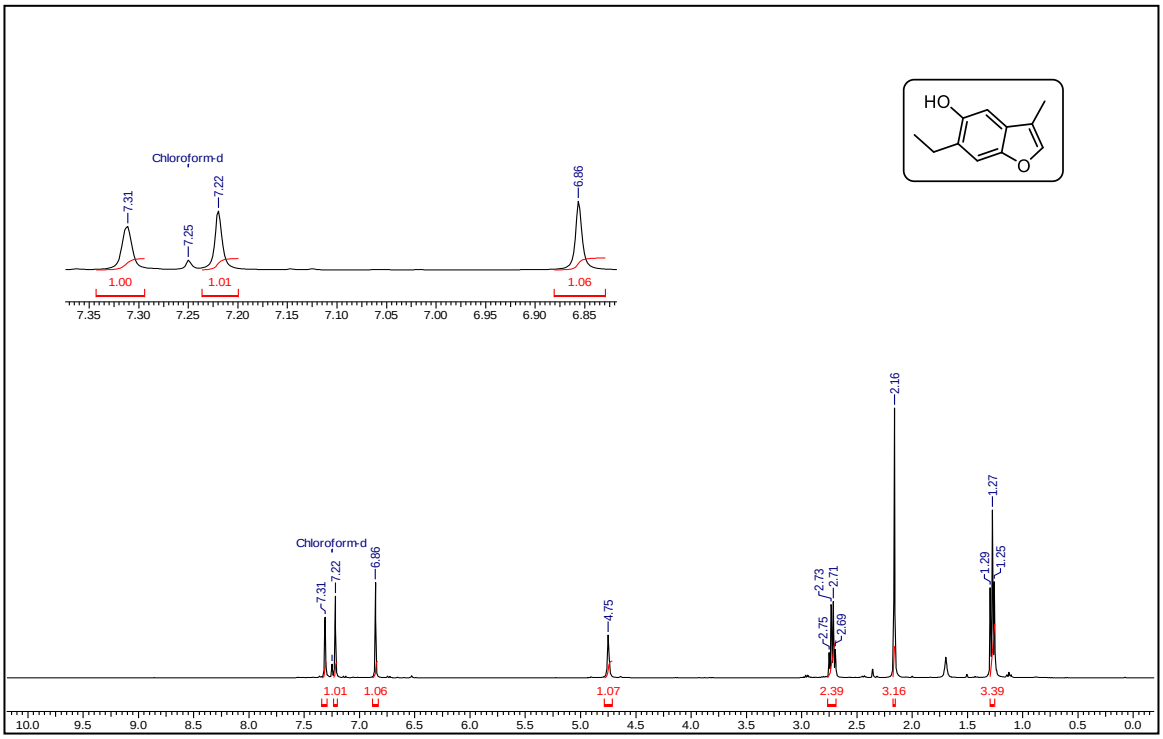
^{13}C NMR Spectrum of 34 in $CDCl_3$



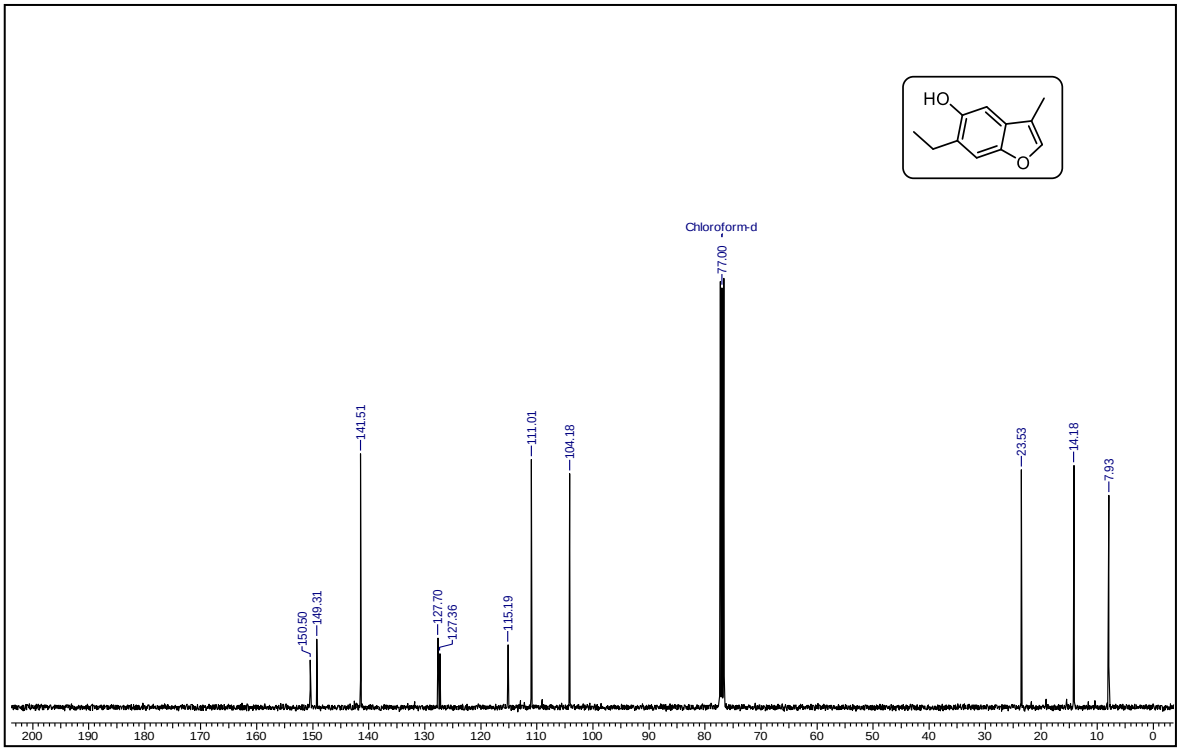
^{1}H NMR Spectrum of 35 in $CDCl_3$



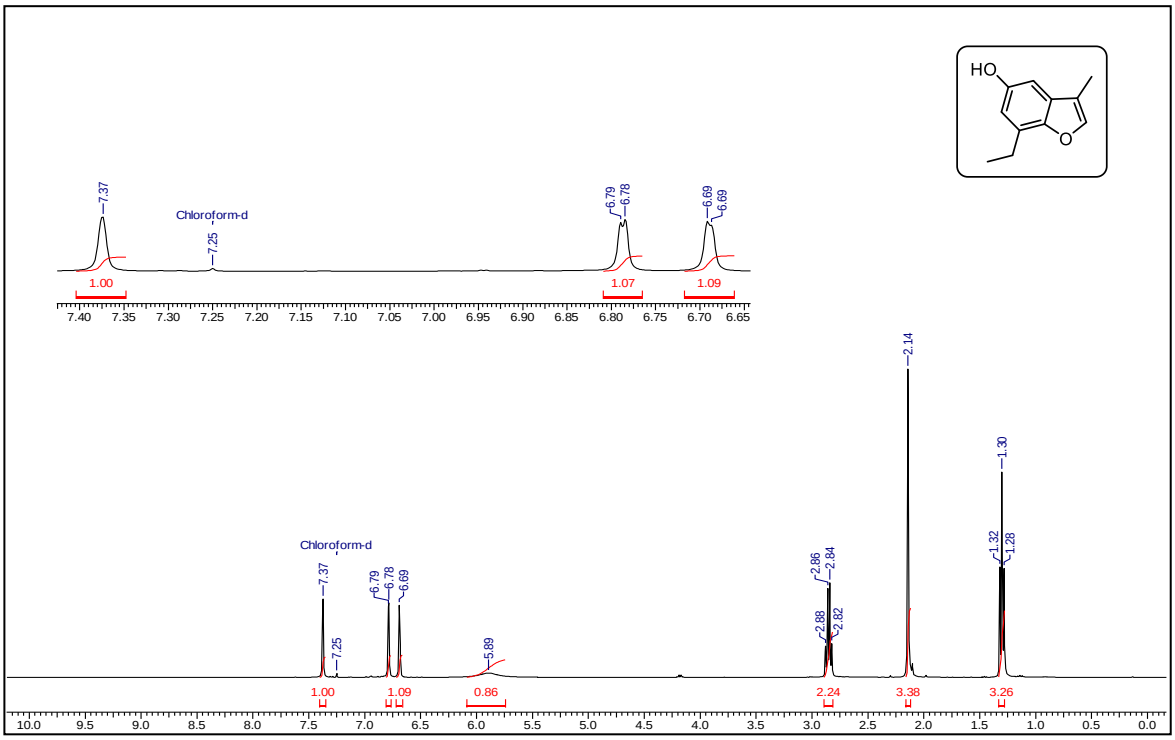
^{13}C NMR Spectrum of 35 in $CDCl_3$



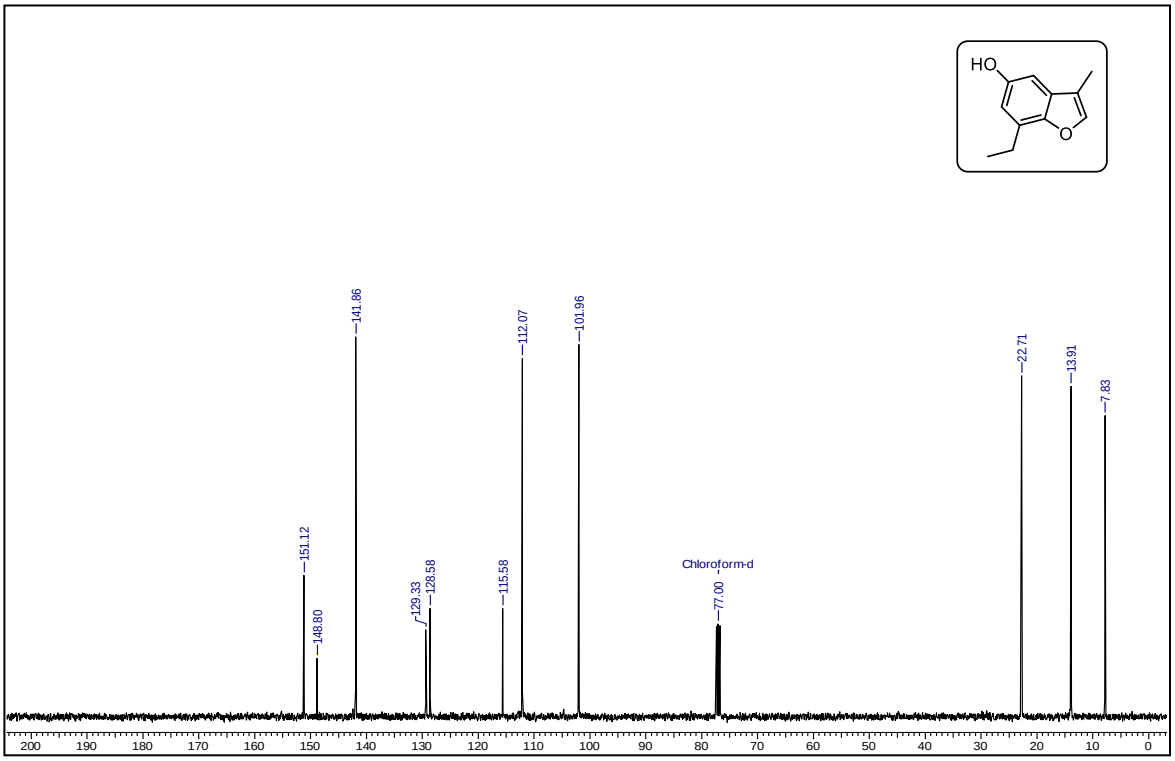
^{1}H NMR Spectrum of 29 in $CDCl_3$



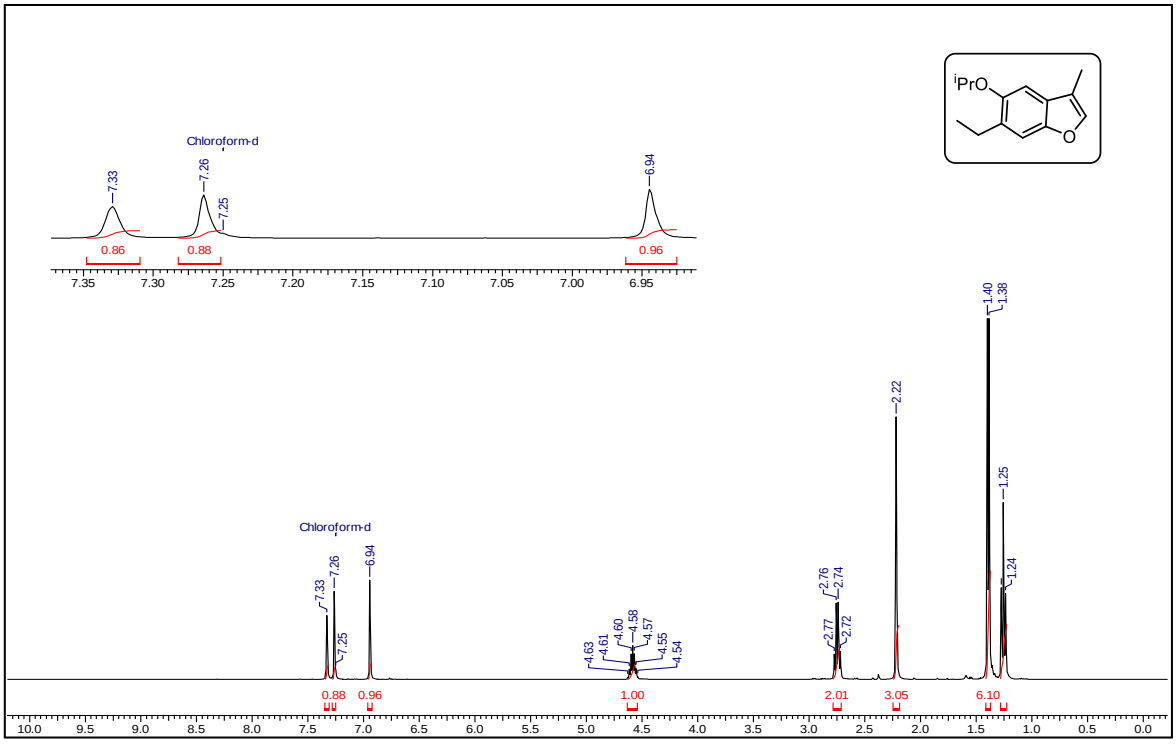
^{13}C NMR Spectrum of 29 in $CDCl_3$



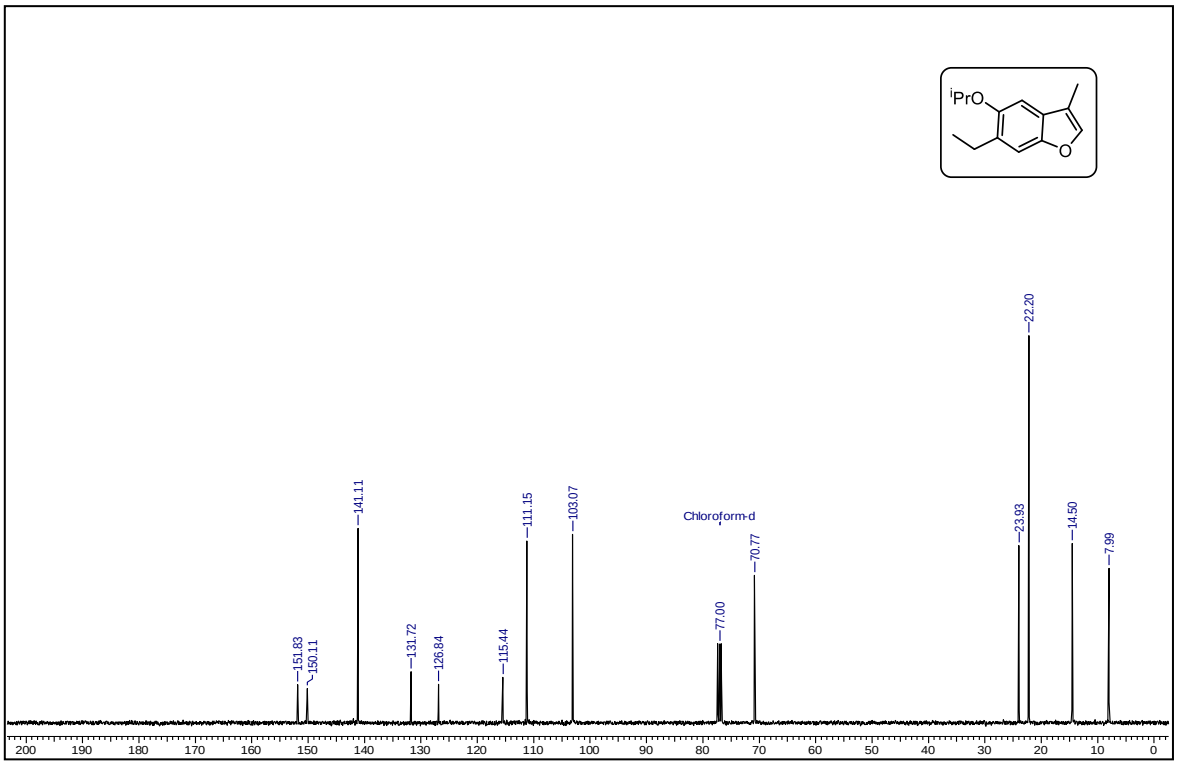
^{1}H NMR Spectrum of 30 in $CDCl_3$



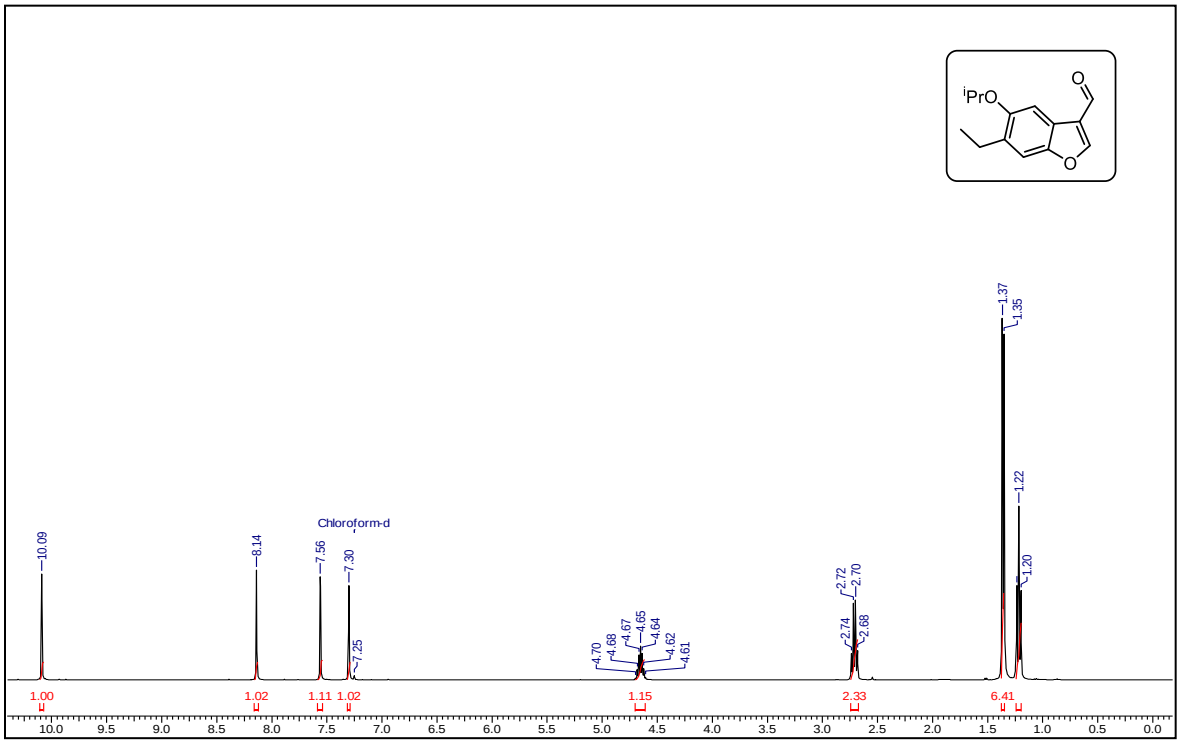
^{13}C NMR Spectrum of 30 in $CDCl_3$



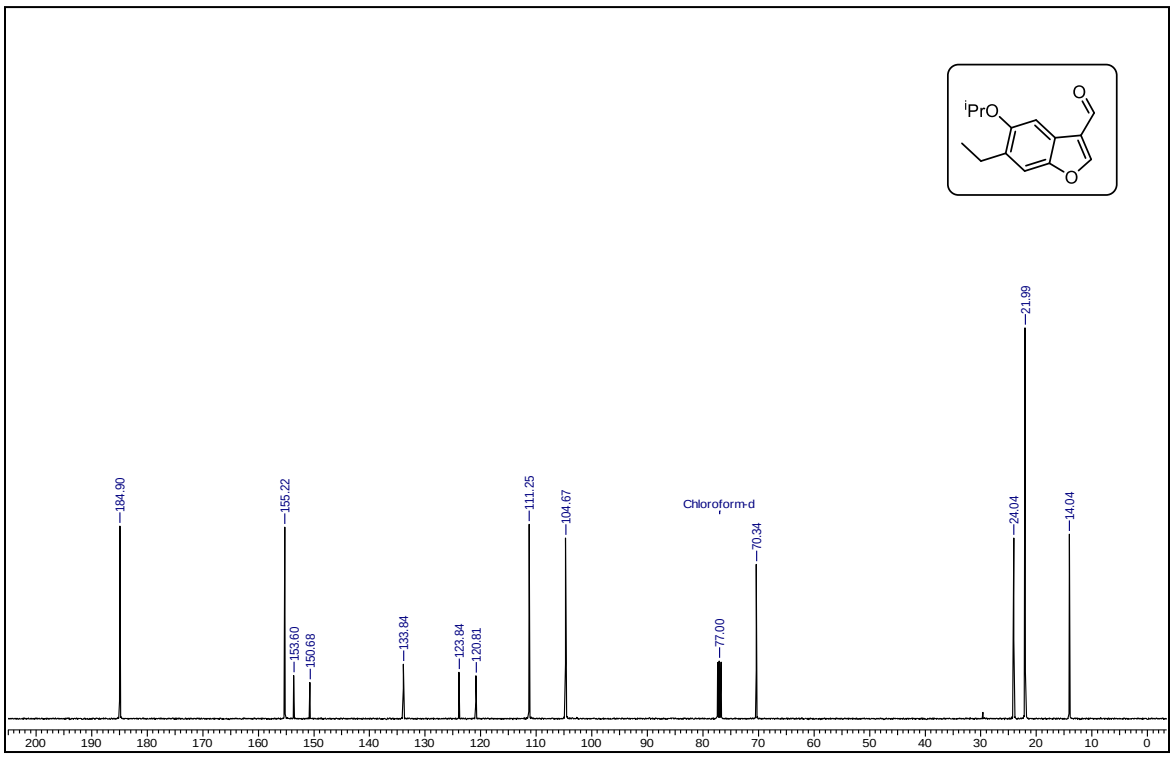
^{1}H NMR Spectrum of 36 in $CDCl_3$



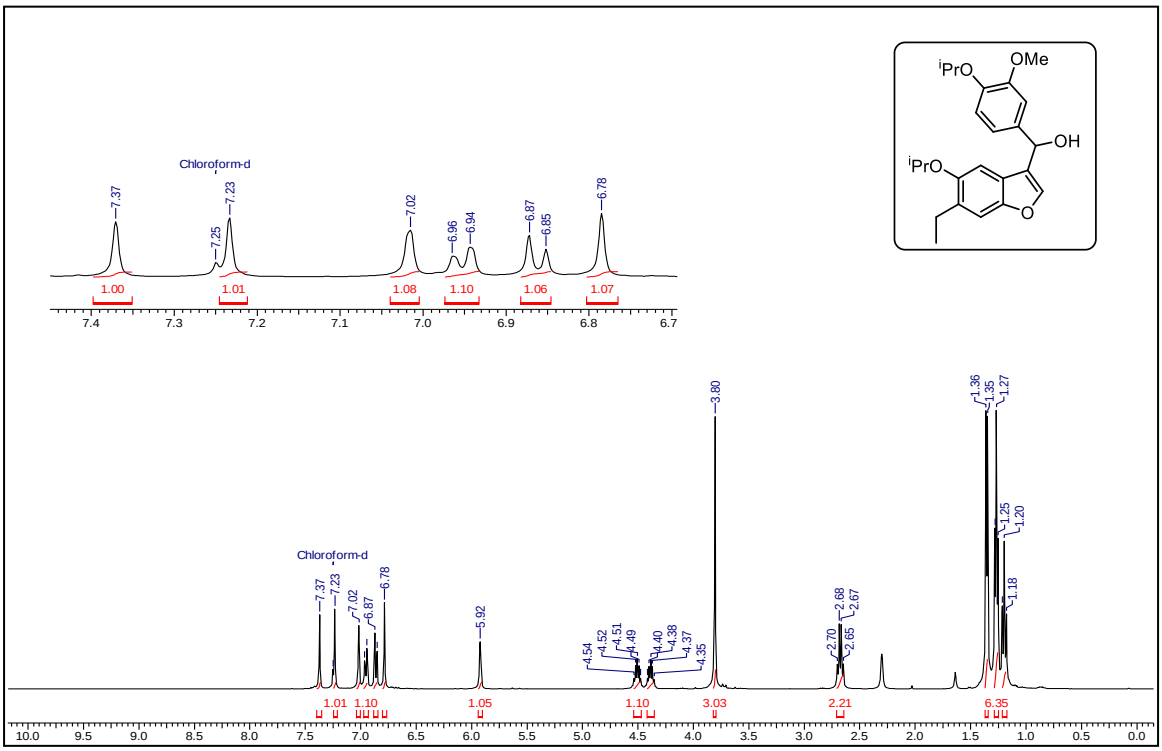
^{13}C NMR Spectrum of 36 in $CDCl_3$



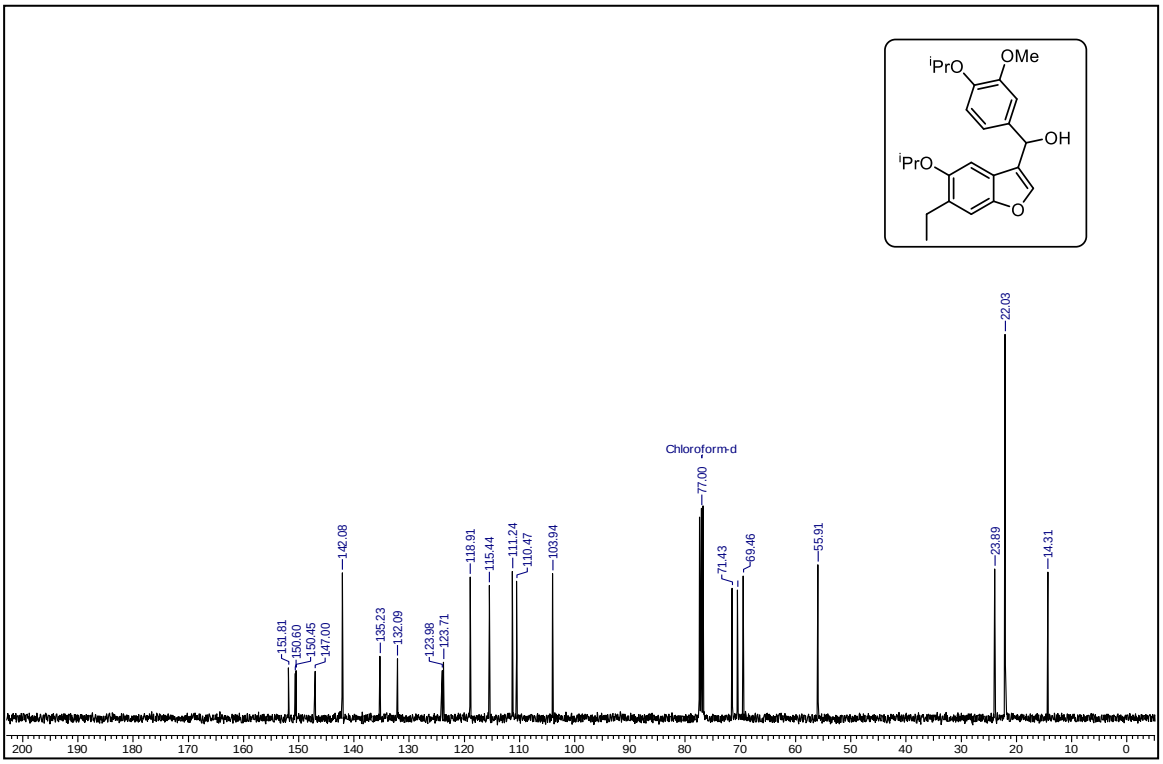
^{1}H NMR Spectrum of 37 in $CDCl_3$



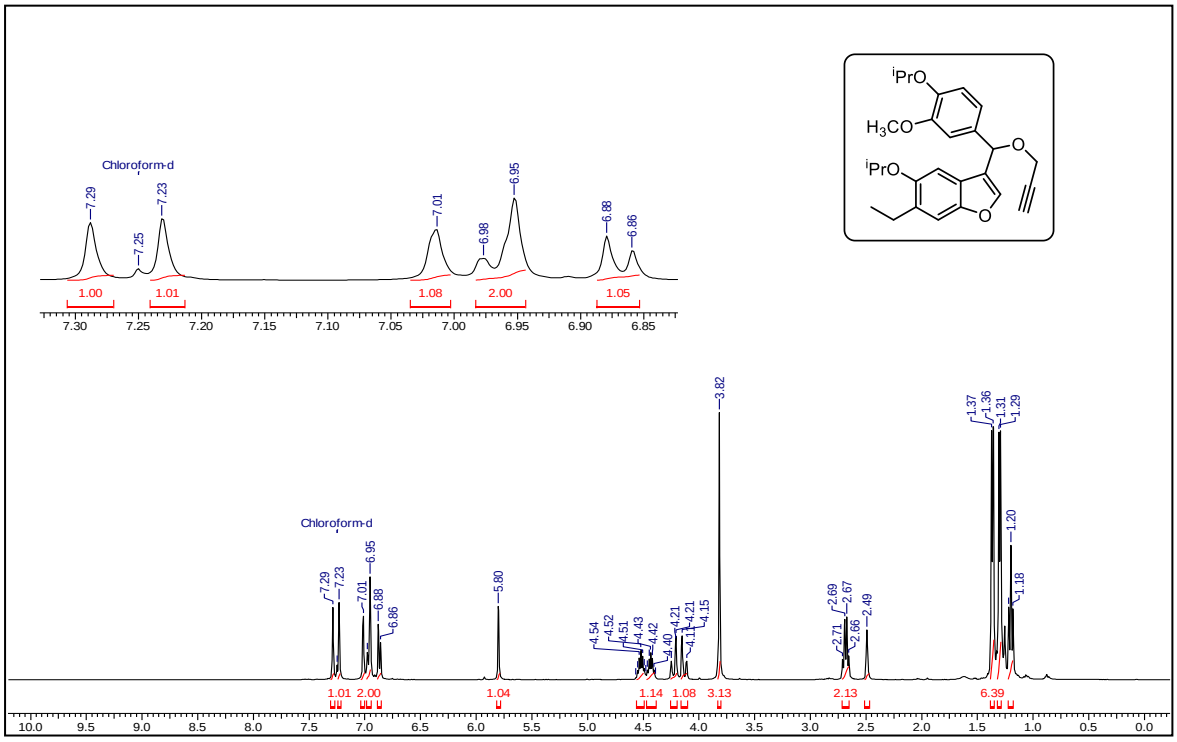
^{13}C NMR Spectrum of 37 in $CDCl_3$



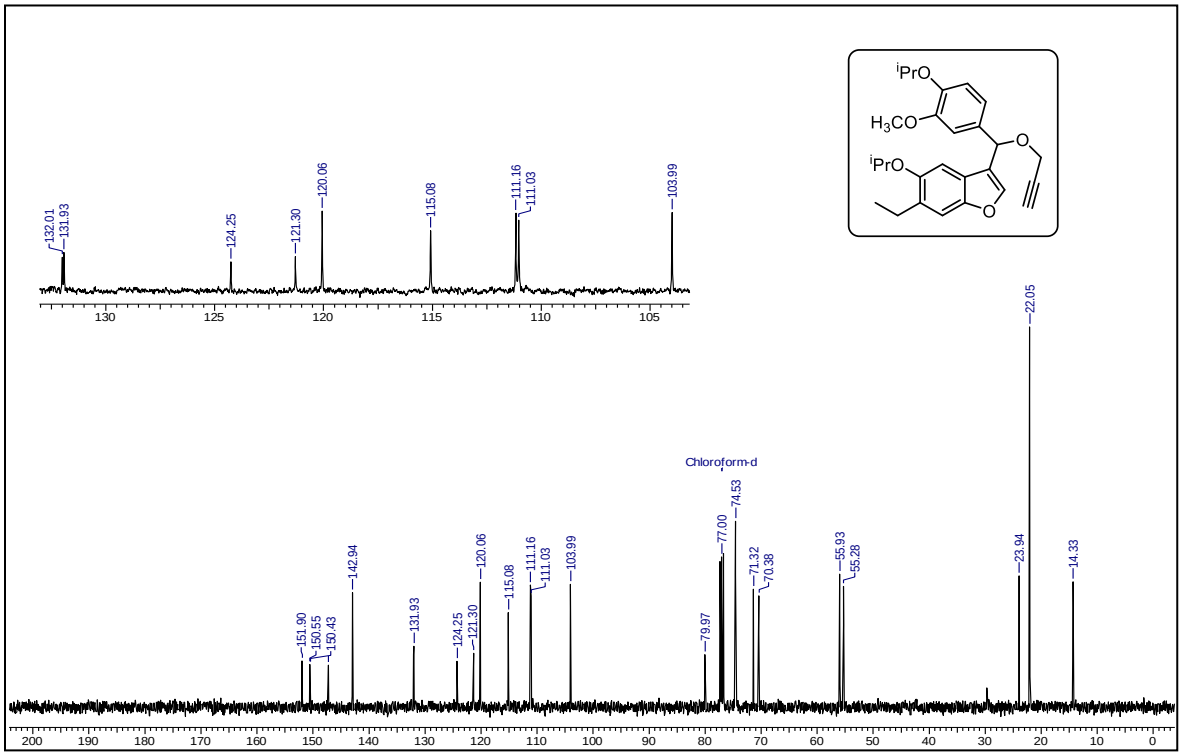
^{1}H NMR Spectrum of 38 in $CDCl_3$



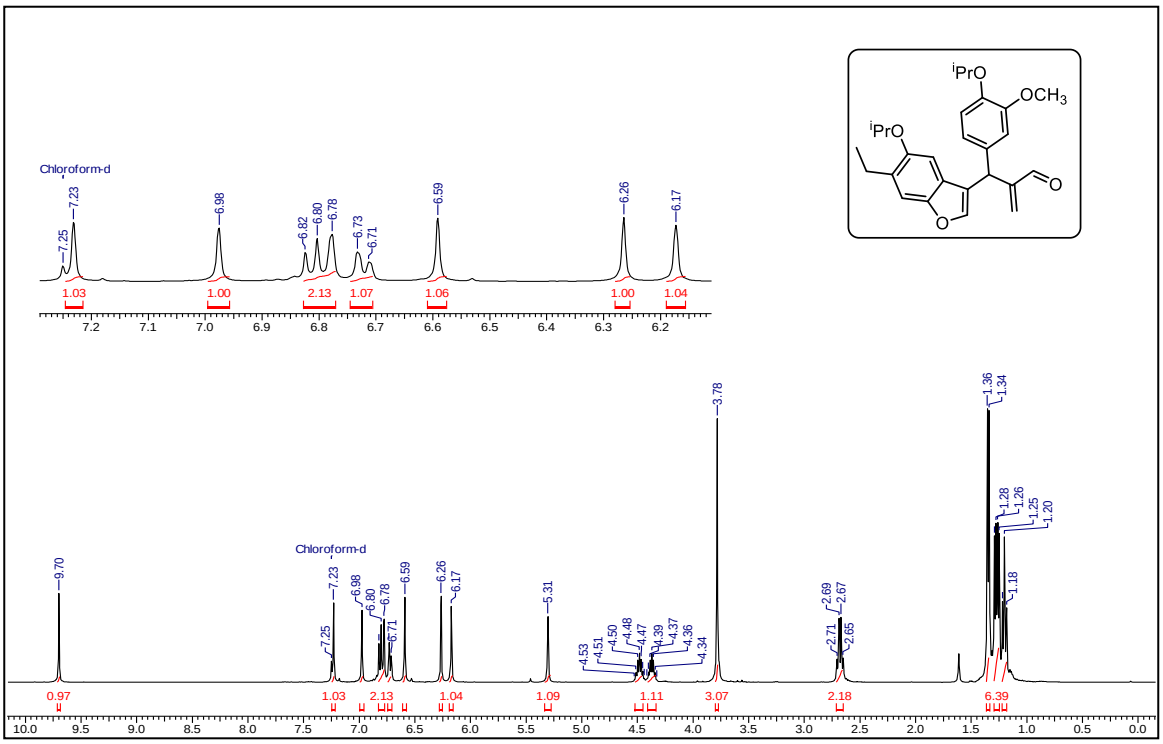
^{13}C NMR Spectrum of 38 in $CDCl_3$



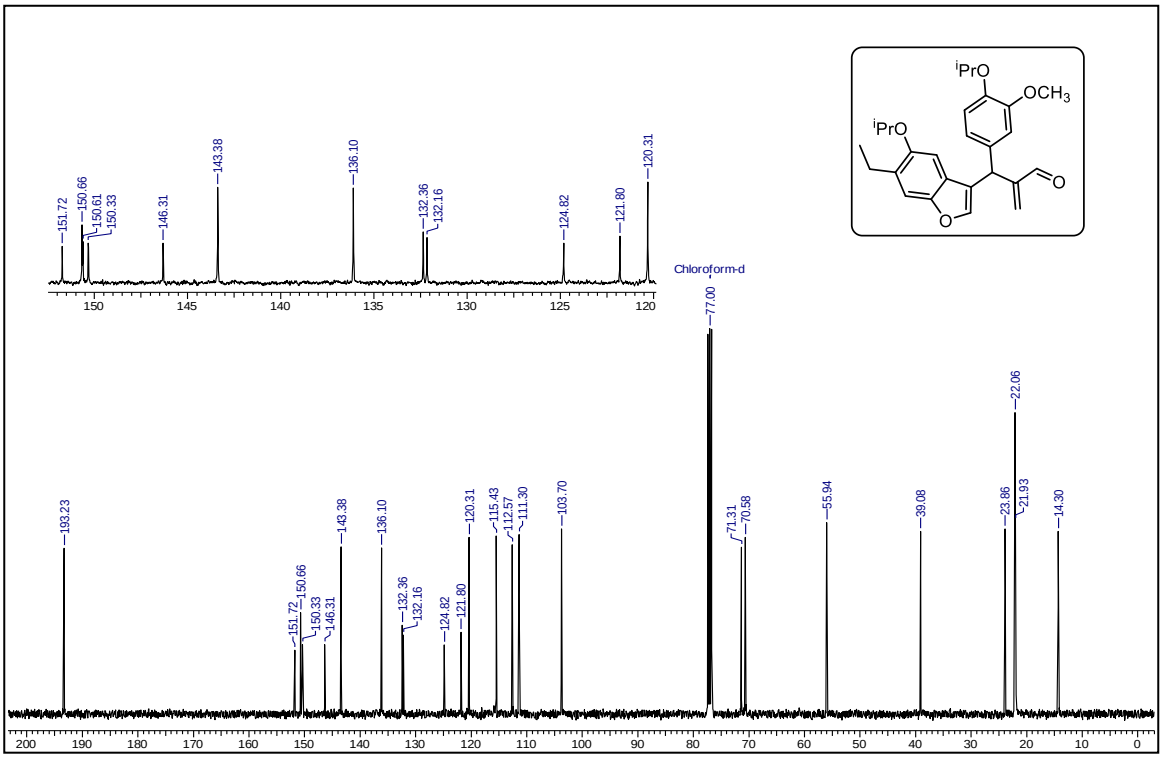
^{1}H NMR Spectrum of 14 in $CDCl_3$



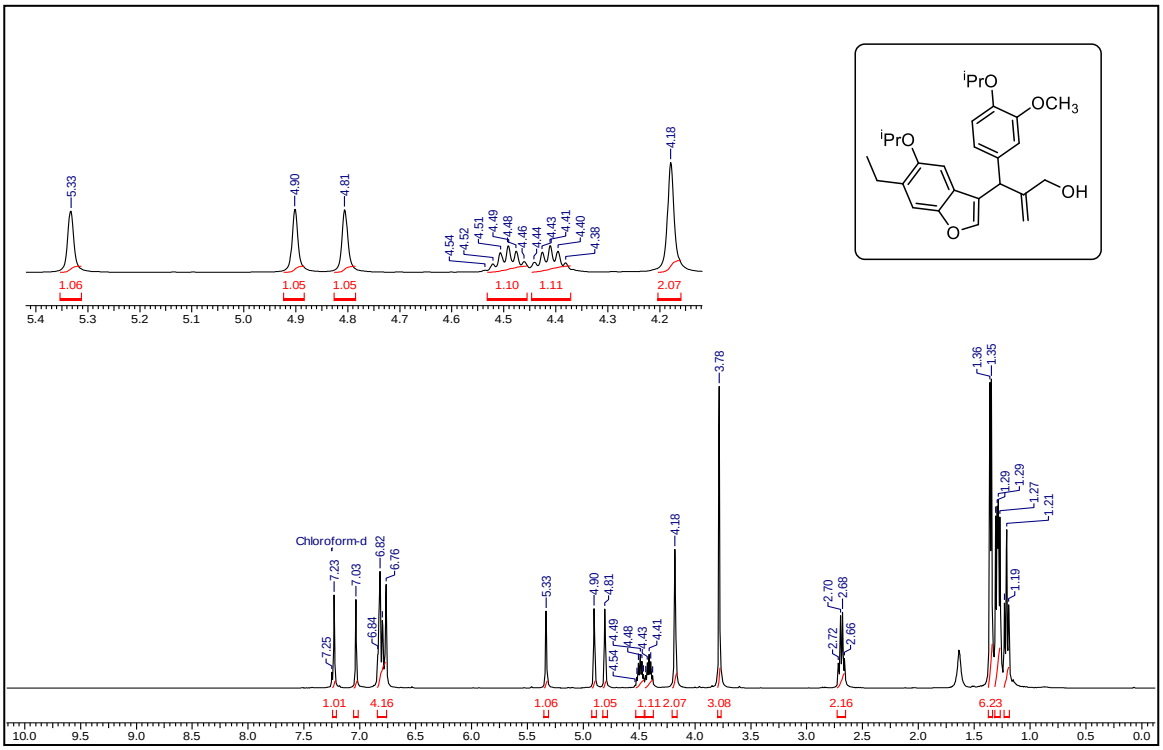
^{13}C NMR Spectrum of 14 in $CDCl_3$



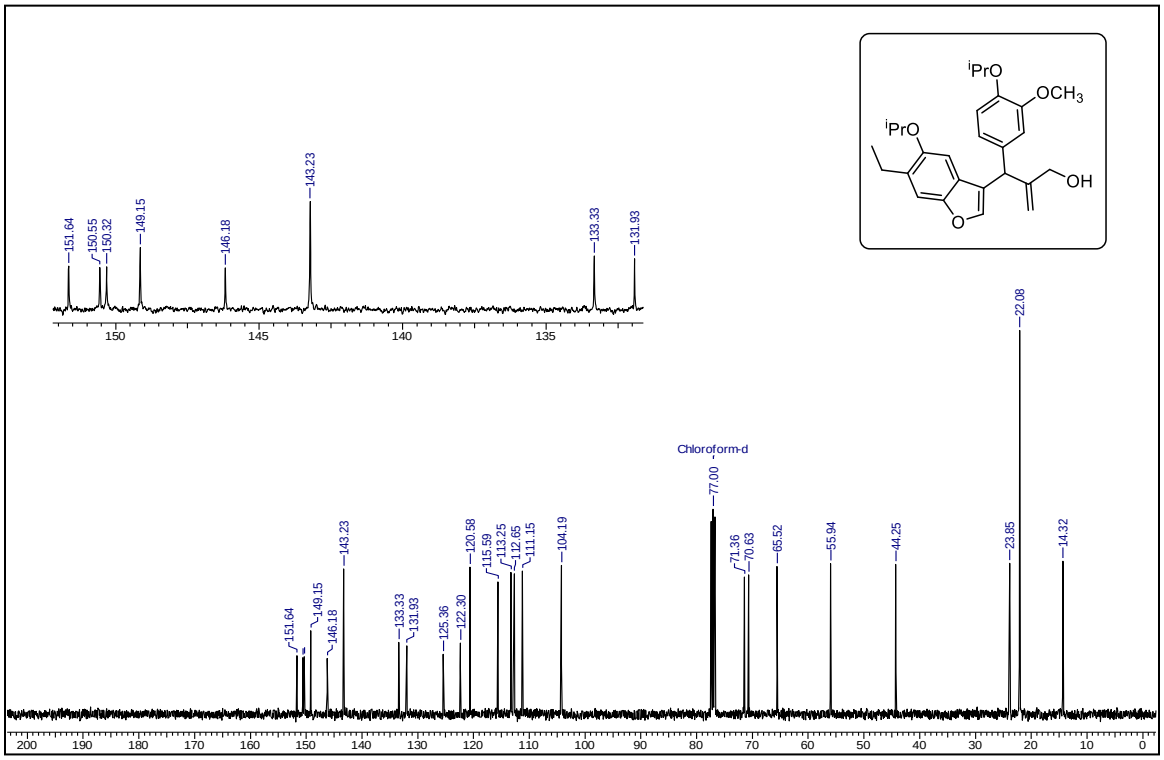
^{1}H NMR Spectrum of 39 in $CDCl_3$



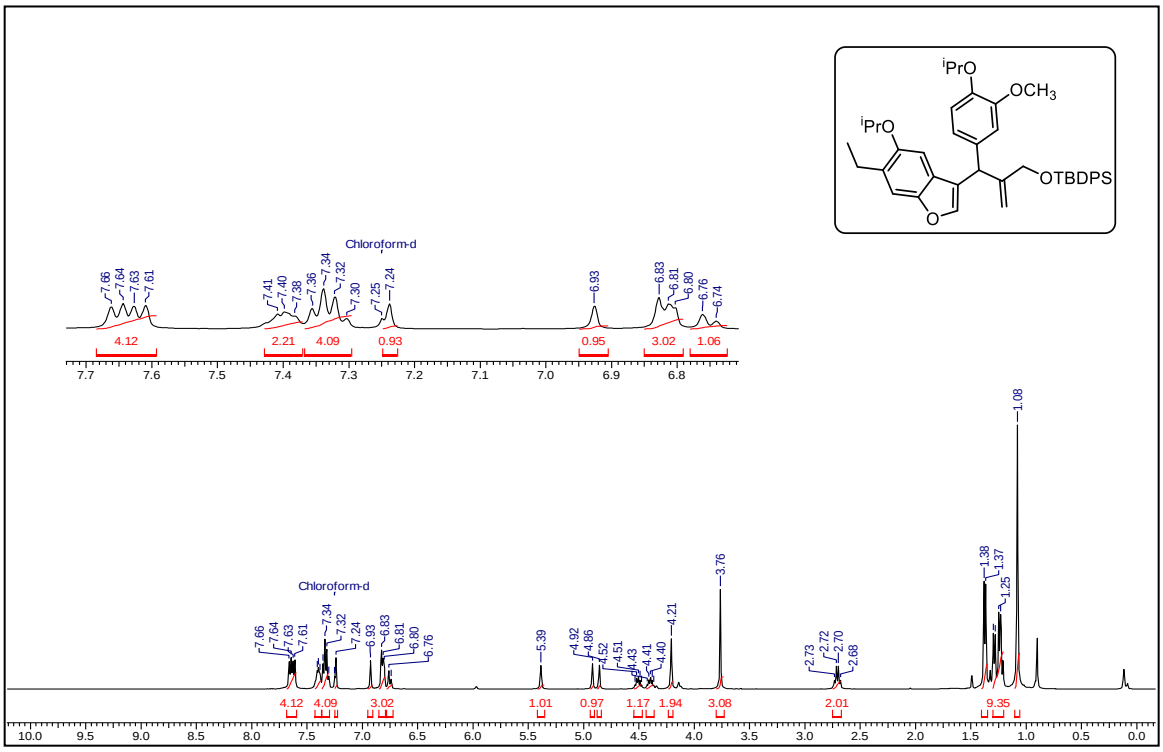
^{13}C NMR Spectrum of 39 in $CDCl_3$



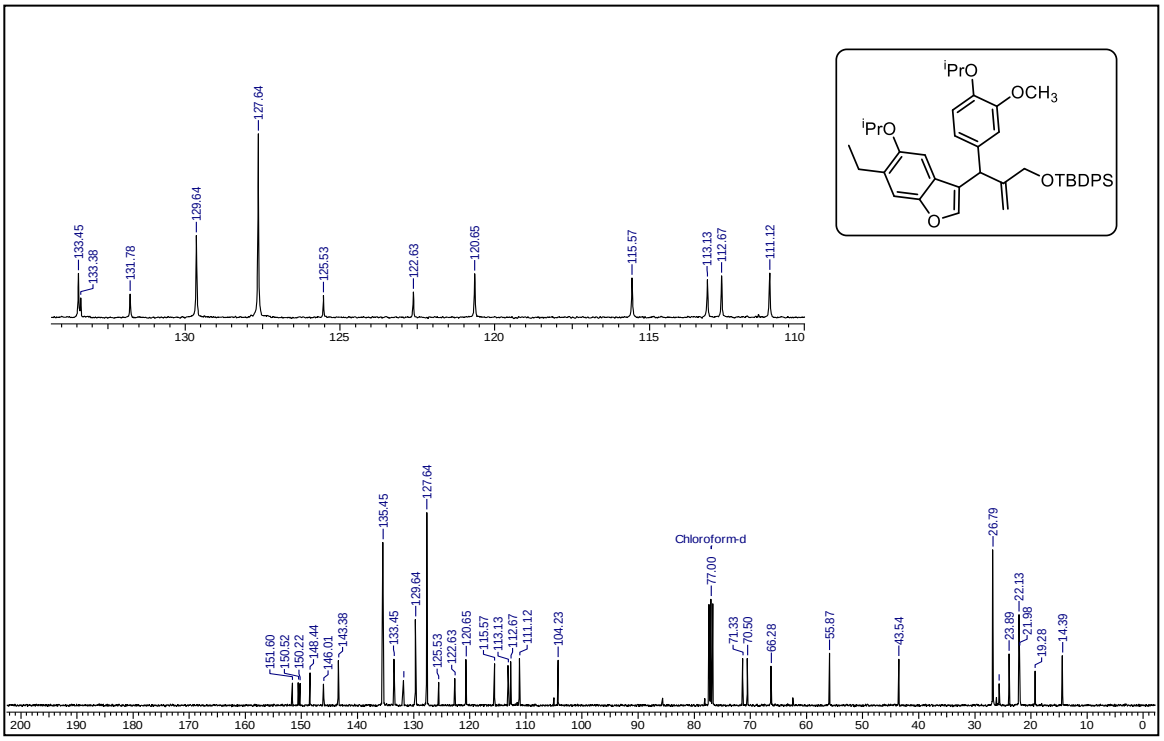
^{1}H NMR Spectrum of 40 in $CDCl_3$



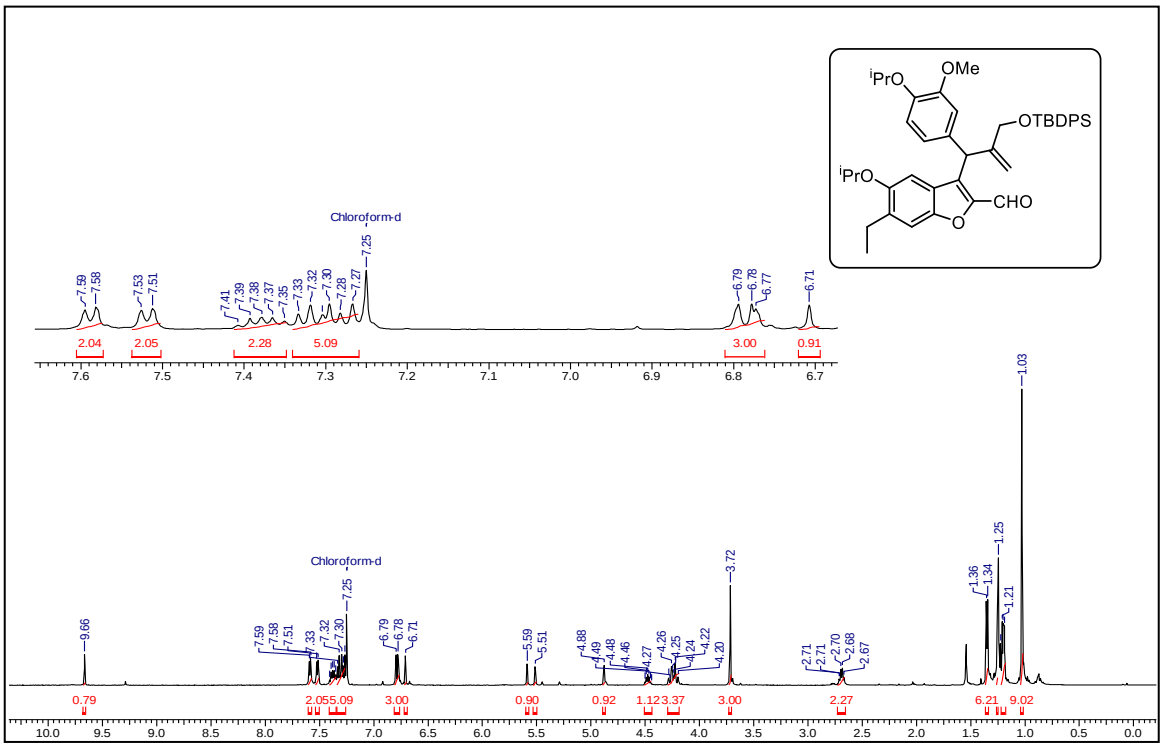
^{13}C NMR Spectrum of 40 in $CDCl_3$



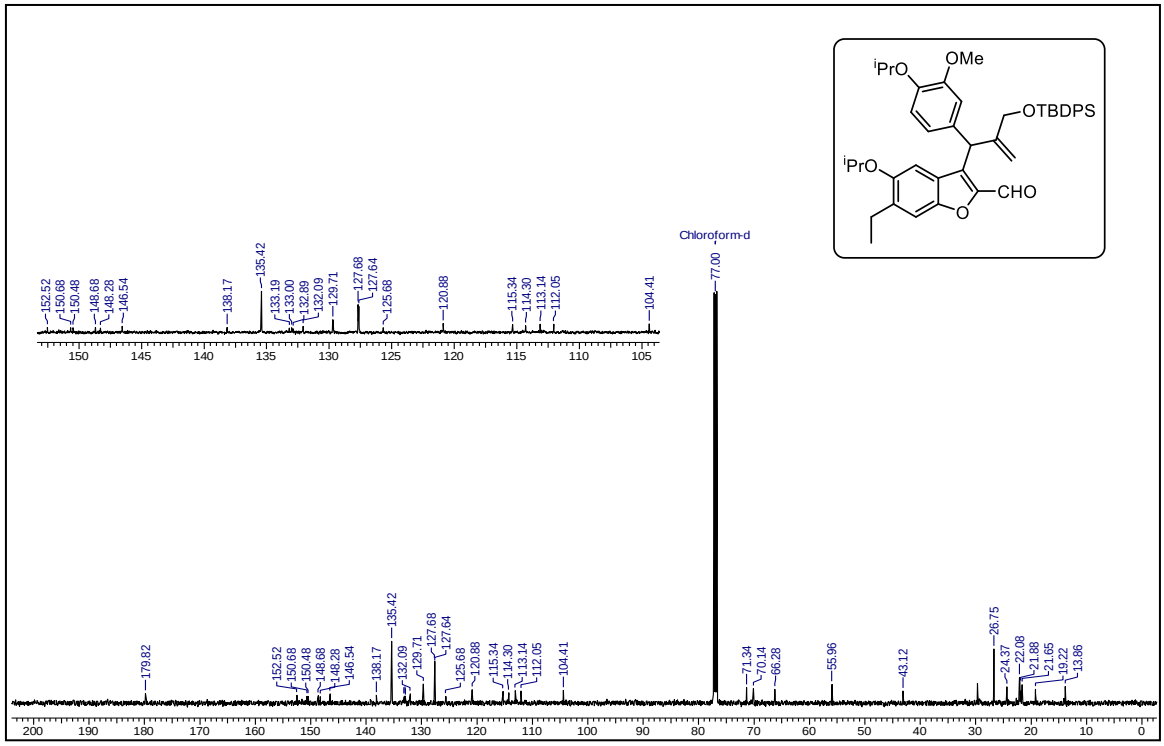
^{1}H NMR Spectrum of 41 in $CDCl_3$



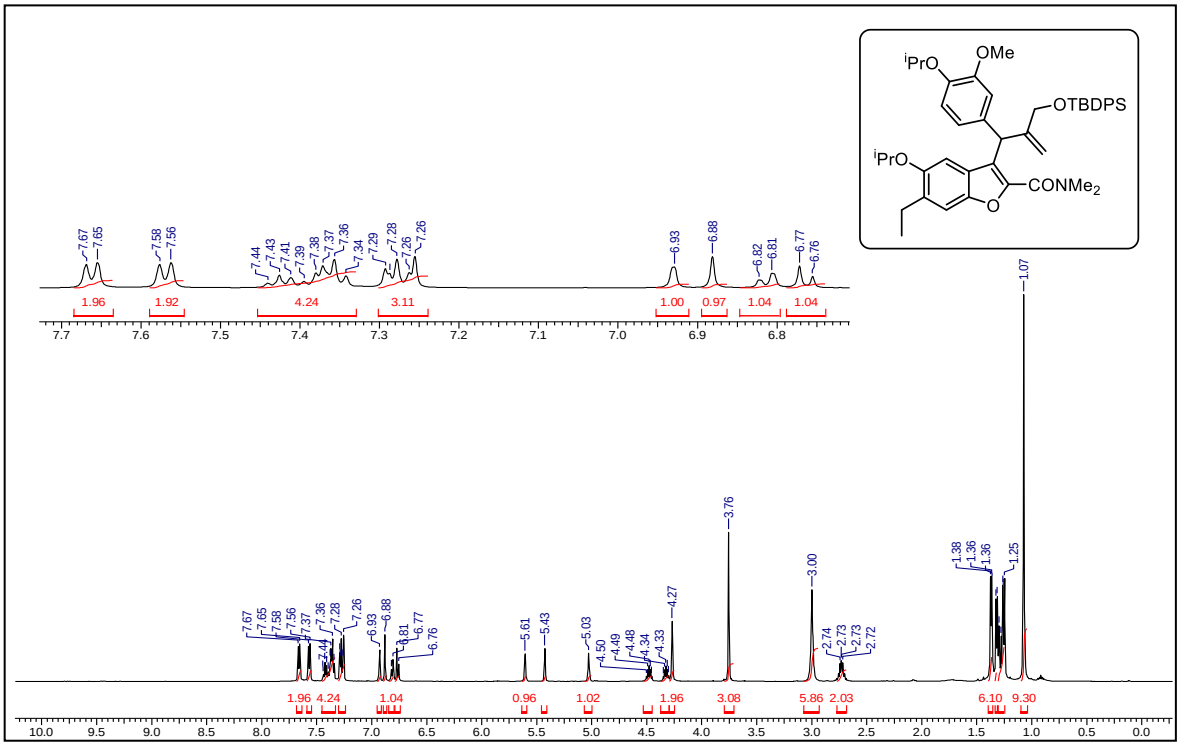
^{13}C NMR Spectrum of 41 in $CDCl_3$



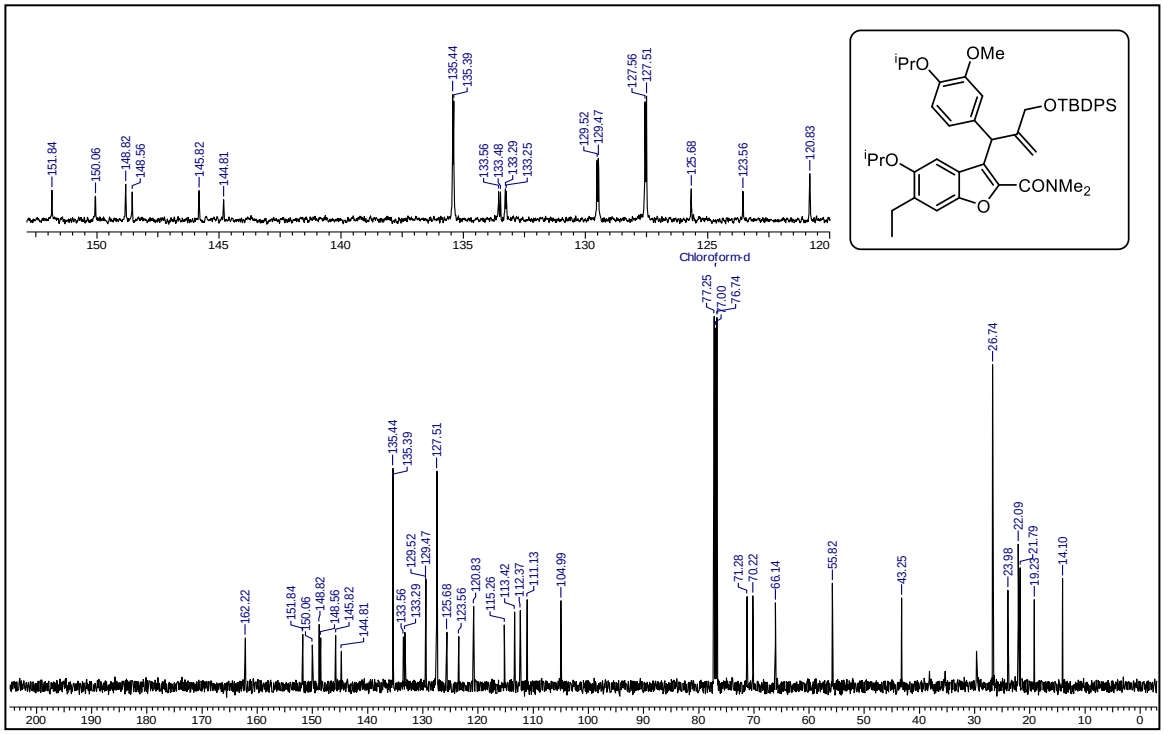
^{1}H NMR Spectrum of 13 in $CDCl_3$



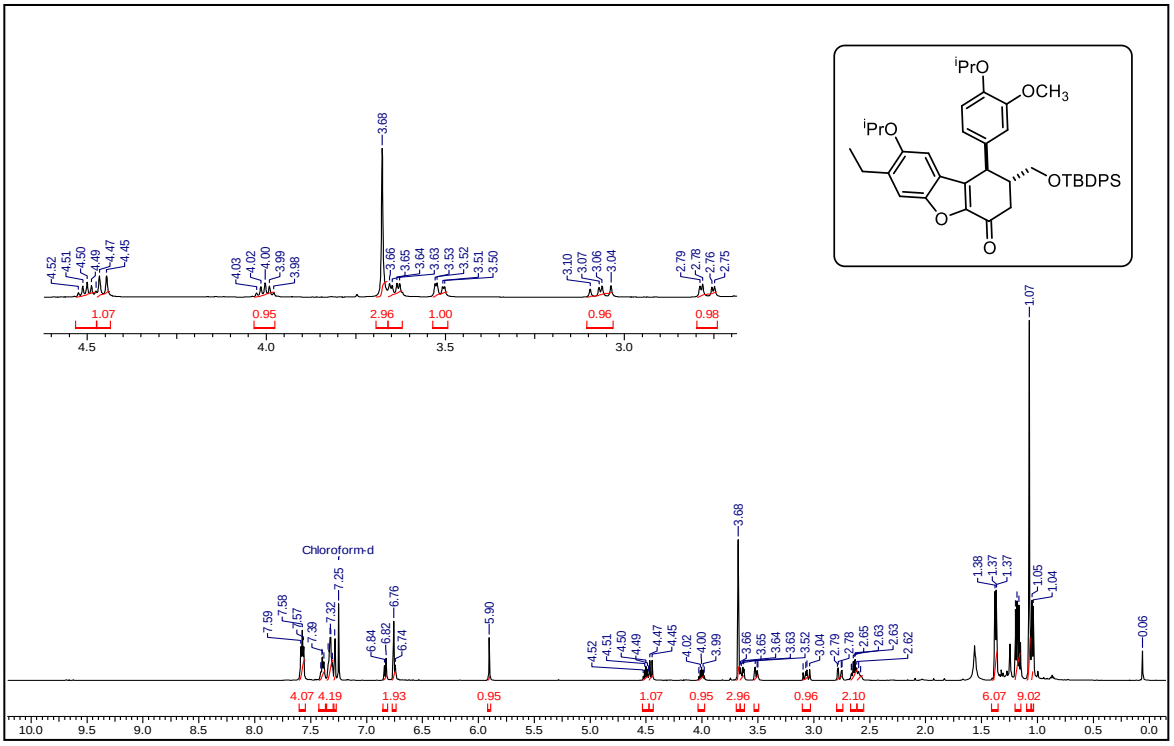
^{13}C NMR Spectrum of 13 in $CDCl_3$



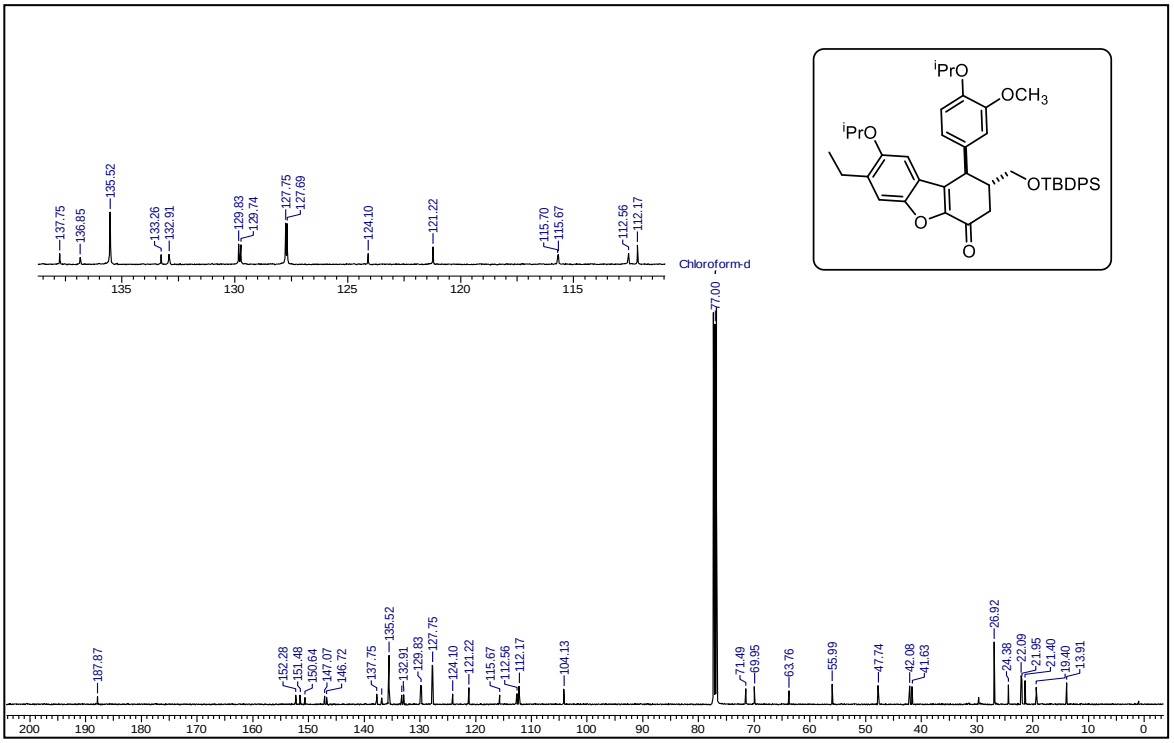
^{1}H NMR Spectrum of 43 in $CDCl_3$



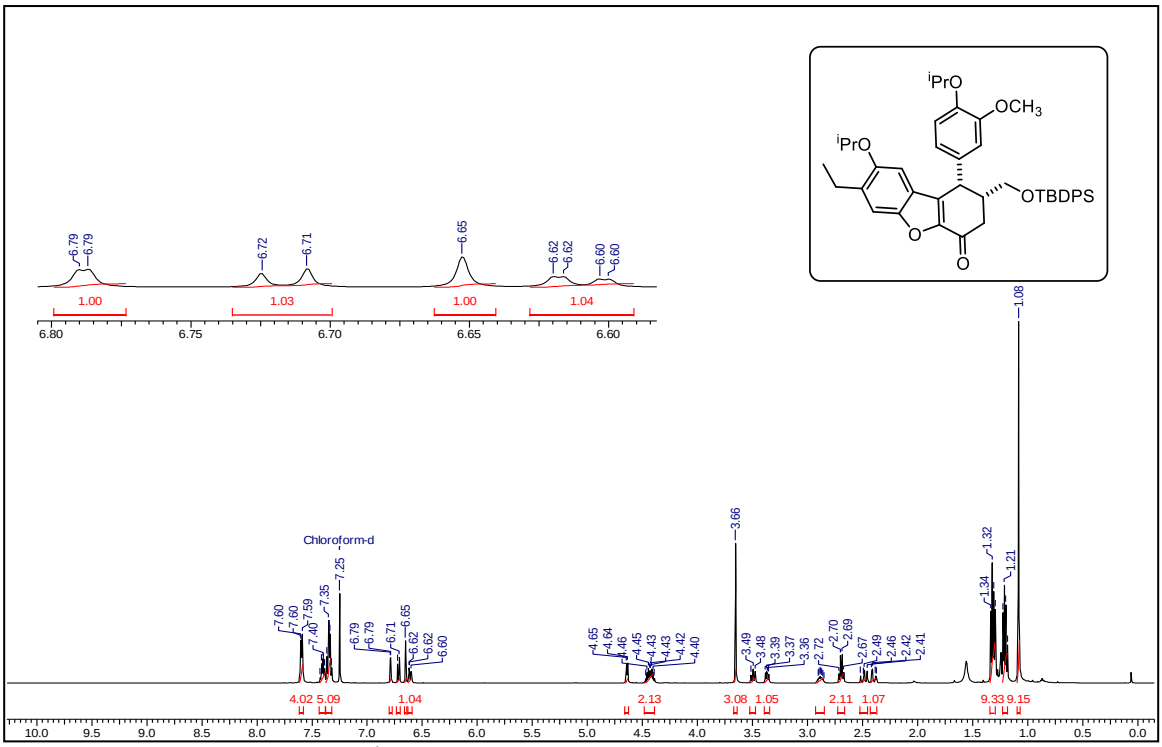
^{13}C NMR Spectrum of 43 in $CDCl_3$



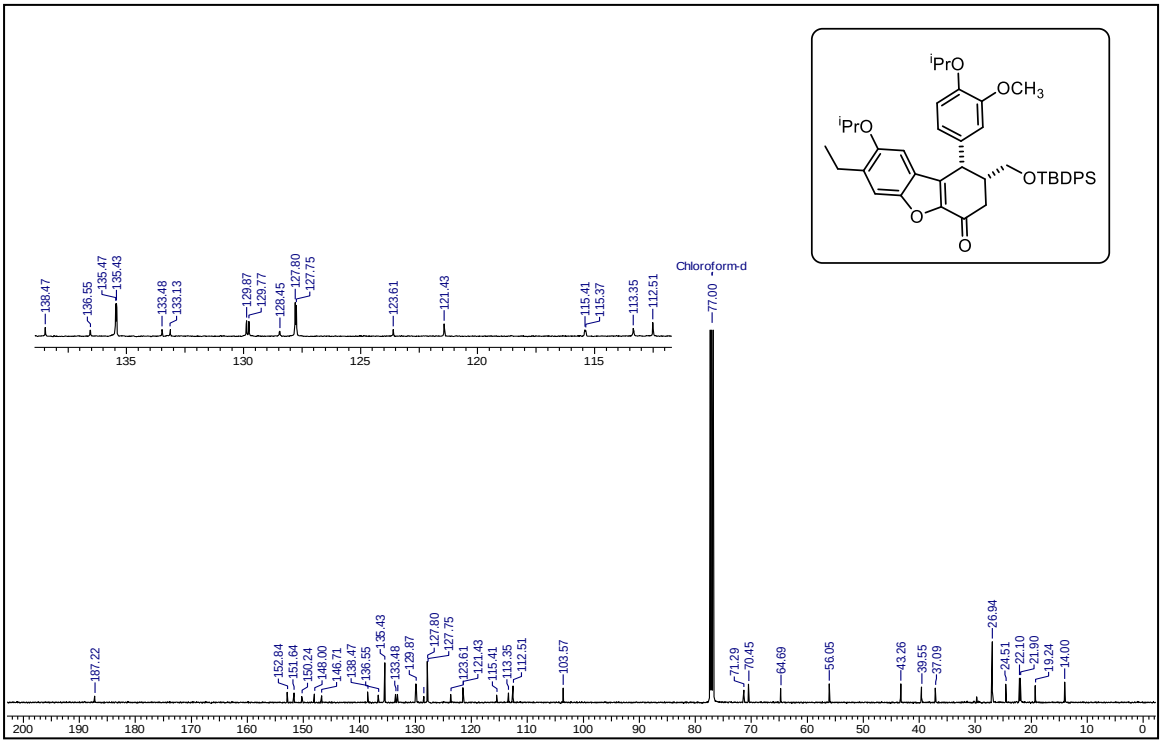
^{1}H NMR Spectrum of *trans*-12 in $CDCl_3$



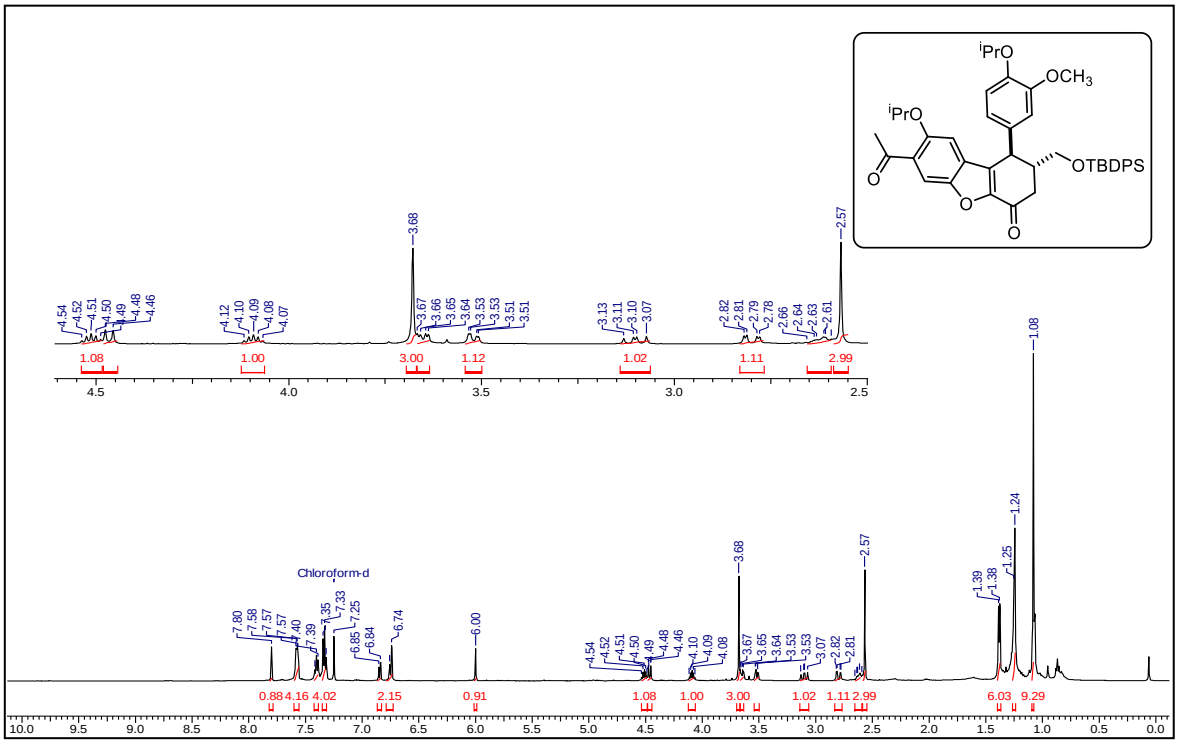
^{13}C NMR Spectrum of *trans*-12 in $CDCl_3$



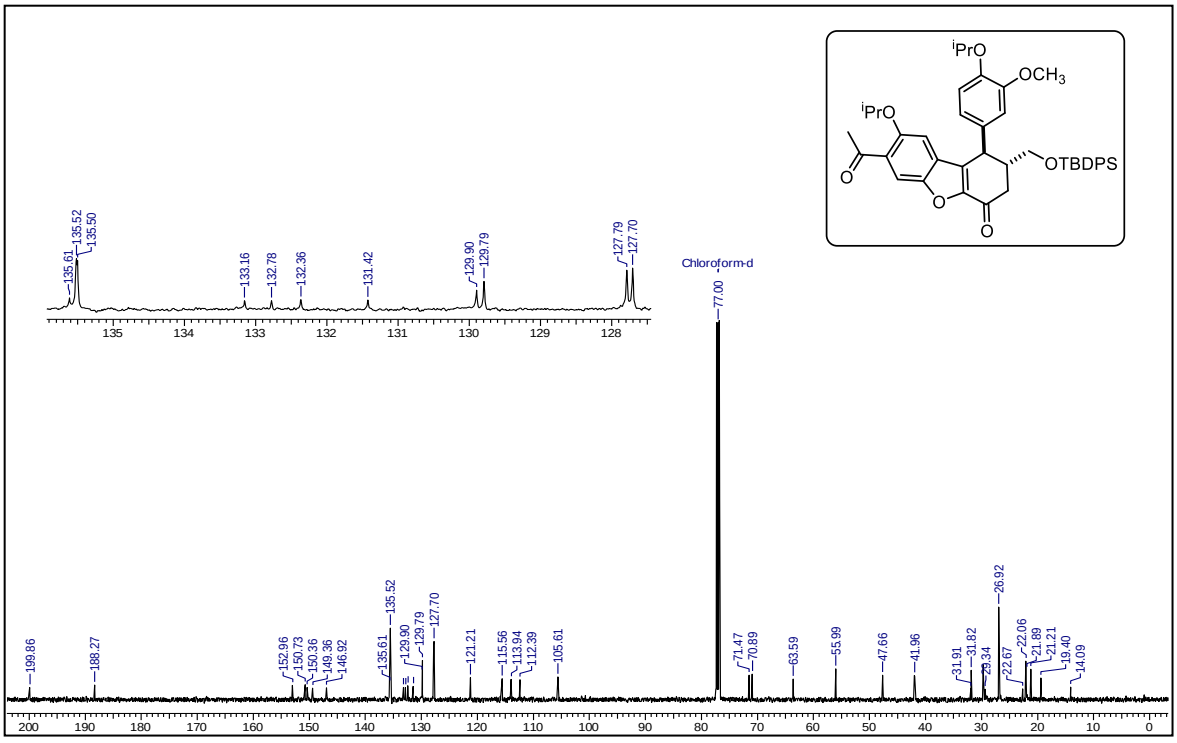
^{1}H NMR Spectrum of *cis*-12 in $CDCl_3$



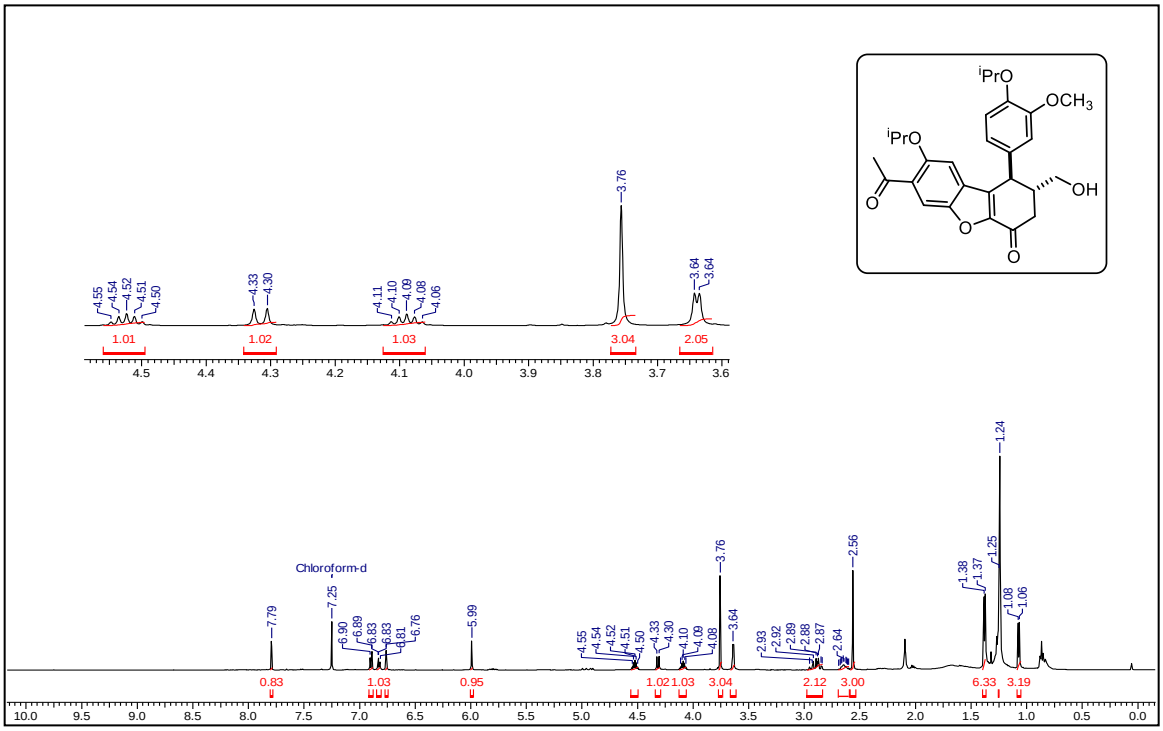
^{13}C NMR Spectrum of *cis*-12 in $CDCl_3$



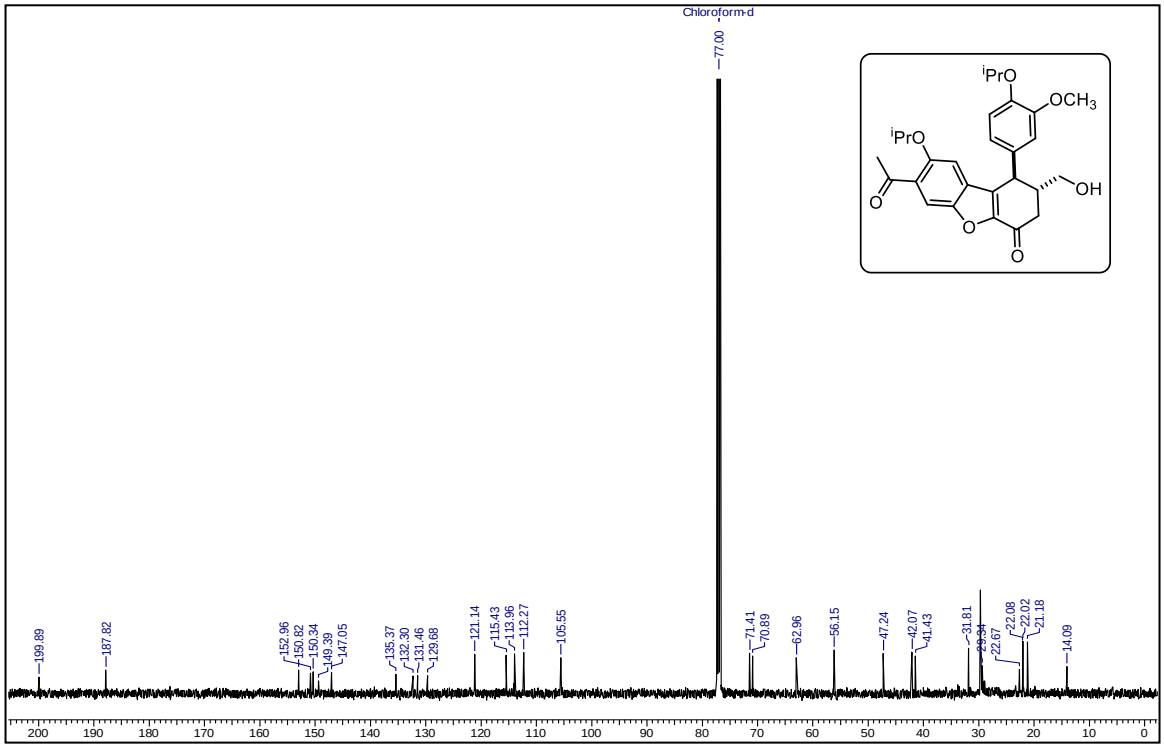
^{1}H NMR Spectrum of 44 in $CDCl_3$



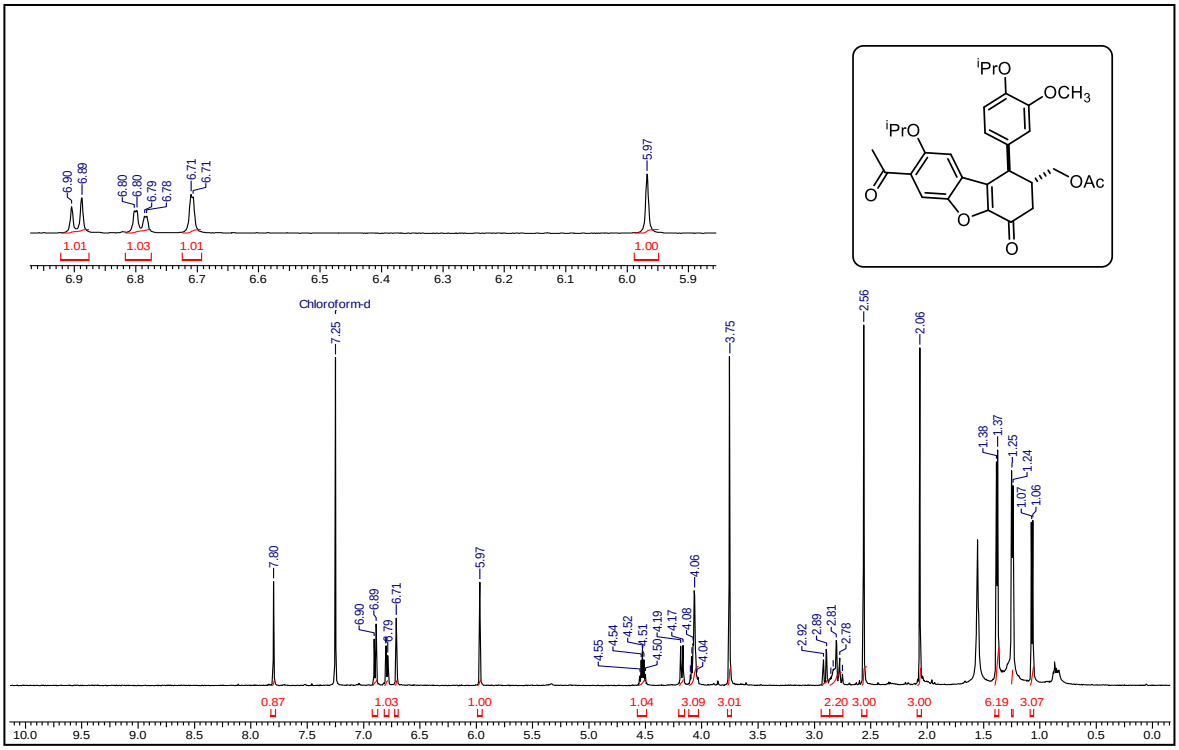
^{13}C NMR Spectrum of 44 in $CDCl_3$



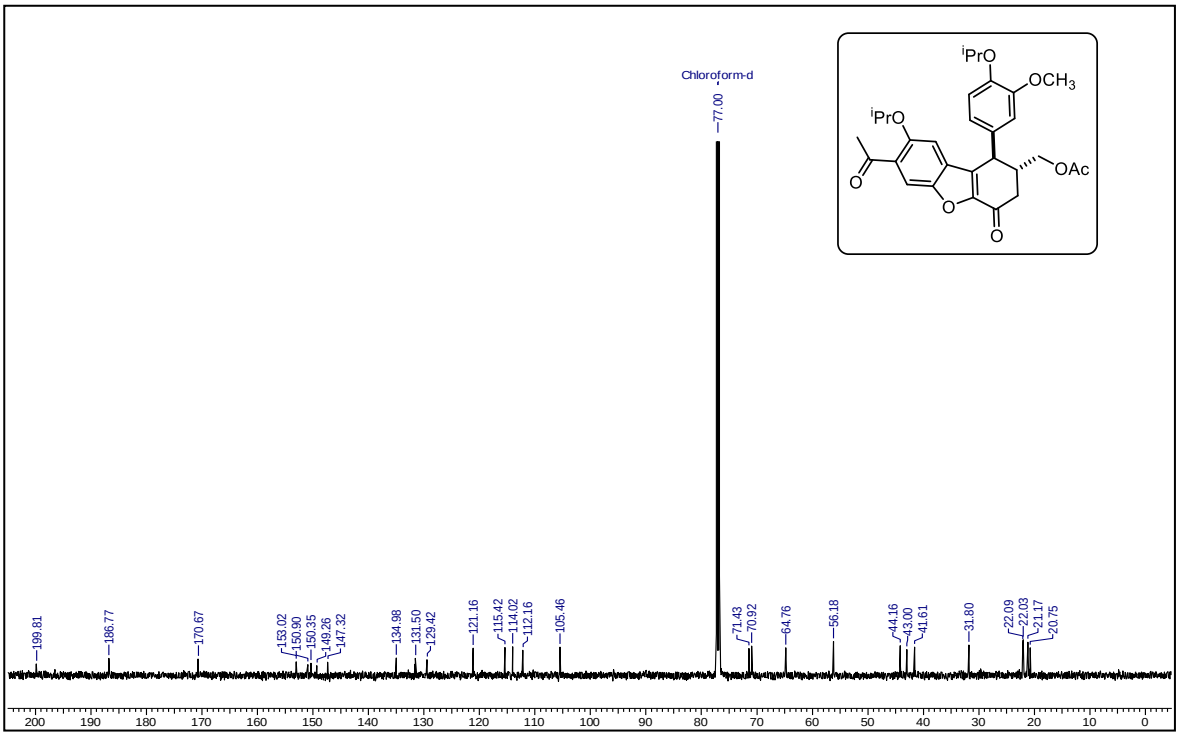
^{1}H NMR Spectrum of 45 in $CDCl_3$



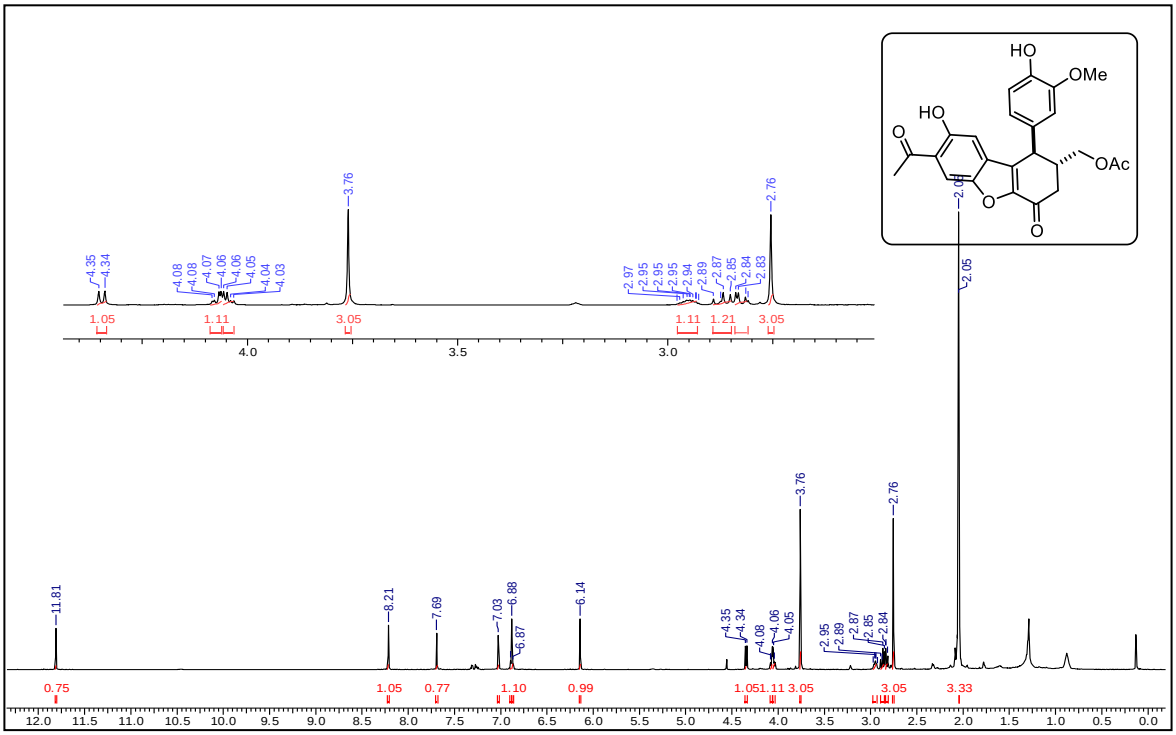
^{13}C NMR Spectrum of 45 in $CDCl_3$



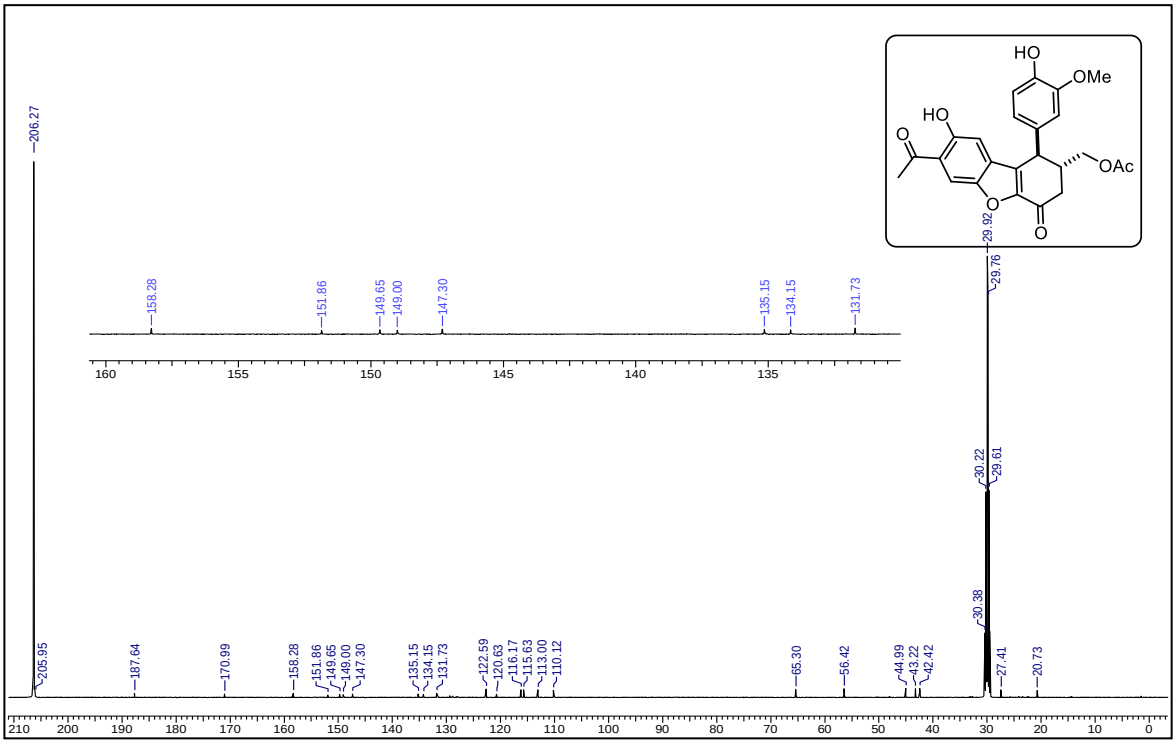
^{1}H NMR Spectrum of 46 in $CDCl_3$



^{13}C NMR Spectrum of 46 in $CDCl_3$



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



^{13}C NMR Spectrum of 1 in $CDCl_3$

1. "Total Synthesis of Propolisbenzofuran B" **Kolluru Srinivas** and Chepuri V. Ramana, *Org. Lett.* (ASAP)

2. "Interrupting Base-Mediated Benzofuran Ring Transformation with Michael Acceptors" **Kolluru Srinivas**, Rashmi Sharma and Chepuri V. Ramana, *J. Org. Chem.* **2017**, *82*, 9816–9823.

3. "Electronic Control on Linear *vs* Branched Alkylation of 2-/3-Aroylbenzofurans with Acrylates: Combined DFT and Synthetic Studies" **Kolluru Srinivas**, Yuvraj B. Dangat, Kumar Vanka and Chepuri V. Ramana, *Chem. Eur. J.* **2017**, *23*, 7570–7581.

4. "Ru-Catalyzed Branched *vs* Linear Selective C3-alkylation of 2-Aroylbenzofurans with Acrylates via C–H Activation" Yadagiri Kommagalla, **Kolluru Srinivas** and Chepuri V. Ramana, *Chem. Eur. J.* **2014**, *20*, 7884–7889.

5. "Cu-Catalyzed Sequential C–N Bond Formations: Expeditious Synthesis of Tetracyclic indoloindol-3-ones" Anand M. kulkarni, **Kolluru Srinivas**, Mukund V. Deshpande and Chepuri V. Ramana, *Org. Chem. Front.* **2016**, *3*, 43–46.

6. "Target Cum Flexibility: Simple Access to Benzofuran Conjugated Sugar Nucleoside derivatives" Yadagiri Kommagalla, **Kolluru Srinivas** and Chepuri V. Ramana, *Tetrahedron Lett.* **2013**, *54*, 1824–1827.

7. "Ruthenium Catalyzed alkylation of 3-formylbenzofurans with acrylates" **Kolluru Srinivas**, Jyothi Mudaliar and Chepuri V. Ramana (*Manuscript under Preparation)*

8. "Synthesis of Indene Conjugated Sugar Nucleosides by rhodium catalyzed Cyclotrimerization strategy" **Kolluru Srinivas**, Manmath Bhusse and Chepuri V. Ramana (*Manuscript under Preparation*)

Patents:

1. "A process for the preparation of anti-inflammatory aroylbenzofuran compounds" Yadagiri Kommagalla, **Kolluru Srinivas** and Chepuri V. Ramana, **US 2016/0229827 A1**

2. "Novel Stereospecific synthesis of (-) (*2S,3S*)-1-Dimethylamino-3-(3-methoxyphenyl)-2-methyl pentan-3-ol" Dodda Mohan Rao, Pingili Krishnareddy, Pingili Ramachandrareddy, Kirla Haritha, **Kolluru Srinivas, US 2013/0296608 A1**