

Synthetic Utilities of *in Situ* Formed Acetal: A Facile Access to Substituted Naphthalene, Benzo[*a*]fluorene and Indene Derivatives

A Thesis Submitted for the Degree of

DOCTOR OF PHILOSOPHY

In Chemistry

by

Seetharaman Manojveer

Reg. No. 09CHPH36

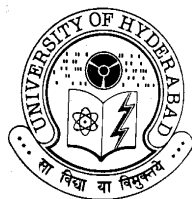
Under the Supervision of

Dr. R. Balamurugan



**SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD 500 046
INDIA**

DECEMBER 2014



School of Chemistry
University of Hyderabad
P.O. Central University
Hyderabad 500 046
India

Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Dr. Rengarajan Balamurugan**.

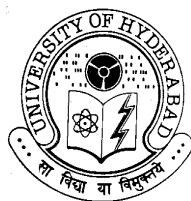
In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

University of Hyderabad

December, 2014

Seetharaman Manojveer

09CHPH36



**School of Chemistry
University of Hyderabad
P.O. Central University
Hyderabad 500 046
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Certificate

Certified that the work embodied in this thesis entitled “**Synthetic Utilities of *in Situ* Formed Acetal: A Facile Access to Substituted Naphthalene, Benzo[a]fluorene and Indene Derivatives**” has been carried out by **Mr. SEETHARAMAN MANOJVEER** under my supervision and the same has not been submitted elsewhere for a degree.

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(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

***GOD GAVE ME NOTHING I WANTED
But, HE GAVE EVERYTHING I NEEDED***

Swami Vivekanandar...

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List of acronyms used

Å	Angstrom
Ac	Acetyl
Anal. Calc'd	Analytically calculated
Aq.	Aqueous
Ar	Aryl
BA	Brønsted acid
Bn	Benzyl
br s	Broad singlet (spectral)
<i>t</i> -Bu	<i>tert</i> -Butyl
°C	Degree Celsius
Calc'd	Calculated
Cat.	Catalytic
cm ⁻¹	Wavenumber(s)
conc.	Concentrated
δ	Chemical shift in parts per million
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets (spectral)
DDL	diacetyldihydrolutidine
dil.	Dilute
DMF	N,N-Dimethylformamide
dr	Diastereomeric ratio
dt	Doublet of triplets (Spectral)
ee	Enantiomeric excess
equiv	Equivalent
ESI	Electron spin ionisation
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
FT	Fourier transformation
g	Gram(s)
h	Hour(s)
HRMS	High resolution mass spectrometry

Hz	Hertz
<i>i</i> -Pr	Isopropyl
IR	Infrared
<i>J</i>	Coupling constant (in NMR Spectroscopy)
K	Kelvin (Temperature)
LA	Lewis acid
LCMS	Liquid chromatography-mass spectrometry
<i>Lit.</i>	Literature
M	Molar (Solution concentration)
m	Multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre (s)
mmol	Millimole(s)
mp	Melting point
MS	Molecular sieves
μL	microlitre
NMR	Nuclear magnetic resonance
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Trifluoromethanesulfonate
Ph	Phenyl
PMA	Phosphomolybdic acid
PTSA/ <i>p</i> -TsOH	<i>p</i> -Toluenesulfonic acid
q	Quartet (spectral)
<i>R_f</i>	Retardation factor
RT	Room temperature
s	Singlet (spectral)
t	Triplet (spectral)
TBDMS	<i>tert</i> -Butyldimethylsilyl ether
td	Triplet of doublets(spectral)
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TMOF	Trimethyl orthoformate
TMSCl	Trimethylsilyl chloride
TTN	thallium(III) trinitrate
UV	Ultraviolet

SYNOPSIS

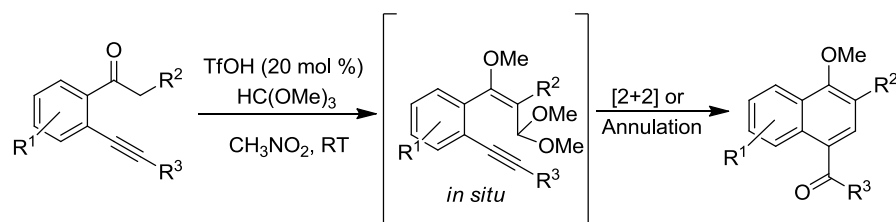
This thesis contains five chapters and one annexure part.

Chapter 1: Survey of Acetal-Assisted Organic Transformations

Chapter 1 describes the synthetic opportunities of acetal and the literature on acetal-assisted organic transformations such as oxidative rearrangements, Mukaiyama-aldol reactions, ketal-Claisen rearrangements, C-C, C-heteroatom bond formations, heteroalkyne metathesis, aryl group and alkoxyl group migrations. Acetal exhibits interesting properties to facilitate useful transformations which are otherwise difficult to achieve or not possible in the absence of acetal. An acetal will be the key functionality/intermediate to achieve the aforementioned transformations. Overall, this chapter will demonstrate the use of acetals beyond its trivial application as protecting group.

Chapter 2: Synthesis of Naphthalene Derivatives From *ortho*-Alkynylacetophenone Derivatives via *in Situ* Incorporation of Acetal

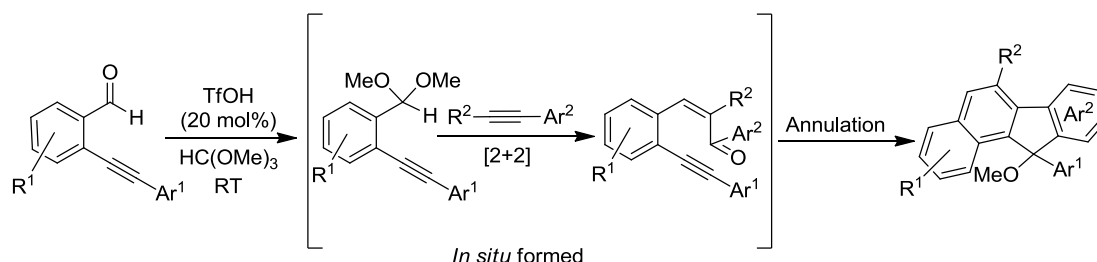
Chapter 2 presents synthesis of naphthalene derivatives from *ortho*-alkynylacetophenone derivatives in the presence of trimethyl orthoformate and triflic acid catalyst. An acetal moiety is incorporated at the α -carbon of *o*-alkynylacetophenone in the presence of trimethyl orthoformate and TfOH. The formed β -ketoacetal undergoes heteroalkyne metathesis/annulation to give substituted naphthalenes (Scheme 1). This transformation shows significant substrate scope which has been discussed in this chapter. Two different mechanistic pathways have been proposed for the construction of naphthalene derivatives. A deuterium incorporation experiment has been carried out to understand the mechanism.



Scheme 1: Incorporation of acetal and alkyne-carbonyl metathesis/annulation of *ortho*-alkynylacetophenone derivatives.

Chapter 3: A Facile Access to Substituted Benzo[*a*]fluorenes from *o*-Alkynylbenzaldehydes via *in Situ* Formed Acetals

Chapter 3 demonstrates the synthesis of substituted benzo[*a*]fluorenes from *o*-alkynylbenzaldehydes and arylalkynes via *in situ* formed acetals (Scheme 2). It is known that the reaction of *o*-alkynylbenzaldehydes and alkynes results in naphthalene derivatives on reaction with Lewis/Brønsted acids. *In situ* formed acetal changes the course of Brønsted acid-catalyzed reaction of *ortho*-alkynylbenzaldehydes with arylalkynes altogether. By utilizing this, an efficient domino approach for the regioselective synthesis of substituted benzo[*a*]fluorenes has been developed under mild reaction conditions. This transformation takes place via [2+2] cycloaddition/alkyne acetal coupling of *in situ* generated acetal followed by double bond isomerization which facilitates the intramolecular cyclization to construct a benzo[*a*]fluorene framework. Substrate scope was studied with both terminal and internal arylalkynes. Several benzo[*a*]fluorene derivatives with different functional groups have been prepared using this method. In order to understand the mechanistic pathway few control experiments were carried out which are discussed in this chapter. These control experiments demonstrate that *in situ* formed acetal not only helps for [2+2] cycloaddition reaction but also assists the *trans-cis* isomerization to undergo annulation to generate fluorene derivatives.

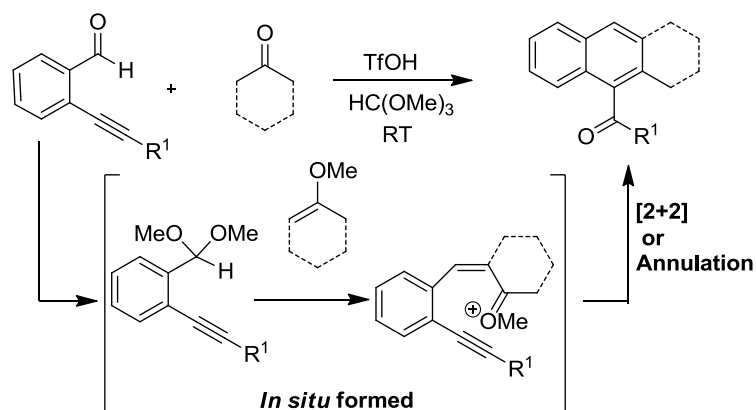


Scheme 2: Synthesis of benzo[*a*]fluorene derivatives from *o*-alkynylbenzaldehydes

Chapter 4: A New Approach to Naphthalene Derivatives from *o*-Alkynylbenzaldehydes and Enolizable Ketones via *in Situ* Formed Acetals

In this chapter a new approach for the synthesis of naphthalene derivatives from *o*-alkynylaldehydes and enolizable ketones (Scheme 3) is described. This cascade reaction involves Claisen-Schmidt condensation followed by heteroalkyne metathesis/annulation. *In situ* formed acetal assists the Claisen-Schmidt condensation between *o*-alkynylbenzaldehydes and enolizable ketones to give chalcone derivatives. This reaction is facilitated by increasing the electrophilicity of carbonyl carbon of *o*-alkynylbenzaldehyde through oxonium ion formation and enhancing the nucleophilicity of α carbon of ketone via the formation of enol ether from enolizable carbonyl compounds. The formed chalcones undergo *trans* to *cis* isomerization to effect heteroalkyne metathesis/annulation to furnish naphthalene derivatives. The substrate scope has been examined by using both cyclic and acyclic ketones with different *o*-alkynylaldehydes to synthesize

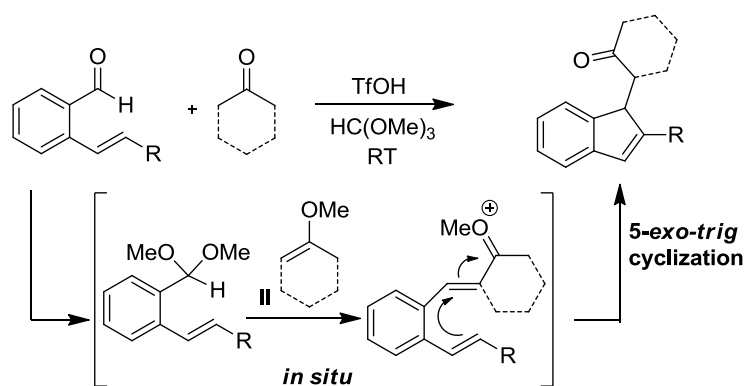
corresponding naphthalene derivatives in good yields. A mechanism has been proposed which contains both heteroalkyne metathesis path and annulation path to construct the naphthalene ring.



Scheme 3: Synthesis of naphthalene derivatives from *o*-alkynylbenzaldehydes

Chapter 5: *In Situ* Formed Acetal-Assisted Synthesis of Substituted Indene Derivatives

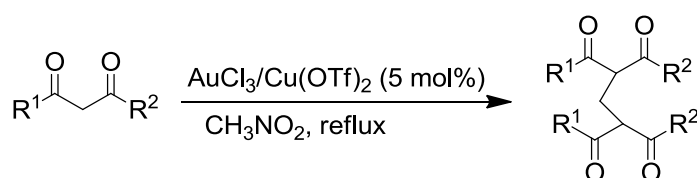
Chapter 5 describes the synthesis of indene derivatives from *o*-alkenylbenzaldehydes and enolizable ketones in the presence of trimethyl orthoformate and triflic acid catalyst (Scheme 4). This domino process involves acetal-assisted Claisen-Schmidt condensation followed by 5-*exo-trig* cyclization/Michael addition. The soft nature of alkene makes it to attack the soft alkene double bond rather than the hard carbonyl carbon during the cyclization step. We have also shown that the chalcones derived from *o*-alkenylbenzaldehydes and ketones can effectively be transformed into indene derivatives in the presence of TfOH catalyst alone. Moreover, it is disclosed that *o*-alkenylbenzaldehyde with electron donating substitution at R group undergoes [4+2] cycloaddition with enolizable carbonyl compounds to afford naphthalene derivative. Separate mechanistic pathways have been proposed for the synthesis of indene and naphthalene derivatives from *o*-alkenylbenzaldehydes.



Scheme 4: Synthesis of indene derivatives from *o*-alkenylbenzaldehydes

Annexure: Gold/Copper-Catalyzed Activation of the *aci*-Form of Nitromethane

Activation of *aci*-form of nitromethane using Lewis acids and its reaction with carbon nucleophiles is presented in the annexure part. 1,3-Dicarbonyl compounds, upon refluxing with catalytic $\text{AuCl}_3/\text{Cu}(\text{OTf})_2$ in nitromethane, gave methylene-bridged bis-1,3-dicarbonyl compounds (Scheme 5). It is envisaged that the bridging methylene group should have come from the solvent nitromethane. The reaction occurs *via* the initial nucleophilic attack of the 1,3-dicarbonyl compound on the *aci*-form activated by Lewis acid, just like the attack of water taking place in the classical Nef reaction (Figure 1). The substrate scope was studied with aryl and alkyl 1,3-diketones, β -ketoesters and 1,3-diester under both gold and copper catalysis separately. Present methodology was extended to other carbon nucleophiles such as indole, xylene, mesitylene, etc., and results have been documented in this chapter.



Scheme 5: Activation of the *aci*-form of nitromethane for the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds

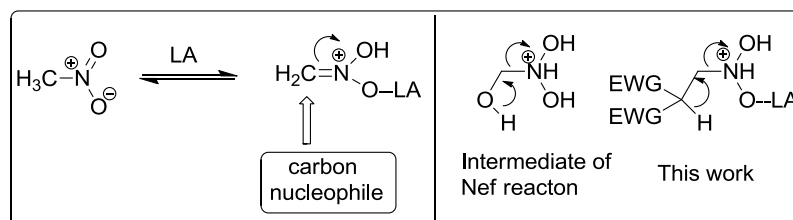


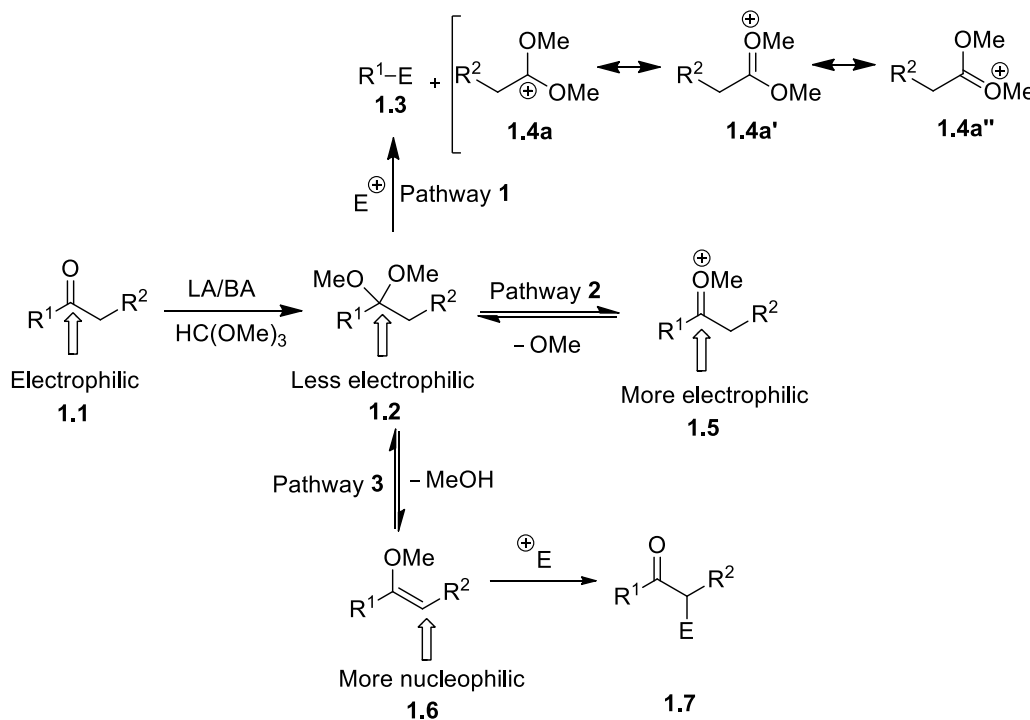
Figure 1

In order to understand the mechanism, trapping experiments and Nash test were carried out which are described in mechanistic part of this chapter.

Survey of Acetal-Assisted Organic Transformations

1. 1 Introduction

Acetals are traditionally used as protecting groups for carbonyl function of ketones and aldehydes due to their chemical inertness under many reaction conditions.¹ However, acetals exhibit interesting properties to facilitate some useful transformations which are otherwise difficult to achieve or not possible in the absence of them. The synthetic opportunities that one can think of using acetal are depicted in Scheme 1.1. The carbonyl compound **1.1** can be converted into its acetal **1.2** in the presence of trialkyl orthoformate (eg. trimethyl orthoformate) and a Lewis acid (LA)/Brønsted acid (BA) catalyst. From acetal **1.2**, R¹ group can migrate to an electrophilic centre to make a new bond. This migration is facilitated by the stabilization of carbocation **1.4a** intermediate by two methoxy groups of acetal (Scheme 1.1, pathway 1). On the other hand, methoxy group can leave from acetal **1.2** to give more reactive oxonium ion **1.5** (Scheme 1.1, pathway 2). When compared to the parent carbonyl compound, **1.1** the oxonium ion **1.5** is more electrophilic in nature and it can undergo new transformations with various nucleophiles under mild reaction conditions. Such intermediate has been utilized extensively in organic synthesis. Alternatively, the acetal can eliminate a molecule of alcohol (here MeOH) to form enol ether **1.6**. This intermediate can advantageously be utilized to obtain the product of α -functionalization of carbonyl compounds (Scheme 1.1, pathway 3).

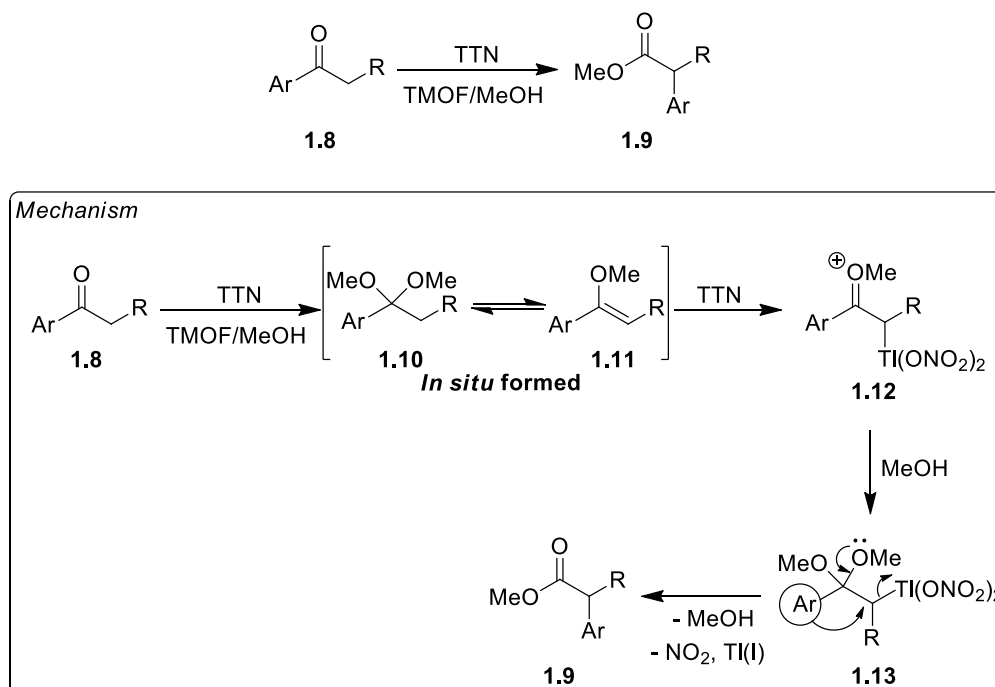
Scheme 1.1: Synthetic opportunities of *in situ* formed acetal

The following section summarizes the reactions carried out using acetals. Many of them employ the acetals formed *in situ*.

1.2 Acetal-assisted reactions

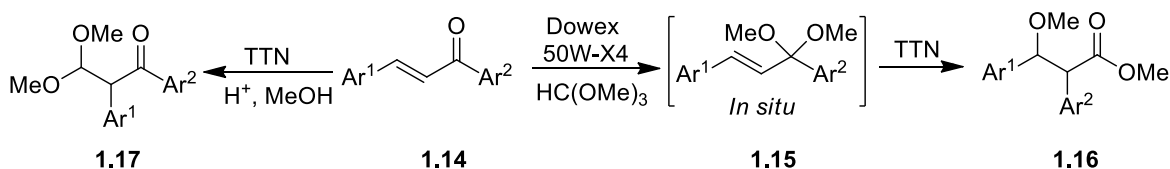
1.2.1 Oxidative rearrangements

Taylor and co-workers disclosed a thallium(III) trinitrate (TTN) mediated oxidative rearrangement of substituted acetophenones **1.8** to methyl arylacetates **1.9** in methanol (Scheme 1.2).² Later, the efficiency and selectivity of this conversion was improved by using trimethyl orthoformate (TMOF) along with methanol. Acetal **1.10** formed from ketone **1.8** generates enol ether **1.11** which attacks TTN to give intermediate **1.12**. Addition of methanol followed by acetal-assisted aryl migration results in ester derivative **1.9** (Scheme 1.2, mechanism).



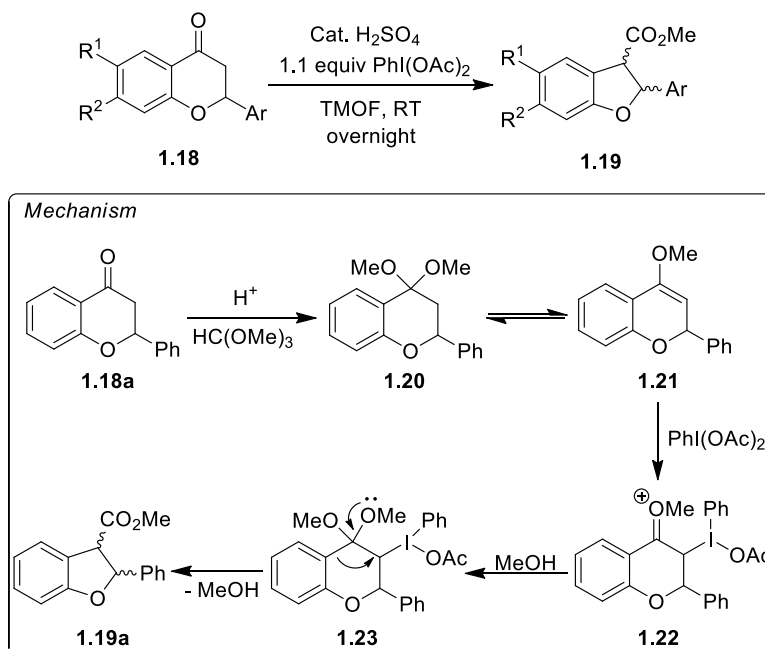
Scheme 1.2: Oxidative rearrangement of acetophenone derivatives

Oxidative rearrangement of chalcone dimethyl acetal **1.15** to methyl 2,3-diaryl-3-methoxypropanoate **1.16** was described by the same group where the chalcone **1.14** was first converted into acetal **1.15** using trimethyl orthoformate and Dowex 50W-X4 cation-exchange resin (Scheme 1.3).³ The acetal **1.15**, upon treatment with thallium(III) trinitrate (TTN), affords methyl 2,3-diaryl-3-methoxypropanoate **1.16** by rearrangement of the Ar² group. On the other hand, Ar¹ migrates to give 3,3-dimethoxy-1,2-diarylpropan-1-ones **1.17** when chalcone **1.14** is treated with TTN in acidic methanol. Thus, the *in situ* formed acetal changes the reactivity of chalcones.



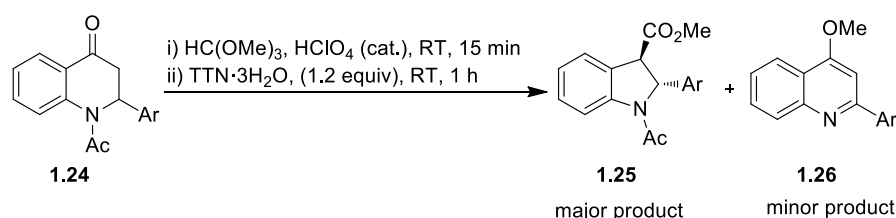
Scheme 1.3: Oxidative rearrangement of chalcones

Ring-contraction of cycloalkanones has been achieved by oxidative rearrangement of *in situ* generated acetal using different oxidizing agents.⁴ For instance, flavanones **1.18** on treatment with hypervalent iodine furnish dihydrobenzofuran derivatives **1.19** in trimethyl orthoformate as solvent (Scheme 1.4a). This ring-contraction involves an electrophilic addition of the iodine(III) reagent on enol ether **1.21** formed from acetal **1.20** to give oxonium ion intermediate **1.22**. Subsequent alcohol addition and aryl group migration in the intermediate acetal **1.23** affords the ring-contraction product dihydrobenzofuran derivative **1.19a** (Scheme 1.4a, mechanism).



Scheme 1.4a: *In situ* acetal-promoted oxidative rearrangement of flavanones

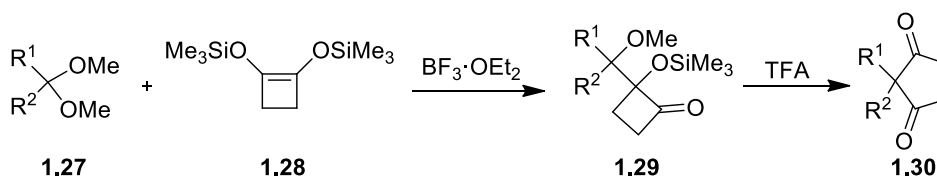
Sundaravadivelu and co-workers reported the oxidative ring-contraction of tetrahydro-4-quinolones **1.24** with TTN in trimethyl orthoformate in the presence of catalytic perchloric acid to make dihydroindole derivatives **1.25** (Scheme 1.4b).⁵ Quinoline derivatives **1.26** were obtained in minor yields due to the aromatization of *in situ* formed acetals. This reaction is stereoselective in nature and follows the same mechanistic route as described in Scheme 1.4a.



Scheme 1.4b: Oxidative rearrangement of tetrahydro-4-quinolones

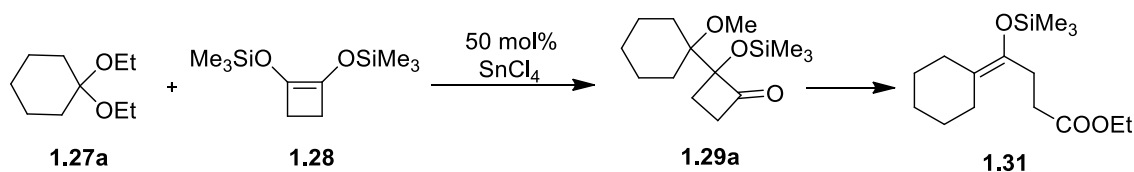
1.2.2 Mukaiyama-aldol type reactions

In 1977, Kuwajima and co-workers utilized the acetals **1.27** for the synthesis of aldol adducts **1.29** using 1,2-bis(trimethylsiloxy)-1-cyclobutene **1.28** in the presence of Lewis acid promotor.⁶ Since the acetal coordinates more strongly with Lewis acid than its carbonyl form, the reaction of acetals gave good yields of products and the reactions were more effective than that of the parent carbonyl compounds. The aldol adducts **1.29** can undergo pinacol rearrangement to afford high yields of cyclopentanediones **1.30** in the presence of TFA at room temperature (Scheme 1.5a).



Scheme 1.5a: Reactions of 1,2-bis(trimethylsilyloxy)cyclobutenes with acetals

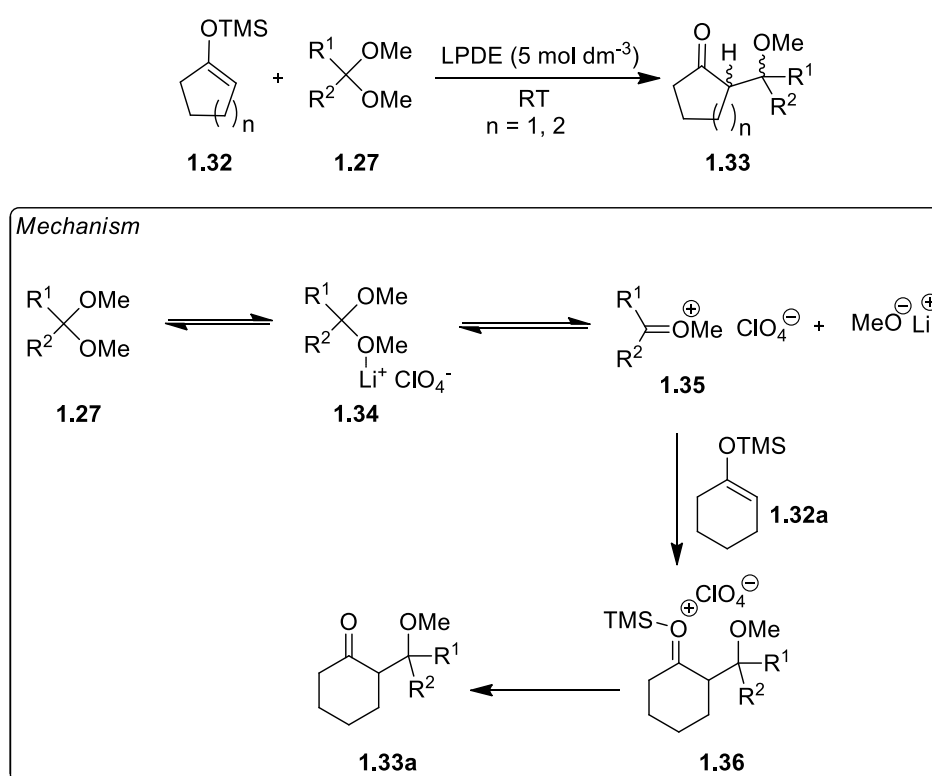
Later, the same group reported the ring-cleavage of aldol adduct **1.29a** to give enol silyl ether derivative **1.31** in the presence of SnCl_4 .⁷ Using 50 mol% SnCl_4 , both aldol and ring-opening reactions were succeeded in single operation to synthesize the compound **1.31** starting from cyclohexanone diethylacetal **1.27a** in 86% yield (Scheme 1.5b).



Scheme 1.5b: SnCl_4 -mediated reactions of 1,2-bis(trimethylsilyloxy)cyclobutenes with acetals

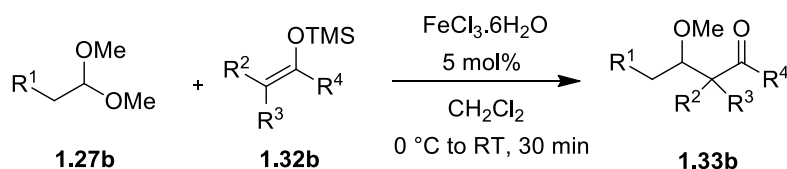
An acetal generates an oxocarbenium ion in the presence of Lewis acid or Brønsted acid catalyst. Thus, formed oxonium ion is more reactive towards various nucleophiles. The reaction of acetal **1.27** with silyl enol ether **1.32** affords the β -methoxy ketone derivative **1.33**. Since strong Lewis acids are required, the chemoselectivity of this bond forming reaction is less. Sankararaman and co-workers described an efficient and chemoselective conversion of acetals **1.27** into corresponding β -methoxy ketone derivative **1.33** upon treatment with silyl enol ether

1.32 in 5 mol dm⁻³ lithium perchlorate-diethyl ether (LPDE) at ambient temperature (Scheme 1.6a).⁸ Under this reaction conditions aldehydes and ketals were unreactive. The chemoselectivity arose due to the fact that mild Lewis acidity of lithium salt is sufficient to activate the acetal to generate more reactive oxocarbenium ion to react with silyl enol ether nucleophiles. The authors showed the evidence for the formation of oxocarbenium ion **1.35** from acetals.^{8b} Based on this the following mechanism was proposed (Scheme 1.6a, mechanism).



Scheme 1.6a: Aldol type condensation of silyl enol ethers with acetals

Very recently, Medio-Simón and co-workers have used acetals of enolizable aldehydes **1.27b** for Mukaiyama-aldol type reactions to make β -methoxycarbonyl compounds **1.33b** in quantitative yields using FeCl₃·6H₂O as catalyst. The authors showed that acetal can be considered as activating groups of carbonyl moiety rather than a protecting group (Scheme 1.6b).⁹



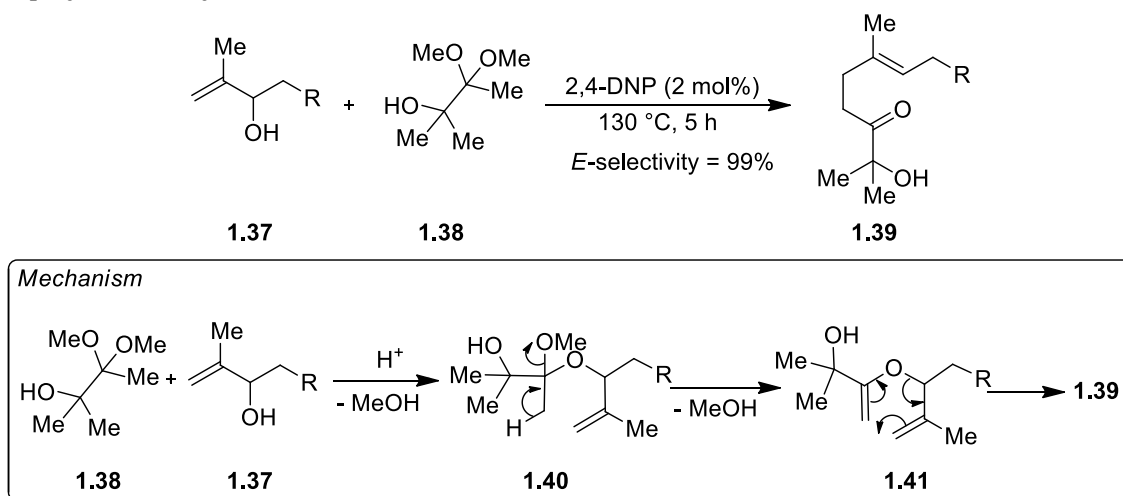
Scheme 1.6b: Mukaiyama-aldol type reactions with enolizable acetals

Thus, the oxocarbenium ion generated from acetals is more electrophilic than the corresponding carbonyl group. The reactions of acetals are more efficient than their parent

carbonyl compounds since the reactions of aldehydes gave β -hydroxycarbonyl compounds in lower yields.

1.2.3 Ketal-Claisen rearrangement

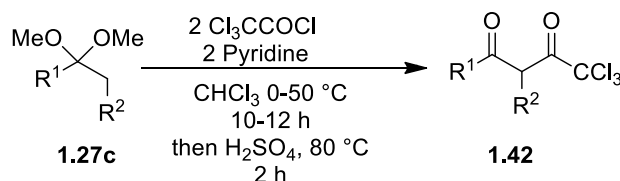
Brønsted acid-catalyzed reaction of allylic alcohol **1.37** with 2,2-dimethoxy-3-methyl-3-butanol **1.38** to make γ - δ -unsaturated ketone was reported by Takayanagi and Morinaka (Scheme 1.7).¹⁰ In the presence of Brønsted acid catalyst, alkyl vinyl ether **1.41** generated from acetal **1.40** undergoes Claisen rearrangement to give α -ketol **1.39** in high yield with good *E*-selectivity (Scheme 1.7, mechanism). The resulting isoprene unit containing product was successfully employed in the synthesis of marine cembranoids.



Scheme 1.7: Ketal-Claisen rearrangement

1.2.4 C-C, C-Heteroatom bond formation from *in situ* formed enol ether

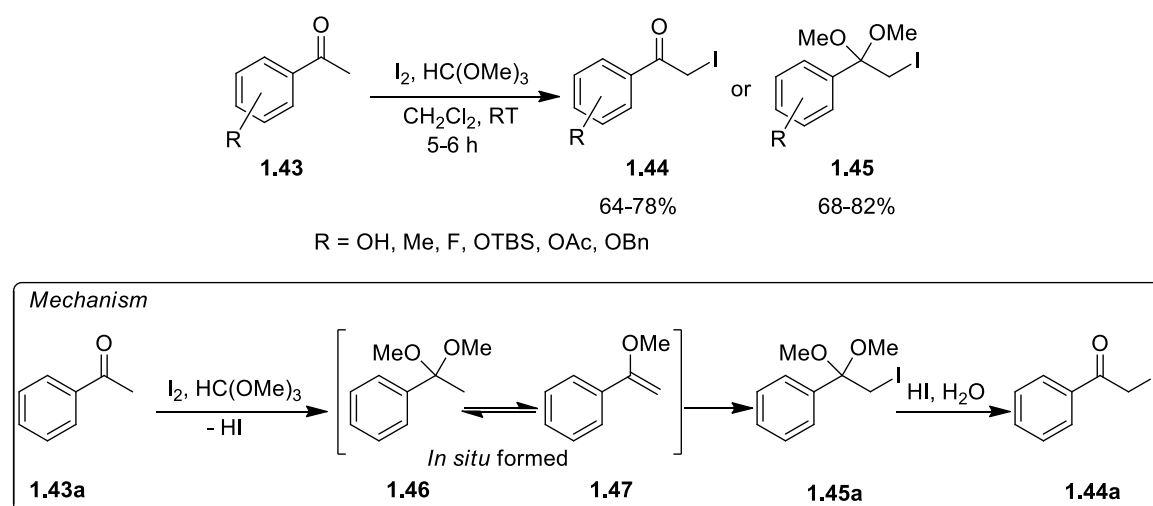
The trihalomethyl- β -diketone **1.42** is a versatile building block for the synthesis of various heterocyclic derivatives.¹¹ Due to the labile nature of perhaloalkyl groups in basic medium, the C-acylation of enolates by Claisen condensation has limited scope to synthesize them. To overcome this, Martins *et al.* developed an improved method for the synthesis of trichloromethyl- β -diketones in which acetals **1.27c** were acylated with trichloroacetyl chloride (Scheme 1.8).^{12a} Here, acetals generate enol ethers which undergo acylation with trichloromethylacetyl chloride to give trichloromethyl- β -diketone **1.42** in good yields under mild reaction conditions.



Scheme 1.8: Acylation of acetal with trichloroacetyl chloride

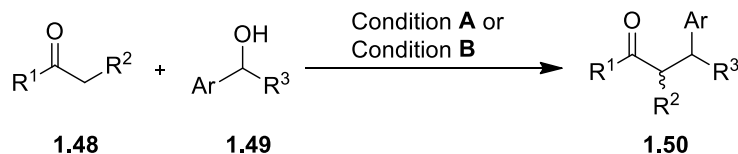
A few years later, the same group established an efficient and green protocol for C-acylation of *in situ* generated enol ether from acetal with trichloroacetyl chloride or trifluoroacetic anhydride in the presence of equimolar amounts of pyridine and imidazolium based ionic liquid.^{12b}

α -Halogenated ketones, particularly α -iodo ketones **1.44**, are useful intermediates in synthetic community.¹³ Several approaches have been established for their synthesis by using various Lewis acid and Brønsted acid catalysts and iodine sources. However, all these reactions require either harsh acidic conditions or toxic metals or elevated temperatures. To overcome these limitations, Yadav and co-workers developed a simple protocol to synthesize α -iodo ketones **1.44** from aryl methyl ketones **1.43** using iodine and trimethyl orthoformate under neutral reaction conditions (Scheme 1.9).¹⁴ The iodination of ketone occurs *via* enol ether **1.47** derived from *in situ* formed acetal **1.46** (Scheme 1.9, mechanism).



Scheme 1.9: Iodination of acetophenones using trimethyl orthoformate and iodine

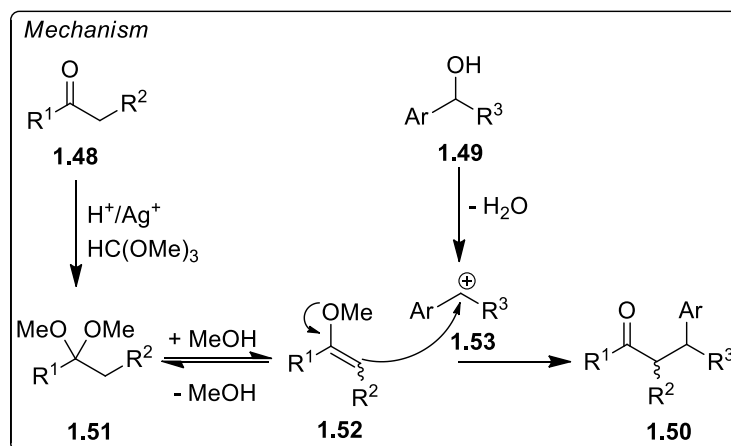
The nucleophilicity of alkyl ketones can be enhanced by converting them into enol ethers which, in turn, could be generated from *in situ* formed acetals. Thus, enol ether can attack an electrophilic centre which is activated by LA/BA catalysts. Using this concept, our research group has developed direct α -alkylation of unactivated ketones **1.48** with various alcohols **1.49** such as diaryl methanol, allyl alcohols and propargyl alcohols having different electrophilicities (Scheme 1.10).¹⁵ Alkyl ketone generates enol ether **1.52** from *in situ* formed acetal **1.51** upon treatment with trimethyl orthoformate in the presence of stoichiometric triflic acid/catalytic AgSbF_6 . The enol ether **1.52** undergoes alkylation with carbocation **1.53** formed from alcohol **1.49** in the same pot to give α -alkylated ketone derivative **1.50** (Scheme 1.10, mechanism).



Condition A: TfOH (1 equiv), HC(OMe)₃ (1 equiv), CCl₄, RT

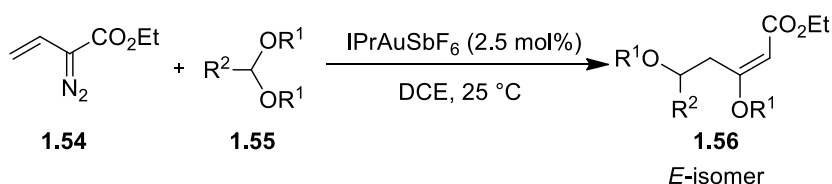
Condition B: AgSbF₆ (10 mol%), HC(OMe)₃ (2 equiv), CH₂Cl₂, RT/heat

R¹ = Aryl/alkyl; R² = H/alkyl; R³ = Aryl/cinnamyl/alkynyl

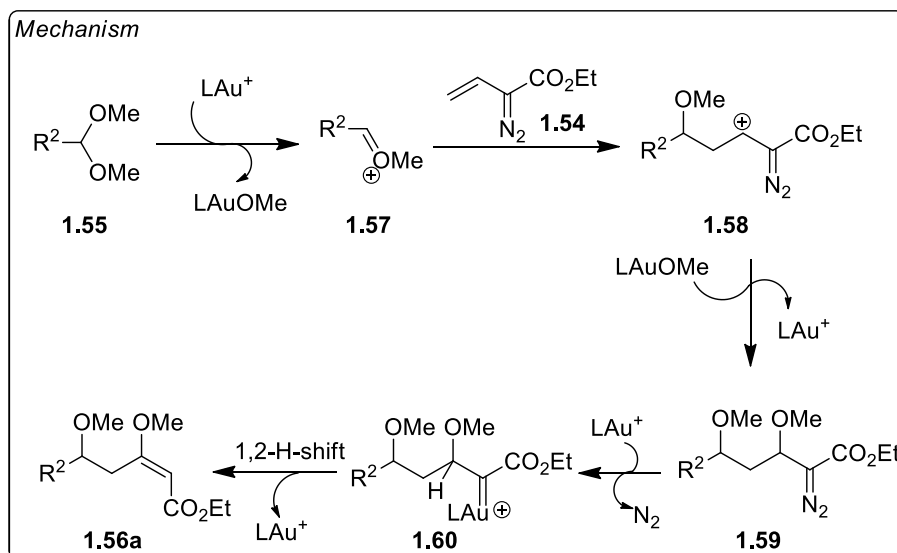


Scheme 1.10: Direct α -alkylation of unactivated ketones

Liu and co-workers have used acetals **1.55** for the carbon-carbon bond formation with vinyl diazo carbonyl compounds **1.54** to make ethyl 3,5-dimethoxy-5-pent-2-enoates **1.56** with exclusive *E*-configuration (Scheme 1.11).¹⁶ This reaction proceeds *via* the formation of oxonium ion **1.57** from acetal **1.55** in the presence of gold-catalyst. Then, Prins-type reaction is initiated by electrophilic addition of alkene to the oxonium ion to form a new carbocation **1.58** which is stabilized by the adjacent diazo group. Gold would react with diazo intermediate to give gold carbene species **1.60** which delivers the final product **1.56a** with *E*-configuration *via* stereoselective 1,2-hydride shift (Scheme 1.11, mechanism).



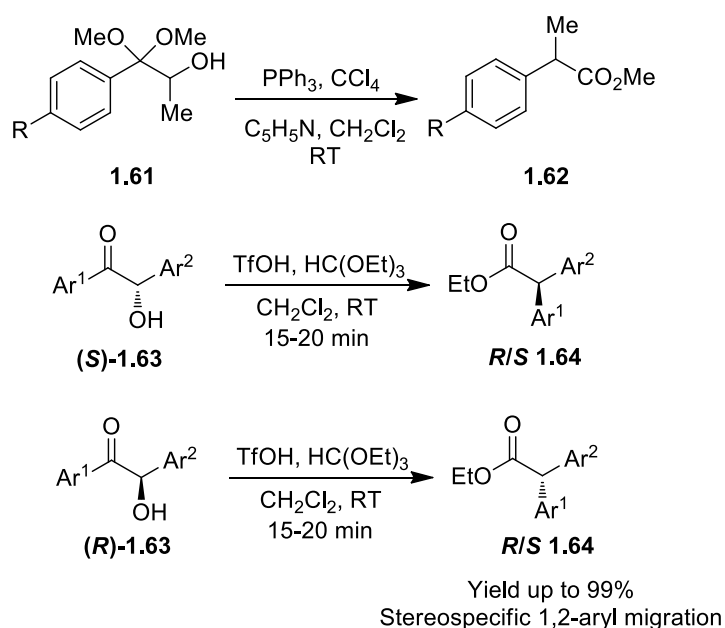
Scheme 1.11: Prins-type reaction between acetals and vinyl diazo carbonyl compounds



Scheme 1.11: Prins-type reaction between acetals and vinyl diazo carbonyl compounds

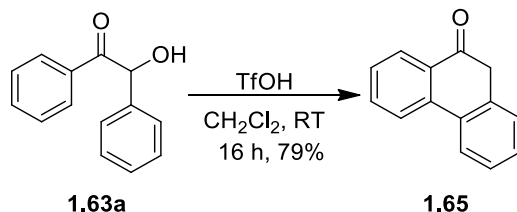
1.2.5 Migration of aryl group from acetal

Miroslav and co-workers utilized *in situ* formed acetals to synthesize α -aryl acetates by 1,2-aryl migration.^{17a} Later, Sonawane group found that 1,2-aryl migration from acetal **1.61** is highly stereospecific under basic conditions (Scheme 1.12). To demonstrate the application of this method, optically pure Ibuprofen and Naproxen were synthesized from corresponding acetals in high yields.^{17b} However, the scope of the aryl migration was not studied fully. Recently our group has reported the reaction of benzoin **1.63** with trimethyl orthoformate in the presence of triflic acid to give α -diarylacetic esters **1.64** (Scheme 1.12).^{17c} This is a simple protocol which involves 1,2-aryl migration from *in situ* formed acetal of benzoin in a stereospecific manner. Using this method, enantioenriched α -diarylacetates can be obtained from chiral benzoin.



Scheme 1.12: *In situ* formed acetal-assisted 1,2-aryl migration

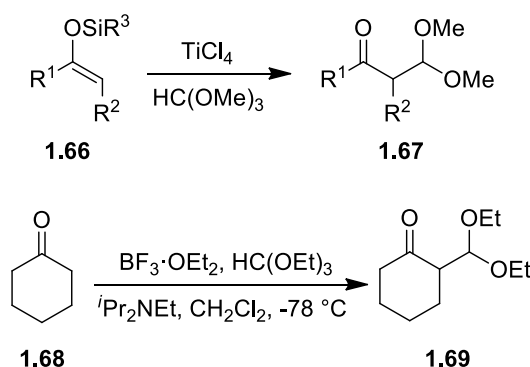
Interestingly, in the presence of TfOH alone benzoin **1.63a** undergoes acid-promoted benzannulation to afford product **1.65**. This was reported by Olah and co-workers in 1991 (Scheme 1.13).¹⁸ Hence, *in situ* formation of acetal is the key for the success of the 1,2-aryl migration of benzoin.



Scheme 1.13: Benzannulation of benzoin

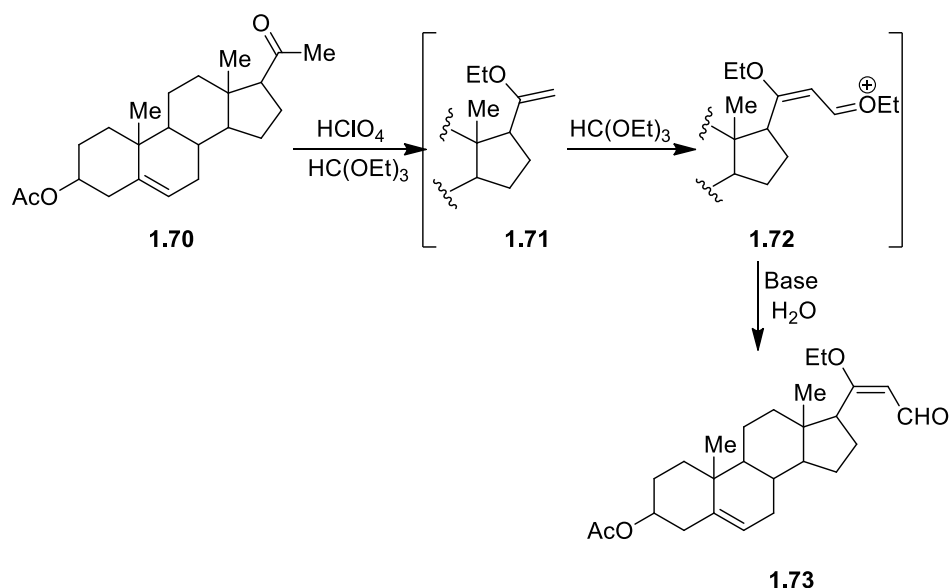
1.2.6 *In situ* acetal incorporation and cyclization

Incorporation of an acetal at the α -carbon of ketones is known to occur in the presence of trialkyl orthoformate and Lewis/Brønsted acids/bases. Mukaiyama and co-workers reported the formation of β -ketoacetal **1.67** from silyl enol ether **1.66** and trimethyl orthoformate in the presence of TiCl_4 (Scheme 1.14).¹⁹ Formation of β -ketoacetals from aliphatic and aromatic ketones was achieved by Mock and Tsou in the presence of *N,N*-diisopropylethylamine and boron trifluoride etherate.²⁰ Here, the reactive species is diethoxy carbonium fluoroborate which is generated under the reaction conditions. For example, cyclohexanone **1.68** on treatment with $\text{BF}_3 \cdot \text{OEt}_2$, triethyl orthoformate and *N,N*-diisopropylethylamine in dichloromethane at -78°C afforded β -ketoacetal **1.69** (Scheme 1.14).



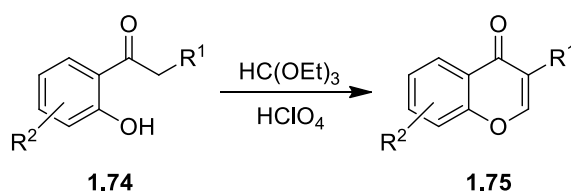
Scheme 1.14: Synthesis of β -ketoacetal using trialkyl orthoformate

Using perchloric acid, Dusza *et al.* developed the alkylation of steroid ketones **1.70** using trialkyl orthoformate.²¹ Under acidic conditions the formyl derivative **1.73** was obtained after hydrolysis of intermediate oxonium ion salt **1.72** formed by electrophilic attack of triethyl orthoformate on enol ether **1.71** (Scheme 1.15).



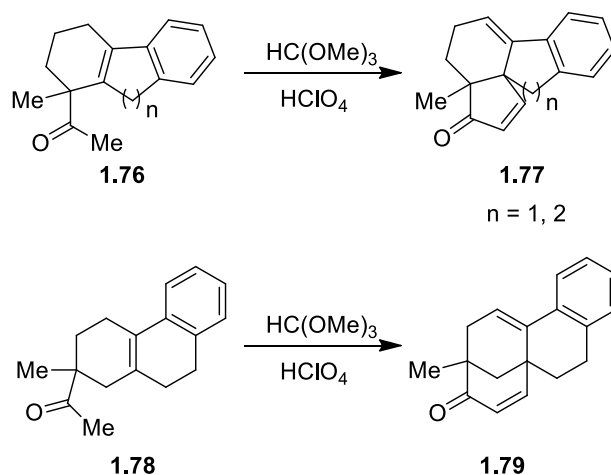
Scheme 1.15: Acid-catalyzed alkylation of steroid ketones with triethyl orthoformate

Dorofeenko and co-workers developed a method for high yielding synthesis of chromones **1.75** from aromatic hydroxy ketones **1.74** and triethyl orthoformate in the presence of perchloric acid (Scheme 1.16).²² Here, formed β -ketoacetal undergoes cyclization with hydroxyl group to give chromone derivatives **1.75**.



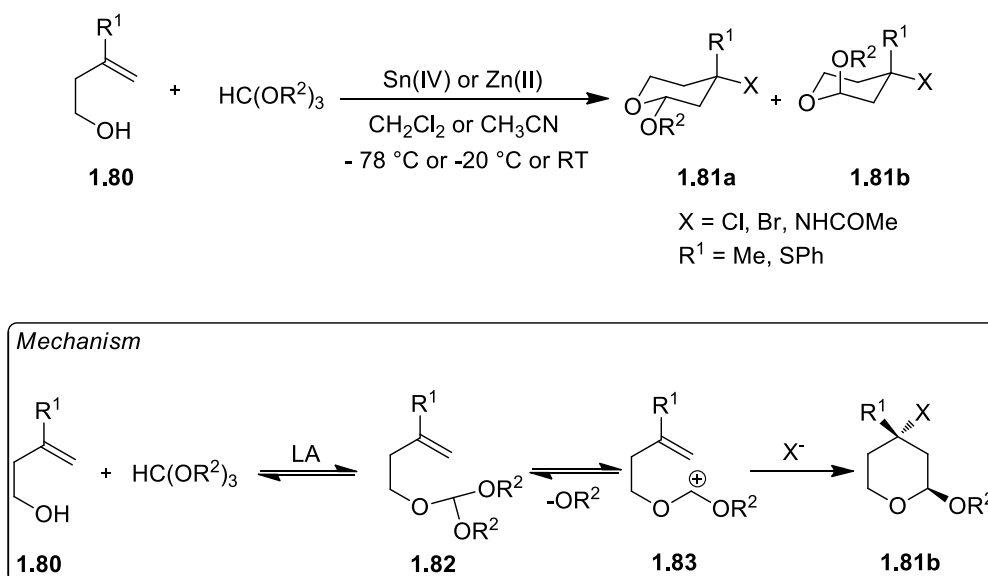
Scheme 1.16: Synthesis of chromones from aromatic *ortho*-hydroxy ketones

Ghatak and co-workers utilized such *in situ* formed β -ketoacetals in the synthesis of polycyclic compounds. This transformation involves one pot perchloric acid-catalyzed *in situ* formylation followed by annulation.²³ For example, β,γ -unsaturated methyl ketones **1.76** were transformed into tetracyclic ketones **1.77** upon treatment with excess trimethyl orthoformate in the presence of perchloric acid. Similarly, the γ,δ -unsaturated methyl ketone **1.78** furnished bridged [3.3.1]nonadienone **1.79** (Scheme 1.17).



Scheme 1.17: Reactions of β,γ - and γ,δ -unsaturated methyl ketones with triethyl orthoformate

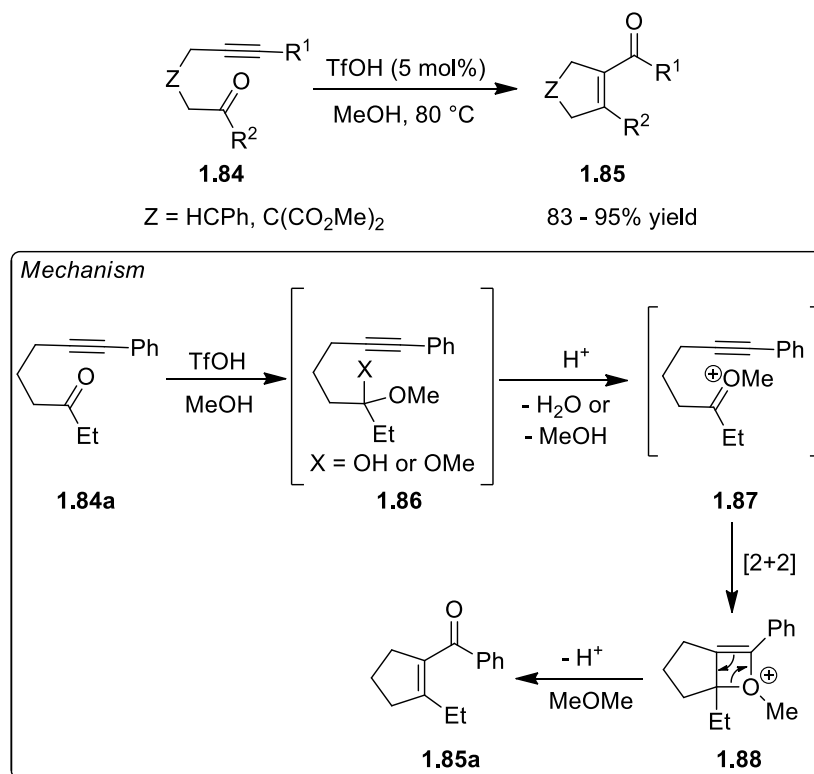
Perron and Albizati described a simple method for the construction of 4-heterosubstituted pyranoside **1.81** from homoallylic alcohol **1.80** and trialkyl orthoformate in the presence of Lewis acid (Scheme 1.18).²⁴ By choosing appropriate Lewis acid and solvent, different heteroatom groups can be incorporated at the 4-position of pyranoside **1.81**. For example, chloride and bromide can be incorporated when the reactions are performed with SnCl_4 and SnBr_4 respectively. The pyranoside ring with an amide group at the 4-position can be obtained by conducting the reaction in acetonitrile solvent. The reaction proceeds through the formation of mixed acetal **1.82** between homoallylic alcohol **1.80** and orthoester followed by cyclization (Scheme 1.18, mechanism). During the cyclization, the nucleophile and the oxonium ion approach the alkene in anti-periplanar fashion to give pyranoside **1.81b** as a major product in which alkoxyl group occupies axial position due to anomeric effect.



Scheme 1.18: Construction of pyranoside ring from homoallylic alcohol *via* orthoester

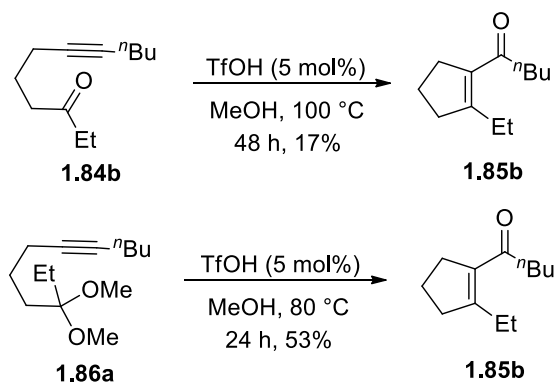
1.2.7 Acetal-assisted heteroalkyne metathesis and cyclization

Yamamoto and co-workers have established a carbocyclization of tethered alkynyl ketones **1.84** to cyclic enones **1.85** using triflic acid catalyst in methanol (Scheme 1.19a).²⁵ They showed that *in situ* formed acetal/hemiacetal **1.86** facilitates the intramolecular [2+2] cycloaddition/heteroalkyne metathesis efficiently to form oxetene intermediate **1.88** with alkyne which eventually gives cyclic enone **1.85a** in excellent yield (Scheme 1.19a, mechanism).



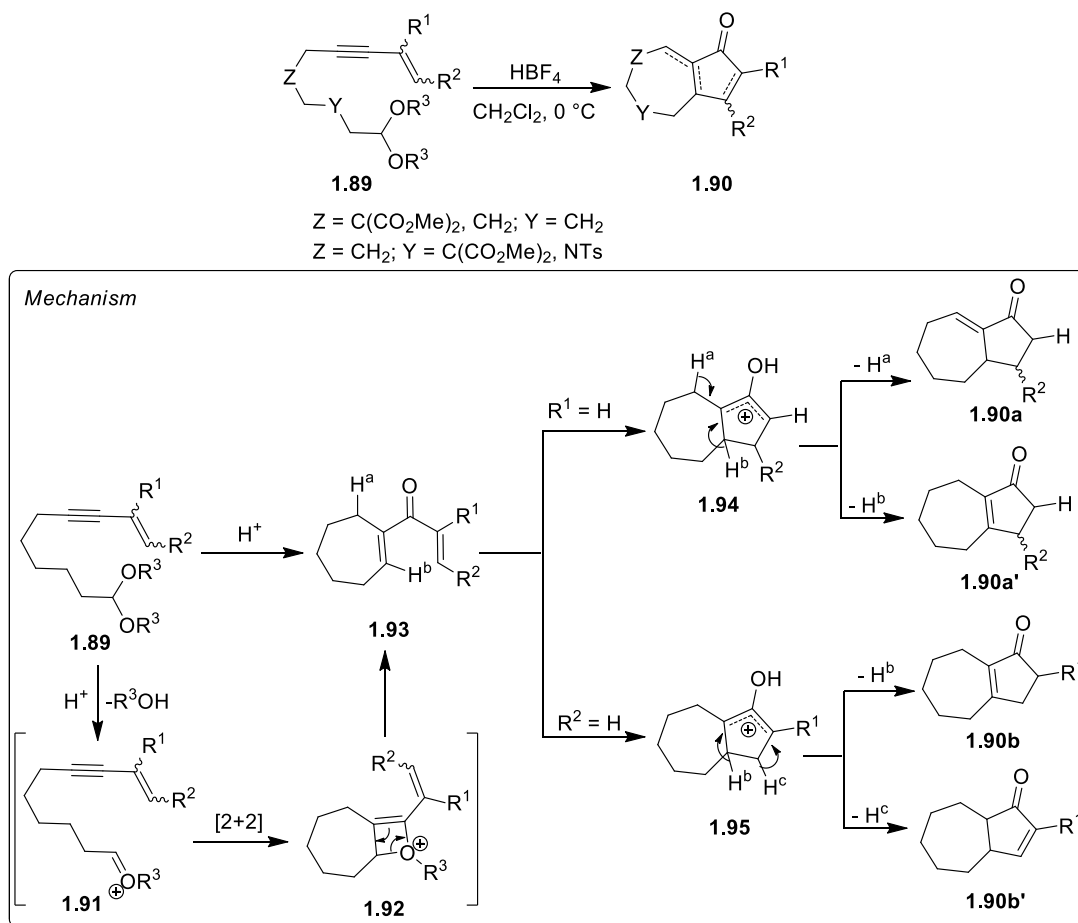
Scheme 1.19a: Carbocyclization of tethered alkynyl ketones *via* acetals/hemiacetals

The reaction of alkynyl ketones having alkyl groups as R¹ did not proceed well. However, corresponding the acetals gave their respective cyclic enones in moderate yields (Scheme 1.19b). Hence, *in situ* generated acetal/hemiacetal **1.86** assists the [2+2] cycloaddition *via* the formation of more active oxonium ion **1.87**.



Scheme 1.19b: Acetal-assisted [2+2] cycloaddition

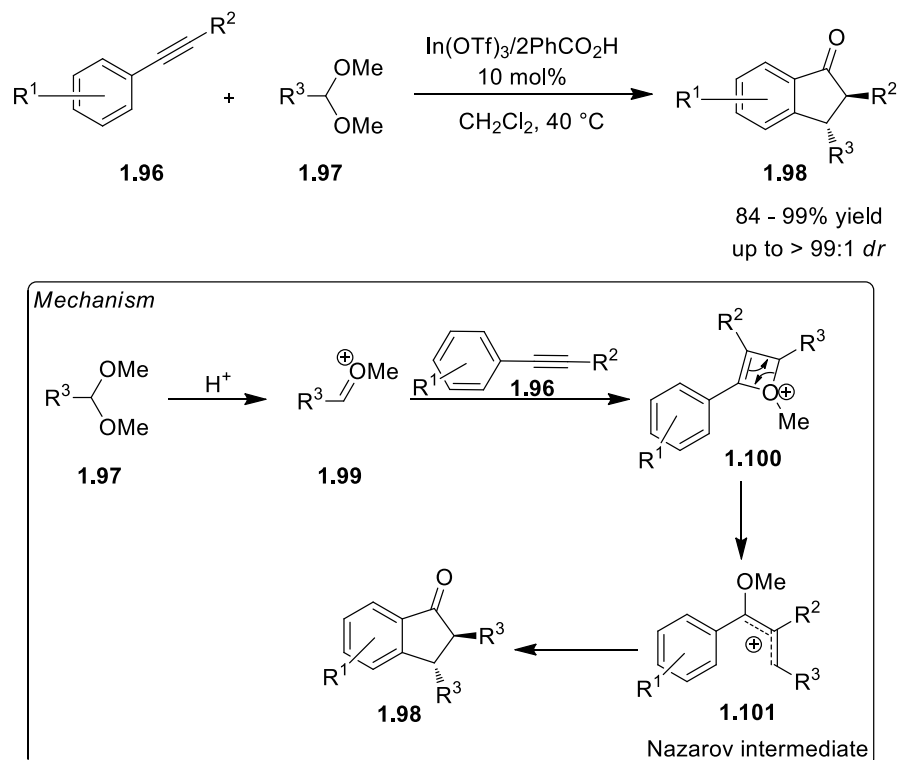
Saá and co-workers utilized linear enyne acetals **1.89** for the synthesis of hydroazulenones **1.90** in the presence of HBF_4 as Brønsted acid (Scheme 1.20).²⁶ The more reactive oxonium ion intermediate **1.91** formed from acetal **1.89** in the presence of Brønsted acid undergoes intramolecular heteroalkyne metathesis with the alkyne to give divinyl ketone **1.93**. Subsequently, stereospecific Nazarov cyclization would happen to afford hydroazulenones **1.90**. Depending on the starting material, elimination of proton will take place from the oxyallyl cation intermediates (**1.94** and **1.95**) to give respective bicyclo[5,3,0]decenones **1.90** (Scheme 1.20, mechanism).



Scheme 1.20: Tandem heteroalkyne metathesis and Nazarov cyclization of enyne acetals

Coupling of arylalkyne **1.96** and acetal **1.97** using combination of $\text{In}(\text{OTf})_3$ and benzoic acid to form 2,3-disubstituted indanone **1.98** in excellent yield and diastereoselectivity was reported by Zhu *et al.* (Scheme 1.21).²⁷ An intermolecular heteroenyne metathesis/[2+2] cycloaddition would take place between alkyne **1.96** and acetal **1.97** via more reactive oxonium ion **1.99** to give oxetene intermediate **1.100** which undergoes cycloreversion to afford Nazarov intermediate **1.101**. Finally, indanone ring will be formed by cyclization and aromatization of intermediate **1.101** (Scheme 1.21, mechanism). Although aldehydes are known to undergo [2+2]

cycloaddition with alkynes, a mixture of products was obtained under the reaction conditions. However, oxonium ion formation from acetal facilitates clean reaction.



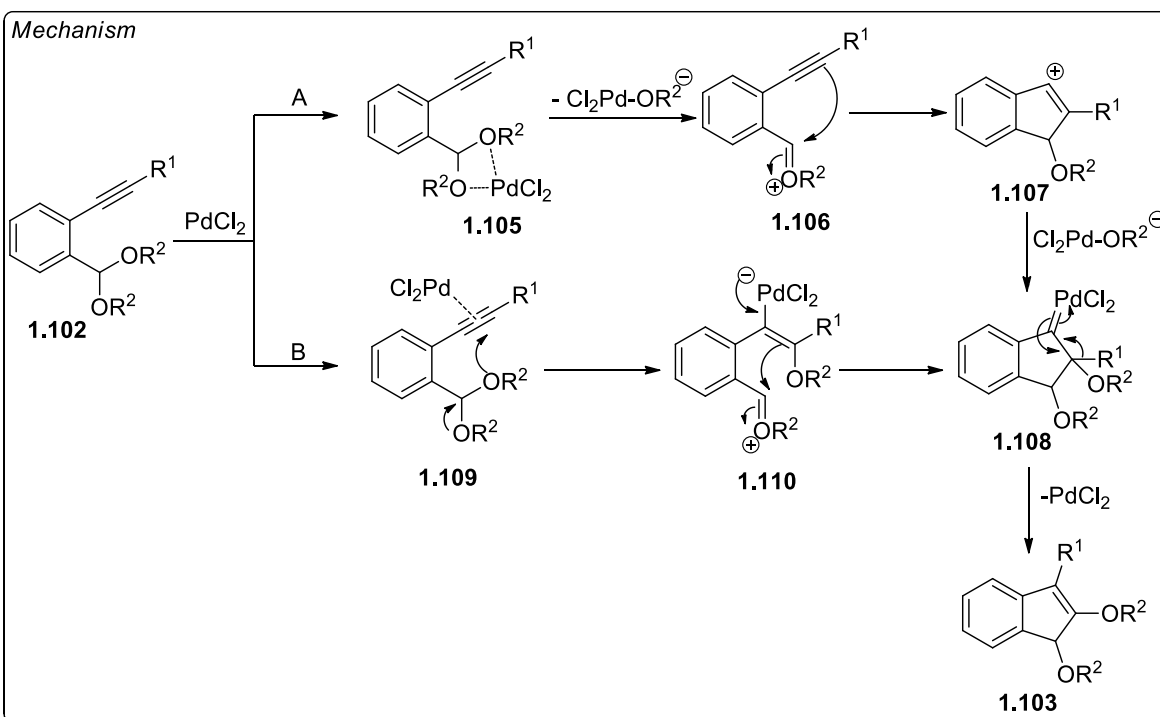
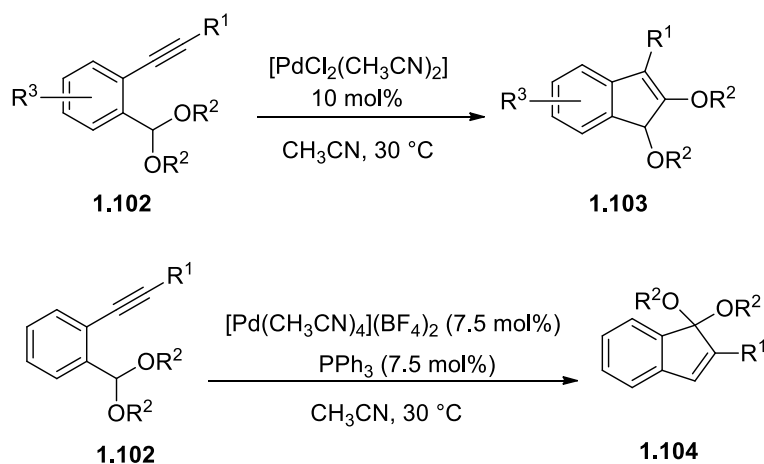
Scheme 1.21: [2 + 2] and subsequent Nazarov cyclization of arylalkynes with acetals

1.2.8 Alkoxy group migration from acetal

Nakamura and Yamamoto disclosed an unprecedented rearrangement of arylalkynes bearing *ortho*-acetals **1.102** to furnish indenol ethers **1.103** in moderate to high yields under Pd-catalysis (Scheme 1.22).²⁸ They proposed two mechanistic pathways for this rearrangement. As shown in pathway A, the rearrangement could be initiated by the coordination of acetal group with electron deficient Pd(II) centre to give the intermediate **1.105**. Oxonium ion **1.106** generated by the cleavage of carbon-oxygen bond in **1.105** undergoes electrophilic addition on the tethered alkyne to form the five membered species **1.107**. Subsequent R¹ group migration in the palladium-carbene complex **1.108** followed by elimination of Pd(II) would produce the indenol ether **1.103**. On the other hand this rearrangement could happen *via* alkoxy group transfer from acetal in **1.109** to the palladium activated carbon-carbon triple bond to give intermediate **1.110**. Nucleophilic attack of the oxonium ion in **1.110** yields palladium-carbene complex **1.108** (Scheme 1.22, mechanism).

Later, the same research group reported the formation of indene derivatives **1.104** from *o*-alkynylbenzaldehyde acetal **1.102** by stepwise delivery of two methoxy groups using cationic

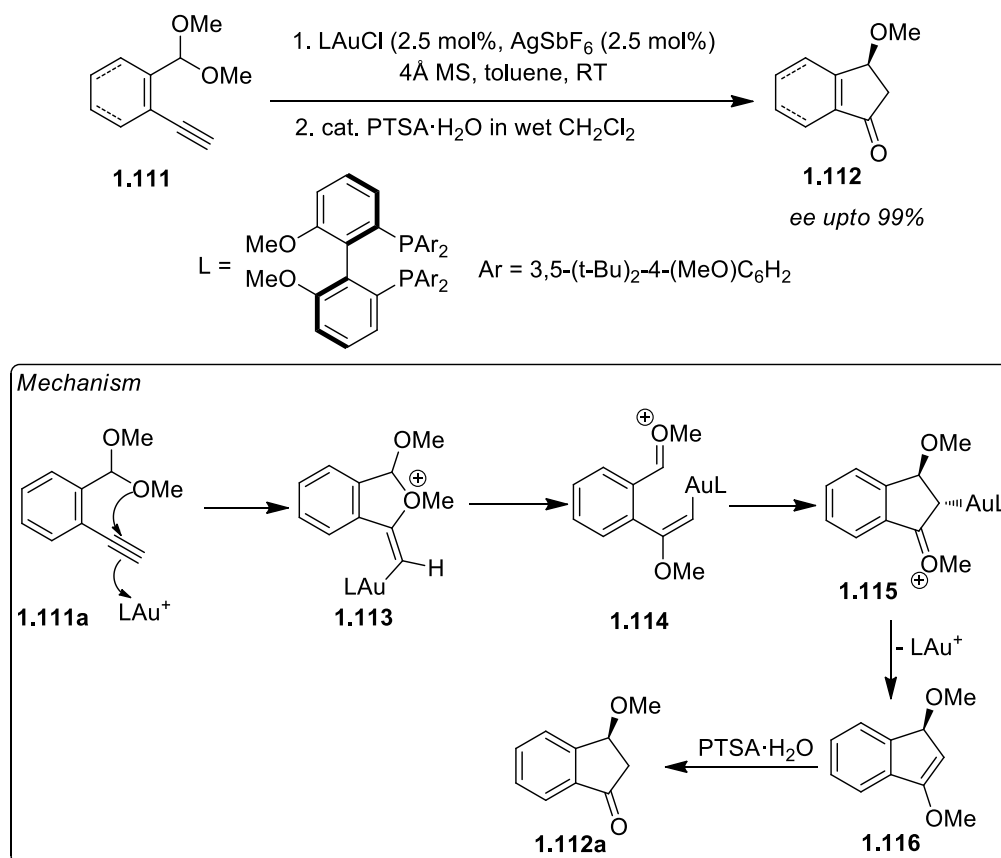
Pd(II) complex (Scheme 1.22).²⁹ Three vacant sites are available with the cationic palladium species which extends the coordination of Pd with aromatic ring of **1.102** to effect stepwise migration of methoxy groups to afford indene derivative **1.104**.



Scheme 1.22: Palladium-catalyzed rearrangement of *o*-alkynylbenzaldehyde acetals

Toste and co-workers have used acetals **1.111** for the enantioselective carboalkoxylation of alkynes to synthesize optically active β -alkoxyindanone and cyclopentenone derivatives **1.112** under cationic (DTBM-MeO-Biphep)-gold(I) catalysis (Scheme 1.23).³⁰ Because of the strong resonance stabilization of oxocarbenium ion, acetal is good nucleophile and attacks the gold activated alkynes to yield intermediate **1.113** which results in **1.114**. The oxonium ion **1.114** undergoes enantioselective cyclization to afford **1.115**. The enol ether **1.116** formed from **1.115**

would undergo hydrolysis with PTSA to provide the final indanone derivative **1.112a** (Scheme 1.23, mechanism).



Scheme 1.23: Gold(I)-catalyzed carboalkoxylation of alkynes using acetals

1.3 Conclusions

Acetals, despite being widely used as protecting groups, have been found useful in developing new reactions. Over the years, there have been reports based on the chemistry of acetals appearing in the literature on regular basis. Recently, acetals have been used in the reactions of aryl group migration, carbon-carbon bond formation, [2+2] cycloadditions/heteroalkyne metathesis, rearrangement reactions etc. In most of the cases it has been shown that the reactions of acetals are more facile and highly efficient than that of corresponding carbonyl compounds. The reason is due to the fact that the reactions of acetals proceed *via* the formation of more reactive oxonium ion. Alkyl ketones generate enol ether from *in situ* formed acetal which is more nucleophilic than respective alkyl ketones. Thus, an alkyl ketone can be used directly in C-C bond formation reaction. Here, it is not necessary to pre-functionalize the alkyl ketone to silyl enol ether/metal enolates/enamines etc. In addition, *in situ* formed acetal changes the original reactivity of a molecule and takes different reaction pathways to result in interesting molecular skeletons. Using trialkyl orthoformate an acetal moiety can be incorporated at α -carbon of an alkyl ketone which has been utilized in intramolecular annulation

reactions to construct different molecular skeletons. Still there is a plenty of scope for the development of reactions using acetals in general and *in situ* generated acetals in particular. We have effectively utilized the *in situ* formed acetal for the synthesis of interesting and useful molecular frameworks from readily available starting materials under mild reaction conditions. The details of these works are discussed in the following chapters.

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Synthesis of Naphthalene Derivatives From *ortho*-Alkynylacetophenone Derivatives via *in Situ* Incorporation of Acetal

2.1 Introduction

The naphthalene core is an important structural motif present in many natural products and bioactive compounds.¹ In addition, it has numerous applications in material science.² Hence development of new methods for the efficient synthesis of substituted naphthalenes has always been an attractive task. Different strategies have been reported for the construction of naphthalene framework. Some of the interesting strategies are shown in Figure 2.1. These include Diels-Alder reaction, annulation reactions, transition metal-mediated cyclization, thermal rearrangement of strained rings, Brønsted acid (BA)/Lewis acid (LA)-catalyzed intramolecular cyclization reactions, anionic ring annulation reactions, thermal/photochemical cyclization reactions etc.. de Koning *et al.* have reviewed the synthetic methods available for the synthesis of naphthalene derivatives till 2002.³ Many metal-mediated cyclizations for the synthesis of substituted naphthalenes have been reported in the last decade using metal catalysts based on Pt, Au, Pd, Rh, Fe, Cu, Ni, Eu, Se, Sc, Ti, Zn, Ga and Re etc. These reactions have been covered in the Ph.D. thesis of Vanajakshi.⁴

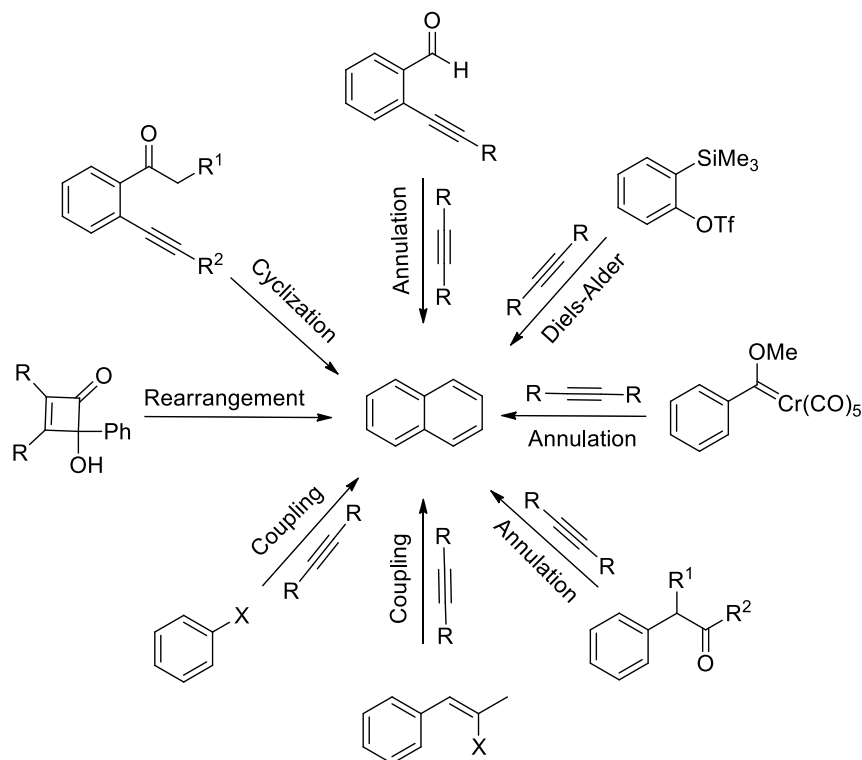


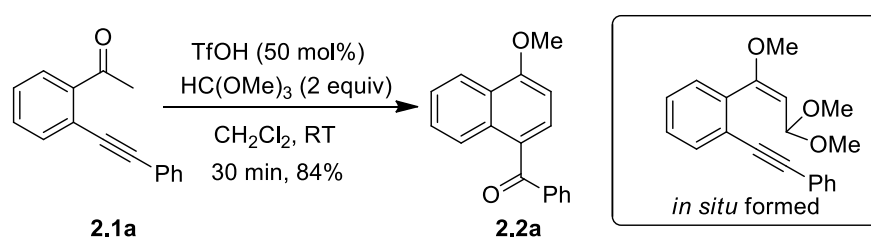
Figure 2.1: Different strategies to construct naphthalene core

In contrast to transition metal-mediated processes, use of Brønsted acids for the construction of naphthalene core is very limited.⁵ Brønsted acid catalysts have their own advantage over transition metal catalysts in the pharmaceutical industries since complete removal of the metal based impurities is a significant task.⁶

2.2 Background

Incorporation of an acetal moiety at the α -carbon of alkyl ketones and their application in the synthesis of different cyclic compounds by intramolecular cyclizations and acetal-assisted heteroalkyne metathesis for the construction of various ring skeletons have been discussed in the first chapter.

It is known that carbonyl compounds (aldehydes/ketones) form acetals in the presence of a Lewis/Brønsted acid and trialkyl orthoformate. During our research endeavour in utilizing such *in situ* formed acetals,⁷ we have found that alkyl ketones can directly be alkylated with diaryl methanols or cinnamyl alcohols or arylpropargyl alcohols *via* its *in situ* acetal generated using trimethyl orthoformate and triflic acid.^{7b} Along these lines, we observed that the reaction of *o*-alkynylacetophenone derivative **2.1a** with trimethyl orthoformate and 0.5 equivalents of triflic acid generated naphthyl ketone derivative **2.2a** efficiently in 84% yield (Scheme 2.1). It is expected that the *in situ* formed acetal incorporates an acetal moiety at the α -carbon which undergoes [2 + 2] heteroalkyne metathesis⁸ or annulation with the alkyne under the influence of acid to form the naphthalene core. Hence the additional carbon atom present in the naphthalene core might be from the trimethyl orthoformate. Impressed by the outcome of the reaction, we proceeded to optimize the reaction conditions.



Scheme 2.1: Incorporation of acetal and alkyne-carbonyl metathesis/annulation of *ortho*-alkynylacetophenone derivative

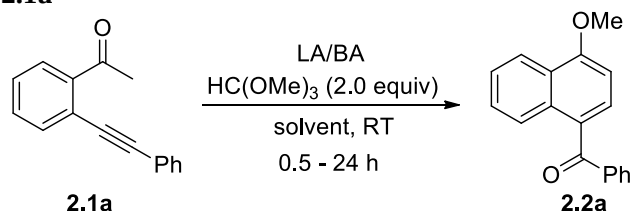
2.3. Results and discussion

2.3.1 Optimization of reaction conditions for the naphthalene synthesis

Using substrate **2.1a**, optimization of the reaction conditions was performed. This substrate was prepared in one step by Sonogashira coupling of commercially available 2'-iodo acetophenone and phenylacetylene. The results of optimization are summarized in Table 2.1. To

begin with we checked the applicability of different Brønsted acids in the present transformation. The reaction did not work with other Brønsted acids such as conc. HCl, TFA, and *p*-TSA (Table 2.1, entries 2–4) even after 24 h. Then, the reaction was attempted with Lewis acids. These were found to be ineffective, as the reaction resulted in either a complex mixture or no reaction (Table 2.1, entries 5–7). Since TfOH alone worked in effecting the reaction, further optimizations were

Table 2.1 Optimization of reaction conditions for naphthyl ketone formation from *o*-alkynylacetophenone **2.1a**



Entry	Solvent	Catalyst	cat. (mol%)	Time (h)	Yield (%) ^a
1	CH ₂ Cl ₂	TfOH	50	0.5	84
2	CH ₂ Cl ₂	Conc. HCl	50	24	NR
3	CH ₂ Cl ₂	TFA	50	24	NR
4	CH ₂ Cl ₂	<i>p</i> -TSA	50	24	NR
5	CH ₂ Cl ₂	AuCl ₃ /AgSbF ₆	5	24	- ^c
6	CH ₂ Cl ₂	AgOTf	5	24	- ^c
7	CH ₂ Cl ₂	Cu(OTf) ₂	5	24	NR
8	DCE	TfOH	50	0.5	76
9	Hexanes	TfOH	50	0.5	34
10	Toluene	TfOH	50	0.5	65
11	Dioxane	TfOH	50	0.5	52
12	CH ₃ CN	TfOH	50	24	NR
13	MeOH	TfOH	50	24	NR
14	CH ₃ NO ₂	TfOH	50	0.5	89
15	CH ₃ NO ₂	TfOH	5	0.5	25
16	CH ₃ NO ₂	TfOH	10	0.5	80
17	CH₃NO₂	TfOH	20	0.5	90
18	CH ₃ NO ₂	TfOH	20	0.5	40 ^b

^a Isolated yield. ^b 1.0 equiv of trimethyl orthoformate was used. NR: no reaction. ^c complex mixture

carried out using TfOH only and changing other parameters such as solvent and catalyst loading. In dichloroethane, the yield of **2.2a** decreased to 76% (Table 2.1, entry 8). In nonpolar solvents such as hexanes and toluene the yields obtained were 34% and 65% respectively (Table 2.1, entries 9 and 10). When the reaction was performed in dioxane, the yield of **2.2a** obtained was 52% (Table 2.1, entry 11). There were no reaction in acetonitrile and methanol even after 24 h (Table 2.1, entries 12 and 13). To our delight, nitromethane was found to be the best solvent, as the yield of **2.2a** was 89% when the reaction was carried out in it (Table 2.1, entry 14). When the amount of catalyst was reduced to 5 mol% and 10 mol%, the yield of **2.2a** dropped to 25% and 80% respectively (Table 2.1, entries 15 and 16). Gratifyingly, the yield of **2.2a** improved to 90% when the loading of TfOH was 20 mol% (Table 2.1, entry 17). Reduction in the amount of trimethyl orthoformate to 1.0 equiv was found to decrease the yield of **2.2a** to 40% (Table 2.1, entry 18).

2.3.2 Scope of naphthyl ketone derivatives synthesis

The scope of this naphthyl ketone formation was evaluated with substrates having different substitution pattern. The reaction condition given in Table 2.1, entry 17, i.e., 20 mol% of TfOH and 2.0 equiv of trimethyl orthoformate in nitromethane solvent at room temperature, was used in these reactions. The results are shown in Figure 2.3. It is important to note that there is no significant influence of electronic effects of the aryl substituents on the outcome of this transformation. Good yields of 1-methoxy-4-naphthyl ketone derivatives **2.2** were obtained with both electron-releasing groups (such as -OMe and Me) and -accepting group (such as -Cl) on the R³ aryl group. The reaction required 60 min for completion when either R² or R³ was an alkyl group. Otherwise the reactions were fast and completed within 30 min. Moderate yields of **2.2d** and **2.2e** were obtained when R³ was an alkyl group such as *n*-hexyl and *n*-butyl. Interestingly, heterocyclic thiophene tolerated the reaction conditions and the corresponding naphthyl ketone derivative **2.2m** was obtained in 72% yield. The structure of compound **2.2c** was further confirmed by single crystal X-ray analysis (Figure 2.2). Unfortunately the reaction was not clean with a terminal alkyne (R³ = H). This may be due to the absence of groups that can stabilize the vinyl carbocation intermediate formed during the reaction. When R² was a phenyl group, the reaction was not clean as it resulted in a complex mixture. A similar reaction with trimethyl orthoacetate gave a complex mixture of products (Scheme 2.2). Since the starting *ortho*-alkynylacetophenones **2.1** were prepared by a Sonogashira coupling reaction, the possible role of trace metal compound

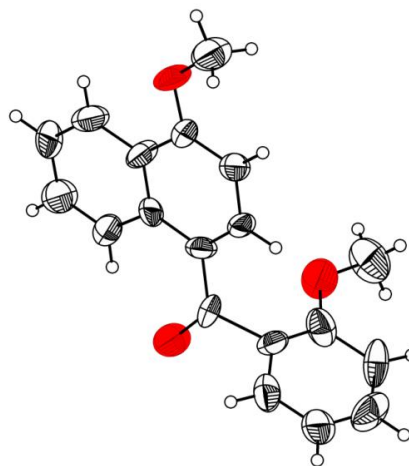
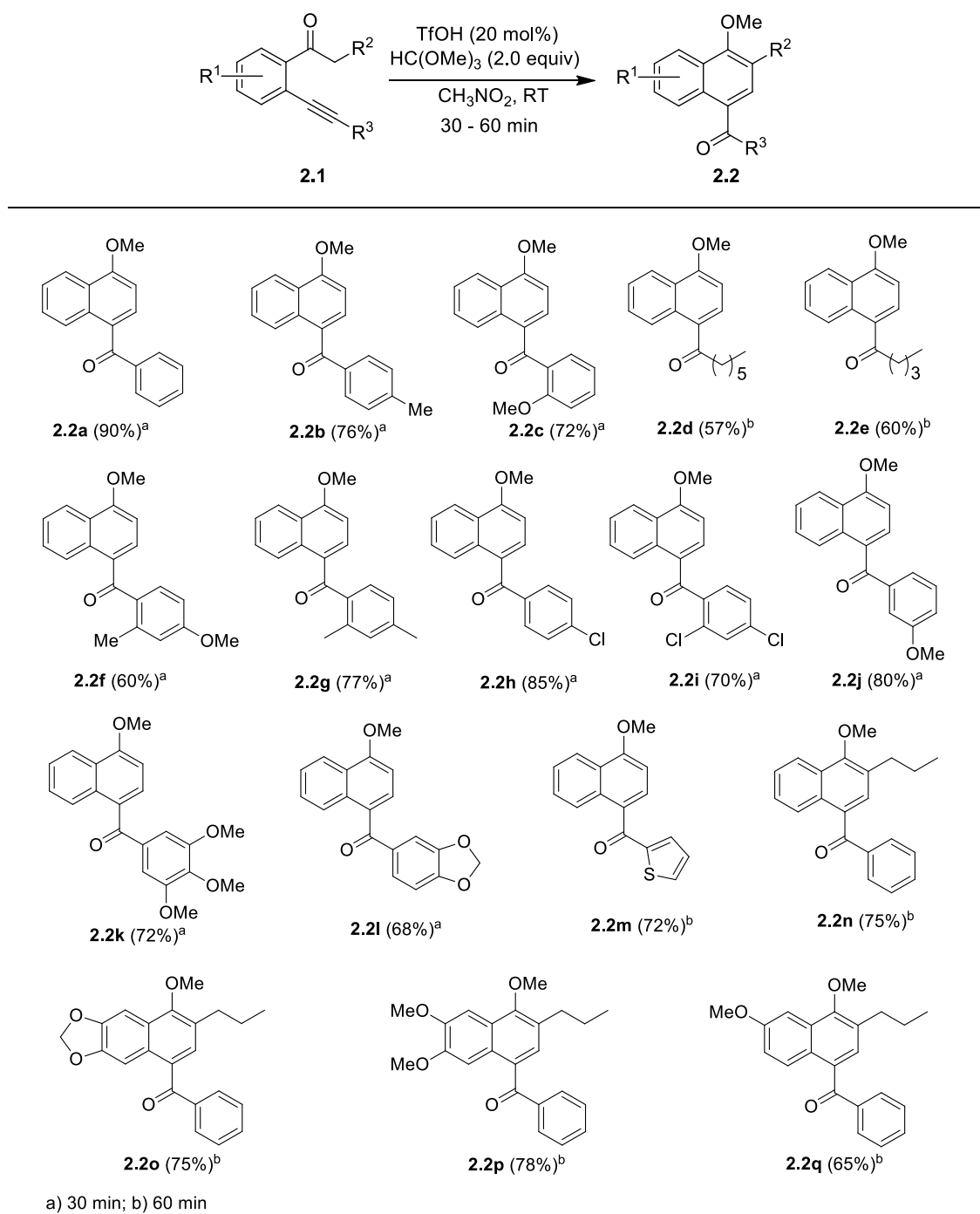
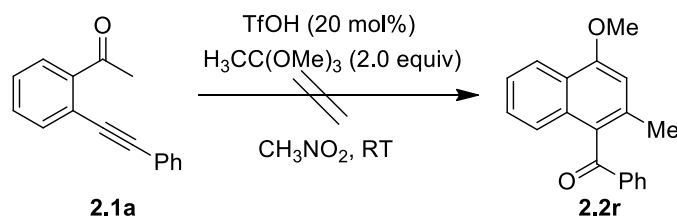


Figure 2.2: ORTEP of compound **2.2c**

impurities (Pd and Cu compounds) as co-catalysts in the present transformation was evaluated by carrying out two control experiments. In the first experiment, the reaction of **2.1a** was carried out in the presence of 2 mol% each of Pd(PPh₃)₄ and CuI along with 20 mol% of TfOH and 2 equiv of trimethyl orthoformate. There was no appreciable acceleration in the reaction rate, as 30 min were required for completion to result in **2.2a** in 88% yield. The above reaction without TfOH did not result in any product even after 24 h. With these experiments, the possibility of the transition metal impurities co-catalyzing the present reaction of **2.1a** could be ruled out.

Figure 2.3: Scope of naphthyl ketone derivatives synthesis

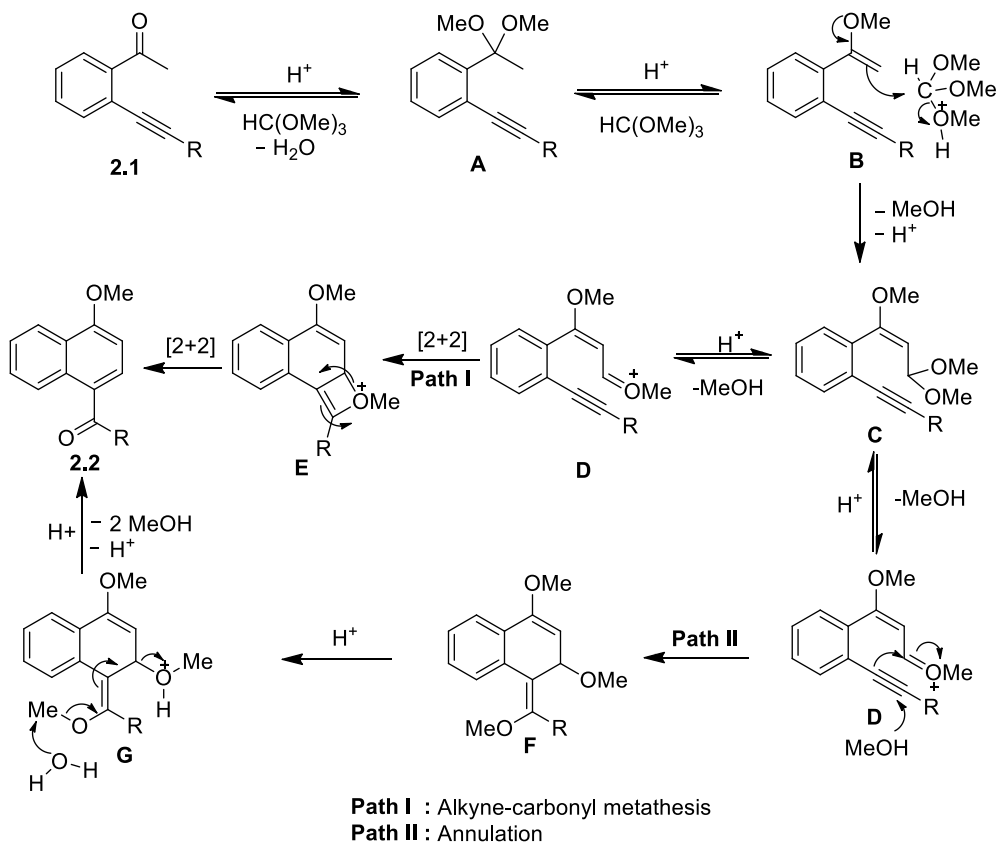




Scheme 2.2: Attempted reaction of **2.1a** with trimethyl orthoacetate

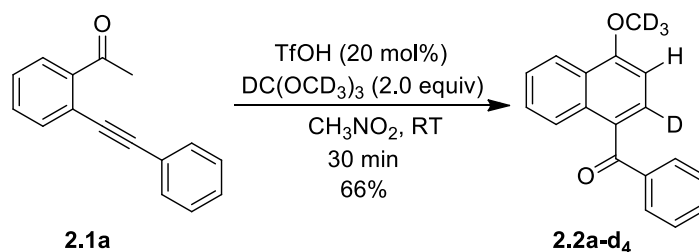
2.3.3 Mechanism of the naphthalene formation

A schematic representation of plausible mechanistic pathways is shown in Scheme 2.3. In the presence of TfOH and trimethyl orthoformate, ketal **A** will form from **2.1** and will be in equilibrium with α -methoxy styrene derivative **B**. The intermediate **B** will attack trimethyl orthoformate to give intermediate **C** which will be in equilibrium with the oxonium ion **D**.⁹ There are two possible pathways (Paths I and II) to construct the naphthalene skeleton **2.2** from **D**. As shown in path I, naphthalene derivative **2.2** will be formed *via* intramolecular [2+2] cycloaddition and cyclcoreversion between the alkyne and oxonium ion of **D** through oxetene intermediate **E** in the presence TfOH. At the same time, the pathway involving annulation could not be excluded (Path II). This is initiated by the electrophilic attack of an oxocarbenium ion on the alkyne. The formed vinylic carbocation is trapped by methanol formed during the reaction to give intermediate **F**. Subsequent elimination of methanol from **F** assisted by the acid present in the reaction would afford naphthalene derivative **2.2**.



Scheme 2.3: Plausible reaction mechanism

In order to confirm the proposed mechanism, fully deuterated trimethyl orthoformate ($\text{DC}(\text{OCD}_3)_3$) was prepared as per reported procedure.¹⁰ The reaction of **2.1a** was carried out with $\text{DC}(\text{OCD}_3)_3$ under optimized reaction conditions (Scheme 2.4). Incorporation of $-\text{OCD}_3$ and D in the naphthalene **2.2a-d₄** was inferred from the ^1H NMR spectrum. The disappearance of a singlet at 4.07 ppm corresponding to OCH_3 protons and doublet at 7.60 ppm were observed in the ^1H NMR spectrum of **2.2a-d₄**. In addition appearance of a singlet at 6.80 ppm which appeared as a doublet in the ^1H spectrum of compound **2.2a** corresponding to the aromatic proton *ortho* to methoxy function on the naphthyl ring was also noted (Figure 2.4). Further, the reaction of **2.1b** was monitored by ^1H NMR to check whether the proposed intermediates are indeed formed in the reaction. Among the proposed intermediates, the formation of acetal **A** intermediate from **2.1b** could only be seen while recording ^1H NMR. The reason for not observing the other intermediates in the ^1H NMR might be due to a fast domino reaction.



Scheme 2.4: Deuterium incorporation study

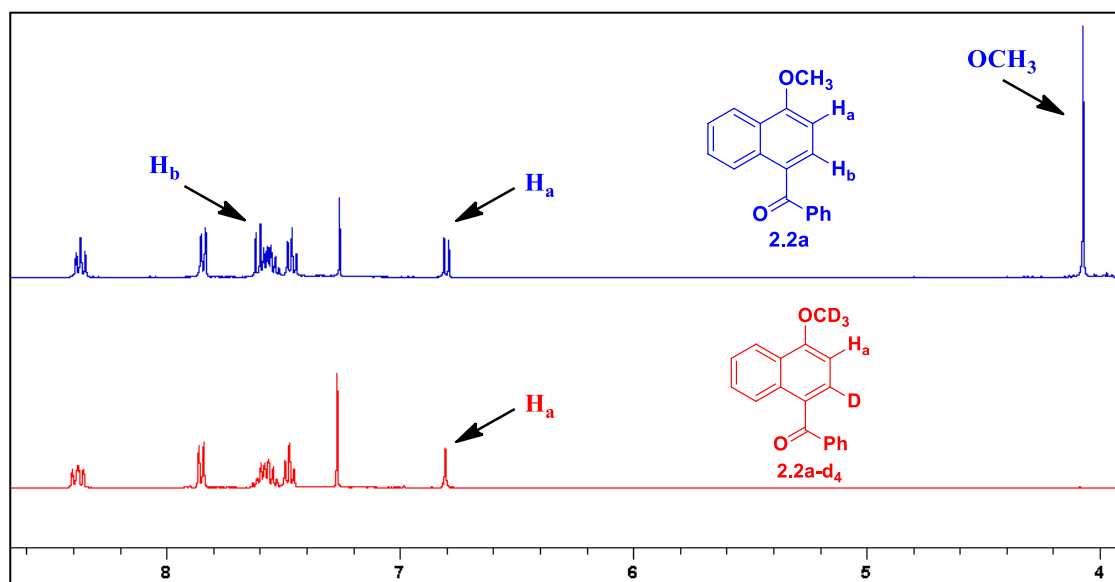


Figure 2.4: Comparison of ^1H NMR spectra of compounds **2.2a** and **2.2a-d₄**

2.4 Conclusions

An interesting domino reaction for the synthesis of substituted naphthyl ketones has been developed using *ortho*-alkynylacetophenone derivatives and trimethyl orthoformate in the presence of triflic acid catalyst. This domino reaction proceeds *via in situ* incorporation of acetal followed by intramolecular heteroalkyne metathesis/annulation. This is a simple and metal free transformation which shows significant substrate scope for the construction of naphthalene core. The products are interesting in the sense that naphthyl ketones with methyl ether function on the naphthyl ring might serve as useful intermediates for the synthesis of natural products. Deuterium incorporation experiment has been carried out to understand the mechanism.

2.5 Experimental section

2.5.1 General information

All solvents and chemicals used in this study were purchased from Merck, Aldrich and local companies. Further distillation/purification was done according to standard procedures wherever required. Dichloromethane was distilled freshly over CaH_2 . THF was dried over sodium and freshly distilled from the still before use. Triethylamine was dried over potassium hydroxide.

Thin layer chromatographies (TLC) were done on aluminum plates coated with silica gel containing F254 indicator and the spots were visualized by UV light and/or by heating the plates sprayed with Seebach solution (phosphomolybdic acid (2.5 g), $\text{Ce}(\text{SO}_4)_2$ (1.0 g), conc. H_2SO_4 (6 mL) and H_2O (94 mL)).

Column chromatography was performed on silicagel 100-200 mesh, using ethyl acetate and hexanes mixture as eluent.

^1H and ^{13}C NMR spectra of the synthesized compounds were recorded in a Bruker 400 or 500 MHz NMR machines using their solutions in CDCl_3 using 5 mm tubes. The ^1H NMR and ^{13}C NMR were referred respectively to TMS used as an internal standard and the central line of CDCl_3 (^1H : $\delta = 0$, ^{13}C : $\delta = 77.0$) and coupling constants (J) were given in Hertz (Hz).

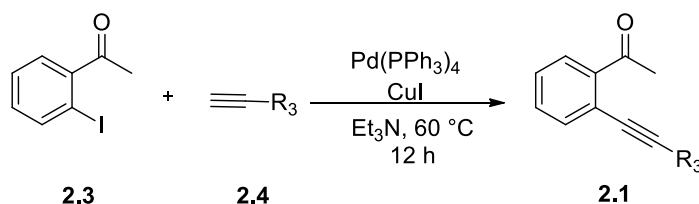
IR spectra were recorded using JASCO FT/IR 5300 spectrometer. Liquid samples were placed directly and solid samples were made into KBr pellets to place on sodium chloride cell. The spectra values are reported as absorption maxima and expressed in cm^{-1} .

High resolution mass spectra (HRMS) were recorded on a Bruker Maxis machine using electrospray ionization.

Melting points were determined by using hot-stage SUPERFIT melting point apparatus or MR-VIS visual melting range apparatus and are uncorrected.

2.5.2 Experimental procedures, spectral and analytical data

General procedure for the synthesis of 2-alkynylacetophenones 2.1a – 2.1m:

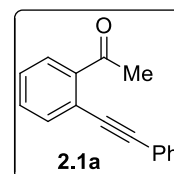


To a solution of 2'-iodoacetophenone **2.3** (1.0 equiv) in triethylamine, the corresponding alkyne **2.4** (1.1 equiv.), Pd(PPh₃)₄ (0.01 equiv) and CuI (0.02 equiv) were added under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 60 °C for 12 h. Then, the suspension was diluted with EtOAc, filtered and evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, hexanes/EtOAc) to give pure product **2.1**.

Analytical data of compounds 2.1a – 2.1m:

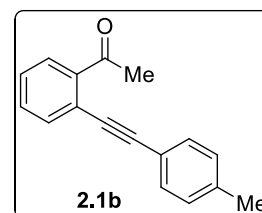
1-(2-(Phenylethynyl)phenyl)ethanone 2.1a:¹¹

It was obtained as pale yellow liquid in 99% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.56-7.54 (m, 2H), 7.48-7.45 (m, 1H), 7.41-7.35 (m, 4H), 2.79 (s, 3H).



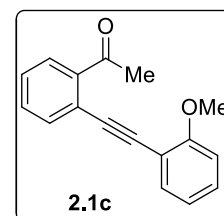
1-(2-(*p*-Tolyethynyl)phenyl)ethanone 2.1b:¹¹

It was obtained as yellow liquid in 88% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.49-7.37 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 2.80 (s, 3H).



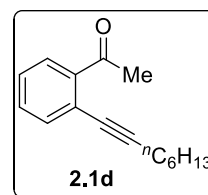
1-(2-((2-Methoxyphenyl)ethynyl)phenyl)ethanone 2.1c:

It was obtained as pale yellow oil in 96% yield. *R*_f = 0.4 (in 30% EtOAc/Hexanes); IR (neat): 3463, 3063, 3002, 2969, 2942, 2838, 2213, 1764, 1676, 1594, 1490, 1457, 1358, 1276, 1249, 1024, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.75 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.65 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.50 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.46 (td, *J* = 1.6, 7.6 Hz, 1H), 7.39 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.36-7.31 (m, 1H), 6.95 (td, *J* = 0.8, 7.6 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.88 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 201.0, 160.2, 140.7, 133.8, 133.3, 131.2, 130.3, 128.5, 128.1, 122.1, 120.5, 112.1, 110.6, 92.3, 92.1, 55.6, 30.3. HRMS (ESI): calcd for C₁₇H₁₄O₂ [*M*+Na]⁺ 273.0891; found 273.0892.

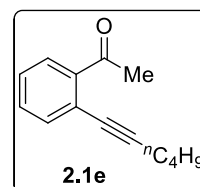


1-(2-(Oct-1-ynyl)phenyl)ethanone 2.1d:¹¹

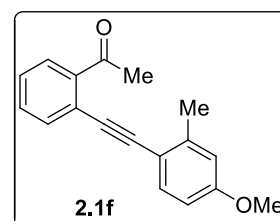
It was obtained as yellow liquid in 80% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.42-7.38 (m, 1H), 7.35-7.31 (m, 1H), 2.73 (s, 3H), 2.46 (t, J = 7.2 Hz, 2H), 1.64-1.28 (m, 8H), 0.90 (t, J = 6.8 Hz, 3H).

**1-(2-(Hex-1-ynyl)phenyl)ethanone 2.1e:¹¹**

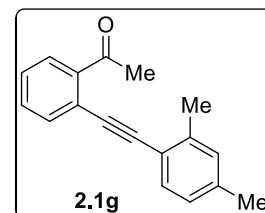
It was obtained as yellow liquid in 86% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.40 (dd, J = 1.2, 7.6 Hz, 1H), 7.34-7.30 (m, 1H), 2.72 (s, 3H), 2.46 (t, J = 7.2 Hz, 2H), 1.61 (quin, J = 7.2 Hz, 2H), 1.48 (sext, J = 7.2 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H).

**1-(2-((2-Methoxy-4-methylphenyl)ethynyl)phenyl)ethanone 2.1f:¹¹**

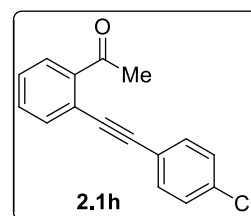
It was obtained as yellow oil in 94% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47-7.44 (m, 2H), 7.39-7.35 (m, 1H), 6.79 (s, 1H), 6.74 (d, J = 7.2 Hz, 1H), 3.82 (s, 3H), 2.79 (s, 3H), 2.53 (s, 3H).

**1-(2-((2,4-Dimethylphenyl)ethynyl)phenyl)ethanone 2.1g:**

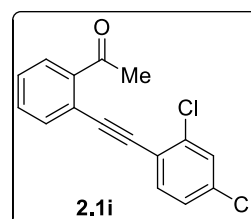
It was obtained as colorless solid in 83% yield. mp 57-59 °C; R_f = 0.3 (in 20% EtOAc/Hexanes); IR (KBr): 2997, 2208, 1665, 1589, 1479, 1408, 1265, 1221, 953, 843, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.48-7.46 (m, 1H), 7.45-7.37 (m, 1H), 7.18 (s, 2H), 7.00 (s, 1H), 2.80 (s, 3H), 2.32 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 200.5, 140.8, 140.7, 138.0, 133.8, 131.2, 130.7, 129.1, 128.6, 128.1, 122.4, 121.9, 95.5, 87.7, 30.1, 21.1. HRMS (ESI): calcd for C₁₈H₁₆O [$M+H$]⁺ 249.1279; found 249.1279.

**1-(2-((4-Chlorophenyl)ethynyl)phenyl)ethanone 2.1h:¹¹**

It was obtained as yellow solid in 82% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.76 (dd, J = 1.2, 8.0 Hz, 1H), 7.62 (dd, J = 1.2, 7.6 Hz, 1H), 7.50-7.39 (m, 4H), 7.36-7.33 (m, 2H), 2.76 (s, 3H).

**1-(2-((2,4-Dichlorophenyl)ethynyl)phenyl)ethanone 2.1i:**

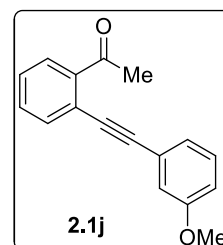
It was obtained as light yellow solid in 93% yield. mp 59-61 °C; R_f = 0.5 (in 20% EtOAc/Hexanes); IR (KBr): 3441, 2214, 1676, 1588, 1479, 1355, 1277, 1231, 1096, 863, 796, 770 cm⁻¹; ¹H NMR (400 MHz,



CDCl₃): δ 7.76 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.52-7.47 (m, 2H), 7.45-7.43 (m, 2H), 7.27-7.23 (m, 1H), 2.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.8, 140.5, 136.6, 135.0, 134.3, 134.0, 131.3, 129.4, 128.8, 128.7, 127.1, 121.5, 120.9, 94.2, 90.5, 29.9. HRMS (ESI): calcd for C₁₆H₁₀Cl₂O [$M+H$]⁺ 289.0187; found 289.0187.

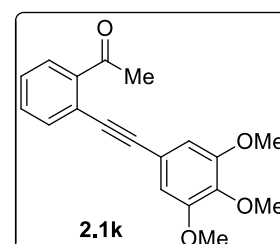
1-(2-((3-Methoxyphenyl)ethynyl)phenyl)ethanone 2.1j:¹²

It was obtained as yellow oil in 80% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.75 (dd, J = 0.8, 7.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.49-7.45 (m, 1H), 7.41-7.37 (m, 1H), 7.29-7.25 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.07-7.06 (m, 1H), 6.92 (dd, J = 2.4, 8.0 Hz, 1H), 3.82 (s, 3H), 2.78 (s, 3H).



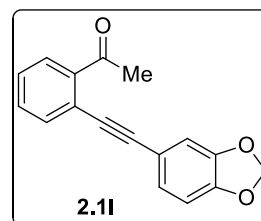
1-(2-((3,4,5-Trimethoxyphenyl)ethynyl)phenyl)ethanone 2.1k:

It was obtained as light yellow solid in 84% yield. mp 52-54 °C; R_f = 0.5 (in 30% EtOAc/Hexanes); IR (KBr): 3430, 2996, 2939, 2830, 1676, 1572, 1500, 1464, 1407, 1350, 1236, 1122, 998, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.50-7.46 (m, 1H), 7.43-7.39 (m, 1H), 6.79 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 200.2, 153.2, 140.6, 139.3, 133.9, 131.3, 128.7, 128.2, 121.6, 117.9, 109.6, 108.7, 94.9, 87.6, 61.0, 56.2, 29.8. HRMS (ESI): calcd for C₁₉H₁₈O₄ [$M+Na$]⁺ 333.1103; found 333.1103.



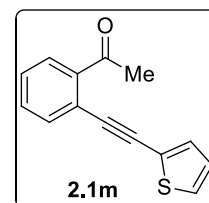
1-(2-(Benzo[d][1,3]dioxol-5-ylethynyl)phenyl)ethanone 2.1l:

It was obtained as colorless solid in 78% yield. mp 94-96 °C; R_f = 0.3 (in 20% EtOAc/Hexanes); IR (KBr): 2915, 2202, 1682, 1561, 1490, 1369, 1326, 1243, 1030, 926, 849, 821, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.08 (dd, J = 1.2, 8.0 Hz, 1H), 6.99 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H), 2.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 200.2, 148.3, 147.5, 140.5, 133.7, 131.3, 128.7, 128.0, 126.3, 121.8, 116.1, 111.3, 108.5, 101.4, 95.0, 87.0, 29.9. HRMS (ESI): calcd for C₁₇H₁₂O₃ [$M+H$]⁺ 265.0865; found 265.0864.



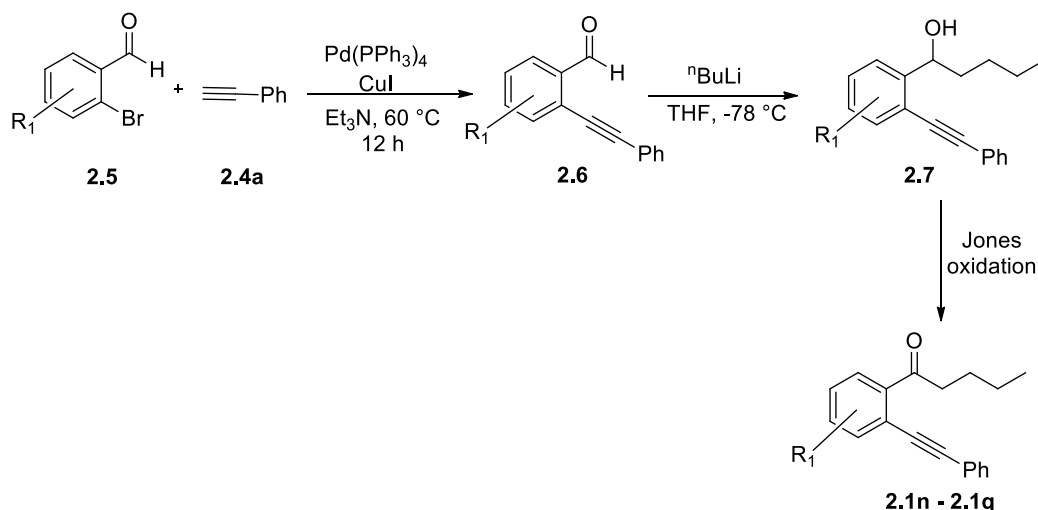
1-(2-(Thiophen-2-ylethynyl)phenyl)ethanone 2.1m:

It was obtained as brown oil in 73% yield. R_f = 0.6 (in 20% EtOAc/Hexanes); IR (neat): 3425, 3104, 2193, 1681, 1588, 1557, 1474, 1417, 1350, 1277, 1246, 1029, 957, 760, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.47 (td, J = 1.2, 7.6 Hz, 1H), 7.41-7.37



(m, 1H), 7.35-7.32 (m, 2H), 7.03 (td, $J = 0.8, 4.4$ Hz), 2.76 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.9, 140.2, 133.5, 132.3, 131.4, 128.8, 128.3, 128.0, 127.2, 122.8, 121.4, 92.3, 88.3, 29.8. HRMS (ESI): calcd for $\text{C}_{14}\text{H}_{10}\text{OS}$ $[M+\text{H}]^+$ 227.0531; found 227.0530.

General procedure for the synthesis of 2-alkynylketones 2.1n – 2.1q:

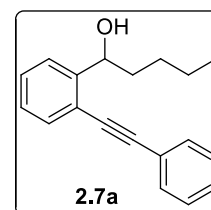


To a solution of 2'-bromobenzaldehyde **2.5** (1.0 equiv) in triethylamine, phenylacetylene **2.4a** (1.1 equiv), $\text{Pd}(\text{PPh}_3)_4$ (0.01 equiv) and CuI (0.02 equiv) were added under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 60 °C for 12 h. Then, the suspension was diluted with EtOAc, filtered and evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, hexanes/EtOAc) to give pure product **2.6**. To a solution of compound **2.6** (1.0 equiv) in dry THF, *n*-butyl lithium (1.1 equiv) was added at -78 °C.¹³ After completion of the reaction as indicated by the TLC, the reaction mixture was quenched with saturated ammonium chloride solution. The suspension was diluted with EtOAc, and then organic layer was separated and washed two times with brine solution and dried over anhydrous sodium sulfate. Then the organic layer was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/EtOAc) to afford the desired product **2.7**. The compounds (**2.1n** – **2.1q**) were obtained by Jones oxidation of **2.7**.¹¹

Analytical data of compounds 2.7a – 2.7d and 2.1n – 2.1q:

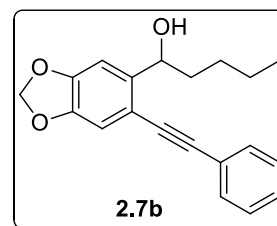
1-(2-(Phenylethynyl)phenyl)pentan-1-ol **2.7a**:¹³

It was obtained as yellow oil in 86% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.56-7.52 (m, 4H), 7.38-7.37 (m, 4H), 7.28-7.24 (m, 1H), 5.25 (d, $J = 4.8$ Hz, 1H), 2.24 (br s, 1H), 1.89-1.81 (m, 2H), 1.56-1.22 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H).

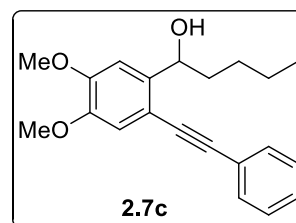


1-(6-(Phenylethynyl)benzo[d][1,3]dioxol-5-yl)pentan-1-ol 2.7b:

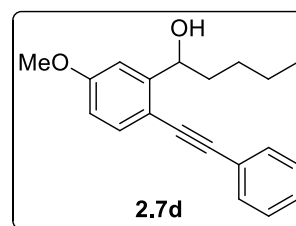
It was obtained as colorless solid in 75% yield. mp 92-94 °C; R_f = 0.3 (in 20% EtOAc/Hexanes); IR (KBr): 30280, 2959, 2918, 2856, 1598, 1500, 1360, 1236, 1138, 1112, 1039, 936, 863, 755, 687 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.50-7.47 (m, 2H), 7.38-7.32 (m, 3H), 7.02 (s, 1H), 6.93 (s, 1H), 5.98 (s, 2H), 5.22 (t, J = 6.4 Hz, 1H), 2.06 (br s, 1H), 1.81-1.75 (m, 2H), 1.49-1.43 (m, 1H), 1.39-1.32 (m, 3H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.4, 146.3, 142.3, 131.3, 128.4, 128.2, 123.2, 113.6, 111.3, 106.0, 101.4, 92.6, 87.2, 72.0, 38.1, 28.0, 22.6, 14.0. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{H}]^+$ 309.1491; found 309.1491.

**1-(4,5-Dimethoxy-2-(phenylethynyl)phenyl)pentan-1-ol 2.7c:**

It was obtained as yellow oil in 90% yield. R_f = 0.2 (in 20% EtOAc/Hexanes); IR (neat): 3472, 3006, 2954, 2933, 2865, 2209, 1598, 1505, 1443, 1345, 1246, 1081, 1024, 869, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.51-7.49 (m, 2H), 7.37-7.33 (m, 3H), 7.04 (s, 1H), 6.97 (s, 1H), 5.22 (t, J = 6.8 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.25 (br s, 1H), 1.83-1.77 (m, 2H), 1.53-1.44 (m, 1H), 1.42-1.33 (m, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.7, 147.5, 140.5, 131.2, 128.4, 128.1, 123.3, 114.1, 112.2, 108.1, 92.6, 87.3, 72.0, 55.9, 55.8, 38.2, 28.1, 22.5, 14.0. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{24}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 347.1623; found 347.1624.

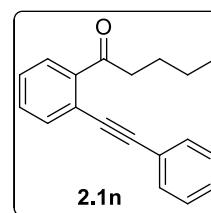
**1-(5-Methoxy-2-(phenylethynyl)phenyl)pentan-1-ol 2.7d:**

It was obtained as light yellow solid in 80% yield. mp 70-72 °C; R_f = 0.2 (in 20% EtOAc/Hexanes); IR (KBr): 3326, 3249, 2953, 2909, 2860, 2208, 1605, 1561, 1495, 1457, 1238, 1167, 1128, 1057, 969, 756, 684 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.48 (dd, J = 2.0, 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.36-7.32 (m, 3H), 7.08 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 2.4, 8.4 Hz, 1H), 5.20 (t, J = 4.8 Hz, 1H), 3.83 (s, 3H), 2.18 (br s, 1H), 1.90-1.73 (m, 2H), 1.53-1.36 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.0, 148.9, 133.6, 131.2, 128.4, 128.0, 123.4, 112.9, 112.6, 110.7, 92.8, 87.2, 72.3, 55.3, 38.0, 28.1, 22.6, 14.0. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{22}\text{O}_2$ $[\text{M}+\text{Na}]^+$ 317.1517; found 317.1518.

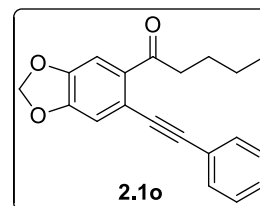


1-(2-(Phenylethynyl)phenyl)pentan-1-one 2.1n:¹³

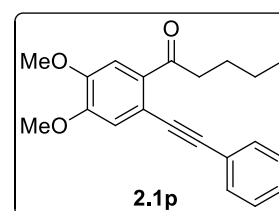
It was obtained as yellow oil in 88.0% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.56-7.53 (m, 2H), 7.47-7.44 (m, 1H), 7.41-7.36 (m, 4H), 3.16 (t, J = 7.6 Hz, 2H), 1.75 (quin, J = 7.6 Hz, 2H), 1.44-1.38 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).

**1-(6-(Phenylethynyl)benzo[d][1,3]dioxol-5-yl)pentan-1-one 2.1o:**

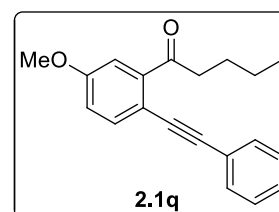
It was obtained as colorless solid in 79% yield; mp 58-60 °C; R_f = 0.5 (in 20% EtOAc/Hexanes); IR (KBr): 2954, 2918, 2866, 1671, 1598, 1505, 1484, 1365, 1236, 1189, 1143, 1039, 853, 760, 687 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.50 (dd, J = 4.0, 7.6 Hz, 2H), 7.36-7.34 (m, 3H), 7.21 (s, 1H), 7.01 (s, 1H), 6.04 (s, 2H), 3.16 (t, J = 7.6 Hz, 2H), 1.76-1.68 (m, 2H), 1.38 (sext, J = 7.6 Hz, 2H), 0.91 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 201.6, 149.8, 148.1, 136.2, 131.3, 128.5, 128.4, 122.9, 116.5, 112.8, 108.6, 107.9, 102.1, 93.6, 88.6, 41.8, 26.8, 22.5, 13.9. HRMS (ESI): calcd for C₂₀H₁₈O₃ [M+H]⁺ 307.1334; found 307.1330.

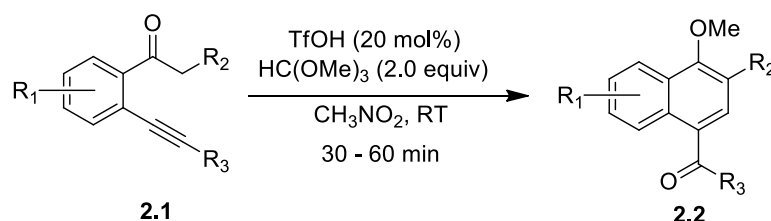
**1-(4,5-Dimethoxy-2-(phenylethynyl)phenyl)pentan-1-one 2.1p:**

It was obtained as colorless solid in 81% yield. mp 93-94 °C; R_f = 0.5 (in 20% EtOAc/Hexanes); IR (KBr): 2954, 2866, 1650, 1593, 15010, 1453, 1443, 1350, 1267, 1215, 1169, 879, 770 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.53 (dd, J = 4.0, 7.6 Hz, 2H), 7.38-7.36 (m, 4H), 7.06 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.28 (t, J = 7.6 Hz, 2H), 1.75 (quin, J = 7.6 Hz, 2H), 1.40 (sext, J = 7.6 Hz, 2H), 0.93 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 201.7, 151.1, 149.1, 133.9, 131.2, 128.6, 128.5, 123.0, 115.5, 115.2, 111.3, 93.8, 89.0, 56.1, 56.0, 41.9, 26.8, 22.6, 14.0. HRMS (ESI): calcd for C₂₁H₂₂O₃ [M+H]⁺ 323.1647; found 323.1651.

**1-(5-Methoxy-2-(phenylethynyl)phenyl)pentan-1-one 2.1q:**

It was obtained as light yellow oil in 86% yield. R_f = 0.5 (in 20% EtOAc/Hexanes); IR (neat): 3435, 2954, 2928, 2866, 1681, 1598, 1500, 1324, 1293, 1226, 1169, 1029, 822, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.54-7.49 (m, 3H), 7.35-7.33 (m, 3H), 7.17 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 2.8, 8.4 Hz, 1H), 3.85 (s, 3H), 3.19 (t, J = 7.2 Hz, 2H), 1.73 (quin, J = 7.6 Hz, 2H), 1.39 (sext, J = 7.6 Hz, 2H), 0.92 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 203.7, 159.4, 142.9, 135.1, 131.2, 128.4, 123.2, 117.2, 113.2, 112.8, 93.0, 88.2, 55.5, 42.0, 26.5, 22.4, 13.9. HRMS (ESI): calcd for C₂₀H₂₀O₂ [M+H]⁺ 293.1542; found 293.1544.

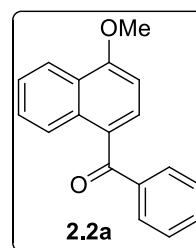


General procedure for the synthesis of naphthalenes 2.2a – 2.2q:

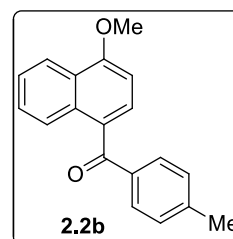
Triflic acid (20 mol%) was charged into a solution of compound **2.1** (1.0 equiv) and trimethyl orthoformate (2.0 equiv) in nitromethane (5 mL/1 mmol). The resulting mixture was stirred at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. After the completion of the reaction, nitromethane was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **2.2**.

Analytical data of compounds 2.2a – 2.2q:**(4-Methoxynaphthalen-1-yl)(phenyl)methanone 2.2a:¹⁴**

It was obtained as light yellow oil in 90% yield. $R_f = 0.5$ (in 20% EtOAc/Hexanes); ^1H NMR (400 MHz, CDCl_3): δ 8.32 (td, $J = 1.6, 8.4$ Hz, 2H), 7.85–7.83 (m, 2H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.58–7.51 (m, 3H), 7.48–7.44 (m, 2H), 6.80 (d, $J = 8.0$ Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.4, 158.3, 139.4, 132.6, 132.5, 131.4, 130.3, 128.2, 128.1, 128.0, 125.8, 125.7, 122.2, 101.9, 55.8.

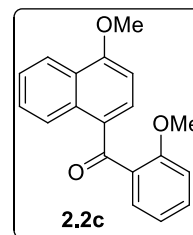
**(4-Methoxynaphthalen-1-yl)(p-tolyl)methanone 2.2b:**

It was obtained as brown oil in 76% yield; $R_f = 0.4$ (in 20% EtOAc/Hexanes); IR (neat): 2939, 1647, 1605, 1577, 1510, 1489, 1257, 1179, 1096, 1055, 1014 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.35–8.29 (m, 2H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.53–7.49 (m, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 6.77 (d, $J = 8.0$ Hz, 1H), 4.04 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.1, 158.0, 143.4, 136.7, 132.5, 130.7, 130.5, 129.2, 129.0, 128.5, 127.8, 125.7, 122.2, 102.0, 55.7, 21.6. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{16}\text{O}_2$ $[\text{M}+\text{H}]^+$ 277.1229; found 277.1230.

**(4-Methoxynaphthalen-1-yl)(2-methoxyphenyl)methanone 2.2c:**

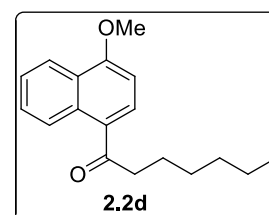
It was obtained as light yellow solid in 72% yield. mp 124–126 °C; $R_f = 0.3$ (in 20% EtOAc/Hexanes); IR (KBr): 2936, 2827, 1638, 1572, 1484, 1457, 1430, 1298, 1276, 1156, 1095,

865, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 9.02 (d, $J = 8.4$ Hz, 1H), 8.33 (d, $J = 8.0$ Hz, 1H), 7.66-7.62 (m, 2H), 7.56-7.52 (m, 1H), 7.48-7.41 (m, 2H), 7.03 (td, $J = 0.8, 7.2$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 4.03 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.0, 159.1, 157.5, 134.5, 132.5, 131.7, 131.0, 130.0, 128.6, 127.9, 126.1, 125.72, 125.65, 122.1, 120.3, 111.6, 102.1, 55.7. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{16}\text{O}_3$ $[\text{M}+\text{H}]^+$ 293.1178; found 293.1178.



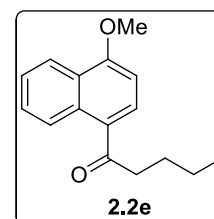
1-(4-Methoxynaphthalen-1-yl)heptan-1-one 2.2d:

It was obtained as light brown oil in 57% yield. $R_f = 0.5$ (in 10% EtOAc/Hexanes); IR (neat): 2923, 2856, 1666, 1572, 1510, 1422, 1226, 1164, 1029 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.84 (d, $J = 9.2$ Hz, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.63-7.59 (m, 1H), 7.54-7.49 (m, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 4.06 (s, 3H), 3.02 (t, $J = 7.2$ Hz, 2H), 1.77 (quin, $J = 7.2$ Hz, 2H), 1.40-1.36 (m, 2H), 1.35-1.28 (m, 4H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.3, 158.7, 132.0, 130.2, 128.5, 128.0, 126.0, 125.8, 125.7, 122.0, 102.0, 55.7, 41.4, 31.7, 29.1, 25.2, 22.5, 14.0. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{22}\text{O}_2$ $[\text{M}+\text{H}]^+$ 271.1698; found 271.1699.



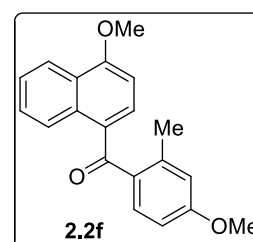
1-(4-Methoxynaphthalen-1-yl)pentan-1-one 2.2e:

It was obtained as light brown oil in 60% yield. $R_f = 0.4$ (in 20% EtOAc/Hexanes); IR (neat): 2942, 2920, 2860, 1676, 1594, 1501, 1479, 1380, 1238, 1183, 1035, 953, 854, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.84 (d, $J = 8.4$ Hz, 1H), 8.31 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.63-7.59 (m, 1H), 7.54-7.50 (m, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 4.06 (s, 3H), 3.03 (t, $J = 7.6$ Hz, 2H), 1.76 (quin, $J = 7.6$ Hz, 2H), 1.48-1.38 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.3, 158.8, 131.9, 130.3, 128.5, 128.0, 126.0, 125.7, 122.0, 102.0, 55.7, 41.1, 27.4, 22.6, 14.0. HRMS (ESI): calcd for $\text{C}_{16}\text{H}_{18}\text{O}_2$ $[\text{M}+\text{H}]^+$ 243.1385; found 243.1385.



(4-Methoxy-2-methylphenyl)(4-methoxynaphthalen-1-yl)methanone 2.2f:

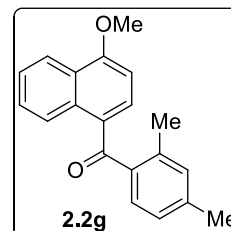
It was obtained as light yellow solid in 60%. mp 95-97 $^{\circ}\text{C}$; $R_f = 0.5$ (in 20% EtOAc/Hexanes); IR (KBr): 2966, 2827, 1632, 1600, 1572, 1556, 1512, 1249, 1161, 1123, 1095, 805, 772 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.59 (d, $J = 8.4$ Hz, 1H), 8.34 (d, $J = 8.0$ Hz, 1H), 7.61-7.57 (m, 1H), 7.55-7.51 (m, 2H), 7.34 (d, $J = 8.4$ Hz, 1H), 6.82 (d, $J = 2.4$ Hz,



1H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.69 (dd, $J = 2.8, 8.4$ Hz, 1H), 4.05 (s, 3H), 3.85 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 198.5, 161.4, 158.5, 141.1, 132.9, 132.8, 132.5, 129.4, 128.2, 125.80, 125.77, 122.2, 116.7, 110.2, 102.0, 55.7, 55.3, 21.1. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{18}\text{O}_3$ $[M+H]^+$ 307.1334; found 307.1337.

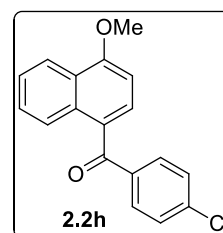
(2,4-Dimethylphenyl)(4-methoxynaphthalen-1-yl)methanone 2.2g:

It was obtained as colorless solid in 77% yield. mp 128-130 °C; $R_f = 0.3$ (in 20% EtOAc/Hexanes); IR (KBr): 2936, 1649, 1578, 1506, 1452, 1419, 1375, 1309, 1227, 1095, 1068, 865, 794, 772 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.35 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.56-7.52 (m, 2H), 7.44 (s, 2H), 7.21 (s, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 4.06 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.8, 158.1, 139.5, 137.9, 134.2, 132.6, 131.1, 128.4, 128.0, 127.9, 125.7, 122.1, 101.9, 55.7, 21.2. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{18}\text{O}_2$ $[M+H]^+$ 291.1385; found 291.1382.



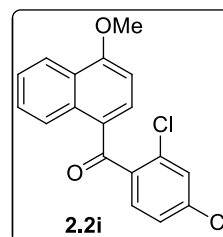
(4-Chlorophenyl)(4-methoxynaphthalen-1-yl)methanone 2.2h:

It was obtained as light yellow solid in 85% yield. mp 123-125 °C; $R_f = 0.5$ (in 20% EtOAc/Hexanes); IR (KBr): 2964, 2939, 1640, 1588, 1500, 1417, 1252, 1096, 1060, 838, 775 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.35 (td, $J = 1.2, 6.8$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.59-7.52 (m, 3H), 7.43 (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.0, 158.5, 138.9, 137.7, 132.5, 131.6, 131.4, 128.6, 127.6, 125.9, 125.8, 125.6, 122.3, 101.9, 55.8. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{13}\text{ClO}_2$ $[M+H]^+$ 297.0682; found 297.0679.



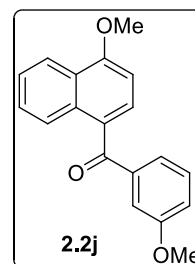
(2,4-Dichlorophenyl)(4-methoxynaphthalen-1-yl)methanone 2.2i:

It was obtained as light yellow solid in 70% yield. mp 85-87 °C; $R_f = 0.6$ (in 20% EtOAc/Hexanes); IR (KBr): 3061, 2928, 2854, 1695, 1670, 1583, 1448, 1396, 1257, 1070, 1008, 947, 686 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 9.12 (d, $J = 8.4$ Hz, 1H), 8.36 (d, $J = 8.0$ Hz, 1H), 7.73-7.69 (m, 1H), 7.60-7.56 (m, 2H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.41-7.34 (m, 2H), 6.73 (d, $J = 8.4$ Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.7, 160.2, 139.0, 136.2, 135.9, 132.6, 132.5, 130.5, 129.9, 129.3, 127.0, 126.2, 126.0, 125.9, 125.8, 122.3, 102.2, 55.9. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{12}\text{Cl}_2\text{O}_2$ $[M+H]^+$ 331.0293; found 331.0292.

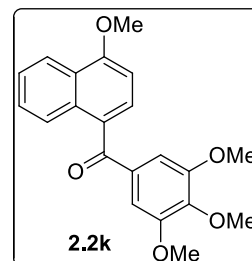


(4-Methoxynaphthalen-1-yl)(3-methoxyphenyl)methanone 2.2j:

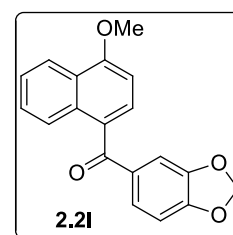
It was obtained as light yellow oil in 80% yield; $R_f = 0.45$ (in 20% EtOAc/Hexanes); IR (neat): 3002, 2936, 2838, 1649, 1578, 1517, 1463, 1424, 1320, 1265, 1095, 1035, 767, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.39-8.34 (m, 2H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.57-7.51 (m, 2H), 7.44-7.43 (m, 1H), 7.35-7.33 (m, 2H), 7.14-7.10 (m, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 4.06 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.1, 159.5, 158.3, 140.7, 132.6, 131.4, 129.2, 128.0, 125.8, 125.7, 123.3, 122.2, 119.1, 114.2, 101.9, 55.8, 55.4. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{16}\text{O}_3$ $[M+H]^+$ 293.1178; found 293.1177.

**(4-Methoxynaphthalen-1-yl)(3,4,5-trimethoxyphenyl)methanone 2.2k:**

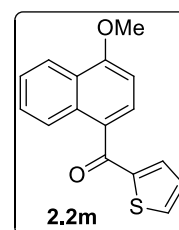
It was obtained as light yellow solid in 72% yield. mp 170-172 $^{\circ}\text{C}$; $R_f = 0.4$ (in 30% EtOAc/Hexanes); IR (KBr): 2958, 2920, 1638, 1578, 1510, 1464, 1329, 1122, 1003, 863, 770 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.36 (d, $J = 7.6$ Hz, 1H), 8.31 (d, $J = 8.8$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.58-7.53 (m, 2H), 7.12 (s, 2H), 6.82 (d, $J = 8.0$ Hz, 1H), 4.09 (s, 3H), 3.95 (s, 3H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.3, 158.2, 152.8, 142.1, 134.4, 132.6, 130.7, 128.2, 128.0, 125.9, 125.7, 122.2, 107.9, 101.9, 61.0, 56.3, 55.8. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{20}\text{O}_5$ $[M+H]^+$ 353.1389; found 353.1390.

**Benzo[d][1,3]dioxol-5-yl(4-methoxynaphthalen-1-yl)methanone 2.2l:**

It was obtained as colorless solid in 68% yield. mp 92-94 $^{\circ}\text{C}$; $R_f = 0.3$ (in 20% EtOAc/Hexanes); IR (KBr): 2938, 1649, 1605, 1578, 1441, 1353, 1249, 1084, 1041, 920, 772 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.33 (d, $J = 9.2$ Hz, 1H), 8.19 (d, $J = 9.2$ Hz, 1H), 7.56-7.50 (m, 3H), 7.42 (d, $J = 1.2$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 6.81-6.78 (m, 2H), 6.04 (s, 2H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.7, 157.8, 151.6, 147.9, 133.7, 132.4, 129.9, 128.6, 127.7, 127.1, 125.72, 125.66, 125.59, 122.2, 109.8, 107.6, 102.0, 101.8, 55.7. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{14}\text{O}_4$ $[M+H]^+$ 307.0970; found 307.0970.

**(4-Methoxynaphthalen-1-yl)(thiophen-2-yl)methanone 2.2m:**

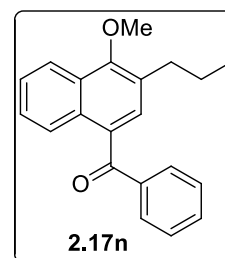
It was obtained as brown oil in 72% yield. $R_f = 0.4$ (in 20% EtOAc/Hexanes); IR (neat): 2939, 1629, 1578, 1505, 1459, 1412, 1329, 1293, 1262, 1096, 1014, 812, 770 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.34 (dd, $J = 1.6, 8.0$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.71 (dd, $J = 1.2, 5.2$ Hz), 7.56-7.51 (m, 3H), 7.12-7.10 (m, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz,



CDCl_3): δ 188.9, 158.1, 145.8, 134.9, 134.2, 132.0, 129.9, 128.2, 127.90, 127.87, 125.9, 125.7, 125.4, 122.2, 101.9, 55.7. HRMS (ESI): calcd for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{S}$ $[M+H]^+$ 269.0636; found 269.0636

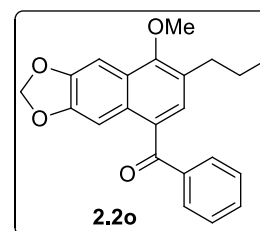
(4-Methoxy-3-propylnaphthalen-1-yl)(phenyl)methanone 2.17n:

It was obtained as light brown oil in 75% yield. R_f = 0.6 (in 20% EtOAc/Hexanes); IR (neat): 2964, 2928, 2866, 1655, 1598, 1572, 1500, 1448, 1376, 1252, 1169, 1101, 993, 863, 770 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.16 (t, J = 8.0 Hz, 2H), 7.88-7.86 (m, 2H), 7.62-7.58 (m, 1H), 7.57-7.53 (m, 1H), 7.49-7.45 (m, 4H), 3.98 (s, 3H), 2.79 (t, J = 8.0 Hz, 2H), 1.69 (quin, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.6, 156.0, 138.7, 133.0, 132.1, 131.5, 130.4, 129.5, 128.5, 128.4, 126.7, 126.4, 126.0, 122.3, 62.2, 31.5, 23.9, 14.1. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{20}\text{O}_2$ $[M+\text{Na}]^+$ 327.1361; found 327.1362.



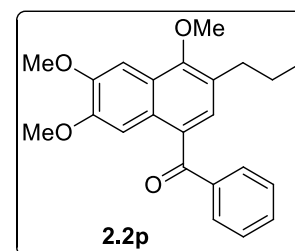
(8-Methoxy-7-propylnaphtho[2,3-d][1,3]dioxol-5-yl)(phenyl)methanone 2.2o:

It was obtained as light brown oil in 75% yield; R_f = 0.4 (in 20% EtOAc/Hexanes); IR (neat): 2954, 2923, 1660, 1500, 1469, 1241, 1127, 1034, 941 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.85-7.83 (m, 2H), 7.61-7.57 (m, 2H), 7.48-7.44 (m, 3H), 7.32 (s, 1H), 6.04 (s, 2H), 3.92 (s, 3H), 2.72 (t, J = 7.6 Hz, 2H), 1.69-1.60 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.7, 155.8, 148.6, 148.1, 138.8, 132.8, 131.0, 130.42, 130.35, 128.8, 128.3, 125.8, 102.7, 101.3, 98.9, 61.8, 31.4, 23.9, 14.1. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{20}\text{O}_4$ $[M+\text{Na}]^+$ 371.1259; found 371.1266.



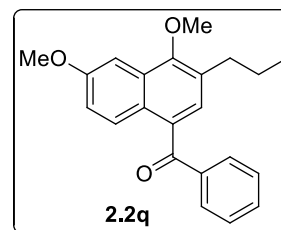
Phenyl(4,6,7-trimethoxy-3-propylnaphthalen-1-yl)methanone 2.2p:

It was obtained as light brown oil in 78% yield. R_f = 0.3 (in 20% EtOAc/Hexanes); IR (neat): 2954, 2923, 2871, 1655, 1578, 1510, 1479, 1433, 1417, 1252, 1221, 1169, 1055, 858, 812, 739 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.85 (d, J = 7.2 Hz, 2H), 7.75 (s, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.44 (s, 1H), 7.38 (s, 1H), 4.05 (s, 3H), 3.97 (s, 3H), 3.91 (s, 3H), 2.74 (t, J = 8.0 Hz, 2H), 1.69-1.61 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 198.0, 155.6, 150.3, 149.8, 139.2, 132.7, 131.4, 130.4, 129.7, 128.3, 127.8, 124.4, 105.0, 100.9, 61.7, 55.85, 55.78, 31.5, 24.0, 14.1. HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{24}\text{O}_4$ $[M+\text{Na}]^+$ 387.1572; found 387.1575.



(4,6-Dimethoxy-3-propylnaphthalen-1-yl)(phenyl)methanone 2.2q:

It was obtained as light brown oil in 65% yield. R_f = 0.4 (in 20% EtOAc/Hexanes); IR (neat): 2954, 2933, 1660, 1624, 1572, 1510, 1448, 1407, 1252, 1221, 1174, 1081, 879, 838 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.08 (d, J = 9.2 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.61-7.57 (m, 1H), 7.48-7.44 (m, 3H), 7.33 (s, 1H), 7.13 (dd, J = 2.4, 9.2 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 2.77 (t, J = 7.6 Hz, 2H), 1.70-1.65 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.7, 158.1, 155.0, 138.7, 132.9, 132.0, 130.4, 130.0, 129.8, 129.2, 128.3, 127.7, 126.9, 119.1, 100.6, 61.6, 55.3, 31.6, 23.9, 14.1. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{22}\text{O}_3$ $[M+H]^+$ 335.1647; found 335.1647.

**Preparation of $\text{DC}(\text{OCD}_3)_3$ and 2.2a-d₄ and analytical data of compound 2a-d₄:**

The fully deuterated trimethyl orthoformate ($\text{DC}(\text{OCD}_3)_3$) was prepared as per reported procedure using CDCl_3 and CD_3OD in the presence of Na metal at 0°C .¹⁰ After 12 h, the reaction mixture was diluted with CH_2Cl_2 and water to quench the excess Na metal. Then, organic layer was separated. The excess CDCl_3 , CD_3OD and CH_2Cl_2 were removed by distillation to get $\text{DC}(\text{OCD}_3)_3$ which was used for reaction of **2.1a** without further purification.

Light yellow oil; R_f = 0.5 (in 20% EtOAc/Hexanes); ^1H NMR (400 MHz, CDCl_3): δ 8.40-8.34 (m, 2H), 7.84 (d, J = 8.0 Hz, 2H), 7.62-7.52 (m, 3H), 7.48-7.44 (m, 2H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.4, 158.3, 139.4, 132.6, 132.5, 130.3, 128.2, 128.04, 127.91, 125.8, 125.7, 122.2, 101.8. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{10}\text{D}_4\text{O}_2$ $[M+H]^+$ 267.1323; found 267.1323.

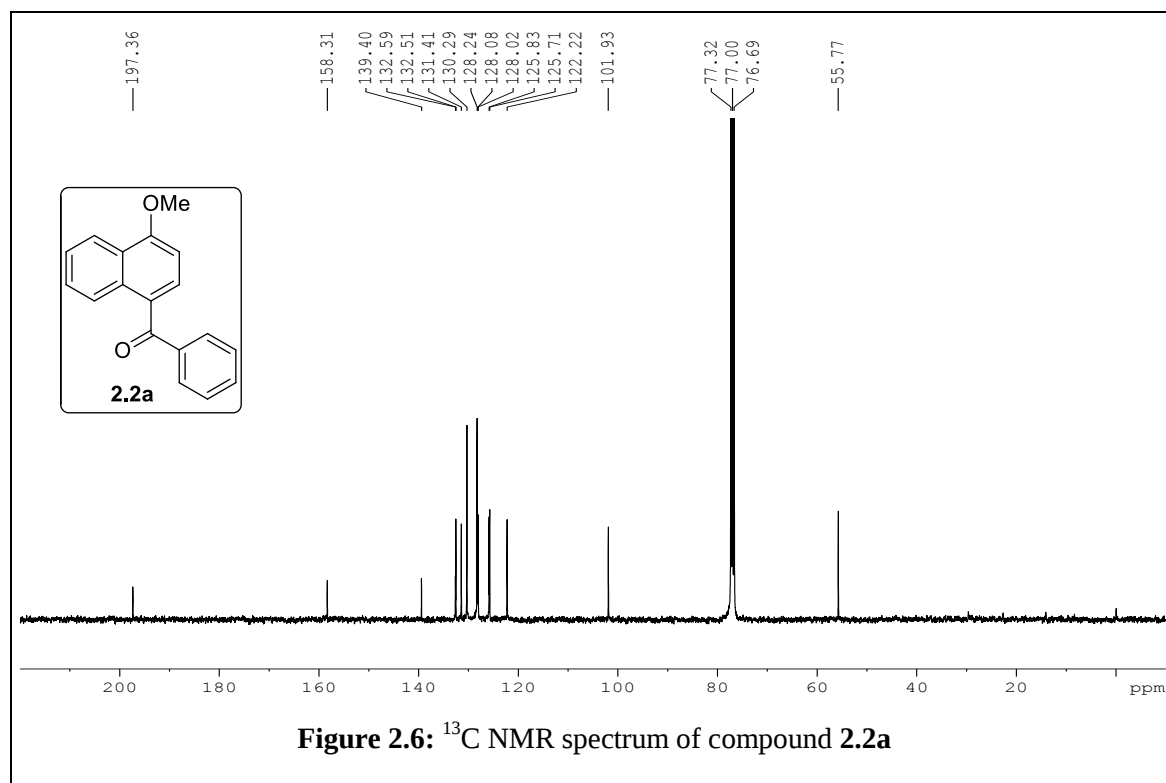
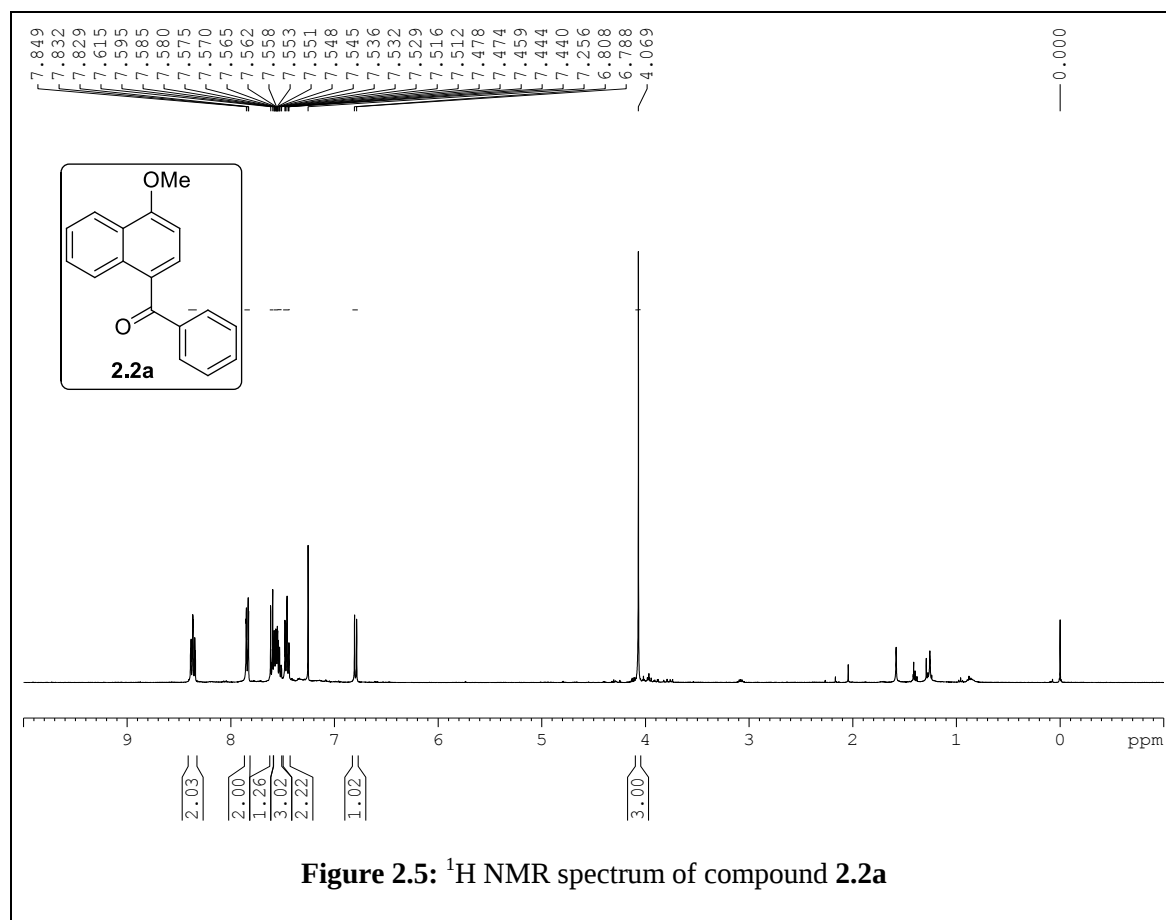
2.6 References

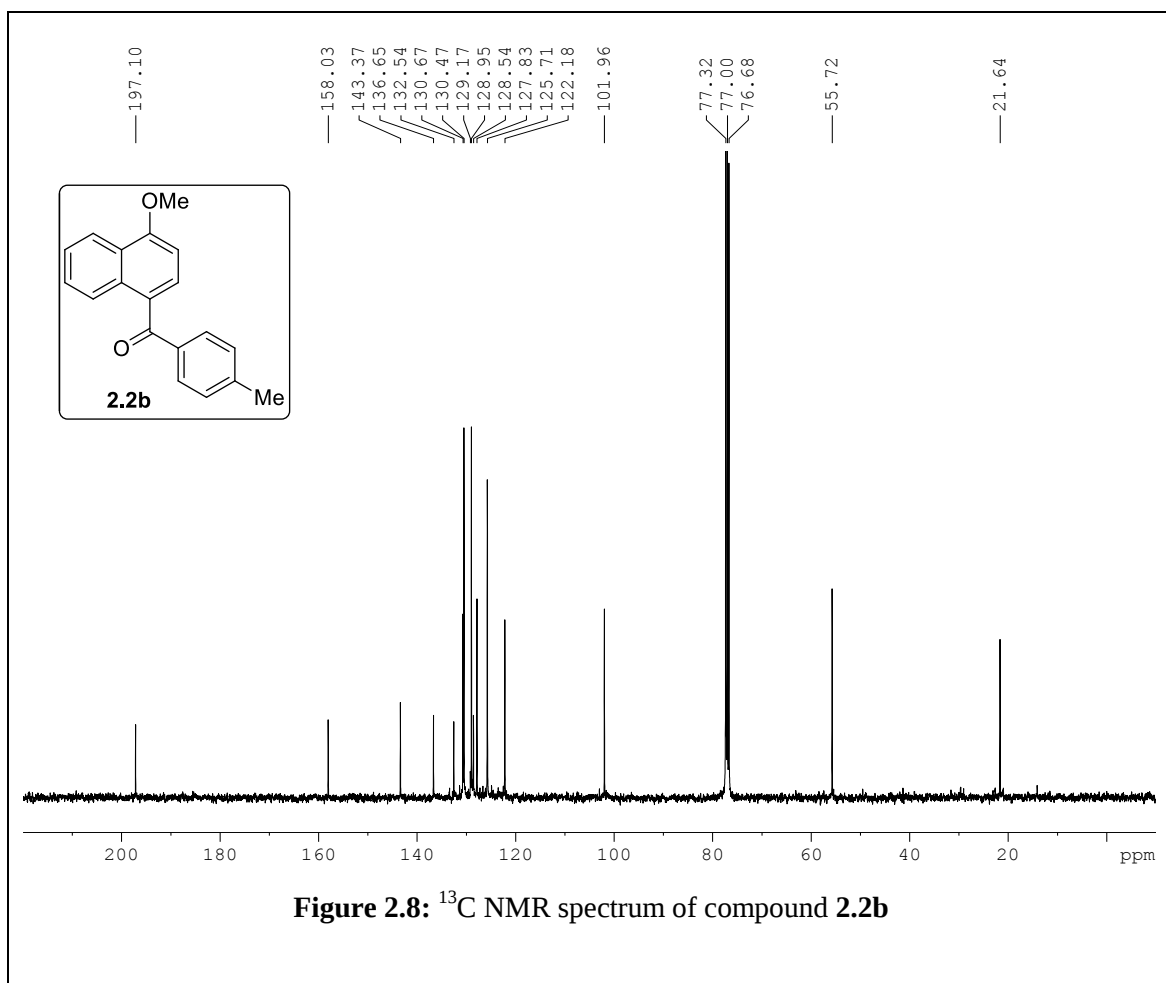
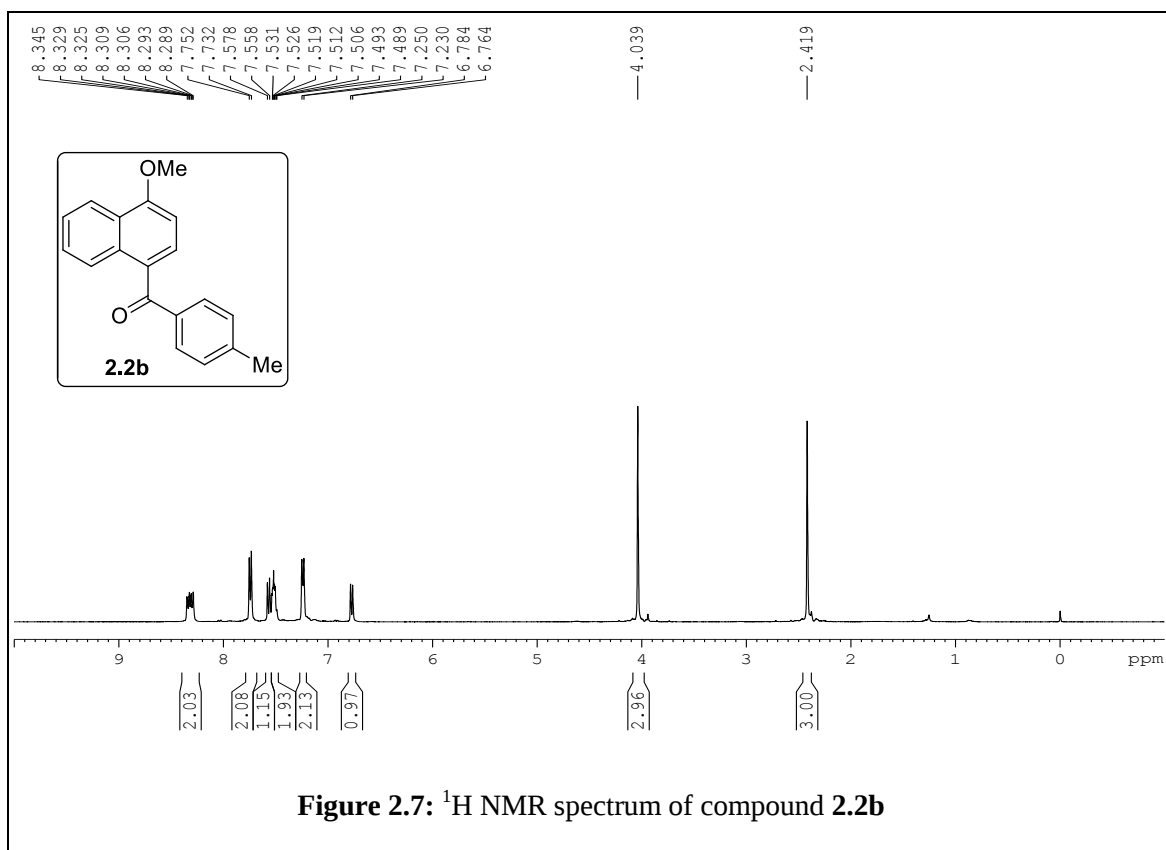
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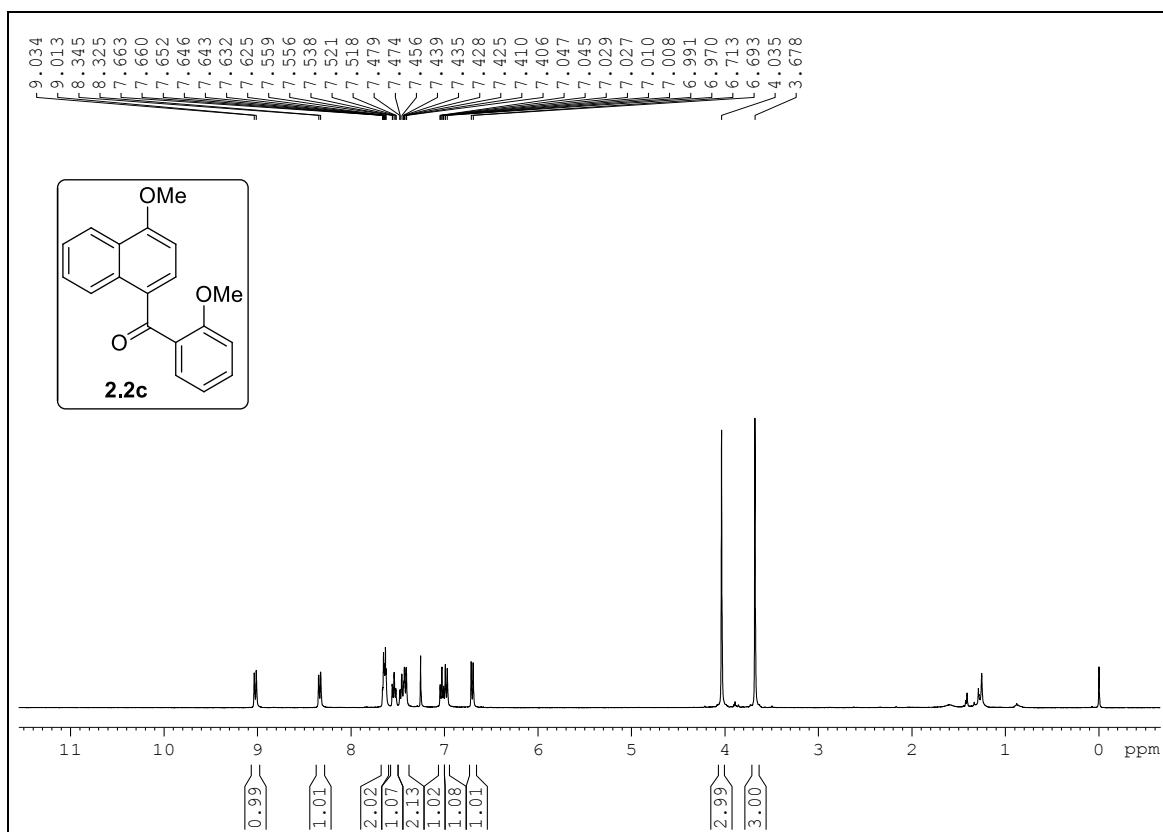
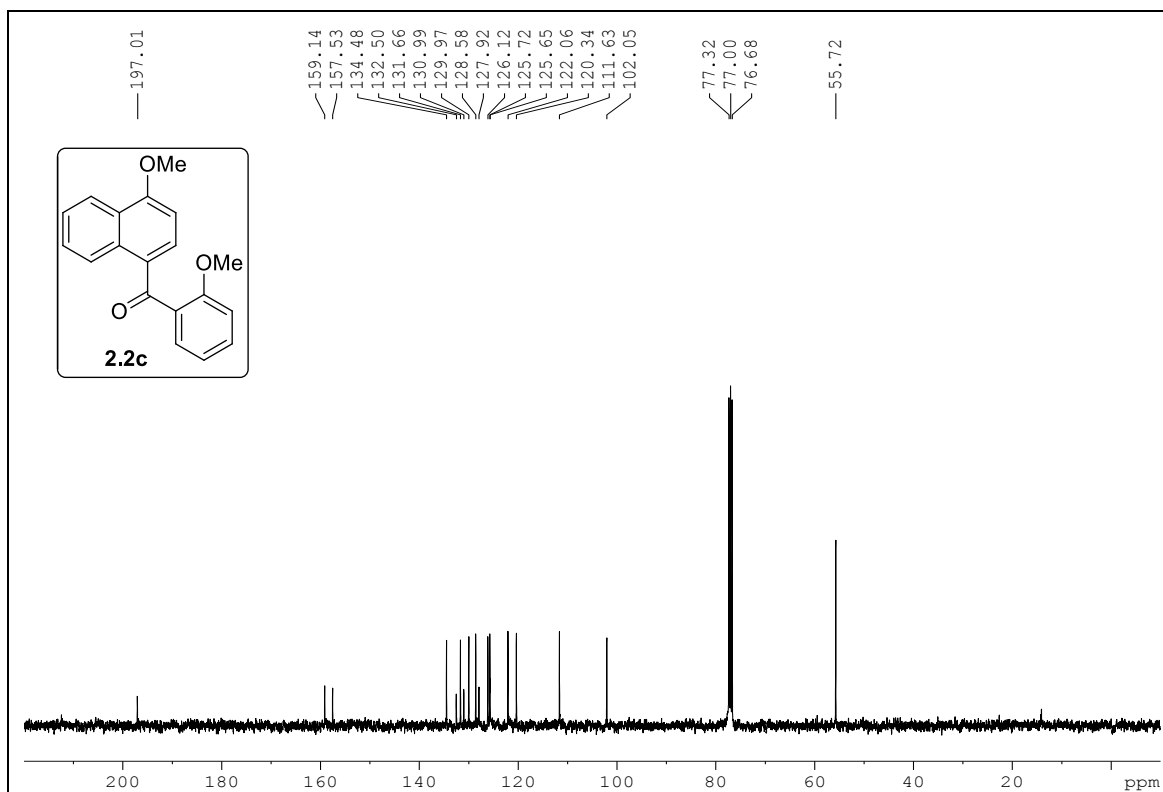
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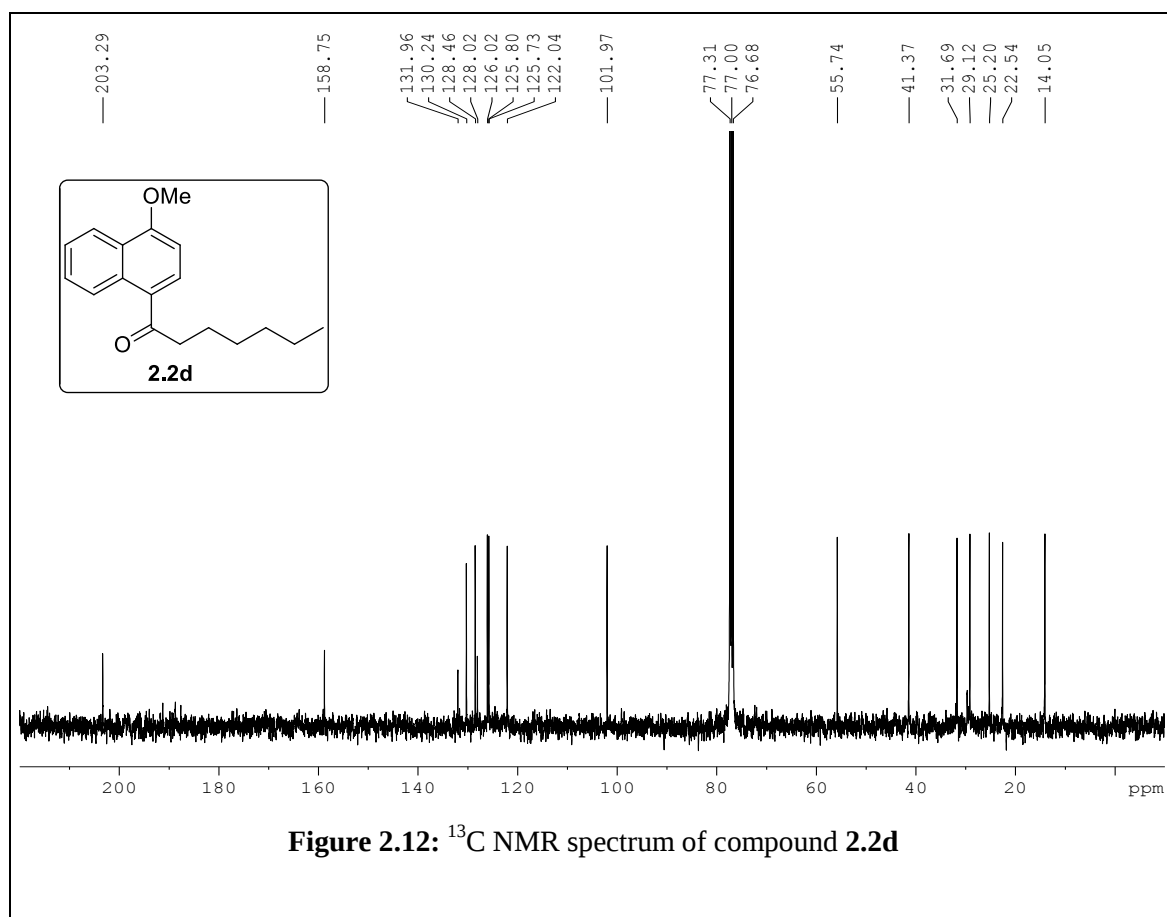
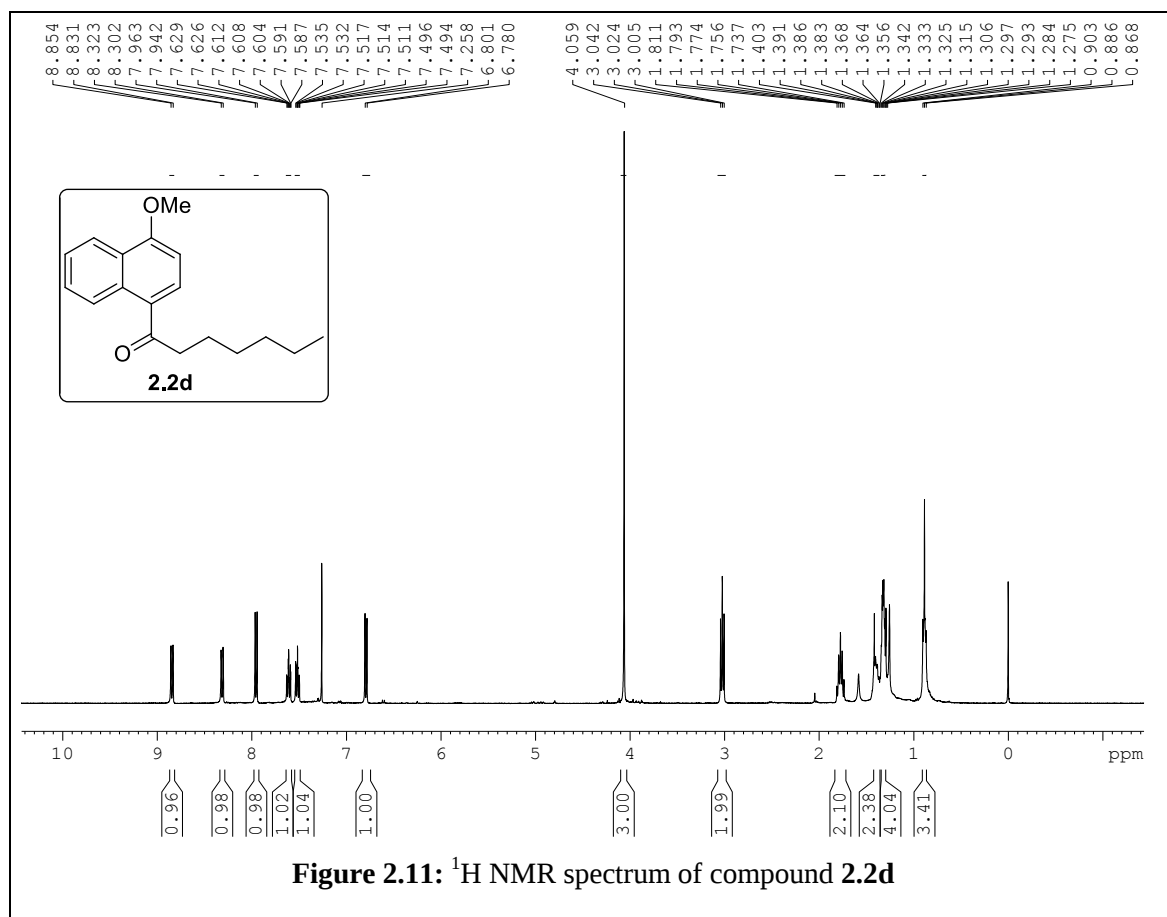
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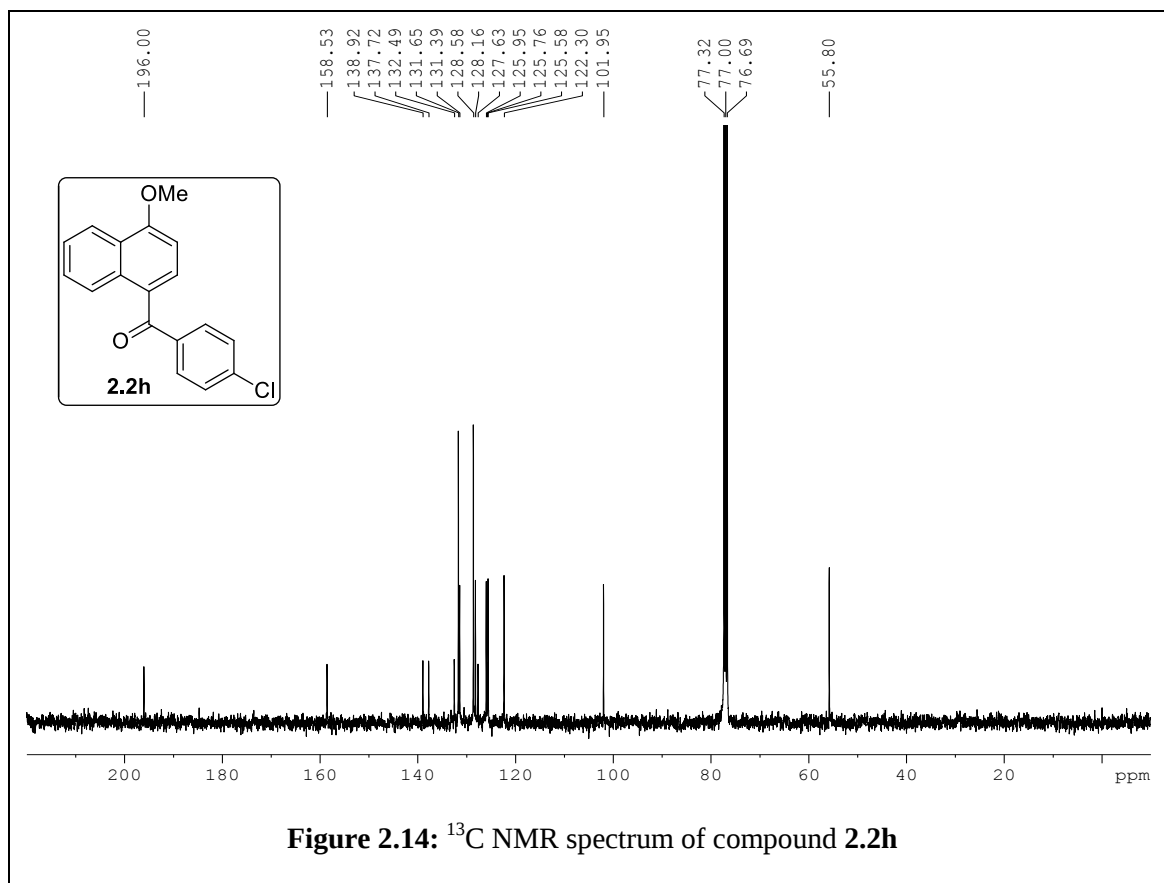
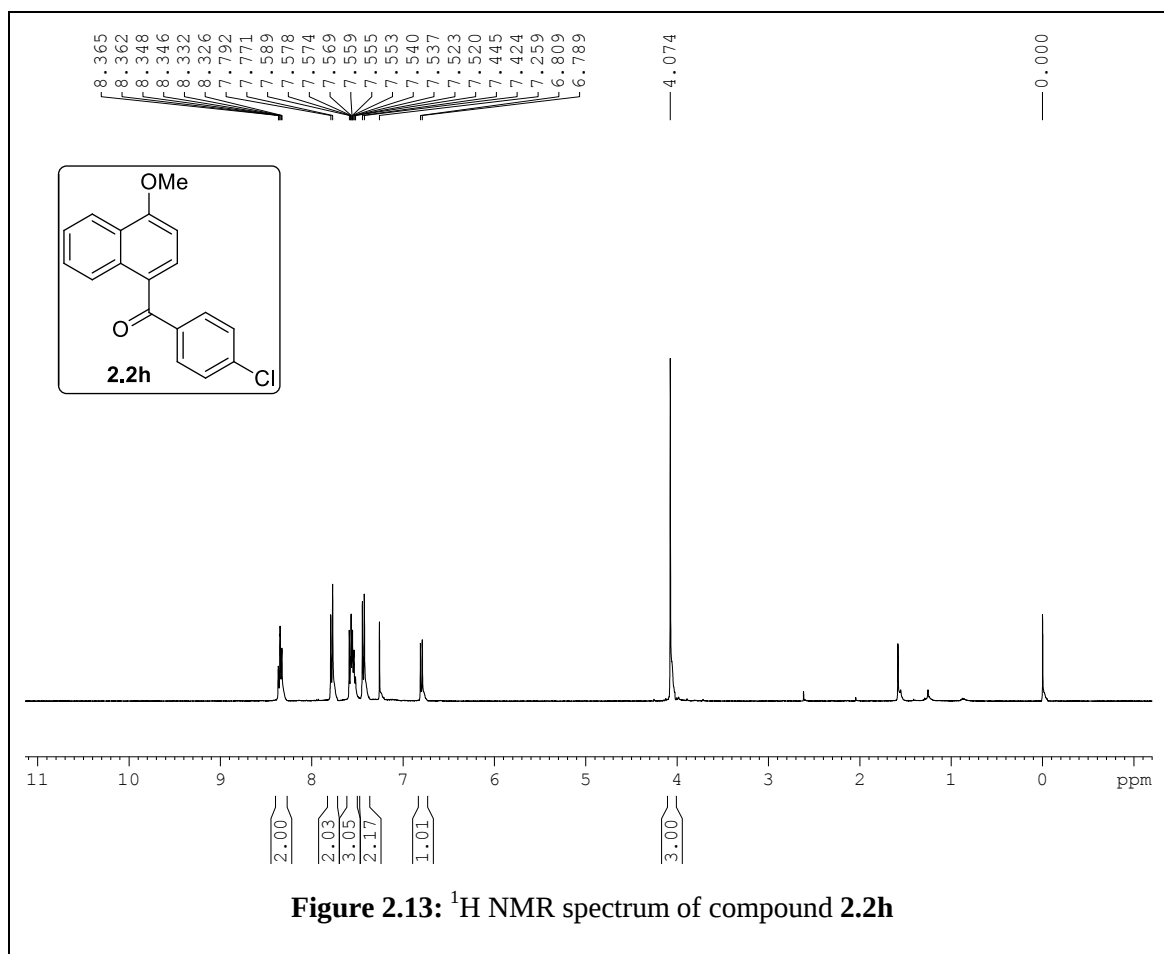
2.7 Representative spectra

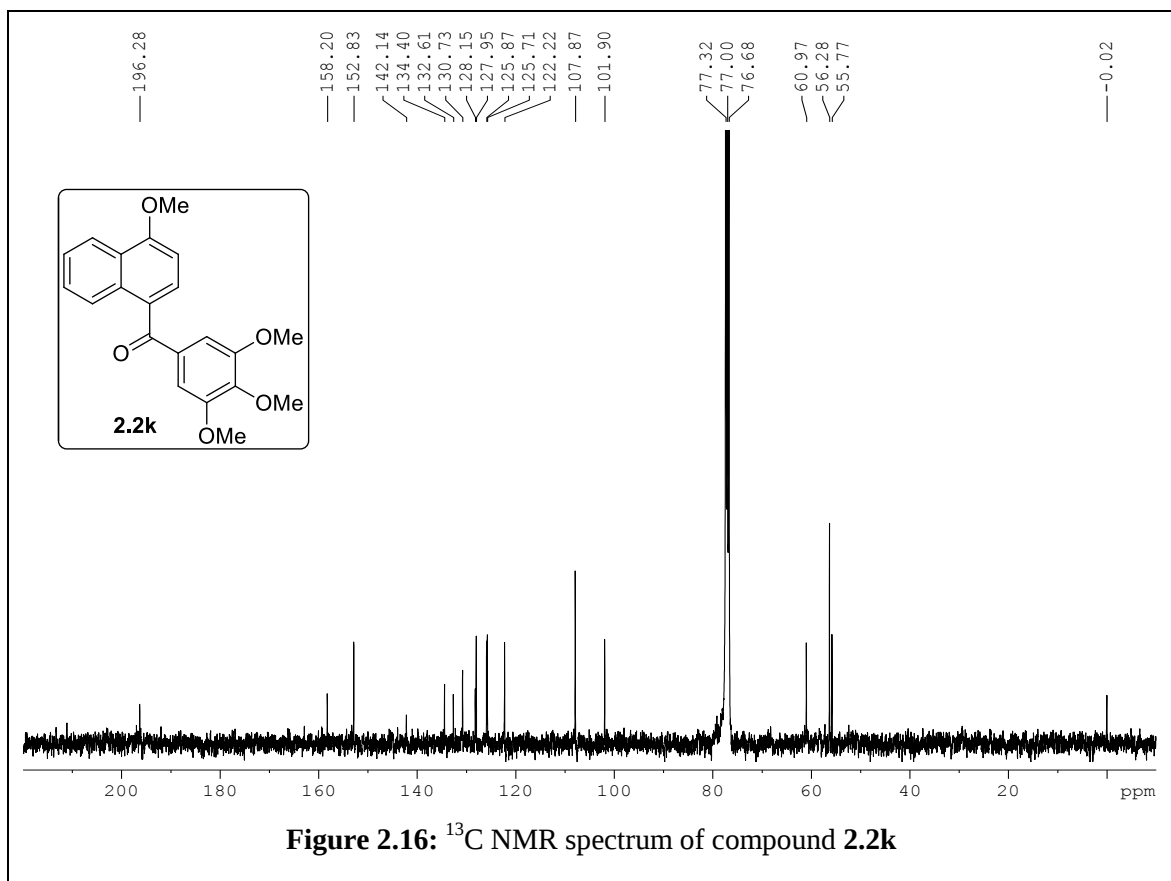
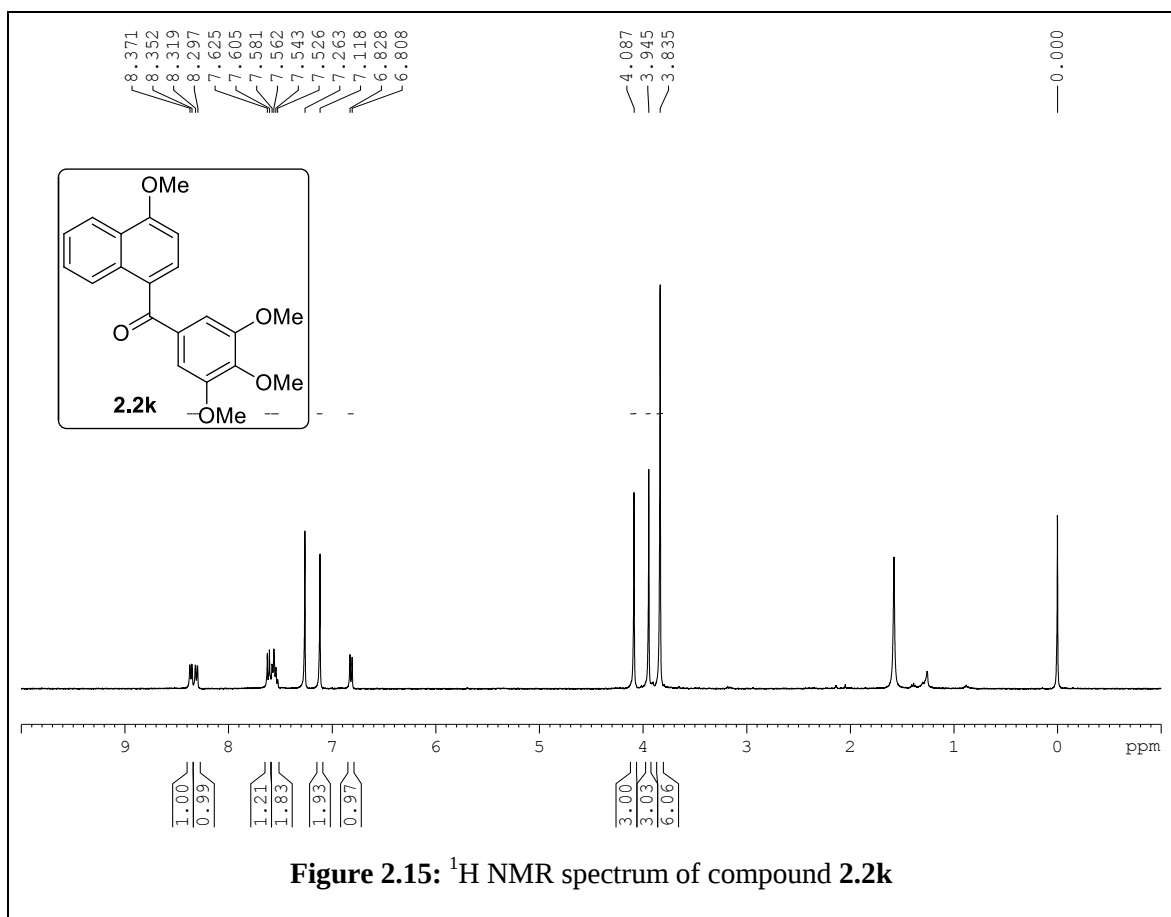


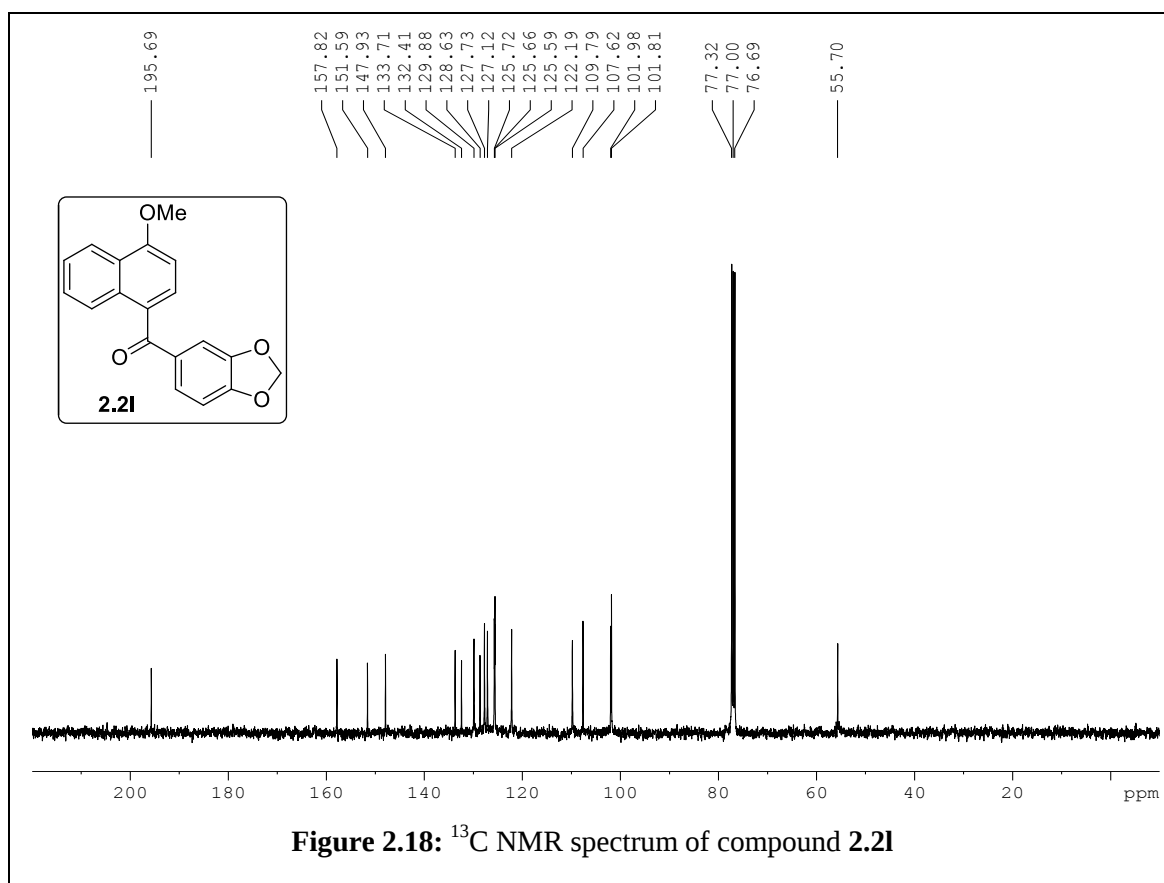
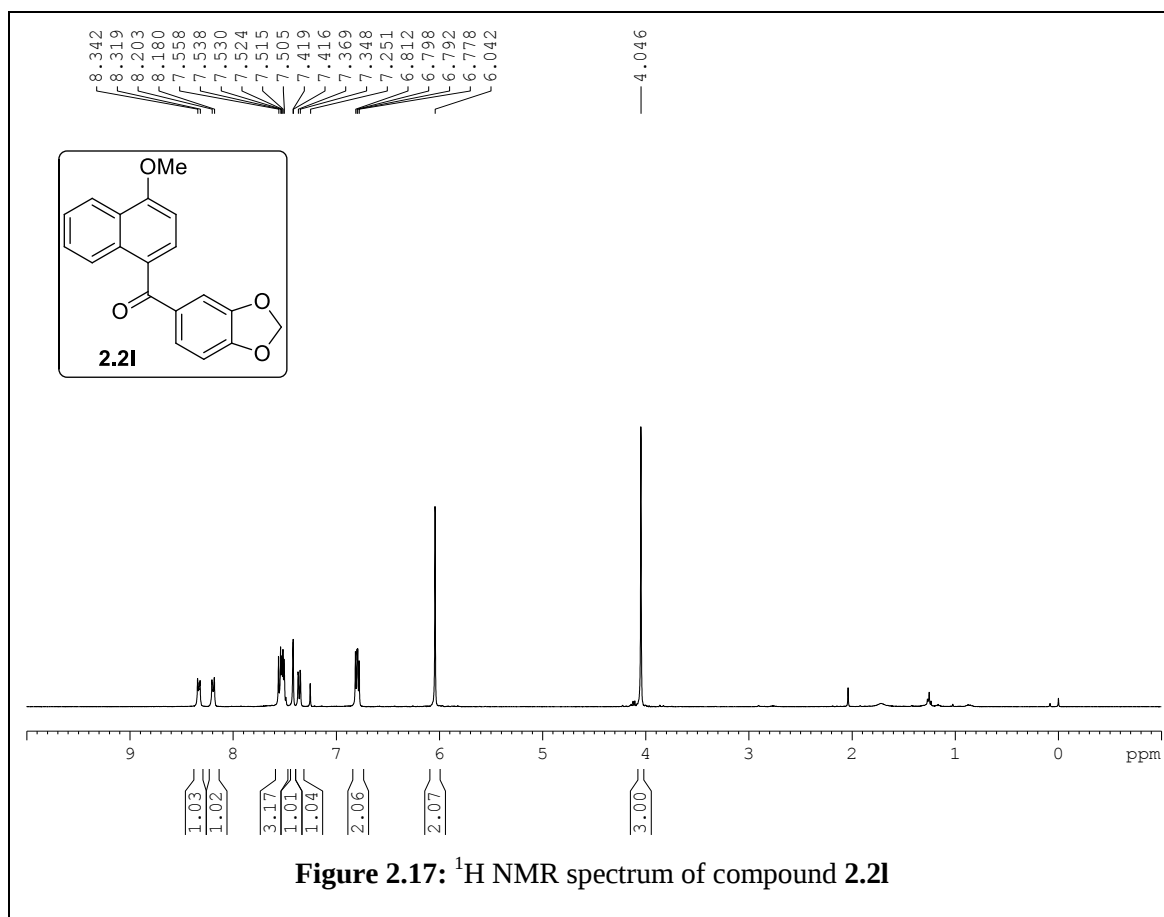


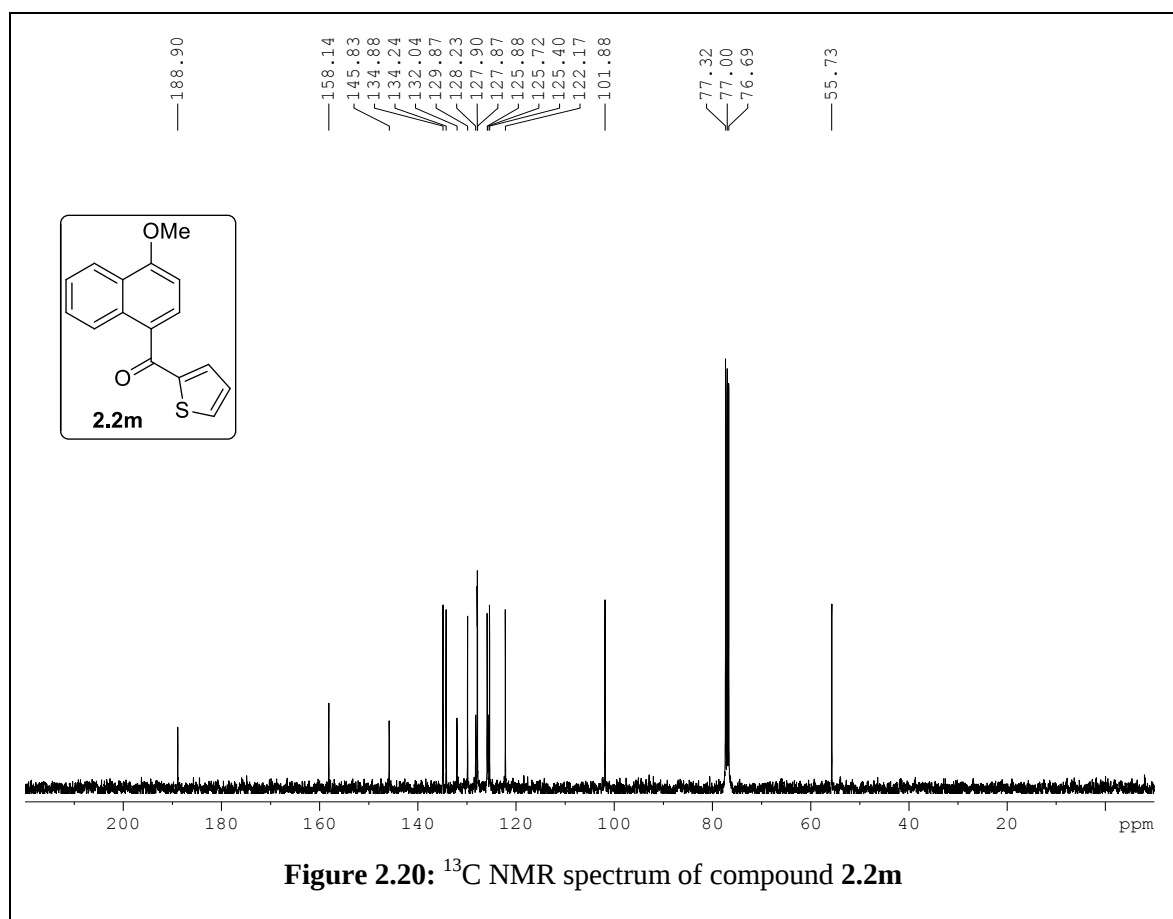
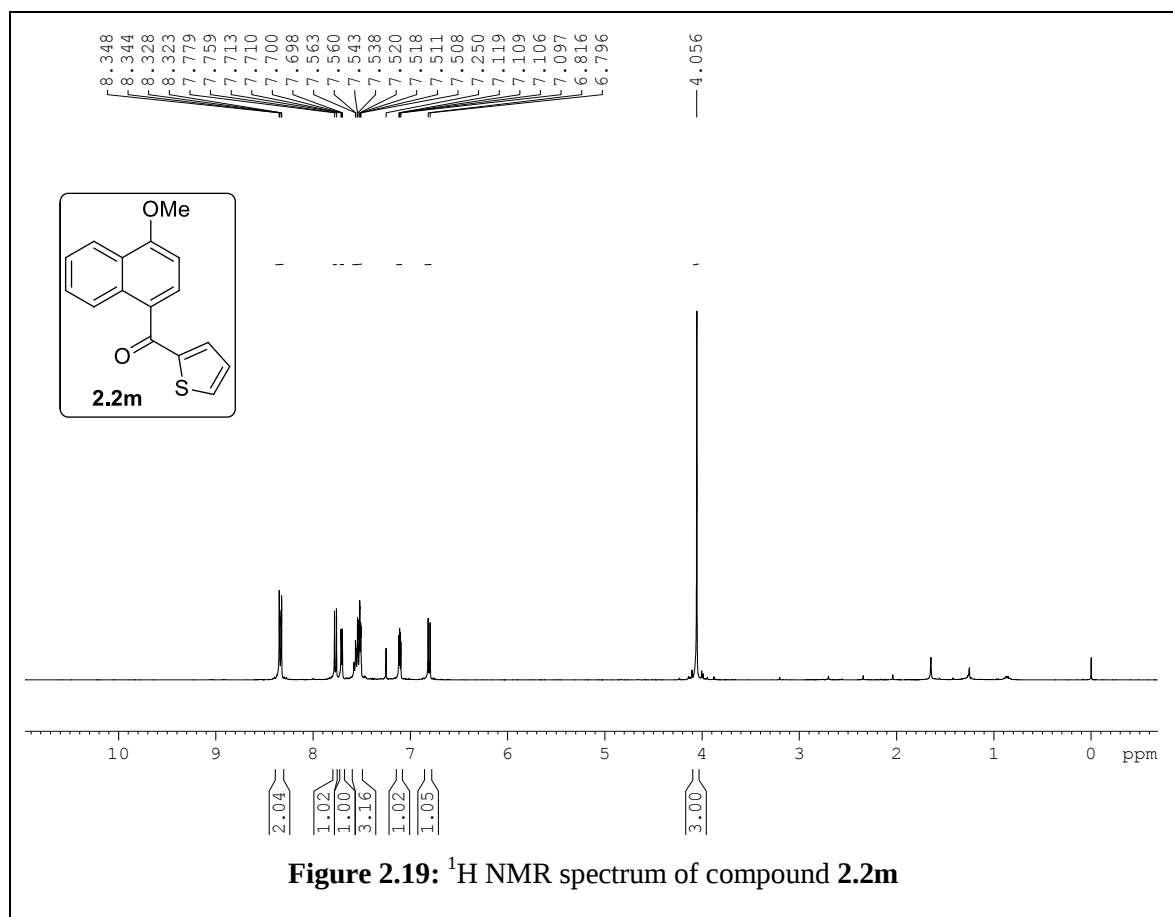
Figure 2.9: ¹H NMR spectrum of compound **2.2c**Figure 2.10: ¹³C NMR spectrum of compound **2.2c**

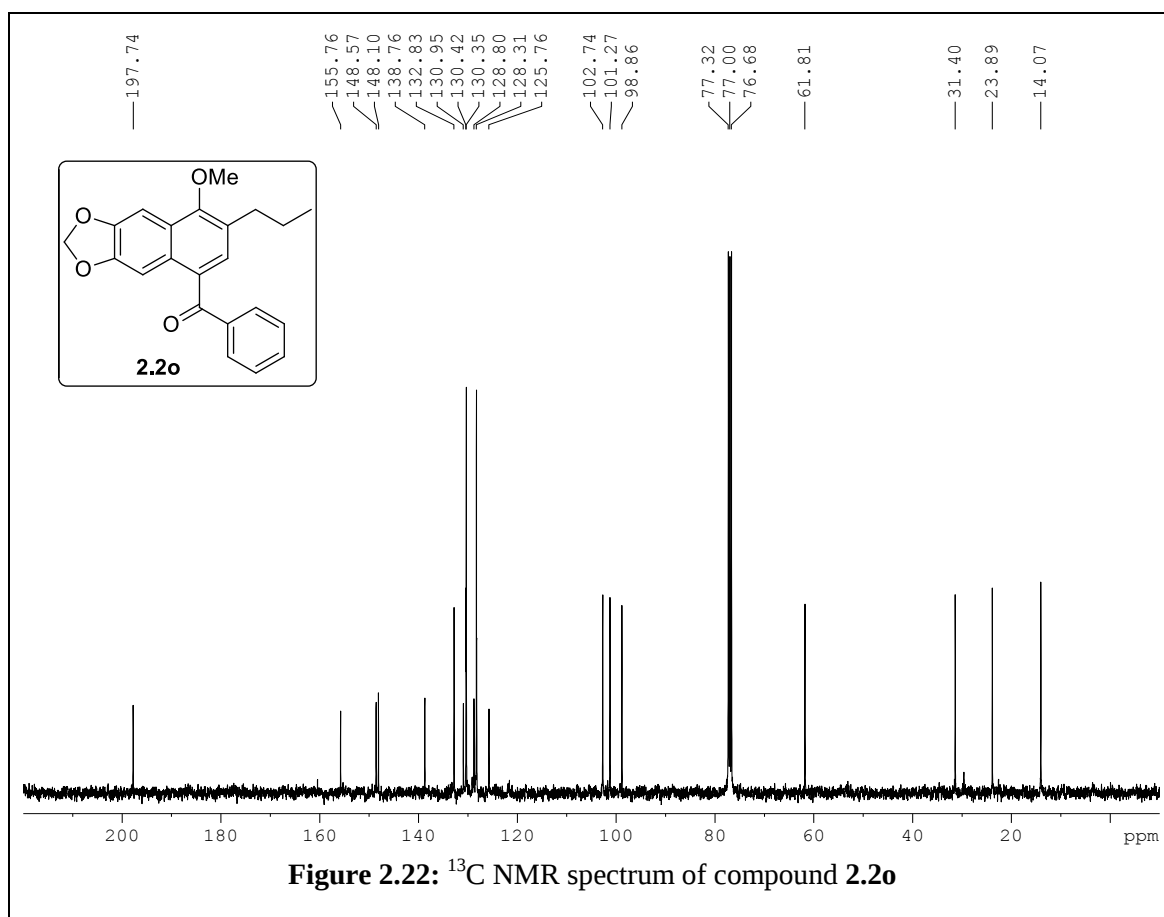
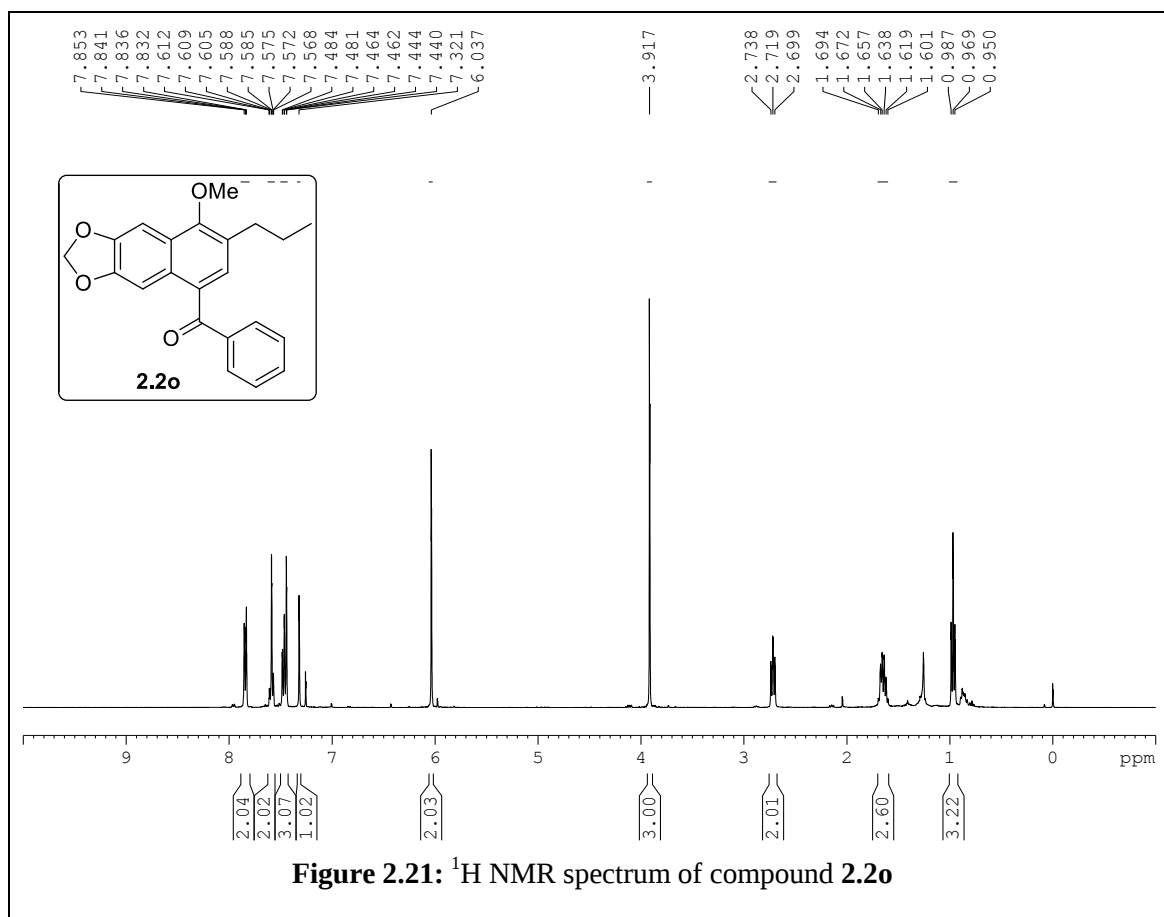


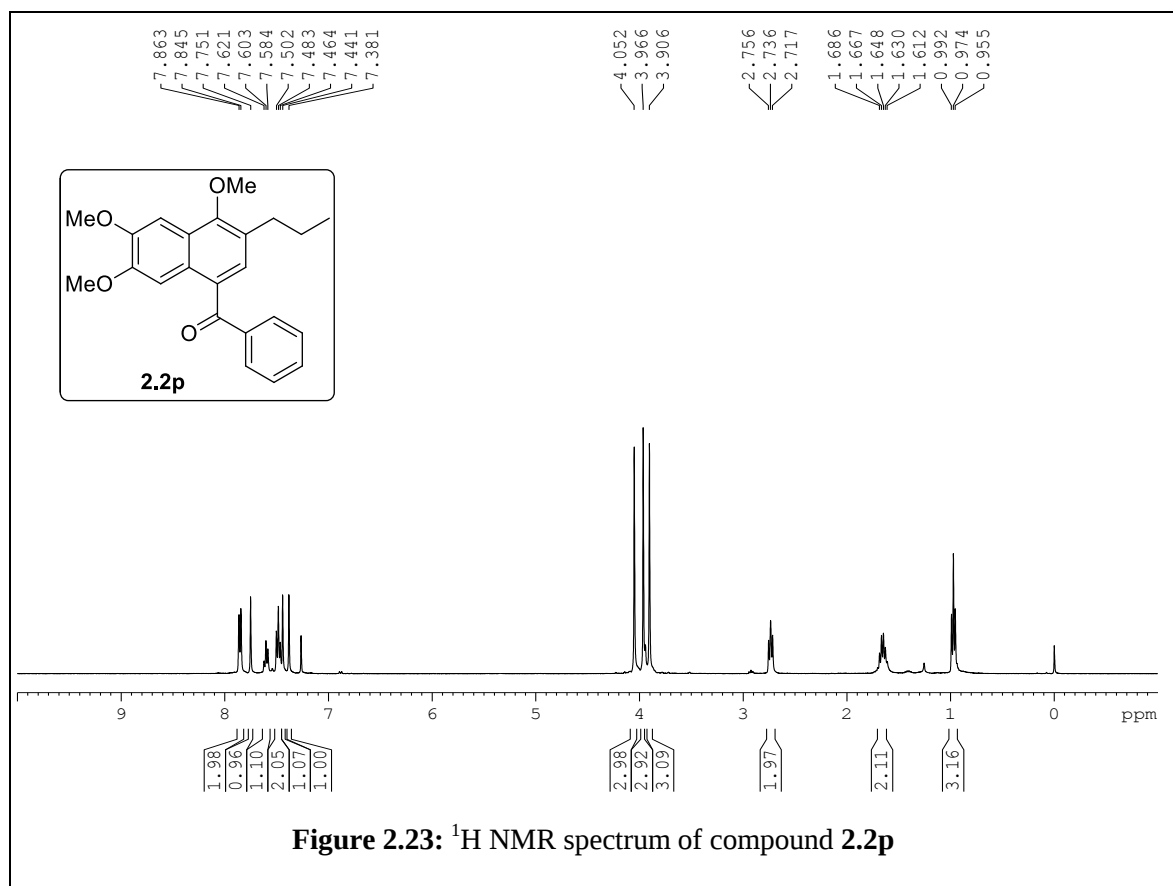
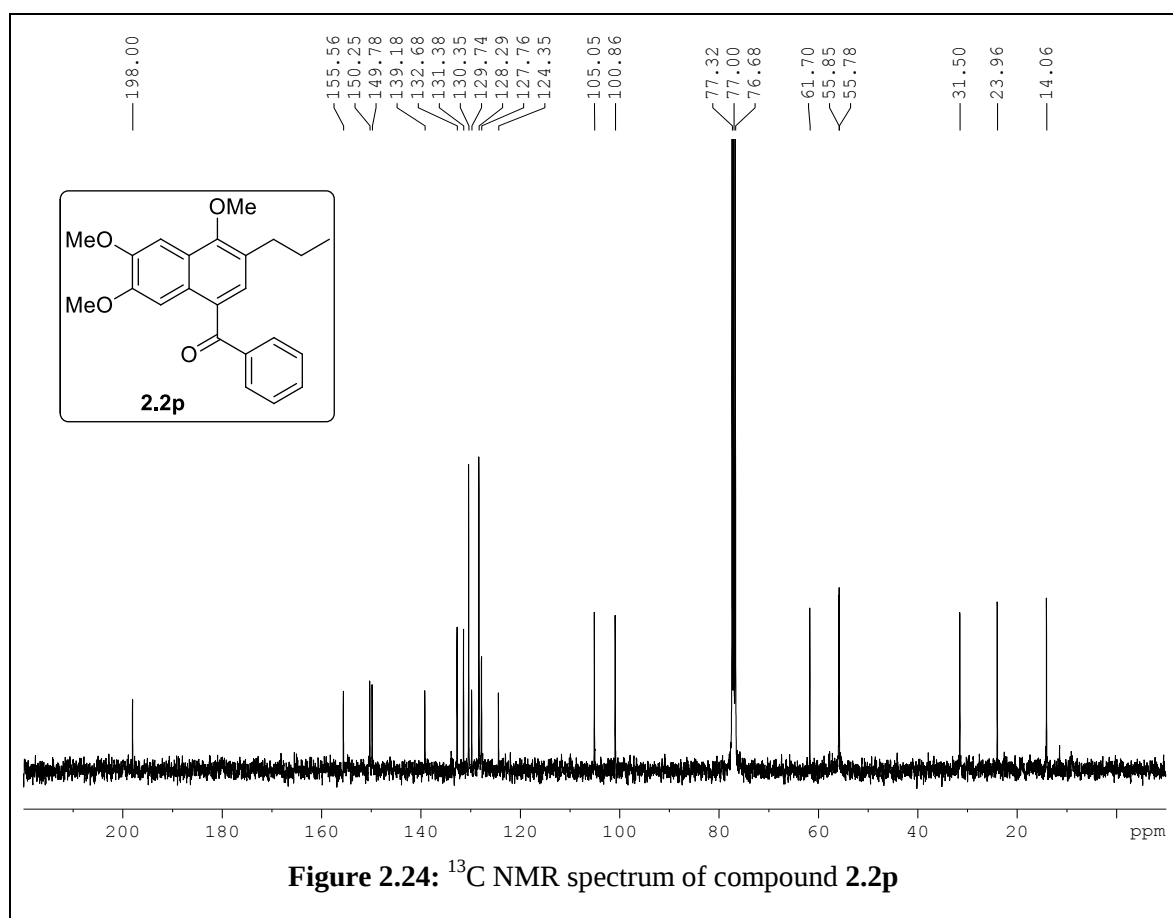


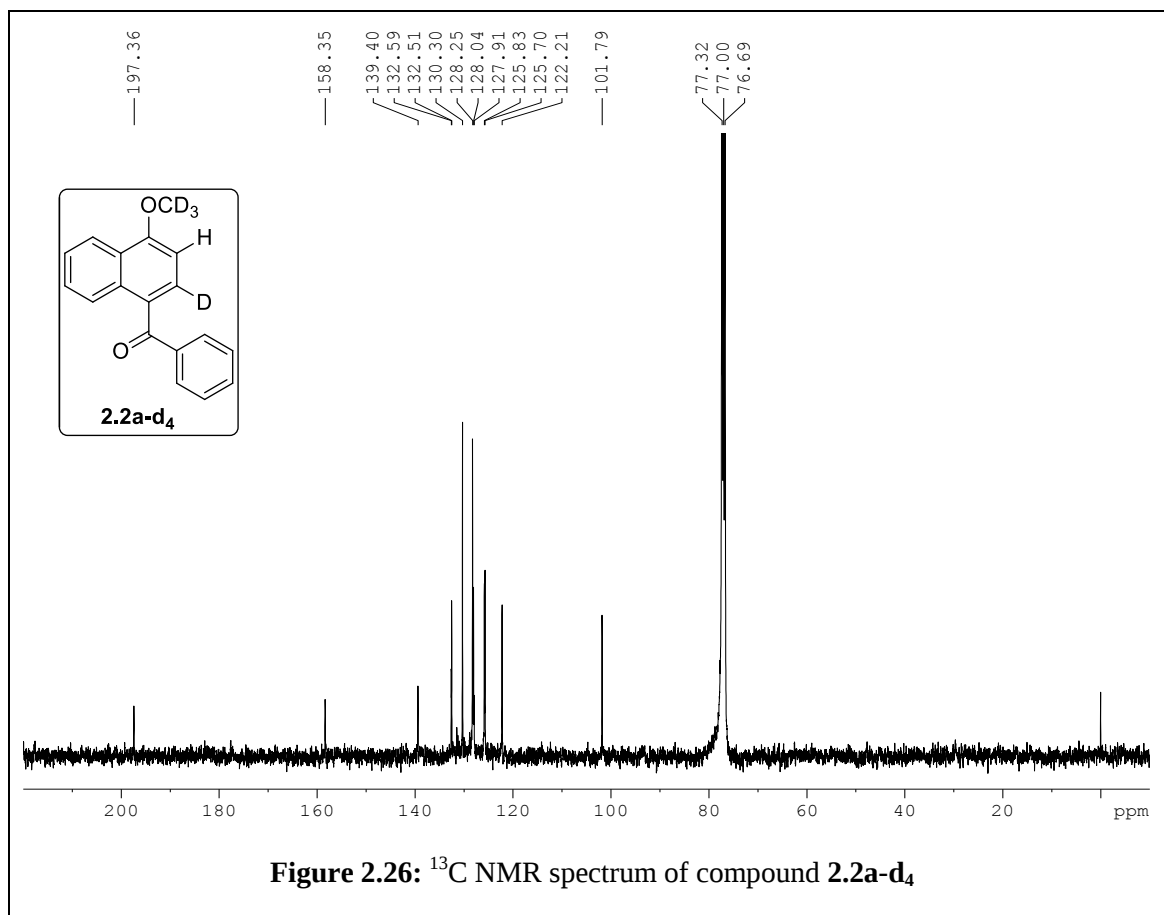
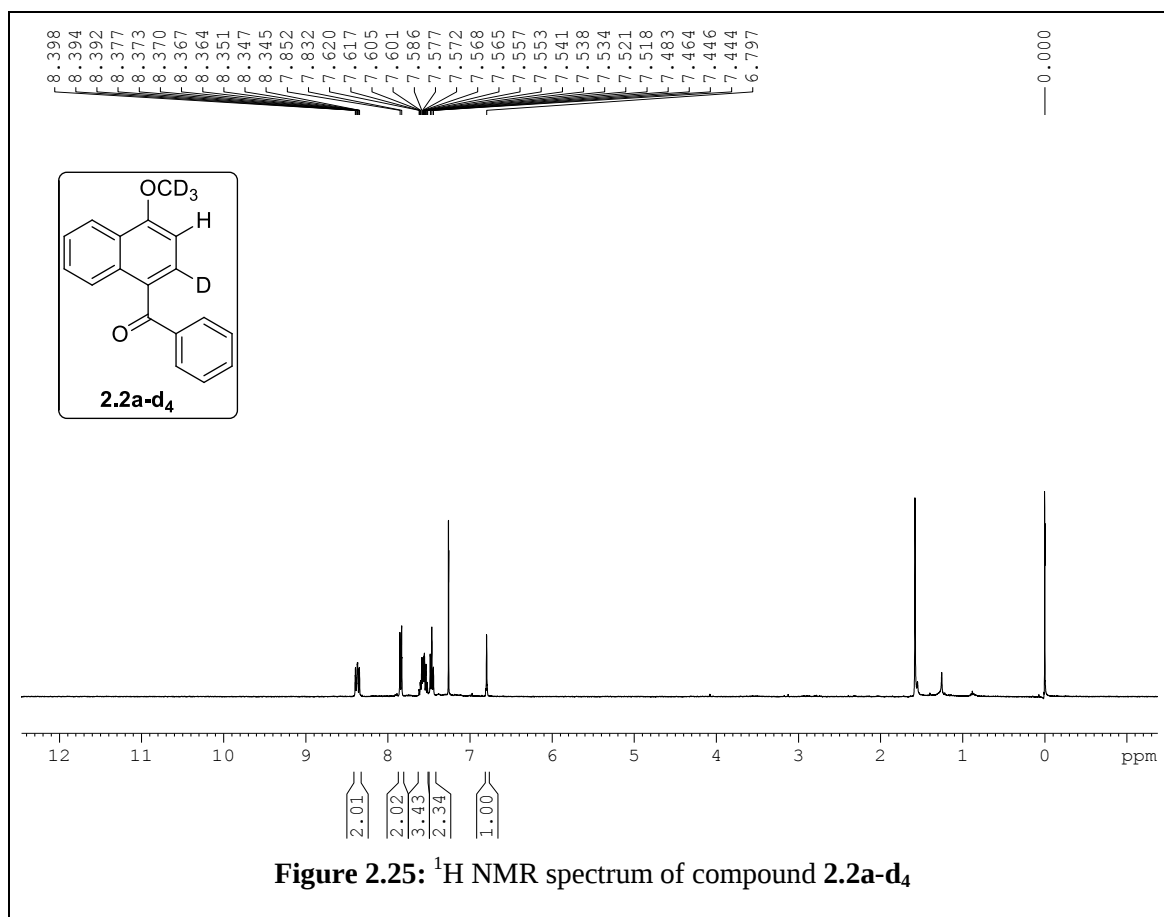








Figure 2.23: ¹H NMR spectrum of compound **2.2p**Figure 2.24: ¹³C NMR spectrum of compound **2.2p**



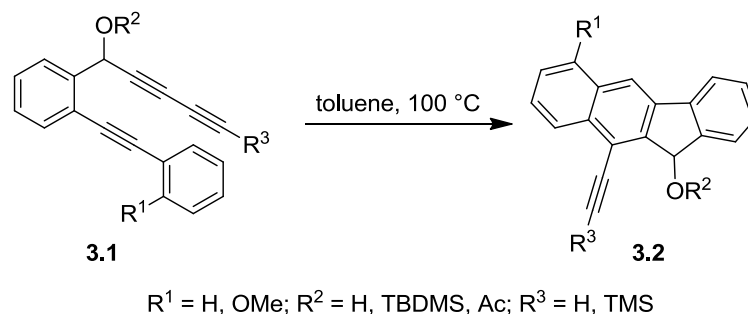
A Facile Access to Substituted Benzo[*a*]fluorenes from *o*-Alkynylbenzaldehydes via *in Situ* Formed Acetals

3.1 Introduction

Polycyclic aromatic hydrocarbons (PAHs) such as naphthalenes, fluorenes, anthracenes, phenanthrenes etc. play an important role in the fields of medicinal and materials chemistry due to their unique properties.¹ For their synthesis in a regioselective manner, cyclization reactions of type [4+2], [2+2], [2+2+2] and domino reactions have been developed.² Among PAHs, fluorene derivatives have widely been utilized in the field of materials science for developing optical materials. Fluorene based compounds have extended π -electron conjugation which leads to high fluorescence efficiency of these compounds and are widely incorporated in oligomers and polymers for NLO applications.³ At the same time these compounds show good thermal and chemical stabilities. In addition, fluorene based compounds can easily be substituted at the 9-position with long alkyl chains to increase its solubility without perturbing its electrochemical properties. This advantage makes the fluorene derivatives to use them in electroluminescent devices, solar cells and chemical sensors.⁴ Hence, development of a simple method for the construction of fluorenes from readily available starting materials is highly desirable. Limited methods are only available in the literature for the construction of fluorene frameworks in general and benzo[*a*]fluorenes in particular.¹² Selected methods on the construction of benzofluorene framework are discussed in the following section.

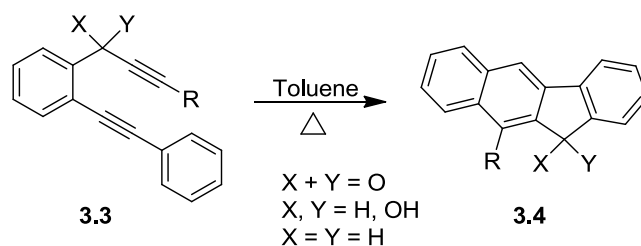
3.1.1 Selected literature survey on fluorene synthesis

In 1999 Saá and co-workers reported a method for the synthesis of benzo[*b*]fluorenes **3.2** from non-conjugated benzotriynes **3.1** where triynes undergo thermal intramolecular radical cyclization followed by hydrogen abstraction to give benzo[*b*]fluorene derivative **3.2** in toluene solvent at 100 °C (Scheme 3.1).⁵



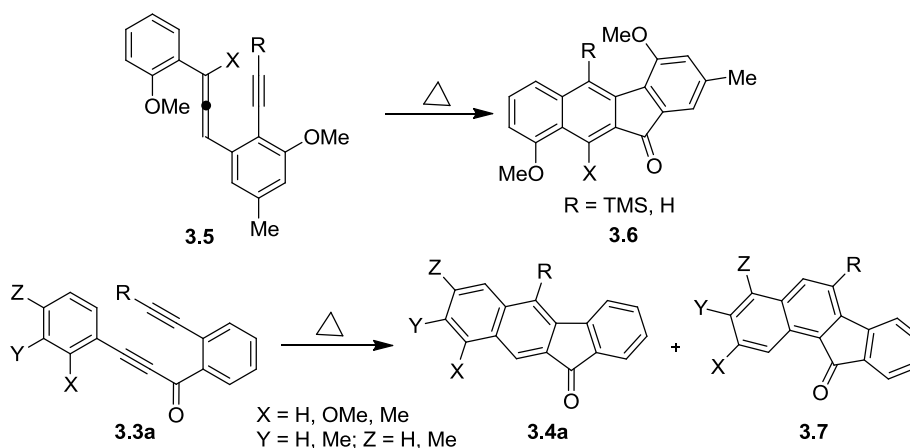
Scheme 3.1: Thermal cyclization of triynes

Few years later the same research group reported a [4+2] cycloaddition of diarylacetylene derivatives **3.3** to furnish benzo[*b*]fluorene derivatives **3.4** in good yields under thermal conditions (Scheme 3.2).⁶ They also found that the reaction depends highly on the nature of hybridization of the carbon linking the reacting alkyne groups. In general, less temperature is required for the reaction of substrates having carbonyl group than substrates with hydroxyl group ($X, Y = H, OH$) or methylene group ($X = Y = H$).



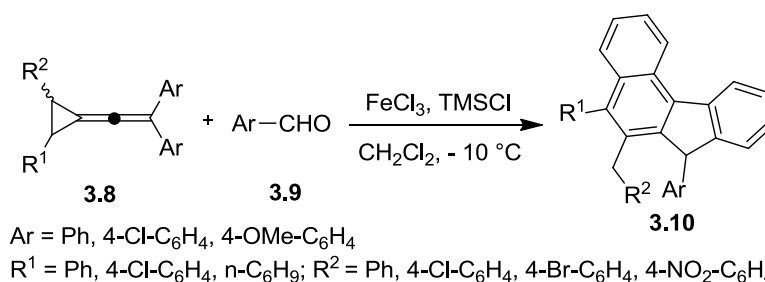
Scheme 3.2: Thermal cyclization of diarylacetylenes

Echavarren group reported an intramolecular cyclization of 1,3-diaryllallene derivatives **3.5** to construct benzo[*b*]fluorenones **3.6** in excellent yields (Scheme 3.3).⁷ They also found that the reaction of **3.3a** to produce benzo[*a*]fluorenones **3.7** in addition to the expected benzo[*b*]fluorenones **3.4a** during cycloaddition. The formation of **3.7** can be suppressed by doing the rearrangement in the presence of phenol which allows to synthesize **3.4a** in excellent yields.



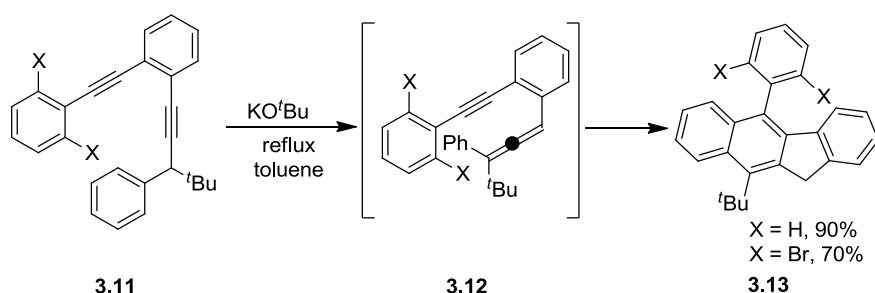
Scheme 3.3: Thermal cyclizations for benzo[*b*]fluorenones synthesis

Vinylidenecyclopropanes **3.8** undergo nucleophilic addition with aromatic aldehydes **3.9** and subsequent Friedel-Crafts reaction and aromatization to afford benzo[*c*]fluorene derivatives **3.10** in moderate to good yields in the presence of $\text{FeCl}_3/\text{TMSCl}$ (Scheme 3.4).⁸



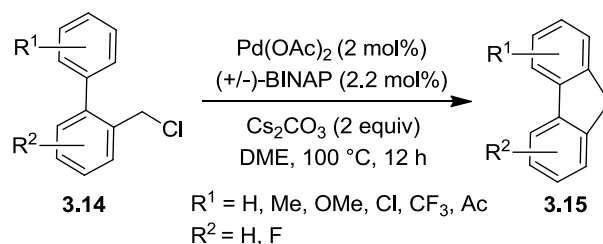
Scheme 3.4: Cycloaddition of vinylidenecyclopropanes with aldehydes

Potassium *tert*-butoxide-mediated cyclization of benzannulated enediynes **3.11** to give benzo[*b*]fluorenes **3.13** was reported by Wang and co-workers (Scheme 3.5).⁹ In this reaction base abstracts a benzylic proton to form allene **3.12** which would undergo cyclization to construct benzo[*b*]fluorene **3.13** in toluene at reflux conditions.



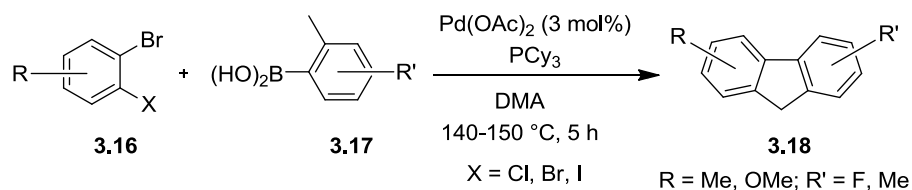
Scheme 3.5: Base-mediated cyclization of benzannulated enediynes

Chang and co-workers developed a facile protocol for the synthesis of fluorene derivatives **3.15** using palladium catalyst (Scheme 3.6).¹⁰ 2-Phenylbenzyl chlorides **3.14** undergo base-assisted C-H activation with impressive functional group tolerance in the presence of palladium acetate to yield a variety of fluorenes **3.15**.



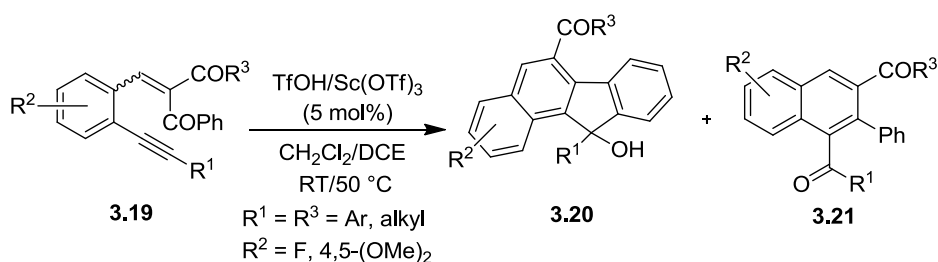
Scheme 3.6: Pd-catalyzed synthesis of fluorene derivatives

Palladium-catalyzed Suzuki cross-coupling of 1,2-dihalobenzenes **3.16** with 2-methylphenylboronic acids **3.17** and subsequent C(sp³)-H activation for further cyclization to form fluorenes **3.18** was demonstrated by Liu *et al.* (Scheme 3.7).¹¹



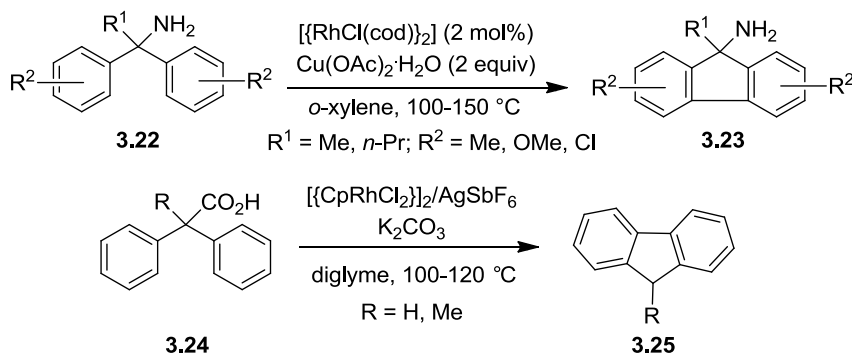
Scheme 3.7: Fluorene synthesis via Pd-catalyzed tandem Suzuki cross-coupling and C(sp³)-H activation

Zhang and co-workers described a method for the synthesis of benzo[*a*]fluorenols **3.20** along with naphthalene derivatives **3.21** from chalcones **3.19** in the presence of triflic acid/Sc(OTf)₃ catalyst systems (Scheme 3.8).¹² In this protocol, chalcones have been prepared from *o*-alkynylbenzaldehydes and 1,3 dicarbonyls which were later subjected to triflic acid/Sc(OTf)₃ catalyzed reaction conditions. Generally, the triflic acid-catalyzed reactions produce benzo[*a*]fluorenols **3.20** as the major product along with corresponding naphthalenes **3.21** as the minor product whereas the reactions of Sc(OTf)₃ result in naphthalenes as the major product.



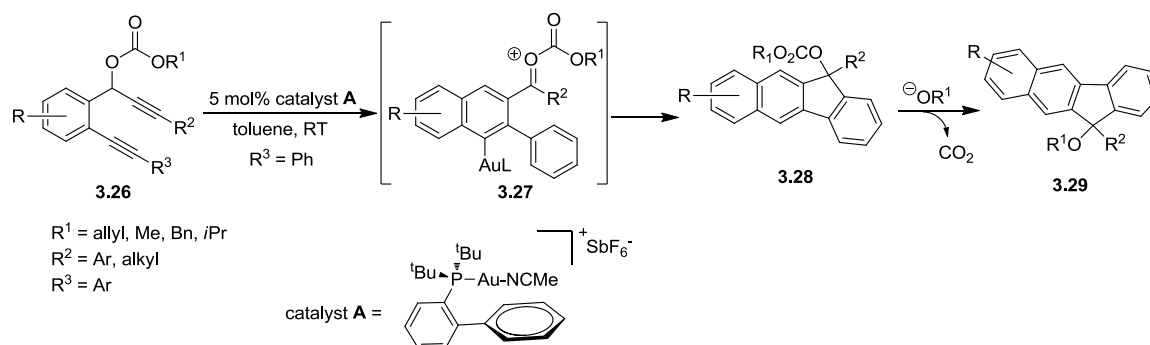
Scheme 3.8: Benzannulation of 2-(2-alkynylarylidene)-1,3-dicarbonyl compounds

Rhodium-catalyzed dehydrogenative cyclization of 1-amino-1,1-diarylalkanes **3.22** to yield fluorene derivatives **3.23** was shown by Miura and co-workers (Scheme 3.9).¹³ Also, they found that 2,2-diphenylalkanoic acids **3.24** undergo dehydrogenative cyclization and subsequent decarboxylation to give fluorene derivatives **3.25** under rhodium catalysis conditions.



Scheme 3.9: Rhodium-catalyzed dehydrogenative cyclization

Chen *et al.* developed a new gold-catalyzed cascade cyclization of 1,6-diynyl carbonates **3.26** to form benzo[*b*]fluorenes **3.29** in toluene at room temperature (Scheme 3.10).¹⁴ This cascade reaction involves [3,3] rearrangement of 1,6-diynyl carbonate to give oxocarbenium ion **3.27** which undergoes arylation followed by decarboxylation from **3.28** to give benzo[*b*]fluorene **3.29**.

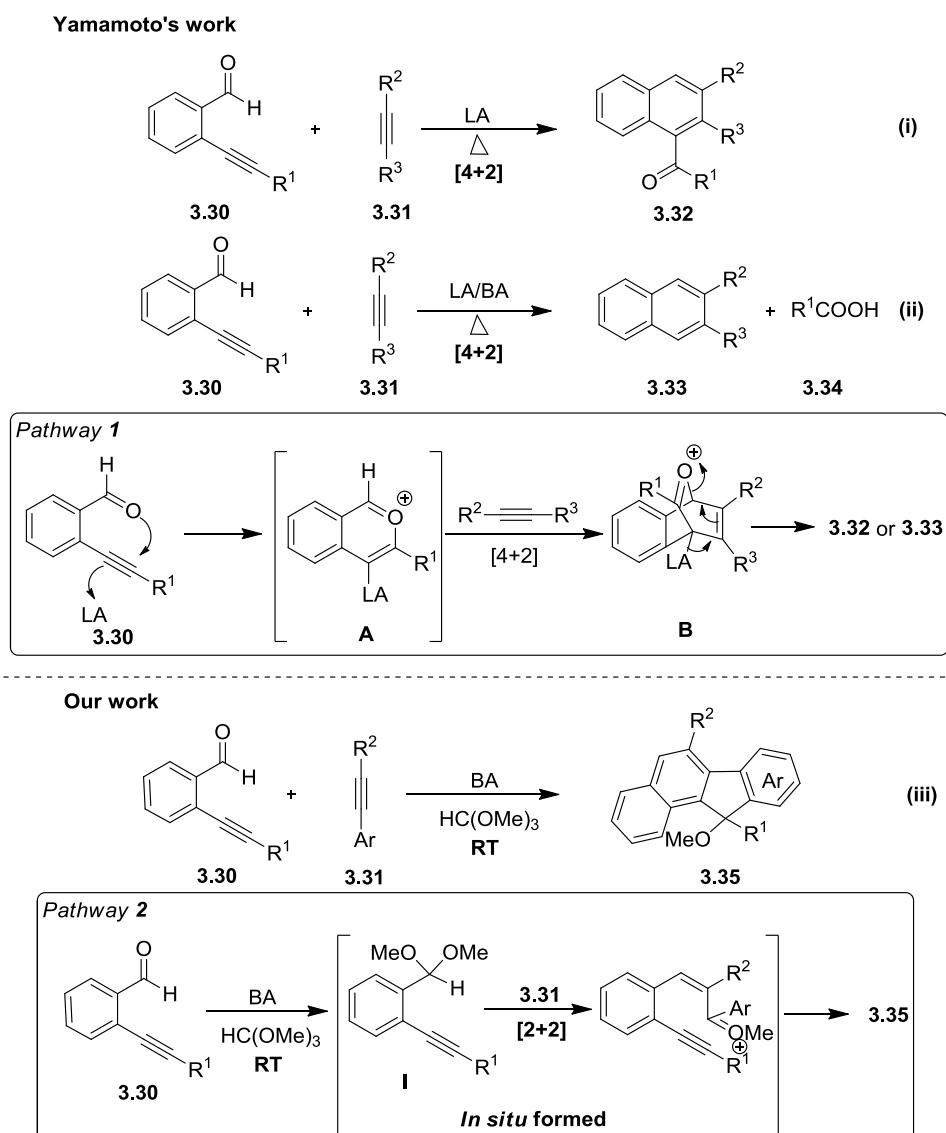


Scheme 3.10: Gold-catalyzed cascade cyclization of 1,6-diynyl carbonates

3.2 Background

Yamamoto and co-workers studied extensively the cyclization involving *o*-alkynylbenzaldehydes **3.30** and alkynes **3.31** under Lewis/Brønsted acid-catalyzed conditions for the synthesis of naphthalenes *via* the [4+2] benzannulation pathway. In this reaction naphthyl ketone **3.32** was the major product with Lewis acid catalyst alone whereas naphthalene derivative **3.33** was the major product in the presence of either Brønsted acid and Lewis acid combination or Brønsted acid alone (Scheme 3.11, eqn (i) and (ii)).¹⁵ In our endeavour to develop reactions using *in situ* generated acetals, we have found that reaction of *o*-alkynylbenzaldehydes **3.30** and alkynes **3.31** in the presence of trimethyl orthoformate and catalytic Brønsted acid results in benzo[*a*]fluorene **3.35** derivatives efficiently (Scheme 3.11, eqn (iii)).

It has to be mentioned that in the reaction reported by Yamamoto and co-workers a cyclic diene **A** is generated (Scheme 3.11, pathway 1) by the attack of the carbonyl oxygen on the activated alkyne. This undergoes cycloaddition with the alkyne to form a [4+2] adduct **B** which subsequently results in either the naphthyl ketone derivative **3.32** or naphthalene derivative **3.33**. Whereas in our reaction the chance for the formation of diene is remote as the starting material, in the presence of trimethyl orthoformate, is converted into its acetal derivative **I** instantly as revealed by the TLC. Moreover the reaction results in the formation of benzo[*a*]fluorene derivative at room temperature itself (Scheme 3.11, pathway 2). This observation and the usefulness fluorene derivatives encouraged us to study the reaction further.



Scheme 3.11: Reaction of *o*-alkynylbenzaldehydes with alkynes under Lewis/Brønsted acid conditions

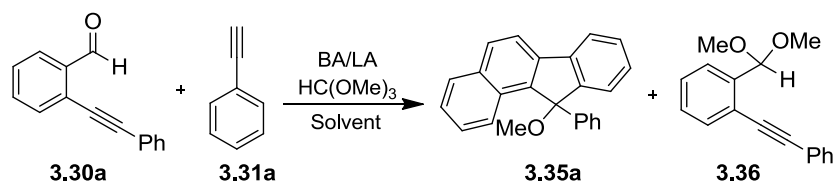
3.3 Results and discussion

3.3.1 Optimization of reaction conditions

At the outset, *o*-alkynylbenzaldehyde **3.30a** was treated with 1.5 equiv of phenylacetylene **3.31a** in the presence of 2.0 equiv of trimethyl orthoformate and 50 mol% of TfOH in dichloromethane solvent at room temperature. Interestingly, the reaction completed in 30 min and resulted in benzo[*a*]fluorene **3.35a** in 72% yield (Table 3.1, entry 1). We turned our attention to

improve the yield of product **3.35a** by changing various parameters. The results are summarized in Table 3.1. Unfortunately, there were no reactions with trifluoroacetic acid and *p*-toluenesulfonic acid even when the reactions were allowed to stir for 24 h at room temperature in dichloromethane solvent (Table 3.1, entries 2 and 3). With super acid $\text{HSbF}_6 \cdot 6\text{H}_2\text{O}$, as the catalyst, product **3.35a** was isolated in 70% yield (Table 3.1, entry 4). Since the reaction required strong Brønsted acids like TfOH, we then focused on finding a better solvent for TfOH-catalyzed reaction. Only moderate yields were obtained when the reaction was carried out separately in dichloroethane, nitromethane and toluene (Table 3.1, entries 5–7). In dioxane, as solvent, the expected product did not form and some unidentified products were obtained. There was no reaction in methanol even after 24 h (Table 3.1, entry 9). Interestingly, a clean reaction was observed when the reaction was performed in acetonitrile and the product was isolated in 86% yield after 4 h (Table 3.1, entry 10). For further optimization, acetonitrile was used as solvent. The amount of TfOH catalyst was reduced to 20 mol% and it was found that there was hardly any appreciable reduction in the yield of the product (85%) (Table 3.1, entry 11). The yield of **3.35a** slightly dropped to 80% when the reaction was conducted with 10 mol% TfOH (Table 3.1, entry 12). There was no change in the yield of the product when 1.2 equiv of **3.31a** was used (Table 3.1, entry 13). Finally, a control reaction was conducted without trimethyl orthoformate using TfOH in dichloromethane solvent. Under this condition, the reaction resulted in 36% of 2-phenylnaphthalene (Scheme 3.14, eqn (1)). This observation clearly indicates that the benzo[a]fluorene formation does not take place through the intermediate proposed in the mechanism by the Yamamoto group for naphthalene synthesis and the importance of trimethyl orthoformate for the formation of benzo[a]fluorenes. The *in situ* formed acetal would generate more electrophilic oxonium ion species in the presence of strong Brønsted acid catalyst which undergoes fast [2+2] cycloaddition reaction than their aldehyde form with alkynes to afford enones.¹⁶

Interestingly, no naphthalene or fluorene derivatives were obtained when the reaction was performed using different Lewis acids such as AuCl_3 , $\text{Cu}(\text{OTf})_2$, $\text{Fe}(\text{OTf})_2$, $\text{Yb}(\text{OTf})_3$ and AgSbF_6 (Table 3.1, entries 14–18). Under these conditions only acetal **3.36** formation was observed at room temperature, which did not give the desired product even under reflux conditions. In the reactions employing $\text{Cu}(\text{OTf})_2$ and AuCl_3 catalysts, the acetal **3.36** was isolated in 99% and 94% respectively. On the other hand, the formed acetal **3.36** converted back to aldehyde **3.30a** with $\text{Fe}(\text{OTf})_2$ or $\text{Yb}(\text{OTf})_3$ as catalyst under reflux conditions. No reaction was observed with AgSbF_6 catalyst even under reflux conditions.

Table 3.1 Optimization study^a

Entry	Solvent	Catalyst	Cat. (mol %)	Time (hours)	Yield (%) ^b	
					3.35a	3.36
1	CH_2Cl_2	TfOH	50	0.5	72	
2	CH_2Cl_2	PTSA	50	24.0	NR	NR
3	CH_2Cl_2	TFA	50	24.0	NR	NR
4	CH_2Cl_2	$\text{HSbF}_6 \cdot 6\text{H}_2\text{O}$	50	12.0	70	
5	$\text{C}_2\text{H}_4\text{Cl}_2$	TfOH	50	0.5	57	
6	CH_3NO_2	TfOH	50	0.5	54	
7	Toluene	TfOH	50	0.5	48	
8	Dioxane	TfOH	50	5.0	---	---
9	CH_3OH	TfOH	50	24.0	NR	NR
10	CH_3CN	TfOH	50	4.0	86	
11	CH_3CN	TfOH	20	4.0	85	
12	CH_3CN	TfOH	10	4.0	80	
13	CH_3CN	TfOH	20	4.0	85^c	
14	$\text{CH}_3\text{CN}^{\text{d}}$	AuCl_3	5	12.0	---	94
15	$\text{CH}_3\text{CN}^{\text{d}}$	Cu(OTf)_2	5	12.0	---	99
16	$\text{CH}_3\text{CN}^{\text{d}}$	Fe(OTf)_2	5	12.0	NR	NR
17	$\text{CH}_3\text{CN}^{\text{d}}$	Yb(OTf)_3	5	12.0	NR	NR
18	$\text{CH}_3\text{CN}^{\text{d}}$	AgSbF_6	5	24.0	NR	NR

^a All the reactions were carried out using **3.30a** (1.0 equiv), **3.31a** (1.5 equiv) and trimethyl orthoformate (2.0 equiv) at RT unless otherwise stated. ^b isolated yield. ^c 1.2 equiv of **3.31a** was used. ^d the reaction was performed under reflux conditions. NR: no reaction.

3.3.2 Substrate scope

The substrate scope was then studied with a variety of substituents using the condition given in entry 13 of Table 3.1 and the results are provided in Figure 3.2. This cascade reaction worked with both terminal as well as internal aromatic alkynes. In general, the reaction completed in 4 h with terminal alkynes and took more time with internal alkynes. It has to be mentioned that dichloromethane is a better solvent for the reactions involving diarylalkynes and high yields were obtained in comparatively shorter reaction times than that in acetonitrile. The reaction of **3.30a** with 1,2-diphenylethyne in CH₃CN furnished 44% of **3.35u** and 20% of **3.30a** was recovered after 24 h. Substrates with substituents like F, Cl, Br, OMe, acetal, cyano and CF₃ tolerated and the corresponding products were obtained in good to excellent yields. The benzo[a]fluorenes with halo substitution (**3.35d**, **3.35e**, **3.35h**, **3.35l**, **3.35n**, **3.35s** and **3.35x**) obtained using this method can, in principle, be functionalized further by transition metal-catalyzed coupling reactions. This method is applicable to aliphatic alkynylaldehydes as well and, for example, products **3.35j** and **3.35k** were obtained in good yields. Only one of the possible regioisomeric products (**3.35v**–**3.35x**) was obtained in good yield with internal unsymmetrical diarylalkynes. To our delight, a pharmaceutically important group such as CF₃ bearing benzo[a]fluorene could be prepared using this methodology (**3.35w**).¹⁷ The structure of **3.35u** was confirmed by single crystal X-ray analysis (Figure 3.1). The structure of **3.35f** was confirmed by COSY and NOESY experiments. The other possible regioisomer, which can in principle form in the second annulation step (5-membered ring formation), was not detected. Unfortunately, this transformation is not applicable when R¹ is an aliphatic group. Only the corresponding acetal was obtained when *o*-alkynylbenzaldehyde with R¹ = C₆H₁₃ was treated with phenylacetylene under the reaction conditions. In addition, there was no reaction when aliphatic terminal alkynes were used as substrates as [2+2] cycloaddition is not possible.

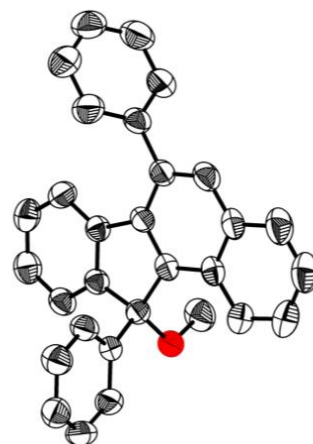
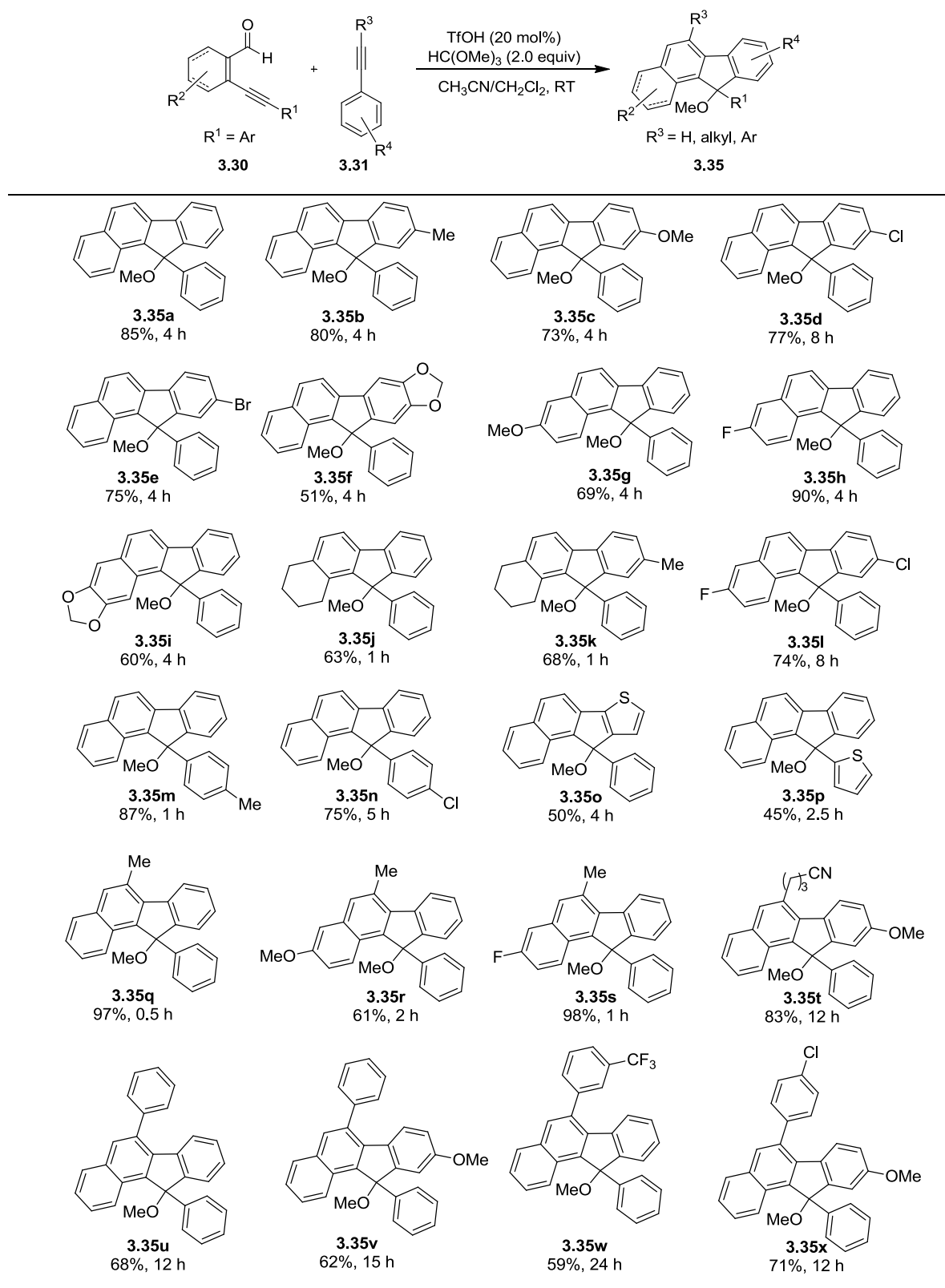


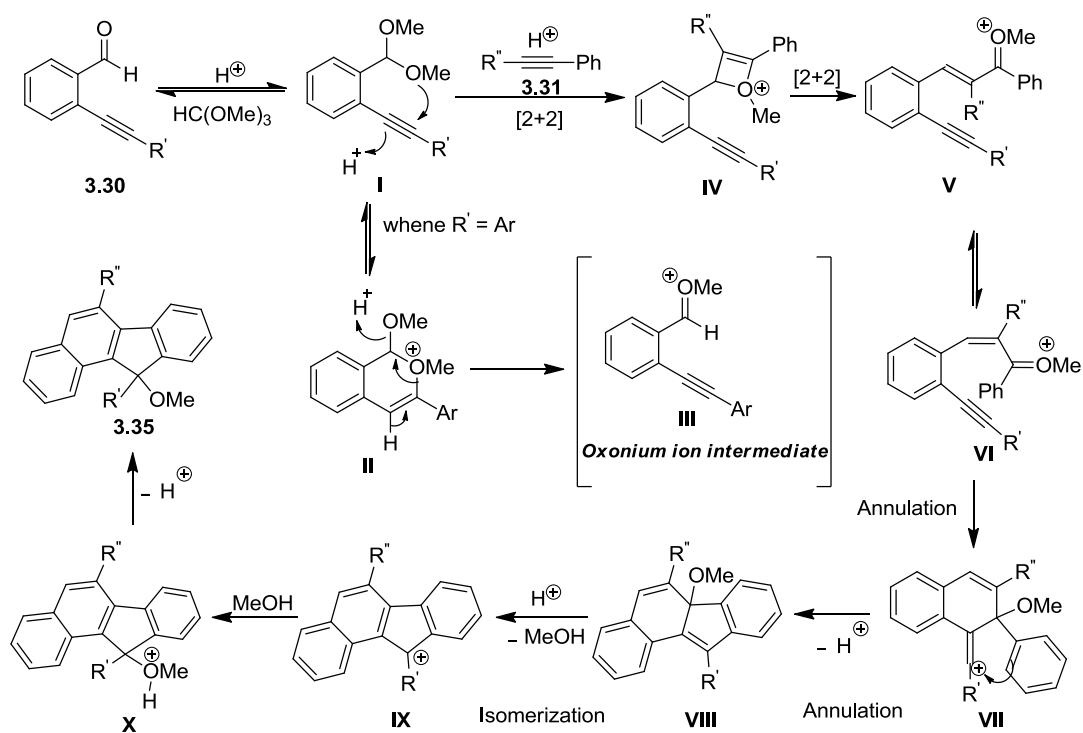
Figure 3.1: ORTEP of compound **3.35u**

Figure 3.2: Substrate scope



3.3.3 Mechanism for the formation of benzo[a]fluorene

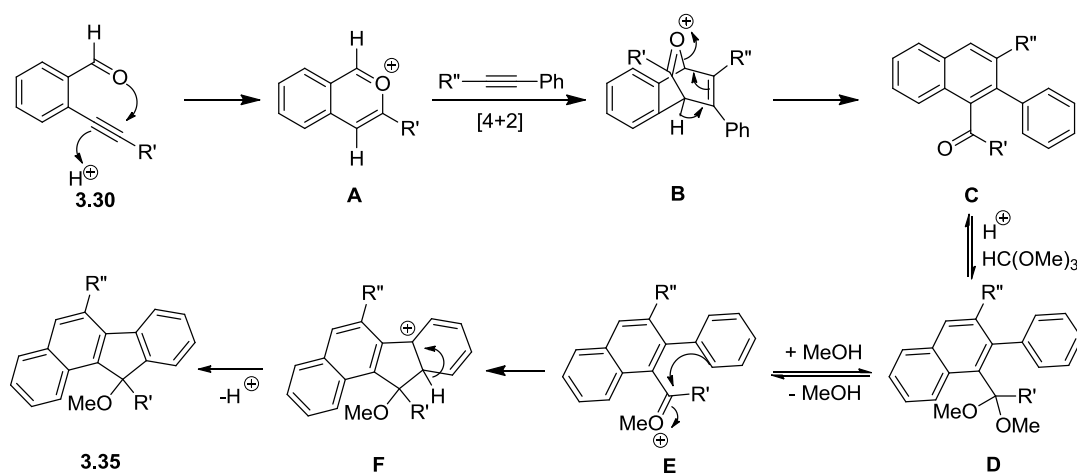
A plausible mechanism for the formation of benzo[a]fluorenes from *o*-alkynylbenzaldehydes is illustrated in Scheme 3.12. The acetal **I** is formed from aldehyde **3.30** in the presence of trimethyl orthoformate and TfOH. Intermolecular alkyne-acetal coupling ([2+2] cycloaddition) would take place between arylalkyne **3.31** and oxocarbenium ion intermediate **III** generated from **I** to give oxetene intermediate **IV**. The outcome of the reaction (i.e. no reaction) of *o*-alkynylbenzaldehyde with alkyl substituent on the alkyne ($R' = C_6H_{13}$) suggests that the triple bond of *o*-alkynylbenzaldehyde **3.30** having aryl as a R' group might participate at the early stage of the reaction. With $R' = Ar$, the formed acetal can attack the triple bond under the influence of acid to give intermediate **II** which can result in the formation of oxocarbenium ion **III** required for the [2+2] cycloaddition. The oxetene formation is regioselective and the oxygen of oxocarbenium will be attached to the alkyne carbon which is attached to an electron rich aryl ring. This is the reason for the formation of benzo[a]fluorene derivatives **3.35q-3.35t** from internal alkynes having both aryl and alkyl substituents as the final cyclization to result in benzo[a]fluorene derivatives is possible only with this regioselectivity. Again it is the reason for the regioselective formation of products **3.35v-3.36x** where diarylalkynes having aryl rings with



Scheme 3.12: Plausible mechanism

different electronic properties were used. Then, [2+2] cycloreversion of **IV** will afford oxocarbenium ion intermediate **V** which will be in equilibrium with its *cis* isomer **VI**.¹⁸ Subsequently, annulation reaction is initiated by intramolecular attack of alkynes on the activated carbonyl group. The formed vinyl carbocation **VII** will be trapped by the aryl group by aromatic electrophilic substitution reaction to give **VIII**. Finally, the benzo[*a*]fluorene **3.35** is formed by isomerization of **VIII** through carbocation intermediate **IX** in the presence of TfOH.

An alternative mechanistic pathway for the formation of benzo[*a*]fluorene derivative could be envisaged involving the diene intermediate (pyrylium ion) proposed by Yamamoto and co-workers.¹⁵ It is depicted in the Scheme 3.13. This pathway involves [4+2] cycloaddition between initially formed pyrylium ion intermediate **A** and alkyne to form bicyclic intermediate **B** which subsequently undergoes ring opening and to give naphthalene **C**. Then annulation would take place through *in situ* formed acetal-assisted electrophilic cyclization to afford benzo[*a*]fluorene. Since in the presence of Brønsted acid pyrylium ion intermediate **A** undergoes [4+2] cycloaddition with an alkyne to give debenzoylated naphthalene derivative (**3.33a**), this mechanistic pathway may be ruled out for the construction of benzo[*a*]fluorene derivative. Moreover the naphthyl ketone **C** was not isolated in any of the reactions even in minor amounts.

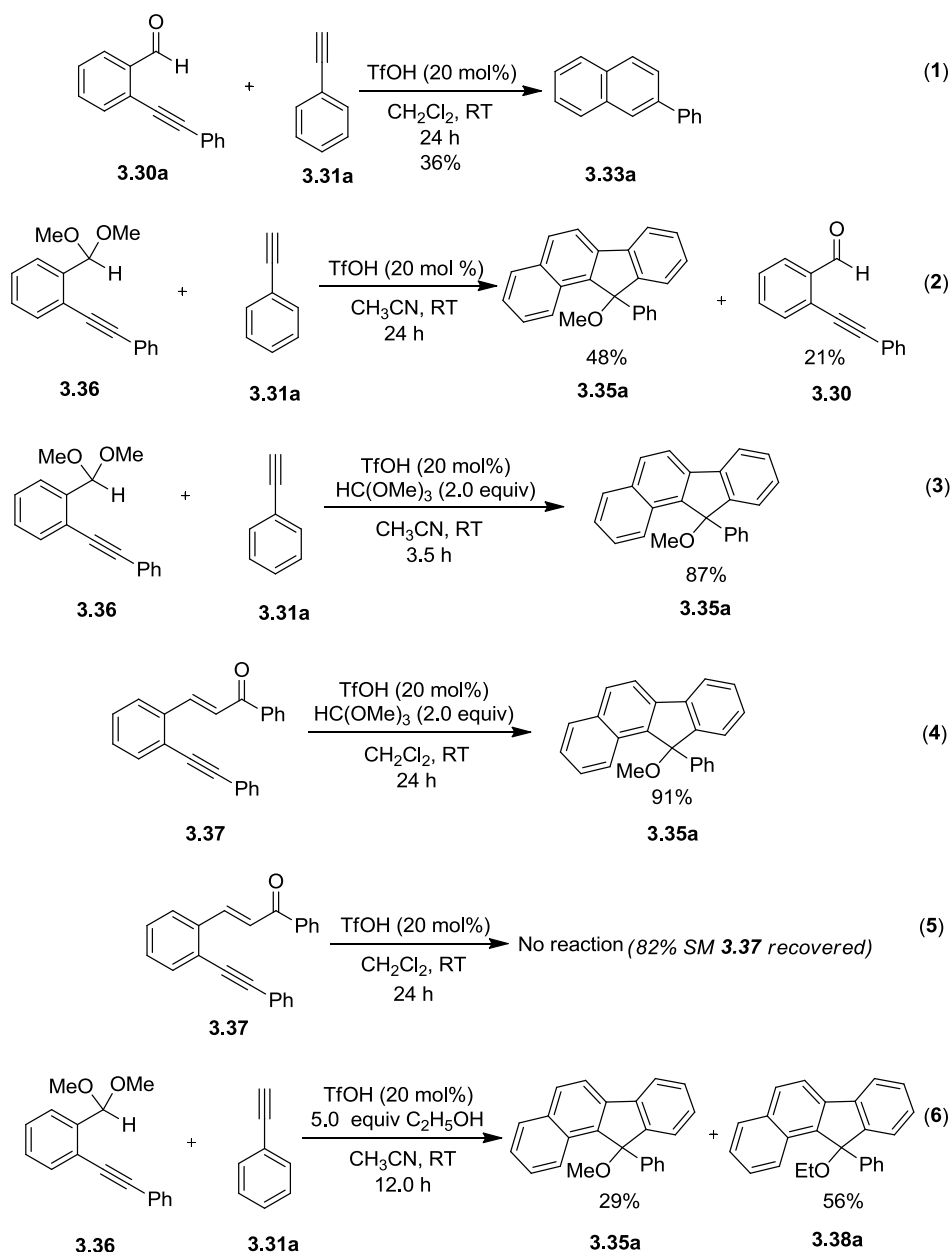


Scheme 3.13: Alternative mechanistic pathway

3.3.4 Control experiments

Control experiments were carried out to check the proposed mechanistic pathway and intermediates (Scheme 3.14). Acetal **3.36** was prepared separately and reacted with phenylacetylene (1.2 equiv) and 20 mol% TfOH in acetonitrile solvent. It resulted in only 48% of benzo[*a*]fluorene derivative **3.35a** and 21% of **3.30a** was recovered (eqn (2)). In another experiment, acetal **3.36** was subjected to standard reaction conditions, which yielded 87% of

3.35a (eqn (3)). Hence it can be argued that, in the presence of trimethyl orthoformate, the concentration of acetal will be kept high as the aldehyde formed by deprotection under acidic conditions will be converted back to acetal. To evaluate the formation of intermediate **VI**, chalcone **3.37** was prepared and treated with TfOH and HC(OMe)₃ in dichloromethane. Gratifyingly, product **3.35a** was isolated in 91% yield after 24 h (eqn (4)) which is quite higher



Scheme 3.14: Control experiments

than that taken for direct conversion of **3.30a** into **3.35a**. The same reaction resulted in 69% of **3.35a** when the reaction was carried out in acetonitrile for 24 h and 20% of starting material **3.37**

was recovered. No reaction was observed in the experiment in which **3.37** was treated with the TfOH catalyst alone in dichloromethane (eqn (5)). Shorter reaction time required for the direct transformation of **3.30a** into **3.35a** (Fig. 1) than **3.37** into **3.35a** might be due to the ease of intermediate **V** to isomerize in to *cis* form than the *trans* enone **3.37**. Furthermore the *trans* enone **3.37** requires time for the formation of acetal and its conversion to oxocarbenium intermediate **V** to effect the *trans* to *cis* isomerization. In order to confirm the formation of carbocation **IX** during the reaction, 5.0 equiv of ethanol was added intentionally as an external nucleophile to trap the carbocation intermediate **IX**. Indeed, the ethanol quenched product **3.38a** was formed along with **3.35a** in the ratio of 1: 0.44 as an inseparable mixture (eqn (6)). Reaction of phenylacetylene alone under the reaction conditions in the absence of *o*-alkynylbenzaldehyde did not give any product even after 24 h. These control experiments demonstrate that *in situ* formed acetal not only helps in [2+2] cycloaddition reaction but also assists the *trans* to *cis* isomerization¹⁸ to undergo annulation in the present transformation. The isomerization is favored as the *cis* product will cyclize to result in a more stable benzo[*a*]fluorene system.

3.4 Conclusions

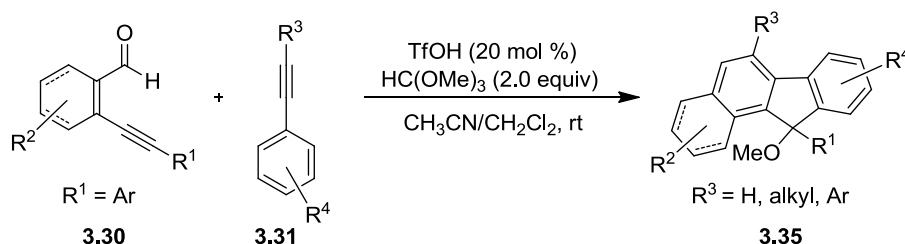
A simple and efficient method has been developed for the regioselective synthesis of substituted benzo[*a*]fluorenes from readily accessible starting materials under mild reaction conditions. Benzo[*a*]fluorene derivatives of material importance could be prepared using the present strategy under metal free mild reaction conditions. In general, methods for the construction of benzo[*a*]fluorene skeleton are less, hence our method gives a route to synthesis variety of benzo[*a*]fluorene derivatives with different substituents. We have shown a significant substrate scope, since the present methodology works with both terminal and internal aryl alkynes. This transformation takes place via [2+2] cycloaddition/alkyne acetal coupling of *in situ* generated acetal followed by double bond isomerization which facilitates the intramolecular cyclization to construct the benzo[*a*]fluorene framework. Control experiments demonstrated that key role of *in situ* formed acetal and formation of intermediates during [2+2] cycloaddition. In addition, it has been shown that the *in situ* formed acetal facilitates *trans* to *cis* isomerization in the annulation step of benzo[*a*]fluorene ring formation. Thus the *in situ* formed acetal can be advantageously used to develop new reactions leading to interesting molecular frameworks.

3.5 Experimental section

For general information see Chapter 2, Section 2.5.1. All the *o*-alkynylaldehydes used in this study were prepared by following the standard Sonogashira coupling reaction of corresponding bromo or iodo compounds and arylalkynes. All the *o*-alkynylaldehydes are reported in the literatures and the data of prepared *o*-alkynylaldehydes matches with those literatures.¹⁵

3.5.1 Experimental procedures, spectral and analytical data

General procedure for the synthesis of benzo[a]fluorene derivatives 3.35a - 3.35x:



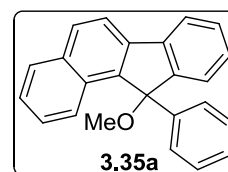
Triflic acid (20 mol%) was charged into a solution of compound **3.30** (1.0 equiv), compound **3.31** (1.2 equiv) and trimethyl orthoformate (2.0 equiv) in acetonitrile solvent (5 mL/1 mmol) at room temperature. The resulting mixture was stirred at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. After the completion of the reaction, ether and water were added and then organic layer was separated and washed with brine solution and dried over anhydrous sodium sulfate. Then the organic layer was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **3.35**.

For internal alkynes **3.31** dichloromethane was used as a solvent. After completion of the reaction, solvent was evaporated under pressure. Then, crude product was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **3.35**.

Analytical data of compounds 3.35a – 3.35x:

11-Methoxy-11-phenyl-11H-benzo[a]fluorene 3.35a:

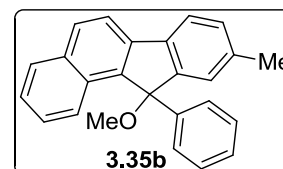
It was obtained as light yellow solid in 85% yield. mp 126-128 °C; R_f = 0.6 (in 10% EtOAc/Hexanes); IR (KBr): 3063, 2931, 1594, 1490, 1454, 1178, 1101, 1073, 821, 756, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, J = 8.0 Hz, 1H), 7.90-7.86 (m, 3H), 7.73 (d, J = 7.6 Hz, 1H), 7.38-7.33 (m, 5H), 7.28 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 6.8 Hz, 1H), 7.19-7.15 (m, 3H), 2.89 (s, 3H); ^{13}C NMR



(100 MHz, CDCl_3): δ 148.7, 143.2, 141.0, 140.6, 139.4, 133.8, 130.5, 129.9, 128.7, 128.2, 127.8, 126.9, 126.8, 125.6, 125.2, 124.6, 119.7, 118.1, 90.1, 51.3. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{18}\text{O}$ $[\text{M}+\text{H}]^+$ 323.1436; found 323.1437.

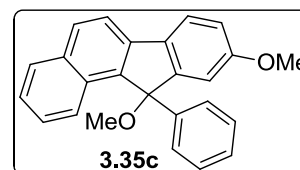
11-Methoxy-9-methyl-11-phenyl-11H-benzo[a]fluorene 3.35b:

It was obtained as yellow solid in 80% yield. mp 142-144 °C; R_f = 0.6 (in 10% EtOAc/Hexanes); IR (KBr): 2931, 2816, 1615, 1484, 1276, 1177, 1100, 1078, 1029, 815, 739, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.92 (d, J = 8.4 Hz, 1H), 7.88-7.82 (m, 3H), 7.60 (d, J = 7.6 Hz, 1H), 7.36-7.30 (m, 4H), 7.18 (d, J = 6.0 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.09 (s, 1H), 2.89 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.9, 143.4, 140.6, 139.6, 138.0, 137.8, 133.5, 130.4, 130.0, 129.4, 129.1, 128.9, 128.7, 128.2, 126.8, 126.7, 125.3, 124.4, 119.5, 118.0, 89.9, 51.3, 21.6. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{20}\text{O}$ $[\text{M}+\text{Na}]^+$ 359.1412; found 359.1408.



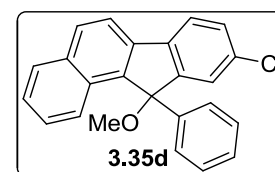
9,11-Dimethoxy-11-phenyl-11H-benzo[a]fluorene 3.35c:

It was obtained as light brown solid in 73% yield. mp 136-138 °C; R_f = 0.4 (in 20% EtOAc/Hexanes); IR (KBr): 2936, 2827, 1610, 1577, 1484, 1429, 1281, 1226, 1106, 1078, 1034, 821, 733, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.93 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.37-7.29 (m, 4H), 7.20-7.14 (m, 3H), 6.89 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 3.78 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.1, 150.8, 143.3, 140.2, 139.5, 133.4, 133.1, 130.5, 130.0, 128.7, 128.2, 126.9, 126.7, 125.2, 125.1, 124.2, 120.5, 117.8, 114.2, 110.5, 89.9, 55.5, 51.4. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{20}\text{O}_2$ $[\text{M}+\text{H}]^+$ 353.1542; found 353.1539.



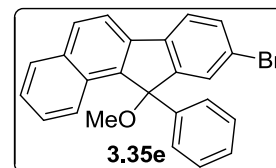
9-Chloro-11-methoxy-11-phenyl-11H-benzo[a]fluorene 3.35d:

It was obtained as light yellow solid in 77% yield. mp 158-160 °C R_f = 0.65 (in 10% EtOAc/Hexanes); IR (KBr): 2986, 2827, 1572, 1495, 1101, 1073, 986, 805, 734, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.99 (d, J = 8.4 Hz, 1H), 7.89 (q, J = 8.4 Hz, 3H), 7.67 (d, J = 8.0 Hz, 1H), 7.45-7.43 (m, 1H), 7.41-7.35 (m, 4H), 7.29 (d, J = 1.6 Hz, 1H), 7.24-7.20 (m, 3H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.6, 142.4, 140.9, 139.1, 138.4, 133.8, 133.6, 130.7, 129.8, 129.0, 128.8, 128.3, 127.2, 127.0, 125.8, 125.2, 125.0, 124.5, 120.7, 118.0, 89.9, 51.5. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{17}\text{ClO}$ $[\text{M}+\text{Na}]^+$ 379.0866; found 379.0866.

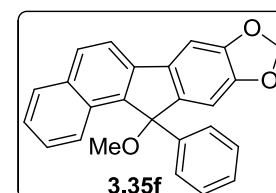


9-Bromo-11-methoxy-11-phenyl-11H-benzo[a]fluorene 3.35e:

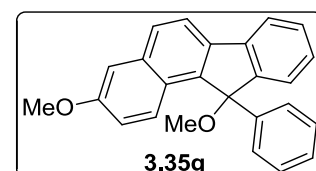
It was obtained as light yellow solid in 75% yield. mp 178-180 °C; R_f = 0.6 (in 10% EtOAc/Hexanes); IR (KBr): 2990, 2820, 1469, 1164, 1096, 1070, 988, 821, 716 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, J = 8.4 Hz, 1H), 7.89-7.83 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.48 (dd, J = 1.6, 8.0 Hz, 1H), 7.42-7.39 (m, 2H), 7.36-7.30 (m, 3H), 7.21-7.18 (m, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.8, 142.4, 140.8, 139.5, 138.4, 133.9, 131.9, 130.8, 129.8, 128.8, 128.3, 127.9, 127.2, 127.0, 125.9, 125.2, 124.5, 121.7, 121.1, 117.9, 89.9, 51.5. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{17}\text{BrO}$ $[M+\text{Na}]^+$ 423.0360; found 423.0360.

**12-Methoxy-12-phenyl-12H-benzo[7,8]fluoreno[2,3-d][1,3]dioxole 3.35f:**

It was obtained as yellow solid in 51% yield. mp 205-207 °C; R_f = 0.4 (in 20% EtOAc/Hexanes); IR (KBr): 2925, 2832, 1582, 1478, 1440, 1319, 1259, 1237, 1073, 1040, 947, 865, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.84 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.6 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.29-7.21 (m, 4H), 7.15-7.08 (m, 4H), 6.68 (s, 1H), 5.87 (d, J = 24.0 Hz, 2H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.4, 147.9, 143.2, 143.0, 140.9, 139.3, 134.5, 133.1, 130.4, 129.7, 128.7, 128.2, 126.9, 126.8, 125.2, 124.1, 117.5, 105.7, 101.4, 100.7, 89.6, 51.2. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{18}\text{O}_3$ $[M+\text{H}]^+$ 367.1334; found 367.1333.

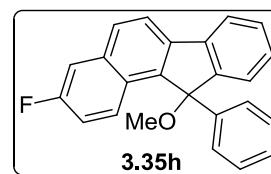
**3,11-Dimethoxy-11-phenyl-11H-benzo[a]fluorene 3.35g:**

It was obtained as light yellow solid in 69% yield. mp 153-155 °C; R_f = 0.4 (in 20% EtOAc/Hexanes); IR (KBr): 2936, 1627, 1594, 1490, 1375, 1243, 1167, 1073, 1019, 865, 832, 750, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.84 (s, 2H), 7.80 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.35-7.32 (m, 3H), 7.27-7.24 (m, 1H), 7.20-7.14 (m, 5H), 7.02 (dd, J = 2.4, 9.2 Hz, 1H), 3.88 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.4, 148.3, 143.3, 141.2, 140.8, 137.3, 135.1, 129.1, 128.7, 128.2, 127.3, 126.9, 126.1, 125.4, 125.2, 124.5, 119.5, 119.4, 118.7, 106.9, 90.0, 55.2, 51.3. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{20}\text{O}_2$ $[M+\text{H}]^+$ 353.1542; found 353.1543.

**3-Fluoro-11-methoxy-11-phenyl-11H-benzo[a]fluorene 3.35h:**

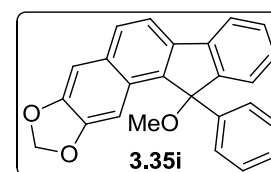
It was obtained as yellow oil in 90% yield. R_f = 0.5 (in 20% EtOAc/Hexanes); IR (neat): 2936, 2821, 1600, 1528, 1479, 1358, 1079, 953, 871, 821, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ

7.92-7.90 (m, 1H), 7.88 (s, 2H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.47 (dd, $J = 2.4, 9.6$ Hz, 1H), 7.36-7.32 (m, 3H), 7.27 (d, $J = 7.2$ Hz, 1H), 7.22-7.09 (m, 5H), 2.88 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.4 (d, $J = 245.0$ Hz), 148.3, 143.0, 141.4, 140.3, 138.7, 134.7 (d, $J = 9.0$ Hz), 129.7 (d, $J = 5.0$ Hz), 128.8, 128.2, 127.8, 127.0, 126.9, 125.2, 124.6, 119.7, 119.3, 117.1 (d, $J = 25.0$ Hz), 111.8 (d, $J = 20.0$ Hz), 90.0, 51.3. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{17}\text{FO}$ $[M+H]^+$ 341.1342; found 341.1343.



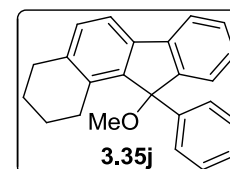
11-Methoxy-11-phenyl-11H-indeno[2',1':5,6]naphtho[2,3-d][1,3]dioxole 3.35i:

It was obtained as light yellow solid in 60% yield. mp 195-197 °C; $R_f = 0.4$ (in 30% EtOAc/Hexanes); IR (KBr): 2980, 2893, 1495, 1457, 1221, 1046, 942, 860, 745, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.76-7.67 (m 3H), 7.34-7.31 (m, 3H), 7.25-7.14 (m, 7H), 5.92 (d, $J = 22.0$ Hz, 2H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.2, 148.1, 147.4, 143.1, 140.6, 140.2, 138.0, 130.9, 129.1, 128.7, 128.2, 127.5, 127.1, 126.9, 125.2, 124.5, 119.5, 116.5, 104.7, 101.0, 100.9, 90.0, 51.2. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{18}\text{O}_3$ $[M+H]^+$ 367.1334; found 367.1333.



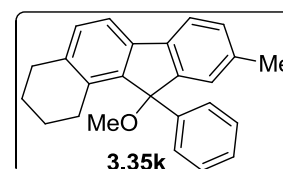
11-Methoxy-11-phenyl-2,3,4,11-tetrahydro-1H-benzo[a]fluorene 3.35j:

It was obtained as brown oil in 63% yield. $R_f = 0.6$ (in 10% EtOAc/Hexanes); IR (neat): 2931, 2821, 1599, 1495, 1451, 1171, 1100, 1078, 1035, 760, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, $J = 7.2$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.32-7.27 (m, 3H), 7.24-7.12 (m, 6H), 2.95 (s, 3H), 2.79-2.73 (m, 3H), 2.14-2.10 (m, 1H), 1.73-1.59 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.8, 143.2, 142.7, 140.5, 139.1, 137.5, 136.0, 130.3, 128.6, 128.0, 127.4, 126.6, 125.3, 124.5, 119.3, 116.9, 89.7, 51.0, 29.9, 24.9, 22.9, 22.6. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{22}\text{O}$ $[M+H]^+$ 327.1749; found 327.1745.



11-Methoxy-9-methyl-11-phenyl-2,3,4,11-tetrahydro-1H-benzo[a]fluorene 3.35k:

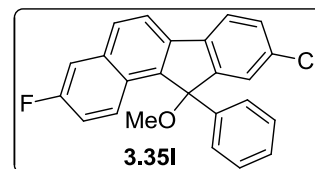
It was obtained as light yellow oil in 68% yield. $R_f = 0.65$ (in 20% EtOAc/Hexanes); IR (neat): 2962, 2821, 1490, 1463, 1101, 1079, 805, 739, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, $J = 7.6$ Hz, 1H), 7.41 (d, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 6.8$ Hz, 2H), 7.24-7.16 (m, 3H), 7.10 (t, $J = 8.0$ Hz, 2H), 6.94 (s, 1H), 2.94 (s, 3H), 2.77-2.71 (m, 3H), 2.27 (s, 3H), 2.13-2.06 (m, 1H), 1.72-1.59 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.0, 143.1, 142.9, 139.2, 137.9,



137.3, 136.9, 135.9, 130.2, 129.4, 129.1, 128.0, 126.5, 125.3, 125.2, 119.1, 116.6, 89.7, 51.0, 29.8, 24.9, 22.9, 22.7, 21.5. HRMS (ESI): calcd for $C_{25}H_{24}O$ $[M+Na]^+$ 363.1725; found 363.1722.

9-Chloro-3-fluoro-11-methoxy-11-phenyl-11H-benzo[a]fluorene 3.35l:

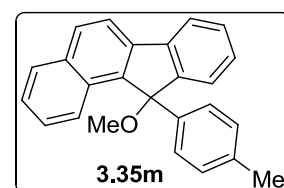
It was obtained as colorless solid in 74% yield. mp 147-149 °C; R_f = 0.6 (in 10% EtOAc/Hexanes); IR (KBr): 2936, 2821, 1600, 1523, 1473, 1161, 1079, 879, 805, 723 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 7.91-7.84 (m 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 2.0, 9.6



Hz, 1H), 7.33 dd, J = 1.6, 8.0 Hz, 1H), 7.31-7.28 (m, 2H), 7.25-7.24 (m, 1H), 7.21-7.19 (m, 3H), 7.13 (td, J = 2.4, 8.8 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5 (d, J = 246.0 Hz), 150.3, 142.3, 141.3, 138.9, 137.7, 134.7 (d, J = 9.0 Hz), 133.7, 133.0 (d, J = 5.0 Hz), 129.1, 128.4, 127.4, 127.0, 126.9, 125.1, 125.0, 120.7, 119.1, 117.4 (d, J = 25.0 Hz), 111.9 (d, J = 21.0 Hz), 89.8, 51.5. HRMS (ESI): calcd for $C_{24}H_{16}ClFO$ $[M+H]^+$ 375.0952; found 375.0947.

11-Methoxy-11-p-tolyl-11H-benzo[a]fluorene 3.35m:

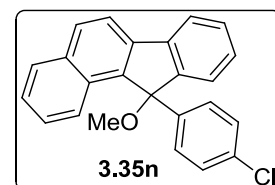
It was obtained as light yellow oil in 87% yield. R_f = 0.6 (in 20% EtOAc/Hexanes); IR (neat): 2926, 2821, 1627, 1517, 1479, 1178, 1095, 1073, 821, 767 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.39-7.32



(m, 3H), 7.29 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 7.2 Hz, 3H), 6.98 (d, J = 8.0 Hz, 2H), 2.88 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 141.0, 140.5, 140.2, 139.3, 136.4, 133.7, 130.4, 130.0, 128.9, 128.7, 128.6, 127.8, 126.7, 125.5, 125.1, 124.6, 124.5, 119.7, 118.1, 90.0, 51.3, 21.0. HRMS (ESI): calcd for $C_{25}H_{20}O$ $[M+H]^+$ 337.1592; found 337.1590.

11-(4-Chlorophenyl)-11-methoxy-11H-benzo[a]fluorene 3.35n:

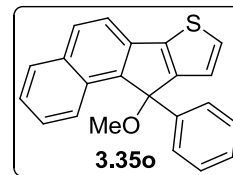
It was obtained as colorless solid in 75% yield. mp 138-140 °C; R_f = 0.5 (in 10% EtOAc/Hexanes); IR (KBr): 2926, 1495, 1342, 1178, 1128, 1079, 832, 761, 701 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 1H), 7.88-7.84 (m, 3H), 7.72 (d, J = 7.6 Hz, 1H), 7.39-7.33 (m,



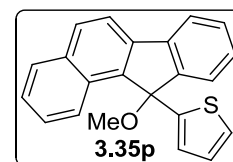
3H), 7.29-7.21 (m, 4H), 7.13 (d, J = 8.8 Hz, 2H), 2.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 141.9, 140.5, 140.4, 139.4, 133.8, 132.6, 130.7, 129.7, 128.9, 128.8, 128.3, 127.9, 126.9, 126.8, 125.7, 124.4, 124.3, 119.9, 118.1, 89.6, 51.4. HRMS (ESI): calcd for $C_{24}H_{17}ClO$ $[M+Na]^+$ 379.0866; found 379.0865.

10-Methoxy-10-phenyl-10H-benzo[4,5]indeno[1,2-b]thiophene 3.35o:

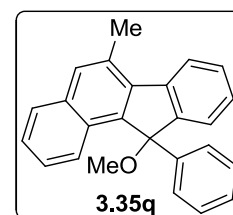
It was obtained as light brown solid in 50% yield. mp 122-124 °C; R_f = 0.45 (in 10% EtOAc/Hexanes); IR (KBr): 2920, 2816, 1616, 1523, 1441, 1095, 1068, 821, 701, 679 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.37-7.30 (m, 4H), 7.24-7.21 (m, 1H), 7.20-7.16 (m, 3H), 6.91 (d, J = 4.8 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 153.5, 143.5, 143.1, 142.0, 136.2, 132.6, 130.4, 129.8, 128.8, 128.3, 127.8, 127.1, 126.8, 125.4, 125.1, 123.9, 122.2, 118.0, 87.9, 51.7. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{16}\text{OS}$ $[\text{M}+\text{H}]^+$ 329.1000; found 329.1002.

**2-(11-Methoxy-11H-benzo[a]fluoren-11-yl)thiophene 3.35p:**

It was obtained as light yellow oil in 45% yield. R_f = 0.65 (in 10% EtOAc/Hexanes); IR (neat): 2931, 1698, 1627, 1473, 1227, 1156, 1101, 1063, 821, 761, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.08-8.06 (m, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.91-7.89 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.45-7.40 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 4.8 Hz, 1H), 6.73 (t, J = 4.8 Hz, 1H), 6.42 (d, J = 3.2 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 147.6, 147.4, 139.9, 139.6, 139.0, 133.8, 130.9, 130.0, 128.9, 128.7, 127.8, 126.9, 126.4, 125.7, 124.8, 124.4, 124.2, 122.9, 119.9, 118.2, 88.7, 51.7. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{16}\text{OS}$ $[\text{M}+\text{H}]^+$ 329.1000; found 329.1001.

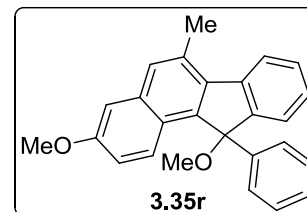
**11-Methoxy-6-methyl-11-phenyl-11H-benzo[a]fluorene 3.35q:**

It was obtained as light yellow solid in 97% yield. mp 128-130 °C; R_f = 0.5 (in 20% EtOAc/Hexanes); IR (KBr): 2931, 2821, 1600, 1501, 1446, 1174, 1073, 1030, 745, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.90 (t, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.38-7.30 (m, 5H), 7.28 (d, J = 7.2 Hz, 1H), 7.25-7.22 (m, 1H), 7.18-7.13 (m, 3H), 2.91 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.2, 143.5, 141.6, 141.4, 138.8, 133.6, 131.1, 130.9, 128.6, 128.3, 128.1, 127.7, 127.2, 126.8, 125.8, 125.7, 125.2, 124.5, 122.9, 89.5, 51.2, 21.6. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{20}\text{O}$ $[\text{M}+\text{H}]^+$ 337.1592; found 337.1591.

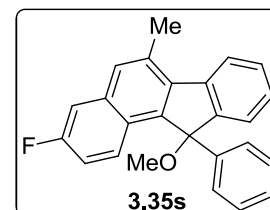


3,11-Dimethoxy-6-methyl-11-phenyl-11H-benzo[a]fluorene 3.35r:

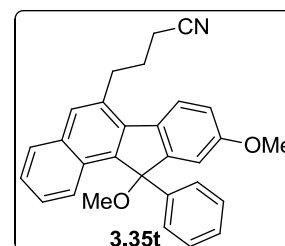
It was obtained as light yellow solid in 61% yield. mp 166-168 °C; R_f = 0.5 (in 20% EtOAc/Hexanes); IR (KBr): 2931, 2821, 1621, 1599, 1484, 1452, 1386, 1320, 1172, 1079, 1030, 882, 838, 761, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.60 (s, 1H), 7.36-7.30 (m, 4H), 7.25-7.11 (m, 5H), 6.95 (dd, J = 2.8, 9.2 Hz, 1H), 3.87 (s, 3H), 2.89 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.6, 148.7, 143.6, 141.8, 141.6, 136.6, 135.0, 131.7, 129.7, 128.6, 128.1, 128.0, 126.82, 126.78, 126.1, 125.2, 124.5, 123.9, 122.5, 118.5, 105.8, 89.4, 55.2, 51.2, 21.6. HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{22}\text{O}_2$ $[M+H]^+$ 367.1698; found 367.1701.

**3-Fluoro-11-methoxy-6-methyl-11-phenyl-11H-benzo[a]fluorene 3.35s:**

It was obtained as yellow solid in 98% yield. mp 131-133 °C; R_f = 0.6 (in 20% EtOAc/Hexanes); IR (KBr): 2925, 2821, 1637, 1517, 1473, 1456, 1221, 1144, 1078, 1034, 749, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.92-7.87 (m, 2H), 7.61 (s, 1H), 7.39-7.29 (m, 5H), 7.21 (d, J = 7.6 Hz, 1H), 7.18-7.12 (m, 3H), 7.03 (td, J = 2.0, 8.8 Hz, 1H), 2.88 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.6 (d, J = 245.0 Hz), 148.8, 143.3, 141.9, 141.2, 138.1, 134.5 (d, J = 9.0 Hz), 132.4, 130.1, 128.7, 128.2, 127.2, 127.1, 127.0, 125.4, 125.1, 124.6, 122.8, 116.2 (d, J = 25.0 Hz), 110.7 (d, J = 21.0 Hz), 89.4, 51.2, 21.6. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{19}\text{FO}$ $[M+H]^+$ 355.1498; found 355.1498.

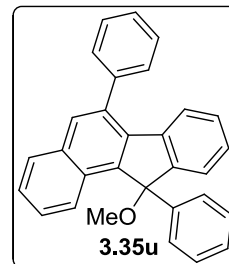
**4-(9,11-Dimethoxy-11-phenyl-11H-benzo[a]fluoren-6-yl)butanenitrile 3.35t:**

It was obtained as light yellow oil in 83% yield. R_f = 0.3 (in 40% EtOAc/Hexanes); IR (neat): 2942, 2827, 2252, 1605, 1484, 1293, 1227, 1073, 1030, 734 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.88 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.72-7.69 (m, 2H), 7.37-7.27 (m, 4H), 7.25-7.13 (m, 3H), 6.91-6.87 (m, 2H), 3.77 (s, 3H), 3.44-3.31 (m, 2H), 2.88 (s, 3H), 2.49 (t, J = 7.2 Hz, 2H), 2.22 (pentet, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.6, 151.5, 143.3, 141.8, 137.8, 132.9, 132.8, 132.2, 130.3, 128.7, 128.2, 127.8, 126.9, 126.3, 125.6, 125.1, 124.2, 123.2, 119.5, 114.0, 110.8, 89.1, 55.4, 51.2, 32.9, 25.3, 16.7. HRMS (ESI): calcd for $\text{C}_{29}\text{H}_{25}\text{NO}_2$ $[M+Na]^+$ 442.1783; found 442.1787.

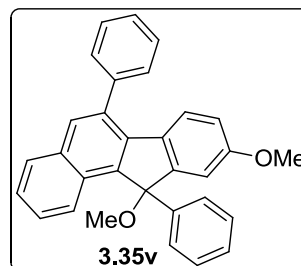


11-Methoxy-6,11-diphenyl-11H-benzo[a]fluorene 3.35u:

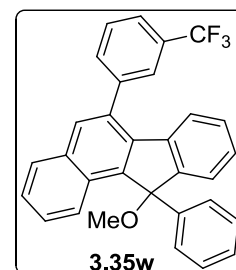
It was obtained as light yellow solid in 68% yield. mp 161-163 °C; R_f = 0.65 (in 10% EtOAc/Hexanes); IR (KBr): 2986, 2821, 1588, 1490, 1462, 1441, 1183, 1101, 1073, 1035, 893, 750, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.01 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.64-7.56 (m, 5H), 7.47-7.42 (m, 3H), 7.37 (t, J = 7.2 Hz, 1H), 7.31-7.23 (m, 3H), 7.21-7.13 (m, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.1, 143.4, 142.1, 140.7, 140.4, 137.3, 135.9, 133.2, 131.3, 129.0, 128.4, 128.2, 127.7, 127.4, 126.9, 126.6, 126.1, 125.2, 124.6, 124.3, 122.9, 89.5, 51.3. HRMS (ESI): calcd for $\text{C}_{30}\text{H}_{22}\text{O}$ $[M+\text{Na}]^+$ 421.1568; found 421.1570.

**9,11-Dimethoxy-6,11-diphenyl-11H-benzo[a]fluorene 3.35v:**

It was obtained as light yellow oil in 62% yield. R_f = 0.4 (in 20% EtOAc/Hexanes); IR (neat): 2931, 2832, 1621, 1489, 1287, 1221, 1073, 1029, 739, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.93 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.59-7.52 (m, 5H), 7.42-7.30 (m, 4H), 7.24-7.16 (m, 3H), 6.81 (s, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 3.71 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.6, 151.3, 143.4, 141.2, 140.8, 137.4, 135.4, 133.2, 132.6, 131.1, 129.1, 128.4, 128.2, 127.7, 126.9, 126.6, 125.6, 125.2, 124.3, 123.7, 113.5, 110.3, 89.3, 55.4, 51.4. HRMS (ESI): calcd for $\text{C}_{31}\text{H}_{24}\text{O}_2$ $[M+\text{Na}]^+$ 451.1674; found 451.1675.

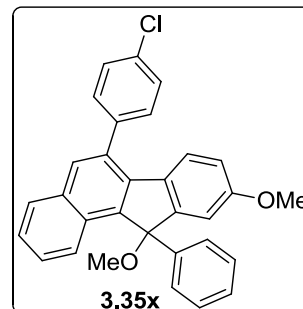
**11-Methoxy-11-phenyl-6-(3-(trifluoromethyl)phenyl)-11H-benzo[a]fluorene 3.35w:**

It was obtained as light yellow oil in 59% yield. R_f = 0.55 (in 10% EtOAc/Hexanes); IR (neat): 2931, 2827, 1627, 1495, 1402, 1172, 1084, 1013, 821, 761 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 3H), 7.74 (d, J = 7.2 Hz, 1H), 7.40-7.28 (m, 8H), 7.25 (s, 1H), 7.22-7.14 (m, 4H), 2.90 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 148.7, 143.2, 141.0, 140.6, 139.4, 133.8, 130.5, 129.9, 128.7, 128.2, 127.8, 126.9, 126.8, 125.6, 124.6, 119.7, 118.1, 90.1, 51.3; ^{19}F NMR (376 MHz, CDCl_3): δ -62.40. HRMS (ESI): calcd for $\text{C}_{31}\text{H}_{21}\text{F}_3\text{O}$ $[M+\text{Na}]^+$ 489.1442; found 489.1440.

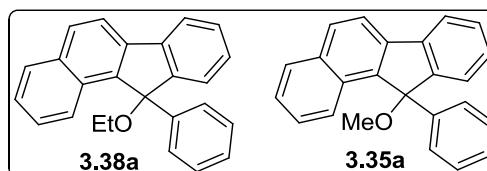


6-(4-Chlorophenyl)-9,11-dimethoxy-11-phenyl-11H-benzo[a]fluorene 3.35x:

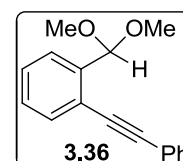
It was obtained as yellow solid in 71% yield. mp 70-72 °C; R_f = 0.55 (in 20% EtOAc/Hexanes); IR (KBr): 2925, 2832, 1604, 1489, 1347, 1292, 1089, 1035, 832, 739, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.93 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.56-7.50 (m, 4H), 7.39 (d, J = 7.2 Hz, 3H), 7.36-7.32 (m, 1H), 7.25-7.16 (m, 3H), 6.81 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.60 (dd, J = 2.0, 8.8 Hz, 1H), 3.72 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.7, 151.3, 143.3, 141.5, 139.2, 137.1, 134.0, 133.7, 132.9, 132.6, 131.2, 129.2, 128.4, 128.2, 126.9, 126.8, 125.8, 125.2, 124.3, 123.5, 113.6, 110.4, 89.3, 55.4, 51.4. HRMS (ESI): calcd for $\text{C}_{31}\text{H}_{23}\text{ClO}_2$ $[M+\text{Na}]^+$ 485.1284; found 485.1285.

**Data of compounds 3.35a and 3.38a:**

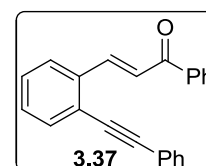
This mixture was obtained as light yellow oil in ratio of 1.0:0.44 in 85% yield. R_f = 0.6 (in 10% EtOAc/Hexanes); ^1H NMR (400 MHz, CDCl_3): δ 7.97-7.93 (m, 2.6H), 7.89-7.85 (m, 3.4H), 7.74-7.71 (m, 1.5H), 7.37-7.32 (m, 8H), 7.29 (d, J = 7.2 Hz, 2H), 7.23-7.13 (m, 7.3H), 3.08-3.01 (m, 1H), 2.95-2.88 (m, 1H), 2.89 (s, 1.3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.5, 148.7, 143.4, 143.2, 141.8, 141.0, 140.6, 140.3, 139.4, 139.0, 133.7, 131.1, 130.5, 130.3, 129.9, 128.7, 128.6, 128.2, 128.1, 127.8, 127.7, 126.9, 126.8, 126.7, 125.5, 125.3, 124.62, 124.56, 124.4, 119.7, 118.1, 90.0, 89.4, 58.9, 51.3, 15.6. HRMS (ESI) for **3.35a**: calcd for $\text{C}_{24}\text{H}_{18}\text{O}$ $[M+\text{H}]^+$ 323.1436; found 323.1437. HRMS (ESI) for **3.38a**: calcd for $\text{C}_{25}\text{H}_{20}\text{O}$ $[M+\text{H}]^+$ 337.1592; found 337.1601.

**1-(Dimethoxymethyl)-2-(phenylethynyl)benzene 3.36:¹⁹**

It was obtained as colorless liquid in 98% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, J = 7.6 Hz, 1H), 7.55 (dd, J = 1.6, 7.2 Hz, 3H), 7.38-7.29 (m, 5H), 5.76 (s, 1H), 3.45 (s, 6H).

**(E)-1-Phenyl-3-(2-(phenylethynyl)phenyl)prop-2-en-1-one 3.37:²⁰**

The compound was prepared by the following the reported procedure.² It was obtained as yellow solid in 76% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.35 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.78-7.75 (m, 1H), 7.64 (d, J = 16.0 Hz, 1H), 7.60-7.58 (m, 1H), 7.55-7.51 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.39-7.34 (m, 6H).

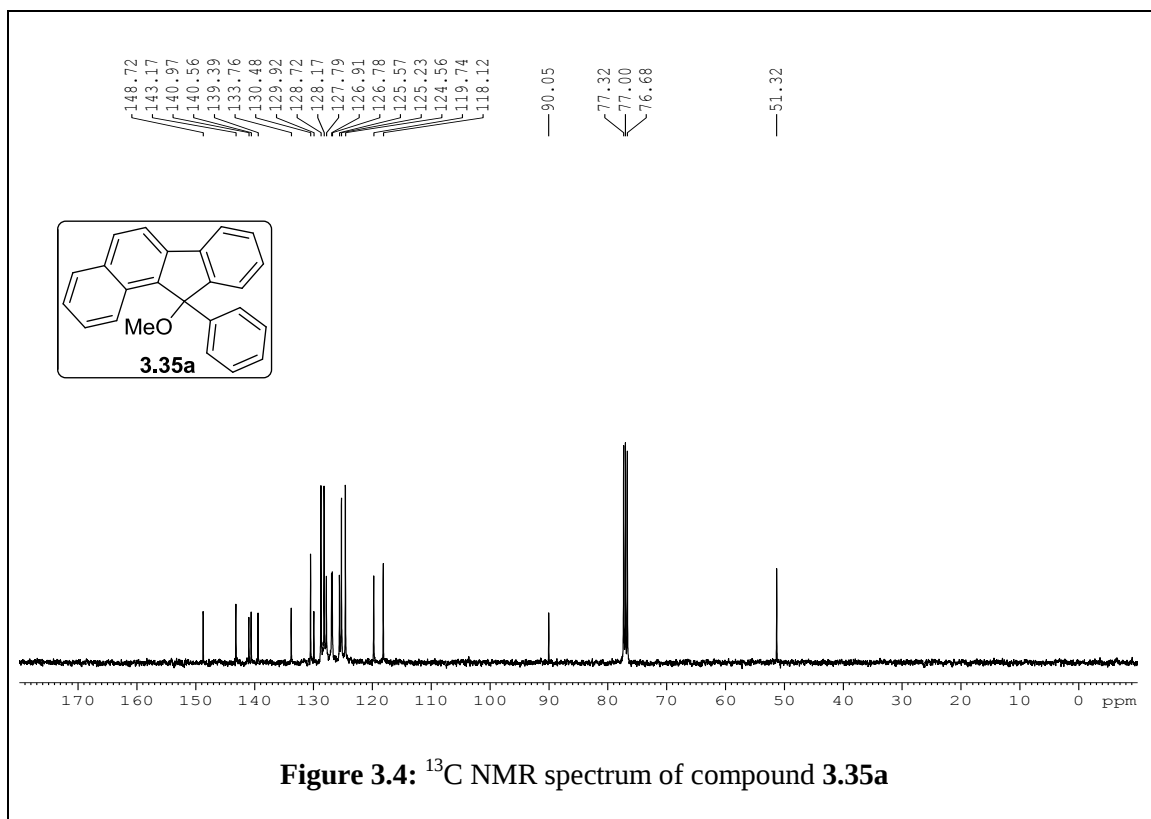
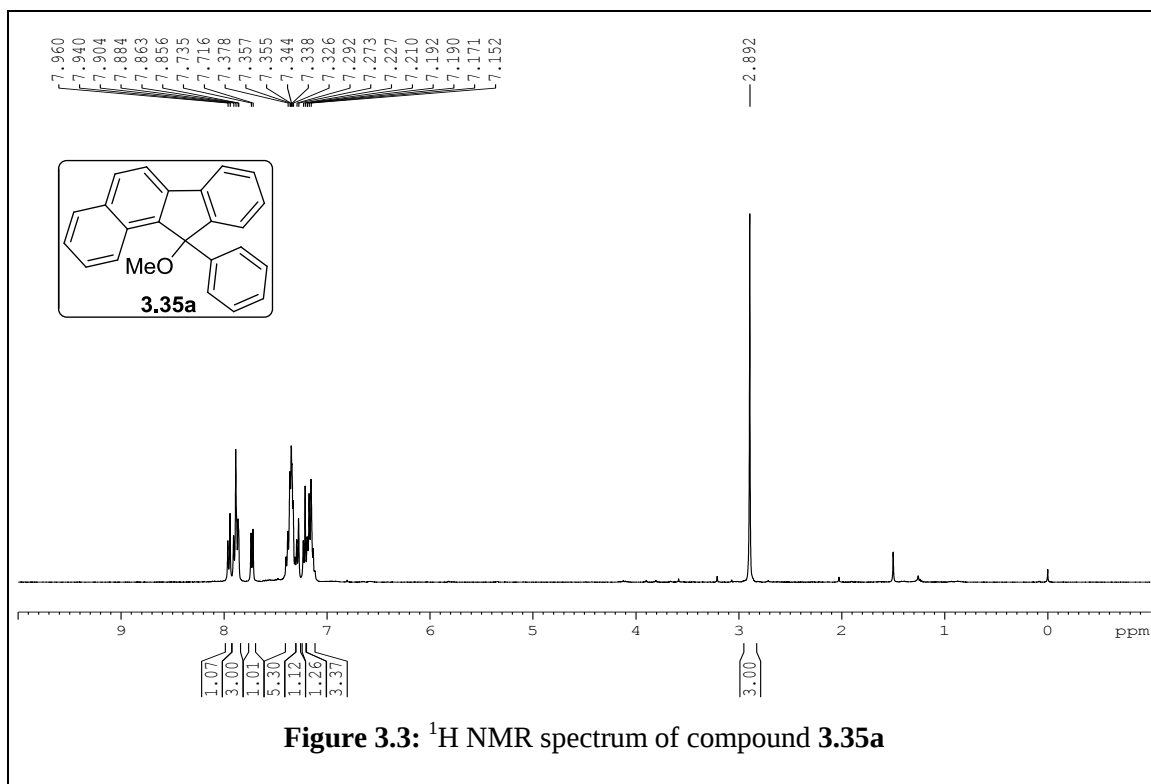


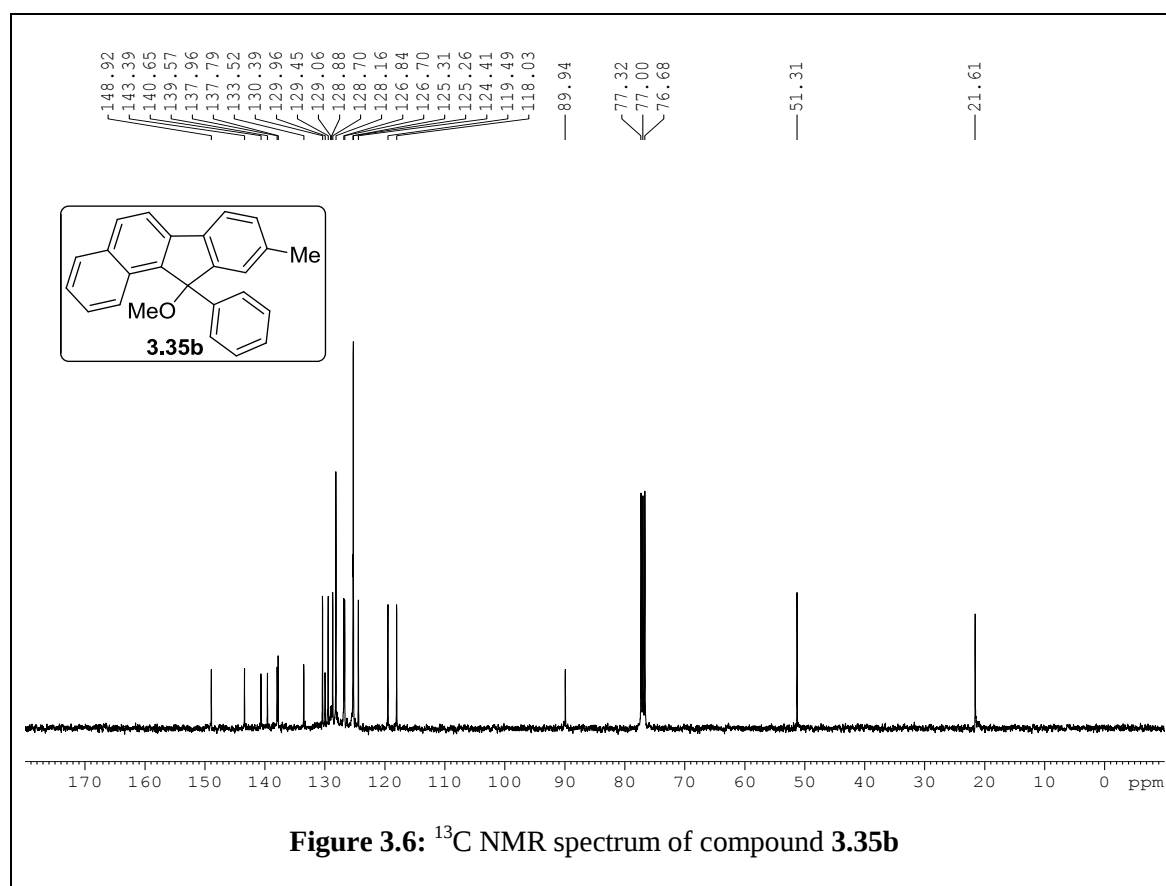
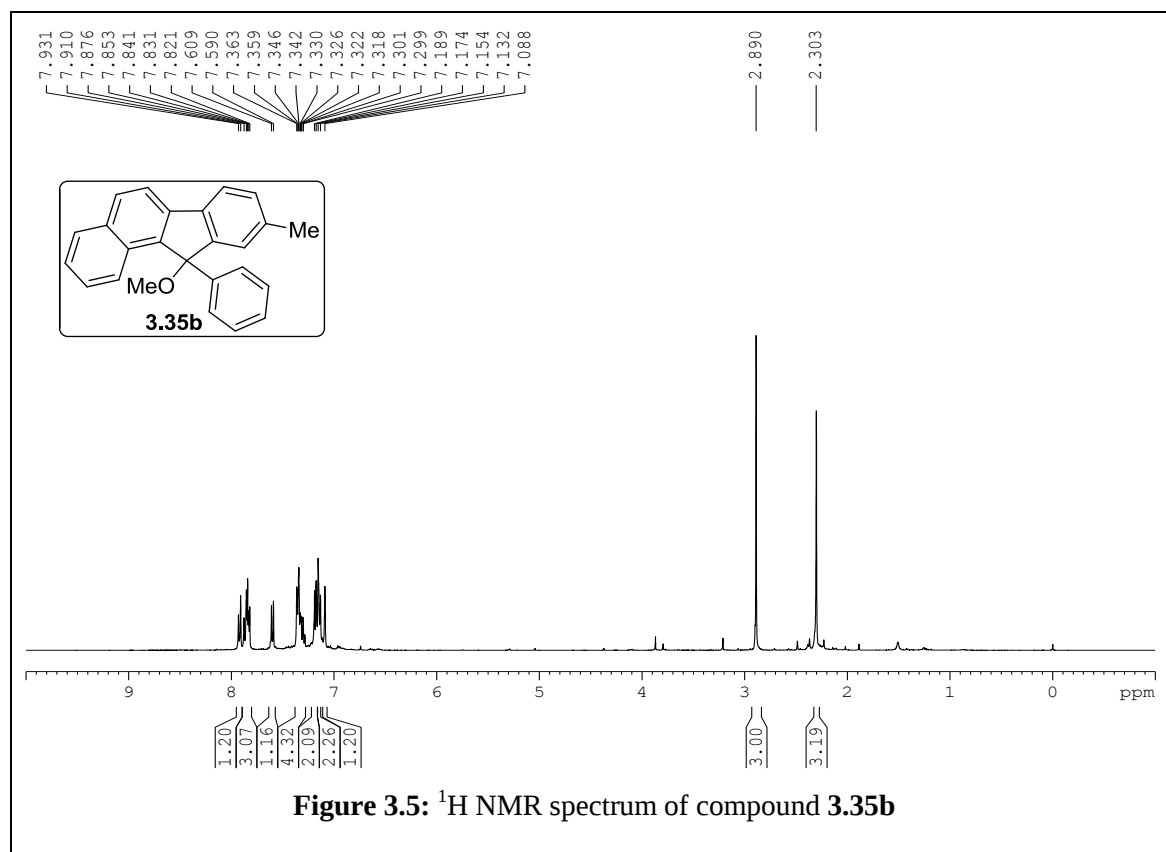
3.6 References

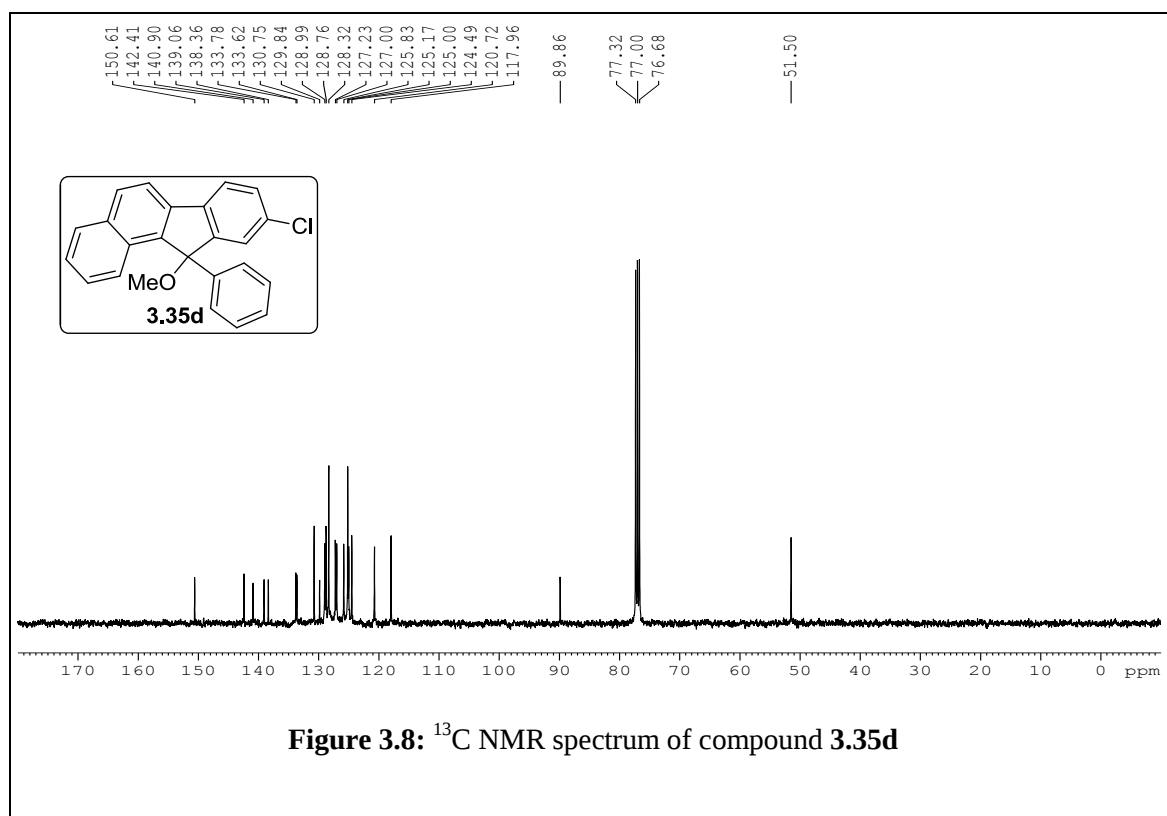
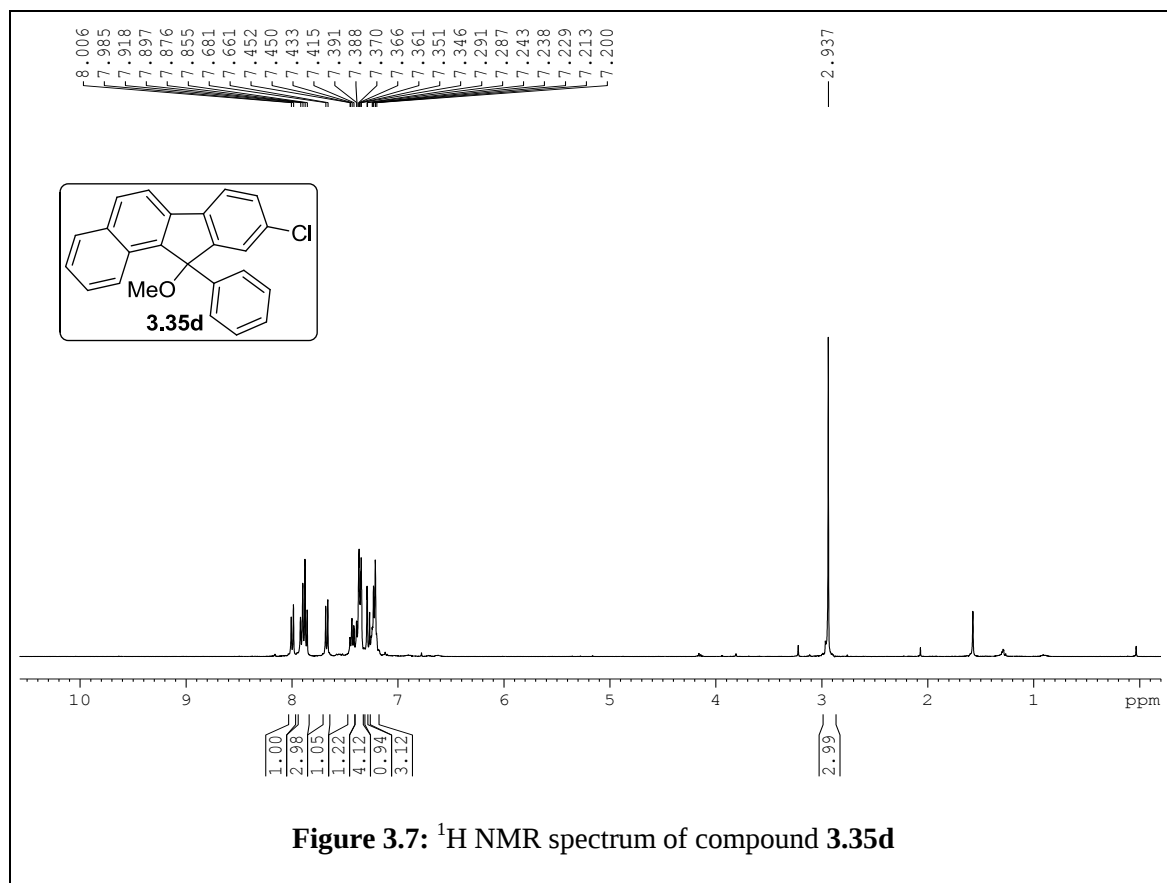
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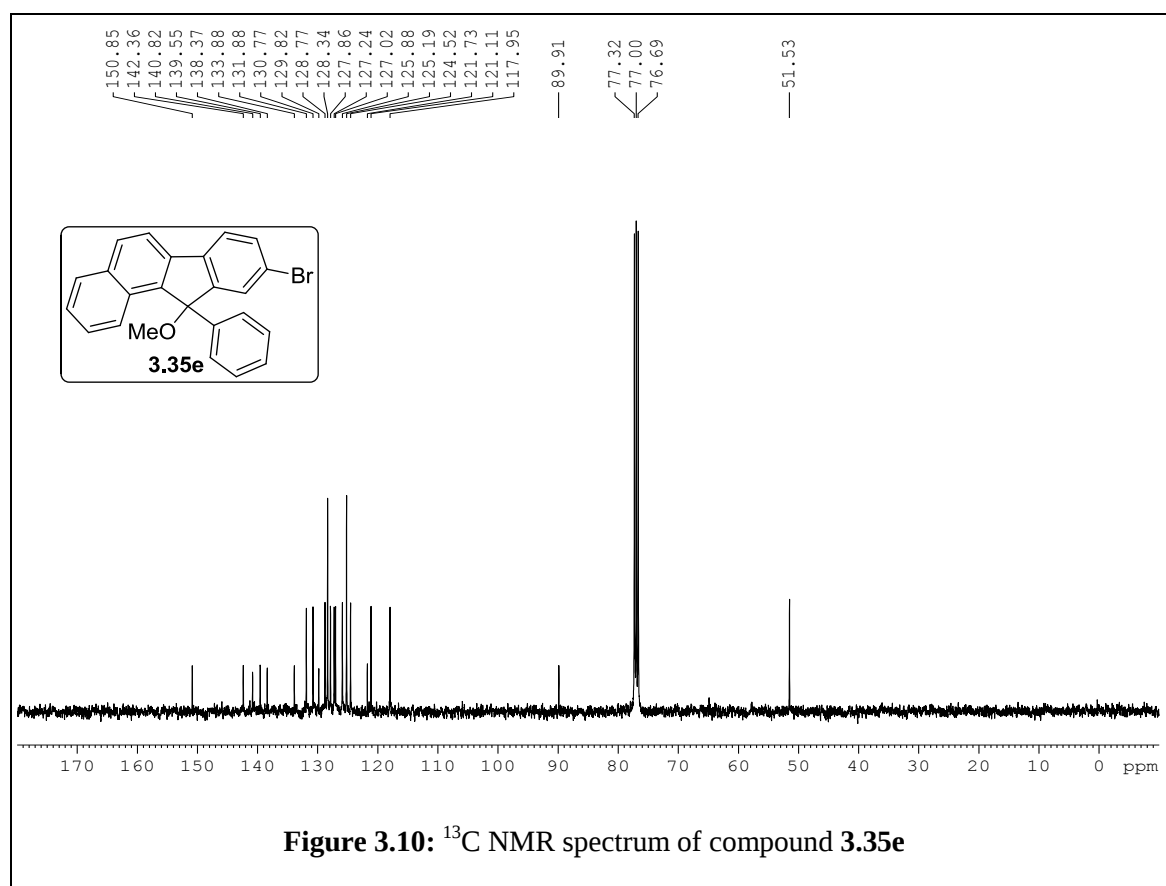
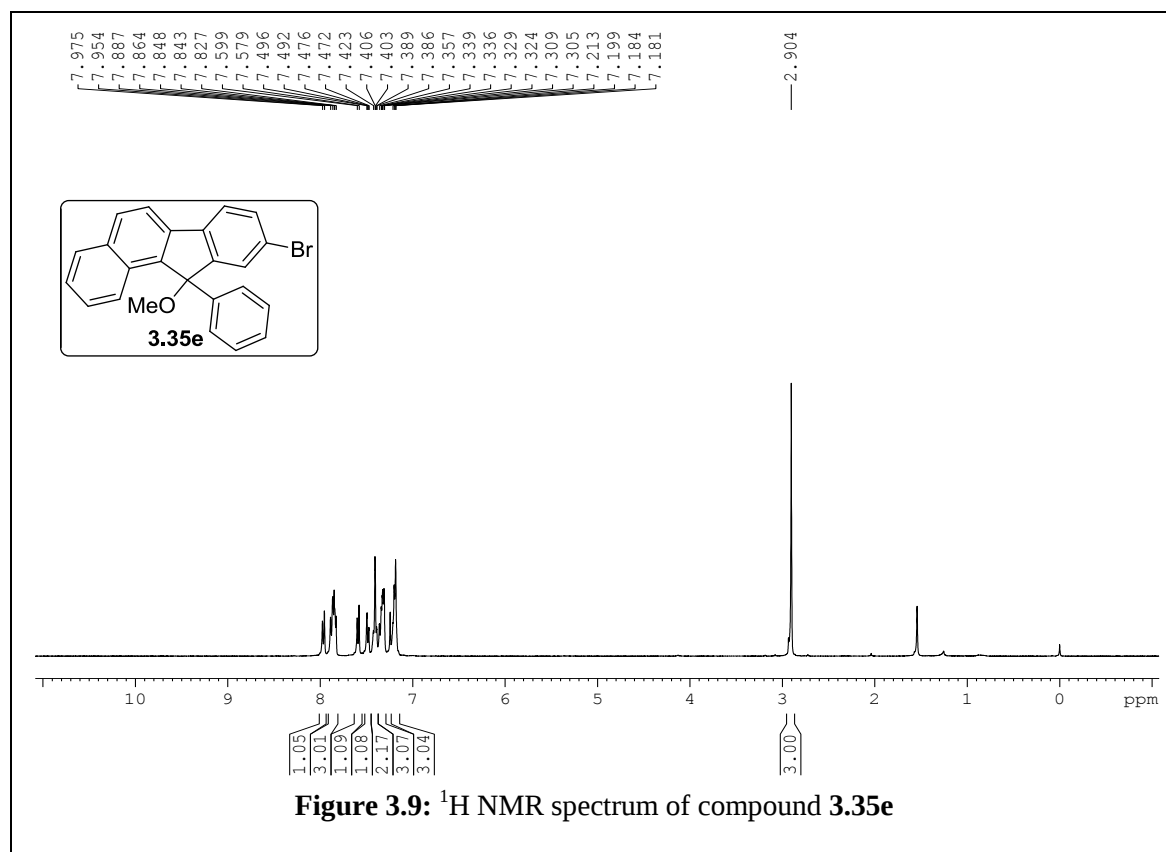
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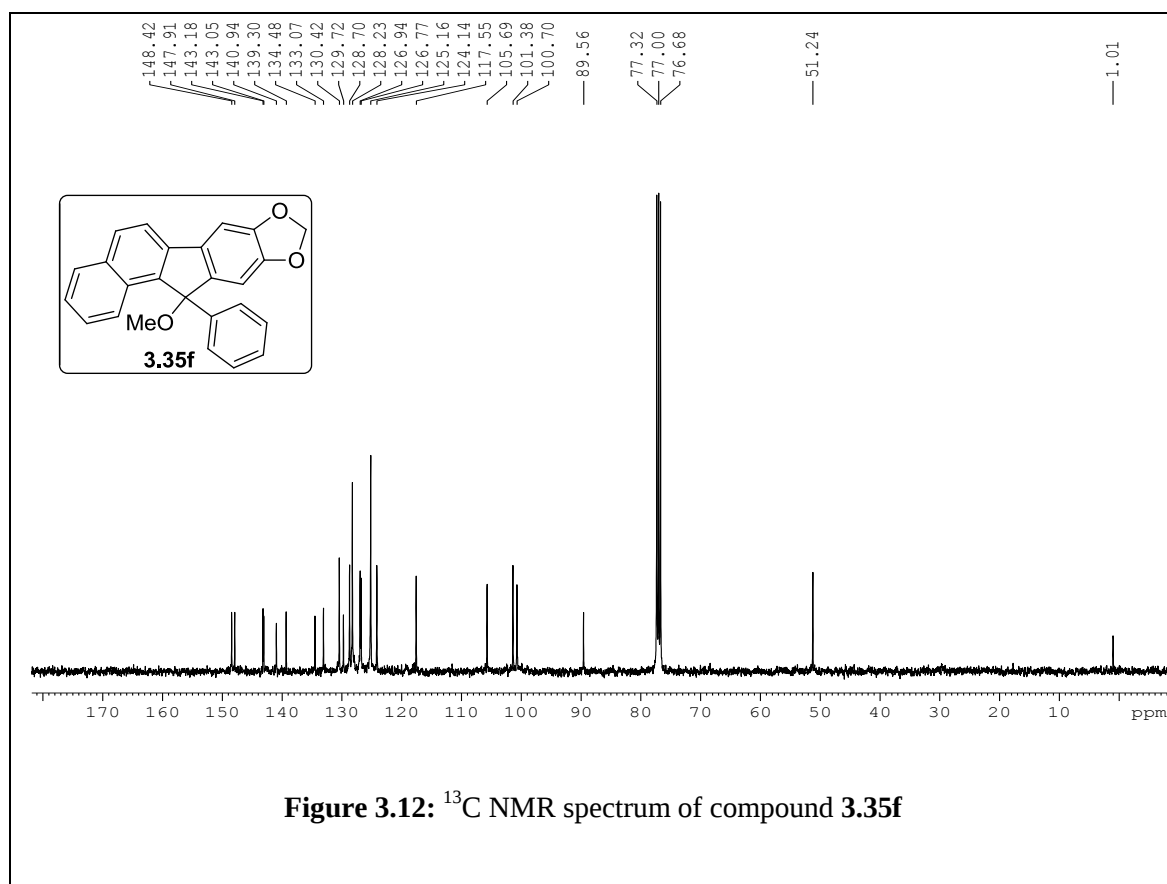
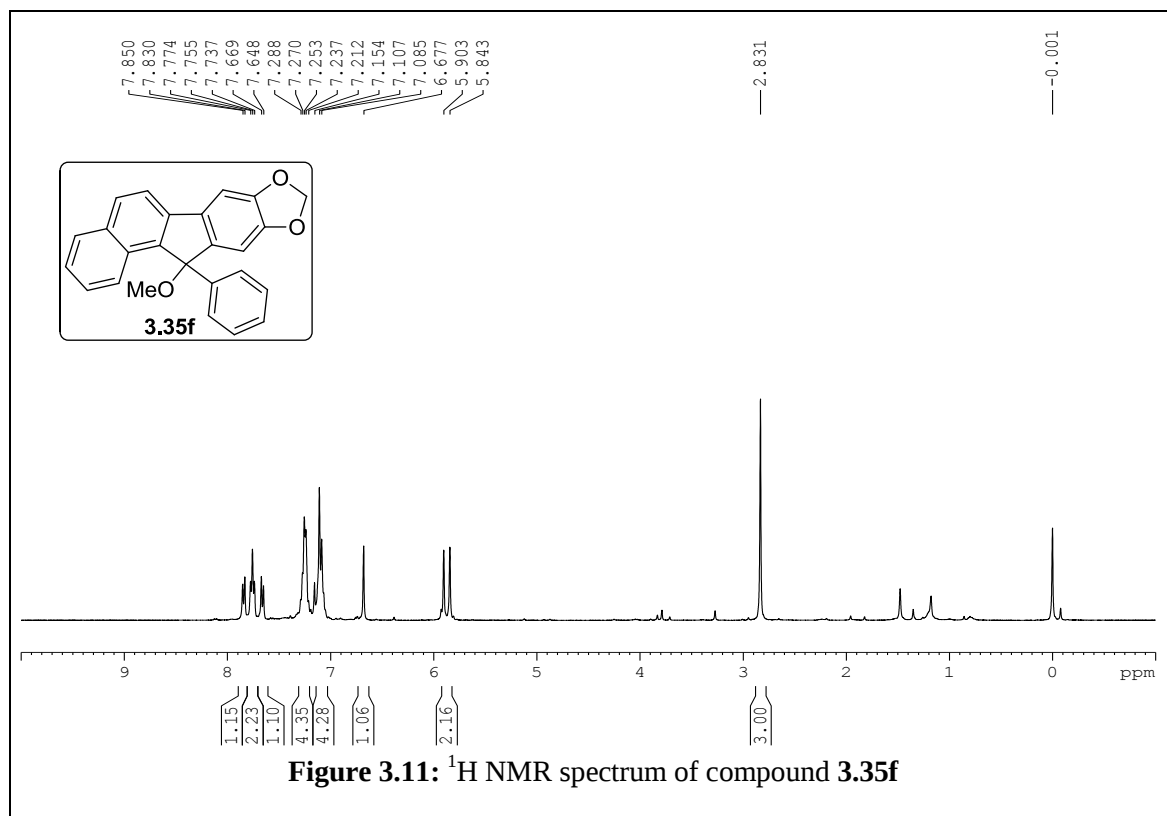
3.7 Representative spectra

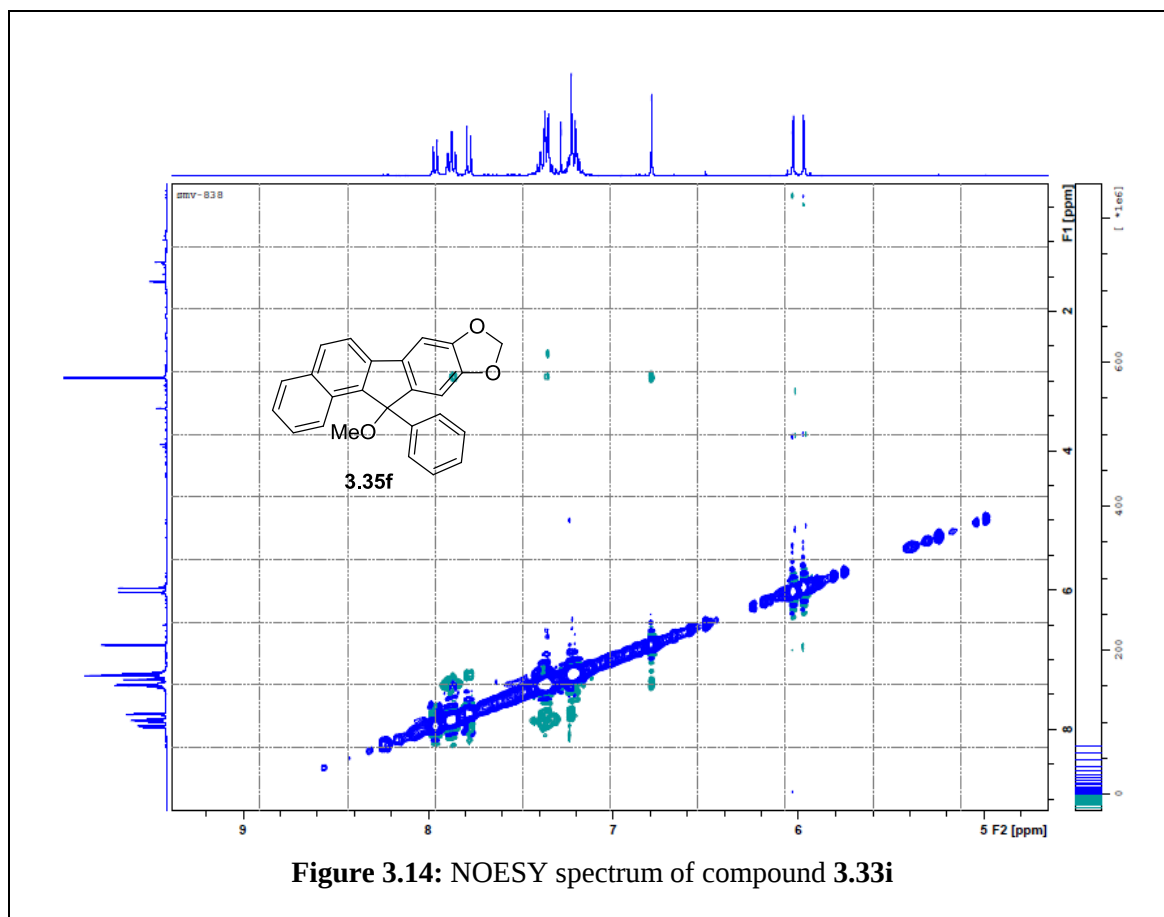
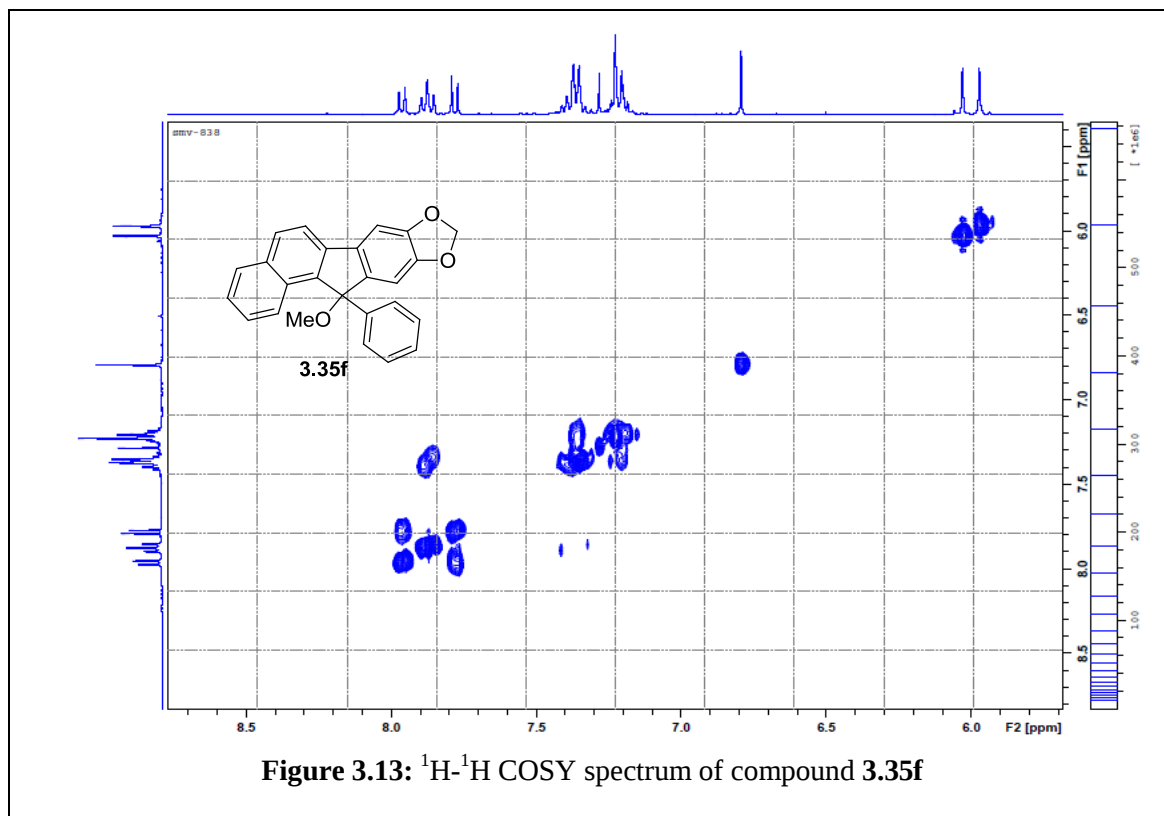


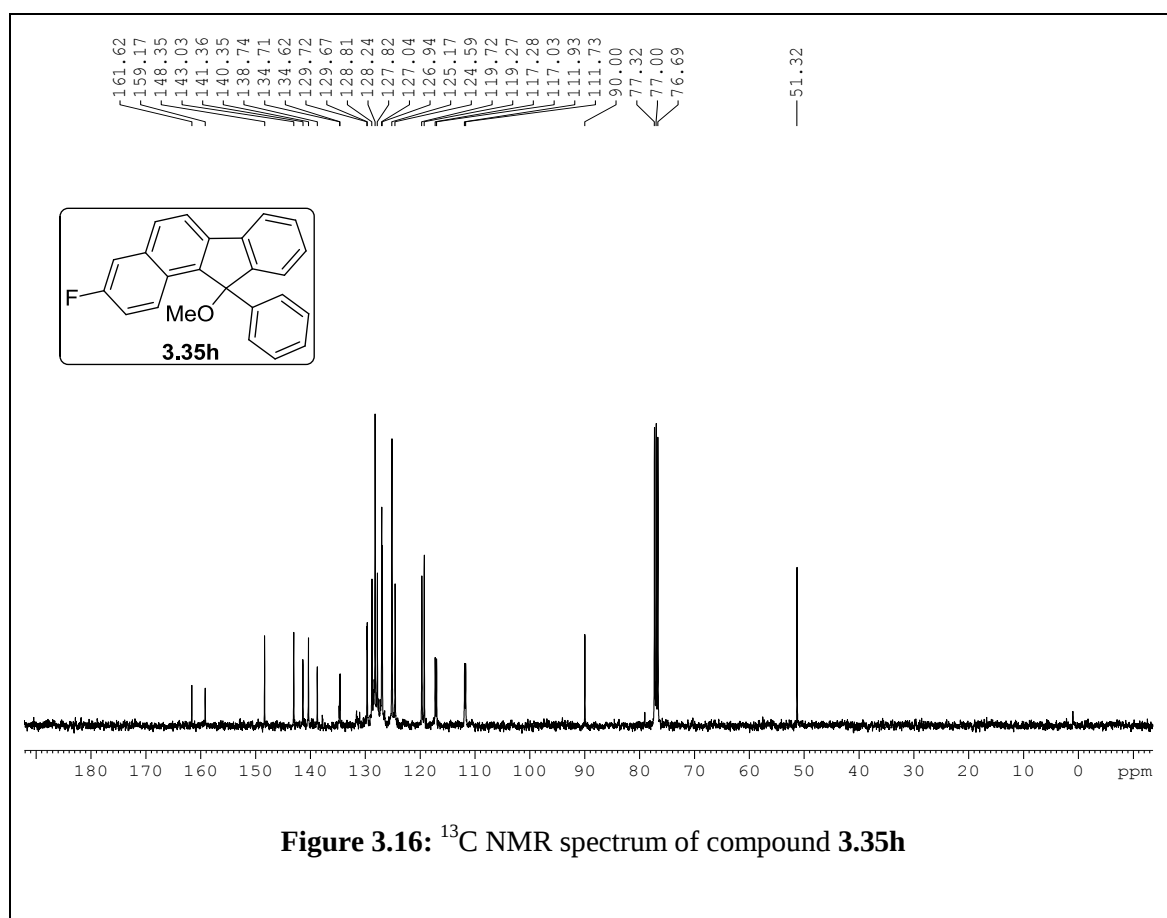
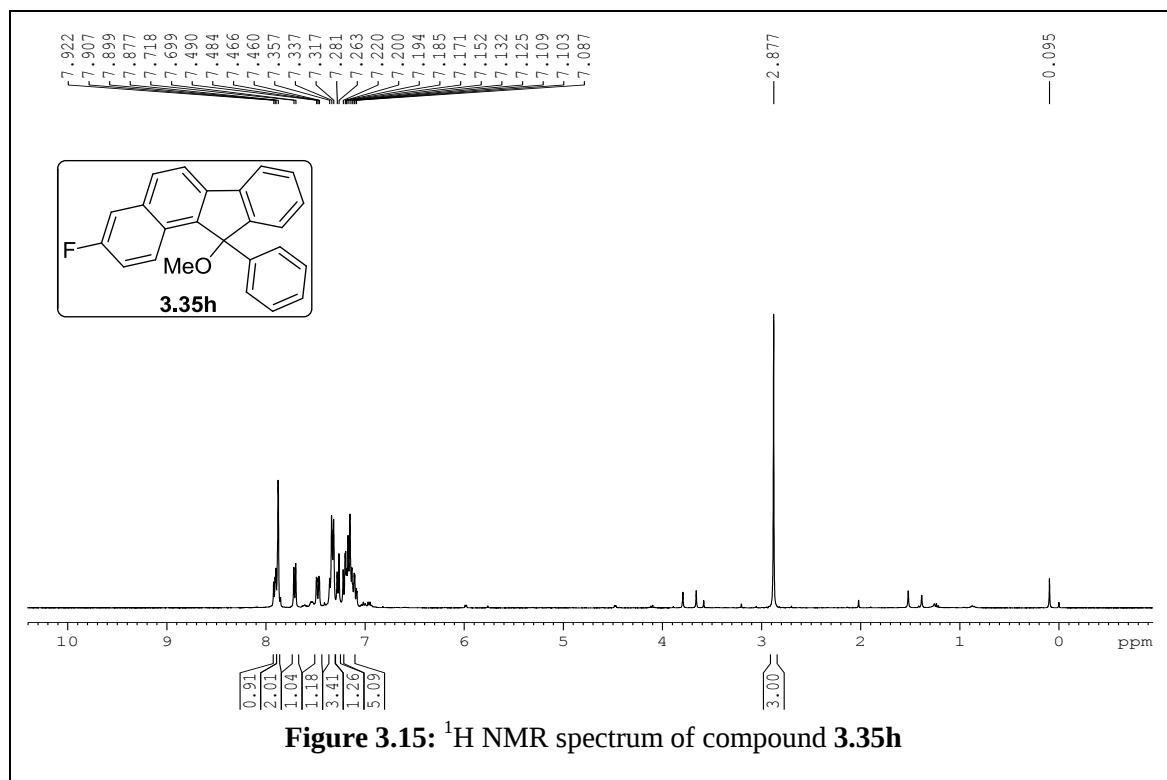


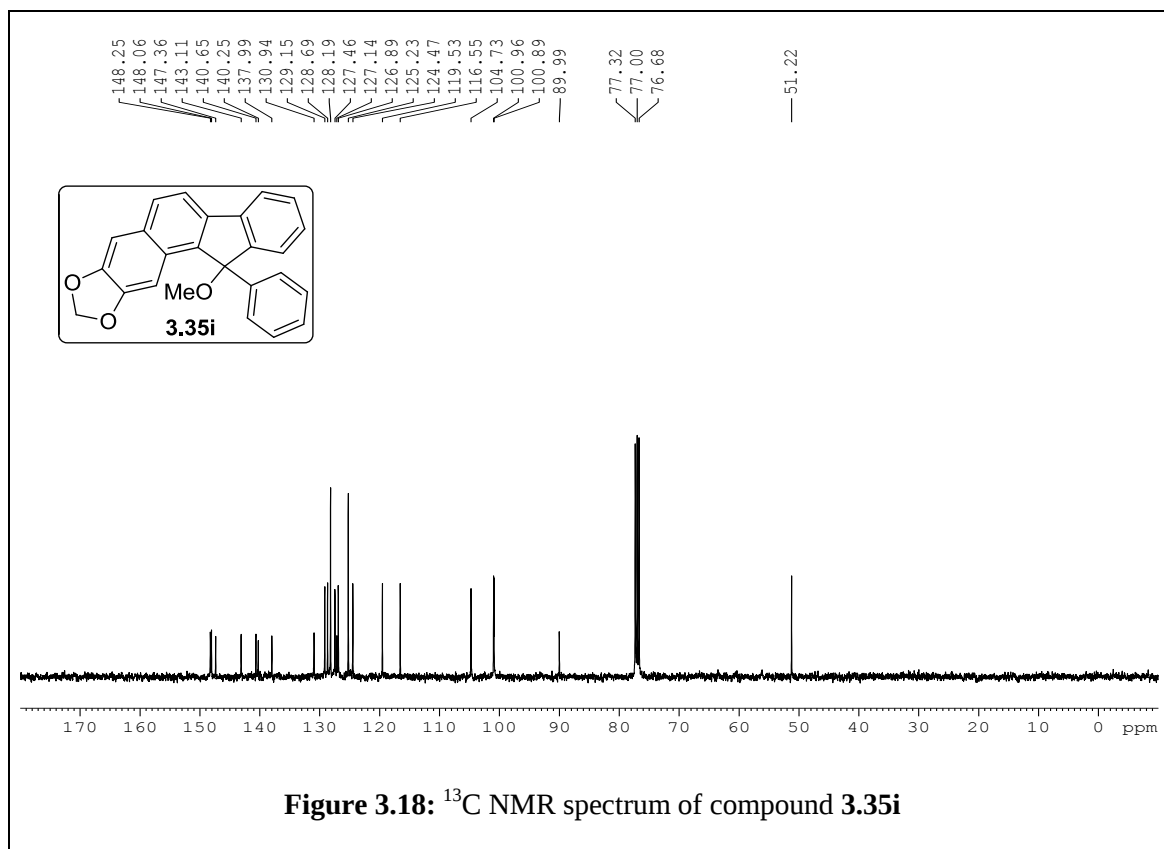
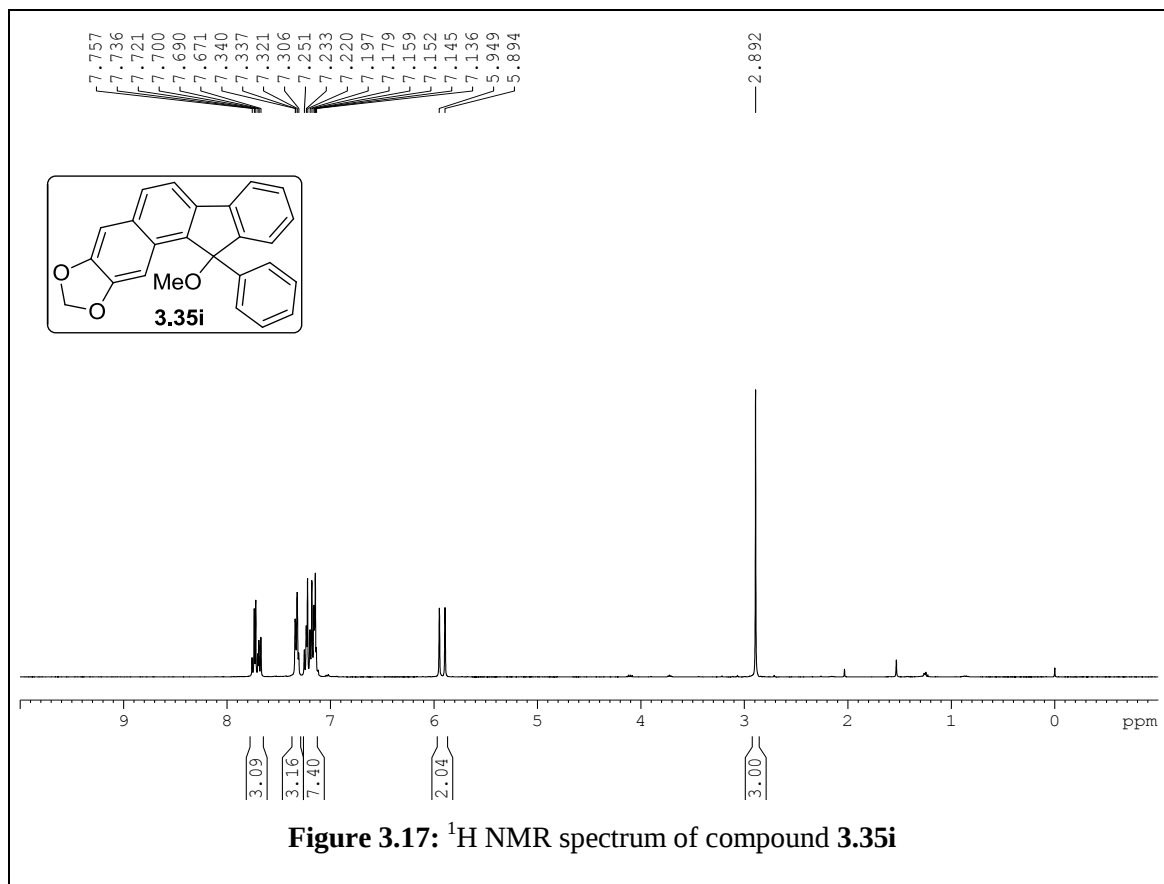


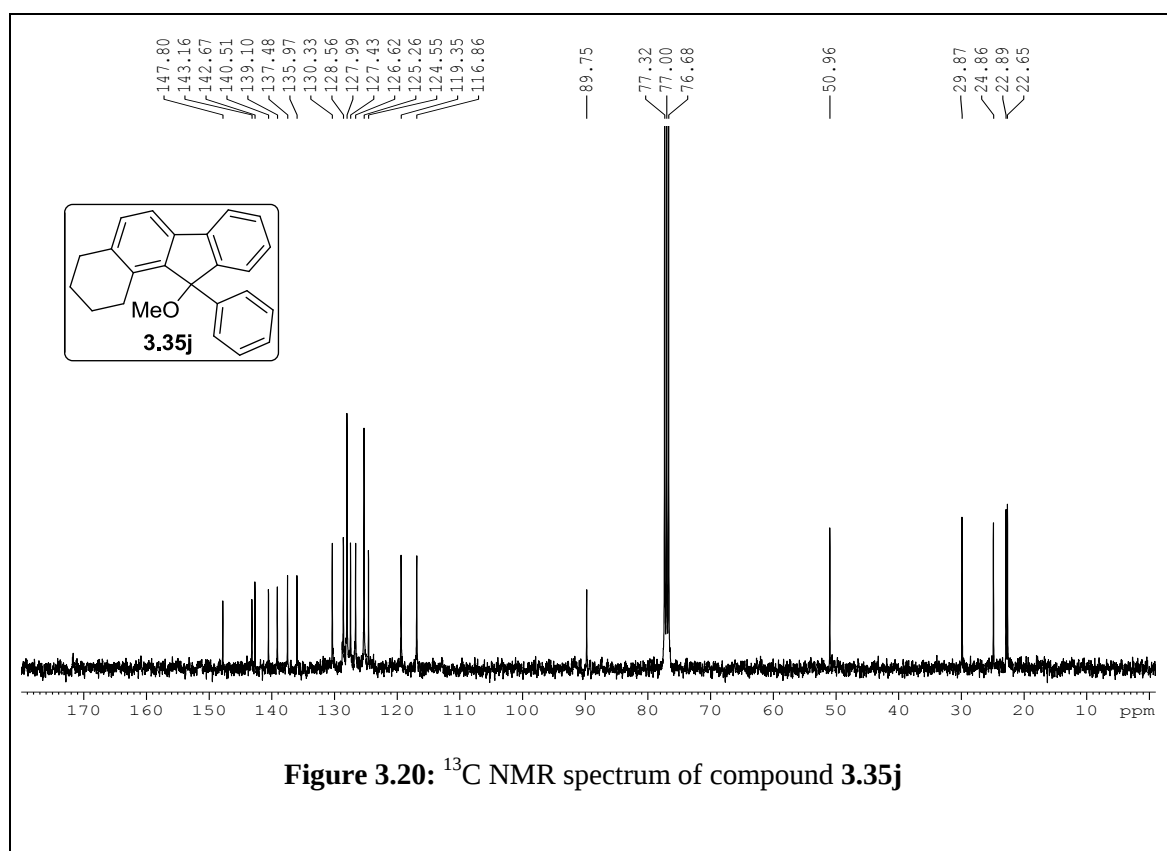
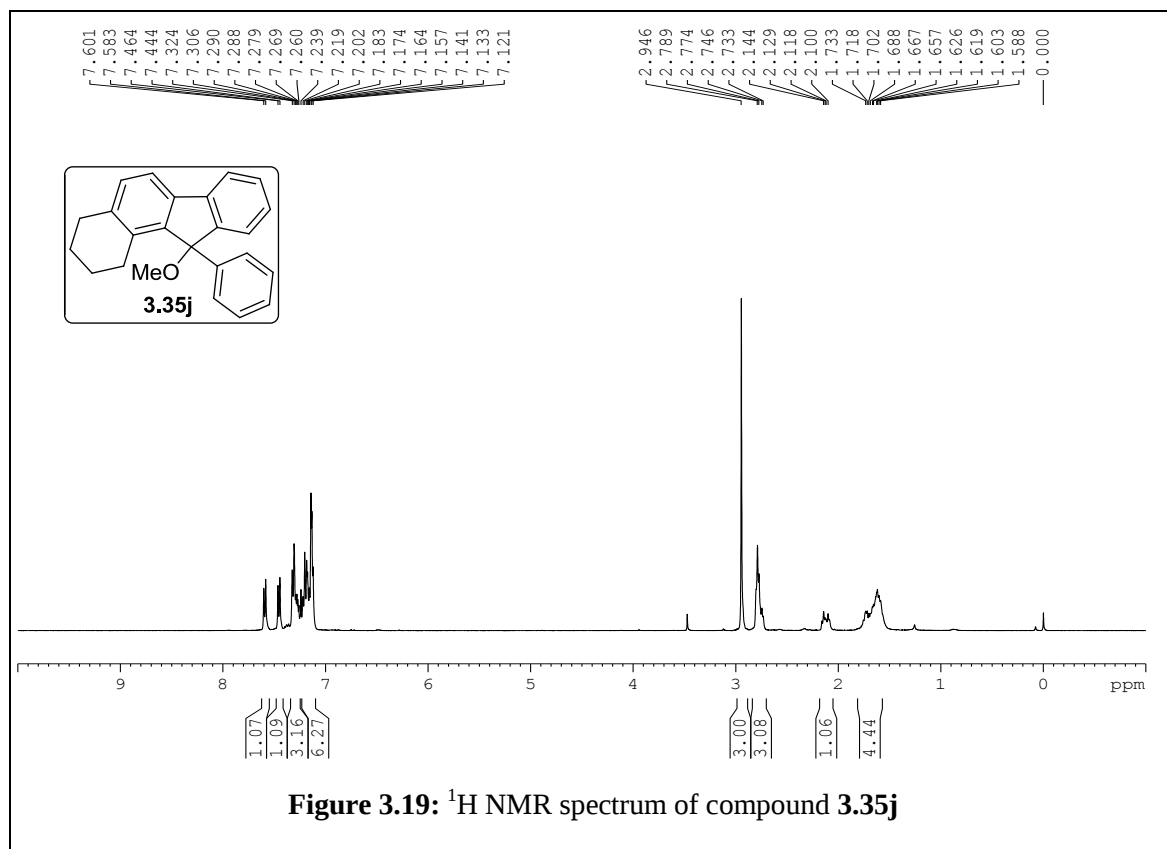


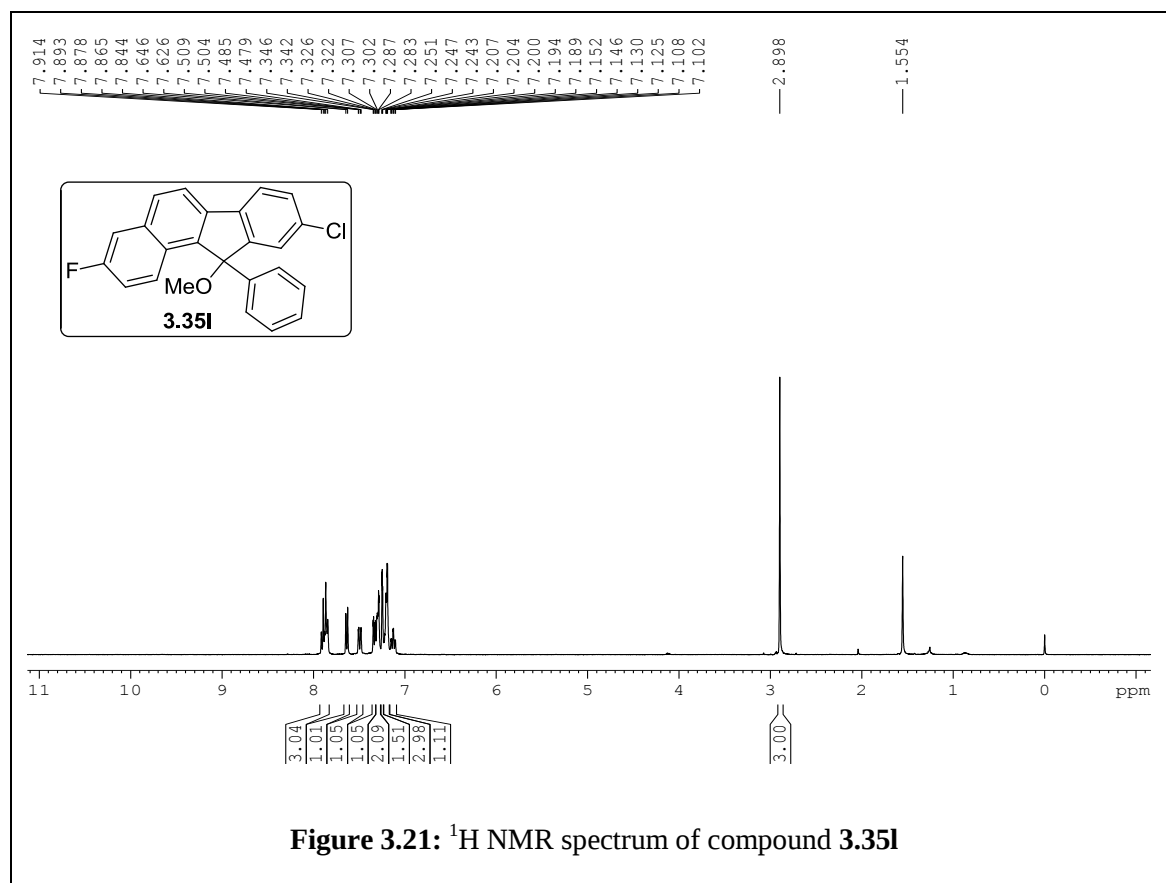
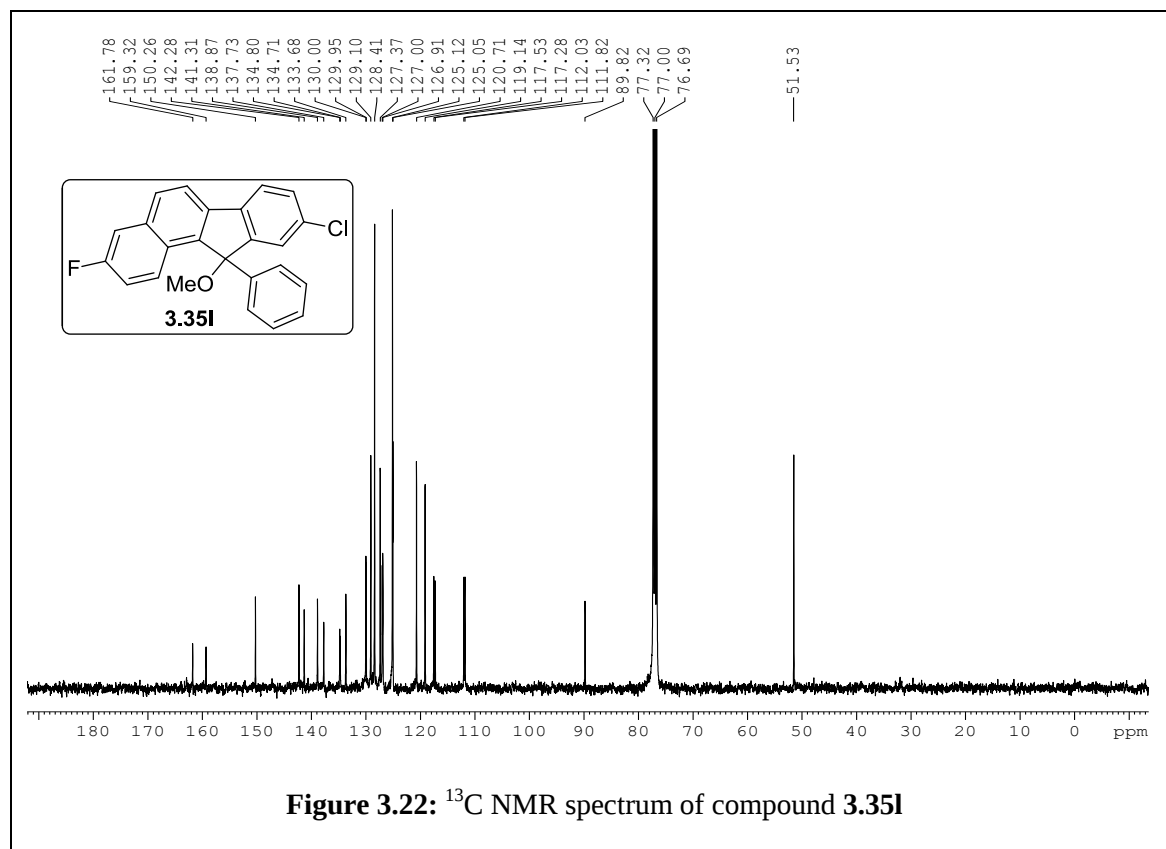


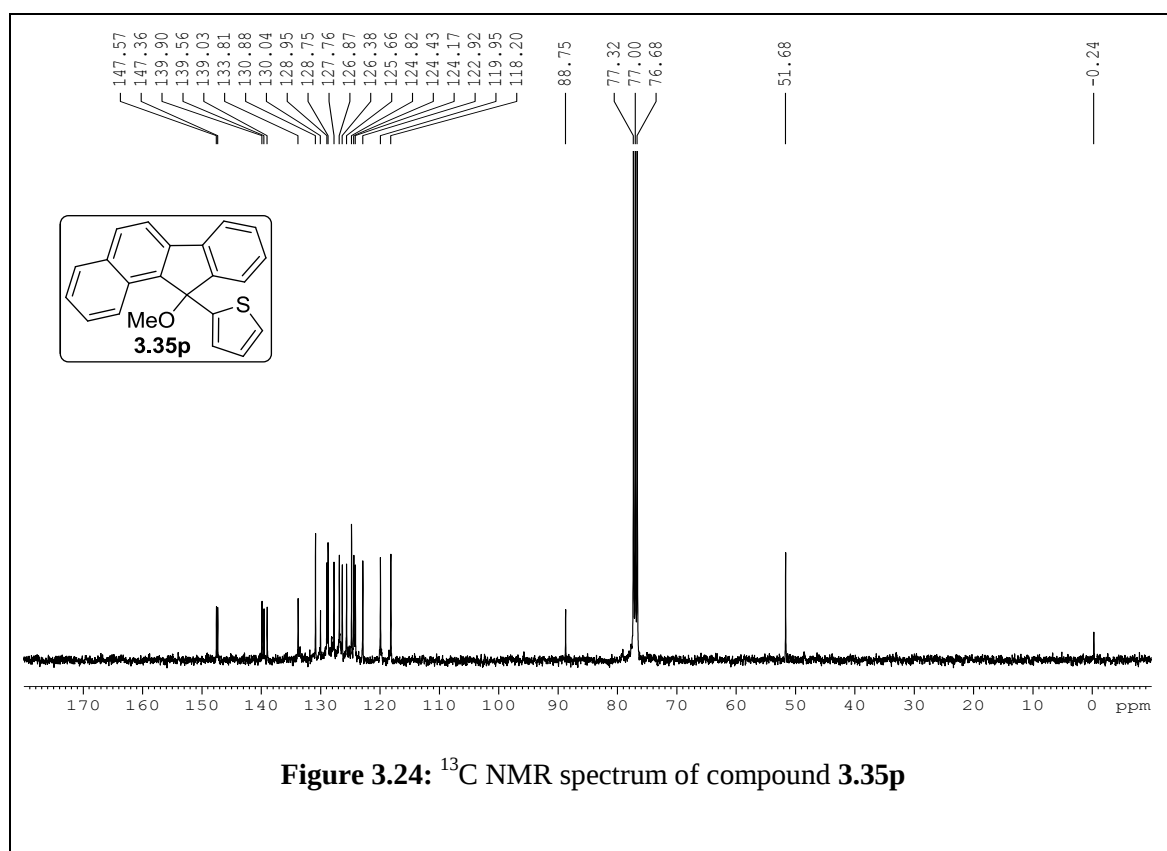
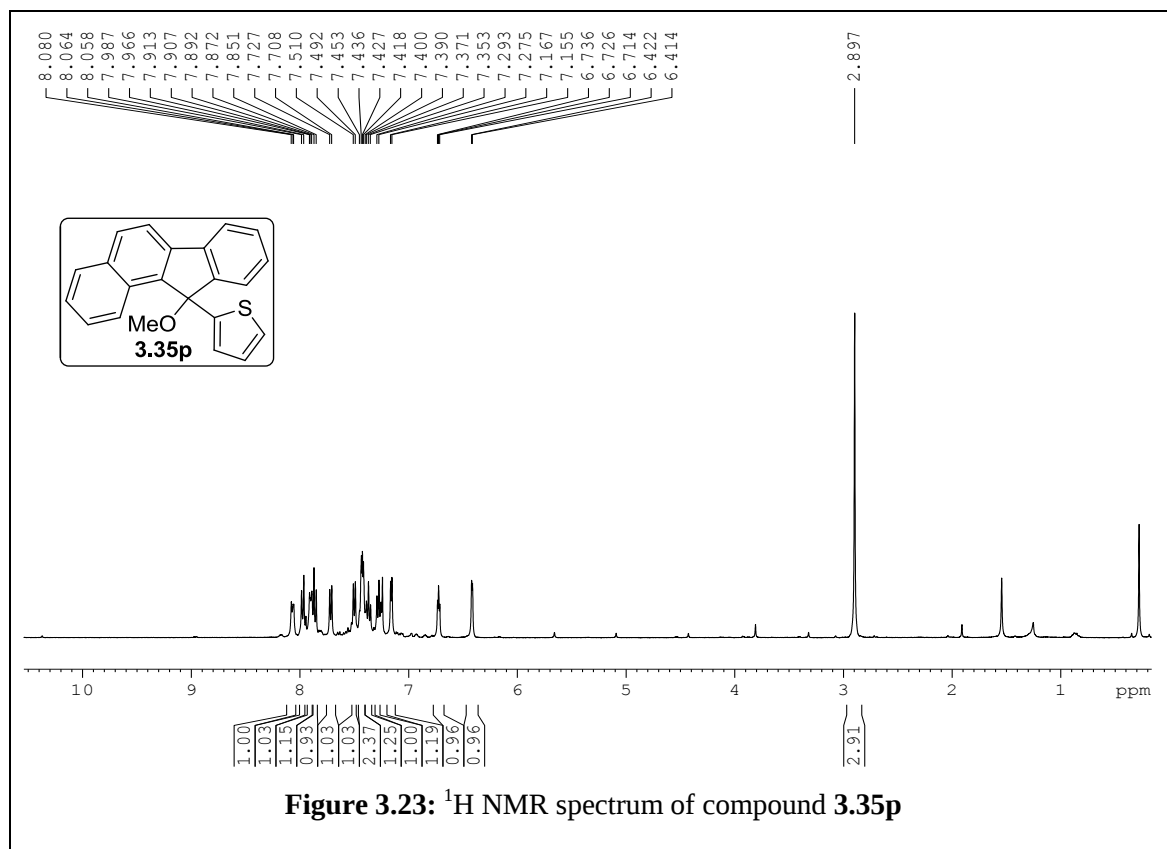


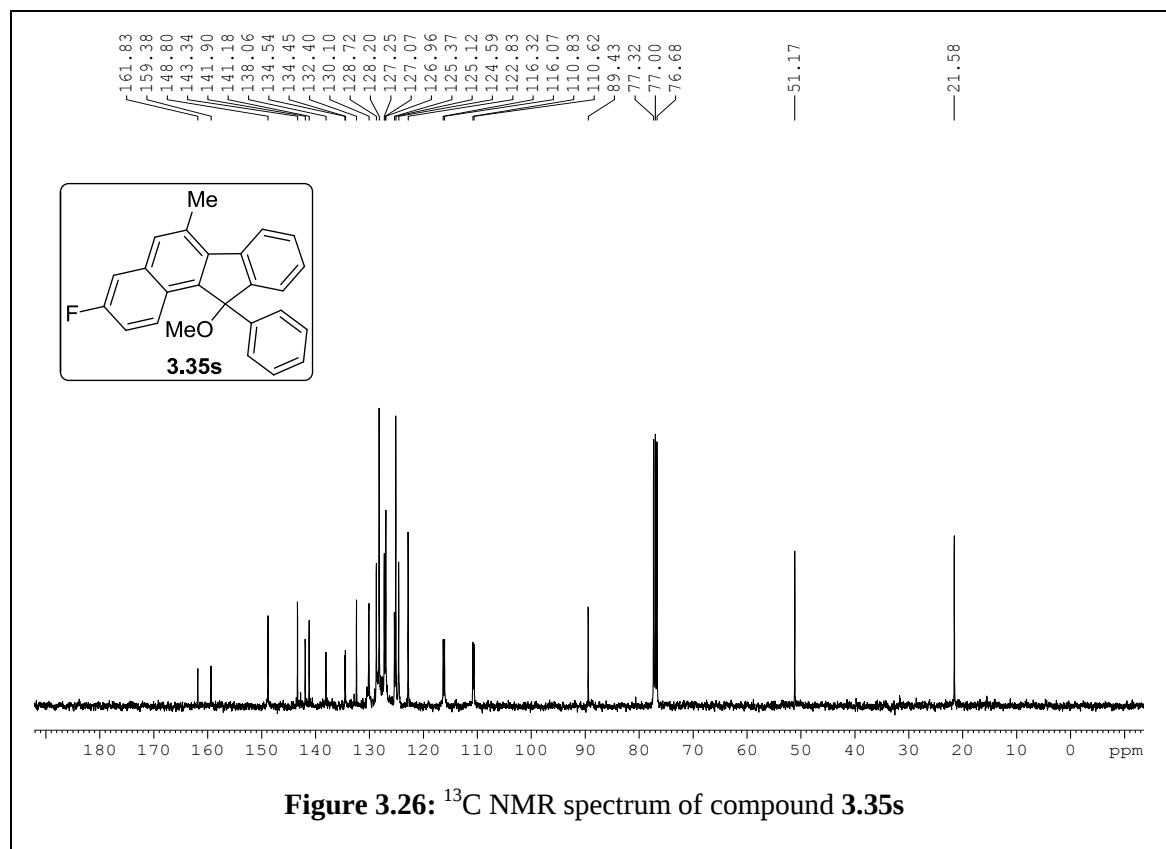
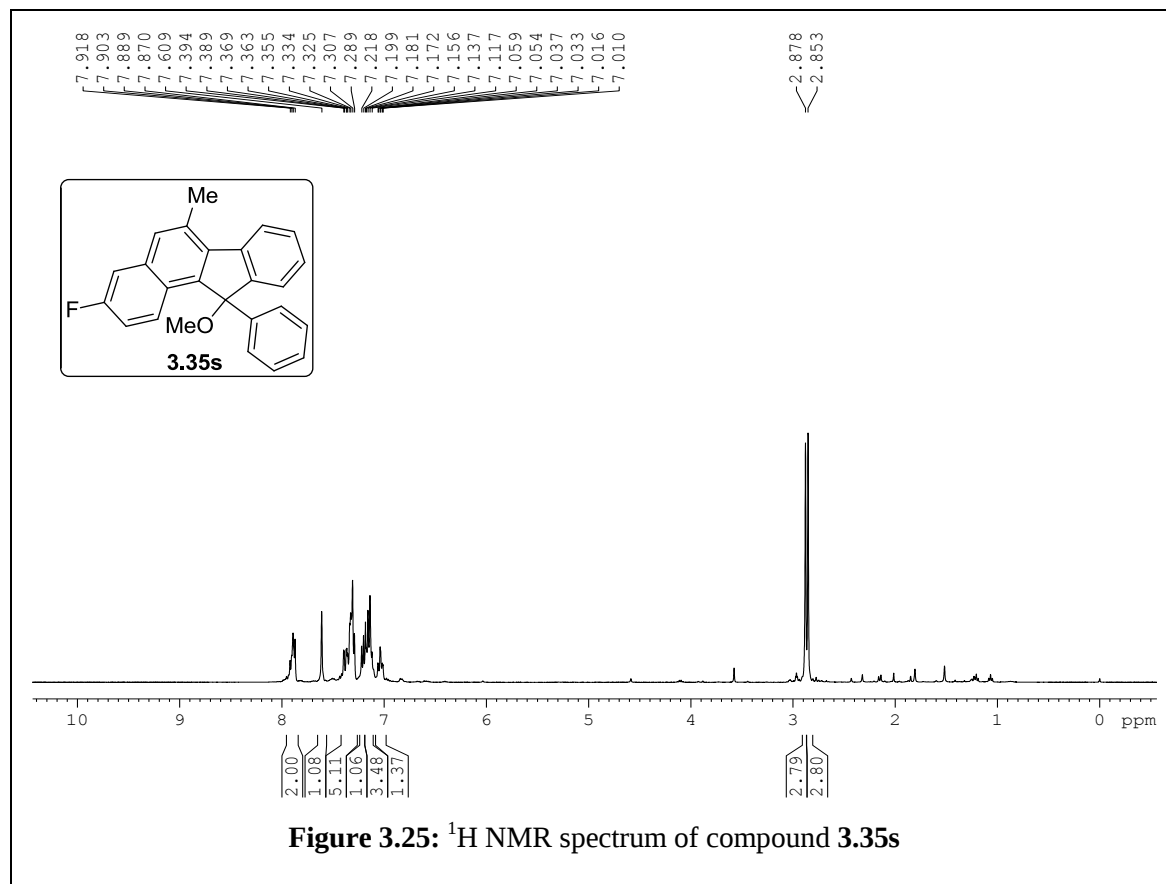


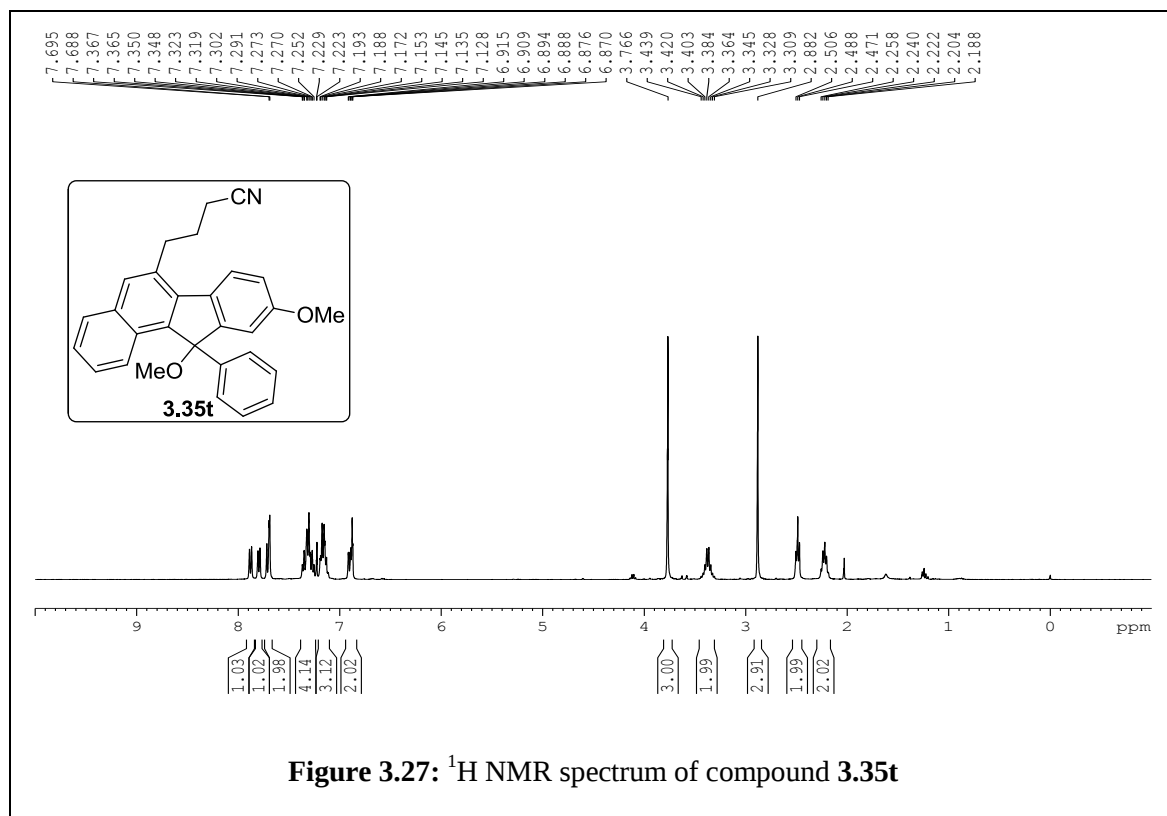
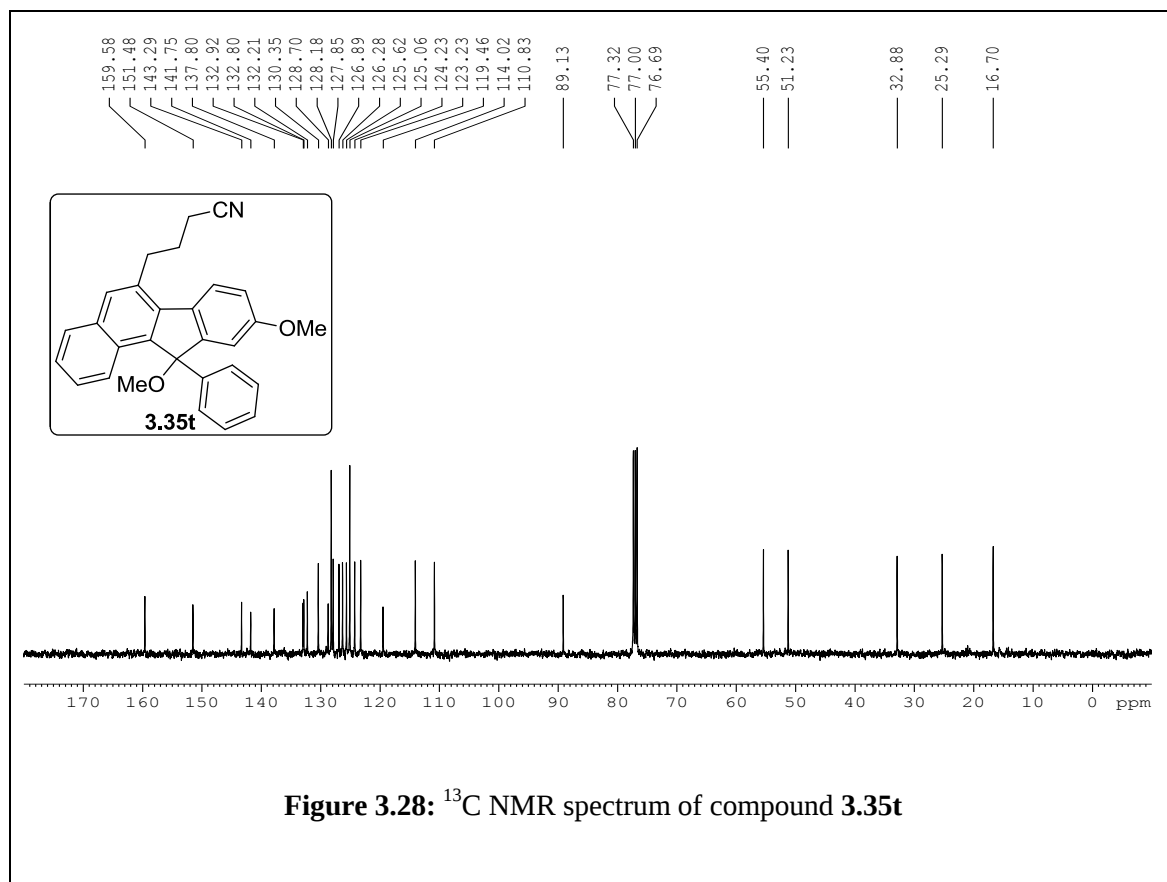


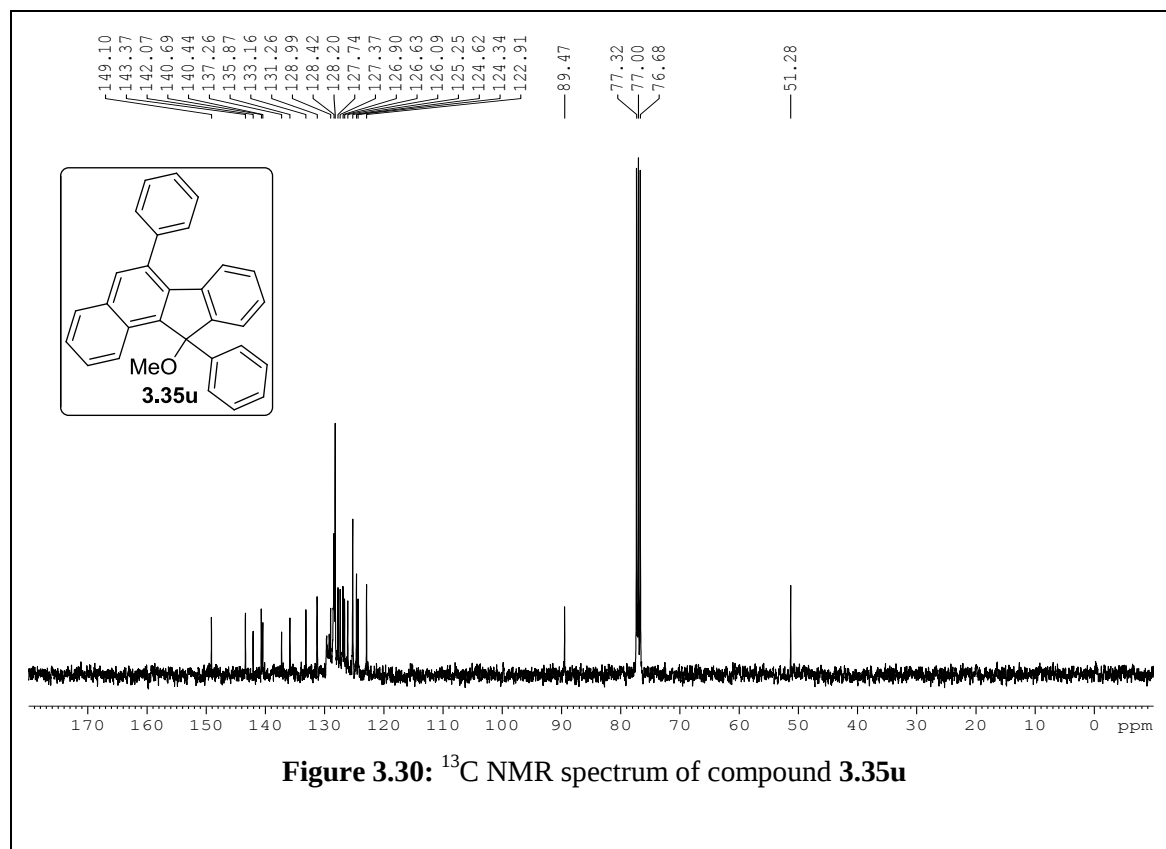
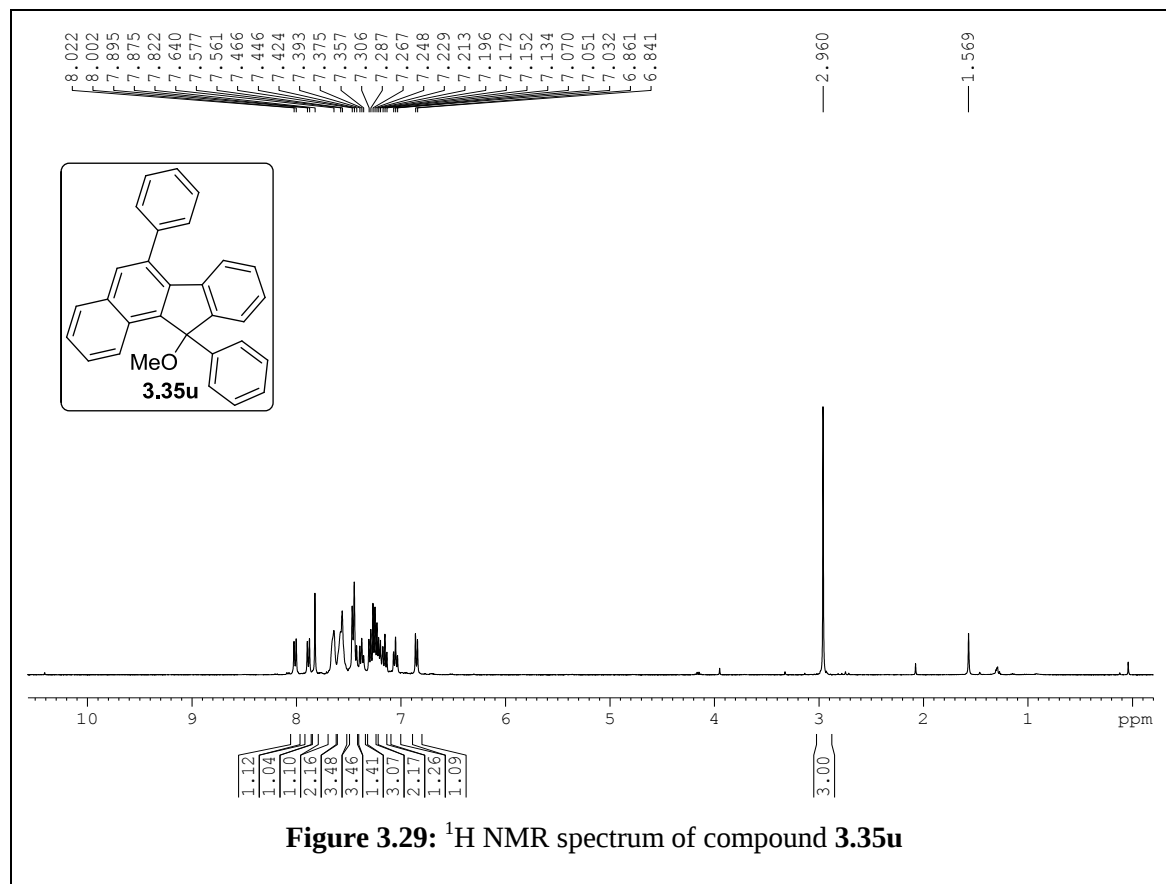


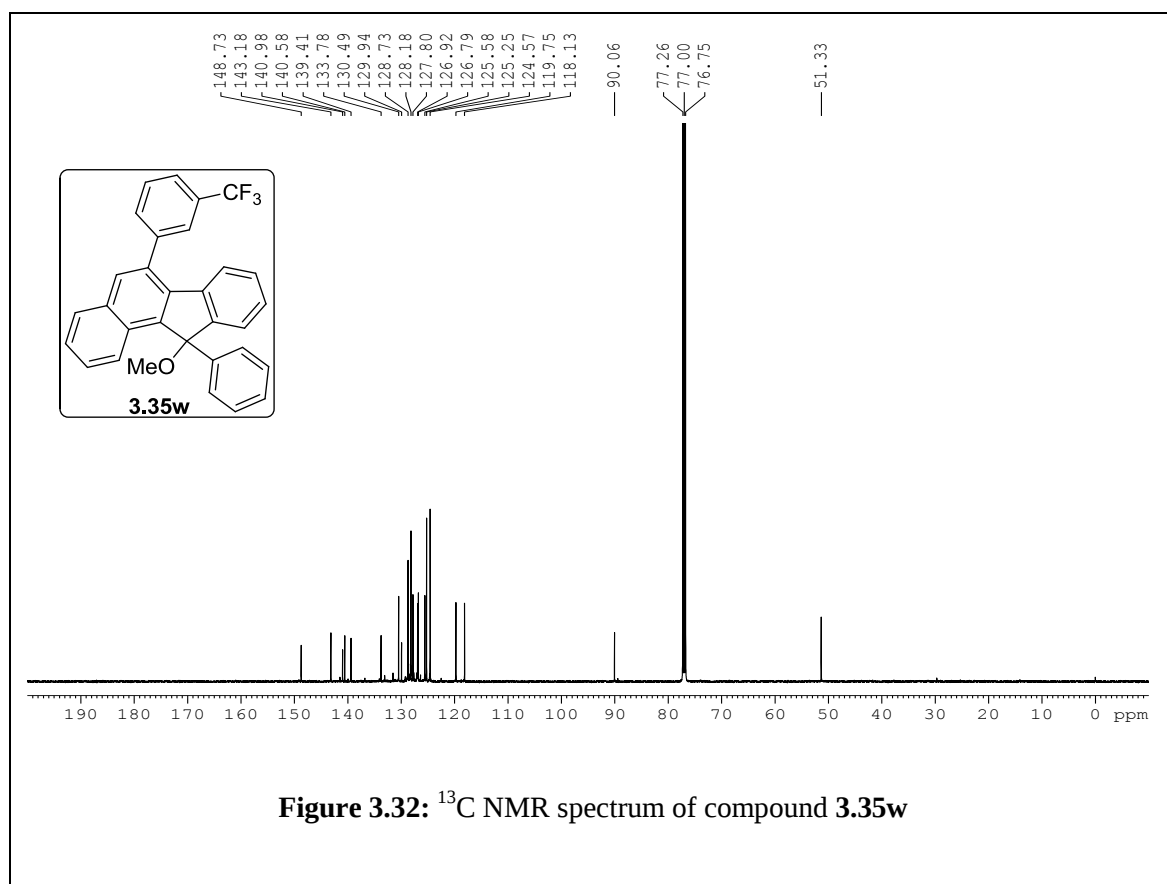
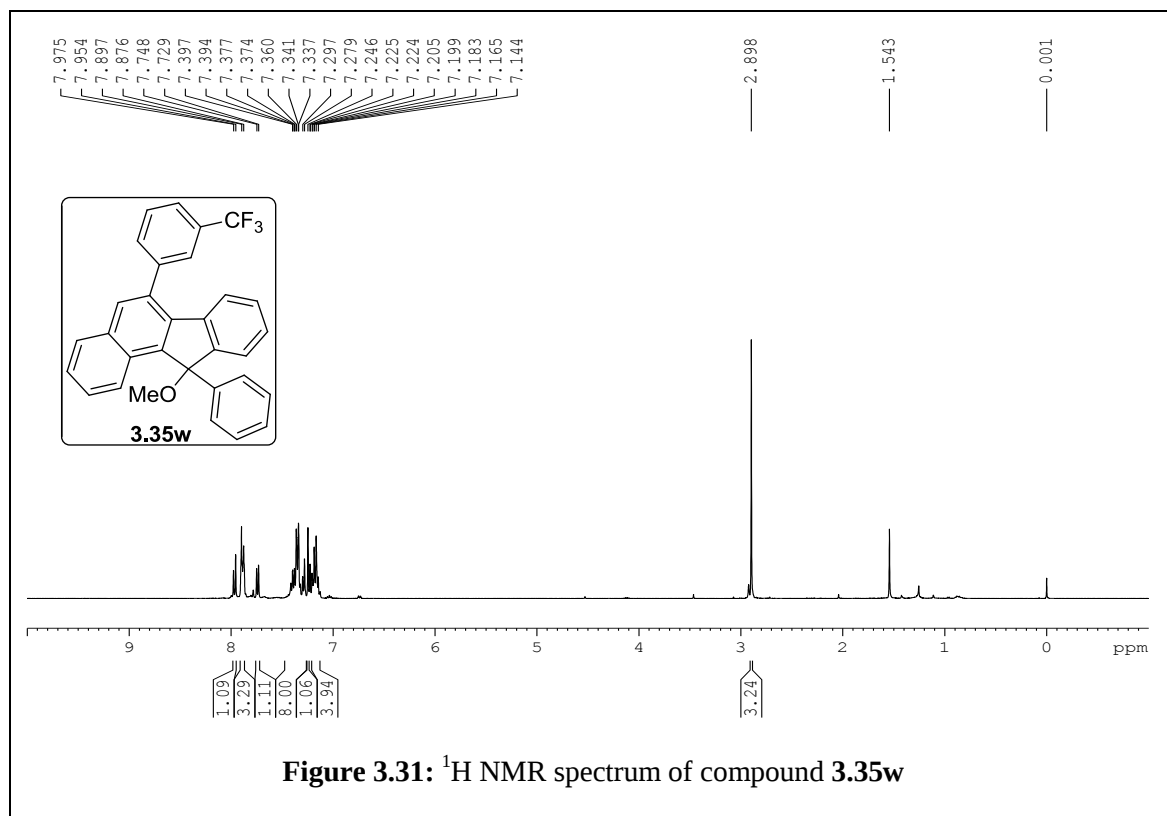
Figure 3.21: ¹H NMR spectrum of compound 3.35IFigure 3.22: ¹³C NMR spectrum of compound 3.35I

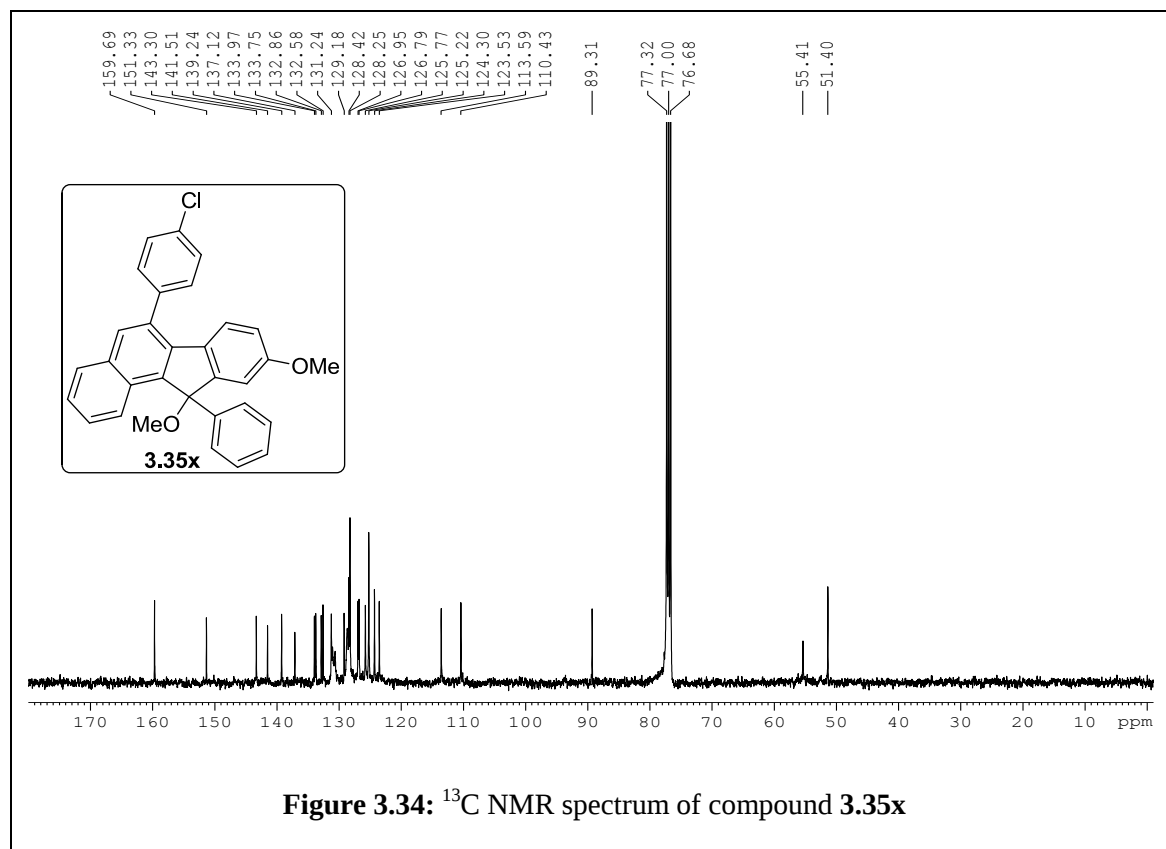
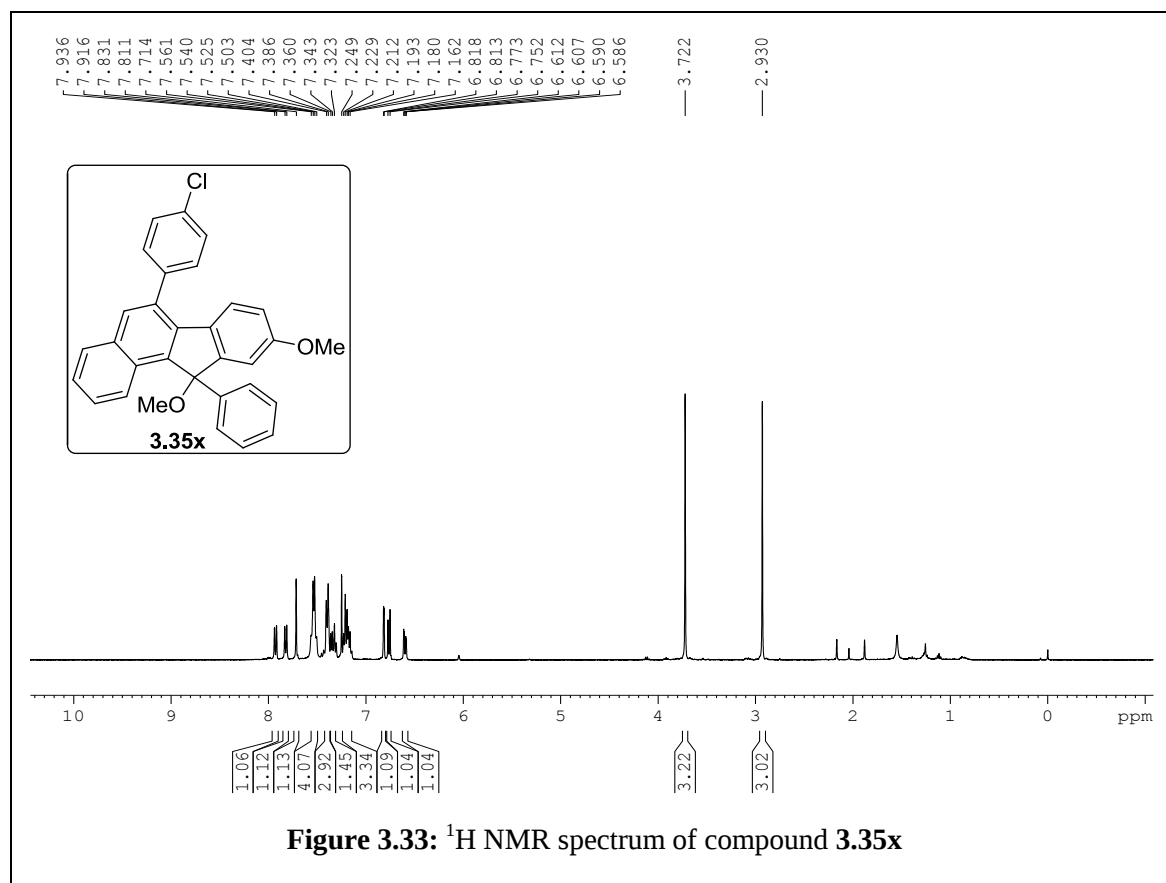




Figure 3.27: ^1H NMR spectrum of compound **3.35t**Figure 3.28: ^{13}C NMR spectrum of compound **3.35t**







Chapter 4

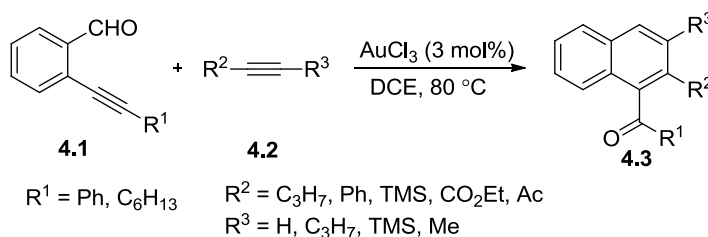
A New Approach to Naphthalene Derivatives from *o*-Alkynylbenzaldehydes and Enolizable Ketones *via in Situ* Formed Acetals

4.1 Introduction

Derivatives of naphthalenes have potential application in the fields of medicinal¹ and material sciences.² In this respect, different approaches have been developed for their synthesis.³ Some of the important methods for the synthesis of naphthalene framework have already been discussed in the introduction part of Chapter 2. An elaborate and a thorough literature on the synthesis of naphthalene derivatives have been covered in the thesis of Vanajakshi.⁴ *o*-Alkynylbenzaldehyde is a versatile building block for the synthesis of naphthalene derivatives. Selected methods for the synthesis of naphthalene derivatives from *o*-alkynylbenzaldehydes and related systems are discussed in the next section.

4.1.1 Synthesis of naphthalene derivatives using *o*-alkynylbenzaldehydes and related systems

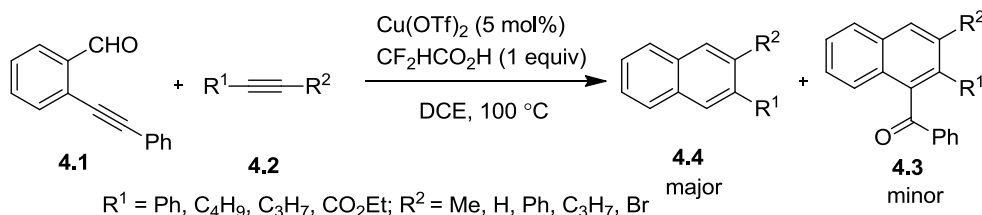
Yamamoto and co-workers reported an AuCl₃-catalyzed formal [4+2] benzannulation between *o*-alkynylbenzaldehydes **4.1** with alkynes **4.2** for the synthesis of naphthyl ketones **4.3** (Scheme 4.1).⁵ This reaction takes place *via* the formation of pyrylium type intermediate followed [4+2] benzannulation with an alkyne to give the naphthyl ketone derivative **4.3**. The mechanistic details have been discussed in the background part of previous chapter (Chapter 3).



Scheme 4.1: Au-catalyzed [4+2] benzannulation of *o*-alkynylbenzaldehydes with alkynes

The yields of naphthalene derivatives **4.3** and the reaction speed have been enhanced by using AuBr₃ instead of AuCl₃ as catalyst as revealed, in their later studies.⁶ In addition to that, they showed a method for the synthesis of naphthalene derivatives **4.4** from *o*-alkynylbenzaldehydes **4.1** and alkynes **4.2** in the presence of Cu(OTf)₂ catalyst and stoichiometric amount of CF₂HCOOH catalyst system at 100 °C (Scheme 4.2). In the presence of Brønsted acid,

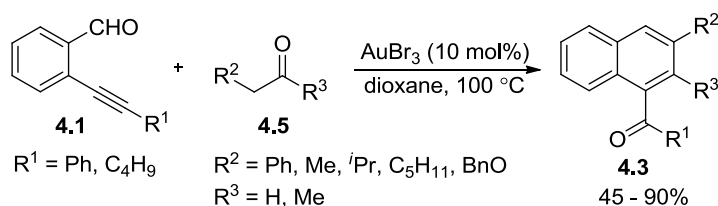
the benzoyl group is cleaved during the annulation process and results in naphthalene derivative **4.4** as the major product.



Scheme 4.2: $\text{Cu}(\text{OTf})_2$ -catalyzed [4+2] benzannulation reaction

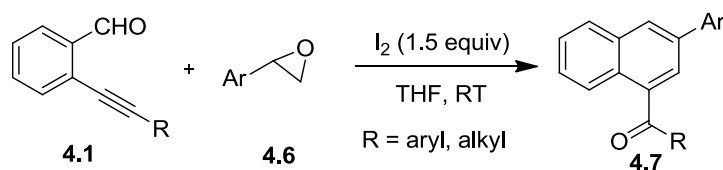
Formation of decarbonylated naphthalene derivatives as the sole product was achieved recently by Li and Nishiyama groups by using ZnCl_2 and $\text{ReBr}(\text{CO})_5$ catalysts respectively.^{7,8}

The Yamamoto group developed an unprecedented [4+2] benzannulation between the *o*-alkynylbenzaldehydes **4.1** and enolizable carbonyl compounds **4.5** for the construction of naphthalene derivatives **4.3** using AuBr_3 catalyst (Scheme 4.3).⁹ Recently, Srinivasan and co-workers reported a method for the selective synthesis of naphthyl ketones by using $\text{In}(\text{OTf})_3$ -catalyst *via* a similar [4+2] benzannulation.¹⁰ The reaction pathway of this annulation reaction is showed in the background Section 4.2 (Scheme 4.7).



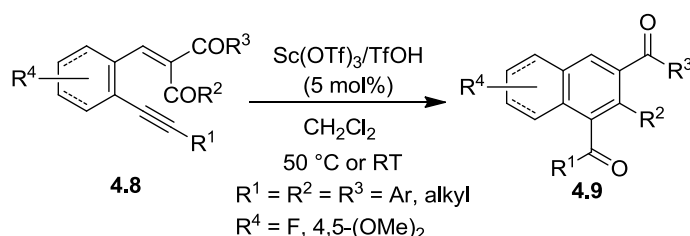
Scheme 4.3: [4+2] benzannulation between *o*-alkynylbenzaldehydes and carbonyl compounds

The [4+2] benzannulation reaction between *o*-alkynylbenzaldehydes **4.1** and styrene oxides **4.6** to form naphthalene derivatives **4.7** in the presence of molecular iodine was demonstrated by Patil and co-workers (Scheme 4.4).¹¹ In this protocol, styrene oxide **4.6** initially undergoes Meinwald rearrangement¹² to furnish arylacetaldehyde in the presence of iodine. Then, enol form of arylacetaldehyde would undergo [4+2] benzannulation with pyrylium intermediate formed from *o*-alkynylbenzaldehyde **4.1** in the presence of iodine, to give naphthyl ketone derivative **4.7**.



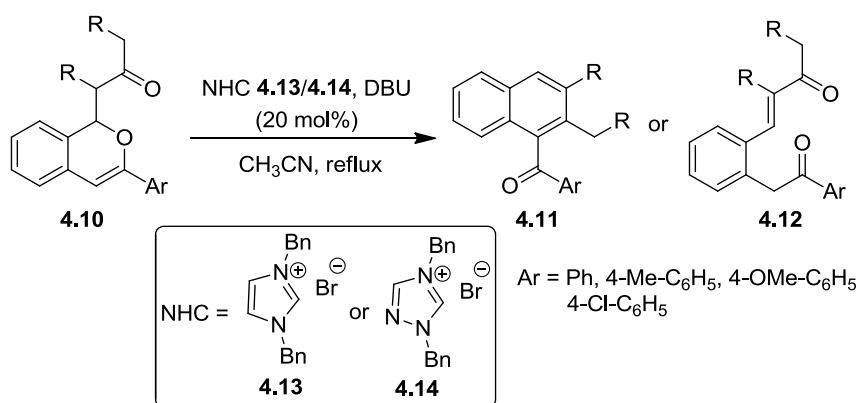
Scheme 4.4: [4+2] benzannulation between *o*-alkynylbenzaldehydes and styrene oxides

Zhang and co-workers described a method for the synthesis of polysubstituted naphthalene derivatives **4.9** from chalcones **4.8** in the presence of $\text{Sc}(\text{OTf})_3$ /triflic acid catalyst system (Scheme 4.5).¹³ It should be noted that, when R^2 is phenyl group, the reaction results in benzo[*a*]fluorenols as the major product under TfOH acid catalysis conditions. The chalcones have been prepared from *o*-alkynylaldehydes and 1,3 dicarbonyls for this protocol.



Scheme 4.5: Synthesis of naphthalenes from 2-(2-alkynylarylidenes)-1,3-dicarbonyl compounds

Cheng and co-workers described the conversion of isochromene derivatives **4.10** into naphthalene derivatives **4.11** and β -(2-(aroylmethylene)phenyl)- α,β -unsaturated ketone derivatives **4.12** in the presence of 20 mol% NHC catalyst in acetonitrile solvent under reflux conditions (Scheme 4.6).¹⁴ The nature of the product depends on the choice of NHC catalyst. The naphthalene derivative **4.11** was obtained when imidazole carbene **4.13** was used as the catalyst. Whereas the triazole carbene catalyst **4.14** favored the formation of α,β -unsaturated ketone derivative **4.12**. Here, the starting isochromene derivatives **4.10** have been prepared from corresponding *o*-alkynylbenzaldehydes and aliphatic cyclic and acyclic ketones under palladium catalysis.

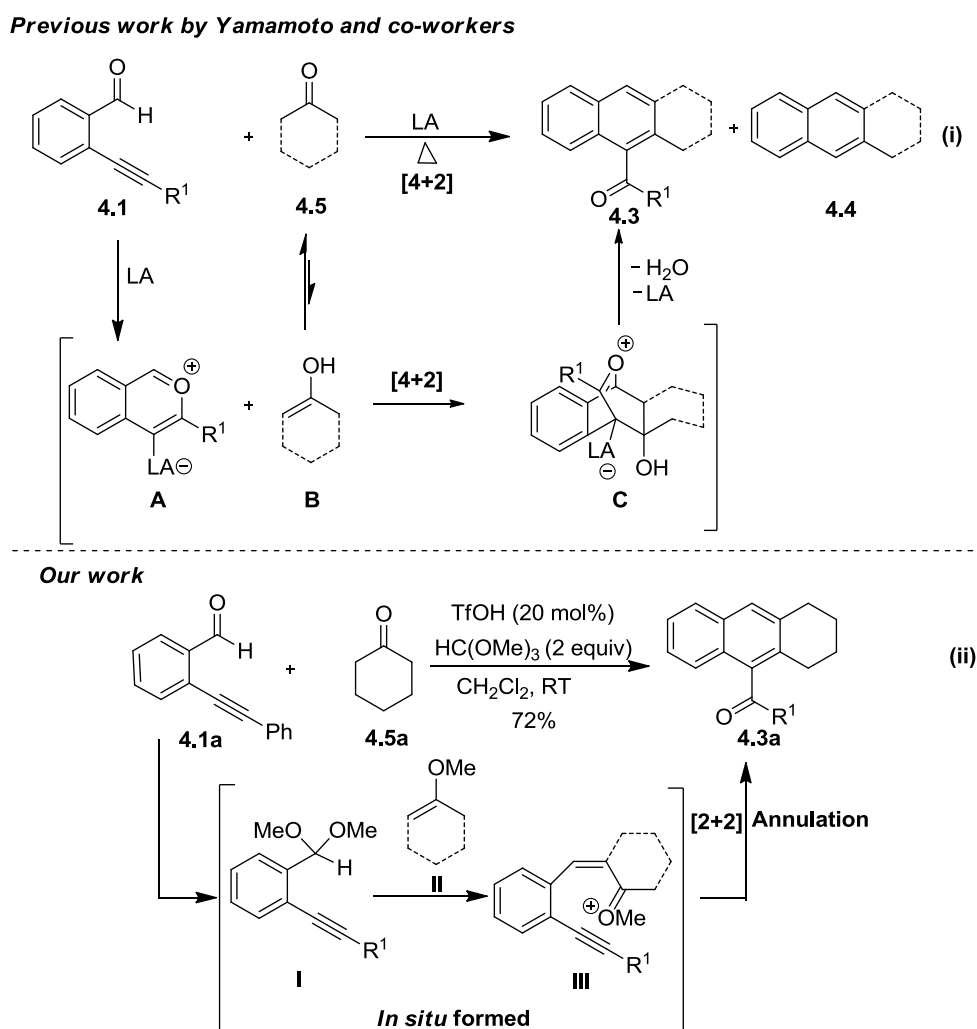


Scheme 4.6: Reaction of isochromene derivatives with NHC catalysts

4.2 Background

In the Yamamoto's work⁹ of synthesis of naphthalene derivatives from *o*-alkynylbenzaldehydes **4.1** and carbonyl compounds **4.5**, hetero-Diels-Alder reaction between the pyrylium intermediate **A** and carbonyl compound **4.5** is the key step. The carbonyl compound **4.5** should be in its enol form **B** to undergo inverse electron demand-type Diels-Alder reaction with the pyrylium intermediate **A** to give naphthalene (Scheme 4.7, eqn i). Since the yield of **4.3** was

dramatically decreased in the presence of 3 Å MS, trace amount of water might play an important role for setting up the keto-enol tautomerization between **4.5** and **B**. In continuation of using enol ether generated from alkyl ketones *via in situ* formed acetal,¹⁵ we have found that the reaction of *o*-alkynylbenzaldehyde **4.1a** and cyclohexanone **4.5a** in the presence of trimethyl orthoformate and catalytic TfOH to result naphthyl ketone **4.3a** in 72% yield at RT (Scheme 4.7, eqn ii). This transformation is expected to take place *via* Claisen-Schmidt condensation between *in situ* formed acetal **I** and enol ether **II** derived from cyclohexanone to give intermediate **III** followed by heteroalkyne metathesis/annulation to furnish naphthyl ketone derivatives **4.3a** in one pot. This transformation is inefficient (i.e. *o*-alkynylbenzaldehyde **4.1a** is decomposed) without trimethyl orthoformate. Thus, the *in situ* formed acetal assists the Claisen-Schmidt condensation by increasing the electrophilicity of carbonyl carbon of *o*-alkynylaldehyde through oxonium ion formation and enhances the nucleophilicity of α -carbon of ketone *via* the formation of enol ether.



Scheme 4.7: Reaction of *o*-alkynylbenzaldehydes with enolizable ketones under Lewis/Brønsted acid conditions

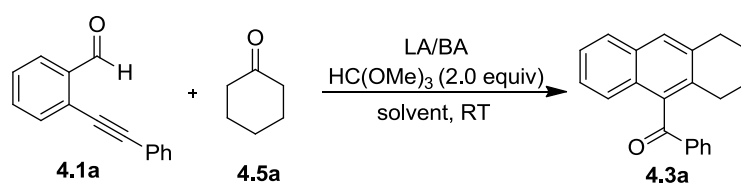
Unlike the methodology developed by Yamamoto⁹ and others our reaction does not require heating and expensive transition metal catalysts. This encouraged us to generalize this method for the synthesis of naphthyl ketone derivatives from *o*-alkynylaldehydes and enolizable ketones under mild reaction conditions.

4.3 Results and discussion

4.3.1 Optimization of reaction conditions for reactions with cyclic ketones

Reaction of 2-(phenylethynyl)benzaldehyde **4.1a** with cyclohexanone **4.5a** was optimized and Table 4.1 summarizes the reaction of this optimization study. Based on our previous experience on the synthesis of benzo[*a*]fluorene derivatives, we investigated the reaction between 2-(phenylethynyl)benzaldehyde **4.1a** and cyclohexanone **4.5a** in the presence of trimethyl orthoformate (2.0 equiv) and TfOH (20 mol%) in dichloromethane solvent at room temperature.

Table 4.1 Results of optimization study with cyclic ketone



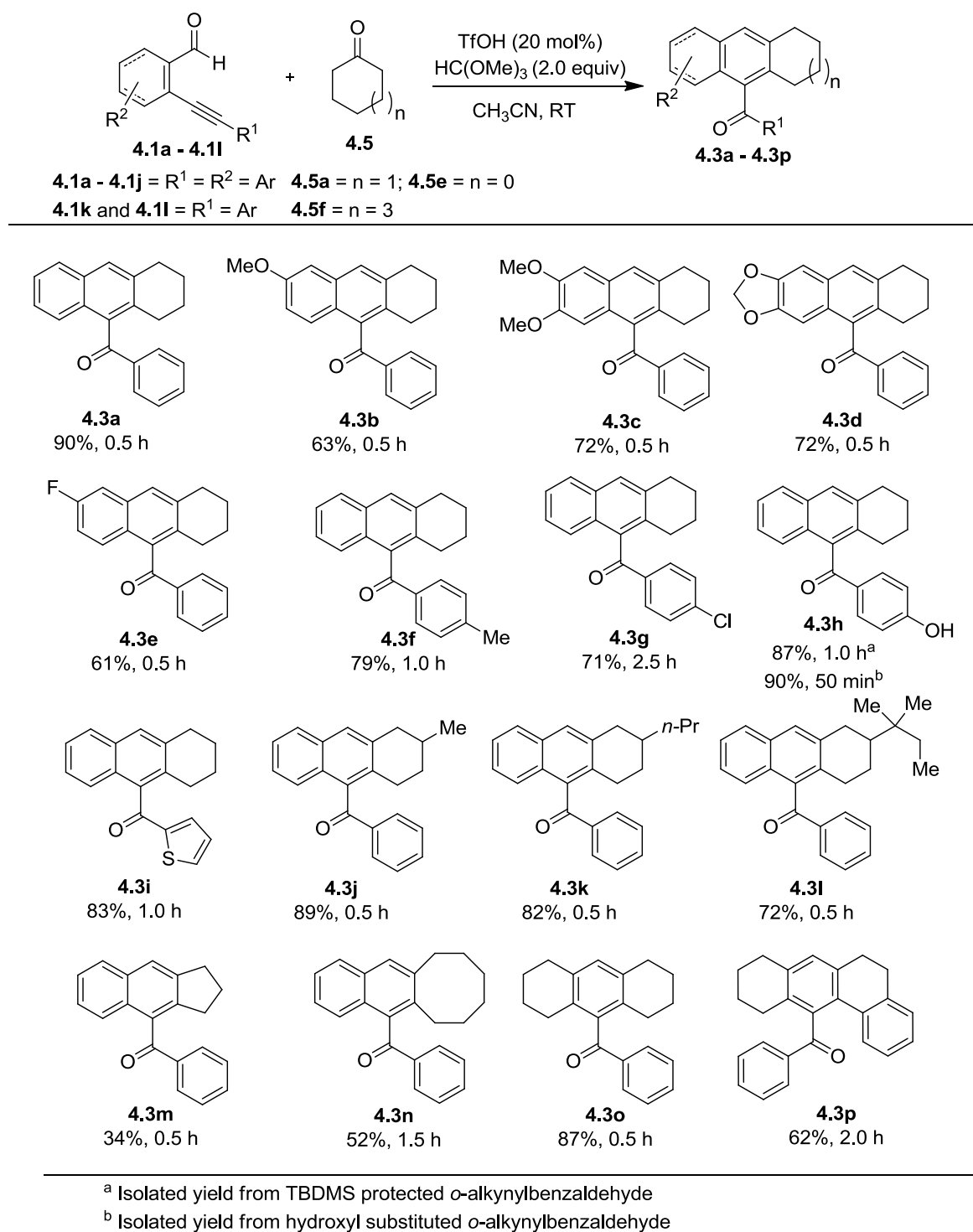
Entry	Solvent	Catalyst	Catalyst amount (mol%)	Time (h)	Yield (%) ^a
1	CH ₂ Cl ₂	TfOH	20	0.5	72
2	CH ₃ CN	TfOH	20	0.5	90
3	CH ₃ CN ^b	TfOH	20	24.0	-
4	CH ₃ CN	TfOH	10	1.0	64
5	CH ₃ CN	HSbF ₆ ·6H ₂ O	20	24.0	NR
6	CH ₃ CN	<i>p</i> -TSA	20	24.0	NR
7	CH ₃ CN	TFA	20	24.0	NR
8	CH ₃ CN	Cu(OTf) ₂	5	6.0	-
9	CH ₃ CN	AuBr ₃	5	5.5	-

^a Isolated yield. ^b without trimethyl orthoformate. NR: no reaction.

The reaction completed in 30 min and the naphthalene product phenyl(1,2,3,4-tetrahydroanthracen-9-yl)methanone **4.3a** was isolated in 72% yield (Table 4.1, entry 1). The yield of **4.3a** increased to 90% when the reaction was conducted in acetonitrile solvent (Table 4.1, entry 2). In the absence of trimethyl orthoformate, the starting material **4.1a** started to degrade (Table 4.1, entry 3). We reduced the amount of TfOH-catalyst loading to 10 mol% and found that yield of **4.3a** reduced to 64% (Table 4.1, entry 4). Then, the reaction was tried with other Brønsted and Lewis acid catalysts using acetonitrile as solvent. However, there was no reaction with TFA, *p*-TSA and $\text{HSbF}_6 \cdot 6\text{H}_2\text{O}$ even after 24 h at room temperature (Table 4.1, entries 5-7). With Lewis acid catalysts such as $\text{Cu}(\text{OTf})_2$ and AuBr_3 , the reactions were not efficient as they resulted in complex reaction mixtures (Table 4.1, entries 8 and 9). Hence the optimized condition is 20 mol% TfOH, 2.0 equiv trimethyl orthoformate and acetonitrile as a solvent at room temperature.

4.3.2 Scope of naphthalene formation with cyclic ketones

Using the optimized conditions, the scope of the reaction was examined with cyclic ketones and the results are presented in Figure 4.1. Saturated ring-fused naphthyl ketone derivatives with various substituents such as methyl, methoxy, acetal, fluoro, chloro and hydroxy were prepared from cyclic ketones in moderate to good yields. TBDMS group did not tolerate the reaction conditions and the corresponding deprotected naphthalene derivative **4.3h** was obtained in good yield. The same product was obtained with slightly improved yield from the corresponding hydroxyl substituted *o*-alkynylbenzaldehyde **4.1h**. To our delight, thiophene tolerated the reaction conditions and the corresponding naphthyl ketone **4.3i** was obtained in 83% yield. Various alkyl substituted cyclohexanones (**4.5b-4.5d**) were examined and the corresponding naphthyl ketone derivatives (**4.3j-4.3l**) were obtained in good yields. With cyclopentanone **4.5e** and cyclooctanone **4.5f**, the corresponding naphthyl ketones (**4.3m** and **4.3n**) were obtained in 34% and 52% yields respectively. Since, larger I-strain associated with enol ether of cyclopentanone (five membered ring) on going from sp^2 to sp^3 hybridization¹⁶ the reaction of **4.1a** with cyclopentanone might have resulted in lower yield of naphthalene derivative **4.3m**. Gratifyingly, the present transformation could be employed on cyclohexene alkynylaldehyde **4.1k** to synthesize product **4.3o** in 87% yield. In addition, alkynylaldehyde **4.1l** prepared from α -tetralone could be used to synthesize polycyclic product **4.3p** in 62% yield. Unfortunately, the present transformation is not suitable when R^1 is alkyl substituent.

Figure 4.1: Scope of naphthalene formation with cyclic ketones

4.3.3 Optimization of reaction conditions for reactions with acyclic ketones

The optimized reaction conditions of the reactions of cyclic ketones were not suitable for acyclic ketone, 3-pentanone **4.5g**, since it resulted in a complex product mixture (Table 4.2, entry 1). Hence, we turned our attention to find out the suitable reaction conditions for the reactions of acyclic ketones and results are shown in Table 4.2. To begin with, TfOH loading was increased to

1.0 equiv to isolate 52% of naphthalene product **4.3q** along with condensation product **4.15** in 28% after 24.0 h (Table 4.2, entry 2). To our delight, the yield of **4.3q** dramatically increased to 82% when the reaction was carried out using 3.0 equiv of trimethyl orthoformate and 1.0 equiv of TfOH for 30 min (Table 4.2, entry 3). In a control reaction, the reaction of **4.1a** and **4.5g** was conducted with 1.0 equiv of TfOH and 2.0 equiv of trimethyl orthoformate in acetonitrile solvent at rt. The reaction resulted in two spots in TLC, one corresponded to the naphthalene product **4.3q** and other spot corresponded to the chalcone **4.15**. This reaction did not complete even after 24.0 h. Then, 1.0 equiv of trimethyl orthoformate was added and found that the polar spot i.e. chalcone **4.15** was completely consumed in 15 min to result in single spot corresponding to the product in TLC. Upon purification 78% of naphthalene derivative **4.3q** was isolated (Scheme 4.8). Thus, the *in situ* formed acetal assists *trans* to *cis* isomerization of chalcone **4.15** to favor the heteroalkyne metathesis/annulation in furnishing the naphthalene derivative. Hence, *in situ* formed acetal not only helps Claisen-Schmidt condensation to occur but also assists the *trans* to *cis* isomerization of chalcone to undergo heteroalkyne metathesis/annulation for the construction of naphthalene derivatives.

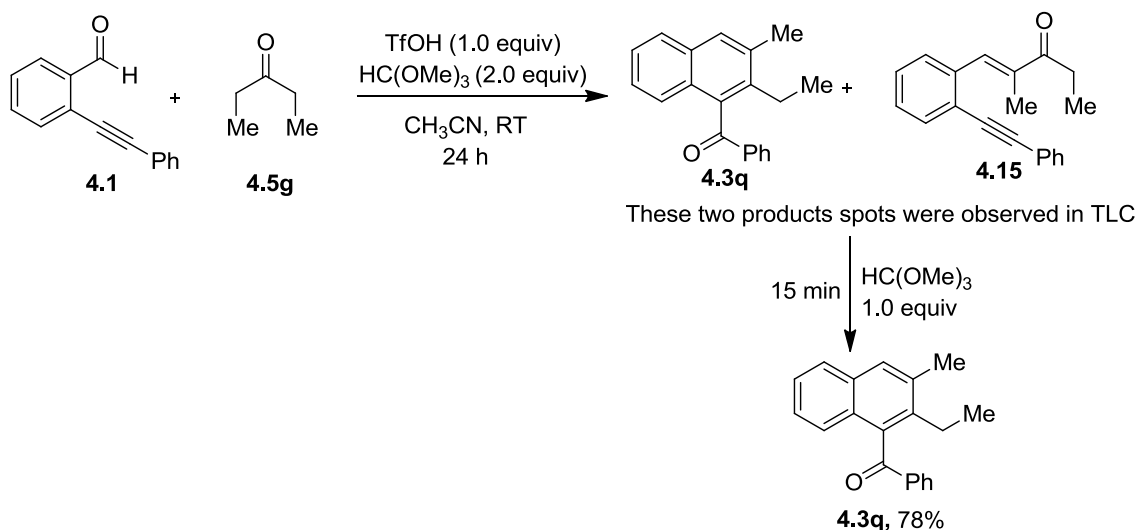
Table 4.2 Results of optimization study with acyclic ketone

Entry	Solvent	Catalyst	Cat. (equiv)	Time (h)	Yield (%) ^a		
					4.3q	4.15	4.16
1	CH ₃ CN	TfOH	0.2	24.0	-	-	-
2	CH ₃ CN	TfOH	1.0	24.0	52	28	-
3	CH₃CN	TfOH^b	1.0	0.5	82	-	-
4	CH ₃ CN	Cu(OTf) ₂	0.05	3.0	-	-	98
5	CH ₃ CN	In(OTf) ₃	0.05	5.0	-	-	80
6	CH ₃ CN	AuCl ₃ /AgSbF ₆	0.05	24.0	61	-	-

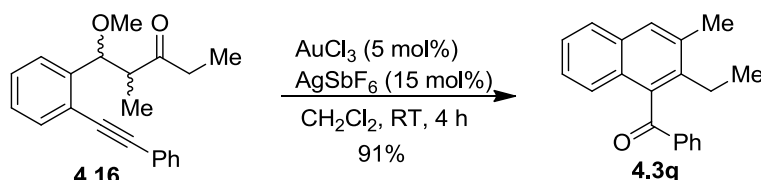
^a Isolated yield. ^b 3.0 equiv of trimethyl orthoformate was used.

Lewis acid catalysts such as Cu(OTf)₂ and In(OTf)₃ promoted the aldol reaction and furnished the product **4.16** in 98% and 80% yields respectively (Table 4.2, entry 4 and 5). Using gold-catalyzed heteroalkyne metathesis¹⁷ the product **4.16** could be converted into naphthalene **4.3q** in excellent yield (Scheme 4.9). However, the same catalysts system was less efficient for the direct synthesis of naphthalene derivative **4.3q** from **4.1a** and **4.5g**, as it resulted in less yield of **4.3q** (Table 4.2,

entry 6). In this experiment, aldehyde **4.1a** and ketone **4.5g** underwent Claisen-Schmidt reaction to afford product **4.15** which then gave the naphthalene product **4.3q** by heteroalkyne metathesis/annulation. This was inferred from the TLC while monitoring the reaction. This result suggests that the formation naphthalene skeleton does not take place *via* [4+2] benzannulation pathway in the presence of trimethyl orthoformate. Thus, the *in situ* formed acetal takes a different path for the construction of naphthalene from *o*-alkynylbenzaldehydes and enolizable ketones.



Scheme 4.8: Control experiment



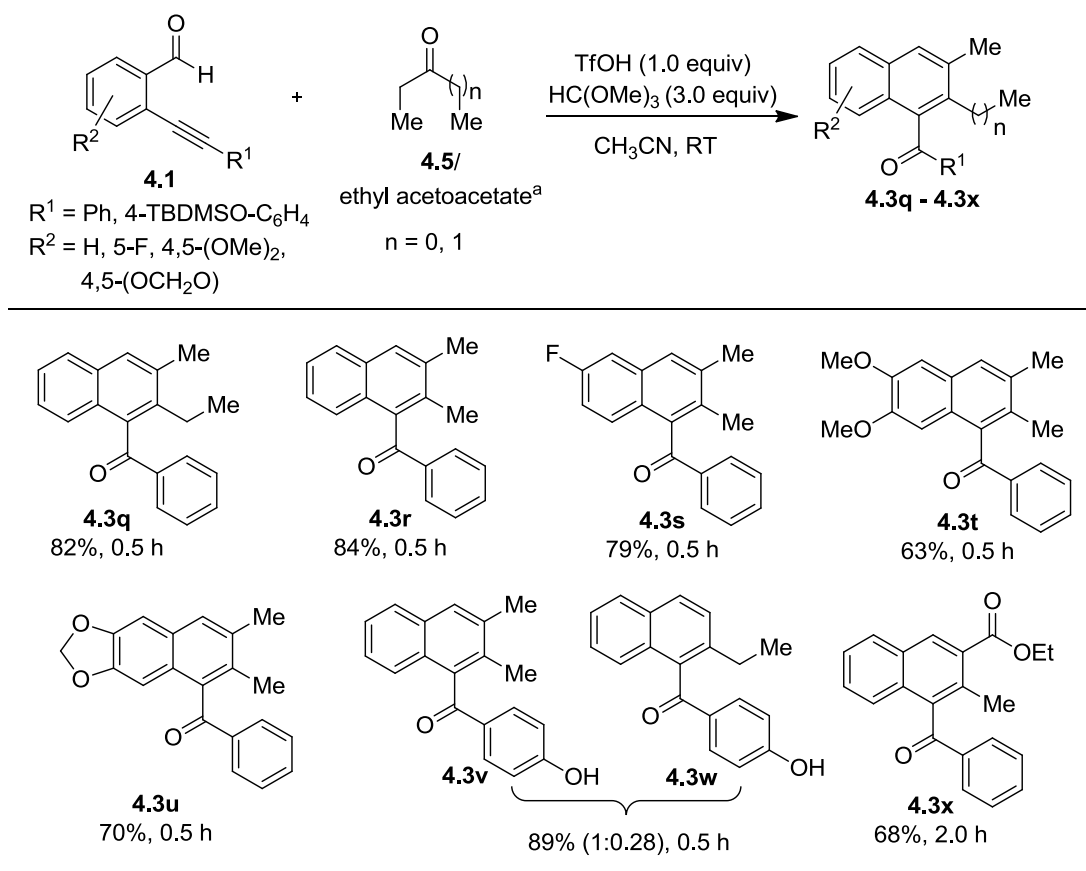
Scheme 4.9: Gold-catalyzed heteroalkyne metathesis

4.3.4 Substrate scope with acyclic ketones

Using stoichiometric amount of TfOH and excess of trimethyl orthoformate, the substrate scope was studied with acyclic ketones. While employing acyclic ketone 2-butanone **4.5h**, only one regioisomeric naphthalene derivatives (**4.3r-4.3u**) were formed with different *o*-alkynylbenzaldehydes. However, two naphthyl ketone derivatives **4.3v** and **4.3w** were obtained in the ratio of 1:0.28 when TBDMS protected *o*-alkynylbenzaldehyde derivative was used. In this reaction, TBDMS group got deprotected and the corresponding hydroxyl substituted naphthyl ketones (**4.3v** and **4.3w**) were obtained in 87% yield as an inseparable mixture. Naphthyl ketone with ester substituent **4.3x** can be prepared from ethyl acetoacetate and **4.1a** in 68% yield. It is

noteworthy to mention that 20 mol% of TfOH is sufficient for synthesis of naphthalene derivative **4.3x**.

Figure 4.2: Scope of naphthalene formation with acyclic ketones

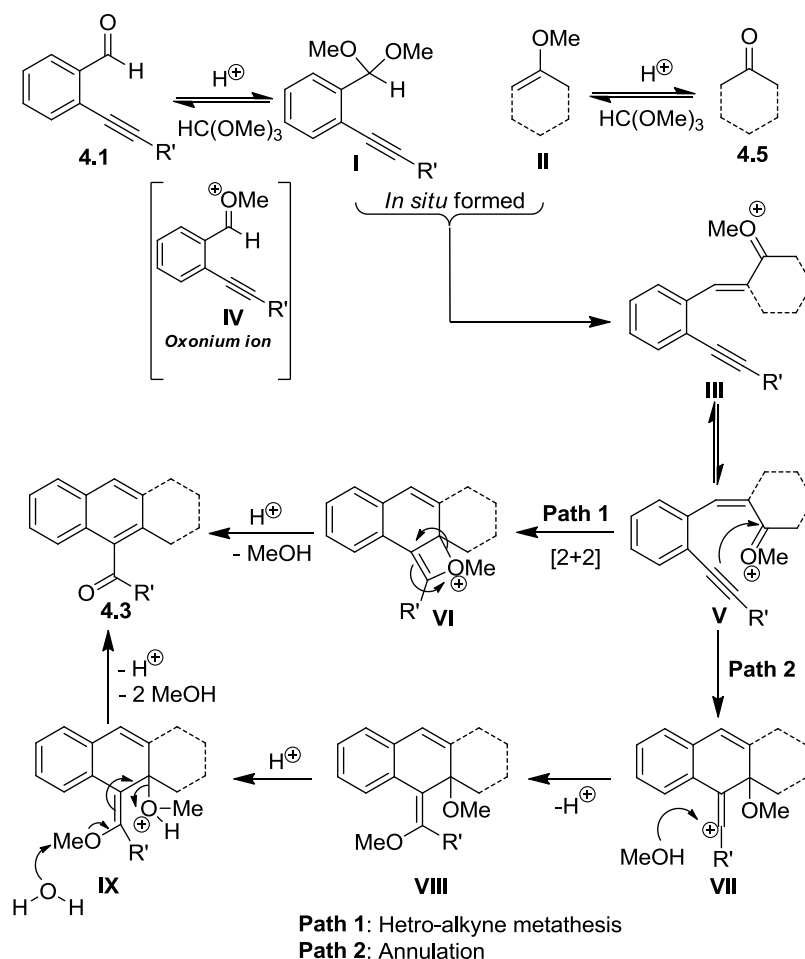


^a 20 mol% TfOH and 2.0 equiv of TMOF were used

4.3.5 Mechanism

Based on the observation made in the above study, a mechanism for the formation naphthyl ketone **4.3** is proposed in Scheme 4.10. Initially, Claisen-Schmidt condensation would take place between *in situ* formed acetal **I** from *o*-alkynylbenzaldehyde **4.1** and enol ether **II** derived from ketone¹⁵ **4.5** in the presence of trimethyl orthoformate and TfOH to afford chalcone type intermediate **III**. This reaction might be facilitated through the formation of highly reactive oxonium intermediate **IV**. The formed intermediate will be in equilibrium with its *cis* isomer. There are two possible pathways to construct the naphthalene core **4.3** from the intermediate **V**. As shown in path 1, naphthalene derivative **4.3** will be formed *via* intramolecular [2+2] cycloaddition and cyclcoreversion between alkyne and oxonium ion through oxetene intermediate **VI** in the presence TfOH. The pathway involving annulation could not be excluded (Path 2). This is initiated by the nucleophilic attack of alkyne on activated carbonyl group. The formed vinylic carbocation **VII** is trapped by methanol formed during the reaction to give intermediate **VIII**.

Subsequent elimination of methanol from **IX** assisted by acid would afford naphthalene derivative **4.3**.



Scheme 4.10: Plausible mechanism

4.4 Conclusions

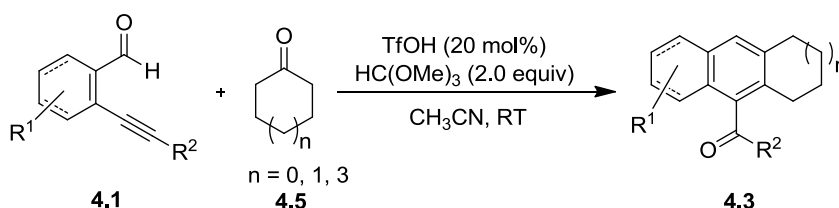
In conclusion, we have developed a domino reaction for the synthesis of naphthyl ketone derivatives from *o*-alkynylbenzaldehydes and ketones in the presence of trimethyl orthoformate and TfOH at room temperature. This cascade reaction involves Claisen-Schmidt condensation followed by heteroalkyne metathesis/annulation. *In situ* formed acetal assists the Claisen-Schmidt condensation by increasing the electrophilicity of carbonyl carbon of *o*-alkynylbenzaldehyde through oxonium ion formation and enhancing the nucleophilicity of α -carbon of ketone via the formation of enol ether. Moreover, the *in situ* formed acetal takes a path for the construction of naphthalene from *o*-alkynylbenzaldehydes and enolizable ketones which is quite different from the one that was reported under gold catalysis by Yamamoto and co-workers. In addition, *trans-cis* isomerization and heteroalkyne metathesis/annulation are facilitated by *in situ* generated acetal.

4.5 Experimental section

For general information see Chapter 2, Section 2.5.1. All the *o*-alkynylaldehydes used in this study were prepared by following the standard Sonogashira coupling reaction of corresponding bromo or iodo compounds and arylalkynes. All the *o*-alkynylaldehydes are reported in the literatures and the data of prepared *o*-alkynylaldehydes matches with those literatures.^{5, 6, 10 and 13}

4.5.1 Experimental procedures, spectral and analytical data

General procedure for the synthesis of naphthalenes 4.3:

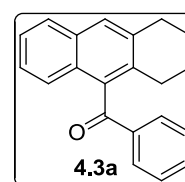


Triflic acid (20 mol%) was charged into a solution of compound **4.1** (1.0 equiv), compound **4.5** (1.2 equiv) and trimethyl orthoformate (2.0 equiv) in acetonitrile solvent (5 mL/1 mmol) at room temperature. The resulting mixture was stirred at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. After the completion of the reaction, solvent was evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **4.3**.

For acyclic ketones, 1.0 equiv of TfOH and 3.0 equiv of trimethyl orthoformate were used.

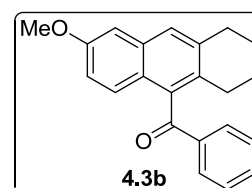
Phenyl(1,2,3,4-tetrahydroanthracen-9-yl)methanone **4.3a**:¹⁴

It was obtained as colourless solid in 90% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45-7.37 (m, 3H), 7.30-7.27 (m, 2H), 3.04 (t, *J* = 6.4 Hz, 4H), 2.82 (br s, 1H), 2.58 (br s, 1H), 2.05-1.82 (m, 1H), 1.79 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 137.4, 135.8, 133.7, 132.7, 131.7, 129.7, 129.2, 128.8, 128.0, 127.4, 125.7, 125.3, 124.6, 30.1, 27.7, 22.9, 22.8.



(3-Methoxy-5,6,7,8-tetrahydroanthracen-9-yl)(phenyl)methanone **4.3b**:

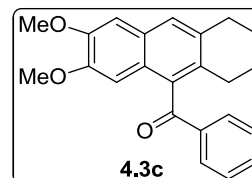
It was obtained as yellow solid in 63% yield. mp 111-113 °C; *R_f* = 0.45 (in 20% EtOAc/Hexanes); IR (KBr): 2936, 1660, 1588, 1454, 1216, 884, 712 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.59-7.57 (m, 1H), 7.55 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.88 (s, 3H), 2.99 (t, *J* = 6.0 Hz, 2H),



2.77 (br s, 1H), 2.53 (br s, 1H), 1.84-1.76 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.9, 157.1, 137.4, 136.3, 135.7, 133.7, 132.9, 130.2, 129.7, 128.8, 127.0, 126.1, 124.7, 118.5, 105.2, 55.2, 30.2, 27.0, 23.0, 22.8. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{20}\text{O}_2$ $[\text{M}+\text{H}]^+$ 317.1542; found 317.1542.

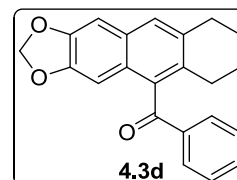
(6,7-Dimethoxy-1,2,3,4-tetrahydroanthracen-9-yl)(phenyl)methanone 4.3c:¹⁰

It was obtained as pale yellow solid in 72% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.82 (d, $J = 7.6$ Hz, 2H), 7.57 (t, $J = 7.6$ Hz, 1H), 7.50 (s, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.05 (s, 1H), 6.65 (s, 1H), 3.97 (s, 3H), 3.70 (s, 3H), 2.97 (t, $J = 6.4$ Hz, 2H), 2.63 (br s, 2H), 1.84-1.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 201.1, 149.2, 149.1, 137.4, 134.4, 133.8, 133.6, 130.8, 129.6, 128.8, 127.7, 126.7, 124.6, 105.7, 103.3, 55.7, 55.6, 29.9, 27.2, 23.0, 22.9.



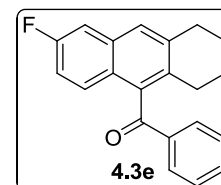
Phenyl(6,7,8,9-tetrahydroanthra[2,3-*d*][1,3]dioxol-5-yl)methanone 4.3d:¹⁰

It was obtained as colourless solid in 72% yield. ^1H NMR (400 MHz, CDCl_3): δ 7.81 (d, $J = 7.6$ Hz, 2H), 7.57 (t, $J = 7.6$ Hz, 1H), 7.45-7.40 (m, 3H), 7.03 (s, 1H), 6.68 (s, 1H), 5.93 (s, 2H), 2.93 (t, $J = 6.0$ Hz, 2H), 2.73-2.49 (m, 2H), 1.82-1.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.8, 147.4, 147.1, 137.2, 135.2, 134.0, 133.8, 130.8, 129.6, 128.8, 127.3, 125.7, 103.2, 100.9, 29.8, 27.1, 23.0, 22.8.



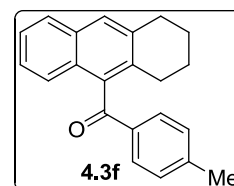
(3-Fluoro-5,6,7,8-tetrahydroanthracen-9-yl)(phenyl)methanone 4.3e:

It was obtained as yellow solid in 61% yield. mp 79-81 °C; $R_f = 0.5$ (in 10% EtOAc/Hexanes); IR (KBr): 2931, 1632, 1594, 1501, 1221, 1139, 887, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.80 (d, $J = 7.6$ Hz, 2H), 7.60 (7.56 (m, 2H), 7.45-7.35 (m, 4H), 7.05 (td, $J = 2.4, 8.4$ Hz, 1H), 3.00 (t, $J = 6.0$ Hz, 2H), 2.78 (br s, 1H), 2.55 (br s, 1H), 1.84-1.77 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.4, 160.2 (d, $J = 245.0$ Hz), 137.2 (d, $J = 9.0$ Hz), 135.9, 133.9, 132.5 (d, $J = 9.0$ Hz), 132.0, 129.6, 129.0, 127.4 (d, $J = 6.0$ Hz), 127.0 (d, $J = 9.0$ Hz), 126.2, 116.1 (d, $J = 25.0$ Hz), 110.3 (d, $J = 20.0$ Hz), 30.1, 27.1, 22.8, 22.6. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{17}\text{FO}$ $[\text{M}+\text{H}]^+$ 305.1342; found 305.1340.



(1,2,3,4-Tetrahydroanthracen-9-yl)(*p*-tolyl)methanone 4.3f:

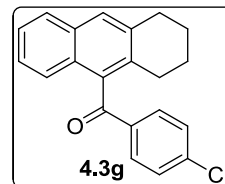
It was obtained as yellow solid in 79% yield. mp 148-150 °C; $R_f = 0.45$ (in 20% EtOAc/Hexanes); Yield = 83.0%. IR (KBr): 2920, 1660, 1610, 1227, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.75 (d, $J = 8.0$ Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 2H), 7.64 (s, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 7.2$



Hz, 1H), 7.25-7.20 (m, 2H), 3.01 (t, $J = 6.4$ Hz, 2H), 2.82 (br s, 1H), 2.55 (br s, 1H), 2.39 (s, 3H), 1.85-1.78 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.4, 144.8, 136.0, 135.8, 135.0, 132.6, 131.7, 129.8, 129.5, 129.1, 127.8, 127.3, 125.6, 125.3, 124.6, 30.1, 27.2, 22.9, 22.8, 21.8. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{20}\text{O}$ $[M+H]^+$ 301.1592; found 301.1592.

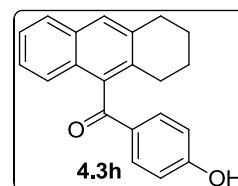
(4-Chlorophenyl)(1,2,3,4-tetrahydroanthracen-9-yl)methanone 4.3g:

It was obtained as yellow solid in 71% yield. mp 139-141 °C; $R_f = 0.45$ (in 20% EtOAc/Hexanes); Yield = 83.0%. IR (KBr): 2926, 1665, 1594, 1446, 1221, 756, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.77-7.74 (m, 3H), 7.66 (s, 1H), 7.40-7.35 (m, 4H), 7.28 (d, $J = 6.8$ Hz, 1H), 3.01 (t, $J = 6.0$ Hz, 2H), 2.80 (br s, 1H), 2.53 (br s, 1H), 1.85-1.77 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.6, 140.3, 135.81, 135.76, 135.1, 132.8, 131.7, 131.0, 129.2, 129.0, 128.2, 127.4, 125.8, 125.4, 124.4, 30.1, 27.3, 22.8, 22.7. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{17}\text{ClO}$ $[M+H]^+$ 321.1046; found 321.1046.



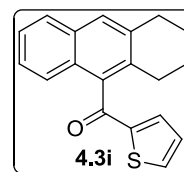
(4-Hydroxyphenyl)(1,2,3,4-tetrahydroanthracen-9-yl)methanone 4.3h:

It was obtained as colourless solid in 87% yield. mp 221-223 °C; $R_f = 0.45$ (in 75% EtOAc/Hexanes); IR (KBr): 2936, 1626, 1561, 1511, 1385, 1292, 1248, 1166, 815, 744 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 6.0$ Hz, 2H), 7.61 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.37-7.33 (m, 1H), 7.27-7.23 (m, 1H), 6.76 (d, $J = 8.8$ Hz, 2H), 6.61 (br s, 1H), 2.99-2.97 (m, 2H), 2.83-2.79 (m, 1H), 2.55-2.51 (m, 1H), 1.83-1.71 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.3, 161.4, 135.8, 135.7, 132.6, 131.7, 130.2, 129.1, 127.9, 127.3, 125.6, 125.3, 124.6, 115.7, 30.1, 27.2, 22.85, 22.78. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{18}\text{O}_2$ $[M+H]^+$ 303.1385; found 303.1386.



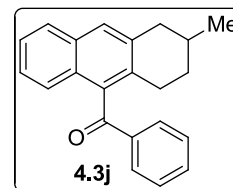
(1,2,3,4-Tetrahydroanthracen-9-yl)(thiophen-2-yl)methanone 4.3i:

It was obtained as yellow solid in 83% yield. mp 124-126 °C; $R_f = 0.45$ (in 20% EtOAc/Hexanes); Yield = 83.0%. IR (KBr): 2920, 1643, 1501, 1408, 1353, 1243, 1227, 1073, 761, 717 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J = 8.0$ Hz, 1H), 7.70 (dd, $J = 0.8, 4.8$ Hz, 1H), 7.63 (s, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 7.2$ Hz, 1H), 7.29 (t, $J = 7.2$ Hz, 1H), 7.24-7.23 (m, 1H), 7.02-7.00 (m, 1H), 3.00 (t, $J = 6.0$ Hz, 2H), 2.94-2.88 (m, 1H), 2.72-2.66 (m, 1H), 1.84-1.75 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 192.7, 145.2, 135.8, 135.6, 135.4, 135.2, 132.8, 131.6, 129.6, 128.4, 128.2, 127.2, 125.7, 125.5, 124.5, 30.0, 27.1, 22.8, 22.7. HRMS (ESI): calcd for $\text{C}_{19}\text{H}_{16}\text{OS}$ $[M+Na]^+$ 315.0820 found 315.0822.

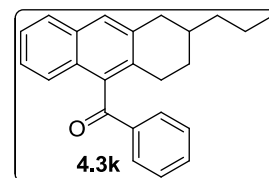


(3-Methyl-1,2,3,4-tetrahydroanthracen-9-yl)(phenyl)methanone 4.3j:

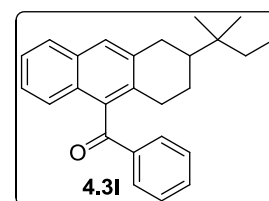
It was obtained as light yellow solid in 89% yield. mp 130-132 °C; R_f = 0.6 (in 10% EtOAc/Hexanes); IR (KBr): 2947, 2914, 1660, 1588, 1501, 1441, 1227, 750, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.81 (d, J = 4.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.43-7.35 (m, 4H), 7.27 (d, J = 7.6 Hz, 1H), 3.08 (dd, J = 8.0, 16.0 Hz, 1H), 2.87 (br s, 1H), 2.64 (d, J = 10.8 Hz, 1H), 2.60 (d, J = 10.8 Hz, 1H), 1.92-1.83 (m, 2H), 1.37 (br s, 1H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.8, 137.3, 135.6, 133.8, 131.7, 129.6, 129.1, 128.8, 128.0, 127.4, 125.7, 125.3, 124.6, 38.8, 31.1, 28.9, 27.0, 21.9. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{20}\text{O}$ $[M+H]^+$ 301.1592; found 301.1592.

**Phenyl(3-propyl-1,2,3,4-tetrahydroanthracen-9-yl)methanone 4.3k:**

It was obtained as pale yellow liquid in 82% yield. R_f = 0.6 (in 10% EtOAc/Hexanes); IR (neat): 2953, 2920, 1665, 1451, 1221, 748, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.81 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 3H), 7.34 (d, J = 7.2 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 3.10 (dd, J = 4.4, 16.0 Hz, 1H), 2.81 (br s, 1H), 2.62 (dd, J = 10.4, 16.0 Hz, 1H), 1.89-1.75 (m, 2H), 1.42-1.33 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.7, 137.4, 135.7, 133.7, 131.7, 129.6, 129.1, 128.8, 128.0, 127.3, 125.6, 125.3, 124.6, 38.6, 36.9, 33.5, 29.2, 27.0, 19.9, 14.3. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{24}\text{O}$ $[M+H]^+$ 329.1905; found 329.1907.

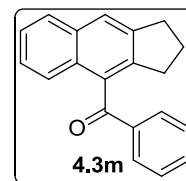
**(3-(tert-Pentyl)-1,2,3,4-tetrahydroanthracen-9-yl)(phenyl)methanone 4.3l:**

It was obtained as light brown liquid in 72% yield. R_f = 0.6 (in 10% EtOAc/Hexanes); IR (neat): 2953, 2920, 1665, 1451, 1221, 748, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.81 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 3H), 7.36 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 3.03 (dd, J = 2.4, 16.0 Hz, 1H), 2.77 (t, J = 12.8 Hz, 2H), 1.86 (d, J = 10.8 Hz, 1H), 1.65-1.59 (m, 1H), 1.42-1.31 (m, 4H), 0.88 (d, J = 6.0 Hz, 6H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 200.7, 137.5, 136.6, 133.7, 131.7, 129.6, 129.1, 128.8, 128.2, 127.3, 125.6, 125.3, 124.6, 41.8, 34.9, 32.4, 31.3, 28.3, 24.0, 23.85, 23.79, 8.1. HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{28}\text{O}$ $[M+H]^+$ 357.2218; found 357.2218.

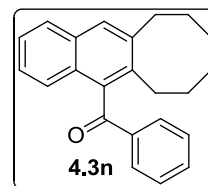


(2,3-Dihydro-1H-cyclopenta[b]naphthalen-4-yl)(phenyl)methanone 4.3m:¹⁴

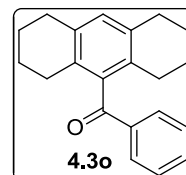
It was obtained as pale yellow liquid in 34% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.84 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.56-7.40 (m, 4H), 7.31 (d, J = 7.6 Hz, 1H), 3.10 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.10 (quint, J = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 200.1, 143.2, 141.3, 137.7, 133.8, 133.2, 132.3, 130.1, 130.0, 128.8, 128.0, 125.8, 125.4, 125.3, 124.1, 32.5, 31.8, 26.1.

**(6,7,8,9,10,11-Hexahydrocycloocta[b]naphthalen-5-yl)(phenyl)methanone 4.3n:**

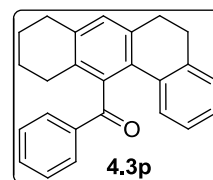
It was obtained as brown oil in 52% yield. R_f = 0.45 (in 20% EtOAc/Hexanes); IR (neat): 2926, 1665, 1594, 1446, 1293, 756, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.81-7.78 (m, 2H), 7.71 (s, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.42-7.36 (m, 4H), 7.27 (d, J = 8.0 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H), 2.88 (br s, 1H), 2.68 (br s, 1H), 1.87 (br s, 1H), 1.72 (br s, 1H), 1.59-1.42 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 200.6, 140.8, 137.9, 136.5, 136.0, 133.7, 132.2, 129.8, 129.6, 128.7, 128.4, 127.4, 126.6, 125.7, 125.4, 124.8, 32.9, 32.7, 31.2, 28.7, 26.3, 25.7. HRMS (ESI): calcd for C₂₃H₂₂O [M+H]⁺ 315.1749; found 315.1748.

**(1,2,3,4,5,6,7,8,8a,10a-Decahydroanthracen-9-yl)(phenyl)methanone 4.3o:**

It was obtained as light yellow solid in 87% yield. mp 104-106 °C; R_f = 0.65 (in 10% EtOAc/Hexanes); IR (KBr): 2925, 1660, 1572, 1452, 1325, 1287, 1161, 761, 706 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 6.88 (s, 1H), 2.75-2.73 (m, 4H), 2.55 (br s, 2H), 2.28 (br s, 2H), 1.74-1.66 (m, 8H); ¹³C NMR (100 MHz, CDCl₃): δ 201.5, 139.3, 137.0, 134.4, 133.5, 130.4, 130.3, 129.2, 128.8, 29.3, 26.4, 23.0, 22.9. HRMS (ESI): calcd for C₂₁H₂₂O [M+H]⁺ 291.1749; found 291.1753.

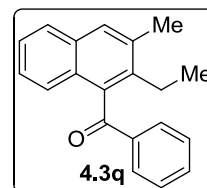
**(5,6,8,9,10,11-Hexahydrotetraphen-12-yl)(phenyl)methanone 4.3p:**

It was obtained as light brown solid in 62% yield. mp 140-142 °C; R_f = 0.45 (in 10% EtOAc/Hexanes); IR (KBr): 2931, 1665, 1572, 1452, 1276, 1210, 783, 750, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, J = 7.6 Hz, 2H), 7.44-7.40 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 7.12-7.10 (m, 2H), 7.00 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 2.85-2.74 (m, 6H), 2.30-2.23 (m, 1H), 1.77-1.74 (m, 3H), 1.67-1.61 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 201.8, 138.7, 137.5, 136.75, 136.66, 136.4, 133.6, 133.2, 132.9, 130.4, 129.4, 129.3, 128.4, 127.5, 127.0, 126.4, 29.9, 29.8, 29.7, 26.9, 23.1, 22.6. HRMS (ESI): calcd for C₂₅H₂₂O [M+H]⁺ 339.1749; found 339.1752.

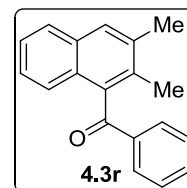


(2-Ethyl-3-methylnaphthalen-1-yl)(phenyl)methanone 4.3q:¹⁴

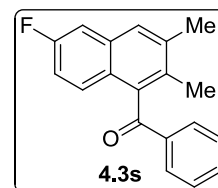
It was obtained as colourless liquid in 82% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.84 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.44-7.38 (m, 4H), 7.29 (d, J = 7.6 Hz, 1H), 2.72 (br s, 1H), 2.56 (s, 4H), 1.11 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 200.5, 137.9, 137.8, 136.0, 134.6, 133.7, 131.9, 129.8, 129.4, 128.7, 127.2, 125.7, 125.5, 124.8, 24.3, 19.6, 14.7.

**(2,3-Dimethylnaphthalen-1-yl)(phenyl)methanone 4.3r:**¹⁰

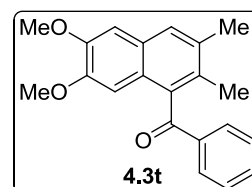
It was obtained as colourless liquid in 84% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.85 (d, J = 7.6 Hz, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.56-7.39 (m, 4H), 7.31 (d, J = 7.6 Hz, 1H), 2.49 (s, 3H), 2.24 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 137.6, 136.1, 135.3, 133.7, 131.9, 131.8, 129.7, 129.4, 128.8, 128.7, 127.3, 125.7, 125.4, 124.7, 20.4, 17.1.

**(6-Fluoro-2,3-dimethylnaphthalen-1-yl)(phenyl)methanone 4.3s:**

It was obtained as yellow solid in 79% yield. mp 47-49 °C; R_f = 0.45 (in 20% EtOAc/Hexanes); IR (KBr): 2958, 1671, 1627, 1600, 1506, 1457, 1221, 1139, 964, 887 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, J = 7.6 Hz, 2H), 7.66 (s, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 2H), 7.42-7.37 (m, 2H), 7.07 (td, J = 2.4, 8.8 Hz, 1H), 2.46 (s, 3H), 2.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 200.4, 160.3 (d, J = 244.0 Hz), 137.4, 136.7, 136.2, 133.9, 132.9 (d, J = 9.0 Hz), 131.1, 129.7, 128.9, 128.0 (d, J = 5.0 Hz), 127.1 (d, J = 9.0 Hz), 126.4, 116.0 (d, J = 25.0 Hz), 110.4 (d, J = 20.0 Hz), 20.5, 17.1. HRMS (ESI): calcd for C₁₉H₁₅FO [M+H]⁺ 279.1185; found 279.1186.

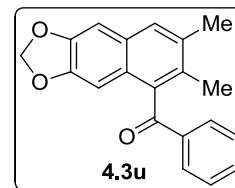
**(6,7-Dimethoxy-2,3-dimethylnaphthalen-1-yl)(phenyl)methanone 4.3t:**¹⁰

It was obtained as yellow solid in 63% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 8.0 Hz, 2H), 7.60-7.56 (m, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.26 (s, 1H), 6.68 (s, 1H), 3.98 (s, 3H), 3.71 (s, 3H), 2.42 (s, 3H), 2.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 201.1, 149.2, 149.0, 137.6, 134.8, 133.7, 133.4, 129.9, 129.7, 128.8, 127.8, 127.5, 124.7, 105.8, 103.6, 55.7, 55.6, 20.2, 17.1.

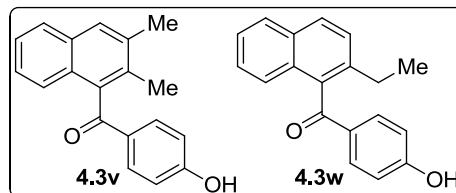


(6,7-Dimethylnaphtho[2,3-*d*][1,3]dioxol-5-yl)(phenyl)methanone 4.3u:¹⁰

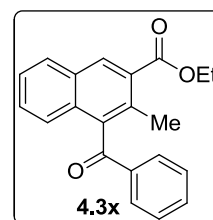
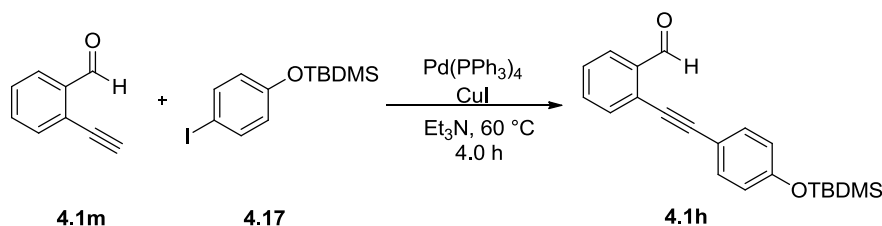
It was obtained as yellow solid in 70% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.06 (s, 1H), 6.71 (s, 1H), 5.94 (s, 2H), 2.40 (s, 3H), 2.15 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 147.5, 147.1, 137.4, 135.6, 133.8, 133.6, 130.0, 129.7, 129.0, 128.8, 128.0, 125.8, 103.4, 101.3, 101.0, 20.2, 16.9.

**(2,3-Dimethylnaphthalen-1-yl)(4-hydroxyphenyl)methanone 4.3v and (2-ethylnaphthalen-1-yl)(4-hydroxyphenyl)methanone 4.3w (1:0.28):**

It was obtained as pale yellow solid in 89% yield. mp 145-147 °C; *R*_f = 0.40 (in 75% EtOAc/Hexanes); IR (KBr): 2969, 1637, 1577, 1511, 1440, 1380, 1292, 1237, 1166, 843, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.83 (d, *J* = 8.4 Hz, 0.3H), 7.79 (d, *J* = 8.0 Hz, 0.3H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.64 (br s, 4H), 7.44 (d, *J* = 8.0 Hz, 0.3H), 7.40-7.73 (m, 2.8H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 2.6H), 2.57 (q, *J* = 7.6 Hz, 0.5H), 2.41 (s, 3H), 2.17 (s, 3H), 1.14 (t, *J* = 7.6 Hz, 0.9H); ¹³C NMR (100 MHz, CDCl₃): δ 200.7, 200.1, 161.8, 138.2, 136.0, 135.2, 132.7, 131.9, 131.7, 130.3, 130.1, 129.3, 129.2, 128.6, 128.0, 127.2, 126.8, 126.6, 125.7, 125.4, 125.0, 124.6, 115.8, 26.7, 20.4, 17.1, 15.5. HRMS (ESI): calcd for C₁₉H₁₆O₂ [M+H]⁺ 277.1229; found 277.1227.

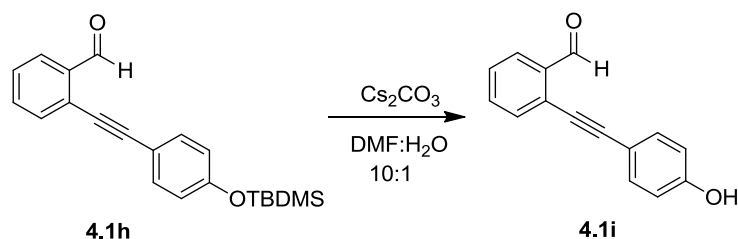
**Ethyl 4-benzoyl-3-methyl-2-naphthoate 4.3x:**¹⁰

It was obtained as colourless liquid in 68% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.52 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.49-7.42 (m, 5H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 199.9, 167.6, 137.8, 137.2, 134.1, 132.3, 131.8, 131.5, 130.8, 129.7, 129.1, 128.9, 128.8, 126.3, 124.8, 61.2, 18.5, 14.3.

**Preparation of 2-((4-((*tert*-butyldimethylsilyl)oxy)phenyl)ethynyl)benzaldehyde 4.1h:**

To a solution of 2-ethynylbenzaldehyde **4.1m** (0.5 g, 3.8 mmol) in triethylamine (15 mL), iodo compound **4.14** (1.54 g, 4.6 mmol), Pd(PPh₃)₄ (44.4 mg, 0.038 mmol) and CuI (7.6 mg, 0.076 mmol) were added under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 60 °C for 4 h. Then, the suspension was diluted with EtOAc, filtered and evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, hexanes/EtOAc) to give pure product **4.1h** as light yellow liquid. Yield 0.96 g (74%); *R_f* = 0.75 (in 20% EtOAc/Hexanes); Yield = 97%. IR (neat): 2958, 2925, 2865, 2207, 1692, 1593, 1506, 1270, 1160, 914, 843, 777 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.64 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.46-7.40 (m, 3H), 6.84 (d, *J* = 8.4 Hz, 2H), 0.99 (s, 9H), 0.22 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 191.8, 156.6, 135.6, 133.7, 133.2, 133.0, 128.2, 127.3, 127.1, 120.4, 115.0, 96.6, 83.8, 25.6, 18.2, -4.4. HRMS (ESI): calcd for C₂₁H₂₄O₂Si [*M*+H]⁺ 337.1624; found 337.1626.

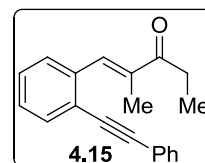
Preparation of 2-((4-hydroxyphenyl)ethynyl)benzaldehyde **4.1i**.



TBDMS group was removed by following the reported procedure,¹⁸ Cs₂CO₃ (145 mg, 0.45 mmol) was added into a solution of *t*-butyldimethylsilyl ether **4.1h** (300 mg, 0.89 mmol) in DMF-H₂O (10:1, 2:0.5 mL). The reaction mixture was allowed to stir at rt for 2.5 h. Then, it was diluted with ether, and then organic layer was separated and washed with brine solution and dried over anhydrous sodium sulfate. Then the organic layer was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/EtOAc) to afford the desired product **4.1i** as colorless solid. Yield 192 mg (97%); mp 172-174 °C; *R_f* = 0.45 (in 75% EtOAc/Hexanes); Yield = 87.0%. IR (KBr): 2854, 2207, 1681, 1588, 1511, 1440, 1270, 832, 804, 777, 678 cm⁻¹; ¹H NMR (400 MHz, Acetone-*d*₆ + CDCl₃): δ 10.62 (s, 1H), 8.76 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 2H), 7.46 (d, *J* = 8.4, 3H), 6.90 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (100 MHz, Acetone-*d*₆ + CDCl₃): δ 190.3, 157.5, 134.7, 133.0, 132.5, 132.1, 127.3, 126.4, 126.1, 114.9, 114.8, 112.3, 96.1, 82.3. HRMS (ESI): calcd for C₁₅H₁₀O₂ [*M*+H]⁺ 223.0759; found 223.0757.

(*E*)-2-Methyl-1-(2-(phenylethynyl)phenyl)pent-1-en-3-one **4.15**:

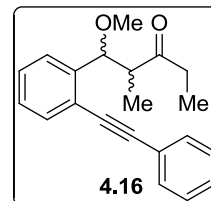
It was obtained as pale yellow oil in 28% yield. *R_f* = 0.3 (in 20% EtOAc/Hexanes); IR (neat): 2975, 1665, 1561, 1534, 1495, 1457, 1200, 1095, 1046, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.93 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.52-7.50 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.40-7.33 (m, 5H), 2.90 (q, *J* = 7.6 Hz, 2H),



2.03 (s, 1H), 1.20 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.1, 137.9, 137.8, 137.1, 132.3, 131.4, 129.1, 128.6, 128.5, 128.2, 128.0, 123.6, 122.9, 95.1, 87.5, 30.9, 13.2, 9.1. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{18}\text{O}$ $[M+H]^+$ 275.1436; found 275.1432.

1-Methoxy-2-methyl-1-(2-(phenylethynyl)phenyl)pentan-3-one 4.16:

Two diastereomers (1:0.5); It was obtained as yellow oil in 98% yield. $R_f = 0.35$ (in 20% EtOAc/Hexanes); IR (neat): 2980, 2931, 1714, 1681, 1495, 1445, 1369, 1089, 941, 766, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.61 (dd, $J = 2.0, 8.0$ Hz, 2H), 7.58-7.53 (m, 2.5H), 7.45 (d, $J = 8.0$ Hz, 1.3H), 7.42-7.35 (m, 6.5H), 7.31-7.26 (m, 2H), 5.25 (d, $J = 4.0$ Hz, 0.5H), 5.08 (d, $J = 9.6$ Hz, 1H), 3.28 (s, 1.3H), 3.13 (s, 3H), 3.05-2.92 (m, 1.6H), 2.67-2.50 (m, 3H), 1.10 (t, $J = 7.2$ Hz, 3H), 1.05-1.00 (m, 2.8H), 0.87 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 214.1, 212.1, 141.6, 132.4, 131.8, 131.5, 128.8, 128.4, 128.3, 127.6, 127.2, 126.5, 126.3, 123.7, 123.1, 122.9, 121.5, 95.0, 94.3, 87.3, 86.8, 82.9, 81.0, 57.4, 56.8, 52.8, 51.1, 36.4, 33.9, 13.4, 9.6, 7.8, 7.5. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{22}\text{O}_2$ $[M+H]^+$ 307.1698; found 307.1697.

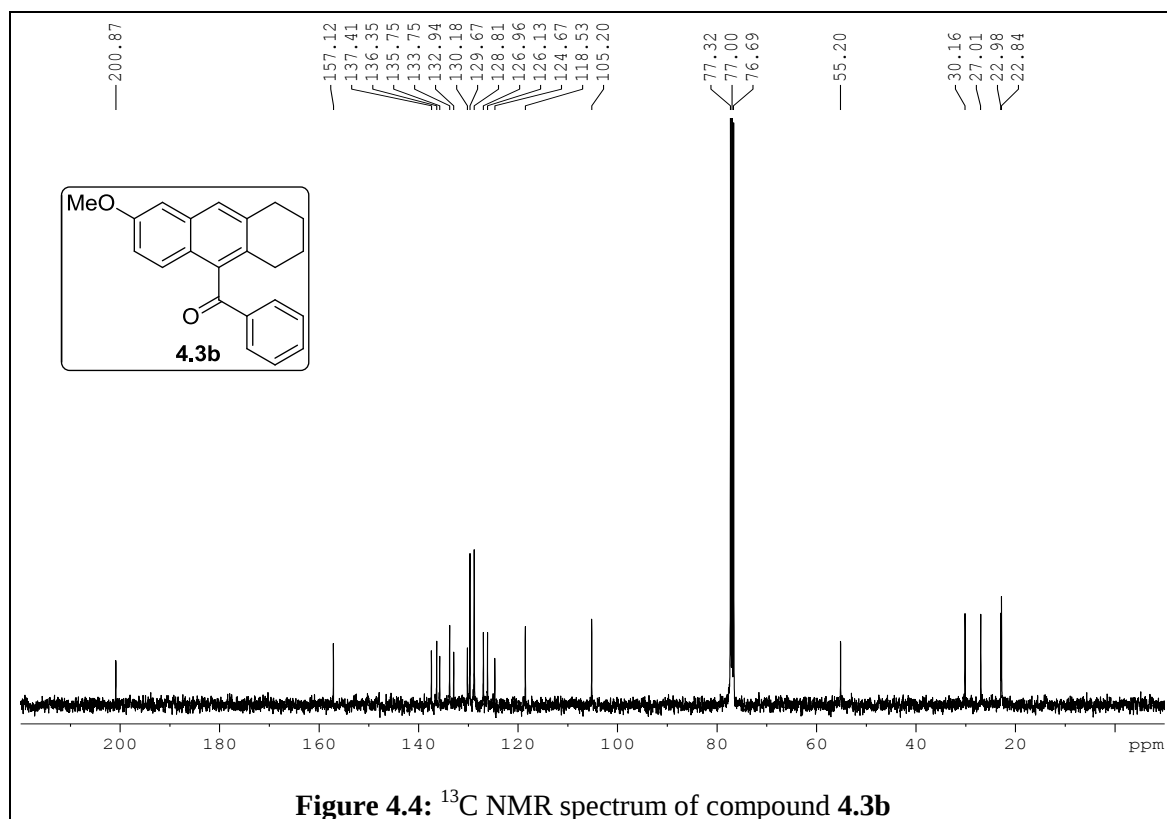
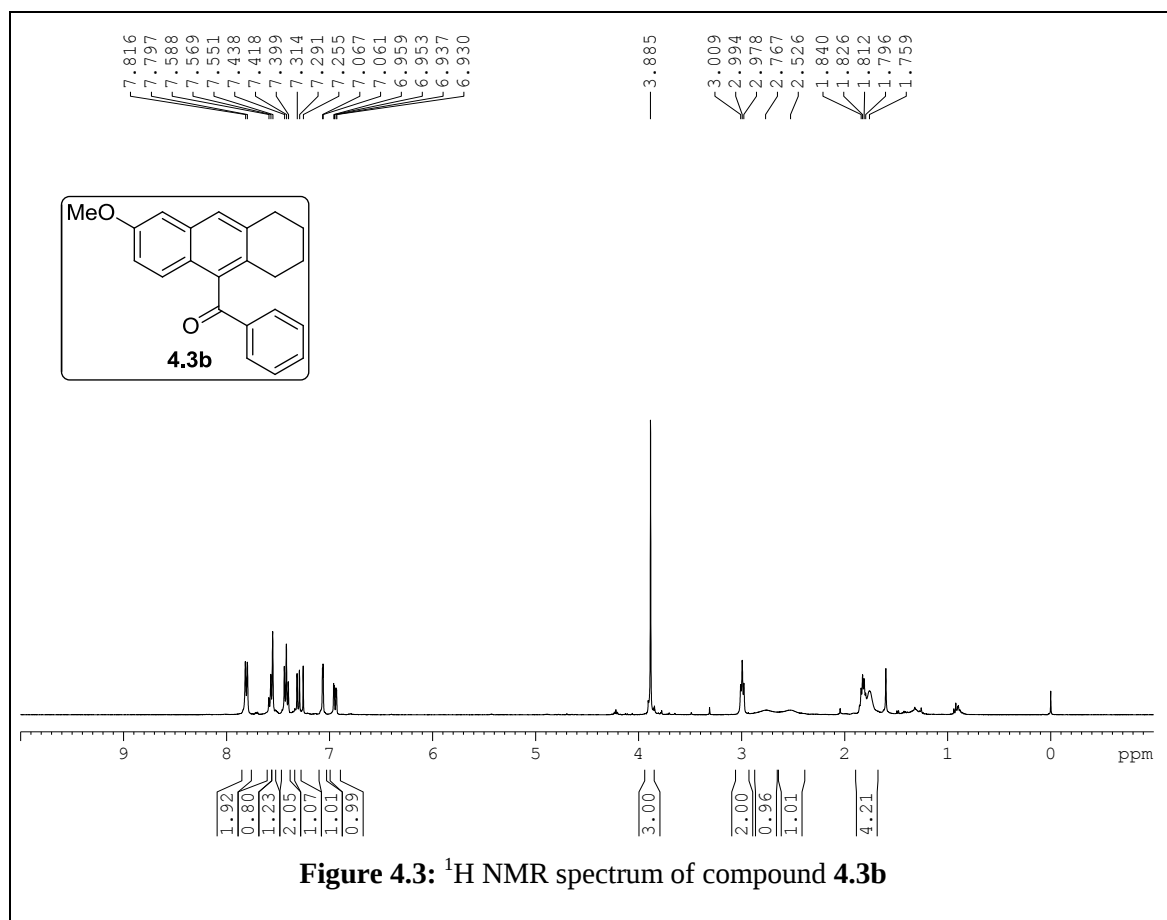


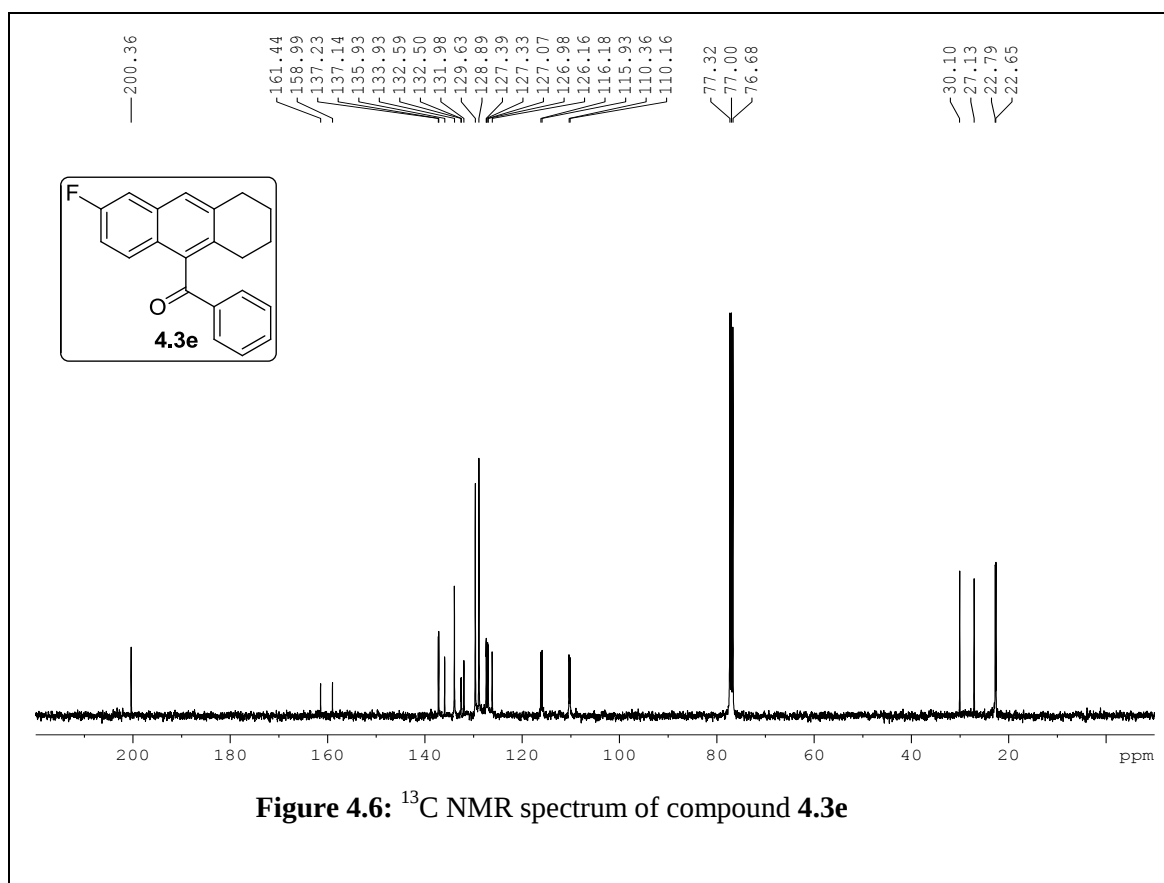
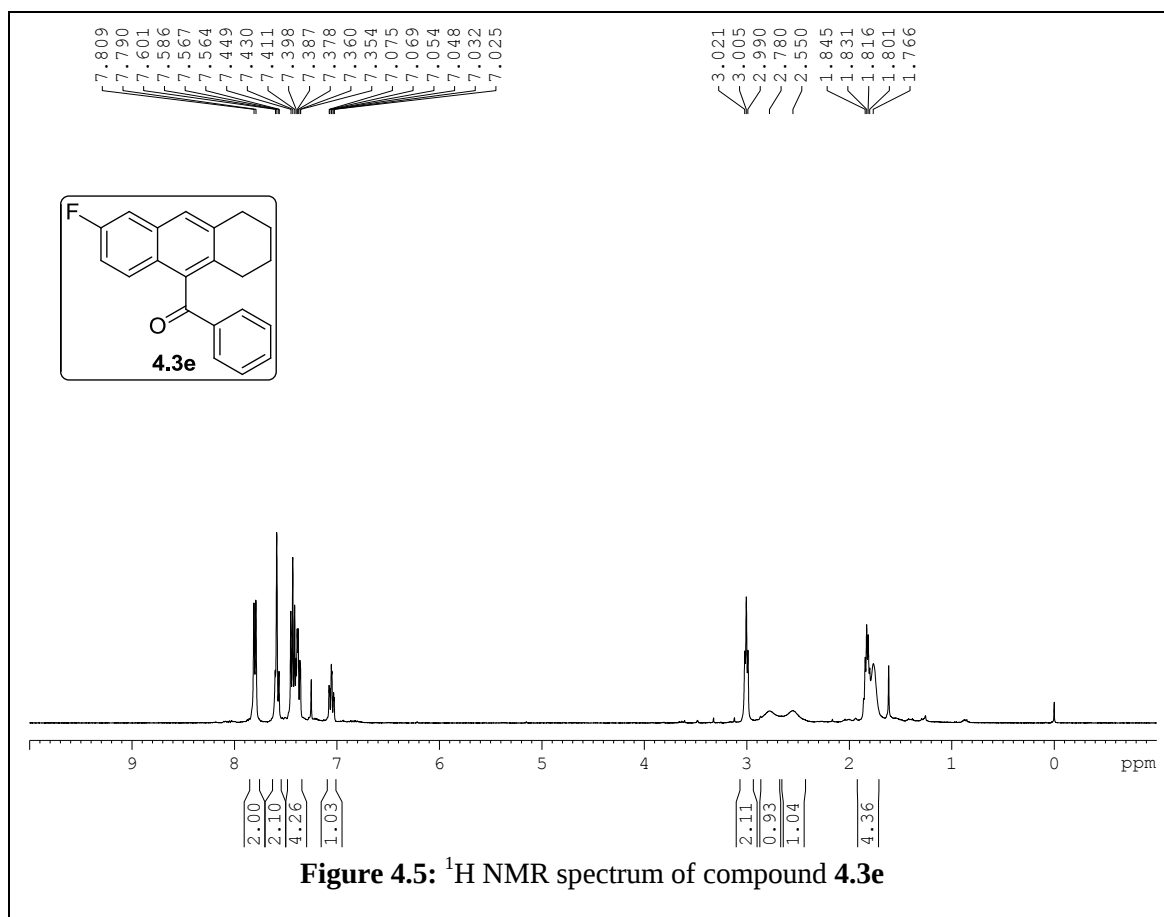
4.6 References

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4.7 Representative spectra





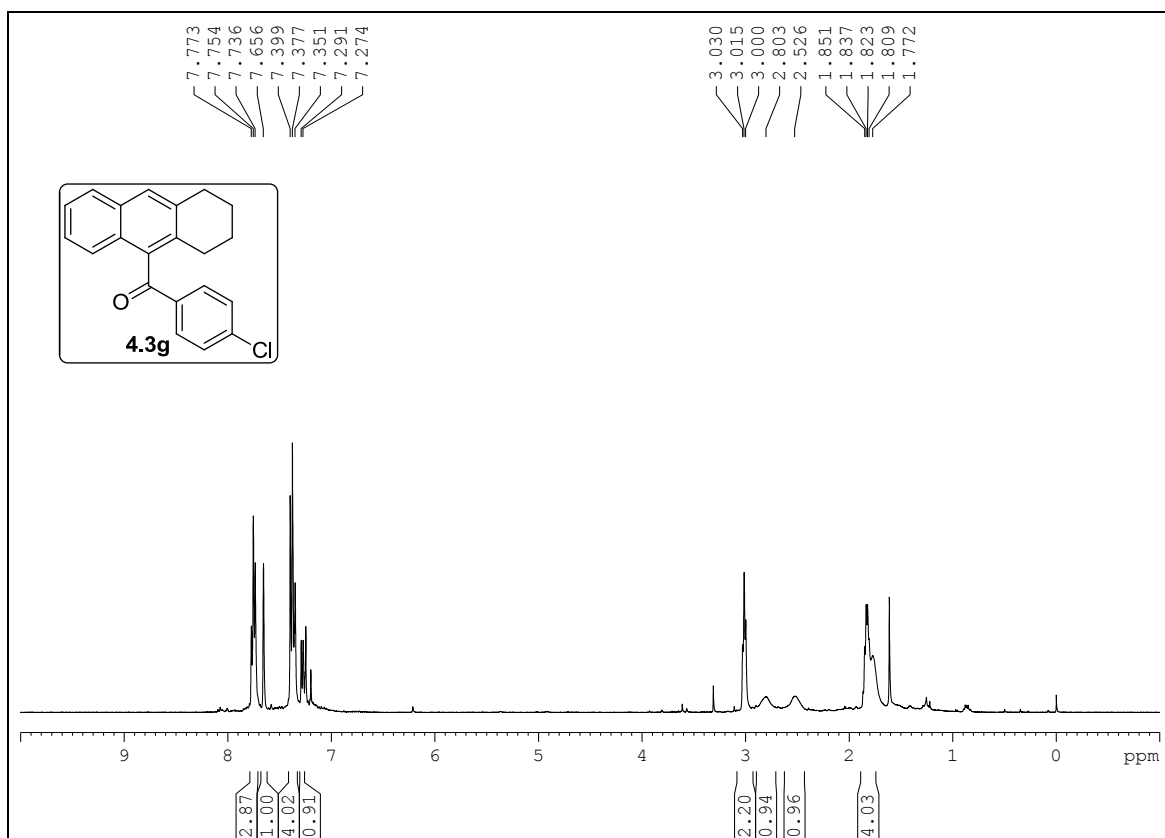


Figure 4.7: ^1H NMR spectrum of compound **4.3g**

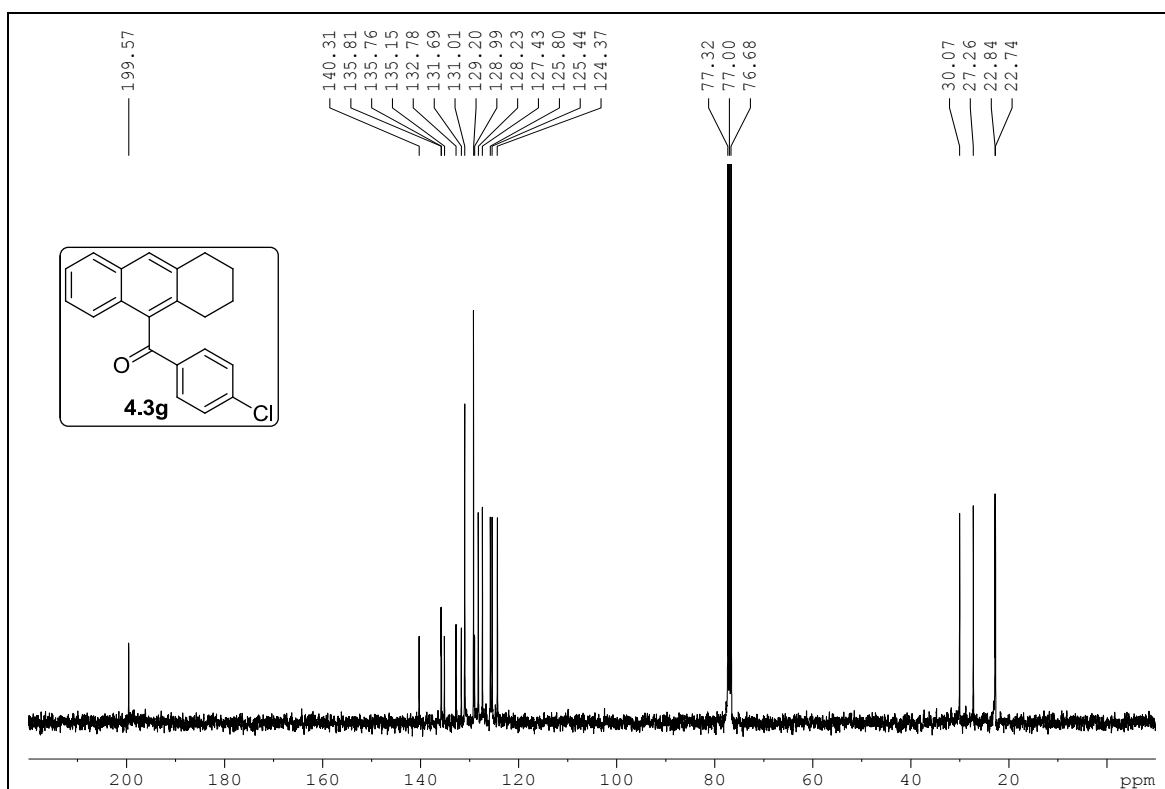
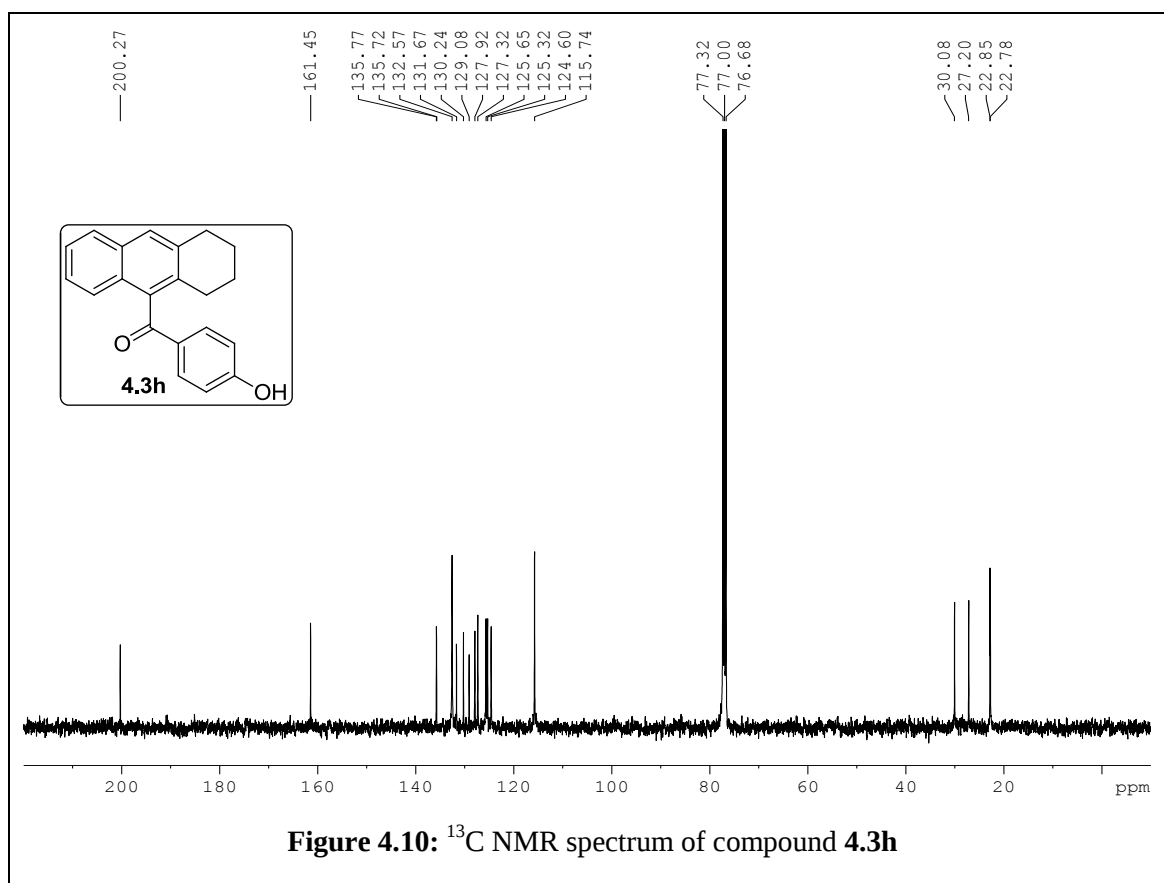
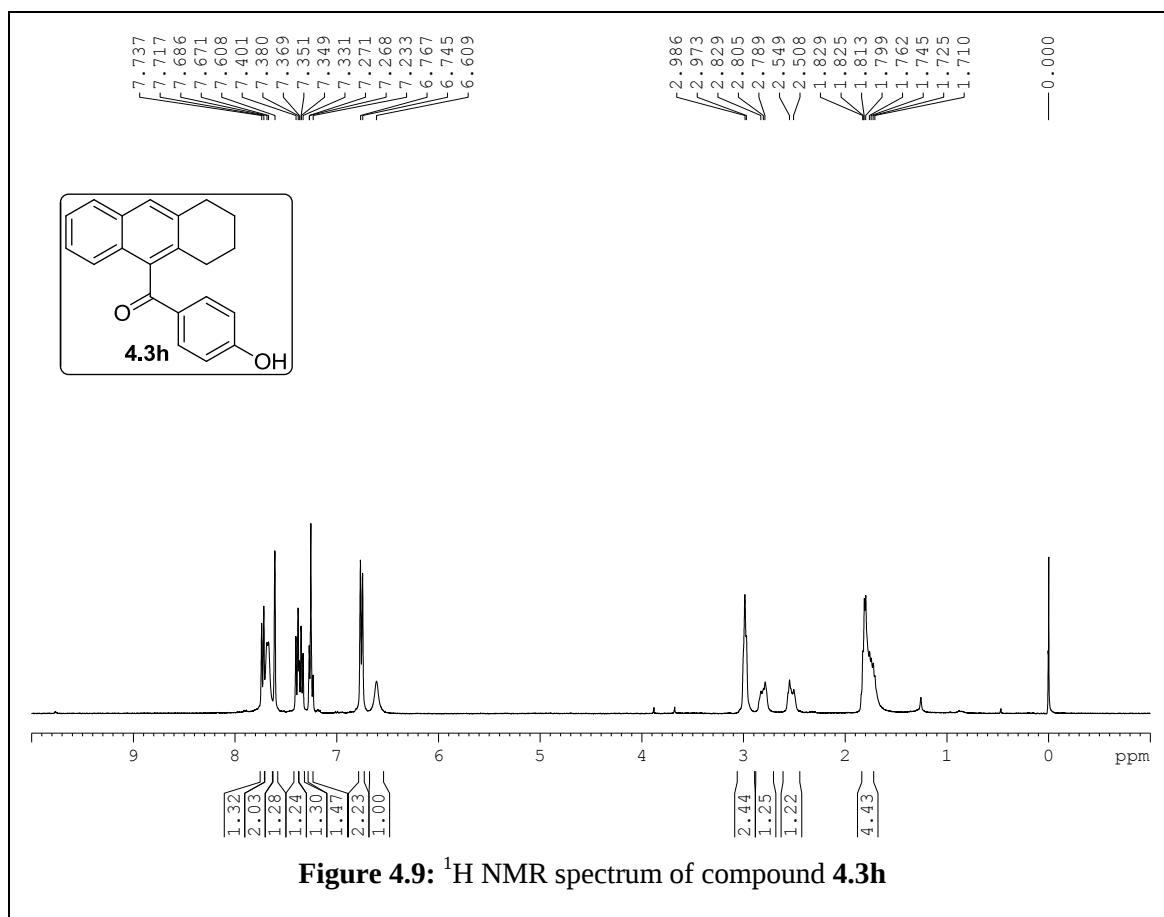
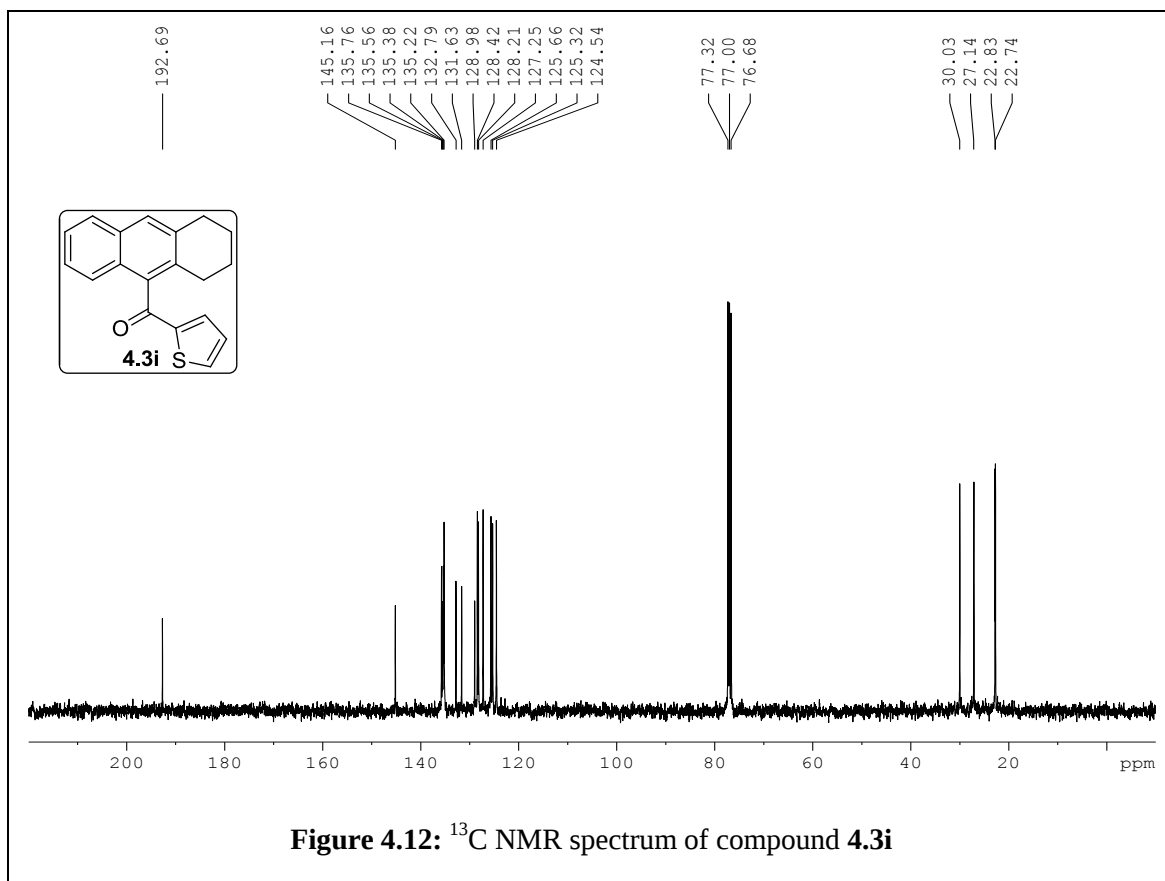
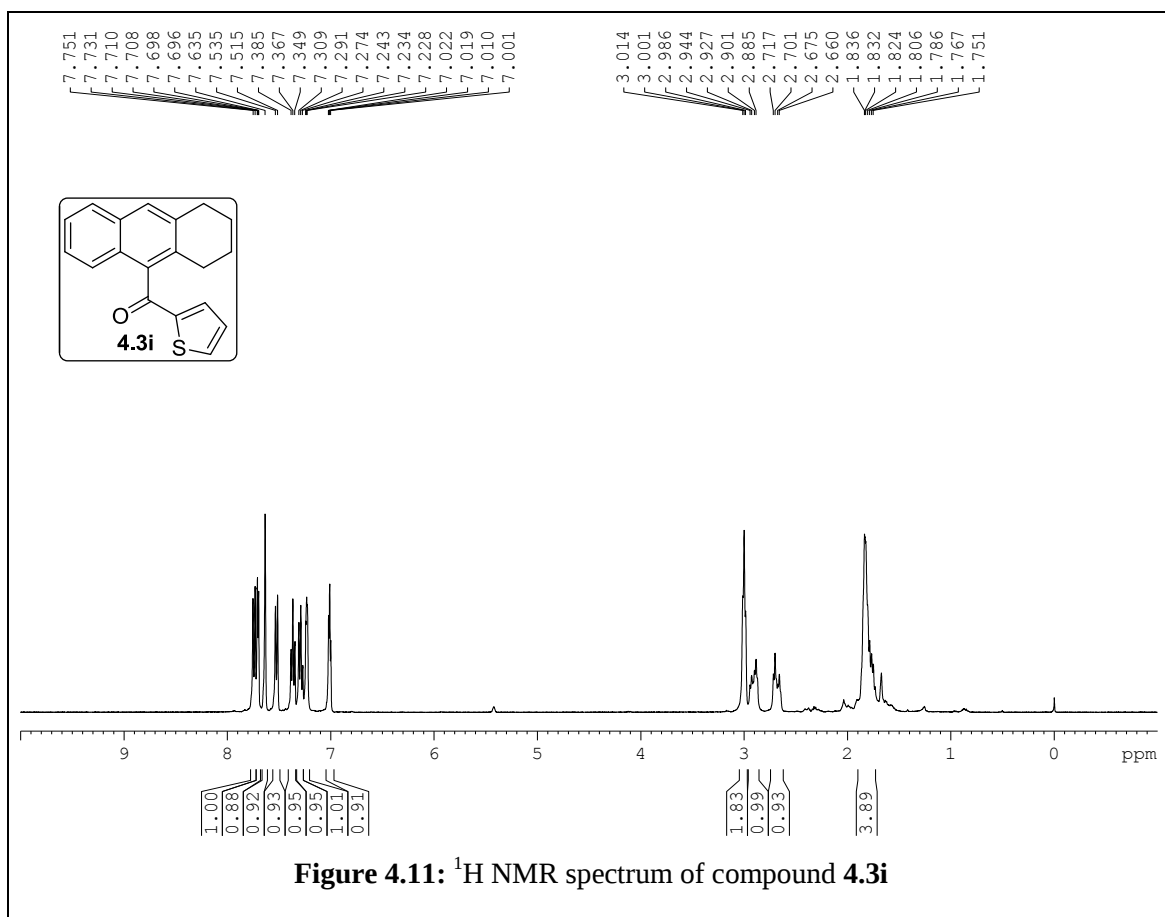
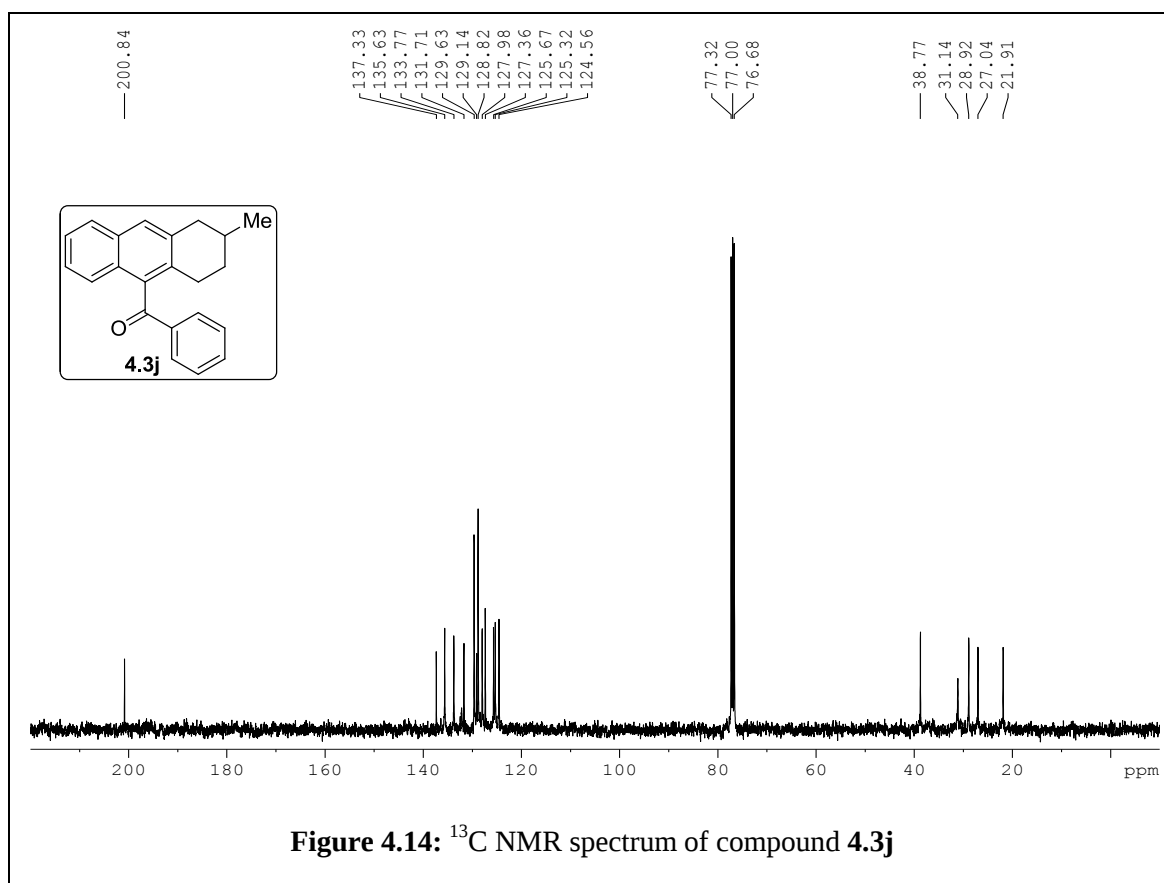
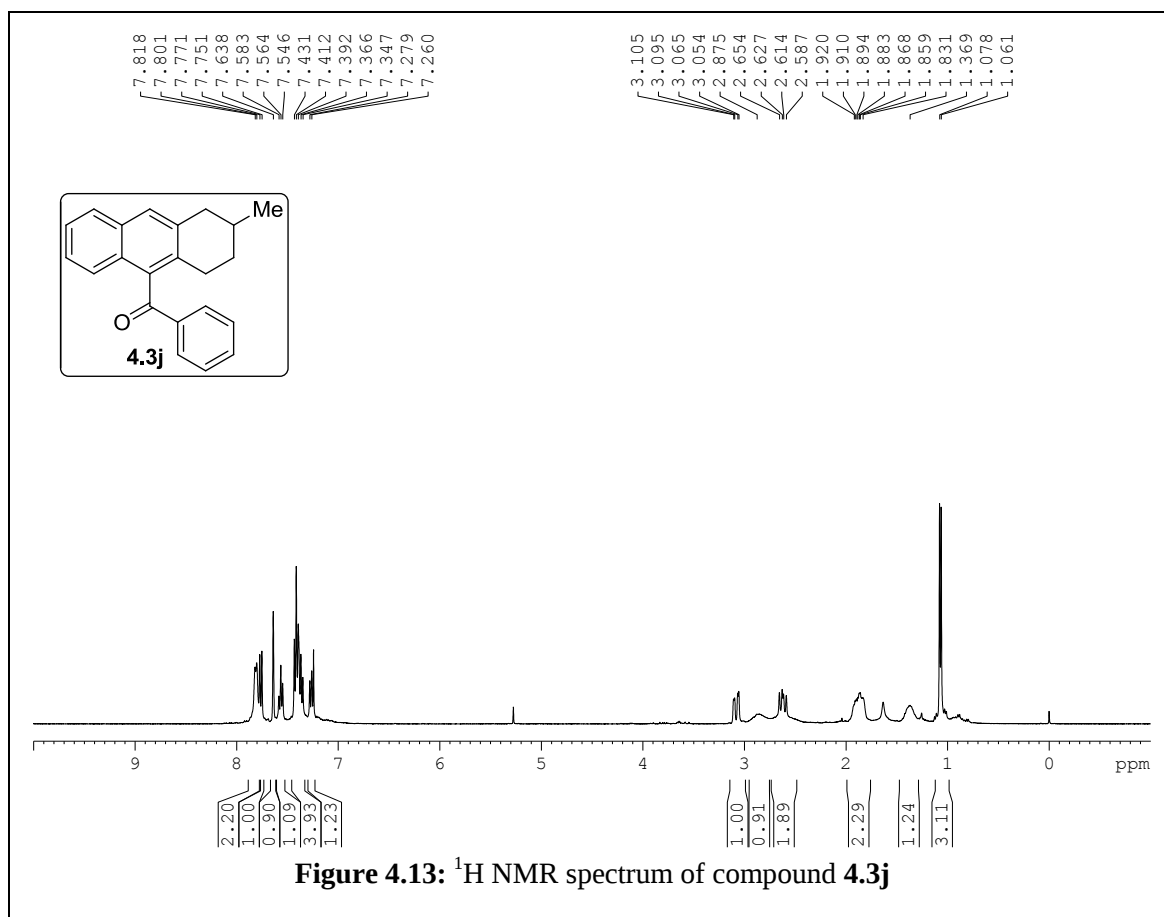
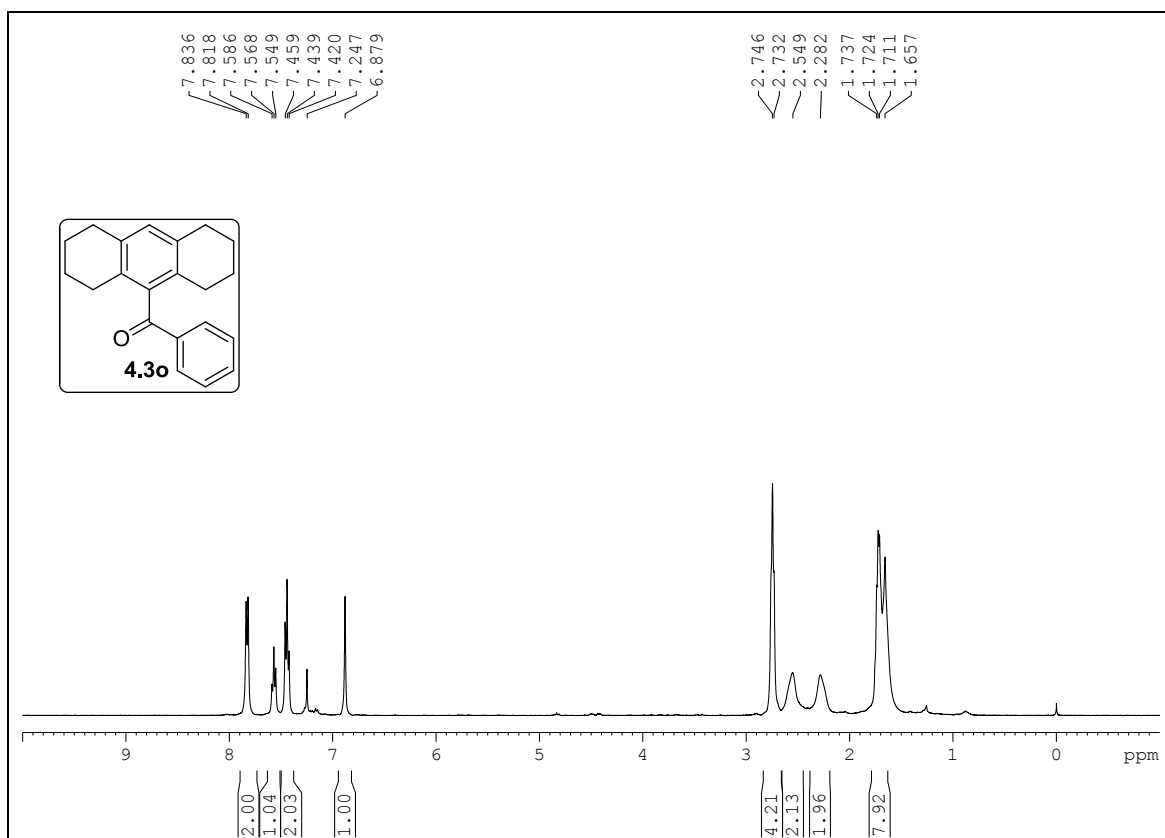
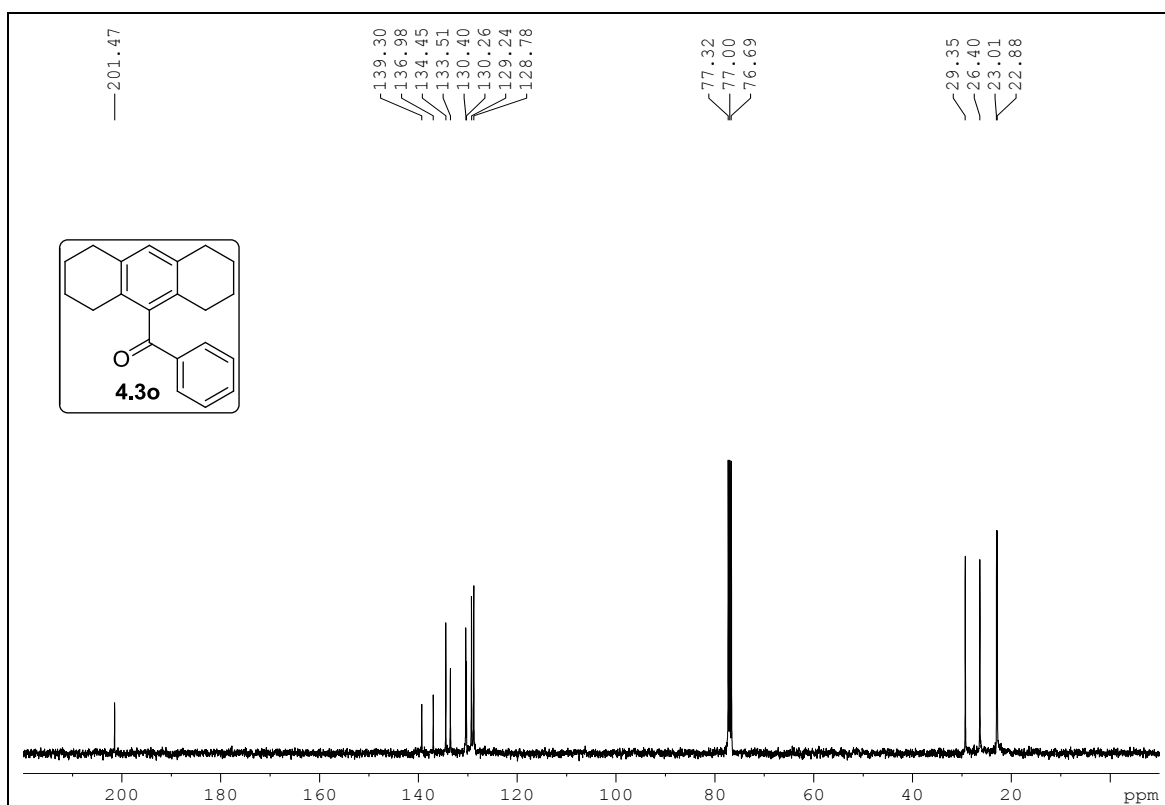


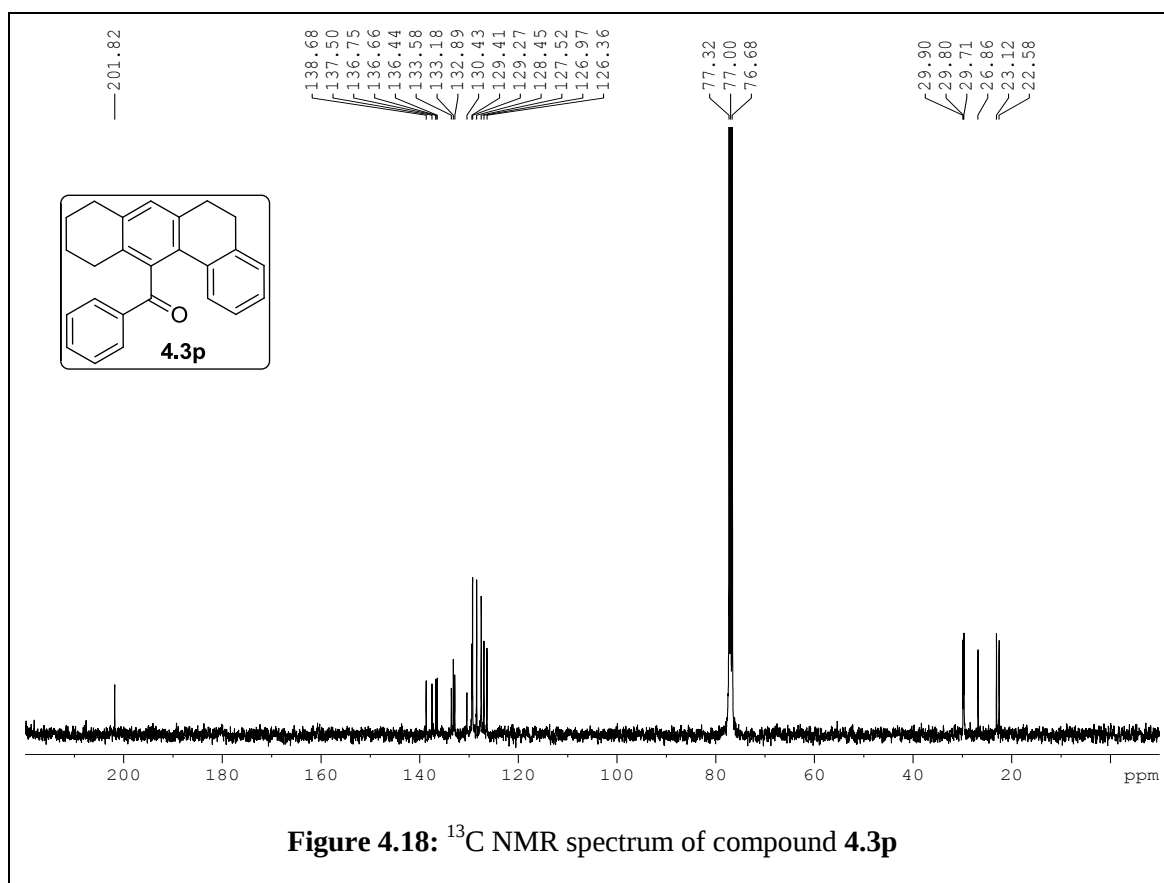
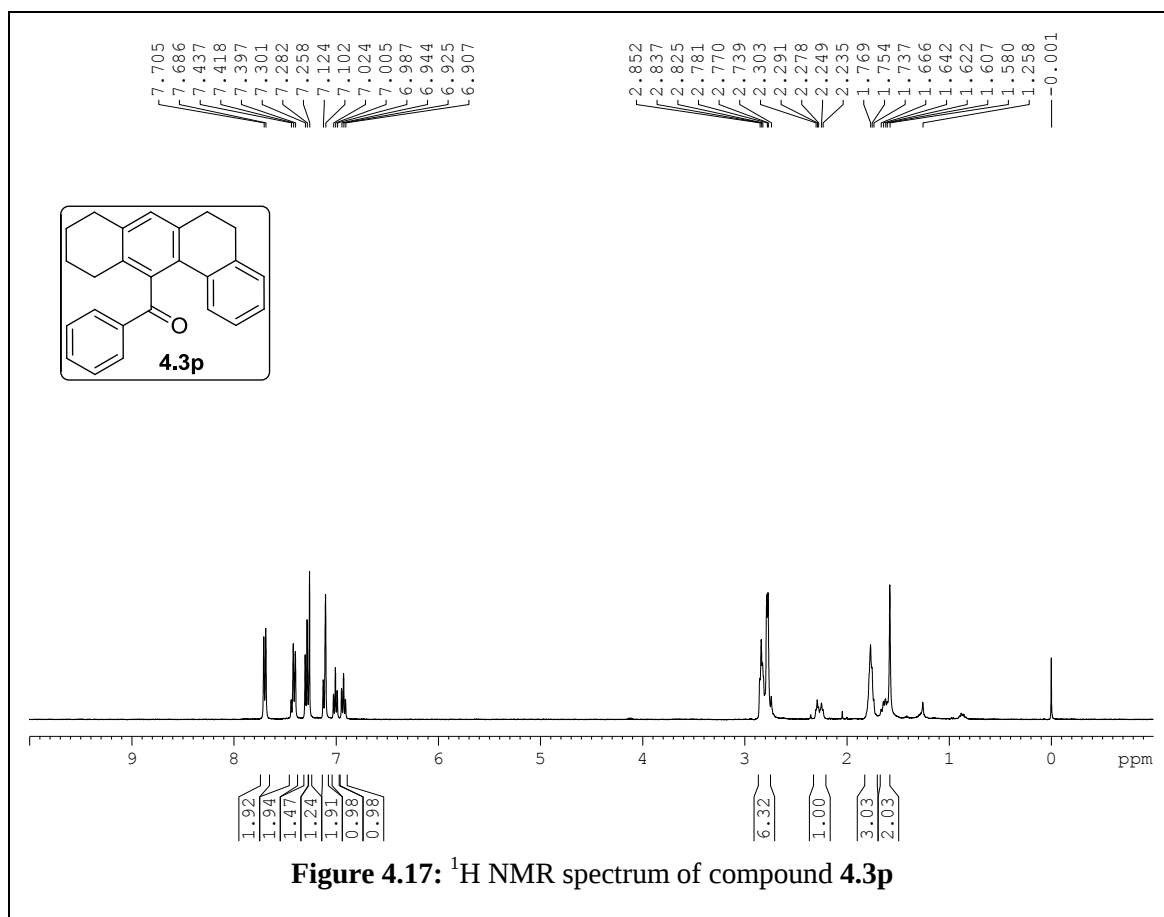
Figure 4.8: ^{13}C NMR spectrum of compound **4.3g**

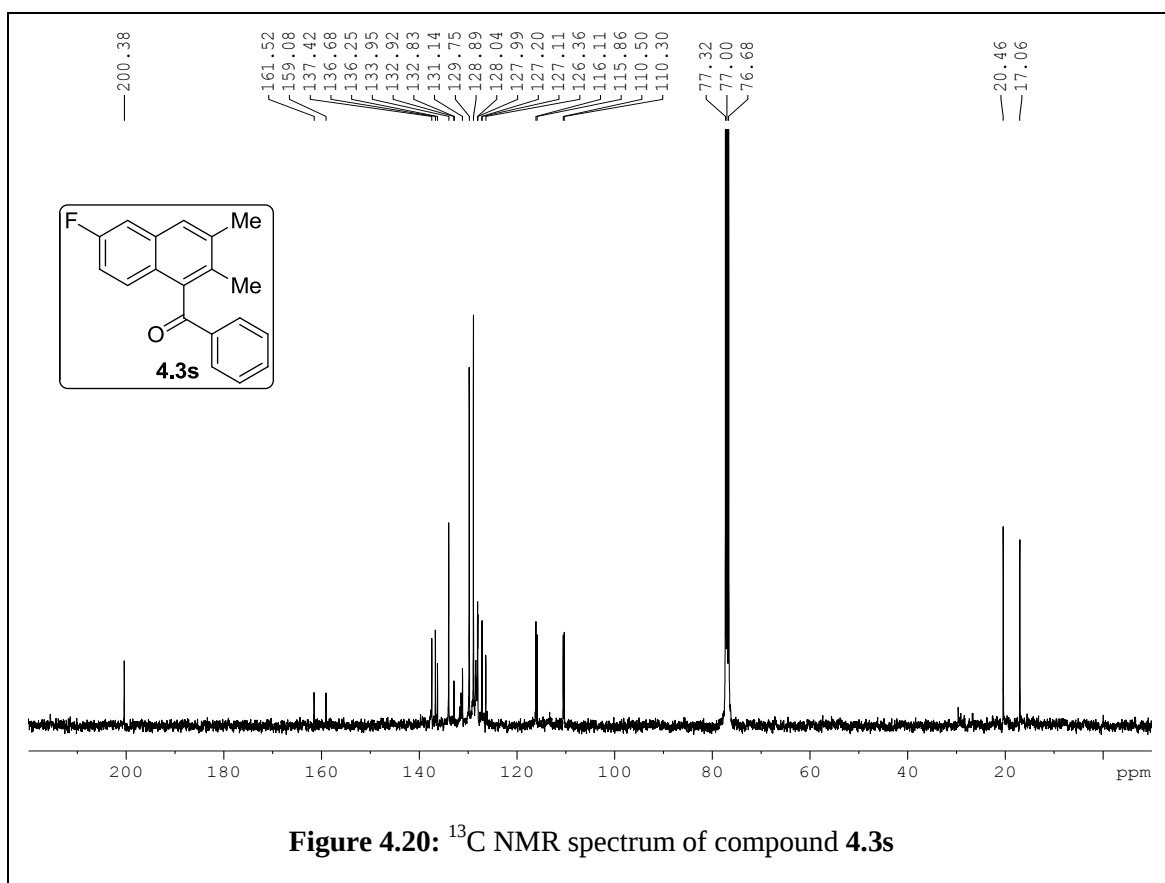
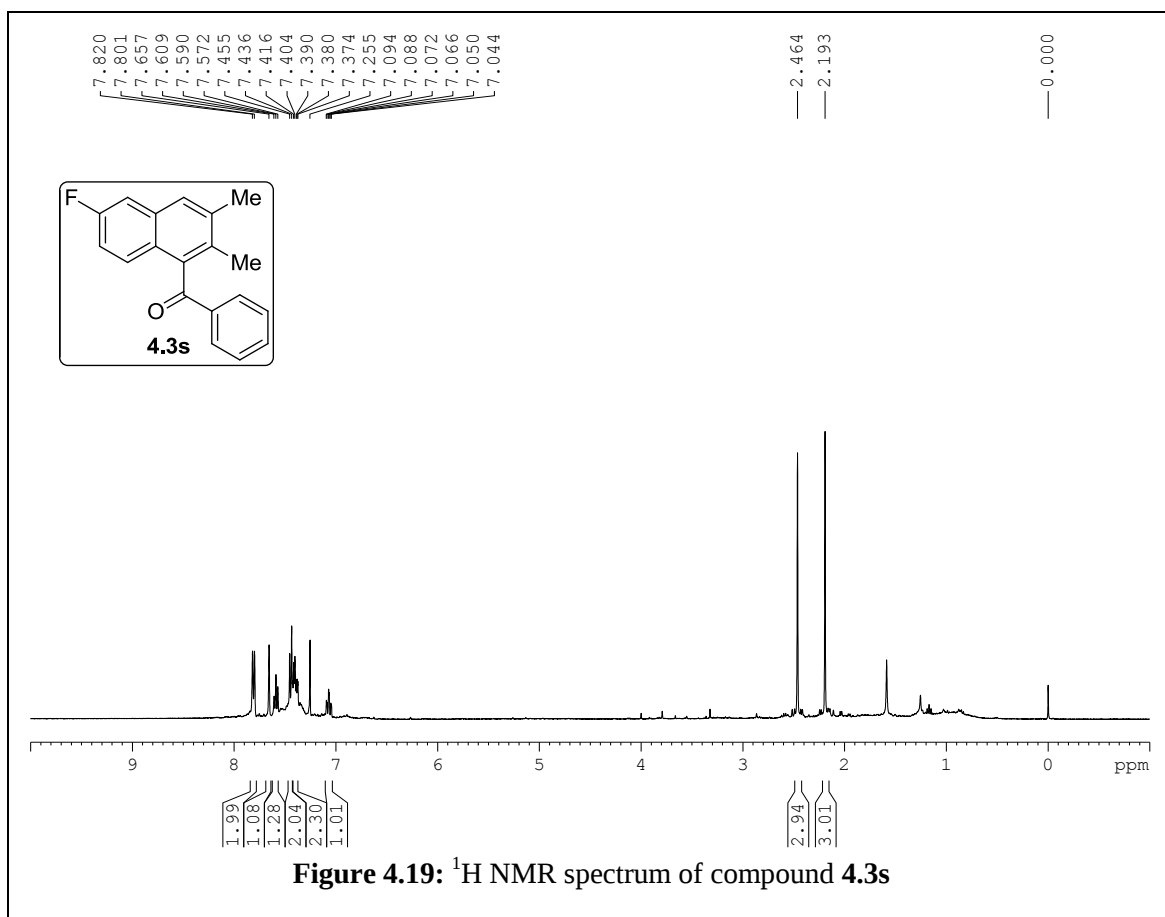


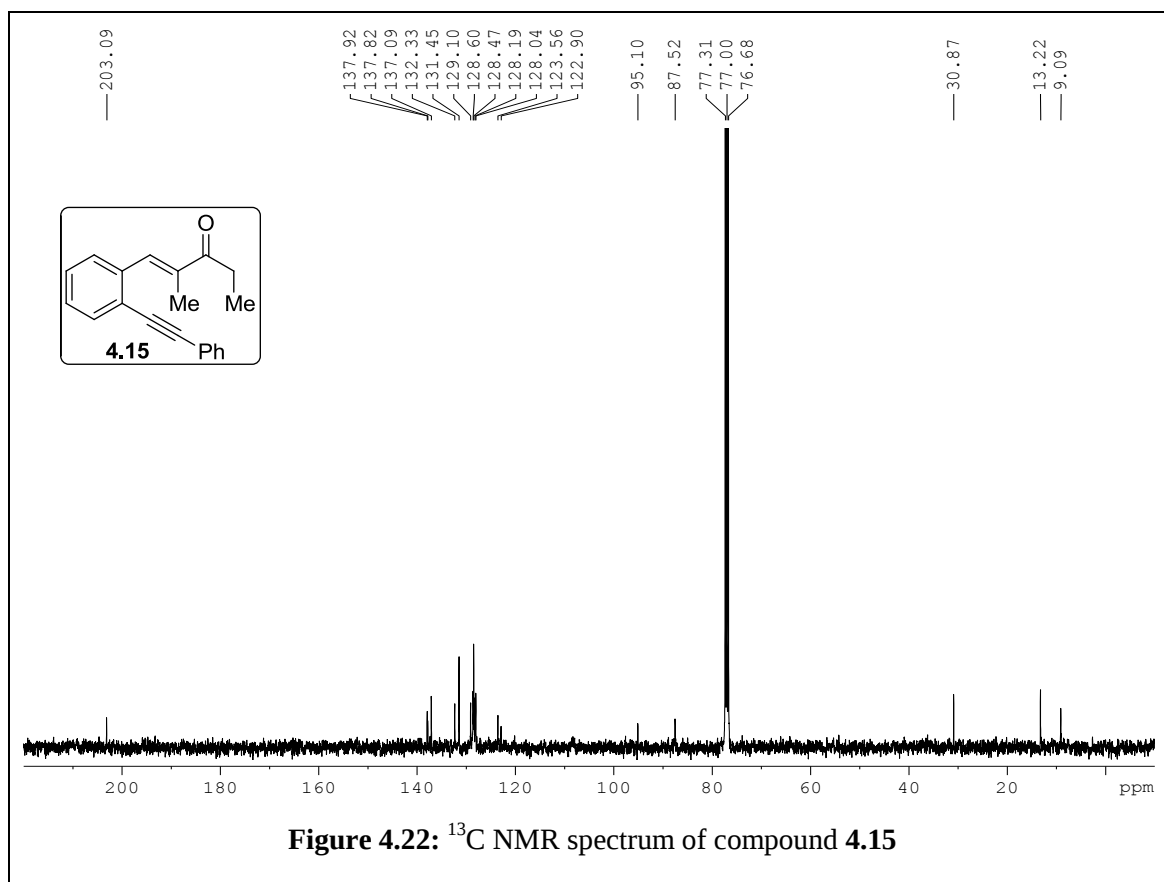
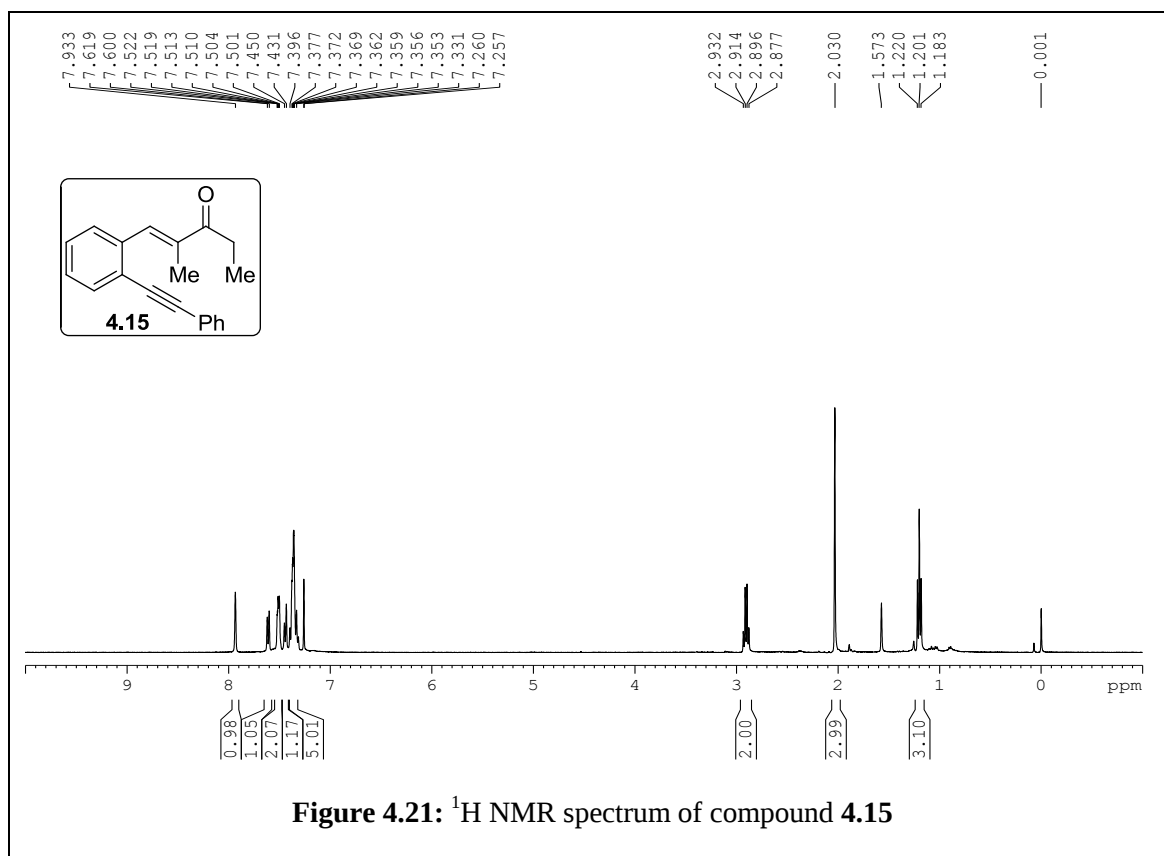


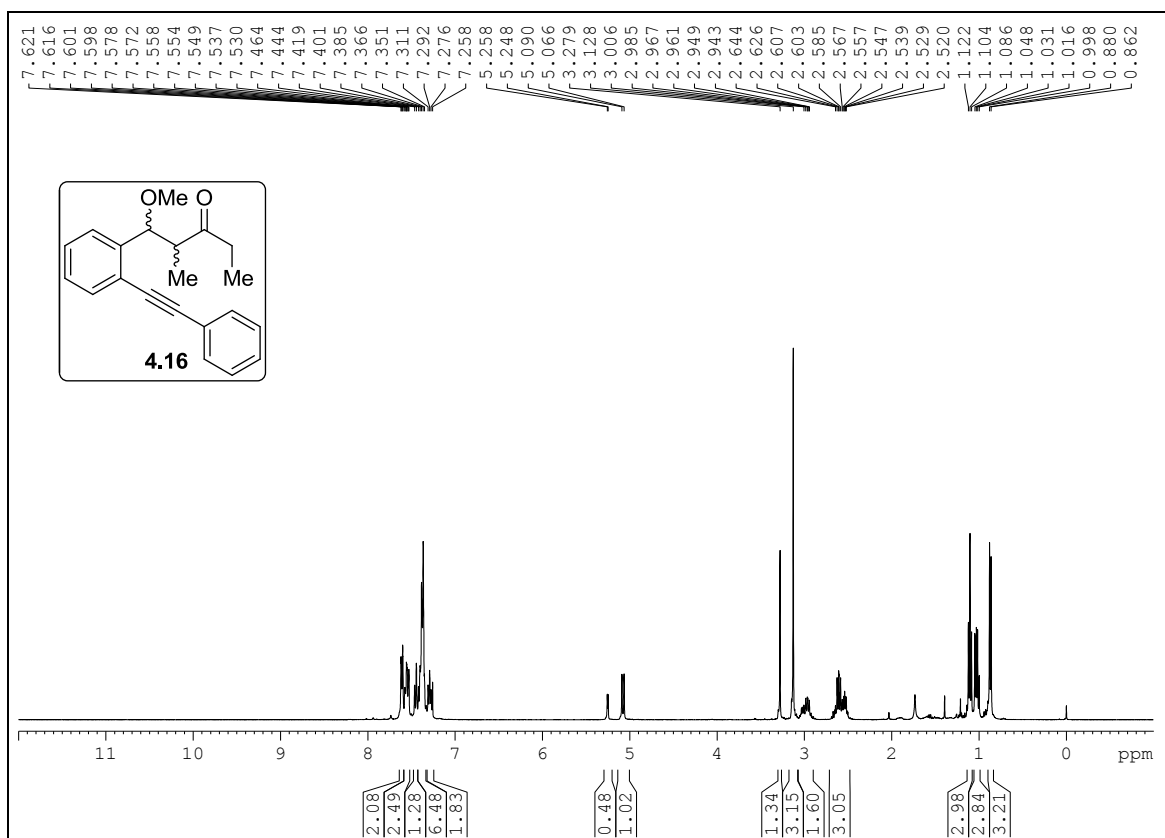
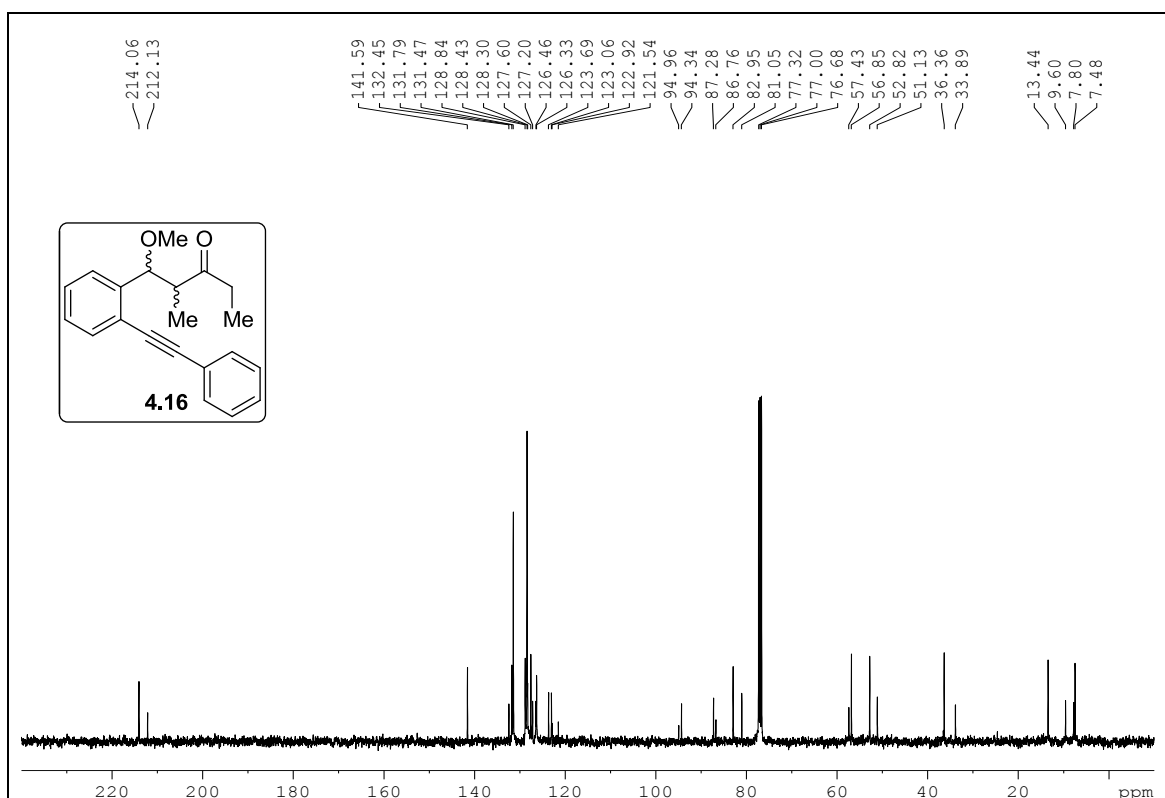


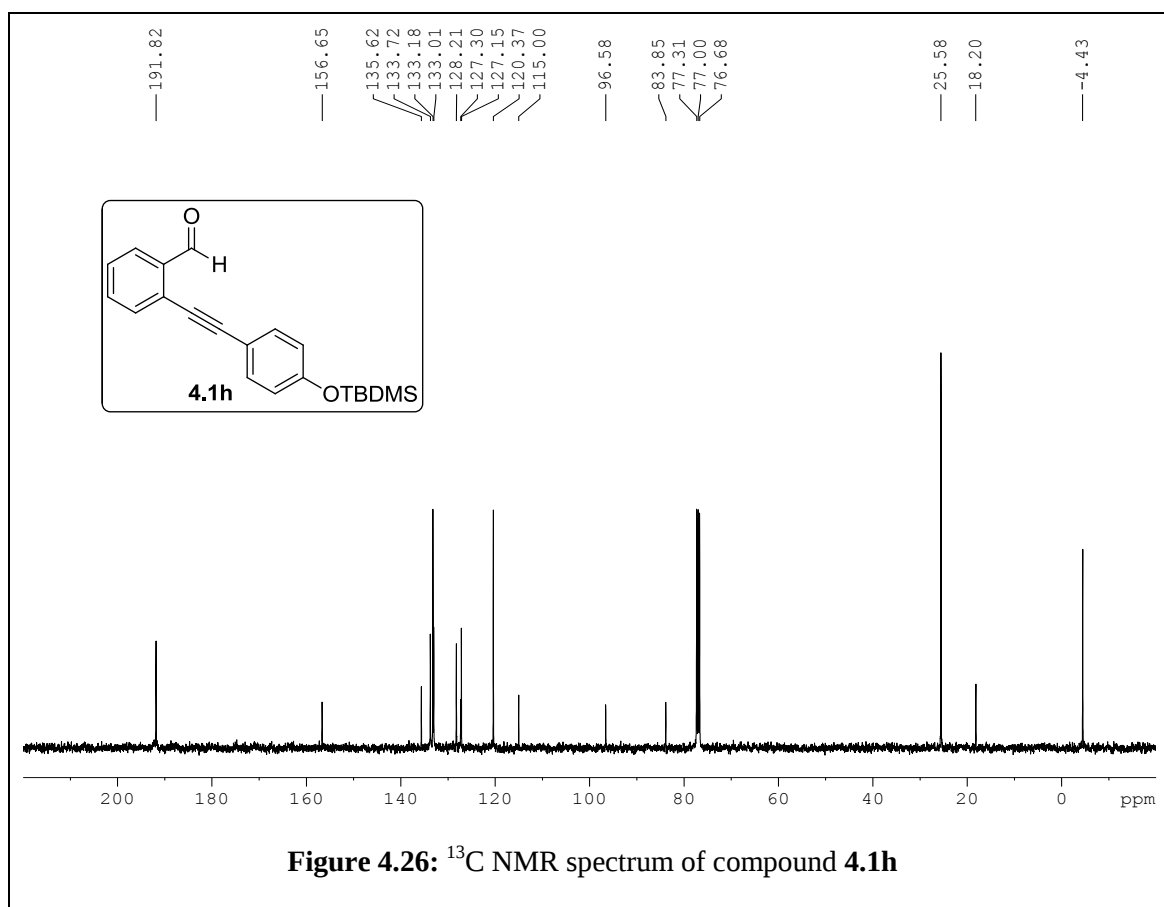
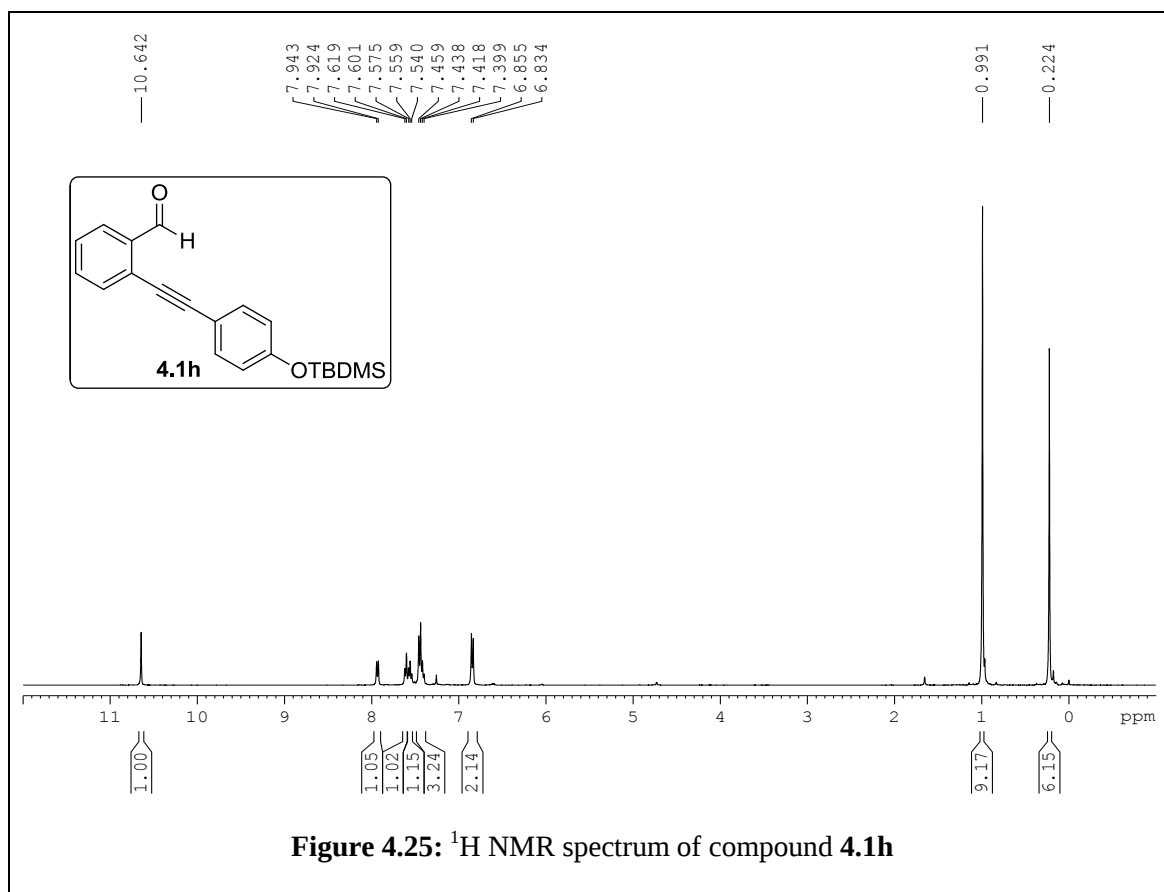
Figure 4.15: ^1H NMR spectrum of compound **4.3o**Figure 4.16: ^{13}C NMR spectrum of compound **4.3o**







Figure 4.23: ¹H NMR spectrum of compound 4.16Figure 4.24: ¹³C NMR spectrum of compound 4.16



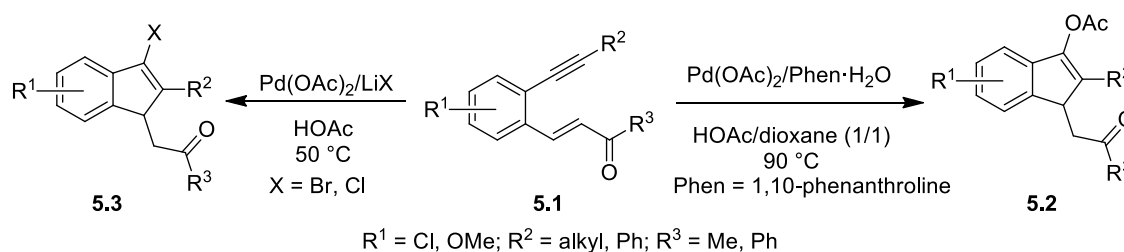
In Situ Formed Acetal-Assisted Synthesis of Substituted Indene Derivatives

5.1 Introduction

Indenes are often encountered in many natural products¹ and functional materials.² Indene derivatives exhibit a wide range of biological properties.³ In addition, they act as ligands to form various metallocene complexes which have been extensively utilized as catalysts in the olefin polymerization process.⁴ For instance, pyridyl substituted indenenes have been utilized to make coordination complexes with metal cations of different metals such as zirconium, manganese and ruthenium. Because of the important of indene moiety, different methods have been established for achieving the indene core. The existing methods mainly involve metal-catalyzed annulation reactions,⁵ ring-expansion of substituted cyclopropenes,⁶ Lewis acid-catalyzed Friedel–Crafts cyclization,⁷ transition metal-catalyzed C-H activation,⁸ and Brønsted acid-catalyzed cyclizations.⁹ Rearrangement reactions of arylalkynes bearing *ortho*-acetals under palladium¹⁰ and gold catalysis¹¹ conditions to form indene skeleton have also been developed. Such rearrangements have been discussed already in the Chapter 1. Some of the interesting and recent literatures on the construction of indene framework are discussed in the next section.

5.1.1 Selected literature survey on indene synthesis

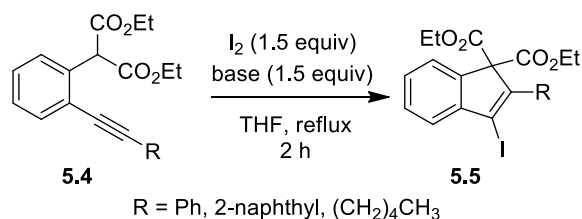
Zhou *et al.* developed an efficient method for the synthesis of functionalized indenenes from *o*-alkynylbenzylidene ketones **5.1** under palladium(II)-catalyzed conditions.¹² This reaction involves *trans*-nucleopalladation of alkynes and conjugate addition. Using this method 3-acetoxy- and 3-halogen-substituted indenenes (**5.2** and **5.3** respectively) could be obtained in high yields (Scheme 5.1).



Scheme 5.1: Pd(II)-catalyzed cyclization of *o*-alkynylbenzylidene ketones

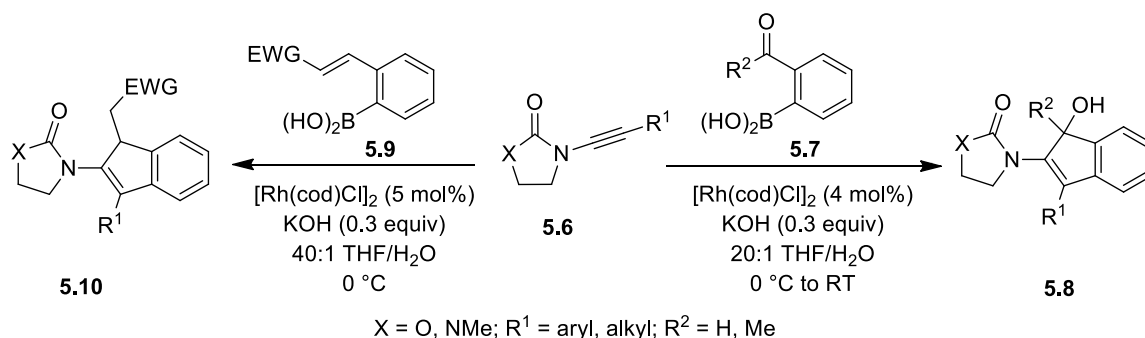
Khan and Wirth reported an iodonium-promoted 5-*endo-dig* carbocyclization of **5.4** to afford 3-iodo-1*H*-indene derivatives **5.5** in good yields (Scheme 5.2).¹³ The products, iodo

substituted indene derivatives were successfully transformed into other derivatives under palladium catalysis conditions.



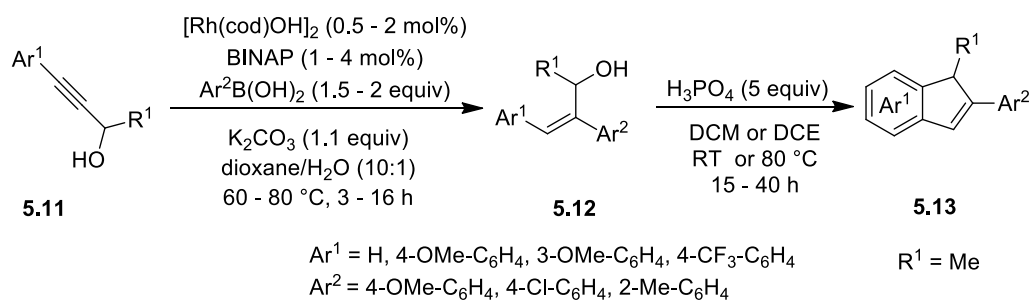
Scheme 5.2: Electrophilic cyclization of 2-substituted ethynylmalonates

Arylboronic acids or esters containing an electrophilic functional group at the *ortho*-position can undergo annulation with ynamides **5.6** under rhodium-catalyzed conditions to give 2-amidoindenols **5.8** or 2-amidoindenenes **5.10** with good regioselectivity as reported by Lam and co-workers.¹⁴ Rh-catalyzed annulation of ynamides **5.6** with 2-acylphenylboronic acids **5.7** afforded 2-amidoindenols **5.8** while 2-alkenylphenylboronic esters **5.9** under Rh-catalysis condition furnished 2-amidoindenenes **5.10** (Scheme 5.3).



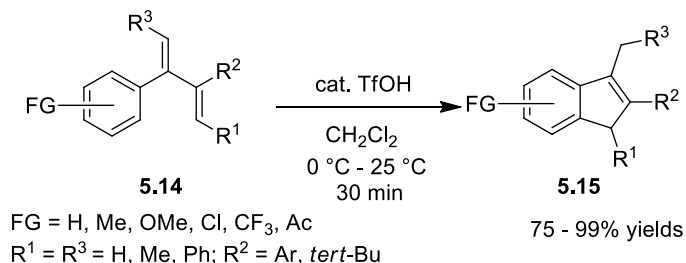
Scheme 5.3: Annulation of ynamides with arylboronic acids or esters

A regio- and stereoselective synthesis of trisubstituted allylic alcohols **5.12** was described by Lautens and co-workers where aryl-substituted propargylic alcohols **5.11** undergo arylation with boronic acids in the presence of rhodium catalyst to give allylic alcohols **5.12** in high yields.¹⁵ The application of the formed allylic alcohols was demonstrated by converting them into valuable indene derivatives **5.13** under phosphoric acid conditions (Scheme 5.4).



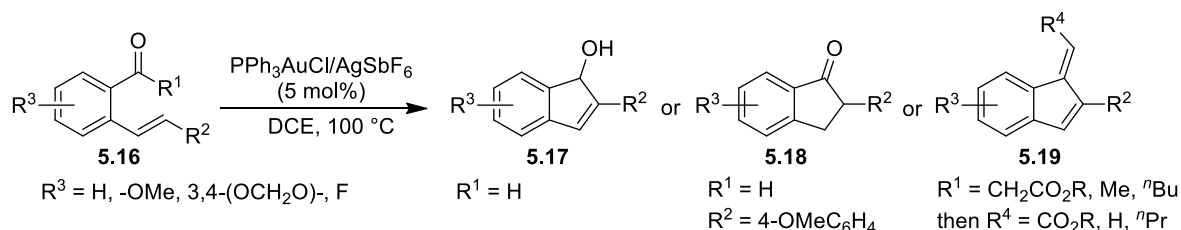
Scheme 5.4: Regio- and stereoselective synthesis of allylic alcohols and their subsequent cyclization

Lee and co-workers reported a Brønsted acid-catalyzed cyclization of diaryl- and alkyl aryl-1,3-dienes **5.14** to synthesize substituted indene derivatives **5.15** under mild reaction conditions.⁹ Treatment of symmetric or unsymmetric diaryl- and alkyl aryl-1,3-dienes **5.14** with a catalytic amount of triflic acid delivered the indene derivatives **5.15** in good to excellent yields (Scheme 5.5).



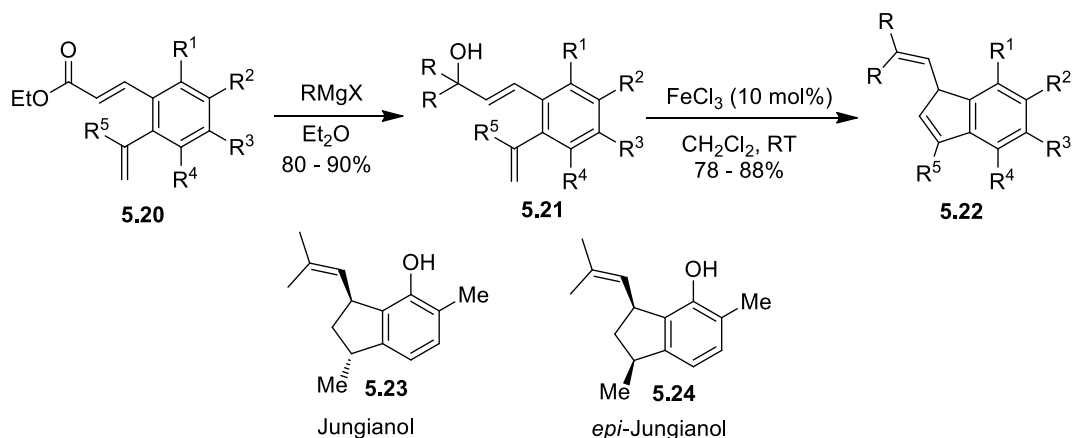
Scheme 5.5: TfOH-catalyzed cyclization of 1,3-dienes

2-Alkenylphenyl carbonyl compounds **5.16** undergo intramolecular cyclization to give a variety of indenols **5.17**, indanones **5.18** and indenes **5.19** under Au(I)-catalysis conditions.¹⁶ The type of indene product formed depends on the nature of substituents present in the 2-alkenylphenyl carbonyl compounds **5.16** (Scheme 5.6).



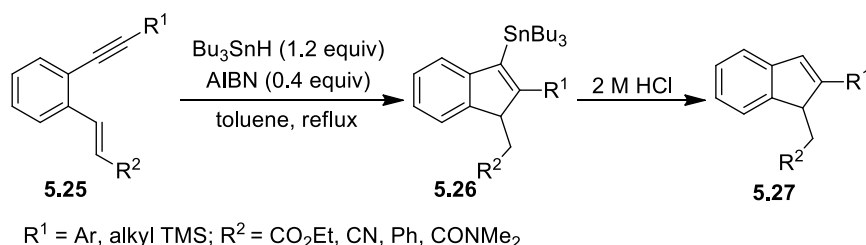
Scheme 5.6: Au(I)-catalyzed intramolecular cyclization of 2-alkenylarylcarbonyls

Using inexpensive and environmentally benign FeCl₃ catalyst Dethe and Murhade described a Prins-type cyclization of allylic alcohols **5.21** to make highly substituted indene derivatives **5.22**.¹⁷ The potential of this novel approach has been shown in the total synthesis of natural products such as jungianol **5.23** and *epi*-jungianol **5.24** in 8.15% and 18.75% overall yields respectively (Scheme 5.7).



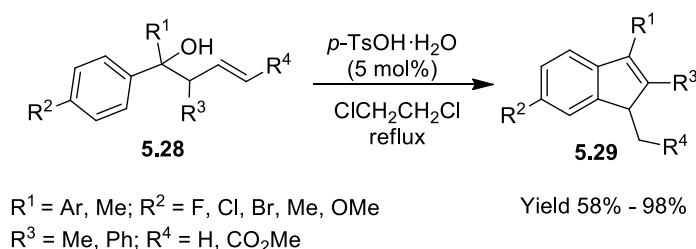
Scheme 5.7: FeCl₃-catalyzed Prins-type cyclization of allylic alcohols

Radical cyclization of enynes **5.25** to give Bu₃Sn-functionalized indenenes **5.26** was developed by Mondal *et al.* (Scheme 5.8).¹⁸ This transformation involves chemo- and regioselective formation of radical followed by intramolecular 5-*exo-trig* closure of the vinyl radical onto the tethered alkene. The resulting Sn-substituted indenenes can be functionalized with various electrophiles to get different indenenes derivatives.



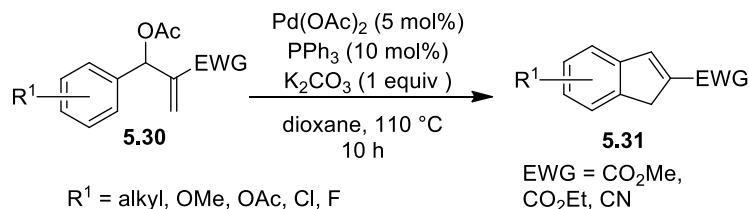
Scheme 5.8: Radical cyclization strategy for substituted indenenes synthesis

Chan and co-workers reported an efficient method for the synthesis of highly substituted indenenes **5.29** by Brønsted-acid catalyzed Friedel-Crafts reaction of homoallylic alcohols **5.28** (Scheme 5.9).¹⁹ However, secondary allylic alcohol did not yield the corresponding indene product under the identical reaction conditions.



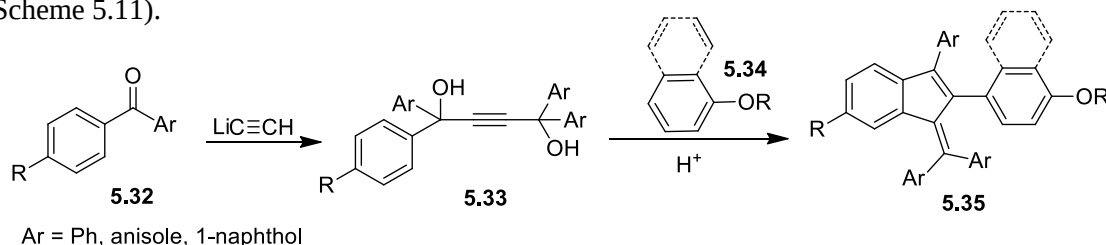
Scheme 5.9: Synthesis of indenenes *via* Friedel-Crafts reaction of homoallylic alcohols

Shao *et al.* have made indene core **5.31** from readily available Baylis–Hillman acetates **5.30** *via* palladium-catalyzed C–H bond activation.²⁰ Since this intramolecular allylic arylation reaction proceeds *via* C–H activation process, it is not required to use prefunctionalized arenes (Scheme 5.10).



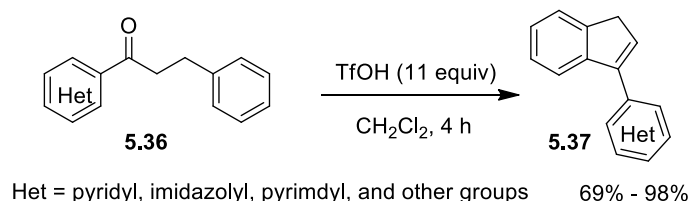
Scheme 5.10: Intramolecular allylic arylation of Baylis–Hillman acetates

Synthesis of polycyclic aromatic indene derivatives **5.35** from tetraarylbut-2-yne-1,4-diols **5.33** using catalytic *p*-TsOH was reported by Sousa *et al.*²¹ This reaction involves the formation of a cationic allenylum intermediate from 1,4-diol **5.33** under acidic condition. Then, a series of cascade reactions would take place to give indene derivative **5.35**. Overall, the indene derivatives could be obtained in two steps from aromatic ketones **5.32** by following this protocol (Scheme 5.11).



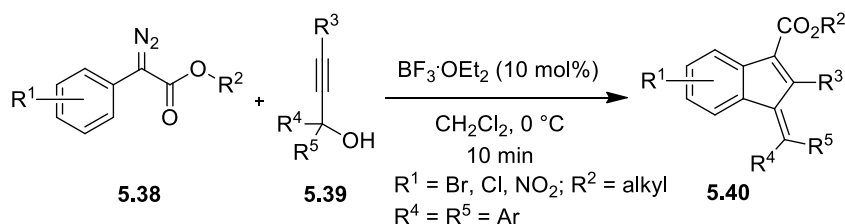
Scheme 5.11: Domino reactions of tetraarylbut-2-yne-1,4-diols

Very recently, Boblak and Klumpp have described a super acid-promoted preparation of indene derivatives **5.37** with *N*-heterocyclic substituents from heterocyclic ketones **5.36** via cyclodehydration process (Scheme 5.12).²² The heterocyclic substituents include pyridyl, imidazolyl and pyrimidyl etc.. The authors showed that a protonated heterocyclic ring lowers the LUMO energy level which makes the cyclodehydration to occur rapidly than the corresponding unprotonated form.



Scheme 5.12: Cyclodehydration of heterocyclic ketones

Muthusamy *et al.* have developed a tandem reaction for the synthesis of highly substituted and conjugated indenenes **5.40** (Scheme 5.13).²³ Propargylic alcohol **5.39**, in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, undergoes Meyer-Schuster rearrangement to give allene carbocation intermediate which is trapped by nucleophilic attack of diazo compound **5.38** followed by Nazarov cyclization and aromatization to afford indene derivative **5.40**. This is an atom economical process which gives biologically important indene systems in excellent yields.

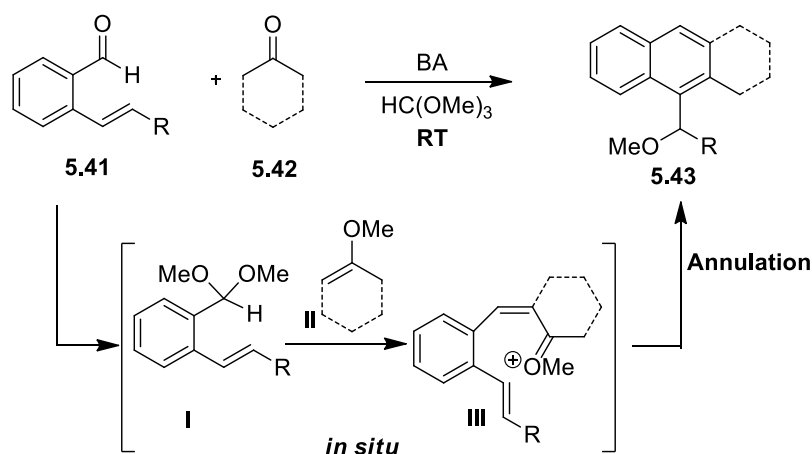


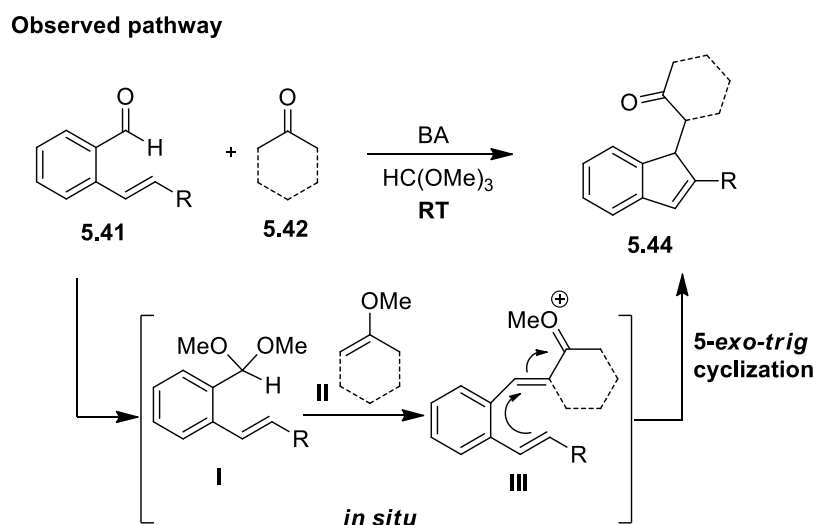
Scheme 5.13: Tandem reaction of propargylic alcohol and α -diazoarylacetic ester

5.2 Background

In Chapter 4, we discussed a different approach for the synthesis of naphthalene derivatives from *o*-alkynylbenzaldehydes and enolizable ketones *via in situ* formed acetals in the presence of trimethyl orthoformate (TMOF) and triflic acid (TfOH) catalyst. This cascade reaction is expected to involve Claisen-Schmidt condensation followed by heteroalkyne metathesis/annulation where *in situ* formed acetal assists both the processes to happen efficiently. Inspired by this acetal-assisted cascade process, we envisioned that a similar cascade with *o*-alkenylbenzaldehyde **5.41** and enolizable ketone **5.42** could result in naphthalene derivative **5.43** (Scheme 5.14, expected pathway). Interestingly, in reality, the reaction takes a different pathway to result in synthetically valuable indene derivative **5.44** (Scheme 5.14, observed pathway). This domino process involves acetal-assisted Claisen-Schmidt condensation followed by 5-*exo-trig* cyclization. Because of the soft nature of alkene, it undergoes, rather, 1,4 addition (Michael addition or 5-*exo-trig* cyclization)²⁴ by attacking the soft electrophilic alkene carbon than attacking the hard electrophilic carbonyl carbon. In the synthesis of naphthalenes from *o*-alkynylbenzaldehydes (Chapter 4), alkyne function of *o*-alkynylbenzaldehyde undergoes intramolecular alkyne-carbonyl metathesis/annulation with the carbonyl carbon because of the hard nature of both alkyne (hard nucleophilic center) and carbonyl (oxocarbenium) carbon (hard electrophilic center).

Expected pathway





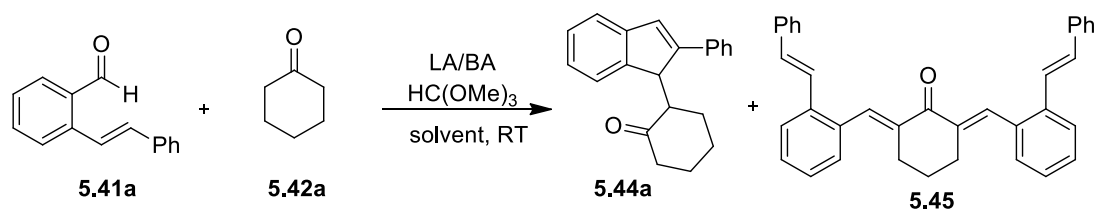
Scheme 5.14: Reaction of *o*-alkenylbenzaldehyde with enolizable ketone

This interesting observation i.e. formation of indene skeleton encouraged us to take it up further.

5.3 Results and discussion

5.3.1 Optimization study

To optimize the reaction conditions, *o*-alkenylbenzaldehyde **5.41a** and cyclohexanone **5.42a** were selected. Initially **5.41a** was treated with 1.2 equiv of cyclohexanone in the presence of 2.0 equiv of trimethyl orthoformate and 20 mol% triflic acid (TfOH) in dichloromethane solvent at room temperature. To our delight, the reaction completed in 30 min and resulted in indene derivative **5.44a** in 75% isolated yield (Table 5.1, entry 1). In order to improve the yield of **5.44a**, we changed parameters such as solvent, catalysts and temperature. Slightly improved yield of the product was noticed when the reaction was conducted in acetonitrile solvent (Table 5.1, entry 2). However, in nitromethane and dioxane it resulted in decomposed mixture and 21% of **5.44a** respectively (Table 5.1, entries 3 and 4). For further optimization study, acetonitrile was chosen as the solvent. Unfortunately, there were no reactions with trifluoroacetic acid and $\text{HSbF}_6 \cdot 6\text{H}_2\text{O}$ even when the reactions were allowed to stir for 24 h at room temperature in acetonitrile solvent (Table 5.1, entries 5 and 6). The aldol condensation product **5.45** was obtained in 36% yield with *p*-toluenesulfonic acid (Table 5.1, entry 7). Then our attention turned into check the present transformation with various Lewis acid catalysts. With $\text{Cu}(\text{OTf})_2$ the aldol product **5.45** was obtained in 69% yield (Table 5.1, entry 8) while the other Lewis acids resulted in either no reaction or decomposed reaction mixture. There were no reactions even under the reflux conditions when the reaction was carried with $\text{Fe}(\text{OTf})_2$, $\text{La}(\text{OTf})_3$, AgOTf , InCl_3 and $\text{BF}_3 \cdot \text{OEt}_2$ (Table 5.1, entries 10-15).

Table 5.1 Optimization study^a

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%) ^b	
				5.44a	5.45
1	TfOH (20)	CH ₂ Cl ₂	0.5	75	--
2	TfOH (20)	CH ₃ CN	0.5	77	--
3	TfOH (20)	CH ₃ NO ₂	1.0	--	--
4	TfOH (20)	Dioxane	0.5	21	--
5	TFA (20)	CH ₃ CN	24.0	NR	NR
6	HSbF ₆ ·6H ₂ O (20)	CH ₃ CN	24.0	NR	NR
7	PTSA (20)	CH ₃ CN	24.0	--	36
8	Cu(OTf) ₂ (5)	CH ₃ CN	24.0	--	69
9	AuCl ₃ (5)	CH ₃ CN	24.0	--	--
10	Fe(OTf) ₂ (5)	CH ₃ CN	24.0	NR	NR
11	La(OTf) ₃ (5)	CH ₃ CN	24.0	NR	NR
12	AgOTf	CH ₃ CN	24.0	NR	NR
13	AgSbF ₆ (5)	CH ₃ CN	24.0	NR	NR
14	InCl ₃ (5)	CH ₃ CN	24.0	NR	NR
15	BF ₃ ·OEt ₂ (10)	CH ₃ CN	24.0	NR	NR
16	TfOH (10)	CH ₃ CN	0.5	61	--
17	TfOH (20)	CH ₃ CN	24.0	51 ^c	--
18	TfOH (20)	CH ₃ CN	0.5	83 ^d	--
19	TfOH (25)	CH₃CN	0.5	87^d	--
20	TfOH (10)	CH ₃ CN	1.0	57 ^e	--

^a All the reactions were carried using 2.0 equiv of HC(OMe)₃ at RT. ^b Isolated yield. ^c Without HC(OMe)₃. ^d 2.5 Equiv of HC(OMe)₃ was used. ^e The reaction was conducted at reflux temperature. NR: no reaction

Since this transformation requires strong Brønsted acid like TfOH, we concentrated on using TfOH for further optimization experiments. The yield of the product was found to be decreased when the amount of catalyst loading was reduced to 10 mol% (Table 5.1, entry 16). Interestingly, this reaction worked without trimethyl orthoformate and gave moderate yield of the product **5.44a** after 24 h (Table 5.1, entry 17). Hence, the presence of trimethyl orthoformate increases both the rate and efficiency of the present transformation by forming more reactive acetal. Finally,

maximum yield of indene derivative **5.44a** (87%) was achieved when the reaction was performed in the presence of 2.5 equiv of trimethyl orthoformate and 25 mol% TfOH catalyst in acetonitrile solvent at RT (Table 5.1, entry 19). Attempt to reduce the amount of catalyst by increasing the reaction temperature failed as it gave only 57% yield of the product at reflux conditions (Table 5.1, entry 20).

5.3.2 Substrate scope

We examined the substrate scope of the present transformation using 2.5 equiv of trimethyl orthoformate and 25 mol% TfOH catalyst in acetonitrile solvent at RT and the results are shown Table 5.2. Moderate to good yields of indene derivatives **5.44** with electron donating (such as OMe, Me) and electron accepting groups (such as F, Cl) were obtained. The reaction of **5.41a** with cyclopentanone resulted in complex mixtures, perhaps due to I-strain associated with cyclopentanone **5.42c** on going from sp^2 to sp^3 hybridization.²⁵ However, the reaction went smoothly with cyclooctanone **5.42d** to give the indene derivative **5.44i** in 70% yield. It is noteworthy to mention that most of the indene derivatives were obtained as single diastereomer except **5.44d** and **5.44i** which were obtained as an inseparable mixture of two diastereomers in 1:0.6 and 1:0.88 ratio respectively. Though 25 mol% of TfOH was not sufficient to form indene derivative with open chain aliphatic ketones such as 3-pentanone **5.42e**, the reaction worked well in the

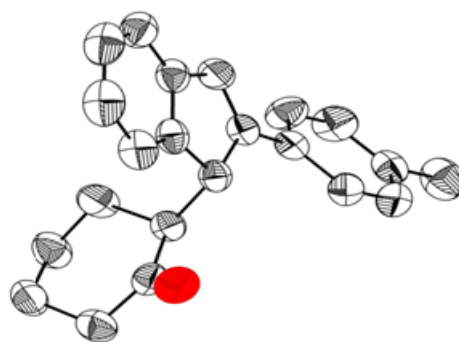


Figure 5.1: ORTEP of compound **5.44i**

presence of stoichiometric amount of TfOH. The reactions of **5.41a** and **5.41c** happened nicely with 3-pentanone in the presence of 1 equiv of TfOH and 2.5 equiv of TMOF to give the corresponding indene derivatives **5.44j** and **5.44k** in 72% and 63% yields respectively. The construction of indene skeleton depends highly on the nature of R^2 group on *o*-alkenylbenzaldehyde **5.41**. If R^2 is *p*-tolyl, corresponding *p*-tolyl substituted indene **5.44l** was furnished in 32% yield only along with 63% of naphthalene derivative **5.46**. The structure of the compound **5.44l** was further confirmed by single crystal X-ray analysis (Figure 5.1). Naphthalene derivative **5.46** was the sole product when R^2 is a better electron donating group such as *p*-anisyl and thiophene. The formation of naphthalene might have taken place *via* [4+2] cycloaddition of pyran intermediate with enol ether of cyclohexanone followed by elimination of aldehyde to generate naphthalene (Scheme 5.16). Thus, electron donating R^2 group facilitate the formation of pyran intermediate to undergo [4+2] cycloaddition reaction with enol ether. To the best of our knowledge this is the first observation where *o*-alkenylbenzaldehyde undergoes [4+2] cycloaddition with enolizable carbonyl compounds to afford naphthalene derivative.²⁶ It should be noted that the substrate (**5.41i** or **5.41j**) decomposed and did not yield naphthalene product in the

absence of trimethyl orthoformate. Hence, the *in situ* formed acetal facilitates the [4+2] benzannulation reaction between *o*-alkenylbenzaldehyde and cyclohexanone. Then the reaction was tried with the substrate **5.41k** having an additional methyl group on the alkene. The reaction resulted in two naphthalene derivatives **5.47** and **5.46** in 26% and 50% yields respectively. The formation naphthalene derivative **5.47** from **5.41k** by intramolecular cyclization is already known in the literature.^{16b} Whereas the naphthalene product **5.46** would have resulted from **5.41k** via [4+2] cycloaddition reaction. The present reaction conditions were not suitable for alkenylaldehyde **5.41l** and acetophenone since the reactions resulted in complex product mixtures (Table 5.2, entries 17 and 18).

Table 5.2 Substrate scope^a

Entry	Substrate	Ketone	Time	Product	Yield (%) ^b
1			30 min		87
2			15 min		79
3			2 h		74
4			15 min		63 <i>dr</i> = 1:0.6

Table 5.2 continued

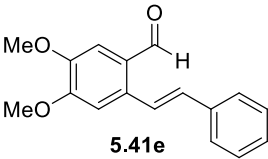
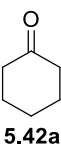
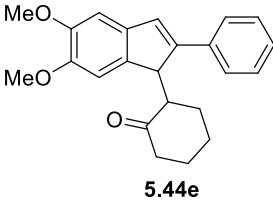
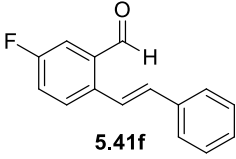
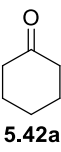
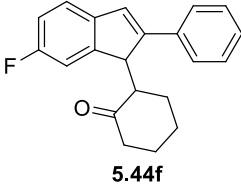
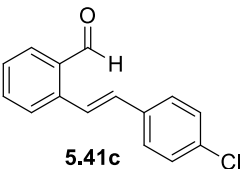
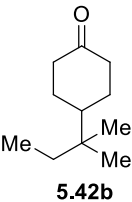
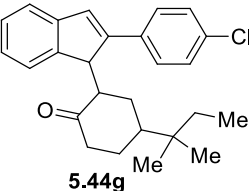
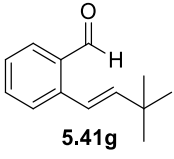
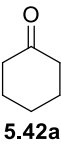
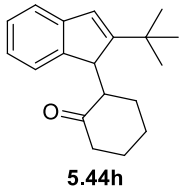
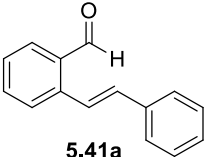
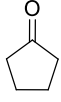
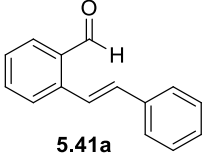
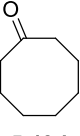
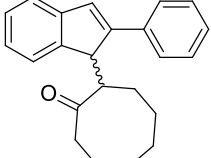
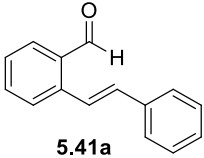
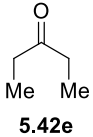
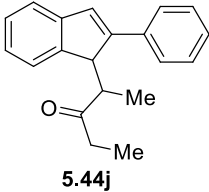
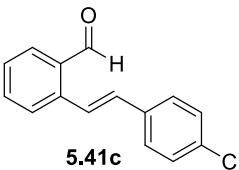
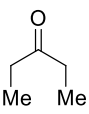
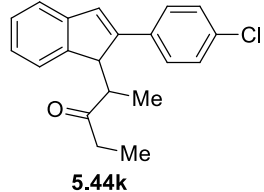
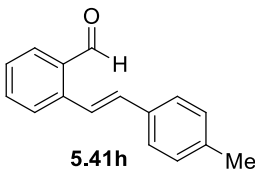
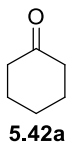
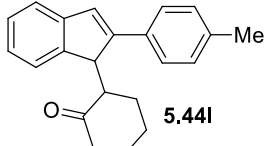
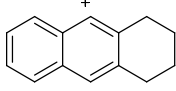
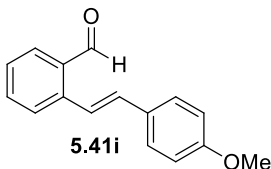
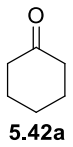
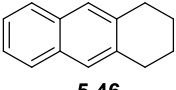
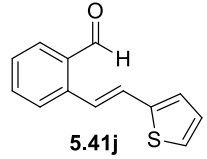
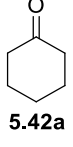
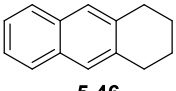
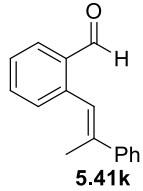
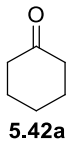
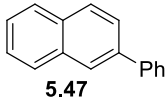
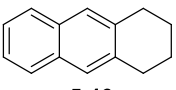
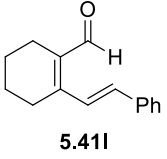
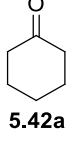
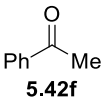
Entry	Substrate	Ketone	Time	Product	Yield (%) ^b
5	 5.41e	 5.42a	15 min	 5.44e	69
6	 5.41f	 5.42a	45 min	 5.44f	77
7	 5.41c	 5.42b	2 h	 5.44g	69
8	 5.41g	 5.42a	30 min	 5.44h	61
9	 5.41a	 5.42c	5 h	Not clean	---
10	 5.41a	 5.42d	1 h	 5.44i <i>dr</i> = 1:0.88	70
11 ^c	 5.41a	 5.42e	30 min	 5.44j	72

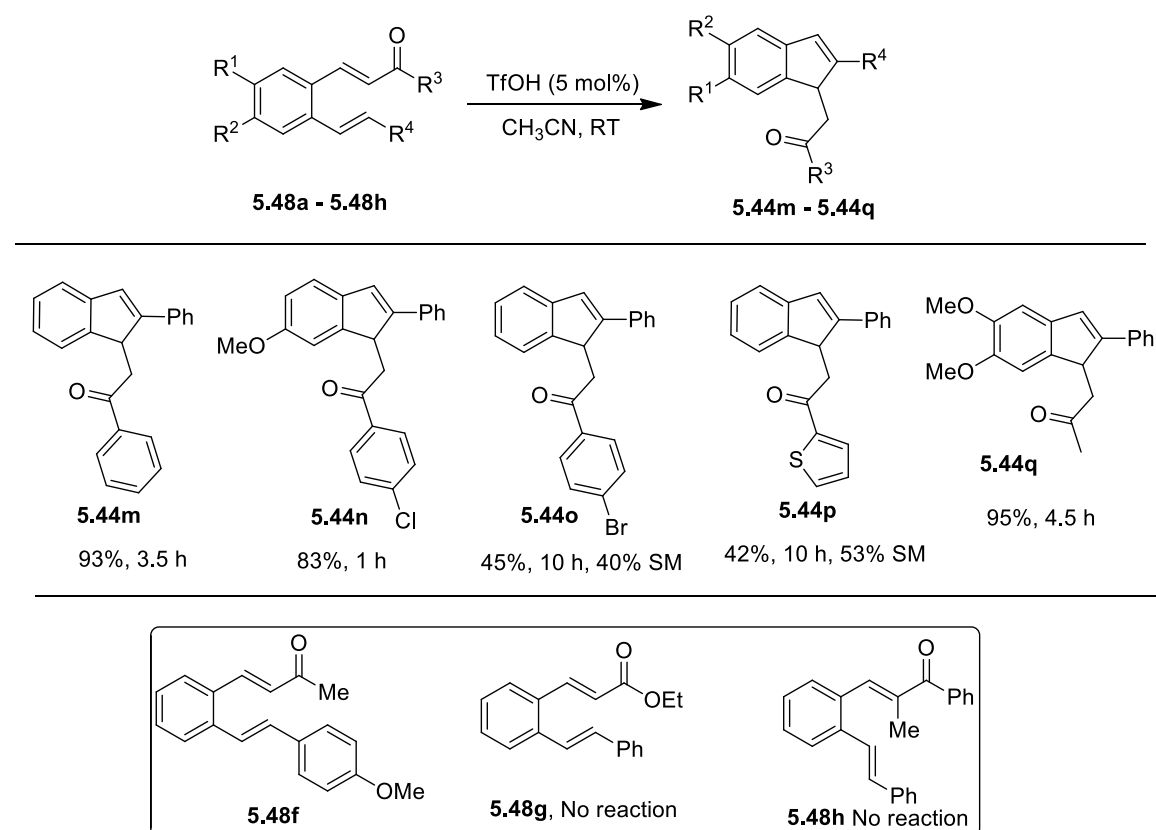
Table 5.2 continued

Entry	Substrate	Ketone	Time	Product	Yield (%) ^b
12 ^c	 5.41c	 5.42e	1 h	 5.44k	63
13	 5.41h	 5.42a	30 min	 5.44l +  5.46	32 63
14	 5.41i	 5.42a	30 min	 5.46	76
15	 5.41j	 5.42a	30 min	 5.46	74
16	 5.41k	 5.42a	30 min	 5.47 +  5.46	26 50
17	 5.41l	 5.42a	15 min	Not clean	---
18	5.41a	 5.42f	24	Not clean	---

^a All the reactions were carried out using 1.0 equiv of *o*-alkenylbenzaldehyde **5.41**, 1.2 equiv of enolizable ketone **5.42**, 2.5 equiv of HC(OMe)₃ and 25 mol% of TfOH at RT. ^b isolated yield. ^c 1.0 equiv of TfOH was used.

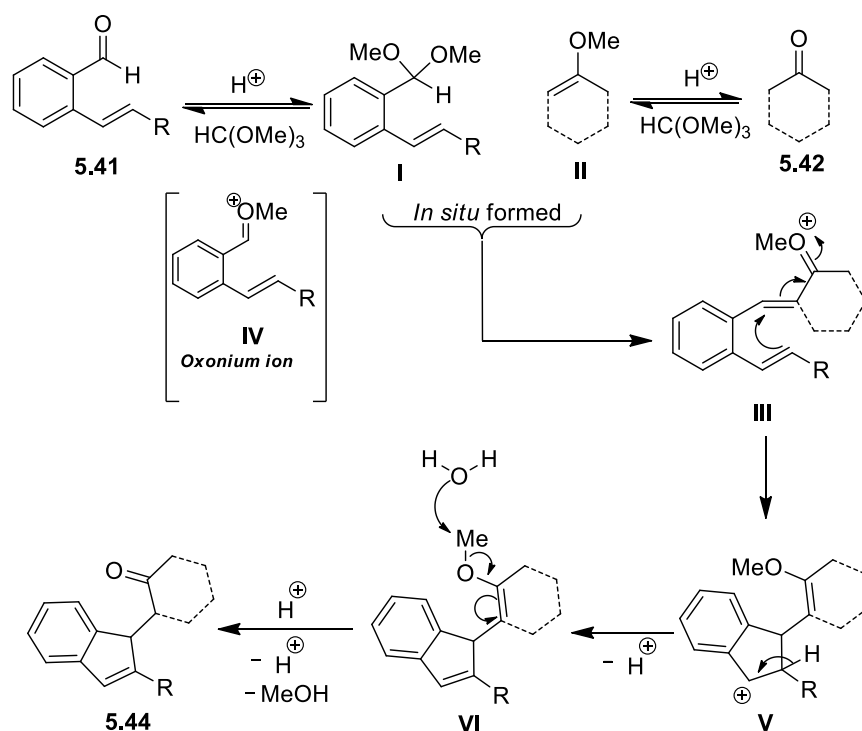
We believe that the reaction proceeds *via* the formation of chalcone type intermediate from aldehyde and enolizable ketone by Claisen-Schmidt condensation followed by 5-*exo-trig* cyclization to afford indene derivatives. Thus, chalcones **5.48** were prepared from corresponding acetophenones and *o*-alkenylbenzaldehydes **5.41** in the presence of KOH in methanol. Then the chalcones **5.48** were subjected separately to our standard reaction conditions. It was found that the reaction proceeded even in the absence of trimethyl orthoformate. The reaction of **5.48a** completed in 3.0 h with clean TLC and resulted in the indene derivative **5.44m** in 91% yield. It should be mentioned that this reaction proceeded in the presence of 5 mol% TfOH alone to give the indene product **5.44m** in excellent yield after 3.5 h. Using this protocol we prepared Cl, Br, OMe and thiophene substituted indene derivatives as shown in Figure 5.2. The reactions were sluggish when R³ of the chalcone is electron donating in nature such as *p*-Br-phenyl and thiophene and the corresponding indene derivatives (**5.44p** and **5.441q**) were isolated in 45% and 40% yields respectively along with their respective starting materials. This may be due to the fact that electrophilicity of carbonyl carbon of substrates is reduced by electron donating nature of Br and thiophene. An unidentified product was obtained when R⁴ of chalcone is 4-methoxy-phenyl substitution **5.48f**. The substrates **5.48g** and **5.48h** did not yield any product under the reaction conditions. The reason for no product formation with **5.48g** may be the electrophilicity of ester carbonyl group of substrate is less than that of carbonyl group.

Figure 5.2: Cyclization of chalcones



5.3.3 Mechanism for the formation of indene

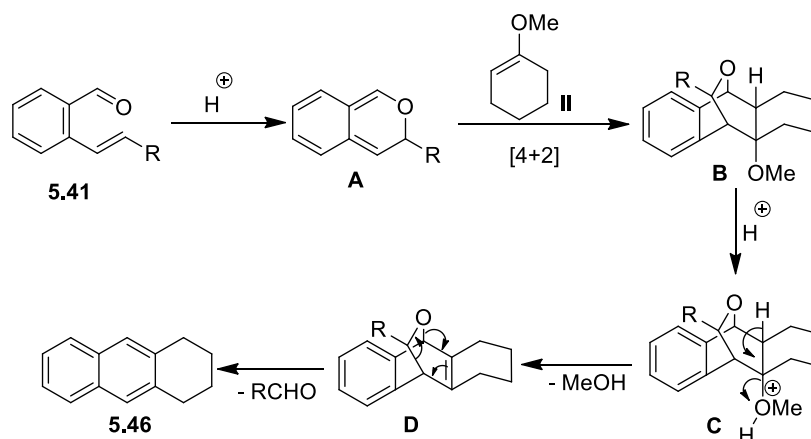
A plausible mechanistic pathway for the construction of indene framework from *o*-alkenylbenzaldehyde is depicted in Scheme 5.15. Initially, Claisen-Schmidt condensation would take place between the *in situ* formed acetal **I** from *o*-alkenylbenzaldehyde **5.41** and the enol ether **II** derived from ketone **5.42** in the presence of trimethyl orthoformate and TfOH to afford chalcone type intermediate **III**. This reaction might be facilitated by highly reactive oxonium ion intermediate **IV** formed from acetal. Intermediate **III** undergoes 5-*exo-trig* cyclization to form stable benzylic carbocation intermediate **V** which results in intermediate **VI** by elimination of proton. Subsequently, indene **5.44** derivative will be formed from **VI** by hydrolysis in the presence of TfOH.



Scheme 5.15: Plausible mechanistic pathway for indene formation

5.3.4 Mechanism for the formation naphthalene via [4+2] benzannulation

A plausible mechanism for the formation of naphthalene from *o*-alkenylbenzaldehyde having electron donating group on the chalcone and enolizable ketone is proposed in Scheme 5.16. Pyran type intermediate²⁷ **A** formed from *o*-alkenylbenzaldehyde **5.41** would undergo [4+2] cycloaddition reaction with enol ether **II** to form intermediate **B**. In the presence of acid, methanol will be eliminated from the intermediate **C** to give intermediate **D** from which naphthalene **5.46** will be formed by the elimination of aldehyde (R-CHO) via sigmatropic rearrangement reaction. The driving force for the reaction may be formation of stable aromatic compound.



Scheme 5.16: Plausible mechanistic pathway for naphthalene formation

5.4 Conclusions

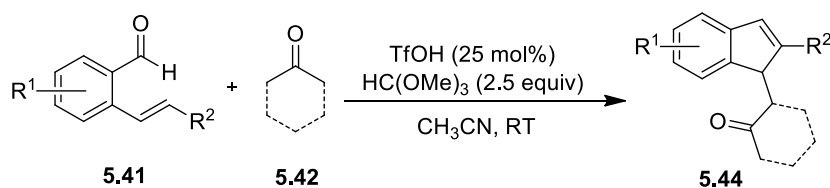
In summary, we have developed a new protocol for the synthesis of indene derivatives from *o*-alkenylbenzaldehydes and enolizable ketones in the presence of trimethyl orthoformate and triflic acid. This cascade reaction involves Claisen-Schmidt condensation followed by 5-*exo-trig* cyclization. *In situ* formed acetal assists the Claisen-Schmidt condensation by increasing the electrophilicity of carbonyl carbon of *o*-alkenylbenzaldehyde through oxonium ion formation and enhances the nucleophilicity of α -carbon of ketone *via* the formation of enol ether. We have also shown that the chalcones derived from *o*-alkenylbenzaldehydes and ketones can effectively be transformed into indene derivatives in the presence TfOH catalyst alone. Moreover, it is disclosed that *o*-alkenylbenzaldehydes with electron donating substitution at R^2 group undergoes [4+2] cycloaddition with enolizable carbonyl compounds to afford naphthalene derivatives.

5.5 Experimental section

For general information see Chapter 2, Section 2.5.1. All the *o*-alkenylbenzaldehydes used in this study were prepared by following the standard Heck coupling reaction of corresponding bromo or iodo compounds and styrene derivatives. All the *o*-alkenylbenzaldehydes are already reported in the literature and the data of the prepared alkenylbenzaldehydes matched with those literature data.¹⁶

5.5.1 Experimental procedures, spectral and analytical data

General procedure for the synthesis of indene derivatives:



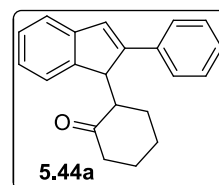
Triflic acid (25 mol%) was charged into a solution of compound **5.41** (1.0 equiv), cyclic ketone **5.42** (1.2 equiv) and trimethyl orthoformate (2.5 equiv) in acetonitrile solvent (5 mL/1 mmol) at room temperature. The resulting mixture was stirred at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. After completion of the reaction, solvent was evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **5.44**.

For acyclic ketone, 1.0 equiv of TfOH and 2.5 equiv of trimethyl orthoformate were used.

Analytical data of compounds **5.44**

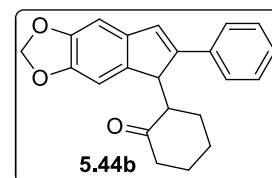
2-(2-Phenyl-1*H*-inden-1-yl)cyclohexanone **5.44a**:

It was obtained as colourless liquid in 87% yield. $R_f = 0.45$ (in 10% EtOAc/Hexanes); IR (neat): 2936, 1709, 1604, 1489, 1462, 1314, 1133, 755, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.46 (d, $J = 7.2$ Hz, 2H), 7.42-7.38 (m, 3H), 7.35 (d, $J = 7.2$ Hz, 1H), 7.31 (d, $J = 7.2$ Hz, 1H), 7.28-7.23 (m, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 7.07 (s, 1H), 4.91 (s, 1H), 2.83 (dd, $J = 4.8, 12.0$ Hz, 1H), 2.58-2.53 (m, 1H), 2.31 (td, $J = 6.4, 14.4$ Hz, 1H), 1.96-1.91 (m, 1H), 1.65-1.42 (m, 2H), 1.37-1.26 (m, 2H), 0.87-0.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.7, 149.6, 145.5, 144.8, 135.2, 128.8, 128.1, 127.5, 126.82, 126.76, 125.2, 124.9, 120.9, 51.4, 47.5, 42.0, 26.4, 25.3, 24.4. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{20}\text{O}$ $[\text{M}+\text{H}]^+$ 289.1592; found 289.1579.



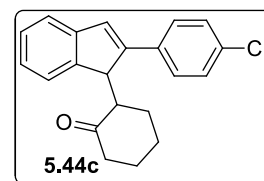
2-(6-Phenyl-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl)cyclohexanone **5.44b**:

It was obtained as yellow oil in 79% yield. $R_f = 0.55$ (in 10% EtOAc/Hexanes); IR (neat): 1703, 1473, 1325, 1232, 1040, 936, 881, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.36 (m, 4H), 7.29-7.26 (m, 1H), 6.96 (s, 2H), 6.83 (s, 1H), 5.94 (d, $J = 1.2$ Hz, 2H), 4.78 (s, 1H), 2.80 (dd, $J = 4.0, 11.6$ Hz, 1H), 2.53 (d, $J = 14.8$ Hz, 1H), 2.33 (dd, $J = 6.4, 13.2$ Hz, 1H), 1.97-1.86 (m, 1H), 1.63-1.48 (m, 2H), 1.38-1.31 (m, 2H), 0.90-0.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.9, 148.6, 146.7, 145.8, 139.7, 138.6, 135.2, 128.8, 127.8, 127.2, 126.5, 106.9, 101.7, 100.9, 51.6, 47.2, 42.0, 26.5, 25.3, 24.5.



2-(2-(4-Chlorophenyl)-1*H*-inden-1-yl)cyclohexanone **5.44c**:

It was obtained as pale yellow solid in 74% yield. mp 83-85 $^{\circ}\text{C}$; $R_f = 0.6$ (in 10% EtOAc/Hexanes); IR (KBr): 2931, 1703, 1489, 1492, 1308, 1188, 1095, 1013, 832, 755 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.40 (m, 6H), 7.25 (t, $J = 7.6$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.06 (s, 1H),

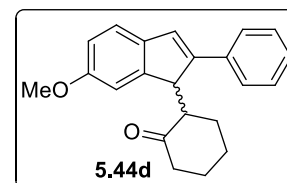


4.87 (s, 1H), 2.76 (dd, $J = 5.2, 12.4$ Hz, 1H), 2.56 (d, $J = 14.8$ Hz, 1H), 2.32 (td, $J = 6.0, 13.6$ Hz, 1H), 1.97-1.92 (m, 1H), 1.58-1.43 (m, 2H), 1.37-1.26 (m, 2H), 0.85-0.76 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.5, 148.3, 145.5, 144.6, 133.6, 133.3, 129.1, 128.7, 128.0, 126.9, 125.2, 125.1, 121.1, 51.3, 47.6, 41.9, 26.3, 25.2, 24.4.

2-(5-Methoxy-2-phenyl-1H-inden-1-yl)cyclohexanone 5.44d:

Two diastereomers (1:0.6); It was obtained as yellow oil in 63% yield.

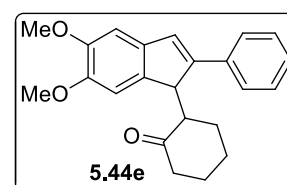
$R_f = 0.4$ (in 10% EtOAc/Hexanes); IR (neat): 2931, 1703, 1604, 1473, 1276, 1221, 1144, 1029, 876, 771, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.46-7.38 (m, 7H), 7.32-7.22 (m, 4H), 7.02 (s, 2H), 6.91 (s,



1H), 6.81 (d, $J = 8.4$ Hz, 0.6H), 6.69 (d, $J = 8.4$ Hz, 1H), 4.86 (s, 0.6H), 4.84 (s, 1H), 3.82 (s, 3.3H), 3.81 (s, 2H), 2.85-2.78 (m, 1.7H), 2.54 (dd, $J = 1.6, 14.8$ Hz, 1.6H), 2.35-2.26 (m, 2.5H), 1.93-1.82 (m, 2.6H), 1.57-1.25 (m, 6.5H), 0.89-0.82 (m, 1.7H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.8, 159.0, 157.9, 151.0, 147.5, 147.4, 146.1, 138.0, 137.7, 135.3, 135.1, 128.8, 128.1, 127.7, 127.6, 127.1, 126.8, 126.5, 125.7, 121.2, 112.4, 111.8, 110.6, 104.5, 55.5, 55.3, 51.5, 47.5, 46.9, 42.0, 27.0, 26.5, 26.4, 25.3, 25.2, 24.4.

2-(5,6-Dimethoxy-2-phenyl-1H-inden-1-yl)cyclohexanone 5.44e:

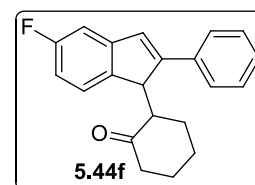
It was obtained as pale yellow solid in 69% yield. mp 135-137 $^{\circ}\text{C}$; $R_f = 0.55$ (in 30% EtOAc/Hexanes); IR (KBr): 2931, 1703, 1593, 1555, 1488, 1462, 1341, 1215, 1100, 876, 771, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.43-7.36 (m, 4H), 7.29-7.26 (m, 1H), 7.03 (s, 1H),



7.00 (s, 1H), 6.91 (s, 1H), 4.80 (s, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 2.83 (dd, $J = 4.0, 12.0$ Hz, 1H), 2.54 (d, $J = 14.8$ Hz, 1H), 2.33 (td, $J = 6.0, 13.6$ Hz, 1H), 1.99-1.95 (m, 1H), 1.59-1.32 (m, 4H), 0.89-0.78 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 212.3, 148.4, 147.1, 138.3, 137.6, 135.2, 128.8, 127.8, 127.1, 126.5, 109.4, 104.3, 56.2, 55.9, 51.6, 47.5, 42.1, 26.7, 25.4, 24.5.

2-(5-Fluoro-2-phenyl-1H-inden-1-yl)cyclohexanone 5.44f:

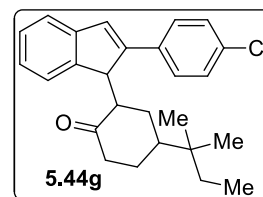
It was obtained as pale yellow liquid in 77% yield; $R_f = 0.4$ (in 10% EtOAc/Hexanes); IR (neat): 1705, 1590, 1464, 1257, 1208, 1093, 880, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.44-7.37 (m, 4H), 7.32-7.30 (m, 1H), 7.26-7.23 (m, 1H), 7.16 (dd, $J = 2.0, 9.6$ Hz, 1H), 7.01 (s, 1H),



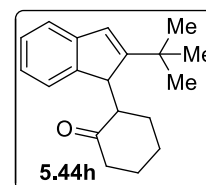
6.95 (td, $J = 2.0, 9.2$ Hz, 1H), 4.87 (s, 1H), 2.83 (dd, $J = 4.8, 12.0$ Hz, 1H), 2.55 (dt, $J = 2.0, 4.0$ Hz, 1H), 2.32 (td, $J = 6.4, 14.8$ Hz, 1H), 1.97-1.92 (m, 1H), 1.58-1.48 (m, 2H), 1.39-1.30 (m, 2H), 0.87-0.76 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.5, 161.3 (d, $J = 242.0$ Hz), 149.4, 147.6 (d, $J = 9.0$ Hz), 140.7, 134.9, 128.9, 127.6 (d, $J = 37.0$ Hz), 126.7, 121.3 (d, $J = 9.0$ Hz), 113.6 (d, $J = 22.0$ Hz), 113.1 (d, $J = 24.0$ Hz), 51.4, 47.8, 41.9, 26.4, 25.3, 24.4.

2-(2-(4-Chlorophenyl)-1H-inden-1-yl)-4-(tert-pentyl)cyclohexanone 5.44g:

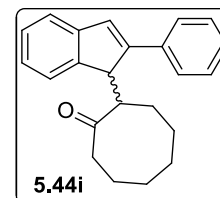
It was obtained as yellow oil in 69% yield. $R_f = 0.45$ (in 10% EtOAc/Hexanes); IR (neat): 2970, 1704, 1599, 1490, 1457, 1188, 1090, 1001, 821, 755, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.32 (m, 5H), 7.25 (t, $J = 5.6$ Hz, 2H), 7.14 (t, $J = 7.2$ Hz, 1H), 7.04 (s, 1H), 4.83 (s, 1H), 2.74 (dd, $J = 4.4, 12.8$ Hz, 1H), 2.57 (d, $J = 14.4$ Hz, 1H), 2.37-2.30 (m, 1H), 1.90-1.87 (m, 1H), 1.30-1.22 (m, 3H), 1.07-1.00 (m, 3H), 0.62-0.59 (m, 6H), 0.54 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.9, 148.5, 145.3, 144.5, 133.9, 133.3, 129.1, 128.9, 128.1, 126.9, 125.2, 125.1, 121.2, 50.9, 47.9, 43.6, 41.4, 34.7, 32.6, 26.8, 25.4, 24.1, 23.9, 7.9.

**2-(2-(tert-Butyl)-1H-inden-1-yl)cyclohexanone 5.44h:**

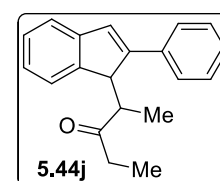
It was obtained as pale yellow liquid in 61% yield. $R_f = 0.6$ (in 10% EtOAc/Hexanes); IR (neat): 2953, 1709, 1463, 1364, 1200, 1128, 1030, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.23 (d, $J = 7.2$ Hz, 1H), 7.19-7.16 (m, 2H), 7.03 (td, $J = 1.2, 7.2$ Hz, 1H), 6.60 (s, 1H), 4.47 (s, 1H), 3.16 (dd, $J = 5.2, 12.8$ Hz, 1H), 2.60-2.56 (m, 1H), 2.43-2.35 (m, 2H), 2.04-2.00 (m, 1H), 1.69-1.66 (m, 1H), 1.53-1.47 (m, 2H), 1.27 (s, 9H), 0.93-0.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.2, 159.3, 145.4, 144.7, 126.7, 126.4, 124.5, 124.0, 120.0, 51.3, 49.0, 42.0, 33.7, 30.9, 26.4, 25.3, 24.7.

**2-(2-Phenyl-1H-inden-1-yl)cyclooctanone 5.44i:**

Two diastereomers (1:0.88); It was obtained as pale yellow oil in 70% yield; $R_f = 0.3$ (in 10% EtOAc/Hexanes); IR (neat): 1688, 1459, 1448, 765, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.55-7.51 (m, 4H), 7.43-7.33 (m, 9H), 7.30-7.25 (m, 4H), 7.20 (td, $J = 1.2, 7.6$ Hz, 1H), 7.15 (td, $J = 1.2, 7.6$ Hz, 1H), 7.08 (s, 1H), 6.94 (s, 1H), 4.46 (s, 1H), 4.27 (d, $J = 4.0$ Hz, 1H), 2.93-2.90 (m, 2H), 2.64-2.57 (m, 1H), 2.52-2.46 (m, 1H), 2.04-1.89 (m, 2H), 1.81-1.69 (m, 3H), 1.57-1.34 (m, 10H), 1.28-1.16 (m, 6H), 1.25-1.05 (m, 2H), 0.96-0.87 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 219.4, 218.3, 150.3, 150.0, 145.9, 145.0, 144.8, 144.4, 136.5, 135.3, 129.1, 128.8, 128.7, 128.4, 127.6, 127.4, 127.3, 127.2, 127.1, 125.1, 124.9, 124.6, 123.7, 121.3, 121.1, 54.2, 53.4, 52.1, 51.4, 41.8, 41.0, 28.6, 27.9, 27.4, 27.3, 26.7, 26.6, 25.2, 24.9, 24.3. HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{24}\text{O}$ $[\text{M}+\text{H}]^+$ 317.1905; found 317.1901.

**2-(2-Phenyl-1H-inden-1-yl)pentan-3-one 5.44j:**

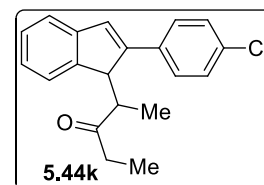
It was obtained as pale yellow liquid in 72% yield. $R_f = 0.6$ (in 10% EtOAc/Hexanes); IR (KBr): 2969, 1703, 1599, 1489, 1462, 1188, 974, 755, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.51 (d, $J = 7.2$ Hz, 2H), 7.42 (t, J



= 7.2 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.28-7.22 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.09 (s, 1H), 4.68 (s, 1H), 2.99 (qd, J = 2.4, 6.8 Hz, 1H), 2.75-2.54 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H), 0.50 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 213.5, 149.7, 144.9, 144.2, 135.2, 128.9, 128.3, 127.6, 127.0, 126.9, 124.8, 124.4, 121.1, 49.6, 46.5, 33.9, 8.8, 8.0. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{20}\text{O}$ $[\text{M}+\text{H}]^+$ 277.1592; found 277.1582.

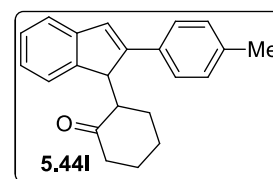
2-(2-(4-Chlorophenyl)-1H-inden-1-yl)pentan-3-one **5.44k**:

It was obtained as pale yellow oil in 63% yield. R_f = 0.45 (in 10% EtOAc/Hexanes); IR (neat): 1709, 1495, 1462, 1380, 1095, 1002, 826, 755 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.43-7.35 (m, 5H), 7.28-7.21 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.07 (s, 1H), 4.63 (s, 1H), 2.93-2.90 (m, 1H), 2.68-2.53 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H), 0.49 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 213.2, 148.4, 144.6, 144.2, 133.7, 133.4, 129.1, 128.8, 128.1, 127.1, 125.1, 124.4, 121.3, 49.6, 46.5, 33.9, 8.8, 8.0.

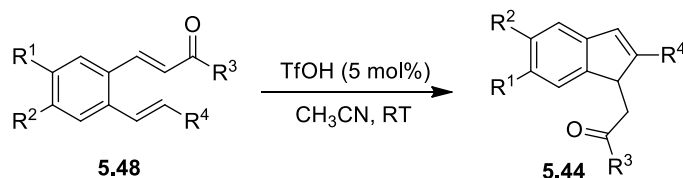


2-(2-(*p*-Tolyl)-1H-inden-1-yl)cyclohexanone **5.44l**:

It was obtained as colourless solid in 32%. mp 124-126 $^{\circ}\text{C}$; R_f = 0.4 (in 10% EtOAc/Hexanes); IR (KBr): 2925, 1709, 1511, 1467, 1314, 1193, 1122, 1023, 821, 755 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.32 (m, 4H), 7.25-7.20 (m, 3H), 7.12 (t, J = 7.2 Hz, 1H), 7.03 (s, 1H), 4.89 (s, 1H), 2.83 (dd, J = 7.8, 12.4 Hz, 1H), 2.57-2.53 (m, 1H), 2.38 (s, 3H), 2.35-2.27 (m, 1H), 1.96-1.91 (m, 1H), 1.56-1.45 (m, 2H), 1.37-1.31 (m, 2H), 0.86-0.75 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 211.8, 149.7, 145.5, 145.0, 137.4, 132.4, 129.6, 127.4, 126.7, 125.2, 124.7, 120.8, 51.5, 47.5, 42.0, 26.4, 25.2, 24.5, 21.2. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{22}\text{O}$ $[\text{M}+\text{H}]^+$ 303.1749; found 303.1748.



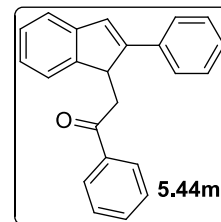
General procedure for cyclization of chalcones



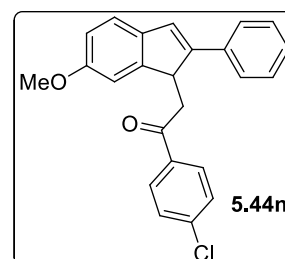
Triflic acid (5 mol%) was charged into a solution of compound **5.48** (1.0 equiv) in acetonitrile solvent (5 mL/1 mmol) at room temperature. The resulting mixture was stirred at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. After the completion of the reaction, solvent was evaporated under reduced pressure. The crude was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **5.44**.

1-Phenyl-2-(2-phenyl-1*H*-inden-1-yl)ethanone 5.44m:

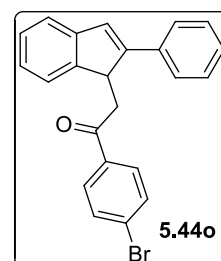
It was obtained as colourless solid in 93% yield. mp 131-133 °C; R_f = 0.65 (in 10% EtOAc/Hexanes); IR (KBr): 1682, 1594, 1495, 1441, 1221, 969, 887, 745. 684 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, J = 7.6 Hz, 2H), 7.54-7.50 (m, 3H), 7.42-7.37 (m, 6H), 7.30-7.24 (m, 2H), 7.16 (s, 1H), 7.10 (t, J = 7.6 Hz, 1H), 4.82 (d, J = 10.0 Hz, 1H), 3.39 (dd, J = 2.4, 18.0 Hz, 1H), 3.00 (dd, J = 10.4, 18.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.1, 150.5, 148.2, 143.6, 136.9, 134.8, 133.2, 128.9, 128.6, 128.1, 127.6, 127.1, 126.8, 125.1, 124.0, 121.1, 44.1, 41.1.

**1-(4-Chlorophenyl)-2-(6-methoxy-2-phenyl-1*H*-inden-1-yl)ethanone 5.44n:**

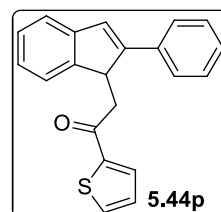
It was obtained as pale yellow solid in 83% yield. mp 113-115 °C; R_f = 0.65 (in 20% EtOAc/Hexanes); IR (KBr): 1682, 1594, 1473, 1435, 1275, 1219, 1086, 870, 763, 691 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.82 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.37-7.35 (m, 4H), 7.29-7.24 (m, 2H), 7.08 (s, 1H), 7.00 (s, 1H), 6.81 (d, J = 6.4 Hz, 1H), 4.74 (d, J = 9.6 Hz, 1H), 3.73 (s, 3H), 3.35 (d, J = 18.0 Hz, 1H), 2.95 (dd, J = 10.4, 18.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 198.0, 158.1, 149.9, 148.1, 139.7, 136.7, 135.2, 134.9, 129.5, 128.8, 127.2, 126.7, 126.4, 121.6, 112.6, 110.7, 55.5, 40.1, 41.2. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{19}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 375.1152; found 375.1149.

**1-(4-Bromophenyl)-2-(2-phenyl-1*H*-inden-1-yl)ethanone 5.44o:**

It was obtained as colourless solid in 45% yield. mp 135-137 °C; R_f = 0.6 (in 10% EtOAc/Hexanes); IR (KBr): 1687, 1578, 1534, 1495, 1397, 1216, 1068, 821, 761, 739, 684 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.75 (d, J = 8.8 Hz, 2H), 7.53 (t, J = 8.4 Hz, 3H), 7.41-7.37 (m, 4H), 7.31-7.25 (m, 2H), 7.16 (s, 1H), 7.11 (td, J = 0.8, 7.2 Hz, 1H), 4.79 (d, J = 10.0 Hz, 1H), 3.34 (dd, J = 2.4, 18.0 Hz, 1H), 2.95 (dd, J = 10.0, 18.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 198.1, 150.3, 147.9, 143.6, 135.6, 134.7, 131.9, 129.7, 128.9, 128.4, 127.7, 127.2, 126.8, 125.2, 123.9, 121.2, 44.0, 41.0. HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{17}\text{BrO}$ $[\text{M}+\text{H}]^+$ 389.0541; found 389.0540.

**2-(2-Phenyl-1*H*-inden-1-yl)-1-(thiophen-2-yl)ethanone 5.44p:**

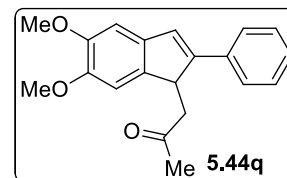
It was obtained as colourless solid in 42% yield. mp 90-92 °C; R_f = 0.55 (in 10% EtOAc/Hexanes); IR (KBr): 1660, 1523, 1452, 1419, 1358, 127, 1073, 936, 761, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, J = 5.2 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 4.0 Hz, 2H), 7.40 (td, J = 0.8, 6.8 Hz,



4H), 7.31-7.25 (m, 2H), 7.16 (s, 1H), 7.11 (t, $J = 7.2$ Hz, 1H), 7.04 (t, $J = 4.0$ Hz, 1H), 4.77 (d, $J = 10.0$ Hz, 1H), 3.35 (dd, $J = 2.4, 17.2$ Hz, 1H), 2.90 (dd, $J = 10.4, 17.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 192.0, 150.2, 147.8, 144.2, 143.6, 134.7, 133.9, 132.2, 128.9, 128.1, 127.6, 127.1, 126.8, 125.2, 123.9, 121.1, 44.2, 41.6.

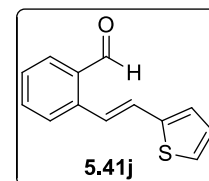
1-(5,6-Dimethoxy-2-phenyl-1*H*-inden-1-yl)propan-2-one 5.44q:

It was obtained as pale brown solid in 95% yield. mp 108-110 °C; $R_f = 0.6$ (in 10% EtOAc/Hexanes); IR (KBr): 1709, 1484, 1462, 1341, 1215, 1095, 1013, 865, 755, 684 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.44 (dd, $J = 1.2, 8.4$ Hz, 2H), 7.39 (t, $J = 7.6$ Hz, 2H), 7.29-7.25 (m, 1H), 7.02 (d, $J = 4.8$ Hz, 2H), 6.94 (s, 1H), 4.45 (d, $J = 10.0$ Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.97 (dd, $J = 2.4, 18.0$ Hz, 1H), 2.35 (dd, $J = 10.4, 18.4$ Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 208.0, 149.0, 148.6, 147.4, 140.6, 136.3, 134.9, 128.8, 127.2, 126.7, 126.4, 108.1, 104.6, 56.2, 56.0, 46.1, 44.0, 30.6. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{H}]^+$ 309.1491; found 309.1489.



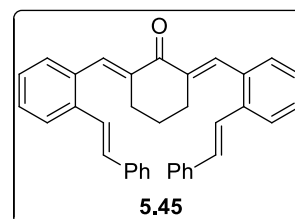
(*E*)-2-(2-(Thiophen-2-yl)vinyl)benzaldehyde 5.41j:

It was obtained as yellow liquid in 77% yield. $R_f = 0.35$ (in 10% EtOAc/Hexanes); IR (neat): 1698, 1627, 1594, 1561, 1479, 1194, 958, 821, 756, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.31 (s, 1H), 7.88-7.81 (m, 2H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.58-7.53 (m, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 5.2$ Hz, 1H), 7.18 (d, $J = 15.6$ Hz, 1H), 7.14 (d, $J = 3.6$ Hz, 1H), 7.02 (dd, $J = 3.6, 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 192.4, 142.4, 139.4, 133.7, 132.7, 132.2, 127.7, 127.5, 127.1, 126.8, 125.5, 124.0.



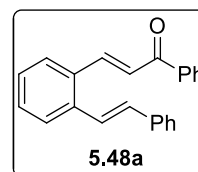
(2*E*,6*E*)-2,6-bis(2-((*E*)-styryl)benzylidene)cyclohexanone 5.45:

It was obtained as yellow solid in 69% yield. mp 108-110 °C; $R_f = 0.45$ (in 10% EtOAc/Hexanes); IR (KBr): 1601, 1475, 1442, 1273, 1164, 967, 765, 689 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.06 (s, 2H), 7.70 (d, $J = 7.6$ Hz, 2H), 7.51 (d, $J = 7.6$ Hz, 4H), 7.35 (t, $J = 7.6$ Hz, 6H), 7.28-7.24 (m, 8H), 7.06 (d, $J = 16.4$ Hz, 2H), 2.68 (t, $J = 5.6$ Hz, 4H), 1.68 (t, $J = 5.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 189.8, 137.9, 137.2, 137.0, 136.1, 134.6, 131.0, 129.5, 128.7, 128.5, 127.9, 127.0, 126.8, 126.2, 125.7, 28.4, 23.2. HRMS (ESI): calcd for $\text{C}_{36}\text{H}_{30}\text{O}$ $[\text{M}+\text{H}]^+$ 479.2375; found 479.2373.

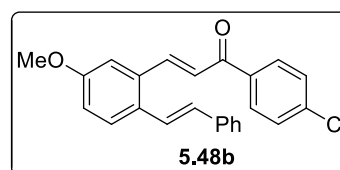


(E)-1-Phenyl-3-(2-((E)-styryl)phenyl)prop-2-en-1-one 5.48a:

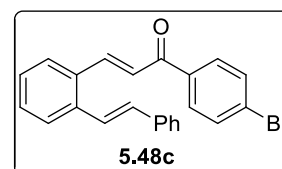
The compound was prepared by the following the reported procedure.²⁸ It was obtained as yellow solid in 83% yield. mp 112-114 °C; R_f = 0.45 (in 20% EtOAc/Hexanes); IR (KBr): 1665, 1605, 1446, 1331, 1205, 1113, 969, 761, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.26 (d, J = 15.6 Hz, 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.69 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.58-7.44 (m, 7H), 7.39-7.25 (m, 5H), 7.01 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 190.2, 142.6, 138.1, 137.0, 133.4, 132.8, 132.7, 130.2, 128.7, 128.6, 128.5, 128.1, 127.7, 127.5, 127.0, 126.8, 125.6, 124.3.

**(E)-1-(4-Chlorophenyl)-3-(5-methoxy-2-((E)-styryl)phenyl)prop-2-en-1-one 5.48b:**

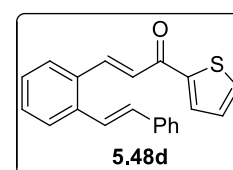
The compound was prepared by the following the reported procedure.²⁸ It was obtained as yellow solid in 76% yield. mp 98-100 °C; R_f = 0.35 (in 20% EtOAc/Hexanes); IR (KBr): 2838, 1643, 1605, 1556, 1473, 1293, 1271, 1172, 1090, 953, 838, 816, 739, 679 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.29 (d, J = 15.2 Hz, 1H), 7.84 (d, J = 2.8 Hz, 1H), 7.66-7.63 (m, 3H), 7.55-7.51 (m, 3H), 7.41-7.24 (m, 6H), 7.16 (s, 1H), 7.01 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 181.8, 145.5, 141.8, 138.1, 137.0, 133.9, 133.2, 132.7, 131.8, 130.3, 128.7, 128.2, 128.1, 127.7, 127.5, 127.0, 126.8, 125.5, 124.0. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{19}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 375.1152; found 375.1152.

**(E)-1-(4-Bromophenyl)-3-(2-((E)-styryl)phenyl)prop-2-en-1-one 5.48c:**

The compound was prepared by the following the reported procedure.²⁸ It was obtained as yellow solid in 74% yield. mp 111-113 °C; R_f = 0.4 (in 10% EtOAc/Hexanes); IR (KBr): 1710, 1588, 1495, 1385, 1303, 1215, 1073, 1007, 963, 826, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.27 (d, J = 15.6 Hz, 1H), 7.89 (dd, J = 1.6, 6.8 Hz, 2H), 7.70-7.64 (m, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.41-7.30 (m, 5H), 7.01 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 189.1, 143.2, 138.2, 137.0, 136.8, 133.2, 132.9, 131.9, 130.5, 130.0, 128.8, 128.2, 128.0, 127.8, 127.5, 127.1, 126.8, 125.5, 123.7. HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{17}\text{BrO}$ $[\text{M}+\text{H}]^+$ 389.0541; found 389.0540.

**(E)-3-(2-((E)-styryl)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one 5.48d:**

The compound was prepared by the following the reported procedure.²⁸ It was obtained as yellow solid in 91% yield. mp 117-119 °C; R_f = 0.5 (in 20% EtOAc/Hexanes); IR (KBr): 1638, 1594, 1523, 1413, 1227, 1057, 958, 871, 756, 723, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.29 (d, J =

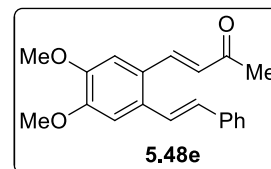


15.2 Hz, 1H), 7.84 (d, $J = 2.8$ Hz, 1H), 7.66-7.63 (m, 3H), 7.55-7.51 (m, 3H), 7.41-7.24 (m, 6H), 7.16 (s, 1H), 7.01 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 181.8, 145.5, 141.8, 138.1, 137.0, 133.9, 133.2, 132.7, 131.8, 130.3, 128.7, 128.2, 128.1, 127.7, 127.5, 127.0, 126.8, 125.5, 124.0. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{16}\text{OS}$ $[\text{M}+\text{H}]^+$ 317.1000; found 317.0996.

(*E*)-4-(4,5-Dimethoxy-2-((*E*)-styryl)phenyl)but-3-en-2-one 5.48e:

The compound was prepared by the following the reported procedure.²⁸

It was obtained as yellow solid in 95% yield. mp 130-132 °C; $R_f = 0.4$ (in 20% EtOAc/Hexanes); IR (KBr): 1649, 1589, 1512, 1446, 1276, 1243, 1200, 1095, 750, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.95

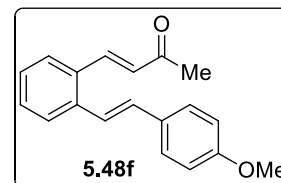


(d, $J = 16.0$ Hz, 1H), 7.53 (d, $J = 7.2$ Hz, 2H), 7.43-7.37 (m, 3H), 7.32-7.26 (m, 1H), 7.07 (s, 2H), 6.90 (d, $J = 16.0$ Hz, 1H), 6.59 (d, $J = 16.0$ Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 198.2, 151.1, 148.9, 140.5, 137.0, 132.0, 131.7, 128.8, 128.0, 126.9, 126.6, 125.3, 125.0, 109.2, 108.9, 56.0, 27.6. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{H}]^+$ 309.1491; found 309.1492.

(*E*)-4-(2-((*E*)-4-Methoxystyryl)phenyl)but-3-en-2-one 5.48f:

The compound was prepared by the following the reported procedure.²⁸

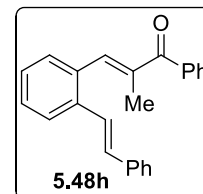
It was obtained as yellow oil in 87% yield. $R_f = 0.45$ (in 20% EtOAc/Hexanes); IR (neat): 2838, 1665, 1605, 1512, 1358, 1254, 1172, 1030, 821, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, $J =$



16.0 Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.28-7.23 (m, 2H), 6.91 (dd, $J = 3.6, 12.4$ Hz, 3H), 6.64 (d, $J = 16.0$ Hz, 1H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 198.1, 159.6, 141.2, 138.1, 132.5, 130.1, 129.7, 128.8, 127.9, 127.4, 127.2, 126.9, 123.1, 114.1, 55.2, 27.7.

(*E*)-2-Methyl-1-phenyl-3-(2-((*E*)-styryl)phenyl)prop-2-en-1-one 5.48h:

The compound was prepared by the following the reported procedure.²⁸ It was obtained as colourless solid in 68% yield. mp 102-104 °C; $R_f = 0.4$ (in 20% EtOAc/Hexanes); IR (KBr): 1638, 1490, 1446, 1385, 1265, 1008, 969, 909, 767, 706 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.81 (d, $J = 7.2$ Hz, 2H), 7.67



(d, $J = 7.2$ Hz, 1H), 7.53-7.25 (m, 12H), 7.16 (d, $J = 16.0$ Hz, 1H), 7.00 (d, $J = 16.0$ Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.3, 140.9, 138.4, 138.3, 137.1, 136.3, 134.3, 131.8, 131.2, 129.4, 129.3, 128.7, 128.5, 128.2, 128.0, 127.2, 126.6, 126.0, 125.8, 14.3. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{20}\text{O}$ $[\text{M}+\text{H}]^+$ 325.1592; found 325.1591.

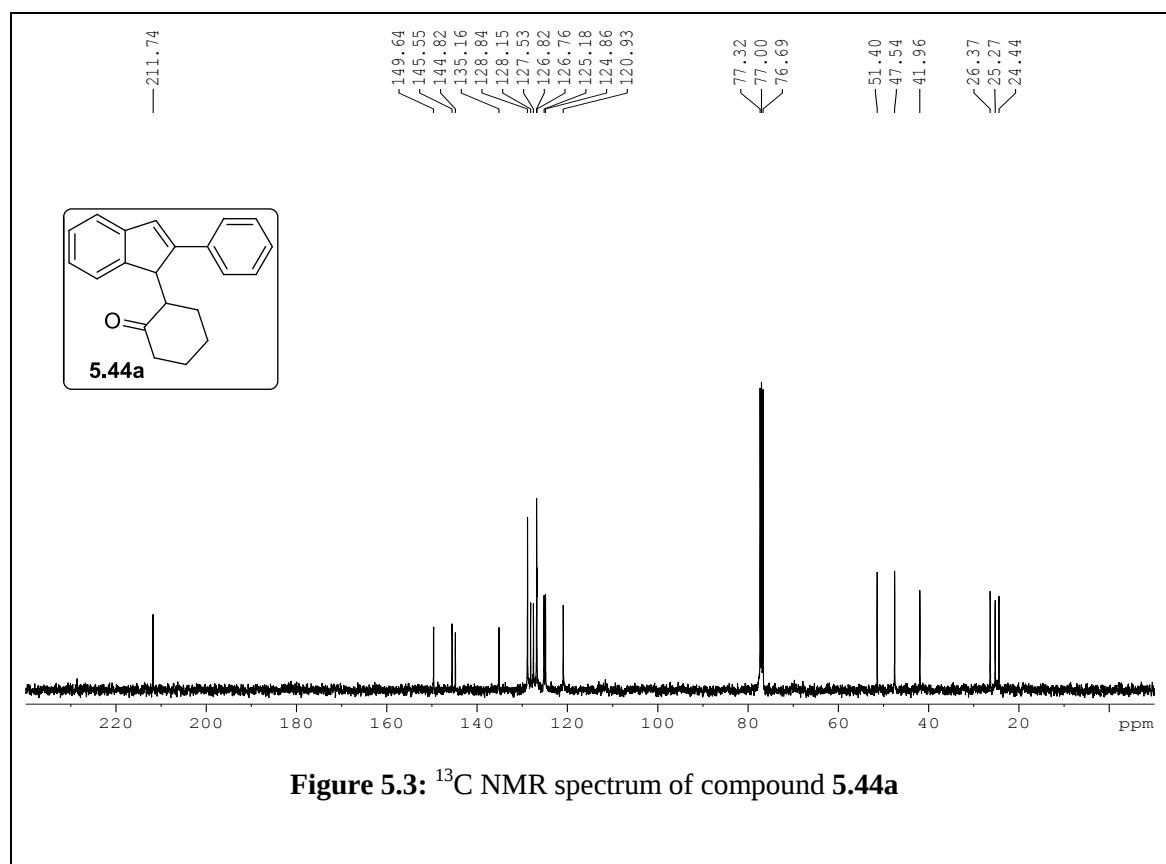
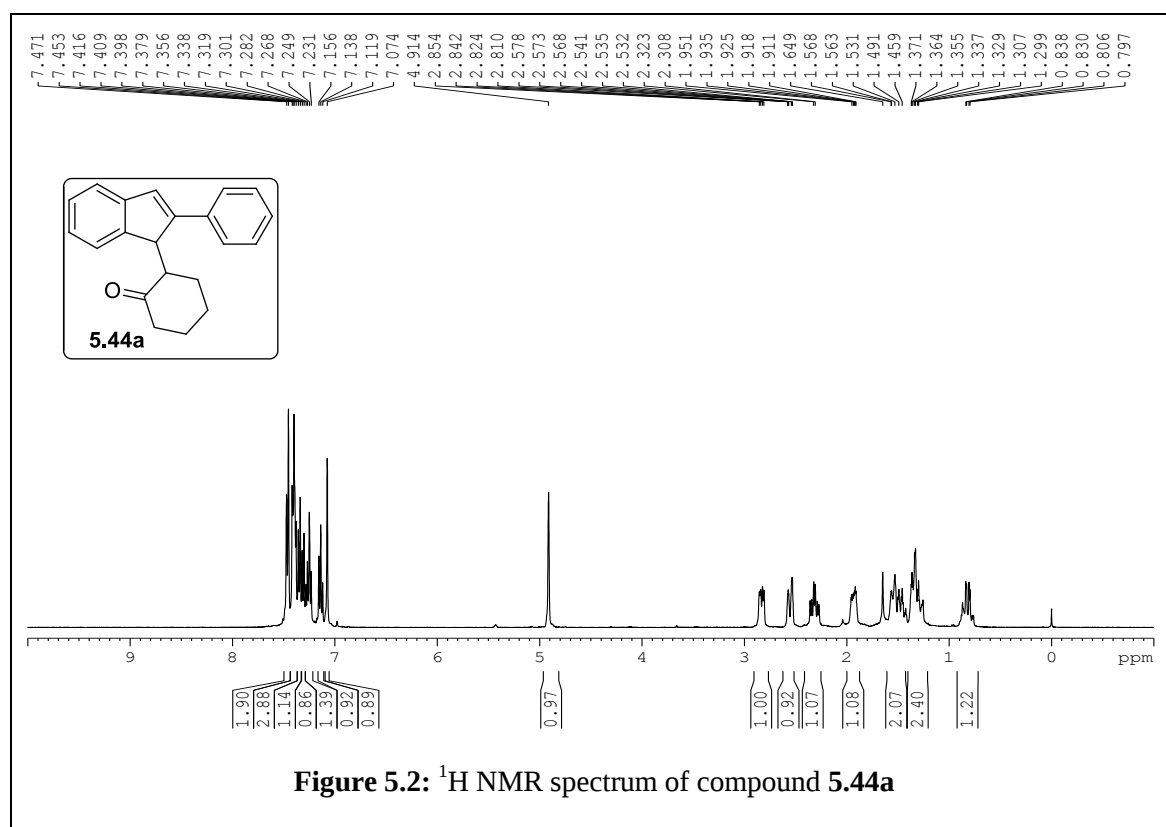
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5.7 Representative spectra



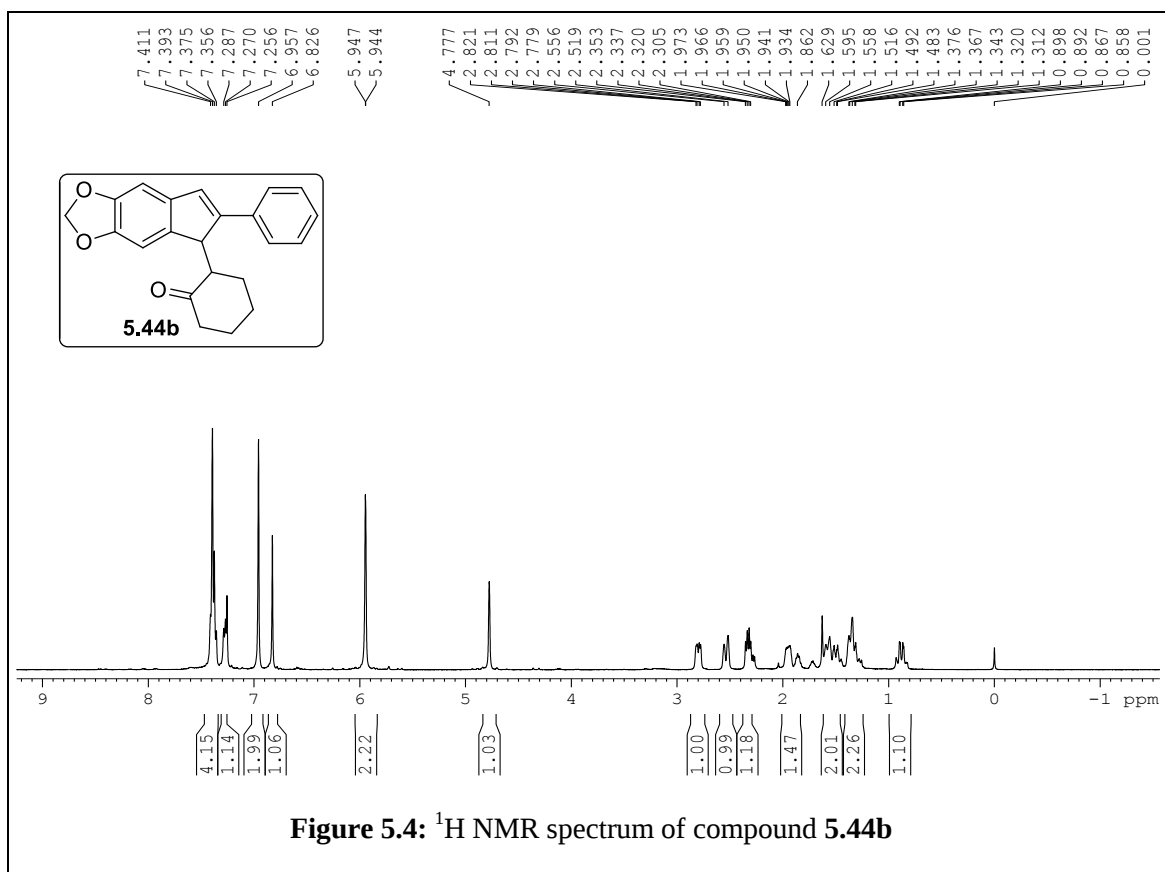


Figure 5.4: ^1H NMR spectrum of compound **5.44b**

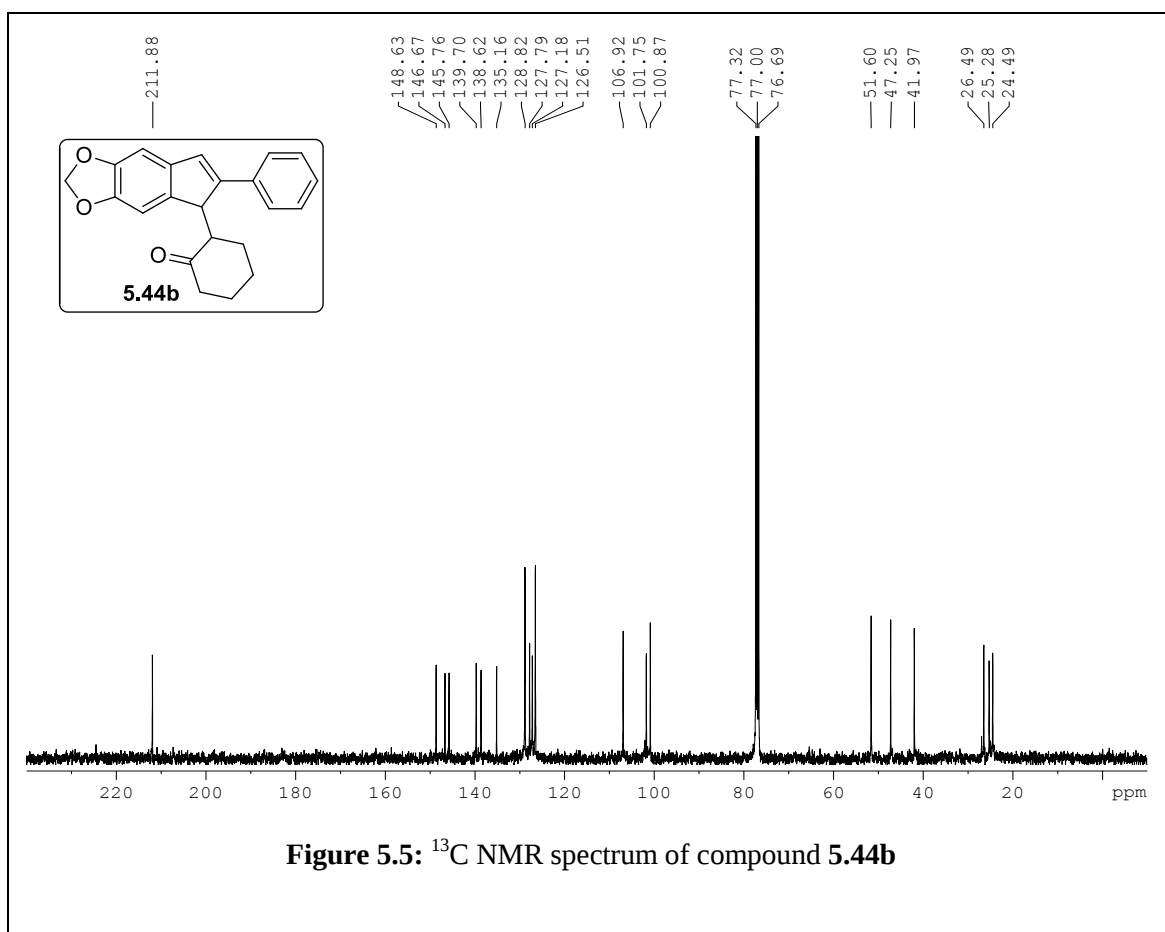
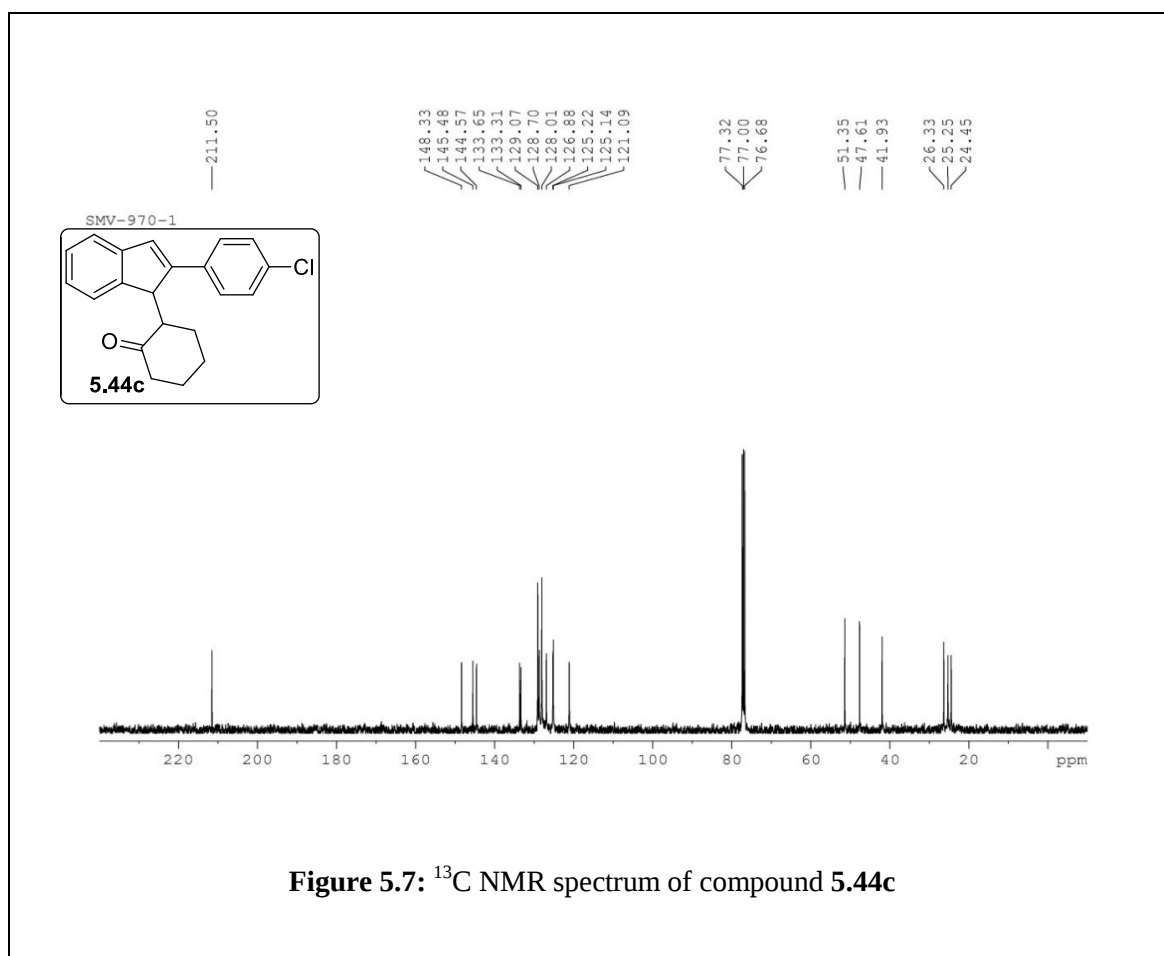
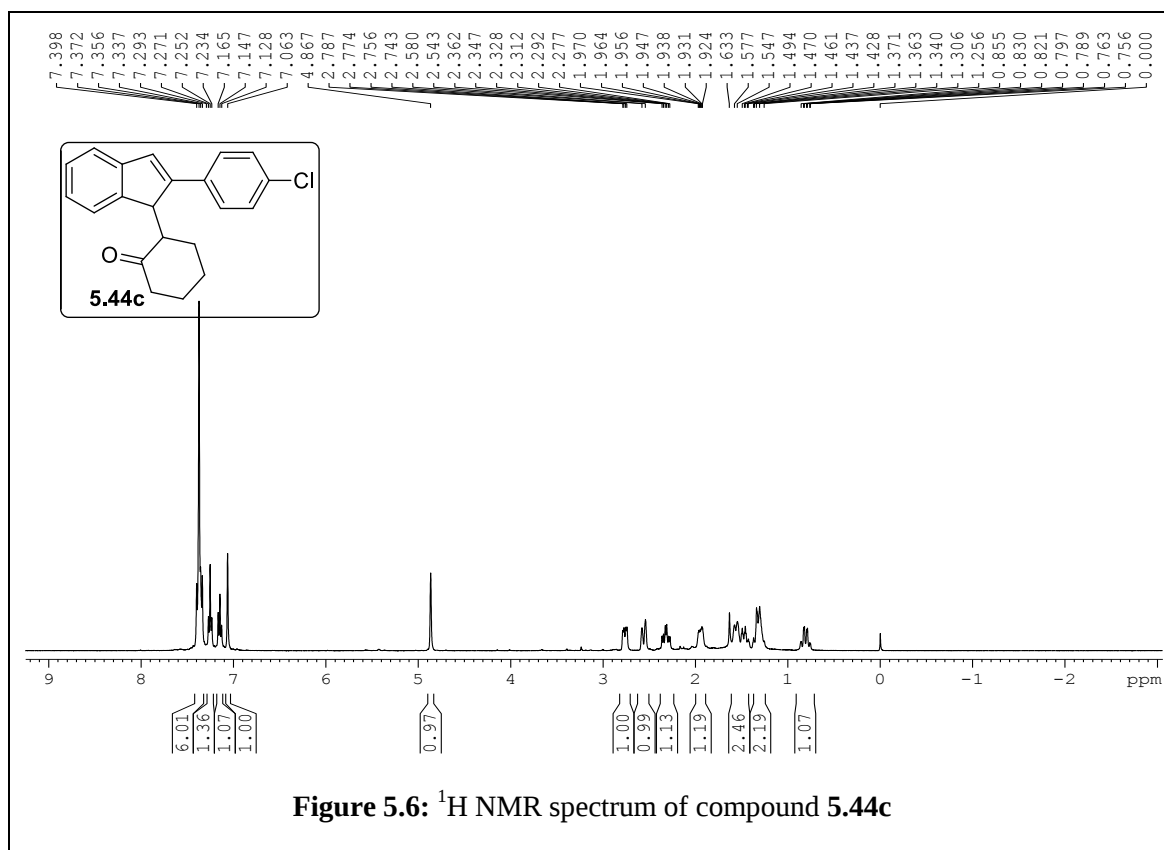
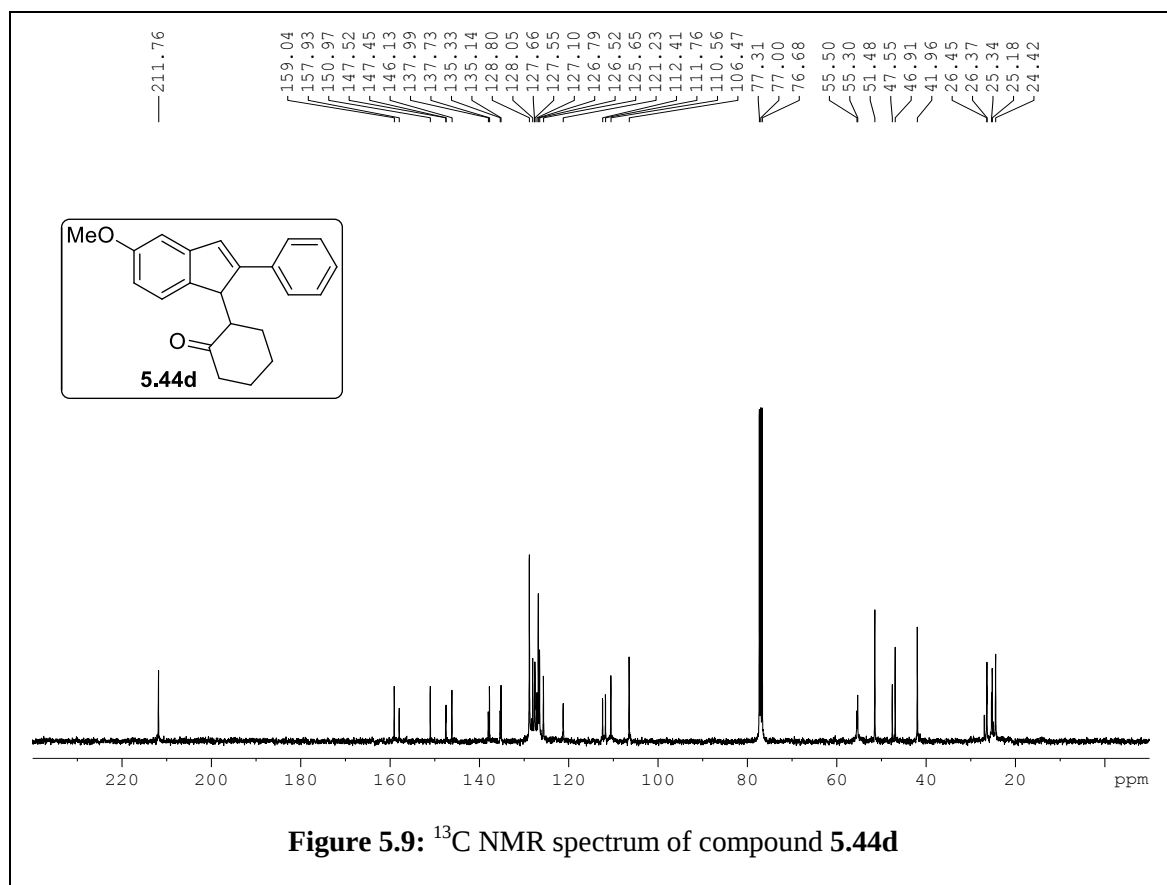
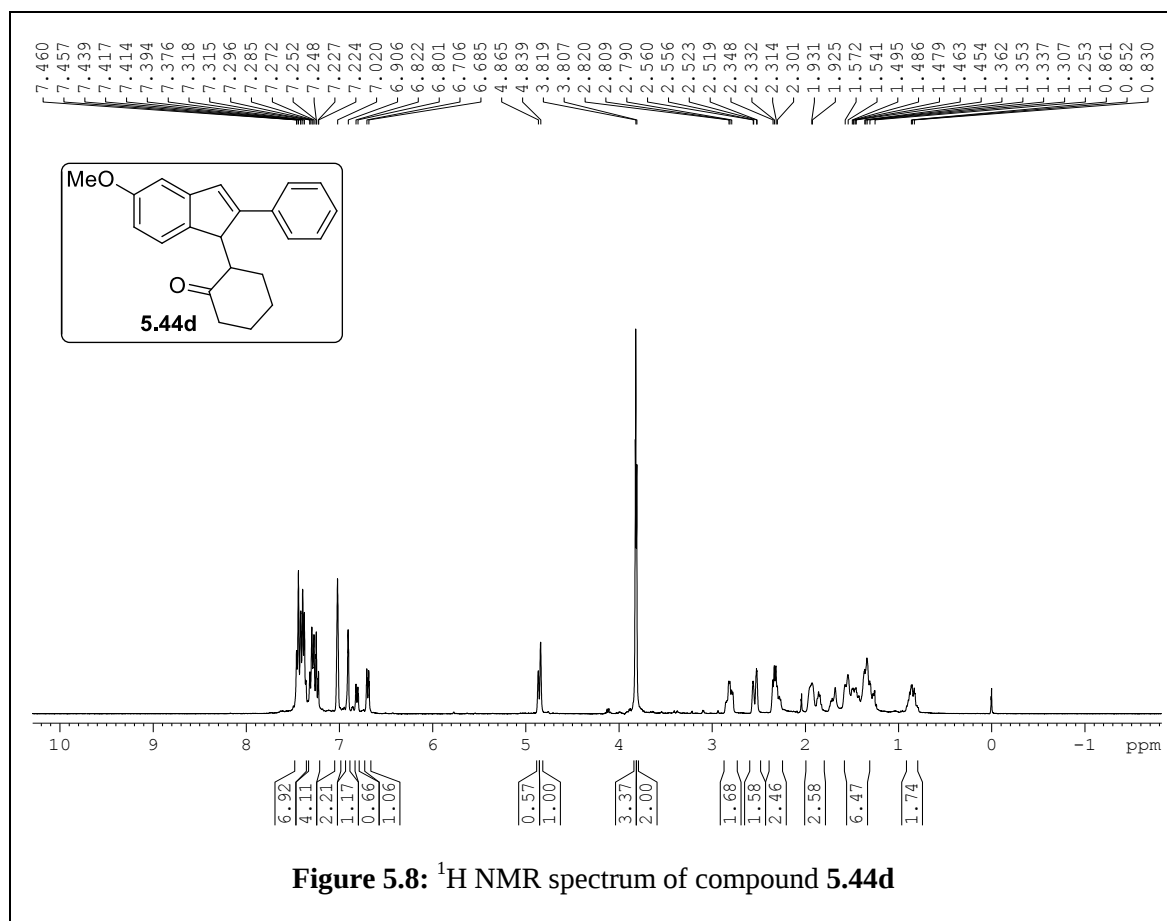
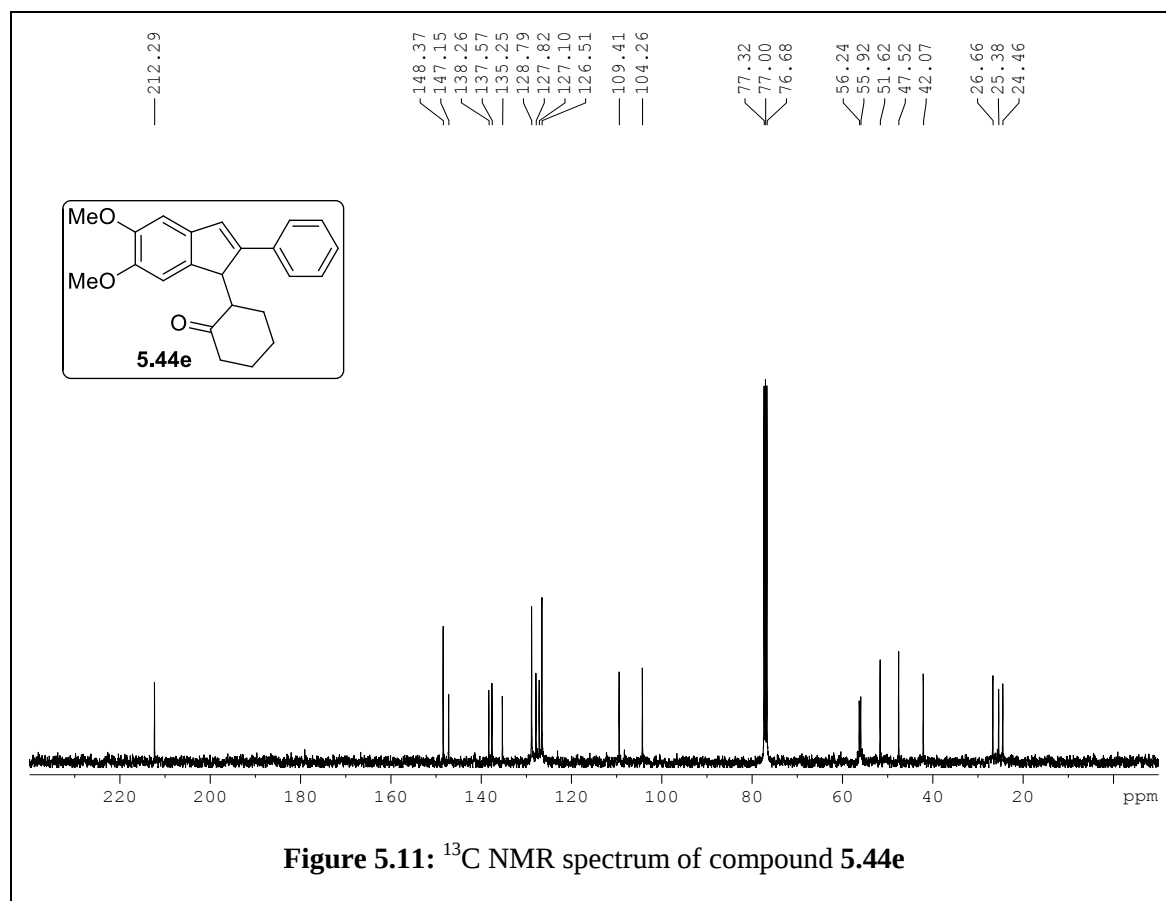
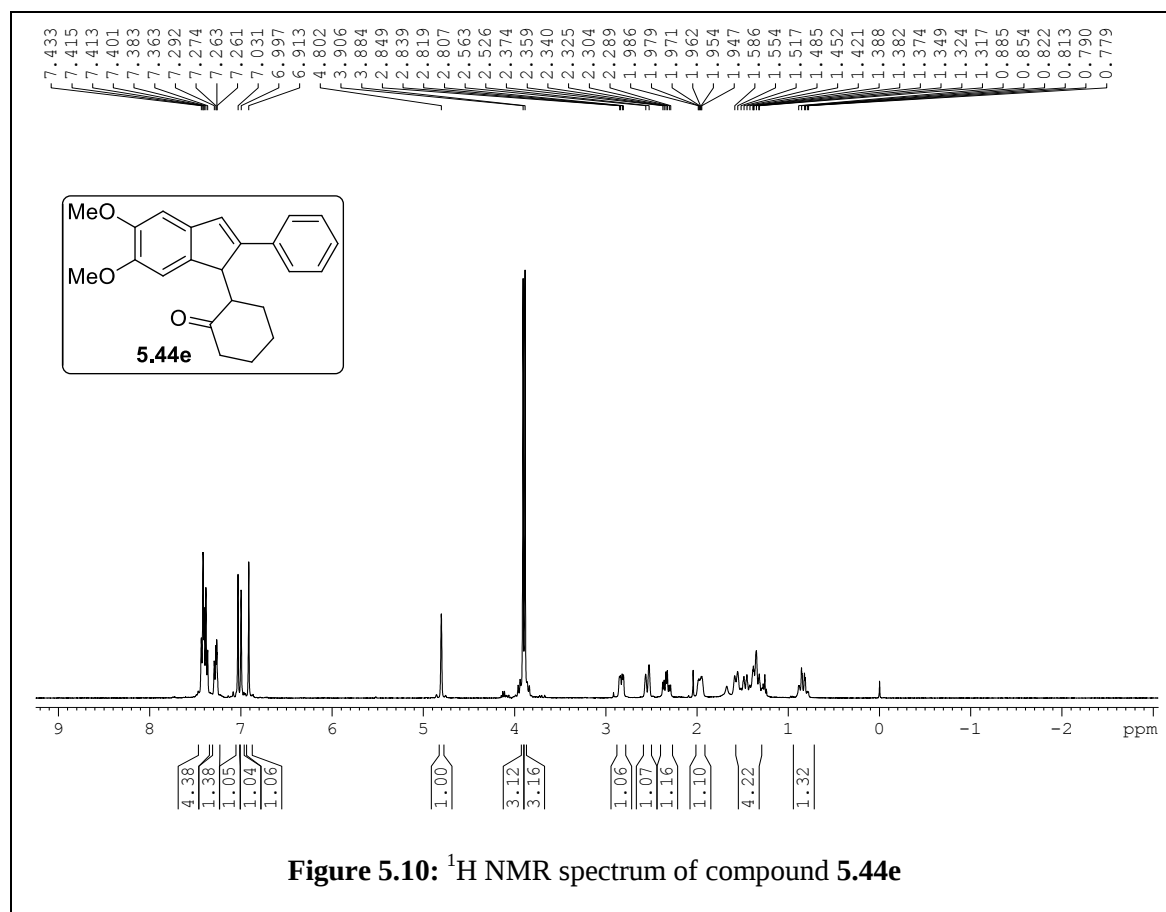
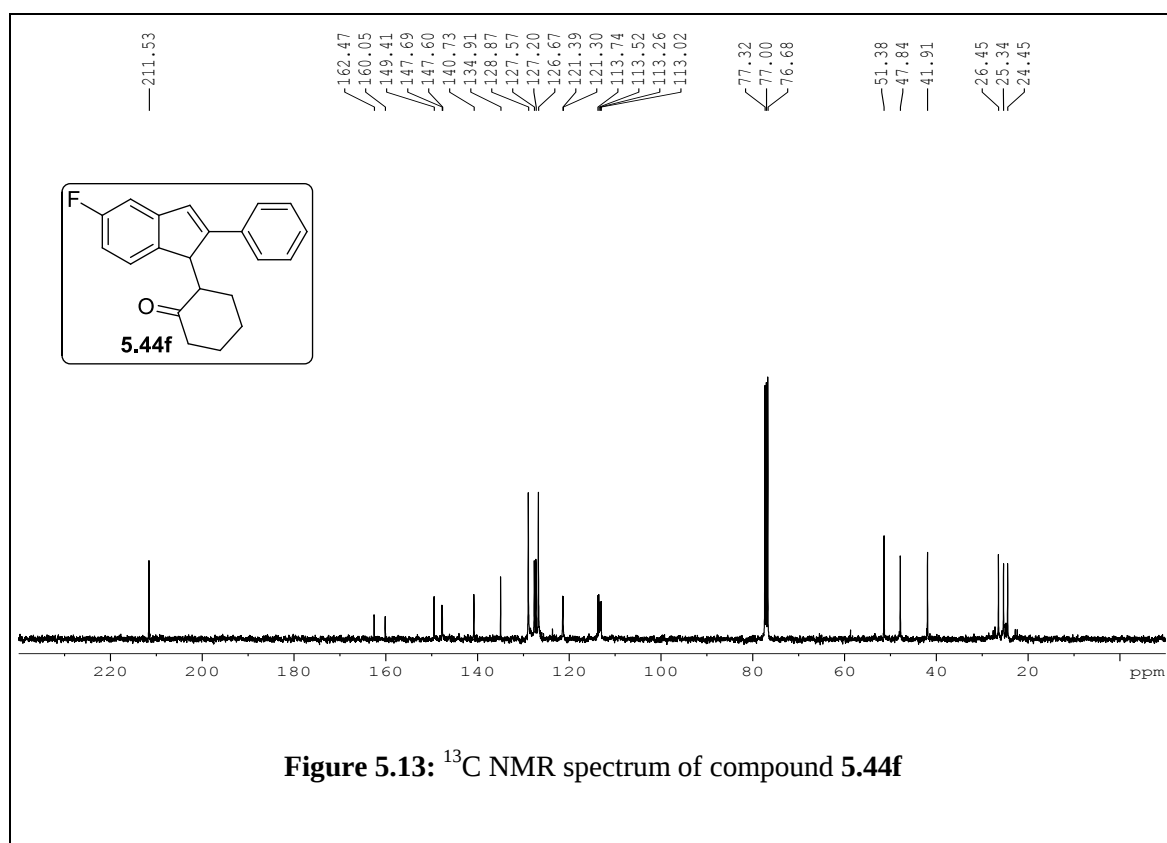
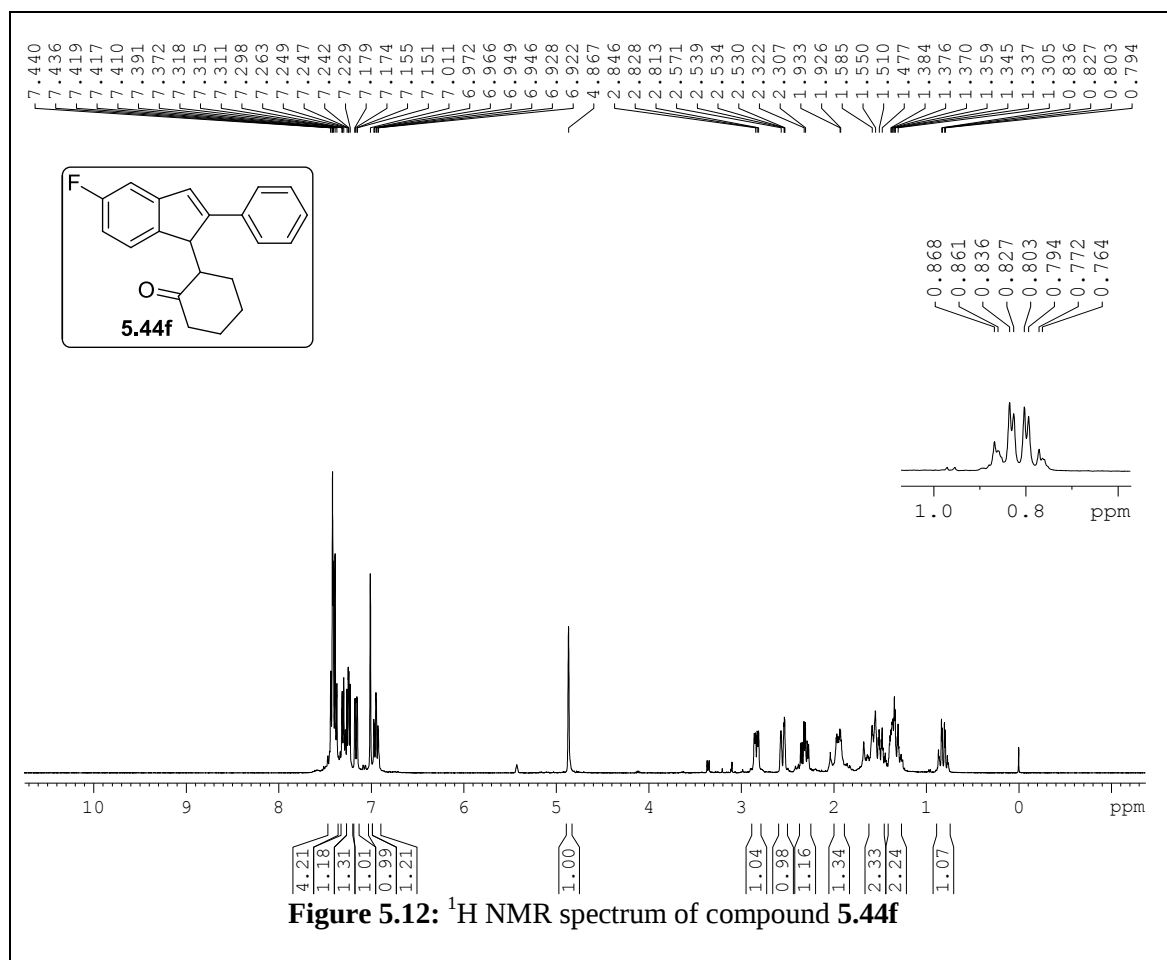


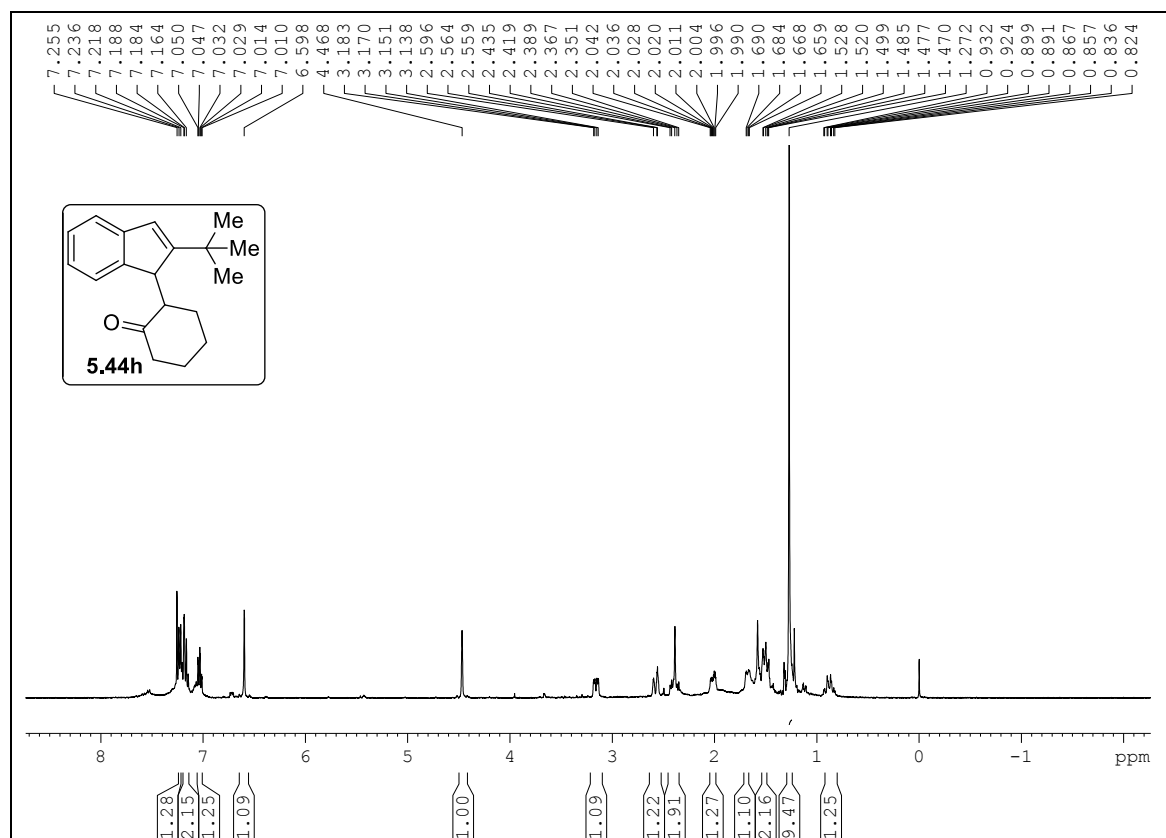
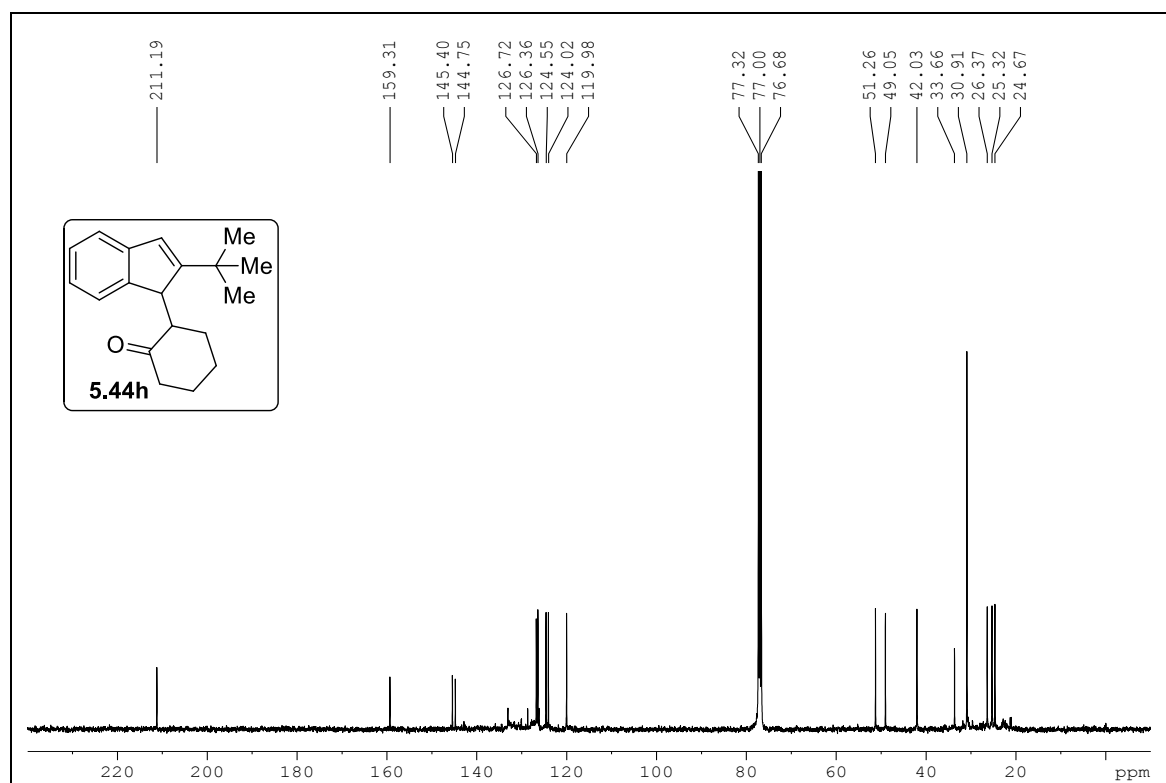
Figure 5.5: ^{13}C NMR spectrum of compound **5.44b**

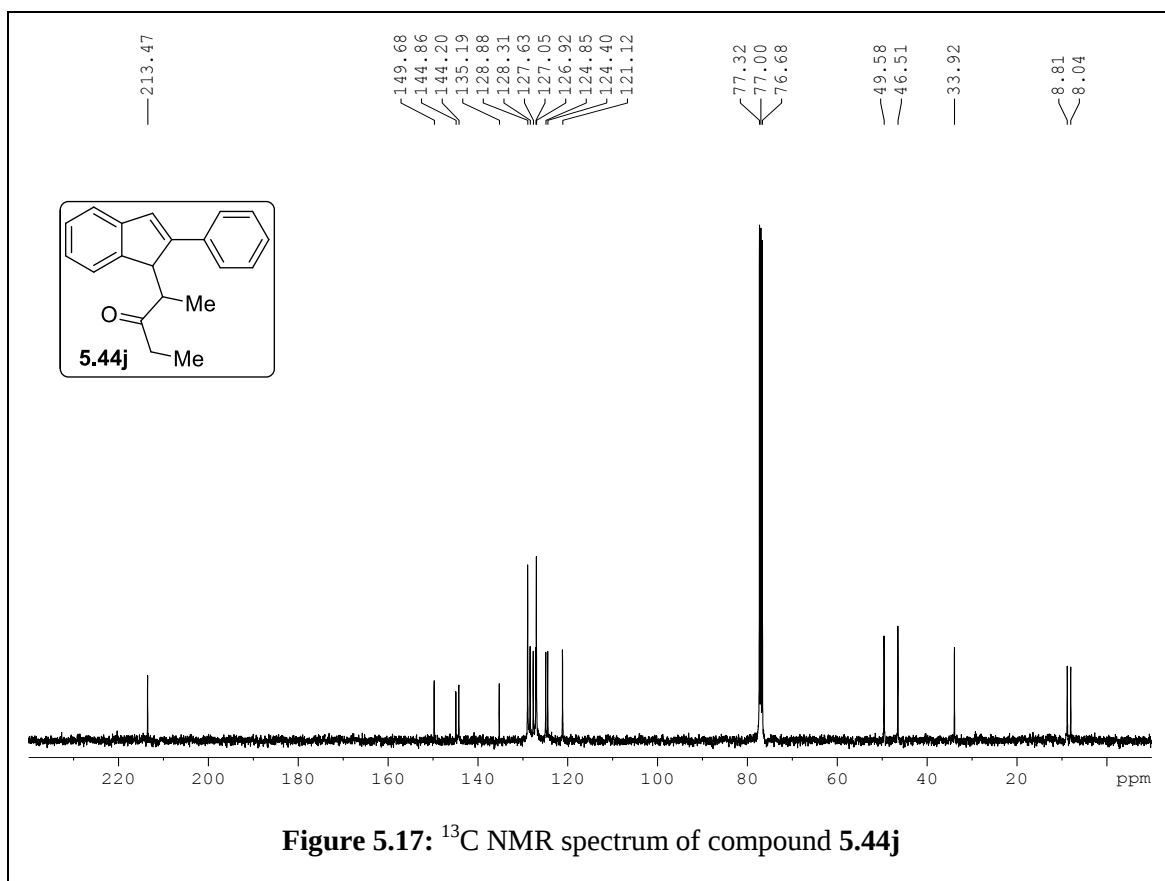
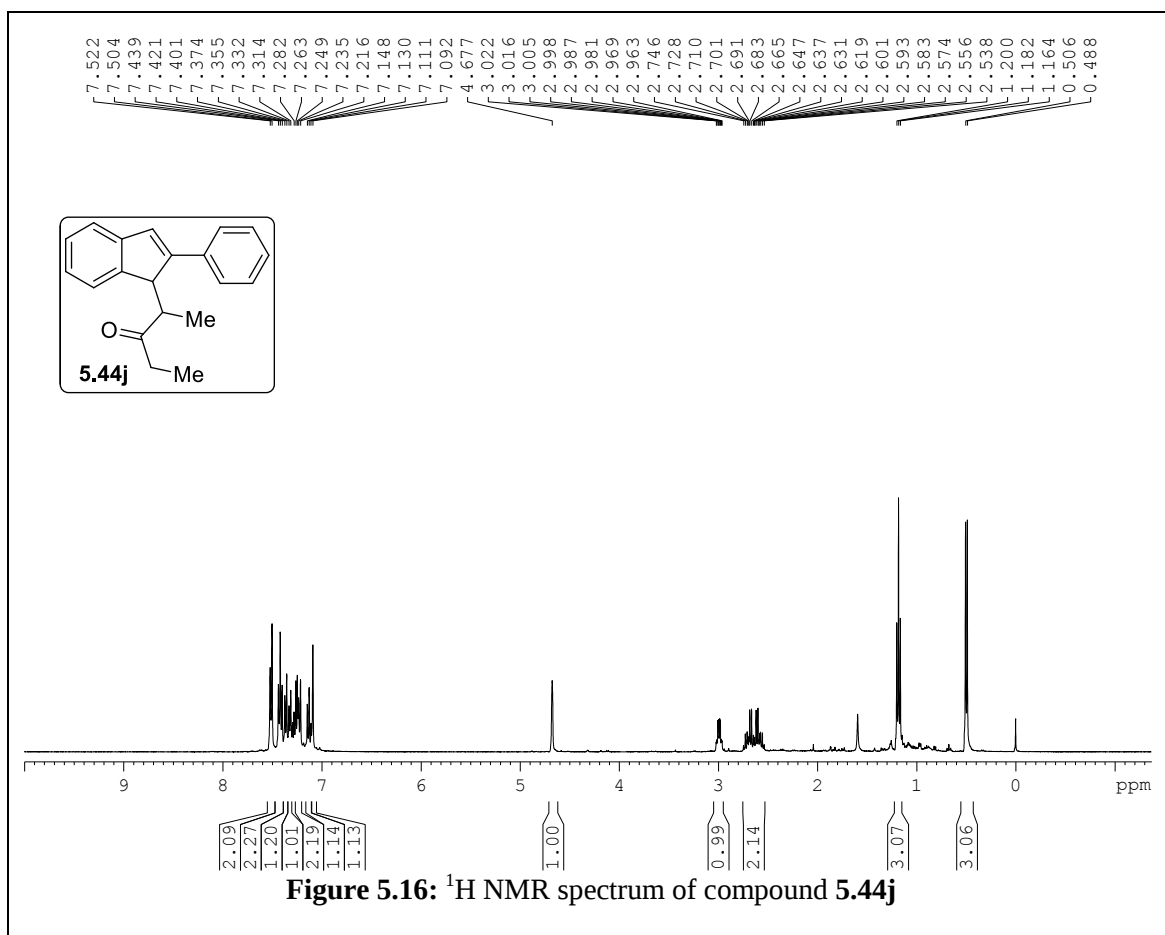


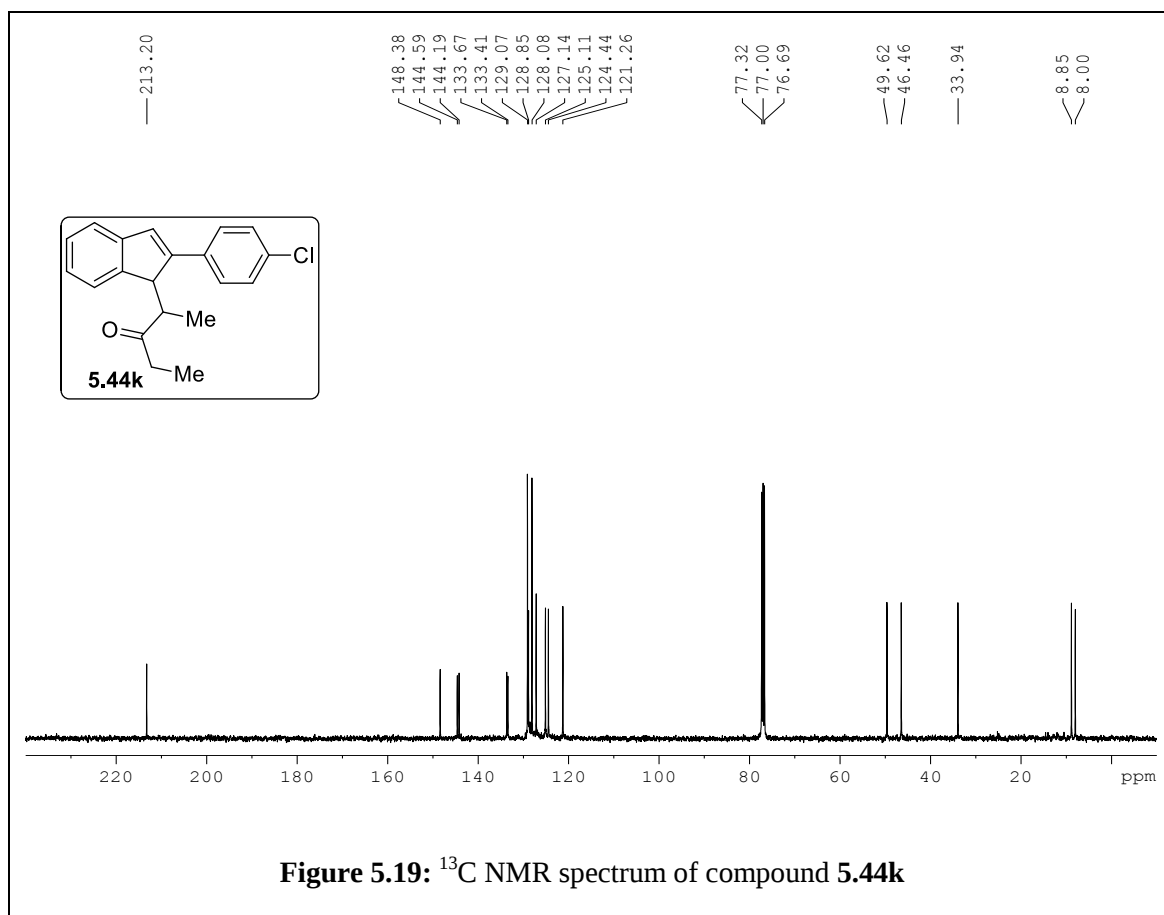
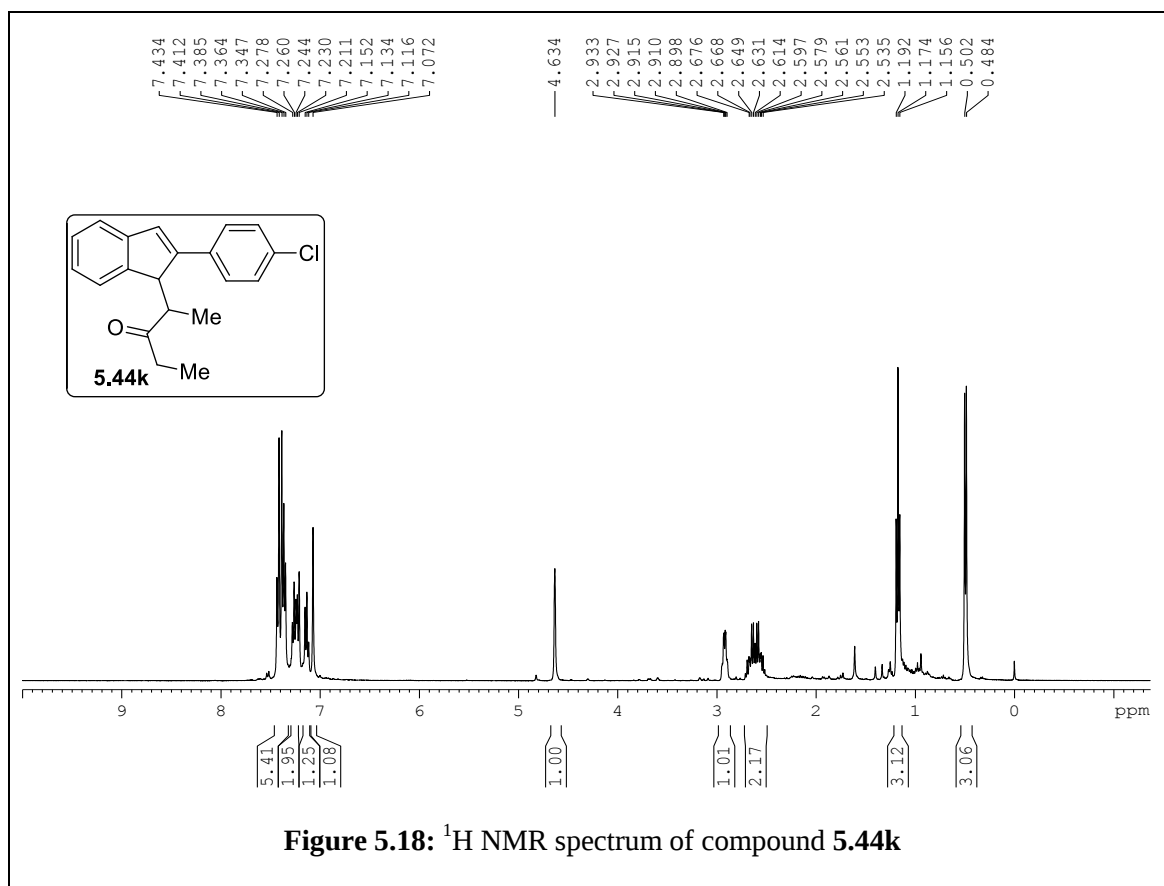


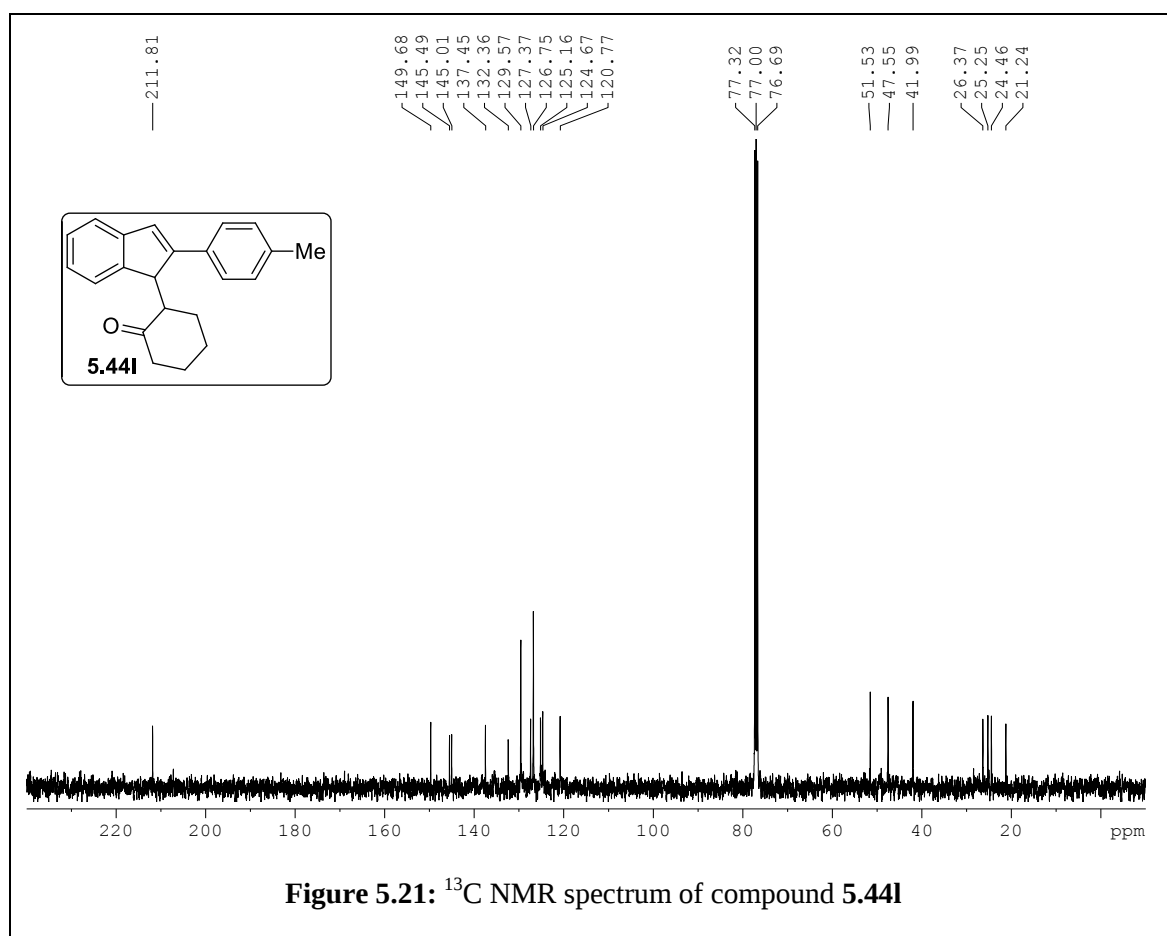
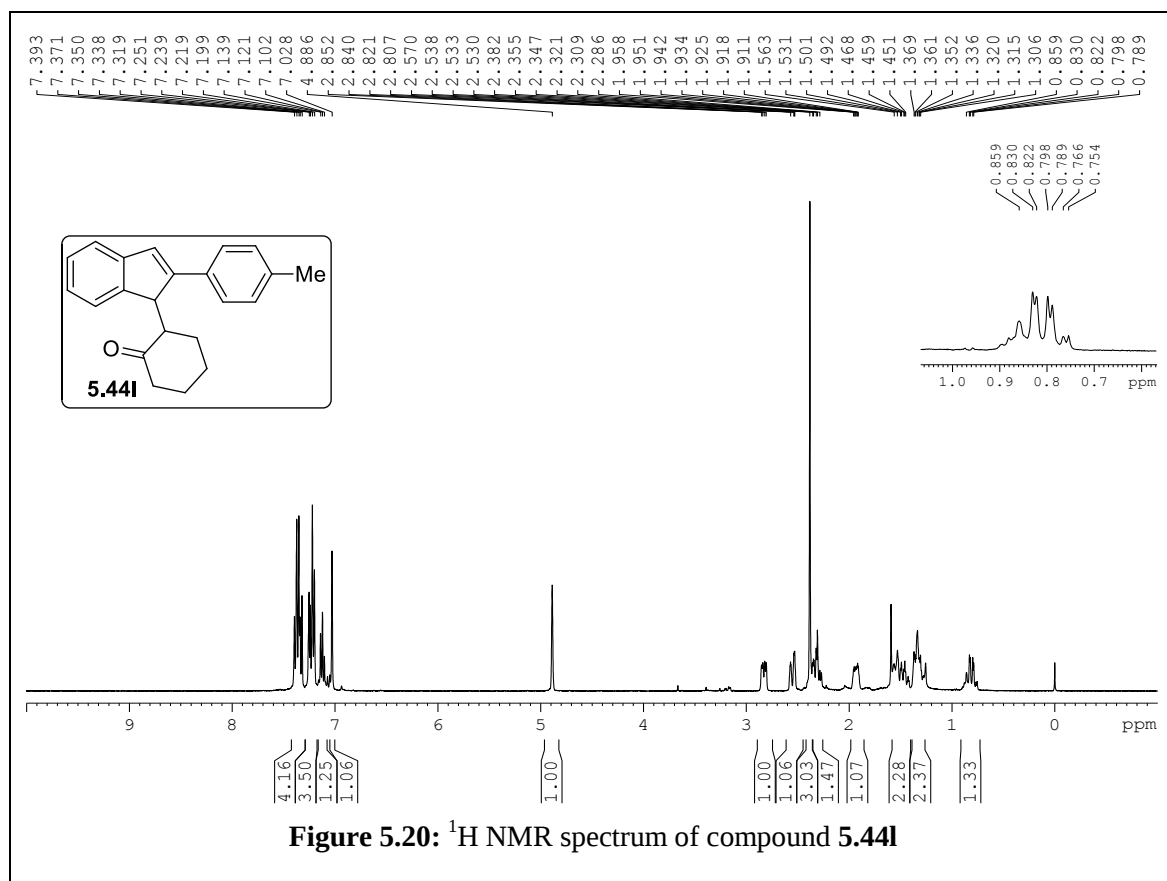


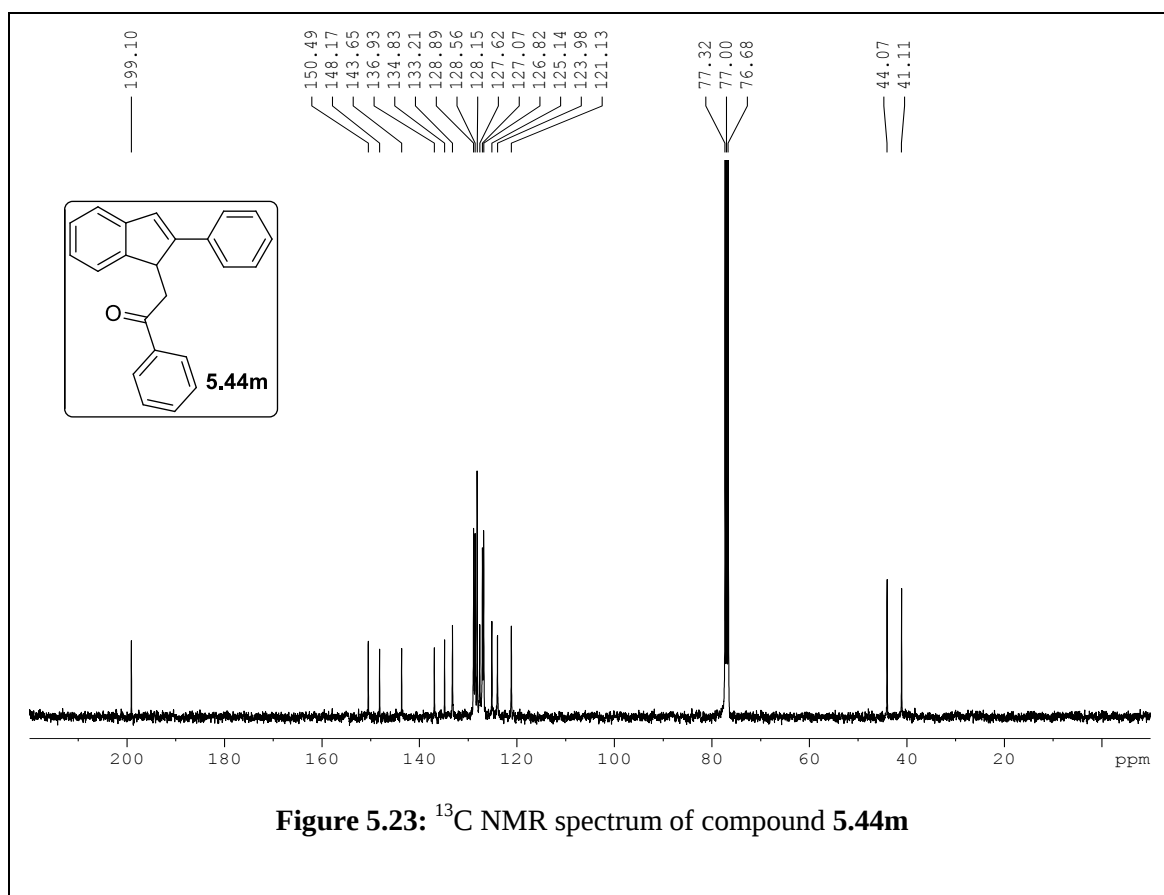
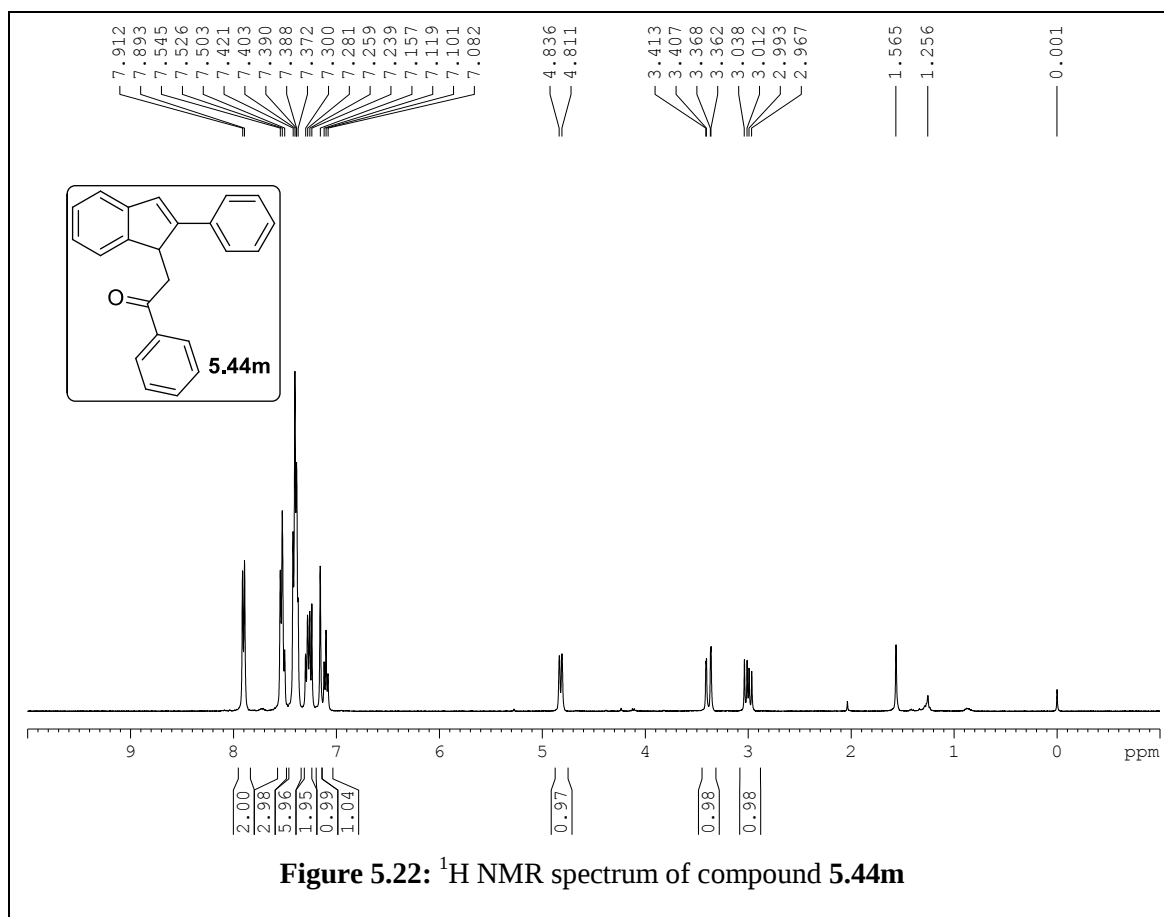


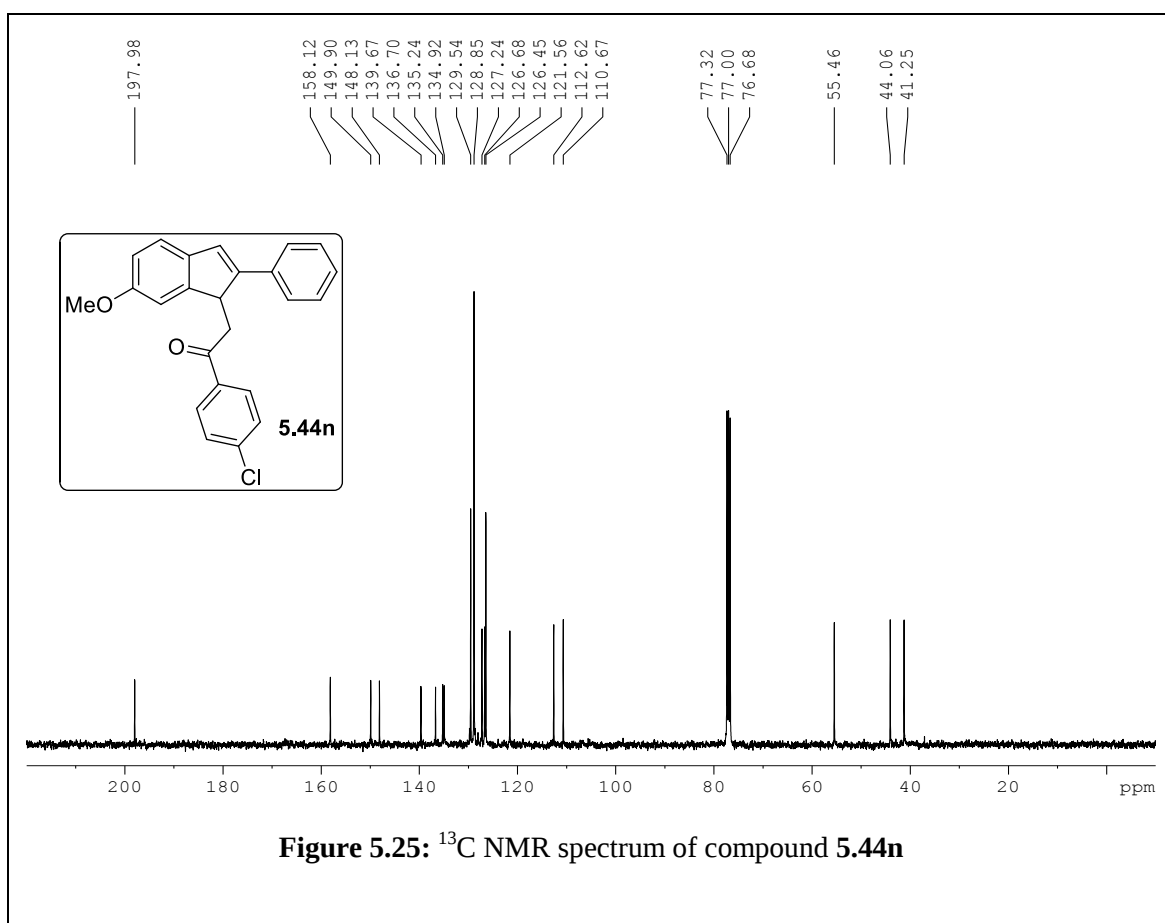
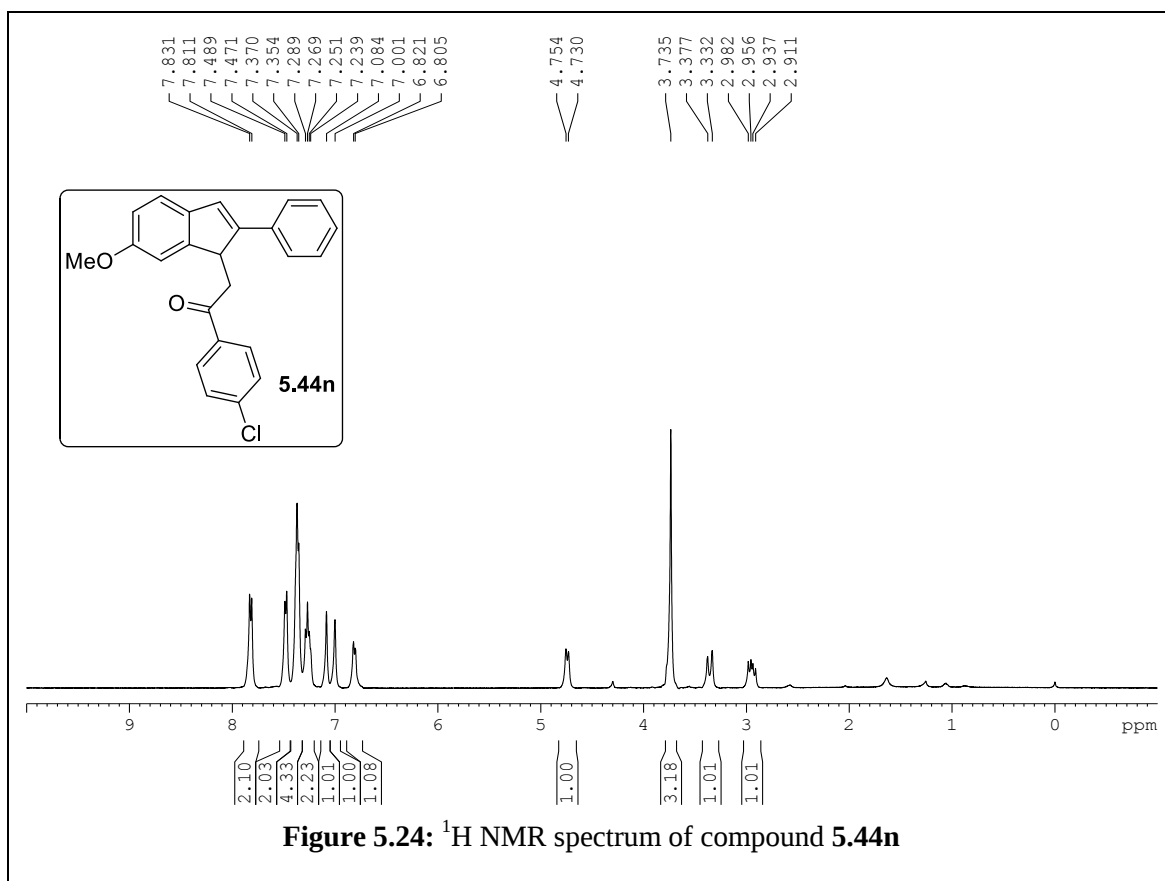

 Figure 5.14: ¹H NMR spectrum of compound 5.44h

 Figure 5.15: ¹³C NMR spectrum of compound 5.44h

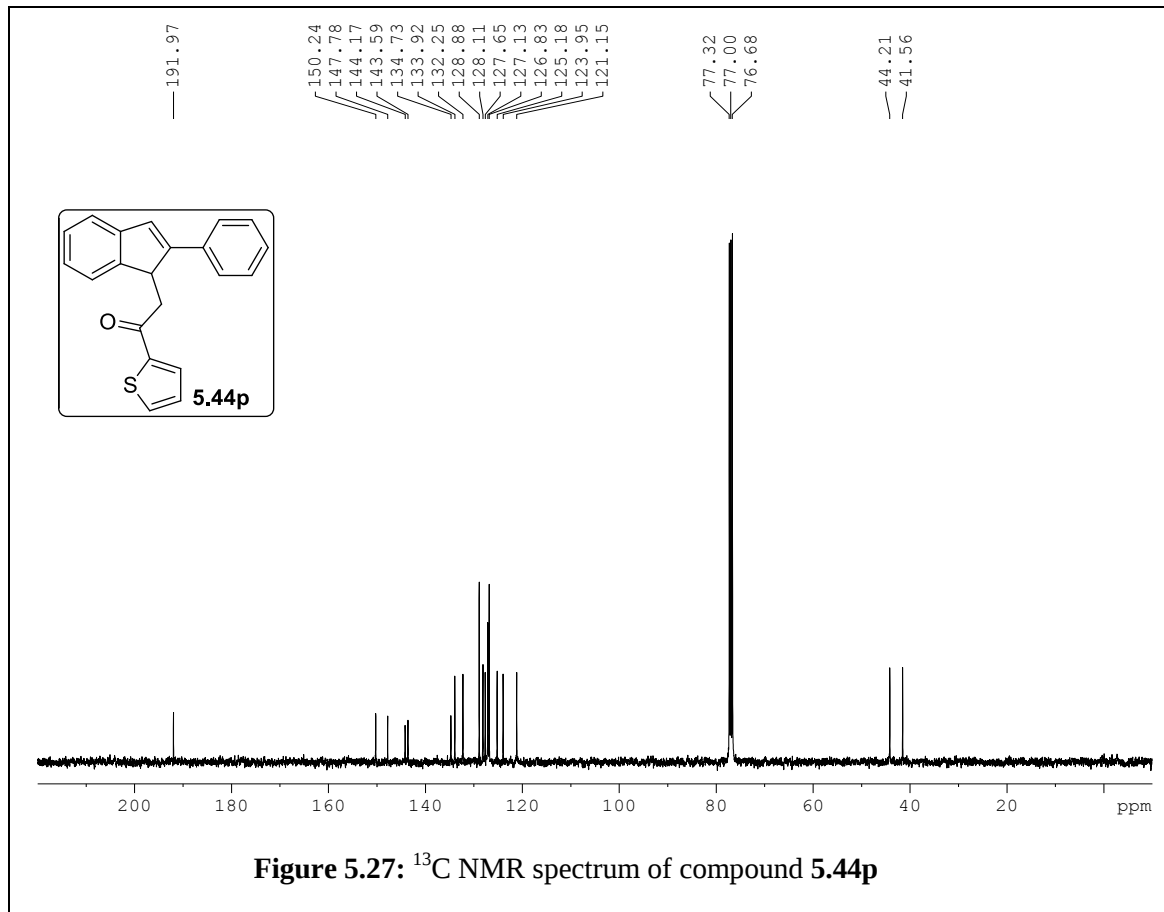
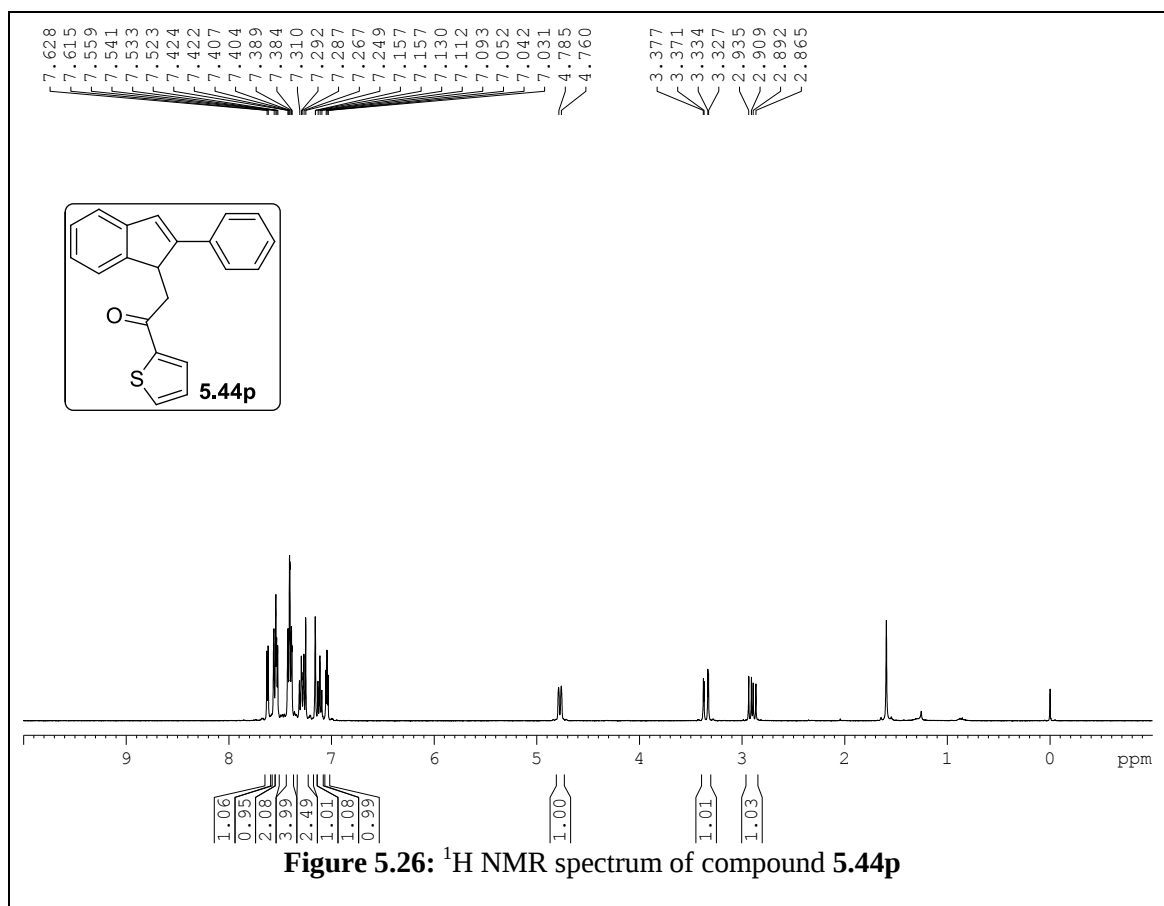


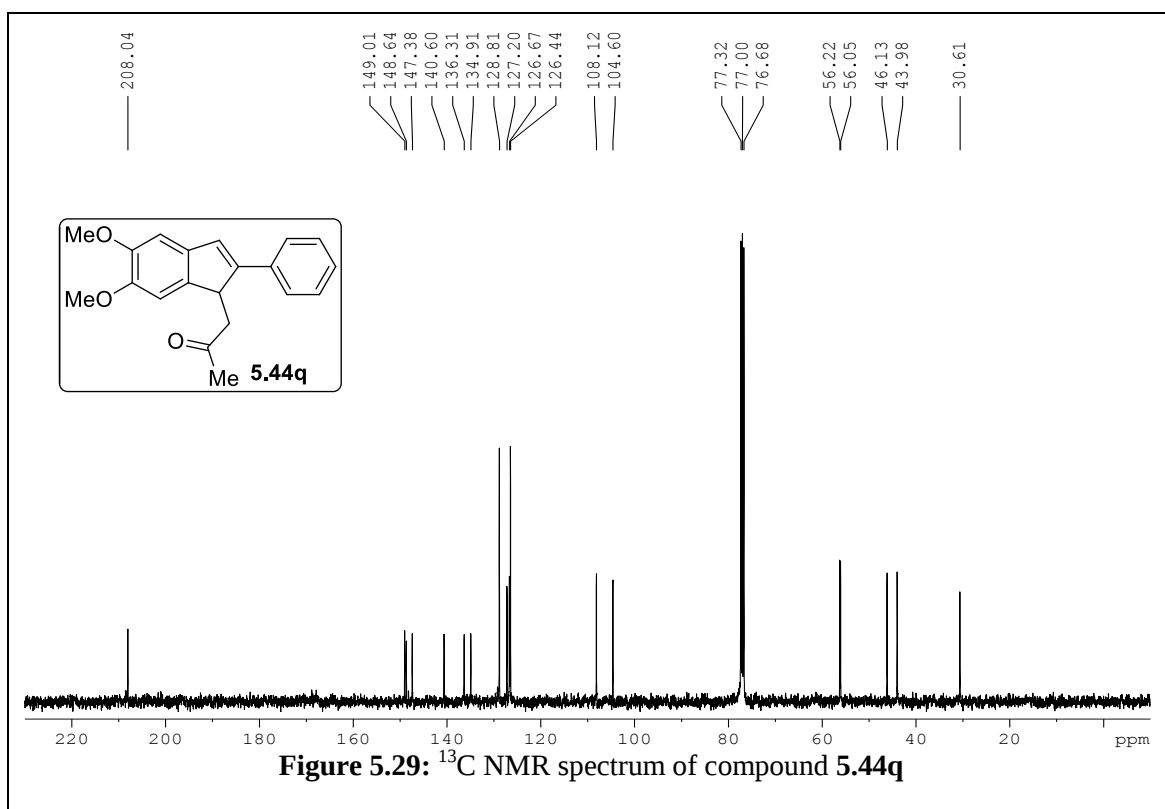
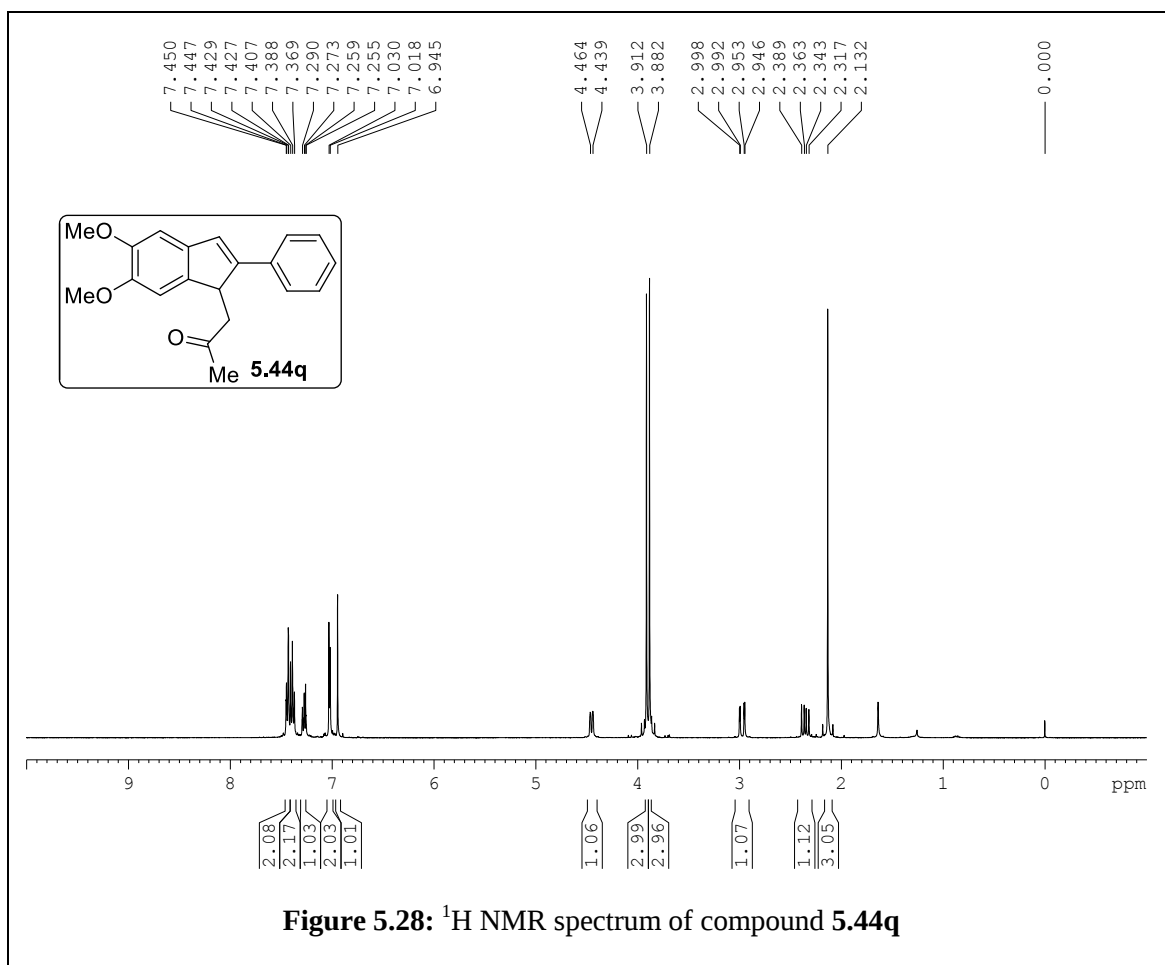












ANNEXURE

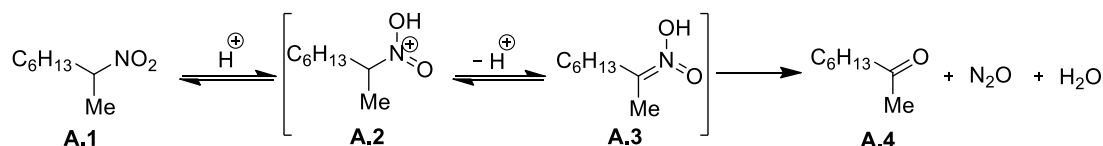
Gold/Copper-Catalyzed Activation of the *aci*-Form of Nitromethane

A.1 Introduction

Nitroalkanes, due to the strong electron withdrawing nature of the nitro group, have become versatile building blocks in the synthesis of a variety of useful molecular scaffolds and fine chemicals.¹ The conversion of nitroalkanes into ketones, known as the Nef reaction,² is achieved by acidic hydrolysis of a nitronate salt made by the basic treatment of an aliphatic nitro compound. Hydrolysis takes place at the stage of protonated *aci*-nitro (nitronic acid) form. In the nitro-*aci*-nitro equilibrium, the *aci*-form is the thermodynamically unfavorable tautomer.³ However, the *aci*-form has been the key intermediate in certain reactions. In the next section, some of the reactions involving *aci*-form (nitronic acid) of nitroalkanes as an intermediate are discussed.

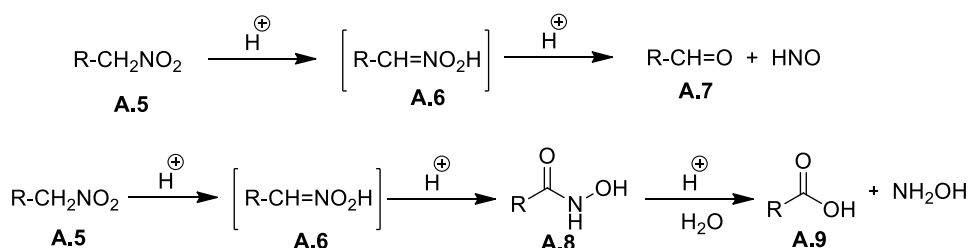
A.1.1 Reactions involving *aci*-form of nitroalkanes

Feuer and Nielsen reported the first example of Nef reaction where 2-nitrooctane **A.1** is directly converted into 2-octanone **A.4** in acidic medium *via* nitronic acid formation (Scheme A.1).⁴ Under acidic condition, the 2-nitrooctane is protonated to give intermediate **A.2** which will be in equilibrium with its *aci*-form **A.3**. Then, hydrolysis of **A.3** would take place to give its carbonyl derivative 2-octanone **A.4**.



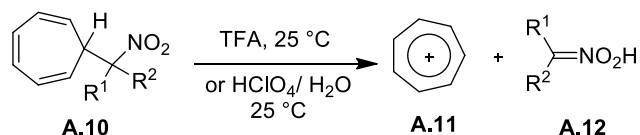
Scheme A.1: Acid-catalyzed conversion of 2-nitrooctane into 2-octanone

Edward and Tremaine showed that the conversion of nitroalkanes **A.5** into their corresponding carbonyl derivatives **A.7** (Nef reaction) and into their carboxylic acid derivatives **A.9** *via* hydroxamic acid intermediate **A.8**. This reaction happens due to the catalytic events that occur after the nitronic acid formation **A.6** (Scheme A.2).⁵



Scheme A.2: Nef and Meyer reactions *via* nitronic acid

Acid-catalyzed nitronic acid formation was achieved by Erden *et al.* Here tropylium ion acts as the electrofuge in the place of proton to generate nitronic acid **A.12** from the nitroalkane **A.10** (Scheme A.3).⁶ In this report, the formation of nitronic acid does not obey the “nitroalkane anomaly” concept.⁷ Thus, the nitronic acid formation depends on the acidity of nitroalkane derivatives where tropylium ion acts as an electrofuge.

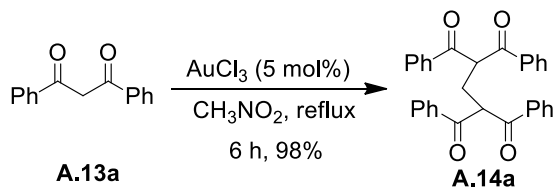


Scheme A.3: Tropylium ion as an electrofuge to generate nitronic acid

Moreover, nitronic acids can be stabilized by aryl substitution⁸ at the α -carbon of a nitroalkane and by H-bonding.⁹ It is therefore evident that the stabilization of nitronic acid is not trivial and hence the limited chemistry of nitronic acids is not surprising.

A.2 Background

During our investigations on exploring the applications of the combined use of oxo- and alkynophilicities of gold catalysts,¹⁰ we found that 1,3-dicarbonyl compound **A.13a**, upon refluxing with catalytic AuCl₃ in nitromethane, gave methylene-bridged bis-1,3-dicarbonyl compound **A.14a** (Scheme A.4).¹¹ It was envisaged that the bridging methylene group should have come from the solvent nitromethane. Furthermore, the reaction could have occurred *via* the initial nucleophilic attack of the 1,3-dicarbonyl compound at the carbon of the *aci*-nitro form activated by AuCl₃, just like the attack of water taking place in the classical Nef reaction (Figure A.1).^{2,12} The *aci*-nitro alkane is generally involved in lower acid concentrations.¹³ However, to the best of our knowledge, direct activation of the *aci*-form of a nitroalkane by a Lewis acid catalyst and attack by a carbon nucleophile on it is not known. Nucleophilic attack of benzene at an *aci*-nitro form generated from nitronate salt is known, however this makes use of very strong acid HF as solvent.¹⁴



Scheme A.4: Activation of the *aci*-form of nitromethane in the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds

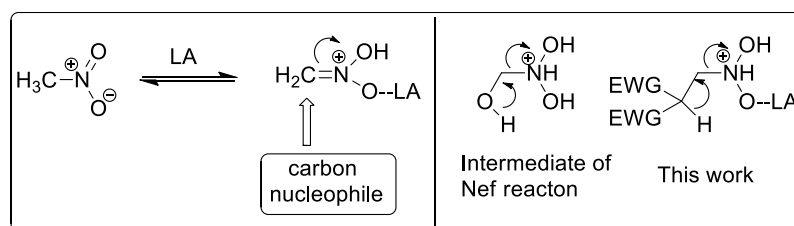


Figure A.1

This new observation of the activation of *aci*-form of nitromethane under Lewis acid catalysis conditions and knowing the importance of methylene-bridged 1,3-dicarbonyl compounds in inorganic chemistry as ligands,^{11b, 15} we got inspiration and proceeded to optimize the reaction conditions.

A.3 Results and Discussion

A.3.1 Optimization of reaction conditions

The reaction of dibenzoylmethane **A.13a** was screened using 5 mol% of selected Lewis and Brønsted acids and the results are summarized in Table A.1.

Among the Lewis acids screened, AuCl₃ and Cu(OTf)₂ were found to be superior catalysts, with the former being the best for the formation of methylenebridged bis-dibenzoylmethane **A.14a** in high yield in a shorter reaction time. Brønsted acids, HCl and HOTf were found to be poorer catalysts. In a different set of experiments, the reaction of dibenzoylmethane was examined in different solvents taking 5 equivalents of nitromethane using AuCl₃ and Cu(OTf)₂ catalysts and

Table A.1 Screening of the catalysts

Entry	Catalyst	Time (h)	Yield ^{a,b}
1	AuCl ₃	6	98
2	AuCl ₃ /AgAbF ₆	3	97
3	AgOTf	24	No reaction
4	Cu(OTf) ₂	5	93
5	InCl ₃	24	5 (94)
6	Sn(OTf) ₂	24	33 (63)
7	CuCl ₂	24	37 (61)
8	FeCl ₃	24	54 (45)
9	BF ₃ OEt ₂	24	24 (25)
10	CuI	24	No reaction
11	HCl	24	10 (80)
12	HOTf	24	6 (86)
13	none	24	No reaction

^a Isolated yield. ^b Values in the parenthesis represent the percentage of recovered unreacted starting material.

results are shown in Table A.2. However, these conditions were not good for the efficiency of the reaction. Perhaps a large quantity of nitromethane is required to have its *aci* form in sufficient amount for the reaction to take place.

Table A.2 Screening of the solvents

	A.13a	A.14a	A.15
Entry	Solvent	Cu(OTf) ₂ A.14a Yield ^{a,b}	AuCl ₃ A.15 Yield ^{a,b}
1	Dichloroethane	1 (91)	14 (84)
2	Toluene	3 (90)	13 (86)
3	Acetonitrile	10 (80)	15 (82)
4	Tetrahydrofuran	5 (91)	10 (88)

^a Isolated yields. ^b values in parenthesis represent the percentage of recovered unreacted starting material.

A.3.2 Substrate scope

The substrate scope was examined with both AuCl₃ and Cu(OTf)₂ separately using a variety of substrates. The substrates include aryl and alkyl 1,3-diketones, β -ketoesters and 1,3-diester. The results are shown in Figures A.2 and A.3. Substrates containing substituents like, I, Br, Cl and OMe on the aryl rings could be handled without any trouble. Substrates with alkyl ketone moieties resulted in slightly lesser yields of the product in the AuCl₃-catalyzed reactions (**A.14i–A.14k**, **A.14x** and **A.14y**). Cu(OTf)₂ was found to be less efficient in these cases, resulting in poor yields of the desired products. It is notable that preparing such compounds by a base-assisted reaction between formaldehyde and 1,3-dicarbonyl compounds is cumbersome due to aldol-related side product formation. The halo substituted methylene-bridged bis-1,3-dicarbonyl compounds (**A.14c**, **A.14d**, **A.14f–A.14h** and **A.14n–A.14q**) can be functionalized under transition metal catalysis conditions. In addition, the reactions could be scaled up. For example, the reaction of **A.13a** on a 1g scale when performed using Cu(OTf)₂ and AuCl₃, the product **A.14a** was obtained in 93% and 95% respectively after 8 h. The reaction of *o*-hydroxy substituted 1,3-aryl diketone **A.13z** i.e 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione resulted in the formation chromone derivative **A.16** i.e 2-phenyl-4*H*-chromen-4-one in excellent yield under both gold/copper catalysis conditions (Scheme A.5).

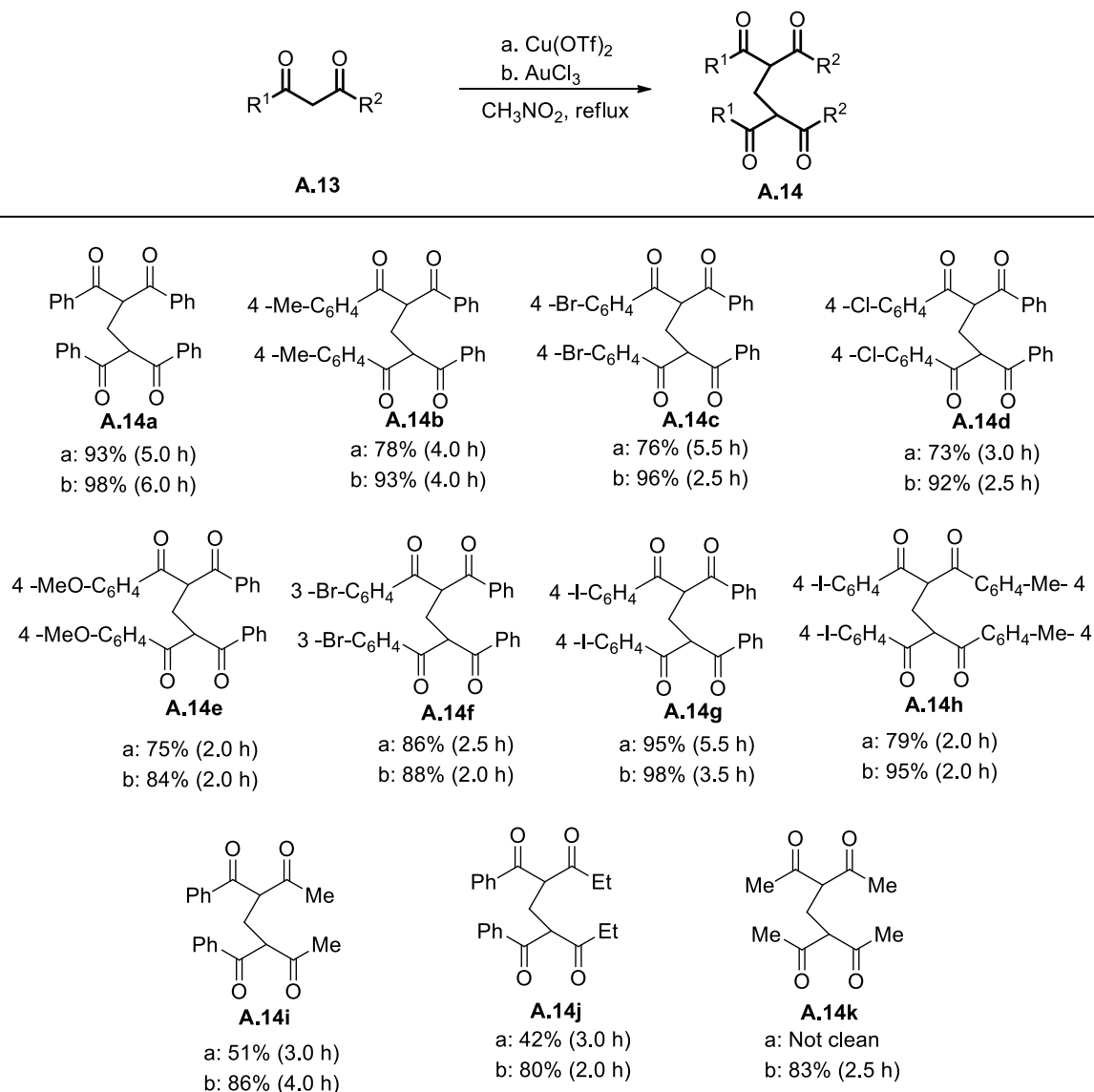
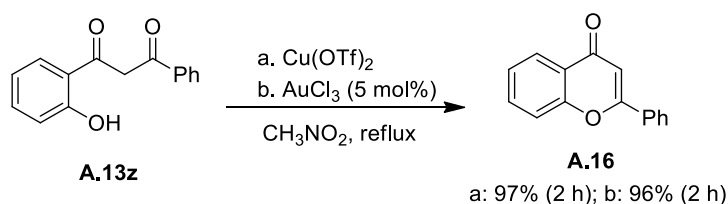
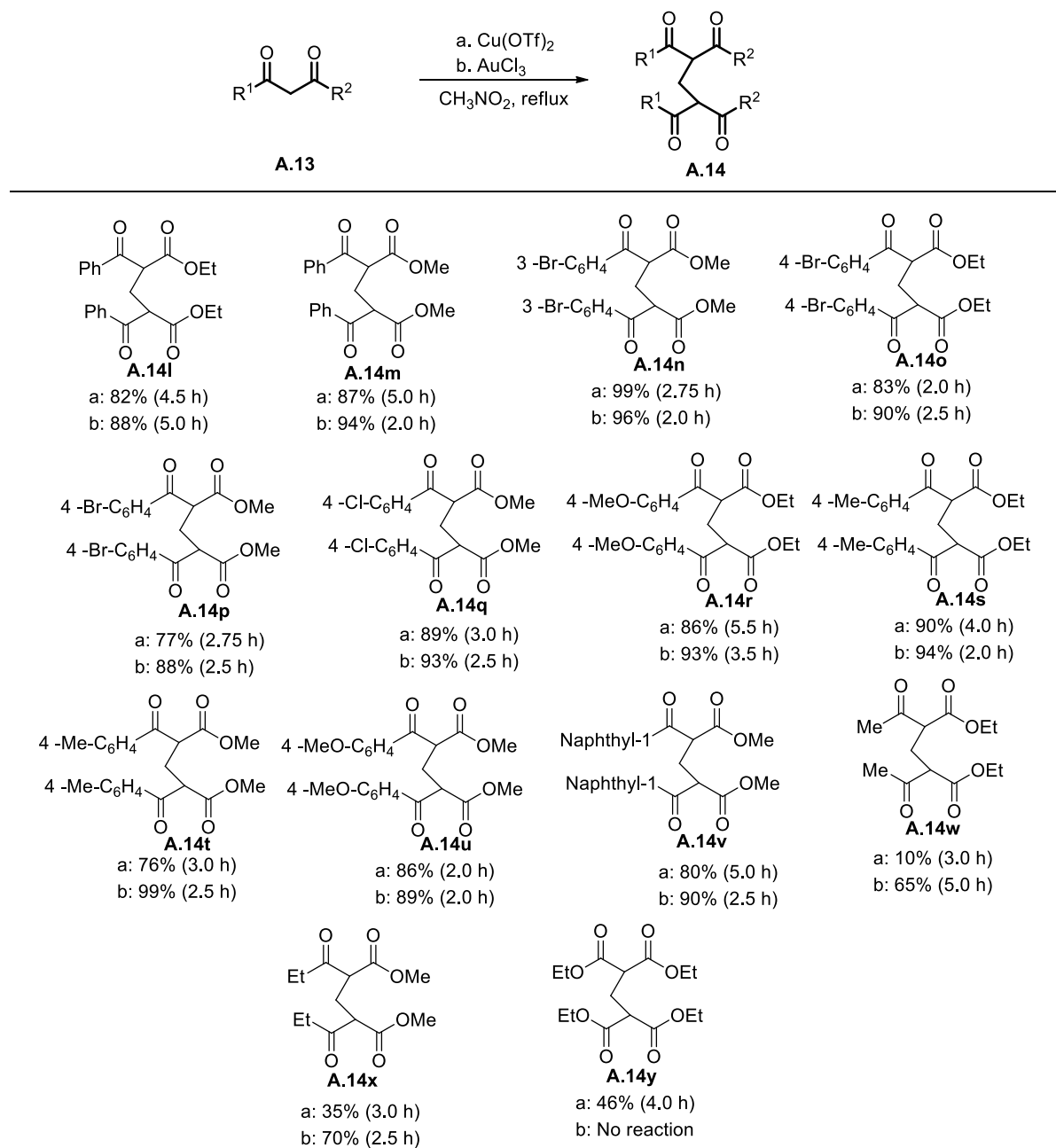
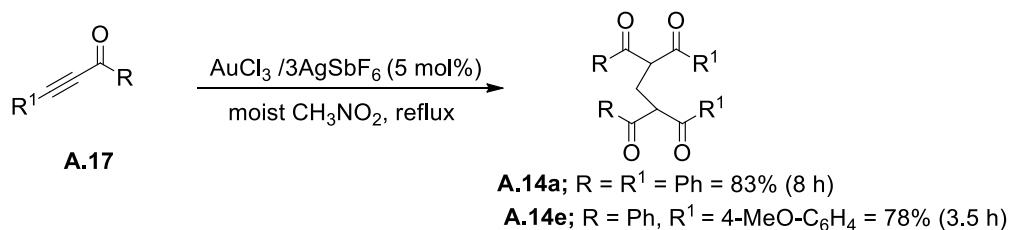
Figure A.2: Substrate scope with aryl and alkyl 1,3-diketones^a^a All the reaction were carried out using 5 mol% catalyst.**Scheme A.5:** Formation 2-phenyl-4*H*-chromen-4-one derivative

Figure A.3: Substrate scope with β -ketoesters and 1,3-diester^a

^a All the reaction were carried out using 5 mol% catalyst.

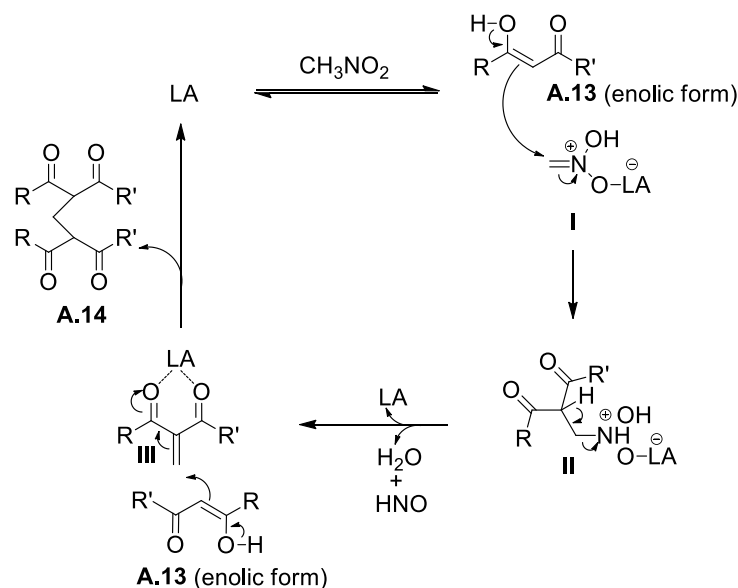
The ability of AuCl_3 to hydrate alkynes¹⁶ could be taken as an advantage to directly convert alkynones into methylenebridged bis-1,3-dicarbonyl compounds in one pot *via* the formation of 1,3-dicarbonyl compounds, using moist nitromethane as shown in the Scheme A.6. This reaction did not take place when $\text{Cu}(\text{OTf})_2$ was used as catalyst. The yields of the final products are, however, lesser than that of same products obtained from the corresponding 1,3-dicarbonyl compounds.



Scheme A.6: Alkynones into methylene-bridged bis-1,3-dicarbonyl compounds

A.3.3 Mechanism for the formation of methylene-bridged bis-1,3-dicarbonyl compounds

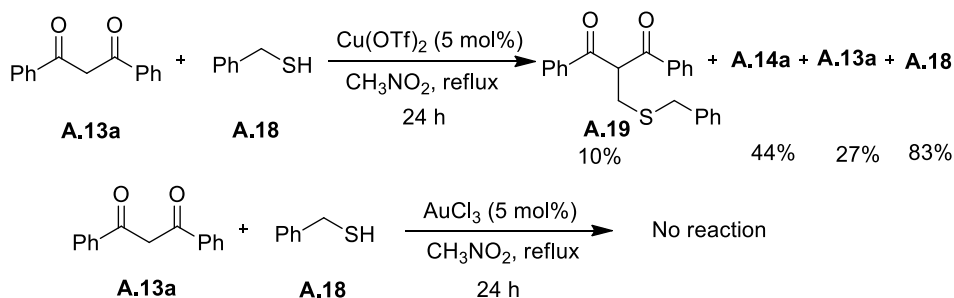
A simple mechanism, as shown in Scheme A.7, could be envisaged although the exact nature of the activated intermediate is unclear.¹⁷ The enolic form of the 1,3-dicarbonyl compound **A.13** could attack the Lewis acid-activated *aci*-nitromethane **I** to account for the first C–C bond formation. Intermediate **II**, on elimination of H₂O and HNO, as known in the mechanism of Nef reaction,² would give the intermediate **III**. This will undergo a fast Lewis acid-catalyzed Michael addition of the 1,3-dicarbonyl compound to furnish **A.14**.



Scheme A.7: Plausible mechanistic pathway

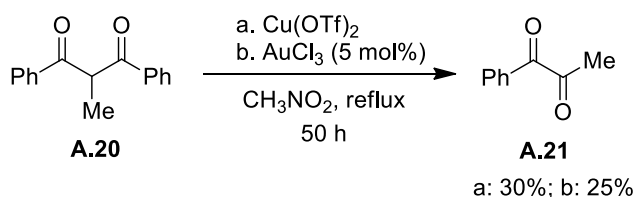
The involvement of intermediate **III** was inferred by trapping it with benzyl thiol **A.18**, which was intentionally added to the reaction of **A.13a** (Scheme A.8). This trapping experiment resulted in 10% of thiol derivative **A.19** which was obtained by the Michael addition of benzyl thiol on the intermediate **III** along with 44% methylene-bridged bis-1,3-dicarbonyl compound **A.14a** under copper-catalyzed reaction conditions after 24 h reflux. In this reaction the unreacted starting materials **A.13a** and **A.18** were isolated in 27% and 83% yields respectively. Due to the

poisoning nature of gold salts by thiol group, the trapping experiment did not provide any result with AuCl_3 (i.e. no reaction).



Scheme A.8: Trapping experiments with benzyl thiol

In another experiment, the reaction of 1,1-dibenzoylpropane **A.20** was studied under the present reaction conditions as the transformation of intermediate **II** into **III** is not possible with this system. However, with both Cu(OTf)_2 and AuCl_3 , only 1-phenylpropane-1,2-dione **A.21**¹⁸ was obtained in 30% and 25%, respectively, after 50 h of reflux (Scheme A.9). The expected nucleophilic attack on the Lewis acid-activated *aci*-nitromethane did not happen, perhaps for the reason that enolization is completely suppressed by the methyl substituent at the central carbon of the 1,3-dione **A.20**.¹⁹



Scheme A.9: Attempt to trap the intermediate **II**

The possibility for the involvement of formaldehyde formed by the Nef-type reaction initiated by traces of water present in the solvent cannot be neglected. A Nash test was carried out to check the formation of formaldehyde.²⁰ The Nash reagent was prepared by dissolving NH_4OAc (15 g, 0.19 mol), 2,4-pentanedione (0.2 ml, 2 mmol) and acetic acid (0.3 ml, 5 mmol) in 100 ml of water. An oven dried RB flask was charged with 5 ml of nitromethane and catalyst (2.5 mol%). Resulting solution was refluxed for 3 hours then cooled down to room temperature. 10 ml of hexane was added into 0.5 ml of the reaction mixture and then stirred it well for 10 minutes at room temperature. 0.01 ml of the reaction mixture in hexane was added to 5 ml of Nash reagent

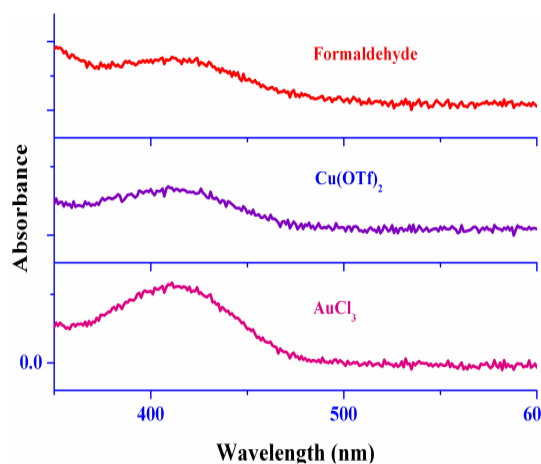


Figure A.4: Nash test

and incubated at 60 °C for 5 minutes. The formaldehyde formation was determined by measuring the absorbance of solution at 412 nm (Figure A.4) which is corresponding to the absorbance of compound diacetyldihydrolutidine (DDL). The formation of DDL is shown in the Figure A.5. Hence, the outcome indicates that some amount of formaldehyde might have formed under the reaction condition. If this had happened at all under the reaction conditions, it is still a new observation as there is no literature precedent for the direct Lewis acid-catalyzed Nef reaction on a nitroalkane.

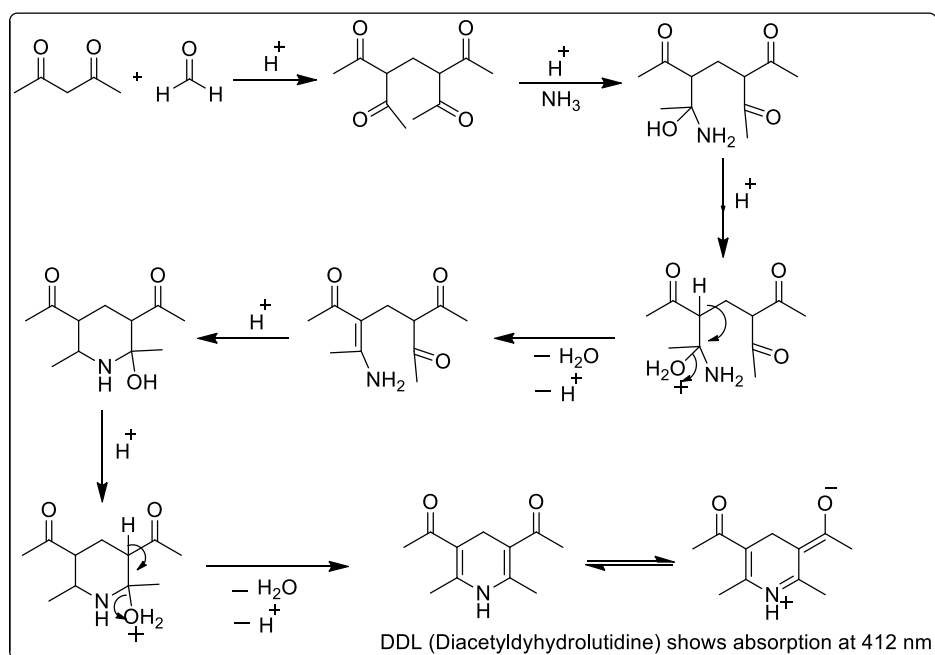


Figure A.5: Pathway for the formation DDL

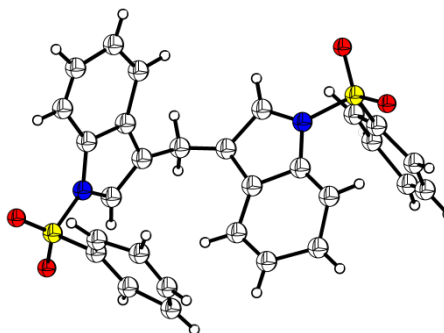
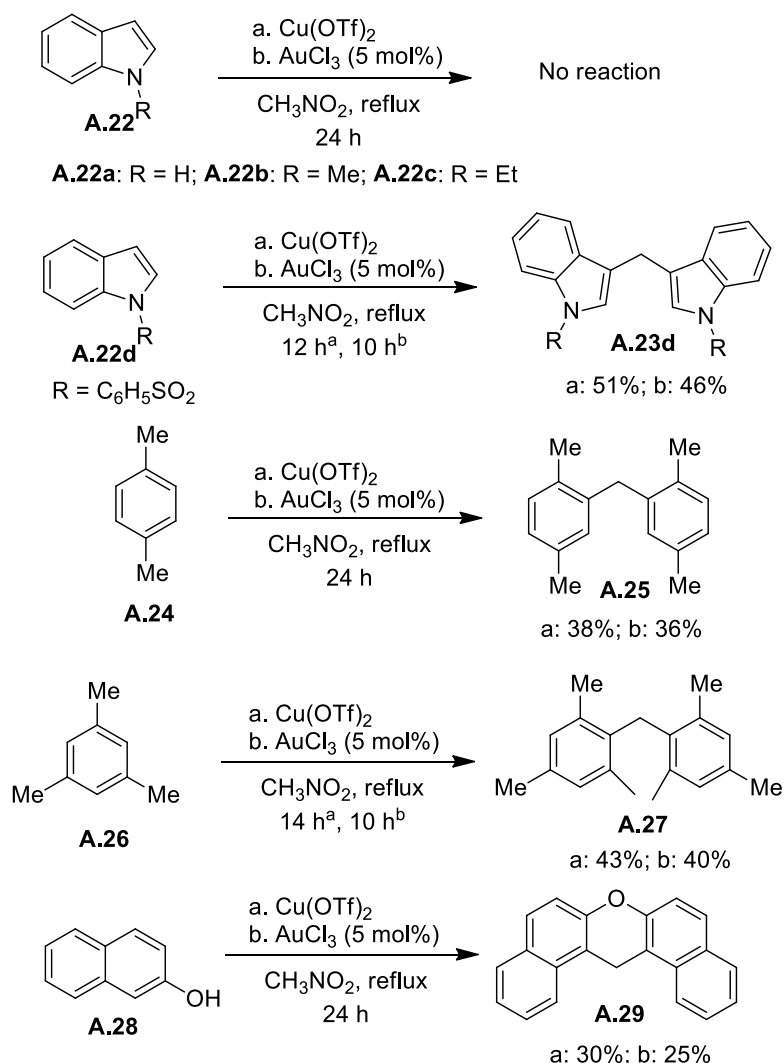
A similar reaction with nitroethane as the solvent did not take place with either AuCl_3 or $\text{Cu}(\text{OTf})_2$. This may be due to the famous ‘nitroalkane anomaly’ that the proton transfer reactions of nitroalkanes show abnormal trends.⁷ Perhaps a detailed theoretical study might give a better picture.

A.3.4 Reactions with other carbon nucleophiles

In order to broaden the scope of the present transformation we tried to find out other carbon nucleophiles (indole, xylene, mesitylene, etc.) to attack the Lewis acid activated *aci*-form of nitromethane which are outlined in Scheme A.10.

Indole, a C-nucleophile, did not result in any product when it was refluxed in nitromethane with either AuCl_3 or $\text{Cu}(\text{OTf})_2$. Similarly, there was no reaction when the indole nitrogen was protected with electron donating group such as Me and Et. The Lewis acid catalyst, at least $\text{Cu}(\text{OTf})_2$ might strongly be coordinating with the electron rich indoles and hence the catalyst may not be available to activate the *aci*-form of nitromethane. To our delight the reaction worked with substrate **A.22d** where indole nitrogen was protected with electron accepting phenyl

sulfonyl group and resulted methylene bridged indole derivative **A.23d**, although in low yield. The structure of compound **A.23d** was confirmed by single crystal X-ray analysis (Figure A.6). Similarly low to moderate yields of methylene bridged derivatives (**A.25** and **A.27**) were obtained when *p*-xylene **A.24** and mesitylene **A.26** were used as carbon nucleophiles to attack Lewis activated *aci*-form of nitromethane. The cyclized product **A.29** formed in moderate yield when β -naphthol **A.28** was used as the substrate. The reason for resulting low to moderate yields of methylene bridged compounds with other carbon nucleophiles (indole, xylene, mesitylene, etc.,) may be due to low nucleophilicity of carbon centre when compared to 1,3-dicarbonyl systems to attack Lewis activated *aci*-form of nitromethane.

Figure A.6: ORTEP of compound **A.23d**Scheme A.10: Different carbon nucleophiles to attack Lewis acid activated *aci*-form of nitromethane

A.4 Conclusions

To summarize, we have developed a method for the activation of *aci*-form of nitromethane using Lewis acids for the attack of carbon nucleophiles. 1,3-Dicarbonyl compounds in the presence of catalytic amounts of AuCl_3 or $\text{Cu}(\text{OTf})_2$ in nitromethane solvent could be converted into methylene-bridged bis-1,3-dicarbonyl compounds. The Lewis acid-activated *aci*-form of nitromethane might have been the key intermediate in the formation of methylene-bridged bis-1,3-dicarbonyls. Significant substrate scope was shown with both AuCl_3 and $\text{Cu}(\text{OTf})_2$ catalysts. We carried out trapping studies and Nash test to understand the mechanistic pathway and possible intermediates during the reaction. We tried to extend the substrate scope by using other carbon nucleophiles such as indole, xylene, mesitylene, etc., to attack Lewis activated *aci*-form of nitromethane and the results are encouraging. Theoretical and experimental studies on the Lewis acid activation of the *aci*-form could expand the scope of nitroalkane chemistry.

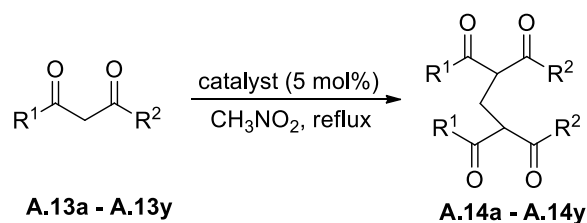
A.5 Experimental section

A.5.1 General information

Chemicals and solvents were obtained from various commercial sources. All starting materials were prepared by following known literature procedures. AuCl_3 , $\text{Cu}(\text{OTf})_2$ and NaH (60% dispersed in mineral oil) were purchased from Aldrich Chemical Co. Nitromethane was obtained from SD-Fine chemicals. Diethyl and dimethyl carbonate were purchased from AVRA synthesis. THF was dried over sodium and freshly distilled before use. ^1H and ^{13}C spectra were recorded on a Bruker Avance 400 MHz using solution in CDCl_3 with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on JASCO FT/IR-5300 spectrometer. Elemental (C, H, N) analysis were done using Thermo Finnigan Flash EA 1112 analyser. UV- Absorption was measured by CARY 100 BIO UV- Visible spectrometer. For TLC, silica gel plates 60 F254 were used and compounds were visualized by UV light and/or by treatment with Seebach solution (phosphomolibdic acid (2.5 g), $\text{Ce}(\text{SO}_4)_2$ (1 g), Conc. H_2SO_4 (6 mL), H_2O (94 mL)) followed by heating. Column chromatography was performed on silica gel (100-200 mesh) using ethyl acetate and hexanes mixture as eluent. The starting material 1,3-dicarbonyl compounds were prepared by following the reported literature procedure.²¹

A.5.2 Experimental procedures, spectral and analytical data

General Procedure for Synthesis of methylene-bridged bis-1,3-dicarbonyl compounds



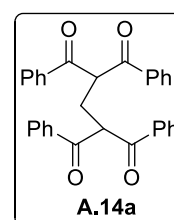
Gold (III) chloride or copper (II) triflate (5 mol%) was charged into a solution of 1,3-dicarbonyl compound **A.13** (1.0 mmol) in nitromethane (10 mL). The resulting mixture was heated to reflux. The reaction was monitored by TLC. After the completion of the reaction, nitromethane was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to furnish the pure compound **A.14**.

The same experimental procedure was followed for the reactions of indole and other carbon nucleophile substrates.

Analytical data of compounds **A.14**

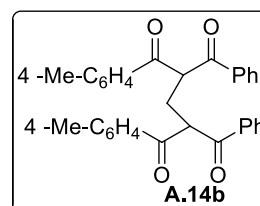
2,4-Dibenzoyl-1,5-diphenylpentane-1,5-dione **A.14a**:^{21b}

Light yellow powder; R_f = 0.4 (in 20% EtOAc/Hexane); ^1H NMR (400 MHz, CDCl_3): δ 8.14 (d, J = 7.2 Hz, 8H), 7.60-7.58 (m, 4H), 7.50-7.46 (m, 8H), 5.74 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.6, 135.4, 133.9, 129.0, 128.8, 53.9, 28.9.



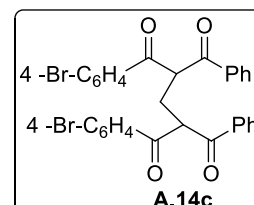
2,4-Dibenzoyl-1,5-di-*p*-tolylpentane-1,5-dione **A.14b**:

Light yellow powder; mp 62-64 °C; R_f = 0.35 (in 20% EtOAc/Hexane); IR (KBr): 3059, 3034, 2922, 1693, 1668, 1604, 1448, 1261, 1182, 949, 688 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.14-8.11 (m, 4H), 8.06-8.03 (m, 4H), 7.55-7.53 (m, 2H), 7.47-7.44 (m, 4H), 7.27-7.23 (m, 4H), 5.72 (t, J = 6.8 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.6, 196.1, 144.8, 135.4, 133.7, 132.9, 132.9, 129.6, 128.9, 128.7, 53.8, 28.9, 21.6; Anal.Calc'd for $\text{C}_{33}\text{H}_{28}\text{O}_4$: C, 81.12; H, 5.78; Found: C, 81.35; H, 5.71.



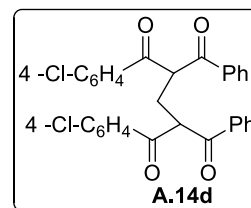
2,4-Dibenzoyl-1,5-bis(4-bromophenyl)pentane-1,5-dione **A.14c**:

Light yellow powder; mp 70-72 °C; R_f = 0.4 (in 20% EtOAc/Hexane); IR (KBr): 3061, 2928, 2854, 1695, 1670, 1583, 1448, 1396, 1257, 1070, 1008, 947, 686 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.12-8.07 (m, 4H), 8.03-7.97 (m, 4H), 7.64-7.57 (m, 6H), 7.51-7.45 (m, 4H), 5.64 (t, J = 6.8 Hz, 2H), 2.78-2.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.2, 195.6, 135.2, 134.0, 132.4, 130.3, 130.2, 129.9, 129.3, 129.1, 128.8, 128.7, 53.9, 28.7; Anal.Calc'd for $\text{C}_{31}\text{H}_{22}\text{Br}_2\text{O}_4$: C, 60.22; H, 3.59; Found: C, 60.35; H, 3.51.

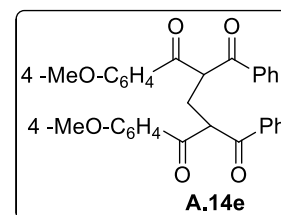


2,4-Dibenzoyl-1,5-bis(4-chlorophenyl)pentane-1,5-dione A.14d:

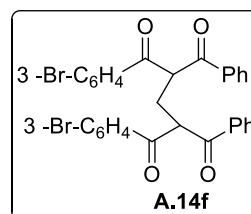
Light yellow powder; mp 62-64 °C; $R_f = 0.4$ (in 20% EtOAc/Hexane); IR (KBr): 3065, 2922, 1695, 1672, 1587, 1487, 1257, 1093, 946, 686 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.13-8.06 (m, 8H), 7.61-7.56 (m, 2H), 7.50-7.44 (m, 8H), 5.66 (t, $J = 6.8$ Hz, 2H), 2.77-2.67 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.2, 195.4, 140.5, 140.4, 135.2, 135.2, 134.0, 133.7, 130.2, 130.1, 129.3, 129.0, 128.7, 128.6, 128.3, 53.9, 28.7; Anal.Calc'd for $\text{C}_{31}\text{H}_{22}\text{Cl}_2\text{O}_4$: C, 70.33; H, 4.19; Found: C, 70.12; H, 4.23.

**2,4-Dibenzoyl-1,5-bis(4-methoxyphenyl)pentane-1,5-dione A.14e:**

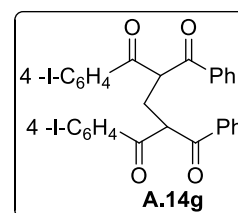
Light yellow powder; mp 66-68 °C; $R_f = 0.3$ (in 33% EtOAc/Hexane); IR (KBr): 3059, 3011, 2932, 2843, 1689, 1664, 1549, 1510, 1421, 1259, 1170, 1026, 949 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.20 (d, $J = 8.8$ Hz, 2H), 8.15-8.11 (m, 4H), 8.06 (d, $J = 7.6$ Hz, 2H), 7.56-7.52 (m, 2H), 7.48-7.41 (m, 4H), 6.98-6.92 (m, 4H), 5.68 (t, $J = 6.8$ Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.74 (t, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.7, 195.1, 195.0, 164.1, 164.0, 135.6, 135.5, 133.7, 133.6, 131.3, 131.1, 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 114.2, 114.1, 55.4, 53.7, 29.1; Anal.Calc'd for $\text{C}_{33}\text{H}_{28}\text{O}_6$: C, 76.14; H, 5.42; Found: C, 76.23; H, 5.38.

**2,4-Dibenzoyl-1,5-bis(3-bromophenyl)pentane-1,5-dione A.14f:**

Light yellow powder; mp 52-54 °C; $R_f = 0.25$ (in 20% EtOAc/Hexane); IR (KBr): 3065, 2928, 2856, 1693, 1670, 1595, 1564, 1446, 1419, 1251, 1188, 1068, 999, 949, 750, 686 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.24 (s, 2H), 8.12 (t, $J = 6.4$ Hz, 3H), 8.06 (t, $J = 7.6$ Hz, 3H), 7.71 (d, $J = 7.2$ Hz, 2H), 7.60 (d, $J = 7.2$ Hz, 2H), 7.53-7.49 (m, 4H), 7.39-7.35 (m, 2H), 5.63 (t, $J = 6.8$ Hz, 2H), 2.75-2.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.2, 195.2, 136.7, 135.1, 134.1, 131.7, 130.6, 129.1, 128.8, 127.3, 123.5, 53.9, 28.6; Anal.Calc'd for $\text{C}_{31}\text{H}_{22}\text{Br}_2\text{O}_4$: C, 60.22; H, 3.59; Found: C, 60.12; H, 3.51.

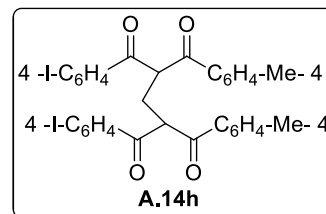
**2,4-Dibenzoyl-1,5-bis(4-iodophenyl)pentane-1,5-dione A.14g:**

Light yellow powder; mp 64-66 °C; $R_f = 0.4$ (in 20% EtOAc/Hexane); IR (KBr): 3057, 2922, 2852, 1693, 1668, 1579, 1446, 1392, 1257, 1180, 1059, 1003, 947, 686 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.12-8.07 (m, 4H), 7.86-7.84 (m, 8H), 7.60-7.59 (m, 2H), 7.51-7.46 (m, 4H), 5.62 (t, $J = 6.8$ Hz, 2H), 2.75-2.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.2, 195.9, 138.4, 135.2, 134.6, 134.1, 130.1, 130.1, 129.1, 128.7, 102.3, 53.8, 28.7; Anal.Calc'd for $\text{C}_{31}\text{H}_{22}\text{I}_2\text{O}_4$: C, 52.27; H, 3.11; Found: C, 52.09; H, 3.18.

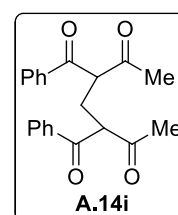


2,4-Bis(4-iodobenzoyl)-1,5-di-*p*-tolylpentane-1,5-dione A.14h:

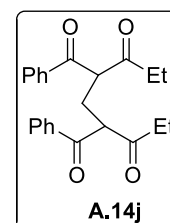
Light yellow powder; mp 88-90 °C; R_f = 0.5 (in 20% EtOAc/Hexane); IR (KBr): 3032, 2922, 1693, 1668, 1604, 1579, 1392, 1259, 1180, 1005, 943 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, J = 7.6 Hz, 4H), 7.83 (s, 8H), 7.27 (d, J = 7.6 Hz, 4H), 5.58 (t, J = 6.8 Hz, 2H), 2.72-2.62 (m, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.0, 195.8, 145.1, 138.3, 134.7, 132.8, 130.0, 129.7, 128.9, 102.2, 53.8, 28.8, 21.7; Anal.Calc'd for $\text{C}_{33}\text{H}_{26}\text{I}_2\text{O}_4$: C, 58.53; H, 3.54; Found: C, 53.42; H, 3.61.

**3,5-Dibenzoylheptane-2,6-dione A.14i:^{21b}**

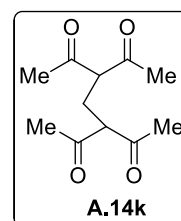
Light yellow solid; R_f = 0.2 (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.3:1. **Two diastereomers;** ^1H NMR (400 MHz, CDCl_3): δ 8.07 (d, J = 7.2 Hz, 2H), 8.03 (d, J = 7.6 Hz, 2H), 7.65-7.58 (m, 2H), 7.54-7.47 (m, 4H), 4.72 (t, J = 6.8 Hz, 1H), 4.65 (t, J = 6.8 Hz, 1H), 2.65-2.45 (m, 2H), 2.19 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.9, 203.4, 196.6, 196.4, 135.9, 135.6, 134.0, 128.9, 128.8, 128.7, 59.3, 59.1, 29.4, 29.1, 27.3, 26.9.

**4,6-Dibenzoylnonane-3,7-dione A.14j:**

Yellow oil; R_f = 0.2 (in 20% EtOAc/Hexane); IR (neat): 2976, 2939, 1720, 1672, 1595, 1448, 1111, 1018 cm^{-1} ; The ratio of two diastereomers is 1:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 8.15-8.10 (m, 1H), 8.06 (d, J = 7.6 Hz, 2H), 8.02 (d, J = 7.6 Hz, 2H), 7.63-7.57 (m, 2H), 7.53-7.46 (m, 5H), 4.75 (t, J = 6.8 Hz, 1H), 4.67 (t, J = 6.8 Hz, 1H), 2.59-2.36 (m, 6H), 1.05 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.7, 206.5, 206.0, 196.7, 196.5, 196.2, 135.9, 135.6, 133.8, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 58.3, 58.1, 53.6, 35.7, 35.5, 35.3, 29.5, 28.1, 27.5, 27.2, 7.6, 7.5; Anal.Calc'd for $\text{C}_{23}\text{H}_{24}\text{O}_4$: C, 75.80; H, 6.64; Found: C, 75.89; H, 6.59.

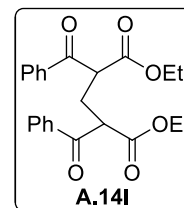
**3,5-Diacetylheptane-2,6-dione A.14k:²²**

Light yellow oil; R_f = 0.25 (in 33% EtOAc/Hexane); ^1H NMR (400 MHz, CDCl_3): δ 3.83 (t, J = 7.2 Hz, 0.4H), 3.68 (t, J = 6.4 Hz, 2H), 2.83 (d, J = 7.2 Hz, 1H), 2.28 (t, J = 6.4 Hz, 2H), 2.22 (s, 6H), 2.21 (s, 5H), 2.17 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.5, 203.1, 191.7, 106.7, 68.1, 64.6, 30.2, 29.4, 26.0, 24.7, 23.1.

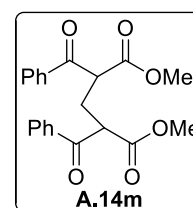


Diethyl 2,4-dibenzoylpentanedioate A.14l:^{21b}

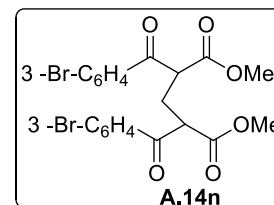
Light yellow oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.1:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 8.05 (d, $J = 7.2$ Hz, 4H), 7.63-7.56 (m, 2H), 7.52-7.45 (m, 4H), 4.63 (t, $J = 7.2$ Hz, 1H), 4.55 (t, $J = 7.2$ Hz, 1H), 4.27-4.18 (m, 2H), 4.13-4.07 (m, 2H), 2.79-2.54 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.1, 194.7, 169.6, 169.2, 135.7, 135.3, 133.7, 128.8, 128.7, 128.0, 61.6, 51.4, 51.2, 28.1, 27.5, 13.9, 13.8.

**Dimethyl 2,4-dibenzoylpentanedioate A.14m:**^{21b}

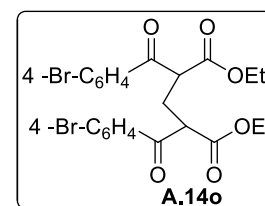
Colourless oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.3:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 8.06 (d, $J = 7.2$ Hz, 4H), 7.62-7.59 (m, 2H), 7.57-7.46 (m, 4H), 4.67 (t, $J = 7.2$ Hz, 1H), 4.58 (t, $J = 7.2$ Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.78-2.54 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.1, 194.6, 170.2, 169.7, 135.6, 135.2, 133.9, 128.9, 128.8, 52.6, 51.2, 50.9, 28.3, 27.7.

**Dimethyl 2,4-bis(3-bromobenzoyl)pentanedioate A.14n:**

Light yellow oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); IR (neat): 3067, 2953, 1747, 1684, 1566, 1435, 1251, 1070, 974 cm^{-1} ; The ratio of two diastereomers is 1.3:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 8.15 (d, $J = 10.4$ Hz, 2H), 7.98 (t, $J = 8.4$ Hz, 2H), 7.73 (t, $J = 8.4$ Hz, 2H), 7.38 (q, $J = 8.0$ Hz, 2H), 4.59 (t, $J = 7.2$ Hz, 1H), 4.51 (t, $J = 7.2$ Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 2.74-2.52 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 193.7, 193.3, 169.6, 169.3, 137.3, 136.9, 136.7, 131.7, 131.6, 130.4, 127.4, 127.3, 123.1, 52.8, 51.0, 50.8, 27.9, 27.4. Anal.Calc'd for $\text{C}_{21}\text{H}_{18}\text{Br}_2\text{O}_6$: C, 47.97; H, 3.45; Found: C, 47.85; H, 3.41.

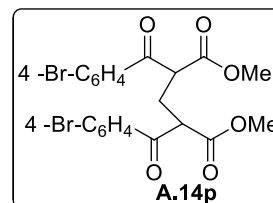
**Diethyl 2,4-bis(4-bromobenzoyl)pentanedioate A.14o:**

Light yellow oil; $R_f = 0.5$ (in 20% EtOAc/Hexane); IR (KBr): 3097, 2986, 1739, 1684, 1585, 1460, 1390, 1248, 1070, 839 cm^{-1} ; The ratio of two diastereomers is 1.2:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 7.91 (d, $J = 8.4$ Hz, 4H), 7.66-7.61 (m, 4H), 4.56 (t, $J = 7.2$ Hz, 1H), 4.47 (t, $J = 7.2$ Hz, 1H), 4.26-4.16 (m, 2H), 4.14-4.07 (m, 2H), 2.74-2.50 (m, 2H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.13 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.1, 193.7, 169.3, 168.9, 134.5, 134.0, 132.1, 130.3, 130.2, 129.2, 129.2, 61.8, 51.3, 51.1, 27.9, 27.3, 13.9, 13.8. Anal.Calc'd for $\text{C}_{23}\text{H}_{22}\text{Br}_2\text{O}_4$: C, 49.84; H, 4.00; Found: C, 49.75; H, 4.08.

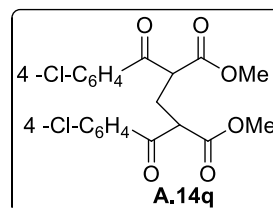


Dimethyl 2,4-bis(4-bromobenzoyl)pentanedioate A.14p: ^{21b}

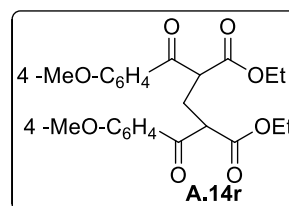
Yellow oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.4:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 7.93-7.89 (m, 4H), 7.66-7.62 (m, 4H), 4.60 (t, $J = 7.2$ Hz, 1H), 4.50 (t, $J = 7.2$ Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.74-2.51 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.1, 193.6, 169.9, 169.4, 134.3, 133.9, 133.2, 130.4, 130.3, 129.4, 52.7, 51.0, 50.8, 28.1, 27.4.

**Dimethyl 2,4-bis(4-chlorobenzoyl)pentanedioate A.14q:** ^{21b}

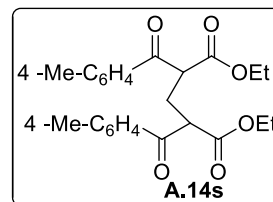
Light yellow oil; $R_f = 0.5$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.2:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 8.02-7.98 (m, 4H), 7.49-7.45 (m, 4H), 4.61 (t, $J = 7.2$ Hz, 1H), 4.51 (t, $J = 7.2$ Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.74-2.50 (m, 2H); ^{13}C NMR (400 MHz, CDCl_3): δ 193.8, 193.4, 169.9, 169.4, 140.6, 133.9, 133.5, 130.3, 130.2, 129.2, 52.7, 51.0, 50.8, 28.1, 27.4.

**Diethyl 2, 4-bis(4-methoxybenzoyl)pentanedioate A.14r:**

Yellow oil; $R_f = 0.35$ (in 33% EtOAc/Hexane); IR (KBr): 2986, 2937, 1739, 1670, 1601, 1510, 1458, 1261, 1172, 1026, 956, 844 cm^{-1} ; The ratio of two diastereomers is 1.3:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 8.05 (d, $J = 8.8$ Hz, 4H), 6.98-6.92 (m, 4H), 4.57 (t, $J = 7.2$ Hz, 1H), 4.49 (t, $J = 7.2$ Hz, 1H), 4.27-4.18 (m, 2H), 4.14-4.06 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.75-2.51 (m, 2H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 193.7, 193.2, 169.9, 169.5, 163.9, 131.3, 131.2, 128.7, 128.2, 113.9, 113.6, 61.4, 55.4, 51.2, 50.9, 28.5, 27.8, 14.1, 13.9, 13.8; Anal.Calc'd for $\text{C}_{25}\text{H}_{28}\text{O}_8$: C, 65.78; H, 6.18; Found: C, 65.85; H, 6.12.

**Diethyl 2,4-bis(4-methylbenzoyl)pentanedioate A.14s:**

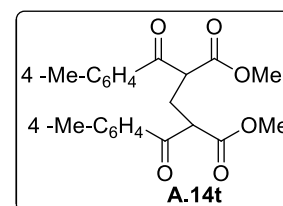
Yellow oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); IR (neat): 3034, 2984, 2935, 1739, 1682, 1606, 1572, 1444, 1257, 1097, 1033, 962 cm^{-1} ; The ratio of two diastereomers is 1.1:1. **Two diastereomers:** ^1H NMR (400 MHz, CDCl_3): δ 7.97-7.92 (m, 4H), 7.30-7.24 (m, 4H), 4.58 (t, $J = 7.2$ Hz, 1H), 4.50 (t, $J = 7.2$ Hz, 1H), 4.25-4.17 (m, 2H), 4.12-4.07 (m, 2H), 2.75-2.52 (m, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.7, 194.4, 169.7, 169.4, 144.7, 133.4, 132.9, 129.4, 129.0, 128.9, 128.1, 61.5, 51.4,



51.2, 28.2, 27.7, 21.6, 13.9, 13.8; Anal.Calc'd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65; Found: C, 70.65; H, 6.59.

Dimethyl 2, 4-bis(4-methylbenzoyl)pentanedioate A.14t:^{21b}

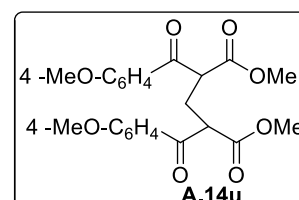
Colourless oil; $R_f = 0.5$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.3:1. **Two diastereomers**; 1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, $J = 7.2$ Hz, 4H), 7.31-7.25 (m, 4H), 4.63 (t, $J = 7.2$ Hz, 1H), 4.55 (t, $J = 7.2$ Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 2.76-2.52



(m, 2H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 194.2, 170.2, 169.8, 144.8, 133.2, 132.7, 129.4, 129.0, 128.9, 52.5, 51.1, 50.8, 28.3, 27.8, 21.6.

Dimethyl 2,4-bis(4-methoxybenzoyl)pentanedioate A.14u:^{21b}

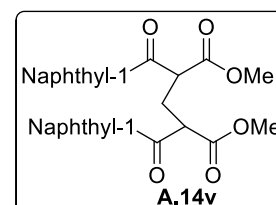
Colourless oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1.3:1. **Two diastereomers**; 1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, $J = 8.0$ Hz, 4H), 6.98-6.93 (m, 4H), 4.6 (t, $J = 7.2$ Hz, 1H), 4.53 (t, $J = 7.2$ Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75 (s,



3H), 3.64 (s, 3H), 2.75-2.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 193.1, 170.4, 169.9, 164.1, 131.1, 131.2, 128.6, 128.1, 113.9, 55.4, 52.4, 50.9, 50.6, 28.6, 27.9.

Dimethyl 2,4-di(1-naphthoyl)pentanedioate A.14v:^{21b}

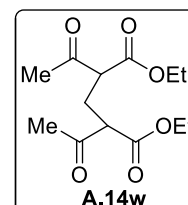
Yellow oil; $R_f = 0.4$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1:1. **Two diastereomers**; 1H NMR (400 MHz, $CDCl_3$): δ 13.15 (s, 0.2H), 8.61-8.57 (m, 2H), 8.01-7.82 (m, 7H), 7.62-7.24 (m, 8H), 4.73 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 0.7H), 3.67 (s, 2.5H), 3.58 (s, 2.1H), 2.91-2.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 197.8,



169.9, 169.8, 134.5, 133.9, 133.8, 133.6, 133.5, 132.9, 130.3, 130.1, 129.9, 128.7, 128.4, 128.3, 127.9, 127.7, 126.6, 126.5, 126.4, 126.2, 125.6, 125.5, 124.8, 124.2, 53.9, 53.8, 52.5, 52.0, 28.4, 27.8, 26.1.

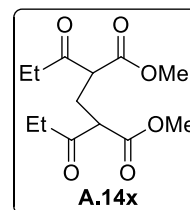
Diethyl 2,4-diacetylpentanedioate A.14w:²³

Yellow oil; $R_f = 0.2$ (in 20% EtOAc/Hexane); The ratio of two diastereomers is 1:1. **Two diastereomers**; 1H NMR (400 MHz, $CDCl_3$): δ 4.26-4.16 (m, 4H), 3.55 and 3.54 (t, $J = 7.2$ Hz, 2H), 2.46-2.31 (m, 2H), 2.26 (s, 6H), 1.30-1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 168.9, 61.6, 56.6, 56.4, 29.4, 29.1, 25.4, 25.3, 13.9.

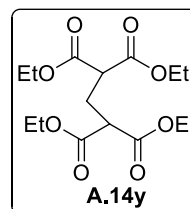


Dimethyl 2,4-dipropionylpentanedioate A.14x:

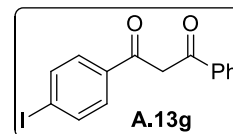
Light yellow oil; $R_f = 0.32$ (in 20% EtOAc/Hexane); IR (KBr): 2976, 2955, 1745, 1716, 1439, 1356, 1170, 1107 1020 cm^{-1} ; The ratio of two diastereomers is 1:1. **Two diastereomers**; ^1H NMR (400 MHz, CDCl_3): δ 3.73 (s, 3H), 3.72 (s, 2H), 3.70 (s, 1H), 3.62-3.56 (m, 2H), 2.65-2.32 (m, 6H), 2.15 (d, $J = 2.4$ Hz, 1H), 1.36 (s, 1H), 1.06 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 205.0, 204.9, 172.6, 169.9, 169.5, 58.4, 55.3, 55.2, 54.4, 54.3, 52.5, 35.7, 35.5, 32.5, 32.3, 26.2, 26.1, 25.8, 25.7, 20.0, 19.8, 7.4; Anal.Calc'd for $\text{C}_{13}\text{H}_{20}\text{O}_6$: C, 57.34; H, 7.40; Found: C, 57.23; H, 7.55.

**Tetraethyl propane-1,1,3,3-tetracarboxylate A.14y:**²⁴

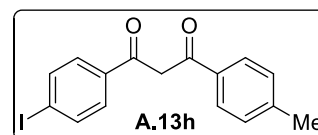
Light yellow oil; $R_f = 0.32$ (in 20% EtOAc/Hexane); ^1H NMR (400 MHz, CDCl_3): δ 4.18 (q, $J = 7.2$ Hz, 8H), 3.45 (t, $J = 7.6$ Hz, 2H), 2.45 (t, $J = 7.6$ Hz, 2H), 1.25 (t, $J = 7.2$ Hz, 12H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.5, 61.6, 49.3, 27.2, 13.9.

**Analytical data of unreported 1,3-dicarbonyl compounds and compound A.19****1-(4-Iodophenyl)-3-phenylpropane-1,3-dione A.13g:**

Yellow solid (82%); mp 104-106 $^{\circ}\text{C}$; Enol form; $R_f = 0.55$ (in 20% EtOAc/Hexane); IR (KBr): 3045, 2916, 1583, 1302, 1064, 1005, 837, 760, 684, 463 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, $J = 7.6$ Hz, 2H), 7.80 (d, $J = 8.0$ Hz, 2H), 7.66 (d, $J = 8.0$ Hz, 2H), 7.56-7.52 (m, 1H), 7.48-7.44 (m, 2H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 185.9, 184.5, 137.8, 135.2, 134.8, 132.5, 128.6, 128.4, 127.1, 99.8, 92.8; Anal.Calc'd for $\text{C}_{15}\text{H}_{11}\text{IO}_2$: C, 51.45; H, 3.17; Found: C, 51.58; H, 3.12.

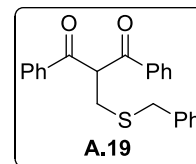
**1-(4-Iodophenyl)-3-*p*-tolylpropane-1,3-dione A.13h:**

White solid (Yield = 65%); mp 174- 176 $^{\circ}\text{C}$; Enol form; $R_f = 0.7$ (in 20% EtOAc/Hexane); IR (KBr): 3034, 2926, 2845, 1738, 1604, 1581, 1510, 1298, 1269, 1182, 1003, 839, 779 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.86 (d, $J = 8.4$ Hz, 2H), 7.81(d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 6.77 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 186.2, 183.9, 143.5, 137.8, 134.9, 132.5, 129.4, 128.4, 127.2, 99.6, 92.5, 21.6; Anal.Calc'd for $\text{C}_{16}\text{H}_{13}\text{IO}_2$: C, 52.77; H, 3.60; Found: C, 52.61; H, 3.68.



2-(Benzylthiomethyl)-1,3-diphenylpropane-1,3-dione A.19:

Yellow oil; $R_f = 0.33$ (in 20% EtOAc/Hexane); IR (neat): 3061, 3028, 2924, 1956, 1903, 1695, 1670, 1597, 1581, 1493, 1448, 1408, 1323, 1286, 1259, 1074, 1028, 1001, 761, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.83 (d, $J = 7.2$ Hz, 4H), 7.55 (t, $J = 7.2$ Hz, 2H), 7.41 (t, $J = 7.2$ Hz, 4H), 7.34-7.28 (m, 5H), 5.32 (t, $J = 6.8$ Hz, 1H), 3.75 (s, 2H), 3.19 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.5, 138.2, 135.7, 133.6, 129.5, 128.9, 128.6, 127.2, 57.6, 37.7, 30.7; Anal.Calc'd for $\text{C}_{23}\text{H}_{20}\text{O}_2\text{S}$: C, 75.64; H, 5.59; Found: C, 76.48; H, 5.65.



The compounds **A.25**, **A.27** and **A.29** were reported in the literature and our prepared compounds data are matching with those literature.²⁵

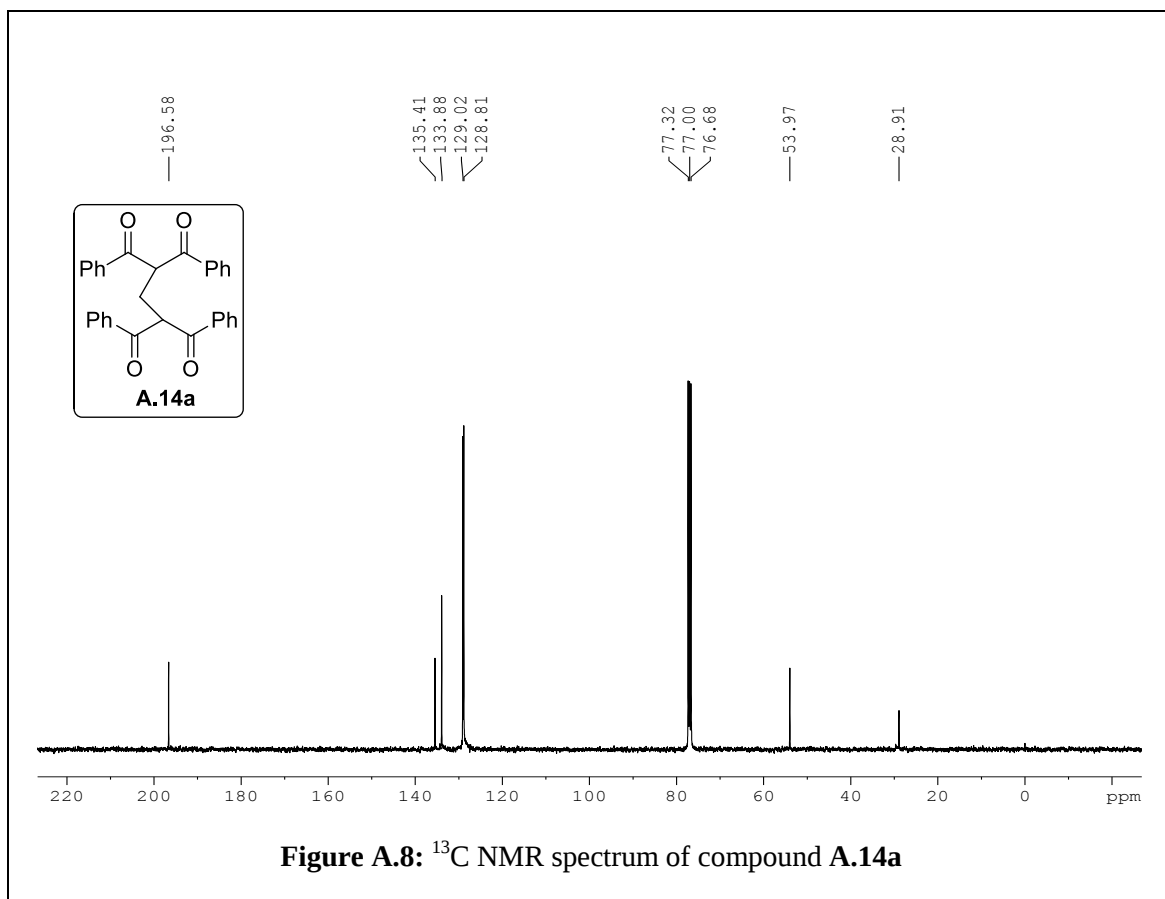
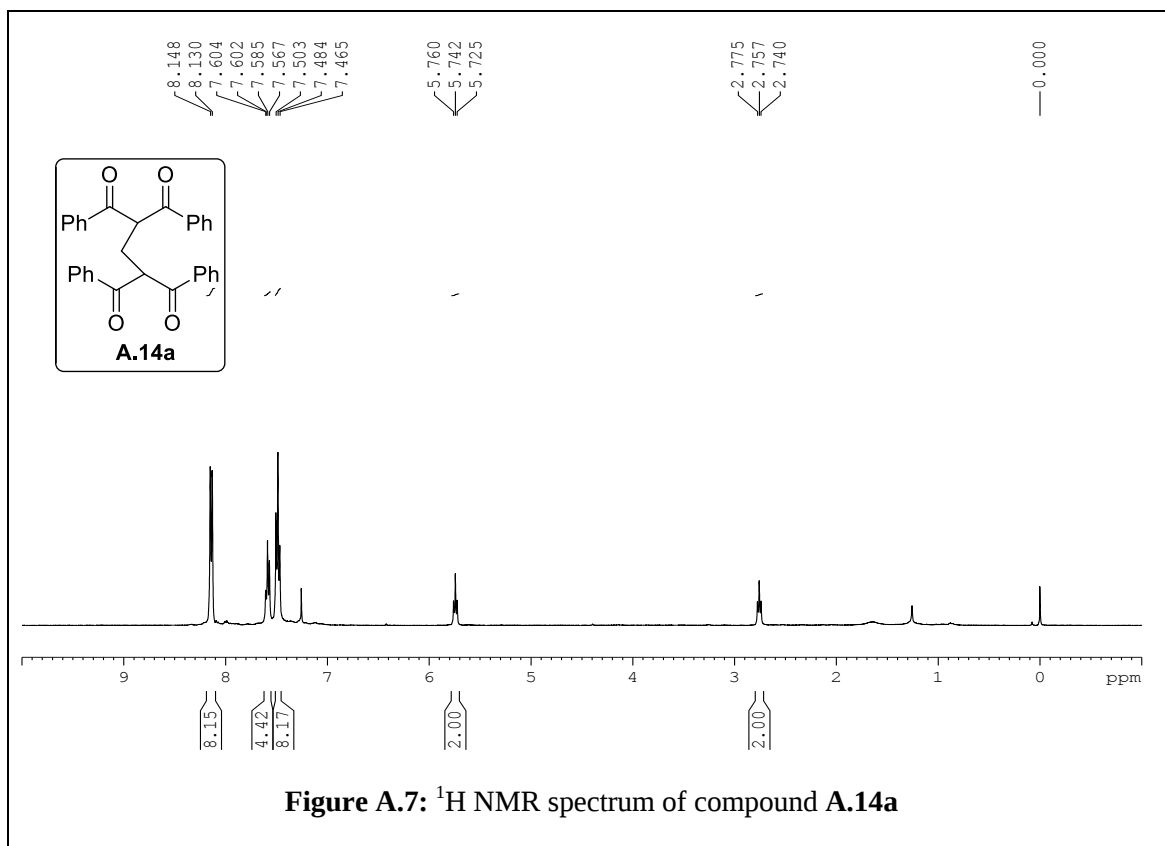
A.6 References

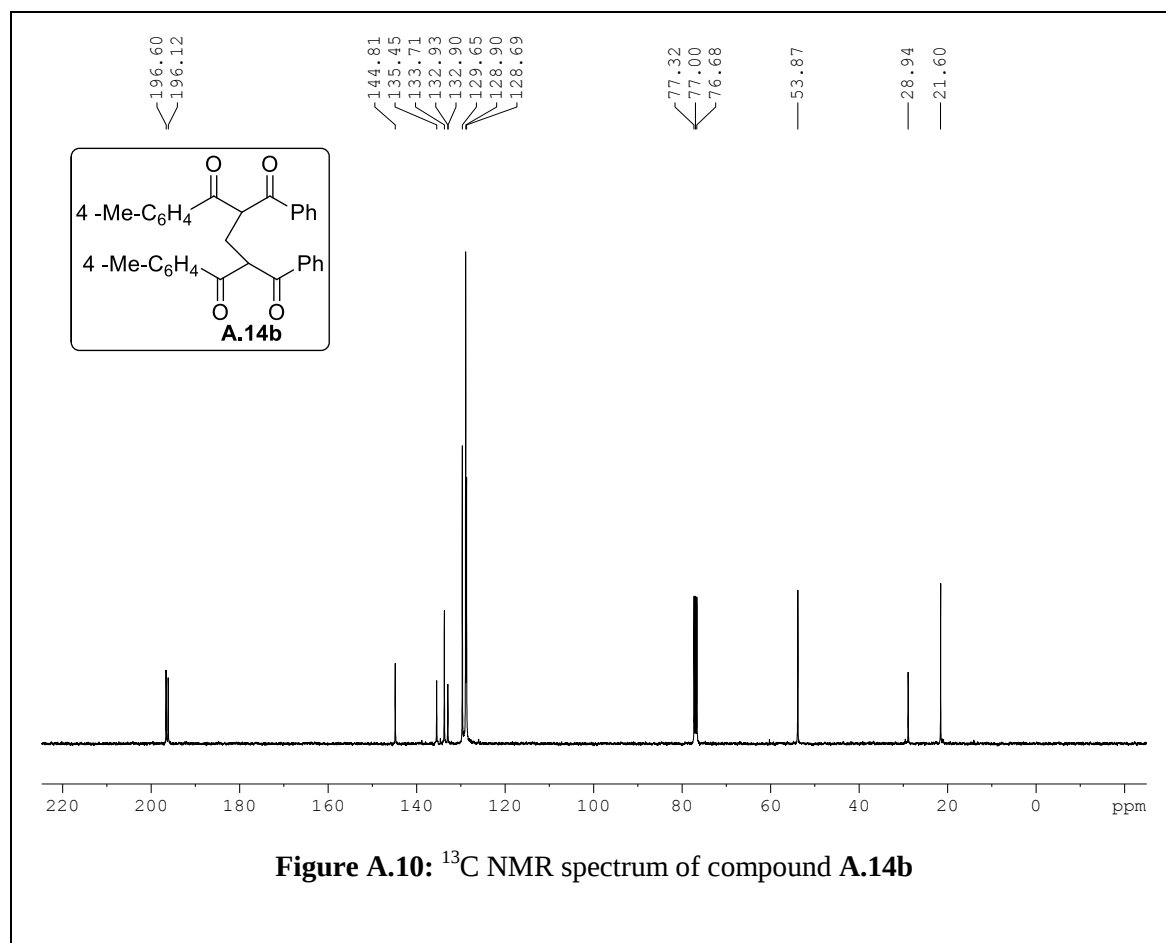
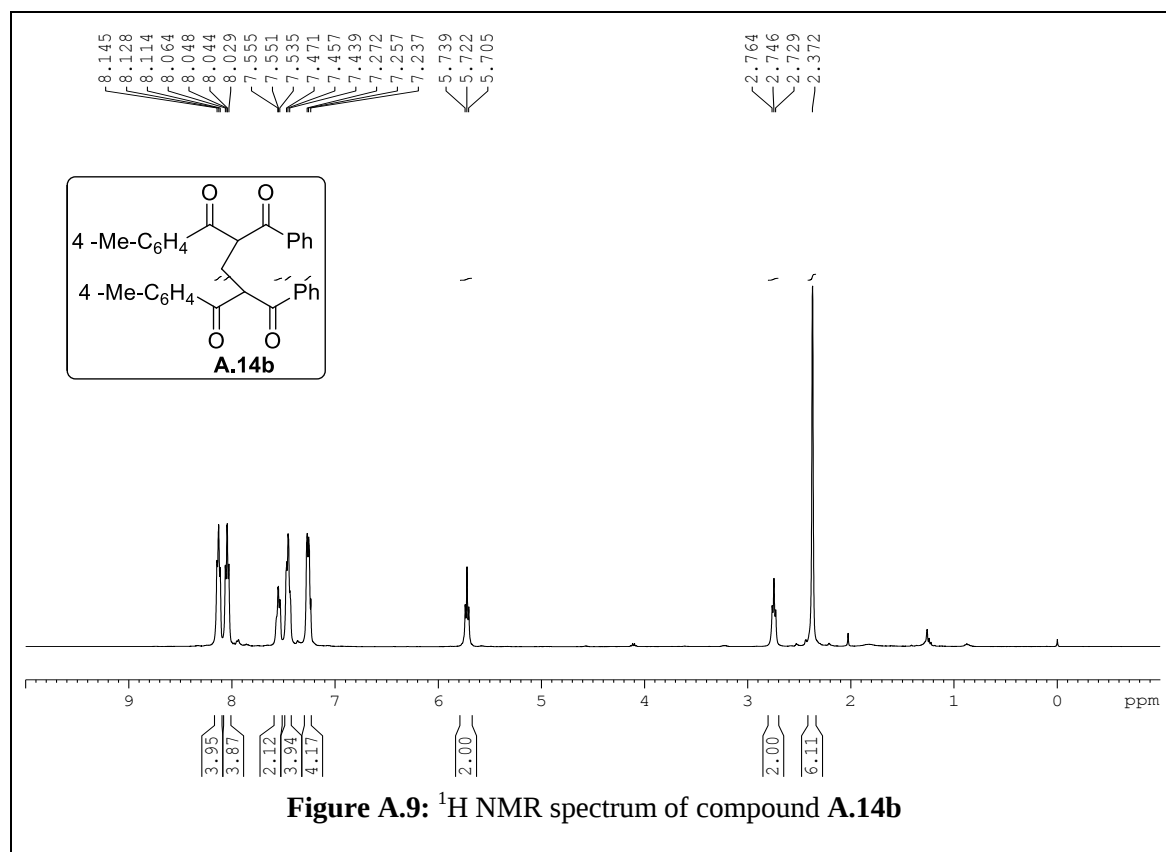
1. For extensive reviews, see: (a) Ballini, R.; Petrini, M. *ARKIVOC* **2009**, 195. (b) Ballini, R.; Palmieri, A.; Barboni, L. *Chem. Commun.* **2008**, 2975. (c) Ballini, R.; Petrini, M.; Rosini, G. *Molecules* **2008**, *13*, 319. (d) Namboothiri, I. N. N.; Rastogi, N. in *Topics in Heterocyclic Chemistry* ed. Hassner, A. Springer-Verlag, Berlin Heidelberg, **2008**, *12*, 1. (e) Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099. (f) Ballini, R.; Palmieri, A. *Curr. Org. Chem.* **2006**, *10*, 2145. (g) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.
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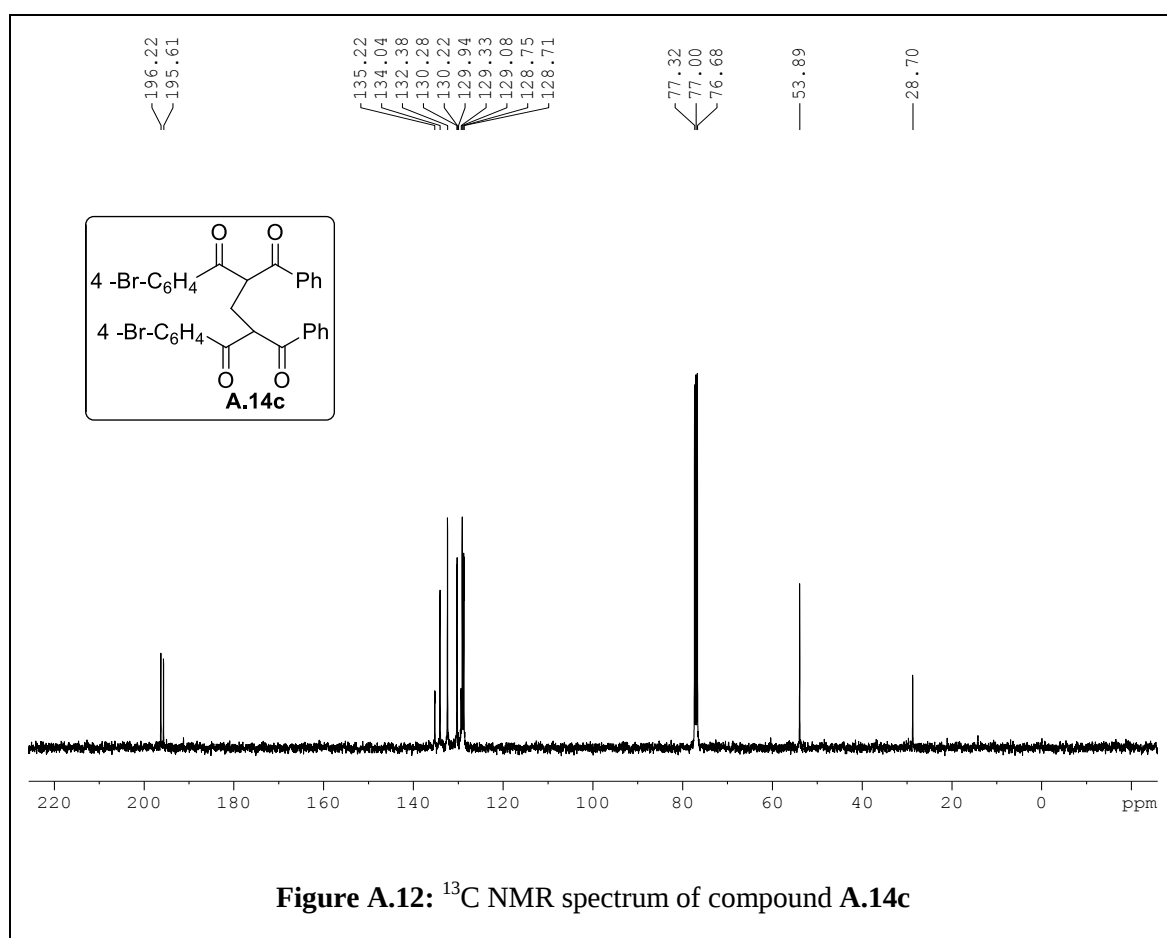
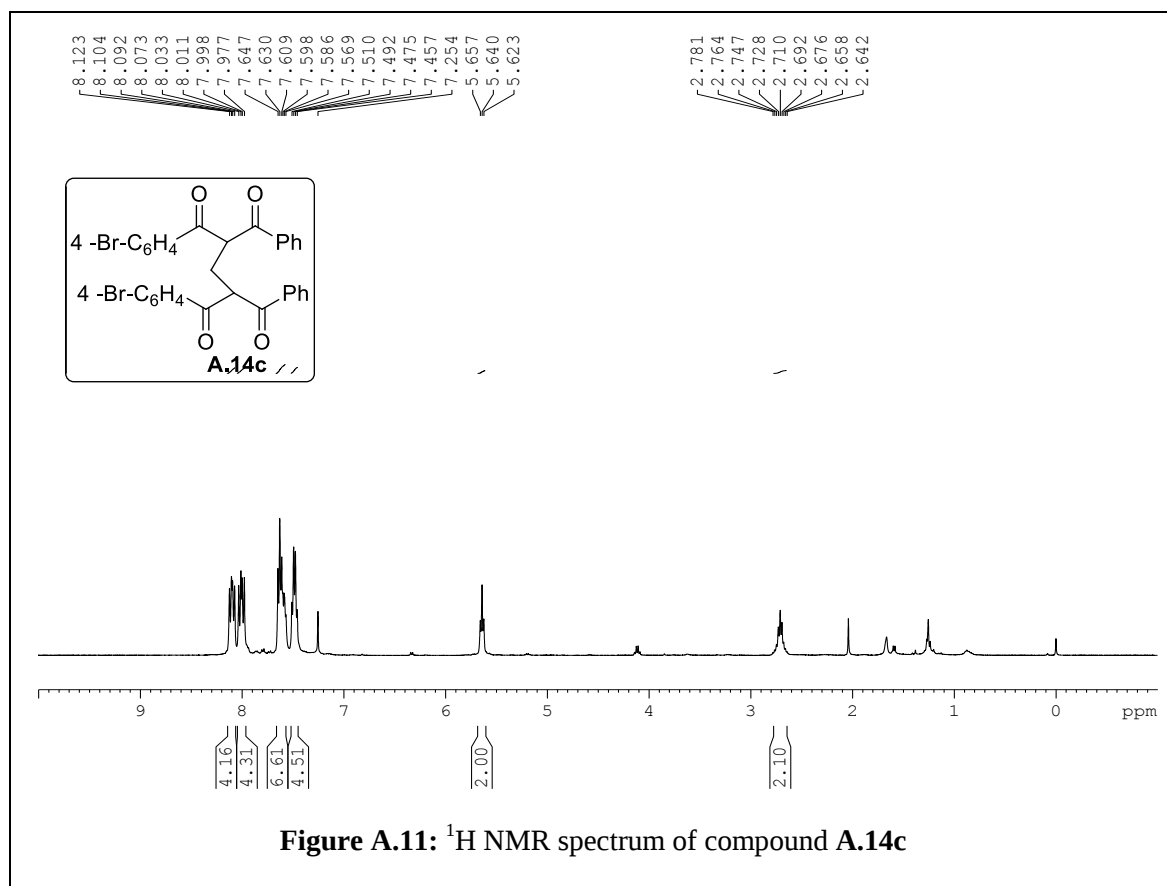
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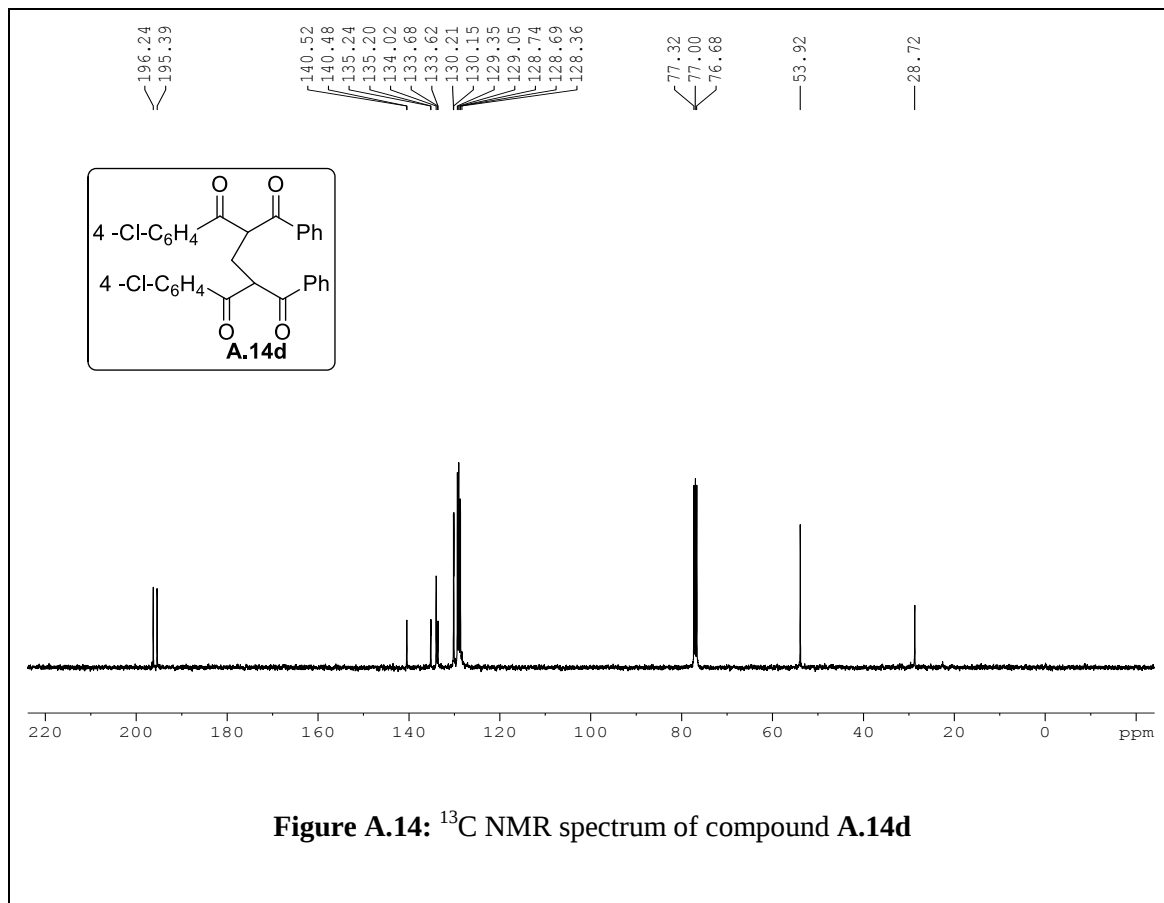
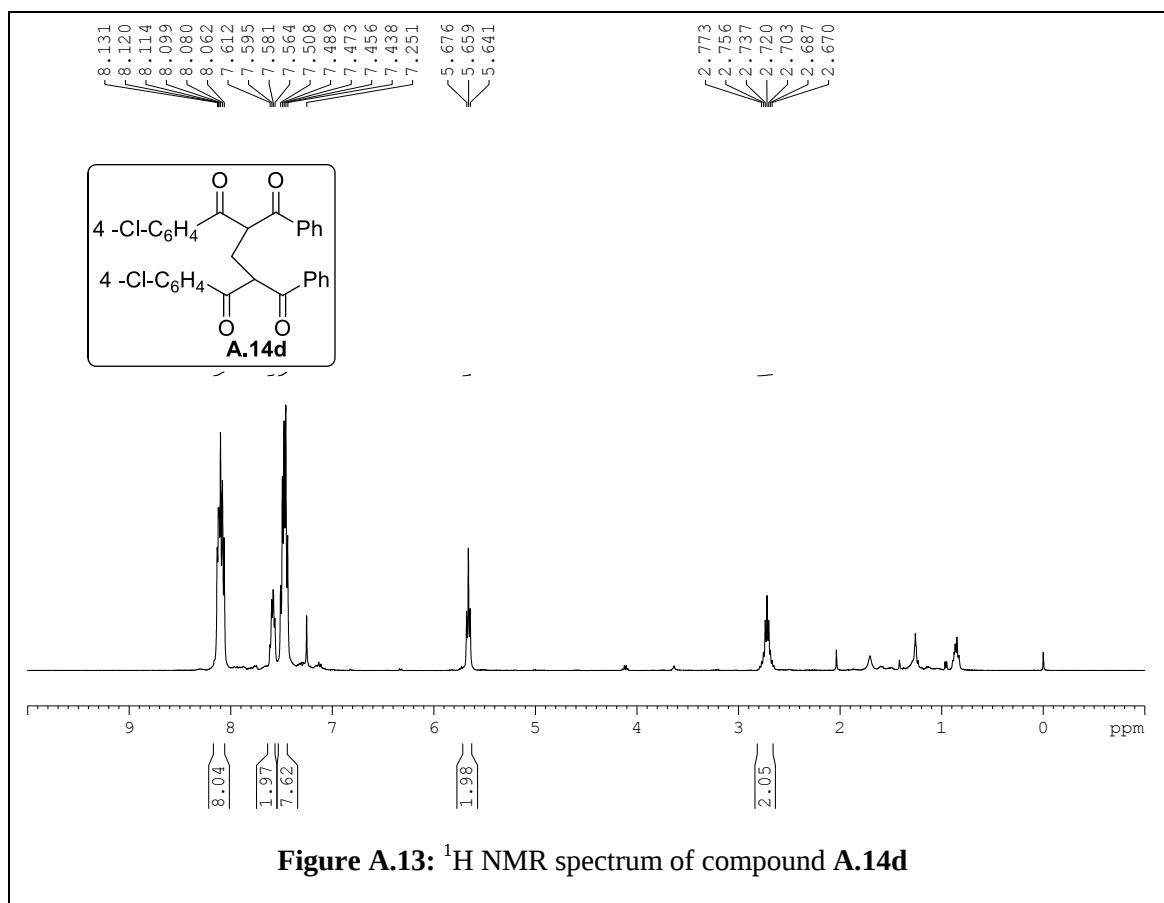
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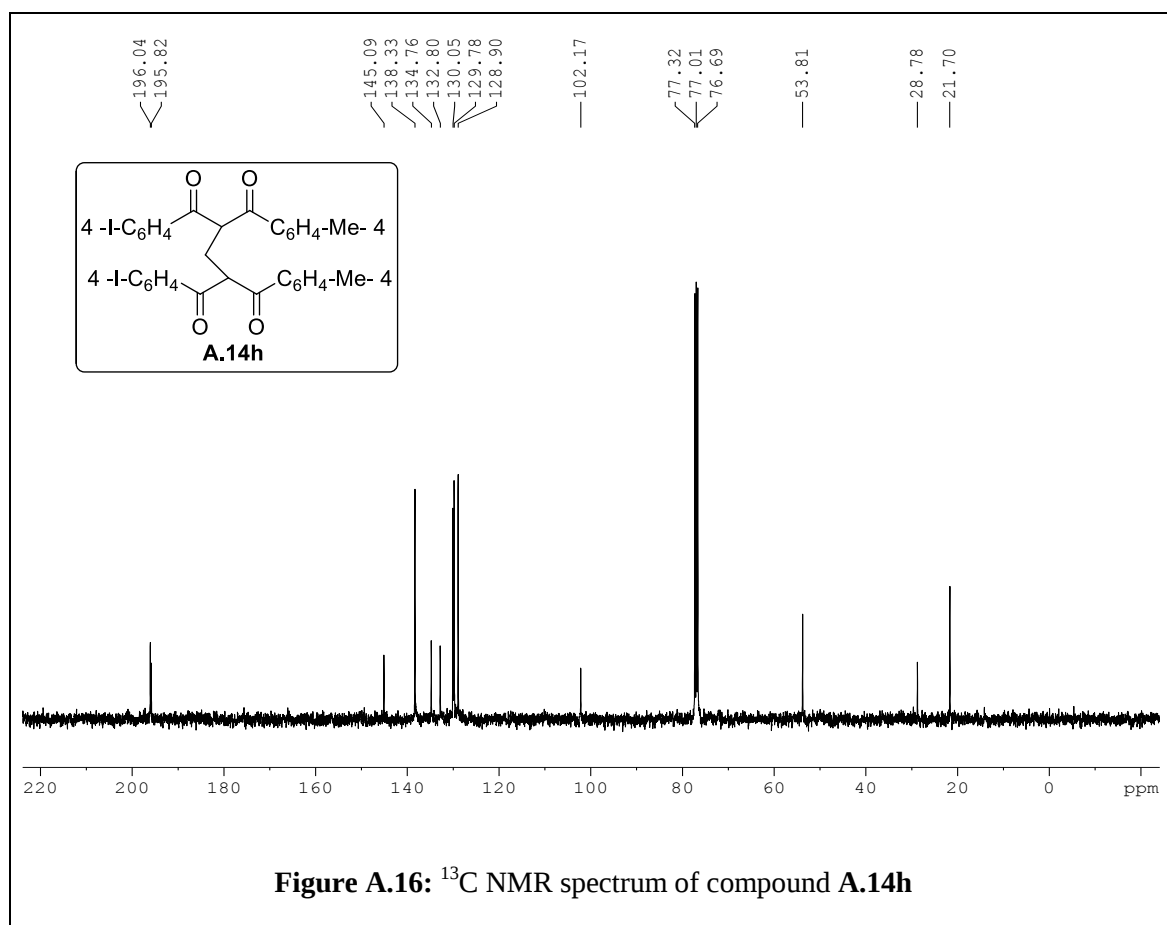
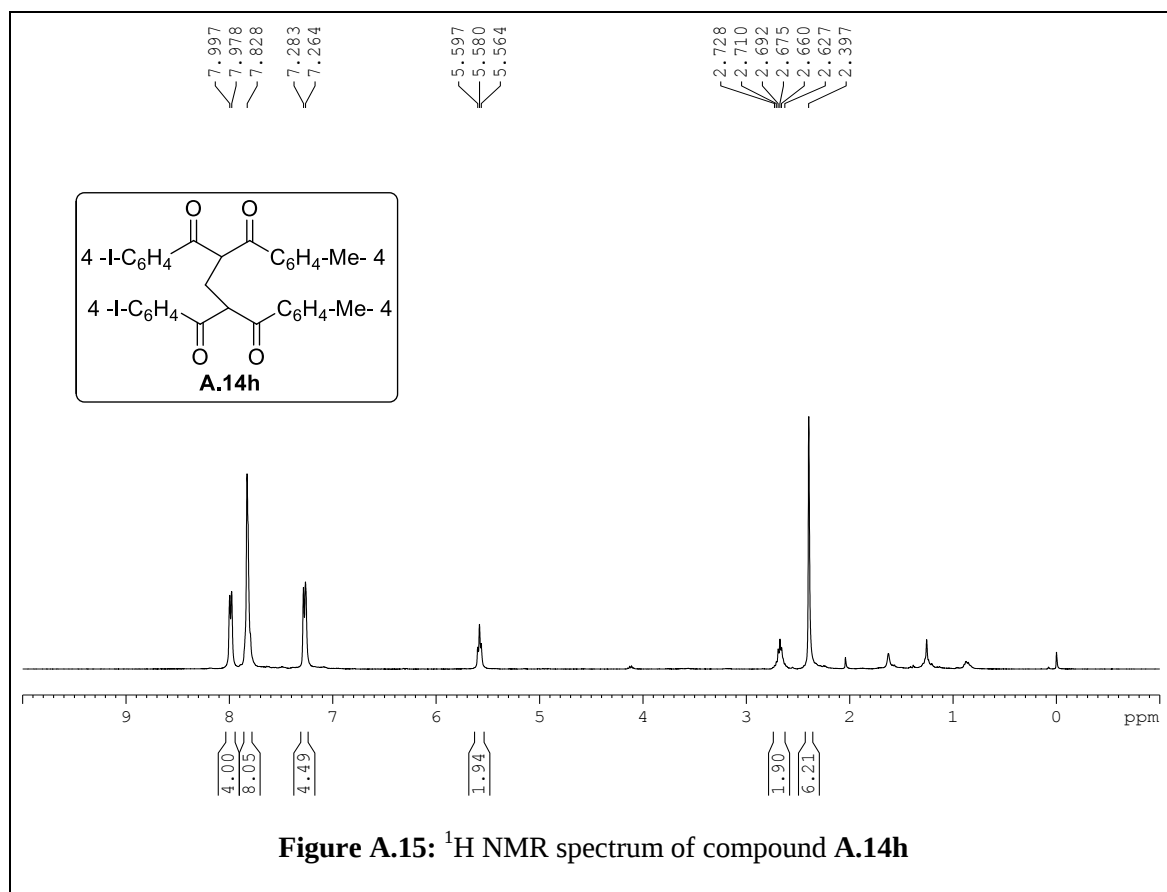
A.7 Representative Spectra

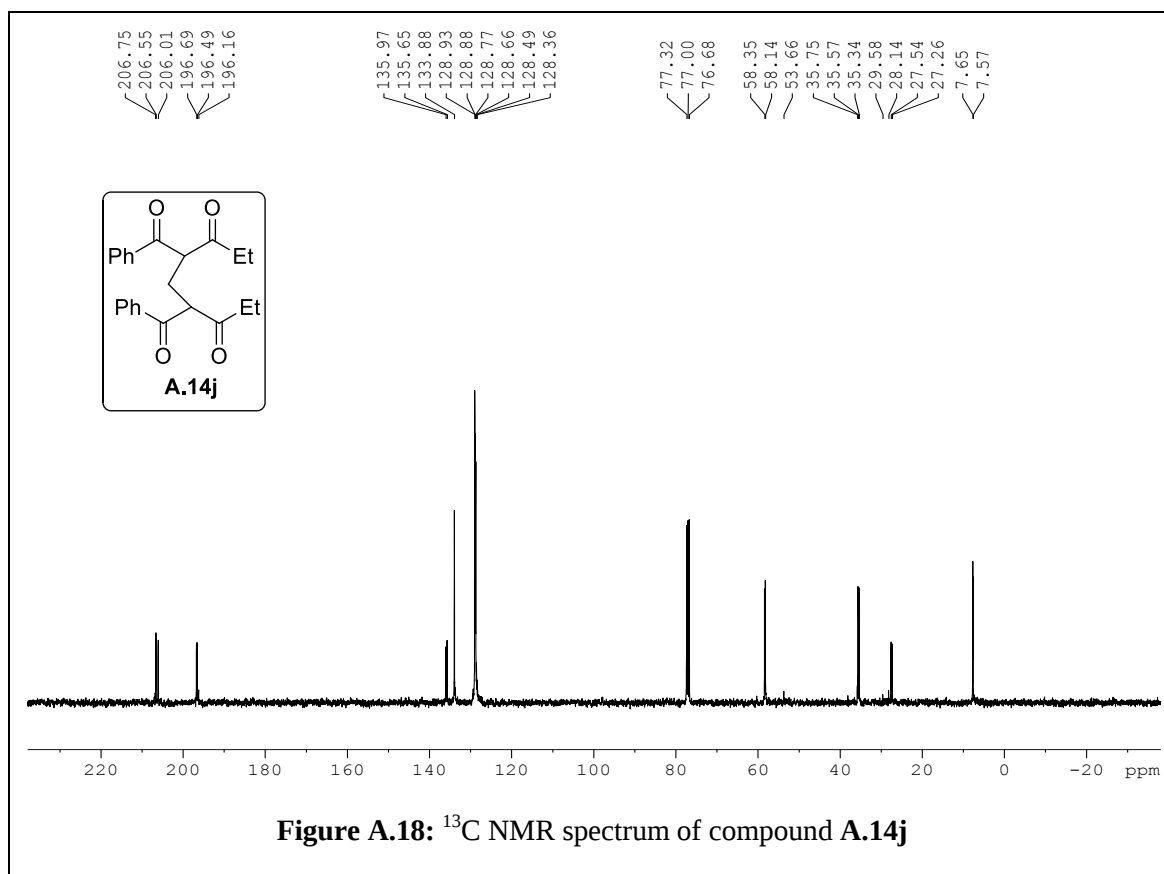
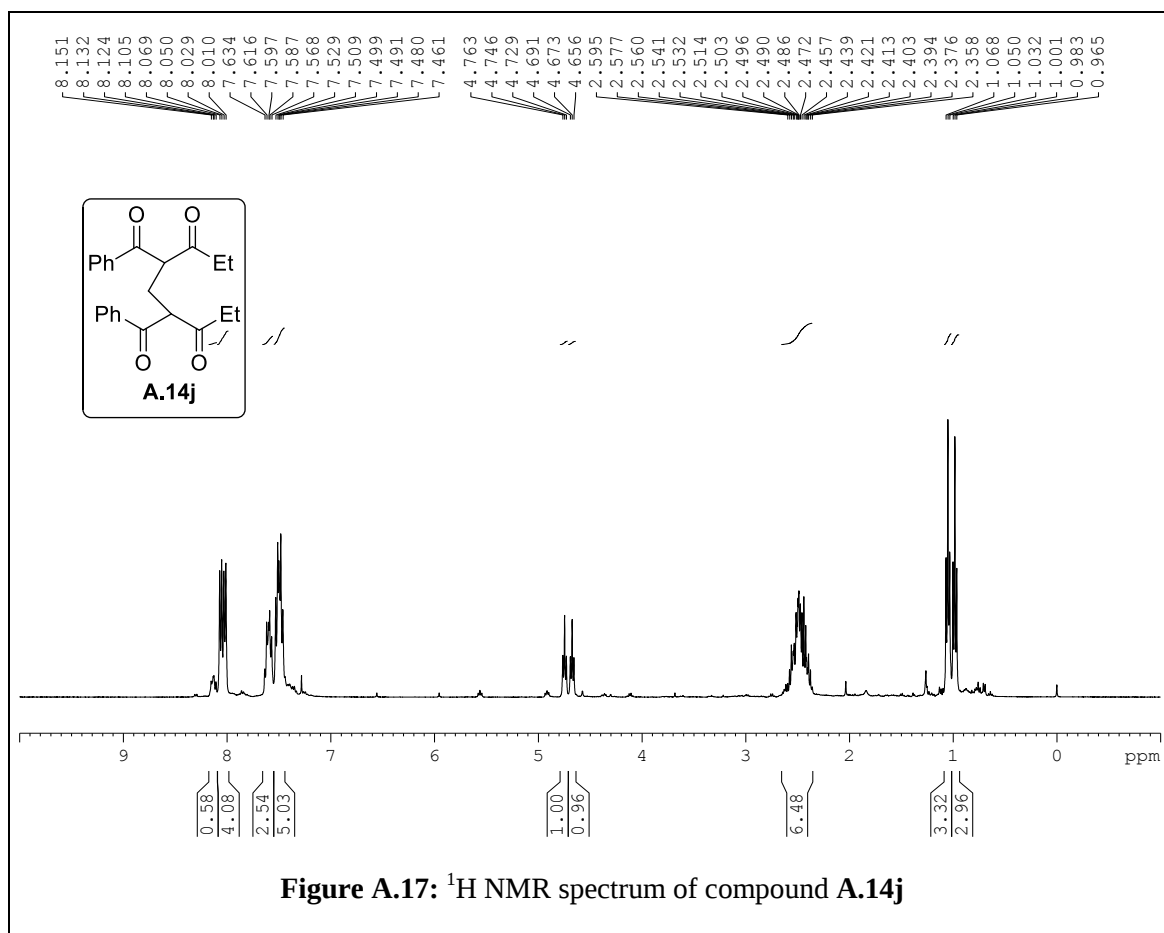


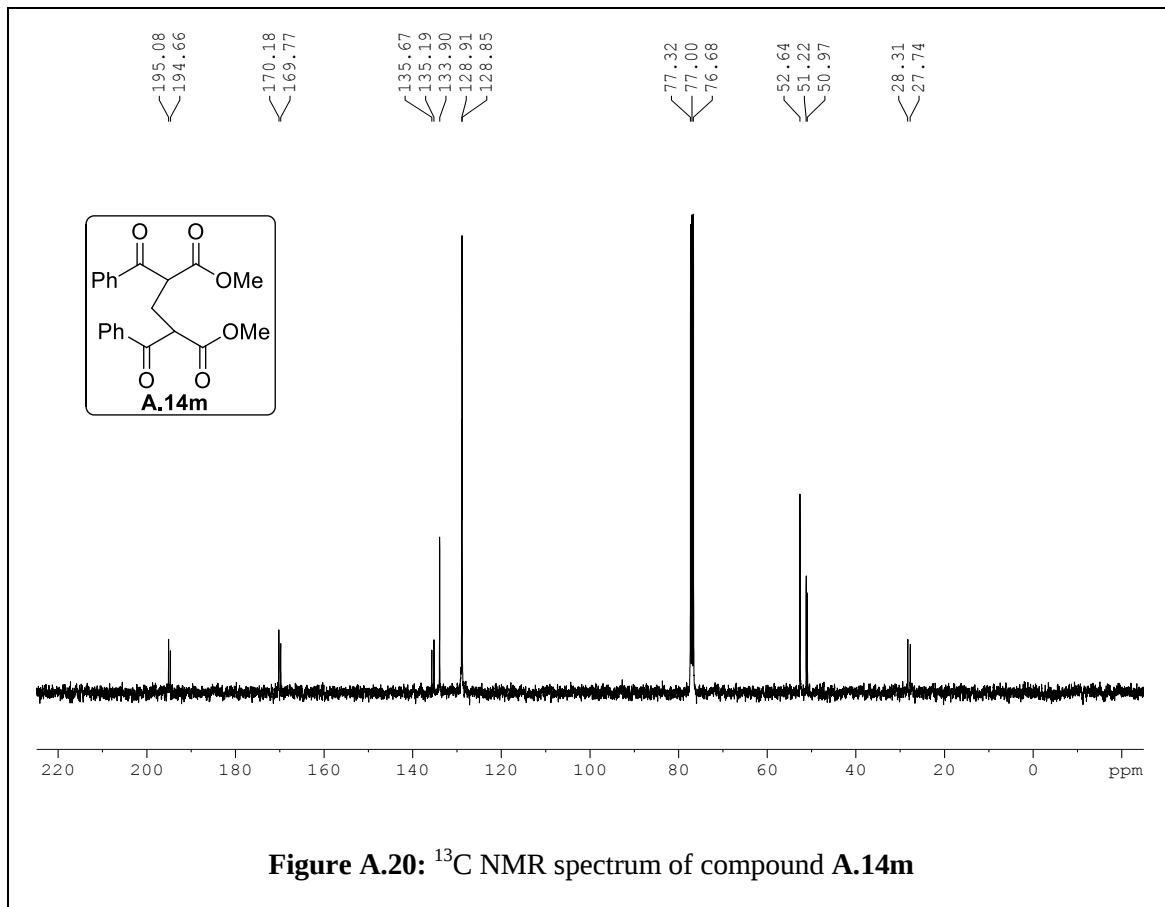
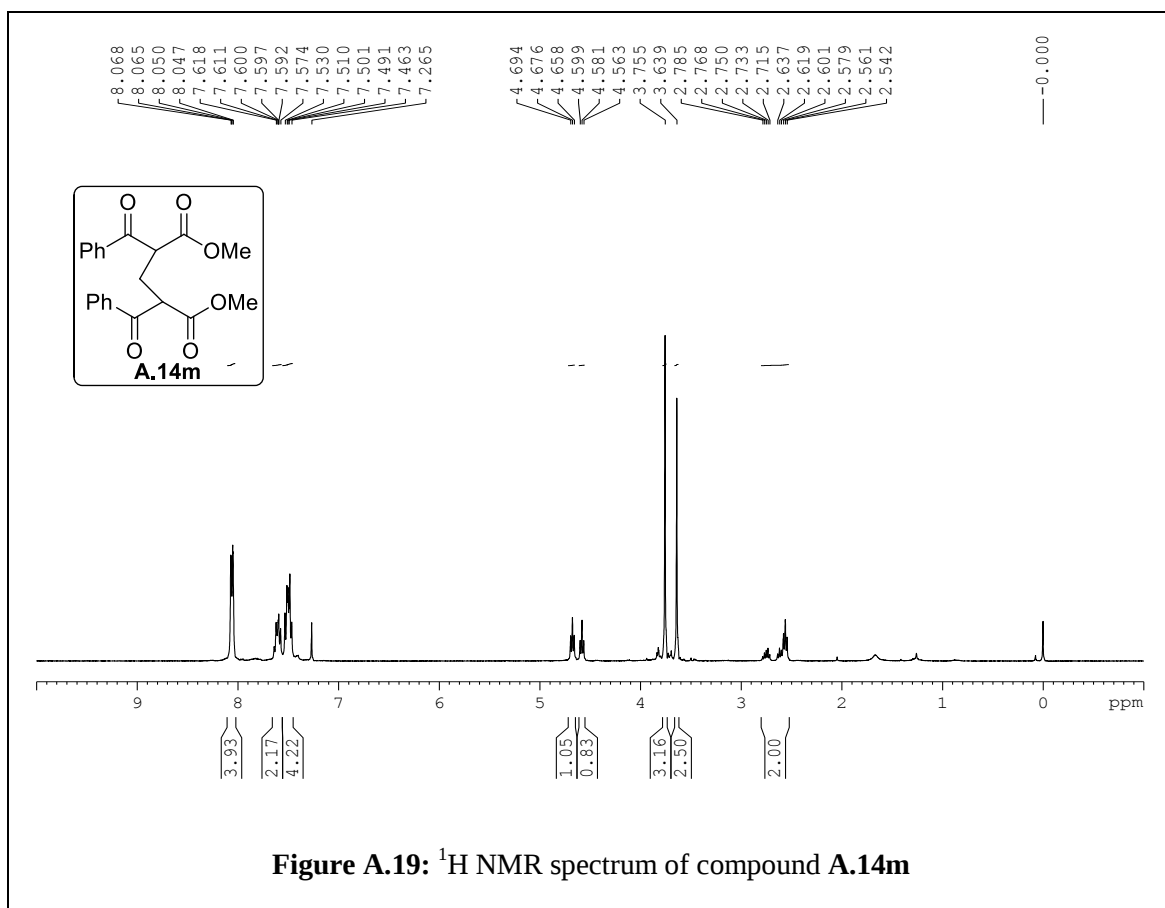


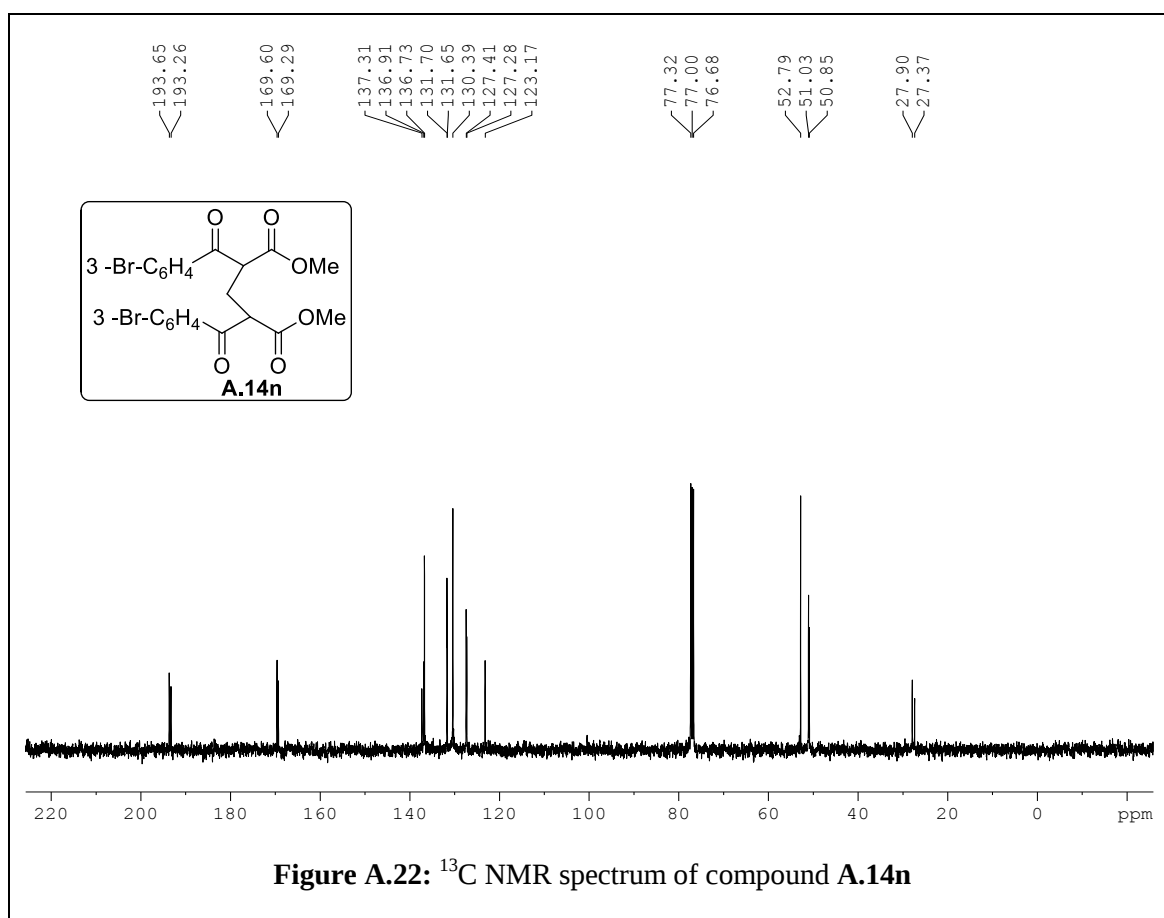
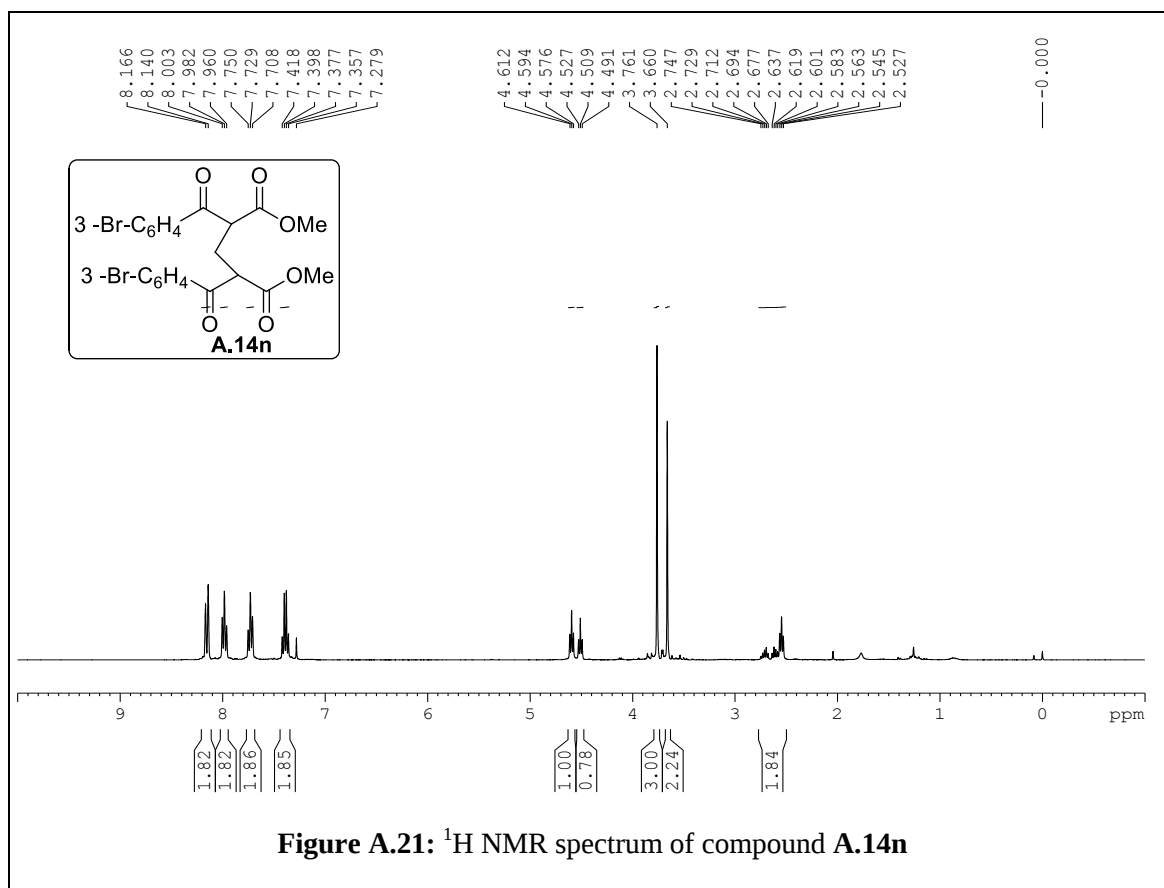


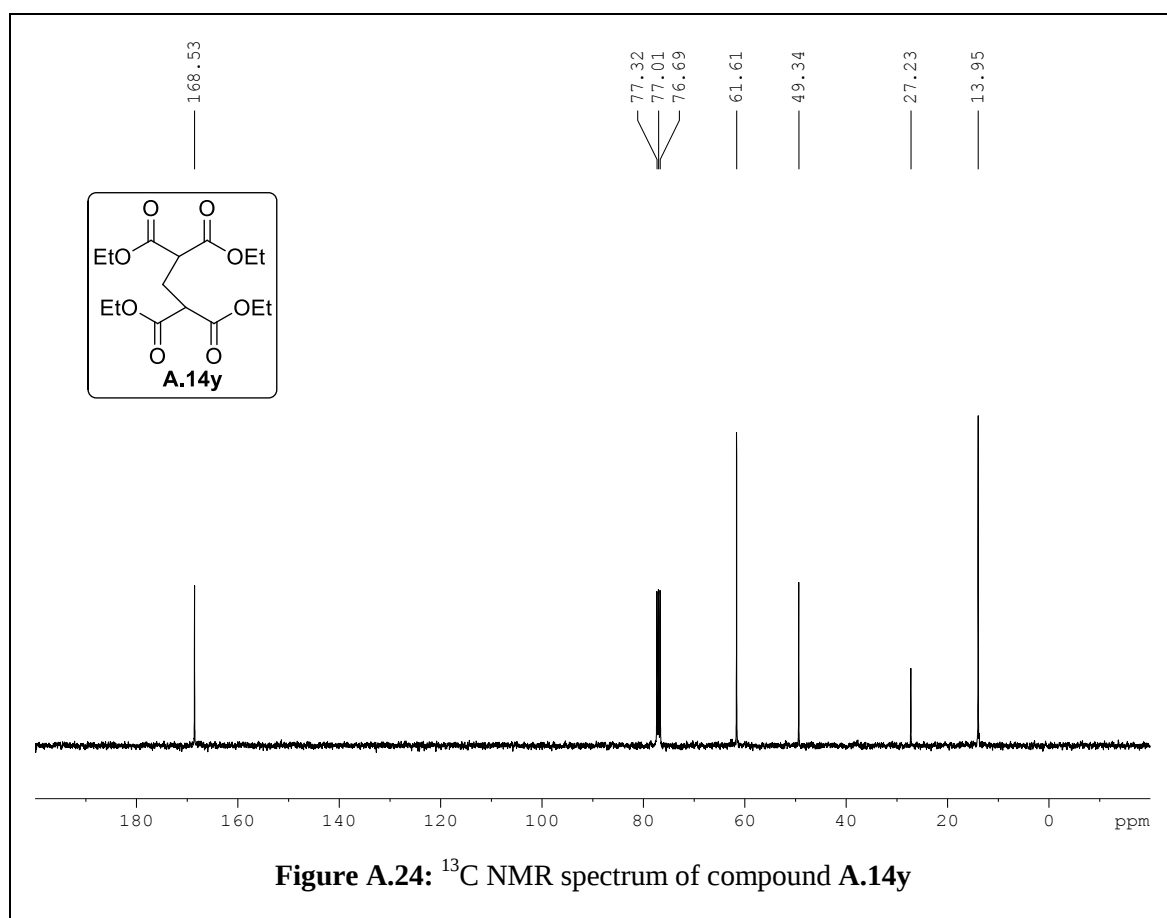
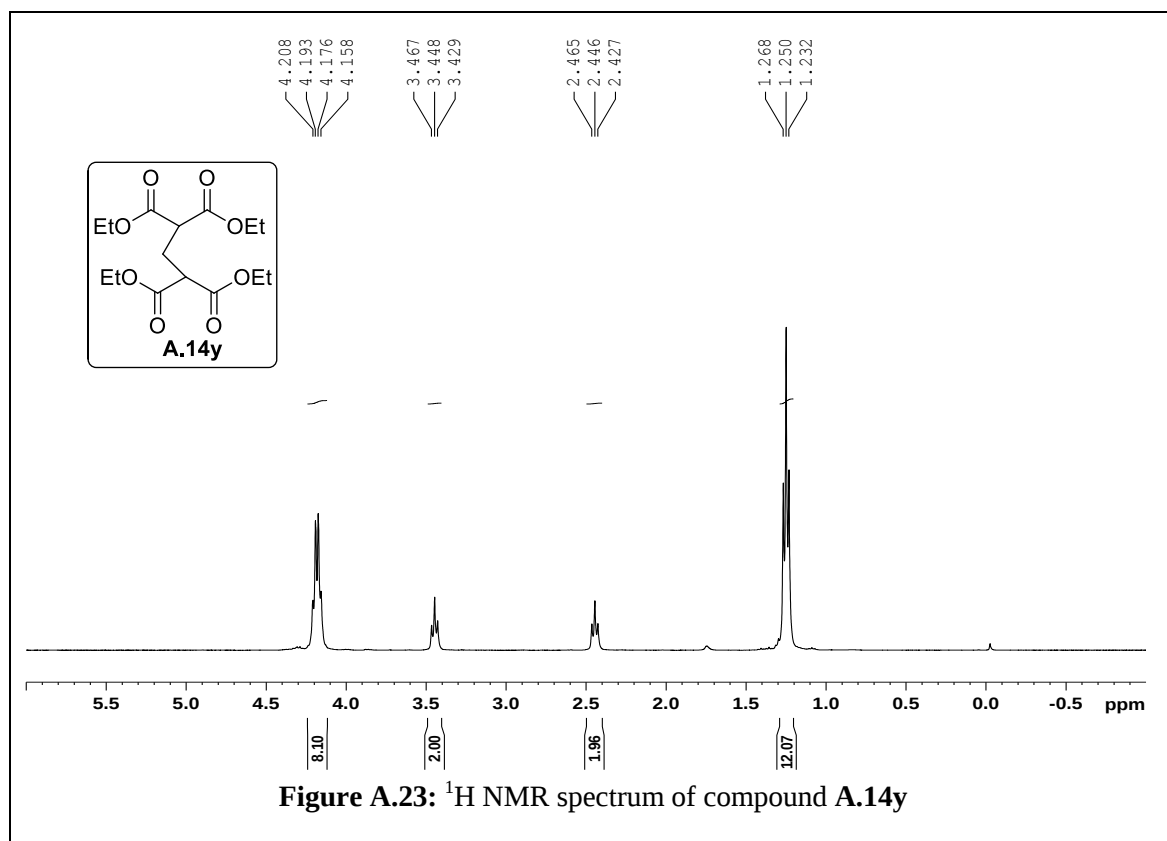


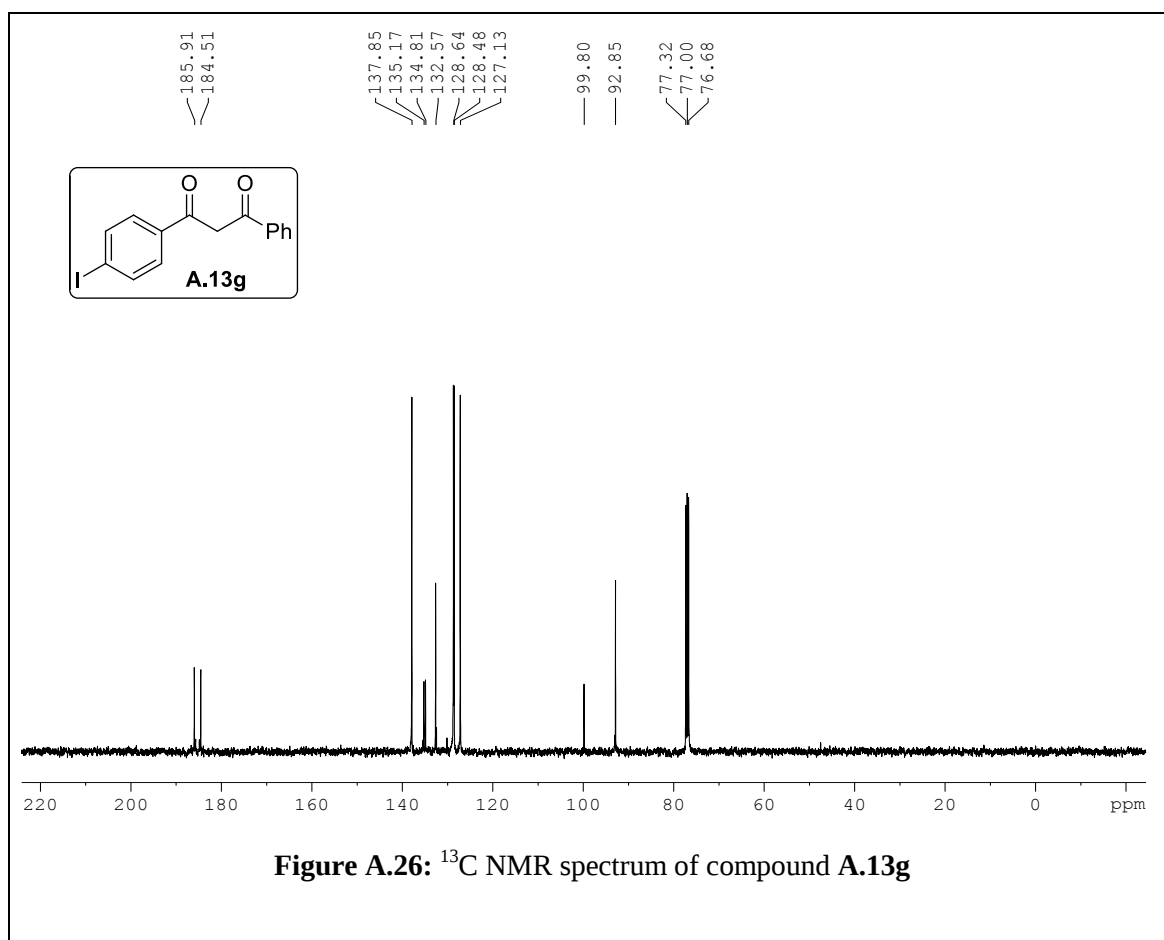
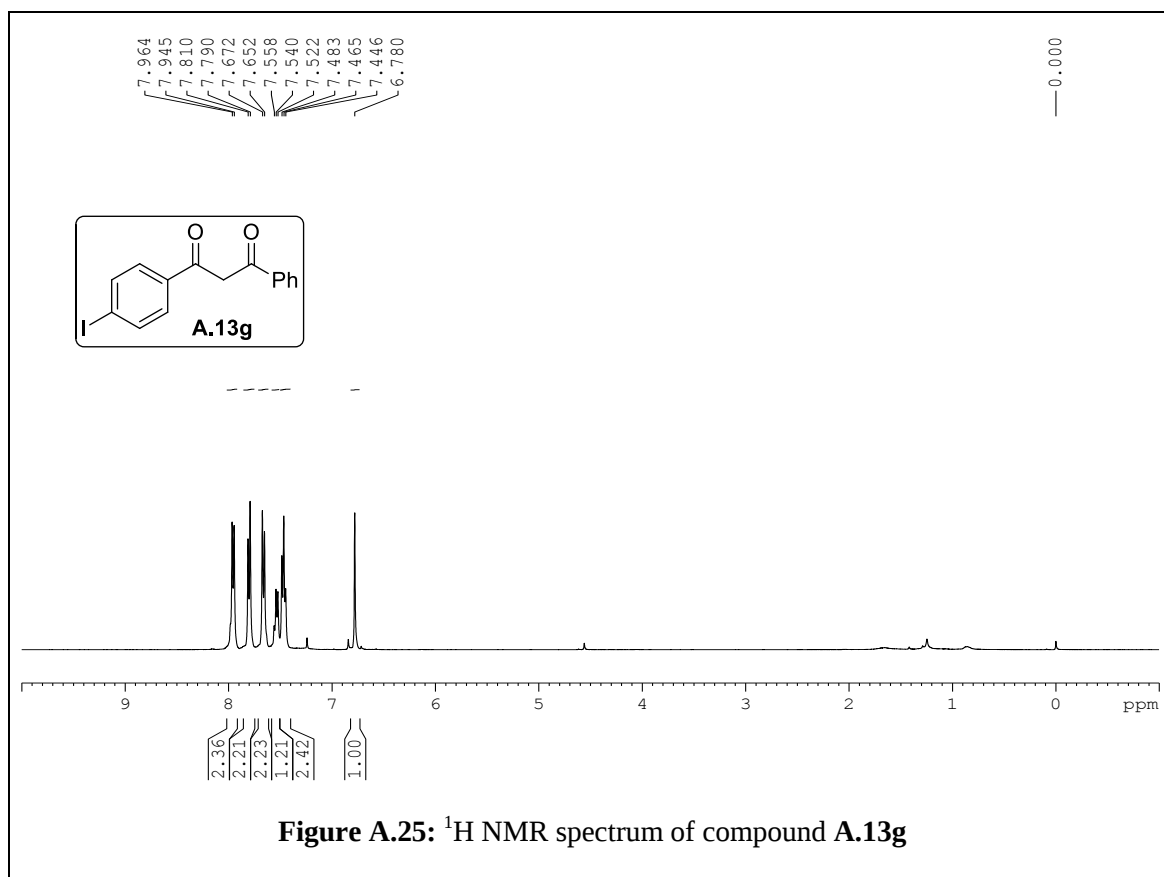












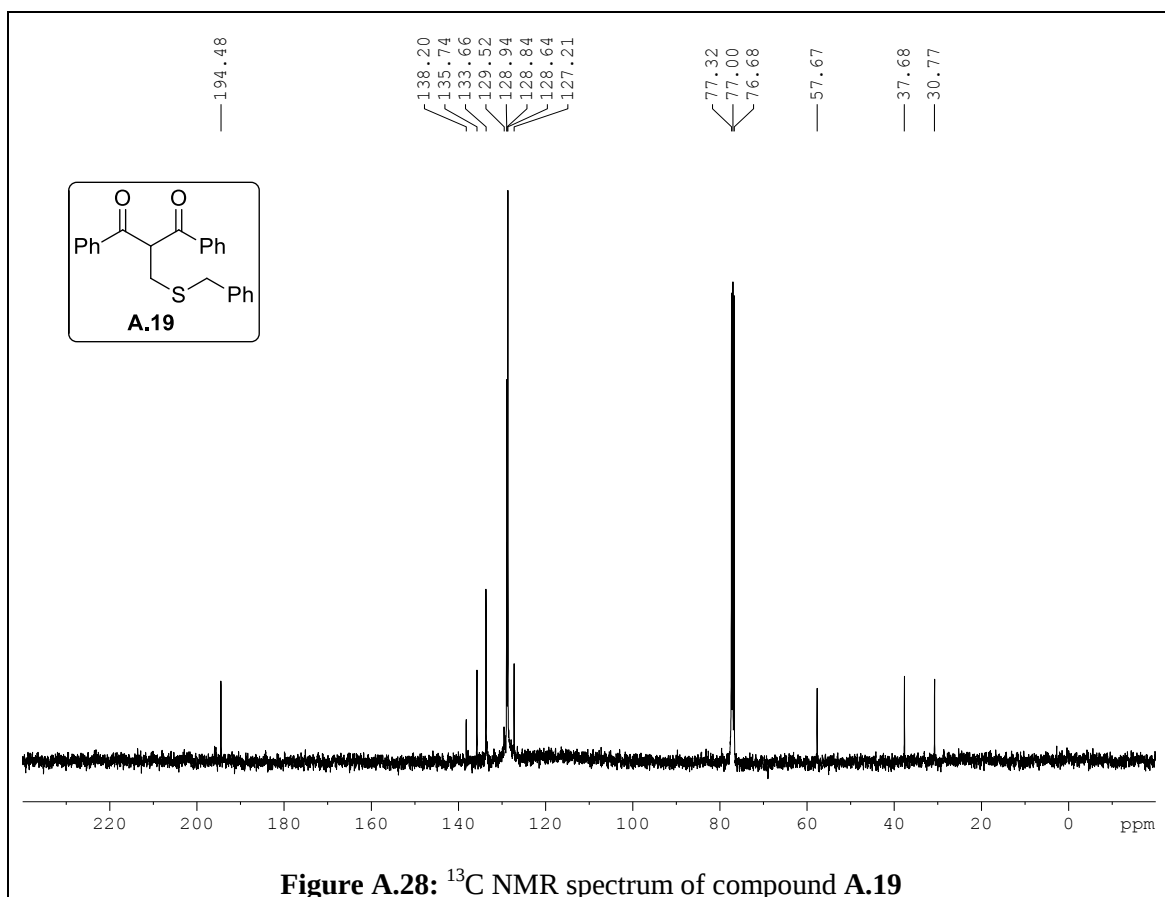
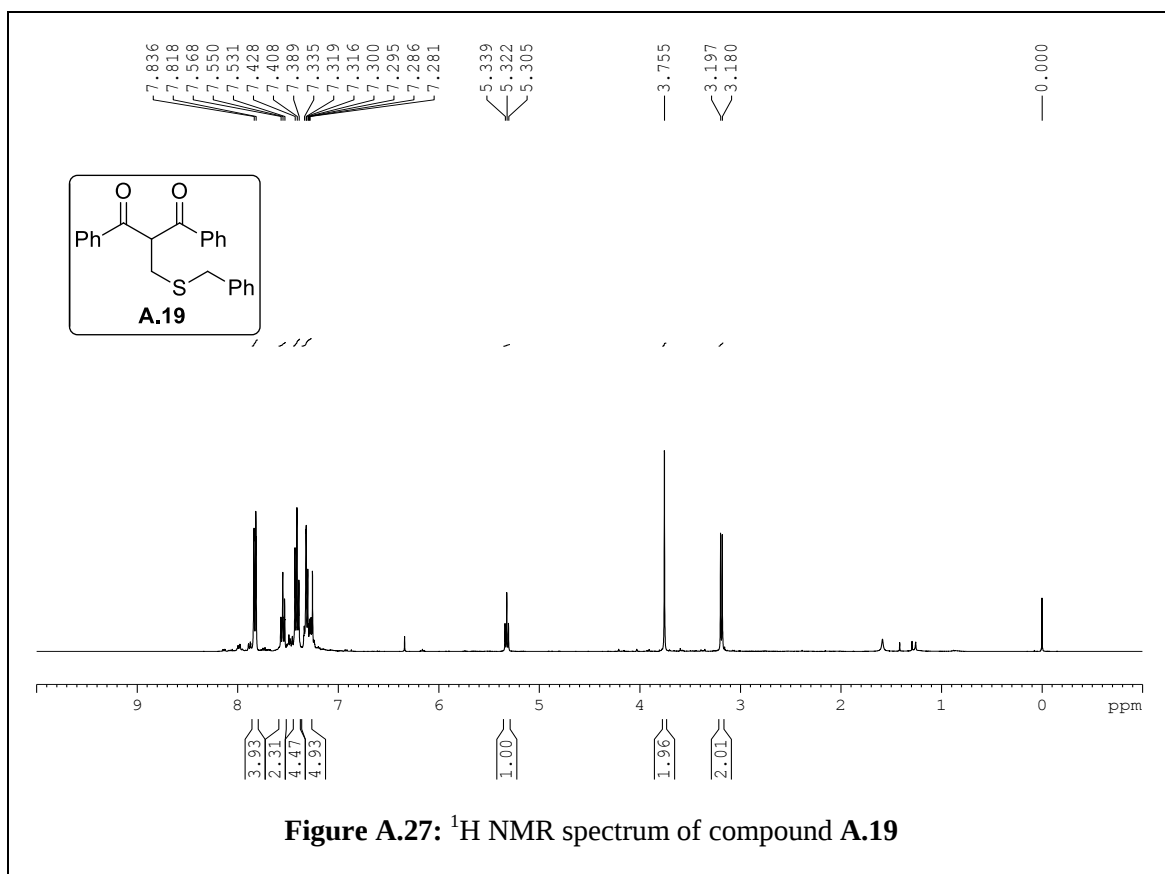


Table 1 Crystal data and structure refinement for **2.2c**

Identification code	2.2c	
Empirical formula	C ₁₉ H ₁₆ O ₃	
Formula weight	292.32	
Temperature	298 K	
Wavelength	71.073 pm	
Crystal system	Monoclinic	
Space group	P 1 2 ₁ /n 1	
Unit cell dimensions	a = 784.2(2) pm	$\alpha = 89.77(3)^\circ$.
	b = 2120.9(10) pm	$\beta = 91.42(2)^\circ$.
	c = 913.0(3) pm	$\gamma = 90.15(3)^\circ$.
Volume	1.5180(9) nm ³	
Z	4	
Density (calculated)	1.279 Mg/m ³	
Absorption coefficient	0.086 mm ⁻¹	
F(000)	616	
Crystal size	0.20 x 0.20 x 0.15 mm ³	
Theta range for data collection	2.77 to 26.37°.	
Index ranges	-9<=h<=7, -26<=k<=13, -11<=l<=10	
Reflections collected	6223	
Independent reflections	3102 [R(int) = 0.2938]	
Completeness to theta = 26.37°	99.8 %	
Max. and min. transmission	0.9872 and 0.9830	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3102 / 0 / 201	
Goodness-of-fit on F ²	0.825	
Final R indices [I>2sigma(I)]	R1 = 0.1079, wR2 = 0.1778	
R indices (all data)	R1 = 0.4259, wR2 = 0.2956	
Largest diff. peak and hole	0.240 and -0.303 e.Å ⁻³	
CCDC	988070	

Table 2 Crystal data and structure refinement for compound **3.35u**

Identification code	3.35u		
Empirical formula	C ₃₀ H ₂₂ O		
Formula weight	398.48		
Temperature	298 K		
Wavelength	0.71073 Å		
Crystal system	monoclinic		
Space group	P 21/n		
Unit cell dimensions	a = 10.7885(9) Å	α = 90°.	
	b = 8.7362(8) Å	β = 91.123(7)°.	
	c = 22.4105(16) Å	γ = 90°.	
Volume	2111.8(3) Å ³		
Z	4		
Density (calculated)	1.346 Mg/m ³		
Absorption coefficient	0.125 mm ⁻¹		
F(000)	885		
Crystal size	0.20 x0.20 x0.15 mm ³		
Theta range for data collection	2.96 to 26.37°.		
Index ranges	-12<=h<=13, -10<=k<=10, -28<=l<=24		
Reflections collected	9034		
Independent reflections	4315 [R(int) = 0.0512]		
Completeness to theta = 26.37°	99.9 %		
Refinement method	Full-matrix least-squares on F ²		
Data / restraints / parameters	4315 / 0 / 281		
Goodness-of-fit on F ²	0.933		
Final R indices [I>2sigma(I)]	R1 = 0.0661, wR2 = 0.1603		
R indices (all data)	R1 = 0.1430, wR2 = 0.2122		
Largest diff. peak and hole	0.167 and -0.164 e.Å ⁻³		
CCDC	993937		

Table 3 Crystal data and structure refinement for compound **5.44I**

Identification code	5.44I	
Empirical formula	C ₂₂ H ₂₂ O	
Formula weight	302.40	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.1622(18) Å	$\alpha = 83.000(16)^\circ$.
	b = 9.508(2) Å	$\beta = 65.519(19)^\circ$.
	c = 10.568(2) Å	$\gamma = 78.417(18)^\circ$.
Volume	820.0(3) Å ³	
Z	23	
Density (calculated)	1.351 Mg/m ³	
Absorption coefficient	0.125 mm ⁻¹	
F(000)	345	
Crystal size	0.30 x 0.20 x 0.15 mm ³	
Theta range for data collection	2.98 to 29.09°.	
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 12, -13 ≤ l ≤ 12	
Reflections collected	5899	
Independent reflections	3702 [R(int) = 0.0221]	
Completeness to theta = 29.09°	84.1 %	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3702 / 0 / 209	
Goodness-of-fit on F ²	1.014	
Final R indices [I > 2σ(I)]	R1 = 0.0526, wR2 = 0.1182	
R indices (all data)	R1 = 0.0882, wR2 = 0.1379	
Largest diff. peak and hole	0.195 and -0.155 e.Å ⁻³	
CCDC	1026819	

Table 4 Crystal data and structure refinement for compound **A.23d**

Identification code	A.23d	
Empirical formula	C ₂₉ H ₂₂ N ₂ O ₄ S ₂	
Formula weight	526.61	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 8.7078(14) Å	α = 77.051(13)°.
	b = 8.8662(13) Å	β = 88.489(13)°.
	c = 16.792(3) Å	γ = 80.107(13)°.
Volume	1244.5(3) Å ³	
Z	2	
Density (calculated)	1.405 Mg/m ³	
Absorption coefficient	0.254 mm ⁻¹	
F(000)	548	
Crystal size	0.20 x 0.20 x 0.15 mm ³	
Theta range for data collection	2.69 to 26.37°.	
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 10, -18 ≤ l ≤ 20	
Reflections collected	9972	
Independent reflections	7284 [R(int) = 0.0641]	
Completeness to theta = 26.37°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9629 and 0.9510	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7284 / 3 / 667	
Goodness-of-fit on F ²	0.952	
Final R indices [I > 2σ(I)]	R1 = 0.1044, wR2 = 0.2928	
R indices (all data)	R1 = 0.2248, wR2 = 0.3493	
Absolute structure parameter	0.1(3)	
Largest diff. peak and hole	0.381 and -0.402 e.Å ⁻³	

List of Publications

1. A Facile Access to Substituted Benzo[a]fluorene Derivatives from *o*-Alkynylbenzaldehydes via *in Situ* Formed Acetals
Manojveer. S.; Balamurugan, R. *Chem. Commun.* **2014**, 50, 9925.
2. Synthesis of Naphthalene Derivatives from *ortho*-Alkynylacetophenone Derivatives via Tandem *in Situ* Incorporation of Acetal and Intramolecular Heteroalkyne Metathesis/Annulation,
Manojveer, S.; Balamurugan, R. *Org. Lett.* **2014**, 16, 1712.
3. Gold/Copper Catalyzed Activation of *aci*-Form of Nitromethane in the Synthesis of Methylene Bridged bis-1,3-Dicarbonyl Compounds,
Balamurugan, R.; **Manojveer, S.** *Chem. Commun.* **2011**, 47, 11143.
4. Homo and Heterocoupling of Terminal Alkynes Using Catalytic CuCl₂ and DBU,
Balamurugan, R.; Naveen, N.; **Manojveer, S.**; Nama, M. V. *Aust. J. Chem.* **2011**, 64, 567.
5. Synthesis and Characterization of 5-Heteroarylsulfanyl-4-aryl-1,2,3-selena/thiadiazoles
Manikannan, R.; Shanmugaraja, M.; **Manojveer, S.**; Muthusubramanian, S. *J. Chem. Sci.* **2012**, 124, 463.
6. A New Approach to Naphthalene Derivatives from *o*-Alkynylbenzaldehydes and Enolizable Ketones via *in Situ* Formed Acetals **Manojveer. S.** Balamurugan, R. *Manuscript to be submitted*
7. *In Situ* Formed Acetal Assisted Synthesis of Substituted Indene Derivatives
Manojveer. S.; Balamurugan, R. *Manuscript under preparation*

Poster and Oral Presentations

1. Presented poster on Gold/Copper Catalyzed Activation of *aci*-Form of Nitromethane in the Synthesis of Methylene Bridged bis-1,3-Dicarbonyl Compounds in the **International Symposium on Chemistry & Complexity** held at **IACS- Kolkata** (Dec-2011).
2. Presented poster on Gold/Copper Catalyzed Activation of *aci*-Form of Nitromethane in the Synthesis of Methylene Bridged bis-1,3-Dicarbonyl Compounds in the **Catalysis Symposium** held at **Dr. Reddy's Laboratory- Hyderabad** (Jan-2011).
3. Presented poster on Gold/Copper Catalyzed Activation of *aci*-Form of Nitromethane in the Synthesis of Methylene Bridged bis-1,3-Dicarbonyl Compounds in the **ChemFest-In house Symposium** held at **University of hyderabad** (Feb-2011).
4. Given talk on Synthesis of Naphthalene Derivatives from *ortho*-Alkynylacetophenone Derivatives *via Tandem in Situ* Incorporation of Acetal and Intramolecular Heteroalkyne Metathesis/Annulation in **IX JNOST** conference held at **IISER-Bhopal** (Dec-2013).
5. Presented poster on *in Situ* Formed Acetal Assisted Intermolecular Heteroalkyne Metathesis and Intramolecular Annulation: A Facile Access to Substituted Fluorene Derivatives in **16th CRSI National Symposium in Chemistry** held at **IIT-Bombay** (Feb-2014).
6. Given talk and presented poster on Synthesis of Naphthalene and Fluorene Derivatives from *in Situ* generated acetal in **ChemFest-In house Symposium** held at **University of hyderabad** (Feb-2014).
7. Presented poster on Synthetic Utilities of *in Situ* Formed Acetal: A Facile Access to Substituted Naphthalene and Benzo[a]fluorene Derivatives in National Symposium on **Transcending Frontiers of Organic Chemistry** held at **NIIST, Thiruvananthapuram** (Oct-2014).
8. Presented poster on Synthetic Utilities of *in Situ* Formed Acetal: A Facile Access to Substituted Naphthalene and Benzo[a]fluorene Derivatives in **The First Indo-Taiwan Symposium on Recent Trends in Chemical sciences** (RTCS-2014) held at **University of hyderabad** (Nov-2014).