Organophosphine Catalyzed Intramolecular Morita-Baylis-Hillman Reaction

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A dissertation submitted for the partial fulfilment of BS-MS dual degree in science

Indian Institute of Science Education and Research Mohali,
April 2019

Dedicated to my parents and beloved friends

Certificate of Examination

This is to certify that the dissertation titled "***Organophosphine catalyzed intramolecular Morita-Baylis-Hillman reaction of biaryl enone-aldehyde***" submitted by Mr. Pinku Tung (Reg. No. MS14143) for the partial fulfilment of BS-MS dual degree program of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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Dated: April 26, 2019

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. S. S. V. Ramasastry at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Pinku Tung

(Candidate)

Dated: April 26, 2019

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

Dr. S. S. V. Ramasastry

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Acknowledgment

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Pinku Tung

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Notations and Abbreviations

δ	Chemical shift in ppm
d	doublet
dd	doublet of doublet
ESI	Electron Spray Ionization
EtOAc	Ethyl acetate
HRMS	High Resolution Mass spectrometry
IR	Infra-red
M	multiplet
MeCN	Acetonitrile
NMR	Nuclear magnetic resonance
Pd	Palladium
ppm	parts per million
S	singlet
t	triplet
TLC	Thin layer chromatography

Abstract

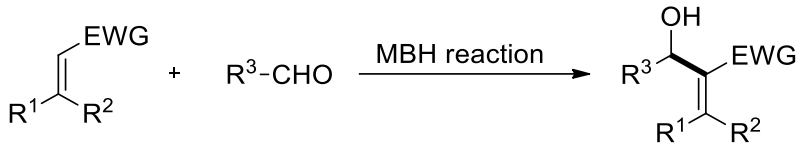
Here we present an organophosphine catalyzed intramolecular Morita-Baylis-Hillman (IMBH) reaction of biaryl enone-aldehyde. The reaction leads to the formation of cyclohepta-fused biaryls bearing arenes and heteroarenes. The reaction occurs at a mild condition, and the substrates are tolerant of a variety of functional groups. An atroposelective Suzuki reaction can be carried out during the starting material synthesis which can deliver an asymmetric IMBH product of various synthetic utility. Towards this different methods have been employed. However, the methods remain quite ineffective in affording either yield or enantioselectivity. Further study on this aspect is underway.

Introduction

1.1 *A general introduction to Morita-Baylis-Hillman reaction:*

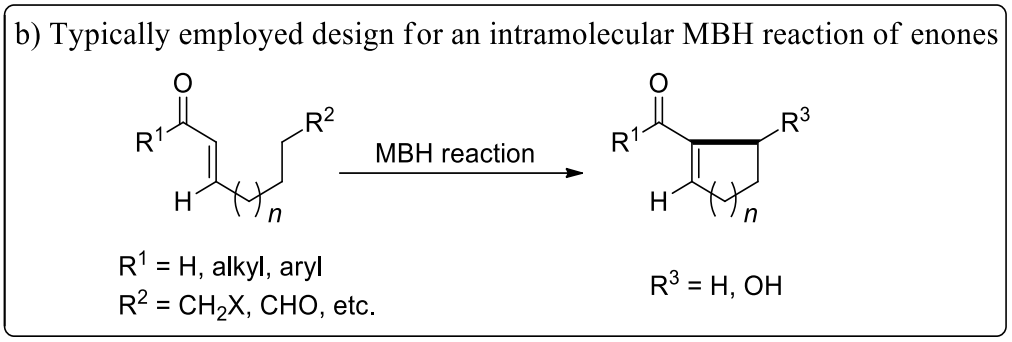
The development of efficient and sustainable methods for the formation of C-C bond has been the lofty goal of chemists over the years. Towards this, many metal mediated coupling reactions have been explored. However, considering the toxicity aspect associated with different metals, synthetic chemists have started focusing on organocatalytic construction of C-C bonds. The Morita-Baylis-Hillman reaction is one of the widely used organocatalytic C-C bond forming reactions (Scheme 1). The reaction proceeds through a sequence of Michael addition of nucleophile over an activated alkene to generate enolate which is then trapped by the electrophile in aldol fashion. Finally, a proton transfer occurs, and subsequent elimination of the catalyst leads to the MBH adduct. This atom-economical reaction offers a variety of advantages by generating a chiral center and many other valuable adducts. [1]

a) General representation of an intermolecular MBH reaction



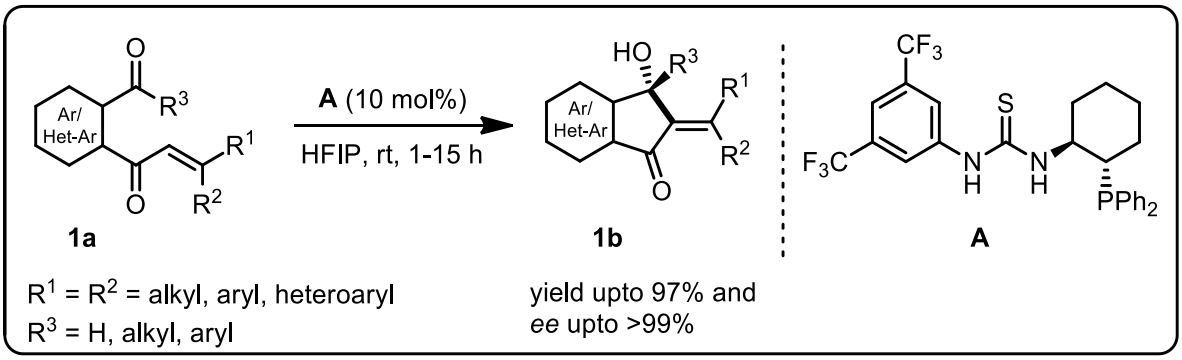
Scheme 1

Intramolecular Morita-Baylis-Hillman (IMBH) has attracted the chemists owing to its potential of providing various rings (Scheme 2). Judicious design of substrate can lead to various annulated products that are abundant core in many natural and non-natural products.



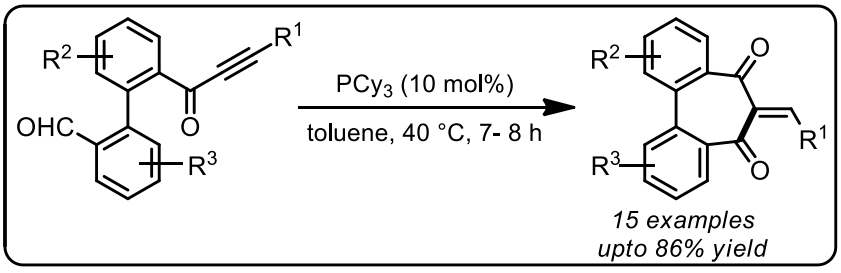
Scheme 2

Our group has previously reported a study where an organocatalytic IMBH reaction of *β,β*-disubstituted enones.[2] This method delivered a variety of cyclopenta[*b*]annulated arenes and heteroarenes in excellent yields and near enantiopurities in remarkably short reaction times (Scheme 3).



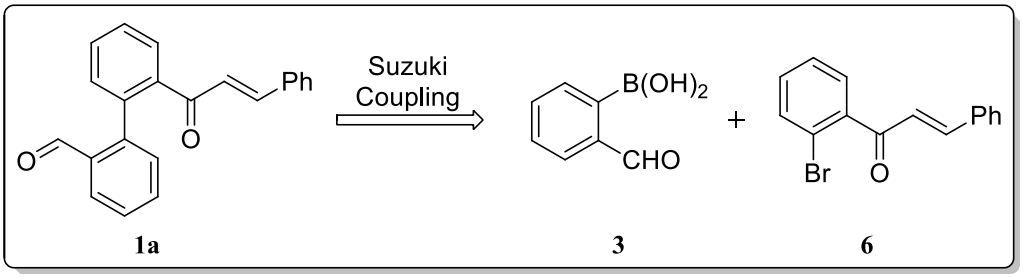
Scheme 3: IMBH reaction of *β,β*-disubstituted enones

In another study, an organophosphine catalyzed IMBH of an activated alkyne was carried out. The overall outcome is a hydroacylated product of *α,β* ynones leading to the formation of 1,3-cyclopenta-, cyclohepta-, and cyclooctadione-fused arenes and heteroarenes (Scheme 4). The method was very well tolerated with both electron donating and withdrawing substituents and provided an excellent yield.[3]

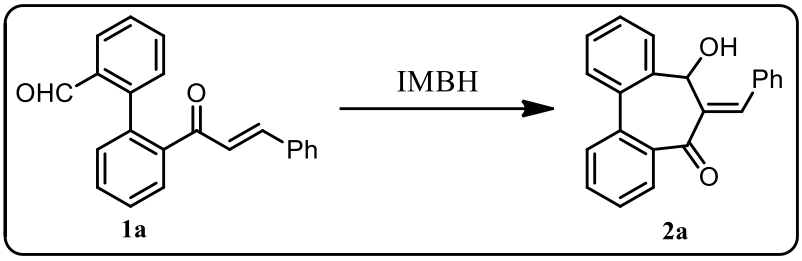


Scheme 4: IMBH of ynone-aldehyde

Motivated by these two studies, we designed our model substrate **1a** which can be obtained by a formal Suzuki coupling of boronic acid **3** and 2-bromo enone **6** (Scheme 5). We hypothesized that the treatment of **1a** in the presence of a catalytic amount of organophosphine can generate the heptannulated product **2a** (Scheme 6).



Scheme 5: Substrate design for the current study



Scheme 6: Possible outcome based on the hypothesis

The product **2a** can be further elaborated to some relevant natural products namely subamol,[4] colchicine,[5] steganacin[6] (Figure 1) etc. possessing immense biological activity.

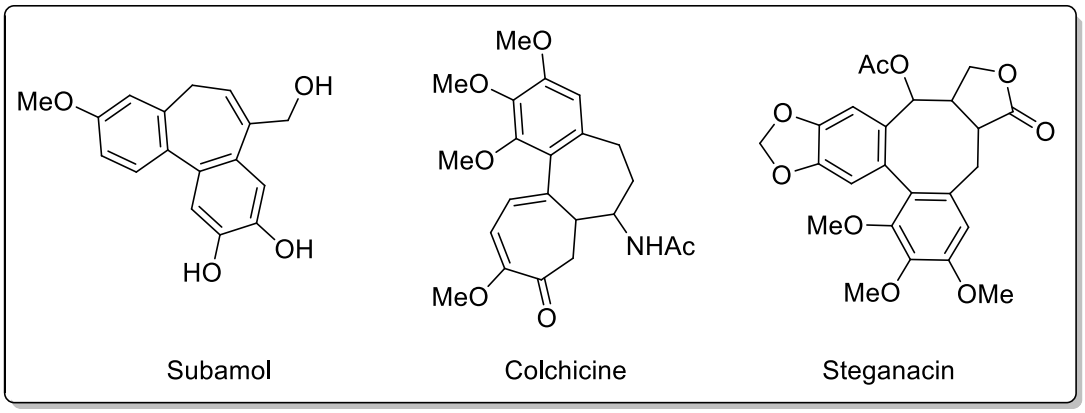
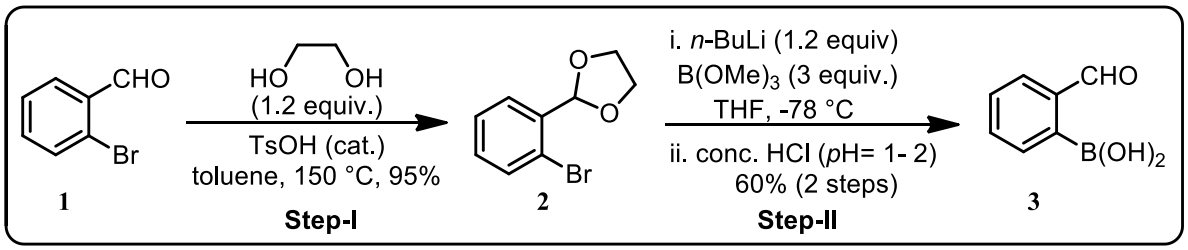


Figure 1

Result and Discussion

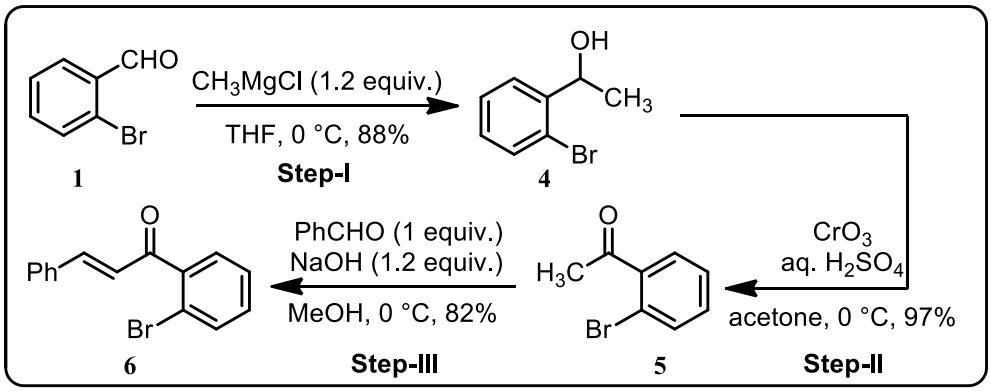
2.1 *Synthesis of the starting material* 1a*:*

To substantiate our hypothesis, we started synthesizing the starting material **1a** for the study following a known procedure. A parallel synthesis strategy was employed at this outset. This involves the synthesis of (2-Formylphenyl)boronic acid by using a two-step protocol. First, the protection of 2-bromo benzaldehyde was carried out. Protected 2-bromo benzaldehyde was then subjected to n-BuLi and trimethyl borate condition followed by acidic work up to deliver the desired product **3** (Scheme 7).[3]



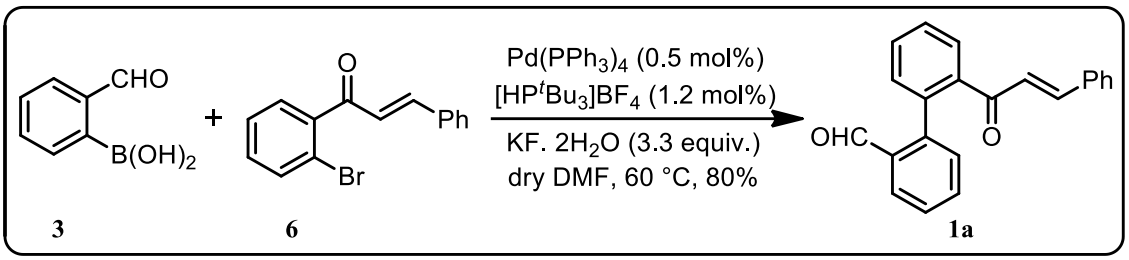
Scheme 7: Synthesis of (2-Formylphenyl)boronic acid

The synthesis of 2-bromo enone can be achieved by a three-step procedure. Methyl Grignard addition to 2-Bromo benzaldehyde **1**, followed by Jones oxidation and subsequently an aldol condensation reaction with benzaldehyde can deliver the desired 2-bromo enone **6** (Scheme 8).[7]



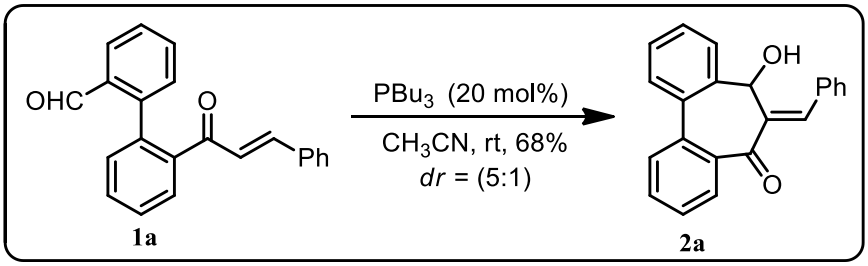
Scheme 8: Synthesis of (*E*)-1-(2-Bromophenyl)-3-phenylprop-2-en-1-one

Compound **3** and **6** were then subjected to Suzuki coupling condition to afford the desired biaryl enone-aldehyde starting material **1a** (Scheme 9).[3]



Scheme 9: Synthesis of biaryl enone aldehyde *via* Suzuki coupling

Later the starting material **1a** was subjected to the catalytic amount of organophosphine PBu_3 (20 mol%) in acetonitrile solvent at room temperature delivering product **2a** with 68% yield. However, the reaction did not go to completion even after 72 hours. The product was isolated and characterized using different spectroscopic tools.

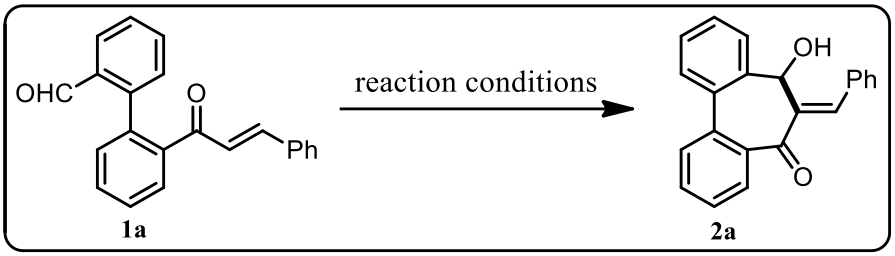


Scheme 10: Organophosphine catalyzed IMBH of biaryl enone-aldehyde

2.2 *Optimization of reaction conditions:*

The next focus was to optimize the reaction condition to improve the reaction yield (Table 1). For that various phosphine catalysts (20 mol%) were screened in acetonitrile solvent at room temperature. However, all other phosphine except tributylphosphine could not deliver the desired product. Then keeping the catalyst fixed, different solvents were screened, and it was found that in both DMF and DMSO solvents, the reaction goes to completion in almost the same time and provides similar yields. Further studies were carried out in DMF solvent. The reaction has been performed with 10 mol% of catalyst giving the same yield as 20 mol%, but considering the practical difficulty, we proceeded with 20 mol% of the catalyst. After a careful evaluation, it was observed that PBu_3 (20 mol%) in DMF at room temperature was optimum for this transformation.

Table 1: Optimization of reaction parameters

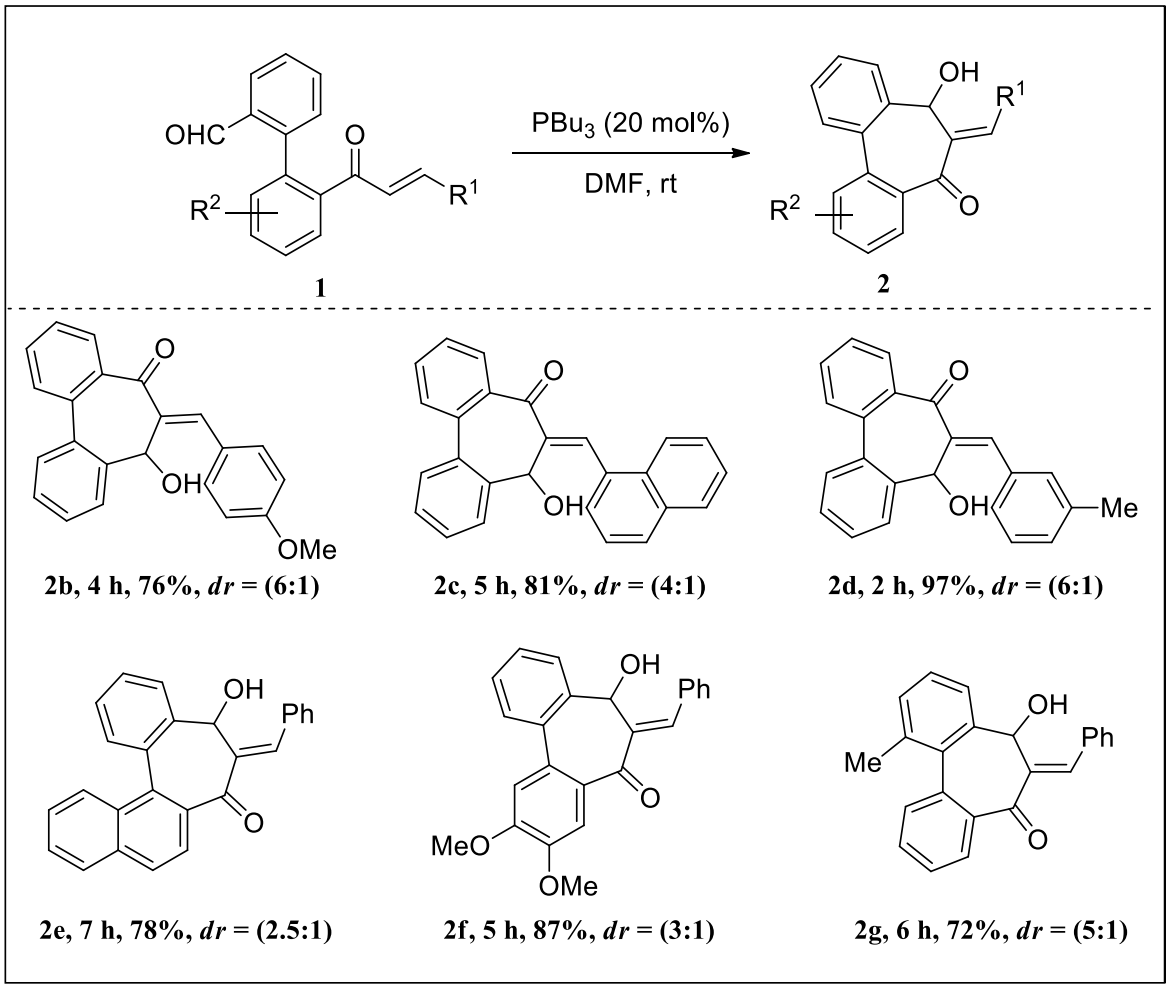


Sl. No.	Phosphine (mol%)	Solvent	Time (h)	Yield (%)
1	PPh_3 (20)	ACN	14	no reaction
2	PCy_3 (20)	ACN	14	no reaction
3	$PEtPh_2$ (20)	ACN	14	no reaction
4	PBu_3 (20)	DCM	31	60
5	PBu_3 (20)	Toluene	28	68
6	**PBu_3 (20)**	**DMF**	**7**	**85**
7	PBu_3 (20)	DMSO	7	86
8	PBu_3 (20)	HFIP	24	no reaction
9	PPh_3 (20)	DMF	24	no reaction
10	PCy_3 (20)	DMF	24	no reaction
11	$PEtPh_2$ (20)	DMF	24	no reaction
12	PBu_3 (10)	DMF	7	88

2.3 *Substrate scope:*

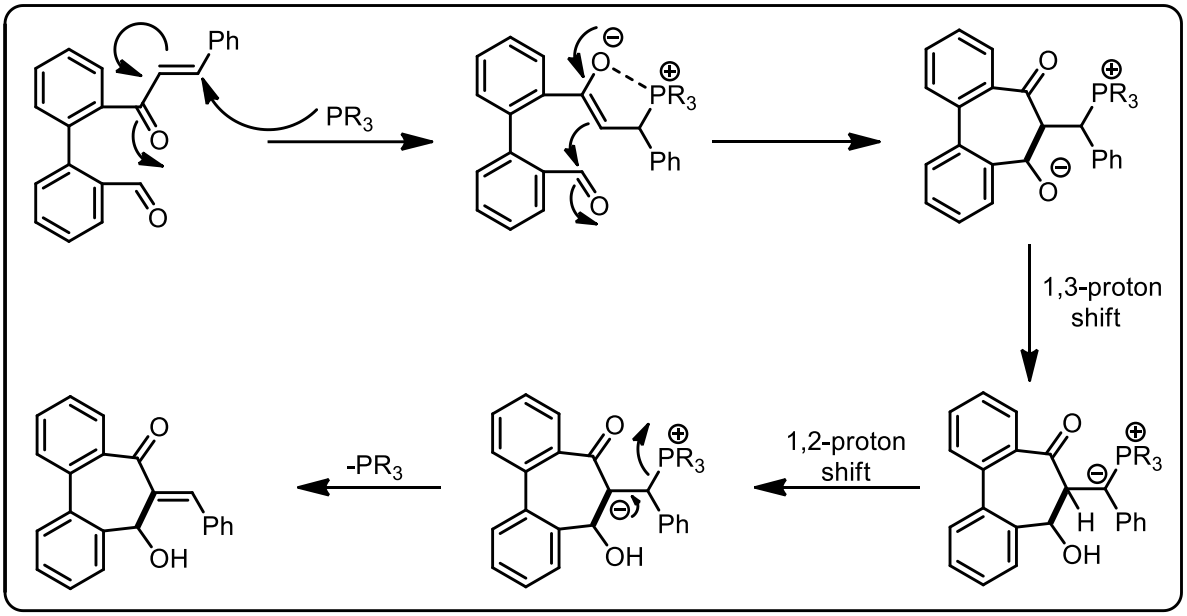
With the optimized condition in hand, we examined the suitability of different substrates (Table 2). It was observed that different substituents at the enone fragment regardless of their electronic nature delivered moderate to good yield in a short time.

Table 2: Substrate scope



2.4 *Plausible mechanism:*

The mechanism for the transformation can be explained through general MBH reaction mechanism (Scheme 11). A phosphine nucleophile adds in 1,4 fashion onto the enone system generating a stable zwitterionic interaction. The enolate generated in the process then attacks the aldehyde electrophile in an intramolecular fashion. Then a 1,3 proton shift followed by a 1,2 proton shift and subsequent elimination of phosphine catalyst generate the desired MBH product.



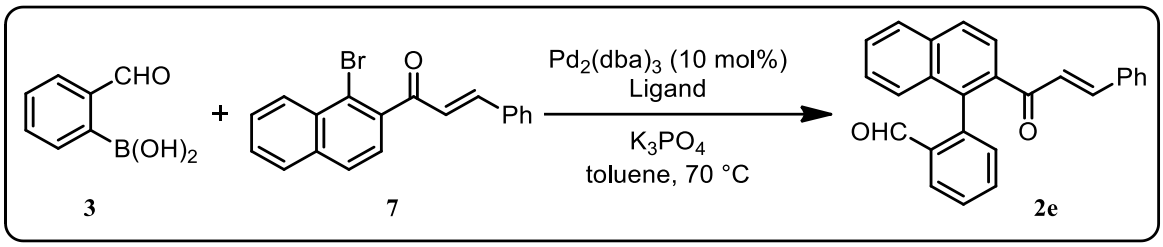
Scheme 11: Plausible mechanism for IMBH of biaryl enone-aldehyde

2.5 *Enantioselective IMBH via atroposelective Suzuki coupling:*

After establishing the racemic study, efforts were made to obtain an enantioselective variant for the MBH product. For that, we envisioned an atroposelective Suzuki coupling reaction to get axially chiral starting material and subsequently the MBH reaction to get the desired chiral compound with significant synthetic utility. A variety of substrates were chosen to carry out the asymmetric Suzuki coupling reaction. Here we discuss several strategies that were employed to substantiate our goal.

Strategy I:

We initiated the enantioselective study on naphthalene enone **7**. Several chiral organophosphine catalysts (Figure 2) were screened in presence of Pd catalyst at 70 °C in toluene solvent (Scheme 12). The reaction did not attain completion, and the product formation was found to be very small. However, in few cases we observed a slight amount of enantiopurity, but there was no improvement in the yield (Table 3).



Scheme 12: Synthesis of atroposelective naphthyl-phenyl enone-aldehyde

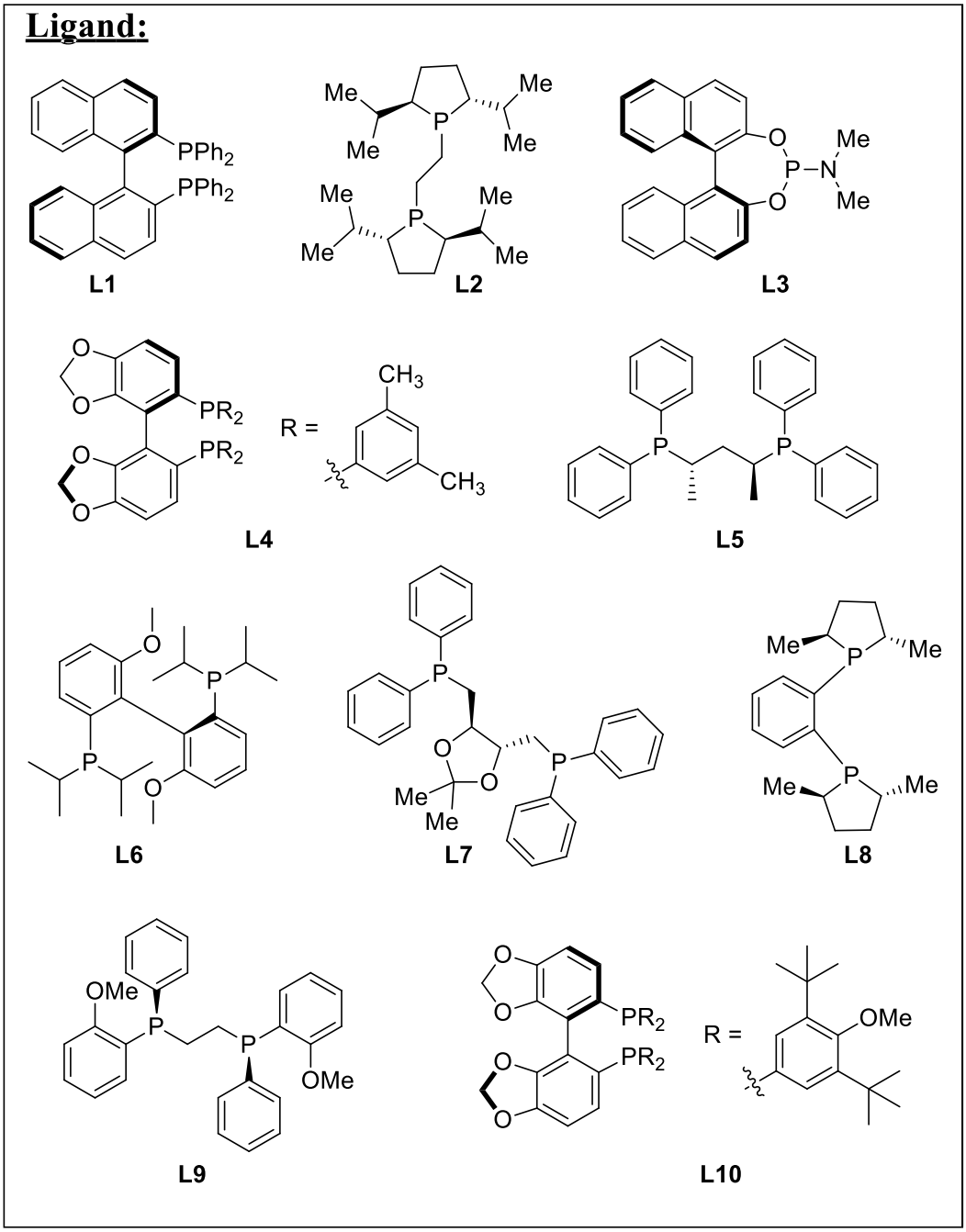


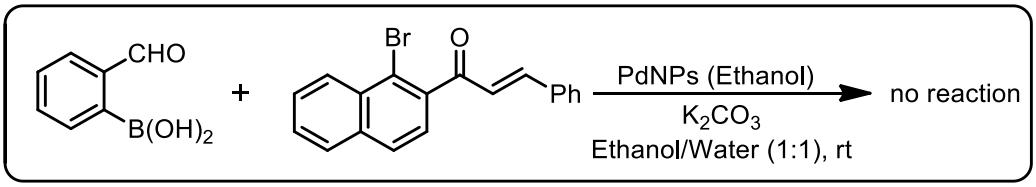
Figure 2

Table 3: Chiral ligand screening

Sl. No.	Ligand (20 mol%)	Time (h)	Yield (%)	*ee* (%)
1	L1	48	Trace	0
2	L2	48	Trace	0
3	L3	48	Trace	0
4	L4	48	Trace	8
5	L5	48	Trace	0
6	L6	48	-	-
7	L7	48	Trace	0
8	L8	48	Trace	0
9	L9	48	20	50
10	L10	48	Trace	13

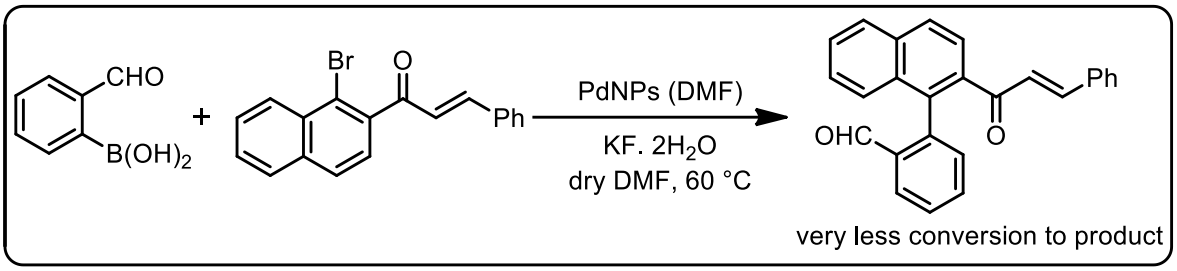
We also thought of introducing chiral Pd nanoparticle for inducing chirality at the Suzuki coupling step.[8] A few racemic conditions were employed (Scheme 13 and Scheme 14), but the conditions were not very feasible for the transformation.

Condition 1:



Scheme 13: Pd nanoparticle-mediated Suzuki coupling

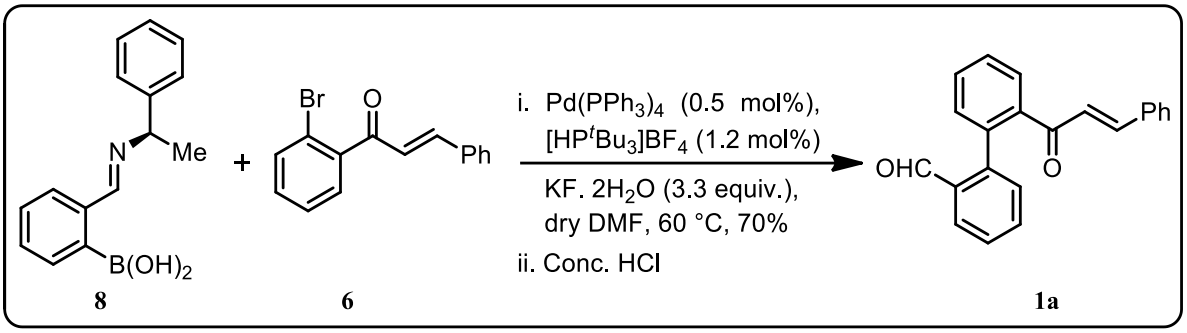
Condition 2:



Scheme 14: Pd nanoparticle-mediated Suzuki coupling

Strategy II:

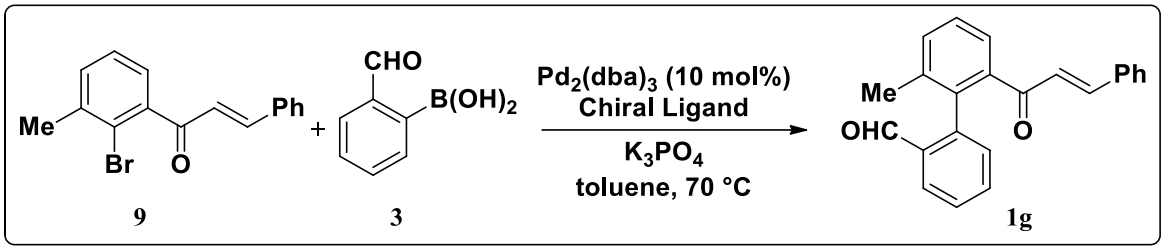
Our next strategy was focused on making the boronic acid fragment chiral instead of employing chiral ligand. For that, the formyl boronic acid was protected with chiral amine (*S*)-(-)-α-Methylbenzylamine[9], and subsequently coupled with the bromo enone fragment (Scheme 15). The desired product **1a** was obtained with good yield after an acidic workup. However, we could not separate the product through the HPLC column. Therefore, the enantioselectivity remained unknown for the method. The same strategy was employed for a few other bromo enone fragments, but the reactions did not proceed in these cases.



Scheme 15: Suzuki coupling between chiral imine and enone

Strategy III:

We thought of introducing an *ortho*-methyl substituent to the bromo enone fragment **9** for the chiral induction (Scheme 16). When the substrate was subjected to chiral coupling condition, the reaction rate was found to be very slow, and a trace amount of product formation was observed. Therefore further study with this substrate was terminated.



Scheme 16: Suzuki coupling between 3-Methyl-2-bromo enone and boronic acid

Experimental Section

General experimental methods:

All the starting compounds and catalysts employed in this study were procured from Sigma-Aldrich and were used without further purification. For thin layer chromatography (TLC), silica aluminium foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Column chromatography was performed using SD Fine silica gel 100-200 mesh (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium and stored over sodium wire. IR spectra were recorded on a Perkin–Elmer FTIR spectrometer as thin films or KBr pellet, as indicated, with ν_{max} in inverse centimetres. Melting points were recorded on a digital melting point apparatus Stuart SMP30 and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz BrukerBiospinAvance III FT-NMR spectrometer. NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Proton chemical shifts are given in δ relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$.Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.1 ppm). High-resolution mass spectra were recorded on a Waters QTOF mass spectrometer. Enantiomeric excess was determined by using Waters Chiral HPLC.

3.1 General Procedure 1: Synthesis of (2-formylphenyl)boronic acid.

(2-Formylphenyl)boronic acid can be synthesized using a two-step protocol.

Representative Procedure for Step I (Scheme 7)

In an oven dried RB flask 2-Bromobenzaldehyde (20 mmol) was dissolved in 20 mL of toluene. Ethylene glycol (24 mmol) was added to it with a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was then subjected to reflux condition at 150 °C with a Dean-Stark apparatus for 7 h. The reaction mixture was then carefully quenched with triethylamine. The reaction mixture was concentrated under reduced pressure and then subsequently extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40-50% EtOAc/hexane) to afford 2-(2-bromophenyl)-1,3-dioxolane.

Representative Procedure for Step II (Scheme 7):

To a 25 mL long neck RB flask equipped with a magnetic stir bar was added 2-(2-bromophenyl)-1,3-dioxolane (5 mmol), dry THF (10 mL) under N_2 atmosphere and stirred at -78 °C for 10 minutes. n-BuLi (1.6M in hexane, 6 mmol) was added dropwise to the above solution and the stirring was continued for 1 h. The trimethyl borate (24 mmol) was then introduced to the reaction mixture at the same temperature and stirred for 1 h. The reaction mixture was kept at room temperature for 5-6 h and then quenched with conc. HCl until the reaction mixture reached *p*H=2 and then extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified using silica gel column chromatography to get the desired (2-Formylphenyl)boronic acid **3**.

3.2 General Procedure 2: Synthesis of 2-bromo enones.

The bromo enone fragment for the compounds **1a**-**1g** was synthesized by using the following three-step protocol. For the different enone backbones, corresponding bromo aldehydes compounds were used.

Representative Procedure for Step I (Scheme 8):

In an oven dried RB flask equipped with magnetic stir bar 2-Bromobenzaldehyde (5 mmol) was dissolved in 10 mL of THF under N_2 atmosphere at 0 °C. To the solution, methylmagnesium chloride (3M in THF, 6 mmol) was added dropwise, and the reaction mixture was allowed to stir for 1 h. The mixture was then quenched with aq. NH_4Cl and subsequently extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-(2-Bromophenyl)ethanol.

Representative Procedure for Step II (Scheme 8):

Chromium trioxide (30 mmol) was dissolved in conc. H_2SO_4 (30 mmol) and H_2O (90 mmol) in an ice bath. This mixture was then added dropwise to 1-(2-Bromophenyl)ethanol in acetone at 0 °C. The reaction was allowed to stir until the TLC showed the complete oxidation of the alcohol. The reaction mixture was then concentrated under reduced pressure to get rid of the acetone and subsequently extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to deliver 1-(2-Bromophenyl)ethanone.

Representative Procedure for Step III (Scheme 8):

In an oven dried RB flask equipped with magnetic stir bar 1-(2-Bromophenyl)ethanone (2.25 mmol) was dissolved in 10 mL of MeOH under at 0 °C. To the solution, benzaldehyde (2.25 mmol) and sodium hydroxide (2.7 mmol) were added. The mixture was allowed to stir for 4-5 hours. The mixture was then concentrated under reduced pressure and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford (*E*)-1-(2-Bromophenyl)-3-phenylprop-2-en-1-one **6**.

3.3 General Procedure 3: Synthesis of biaryl enone-aldehyde.

The biaryl compounds **1a**-**1g** were synthesized via Suzuki coupling as discussed below.

Representative Procedure (Scheme 9):

In an oven dried seal tube (*E*)-1-(2-Bromophenyl)-3-phenylprop-2-en-1-one (1 mmol), (2-Formylphenyl)boronic acid (2 mmol), $Pd(PPh_3)_4$ (0.5 mol%), $[HP^tBu_3]BF_4$ (1.2 mol%) and KF. $2H_2O$ (3.3 mmol) were dissolved in dry DMF under an inert atmosphere. The reaction mixture was kept for stirring for 7-8 hours at 60 °C. The mixture was then quenched with ice and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to deliver desired 2'-Cinnamoyl-[1,1'-biphenyl]-2-carbaldehyde **1a** with 80% yield.

3.4 General Procedure 4: Synthesis of IMBH adducts.

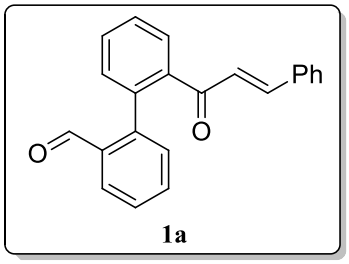
The following method describe the synthesis of the IMBH adducts **2a**-**2g**.

Representative Procedure (Scheme 10):

In a dry vial compound **1a** (10 mmol) was dissolved in dry DMF. Then tributylphosphine (20 mol%) was added to it. The reaction mixture was allowed to stir until the TLC indicated the completion of the starting material. The mixture was then quenched with ice and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to deliver (*E*)-6-Benzylidene-7-hydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one **2a**.

2'-Cinnamoyl-[1,1'-biphenyl]-2-carbaldehyde (1a).

This compound was prepared by following the general procedure 3 (Scheme 9) and isolated as

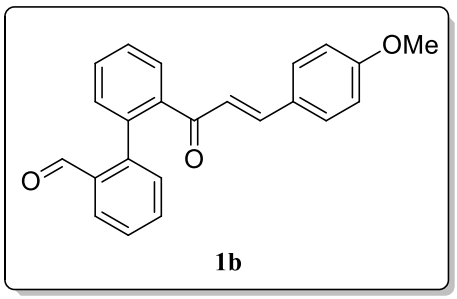


1a

yellow semi solid. R_f = 0.5 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3060.5, 3027.4, 1694.3, 1667.5, 1597.6, 1208.8, 757.9**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.96 (s, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.78-7.76 (m, 1H), 7.60-7.55(m, 3H), 7.49-7.42 (m, 2H), 7.38-7.31 (m, 7H), 6.78 (d, *J* = 15.96 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.6, 191.6, 145.4, 143.9, 140.0, 137.1, 134.2, 134.0, 133.4, 131.7, 131.1, 130.7, 130.5, 128.9 (2C), 128.6, 128.37 (2C), 128.32, 128.2, 128.1, 125.8. **HRMS (ESI):** *m/z* calculated for $C_{22}H_{16}O_2$ $(M+Na)^+$: 335.1048. Found: 335.1055.

(*E*)-2'-(3-(4-Methoxyphenyl)acryloyl)-[1,1'-biphenyl]-2-carbaldehyde (1b).

This compound was prepared by following the general procedure 3 and isolated as yellow oil.

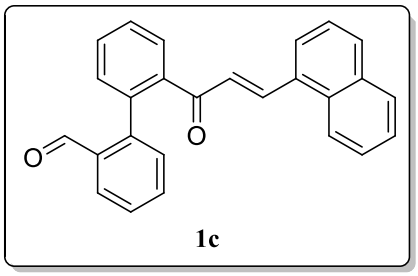


1b

R_f = 0.3 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3064.8, 3016.2, 2933.9, 1692.9, 1636.0, 1595.9, 1255.1, 757.8**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 7.99 (dd, *J* = 1.08 Hz, 7.76 Hz, 1H), 7.75-7.73 (m, 1H), 7.59-7.54 (m, 3H), 7.38-7.29 (m, 5H), 6.85 (d, *J* = 8.76 Hz, 2H), 6.65 (d, *J* = 15.88, 1H), 3.82 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.7, 191.6, 161.8, 145.3, 144.0, 140.3, 137.0, 134.0, 133.3, 131.7, 131.0, 130.2, 130.1 (2C), 128.5, 128.2 (2C), 127.9, 126.9, 123.8, 114.3 (2C), 55.4. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{18}O_3$ $(M+H)^+$: 343.1334. Found: 343.1341.

(*E*)-2'-(3-(Naphthalen-1-yl)acryloyl)-[1,1'-biphenyl]-2-carbaldehyde (1c).

This compound was prepared by following the general procedure 3 and isolated as yellow gel.

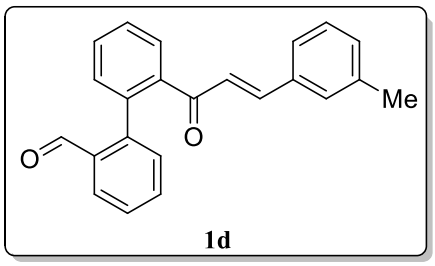


1c

R_f = 0.6 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3079.8, 3059.3, 3042.4, 1694.1, 1662.2, 1597.1, 1252.1, 756.3**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.99 (s, 1H), 8.30 (d, *J* = 15.64 Hz, 1H), 8.06-8.01 (m, 2H), 7.87 (t, *J* = 7.44 Hz, 3H), 7.66-7.50 (m, 6H), 7.47-7.38 (m, 4H), 6.89 (d, *J* = 15.64 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.1, 191.5, 144.0, 141.8, 140.1, 137.2, 134.1, 133.6, 133.4, 131.8, 131.7, 131.5, 131.2, 130.9, 130.6, 128.7 (2C), 128.3 (2C), 128.1 (2C), 127.0, 126.3, 125.3, 125.2, 123.2. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{18}O_2$ $(M+Na)^+$: 385.1204. Found: 385.1226.

(*E*)-2'-(3-(m-Tolyl)acryloyl)-[1,1'-biphenyl]-2-carbaldehyde (1d).

This compound was prepared by following the general procedure 3 and isolated as yellow oil.

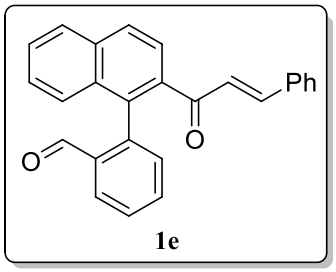


1d

R_f = 0.5 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3059.8, 3023.7, 2982.5, 2922.9, 1694.3, 1644.6, 1598.8, 1239.1, 770.7**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.96 (s, 1H), 8.00 (d, *J* = 7.76 Hz, 1H), 7.77 (d, *J* = 7.12 Hz, 1H), 7.62-7.56 (m, 3H), 7.48 (t, *J* = 7.52 Hz, 1H), 7.39-7.32 (m, 3H), 7.25-7.17 (m, 4H), 6.78 (d, *J* = 15.96 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.6, 191.5, 145 .6, 143.9, 140.1, 138.5, 137.1, 134.2, 134.1, 133.3, 131.7, 131.5, 131.0, 130.4, 129.0, 128.7, 128.5, 128.28, 128.23, 128.0, 125.8, 125.5, 21.2. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{18}O_2$ $(M+Na)^+$: 349.1204. Found: 349.1212.

(*E*)-2-(2-Cinnamoylnaphthalen-1-yl)benzaldehyde (1e).

This compound was prepared by following the general procedure 3 and isolated as pale yellow



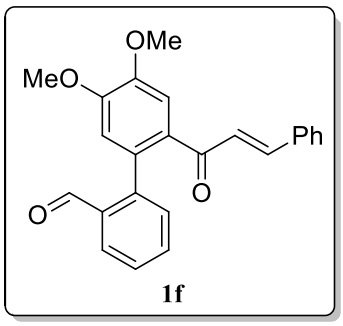
1e

oil. R_f = 0.5 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3061.0, 3023.7, 1701.0, 1642.3, 1596.2, 1217.1, 766.2**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.70 (s, 1H), 8.08 (dd, *J* = 7.68 Hz, 14.68 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.48 Hz, 1H), 7.67-7.55 (m, 3H), 7.48 (t, *J* = 7.56 Hz, 1H), 7.43-7.39 (m, 2H), 7.37-7.35 (m, 6H), 6.81 (d, *J* = 16.04 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.7, 191.4, 145.7,

141.1, 137.6, 135.4, 134.5, 134.2, 133.9, 133.6, 132.9, 131.8, 130.7, 128.9 (2C), 128.77, 128.72, 128.4 (2C), 128.3, 127.7, 127.55, 127.53, 126.8, 126.4, 124.3. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{18}O_2$ $(M+H)^+$: 363.1385. Found: 363.1398.

2'-Cinnamoyl-4',5'-dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (1f).

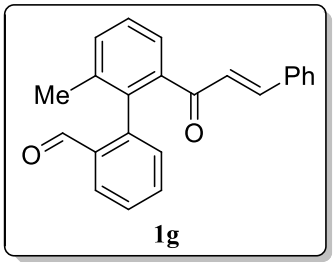
This compound was prepared by following the general procedure 3 and isolated as dark yellow semi solid. R_f = 0.2 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3061.0, 3001.2, 2970.2, 2933.9, 1693.2, 1658.8, 1596.5, 1232.9, 773.5**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.98 (s, 1H), 8.00 (d, J = 7.72 Hz, 1H), 7.60 (t, J = 7.48 Hz, 1H), 7.50-7.44 (m, 2H), 7.40-7.34 (m, 3H), 7.32-7.30 (m, 2H), 7.23-7.22 (m, 2H), 6.82 (s, 1H), 6.61 (d, J = 15.76 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.6, 191.5, 150.8, 148.7, 144.2, 143.7, 134.5, 134.3, 133.5, 132.8, 131.4, 130.9, 130.4, 128.7 (2C), 128.3, 128.2 (2C), 128.0, 125.6, 114.1, 111.9, 56.2 (2C). **HRMS (ESI):** *m/z* calculated for $C_{24}H_{20}O_4$ $(M+Na)^+$: 395.1259. Found: 395.1274.



1f

2'-Cinnamoyl-6'-methyl-[1,1'-biphenyl]-2-carbaldehyde (1g).

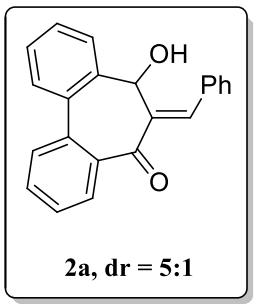
This compound was prepared by following the general procedure 3 and isolated as yellow semi solid. R_f = 0.6 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3064.8, 3034.9, 2971.3, 1694.2, 1644.2, 1596.6, 1229.4, 763.6**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.83 (s, 1H), 7.99 (d, *J* = 7.72 Hz, 1H), 7.60-7.56 (m, 1H), 7.54-7.51 (m, 1H), 7.49-7.46 (m, 3H), 7.42-7.40 (m, 2H), 7.39-7.36 (m, 2H), 7.34-7.32 (m, 2H), 7.20 (d, *J* = 7.56 Hz, 1H), 6.80 (d, *J* = 16.04, 1H), 2.08 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.5, 191.8, 145.7, 142.5, 140.1, 137.6, 136.2, 134.34, 134.31, 133.7, 132.1, 130.7 (2C), 128.9 (2C), 128.3 (2C), 128.2, 127.95, 127.93, 126.3, 125.6, 20.6. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{18}O_2$ $(M+Na)^+$: 349.1204. Found: 349.1213.



1g

(*E*)-6-Benzylidene-7-hydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (2a).

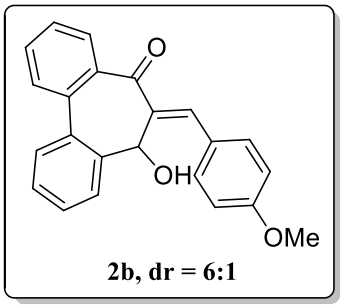
This compound was prepared by following the general procedure 4 (Scheme 10) and isolated as yellow oil. R_f = 0.4 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3434.9, 3061.8, 3023.7, 2960.0, 1660.4, 1597.2, 743.0**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.94 (s, 1H), 7.85 (d, *J* = 7.68 Hz, 1H), 7.66 (t, *J* = 7.52 Hz, 1H), 7.57-7.53 (m, 2H), 7.52-7.48 (m, 5H), 7.46-7.44 (m, 2H), 7.35-7.32 (m, 1H), 7.22 (d, *J* = 7.52 Hz, 1H), 5.94 (d, *J* = 3.36 Hz, 1H), 2.15 (d, *J* = 4.52 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.8, 141.7, 139.9, 139.1, 138.9, 138.1, 134.9, 132.4 (2C), 131.2, 129.9 (2C), 129.49, 129.43 (3C), 129.0, 128.6 (2C), 128.4, 128.1, 71.5. **HRMS (ESI):** *m/z* calculated for $C_{22}H_{16}O_2$ $(M+Na)^+$: 335.1048. Found: 335.1058.



2a, dr = 5:1

(*E*)-7-Hydroxy-6-(4-methoxybenzylidene)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (2b).

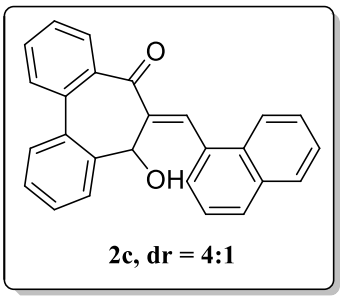
This compound was prepared by following the general procedure 4 and isolated as yellow viscous oil. R_f = 0.25 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3440.5, 3061.0, 2960.0, 2930.1, 1654.8, 1597.5, 742.4**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (s, 1H), 7.83 (d, *J* = 7.52 Hz, 1H), 7.70-7.63 (m, 1H), 7.57-7.51 (m, 4H), 7.49-7.42 (m, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.27-7.22 (m, 1H), 7.02 (d, *J* = 8.52 Hz, 2H), 6.00 (d, *J* = 4.48 Hz, 1H), 3.90 (s, 3H) 2.16 (d, *J* = 4.92 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.0, 160.5, 140.2, 139.93, 139.91, 139.4, 139.1, 137.9, 132.2, 131.5 (2C), 131.1, 129.8, 129.37, 129.33, 128.4, 128.1, 127.1, 114.2 (3C), 71.7, 55.3. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{18}O_3$ $(M+Na)^+$: 365.1154. Found: 365.1163.



2b, dr = 6:1

(*E*)-7-Hydroxy-6-(naphthalen-1-ylmethylene)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (2c).

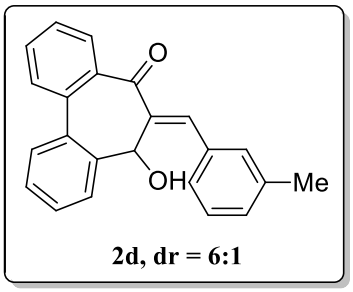
This compound was prepared by following the general procedure 4 and isolated as dark yellow semi solid. R_f = 0.4 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3441.5, 3060.0, 2925.9, 1660.7, 1596.6, 742.0**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.42 (s, 1H), 7.96-7.91 (m, 4H), 7.69-7.65 (m, 1H), 7.61-7.59 (m, 1H), 7.58-7.55 (m, 4H), 7.53-7.51 (m, 2H), 7.46 (t, J = 7.72 Hz, 1H), 7.28 (d, J = 14.8 Hz, 1H), 7.04 (d, J = 7.36 Hz, 1H), 5.78 (s, 1H), 2.10 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.3, 143.4, 139.0, 138.9, 138.4, 133.5, 132.5 (2C), 131.6, 131.1, 130.1 (2C), 129.6, 129.36 (2C), 129.3, 128.5 (2C), 128.4, 128.1, 126.7, 126.6, 126.5, 125.2, 125.1, 72.0. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{18}O_2$ $(M+Na)^+$: 385.1204. Found: 385.1221.



2c, dr = 4:1

(*E*)-7-Hydroxy-6-(3-methylbenzylidene)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (2d).

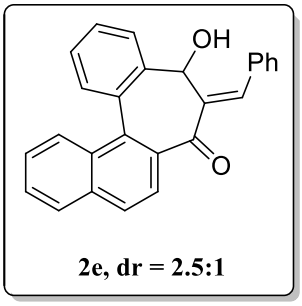
This compound was prepared by following the general procedure 4 and isolated as yellow oil. R_f = 0.4 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3443.8, 3064.8, 3027.4, 2982.5, 2960.0, 1658.0, 1597.5, 741.8**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 (s, 1H), 7.85 (dd, *J* = 1.08 Hz, 7.72 Hz, 1H), 7.67-7.63 (m, 1H), 7.57-7.54 (m, 2H), 7.52-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.34-7.32 (m, 1H), 7.30 (m, 1H), 7.27-7.23 (m, 2H), 5.95 (d, *J* = 5.4 Hz, 1H), 2.45 (s, 3H), 2.14 (d, *J* = 5.48 Hz, 1H), 1.28 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.8, 141.6, 140.1, 139.2, 139.0, 138.3, 138.1, 134.9, 132.4, 131.1, 130.1 (2C), 129.9 (2C), 129.8, 129.5, 129.3, 128.5, 128.4, 128.1, 126.4, 71.5, 21.4. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{18}O_2$ $(M+Na)^+$: 349.1204. Found: 349.1227.



2d, dr = 6:1

(*E*)-8-Benzylidene-9-hydroxy-8,9-dihydro-7*H*-benzo[6,7]cyclohepta[1,2-*a*]naphthalen-7-one (2e).

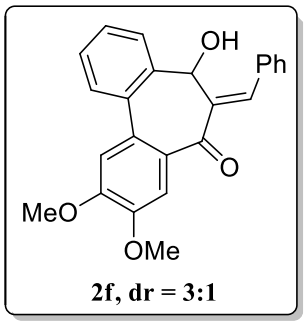
This compound was prepared by following the general procedure 4 and isolated as dark yellow semi solid. R_f = 0.4 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3443.8, 3057.3, 3031.1, 2967.5, 2925.4, 1660.3, 1592.4, 763.6**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.14 (d, *J* = 8.44 Hz, 1H), 7.96-7.94 (m, 2H), 7.87 (s, 1H), 7.77 (d, *J* = 8.52 Hz, 1H), 7.64-7.60 (m, 1H), 7.58-7.56 (m, 2H), 7.52-7.50 (m, 4H), 7.48-7.42 (m, 2H), 7.35-7.32 (m, 1H), 7.23 (d, *J* = 7.48 Hz, 1H), 5.91 (d, *J* = 6.32 Hz, 1H), 2.29 (d, *J* = 6.52 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.2, 142.7, 139.8, 139.5, 136.8, 136.4, 135.8, 134.7, 134.1, 134.0, 130.9, 129.6 (2C), 129.2, 128.7 (2C), 128.64, 128.62, 128.5, 128.4, 128.1, 127.6, 127.1, 126.9, 125.1, 71.6. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{18}O_2$ $(M+Na)^+$: 385.1204. Found: 385.1219.



2e, dr = 2.5:1

(*E*)-6-Benzylidene-7-hydroxy-2,3-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (2f).

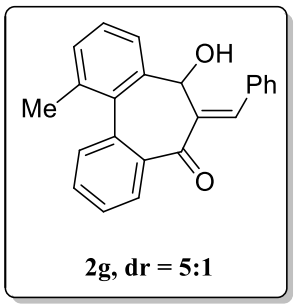
This compound was prepared by following the general procedure 4 and isolated as yellow gel. R_f = 0.15 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3479.2, 3076.0, 3064.8, 2956.3, 2932.6, 1651.6, 1586.8, 1268.5, 760.7**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.93 (s, 1H), 7.54-7.52 (m, 1H), 7.49-7.47 (m, 5H), 7.45-7.42 (m, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 7.24 Hz, 1H), 7.02 (s, 1H), 5.93 (d, J = 5.08 Hz, 1H), 4.03 (s, 3H), 4.01 (s, 3H), 2.31 (d, J = 5.64 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.9, 152.4, 148.7, 141.8, 139.9, 138.7, 135.1, 132.3, 131.3, 130.8, 129.3 (3C), 129.2, 128.9, 128.6 (3C), 128.1, 112.7, 112.1, 71.6, 56.1, 56.0. **HRMS (ESI):** *m/z* calculated for $C_{24}H_{20}O_4$ $(M+Na)^+$: 395.1259. Found: 395.1273.



2f, dr = 3:1

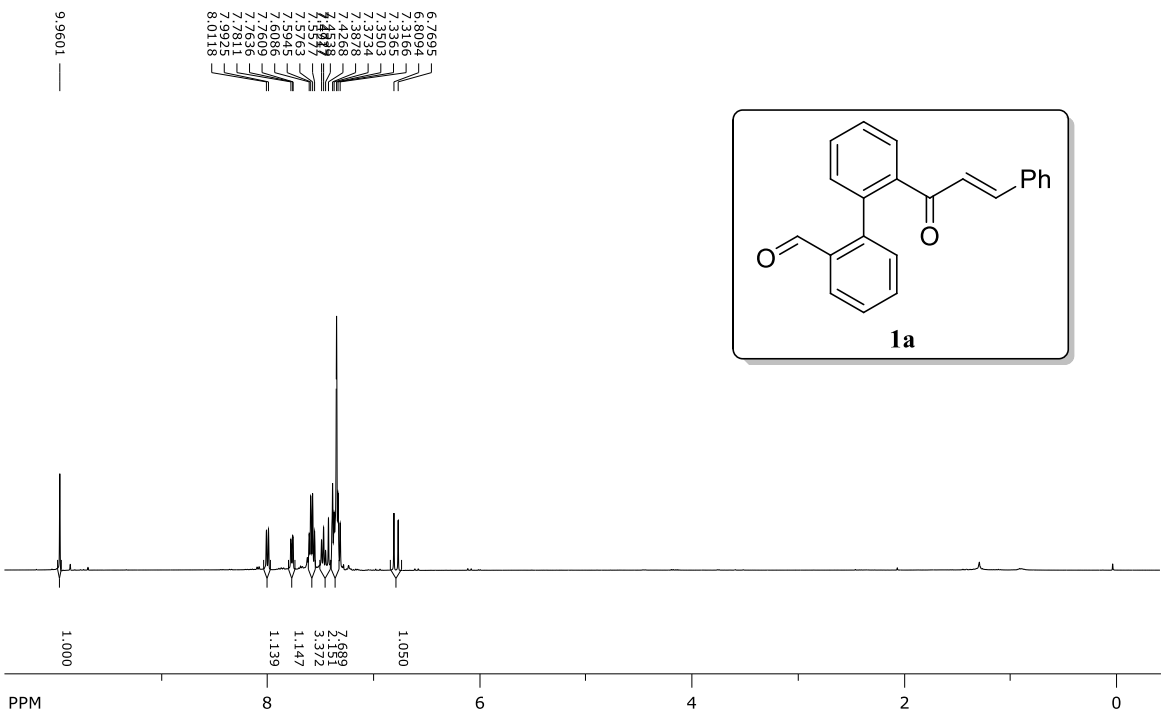
(*E*)-6-Benzylidene-7-hydroxy-11-methyl-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-one (2g).

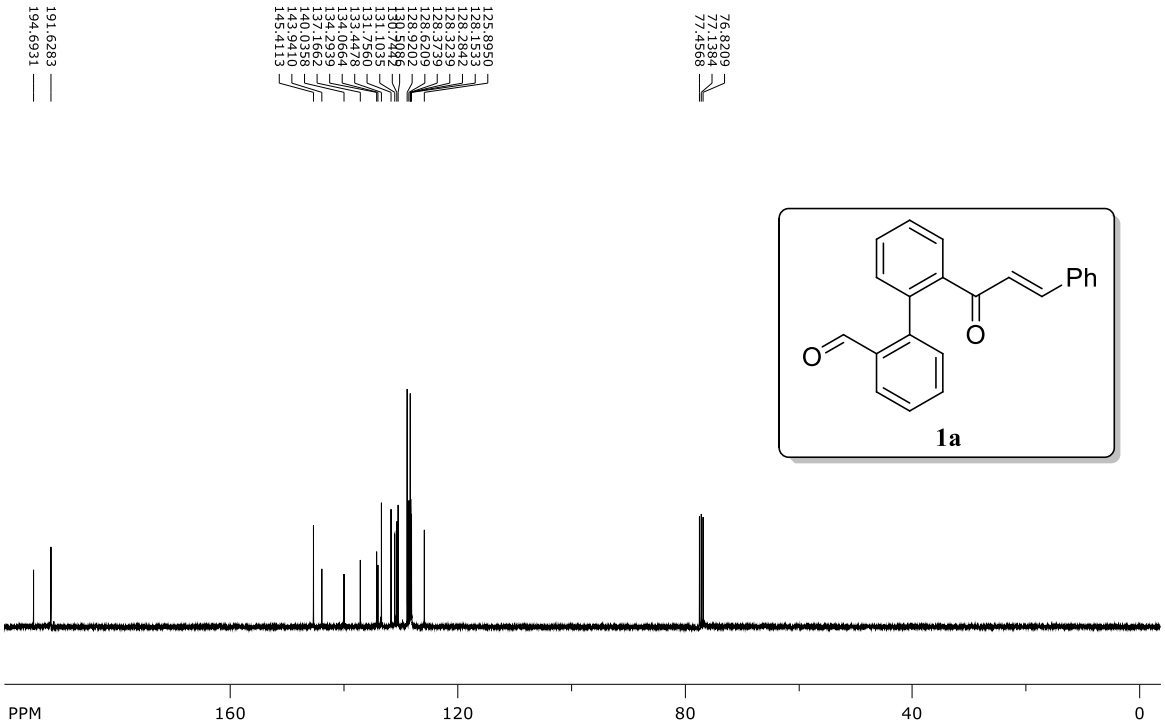
This compound was prepared by following the general procedure 4 and isolated as yellow brown viscous oil. R_f = 0.5 (hexane/EtOAc = 4/1). **IR (thin film, neat):** ν_{max}/cm^{-1} 3445.0, 3064.8, 3027.4, 2971.3, 2926.2, 1661.7, 1593.4, 748.1**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 (s, 1H), 7.56-7.52 (m, 4H), 7.49-7.44 (m, 3H), 7.40-7.36 (m, 3H), 7.25 (m, 1H), 7.13 (d, *J* = 7.56 Hz, 1H), 5.81 (d, *J* = 7.2 Hz, 1H), 2.43 (s, 3H), 2.26 (d, *J* = 7.28 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.5, 142.5, 140.6, 139.1, 138.8, 136.8, 135.8, 134.9, 134.6 (2C), 132.6, 129.6 (2C), 129.1, 128.7 (2C), 128.26, 128.24, 128.1, 128.0, 126.7, 71.5, 21.3. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{18}O_2$ $(M+Na)^+$: 349.1204. Found: 349.1214.

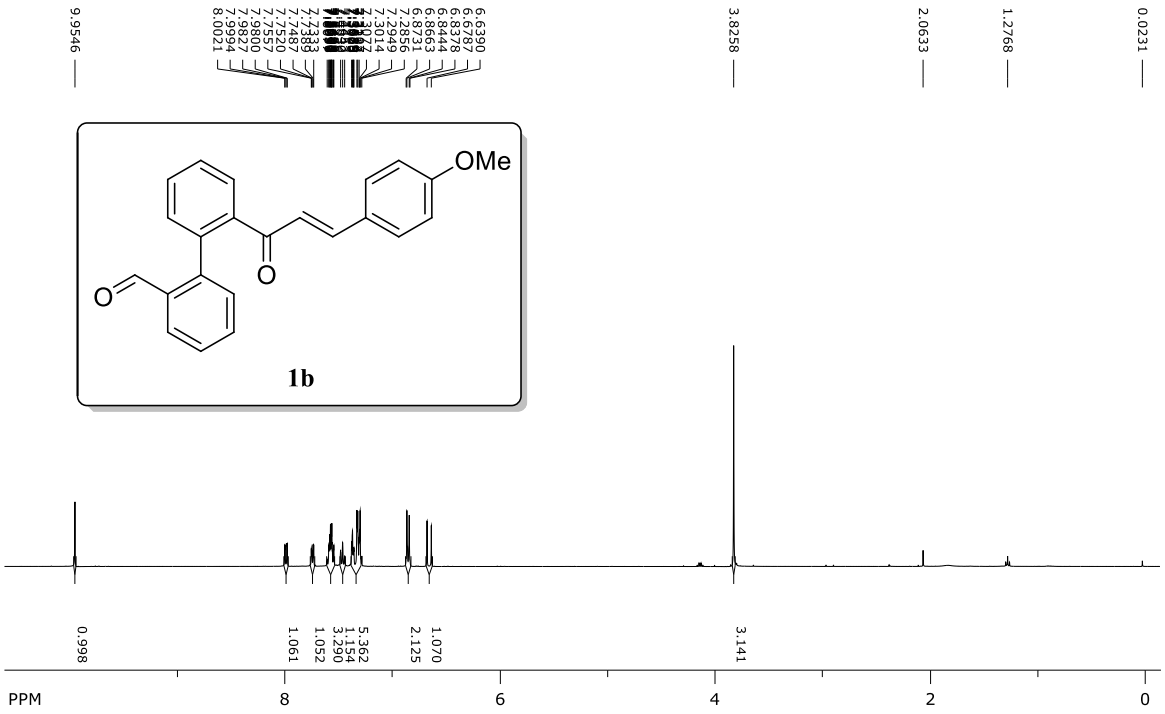


2g, dr = 5:1

Copies of ^{1}H and ^{13}C-NMR spectra of all the new compounds reported in this study:



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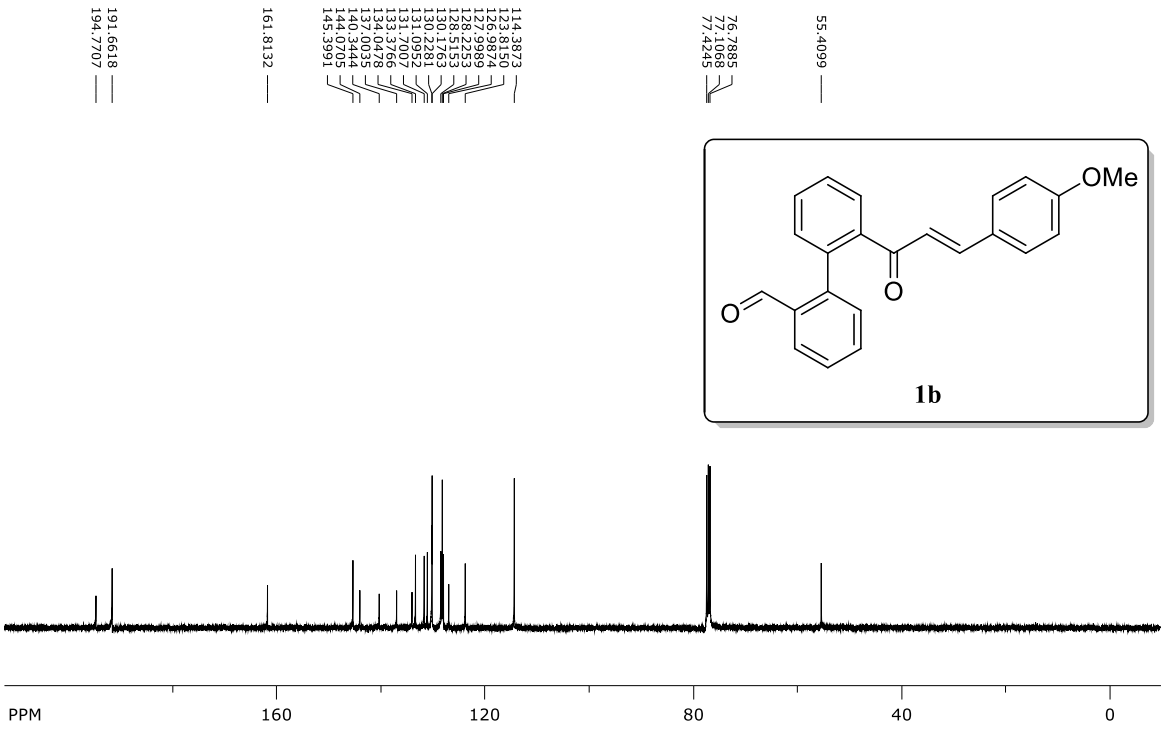
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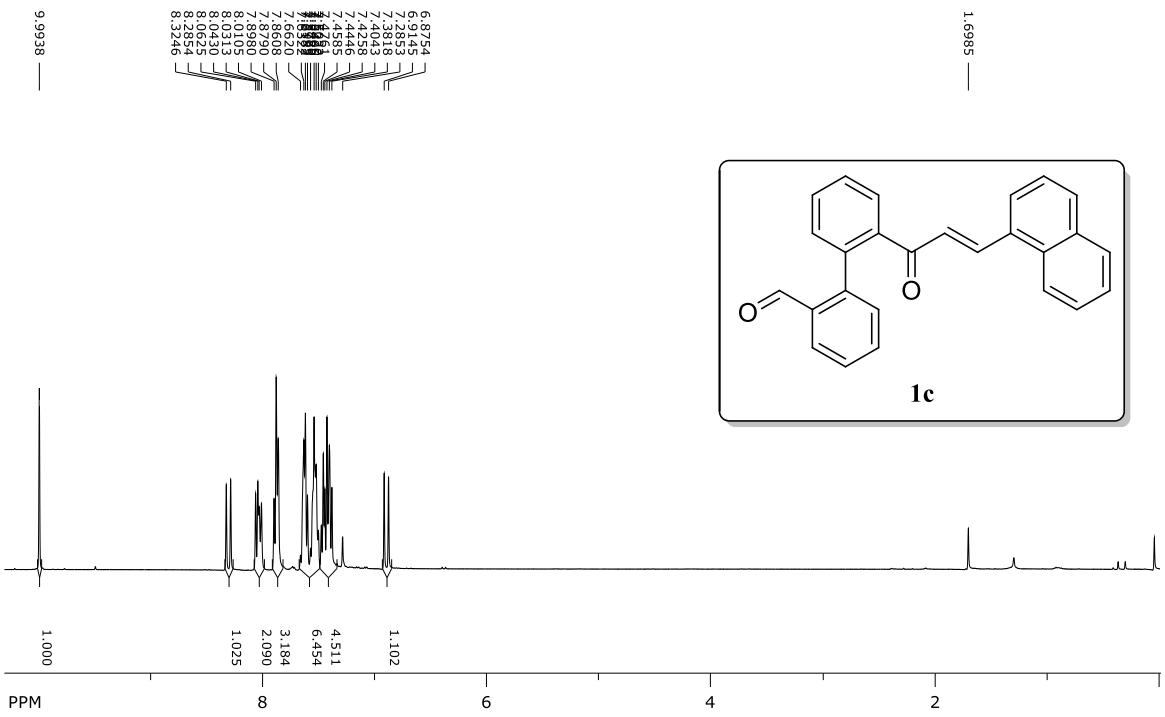
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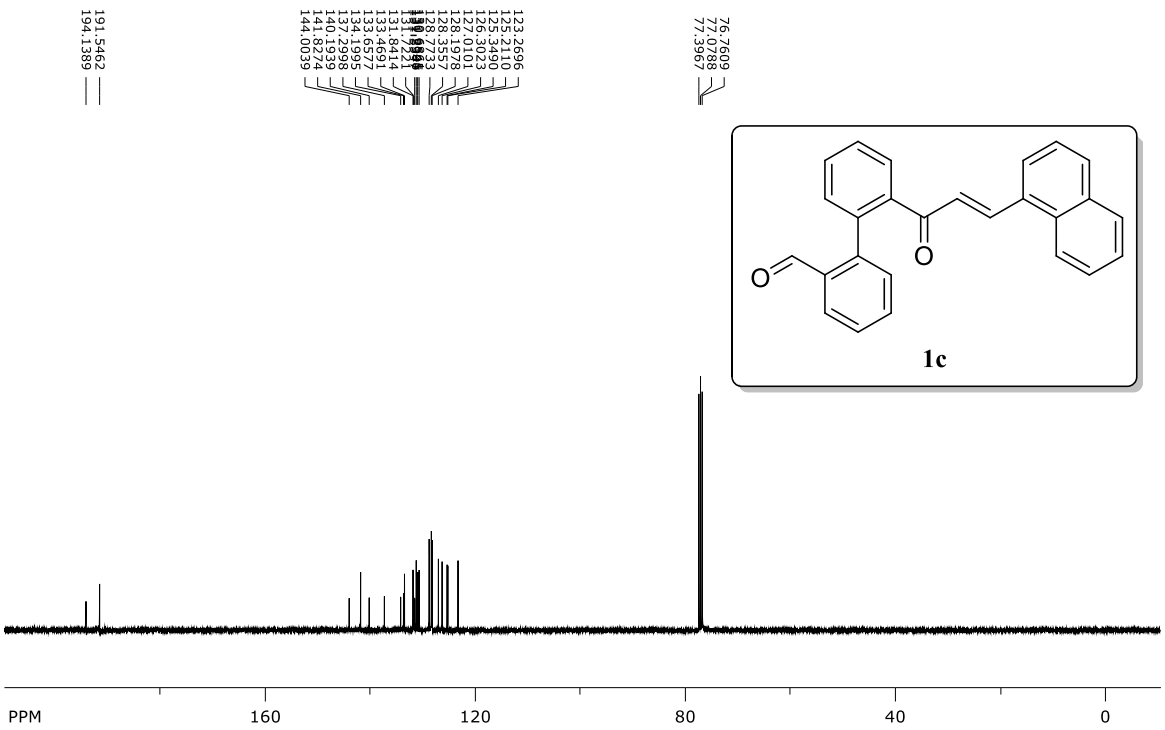
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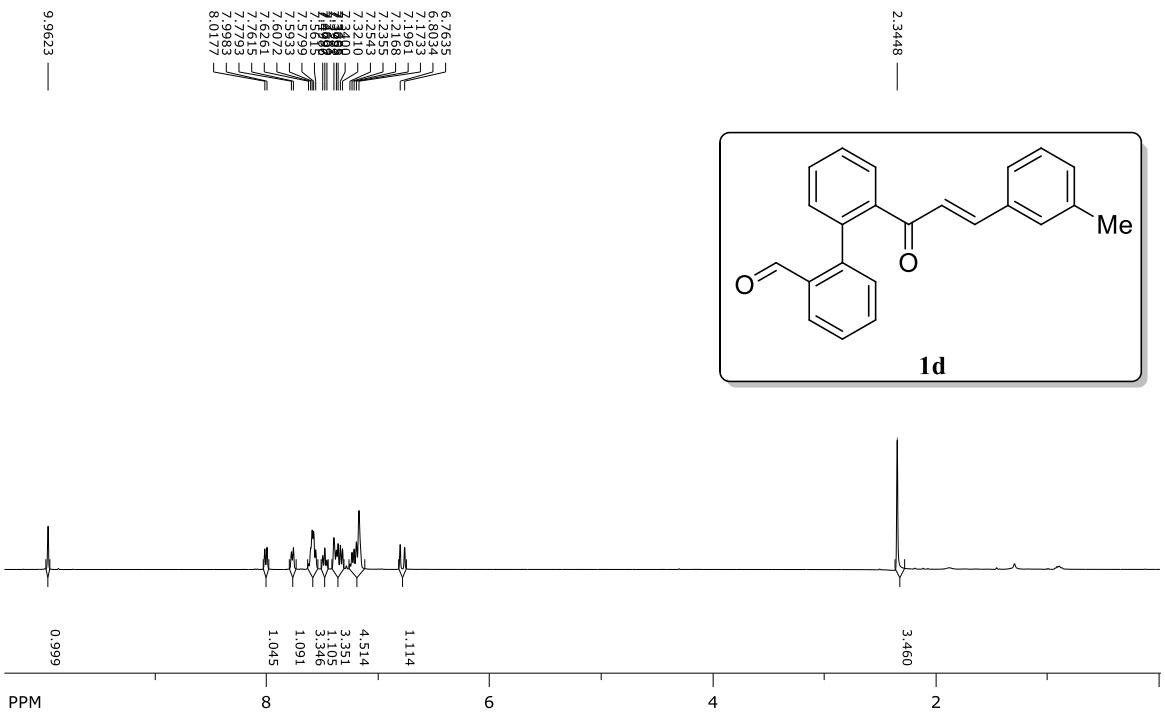
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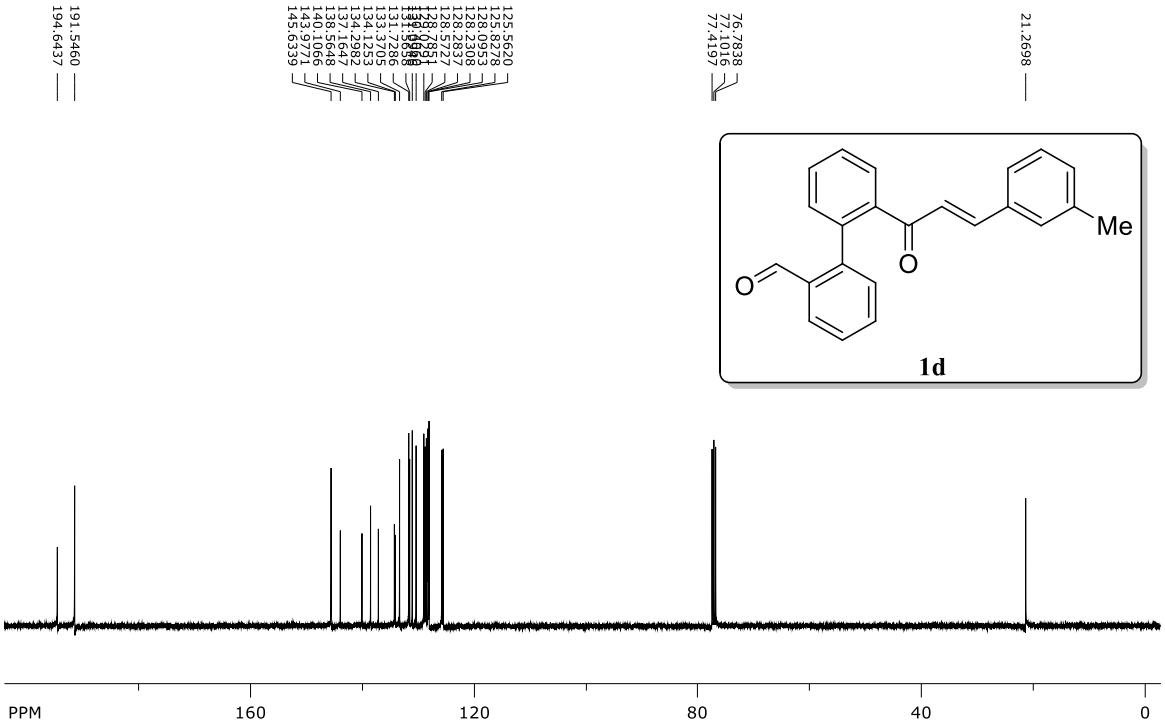
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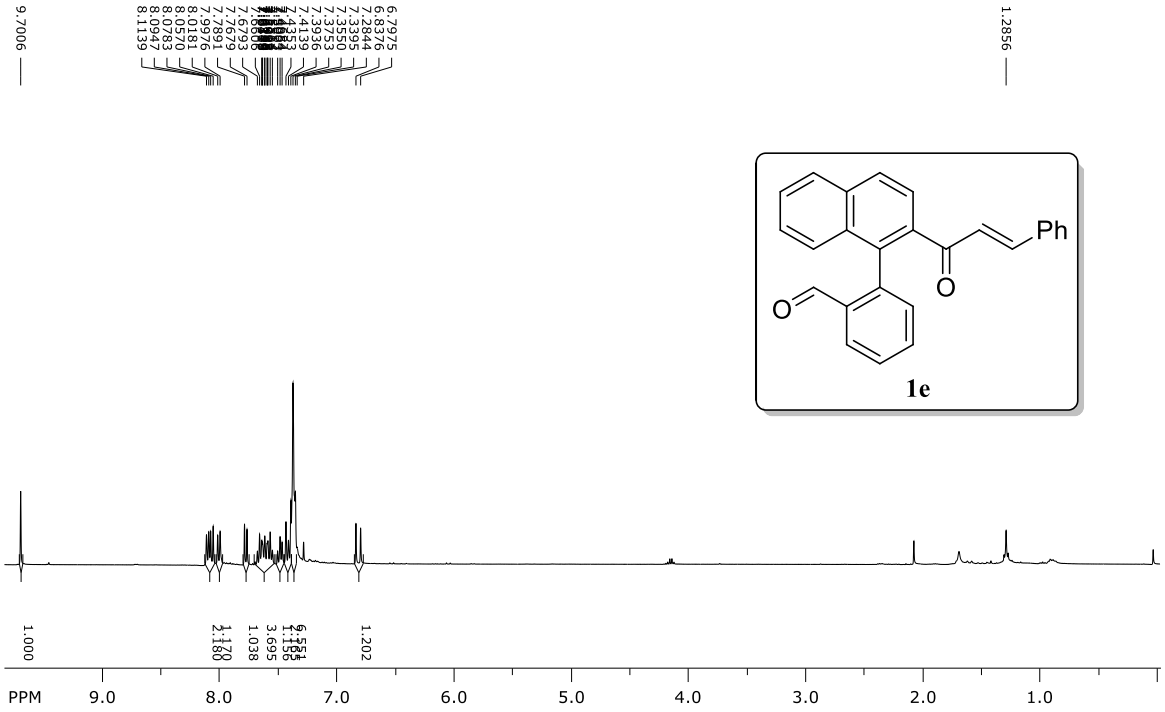
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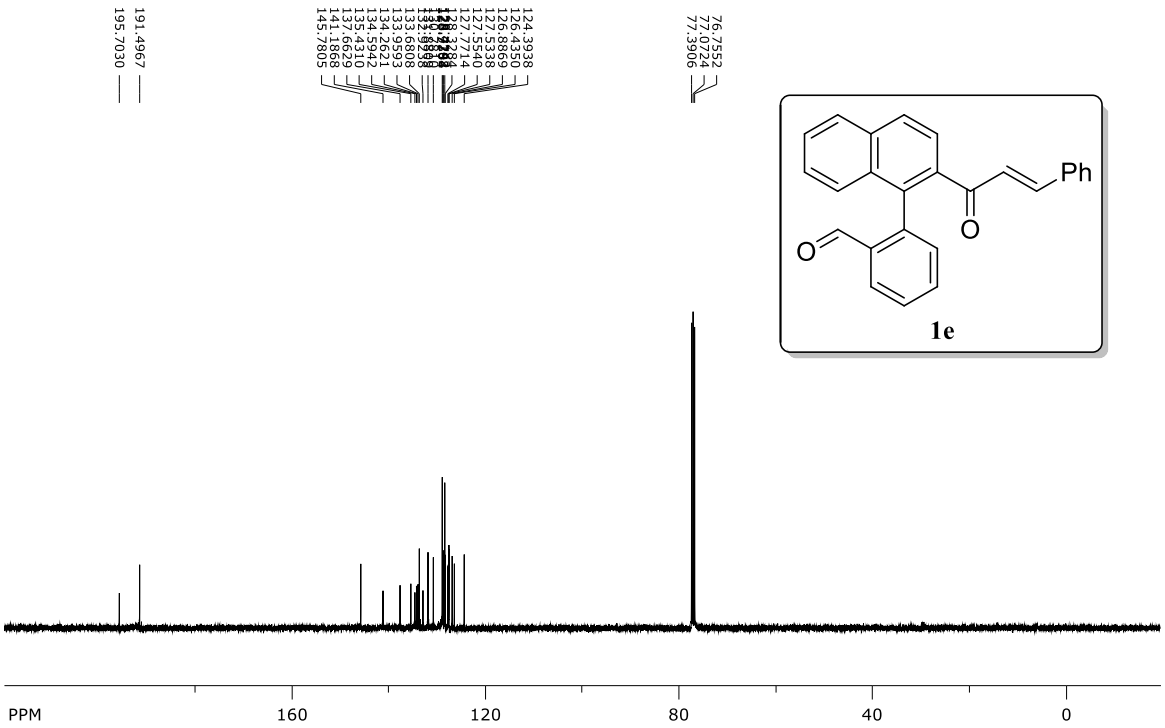
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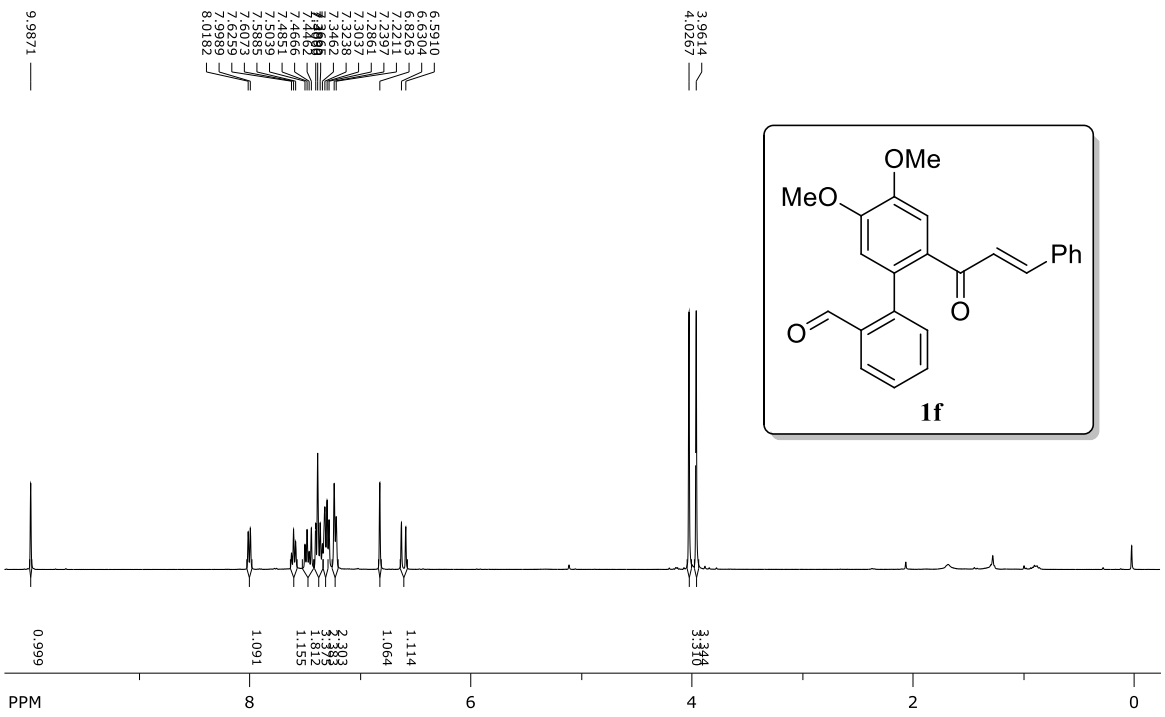
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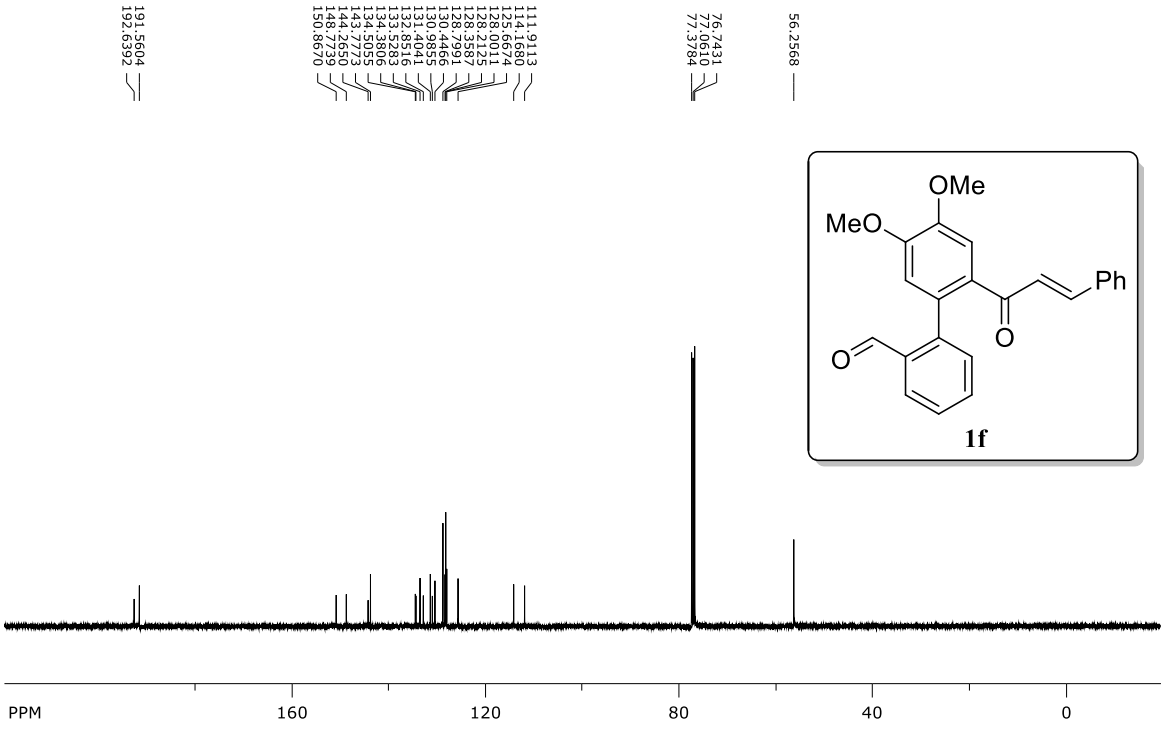
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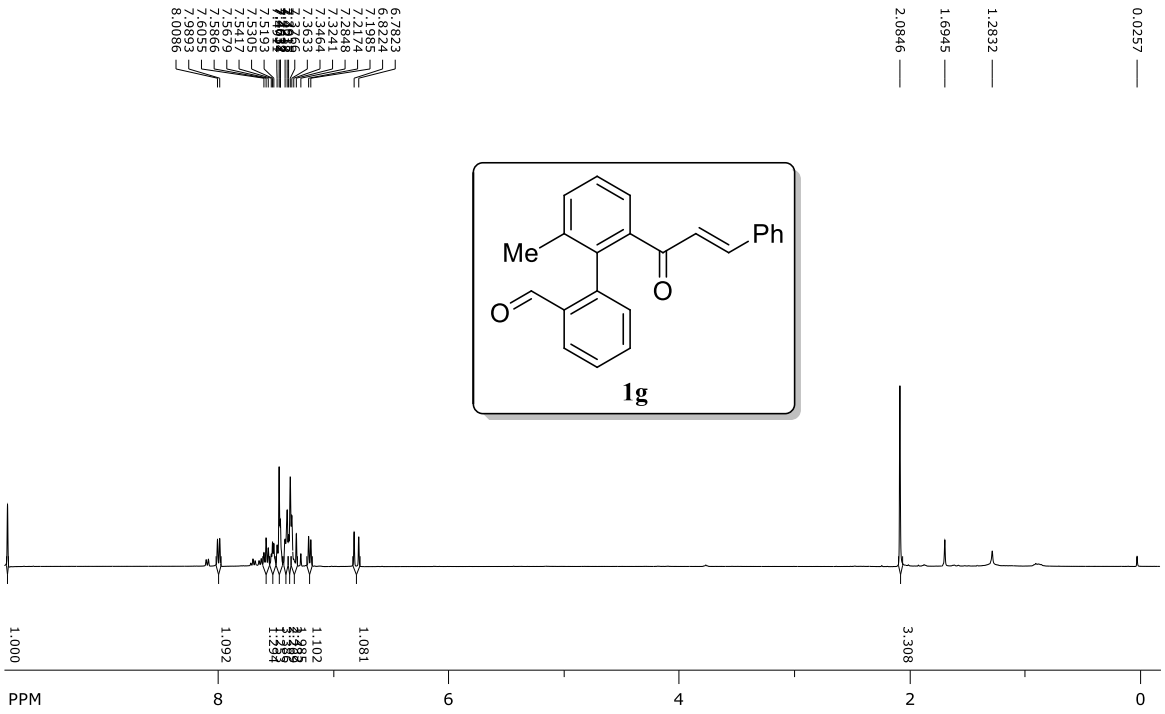
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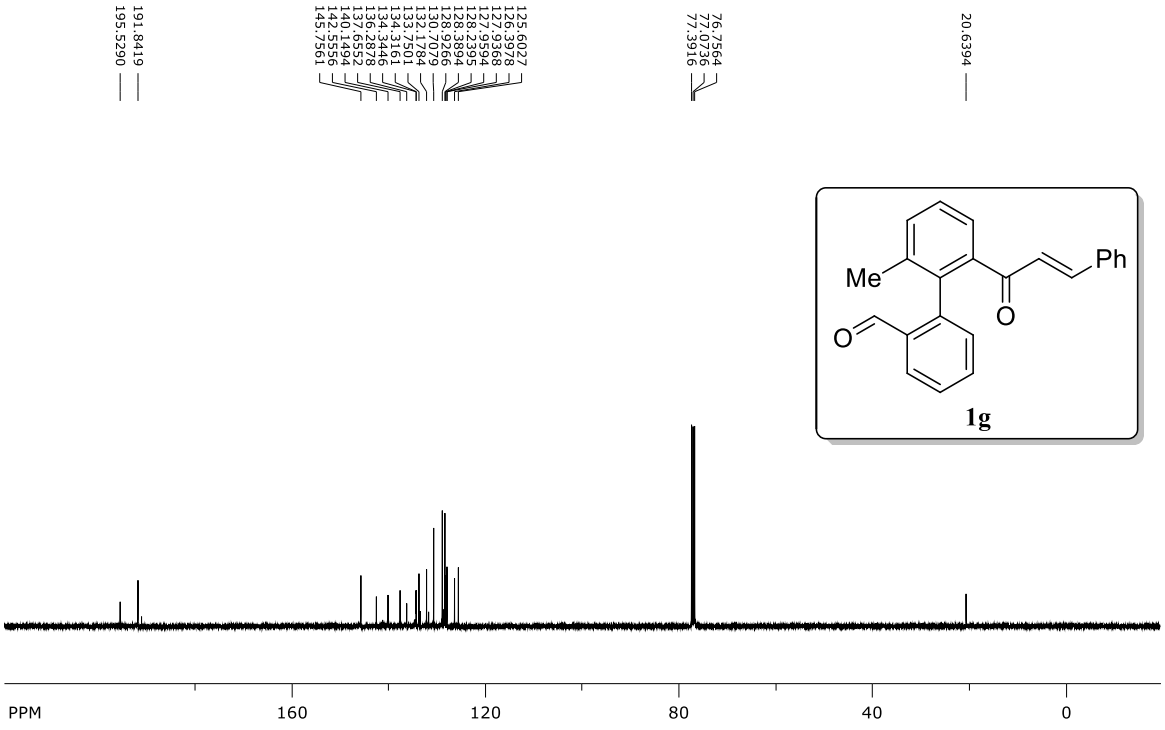
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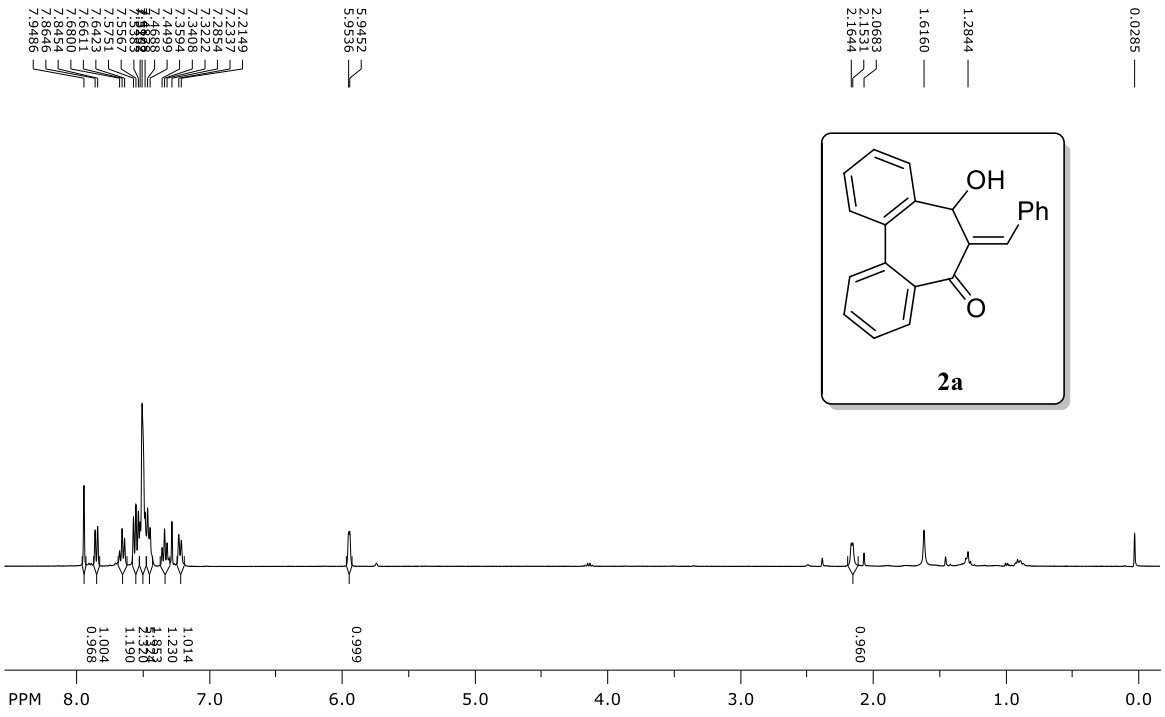
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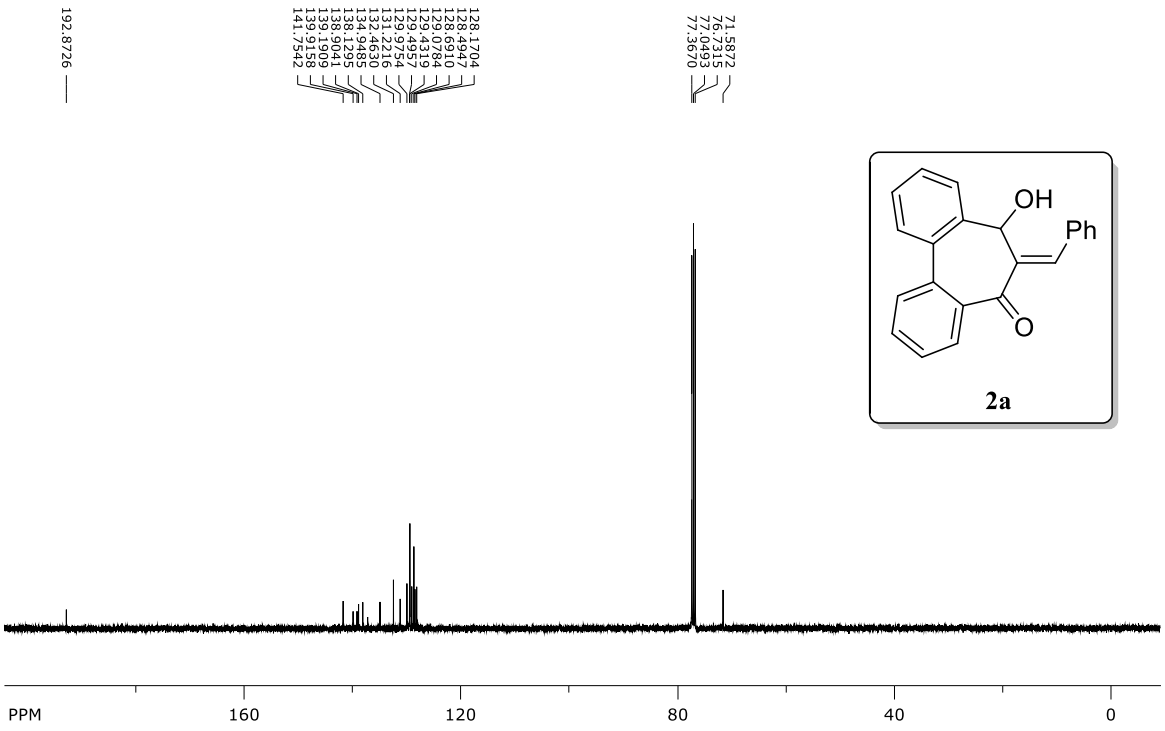
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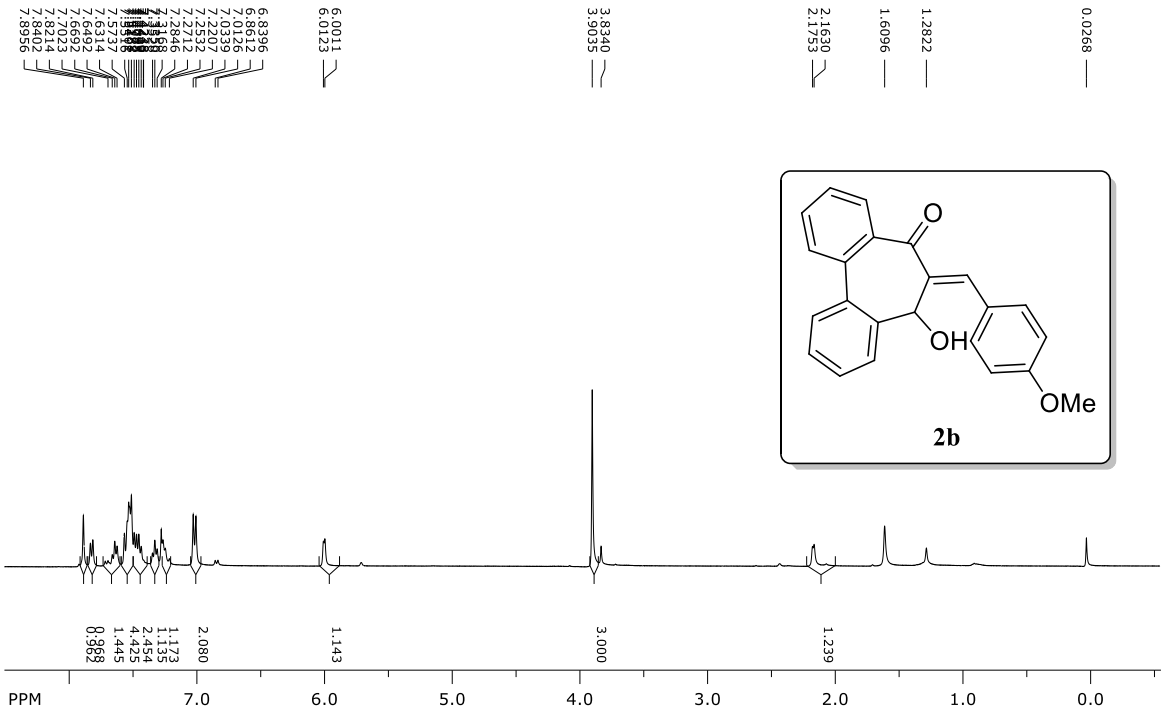
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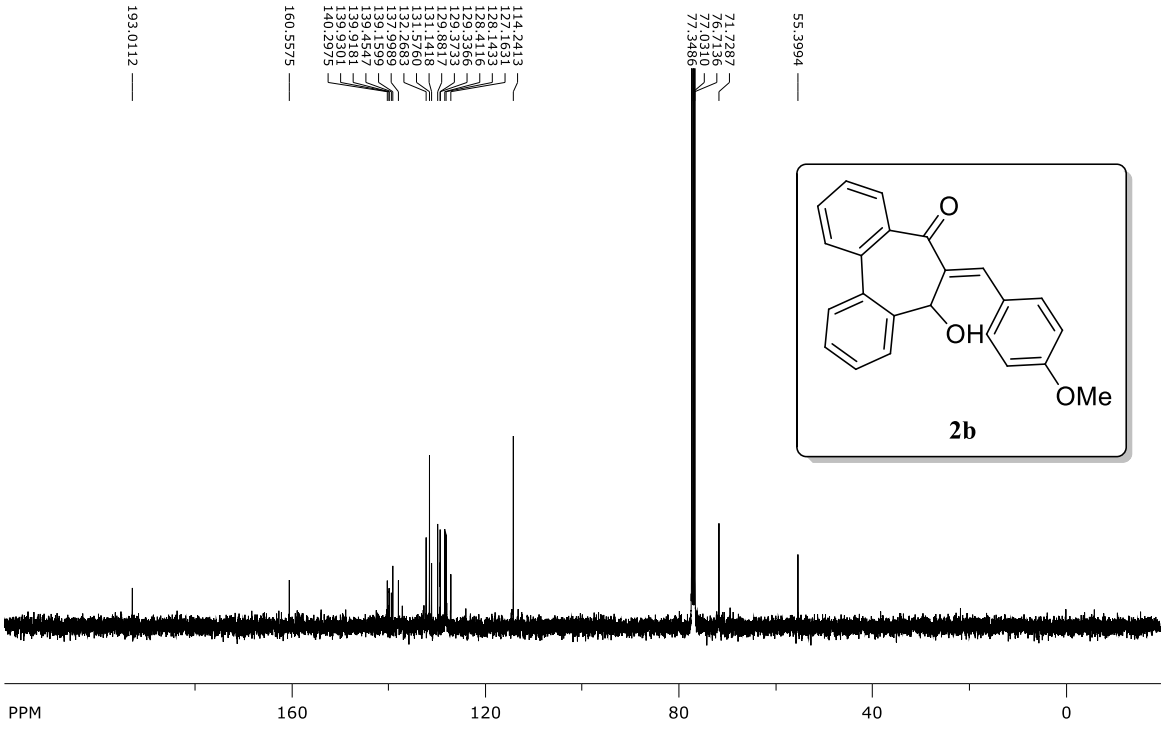
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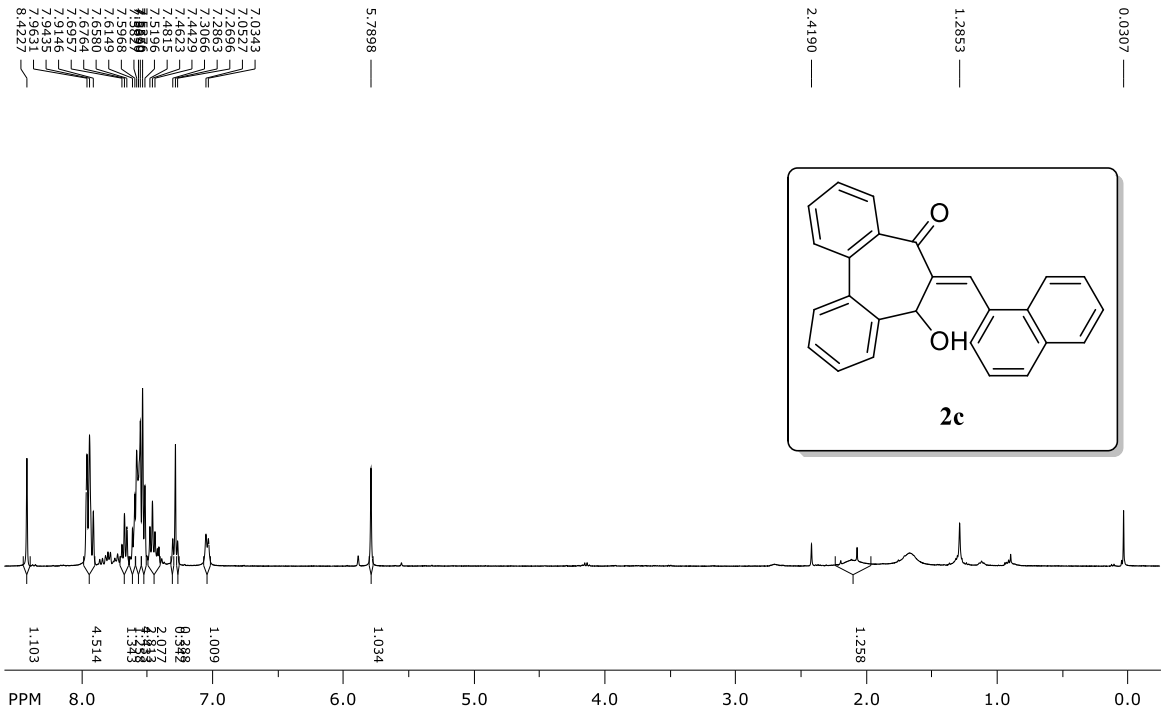
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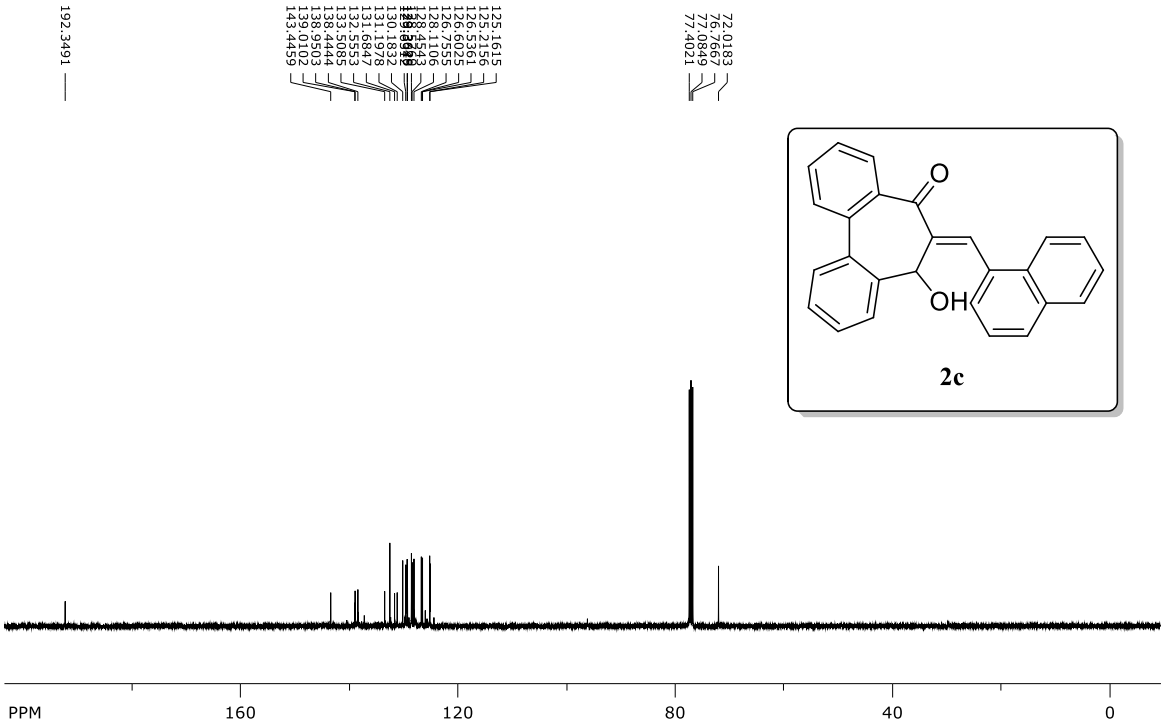
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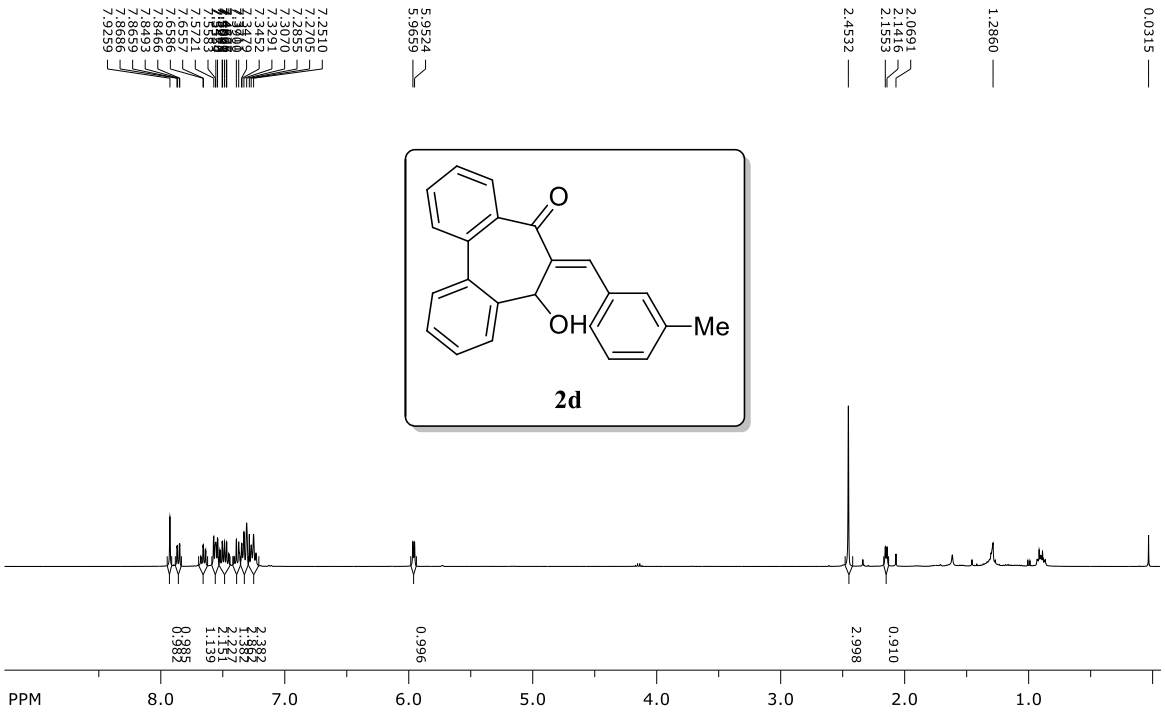
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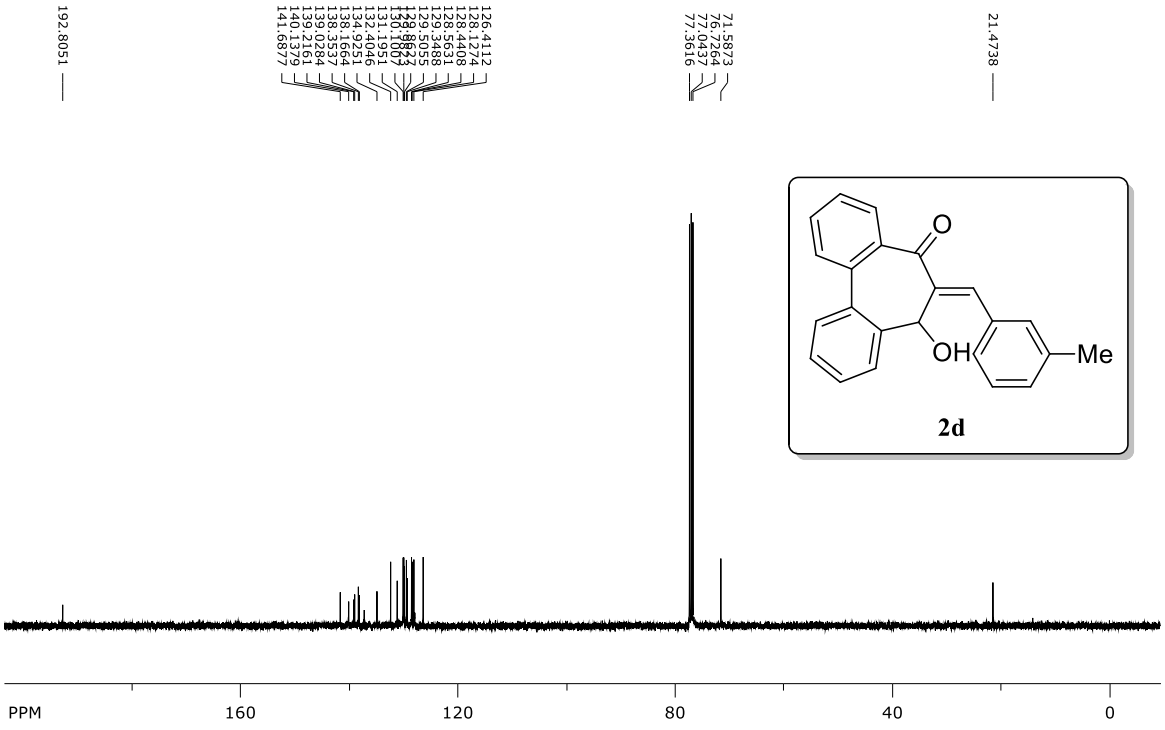
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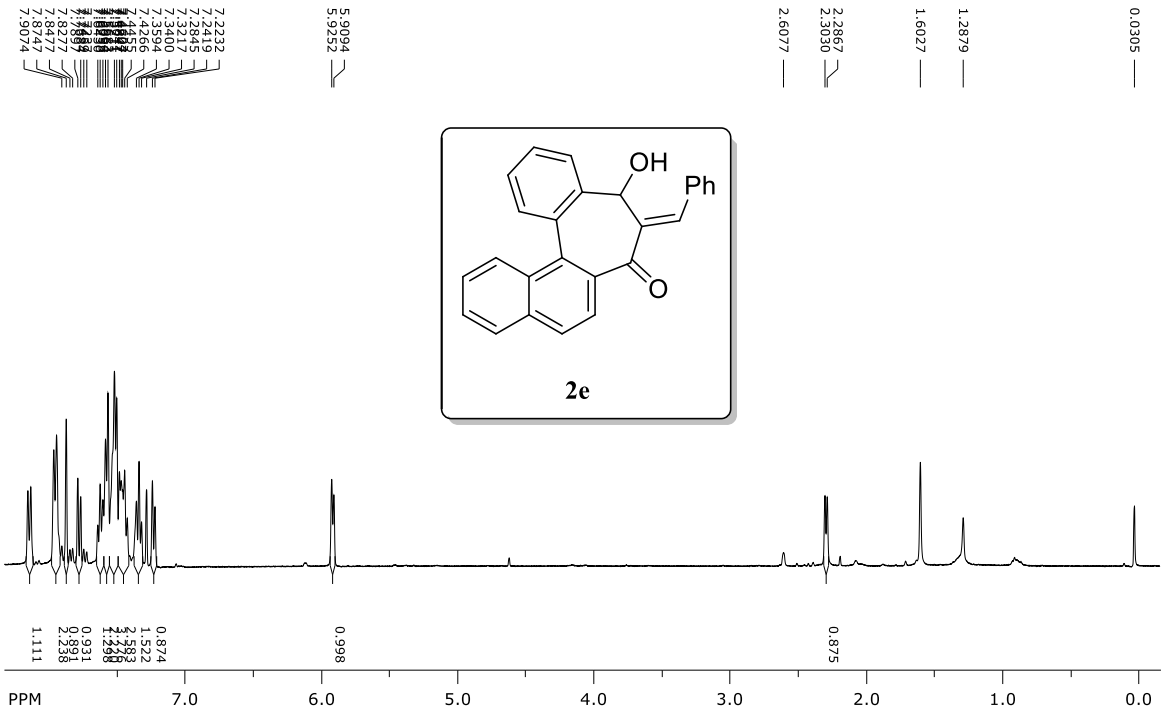
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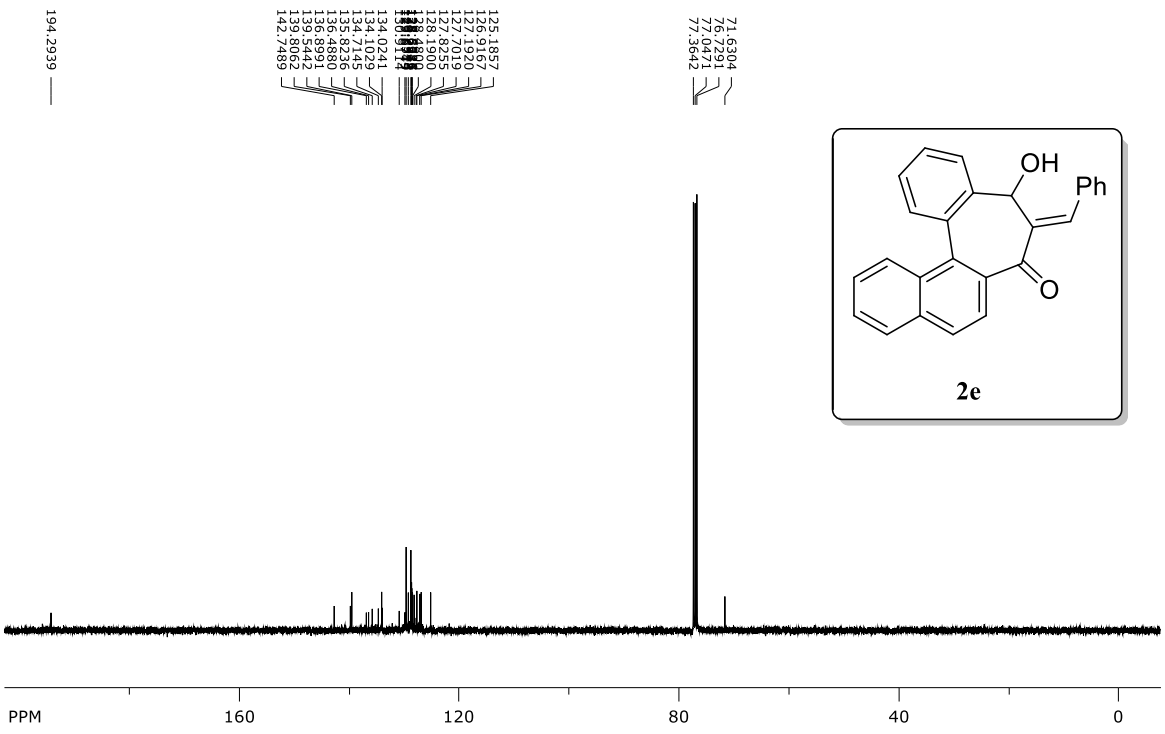
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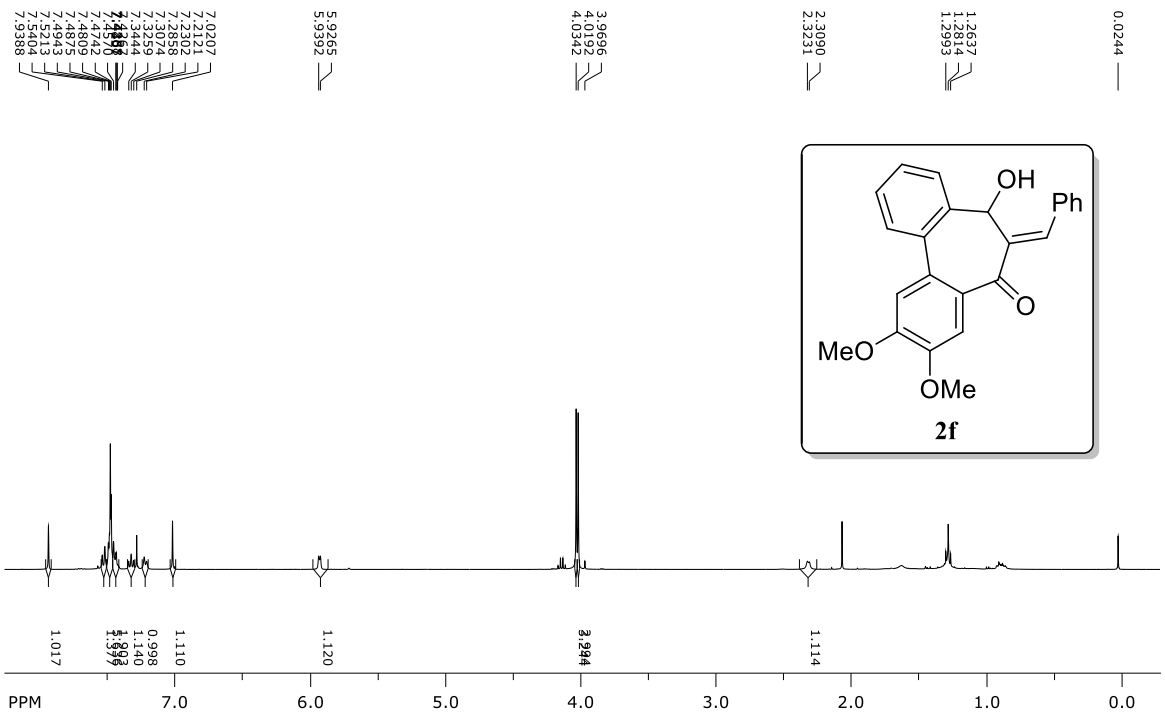
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OMe
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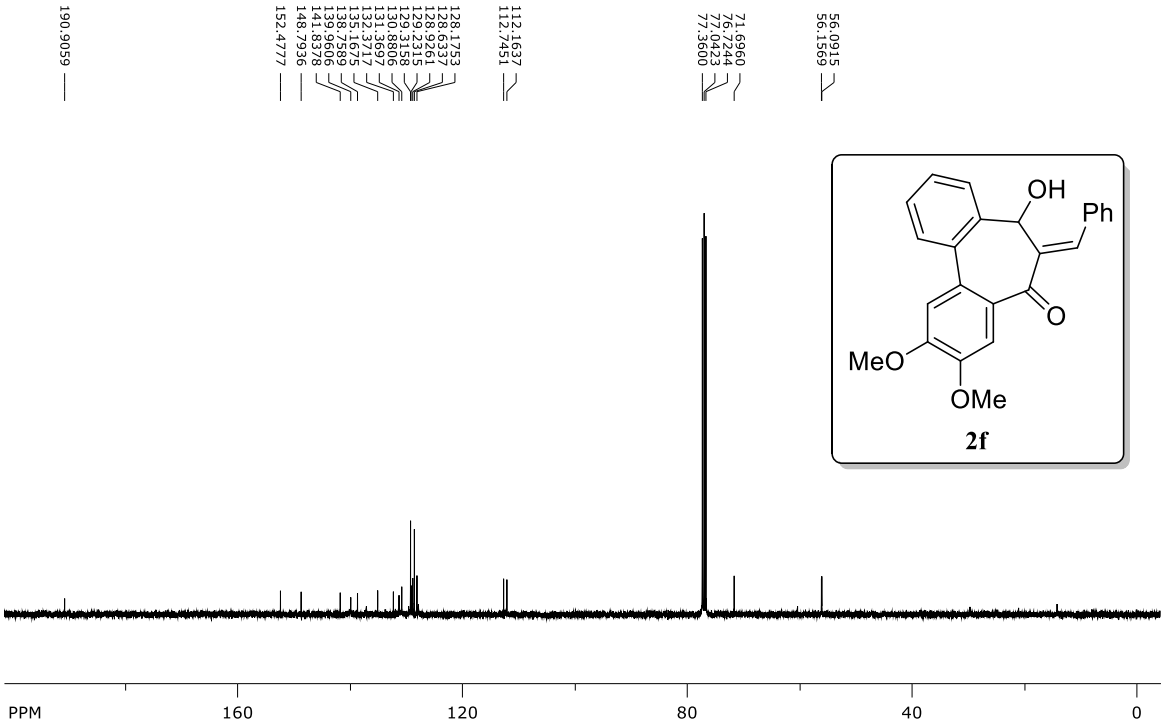
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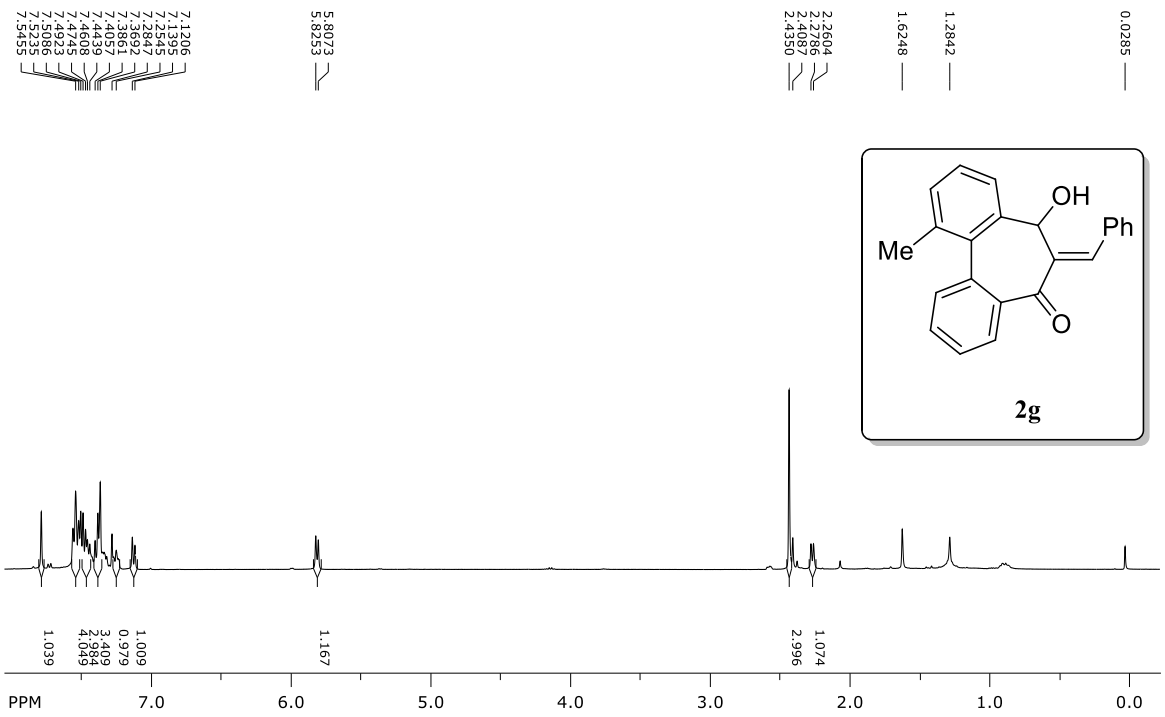
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O
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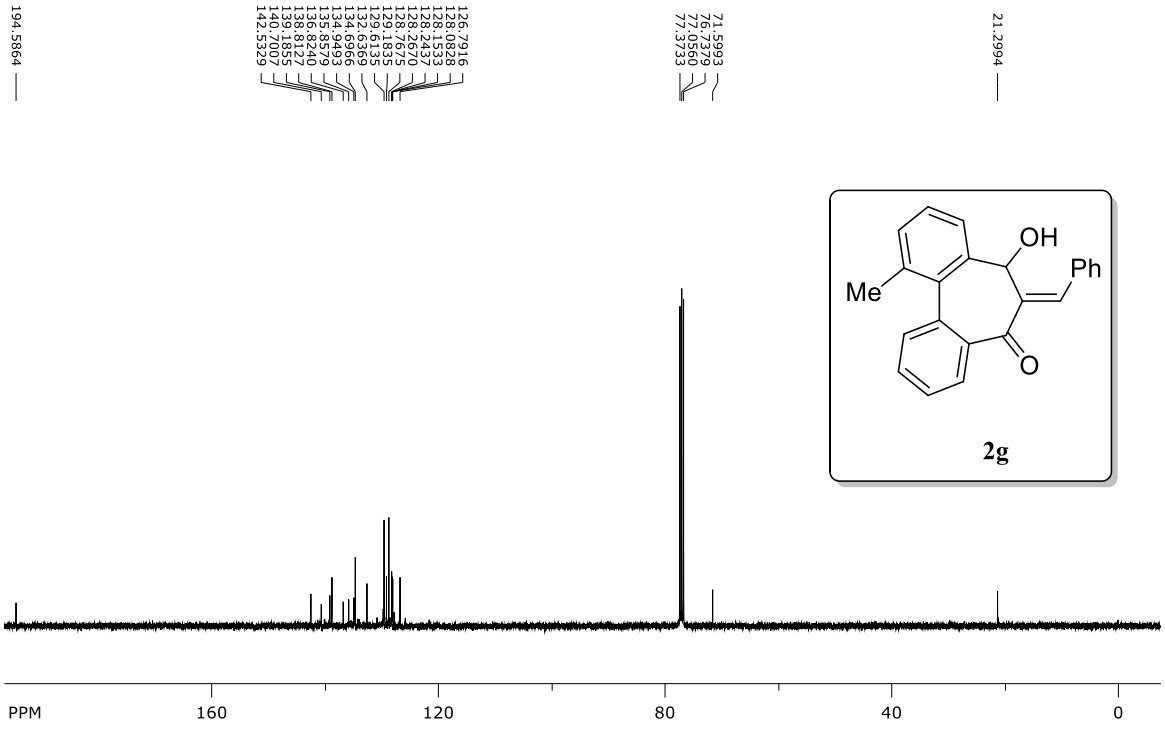
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Ph
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2g
PPM
160
120
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Conclusion

To conclude, we were able to successfully validate our hypothesis by carrying out an IMBH on enone-aldehyde system. A wide range of substrates was synthesized by using this method with excellent yield in short reaction time. Several efforts were made to obtain an enantioselective variant of the method. However, all the methods above were unable to provide a reasonable yield and enantioselectivity. Further enantioselective studies and some useful elaborations are underway.

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