Unsaturated Sulfones as Versatile Building Blocks for Carbocyclic and Heterocyclic Construction

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in

Chemistry

By

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Dedicated

to

My Family and Friends

CONTENTS

DECLARATION

(*As required under clause I2 of Ordinance IIA of the Central University of Haryana*)

This is to certify that the material embodied in the present work, entitled **"Unsaturated sulfones as versatile building blocks for carbocyclic and heterocyclic construction"**, is based on my original research work. The research work was carried out under the joint supervision of **Dr. Rajeev S. Menon (Supervisor),** Central University of Haryana and **Professor Sunil K. Sharma (Co-Supervisior),** University of Delhi. This work has not been submitted, in part or full, for any other diploma or degree of any University/Institution Deemed to be University and College/Institution of National Importance. References from other works have been duly cited at the relevant places.

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It is difficult to mention all who helped me during this beautiful journey. I must thank all those whom I have failed to state and helped me in various ways for achieving my goal.

Finally, I would like to thank almighty god for giving me immense strength and only with his blessings this journey could have been so wonderful and peaceful.

Deepak Yadav

ABBREVIATIONS

CAN	Cerium Ammonium Nitrate
DMA	Dimethylacetamide
RCM	Ring Closing Metathesis
DCE	1,2-Dichloroethane
TBAT	Tetrabutylammonium triphenyldifluorosilicate
BHT	Butylated hydroxytoluene
THF	Tetrahydrofuran
DBU	1,8-Diazabicyclo[5.4. 0]undec-7-ene
PCC	Pyridinium chlorochromate
DMF	Dimethylformamide
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
DMSO	Dimethyl sulfoxide
DTBP	Di-tert-butyl peroxide
DABCO	1,4-diazabicyclo[2.2. 2]octane
TBHP	tert-Butyl hydroperoxide
PEG	Polyethylene Glycol
TLC	Thin-layer chromatography
COX	Cyclooxygenase
rt	Room temperature

LIST OF PUBLICATIONS

1. **Deepak Yadav**, Sunil K. Sharma, Rajeev S. Menon. Facile synthesis of biarylmethanes and tetrasubstituted arenes *via* a base-mediated [3+3] benzannulation reaction of Morita-Baylis-Hillman adducts and unsaturated sulfones. *Org. Biomol. Chem.*, **2019**, *17*, 4073.

2. Ayushi Mittal, Shweta Kumari, Parmanand, **Deepak Yadav**, Sunil K. Sharma. A new copper complex on graphene oxide: a heterogeneous catalyst for N-arylation and C–H activation. *Appl. Organomet. Chem.*, **2019**, e5362.

3. **Deepak Yadav**, Rajeev S. Menon. Recent developments in the chemistry of allenyl sulfones. *Org. Biomol. Chem.*, **2020**, *18*, 365-378

4. Krishna, Shweta Kumari, **Deepak Yadav**, Sunil K. Sharma. Cu (II) Schiff base complex grafted guar gum: Catalyst for benzophenone derivatives synthesis. *Applied Catalysis A, General* 601 (**2020**) 117529.

5. **Deepak Yadav**, Parbhakar Joshi, Sunil K. Sharma, Rajeev S. Menon. Regioselective synthesis of arylsulfonyl benzophenones via aerobic oxidative [3+3] benzannulation reactions. *Eur. J. Org. Chem.* ***(communicated).***

6. **Deepak Yadav**, Krishna, Sunil K. Sharma, Rajeev S. Menon. Regioselective synthesis of arylsulfonyl heterocycles from bromoallyl sulfones via sequential formal vinylic substitution reaction and intramolecular Heck coupling reaction. *Org. Biomol. Chem.* ***(communicated).***

Chapter I

Part A: Introduction and development of benzannulation chemistry

1.1. Introduction to benzannulation reactions

Aromatic hydrocarbons constitute important building blocks in organic synthesis due to their extra stability, abundance and their ready reactivity in substitution reactions in comparison with non-aromatic hydrocarbons. The concept of aromaticity is important in order to understand the stability, bonding, structure, reaction and properties of conjugated cyclic molecules. Benzene is the quintessential aromatic hydrocarbon and can be transformed into various other aromatic hydrocarbons. Numerous electrophilic and nucleophilic aromatic substitutions reactions on phenyl ring form a significant chunk in organic chemistry literature. Due to their special properties, aromatic compounds find a variety of applications.[1,2] As a consequences, a number of synthetic methods have been developed for construction of aromatic compounds and organic chemists continue to develop new strategies for their synthesis.

Substituted arenes are generally prepared from aromatic precursors *via* introduction of substituents on aromatic ring or by manipulating pre-installed functional groups. The pre-installed group alters the reactivity pattern of arene core and occasionally prevents the formation of desired regioisomers when syntheses of di-, tri- and tetra-substituted arenes are attempted. To overcome these issues alternate approaches for synthesis of poly-substituted arenes such as transition metal mediated coupling reactions[3] and directed metallation reactions[4] have been developed.

Benzannulation, a nonconventional approach, wherein arenes are constructed from acyclic precursors, addresses above mentioned challenges significantly. In benzannulation

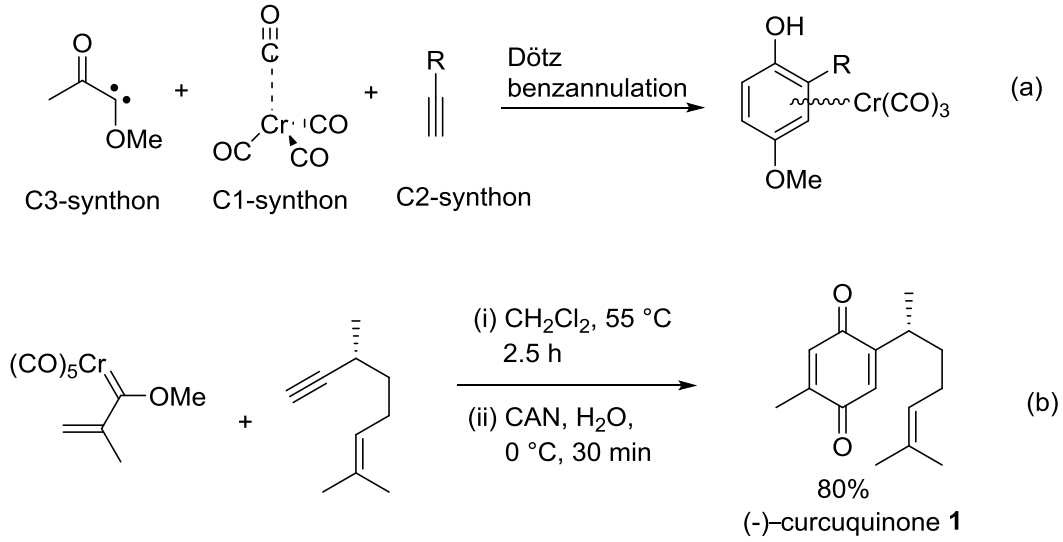
reactions a variety of acyclic components can be combined in various ways to afford a benzenoid aromatic product. These reactions can be either intramolecular (one-component) or intermolecular (two- or multi-component) in nature. The acyclic components can be of various sizes, nature and their union may be catalyzed or mediated by various catalysts, acid, base, light or metal complexes . Dotz reaction[5] and Danheiser annulation[6] are important and well known transformations which demonstrate the strength of benzannulation approach in synthesis. The availability of a diverse array of acyclic precursors, reaction conditions and different mechanistic types makes benzannulation strategy superior to aromatic substitution reactions for construction of substituted arenes.

The most general and common classification of benzannulation reactions is based on the number of carbon atoms contributed by each acyclic component to the final product. Accordingly, benzannulation reaction are categorized as [2+2+2], [3+2], [4+2], [5+1], [3+3], *etc* types. In addition, they can also be classified based on the mechanistic or type of reaction involved. Some of such categories include, cycloaddition, ring-closing metathesis, base mediated, Lewis acid catalyzed, light induced, transition-metal promoted, electrocyclic ring closure, *etc*. The work presented in the first two chapters of this thesis focuses on benzannulation reactions. Therefore, for presenting the work in proper context, a discussion on various benzannulation reactions is given below.

1.2. Various types of benzannulation reactions

1.2.1. Transition metal-mediated benzannulation reactions

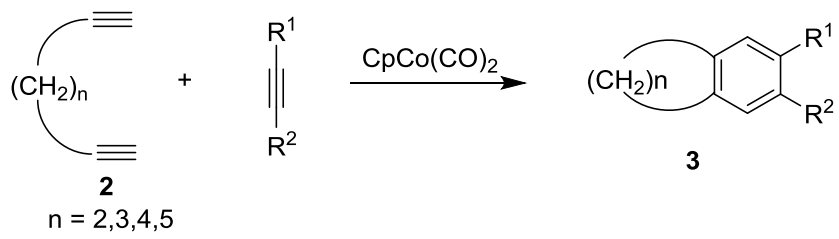
Dötz benzannulation is one of the most widely used transition metal-mediated benzannulation reaction for the construction of substituted arene derivatives.[5]



Scheme 1: (a) Schematic representation of Dötz benzannulation reaction (b) synthesis of (-)-curcuquinone via Dötz benzannulation reaction

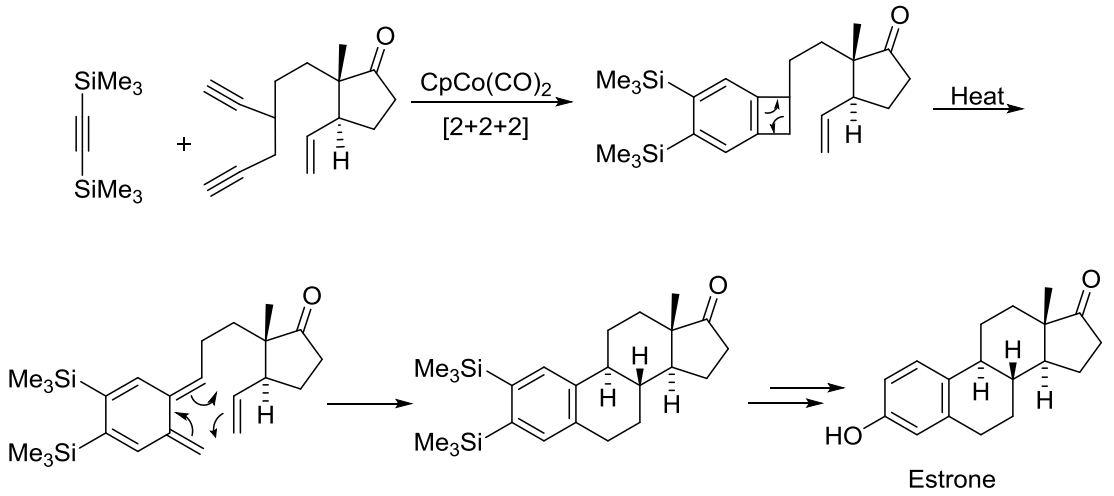
The reaction may be viewed as a [3+2+1] cycloaddition reaction which involves α,β-unsaturated Fischer carbene ligand, an alkyne and a carbon monoxide ligand on chromium (Scheme 1a). Dötz benzannulation reaction has found numerous applications in synthesis. For example, Dötz and co-workers reported a total synthesis of natural product (-)-curcuquinone **1** *via* chromium-mediated regioselective [3+2+1] benzannulation reaction (Scheme 1b).[7]

Vollhardt and co-workers found that cobalt complex $CpCo(CO)_2$ have ability to catalyze [2+2+2] cyclisation of α,ω-diynes such as **2** and alkynes to generate benzene derivatives **3** (Scheme 2).



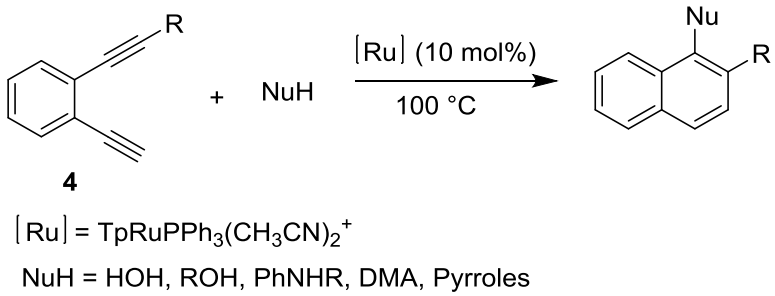
Scheme 2: Co-catalyzed cross-trimersiation of diyne with alkyne

This [2+2+2] cycloaddition reaction has wide scope and has been employed in synthesis of various natural products such as Estrone, as depicted in Scheme 3.[8]



Scheme 3: $CpCo(CO)_2$ -catalysed steroid synthesis via [2+2+2] benzannulation

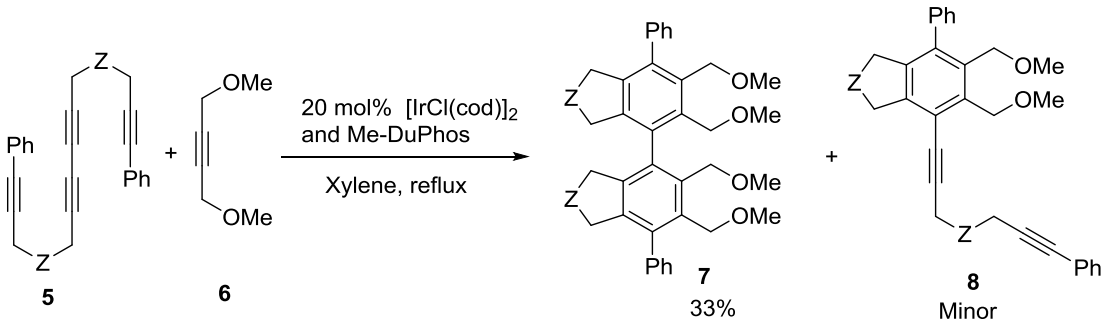
An efficient Ru-catalyzed cyclisation of enediyne system **4** with various nucleophiles affords naphthalene derivatives (Scheme 4). The reaction proceeds *via* regioselective addition of nucleophiles to the Ru-alkyne π-complex. The addition occurs regioselectively at the internal carbon of alkyne.[9]



Scheme 4: Ru-catalyzed regioselective aromatization of enediynes with nucleophiles

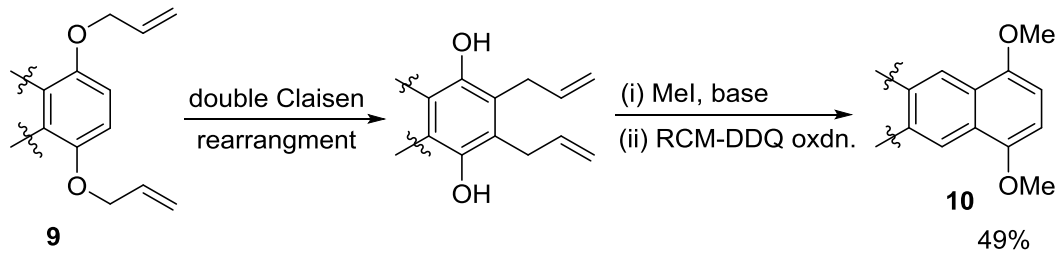
An enantioselective [2+2+2] cycloaddition reaction of carbon tethered tetrayene **5** and alkyne **6** catalyzed by a chiral iridium complex afforded axially chiral compound **7**

along with a mono-cyclized product **8** (Scheme 5).[10] The catalytically active species is generated *in situ* from $[IrCl(cod)]_2$ and the chiral ligand Me-DuPhos.



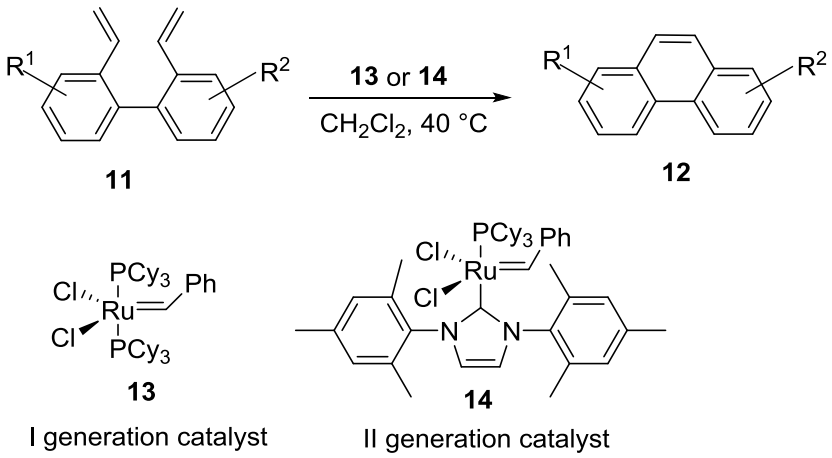
Scheme 5: Iridium-catalyzed [2+2+2] cycloaddition reaction

Ring-closing metathesis (RCM) constitutes a powerful tool for construction of carbocycles. The pioneering efforts of Grubbs, Hoveyda and Schrock, have led to the development of a wide variety of metathesis catalysts for promoting olefin metathesis of challenging substrates.[11] These reactions can be conveniently employed for the construction of aromatic carbocycles from suitable acyclic precursors such as terminal dienes. Kotha and co-workers have developed a methodology for the construction of hydroquinone derivative **10** from bis-allyl aryl ethers **9** *via* sequential double Claisen rearrangement, one pot RCM and DDQ oxidation as depicted in scheme 6.[12]



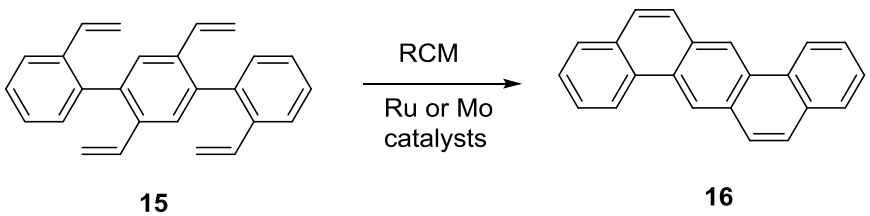
Scheme 6: Double Claisen rearrangement-RCM-oxidation sequence of bis-allyl phenyl ether

First and second generation ruthenium catalysts **13** and **14** promoted ring-closing metathesis of 2,2'-divinylbiphenyls **11** to afford substituted phenanthrenes **12** (Scheme 7). The reaction proceeds under very mild conditions and can tolerate a number of functional groups present on the biphenyl moiety.[13]



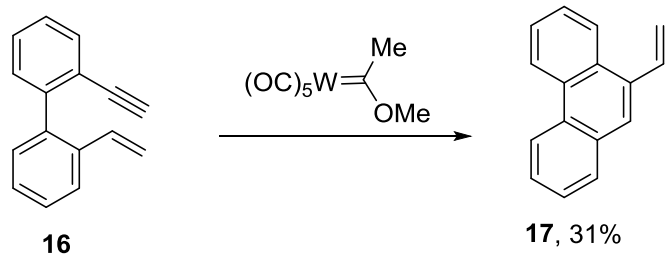
Scheme 7: RCM of 2,2'-divinylbiphenyls to generate phenanthrene derivatives

King and co-workers have developed a methodology for construction of polycyclic aromatic hydrocarbons (PAHs) *via* double ring closing metathesis of pendant olefins on a phenylene backbone. The ring closing metathesis of vinyl-substituted terphenyl derivatives **15** in presence of Grubbs I catalyst afforded dibenzanthracene derivative **16** (Scheme 8).[14]



Scheme 8: Synthesis of PAHs by ring closing metathesis of polyenes

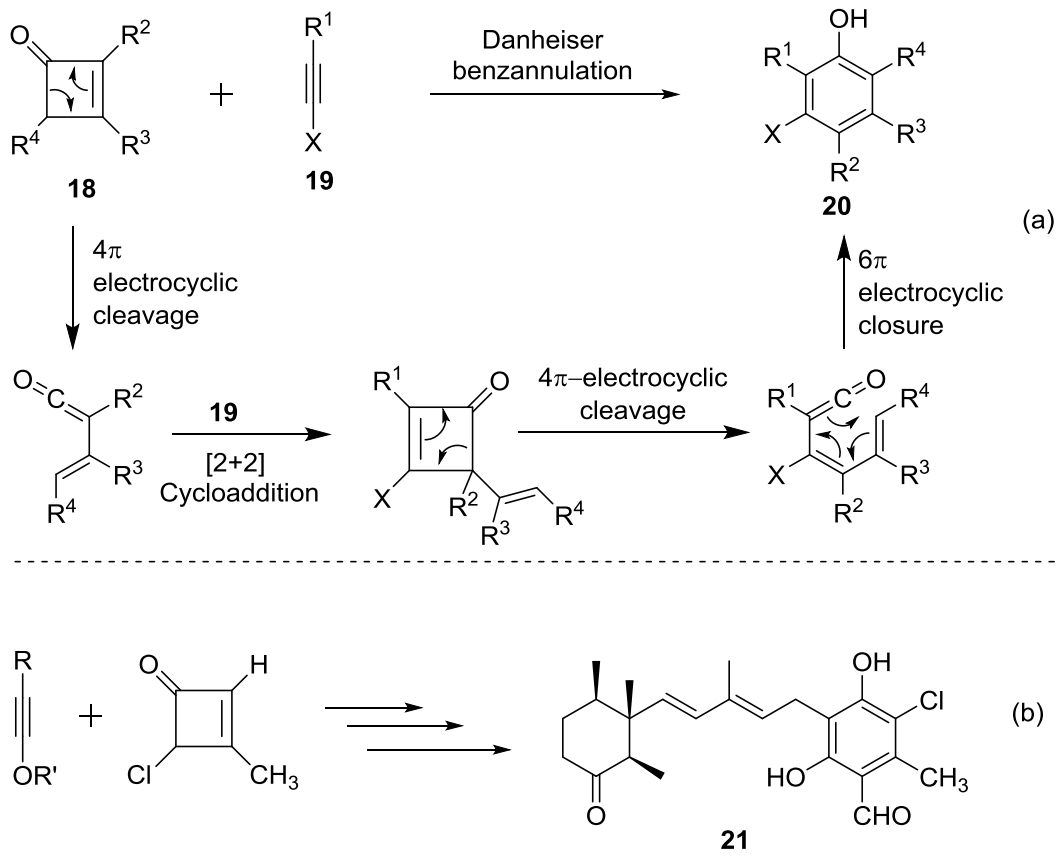
In addition to olefin metathesis, enyne metathesis strategy has also been found useful for synthesis of various aromatic hydrocarbons. In 1985, Katz has developed the first intramolecular enyne ring closing metathesis for construction of construction of 9-vinylphenanthrene **18** from enyne derivative **17** using a Fischer tungsten-carbene complex (Scheme 9).[15]



Scheme 9: Synthesis of phenanthrene by enyne ring closing metathesis

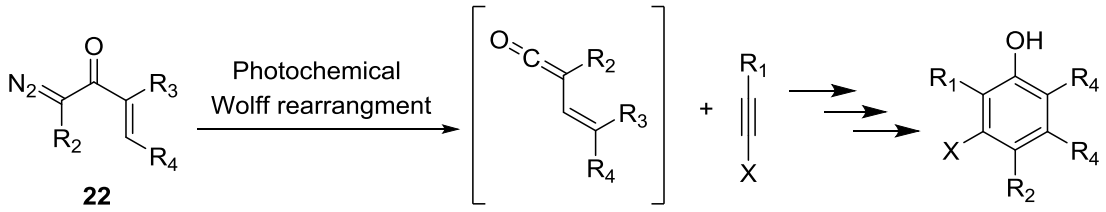
1.2.2. Electrocyclic benzannulation reaction

Danheiser has developed a regiocontrolled annulation wherein cyclobutenones **18** reacted with substituted acetylenes **19 to** afford highly substituted phenol derivatives **20**.[6a] The reaction involves sequential 4л electrocyclic cleavage, [2+2] cycloaddition, 4л electrocyclic cleavage and 4л electron electrocyclic closure reactions as depicted in scheme 10. This reaction has wide applications for example used as key step for total synthesis of (-)-ascochlorin **21** (Scheme 10).[16]



Scheme 10: (a) Danheiser benzannulation reaction, (b) Synthesis of (-)-ascochlorin via Danheiser benzannulation

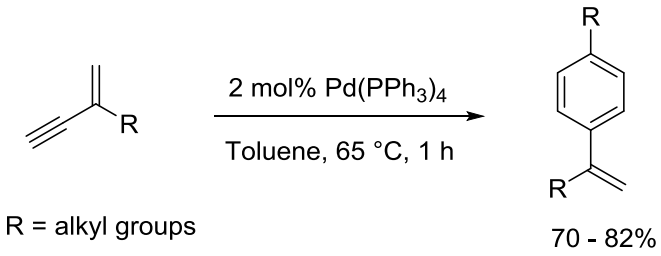
The modified Danheiser reaction involves the annulation of α-diazoketone **22** with acetylene derivatives to generate functionalized polycyclic aromatic and heteroaromatic compounds (Scheme 11).[6b] The reaction proceeds via photochemical Wolff rearrangement of α-diazoketone **22** to generate a vinyl ketene, followed by cycloaddition and electrocyclic reactions.



Scheme 11: Modified Danheiser benzannulation reaction of α-diazoketone

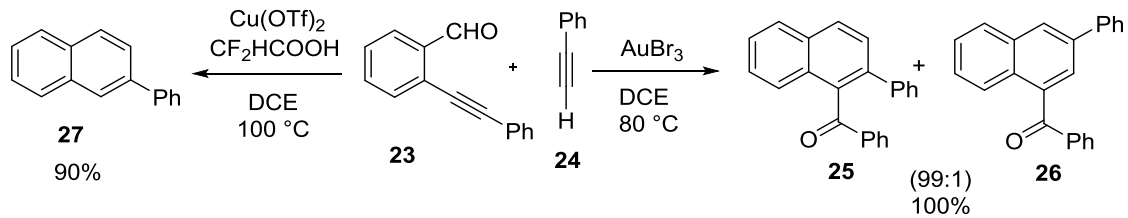
1.2.3. Dies-Alder type benzannulation reactions

The Dies-Alder [4+2] cycloaddition of suitably substituted dienes and a dienophiles has been widely used for synthesis of various polycyclic hydrocarbons. Many of the [4+2] cycloadditions are followed by an oxidative aromatization, either as spontaneous aerial oxidation or by the addition of oxidants such as DDQ. Yamamoto and co-workers has reported a palladium catalyzed benzannulation of conjugated enyne systems. The reaction proceeds *via* a [4+2] dimerisation of the enyne to generate 1,4-disubstituted benzenes (Scheme 12).[17]



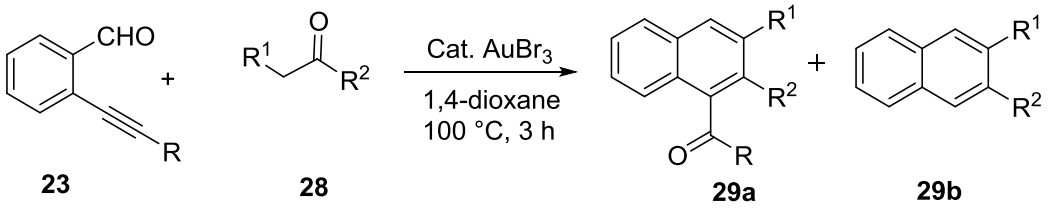
Scheme 12: [4+2] dimerizatiom of conjugated enynes

Lewis acid-promoted [4+2] benzannulation reaction for the construction of polysubstitued aromatic compounds was developed by Asao and Yamamoto. For example, the cycloaddition reaction of o-(alkynyl)benzaldehyde **23** with alkyne **24** in presence of $AuBr_3$ produced naphthyl ketones **25** and **26**. On the other hand, the same pair of reactants combined in the presence of $Cu(OTf)_2$ and and a Brønsted acid to afford a decarbonylated naphthalene derivative **27** (Scheme 13).[18]



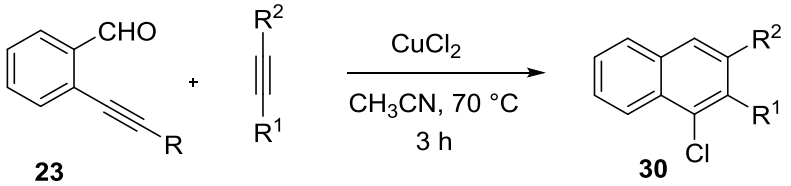
Scheme 13: [4+2] benzannulation of o-(alkynyl)benzaldehyde and alkyne

A gold-catalyzed [4+2] benzannulation of o-(alkynyl)benzaldehyde **23** and ketone **28** generated naphthalene derivative **29a-b** (Scheme 14).[19] The transformation may be viewed as a Diels-Alder reaction of pyrylium species derived from o-(alkynyl)benzaldehyde under gold catalysis and the enol form of **28**.



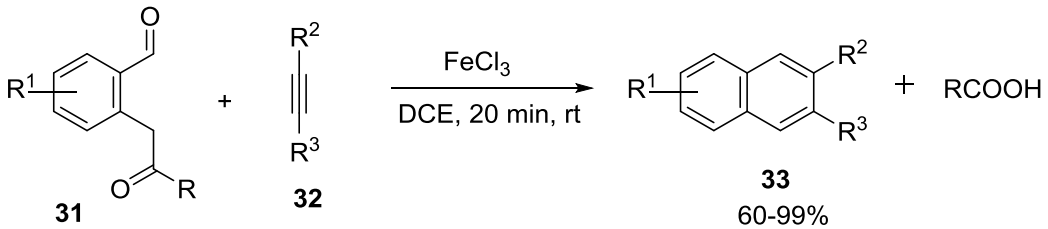
Scheme 14: Gold-catalyzed [4+2] benzannulation of o-(alkynyl)benzaldehyde and enol

Asao reported a $CuCl_2$-promoted [4+2] benzannulation of o-(alkynyl)benzaldehyde **23** with alkynes for the stereoselective synthesis naphthyl halides **30** (Scheme 15).[20]



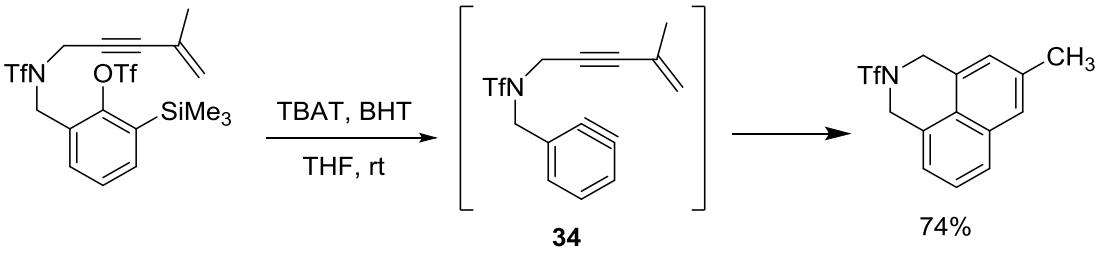
Scheme 15: Cu-catalyzed benzannulation of *o*-(alkynyl)benzaldehyde and alkynes

The iron-catalyzed benzannulation of 2-alkylbenzaldehyde with alkynes is another useful annulation reaction of *o*-substituted benzaldehyde for the synthesis of various aromatic compounds. For example, the reaction of 2-(2-oxyethyl)-benzaldehyde **31** with alkyne **32** in presence of $FeCl_3$ produced substituted naphthalene derivatives **33** (Scheme 16).[21]



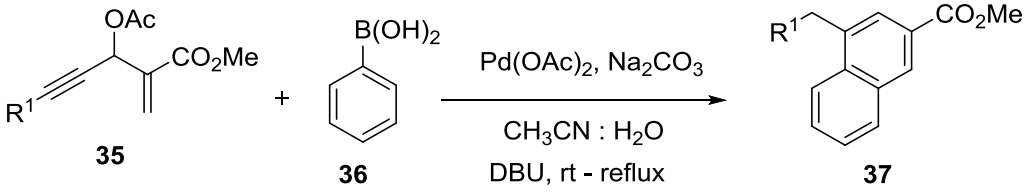
Scheme 16: Iron(III)-catalyzed cyclisation of 2-alkylbenzaldehyde

The intramolecular [4+2] cycloaddition of conjugated enynes with *in situ* generated benzyne furnished highly condensed polycyclic aromatic compounds. The benzyne intermediate **34** was generated *via* TBAT-prompted 1,2-elimination of o-(trimthylsilyl)aryl triflate (Scheme 17).[22]



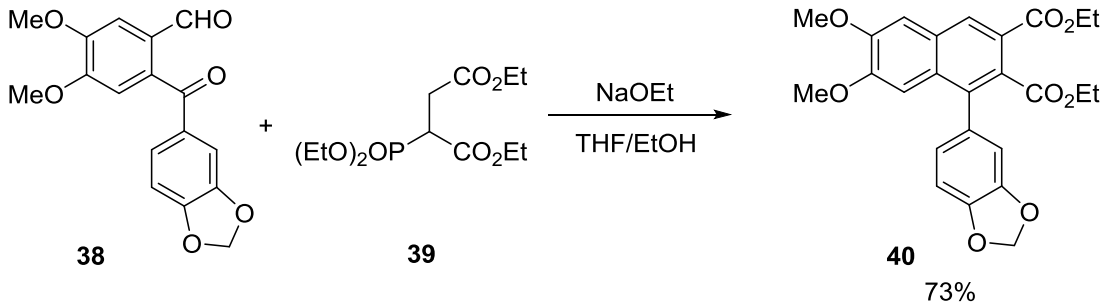
Scheme 17: Intramolecular [4+2] benzannulation of enynes with *in situ* generated benzyne

The reaction of Morita-Baylis-Hillman (MBH) acetate **35** derived from acetylenic aldehydes with boronic acid **36** to afford naphthalene derivative **37** was reported by Reddy and co-workers (Scheme 18).[23] This $Pd(OAc)_2$ catalysed [4+2] benzannulation proceeds via tandem allylic substitution/hydroarylative cycloisomerisation reactions.



Scheme 18: [4+2] benzannulation of MBH acetate with boronic acids

Base induced annulation reaction of ketoaldehyde **38** and phosphonate **39** was developed by Harrowven and co-workers. The reaction proceeded through sequential Wadsworth-Emmons and Claisen condensation reactions to afford substituted naphthalene derivative **40** that incorporated structural features of HIV-1 reverse transcriptase enzyme inhibiting natural products justicidine B and retrojusticidin B (Scheme 19).[24]

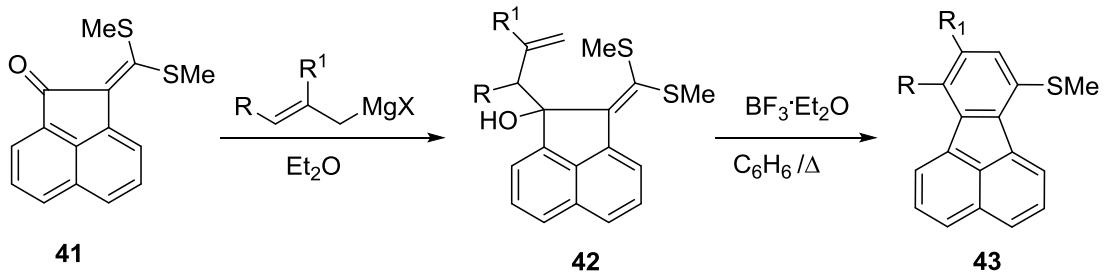


Scheme 19: Cyclisation of ketoaldehyde and phosphonate via Wadsworth-Emmons reaction

1.2.4. [3+3] benzannulation reactions

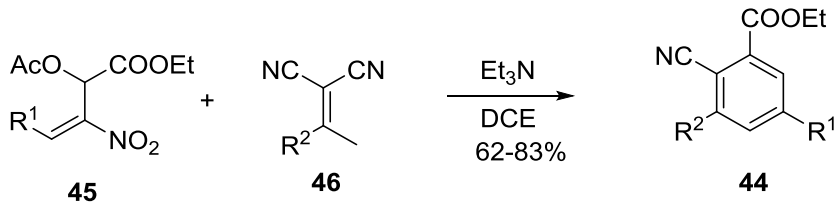
In [3+3] benzannulation approach, the union of two acyclic three-carbon components generates an arene product. The easy availability of a variety of precursors makes this strategy promising for construction of poly-substituted aromatic compounds, provided that the regiochemical challenges are overcome. Generally, [3+3] benzannulation reaction involves sequential nucleophilic attack on electrophilic partner, cyclisation and aromatization through elimination or oxidation.

Junjappa and co-workers have developed an efficient synthesis for the construction of fluoranthene derivatives **43** *via* a [3+3] benzannulation reaction of carbinol acetal **42**, which was derived by treatment of α-oxoketene dithioacetal **41** with allylic Grignard reagents (Scheme 20).[25]



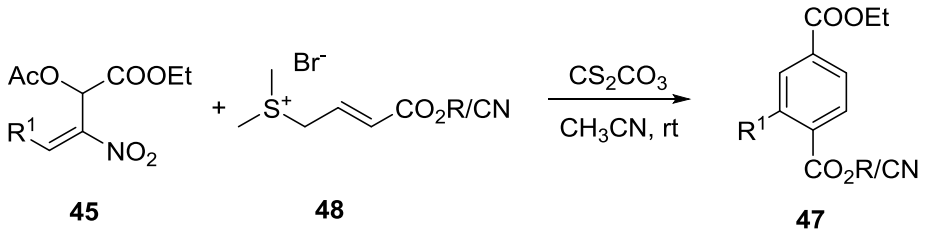
Scheme 20: Synthesis of fluoranthene *via* [3+3] benzannulation method

One-pot [3+3] benzannulation reaction for synthesis of *m*-terphenyls **44** has been developed by Namboothiri and co-workers. The reaction involves a base promoted regioselective cyclisation of Morita-Baylis-Hillman (MBH) acetates **45** of nitroalkenes and alkylidenemalononitriles **46** to afford a variety of polysubstituted meta-terphenyls **44** (Scheme 21).[26]



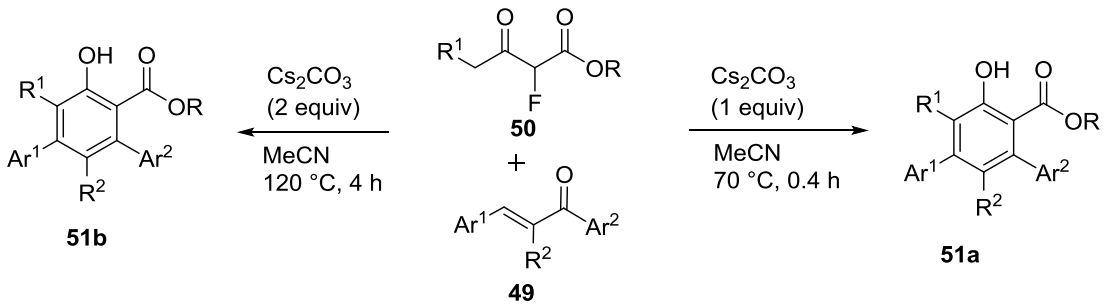
Scheme 21: [3+3] benzannulation for synthesis of m-terphenyls

Namboothiri's group also developed another interesting [3+3] benzannulation reaction for the synthesis of 2-aryl terephthalates **47** from MBH acetates **45** and stabilized sulfur ylides **48** (Scheme 22).[27] The products 2-aryl terephthalates **47** are useful precursors for the synthesis of many farnesyltransferase inhibitors.



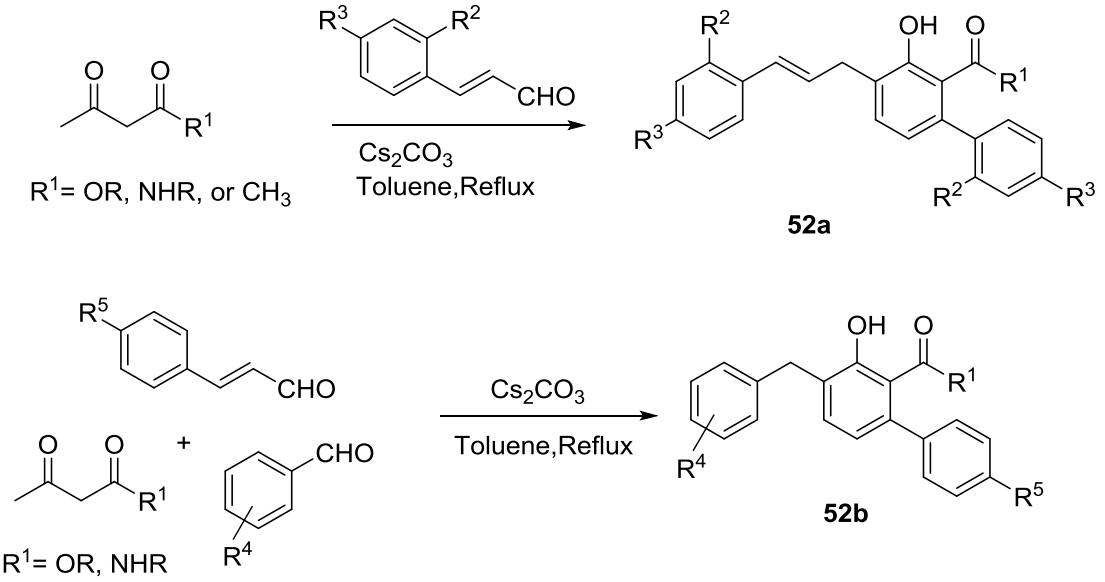
Scheme 22: [3+3] benzannulation for the synthesis of 2-aryl terephthalates

Polysubstituted phenols can be synthesized via the Robinson annulation reaction of α,β-unsaturated ketones **49** with α-fluoro-β-ketoesters **50**. The Robinson annulation is followed by a dehydrofluorination and subsequent tautomerization to afford substituted phenols **51a-b** (Scheme 23).[28]



Scheme 23: Robinson annulations for synthesis of substituted phenols

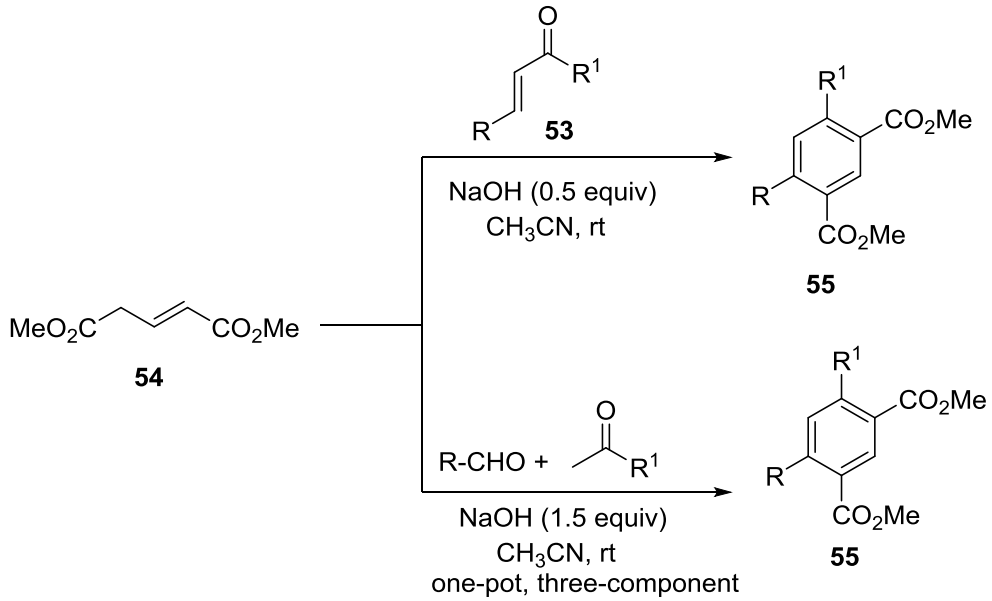
A transition-metal free benzannulation of readily available β-ketoester, β-ketoamides or 1,3-diketones with cinnamaldehyde or aryl aldehydes afforded polyfunctionalised biaryls **52a-b** (Scheme 24).[29] This base assisted cascade transformation involves the formation of three new bonds through multicomponent reactions.



Scheme 24: Transition metal free benzannulation reaction for synthesis of biaryl phenols

Zhao and Liu have developed a base-promoted, aerobic oxidative [3+3] benzannulation reaction of α,β-unsaturated carbonyls **53** with dimethylglutaconate **54**. The reaction afforded substituted benzene derivatives **55** in good yields. Furthermore, one-pot aromatization can also be carried out more conveniently through in situ generation of

α,β-unsaturated carbonyl compound from aldehyde and ketone via base-mediated aldol reaction prior to the benzannulation step (Scheme 25).[30]



Scheme 25: Base mediated [3+3] benzannulation reaction of α,β-unsaturated carbonyls with dimethylglutaconate

1.3. Conclusion

From the above discussion, it is evident that the benzannulation approach is a highly diverse and powerful tool for generation of functionalized arenes. The availability of a variety of reaction components, reaction conditions, scope for catalysis, multitudes of mechanistic types, and possibility of multicomponent protocols are some of the features that make benzannulation reactions a highly useful method for the constructions of substituted arenes. Additionally, a number of benzannulation reactions can be carried out in aqueous reaction medium, in open-flasks and utilizes atmospheric air as an oxidant. The results of our investigations in this area are presented in detail in the following chapters of this thesis.

Part B: Introduction and synthetic applications of allenyl sulfones

1.4. Allenyl sulfones-An introduction

Allenes are cumulated dienes in which two double bonds share a single sp-hybridized carbon atom (Figure 1). The two double bonds of allene molecule are not conjugated and are less stable in comparison to either conjugated or isolated double bonds. Unlike conjugated dienes, allenes are often more reactive and the double bonds in substituted allenes may be differentiated in chemical reactions.

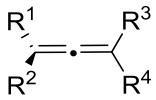


Figure 1: General structure of an allene

Substituted allenes may behave as electron deficient or electron rich entities depending on the nature of substituents. Allenes endowed with one or more electron withdrawing groups are known as electron deficient allenes. Allenoates ie., allenes possessing an ester substituent belongs to a well-studied class of electron deficient allenes and have been used in various addition and cyclisation reactions.[31] A closely related class of allenes, viz., allenyl sulfones (or sulfonyl allene) constitute another important class of electron deficient allenes. Fuchs in a seminal *Chemical Reviews* article has summarized the unique features of sulfonyl, especially arylsulfonyl group.[32] These include (i) tendency of vinyl sulfones to undergo base-catalyzed isomerisation to allyl sulfones (ii) leaving group capacity of sulfinate anions under both acidic and basic conditions (iii) capacity of sulfonyl group to stabilize negative charge adjacent to it. These features of allenyl sulfones influence the reactivity of allenyl framework and make it a unique class of electron deficient allenes. Generally, the addition of nucleophiles to electrophilic allenes

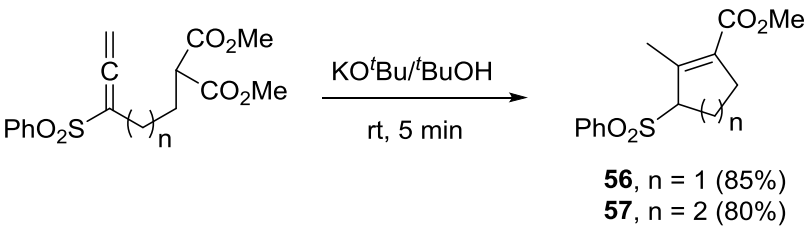
(electron deficient allenes) generates conjugated (vinyl) final products, however, in case of allenyl sulfones the nucleophilic addition proceeds *via* generation of stabilized α-sulfonyl carboanions which on protonation afford allyl sulfones as final products. The unique and highly unusual tendency of arylsulfoyl unit to *de-conjugate* the double bond adjacent to it combined with their leaving group ability make the sulfonyl group a versatile functional group. The work presented in last chapter of this thesis is based on allenyl sulfones. Therefore, for convenience and better understanding of the work, some important aspects of the chemistry of allenyl sulfones are presented below.

1.5. Reactions of allenyl sulfones

The sulfonyl group makes allenyl sulfones electrophilic in nature and majority of reactions involves addition of nucleophiles to the central carbon atom of allene. A number of nucleophiles undergo such conjugate addition reactions. Additionally, allenyl sulfones behave as dienophiles or dipolarophiles and readily engage in various cycloaddition reactions with dienes or dipoles. Other synthetic applications of allenyl sulfones such as electrophilic additions, transition-metal mediated processes and isomerisation reactions are also well investigated. A brief overview of important transformations of allenyl sulfones is presented in the following section.

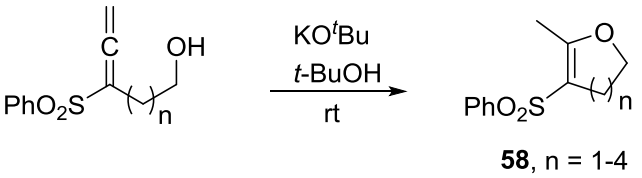
1.5.1. Conjugate addition reactions

Mukai and co-workers developed a method for construction for five- and six-membered carbocycles through endo-mode, Michael addition to allenyl sulfones. The base promoted intramolecular Michael addition of stabilized nucleophile to an allenyl sulfone moiety afforded tri-substituted cyclopentene and cyclohexene derivatives **56** and **57** (Scheme 26).[33]



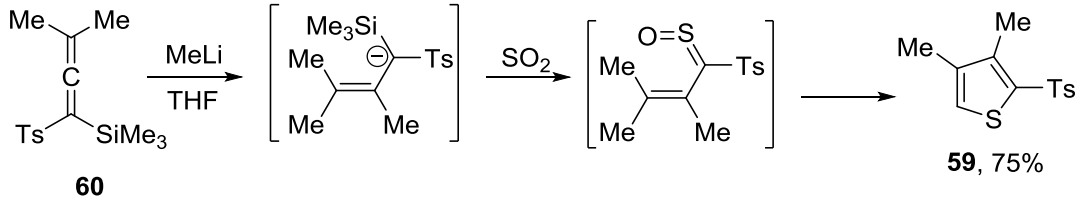
Scheme 26: Intramolecular conjugate addition of nucleophile to allenyl sulfones

Additionally, five to eight membered oxa-heterocycles **58** can also be synthesized via this route (Scheme 27). In presence of base, allenyl sulfones tethered to a terminal primary alcohol group, undergo oxa-Michael cyclisation to generate cyclic enol ethers **58** in high yields.[34]



Scheme 27: Intramolecular oxa-Michael addition of alcohols to allenyl sulfones

The thiophene derivative **59** can be synthesized from α-silylated allenyl sulfones **60** *via* a sequential Michael-type addition of an organolithium reagent to allenyl sulfone **60**, generation of α,β-unsaturated sulfine, and cyclisation as depicted in Scheme 28.[35]

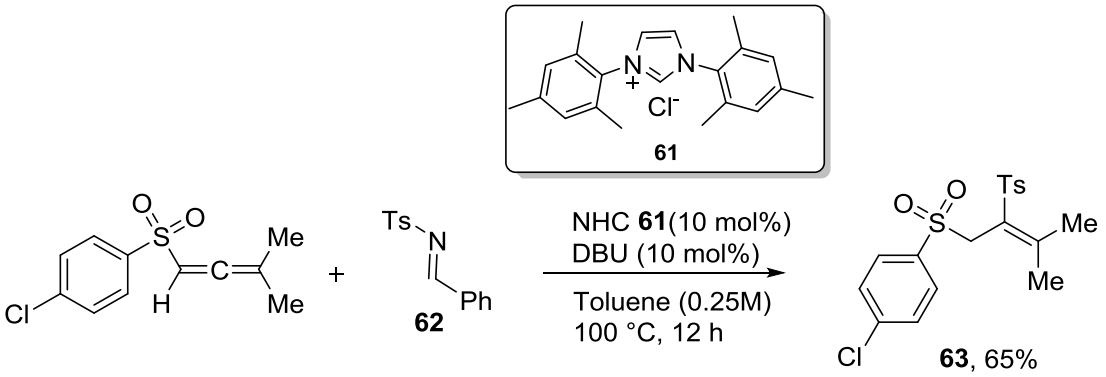


60

Scheme 28: Synthesis of thiophenes from allenyl sulfones

The N-heterocyclic carbene (NHC) **61** catalyzed reaction of allenyl sulfones with the aldimine derivative **62** in presence of DBU afforded tosylated allylic sulfones **63**

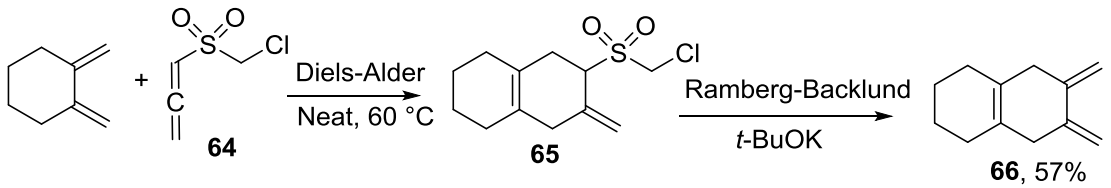
(Scheme 29).[36] The tosyl anion, generated from N-tosyl aldimine attacked selectively at the β-position of allenyl sulfones *via* sulfur atom to afford the final product.



Scheme 29: NHC catalyzed synthesis of allylic sulfones from allenyl sulfones

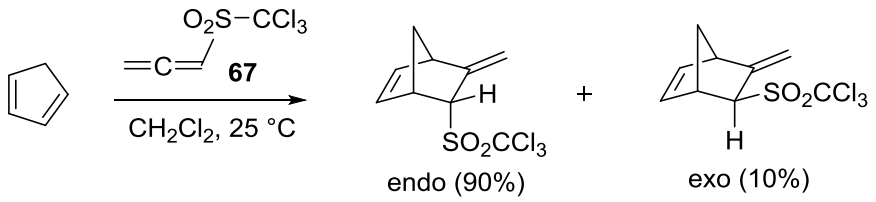
1.5.2. Cycloaddition reactions

Block and Putnam reported the [4+2] cycloaddition reaction of allenyl chloromethyl sulfones **64** with dienes.[37] The treatment of initial cycloadduct **65** with base generated a new 1,4-diene moiety **66** *via* Ramberg-Backlund rearrangement (Scheme 30). The overall reaction may be considered as a cyclo-homologation of the diene.



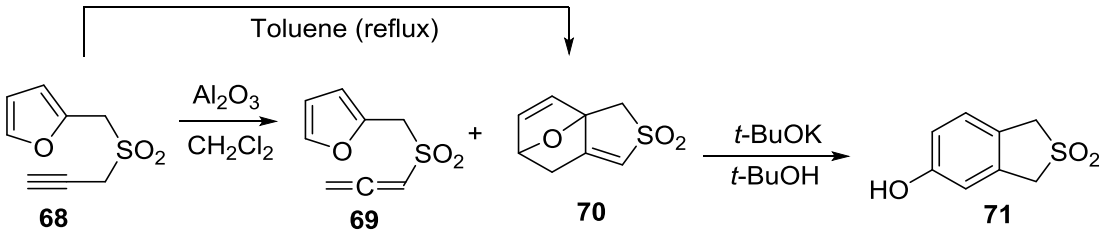
Scheme 30: Cyclo-homologation of diene via Dies-Alder reaction with allenyl sulfone

Dies-Alder reaction of allenyl trichloromethylsulfones **67** and cyclopentadiene were reported by Braverman. The cycloaddition reaction proceeded with good regio- and stereoselectivity (Scheme 31).[38] The trichloromethyl group enhanced the reactivity of allene and even less reactive dienes such as furan also underwent the cycloadditon reactions.



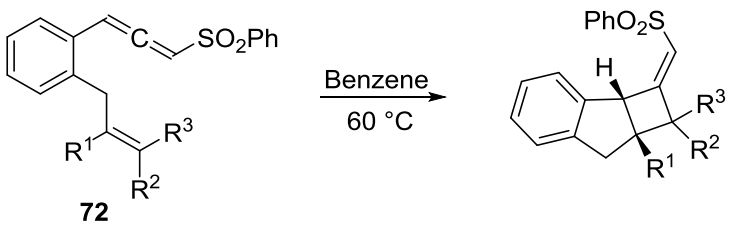
Scheme 31: [4+2] cycloaddition reaction of allenyl trichloromethylsulfones

The reaction of furfural propargyl sulfone **68** with catalytic amount of aluminium oxide produced allenyl furfural sulfone **69** along with cycloadduct **70**. When this mixture was refluxed in toluene, a single cycloadduct **70** was obtained. The cycloadduct **70**, on treatment with base afforded 5-hydroxy benzosulfolene **71** *via* base-mediated aromatization (Scheme 32).[39]



Scheme 32: Intramolecular Diels-Alder reaction of allenyl sulfones

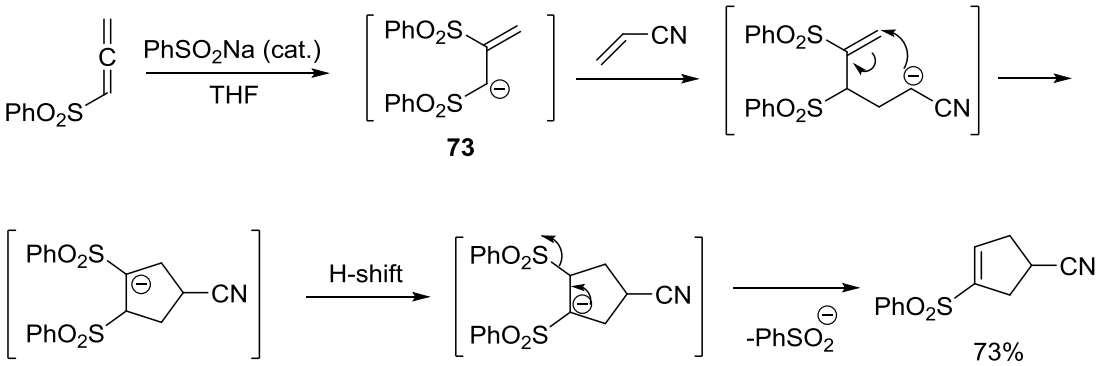
Padwa has extensively investigated the chemistry of allenyl sulfones. A highly regio- and stereospecific intramolecular [2+2] thermal cycloaddition reaction of ene-allenyl sulfones **72** was reported by Padwa. It may be noted that a non-activated double bond of allene participated in cycloaddition reaction (Scheme 33).[40]



Scheme 33: Intramolecular [2+2] cycloaddition reaction of allenyl sulfones

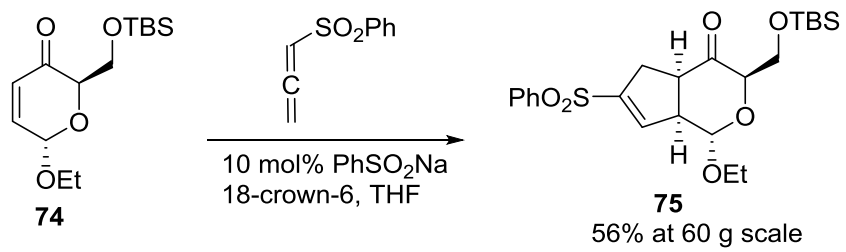
1.5.3. Sulfinate-triggered reactions

In addition to various cycloaddition reactions of allenyl sulfones, sulfinate anion-catalyzed [3+2] cycloaddition reactions of allenyl sulfones were also developed by Padwa.[41] In these reactions allenyl sulfones functioned as three-atom components and sulfinate salts performed the role of catalysts. The reaction is initiated by addition of sulfinate anion to electrophilic carbon of allene to generate an α-sulfonyl carbanioic intermediate **73**, which undergo cycloaddition reaction with electron deficient 2-atom component. A representative example of such cyclisation is presented in scheme 34.



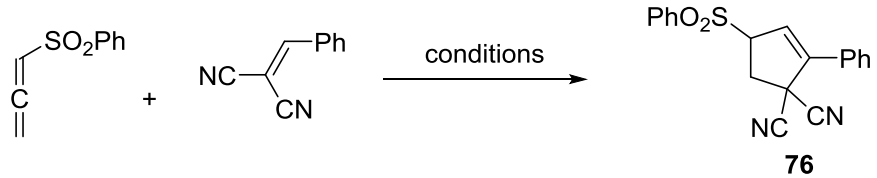
Scheme 34: Padwa anionic [3+2] cycloaddition of allenyl sulfones

Hale reported the total synthesis of (-)-echinosporin, 4-epi-brefeldin A and (+)-brefeldin A *via* Padwa anionic [3+2] cycloadditon.[42] The sulfinate catalysed cyclisation of allenyl sulfone with olefin **74** derived from D-glucal generated the desired bicyclic ketone **75**, which served as a common building block for synthesis of above mentioned natural products (Scheme 35).



Scheme 35: Padwa anionic [3+2] cycloadditon step in the total synthesis of (-)-echinosporin, 4-epi-brefeldin A and (+)-brefeldin A

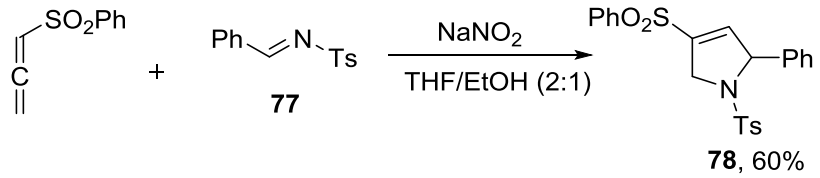
The extension of this annulations reaction to other electron deficient components such as 1,1-dicyano olefins and other catalyst like NHCs was carried out by Perrio and Kuwano respectively (Scheme 36).[43,44] Interestingly, these modified annulation reactions afforded allyl sulfones **76**, whereas, vinyl sulfones were formed in Padwa's [3+2] cycoaddition. (see, Scheme 34).



Perrio's method: $PhSO_2Na$, n-Bu_4NBr (10 mol% each), CH_3CN
Kuwano's method: Triphenyltriazolium salt (NHC precursor), Cs_2CO_3, THF

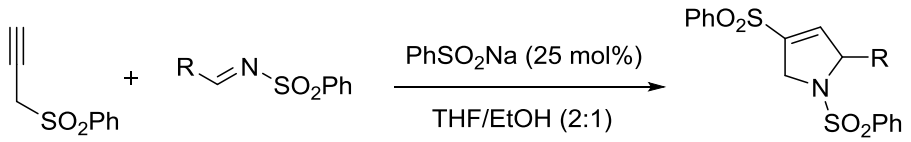
Scheme 36: Modification of Padwa's anionic [3+2] cycloaddition by Perrio and Kuwano

A [3+2] cyclisation reaction of electron deficient N-tosyl imine **77** and allenyl sulfone was developed by Robina (Scheme 37). This sodium nitrite promoted reaction afforded 3-pyrollines **78**. However, controlled experiment revealed that in situ generated sulfinate anion was involved in the reaction and its addition increased the overall yield of reaction.[45]



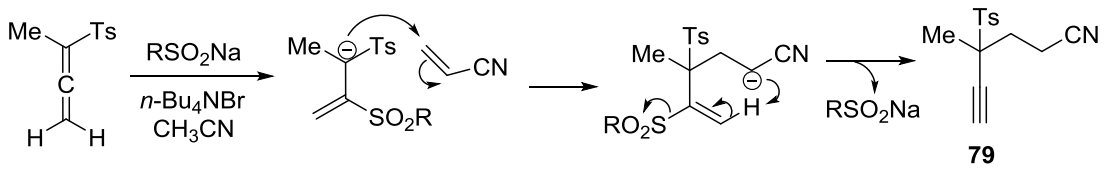
Scheme 37: [3+2] cyclisation of allenyl sulfones with N-tosyl imines

The same class of products can be synthesized from propargyl sulfones. Perrio and co-workers reported that allenyl sulfone was generated from propargyl sulfone *via* sulfinate anion promoted isomerisation (Scheme 39). The ensuing [3+2] cycloaddition proceeded as depicted in Scheme 38.[46]



Scheme 38: Synthesis of 3-pyrrolines from propargyl sulfones

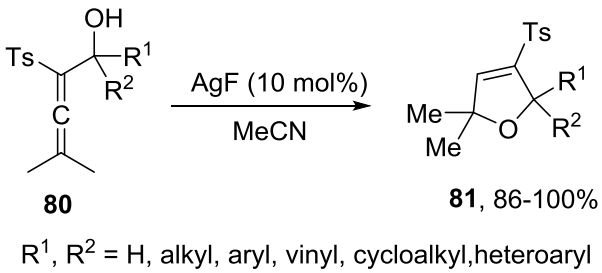
Same group have shown that the umpolung conjugate addition of α-substituted allenyl sulfones to Michael acceptors like acrylonitrile, acrylates and vinyl sulfones could catalyzed by sulfinate salt. In initial steps the process is similar to Padwa's [3+2] cyclisation, however, proton abstraction at later stage afforded alkyne derivatives **79** along with regeneration of sulfinate catalyst (Scheme 39).[47]



Scheme 39: Sulfinate catalyzed umpolung conjugate addition of α-substituted allenyl sulfones

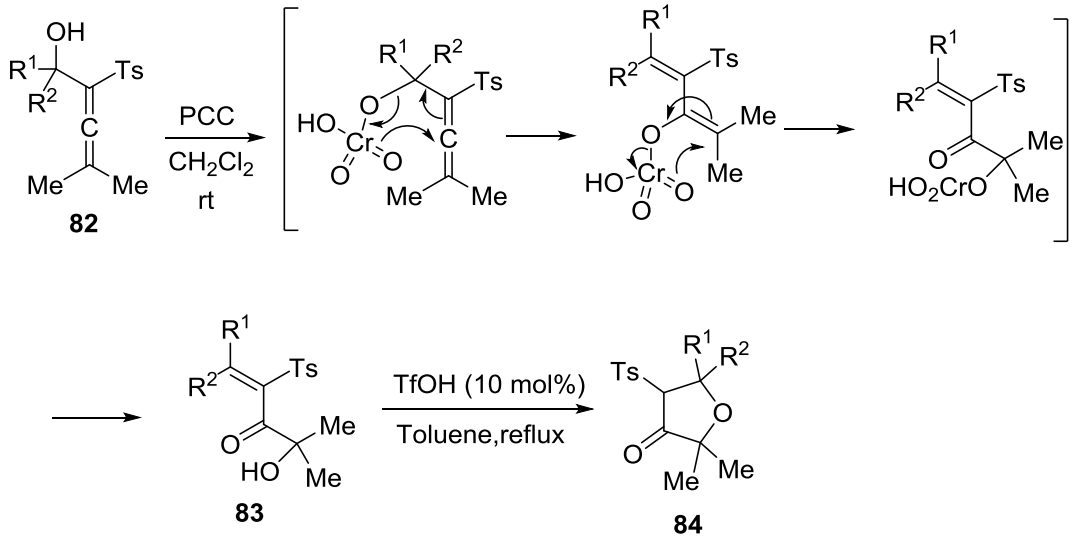
1.5.4. Miscellaneous reactions

Harmata has developed a number of important cyclisation and rearrangement reactions of functionalized allenyl sulfones. A facile Ag(I)-catalyzed 5-*endo*-trig cyclisation reaction of α-hydroxy allenyl sulfones **80** afforded dihydrofuran derivatives **81** (Scheme 40).[48]



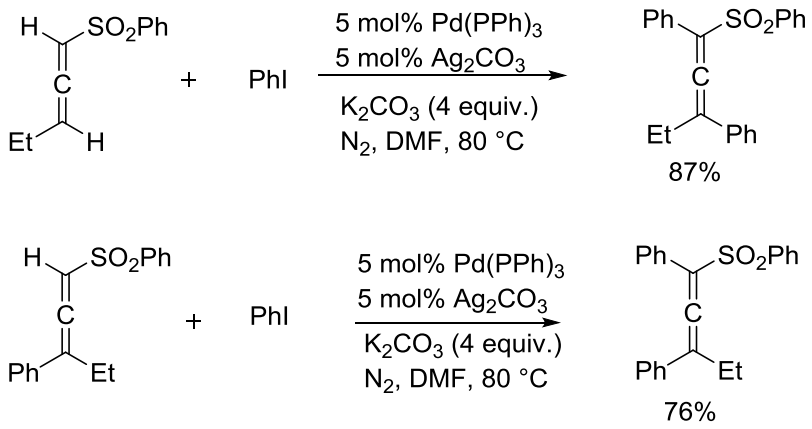
Scheme 40: Ag(I)-catalyzed cyclisation of α-hydroxy allenyl sulfones

A Cr(VI) triggered rearrangement reaction of sulfonyl allenols **82** was reported by same group in 2014. The reaction proceeded *via* a sequence of sigmatropic shifts to generate α'-hydroxydienones **83** in moderate yields.[49] The acid catalyzed cyclisation of α'-hydroxydienones **83** readily converted them into dihydrofuran-3(2H)-ones **84** (Scheme 41).[50]



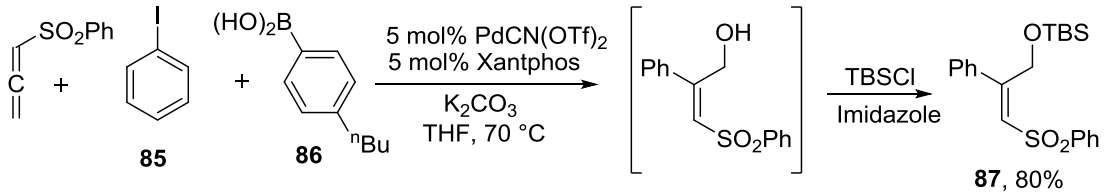
Scheme 41: Cr(VI) promoted rearrangement of sulfonyl allenols and subsequent acid catalysed cyclisation

Recently, numerous transition metal catalyzed carbon-carbon bond forming reaction of allenyl sulfones have been developed. In 2005, the first Heck-type coupling of allenyl sulfones with aryl halides was reported by Fu and Ma.[51] It was observed only terminal carbons of allenyl sulfones partake in coupling with aryl halides and allenic unit was left intact in the final product (Scheme 42).



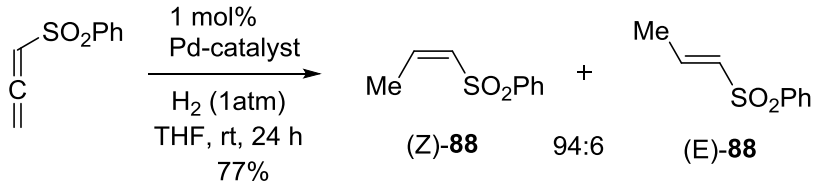
Scheme 42: Heck-type coupling of allenyl sulfones with aryl halides

Pd(0)-catalyzed reaction of allenyl sulfones with aryl iodides **85** and organoboronic acids **86** generated (Z)-allylic alcohols **87** in good regio- and stereoselectivity (Scheme 43).[52] Here, boronic acid **86** acts as a source of hydroxide ion, which can be trapped by the л-allyl palladium complex to form a C-OH bond.



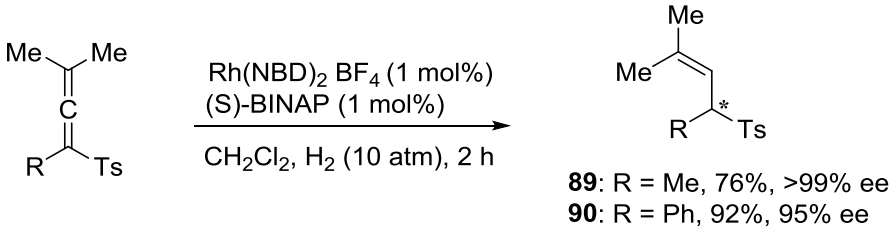
Scheme 43: Pd-catalyzed generation of (Z)-allylic alcohols from allenyl sulfones

Regoi- and enantio-controlled reduction of conjugated unsaturated bonds is always challenging. The stereoselective palladium-catalyzed semi-hydrogenation of allenyl sulfones was reported to produce vinyl sulfones **88** (Scheme 44).[53]



Scheme 44: Stereoselective semi-hydrogenation of allenyl sulfones

On the other hand, allenyl sulfones could be enantioselectively converted into chiral allylic sulfones **89-90** by semi-hydrogenation in presence of rhodium based catalyst (Scheme 45).[54]



Scheme 45: Asymmetric hydrogenation of allenyl sulfones by Rh-based catalyst

1.6. Conclusion

Allenyl sulfones (sulfonyl allene), an important class of electron deficient allene have received less attention than other electron deficient allenes. From the foregoing discussion, it is clear that allenyl sulfones can be employed in numerous useful and novel reactions. Michael-type addition reactions and cycloaddition reactions are the most commonly reported reactions of allenyl sulfones. However, recent reports on novel asymmetric transformations, catalytic addition, and applications in targeted synthesis have enriched the chemistry of allenyl sulfones. Investigations by our group led to the development of a new synthetic surrogate for allenyl sulfones, which can be further utilized for construction of various carbocyclic and hetrocyclic derivatives. The results of our recent investigations are presented in detail in the introduction to chapter IV of this thesis.

1.7. References

1. (a) Liu, Y.; Young, K.; Rakotondraibe, L. H.; Brodie, P. J.; Wiley, J. D.; Cassera, M. B.; Callmander, M. W.; Rakotondrajaona, R.; Rakotobe, E.; Rasamison, V. E.; TenDyke, K.; Shen, Y.; Kingston, D. G. I. *J. Nat. Prod.* **2015**, *78*, 1543. (b) Mbotchak, L.; Le Morvan, C.; Duong, K. L.; Rousseau, B.; Tessier, M.; Fradet, A. *J. Agric. Food Chem.* **2015**, *63*, 5178. (c) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Takahashi, M.; Kotera, J.; Ikeo, T. *J. Med. Chem.* **1999**, *42*, 1293.

2. (a) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, *0*, 5075. (b) Straub, B. F. *Chem. Commun.* **2004**, *0*, 1726. (c) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (d) Viswanathan, G. S.; Wang, M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2138.

3. (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Zhang, L.; Wu, J. *J. Am. Chem. Soc*. **2008**, *130*, 12250. (e) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925. (f) Goossen, L. J.; Lange, P. P.; Rodrıguez, N.; Linder, C. *Chem. Eur. J.* **2010**, *16*, 3906. (g) Zhang, R.; Miao, C.-X.; Wang, S.; Xia, C.; Sun, W. *Chem. Cat. Chem.* **2012**, *4*, 192. (h) Chinnagolla, R. K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 5246.

4. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

5. Dötz, K. H. *Angew. Chem., Int. Ed. Engl*. **1975**, *14*, 644.

6. (a) Danheiser R. L.; Gee, S.K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc*. **1990**, *112*, 3093.

7. Minatti, A.; Dotz, K. H. *J. Org. Chem.* **2005**, *70*, 3745.

8. Vollhardt, K. P. C. *Angew. Chem. Int. Ed.* **1984**, *23*, 539.

9. Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc*.**2005**, *127*, 3406.

10. Washakoon, N.; Rigby, J. *J. Org. Chem.* **1996**, *61*, 7644.

11. Grubbs, R. H.; Brunck, T. K. *J. Am. Chem. Soc.* **1972**, *94*, 2538.

12. (a) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 2585. (b) Kotha, S.; Shah, V. R.; Mandal, K. *Adv. Synth. Catal*. **2007**, *349*, 1159.

13. Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711.

14. Bonifacio, M. C.; Robertson, C. R.; Jung, J.-Y.; King, B. T. *J. Org. Chem.* **2005**, *70*, 8522.

15. Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737.

16. Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.*, **2000**, *2*, 3407.

17. Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970.

18. Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.***2003**, *125*, 10921.

19. Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458.

20. Isogai, Y.; Menggenbateer; Khan, F. N.; Asao, N. *Tetrahedron* **2009**, *65*, 9575.

21. Zhu, S.; Xiao, Y.; Guo, Z.; and Jiang, H. *Org. Lett.*, **2013**, *15*, 898.

22. Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett*. **2005**, *7*, 3917.

23. Reddy, C. R.; Dilipkumar, U.; Reddy, D. M. *Org. Lett*. **2014**, *16*, 3792.

24. Harrowven, D. C.; Bradley, M.; Castro, J. L.; Flanagan, S. R. *Tetrahedron Lett.* **2001**, *42*, 6973.

25. Panda, K.; Venkatesh, C.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2005**, *2005*, 2045.

26. Gopi, E.; Namboothiri, I. N. N. *J. Org. Chem.* **2014**, *79*, 7468.

27. Satham, L.; Namboothiri, I. N. N. *J. Org. Chem*. **2018**, *83*, 9471.

28. Qian, J.; Yi, W.; Huang, X.; Miao, Y.; Zhang, J.; Cai, C.; Zhang, W. *Org. Lett*. **2015**, *17*, 1090.

29. Poudel, T. N.; Lee, Y. R. *Org. Lett.* **2015**, *17*, 2050.

30. Diallo, A.; Zhao, Y.-L.; Wang, H.; Li, S.-S.; Ren, C.-Q.; Liu, Q. *Org. Lett*. **2012**, *14*, 5776.

31. (a) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.*, **2009**, 38, 3102. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res*., **2001**, *34*, 535.

32. El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L. *Chem. Rev*. **2009**, *109*, 2315.

33. Mukai, C.; Ukon, R.; Kuroda, N. *Tetrahedron Lett*., **2003**, *44*, 1583.

34. Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett*., **2001**, *3*, 3385.

35. Linden, J. B.; Van Asten, P. F. T. M.; Braverman, S.; Zwanenburg, B. *Red. Trav. Chim. Pays-Bas*, **1995**, *114*, 51.

36. Swamy, K. C. K.; Suresh, R. R.; Gangadhararao, G.; Anitha, M. *Synthesis*, **2017,** *49*, 2275.

37. Block, E.; Putman, D. *J. Am. Chem. Soc*., **1990**, *112*, *10*, 4073.

38. Braverman, S.; Lior, Z. *Tetrahedron Lett.*, **1994**, *35*, *36*, 6725.

39. Kanematsu, K.; Kinoyama, I. *J. Chem. Soc., Chem., Commun.* **1992**, 735.

40. Padwa, A.; Lipka, H.; Watterson, S. H.; and Murphree, S. S. *J. Org. Chem*., **2003**, *68*, 6238.

41. (a) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc*. **1988**, *110*, 1617. (b) Padwa, A.; Yeske, P. E. *J. Org. Chem*., **1991**, *56*, 6386.

42. (a) Flasz, J. J.; Hale, K. J. *Org. Lett*., **2012**, *14*, 3024. (b) Xiong, Z.; Hale, K. L. *Org. Lett.*, **2016**, *18*, 4254.

43. Martzel, T.; Lohier, J. F.; Gaumont, A. C.; Brière, J. F.; Perrio, S. *Adv. Synth. Catal.*, **2018**, *360*, 2696.

44. Kuwano, S.; Masuda, T.; Yamaguchi, K.; Arai, T. *Heterocycles*, **2017**, *95*, 232.

45. Moreno-Clavijo, E.; Carmona, A. T.; Reissig, H.-U.; Moreno-Vargas, A. J.; Alvarez, E.; Robina, I. *Org Lett*., **2009**, *11*, 4778.

46. Martzel, T.; Lohier, J. F.; Gaumont, A. C.; Brière, J. F.; Perrio, S. *Eur. J. Org. Chem.*, **2018**, 5069.

47. Martzel, T.; Lohier, J. F.; Gaumont, A. C.; Brière, J. F.; Perrio, S. *Chem. Eur. J.*, **2017**, *359*, 96.

48. Tata, R. R.; and Harmata, M. *Org. Lett*., **2016**, *18*, 5684.

49. Tata, R.; Hampton, C. S.; Altenhofer, E. F.; Topinka, M.; Ying, W.; Gao, X.; Harmata, M. *Chem. Eur. J*., **2014**, *20*, 13547.

50. Tata, R. R.; and Harmata, M. *J. Org. Chem.*, **2015**, *80*, 6839.

51. Fu, C.; and Ma, S. *Org. Lett*., **2005**, *7*, 1605.

52. Bai, T.; Yang, Y.; Janes, T.; Song, D.; Guo, Z. *Tetrahedron*, **2017**, *73*, 5784.

53. Guo, H.; Zheng, Z.; Yu, F.; Ma, S.; Holuigue, A.; Tromp, D. S.; Elsevier, C. J.; Yu, Y. *Angew. Chem. Int. Ed*., **2006**, *45*, 4997.

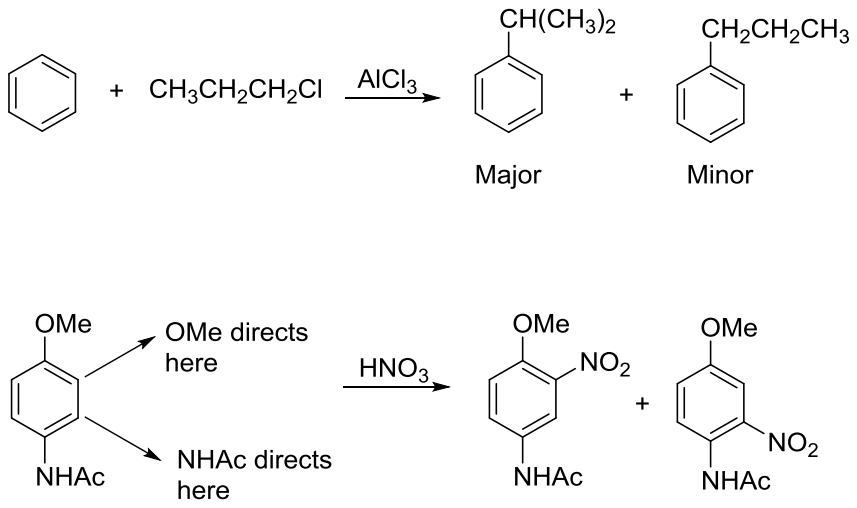
54. Long, J.; Shi, L.; Li, X.; Lv, H.; Zhang, X. *Angew. Chem. Int. Ed*., **2018**, *57*, 13248.

Chapter II

Base-mediated [3+3] benzannulation reactions of bis-sulfonyl propenes and Morita-Baylis-Hillman (MBH) bromides for the synthesis of highly substituted arenes

2.1. Introduction

Substituted arene units are widely prevalent in organic chemistry and are routinely found as the core unit of many natural products and synthetic molecules.[1] The arene scaffold constitute an excellent building block as it can be conveniently transformed into various desired target molecules. Organic chemists strive continuously to develop methods to synthesize arenes. Generally, substituted arenes are constructed by stepwise introduction of functional group via electrophilic aromatic substitution reactions.[2] Friedel-Crafts reaction is a well established and one of the oldest among such methods.[3] This reaction has wide application for synthesis of mono-substituted arenes while regioselective synthesis of di-, tri- and tetra-substituted arenes often becomes challenging via aromatic substitution reactions. The directing effect of groups present on aryl ring decides the regiochemical outcome of the reaction and may prevent the formation of a desired regioisomer. The structural rearrangement of electrophile (carbocation) generated during the course of electrophilic substitution reaction can lead to the formation of unwanted side-products. Electron withdrawing groups on the arene ring deactivate them and bulky substituents repel the approach of electrophiles thereby making such electrophilic substitutions problematic. Some examples of above mentioned problems complicate the outcomes of aromatic electrophilic substitutions are depicted in scheme 1.



Scheme 1: Regiochemical control challenges in electrophilic aromatic substitution

Modern synthetic methods such as transition metal mediated cross-coupling reactions[4] and directed metallation reactions[5] address these issues significantly. These methods, however, employ arenes preinstalled with groups which become involved in coupling reaction. Most of the reactive groups on such pre-functionalised arene are introduced via aromatic substitution reaction. Their synthesis, especially when a poly-substituted arene is required, again faces the same issues described above.

An alternative approach of arene construction is highly desirable to overcome these issues. *Benzannulation reactions*, where the union of two acyclic precursors affords an arene product address above-mentioned aspects to some extent. This method has become a powerful tool for the synthesis of arenes due to its many favorable virtues. Dotz reaction[6] and Danheiser benzannulation[7] are important and well known transformations that demonstrate the potential of this strategy in organic synthesis. In a benzannulation reaction the acyclic precursor can be of various sizes and type, the assembly of two or more components may be catalyzed or mediated by metal

complexes, acids, bases or light. The combination of two, three or more acyclic building blocks may result in an efficient synthesis of arenes. Different varieties of benzannulation reactions are developed and can be classified into various categories depending on the number of carbon atoms contributed by each of acyclic building block to final product, such as [3+3], [4+2], [5+1], [2+2+2], *etc*. Benzannulation reactions of the [3+3] class are more pertinent to work presented in this chapter.[8] Elegant applications of this strategy in the total synthesis of arene containing natural products reveal the power of this method.[9] A detailed discussion on benzannulation reactions may be found in chapter 1.

In the following passages, a novel [3+3] benzannulation reaction of Morita-Baylis-Hillman bromides and unsaturated sulfones that affords tetra-substituted bis-sulfonylarenes is described. To present the results in context, a brief overview of arysulfones is presented in following sections.

2.2. Aryl sulfones

Arylsulfones are important synthetic targets owing to their synthetic utility and favorable properties.[10] A number of aryl sulfones exhibit biological activities such as inhibitory activities against various enzymes.[11] In addition, some arylsulfones shows excellent coordinating properties,[12] which enhances their demand. The anti-leprosy drug dapsone and the anti- ischemic agent cariporide are important aryl sulfones in pharmacology. Some important aryl sulfones are depicted in figure 1.

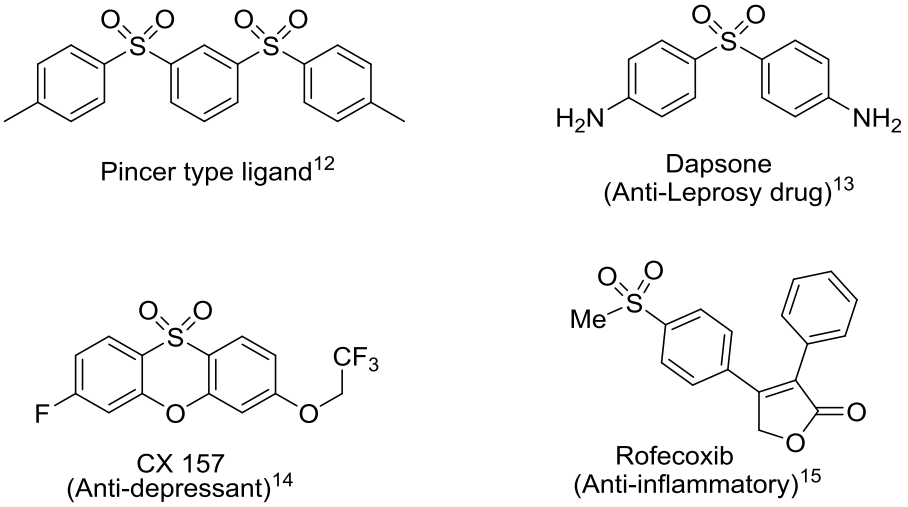


Figure 1: Some important biological active aryl sulfones

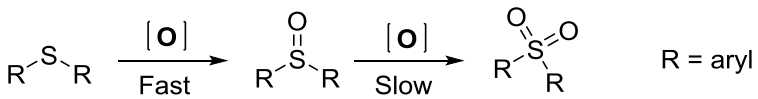
As a consequence, a number of methods have been developed for their synthesis and a few selected methods are presented below.

2.3. Synthesis of aryl sulfones

Commonly used methods for synthesis of aryl sulfones are, (i) oxidation of aryl sulfides,[16] (ii) sulfonylation of arenes[17] and (iii) coupling of sulfinates with aryl halides or tosylates.[18] Each of these three methods are described with examples in the following sections.

2.3.1. Oxidation of aryl sulfides

A general route for synthesis of aryl sulfones involves oxidation of corresponding aryl sulfides. Peroxyacids and peroxides are the common oxidants used for oxidation of sulfides and sulfoxide into sulfones. A general approach for oxidation of sulfides is described in scheme 2.

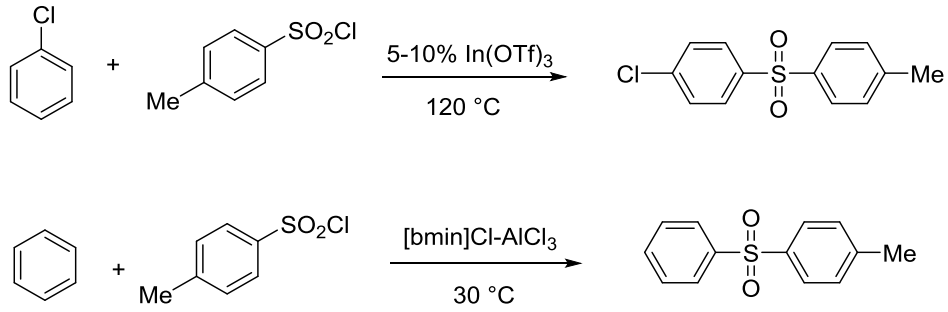


Scheme 2: General method for oxidation of sulfides into sulfones

Initially, sulfides are oxidized to sulfoxides which can be further oxidized to sulfones. Some other reagents such as potassium permanganate, osmium tetraoxide and HOF.CH_3CN complex are also effective in oxidation of sulfides into sulfones.

2.3.2. Sulfonylation of arenes by sulfonyl chlorides

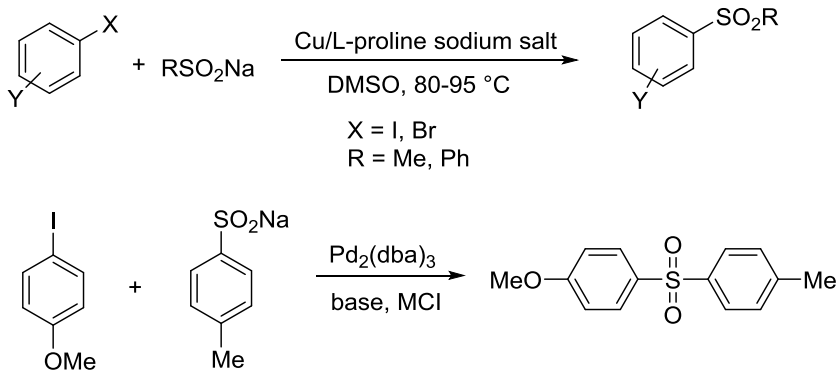
Arenes undergo sulfonylation by sulfonyl chloride in presence of Lewis acids. Both activated and deactivated arenes are reactive towards sulfonylation reaction and generate the corresponding aryl sulfones. Two examples of Lewis acid-mediated sulfonylation reactions of arenes with *p*- toluenesulfonyl chloride are depicted in scheme 3.



Scheme 3: Synthesis of aryl sulfones *via* sulfonylation

2.3.3. Coupling of sulfinates with aryl halides

Metal mediated coupling of aryl halides with sodium salt of sulfinic acids affords aryl sulfones in good yields (scheme 4). Symmetrical and unsymmetrical aryl sulfones can be synthesized *via* this coupling reaction.

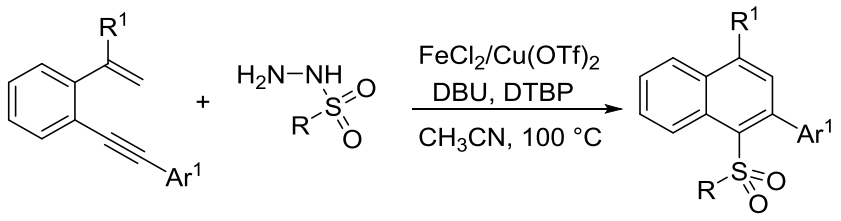


Scheme 4: Synthesis of aryl sulfones via coupling of sodium sulfinate salt with aryl halides

It is notable that in all of the above mentioned methods, pre-functionalised arenes are used for sulfonylation that affords a number of simple aryl sulfones, however, synthesis of more substituted aryl sulfones would be difficult by using these methods. For such substituted sulfones, the di-, tri-, and tetra-substituted arene building blocks are not readily available. In addition, the already present functionalities on arene building blocks may interfere with regiochemistry and reactivity of sulfonylation reaction. *Benzannulation approach* for synthesis of aryl sulfones may address some of these challenges. This approach, however, has been applied only rarely and the available examples are presented below.

2.4. Synthesis of aryl sulfones via benzannulation reactions

An acyclic sulfone moiety can be converted into arene *via* annulation reaction with another suitable precursor. The acyclic sulfone precursor may be prepared by nucleophilic displacement reaction of leaving group by aryl sodium sulfinate salt. Unlike other methods, in benzannulation strategy the sulfone group is introduced on the arene ring as it is formed. The innate simplicity and verstility of this approach make it a promising strategy for synthesis of aryl sulfones. For example, Fe-Cu co-catalyzed oxidative benzannulation of enynes and sulfonyl hydrazides afforded sulfonyl naphthalene derivatives (Scheme 5) [19]

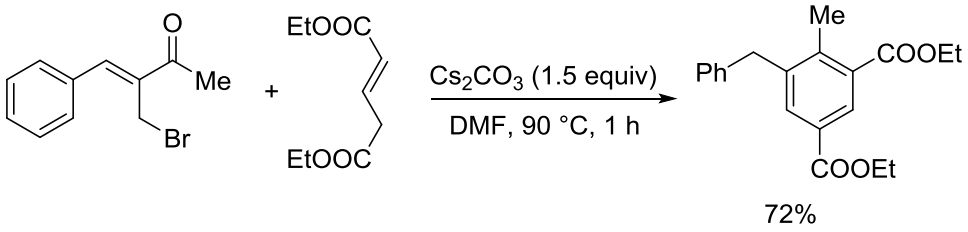


Scheme 5: Synthesis of aryl sulfones via benzannulation reaction of enynes and sulfonyl hydrazides

2.5. Statement of the problem

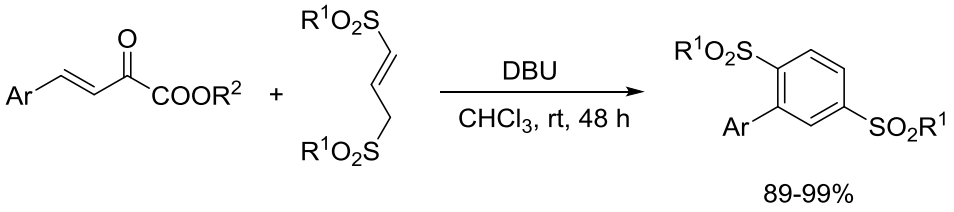
It is worth noting that a highly substituted arene with deactivating groups can be readily synthesized via benzannulation method, however, the introduction of more than one electron withdrawing group is much difficult via electrophilic substitution reaction. Additionally, the regiochemical outcome in electrophilic substitution reactions is determined by the group present on arene ring. As consequences of above discussion, a benzannulation approach for synthesis of highly functionalized sulfonyl arenes appears highly attractive. Our investigations towards this end, led to the development of a convenient and regioselective method for the rapid synthesis of biarylmethanes from simple precursors.

Kim and co-workers in 2013 described a base mediated [3+3] benzannulation reaction of Morita-Baylis-Hillman (MBH) adducts and glutacnoates to afford poly-substituted arene derivatives bearing 1,3-dicarboxylates group (Scheme 6).[20] The MBH adduct contains three electrophilic centers, and the reaction is initiated by displacement of allylic bromide in MBH adduct by nucleophilic end of the 1,3-dicarboxylate anion.



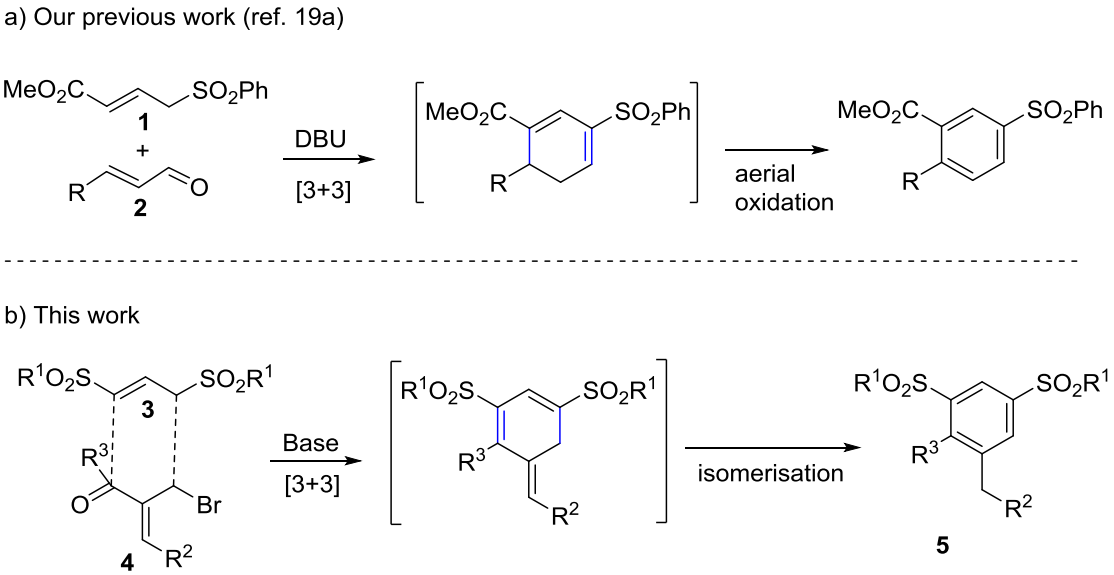
Scheme 6: [3+3] benzannulation of MBH bromide and glutaconates

In 2018 Zhang, Yan and co-workers reported a facile synthesis of aryl sulfones via a base mediated [3+3] benzannulation reaction of 1,3-bis(sulfonyl)propene and β,γ-unsaturated α-ketoester (Scheme 7).[21]



Scheme 7: [3+3] benzannulation of β,γ-unsaturated α-ketoesters and 1,3-bis(sulfonyl)propene

Recently, our group developed an aerial oxidative, [3+3] benzannulation reaction mediated by base that afforded aryl sulfones from 4-sulfonyl crotonates **1** (a bis-nucleophile) and α,β-unsaturated aldehydes and ketones **2** (a 1,3-bis-electrophile) (Scheme 8a).[19a] We surmised that the benzannulation reaction of sulfone bearing symmetric 1,3-bis-nucleophile and a suitable electrophile partner could potentially afford substituted bis-sulfonylarenes (Scheme 8b). For this, we selected Morita-Baylis-Hillman adduct-derived bromide **4** as 3-atom bis-electrophilic building block and 1,3-bis-sulfonylpropene **3** as the bis-nucleophile.



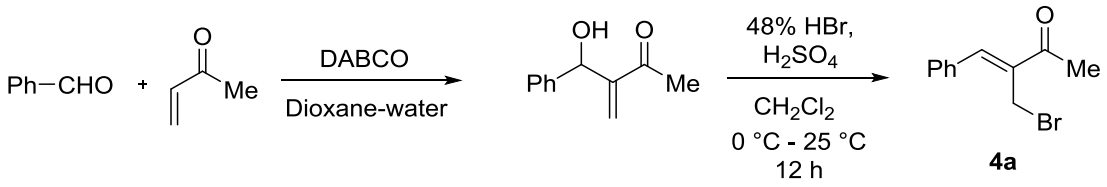
Scheme 8: (a) Benzannulation of enals and bis-sulfonylpropene (b) the present work

Indeed, the MBH bromide **4** incorporates three different electrophilic centers and it was interesting to test its reactivity and regiochemical preferences in a reaction with bis-

nucleophiles **3**. Additional impetus for the exploration came from the easy availability of both the 3-carbon building blocks.

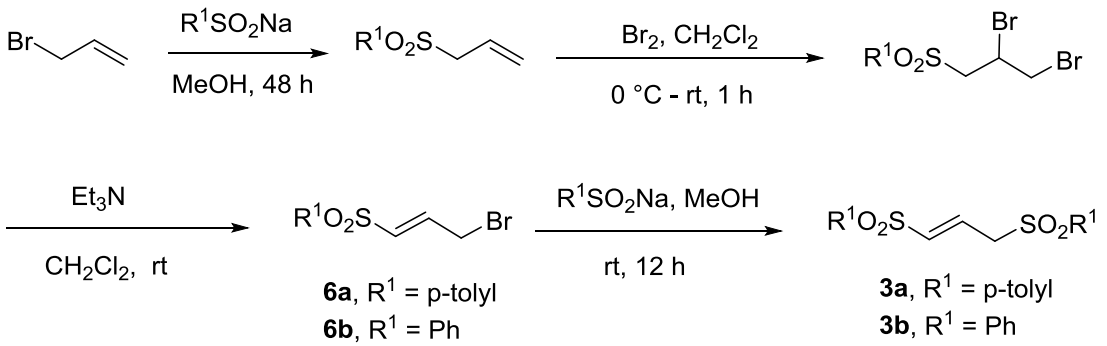
2.6. Results and discussion

In order to test the feasibility of the proposed benzannulation reaction, the required MBH bromide **4a** was prepared from the reaction of benzaldehyde with methyl vinyl ketone in presence of DABCO and followed by bromination with HBr as reported earlier (Scheme 9).[22]



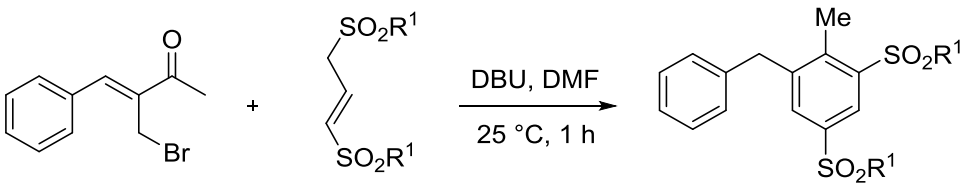
Scheme 9: Preparation of MBH bromide **4a**

The nucleophilic partners, 1,3-bistoluenelsulfonylpropene **3a** and 1,3-bisphenylsulfonylprpopene **3b** were easily prepared via a nucleophilic displacement reaction from the corresponding known bromides **6a, 6b**.[23] These, in turn were assembled from allyl bromide via substitution-bromination-elimination sequence (Scheme 10).



Scheme 10: Preparation of 1,3-bis-arylsulfonylprpopenes **6a-b** from allyl bromide

Once both the reaction partners **4a** and **3a** were at hand, we started our investigations by their union in a benzannulation reaction. Initially, **4a** and **3a** were treated under the conditions of our previously reported benzannulation protocol.[19a] Pleasingly, an aromatic product incorporating both the arenesulfonyl groups was obtained which was assigned the structure **5aa** (Scheme 10). The structure of benzannulated product was assigned on the basis of spectroscopic analysis. The product was isolated as a white crystalline product. The ^{1}H NMR spectrum of **5aa** exhibited a singlet at δ 3.99 (2H) indicating the presence of a methylene group incorporated between two benzene rings. Another singlet at δ 2.35 corresponding to three protons was assigned to methyl group, attached to arene product. Two different doublets at δ 8.63 (d, J = 2.0Hz, 1H) and δ 7.87 (d, J = 2.0, 1H) was assigned to two mutually coupled protons on newly formed arene. Other aliphatic and aromatic hydrogen signals indicated the attachment of tosyl group to benzannulated product. In ^{13}C NMR spectrum signals at δ 39.7 and δ 16.3 confirmed the presence of benzylic methylene and methyl groups in product **5aa**, respectively. All other peaks and other characterization data were also in agreement with the assigned structure (Scheme 11).



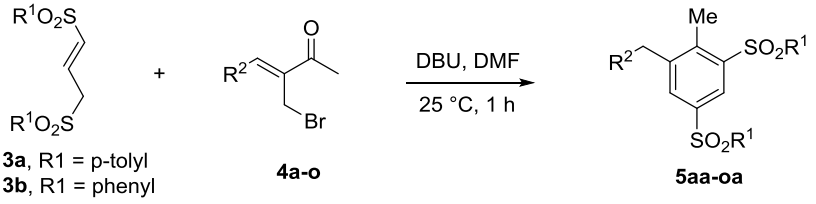
4a **3a**, R^1 = *p*-tolyl **5aa**, 74%

Scheme 11: Benzannulation reaction of **4a** and **3a**

The facile formation of a tetra-substitutes arene from two acyclic precursors prompted us to explore the generality and scope of the benzannulation reaction. For further investigations towards this end, a number of MBH bromides were prepared by

following same method as described in Scheme 8. All of these MBH bromides were then treated with 1,3-bis-arylsulfonyl propene **3a** and **3b** under the optimal conditions of benzannulation reaction. The results are presented in table 1.

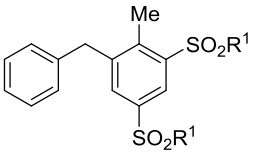
Table 1: Substrate scope of benzannulation reaction[a]



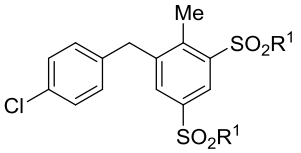
3a, R1 = p-tolyl
3b, R1 = phenyl

4a-o

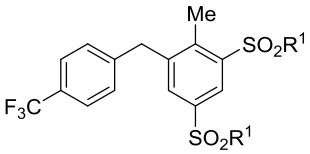
5aa-oa



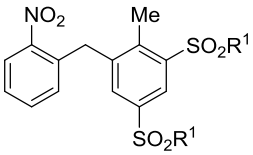
5aa, R^1 = p-tolyl, 74%
5ab, R^1 = phenyl, 75%



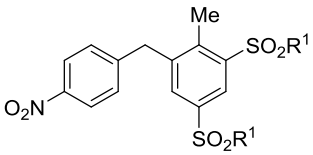
5ba, R^1 = p-tolyl, 71%
5bb, R^1 = phenyl, 74%



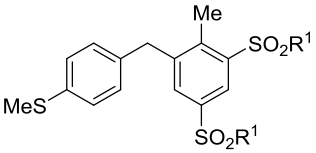
5ca, R^1 = p-tolyl, 66%
5cb, R^1 = phenyl, 69%



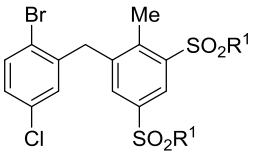
5da, R^1 = p-tolyl, 58%



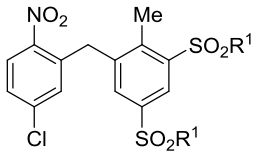
5ea, R^1 = p-tolyl, 56%



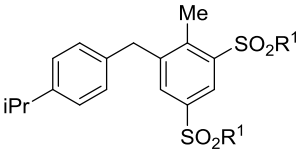
5fa, R^1 = p-tolyl, 78%



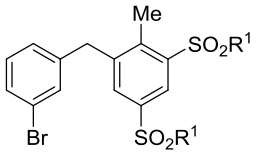
5ga, R^1 = p-tolyl, 67%



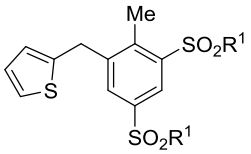
5ha, R^1 = p-tolyl, 62%



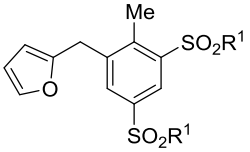
5ia,R^1 = p-tolyl, 75%



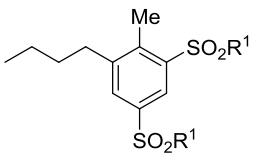
5ja, R^1 = p-tolyl, 73%
5jb, R^1 = phenyl, 76%



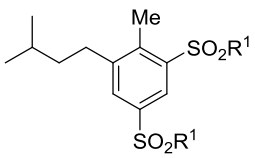
5ka, R^1 = p-tolyl, 72%
5kb, R^1 = phenyl, 74%



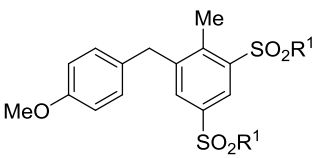
5la, R^1 = p-tolyl, 69%
5lb, R^1 = phenyl, 71%



5ma, R^1 = p-tolyl, 72%



5na, R^1 = p-tolyl, 73%

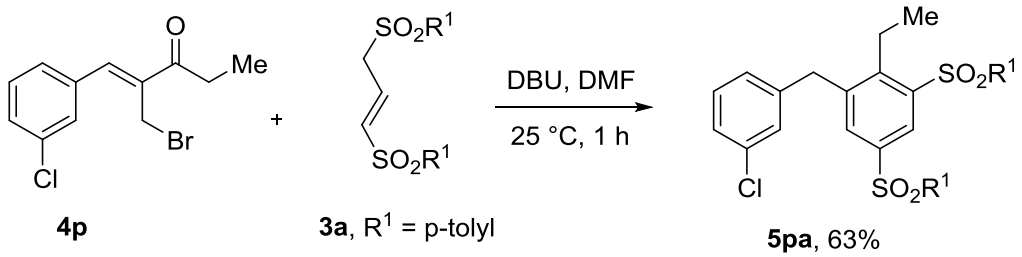


5oa,R^1 = p-tolyl, 82%

[a]reaction conditions: **4** (0.3mmol), **3** (0.33mmol), DBU (0.45mmol), DMF (5ml), 1 h, 25 °C

A variety of MBH adducts **4a-4o** derived from different substituted aldehydes were employed in study reacted smoothly and afforded corresponding tetra-substituted bis-sulfonylarenes **5aa-5oa**. It may be noted that, different groups such as nitro, trifluromethyl, chloro, thiomethyl and bromo can be easily incorporated in biarylmethane products. Electron rich MBH bromide such as *p*-methoxyphenyl ring was also tolerated in the benzannulation reaction. Heteroaryl rings such as thiophene- and furan-bearing biarymethane products (**5ka, 5kb, 5la and 5lb**) may also be synthesized *via* this method. It is worth noting that the reaction is not limited to aryl substrates, alkyl group bearing MBH bromide reacted smoothly to generate corresponding arene **5ma** and **5na**. We tested the scalability of the reaction with 1 g of MBH bromide **4j** and pleasingly, the desired product **5ja** was isolated in 71% yield.

The benzannulation reaction was then tested with an MBH bromide **4p** derived from ethyl vinyl ketone. The treatment of **4p** with **3a** under the conditions of benzannulation reaction afforded ethyl-substituted bis-sulfonylarene **5pa** (Scheme 12).

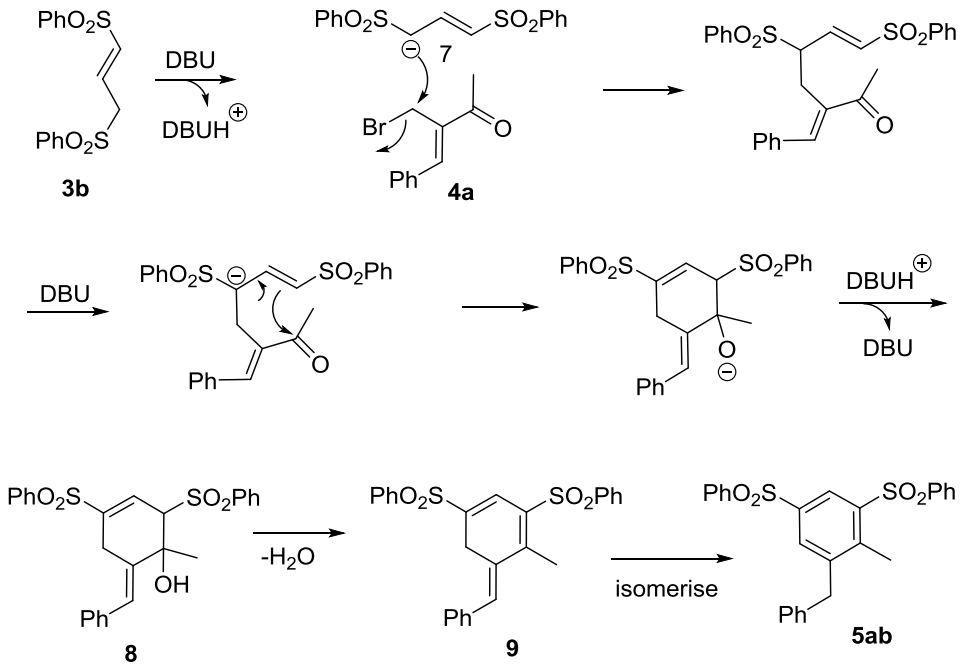


Scheme 12: Benzannulation reaction with MBH bromide derived from ethyl vinyl ketone

It is noteworthy that all the bis-sulfonylarene products are novel molecules. Their synthesis by conventional methods would not be trivial. Additionally, the bis-sulfonylarene products **5aa-5pa** may assume special importance in view of utility as pincer-type ligands.[12]

2.7. Plausible mechanism for benzannulation reaction

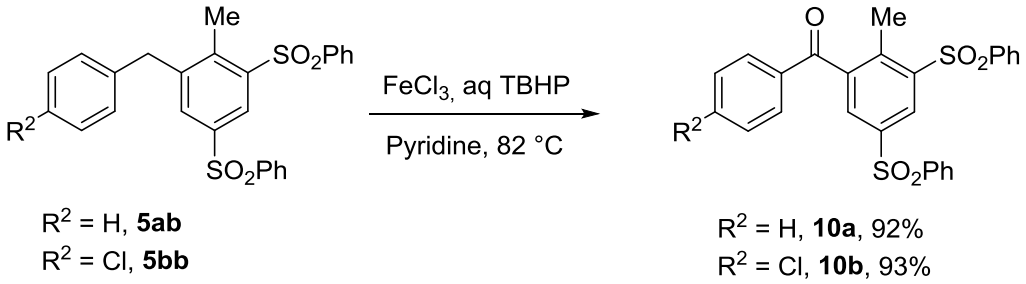
A mechanistic proposal depicted in scheme 12 may be advanced to explain the formation of arene products **5**. Initially, DBU deprotonates 1,3-bisphenylsulfonylprpopene **3b** to afford a stabilized carbanion **7**. This carbanion may interact with MBH bromide **4a** at three different electrophilic sites. These are: (i) 1,2- addition at carbonyl group (ii) 1,4-addition conjugate to the carbonyl group or, (iii) displacement of allylic bromide. It is presumable that the bromine containing carbon is least hindered electrophilic site in MBH bromide **4a** and carbanion **7** displaces bromide in **4a**. It is also noteworthy that the allylic bromide is considered as an activated electrophile in nucleophilic substitution reactions. Further deprotonation and intramolecular cyclisation forms cyclohexenol derivative **8**. It is presumable that intramolecular 1,2-addition of the carbanion to enone moiety is favored over Michael addition due to high steric demands. Dehydration of carbinol **8** then produces cyclohexadiene derivative **9**. The cyclohexadiene readily undergoes isomerisation via [1,3]-H shift to furnish the aromatic product **5ab** (Scheme 13).



Scheme 13: Plausible mechanism of benzannulation reaction

2.8. Synthetic modification of biarylmethane derivatives

The biarylmethane products are amenable to further synthetic modifications. Benzylic oxidation[24] of biarymethanes by *tert*-butyl hydroperoxide (TBHP) and $FeCl_3$ afforded corresponding benzophenone derivatives in excellent yields (Scheme 14). It is important to note that oxidation proceeds selectively at methylene group and methyl group present on phenyl ring was unaffected. Importantly, similar substituted benzophenones are highly sought-after targets for applications in medicinal chemistry, UV-blocking agents and photocatalysis.



R^2 = H, **5ab**
R^2 = Cl, **5bb**

R^2 = H, **10a**, 92%
R^2 = Cl, **10b**, 93%

Scheme 14: Benzophenone synthesis via site-selective oxidation of biarylmethanes

2.9. Conclusion

In conclusion, a [3+3] benzannulation reaction of two readily available, acyclic precursors viz., 1,3-bissulfonyl propenes and MBH-bromides to afford highly substituted bis-sulfonyl arenes has been developed. The newly formed phenyl ring contains two arenesulfonyl groups which are difficult to introduce by other methods. The benzannulation reaction developed here is metal free, mediated by base (DBU) and proceeds at room temperature to generate a highly substituted product. The biarylmethane derivatives can be readily converted into corresponding benzophenone derivatives *via* site-selective oxidation by TBHP and $FeCl_3$. It is presumable that the present benzannulation reaction may find application as a valuable and powerful synthetic tool for the construction of highly substituted arenes.

2.10. Experimental section

General information

All ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solvent at ambient temperature, chemical shift δ are given in ppm on a scale downfield from tetramethylsilane (TMS), and the coupling constant *J* are in Hz. The signal patterns are indicated as follows: s, Singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; brs = broad). FTIR spectra were recorded as neat. Melting points were recorded on an electrothermal apparatus and are uncorrected. All solvents and reagents were used without further purification unless specified otherwise. Technical grade petroleum ether and ethyl acetate used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh and 100-200 mesh) packed in glass columns. All reactions were performed in oven-dried glassware with magnetic stirring. TLC analysis was performed on 60 F_{254} silica gel plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining by $KMnO_4$. High-resolution mass spectra were recorded with q-TOF electrospray mass spectrometer. All purchased chemicals were used as received.

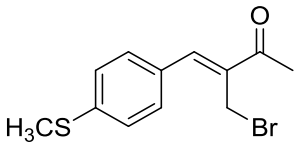
Preparatiom of MBH adduct

In a RB flask a solution of aldehyde (5.0 mmol) and methyl vinyl ketone or ethyl vinyl ketone (7.5 mmol) in 20 ml of 1,4-dioxane-water (1:1, v/v) was stirred at room temperature in presence of DABCO (2 mmol). The reaction progress was monitored by TLC. Upon completion the reaction, mixture was diluted with water and extracted with ether (3×20 ml). The organic layer was washed with brine, dried over sodium sulfate and solvent was evaporated by using rotavapour. The crude product was purified by column charomatography on silica gel using ethyl acetate-petroleum ether as eluent to give desired MBH adduct.

Preparation of MBH bromides 4a-4p[22]

In a RB flask a solution of MBH adduct in DCM (3ml/mmol) kept at 0 ˚C, to this 48% HBr solution (0.4ml/mmol of MBH adduct) was added dropwise. Then, conc. H_2SO_4 (0.3ml/mmol of MBH adduct) was added and stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with DCM (3×10ml). The combined organic layer was dried over sodium sulfate and solvent was evaporated by using rotavapour. The pure product MBH bromide was isolated after column charomatography on silica gel using ethyl acetate-petroleum ether as eluent.

Spectroscopic data for novel MBH bromides



4f, (Z)-3-(bromomethyl)-4-(4-(methylthio)phenyl)but-3-en-2-one

Colorless crystal, 558 mg, 87% (from 500 mg of MBH adduct)

R_f = 0.8 (20% ethyl acetate in hexanes)

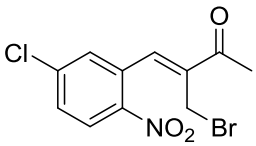
Melting point: 93-94 ˚C

IR (KBr) υ**max**: 2922, 2852, 1657, 1614, 1587, 1489, cm^{-1}

^{1}H NMR (400 MHz, CDCl3) δ 7.58 (s, 1H), 7.55(d, *J* = 8.4Hz, 2H), 7.32(d, *J* = 8.4Hz, 2H), 4.38(s, 2H), 2.53 (s, 3H), 2.50(s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ 197.1, 142.6, 142.5, 142.0, 136.3, 130.4, 125.8, 25.9, 25.4, 15.0

HRMS calcd for $C_{12}H_{13}BrOS$ (M+H) 284.9949; found 284.9949.



4h, (Z)-3-(bromomethyl)-4-(5-chloro-2-nitrophenyl)but-3-en-2-one

Pale yellow solid, 553 mg, 89% (from 500 mg of MBH adduct)

R_f = 0.6 (20% ethyl acetate in hexanes)

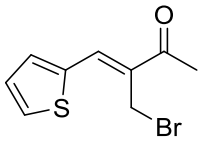
Melting point: 108-109 ˚C

IR (KBr) υ**max**: 1676, 1599, 1560, 1523, 1464, 1427, 1338, 906, 813, 679, 526 cm^{-1}

^{1}H NMR (400 MHz, CDCl3) δ 8.21(d, *J* = 8.8Hz, 1H), 7.88(s, 1H), 7.75(d, *J* = 2.2Hz, 1H), 7.57 (dd, *J* = 8.8, 2.2Hz, 1H), 4.06(s, 2H), 2.53 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ 196.4, 145.3, 140.9, 138.6, 138.2, 132.2, 130.3, 129.9, 127.0, 26.2, 23.6

HRMS calcd for $C_{11}H_9BrClNO_3$ (M+H) 317.9533; found 317.9544



4k, (Z)-3-(bromomethyl)-4-(thiophen-2-yl)but-3-en-2-one

Yellow solid, 531 mg, 79% (from 500 mg of MBH adduct)

R_f = 0.7 (20% ethyl acetate in hexanes)

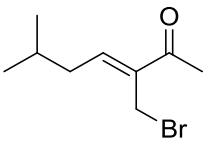
Melting point: 129-131 ˚C

IR (KBr) υ_{max}: 2922, 1659, 1603, 1414, 1203, 700 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.68 (dd, *J* = 5.2, 0.4 Hz, 1H), 7.51 (dd, *J* = 3.6, 0.4 Hz, 1H), 7.20 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.55 (s, 2H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 137.1, 135.5, 134.1, 133.6, 132.6, 128.3, 25.8, 25.0

HRMS calcd for $C_9H_{10}BrOS$ (M+H) 244.9636; found 244.9636.



4n, (Z)-3-(bromomethyl)-6-methylhept-3-en-2-one

Pale Yellow oil, 505 mg, 72% (from 500 mg of MBH adduct)

R_f = 0.7 (20% ethyl acetate in hexanes)

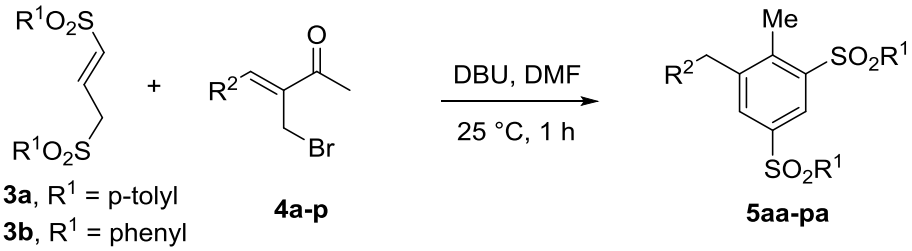
IR (KBr) υ_{max}: 2957, 1670, 1462, 412 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (t, J = 7.5Hz, 1H), 4.16 (s, 2H), 2.33 (s, 3H), 2.25–2.21 (m, 2H), 1.87–1.79 (m, 1H), 0.96 (d, J = 6.7Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 147.7, 139.0, 38.3, 28.3, 25.6, 22.8, 22.7

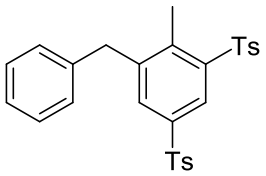
HRMS calcd for $C_9H_{16}BrO$ (M+H) 219.0385; found 219.0379.

General procedure for the DBU-mediated benzannulation reaction



DBU (0.45 mmol) was added to a solution of MBH bromide **4a-p** (0.30 mmol) and 1,3-bissulfonylpropene **3a-b** (0.33 mmol) in DMF (5 mL). The reaction mixture was stirred at 25 ˚C for 1h. After completion of the reaction, 10 mL deionized water was added and the solution was extracted with ethylacetate (3×10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and the solvent was evaporated off on a rotavpor under reduced pressure. The residue was subjected to column charomatography on silica gel using petroleum ether-ethyl acetate as eluent to afford analytically pure sample of the product.

Spectroscopic data for the products 5aa-5pa



5aa, 4,4'-(5-benzyl-4-methyl-1,3-phenylenedisulfonyl)bis(methylbenzene)

White solid, 110 mg, 75%

R_f = 0.6 (20% ethyl acetate in hexanes)

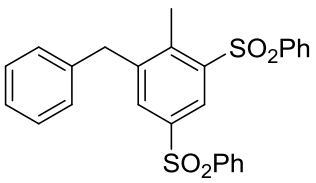
Melting point: 189-191 ˚C

IR (KBr) υ_{max}: 3082, 2926, 1591, 1492, 1442, 1319, 1294, 1147, 540 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 2.0, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.33–7.29 (m, 4H), 7.27–7.20 (m, 3H), 6.94 (d, *J* = 6.5Hz, 2H), 4.00 (s, 2H), 2.43 (s, 6H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 143.7, 142.3, 141.9, 140.3, 137.9, 137.7, 137.4, 133.2, 130.2, 130.0, 128.9, 128.6, 128.0, 127.9, 126.9, 39.7, 21.7, 16.3

HRMS calcd for $C_{28}H_{27}O_4S_2$ (M+H) 491.1351; found 491.1346.



5ab, (5-benzyl-4-methyl-1, 3-phenylenedisulfonyl)dibenzene

White solid, 108 mg, 75%

R_f = 0.6 (20% ethyl acetate in hexanes)

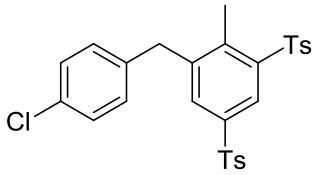
Melting point: 160-162 ˚C

IR (KBr) υ_{max}: 3086, 3059, 1583, 1496, 1446, 1315, 1147, 835, 567 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.89 (d, *J* = 2.0, 1H), 7.82 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.61 (t, *J* = 7.2, 2H), 7.65–7.48 (m, 4H), 7.28–7.17 (m, 3H), 6.94 (d, *J* = 6.8Hz, 2H), 4.00 (s, 2H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 142.7, 141.6, 140.9, 140.3, 140.0, 137.6, 133.8, 133.5, 129.6, 129.4, 129.0, 128.5, 127.9, 127.1, 126.9, 39.7, 16.4.

HRMS calcd for $C_{26}H_{23}O_4S_2$ (M+H) 463.1038; found 463.1049.



5ba, 4,4'-[5-(4-chlorobenzyl)-4-methyl-1,3-phenylenedisulfonyl]bis(methylbenzene)

White solid, 112 mg, 71%

R_f = 0.6 (20% ethyl acetate in hexanes)

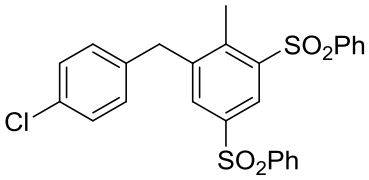
Melting point: 192-194 ˚C

IR (KBr) υ_{max}: 3066, 2920, 1595, 1492, 1435, 1404, 1303, 1143, 817, 711, 667 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz, 1H), 7.83 (d, *J* = 2.0, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4, 2H), 7.33–7.29 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4, 2H), 3.95 (s, 2H), 2.42 (s, 6H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (2), 143.1, 142.2, 142.1, 140.5, 137.8, 137.3, 136.3, 133.1, 132.7, 130.3, 130.0, 129.9, 129.0, 128.0, 127.9, 127.0, 39.0, 21.74, 16.3.

HRMS calcd for $C_{28}H_{26}ClO_4S_2$ (M+H) 525.0961; found 525.0978.



5bb, (5-(4-chlorobenzyl)-4-methyl-1, 3-phenylenedisulfonyl)dibenzene

White solid, 112 mg, 74%

R_f = 0.4 (20% ethyl acetate in hexanes)

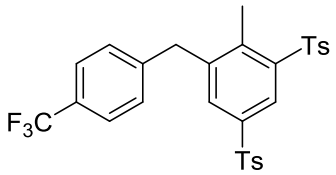
Melting point: 147-149 ˚C

IR (KBr) υ_{max}: 3082, 1581, 1489, 1442, 1315, 1149, 559 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.64–7.59 (m, 2H), 7.55(d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 8.4Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.97 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 142.5, 141.8, 140.7, 140.2, 136.1, 133.8, 133.4, 132.8, 129.9, 129.7, 129.4, 129.1, 127.9, 127.3, 39.0, 16.4.

HRMS calcd for $C_{26}H_{22}ClO_4S_2$ (M+H) 497.0648; found 497.0631.



5ca, 4,4'-{4-methyl-5-[4-(trifluromethyl)benzyl]-1,3-phenylenedisulfonyl} bis(methylbenzene)

White solid, 110 mg, 66%

R_f = 0.6 (20% ethyl acetate in hexanes)

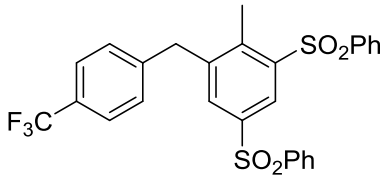
Melting point: 187-189 ˚C

IR (KBr) υ_{max}: 3082, 2925, 1593, 1419, 1323, 1149, 1112, 812, 709, 659 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 2.0, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4, 2H), 7.49 (d, *J* = 8.1, 2H), 7.33–7.28 (m, 4H), 7.05 (d, *J* = 8.1, 2H), 4.05 (s, 2H), 2.42 (s, 6H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 144.8, 142.4, 142.1 (2), 140.5, 137.6, 137.1, 133.1, 130.2, 129.9, 128.7, 127.9, 127.8, 127.1, 125.7(q, *J* = 3.8Hz), 39.3, 21.6 (2), 16.3

HRMS calcd for $C_{29}H_{26}F_3O_4S_2$ (M+H) 559.1225; found 559.1206.



5cb, {4-methyl-5-[4-(trifluromethyl)benzyl]-1,3-phenylenedisulfonyl}dibenzene

White solid, 110 mg, 69%

R_f = 0.5 (20% ethyl acetate in hexanes)

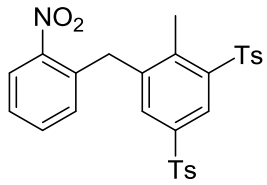
Melting point: 156-157 ˚C

IR (KBr) υ_{max}: 3066, 1583, 1448, 1325, 1298, 1142, 1112, 1070, 690, 549 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.63–7.54 (m, 2H), 7.53-7.49 (m, 6H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.07 (s, 2H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 142.4, 141.9, 141.7, 140.5, 140.2, 140.0, 133.8, 133.7, 133.4, 129.6, 129.3, 128.7, 127.8 (2), 127.3, 125.8 (q, *J* = 3.6 Hz), 39.3, 16.3

HRMS calcd for $C_{27}H_{22}F_3O_4S_2$ (M+H) 531.0912; found 531.0930.



5da, 4,4'-[4-methyl-5-(2-nitrobenzyl)-1,3-phenylenedisulfonyl]bis(methylbenzene)

White solid, 93 mg, 58%

R_f = 0.4 (20% ethyl acetate in hexanes)

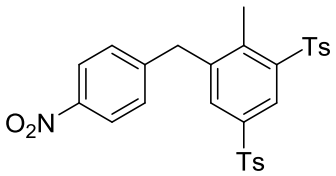
Melting point: 170-172 ˚C

IR (KBr) υ_{max}: 3059, 2922, 1593, 1523, 1435, 1348, 1315, 1143, 837, 659 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 1.6 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.73 (d, *J* = 8.4Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.53–7.40 (m, 2H), 7.32–7.28 (m ,4H), 6.92 (d, *J* = 7.6Hz, 1H), 4.28 (s, 2H), 2.41 (s, 6H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 144.9, 142.1(2), 141.8, 140.6, 137.7, 137.2, 133.8, 132.8, 132.3, 131.6, 130.2, 130.0, 128.5, 128.0, 127.9, 127.1, 125.5, 36.6, 21.8, 16.3.

HRMS calcd for $C_{28}H_{26}NO_6S_2$ (M+H) 536.1202; found 536.1243.



5ea, 4,4'-[4-methyl-5-(4-nitrobenzyl)-1,3-phenylenedisulfonyl]bis(methylbenzene)

White solid, 90 mg, 56%

R_f = 0.4 (20% ethyl acetate in hexanes)

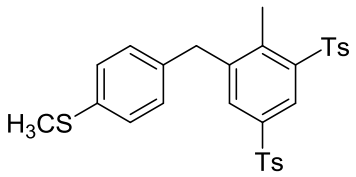
Melting point: 122-124 ˚C

IR (KBr) υ_{max}: 3072, 2924, 1597, 1519, 1492, 1438, 1348, 1309, 1145, 837, 812, 705, 661 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.6 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 1.6 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.33–7.29 (m, 4H), 7.10 (d, *J* = 8.5Hz, 2H), 4.10 (s, 2H), 2.42 (s, 6H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 145.5, 145.1(2), 142.4, 142.2, 141.8, 140.8, 137.6, 137.0, 133.2, 130.4, 130.1, 129.3, 128.0, 127.9, 127.4, 124.1, 39.5, 21.8, 16.4

HRMS calcd for $C_{28}H_{26}NO_6S_2$ (M+H) 536.1202; found 536.1225.



5fa, 4,4'-[4-methyl-5-(4-methylthiobenzyl)-1,3-phenylenedisulfonyl]bis(methylbenzene)

White solid, 126 mg, 78%

R_f = 0.5 (20% ethyl acetate in hexanes)

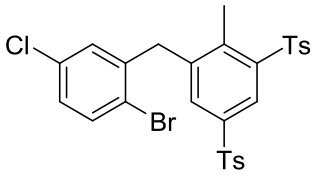
Melting point: 145-147 ˚C

IR (KBr) υ_{max}: 3062, 2924, 1593, 1492, 1436, 1319, 1147, 1085, 707, 671, 545 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.5 Hz, 1H), 7.86 (d, *J* = 1.5 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.32–7.28 (m, 4H), 7.12 (d, *J* = 8.2Hz, 2H), 6.85 (d, *J* = 8.2Hz, 2H), 3.94 (s, 2H), 2.45 (s, 3H), 2.42 (s, 6H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 143.4, 142.1, 141.8, 140.2, 137.7, 137.2, 136.8, 134.4, 133.0, 130.1, 129.9, 129.8, 128.9, 127.8, 126.9, 39.0, 21.6, 16.2, 15.8

HRMS calcd for $C_{29}H_{29}O_4S_3$ (M+H) 537.1228; found 537.1247.



5ga, 4,4'-[5-(2-bromo-5-chlorobenzyl)-4-methyl-1,3-phenylenedisulfonyl] bis(methylbenzene)

White solid, 121 mg, 67%

R_f = 0.5 (20% ethyl acetate in hexanes)

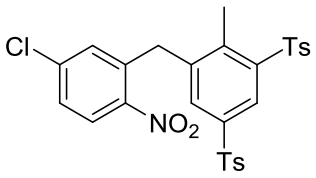
Melting point: 189-191 ˚C

IR (KBr) υ_{max}: 3062, 2924, 1593, 1448, 1317, 1143, 1087,812, 711, 549 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 1.8 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3Hz, 2H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.50(d, *J* = 8.5, 1H), 7.31 (d, *J* = 8.4 Hz, 4H), 7.11 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 4.00 (s, 2H), 2.42 (s, 6H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.2, 142.0, 141.5, 140.6, 139.0, 137.7, 137.2, 134.3, 134.2, 134.0, 132.7, 130.3(2), 130.1, 130.0, 129.0, 127.9, 127.1, 122.7, 39.7, 21.8, 21.73, 16.3.

HRMS calcd for $C_{28}H_{25}BrClO_4S_2$ (M+H) 603.0066; found 603.0076.



5ha, 4,4'-[5-(5-chloro-2-nitrobenzyl)-4-methyl-1,3-phenylenedisulfonyl] bis(methylbenzene)

White solid, 106 mg, 62%

R_f = 0.5 (20% ethyl acetate in hexanes)

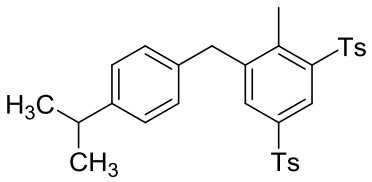
Melting point: 182-184 ˚C

IR (KBr) υ_{max}: 3067, 2927, 1525, 1440, 1313, 1296, 1145,813, 549 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.6 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 1.6, 1H), 7.42 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.32 (d, *J* = 8.0, 4H), 6.81 (d, *J* = 2.0, 1H), 4.28 (s, 2H), 2.42 (s, 6H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 145.0(2), 142.3, 142.0, 140.8(2), 140.3, 137.6, 137.2, 135.0, 132.3, 131.4, 130.3, 130.1, 128.7, 128.0, 127.9, 127.4, 127.0, 36.5, 21.7, 16.3.

HRMS calcd for $C_{28}H_{25}ClNO_6S_2$ (M+H) 570.0812; found 570.0832.



5ia, 4,4'-[5-(4-isopropylbenzyl)-4-methyl-1,3-phenylenedisulfonyl]bis(methylbenzene)

White solid, 120 mg, 75%

R_f = 0.7 (20% ethyl acetate in hexanes)

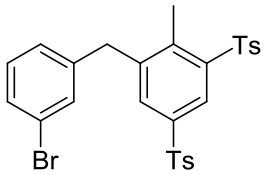
Melting point: 167-168 ˚C

IR (KBr) υ_{max}: 3078, 2964, 1593, 1425, 1319, 1139, 1083, 808, 705, 671, 565 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.8 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2Hz, 2H), 7.32-7.28 (m, 4H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.95 (s, 2H), 2.89-2.80 (m, 1H), 2.42 (s, 6H), 2.35 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 144.8(2), 144.0, 142.3, 141.8, 140.2, 138.0, 137.4, 135.0, 133.2, 130.2, 130.0, 128.4, 128.0, 127.9, 126.9, 126.8, 39.2, 33.7, 24.0, 21.74, 21.72, 16.4

HRMS calcd for $C_{31}H_{33}O_4S_2$ (M+H) 533.1820; found 533.1829.



5ja, 4,4'-[5-(3-bromobenzyl)-4-methyl-1,3-phenylenedisulfonyl]bis(methylbenzene)

White solid, 125 mg, 73%

R_f = 0.6 (20% ethyl acetate in hexanes)

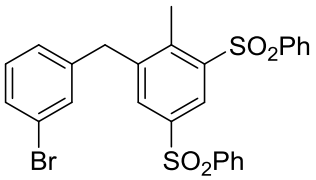
Melting point: 204-206 ˚C

IR (KBr) υ_{max}: 3072, 2924, 1591, 1566, 1446, 1294, 1141, 840, 812, 709, 661, 545 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 1.6Hz, 1H), 7.79 (d, *J* = 8.3Hz, 2H), 7.70 (d, *J* = 8.3Hz, 2H), 7.35-7.29 (m, 5H), 7.14–7.10 (m, 1H), 7.05 (s, 1H), 6.87 (d, *J* = 7.7Hz, 1H), 3.96 (s, 2H), 2.42 (s, 6H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 144.7, 142.6, 142.1, 141.9, 140.4, 139.9, 137.6, 137.1, 133.0, 131.4, 130.3, 130.2, 129.9, 127.8, 127.8, 127.1, 126.9, 122.8, 39.2, 21.6 (2), 16.2

HRMS calcd for $C_{28}H_{26}BrO_4S_2$ (M+H) 569.0456; found 569.0444.



5jb, [5-(3-bromobenzyl)-4-methyl-1,3-phenylenedisulfonyl]dibenzene

White solid, 124 mg, 76%

R_f = 0.5 (20% ethyl acetate in hexanes)

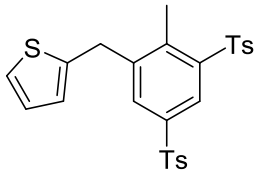
Melting point: 156-157 ˚C

IR (KBr) υ_{max}: 3064, 1568, 1446, 1309, 1143, 1978, 684, 567 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 2H), 7.87 (d, J = 1.6 Hz, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.62–7.60 (m, 2H), 7.56-7.50 (m, 4H), 7.34 (d, J = 7.4 Hz, 1H), 7.14-7.01 (m, 1H), 7.07 (s, 1H), 6.86 (d, J = 7.4 Hz, 1H), 3.97 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.6, 141.8, 140.7, 140.2, 139.9, 133.9, 133.8, 133.5, 131.5, 130.5, 130.2, 129.7, 129.5, 127.9, 127.3, 127.2, 123.0, 39.2, 16.4.

HRMS calcd for $C_{26}H_{22}BrO_4S_2$ (M+H) 541.0143; found 541.0122.



5ka, 2-(2-methyl-3,5ditosylbenzyl)thiophene

White solid, 107 mg, 72%

R_f = 0.6 (20% ethyl acetate in hexanes)

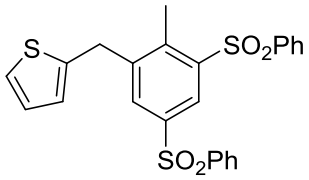
Melting point: 199-201 ˚C

IR (KBr) υ_{max}: 2924, 1591, 1498, 1436, 1315, 1294, 1143, 1083,812, 542 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 4H), 7.14 (d, J = 5.1 Hz, 1H), 6.88 (dd, J = 5.1, 3.5 Hz, 1H), 6.58 (d, J = 3.5 Hz, 1H), 4.14 (s, 2H), 2.41 (s, 6H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 143.2, 142.0, 141.9, 140.5, 140.4, 137.9, 137.3, 132.8, 130.2, 130.0, 128.0, 127.9, 127.2, 125.9, 124.8, 124.7, 34.0, 21.8, 16.2.

HRMS calcd for $C_{26}H_{25}O_4S_3$ (M+H) 497.0915; found 497.0933.



5kb, 2-[2-methyl-3,5bis(phenylsulfonyl)benzyl]thiophene

White solid, 104 mg, 74%

R_f = 0.5 (20% ethyl acetate in hexanes)

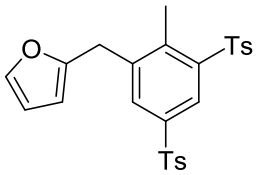
Melting point: 187-189 ˚C

IR (KBr) υ_{max}: 3082, 2362, 1581, 1444, 1311, 1147, 1089, 725, 686, 570 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.83 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62–7.60 (m, 2H), 7.56 – 7.52 (m, 4H), 7.14 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.2, 3.6Hz, 1H), 6.59 (dd, *J* = 3.6, 1.2Hz, 1H), 4.16 (s, 2H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.3, 141.7, 140.8, 140.3, 140.2(2), 133.8, 133.1, 129.7, 126.4, 127.9, 127.4, 127.2, 126.0, 124.8, 34.0, 16.2.

HRMS calcd for $C_{24}H_{21}O_4S_3$ (M+H) 469.0602; found 469.0590.



5la, 2-(2-methyl-3,5-ditosylbenzyl)furan

White solid, 100 mg, 70%

R_f = 0.5 (20% ethyl acetate in hexanes)

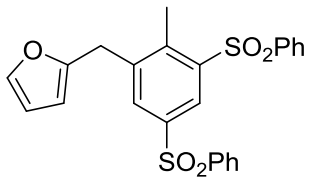
Melting point: 203-204 ˚C

IR (KBr) υ_{max}: 2926, 1593, 1498, 1440, 1315, 1294, 1143, 1083,810, 707, 553 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 1.9 Hz, 1H), 7.90 (d, *J* = 1.9 Hz, 1H), 7.81 (d, *J* = 8.3Hz, 2H), 7.71 (d, *J* = 8.3Hz, 2H), 7.32–7.30 (m, 4H), 7.28 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.25 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.87 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.95 (s, 2H), 2.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 144.8, 142.1, 142.0, 141.8, 141.2, 140.4, 137.9, 137.3, 133.0, 130.3, 130.0, 128.0, 127.9, 127.2, 110.6, 110.5, 107.5, 107.4, 32.5, 21.7, 16.1.

HRMS calcd for $C_{26}H_{25}O_5S_2$ (M+H) 481.1143; found 481.1166.



5lb, 2-[2-methyl-3,5bis(phenylsulfonyl)benzyl]furan

White solid, 97 mg, 71%

R_f = 0.5 (20% ethyl acetate in hexanes)

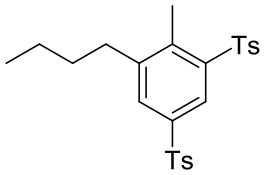
Melting point: 175-177 ˚C

IR (KBr) υ_{max}: 2922, 2855, 2306, 1585, 1444,1307, 1145, 725, 535 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.0 Hz, 1H), 7.97–7.88 (m, 3H), 7.83 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.64–7.56 (m, 2H), 7.56–7.48 (m, 4H), 7.28 (dd, *J* = 2.0, 0.8Hz, 1H), 6.26 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.88 (dd, *J* = 3.2, 0.8 Hz, 1H), 3.96 (s, 2H), 2.42 (s, 3H).).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 141.6, 141.4, 140.3, 140.1, 133.8, 133.3, 129.6, 129.4, 127.9, 110.6(2), 107.5(2), 32.5, 16.2.

HRMS calcd for $C_{24}H_{21}O_5S_2$ (M+H) 453.0830; found 453.0840.



5ma, 4, 4'-(5-butyl-4-methyl-1,3-phenylenedisulfonyl)bis(methylbenzene)

White solid, 99 mg, 72%

R_f = 0.7 (20% ethyl acetate in hexanes)

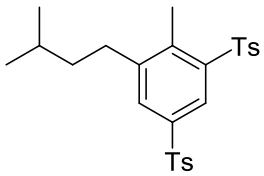
Melting point: 146-148 ˚C

IR (KBr) υ_{max}: 3068, 2953, 2924, 2864, 1593, 1442, 1309, 1296, 1145, 1085, 813, 565, 549 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 2.0Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.32-7.25 (m, 4H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 6H), 2.38 (s, 3H), 1.48-1.44 (m, 2H), 1.35-1.29 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 144.8, 144.7, 141.5, 141.4, 140.0, 138.1, 137.5, 132.2, 130.2, 130.0, 128.0, 127.9, 126.3, 33.5, 31.9, 22.6, 21.7, 15.8, 13.9.

HRMS calcd for $C_{25}H_{29}O_4S_2$ (M+H) 457.1507; found 457.1499.



5na, 4, 4'-(5-isopentyl-4-methyl-1,3-phenylenedisulfonyl)bis(methylbenzene)

White solid, 103 mg, 73%

R_f = 0.7 (20% ethyl acetate in hexanes)

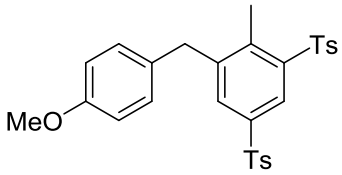
Melting point: 165-167 ˚C

IR (KBr) υ_{max}: 3072, 2958, 2908, 1593, 1442, 1313, 1296, 1145, 1083, 812, 549 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.0 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.33–7.26 (m, 4H), 2.60 (t, *J* = 8Hz, 2H), 2.42 (s, 6H),2.39 (s, 3H), 1.59–1.56 (m, 1H), 1.38-1.32 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 144.7(2), 141.5, 141.3, 140.1, 138.1, 137.5, 132.1, 130.2, 130.0, 128.0, 127.9, 126.3, 39.0, 31.7, 28.3, 22.4, 21.7, 15.7.

HRMS calcd for $C_{26}H_{31}O_4S_2$ (M+H) 471.1664; found 471.1657.



5oa, 4,4'-(5-(4-methoxybenzyl)-4-methyl-1,3-phenylenedisulfonyl)bis(methylbenzene)

White solid, 128 mg, 82%

R_f = 0.5 (20% ethyl acetate in hexanes)

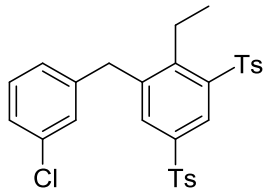
Melting point: 167-169 ˚C

IR (KBr) υ**max**: 2926, 1591, 1510, 1444, 1315, 1246, 1150, 567, 545 cm-1

1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.8 Hz, 1H), 7.84 (d, *J* = 1.8Hz, 1H), 7.78 (d, *J* = 8.2Hz, 2H), 7.69 (d, *J* = 8.2Hz, 2H), 7.29(dd, *J* = 7.9, 5.9Hz, 4H), 6.85 (d, *J* = 8.5Hz, 2H), 6.77 (d, *J* = 8.5Hz, 2H), 3.91 (s, 2H), 3.76 (s, 3H), 2.40(s, 6H), 2.34 (s, 3H).

13C NMR (100 MHz, $CDCl_3$) δ 158.4, 144.8, 144.7, 144.2, 142.2, 141.8, 140.2, 137.9, 137.4, 133.0, 130.2, 129.9.8, 129.6, 128.0, 127.9, 126.7, 114.3, 55.3, 38.8, 21.7, 16.2

HRMS calcd for $C_{29}H_{28}O_5S_2$ (M+H) 521.1457; found 521.1479.



5pa, 4,4'-(5-(3-chlorobenzyl)-4-ethyl-1,3-phenylenedisulfonyl)bis(methylbenzene)

White solid, 102 mg, 63 %

R_f = 0.6 (20% ethyl acetate in hexanes)

Melting point: 146-148 ˚C

IR (KBr) υ**max**: 2976, 1591, 1475, 1429, 1317, 1294, 1147, 669, 559 cm-1

1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.6 Hz, 1H), 7.74–7.69 (m, 5H), 7.31 (dd, *J* = 8.4, 2.0Hz, 4H), 7.20-7.18 (m, 2H), 6.89(s, 1H), 6.84 (dd, *J* = 8.4, 1.6Hz, 1H), 3.99 (s, 2H), 2.89 (q, *J* = 7.4Hz 2H), 2.41(s, 6H), 0.88 (t, *J* = 7.4Hz, 3H).

13C NMR (100 MHz, $CDCl_3$) δ 147.7, 144.9, 144.8, 142.7, 141.9, 140.5, 140.4, 137.9, 137.7, 134.8, 133.7, 130.3, 130.2, 130.1, 128.7, 128.0, 127.9, 127.3, 127.2, 126.9, 37.6, 22.9, 21.7, 14.1.

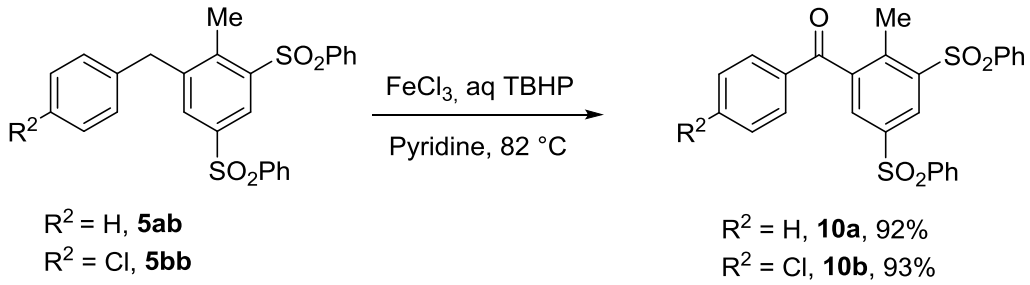
HRMS calcd for $C_{29}H_{27}ClO_4S_2$ (M+H) 539.1118; found 539.1121.

Procedure for gram scale benzannulation reaction

DBU (0.88ml, 5.88 mmol) was added to a solution of MBH bromide **4j** (1g, 3.92 mmol) and 1,3-bissulfonylpropene **3a-b** (1.51g, 4.31 mmol) in DMF (15 mL). The reaction mixture was stirred at 25 ˚C for 1h. After completion of the reaction, 50 mL deionized water was added and the solution was extracted with ethylacetate (3×30 mL). The combined organic layers were washed with brine, dried over sodium sulfate and the solvent was evaporated off on a rotavpor under reduced pressure. The residue was subjected to column charomatography on silica gel using petroleum ether-ethyl acetate

as eluent to afford analytically pure sample of the product. A white solid (1.58g, 71%) which was identical to the product **5ja** obtained in the low-scale reaction.

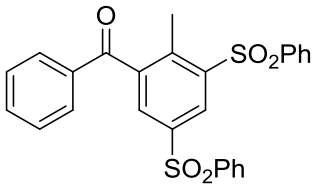
General procedure for $FeCl_3$-TBHP mediated benzylic oxidation



R^2 = H, **5ab**
R^2 = Cl, **5bb**

R^2 = H, **10a**, 92%
R^2 = Cl, **10b**, 93%

To a solution of $FeCl_3.6H_2O$ (2.2 mg, 0.008 mmol) in pyridine (0.5 mL), the bis-sulfonyl arene **5ab** or **5bb** (0.22 mmol) was added. To this, tert-butyl hydroperoxide (0.05 mL, 0.33 mmol) was added and the reation mixture heated at 82 ˚C for 24 h. Then the reaction mixture was poured into a separating funnel containing 10 mL 1N HCl. The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with anhydrous sodium sulphate, filtered and the solvent was evaporated off on a rotavapor under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether-ethyl acetate as eluent to afford the benzphenones **10a-b** in analytically pure form.



10a, [2-methyl-3,5-bis(phenylsulfonyl)phenyl](phenyl)methanone

White solid, 96 mg, 92%

R_f = 0.5 (20% ethyl acetate in hexanes)

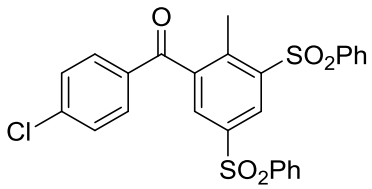
Melting point: 168-170 ˚C

IR (KBr) υ_{max}: 3066, 1664, 1583, 1442, 1296, 1145, 1078, 727, 684, 559 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 1.9 Hz, 1H), 8.03 (d, *J* = 1.9 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.67–7.63 (m, 5H), 7.58– 7.53 (m, 4H), 7.46 (t, *J* = 8.0 Hz, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 143.4, 142.3, 141.6, 140.5, 140.3, 139.6, 135.7, 134.8, 134.1, 130.8, 130.2, 129.8, 129.6, 129.1, 128.1, 128.0, 17.4.

HRMS calcd for $C_{26}H_{21}O_5S_2$ (M+H) 477.0830; found 477.0852.



10b, (4-chlorophenyl)[2-methyl-3,5-bis(phenylsulfonyl)phenyl]methanone

White solid, 102 mg, 91%

R_f = 0.6 (20% ethyl acetate in hexanes)

Melting point: 153-155 ˚C

IR (KBr) υ_{max}: 3068, 2974, 1672, 1585, 1444, 1317, 1143, 1085, 723, 688, 559 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 1.9 Hz, 1H), 8.00 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.85 (d, *J* = 7.6, 2H), 7.67–7.53(m, 8H), 7.43 (d, *J* = 8.5, 2H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 142.8, 142.5, 141.6, 141.5, 140.7, 140.3, 139.6, 134.2, 134.1, 131.5, 130.7, 129.8, 129.6, 128.2, 128.0, 17.4.

HRMS calcd for $C_{26}H_{20}ClO_5S_2$ (M+H) 511.0441; found 511.0461.

2.11. References

1. Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775.

2. (a) Snieckus, V. *Beilstein J. Org. Chem.* **2011**, *7*, 1215 and references cited therein. (b) Bunnett, J.F. *Acc. Chem. Res*. **1978**, *11*, 413. (c) Smith, M. B.; March, J. Aromatic Substitution, Nucleophilic and Organometallic. *March's Advanced Organic Chemistry, 6th ed*.; John Wiley & Sons: Hoboken, NJ, **2007**; pp 853.

3. Calloway, N.O. *Chemical Reviews* **1935,** *17*, 327. (b) Olah, G. A. Friedel –Craftes chemistry; Wiley & Sons: New York, **1973**. (c) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.***2010**, *6*, No. 6.

4. (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508. (c) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.: Heydari, M.; Malmir, M. *J. Organomet. Chem*. **2018**, *861*, 17.

5. Snieckus, V. *Chem. Rev*. **1990**, *90*, 879. (b) Kuhl, N.; Hopkinson, M.N.; Delord, J. W.; Glorius, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 2. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147.

6. (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl*. **1975**, *14*, 644. (b) Waters, M. L.; Wulff, W. D. *Org. React.* **2008**, *70*, 121.

7. (a) Danheiser R. L.; Gee, S.K. *J. Org. Chem*. **1984**, *49*, 1672. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc*. **1990**, *112*, 3093.

8. (a) Katritzky, A. R.; Lie, Xie, L. *Tetrahedron*, **1999**, *55*, 8263. (b) Feng, J.; Liu, B. *Tetrahedron Lett*. **2015**, *56*, 1474. (c) Diallo, A.; Zhao, Y. L.; Wang, H.; Li, S. S.; Ren, C. Q.; Liu, Q. *Org. Lett*. **2012**, *14*, 5776. (d) Li, L.; Zhao, Y. L.; Wang, H.; Li, Y. J.; Xu, X.; Liu, Q. *Chem. Commun.* **2014**, *50*, 6458. (e) Gopi, E.; Namboothiri, I. *J. Org. Chem*. **2014**, *79*, 7468. (f) Satham, L.; Namboothiri, I. *J. Org. Chem*. **2018**, *83*, 9471. (g) Xie, P.; Huang, Y.; Chen, R. *Chem. Eur. J*. **2012,** *18*, 7362.

9. Li, H.; Chen, Q.; Lu, Z.; Li, A. *J. Am. Chem. Soc*. **2016**, *138*, 15555. (b) Yang, P.; Yao, M.; Li, J.; Li, Y.; Li, A. *Angew. Chem. Int. Ed*. **2016**, *55*, 6964. (c) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852. (d) Finkbeiner, P.; Murai, K.; Röpke, M.; Sarpong, R. *J. Am. Chem. Soc.* **2017**, *139*, 11349.

10. (a) Alba, A.-R.; Companyó, X.; Rios, R. *Chem. Soc. Rev*. **2010**, *39*, 2018. (b) Nenajdenko, V. G.; Krasovskiy, A. L.; Balenkova E. S. *Tetrahedron* **2007**, *63*, 12481.

11. (a) Dinsmore, C. J.; Williams, T. M.; O'Neill, T. J.; Liu, D.; Rands, E.; Culberson, J. C.; Lobell, R. B.; Koblan, K. S.; Kohl, N. E.; Gibbs, J. B. *Bioorg. Med. Chem. Lett*. **1999**, 9, 3301. (b) Neamati, N.; Mazumder, A.; Zhao, H.; Sunder, S.; Burke, T. R., Jr.; Schultz, R. J.; Pommier, Y. *Antimicrob. Agents Chemother*. **1997**, 41, 385. (c) Harguindey, S.; Arranz, J. L.; Orozco, J. D. P.; Rauch, C.; Fais, S.; Cardone, R. A.; Reshkin, S. J. *J. Transl. Med*. **2013**, 11, 282.

12. Ezzi, M. L.; Lenk, R.; Madec, D.; Sotiropoulos, J.-M.; Mallet- Ladeira, S.; Castel, A. *Angew. Chem., Int. Ed*. **2015**, *127*, 819.

13. Zhu, Y. I.; Stiller, M. J. *J. Am. Acad. Dermatol*. 2001, *45*, 420.

14. Fowler, J. S.; Logan, J.; Azzaro, A. J.; Fielding, R. M.; Zhu, W.; Poshusta, A. K.; Burch, D.; Brand, B.; Free, J.; Asgharnejad M.; , Wang, G. J.; Telang, F.; Hubbard, B.; Jayne, M.; King, P.; Carter, P.; Carter, S.; Xu, Y.; Colleen Shea, C.; Muench, L.; Alexoff, D.; Shumay, E.; Schueller, M.; Donald Warner, D.; Apelskog-Torres, K. *Neuropsychopharmacology* **2010**, *35*, 623

15. Madhava, G.; Ramana, K. V.; Sudhana, S. M.; Rao, D. S.; Kumar, K. H.; Lokanatha, V.; Rani, A. U.; Raju, C. N. *Medicinal Chemistry* **2017**, *13*, 484.

16. Ward, R. S.; Diaper, R. L. *Sulfur Rep*. **2001**, *22*, 251.

17. Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Synlett* **2001**, 830.

18. (a) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608.

19. (a) Joshi, P.R.; Undeela, S.; Reddy, D.D.; Singarapu. K.K.; Menon.. R. S. *Org. Lett*. **2015**, *17*, 1449. (b) Fu, R.; Hao, W. J.; Wu, Y. N.; Wang, N. N.; Tu, S. J.; Li, G.; Jiang, B. *Org. Chem. Front.* **2016**, *3*, 1452.

20. Lim, J. W.; Kim, S, H.; Yu, J.; Kim, N. J. *Bull. Korean Chem. Soc*. **2013**, *34*, 3503.

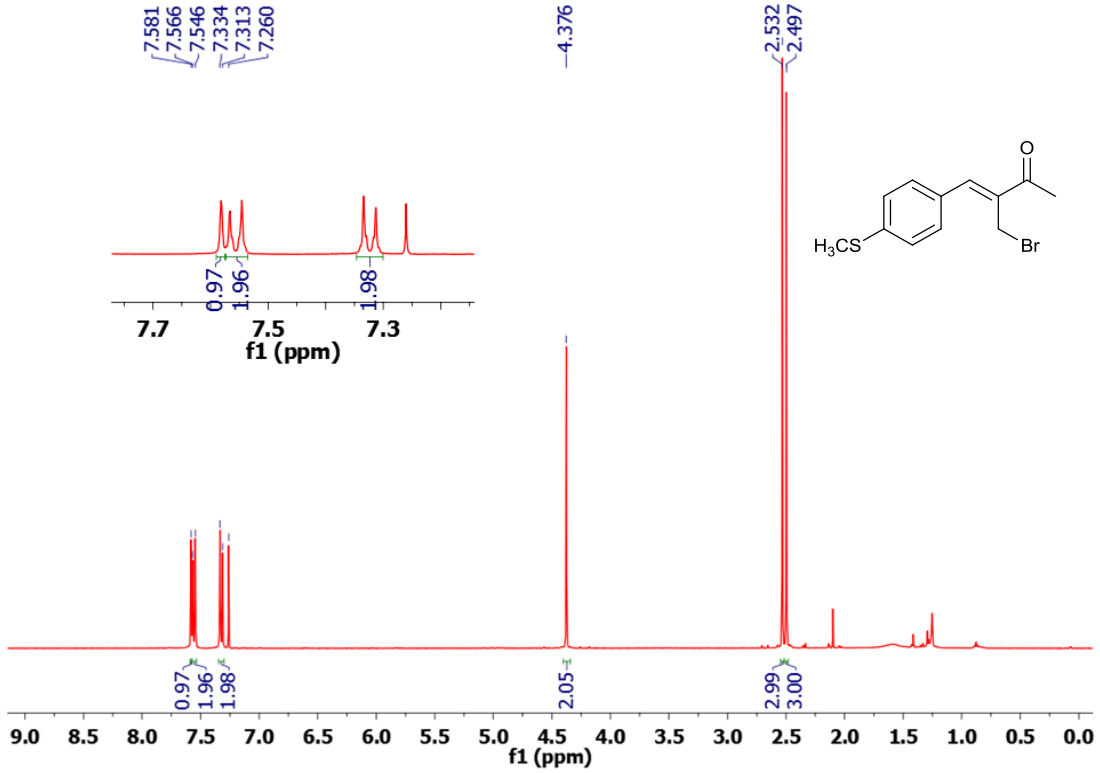
21. Tang, X. Z.; Tong, L.; Liang, H.; Liang, J.; Zou, Y.; Zhang, X.; Yan, M.; Chan, A. S. C. *Org. Biomol. Chem*. **2018**, *16*, 3560.

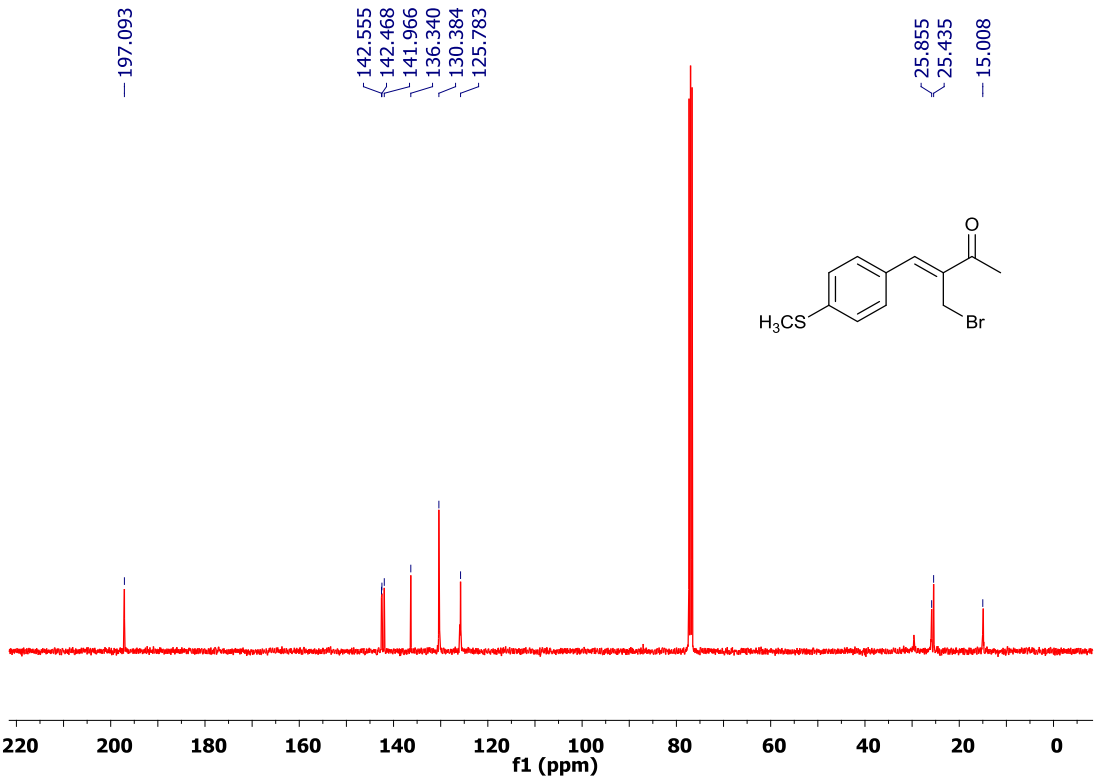
22. (a) Buchholz, R.; Hoffman, H. M. R. *Helc. Chim. Acta*. **1991**, 74, 1213. (b). Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishna macharyulu, M. *Tetrahedron* **1999**, *55*, 6971.

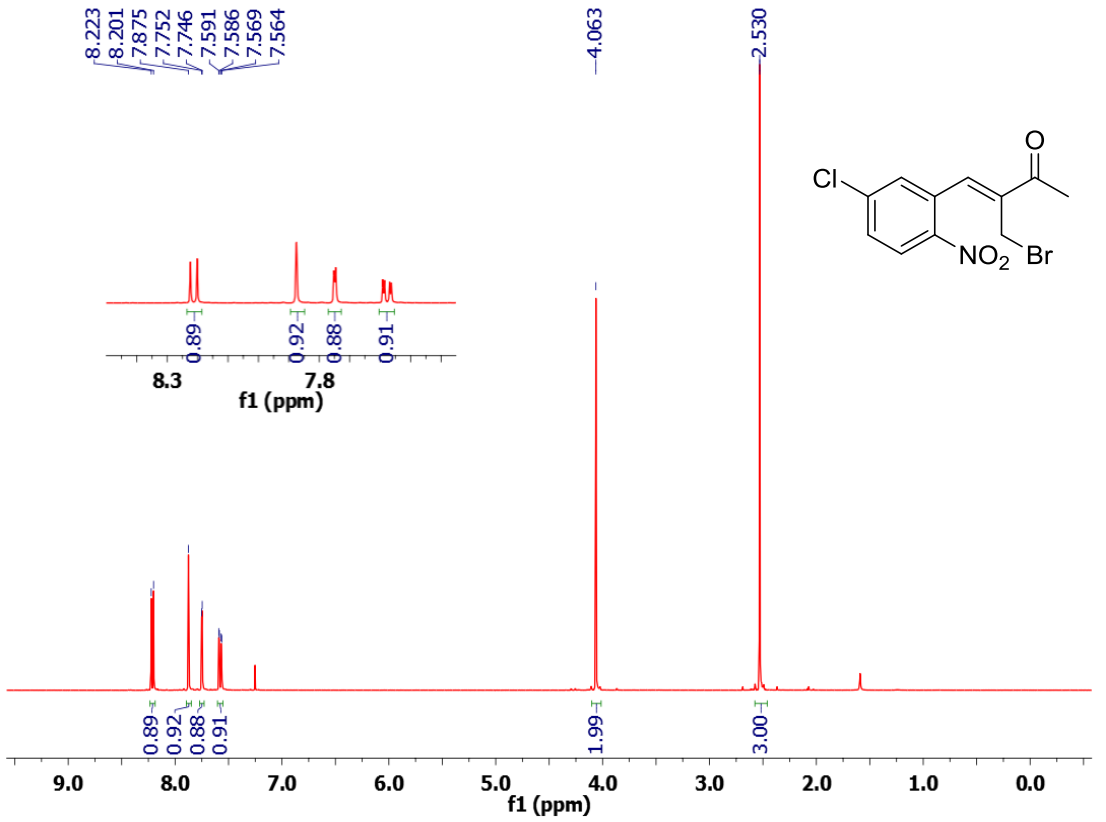
23. Gallagher, E. T.; Grayson, D. H. *Org. Biomol. Chem*. **2003**, *1*, 1374. (b) (b) Padwa, A.; Gareau, Y.; Harrison, B.; Brian, N.; Bryan, H. *J. Org. Chem*. **1991**, *56*, 2713

24. Nakanishi, M.; Bolm, C. *Adv. Synth. Catal*. **2007**, *349*, 861-864.

2.12. NMR spectra of new compounds [^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)]



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O
NO2
Br
0.89
0.92
0.88
0.91
8.3
7.8
f1 (ppm)
1.99
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
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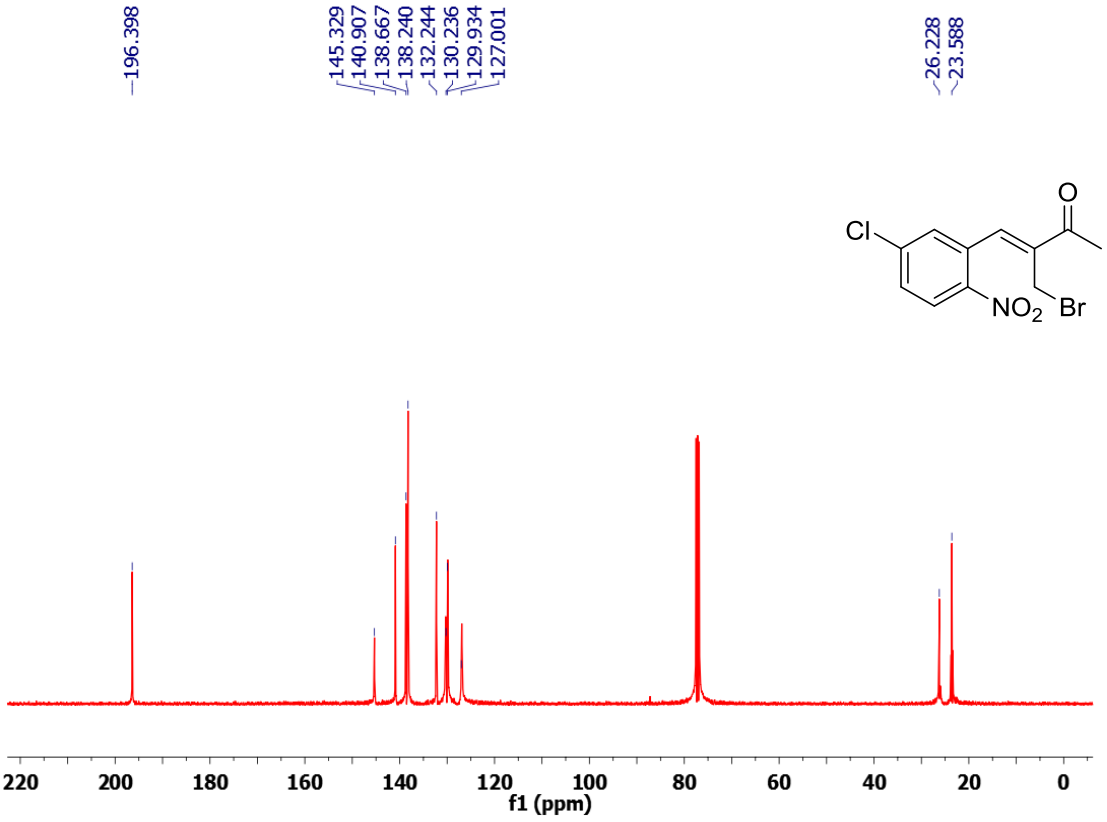
0.0
f1 (ppm)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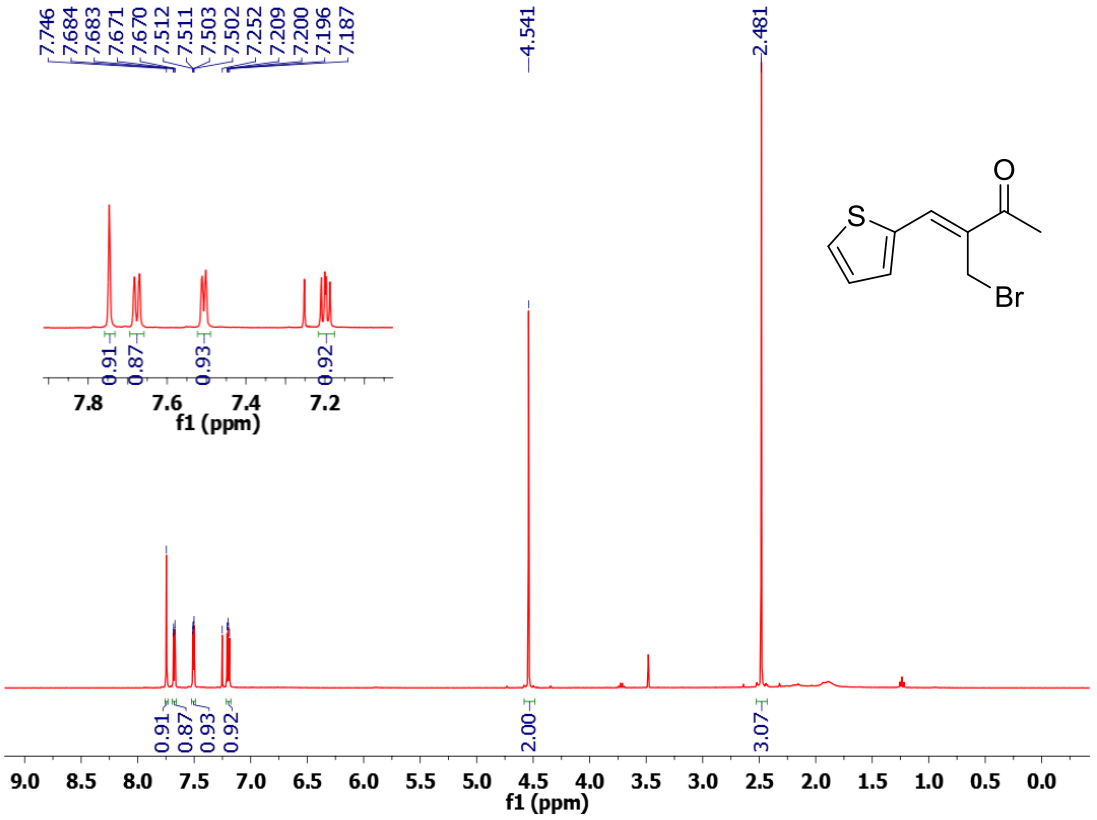
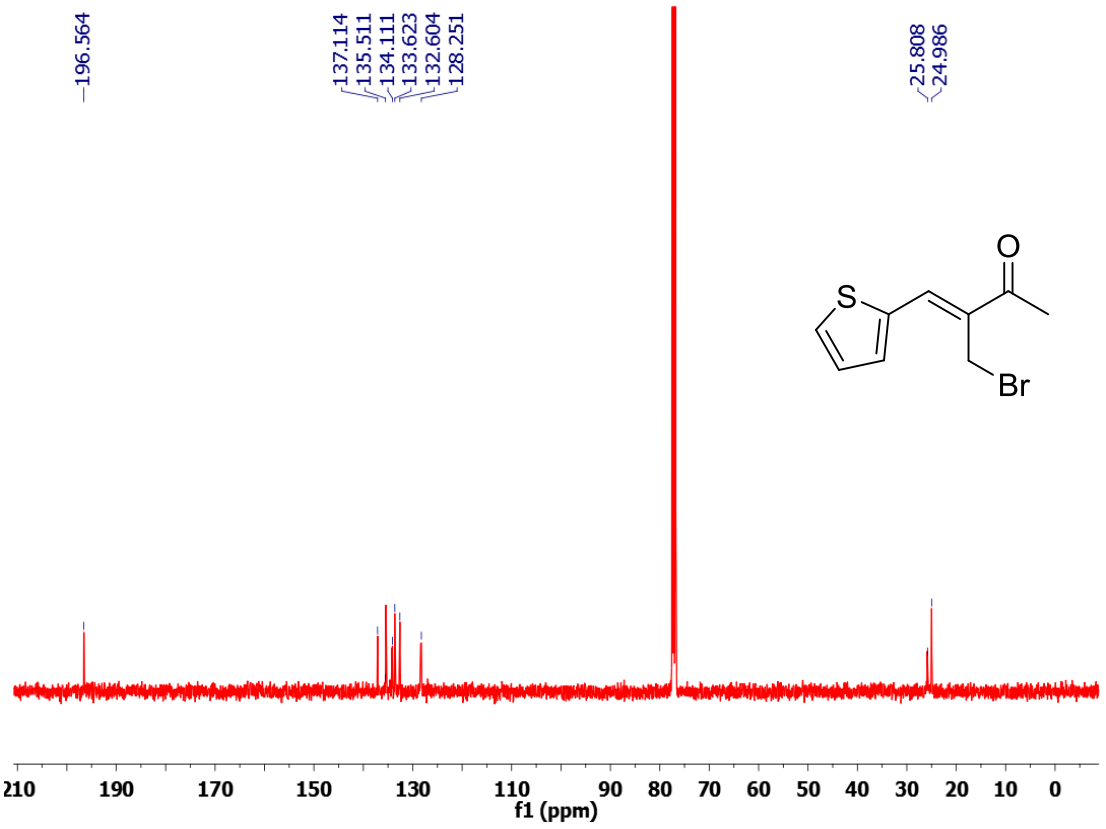
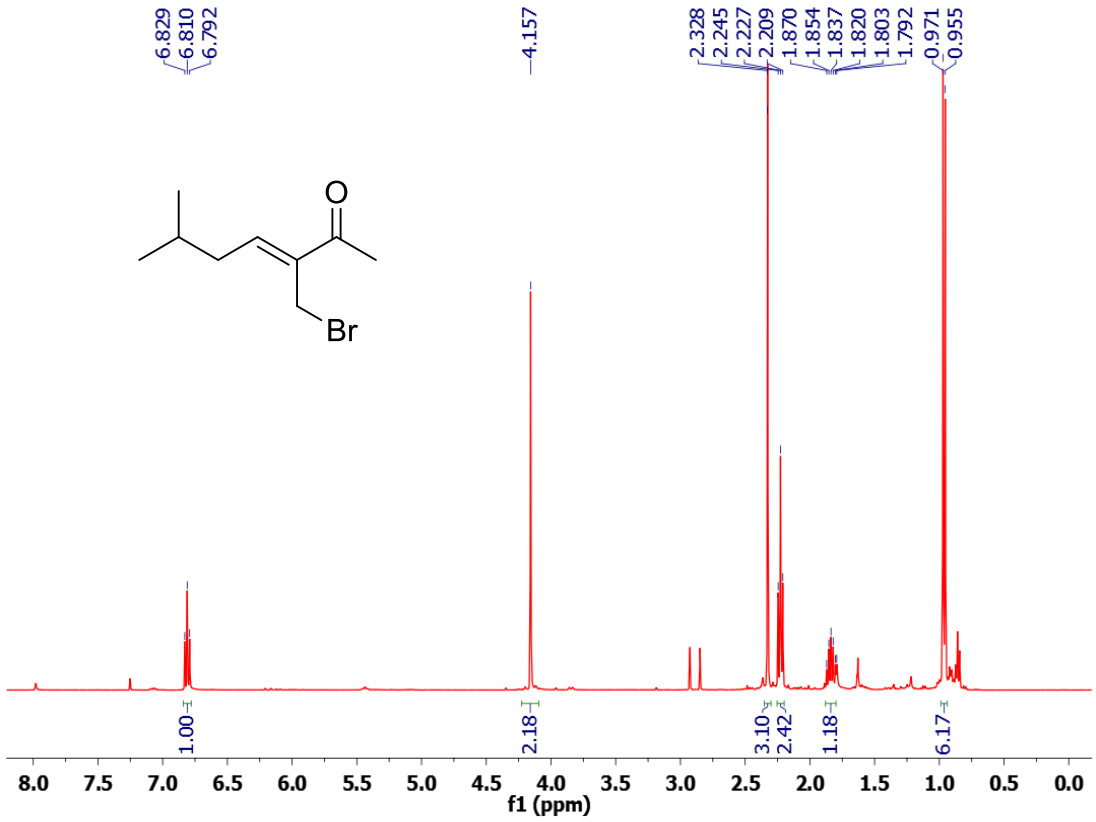
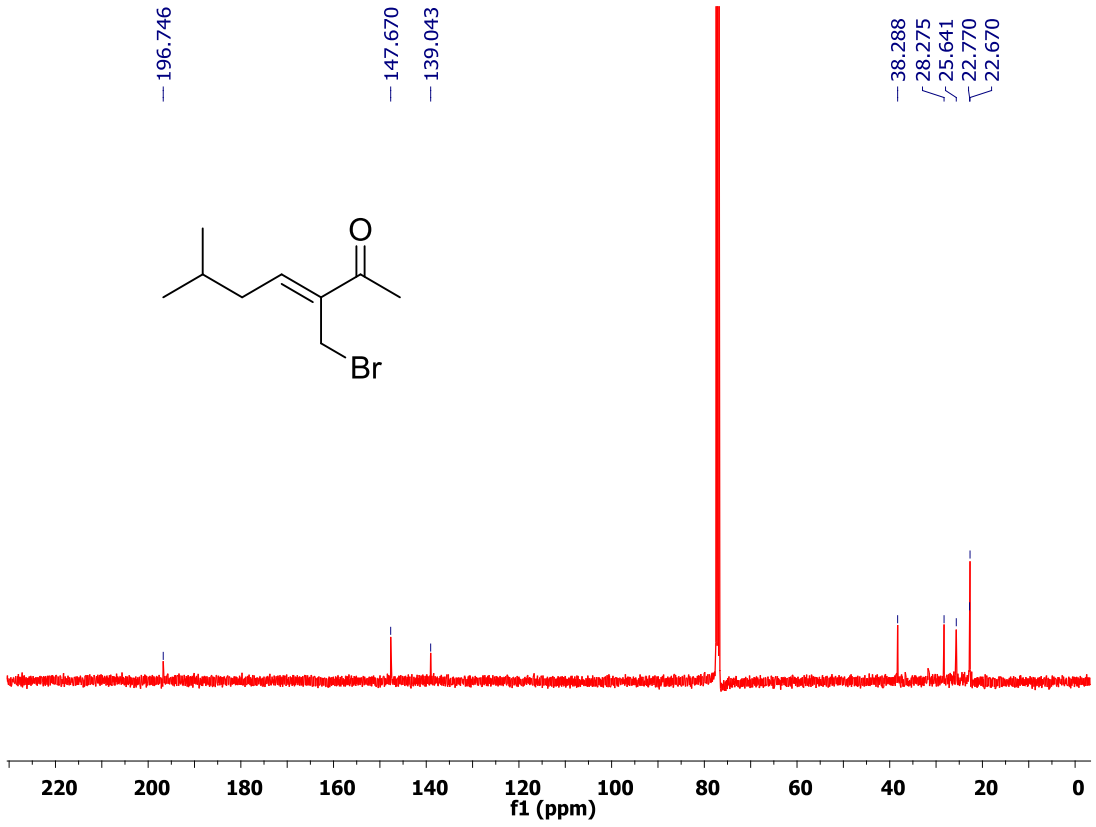
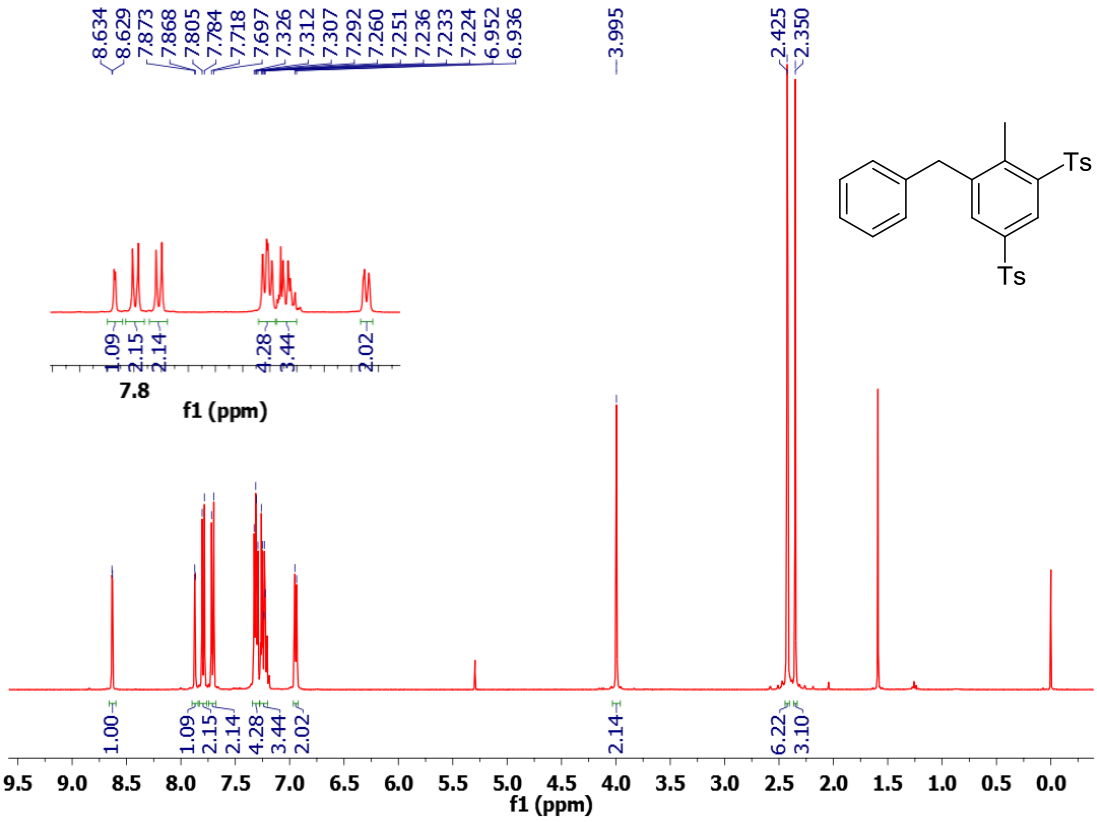
NO2
Br
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

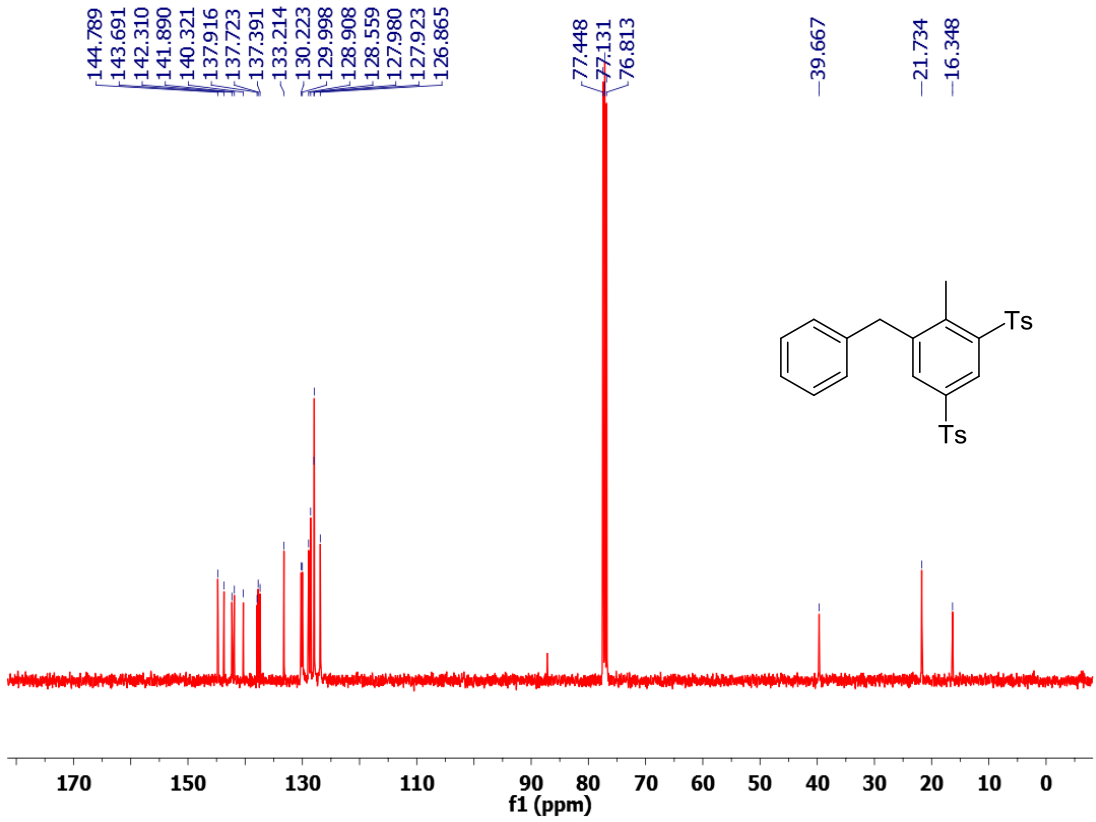

7.746
7.684
7.683
7.671
7.670
7.512
7.511
7.503
7.502
7.252
7.209
7.200
7.196
7.187
4.541
2.481
O
S
Br
0.91
0.87
0.93
0.92
7.8
7.6
7.4
7.2
f1 (ppm)
0.91
0.87
0.93
0.92
2.00
3.07
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

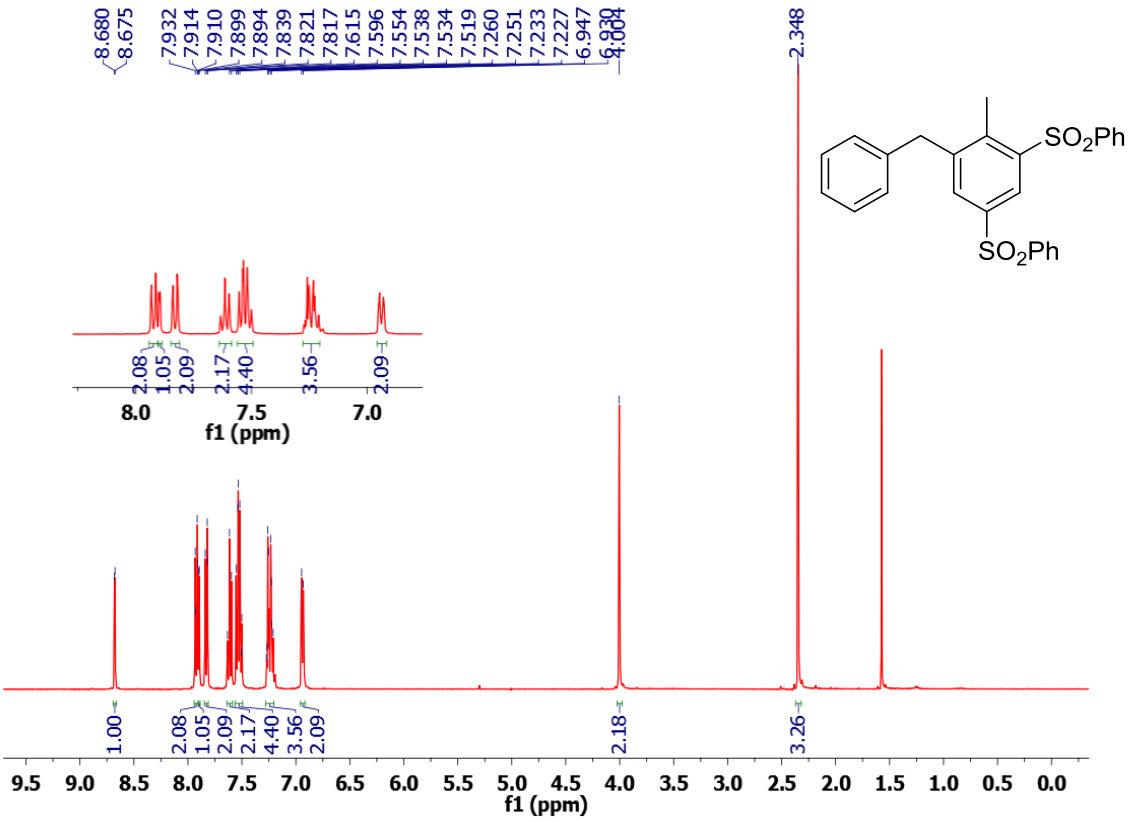

196.564
137.114
135.511
134.111
133.623
132.604
128.251
25.808
24.986
O
S
Br
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

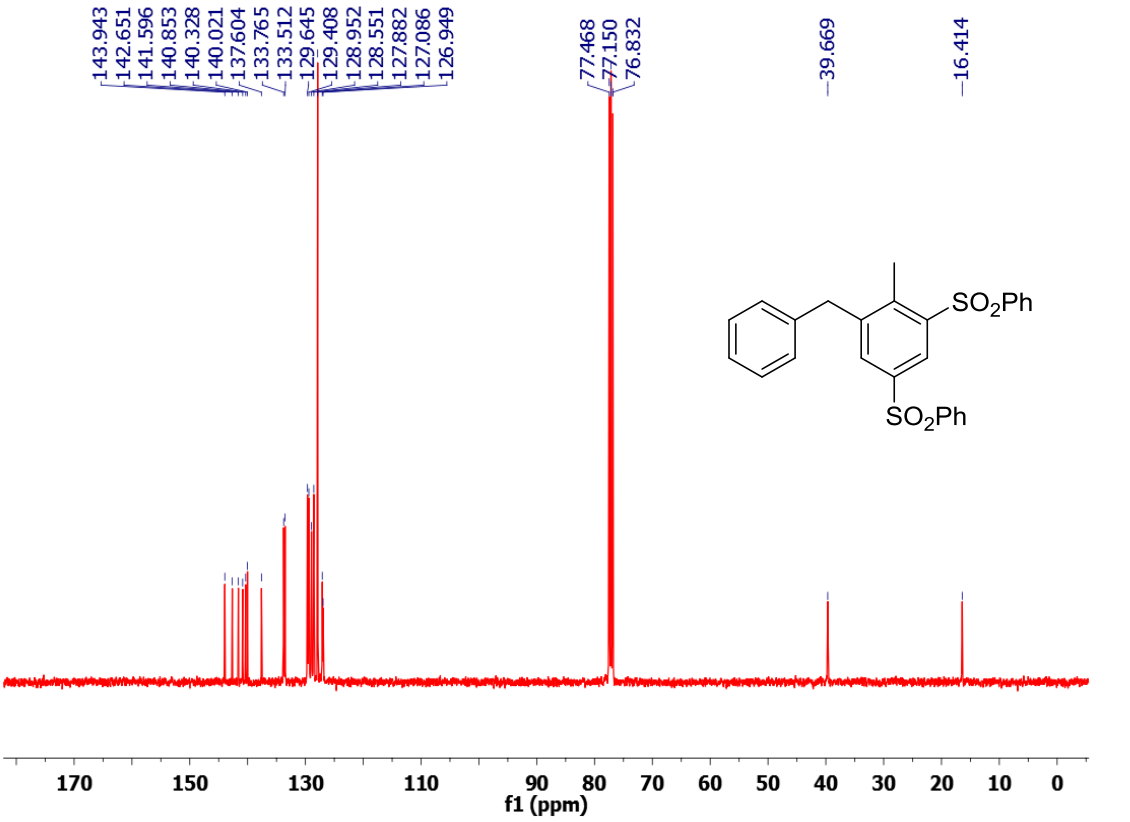

6.829
6.810
6.792
4.157
2.328
2.245
2.227
2.209
1.870
1.854
1.837
1.820
1.803
1.792
0.971
0.955
O
Br
1.00
2.18
3.10
2.42
1.18
6.17
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

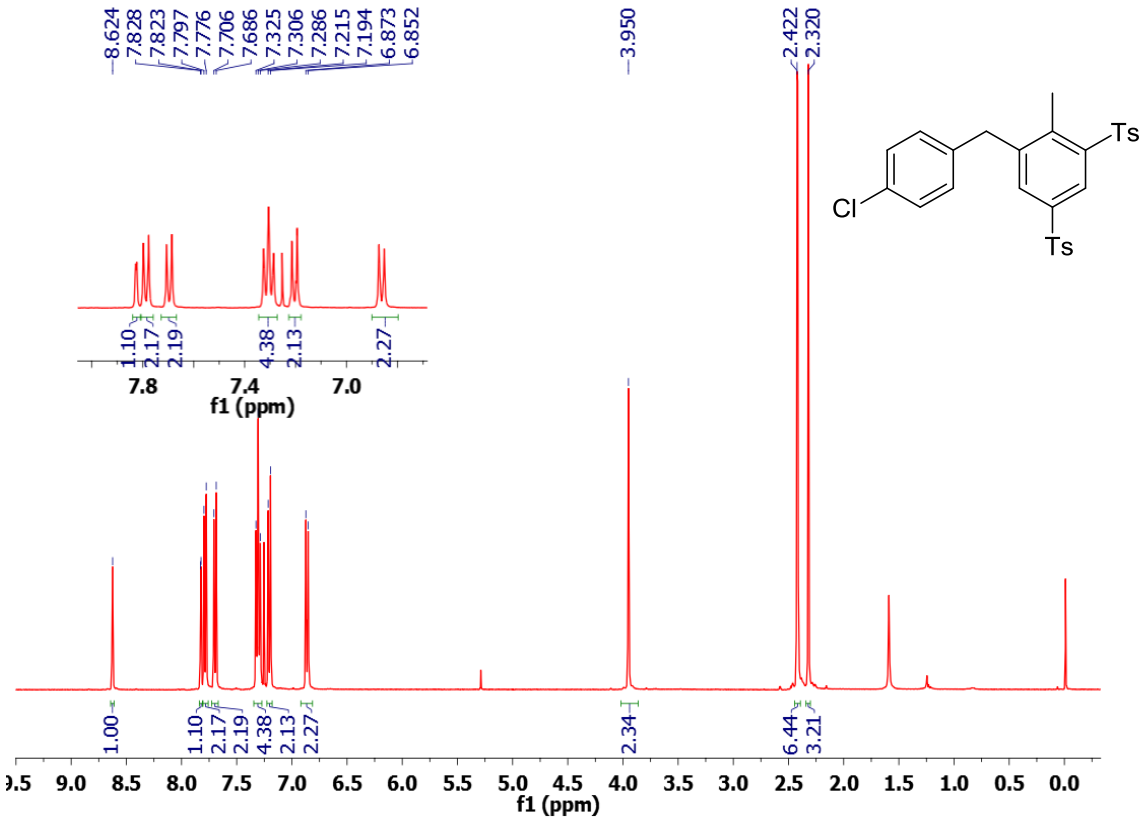

196.746
147.670
139.043
38.288
28.275
25.641
22.770
22.670
O
Br
220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

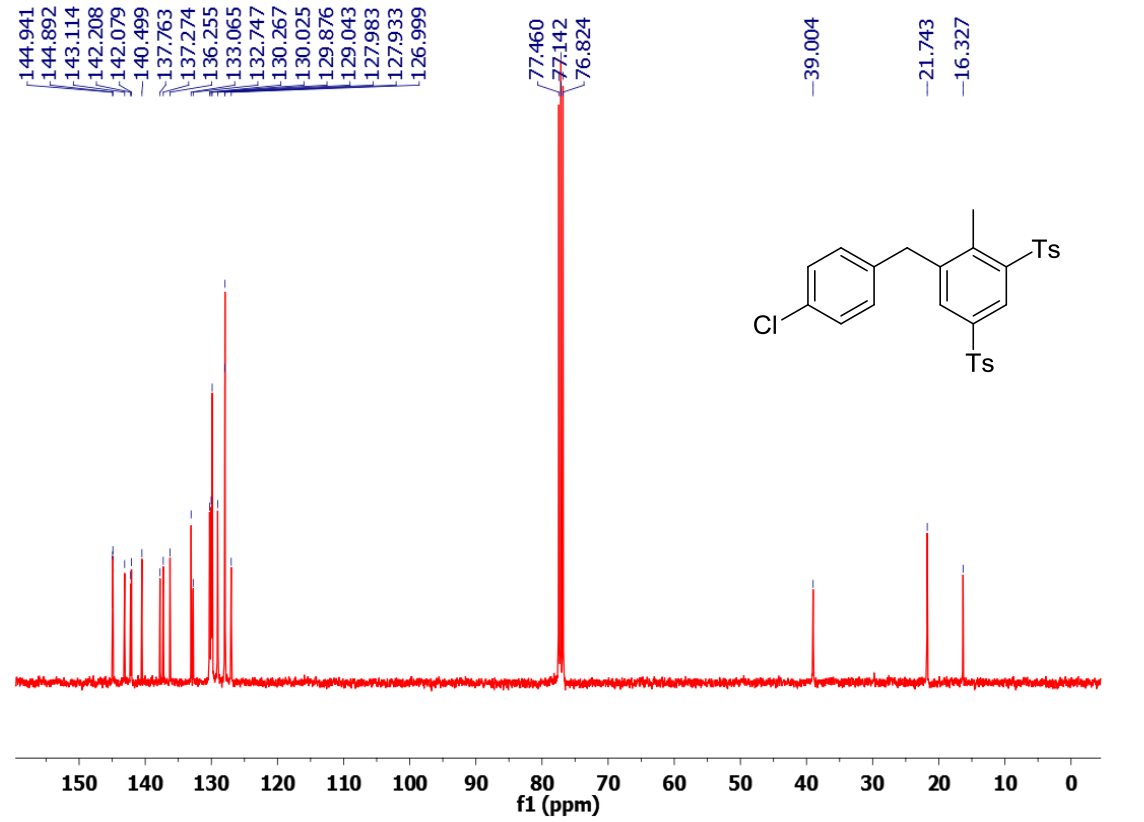

8.634
8.629
7.873
7.868
7.805
7.784
7.718
7.697
7.326
7.312
7.307
7.292
7.260
7.251
7.236
7.233
7.224
6.952
6.936
3.995
2.425
2.350
Ts
Ts
1.09
2.15
2.14
4.28
3.44
2.02
7.8
f1 (ppm)
1.00
1.09
2.15
2.14
4.28
3.44
2.02
2.14
6.22
3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

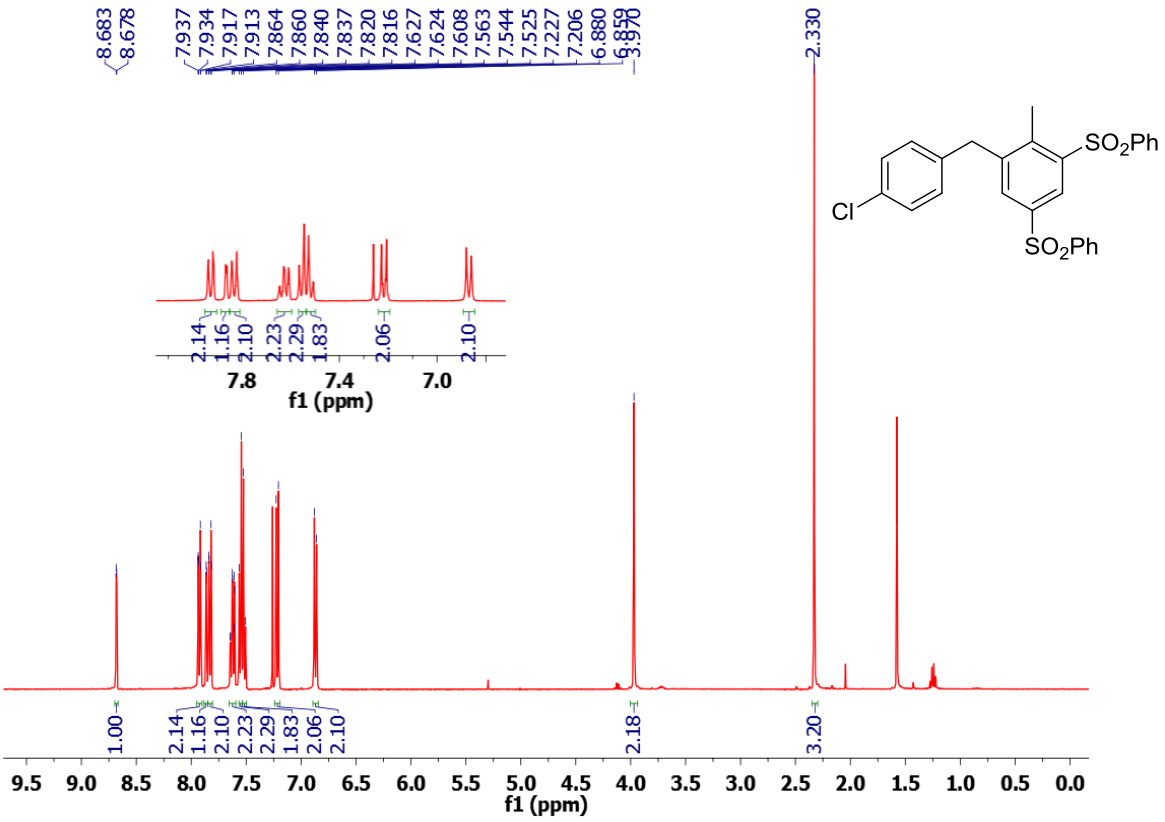

144.789
143.691
142.310
141.890
140.321
137.916
137.723
137.391
133.214
130.223
129.998
128.908
128.559
127.980
127.923
126.865
77.448
77.131
76.813
39.667
21.734
16.348
Ts
Ts
170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.680
8.675
7.932
7.914
7.910
7.899
7.894
7.839
7.821
7.817
7.615
7.596
7.554
7.538
7.534
7.519
7.260
7.251
7.233
7.227
6.947
6.938
4.004
2.348
SO2Ph
SO2Ph
2.08
1.05
2.09
2.17
4.40
3.56
2.09
8.0
7.5
7.0
f1 (ppm)
1.00
2.08
1.05
2.09
2.17
4.40
3.56
2.09
2.18
3.26
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


143.943
142.651
141.596
140.853
140.328
140.021
137.604
133.765
133.512
129.645
129.408
128.952
128.551
127.882
127.086
126.949
77.468
77.150
76.832
39.669
16.414
SO2Ph
SO2Ph
170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.624
7.828
7.823
7.797
7.776
7.706
7.686
7.325
7.306
7.286
7.215
7.194
6.873
6.852
3.950
2.422
2.320
Ts
Cl
Ts
1.10
2.17
2.19
4.38
2.13
2.27
7.8
7.4
7.0
f1 (ppm)
1.00
1.10
2.17
2.19
4.38
2.13
2.27
2.34
6.44
3.21
f1 (ppm)


144.941
144.892
143.114
142.208
142.079
140.499
137.763
137.274
136.255
133.065
132.747
130.267
130.025
129.876
129.043
127.983
127.933
126.999
77.460
77.142
76.824
39.004
21.743
16.327
Ts
Cl
Ts
f1 (ppm)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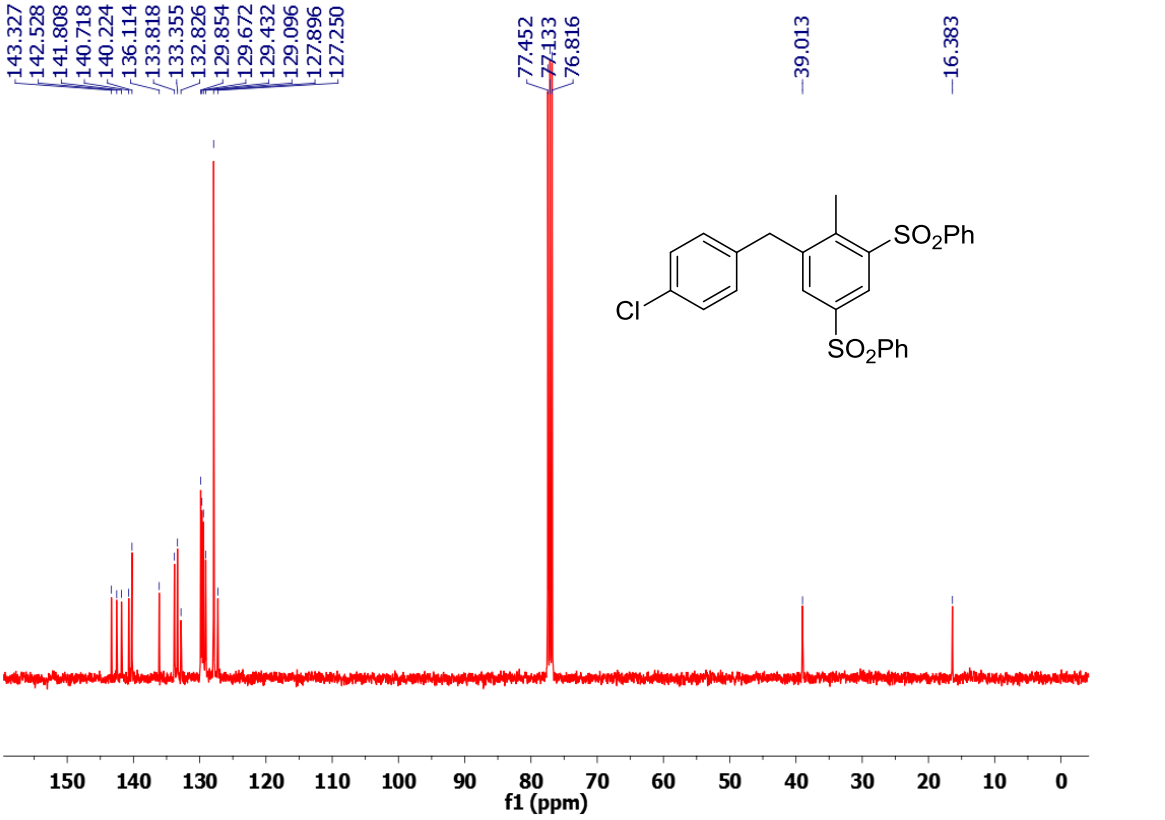
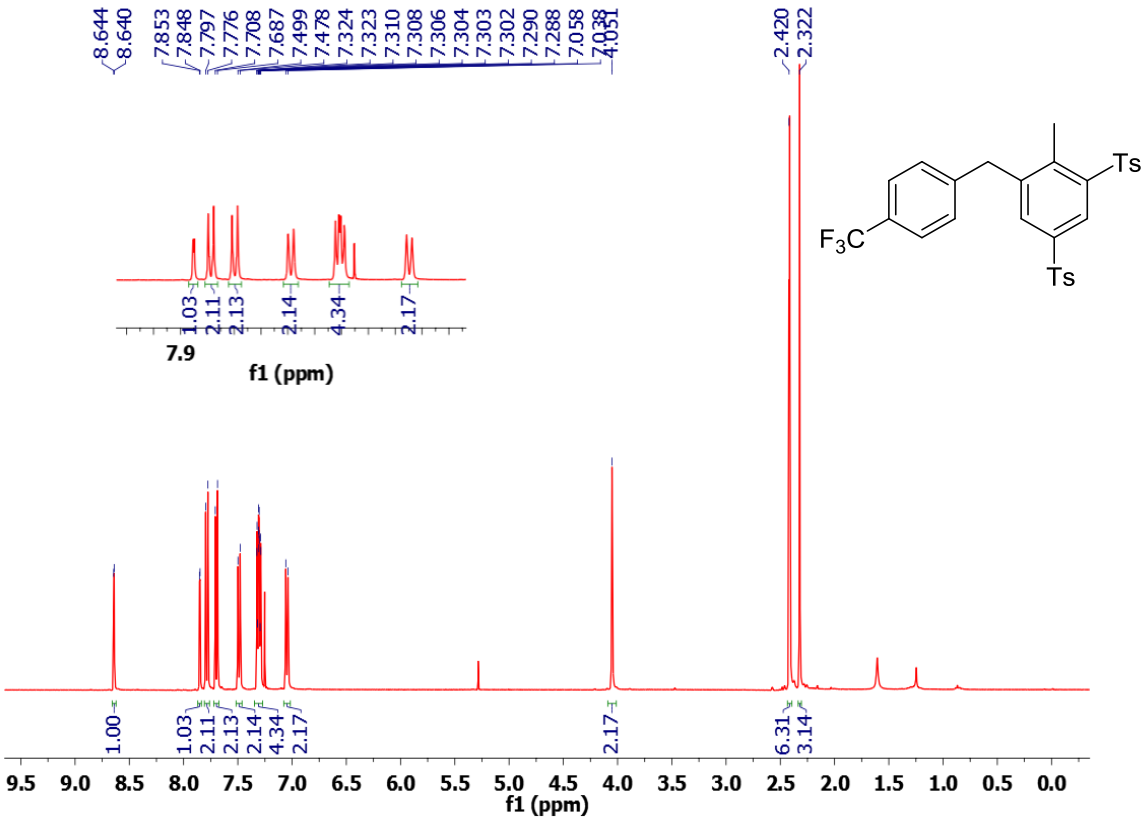
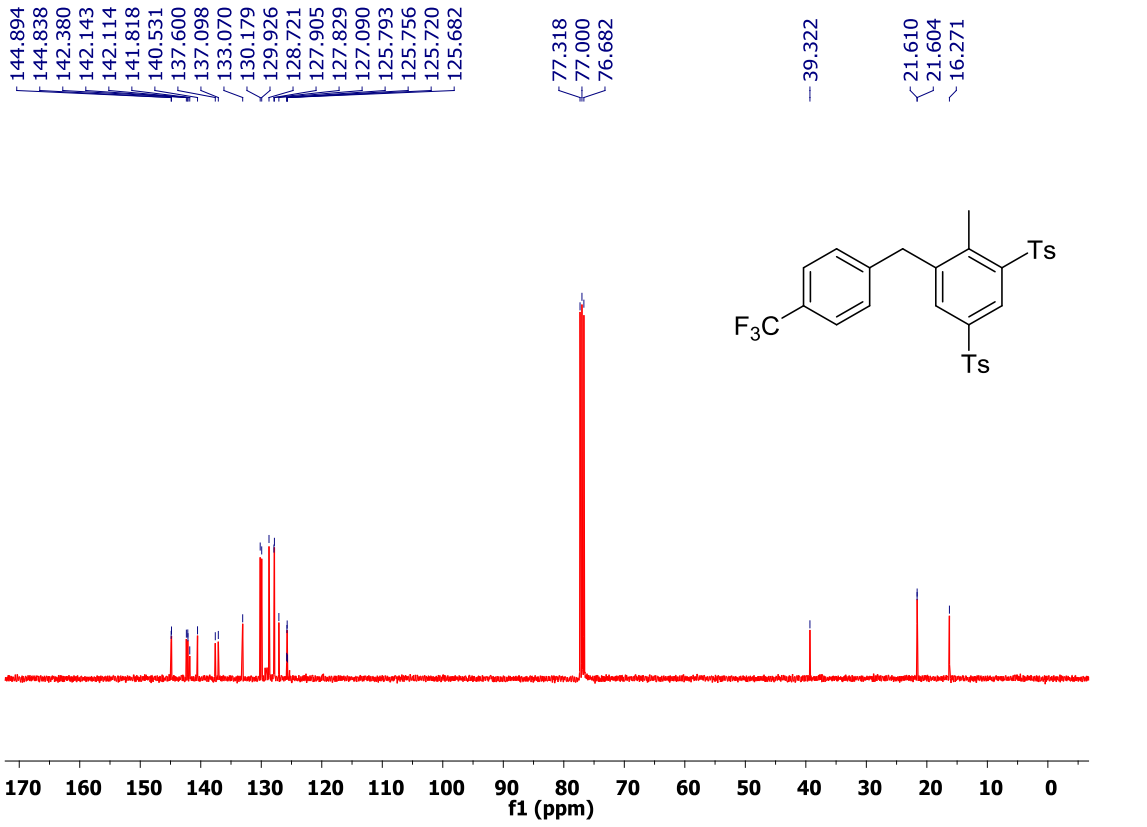
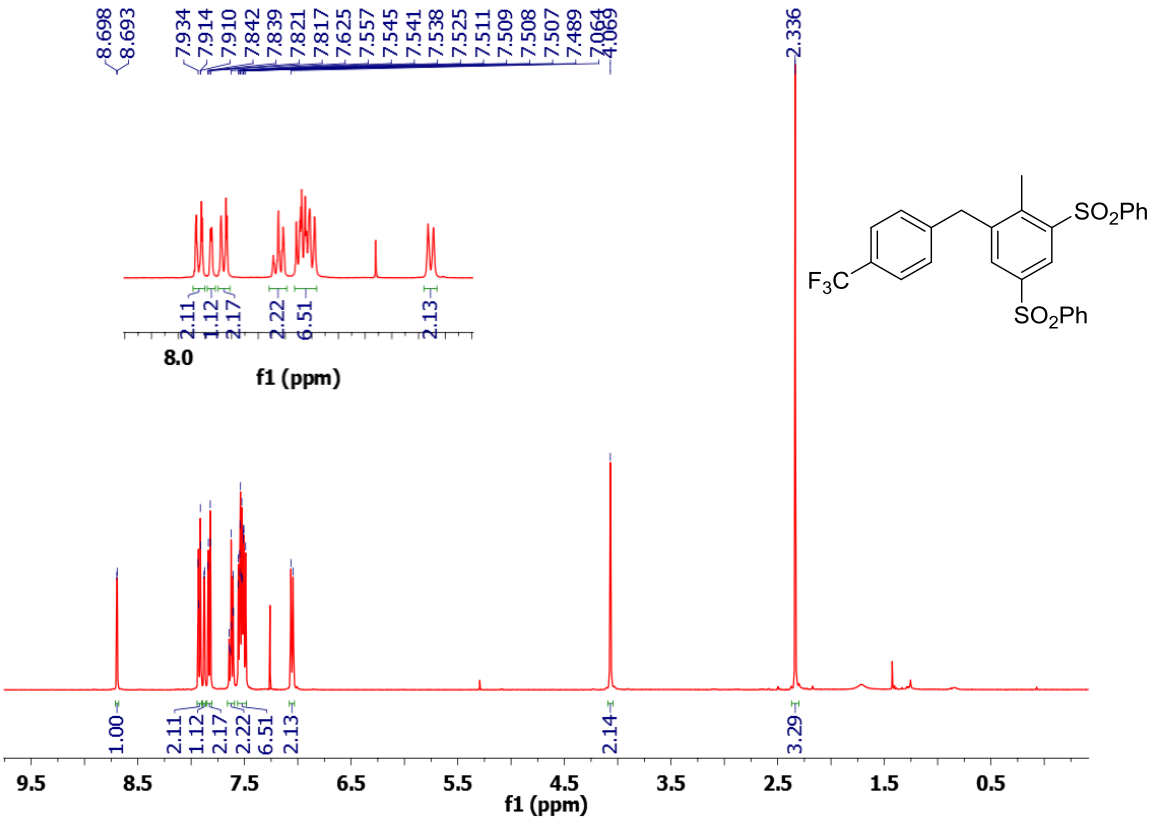
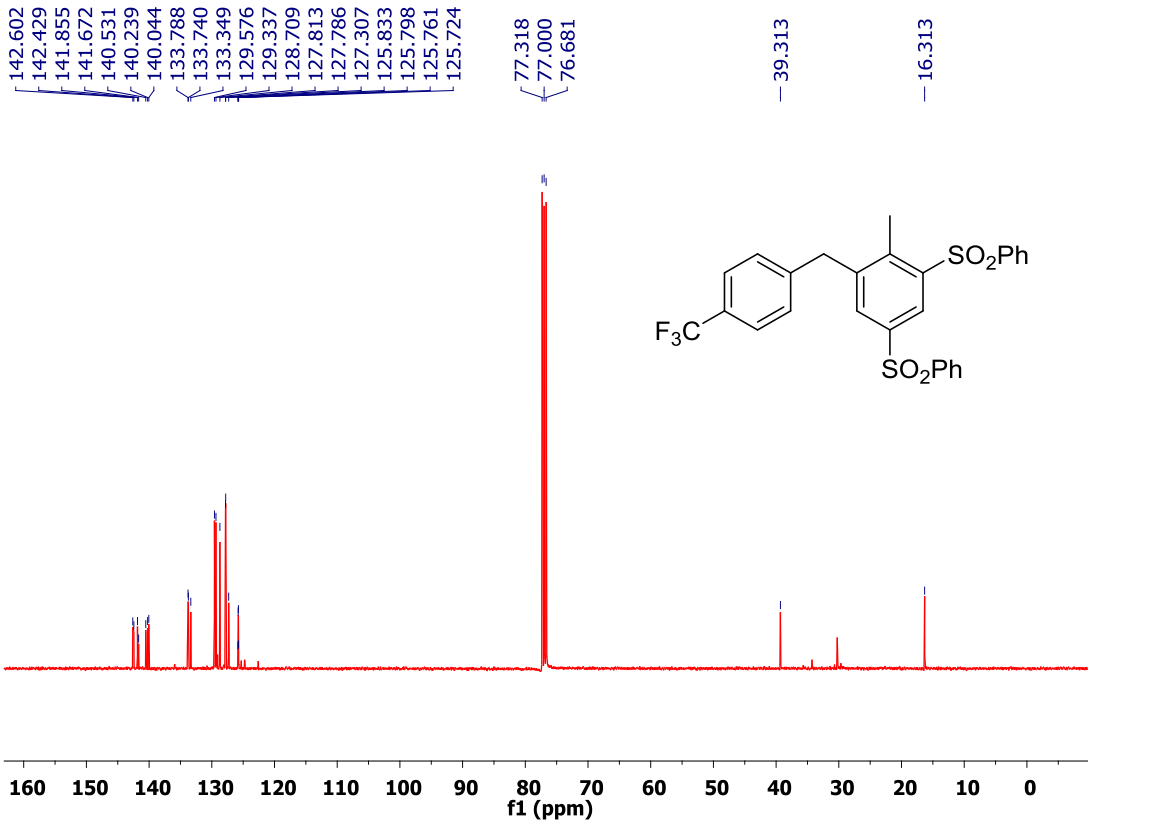
8.678
7.937
7.934
7.917
7.913
7.864
7.860
7.840
7.837
7.820
7.816
7.627
7.624
7.608
7.563
7.544
7.525
7.227
7.206
6.880
6.859
3.970
2.330
SO2Ph
Cl
SO2Ph
2.14
1.16
2.10
2.23
2.29
1.83
2.06
2.10
7.8
7.4
7.0
f1 (ppm)
1.00
2.14
1.16
2.10
2.23
2.29
1.83
2.06
2.10
2.18
3.20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


143.327
142.528
141.808
140.718
140.224
136.114
133.818
133.355
132.826
129.854
129.672
129.432
129.096
127.896
127.250
77.452
77.133
76.816
39.013
16.383
SO2Ph
Cl
SO2Ph
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.644
8.640
7.853
7.848
7.797
7.776
7.708
7.687
7.499
7.478
7.324
7.323
7.310
7.308
7.306
7.304
7.303
7.302
7.290
7.288
7.058
7.038
4.051
2.420
2.322
1.03
2.11
2.13
2.14
4.34
2.17
7.9
f1 (ppm)
Ts
F3C
Ts
1.00
1.03
2.11
2.13
2.14
4.34
2.17
2.17
6.31
3.14
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


144.894
144.838
142.380
142.143
142.114
141.818
140.531
137.600
137.098
133.070
130.179
129.926
128.721
127.905
127.829
127.090
125.793
125.756
125.720
125.682
77.318
77.000
76.682
39.322
21.610
21.604
16.271
Ts
F3C
Ts
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.698
8.693
7.934
7.914
7.910
7.842
7.839
7.821
7.817
7.625
7.557
7.545
7.541
7.538
7.525
7.511
7.509
7.508
7.507
7.489
7.064
4.069
2.336
2.11
1.12
2.17
2.22
6.51
2.13
8.0
f1 (ppm)
SO2Ph
F3C
SO2Ph
1.00
2.11
1.12
2.17
2.22
6.51
2.13
2.14
3.29
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)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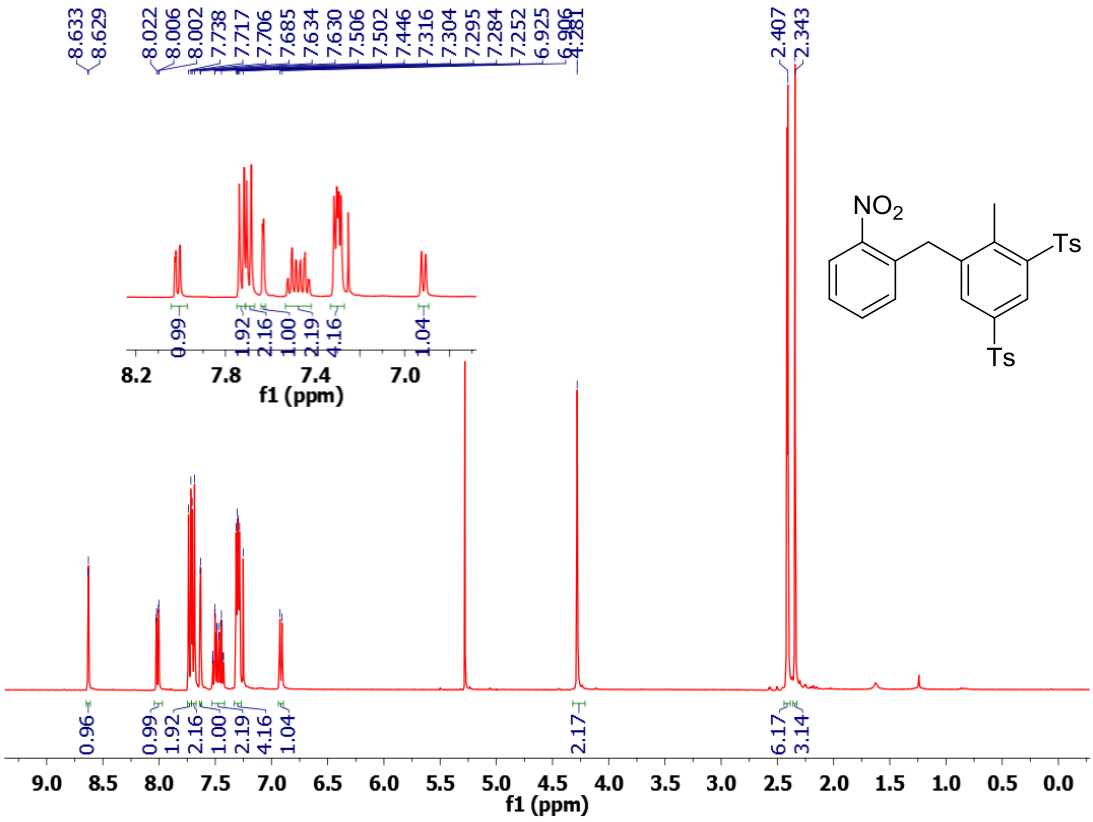
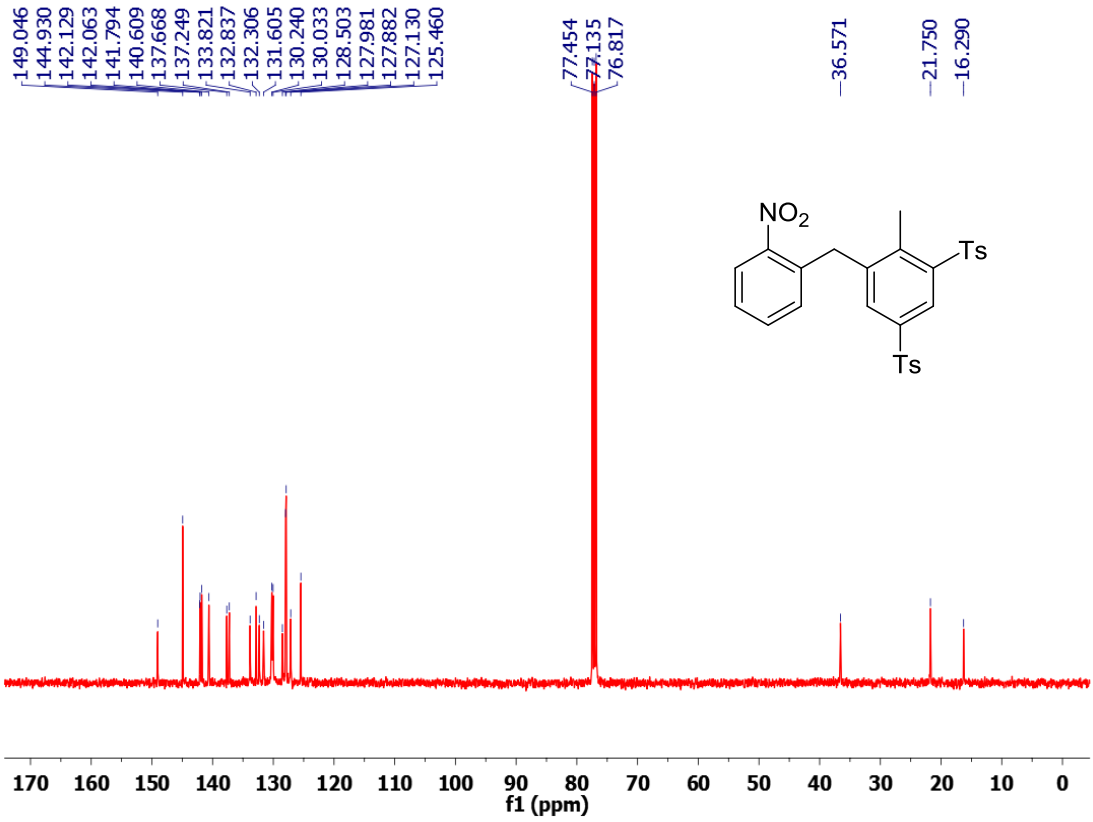
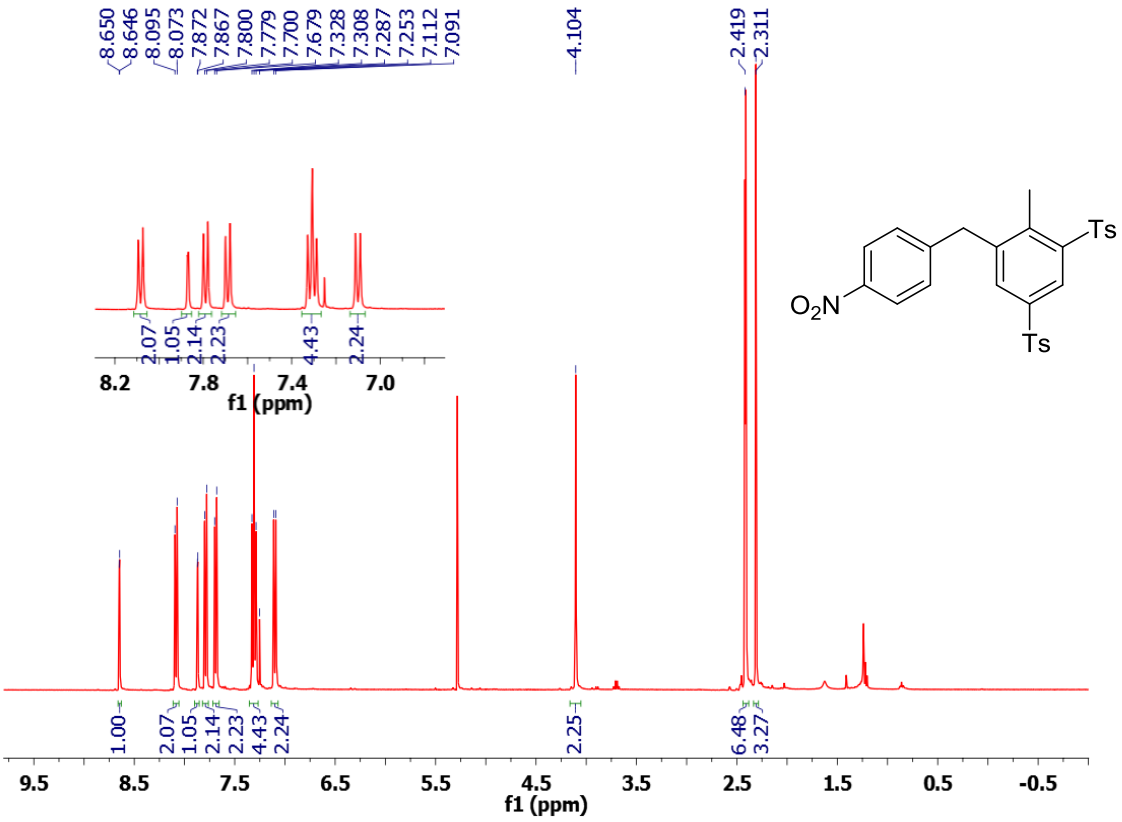
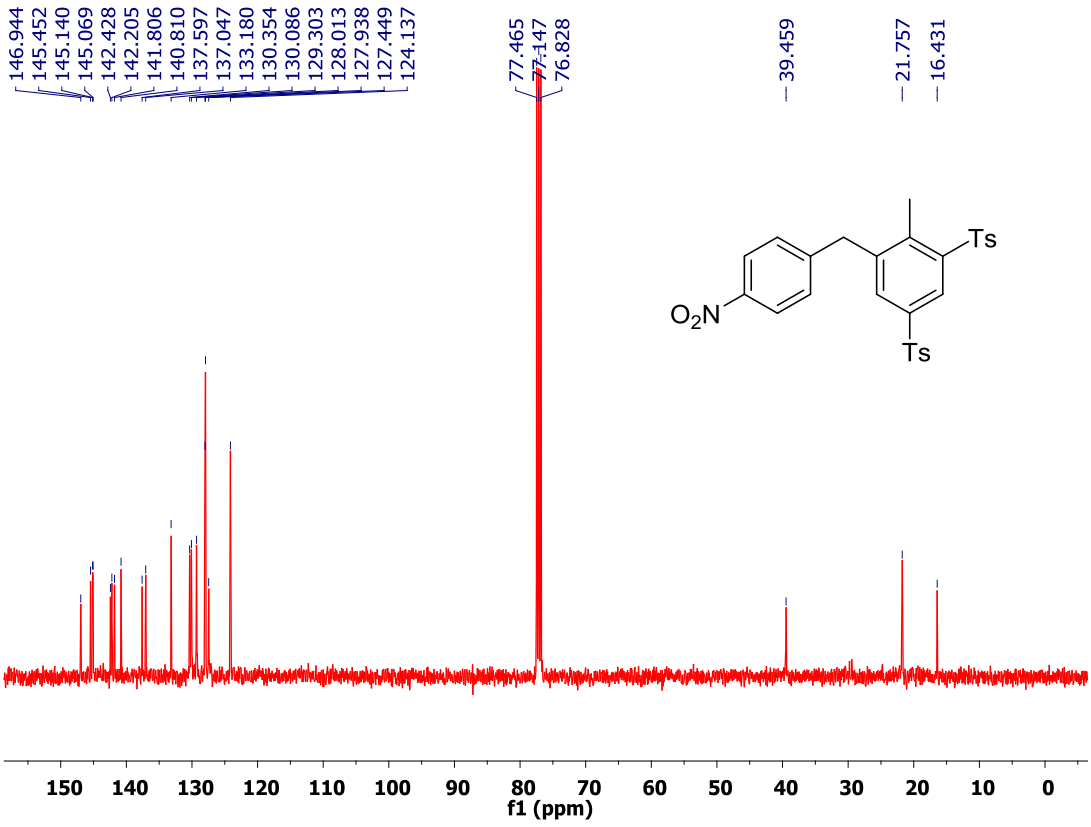
142.429
141.855
141.672
140.531
140.239
140.044
133.788
133.740
133.349
129.576
129.337
128.709
127.813
127.786
127.307
125.833
125.798
125.761
125.724
77.318
77.000
76.681
39.313
16.313
SO2Ph
F3C
SO2Ph
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.633
8.629
8.022
8.006
8.002
7.738
7.717
7.706
7.685
7.634
7.630
7.506
7.502
7.446
7.316
7.304
7.295
7.284
7.252
6.925
2.407
2.343
NO2
Ts
Ts
0.99
1.92
2.16
1.00
2.19
4.16
1.04
8.2
7.8
7.4
7.0
f1 (ppm)
0.96
0.99
1.92
2.16
1.00
2.19
4.16
1.04
2.17
6.17
3.14
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


149.046
144.930
142.129
142.063
141.794
140.609
137.668
137.249
133.821
132.837
132.306
131.605
130.240
130.033
128.503
127.981
127.882
127.130
125.460
77.454
77.135
76.817
36.571
21.750
16.290
NO2
Ts
Ts
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.650
8.646
8.095
8.073
7.872
7.867
7.800
7.779
7.700
7.679
7.328
7.308
7.287
7.253
7.112
7.091
4.104
2.419
2.311
2.07
1.05
2.14
2.23
4.43
2.24
8.2
7.8
7.4
7.0
f1 (ppm)
Ts
O2N
Ts
1.00
2.07
1.05
2.14
2.23
4.43
2.24
2.25
6.48
3.27
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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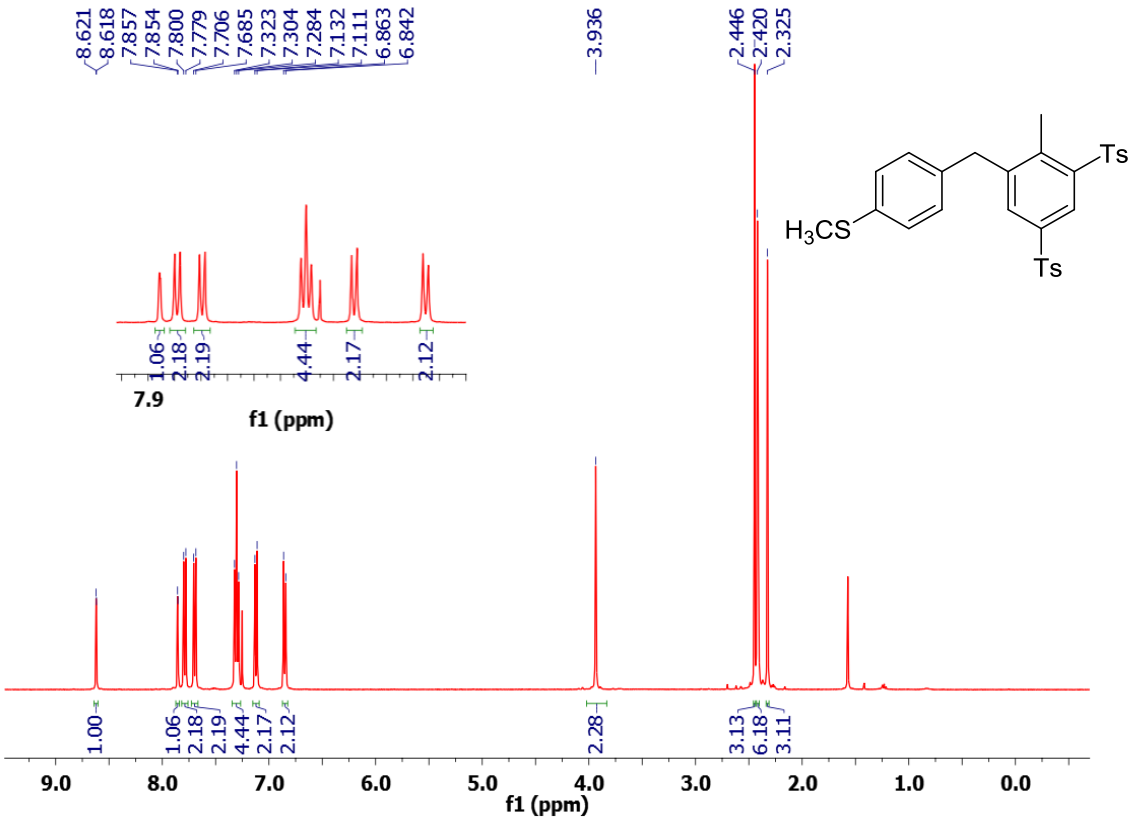
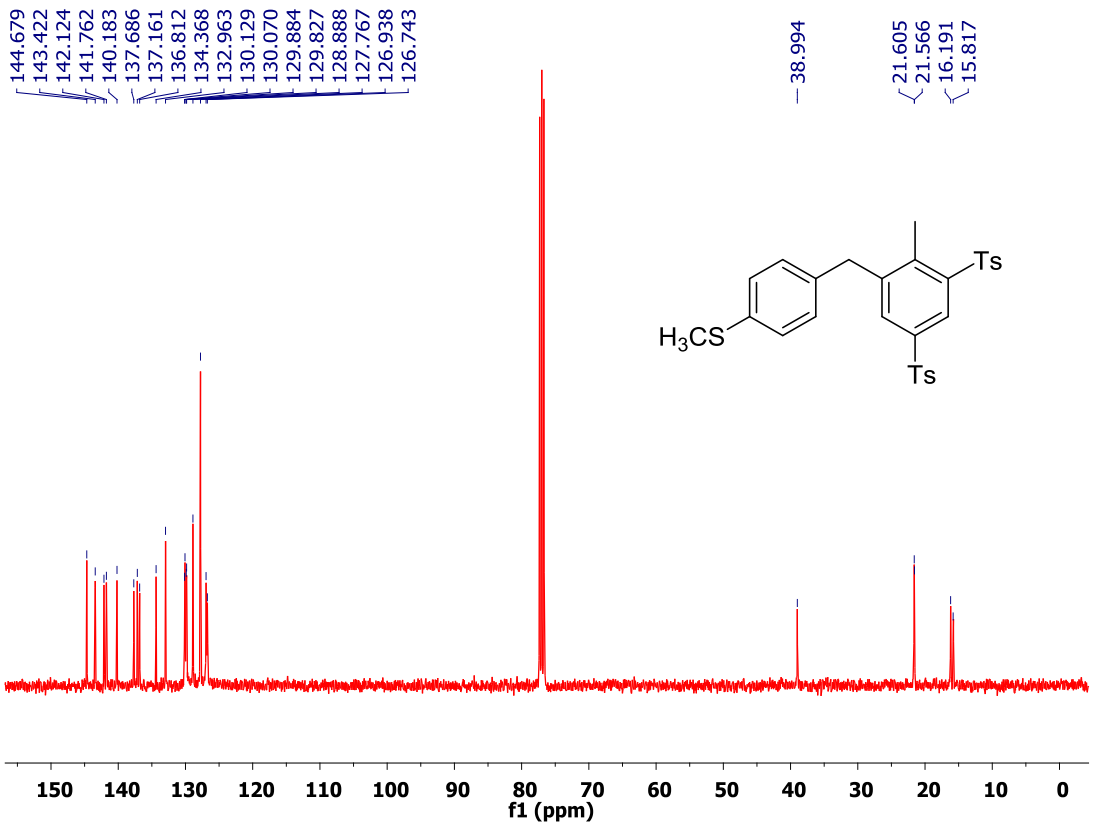
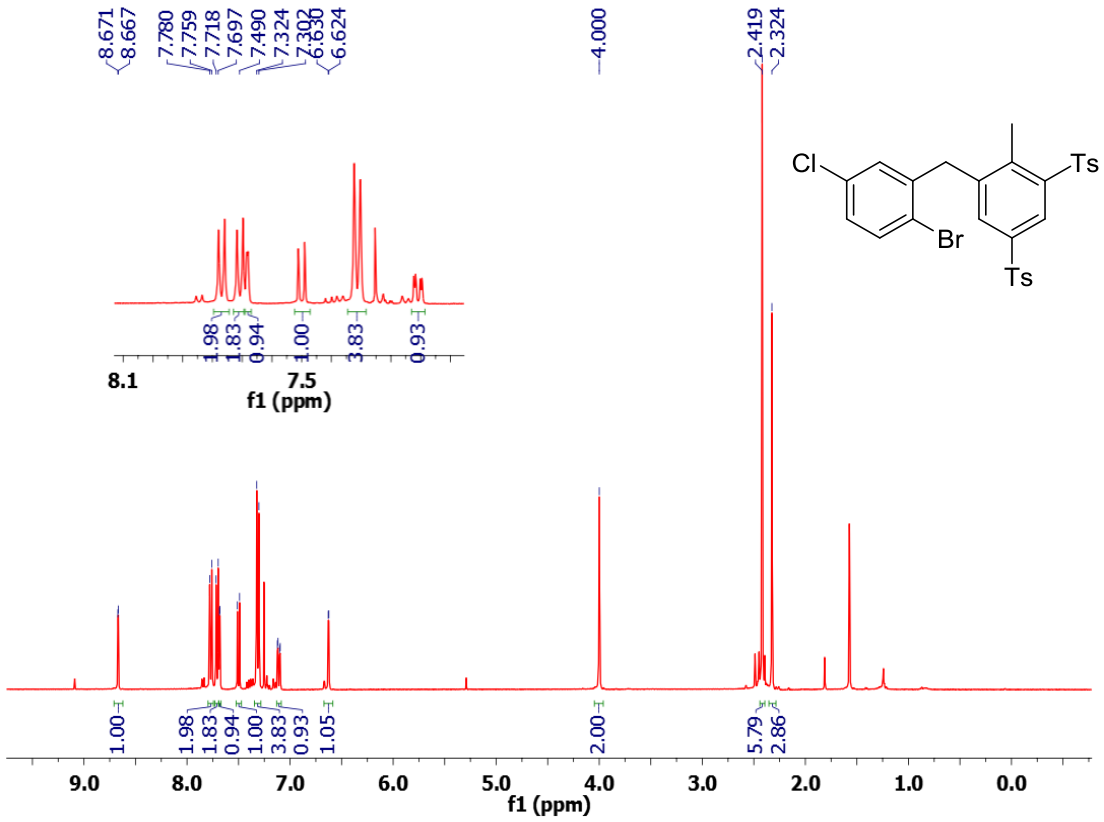
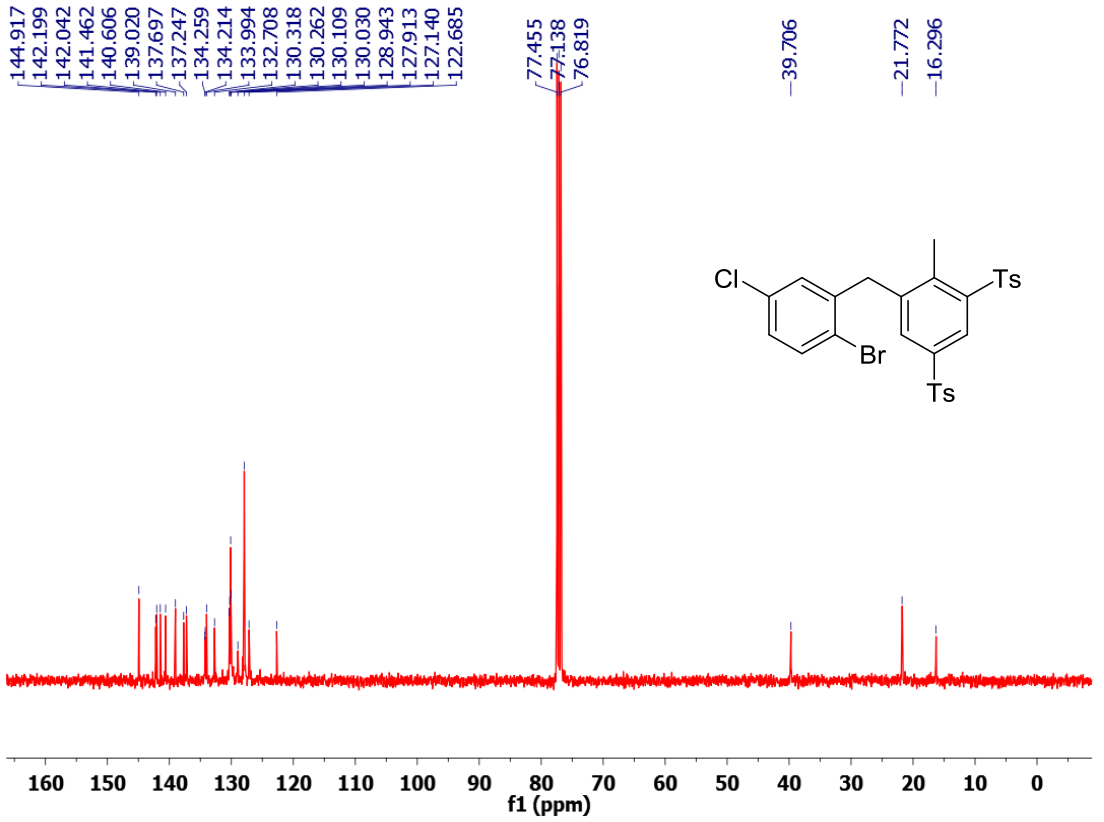
145.452
145.140
145.069
142.428
142.205
141.806
140.810
137.597
137.047
133.180
130.354
130.086
129.303
128.013
127.938
127.449
124.137
77.465
77.147
76.828
39.459
21.757
16.431
Ts
O2N
Ts
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.621
8.618
7.857
7.854
7.800
7.779
7.706
7.685
7.323
7.304
7.284
7.132
7.111
6.863
6.842
3.936
2.446
2.420
2.325
Ts
H3CS
Ts
1.06
2.18
2.19
4.44
2.17
2.12
7.9
f1 (ppm)
1.00
1.06
2.18
2.19
4.44
2.17
2.12
2.28
3.13
6.18
3.11
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


144.679
143.422
142.124
141.762
140.183
137.686
137.161
136.812
134.368
132.963
130.129
130.070
129.884
129.827
128.888
127.767
126.938
126.743
38.994
21.605
21.566
16.191
15.817
Ts
H3CS
Ts
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.671
8.667
7.780
7.759
7.718
7.697
7.490
7.324
7.302
6.630
6.624
4.000
2.419
2.324
Cl
Ts
Br
Ts
1.98
1.83
0.94
1.00
3.83
0.93
8.1
7.5
f1 (ppm)
1.00
1.98
1.83
0.94
1.00
3.83
0.93
1.05
2.00
5.79
2.86
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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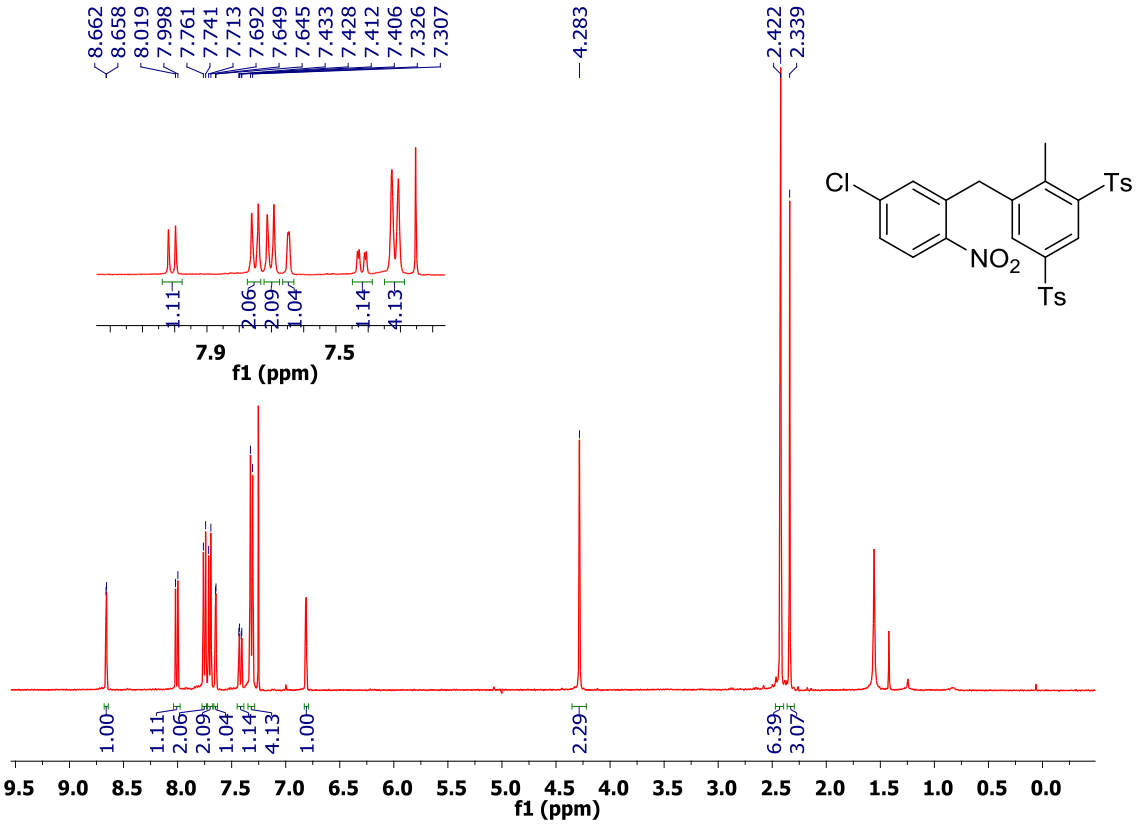
142.199
142.042
141.462
140.606
139.020
137.697
137.247
134.259
134.214
133.994
132.708
130.318
130.262
130.109
130.030
128.943
127.913
127.140
122.685
77.455
77.138
76.819
39.706
21.772
16.296
Cl
Ts
Br
Ts
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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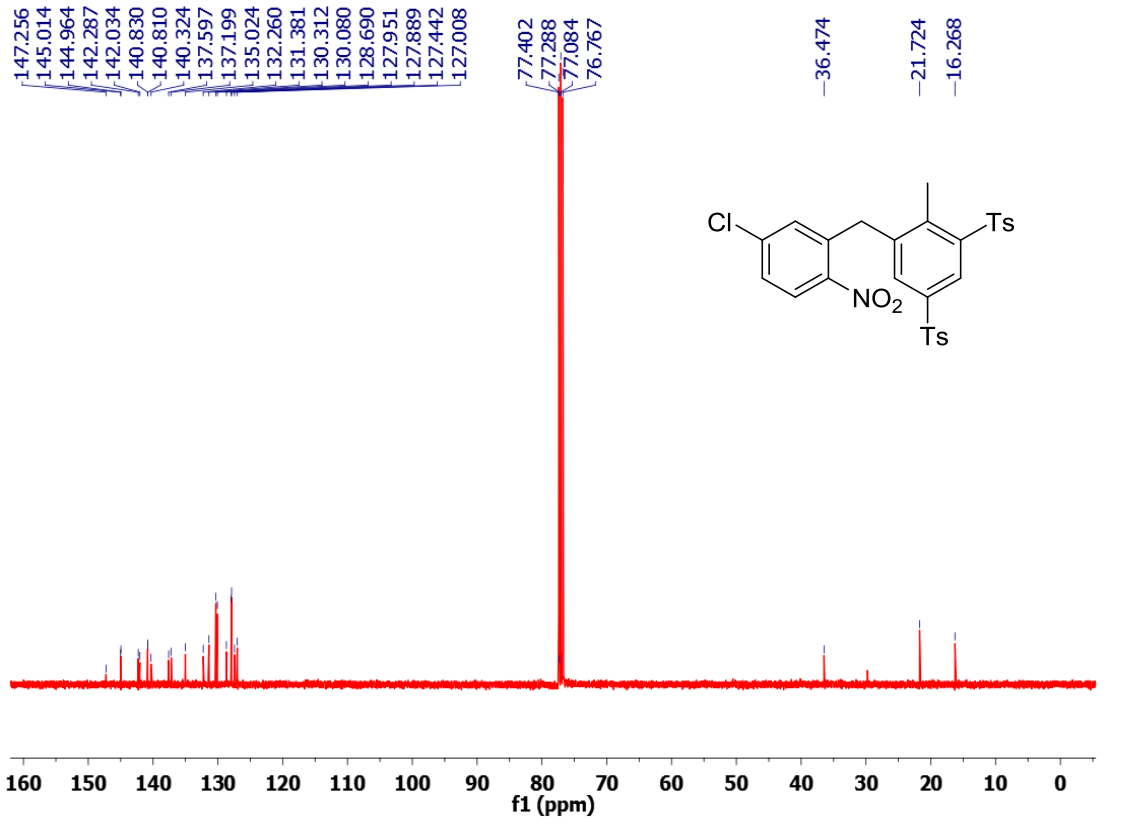
8.658
8.019
7.998
7.761
7.741
7.713
7.692
7.649
7.645
7.433
7.428
7.412
7.406
7.326
7.307
4.283
2.422
2.339
Cl
Ts
NO2
Ts
1.11
2.06
2.09
1.04
1.14
4.13
7.9
7.5
f1 (ppm)
1.00
1.11
2.06
2.09
1.04
1.14
4.13
1.00
2.29
6.39
3.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.964
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140.830
140.810
140.324
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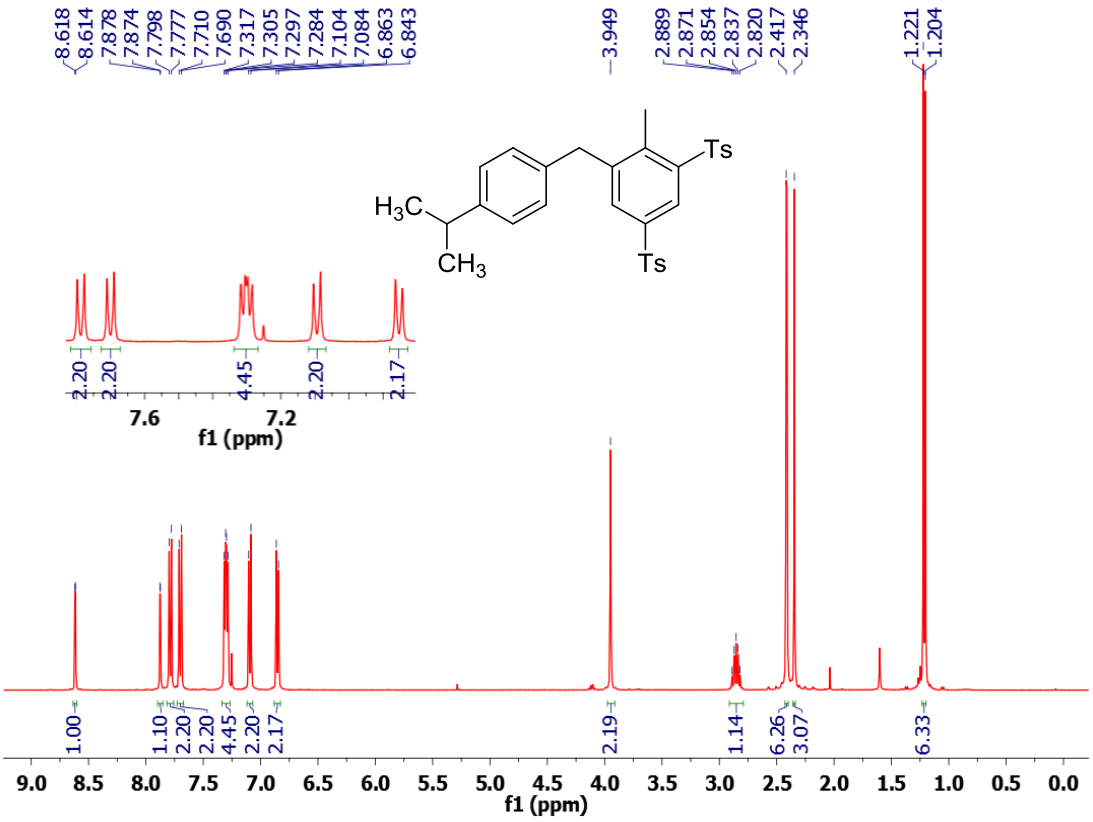
137.199
135.024
132.260
131.381
130.312
130.080
128.690
127.951
127.889
127.442
127.008
77.402
77.288
77.084
76.767
36.474
21.724
16.268
Cl
Ts
NO2
Ts
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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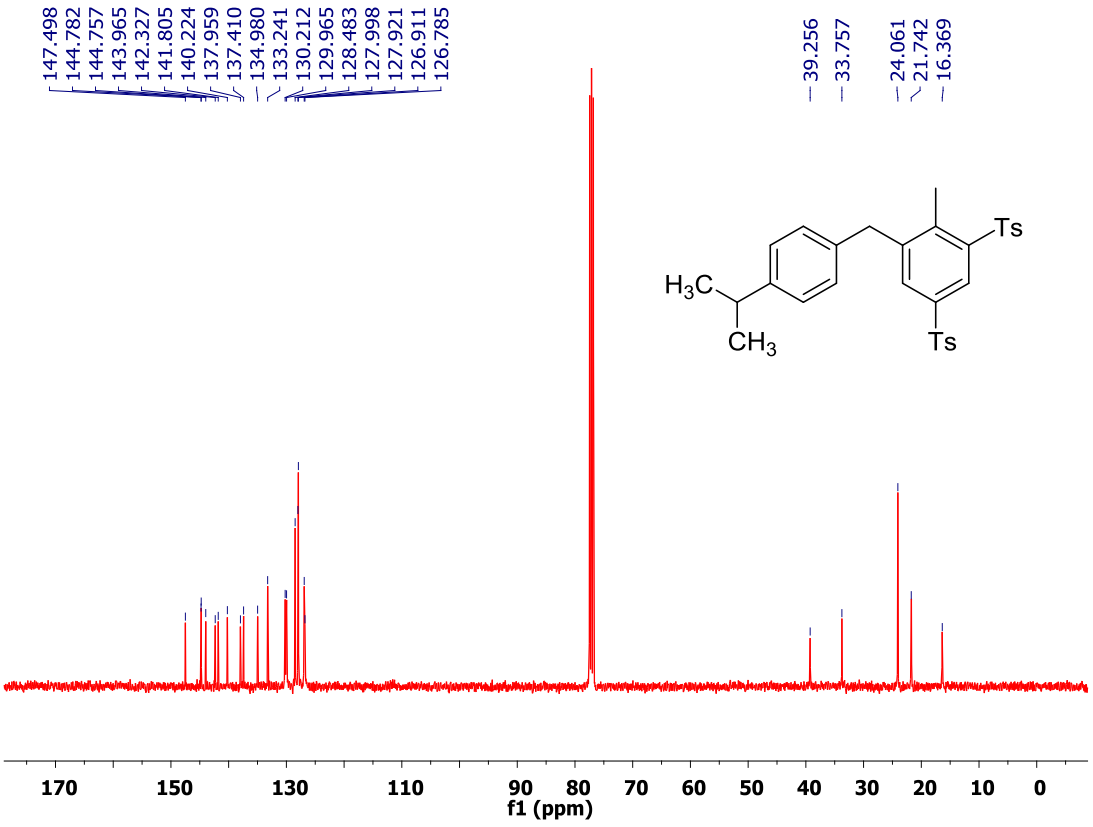
8.614
7.878
7.874
7.798
7.777
7.710
7.690
7.317
7.305
7.297
7.284
7.104
7.084
6.863
6.843
3.949
2.889
2.871
2.854
2.837
2.820
2.417
2.346
1.221
1.204
Ts
H3C
CH3
Ts
2.20
2.20
4.45
2.20
2.17
7.6
7.2
f1 (ppm)
1.00
1.10
2.20
2.20
4.45
2.20
2.17
2.19
1.14
6.26
3.07
6.33
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.782
144.757
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140.224
137.959
137.410
134.980
133.241
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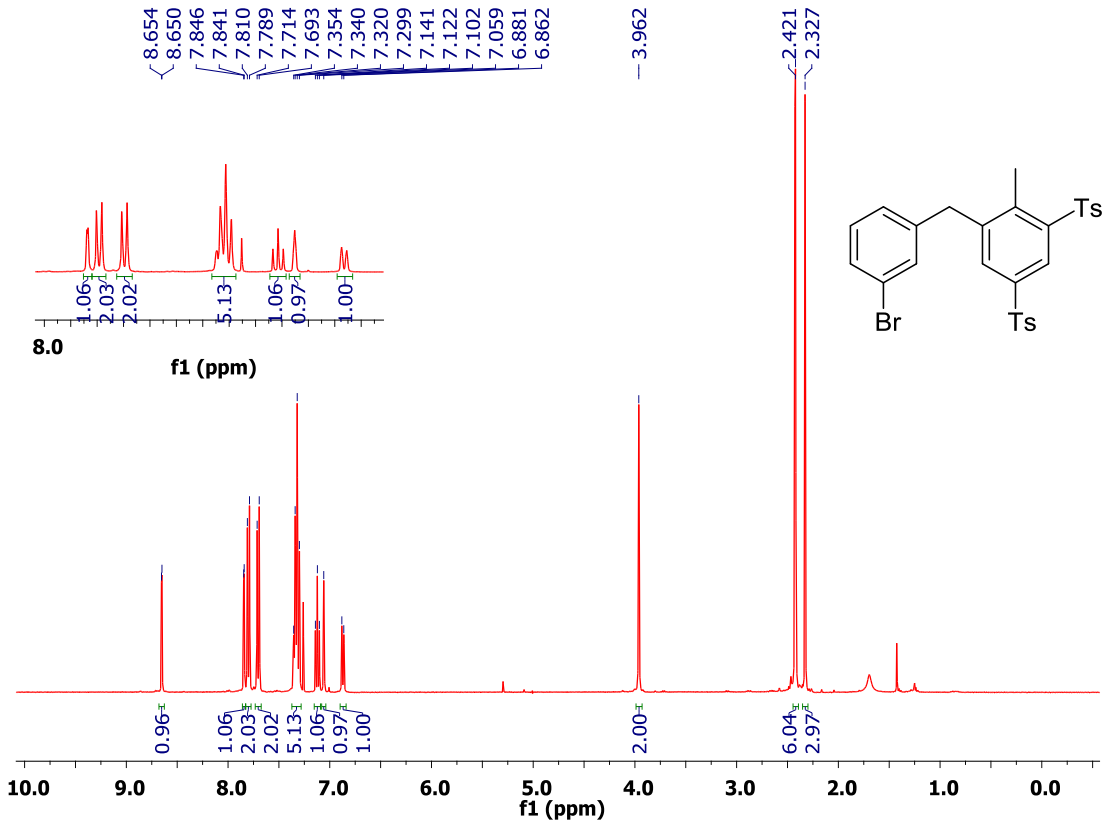
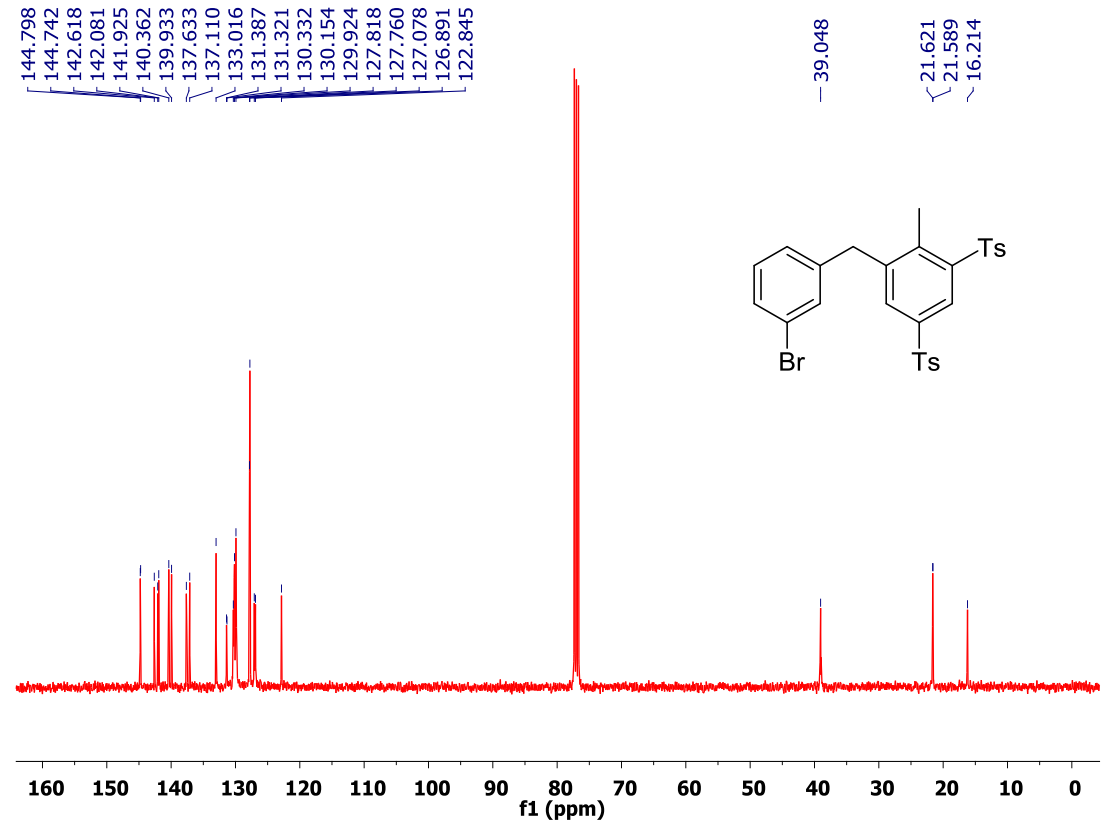
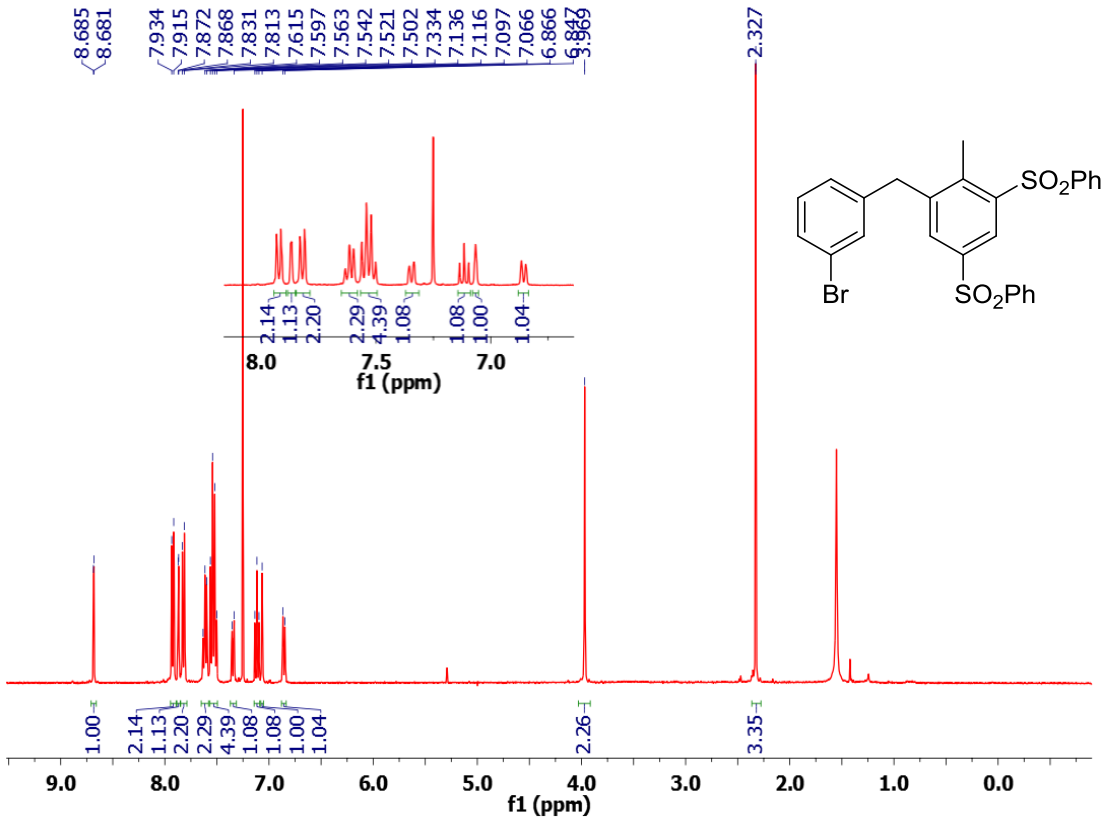
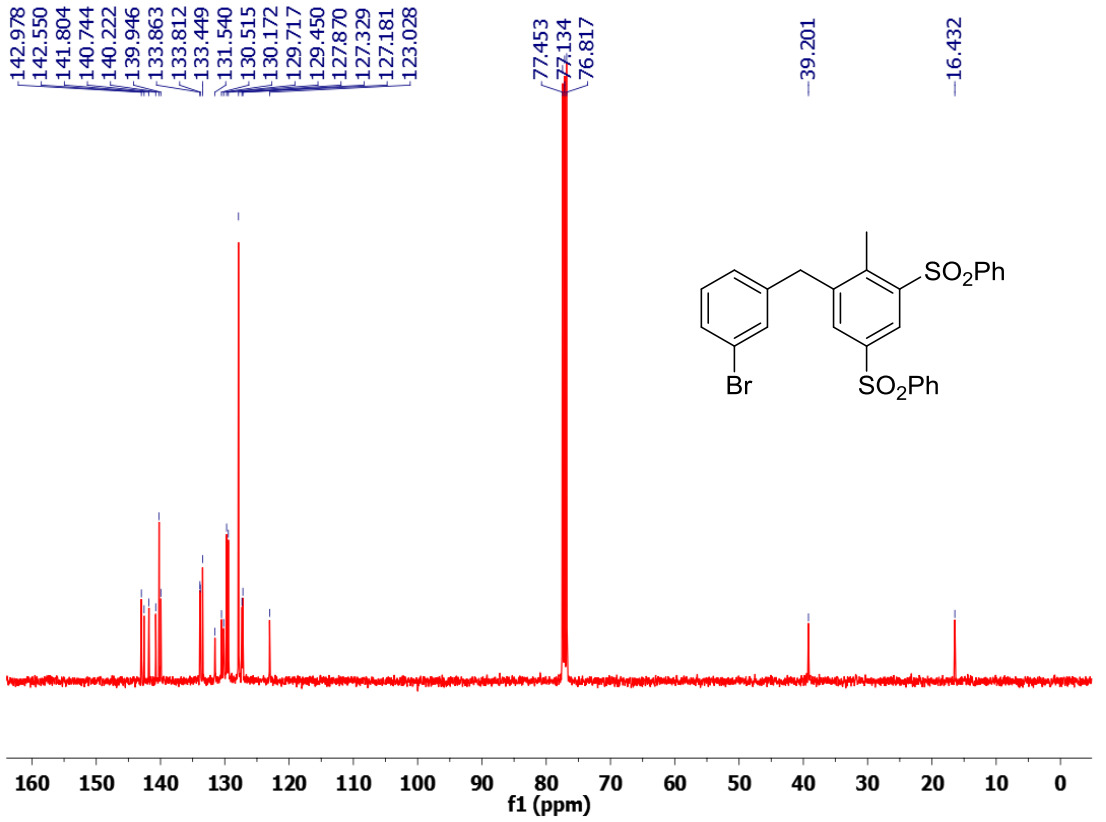
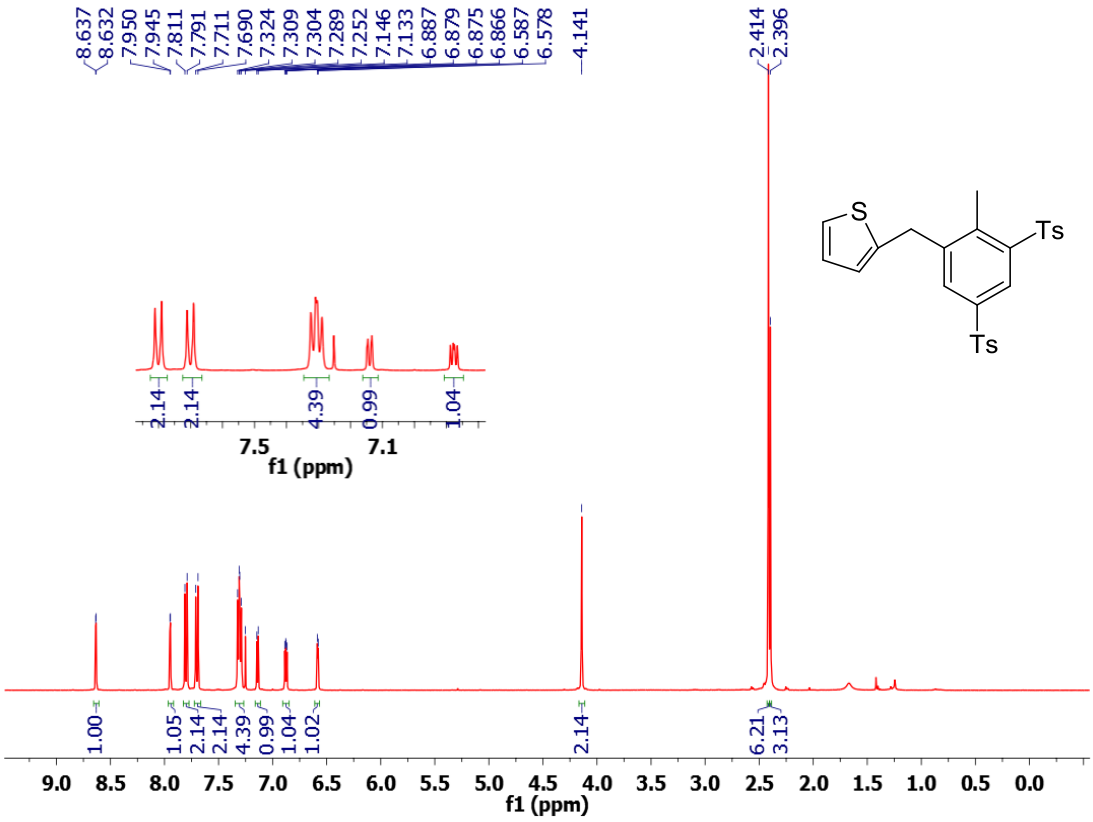
129.965
128.483
127.998
127.921
126.911
126.785
39.256
33.757
24.061
21.742
16.369
Ts
H3C
CH3
Ts
170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

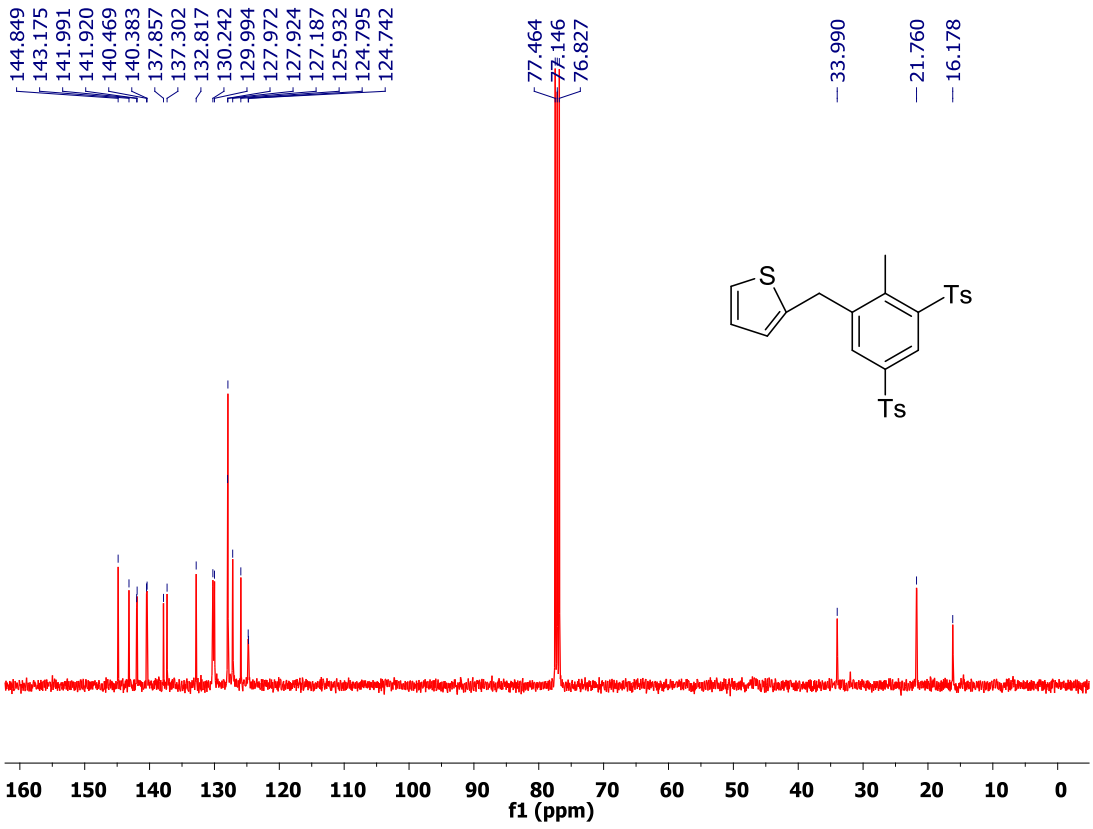

8.654
8.650
7.846
7.841
7.810
7.789
7.714
7.693
7.354
7.340
7.320
7.299
7.141
7.122
7.102
7.059
6.881
6.862
3.962
2.421
2.327
1.06
2.03
2.02
5.13
1.06
0.97
1.00
8.0
f1 (ppm)
Ts
Br
Ts
0.96
1.06
2.03
2.02
5.13
1.06
0.97
1.00
2.00
6.04
2.97
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


144.798
144.742
142.618
142.081
141.925
140.362
139.933
137.633
137.110
133.016
131.387
131.321
130.332
130.154
129.924
127.818
127.760
127.078
126.891
122.845
39.048
21.621
21.589
16.214
Ts
Br
Ts
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.685
8.681
7.934
7.915
7.872
7.868
7.831
7.813
7.615
7.597
7.563
7.542
7.521
7.502
7.334
7.136
7.116
7.097
7.066
6.866
6.847
3.969
2.327
2.14
1.13
2.20
2.29
4.39
1.08
1.08
1.00
1.04
8.0
7.5
7.0
f1 (ppm)
SO2Ph
Br
SO2Ph
1.00
2.14
1.13
2.20
2.29
4.39
1.08
1.08
1.00
1.04
2.26
3.35
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


142.978
142.550
141.804
140.744
140.222
139.946
133.863
133.812
133.449
131.540
130.515
130.172
129.717
129.450
127.870
127.329
127.181
123.028
77.453
77.134
76.817
39.201
16.432
SO2Ph
Br
SO2Ph
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.637
8.632
7.950
7.945
7.811
7.791
7.711
7.690
7.324
7.309
7.304
7.289
7.252
7.146
7.133
6.887
6.879
6.875
6.866
6.587
6.578
4.141
2.414
2.396
S
Ts
Ts
2.14
2.14
4.39
0.99
1.04
7.5
7.1
f1 (ppm)
1.00
1.05
2.14
2.14
4.39
0.99
1.04
1.02
2.14
6.21
3.13
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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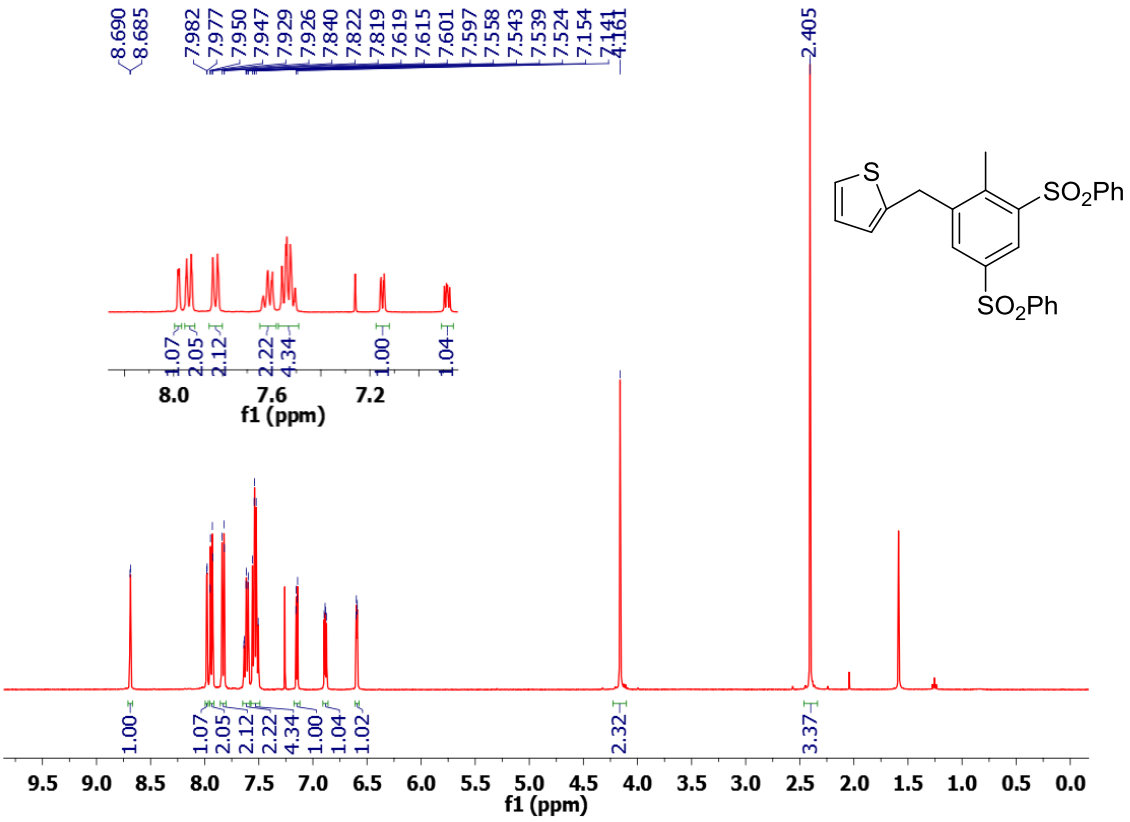
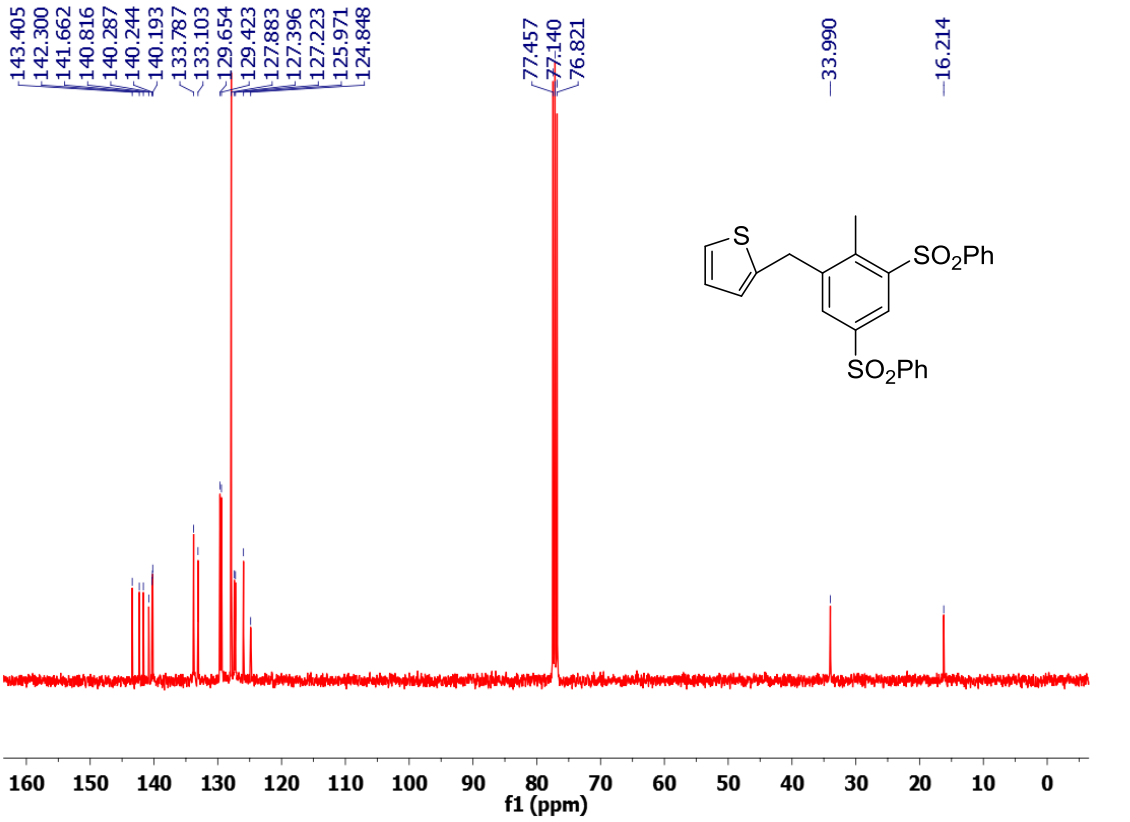
143.175
141.991
141.920
140.469
140.383
137.857
137.302
132.817
130.242
129.994
127.972
127.924
127.187
125.932
124.795
124.742
77.464
77.146
76.827
33.990
21.760
16.178
S
Ts
Ts
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.690
8.685
7.982
7.977
7.950
7.947
7.929
7.926
7.840
7.822
7.819
7.619
7.615
7.601
7.597
7.558
7.543
7.539
7.524
7.154
7.141
4.161
2.405
S
SO2Ph
SO2Ph
1.07
2.05
2.12
2.22
4.34
1.00
1.04
8.0
7.6
7.2
f1 (ppm)
1.00
1.07
2.05
2.12
2.22
4.34
1.00
1.04
1.02
2.32
3.37
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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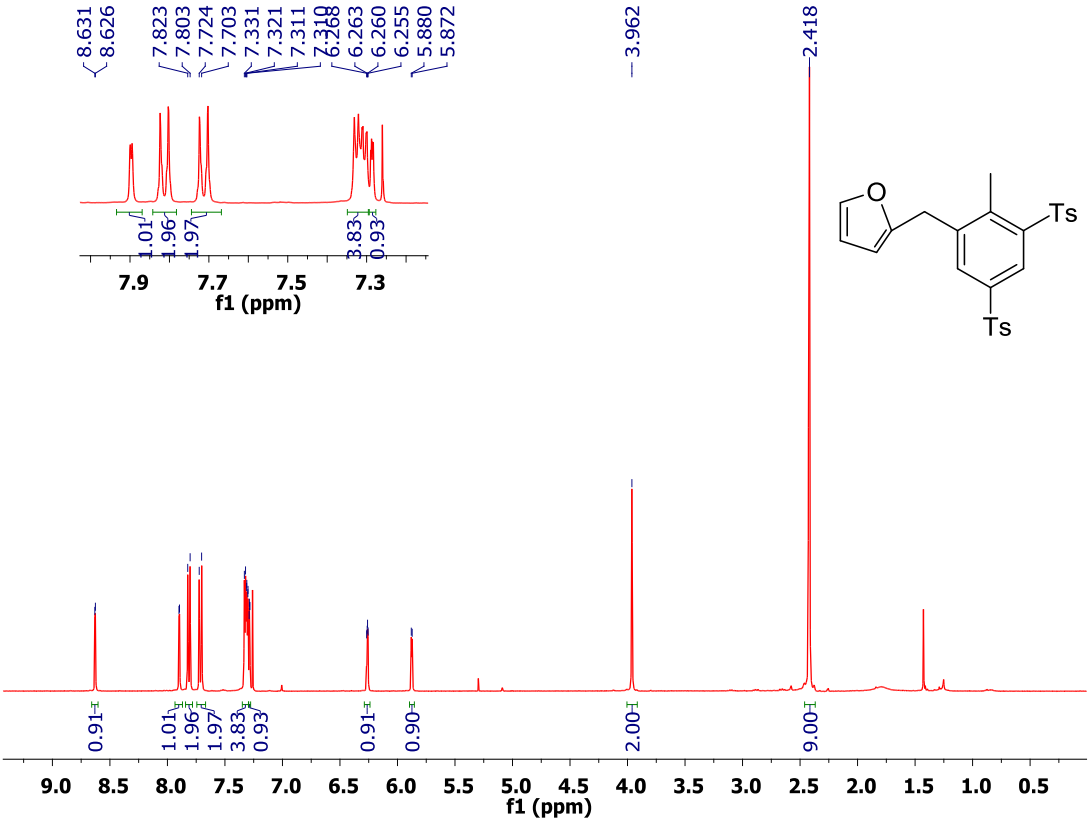
142.300
141.662
140.816
140.287
140.244
140.193
133.787
133.103
129.654
129.423
127.883
127.396
127.223
125.971
124.848
77.457
77.140
76.821
33.990
16.214
S
SO2Ph
SO2Ph
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.631
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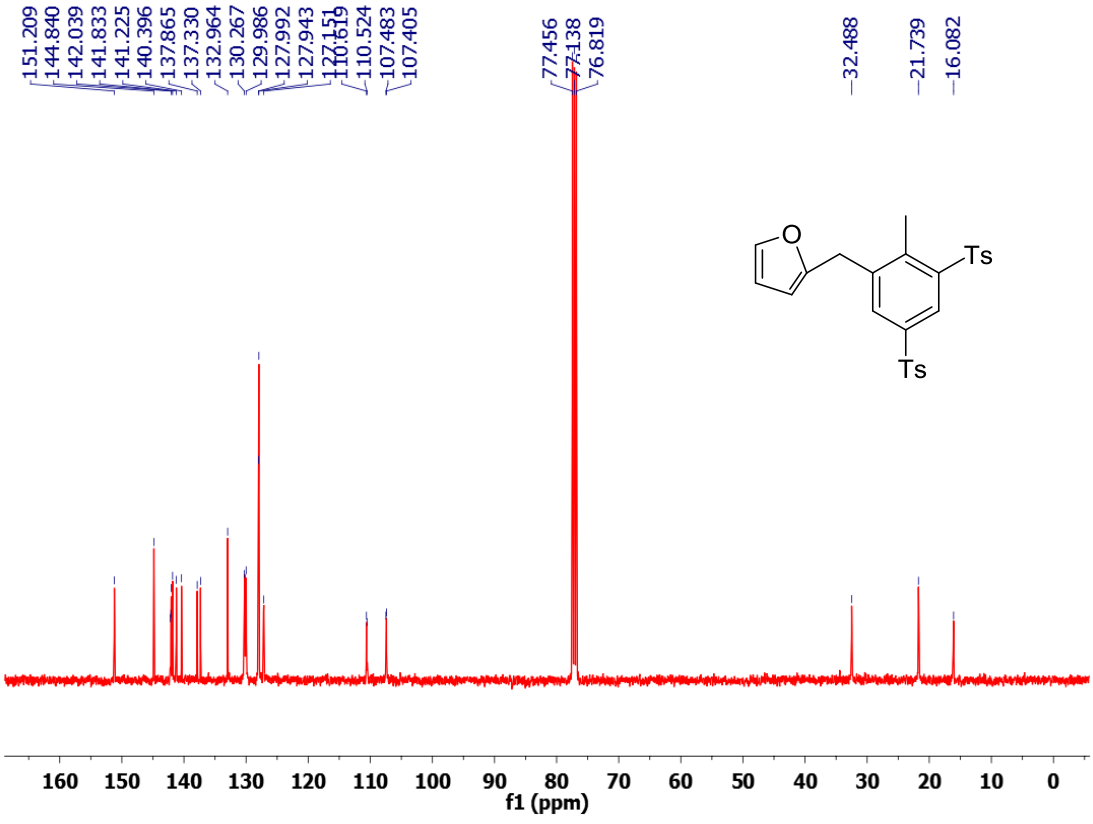
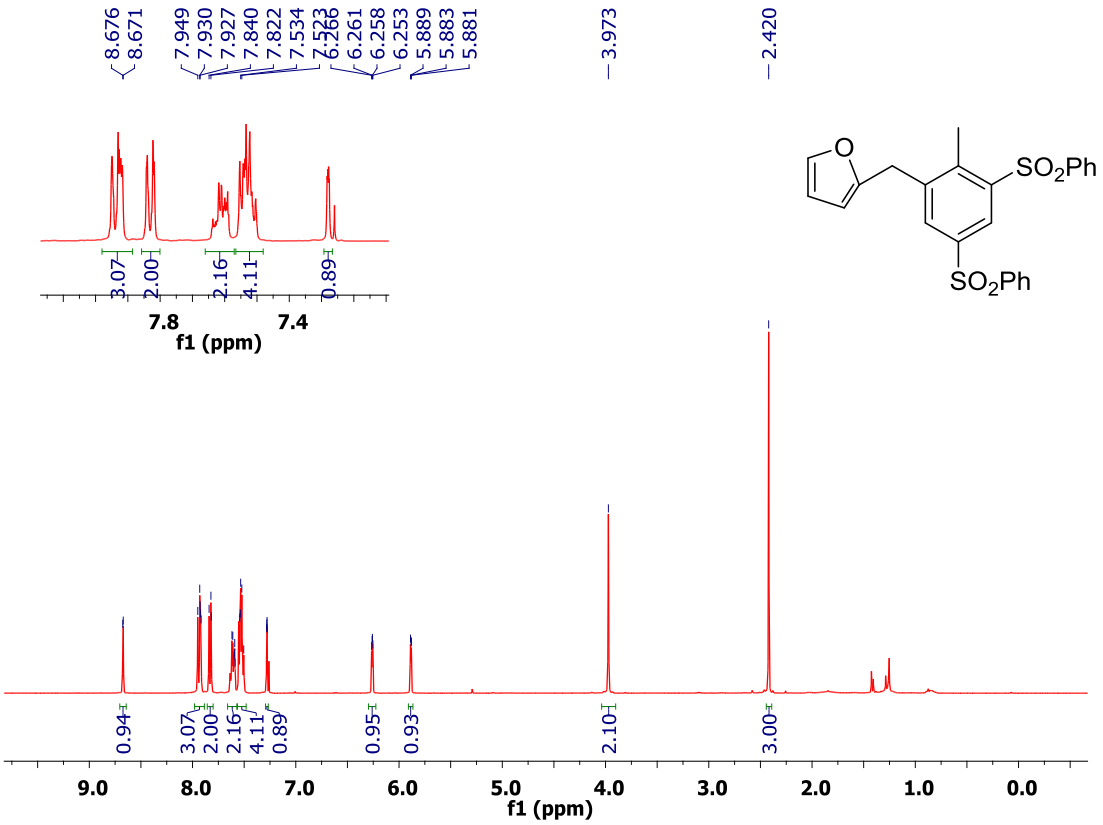
7.823
7.803
7.724
7.703
7.331
7.321
7.311
6.263
6.260
6.255
5.880
5.872
3.962
2.418
1.01
1.96
1.97
3.83
0.93
7.9
7.7
7.5
7.3
f1 (ppm)
O
Ts
Ts
0.91
1.01
1.96
1.97
3.83
0.93
0.91
0.90
2.00
9.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


151.209
144.840
142.039
141.833
141.225
140.396
137.865
137.330
132.964
130.267
129.986
127.992
127.943
110.524
107.483
107.405
77.456
77.138
76.819
32.488
21.739
16.082
O
Ts
Ts
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.930
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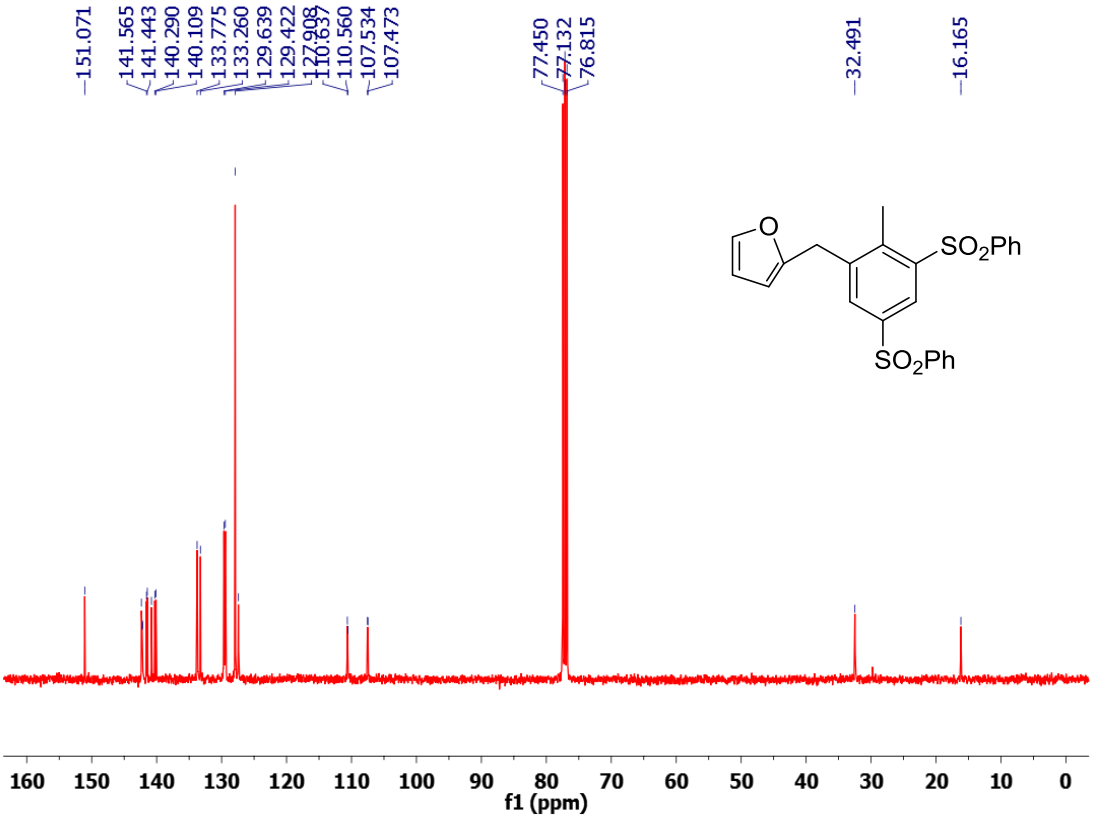
7.822
7.534
7.523
6.266
6.261
6.258
6.253
5.889
5.883
5.881
3.973
2.420
O
SO2Ph
SO2Ph
3.07
2.00
2.16
4.11
0.89
7.8
7.4
f1 (ppm)
0.94
3.07
2.00
2.16
4.11
0.89
0.95
0.93
2.10
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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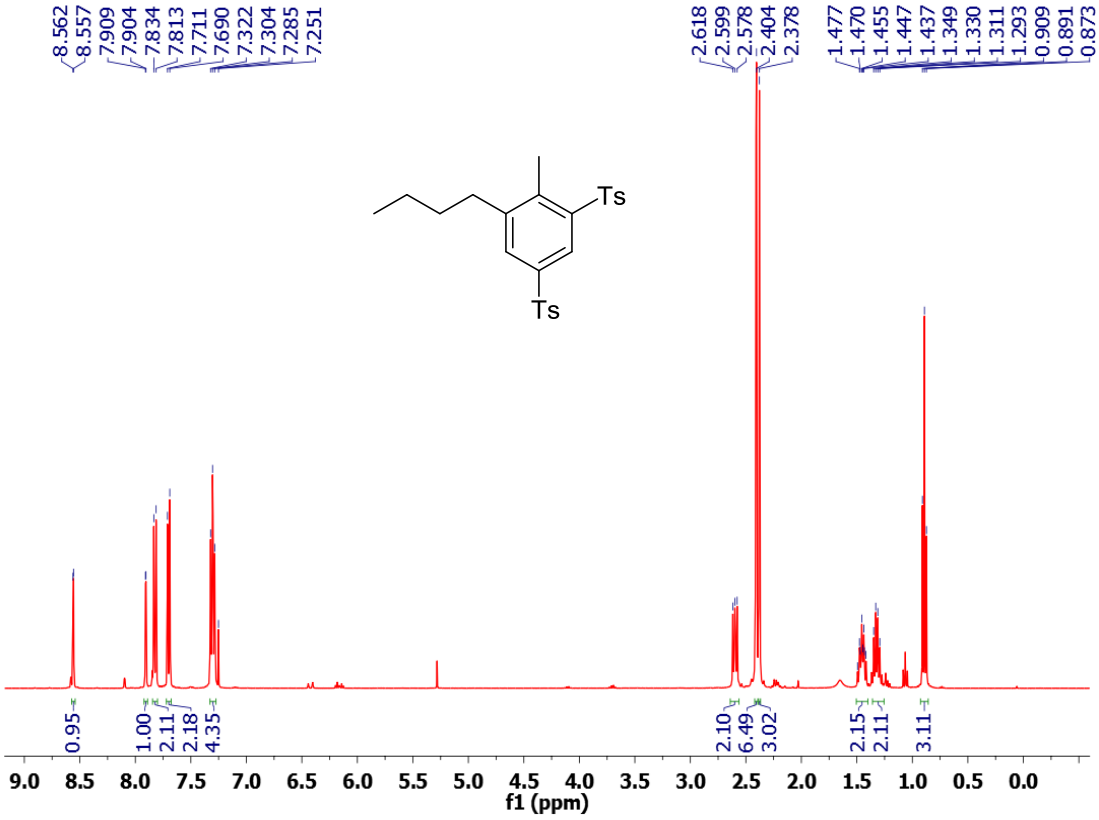
141.443
140.290
140.109
133.775
133.260
129.639
129.422
127.908
110.637
110.560
107.534
107.473
77.450
77.132
76.815
32.491
16.165
O
SO2Ph
SO2Ph
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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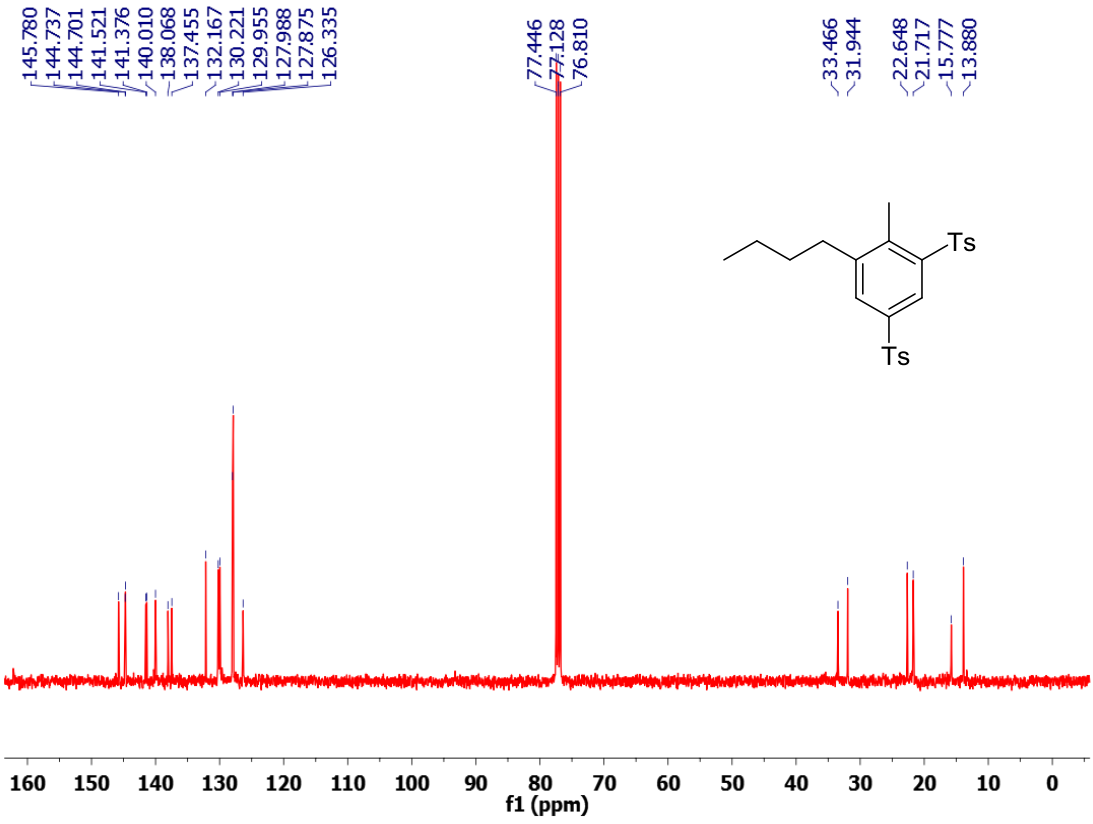
7.909
7.904
7.834
7.813
7.711
7.690
7.322
7.304
7.285
7.251
2.618
2.599
2.578
2.404
2.378
1.477
1.470
1.455
1.447
1.437
1.349
1.330
1.311
1.293
0.909
0.891
0.873
Ts
Ts
0.95
1.00
2.11
2.18
4.35
2.10
6.49
3.02
2.15
2.11
3.11
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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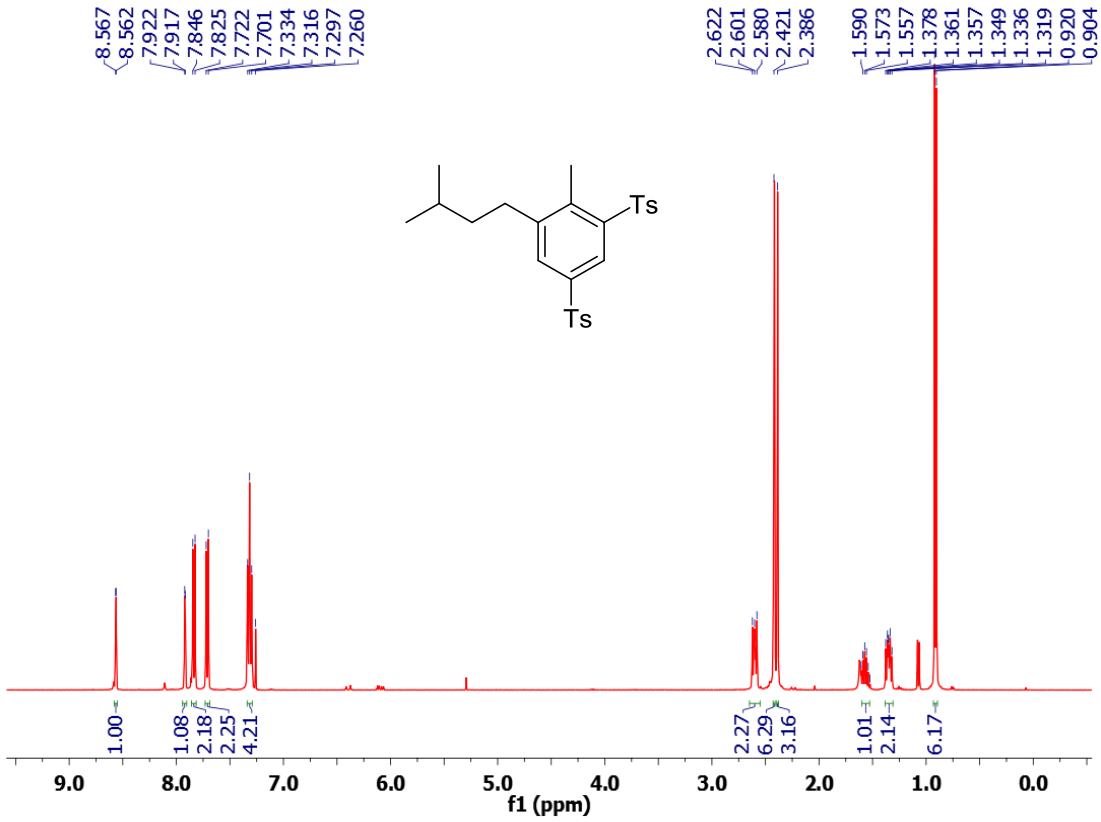
144.701
141.521
141.376
140.010
138.068
137.455
132.167
130.221
129.955
127.988
127.875
126.335
77.446
77.128
76.810
33.466
31.944
22.648
21.717
15.777
13.880
Ts
Ts
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.922
7.917
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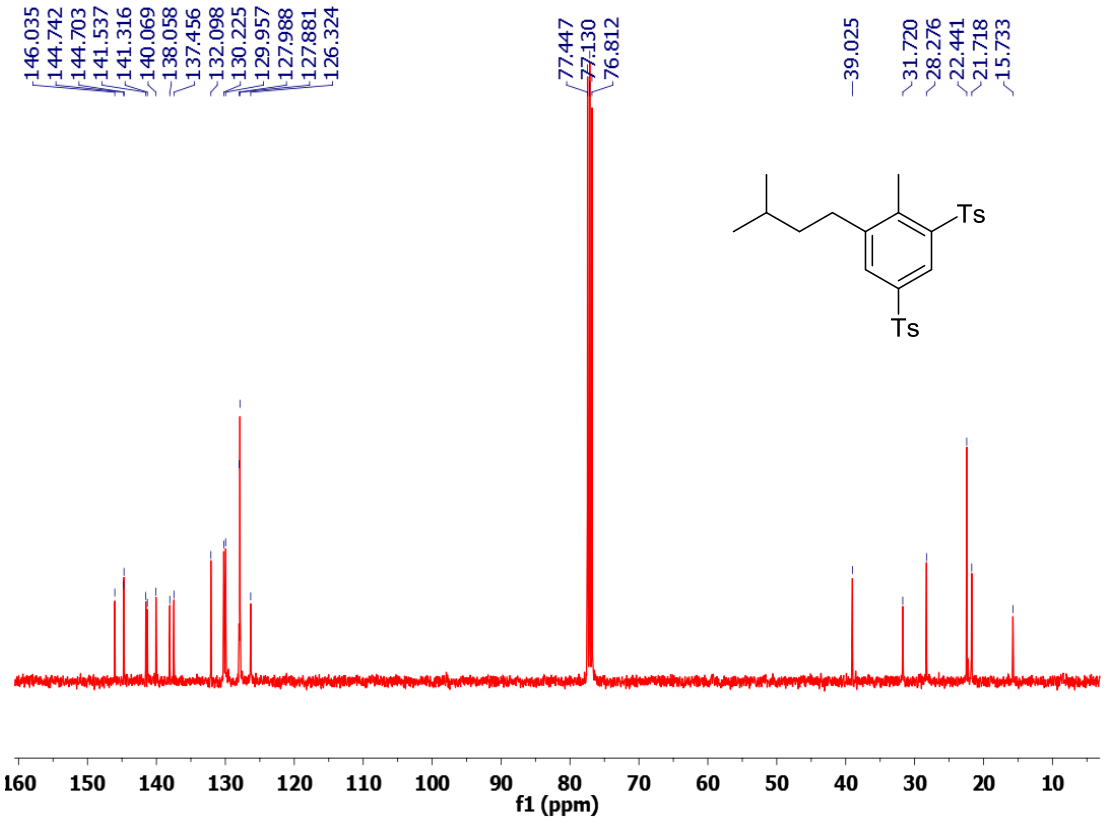
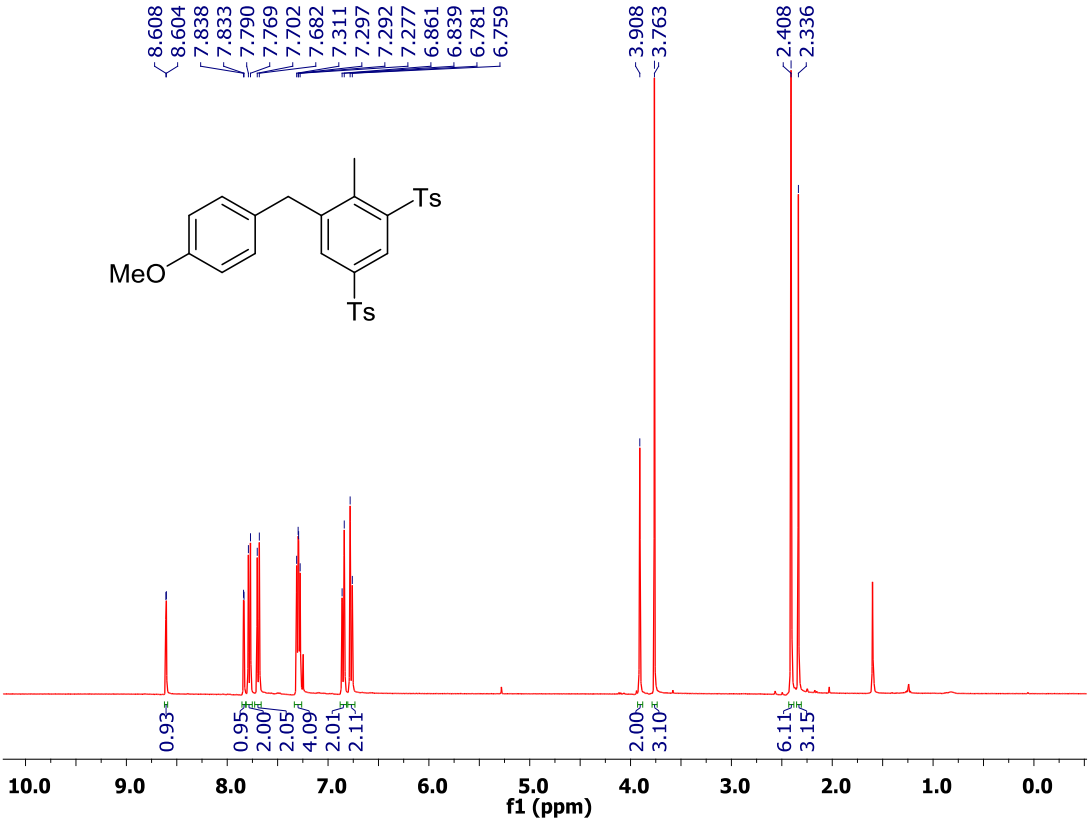
7.722
7.701
7.334
7.316
7.297
7.260
2.622
2.601
2.580
2.421
2.386
1.590
1.573
1.557
1.378
1.361
1.357
1.349
1.336
1.319
0.920
0.904
Ts
Ts
1.00
1.08
2.18
2.25
4.21
2.27
6.29
3.16
1.01
2.14
6.17
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


146.035
144.742
144.703
141.537
141.316
140.069
138.058
137.456
132.098
130.225
129.957
127.988
127.881
126.324
77.447
77.130
76.812
39.025
31.720
28.276
22.441
21.718
15.733
Ts
Ts
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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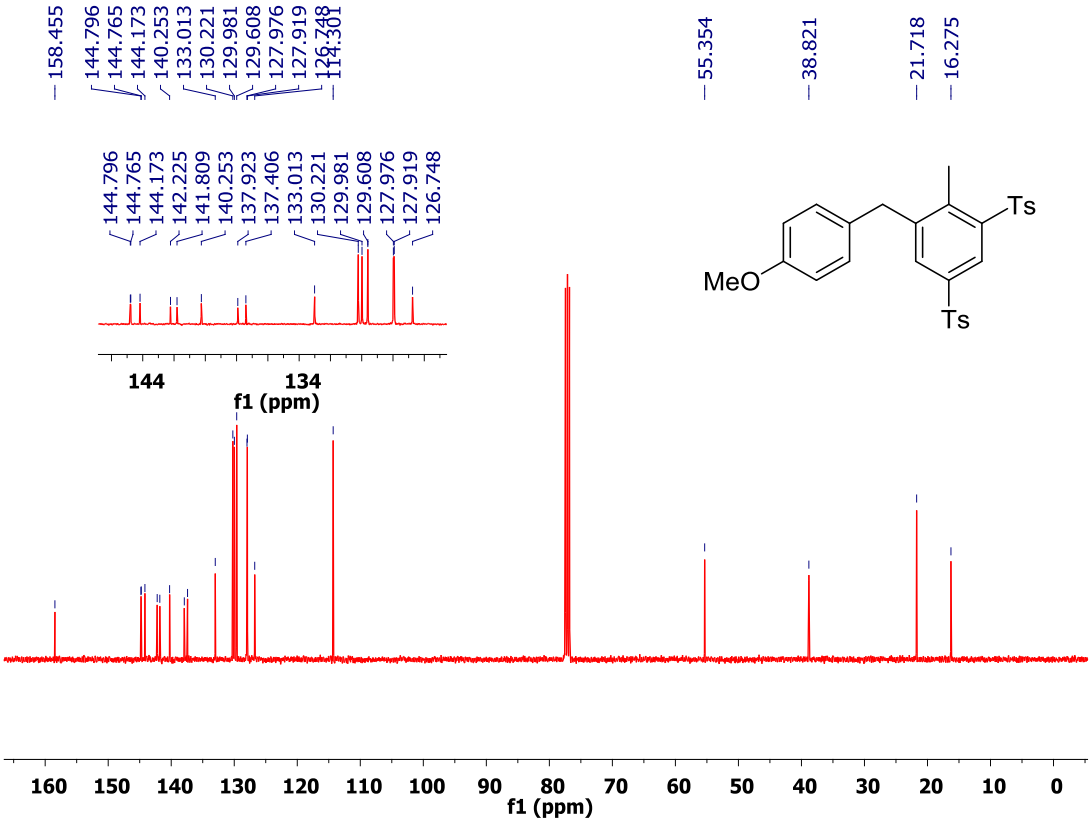
8.604
7.838
7.833
7.790
7.769
7.702
7.682
7.311
7.297
7.292
7.277
6.861
6.839
6.781
6.759
3.908
3.763
2.408
2.336
Ts
MeO
Ts
0.93
0.95
2.00
2.05
4.09
2.01
2.11
2.00
3.10
6.11
3.15
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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144
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f1 (ppm)
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MeO
Ts
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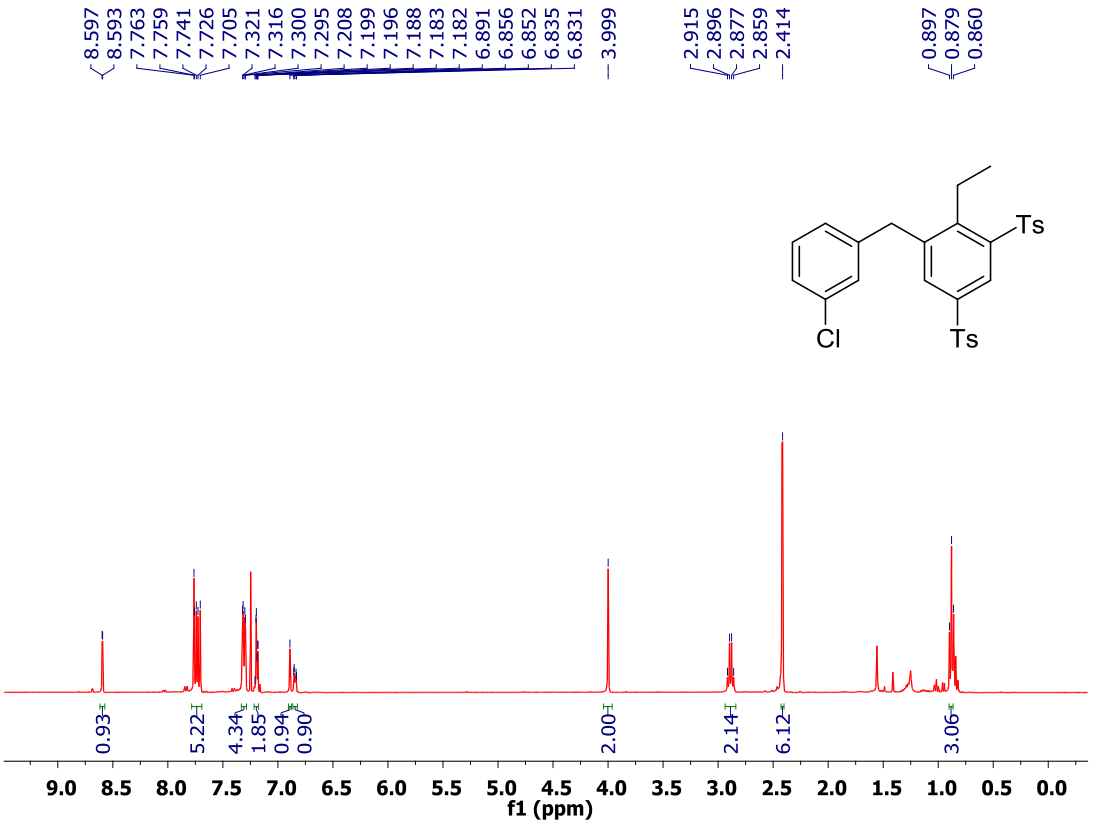
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Cl
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1.85
0.94
0.90
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2.14
6.12
3.06
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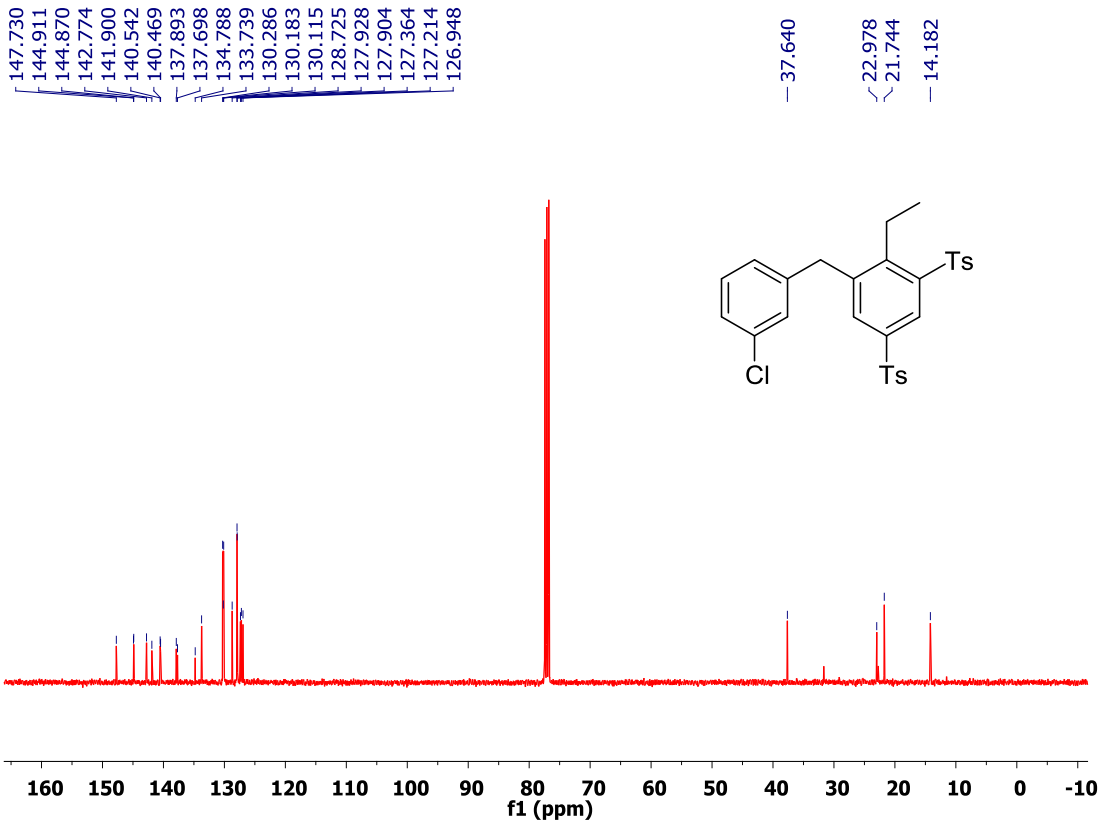
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Cl
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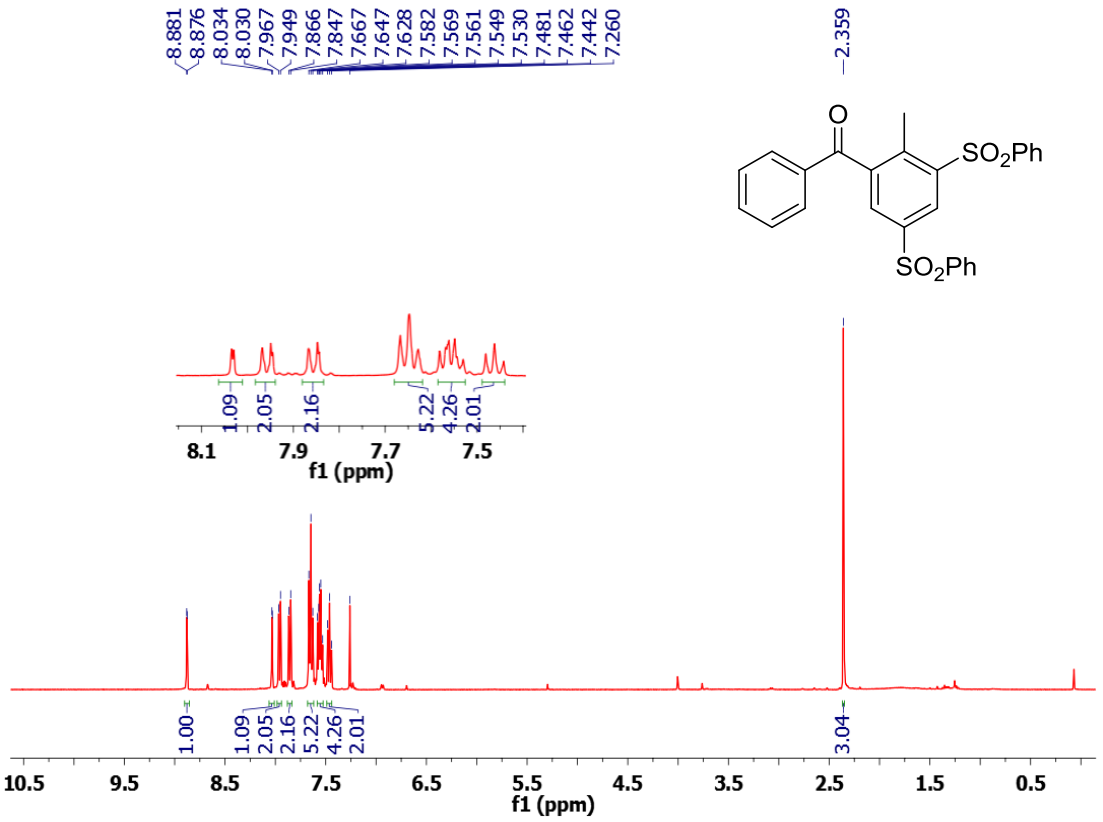
f1 (ppm)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7.260
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SO2Ph
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2.05
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7.7
7.5
f1 (ppm)
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5.22
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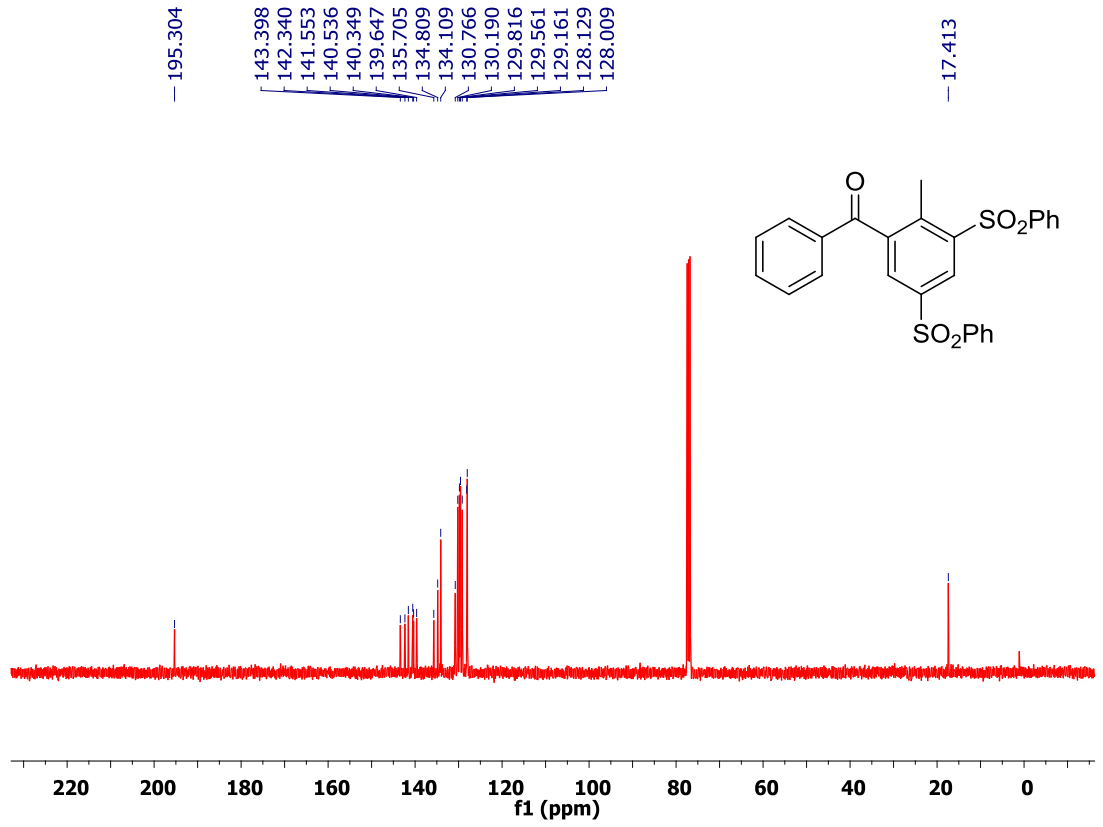
f1 (ppm)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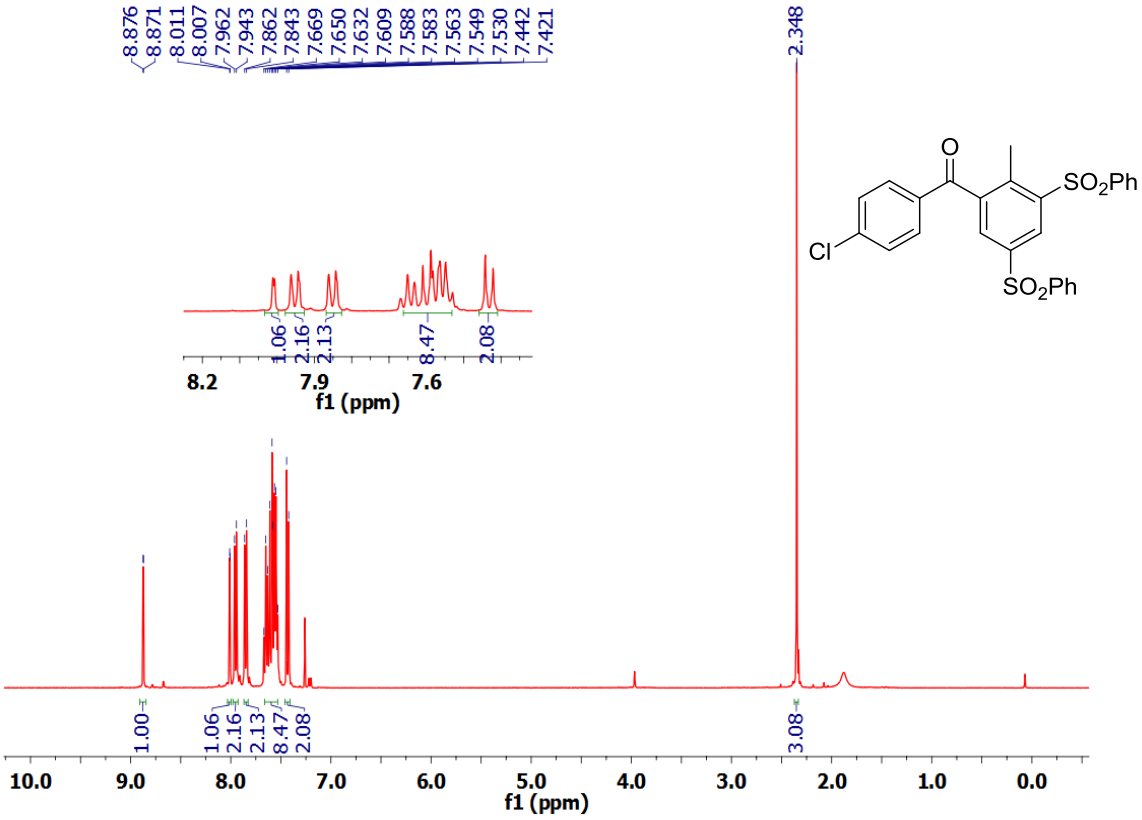
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7.563
7.549
7.530
7.442
7.421
2.348
1.06
2.16
2.13
8.47
2.08
8.2
7.9
7.6
f1 (ppm)
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2.08
3.08
10.0
9.0
8.0
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0.0
f1 (ppm)
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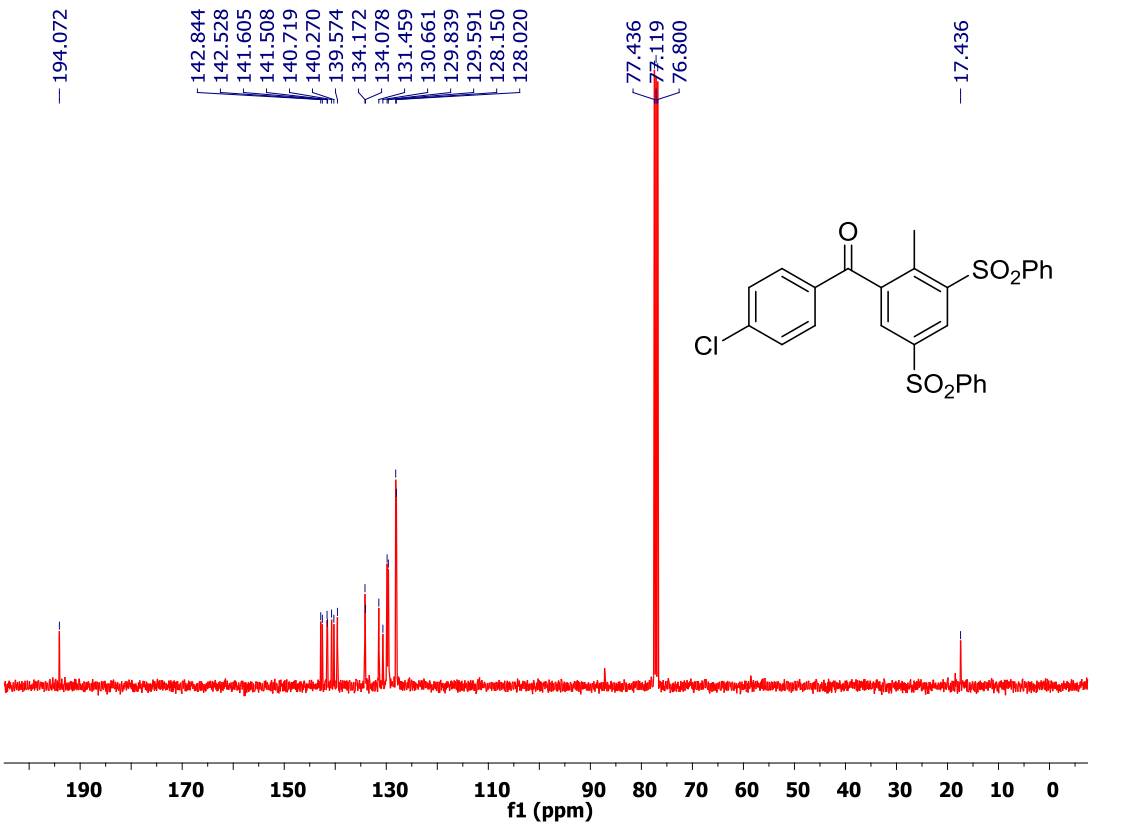
SO2Ph
Cl
SO2Ph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110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
O
SO2Ph
Cl
SO2Ph

Chapter III

Regioselective and oxidative [3+3] benzannulation reactions for the synthesis of highly substituted benzophenone derivatives

3.1. Introduction

Benzophenone is a privileged structural motif that is found in a variety of biologically active natural products and pharmaceuticals.[1] A number of benzophenone containing naturally occurring molecules exhibits a wide range of biological effects such as anti-inflammatory,[2] anti-microbial,[3] antioxidant,[4] anti-viral[5] and antiparasitic activities.[6] For example, cariphenone A, exhibits antioxidant activity and pestalone shows potent antibiotic activity against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecium (VREF). Additionally, cytotoxicity and anti-proliferative activity against cancer cells is commonly reported biological activity of a number of benzophenones.[7] Some important naturally occurring biologically active benzophenones are depicted in figure 1.

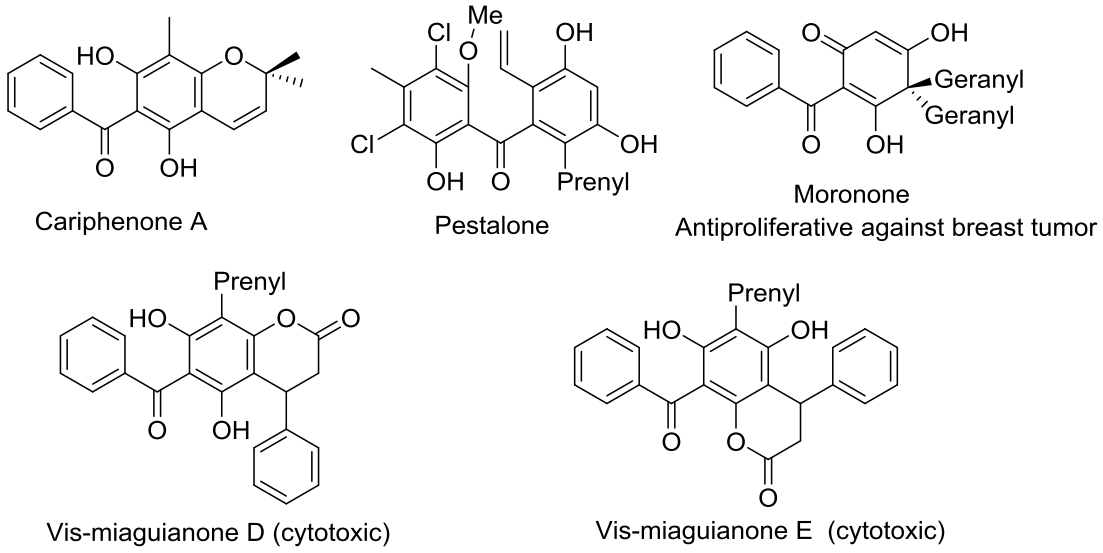


Figure 1: Some important naturally occurring biological active benzophenones

In addition to these biological activities, benzophenone represents one of the important classes of compounds in photochemical applications. Benzophenones show a significant absorption of ultra-violet (UV) light. Owing to their remarkable photochemistry they also find applications as photosenitizer,[8] photoredox catalysts[9] and active ingredients in sunscreens such as oxybenzone (Figure 2).[10] Additionally, a number of synthetic benzophenone derivatives are marketed as successful drugs. Tolcapone, a catechol-O-methyltranferase (COMT) inhibitor for the treatment of Parkinson's disease,[11] fenofibrate, a blood cholesterol reducing agent[12] and ketoprofen an antinflammatory drug, are three notable examples among these (Figure 2).

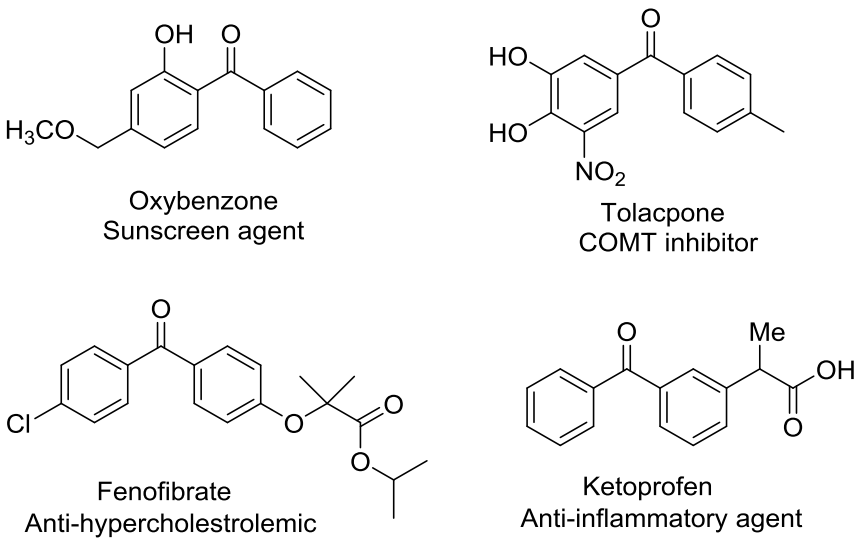


Figure 2: Selected examples of synthetic benzophenone-based drugs/cosmetics

Owing to their importance as building blocks in synthesis of many pharmacological compounds and photochemical properties, a number of synthetic methods for the construction of benzophenones have been developed. The most common among such methods is Friedel-Crafts benzoylation reactions.[14] The regiochemical outcome in these

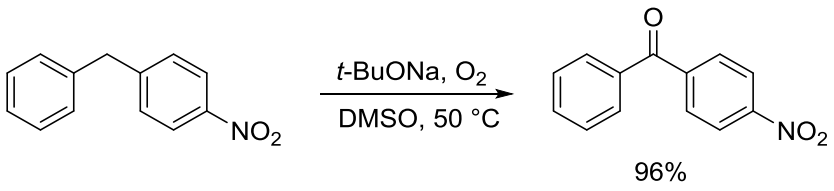
reactions is determined by the directing effect of the existing substituents on aryl ring. This feature may or may not lead to the selective formation of a desired regioisomer when the construction of poly-substituted benzophenone is attempted. Steric hinderence and deactivating effects of electron withdrawing groups also pose challenges in the synthesis of poly-substituted benzophenones.

To overcome these challenges, alternate methods such as oxidation of biarylmethanes,[15] oxidation of secondary alcohols,[16] metal-catalyzed coupling reactions,[17] oxidative cleavage of C-C double bonds[18] and direct addition of Grignard reagents to acyl chlorides[19] have been developed for their synthesis. Yet another alternative method is benzannulation reaction, wherein two acyclic precursors are combined together to form a benzene ring. The advantages of benzannulation reaction have been discussed in detail in chapter II. A brief overview of some of above-mentioned methods is described in following section.

3.2. Methods for the synthesis of benzophenone derivatives

3.2.1. Oxidation of biarylmethanes

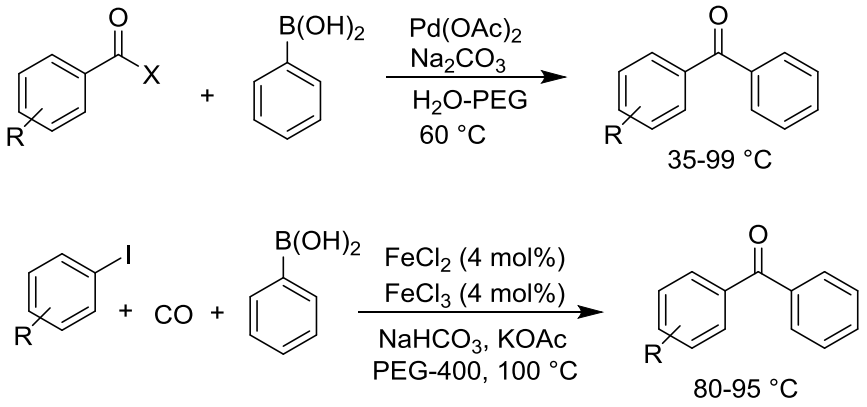
Li and co-workers developed a transition metal-free oxidation of benzylic sp^3 C-H bonds of biarylmethanes by O_2 and *t*-BuONa to generate the corresponding benzophenones (Scheme 1).[15a]



Scheme 1: Base and oxygen-mediated oxidation of biarymethanes to benzophenones

3.2.2. Transition metal-catalyzed coupling reactions

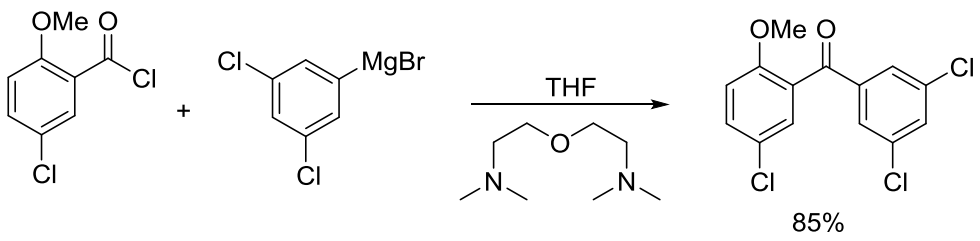
A variety of cross-coupling reactions for the synthesis of biaryl ketones are reported. Palladium-catalyzed cross coupling reactions of arylboronic acids with acyl halides, anhydrides or carboxylic acids is one among them.[17b] In addition, carbonylative coupling reaction is a widely used method for the construction of symmetrical and unsymmetrical benzophenones (Scheme 2).[17c]



Scheme 2: Synthesis of benzophenones via transition metal-catalyzed coupling reactions

3.2.3. Direct addition of Grignard reagents to acid chlorides

The addition of arylmagnesium halides to acid chlorides was reported by Wang and co-workers. The reaction afforded various aryl ketones in good yield when carried out in the presence of a simple tridentate ligand, *bis*-[2(N,N-dimethylamino)ethyl]ether (Scheme 3).[19]

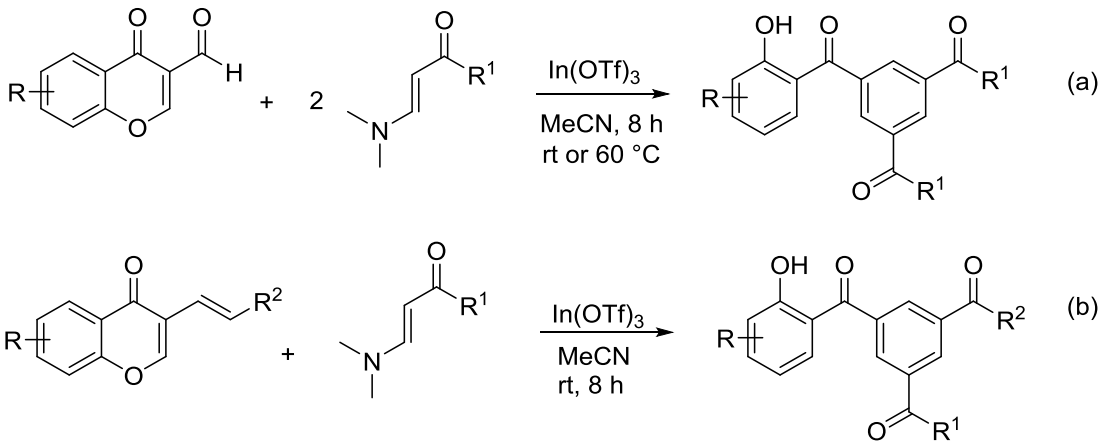


Scheme 3: Addition of arylmagnesium bromide to an acid chloride

It may be noted that the above discussed methods utilize precursors having pre-existing arene rings and conveniently provide access to a number of simple benzophenone derivatives. However, their scopes are limited when poly-functional benzophenones are required as the necessary building blocks would not be readily available. As stated above, benzannulation reactions, offer a number of advantages in such situations. Benzannulation reactions are superior to conventional methods in terms of variety of available reaction components, scope of catalysis and versatility of reaction conditions. A selection of benzannulation-based synthesis of benzophenone derivatives are described below to illustrate these virtues.

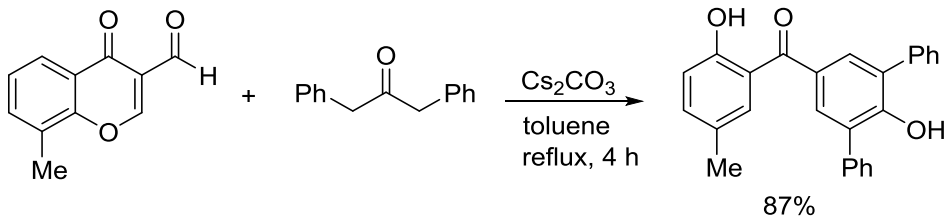
3.2.4. Benzannulation-based methods for synthesis of benzophenone derivatives

Lee and co-workers reported the construction of 2-hydroxybenzophenone derivatives *via* Indium(III)-catalyzed [2+2+2] benzannulation reaction of 3-formylchromones with β-enamino ketones or esters (Scheme 4a). In addition, they developed a [4+2] benzannulation reaction of 3-substituted chromen-4-ones with β-enamino ketones or esters that lead to the same class of products (Scheme 4b).[20]



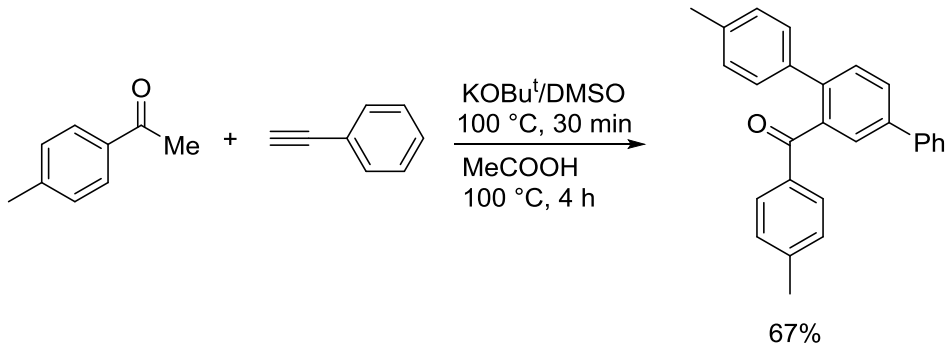
Scheme 4: Construction of 2-hydroxybenzophenone derivatives *via* [2+2+2] and [4+2] benzannulation reactions

A Cs_2CO_3-promoted benzannulation of 3-formyl chromones amd 1,3-diphenyl-2-propanone was also developed by Lee and co-workers. The reaction proceeds through an initial Knoevenagel condensation which is followed by an intramolecular Michael addition to generate substituted benzophenone derivatives (Scheme 5).[21]



Scheme 5: Synthesis of benzophenone derivatives from 3-formyl chromones and 1,3-diphenyl-2-propanone

A base-promoted reaction of acetylarenes with arylacetylenes furnished benzophenone derivatives. The reaction proceeds by the addition of enolate derived from acetylarene to arylacetylene to afford β,γ-unsaturated ketones. Subsequent [3+3] annulation reaction of the newly generated ketone with another molecule of β,γ-unsaturated ketone leads to the formation of benzophenone derivative (Scheme 6).[22]



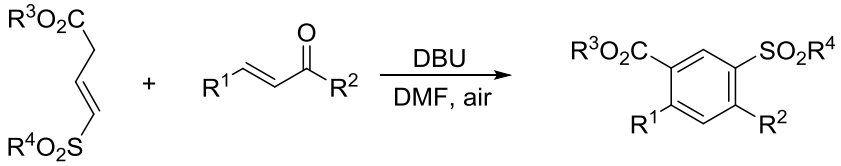
Scheme 6: Base-mediated synthesis of benzophenones from acetylarenes and arylacetylenes

3.3. Background to the present work

In view of the above-mentioned importance of benzophenone derivatives as well as the advantages of benzannulation reactions, we became interested in developing a convenient

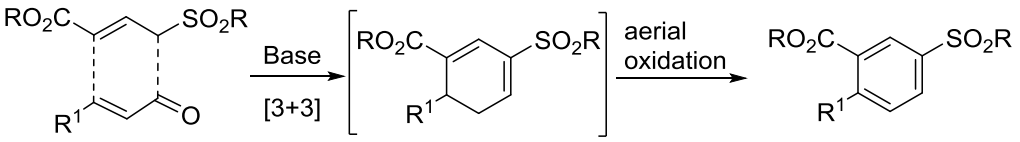
benzannulation-based route to benzophenones. The successful development of aerobic oxidative [3+3] benzannulation reaction of α,β-unsaturated carbonyl compounds with 4-sulfonyl crotonates to afford poly-substituted arenes (Scheme 7a)[23] and a related report[24] encouraged us to undertake this exploration. Mechanistically, our method involved a cyclocondensation of a bis-nucleophile and a bis-electrophile to generate a cyclohexadiene intermediate which underwent in situ aerial oxidation to the arene product (Scheme 7b). The bis-nucleophile (4-sulfonyl crotonate) may be viewed as a propene substituted with two electron withdrawing groups (ester and sulfonyl) at both ends. It was of interest to explore whether the ester group can be replaced with a ketone functionality (compound **1**). A parallel mechanistic scenario can be contemplated lading to the formation of a benzophenone product from **1** and enal **2** in the case of aroyl ketone (Scheme 7c).

Our previous work:



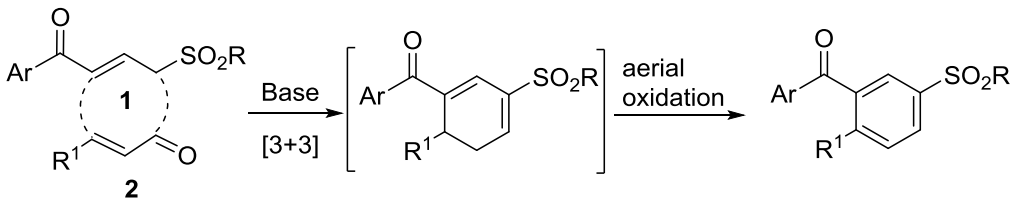
(a)

Simplified mechanistic overview:



(b)

Proposed benzannulation reaction:



(c)

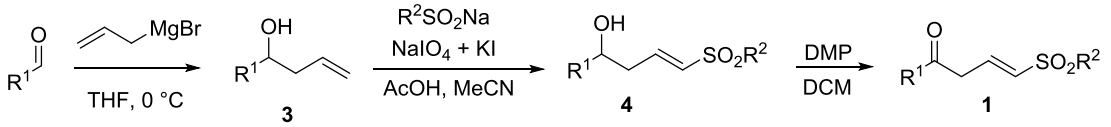
Scheme 7: [3+3] benzannulation reaction of α,β-unsaturated carbonyl compounds (a) with 4-sulfonyl crotonates (b) simplified mechanistic overview (c) Proposed benzannulation reaction

The implementation of the plan, however, posed two serious challenges: (i) ready availability of the 3-carbon nucleophilic component and (ii) the steric demands of a arylketo group would only be slightly different from that of the sulfonyl group thereby making steric differentiation of both ends of the propene unit by the bis-electrophile more challenging (the ester unit in the previous study is considerably smaller than the arylsulfonyl groups). This might lead to non-regioselective outcomes. However, in view of the importance of the product class and previous success we undertook the studies.

Our efforts towards this end, resulted in the discovery of a base-mediated, aerial oxidative [3+3] benzannulation reaction that afforded benzophenone/arene derivatives in excellent regioselectivity. The results of this study are presented in the following passages.

3.4. Results and discussion

In order to test our hypothesis, a convenient access to the required 1,3-bis-nucleophile **1** (1,3-disubstituted propene) was necessary and a three-step preparation from aldehydes was developed. The homoallylic alcohols **3** formed *via* allylation of aldehydes were treated with sodium arylsulfinates, $NaIO_4$ and KI to furnish the vinyl sulfones **4**.[25] This reaction proceeds via the iodosulfonylation of the terminal alkene and subsequent dehydroiodination. Oxidation of the secondary alcohol **4** using Dess-Martin periodinane (DMP) afforded the desired keto-sulfone **1** (Scheme 8).



Scheme 8: Preparation of the nucleophilic three-carbon building block **1** for the proposed benzannulation

Pleasingly this reaction was applicable to a number of aldehydes and a number of 1,3-bis-nucleophiles **(1a-1h)** were synthesized in good yields. A summary is depicted table 1. Substituted aryl ketones (**1a-f**, entries 1-6) were readily prepared from corresponding araldehydes, an alkyl derivative (**1g**, entry 7) was made from isovaleraldehyde and a heterocyclic analogue (**1h**, entry 8) from 2-formyl thiophene.

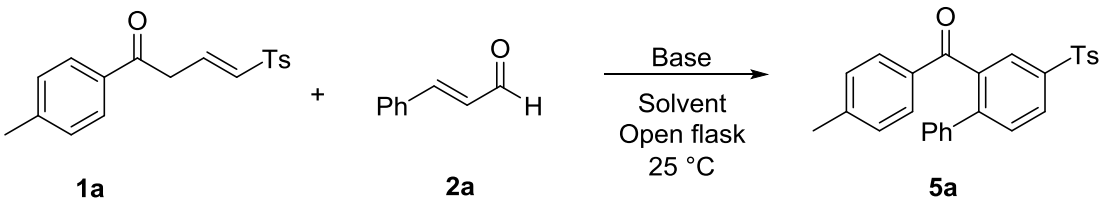
Table 1: Substrate scope for the preparation of 1,3-bis-nucleophile component 1

Entry	R^1	R^2	Isolated yield of **4** (%)	Isolated yield of **1** (%)
1	*p*-tolyl	*p*-tolyl	**4a**, 76	**1a**, 89
2	*p*-tolyl	Ph	**4b**, 74	**1b**, 87
3	phenyl	*p*-tolyl	**4c**, 75	**1c**, 89
4	4-bromophenyl	*p*-tolyl	**4d**, 81	**1d**, 91
5	2,3,4-trimethoxyphenyl	*p*-tolyl	**4e**, 78	**1e**, 89
6	4-isopropylphenyl	*p*-tolyl	**4f**, 73	**1f**, 84
7	isobutyl	*p*-tolyl	**4g**, 71	**1g**, 82
8	thiophene-2-yl	*p*-tolyl	**4h**, 68	**1h**, 78

Following the synthesis of precursors, we started our investigations with the benzannulation reaction of **1a** with a simple electrophilic partner cinnamaldehyde **2a**. Initially, these two reactants were treated under the optimized conditions for previously developed benzannulation reaction of sulfonyl crotonates (entry 1, Table 2). Reaction was carried out in open flask to promote aromatization via aerial oxidation. Pleasingly, a crystalline product was isolated after standard work-up and column chromatography. The product was tentatively assigned the structure **5a** on the basis of spectroscopic analysis. In the ^{1}H NMR spectrum of **5a** two different singlets at δ 2.34 (3H) and δ 2.42 (3H) were visible, indicating the presence of two methyl groups on aryl rings in the

final product. In ^{13}C NMR spectrum, the signals at δ 21.8 and δ 21.7 confirmed the presence of these two methyl groups. The signal at δ 8.01 (d, J = 2.0Hz, 1H) was assigned to proton that is sandwiched between the carbonyl and sulfonyl group on the newly formed ring. The other hydrogens in aromatic region gave the expected resonance pattern. In ^{13}C NMR spectrum, the signal at δ 196.3 indicated the presence of ketone carbon in the product. An absorption band at 1741 cm^{-1} in IR spectrum also agreed with this assignment. Other spectroscopic features were also in agreement with the assigned structure. It may be noted that the depicted regiochemistry was tentatively assigned at this stage for the compound **5a**.

Table 2: Optimization of reaction conditions for benzannulation reaction of 1,3-bis nucleophile 1a and cinnamaldehyde 2a[a]



1a **2a** **5a**

Entry	Base (mmol)	Solvent	Time (h)	Product (yield %)[b]
1	DBU (1.1)	DMF	2	54
2	DBU (1.1)	CH_3CN	2	43
3	DBU (1.1)	THF	2	49
4	DBU (1.1)	DMSO	2	42
5	DBU (1.1)	1,4-dioxane	2	29
6	DBU (1.1)	CH_2Cl_2	2	36
7	**DBU (2)**	**DMF**	**1**	**74**
8	Cs_2CO_3 (2)	DMF	1	41
9	Pyridine (2)	DMF	1	32
10	t-BuOK (2)	DMF	1	40
11[c]	DBU (2)	DMF	1	72

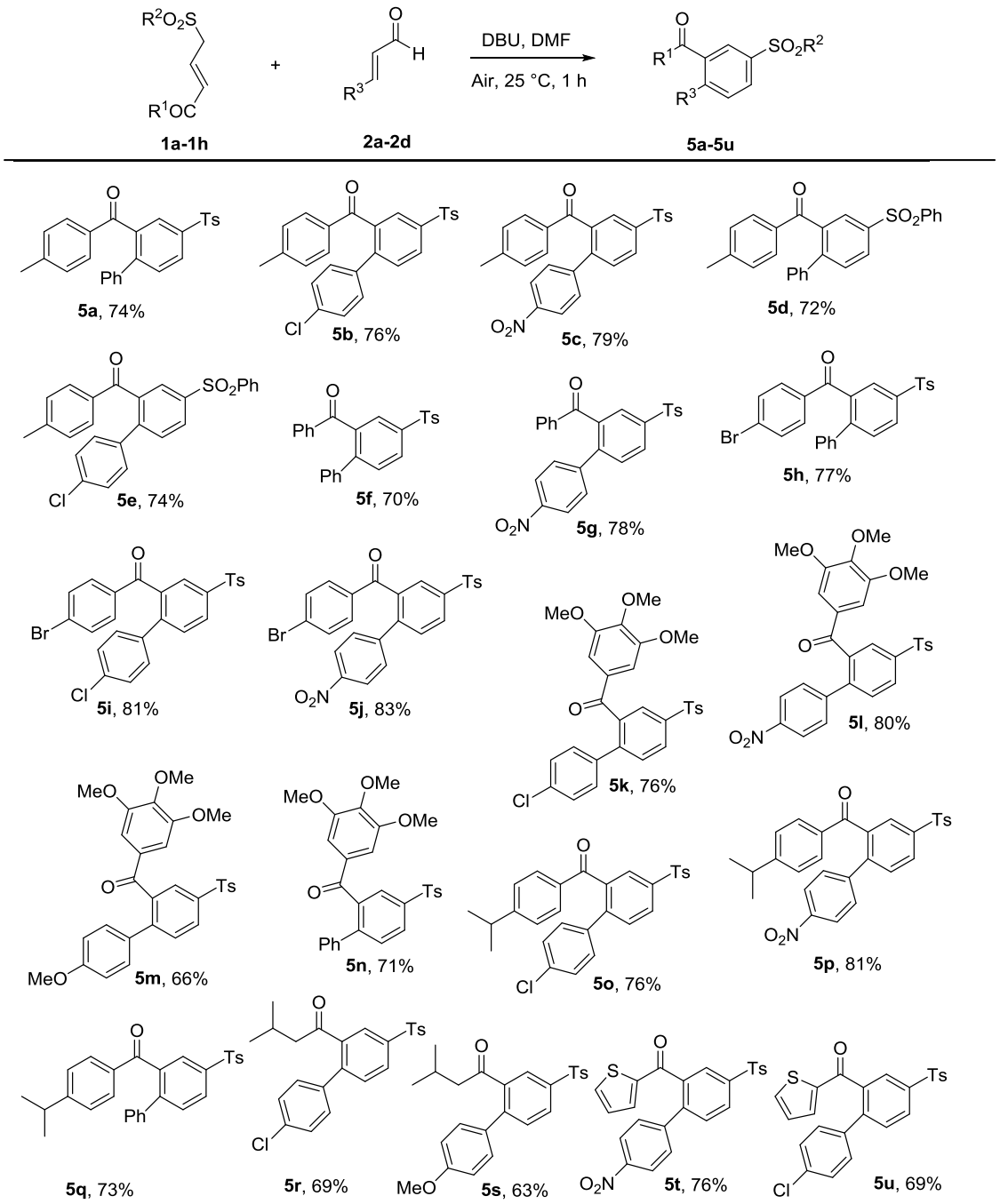
[a]Reaction conditions: **1a** (0.11 mmol), **2a** (0.1mmol), DMF (1 ml), 25 °C. [b]Yield of isolated product. [c]under oxygen atmosphere.

Although the product **5a** could be isolated and identified, the yield (54%) was less than satisfactory. Therefore, a number of reaction conditions were investigated by varying the nature and amount of base in various solvents. The same product **5a** was obtained in all cases in varying yields. The best result was obtained when the reactants were exposed to two molar equivalent of DBU in DMF for 1h (entry 7, table 2). Other bases such as cesium carbonate (entry 8), pyridine (entry 9), potassium tert-butoxide (entry 10) and solvents (entry 2-6) were less effective in promoting the benzannulation reaction. There was no significant change in yield when the reaction was carried out under an oxygen atmosphere (entry 11, table 2).

The pleasing outcome encouraged us to explore the substrate scope and generality for this benzannulation reaction. The various 1,3-bis-nucleophiles **1a-h** and α,β-unsaturated aldehydes were subjected to the optimized benzannulation conditions. Delightfully, the corresponding benzophenone derivatives isolated in all the cases. The results are summarized in Table 3.

All the 1,3-bis nucleophiles **1a-h** reacted smoothly with different α, β- unsaturated aldehydes and afforded a wide variety of highly substituted sulfone-bearing benzophenone and arene derivatives. Both electron withdrawing groups such as nitro **(5g, 5l, 5p, 5t)** and electron donating group such as methoxy **(5m, 5s)** are tolerated in benzannulation reaction. A heterocyclic residue such as thiophene can also be easily incorporated into final product by using the corresponding 1,3-bis-nucleophile **1h**.It is important to note that the reaction is not limited to aryl 1,3-bis-nucleophile. The alkyl ketone **1g** reacted smoothly with various enals in the benzannulation reaction to afford the corresponding substituted isobutyl aryl ketones **(5r, 5s)**.

Table 3: Generality and scope of the benzannulation reaction[a]



[a]Reaction conditions: **2a** (0.3mmol), 1,3-bis-nucleophile **1a-h** (0.33 mmol), DBU (0.45 mmol) DMF (4 ml), 25 °C, 1h. Yield of isolated products given.

Single crystal X-ray analysis of a representative product **5h** was also obtained at this stage (Figure 4). Thus the structure and regiochemistry assignment of the products **5a-u** were unambiguously established.

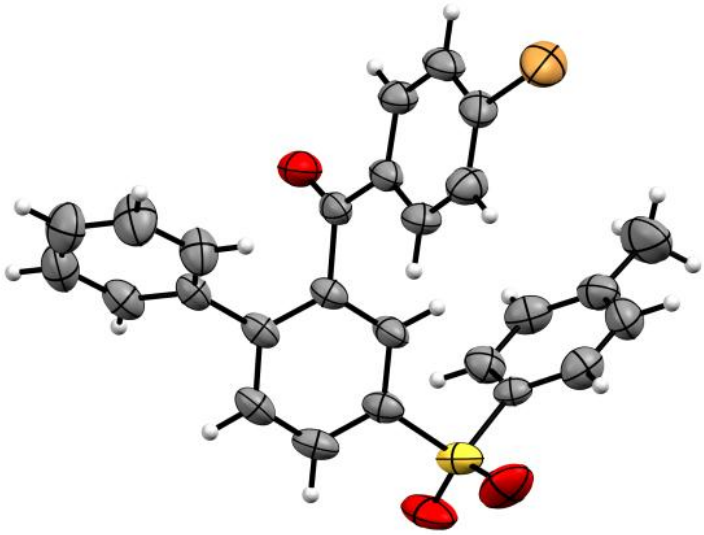
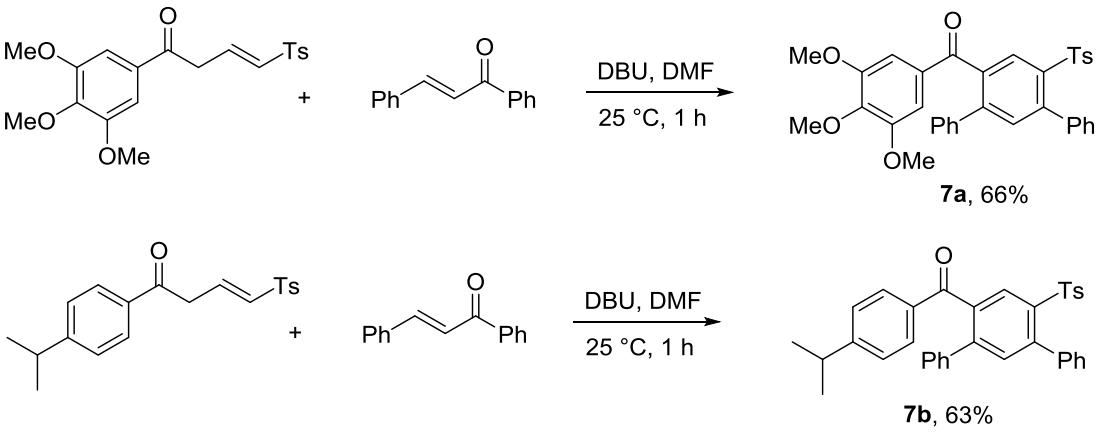


Figure 4: ORTEP diagram of **5h**

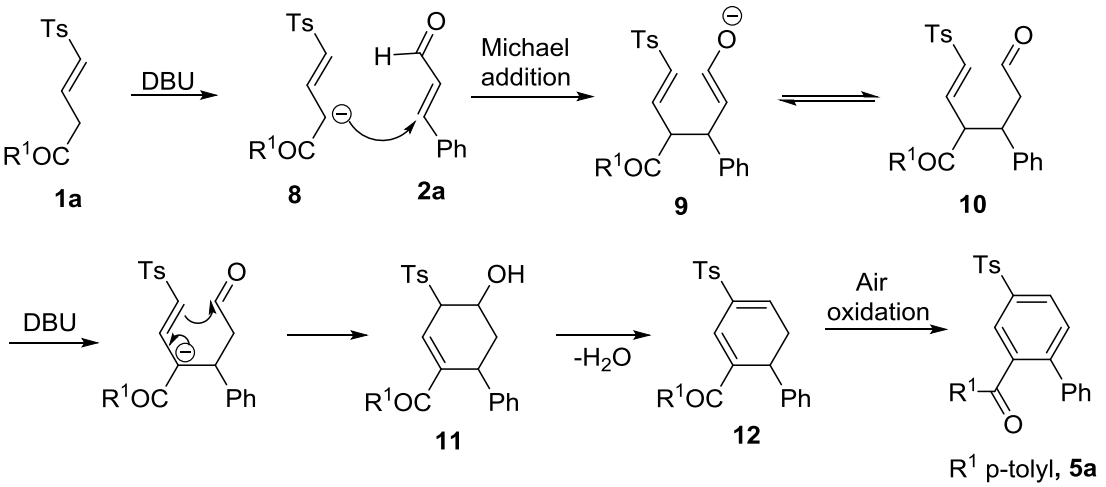
The promising results of benzannulation reaction with α, β- unsaturated aldehydes prompted us to explore its applicability to enones. Readily prepared chalcone **6** was chosen as a representative unsaturated ketone for this purpose. Smooth conversions of **6** to the highly substituted benzophenone derivatives **7a-b** were observed when the former was reacted with trimethoxyphenyl (**1e**) as well as isopropyl (**1f**) keto-sulfones, albeit in slightly reduced yields (Scheme 9). It may be noted that the newly installed benzene ring is endowed with four rather bulky substituents at well defined positions.



Scheme 9: Benzannulation reaction of trans-chalcone **6** and enals

3.5. Plausible mechanism of the benzannulation reaction

A simplified plausible mechanism for the benzannulation reaction is depicted in Scheme 10. It is likely that reaction is initiated by deprotonation of 1,3-substituted propene **1a** by DBU to generate the stabilized carbanion **8**. The latter may undergo an intermolecular Michael addition with enals/enones **2**. It may be noted that carbanion may react via either of its terminal carbons. It is presumable that the carboanion **8** reacts via the sterically less hindered α-carbonyl end with enal **2**, which results in the formation of enolate **9**. Further, deprotonation and intramolecular nucleophilic addition of the resulting carbanion to the aldehyde affords the cyclohexenol derivative **11**. The dehydydaration of **11** generates cyclohexadiene **12**. The final aromatic product **5a** is then formed via oxidation of **12** by atmospheric oxygen.



Scheme 10: Plausible mechanism for benzannulation reaction

It is worth to note that the cyclohexadiene moiety **12** can also undergo aromatization by eliminating tosyl moiety via base promoted H-shift and then β-elimination. This is presumably slower than the aerial oxidation and the sulfonyl moiety is retained in the final product.

3.6. Conclusion

In conclusion, a base promoted regioselective synthesis of substituted benzophenone/ arenes via aerobic oxidative [3+3] benzannulation reaction of α,β-unsaturated carbonyl compounds and 1,3-bisnucleophile (1,3-disubstituted propene) was developed. In this reaction two acyclic precursors were assembled to afford arylsulfonyl bearing benzophenone. The reaction described here proceeds at room temperature in an open flask, in presence of DBU under mild conditions. Additionally, the reaction uses no metals and utilizes atmospheric oxygen for oxidation. The benzannulation method is notable for its efficiency, scope and generality. The reaction afforded highly substituted sulfonyl containing benzophenone derivatives which are difficult to synthesize via conventional methods. It is presumable that the method may find applications in the targeted synthesis of designer benzophenone derivatives of importance.

3.7. Experimental section

General information

All ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solvent at ambient temperature, chemical shift δ are given in ppm on a scale downfield from TMS, and the coupling constant *J* are in Hz. The signal patterns are indicated as follows: s, Singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; brs = broad). FTIR spectra were recorded as neat. Melting points were recorded on an electrothermal apparatus and are uncorrected. All the reagents and solvents were used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh and 100- 200

mesh) packed in glass columns. All reactions were performed in oven-dried glassware with magnetic stirring. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining by $KMnO_4$. High-resolution mass spectra were recorded with q-TOF electrospray mass spectrometer. All purchased chemicals were used as received.

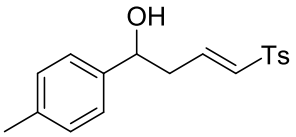
Synthesis of Alkene 3: General Procedure[25]

A solution of allyl magnesium bromide (1M in diethyl ether, 1.5 equiv) was added dropwise to a solution of aldehyde (1 equiv) in anhydrous diethyl ether at 0 ˚C. The reaction mixture was allowed to warm to room temperature and stirred for overnight. After completion of reaction an aqueous solution of NH_4Cl was added at 0 ˚C. The organic layer was extracted ether. The combined organic layer was dried over sodium sulfate and solvent was evaporated on rotavapour. The crude material was purified by Column chromatography on silica gel using ethyl acetate-petroleum ether as eluent to afford pure homoallylic alcohols **3**.

Synthesis of Vinyl Sulfones: General Procedure[26]

To a stirred solution of alkene **3** (2.0 mmol) and $ArSO_2Na$ (2 equiv) in MeCN (20 mL), $NaIO_4$ (10mol %), KI (10 mol %) and 2-3 drops of AcOH were added. The reaction mixture was stirred at room temperature for 24h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched by adding sat. aq $Na_2S_2O_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The extract was dried with anhydrous sodium sulfate and solvent was evaporated on a rotavapor. Column chromatography of the resulting residue on silica gel using ethyl acetate-petroleum ether as eluent afforded analytically pure samples of the vinyl sulfones **4a-h**.

Spectroscopic data for vinyl sulfones



4a, (E)-1-(p-tolyl)-4-tosylbut-3-en-1-ol

White solid, 480 mg, 76%

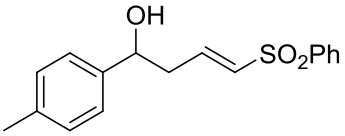
Melting point: 102-104˚C

IR (KBr) υ_{max}: 3508, 3041, 2922, 2883, 1635, 1595, 1440, 1267, 1138, 1031, 813, 522

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3Hz, 2H), 7.30 (d, J = 8.0Hz, 2H), 7.17 (d, J = 8.3Hz, 2H), 7.11 (d, J = 8.0Hz, 2H), 6.98–6.88(m, 1H), 6.32 (d,t, J = 15.2, 1.4Hz, 1H), 4.79 (d,d, J = 7.0, 5.8Hz, 1H), 2.71–2.53 (m, 2H), 2.43 (s, 3H), 2.32(s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 142.4, 140.1, 137.8, 137.5, 132.9, 129.9, 129.4, 127.7, 125.7, 72.6, 40.8, 21.7, 21.2

HRMS calcd for $C_{18}H_{22}O_4S$ (M+H_2O) 334.1239 ; found 334.1437



4b, (E)-4-(phenylsulfonyl)-1-(p-tolyl)but-3-en-1-ol

White solid, 447 mg, 74%

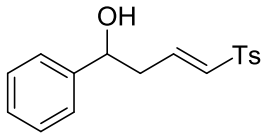
Melting point: 106-107˚C

IR (KBr) υ_{max}: 3535, 2889, 1629, 1583, 1444, 1419, 1300, 1138, 1047, 748, 580

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1Hz, 2H), 7.61(t, J = 7.4Hz, 1H), 7.51(t, J = 7.7Hz, 2H), 7.18 (d, J = 8.1Hz, 2H), 7.12 (d, J = 8.1Hz, 2H), 7.03–6.94 (m, 1H), 6.35 (dt, J = 15.1, 1.2Hz, 1H), 4.84–4.79 (m, 1H), 2.74-2.57 (m, 2H), 2.32 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.5, 140.0, 137.9, 133.3, 132.7, 129.4, 129.2, 127.6, 125.6, 72.6, 40.8, 21.1

HRMS calcd for $C_{17}H_{20}O_4S$ ($M+H_2O$) 320.1082 ; found 320.1283



4c, (E)-1-phenyl-4-tosylbut-3-en-1-ol

White solid, 453 mg, 75%

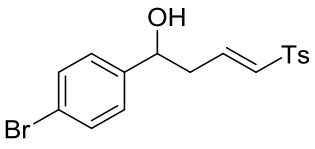
Melting point: 109-110˚C

IR (KBr) υ_{max}: 3491, 3064, 2926, 2870, 1624, 1593, 1450, 1398, 1284, 1139, 1078, 756, 673

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3Hz, 2H), 7.37–7.21 (m, 7H), 6.97-6.90 (m, 1H), 6.33 (d,t, J = 14.3, 1.2Hz, 1H), 4.82 (dd, J = 7.5, 5.2Hz, 1H), 2.71–2.54 (m, 2H), 2.42 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.1, 142.3, 137.4, 133.0, 129.9, 128.7, 128.1, 127.7, 125.7, 72.7, 40.8, 21.7

HRMS calcd for $C_{17}H_{20}O_4S$ ($M+H_2O$) 320.1082 ; found 320.1281



4d, (E)-1-(4-bromophenyl)-4-tosylbut-3-en-1-ol

Yellow solid, 617 mg, 81%

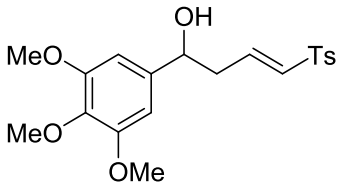
Melting point: 107-108˚C

IR (KBr) υ_{max}: 3510, 3047, 2879, 1635, 1593, 1483, 1309, 1280, 1141, 1041, 813, 657, 524

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0Hz, 2H), 7.41 (d, *J* = 8.4Hz, 2H), 7.31 (d, *J* = 8.0Hz, 2H), 7.15 (d, *J* = 8.4Hz, 2H), 6.94–6.87 (m, 1H), 6.30 (dt, *J* = 15.1, 1.3Hz, 1H), 4.83 (dd, *J* = 7.0, 5.5Hz, 1H), 2.68–2.54 9m, 2H), 2.44 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 142.0, 141.6, 137.3, 133.4, 131.8, 129.9, 127.6, 127.4, 121.8, 72.0, 40.8, 21.7

HRMS calcd for $C_{17}H_{19}BrO_4S$ (M+ H_2O) 398.0187; found 398.0406



4e, (E)-4-tosyl-1-(3,4,5-trimethoxyphenyl)but-3-en-1-ol

White solid, 612 mg, 78%

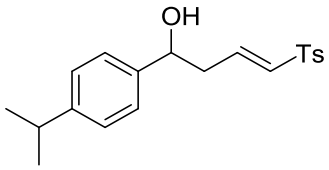
Melting point: 140-142˚C

IR (KBr) υ_{max}: 3512, 2935, 1589, 1485, 1419, 1305, 1235, 1122, 1082, 655, 534

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4Hz, 2H), 7.28 (d, *J* = 8.4Hz, 2H), 6.98–6.91 (m, 1H), 6.49 (s, 2H), 6.34 (dt, *J* = 15.2, 1.2Hz, 1H), 4.74 (dd, *J* = 7.3-5.2Hz, 1H), 3.80 (s, 6H), 3.78 (s, 3H), 2.62-2.56 (m, 2H), 2.39 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.38, 153.36, 144.4, 142.4, 139.0, 137.4, 132.8, 129.9, 127.6, 102.5, 72.8, 60.8, 56.1, 40.9, 21.6

HRMS calcd for $C_{20}H_{26}O_7S$ (M+H_2O) 410.1399 ; found 410.1643



4f, (E)-1-(4-isopropylphenyl)-4-tosylbut-3-en-1-ol

White solid, 502 mg, 73%

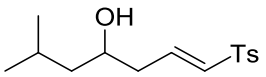
Melting point: 107-109˚C

IR (KBr) υ_{max}: 3566, 3047, 2958, 1629, 1593, 1458, 1415, 1300, 1139, 1082, 812, 661, 528

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2Hz, 2H), 7.30 (d, J = 8.4Hz, 2H), 7.21-7.15 (m, 4H), 6.99–6.94 (m, 1H), 6.34 (dt, J = 14.9, 1.2Hz, 1H), 2.90-2.83 (m, 1H), 2.68-2.59 (m, 2H), 2.40 (m, 3H), 1.22 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 144.3, 142.4, 140.4, 137.5, 133.0, 129.9, 127.7, 126.8, 125.7, 72.7, 40.7, 33.9, 24.03, 24.02, 21.6

HRMS calcd for $C_{20}H_{26}O_4S$ (M+H_2O) 362.1552 ; found 362.1793



4g, (E)-6-methyl-1-tosylhept-1-en-4-ol

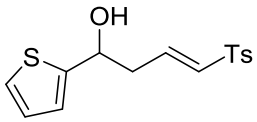
Yellow viscous liquid, 401 mg, 71%

IR (KBr) υ_{max}: 3506, 3047, 2954, 1631, 1597, 1462, 1402, 1288, 1139, 1085, 810, 661

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0Hz, 2H), 7.29 (d, J = 8.0Hz, 2H), 7.00-6.93 (m, 1H), 6.37 (d, J = 15.1Hz, 1H), 3.82–3.77 (m, 1H), 2.39 (s, 3H), 2.32–2.26 (m, 2H), 1.74–1.67 (m, 1H), 1.41-1.34 (m, 1H), 1.20–1.14 (m, 1H), 0.86 (t, J = 7.1Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 143.2, 137.5, 132.6, 129.9, 127.7, 68.2, 46.3, 39.8, 24.5, 23.3, 21.9, 21.6

HRMS calcd for $C_{15}H_{24}O_4S$ (M+H) 300.1395 ; found 300.1636



4h, (E)-1-(thiophen-2-yl)-4-tosylbut-3-en-1-ol

Reddish Solid, 419 mg, 68%

Melting point: 104-105˚C

IR (KBr) υ_{max}: 3483, 3049, 1631, 1597, 1492, 1402, 1286, 1139, 1082, 810, 659

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.1Hz, 2H), 7.28 (d, J = 7.8Hz, 2H), 7.19 (dd, J = 5.6, 2.9Hz, 1H), 6.94–6.88 (m, 3H), 6.34 (d, J = 15.0Hz, 1H), 5.03 (s, 1H), 2.76-2.63 (m, 2H), 2.40 (s, 3H)

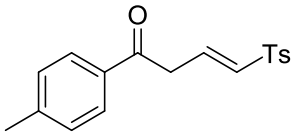
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 144.4, 141.9, 137.2, 133.1, 129.9, 127.7, 126.8, 125.0, 124.1, 68.5, 41.0, 21.7

HRMS calcd for $C_{15}H_{18}O_4S_2$ (M+H) 326.0647 ; found 326.0878

Synthesis of 1, 3-bisnucleophile: General procedure

To a solution of Dess-Martin Periodinane (2.0 mmol) in CH_2Cl_2 (10 ml) at room temperature was added a solution of vinyl sulfone (1.0 mmol) in CH_2Cl_2 (10 ml). After 1 h of stirring (reaction was monitored by TLC), the mixture was diluted with diethyl ether (20 mL) and quenched with 1/1 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ solution followed by brine. The extract was dried over anhydrous sodium sulfate and concentrated on a rotavapor. Column chromatography of the resulting residue on silica gel using ethyl acetate-petroleum ether as eluent afforded analytically pure samples of 1, 3-bisnucleophile **1a-h**.

Spectroscopic data of 1, 3-bisnucleophile



1a, (E)-1-(p-tolyl)-4-tosylbut-3-en-1-one

White solid, 279 mg, 89%

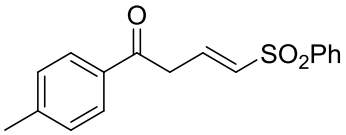
Melting point: 111-113˚C

IR (KBr) υ_{max}: 2980, 2929, 1664, 1624, 1598, 1450, 1409, 1319, 1288, 1143, 821

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.70 (m, 4H), 7.33 (d, *J* = 8.0Hz, 2H), 7.23 (d, *J* = 8.4Hz, 2H), 6.89 (d, *J* = 15.4Hz, 1H), 6.76–6.68 (m, 1H), 4.00 (dd, *J* = 7.7, 1.0Hz), 2.42 (s, 3H), 2.39(s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.75, 145.3, 144.4, 135.3, 134.3, 133.5, 132.0, 130.0, 129.4, 128.8, 128.5, 59.7, 21.7

HRMS calcd for $C_{18}H_{18}O_3S$ (M+H) 315.1056 ; found 315.1061



1b, (E)-4-(phenylsulfonyl)-1-(p-tolyl)but-3-en-1-one

White solid, 261 mg, 87%

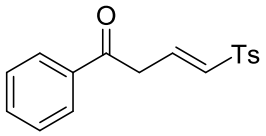
Melting point: 108-109˚C

IR (KBr) υ_{max}: 2974, 2918, 1664, 1608, 1448, 1408, 1292, 1145, 979, 727, 584

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.4, 1.2Hz, 2H), 7.72 (d, *J* = 8.0Hz, 2H), 7.69–7.64 (m, 1H), 7.56 (t, *J* = 7.7Hz, 2H), 7.24 (d, *J* = 8.0Hz, 2H), 6.90 (dt, *J* = 15.4, 1.0Hz, 1H), 6.77-6.70 (m, 1H), 4.03 (dd, 8.0, 1.0Hz, 2H), 2.4 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 144.5, 138.2, 134.3, 134.2, 133.6, 131.7, 129.5, 129.4, 128.8, 128.5, 59.6, 21.7

HRMS calcd for $C_{17}H_{16}O_3S$ (M+H) 301.0899 ; found 301.0901



1c, (E)-1-phenyl-4-tosylbut-3-en-1-on

White solid, 267 mg, 89%

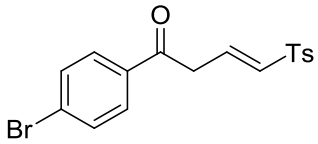
Melting point: 113-114˚C

IR (KBr) υ_{max}: 3082, 2978, 2918, 1658, 1624, 1446, 1409, 1317, 1292, 1139, 696, 516

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.6Hz, 2H), 7.75 (d, *J* = 8.4Hz), 7.59-7.53 (m, 1H), 7.44 (t, *J* = 8.0Hz, 2H), 7.34 (d, *J* = 8.0Hz, 2H), 6.90 (dt, 15.4, 1.0Hz, 1H), 6.78–6.70 (m, 1H), 4.01 (dd, 7.6, 1.0Hz, 2H), 2.42(s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 145.3, 136.8, 135.3, 133.5, 133.4, 132.5, 130.1, 128.8, 128.7, 128.5, 59.7, 21.7

HRMS calcd for $C_{17}H_{16}O_3S$ (M+H) 301.0899 ; found 301.0904



1d, (E)-1-(4-bromophenyl)-4-tosylbut-3-en-1-one

Yellow solid, 345 mg, 91%

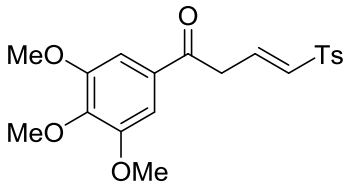
Melting point: 116-117˚C

IR (KBr) υ_{max}: 2924, 1668, 1622, 1581, 1487, 1444, 1286, 1134, 812, 513

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8Hz, 2H), 7.35 (d, J = 8.0Hz, 2H), 6.88 (d, J = 15.4Hz, 1H), 6.79-6.71 (m, 1H), 4.01 (dd, J = 7.6, 0.8Hz, 2H), 2.43 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 135.5, 135.3, 133.1, 132.9, 132.1, 130.2, 130.1, 128.7, 128.4, 59.6, 21.7

HRMS calcd for $C_{17}H_{15}BrO_3S$ (M+H) 379.0004 ; found 378.9996



1e, (E)-4-tosyl-1-(3,4,5-trimethoxyphenyl)but-3-en-1-one

White solid, 347 mg, 89%

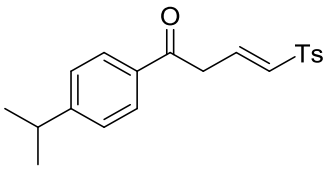
Melting point: 168-169˚C

IR (KBr) υ_{max}: 2951, 2839, 1668, 1625, 1583, 1460, 1413, 1307, 1116, 767, 516

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4Hz, 2H), 7.35 (d, J = 8.4Hz, 2H), 7.13 (s, 2H), 6.91 (d, J = 15.4Hz, 1H), 6.76–6.68 (m, 1H), 4.01 (dd, J = 7.6, 0.8Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.42 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 153.2, 145.4, 143.0, 135.4, 133.4, 132.1, 132.0, 130.1, 128.4, 106.4, 61.0, 59.6, 56.4, 21.7

HRMS calcd for $C_{20}H_{22}O_6S$ (M+H) 391.1216 ; found 391.1211



1f, (E)-1-(4-isopropylphenyl)-4-tosylbut-3-en-1-one

White solid, 288 mg, 84%

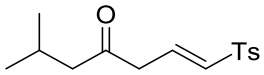
Melting point: 112-113˚C

IR (KBr) υ_{max}: 2969, 2927, 1659, 1598, 1463, 1409, 1292, 1139, 669, 518

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.75 (m , 4H), 7.35 (d, *J* = 8.0Hz, 2H), 7.31 (d, *J* = 8.0Hz, 2H), 6.90 (d, *J* = 15.4Hz, 1H), 6.77–6.69 (m, 1H), 4.02 (dd, *J* = 7.6, 0.8Hz, 2H), 3.00–2.93 (m, 1H), 2.44 (s, 3H), 1.27 (d, *J* = 6.8Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 155.1, 145.2, 135.3, 134.6, 133.6, 132.1, 130.0, 129.0, 128.5, 126.9, 59.7, 34.3, 23.7, 21.7

HRMS calcd for $C_{20}H_{22}O_3S$ (M+H) 343.1369 ; found 343.1363



1g, (E)-6-methyl-1-tosylhept-1-en-4-one

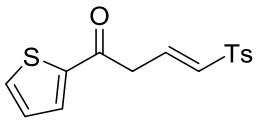
Yellow viscous liquid, 230 mg, 82%

IR (KBr) υ_{max}: 2958, 1707, 1670, 1597, 1429, 1404, 1292, 1141, 813, 516

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2Hz, 2H), 7.32 (d, *J* = 8.2Hz, 2H), 6.61–6.52 (m, 1H), 6.02 (dt, *J* = 16.0, 1.2Hz, 1H), 3.90 (dd, *J* = 7.6, 1.2Hz, 2H), 2.42 (s, 3H), 2.35 (d, 7.2Hz, 2H), 2.09–2.02 (m, 1H), 0.88 (d, *J* = 6.6Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 145.4, 137.3, 135.1, 130.8, 130.0, 128.4, 59.5, 49.4, 25.0, 22.6, 21.7

HRMS calcd for $C_{15}H_{20}O_3S$ (M+H) 281.1212 ; found 2811.1206



1h, (E)-1-(thiophen-2-yl)-4-tosylbut-3-en-1-one

Yellow solid, 239 mg, 78%

Melting point: 123-125˚C

IR (KBr) υ_{max}: 3039, 2972, 2906, 1649, 1616, 1512, 1408, 1290, 1139, 754, 518

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0Hz, 2H), 7.68–7.63 (m, 2H), 7.33 (d, *J* = 8.0Hz, 2H), 7.13 (t, *J* = 4.2 Hz, 1H), 6.83–6.74 (m, 2H), 4.01 (d, *J* = 4.8Hz, 2H), 2.42 (s, 3H)

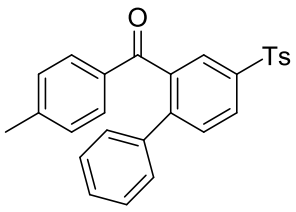
^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 145.4, 144.2, 135.3, 135.0, 132.9, 132.8, 131.9, 130.1, 128.5, 128.4, 59.5, 21.7

HRMS calcd for $C_{15}H_{14}O_3S_2$ (M+H) 307.0463; found 307.0458

DBU-mediated benzannulation reaction: General method

DBU (0.45 mmol) was added to a solution cinnamaldehyde **2** (0.3 mmol) and 1, 3-bis-nucleophile **1** (0.33 mmol) in DMF (4 mL). The reaction mixture was stirred at 25 °C for 1h. After completion of the reaction, 10 mL deionized water was added and the solution was extracted with ethylacetate (3×10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and the solvent was evaporated on a rotavapor under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether-ethyl acetate as eluent to afford analytically pure sample of the product.

Spectroscopic data for the products



5a, p-tolyl(4-tosyl-[1,1'-biphenyl]-2-yl)methanone

White solid, 95 mg, 74%

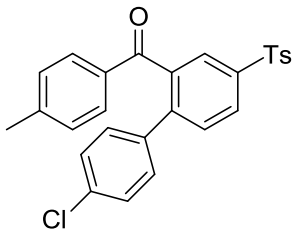
Melting point: 143-144˚C

IR (KBr) υ_{max}: 3022, 2970, 1741, 1660, 1598, 1369, 1153, 1097, 664, 532

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.0, 2.0Hz, 1H), 8.01 (d, *J* = 2.0Hz, 1H), 7.85 (d, *J* = 8.4Hz, 2H), 7.60 (d, *J* = 8.4Hz, 1H), 7.52 (d, *J* = 8.0Hz, 2H), 7.32 (d, *J* = 8.4Hz, 2H), 7.22 (s, 5H), 7.11 (d, *J* = 8.4Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 145.6, 144.7, 144.6, 140.8, 140.1, 138.5, 138.2, 133.9, 131.2, 130.2, 130.1, 129.2, 128.8, 128.6, 128.4, 127.9, 127.6, 21.8, 21.7

HRMS calcd for $C_{27}H_{22}O_3S$ (M+H) 427.1369 ; found 427.1390



5b, (4'-chloro-4-tosyl-[1,1'-biphenyl]-2-yl)(p-tolyl)methanone

White solid, 105 mg, 76%

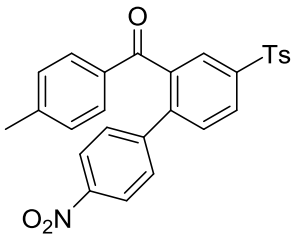
Melting point: 153-154˚C

IR (KBr) υ_{max}: 3010, 2982, 1746, 1621, 1570, 1388, 1190, 1060, 765, 540

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.4, 2.0Hz, 1H), 7.99 (d, *J* = 2.0Hz, 1H), 7.84–7.81 (m, 2H), 7.55 (d, *J* = 8.0Hz, 1H), 7.52 (d, *J* = 8.4Hz, 2H), 7.31 (dd, *J* = 8.4, 0.8Hz, 2H), 7.21–7.17 (m, 2H), 7.16–7.11(m, 4H), 2.40 (s, 3H), 2.35 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 145.0, 144.7, 144.3, 141.1, 140.0, 138.1, 136.9, 134.7, 133.7, 131.1, 130.25, 130.21, 130.1, 129.4, 128.9, 128.8, 127.9, 127.6, 21.8, 21.7

HRMS calcd for $C_{27}H_{21}ClO_3S$ (M+H) 461.0979 ; found 461.0959



5c, (4'-nitro-4-tosyl-[1,1'-biphenyl]-2-yl)(p-tolyl)methanone

Yellow solid, 112 mg, 79%

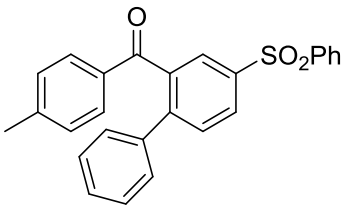
Melting point: 157-158˚C

IR (KBr) υ_{max}: 2924, 1660, 1597, 1512, 1448, 1408, 1340, 1249, 1157, 1157, 682, 596

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.09 (m, 3H), 8.04 (d, *J* = 1.2Hz, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.0Hz, 2H), 7.39 (d, *J* = 8.4Hz, 2H), 7.33 (d, *J* = 8.0Hz 2H), 7.16 (d, *J* = 8.0Hz, 2H), 2.41 (s, 3H), 2.37 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 147.6, 145.5, 145.1, 144.9, 143.2, 142.2, 140.2, 137.8, 133.6, 131.1, 130.2, 129.7, 129.6, 129.1, 128.0, 127.8, 123.8, 21.8, 21.7

HRMS calcd for $C_{27}H_{21}NO_5S$ (M+H) 472.1219 ; found 472.1242



5d, (4-(phenylsulfonyl)-[1,1'-biphenyl]-2-yl)(p-tolyl)methanone

White solid, 89 mg, 72%

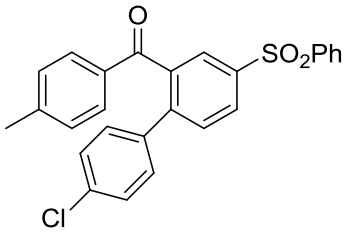
Melting point: 141-142˚C

IR (KBr) υ_{max}: 3017, 2951, 1744, 1634, 1568, 1440, 1370, 1110, 1012, 840, 548

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.4, 2.0Hz, 1H), 8.02 (d, *J* = 2.0Hz,1H), 7.97 (d, *J* = 7.6Hz, 2H), 7.59 (t, *J* = 7.6Hz, 2H), 7.52 (t, *J* = 8.0Hz, 4H), 7.21 (s, 5H), 7.10 (d, *J* = 8.4Hz, 2H), 2.33 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 145.8, 144.7, 141.2, 140.4, 140.2, 138.4, 133.9, 133.5, 131.2, 130.2, 129.5, 129.2, 129.0, 128.8, 128.6, 128.4, 127.8, 127.7, 21.8

HRMS calcd for $C_{26}H_{20}O_3S$ (M+H) 413.1209 ; found 413.1206



5e, (4'-chloro-4-(phenylsulfonyl)-[1,1'-biphenyl]-2-yl)(p-tolyl)methanone

White solid, 99 mg, 74%

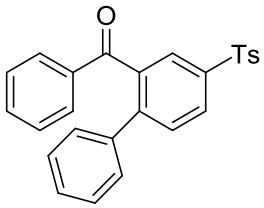
Melting point: 151-153˚C

IR (KBr) υ_{max}: 3045, 2981, 1745, 1654, 1520, 1448, 1358, 1138, 1028, 765, 535

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.0, 1.6Hz, 1H), 8.01 (d, J = 1.6Hz, 1H), 7.96 (d, J = 7.2Hz, 2H), 7.59–7.50 (m, 6H), 7.21-7.12 (m, 6H), 2.36 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 145.1, 144.5, 141.1, 140.7, 140.1, 136.9, 134.7, 133.7, 133.6, 131.2, 130.2, 130.1, 129.5, 129.4, 129.1, 128.9, 127.9, 127.7, 21.8

HRMS calcd for $C_{26}H_{19}ClO_3S$ (M+H) 447.0822 ; found 447.0842



5f, phenyl(4-tosyl-[1,1'-biphenyl]-2-yl)methanone

White solid, 86 mg, 70%

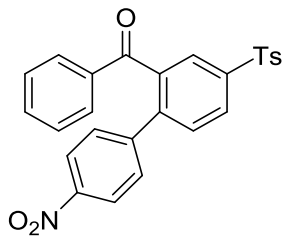
Melting point: 139-141˚C

IR (KBr) υ_{max}: 2922, 1666, 1591, 1446, 1400, 1315, 1248, 1149, 675, 548

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.0, 2.0Hz, 1H), 8.04 (d, J = 2.0Hz, 1H), 7.85 (d, J = 8.4Hz, 2H), 7.60–7.57 (m, 3H), 7.44 (t, J = 7.4Hz, 1H), 7.33–7.26 (m, 4H), 7.19 (s, 5H), 2.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 145.7, 144.6, 140.9, 139.9, 138.4, 138.2, 136.4, 133.5, 131.2, 130.2, 129.9, 129.0, 128.9, 128.6, 128.4, 127.9, 127.7, 21.7

HRMS calcd for $C_{26}H_{20}O_3S$ (M+H) 413.1212 ; found 413.1194



5g, (4'-nitro-4-tosyl-[1,1'-biphenyl]-2-yl)(phenyl)methanone

Yellow solid, 107 mg, 78%

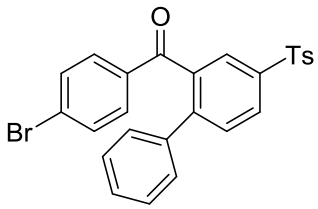
Melting point: 153-154˚C

IR (KBr) υ_{max}: 3022, 2970, 1739, 1589, 1367, 1224, 1037, 532

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.4, 2.0Hz, 1H), 8.12-8.08 (m, 3H), 7.86 (dt, J = 8.0, 2.0Hz, 2H), 7.64–7.59 (m, 3H), 7.55–7.51 (m, 1H), 7.40–7.33 (m, 6H), 2.42 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 147.6, 145.0, 143.4, 142.3, 139.9, 137.8, 136.1, 134.2, 131.2, 130.3, 130.0, 129.8, 128.8, 128.0, 127.9, 123.8, 21.7

HRMS calcd for $C_{26}H_{19}NO_5S$ (M+H) 458.1063 ; found 458.1038



5h, (4-bromophenyl)(4-tosyl-[1,1'-biphenyl]-2-yl)methanone

Yellow solid, 113 mg, 77%

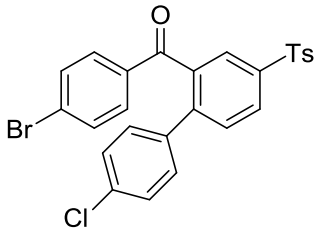
Melting point: 158-159˚C

IR (KBr) υ_{max}: 3012, 2967, 1735, 1665, 1570, 1443, 1361, 1047, 840, 546

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.0, 2.0Hz, 1H), 8.02 (d, *J* = 2.0Hz, 1H), 7.85 (dt, *J* = 8.4, 1.6Hz, 2H), 7.59 (d, *J* = 8.0Hz, 1H), 7.42–7.38 (m, 4H), 7.32 (d, *J* = 8.0Hz, 2H), 7.22–7.16 (m, 5H), 2.41 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 145.6, 144.7, 141.2, 139.3, 138.2, 138.1, 135.2, 131.8, 131.28, 131.22, 130.2, 129.3, 128.9, 128.8, 128.7, 128.6, 127.9, 127.7, 21.7

HRMS calcd for $C_{26}H_{19}BrO_3S$ (M+H) 491.0317 ; found 491.0292



5i, (4-bromophenyl)(4'-chloro-4-tosyl-[1,1'-biphenyl]-2-yl)methanone

Yellow solid, 128 mg, 81%

R_f = 0.7 (20% ethyl acetate in hexanes)

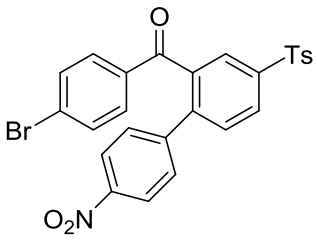
Melting point: 170-171˚C

IR (KBr) υ_{max}: 3064, 1668, 1581, 1494, 1469, 1292, 1147, 813, 648, 584

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.4, 2.0Hz, 1H), 8.00 (d, *J* = 2.0Hz, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.56 (d, *J* = 8.4Hz, 1H), 7.47–7.42 (m, 4H), 7.32 (d, *J* = 8.4Hz), 7.21 (d, *J* = 8.5Hz, 2H), 7.12 (d, *J* = 8.5Hz, 2H), 2.41 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 144.8, 144.2, 141.5, 139.2, 139.2, 137.9, 136.6, 135.0, 132.0, 131.3, 131.2, 130.2, 130.0, 129.3, 129.0, 127.9, 127.7, 21.7

HRMS calcd for $C_{26}H_{18}BrClO_3S$ (M+H) 524.9928 ; found 524.9939



5j, (4-bromophenyl)(4'-nitro-4-tosyl-[1,1'-biphenyl]-2-yl)methanone

Yellow solid, 133 mg, 83%

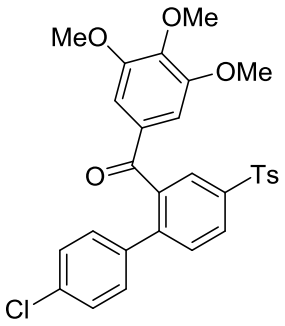
Melting point: 176-178˚C

IR (KBr) υ_{max}: 3057, 1668, 1585, 1517, 1396, 1344, 1151, 657, 584

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.0, 2.0Hz, 1H), 8.11 (d, *J* = 8.8Hz, 2H), 8.04 (d, *J* = 2.0Hz, 1H), 7.84 (d, *J* = 8.0Hz, 2H), 7.60 (d, *J* = 8.0Hz, 1H), 7.51-7.46 (m, 4H), 7.38–7.32 (m, 4H), 2.42 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 147.7, 145.1, 144.8, 143.2, 142.5, 139.3, 137.7, 134.8, 132.2, 131.3, 130.3, 129.7, 129.5, 128.0, 127.8, 123.9, 21.7

HRMS calcd for $C_{26}H_{18}BrNO_5S$ (M+H) 536.0168 ; found 536.0189



5k, (4'-chloro-4-tosyl-[1,1'-biphenyl]-2-yl)(3,4,5-trimethoxyphenyl)methanone

White solid, 121 mg, 76%

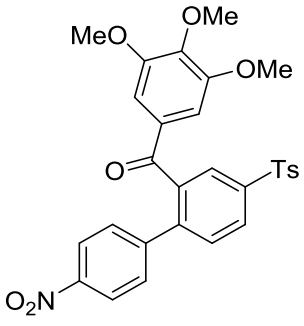
Melting point: 159-161˚C

IR (KBr) υ_{max}: 2931, 1743, 1662, 1583, 1498, 1460, 1409, 1321, 1120, 655, 584

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.0, 1.6Hz, 1H), 8.01 (d, *J* = 1.6Hz, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.57 (d, *J* = 8.0Hz, 1H), 7.31 (d, *J* = 8.4Hz, 2H), 7.23 (d, *J* = 8.4Hz, 2H), 7.15 (d, *J* = 8.4Hz, 2H), 6.87 (s, 2H), 3.89 (s, 3H), 3.74 (s, 6H), 2.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 144.8, 144.5, 143.3, 141.1, 139.6, 138.0, 136.9, 134.8, 131.26, 131.21, 130.2, 130.0, 129.1, 129.0, 127.94, 127.90, 107.7, 61.0, 56.3, 21.7

HRMS calcd for $C_{29}H_{25}ClO_6S$ (M+H) 537.1139 ; found 537.1143



5l, (4'-nitro-4-tosyl-[1,1'-biphenyl]-2-yl)(3,4,5-trimethoxyphenyl)methanone

Yellow solid, 131 mg, 80%

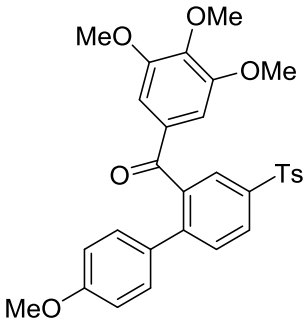
Melting point: 163-165 ˚C

IR (KBr) υ_{max}: 2973, 1758, 1648, 1582, 1469, 1454, 1413, 1308, 1164, 723, 567

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.11 (m , 3H), 8.05 (d, *J* = 2.0Hz, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.61 (d, *J* = 8.0Hz, 1H), 7.40 (d, *J* = 8.8Hz, 2H), 7.32 (d, *J* = 8.4Hz, 2H), 6.90 (s, 2H), 3.90 (s, 3H), 3.75 (s, 6H), 2.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 153.1, 147.7, 145.1, 145.0, 143.7, 143.6, 142.1, 139.7, 137.8, 131.4, 130.9, 130.3, 129.7, 129.3, 128.0, 127.9, 123.9, 107.8, 61.1, 56.3, 21.7

HRMS calcd for $C_{29}H_{25}NO_8S$ (M+H) 548.1380 ; found 548.1353



5m, (4'-methoxy-4-tosyl-[1,1'-biphenyl]-2-yl)(3,4,5-trimethoxyphenyl)methanone

White solid, 105 mg, 66%

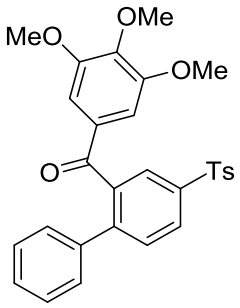
Melting point: 178-179˚C

IR (KBr) υ_{max}: 2933, 2837, 1664, 1583, 1508, 1458, 1409, 1321, 1153, 1006, 657, 567

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.0, 2.0Hz, 1H), 7.98 (d, *J* = 2.0Hz, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.58 (d, *J* = 8.0Hz, 1H), 7.30 (d, *J* = 8.4Hz, 2H), 7.15 (d, *J* = 8.8Hz, 2H), 6.87 (s, 2H), 6.76 (d, *J* = 8.8Hz, 2H), 3.87 (s, 3H), 3.73 (s, 6H), 3.72(s, 3H), 2.39 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 159.9, 152.9, 145.3, 144.6, 143.0, 140.2, 139.4, 138.2, 131.3, 131.0, 130.8, 130.16, 130.10, 129.0, 127.8, 114.2, 107.7, 61.0, 56.3, 55.2, 21.6

HRMS calcd for $C_{30}H_{28}O_7S$ (M+H) 533.1635 ; found 533.1631



5n, (4-tosyl-[1,1'-biphenyl]-2-yl)(3,4,5-trimethoxyphenyl)methanone

White solid, 107 mg, 71%

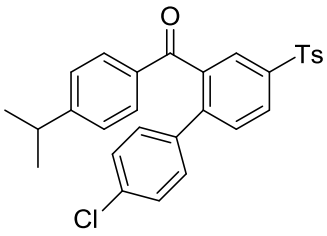
Melting point: 145-146˚C

IR (KBr) υ_{max}: 3053, 2933, 1664, 1583, 1498, 1454, 1323, 1226, 1118, 1004, 654, 574

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.4, 2.0Hz, 1H), 8.02 (d, J = 2.0Hz, 1H), 7.85 (d, J = 8.4Hz, 2H), 7.61 (d, J = 8.4Hz, 1H), 7.31 (d, J = 8.0Hz, 2H), 7.24–7.20 (m, 5H), 6.85 (s, 2H), 3.80 (s, 3H), 3.72 (s, 6H), 2.39 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 152.8, 145.7, 144.7, 143.0, 140.8, 139.7, 138.4, 138.2, 131.3, 131.2, 130.2, 129.0, 128.8, 128.7, 128.5, 127.93, 127.90, 107.7, 60.9, 56.3, 21.6

HRMS calcd for $C_{29}H_{26}O_6S$ (M+H) 503.1529 ; found 503.1524



5o, (4'-chloro-4-tosyl-[1,1'-biphenyl]-2-yl)(4-isopropylphenyl)methanone

White solid, 111 mg, 76%

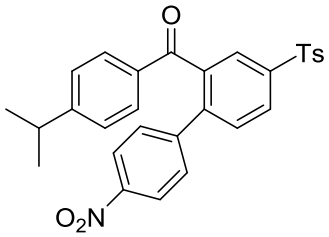
Melting point: 152-154˚C

IR (KBr) υ_{max}: 3057, 2960, 1664, 1598, 1465, 1411, 1292, 1151, 810, 665, 586

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.4, 2.0Hz, 1H), 8.00 (d, *J* = 2.0Hz, 1H), 7.83 (d, *J* = 8.4Hz, 2H), 7.56–7.53 (m, 3H), 7.31 (d, *J* = 8.0Hz, 2H), 7.20–7.12 (m, 6H), 2.94-2.87 (m, 1H), 2.40 (s, 3H), 1.23 (d, *J* = 7.2Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 155.6, 144.7, 144.5, 141.1, 140.1, 138.1, 137.0, 134.6, 134.0, 131.1, 130.4, 130.2, 130.1, 128.9, 128.8, 127.9, 127.7, 126.8, 34.3, 23.6, 21.9

HRMS calcd for $C_{29}H_{25}ClO_3S$ (M+H) 489.1292 ; found 489.1272



5p, (4-isopropylphenyl)(4'-nitro-4-tosyl-[1,1'-biphenyl]-2-yl)methanone

Yellow solid, 121 mg, 81%

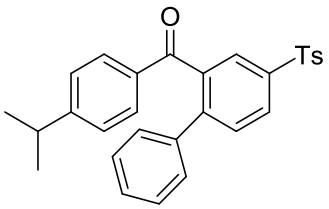
Melting point: 160-161˚C

IR (KBr) υ_{max}: 3061, 2962, 1662, 1598, 1517, 1462, 1413, 1344, 1286, 1153, 1101, 810, 586

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10 (m, 3H), 8.05 (d, *J* = 2.0Hz, 1H), .84 (d, *J* = 8.4Hz, 2H), 7.59-7.56 (m, 3H), 7.31 (d, *J* = 8.8Hz, 2H), 7.33 (d, *J* = 8.0Hz, 2H), 7.22 (d, *J* = 8.4Hz, 2H), 2.95–2.89 (m, 1H), 2.41 (s, 3H), 1.23 (d, *J* = 6.8Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 156.1, 147.6, 145.1, 144.9, 143.4, 142.1, 140.2, 137.8, 134.0, 131.2, 130.5, 130.2, 129.8, 129.2, 128.0, 127.8, 127.0, 123.7, 34.4, 23.5, 21.7

HRMS calcd for $C_{29}H_{25}NO_5S$ (M+H) 500.1542 ; found 500.1538



5q, (4-isopropylphenyl)(4-tosyl-[1,1'-biphenyl]-2-yl)methanone

White solid, 99 mg, 73%

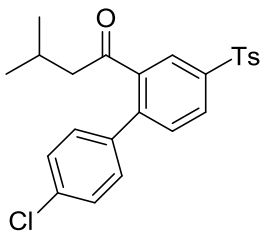
Melting point: 151-153˚C

IR (KBr) υ_{max}: 3057, 2964, 1666, 1597, 1465, 1413, 1315, 1151, 1101, 813, 578

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.4, 2.0Hz, 1H), 8.00 (d, *J* = 2.0Hz, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.59 (d, *J* = 8.4Hz, 1H), 7.56 (d, *J* = 8.4Hz, 2H), 7.31 (d, *J* = 8.0Hz, 2H), 7.21 (s, 5H), 7.16 (d, *J* = 8.4Hz, 2H), 2.92–2.85 (m. 1H), 2.40 (s, 3H), 1.21 (d, *J* = 6.8Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 155.3, 145.8, 144.6, 140.7, 140.1, 138.5, 138.2, 134.3, 131.3, 130.4, 130.1128.8, 128.5, 128.3, 127.9, 127.6, 126.6, 34.3, 32.6, 21.6

HRMS calcd for $C_{29}H_{26}O_3S$ (M+H) 455.1682 ; found 455.1661



5r, 1-(4'-chloro-4-tosyl-[1,1'-biphenyl]-2-yl)-3-methylbutan-1-one

White solid, 88 mg, 69%

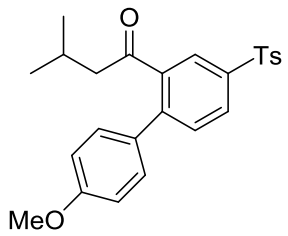
Melting point: 114-115˚C

IR (KBr) υ_{max}: 2958, 2927, 1689, 1591, 1496, 1463, 1317, 1296, 1151, 1089, 815, 659

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.97 (m, 2H), 7.84 (d, *J* = 8.4Hz, 2H), 7.44 (dd, *J* = 8.0, 0.4Hz, 1H), 7.38 (d, *J* = 8.8Hz, 2H), 7.31 (d, *J* = 8.0Hz, 2H), 7.19 (d, *J* = 8.8Hz, 2H), 2.39 (s, 3H), 2.19 (d, *J* = 6.8Hz, *J*, 2H), 2.00–1.90 (m, 1H), 0.74 (d, *J* = 6.4Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 144.7, 143.2, 142.0, 141.6, 138.0, 137.2, 135.1, 131.3, 130.2, 130.1, 129.1, 129.0, 127.9, 126.7, 51.7, 24.7, 22.4, 21.7

HRMS calcd for $C_{24}H_{23}ClO_3S$ (M+H) 427.1135 ; found 427.1122



5s, 1-(4'-methoxy-4-tosyl-[1,1'-biphenyl]-2-yl)-3-methylbutan-1-one

White solid, 80 mg, 63%

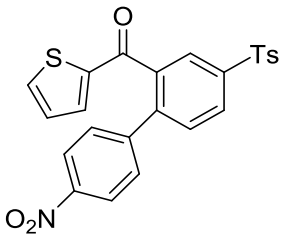
Melting point: 104-105˚C

IR (KBr) υ_{max}: 2964, 2927, 1691, 1606, 1516, 1463, 1392, 1247, 1147, 1095, 665, 536

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.2, 2.0Hz, 1H), 7.93 (d, *J* = 2.0, 1H), 7.84 (d, *J* = 8.4Hz, 2H), 7.46 (d, *J* = 8.2Hz, 1H), 7.30 (d, *J* = 8.4Hz, 2H), 7.19 (d, *J* = 8.8Hz, 2H), 6.93 (d, *J* = 8.8Hz, 2H), 3.82 (s, 3H), 2.39 (s, 3H), 2.12 (d, *J* = 6.8Hz, 2H), 1.95-1.88 (m, 1H), 0.71 (d, j = 6.8Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 160.2, 144.5, 144.1, 142.0, 140.8, 138.3, 131.1, 131.0, 130.16, 130.13, 128.8, 127.9, 126.7, 114.4, 55.4, 51.6, 24.9, 22.4, 21.6

HRMS calcd for $C_{25}H_{26}O_4S$ (M+H) 423.1631 ; found 423.1618



5t, (4'-nitro-4-tosyl-[1,1'-biphenyl]-2-yl)(thiophen-2-yl)methanone

Yellow solid, 106 mg, 76%

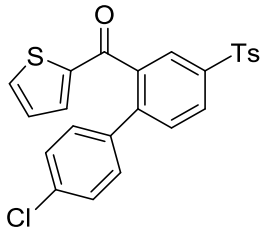
Melting point: 165-167˚C

IR (KBr) υ_{max}: 2967, 1649, 1584, 1487, 1458, 1309, 1137, 1058,819, 567

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.12 (m, 4H), 7.85 (d, *J* = 8.0Hz, 2H), 7.72 (dd, *J* = 4.8, 0.8Hz, 1H), 7.60 (d, *J* = 8.0Hz, 1H), 7.44 (d, *J* = 8.4Hz, 2H), 7.34–7.30 (m, 3H), 7.05 (dd, *J* = 4.8, 4.0Hz), 2.41 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 147.7, 145.0, 144.9, 143.4, 143.1, 142.3, 139.7, 137.7, 136.6, 136.1, 131.4, 130.3, 129.7, 129.5, 128.6, 128.0, 127.7, 123.9, 21.7

HRMS calcd for $C_{24}H_{17}NO_5S_2$ (M+H) 464.0627 ; found 464.0614



5u, (4'-chloro-4-tosyl-[1,1'-biphenyl]-2-yl)(thiophen-2-yl)methanone

Yellow solid, 94 mg, 69%

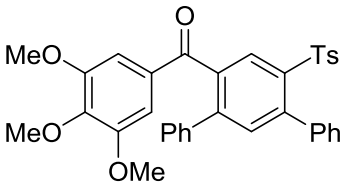
Melting point: 156-157˚C

IR (KBr) υ_{max}: 2924, 1656, 1591, 1496, 1441, 1318, 1143, 1081,829, 545

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.06 (m, 2H), 7.84 (d, *J* = 8.4Hz, 2H), 7.67 (dd, *J* = 4.8, 1.2Hz, 1H), 7.56 (d, *J* = 8.4Hz, 1H), 7.32 (d, *J* = 8.4Hz, 2H), 7.25–7.18 (m, 5H), 7.00 (dd, *J* = 4.8, 4.0Hz, 1H), 2.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 144.8, 144.1, 143.6, 141.2, 139.6, 138.0, 136.8, 136.0, 135.9, 134.8, 131.3, 130.2, 130.0, 129.2, 129.0, 128.4, 127.9, 127.5, 21.7

HRMS calcd for $C_{24}H_{17}ClO_3S_2$ (M+H) 453.0387 ; found 453.0380



7a, (6'-tosyl-[1,1':3',1''-terphenyl]-4'-yl)(3,4,5-trimethoxyphenyl)methanone

White solid, 114 mg, 66%

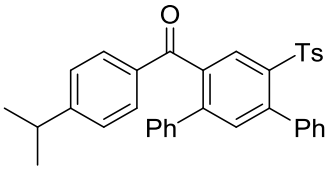
Melting point: 181-183˚C

IR (KBr) υ_{max}: 2926, 1658, 1583, 1498, 1454, 1325, 1122, 1001, 698, 578

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.35 (t, *J* = 7.2Hz, 2H), 7.28–7.22 (m, 7H), 7.15 (d, *J* = 8.4Hz, 2H), 7.08 (d, *J* = 8.4Hz, 2H), 7.01 (d, *J* = 7.6Hz, 4H), 3.89 (s, 3H), 3.82(s, 6H), 2.33 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 152.9, 143.9, 143.1, 138.8, 138.2, 137.9, 137.5, 137.4, 134.6, 131.6, 129.9, 129.3, 129.1, 128.4, 128.7, 128.6, 128.1, 128.0, 127.5, 107.9, 61.0, 56.4, 21.6

HRMS calcd for $C_{35}H_{30}O_6S$ (M+H) 579.1842 ; found 579.1823



7b, (4-isopropylphenyl)(6'-tosyl-[1,1':3',1''-terphenyl]-4'-yl)methanone

White solid, 100 mg, 63%

Melting point: 195-196˚C

IR (KBr) υ_{max}: 2958, 1664, 1600, 1537, 1492, 1448, 1290, 1143, 954, 700, 569

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.73 (d, *J* = 8.4Hz, 2H), 7.63–7.32 (m, 2H), 7.28–7.23 (m, 9H), 7.14 (d, *J* = 8.4Hz, 2H), 7.06 (d, *J* = 8.4Hz, 2H), 7.01 (d, *J* = 8.0Hz, 2H), 2.97-2.90 (m, 1H), 2.33 (s, 3H), 1.25 (d, *J* = 7.2Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 155.3, 145.6, 143.7, 143.6, 138.5, 138.36, 138.34, 137.6, 137.5, 134.7, 134.5, 130.6, 130.0, 129.1, 129.0, 128.8, 128.6, 128.3, 128.08, 128.04, 127.4, 126.7, 34.4, 23.6, 21.6

HRMS calcd for $C_{35}H_{30}O_3S$ (M+H) 531.1995 ; found 531.1983

3.8. References

1. (a) Wu, S.-B.; Long, C.; Kennelly E. J. *Nat. Prod. Rep*. **2014**, *31*, 1158. (b) Surana, K.; Chaudhary, B.; Diwakar, M.; Sharma, *S. Med. Chem. Comm*. **2018**, *9*, 1803.

2. Chen, J.-J.; Ting, C.-W.; Hwang, T.-L.; Chen, I.-S. *J. Nat. Prod*. **2009**, *72*, 253.

3. (a) Cueto, M.; Jensen, P. R.; Kauffman, C.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2001**, *64*, 1444. (b) Lokvam, J.; Braddock, J. F.; Reichardt, P. B.; Clausen, T. P. *Phytochemistry* **2000**, *55*, 29.

4. (a) Sang, S.; Pan, M.-H.; Cheng, X.; Bai, N.; Stark, R. E.; Rosen, R.T.; Lin-Shiau, S.-Y.; Lin, J.K.; Ho, C.-T. *Tetrahedron* **2001**, *57*, 9931. (b) Bernardi, A. P. M.; Ferraz, A. B. F.; Albring, D. V.; Bordignon, S. A. L.; Schripsema, J.; Bridi, R.; Dutra-Filho, C. S.; Henriques, A. T.; Von Poser, G. L. *J. Nat. Prod*. **2005**, *68*, 784.

5. (a) Fuller, R. W.; Blunt, J. W.; Boswell, J. L.; Cardellina, J. H.; Boyd, M. R. J. Nat. Prod. **1999**, *62*, 130-132. (b) Globulifera, S.; Livingstonel, G.; Ovalifolia, G.; Rosea, C. *Tetrahedron* **1992**, *48*, 10093.

6. Abe, F.; Nagafuji, S.; Okabe, H.; Akahane, H.; Estrade-Muniz, E,; Huerta-Reyes, M.; Reyes-Chilpa, R. *Biol. Pharm. Bull* **2004**, *27*, 141.

7. (a) Datta, S.; Li, J.; Mahdi, F.; Jekabsons, M. B.; Nagle, D. G.; Zhou, Y.-D. *J. Nat. Prod.* **2012**, *75*, 2216. (b) Ee, G. C. L.; The, S. S.; Kwong, H. C.; Mah, S. H.; Lim, Y. M.; Rahmani, M. *Phytochemistry Letters* **2012**, *5*, 545.

8. (a) Cuquerella, M. C.; Lhiaubet-Vallet, V.; Cadet, J.; Miranda, M. A. *Accounts of Chemical Research* **2012**, *45*, 9, 1558. (b) Dumont, E.; Wibowo, M.; Roca-Sanjuan, D.; Garavelli, M.; Assfelsd, X.; Monari, A. *J. Phys. Chem. Lett.* **2015**, *6*, 576.

9. Romero, N. A.; Nicewicz, S. A. *Chem. Rev*. **2016**, *116*, 10075.

10. (a) Klimová, Z.; Hojerová, J.; Beranková, M. *Food and Chem. Toxicol*. **2015**, *83*, 237. (b) Baker, L. A.; Horbury, M. D.; Greenough, S. E.; Coulter, P. M.; Karsili, T. N. V.; Roberts, G. M.; Orr-Ewing, A. J.; Ashfold, M. N. R.; Stavros, V. G. *The Journal of Physical Chemistry Letters* **2015**, *6*, *8*, 1363

11. Dingemanse, J.; Jorga, K.; Zürcher, G.; Schmitt, M.; Sedek, G.; Prada, M. D.; Brummelen, P. V. *Br J Clin Pharmacol* **1995**, *40*, 253.

12. Wong, T. Y.; Simó, R.; Mitchell, P. *Am. J. Ophthalmol*. **2012**, *154*, 6.

13. Kantor, T. G. *Pharmacotherapy* **1986**, *6*, 93.

14. (a) Vekariya, R. H.; Aubé, J. *Org. Lett*. **2016**, 18, 3534. (b) Sarvari, M. H.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953.

15. (a) Li, J.-S.; Yang, F.; Yang, Q.; Li, Z.-W.; Chen, G.-Q.; Da, Y.-D.; Huang, P.-M.; Chen., C.; Zhang, Y.; Huang, L.-Z. *Synlett* **2017,** *28*, 994. (b) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal*. **2007**, *349*, 861.

16. (a) Velusamy, S.; Punniyamurthy, T. *Org. Lett.* **2004**, *6*, 2, 217. (b) Tamura, N.; Aoyama, T.; Takido, T.; Kodomari, M. *Synlett* **2012**, *23*, 1397.

17. (a) Ekoue-Kovi, K.; Xu, H.; Wolf, C. *Tetrahedron Letters* **2008**, *49* 5773. (b) Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem*. **2006**, *71*, 5725. (c) Zhong, Y.; Han, W. *Chem. Commun.* **2014**, *50*, 3874

18. (a) Wang, G.-Z.; Li, X.-L.; Dai, J.-J; Xu, H.-J. *J. Org. Chem*. **2014**, *79*, 7220. (b) Lin, R.; Chen, F.; Jiao, N. *Org. Lett.* **2012**, *14*, *16*, 4158

19. Wang, X.-J.; Zhang, Li.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. Org. Lett. **2005,** *7*, 5593

20. Cai, H.; Xia, L.; Lee, Y. R. *Chem. Commun.* **2016**, *52*, 7661.

21. Tamargo, R. J. I.; Poudel, T. N.; Lee, Y. R. *RSC Adv*. **2016**, *6*, 70311.

22. Schmidt, E. Y.; Ivanova, E. V.; Tatarinova, I. V.; Ushakov, I. A.; Semenova, N. V.; Vashchenko, A. V.; Trofimov, B. A. *Org. Lett.* **2016**, *18*, *9*, 2158.

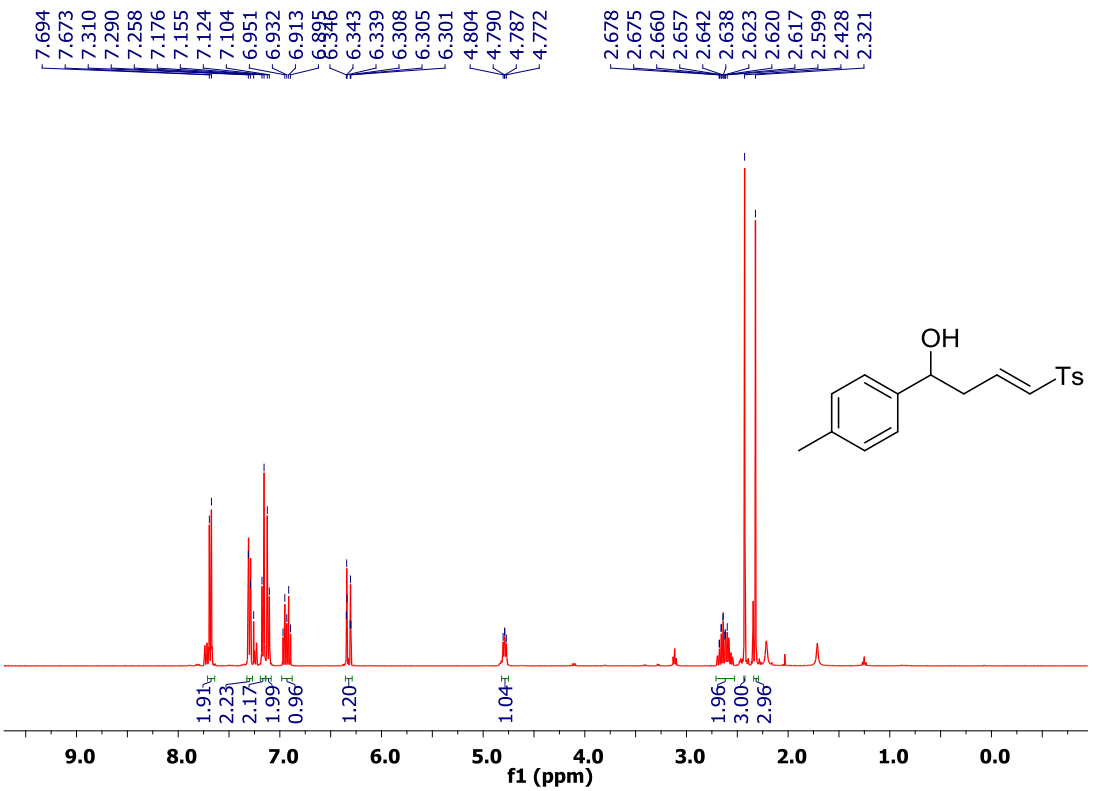
23. Joshi, P. R.; Undeela, S.; Reddy, D. D.; Singarapu, K.K.; Menon, R. S. *Org. Lett*. **2015**, *17*, 1449.

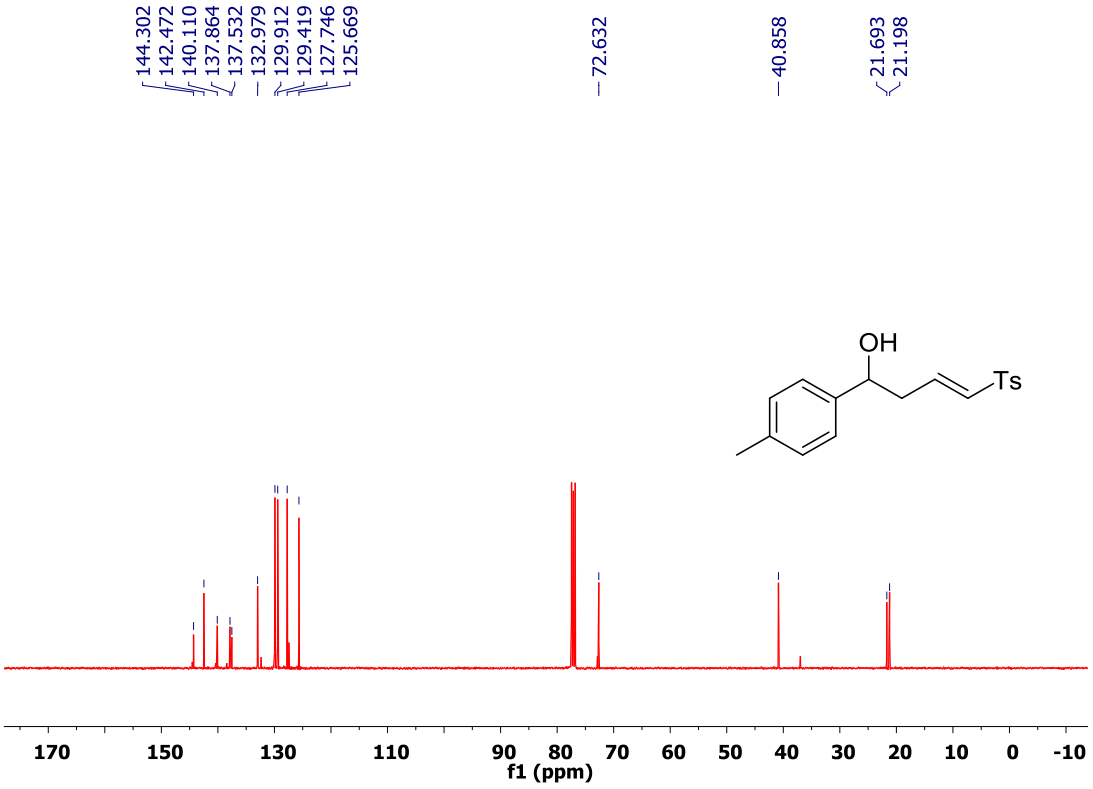
24. Diallo, A.; Zhao, Y. -L.; Wang, H.; Li, S. -S.; Ren, C. -Q.; Liu, Q. *Org. Lett.* **2012**, *14*, 5776.

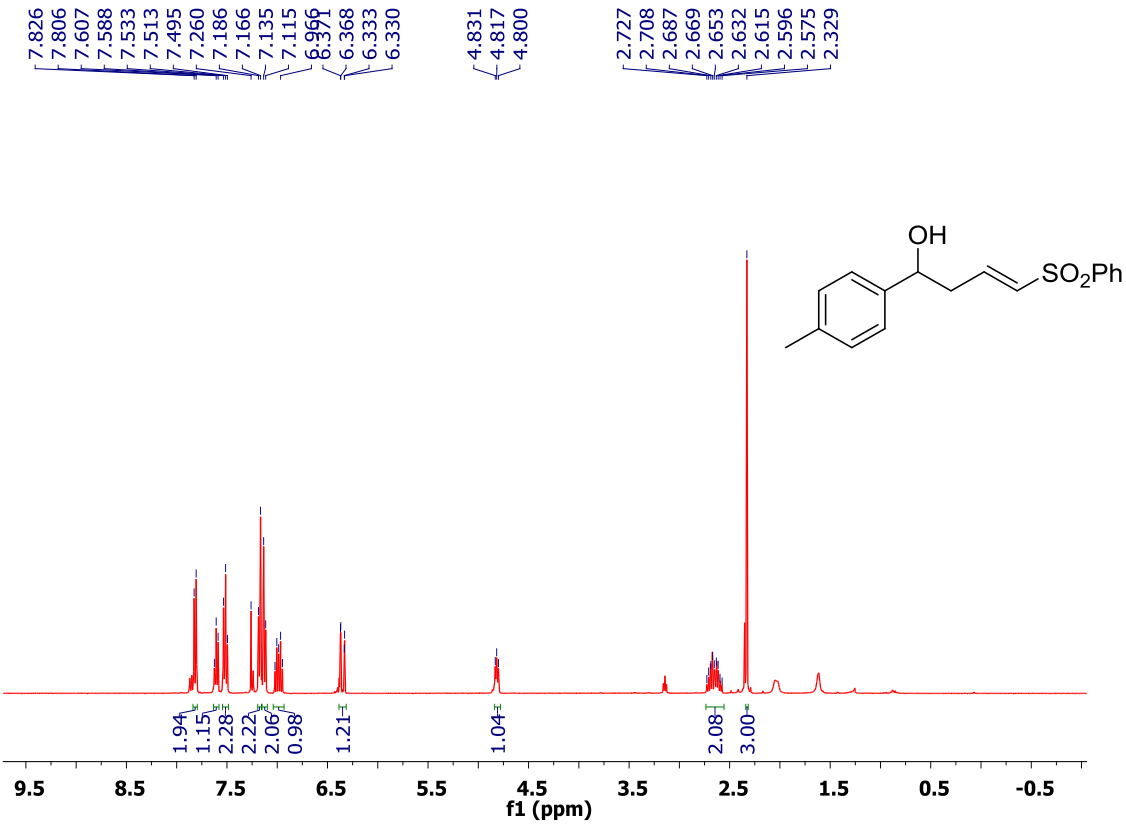
25. Jiang, D.; Peng, J.; Chen, Y. *ChemInform* **2008**, *39*, 37

26. Das, B.; Lingaiah, M.; Damodar, K.; Bhunia, N. *Synthesis* **2011**, *18*, 2941.

3.9. NMR spectra of new compounds [^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)]



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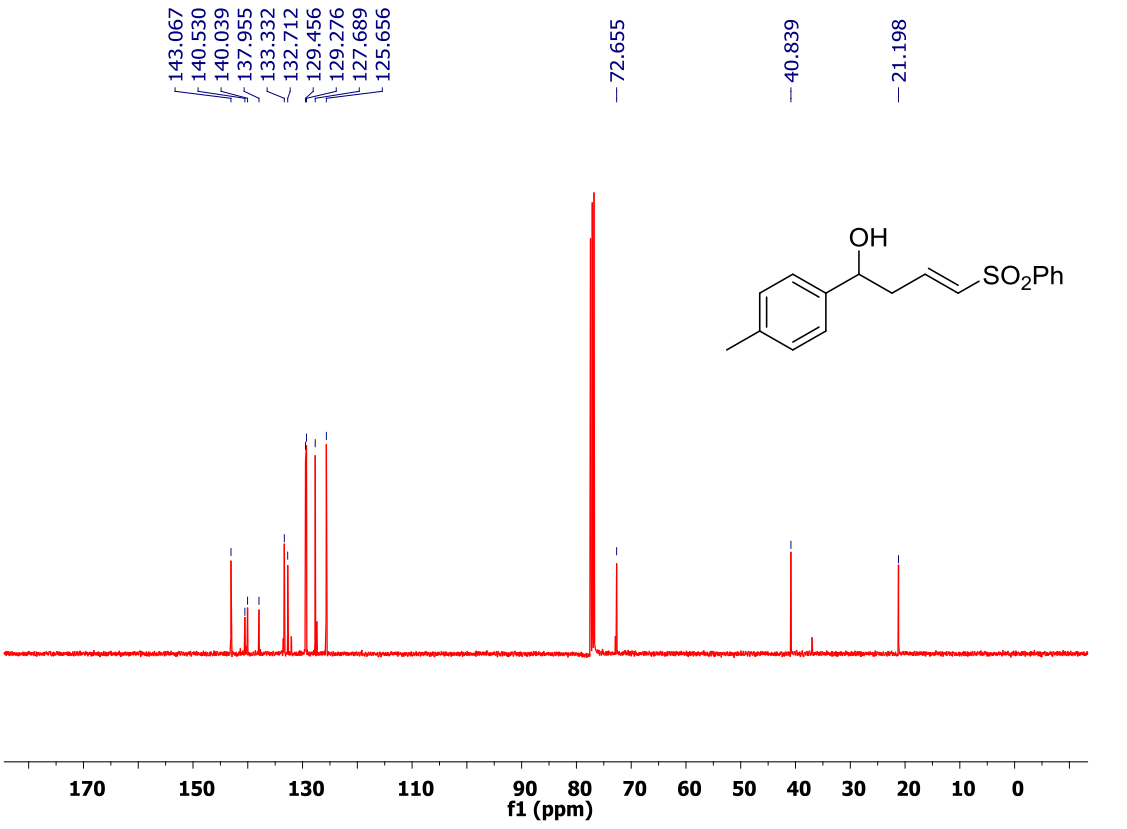
6.371
6.368
6.333
6.330
4.831
4.817
4.800
2.727
2.708
2.687
2.669
2.653
2.632
2.615
2.596
2.575
2.329
OH
SO2Ph
1.94
1.15
2.28
2.22
2.06
0.98
1.21
1.04
2.08
3.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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125.656
72.655
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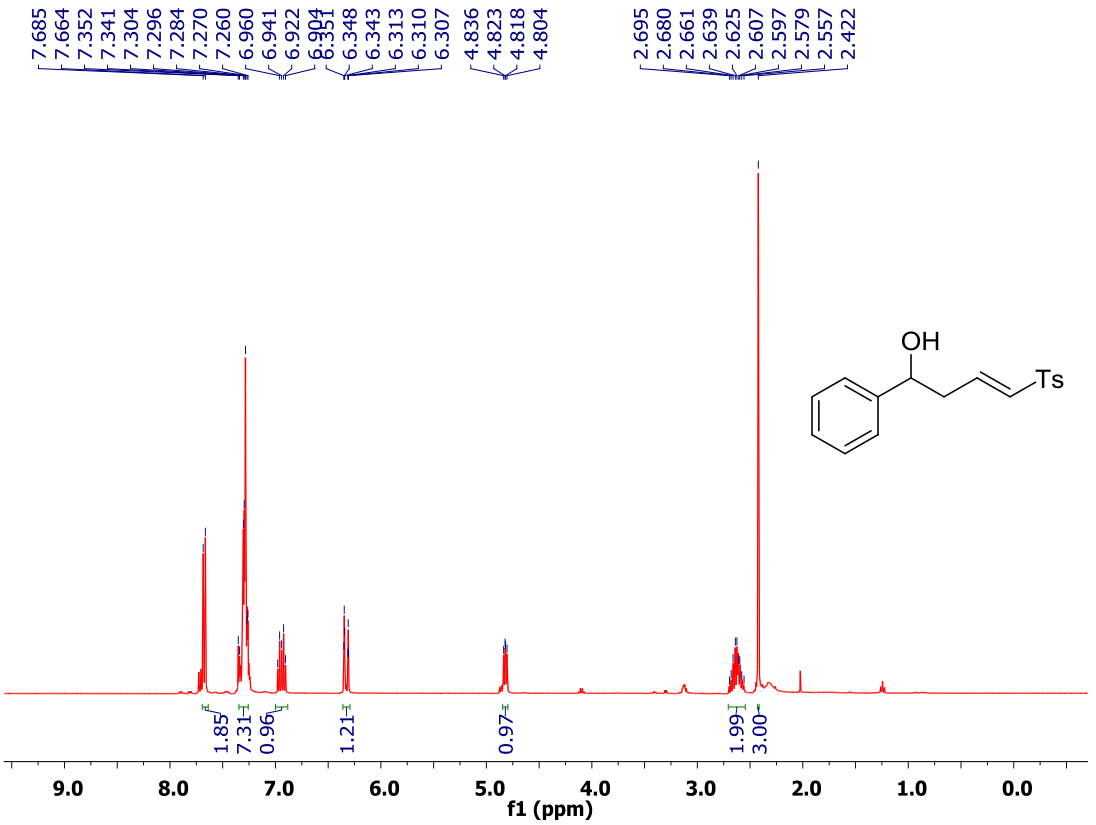
OH
SO2Ph
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.664
7.352
7.341
7.304
7.296
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7.270
7.260
6.960
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6.922
6.904
6.351
6.348
6.343
6.313
6.310
6.307
4.836
4.823
4.818
4.804
2.695
2.680
2.661
2.639
2.625
2.607
2.597
2.579
2.557
2.422
OH
Ts
1.85
7.31
0.96
1.21
0.97
1.99
3.00
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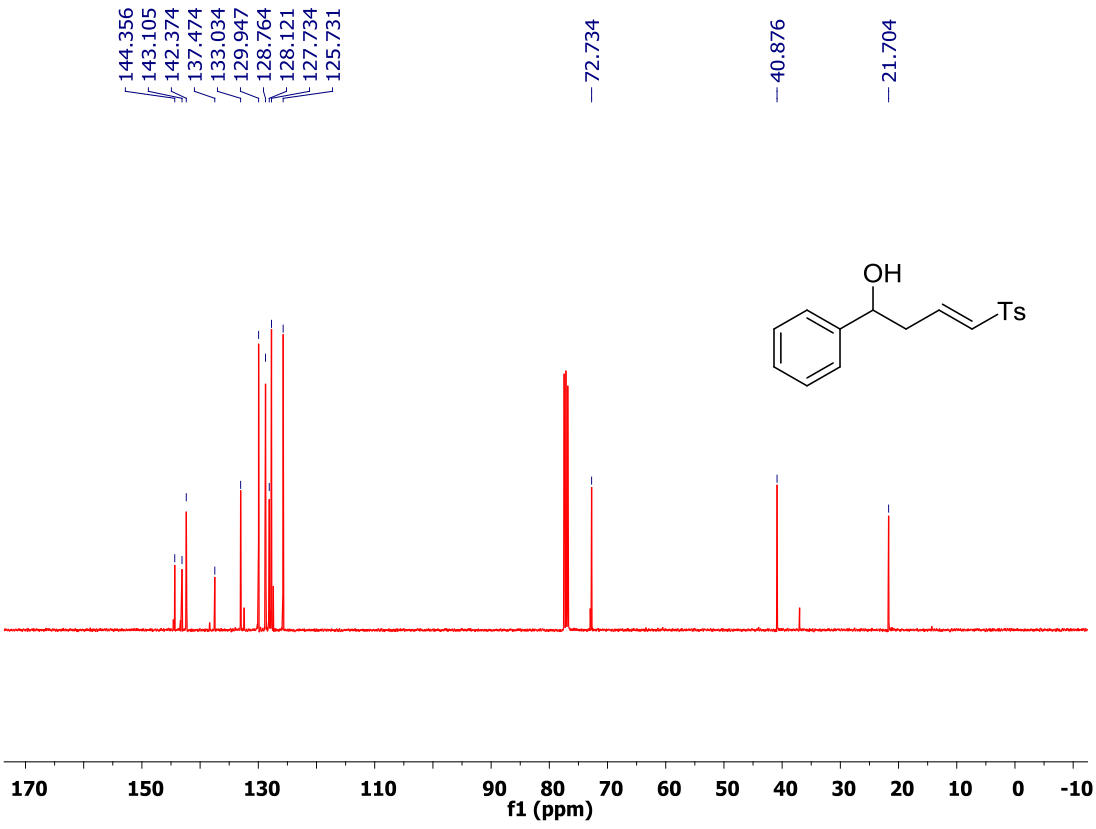
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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142.374
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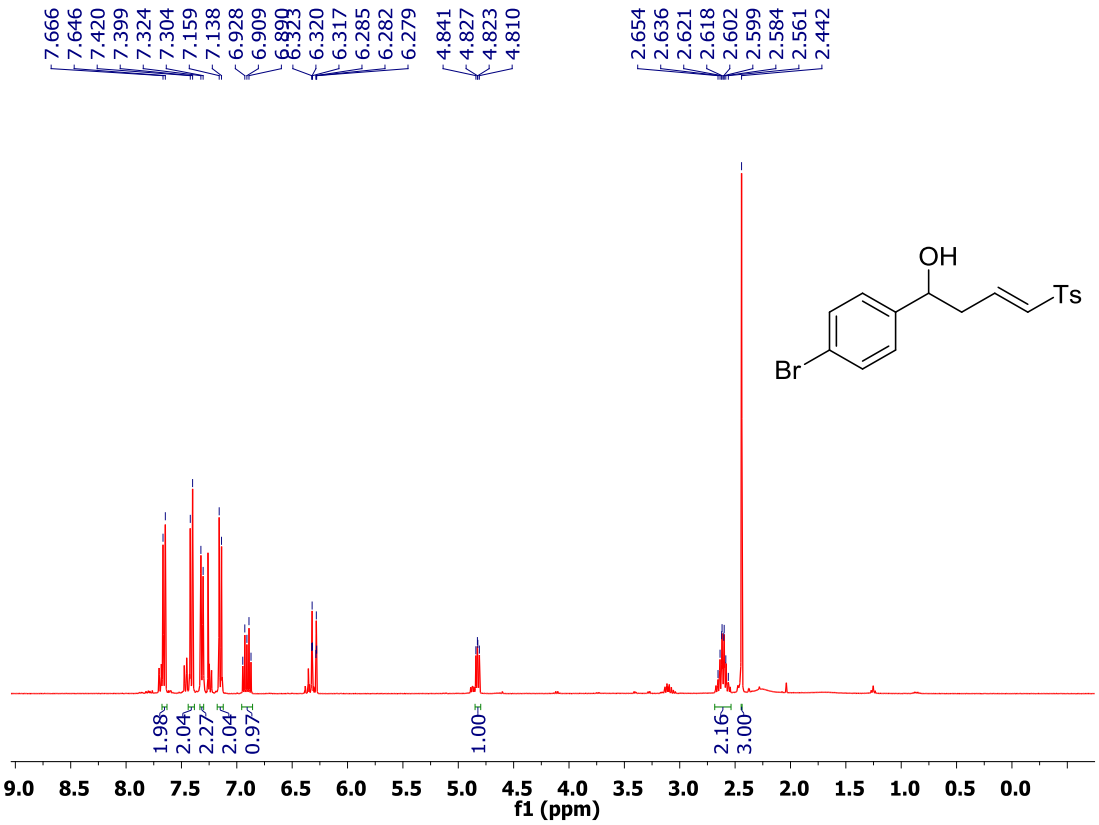
129.947
128.764
128.121
127.734
125.731
72.734
40.876
21.704
OH
Ts
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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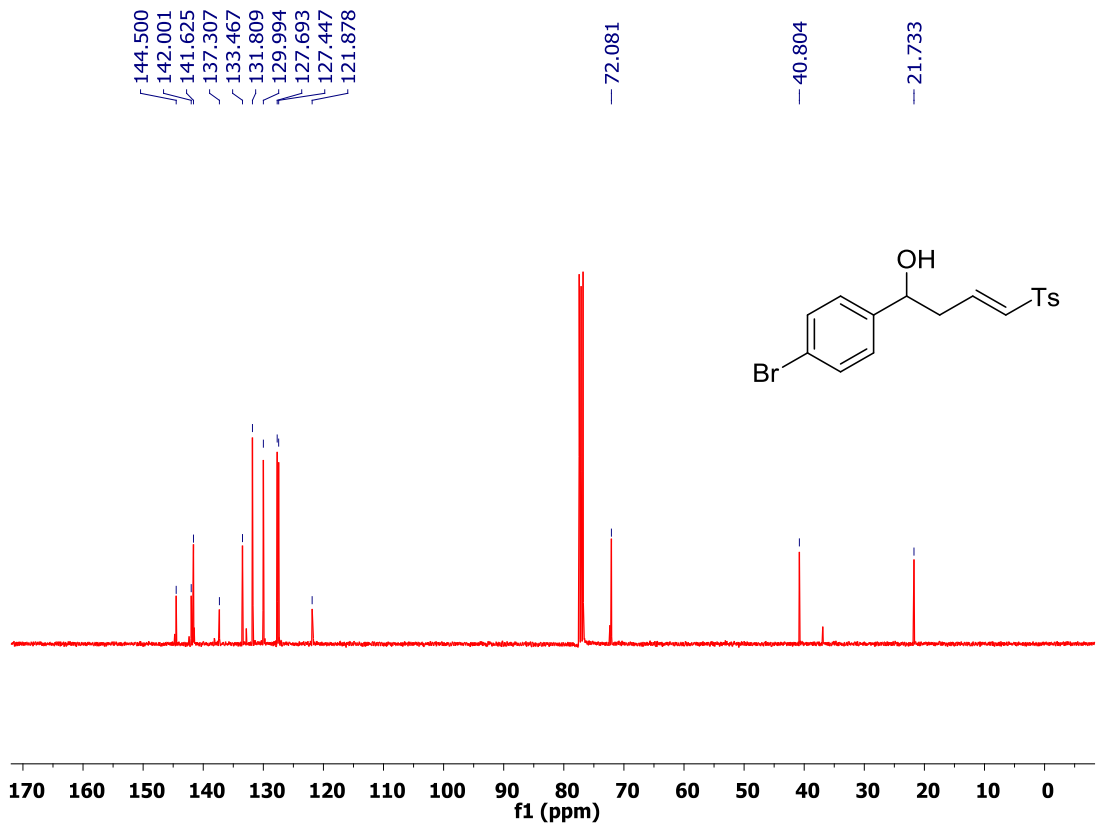
7.420
7.399
7.324
7.304
7.159
7.138
6.928
6.909
6.320
6.317
6.285
6.282
6.279
4.841
4.827
4.823
4.810
2.654
2.636
2.621
2.618
2.602
2.599
2.584
2.561
2.442
OH
Ts
Br
1.98
2.04
2.27
2.04
0.97
1.00
2.16
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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142.001
141.625
137.307
133.467
131.809
129.994
127.693
127.447
121.878
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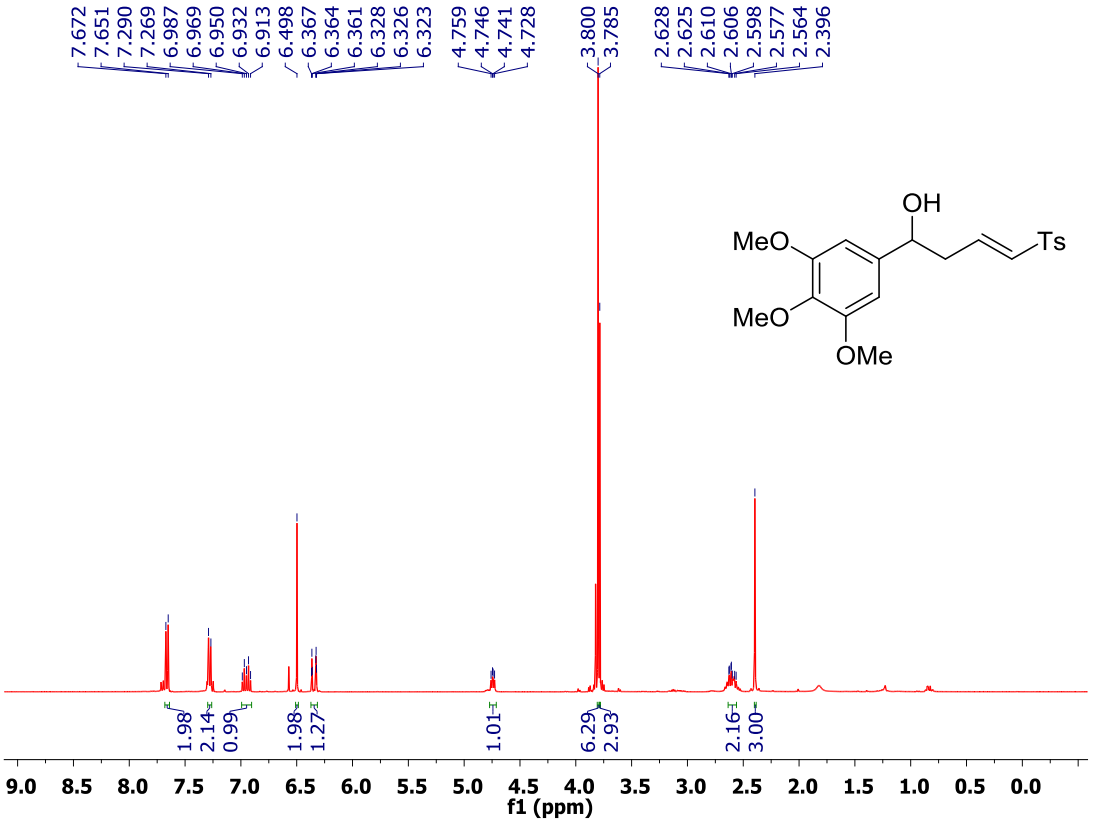
40.804
21.733
OH
Ts
Br
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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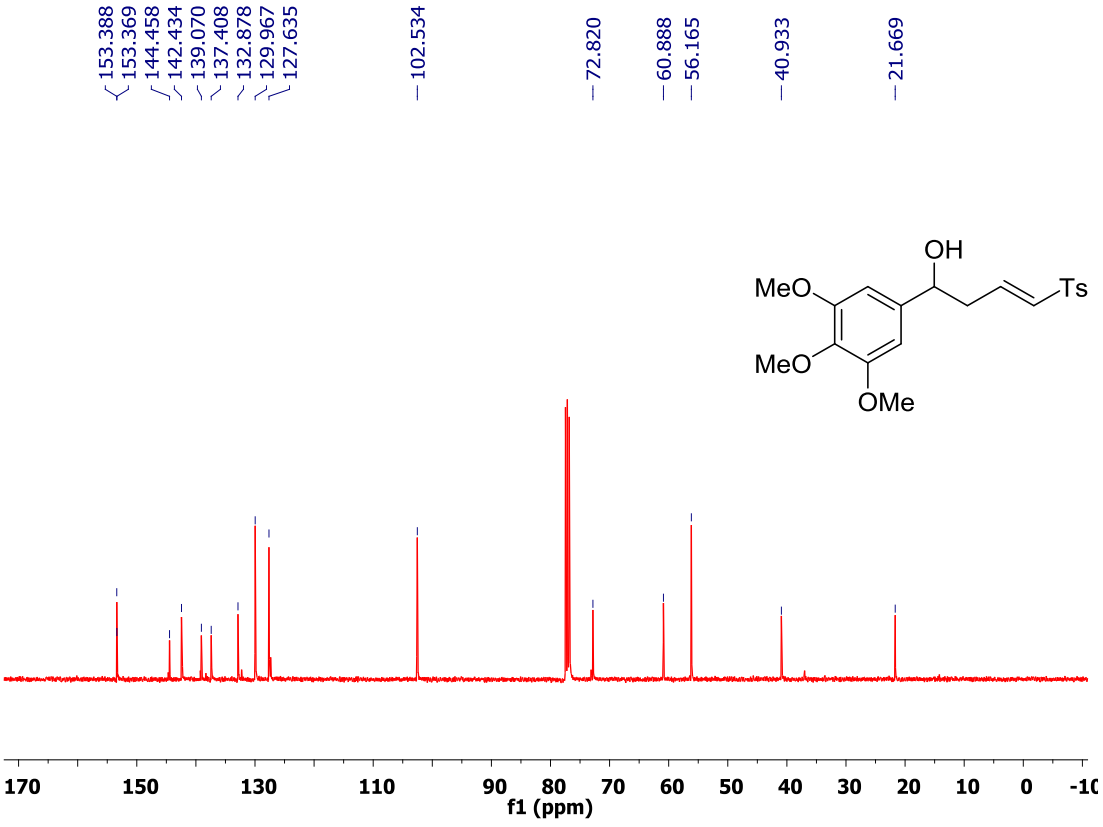
6.364
6.361
6.328
6.326
6.323
4.759
4.746
4.741
4.728
3.800
3.785
2.628
2.625
2.610
2.606
2.598
2.577
2.564
2.396
OH
MeO
Ts
MeO
OMe
1.98
2.14
0.99
1.98
1.27
1.01
6.29
2.93
2.16
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.967
127.635
102.534
72.820
60.888
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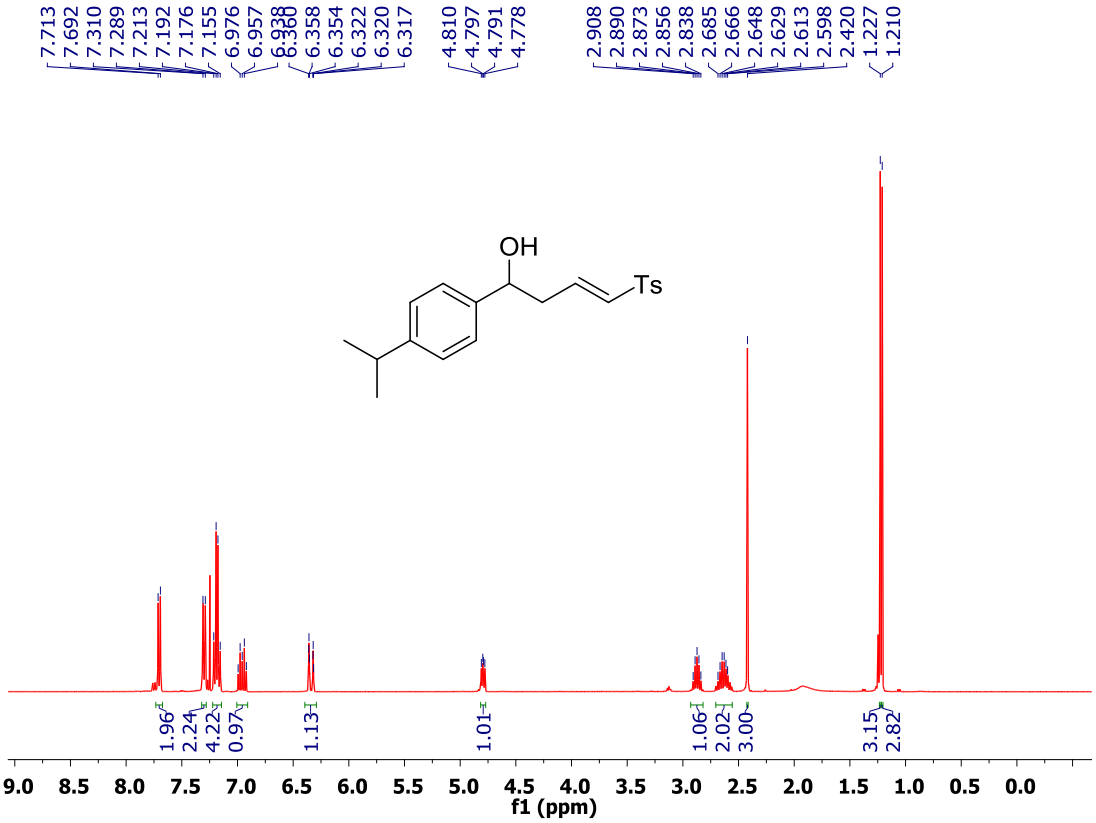
21.669
OH
MeO
Ts
MeO
OMe
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.155
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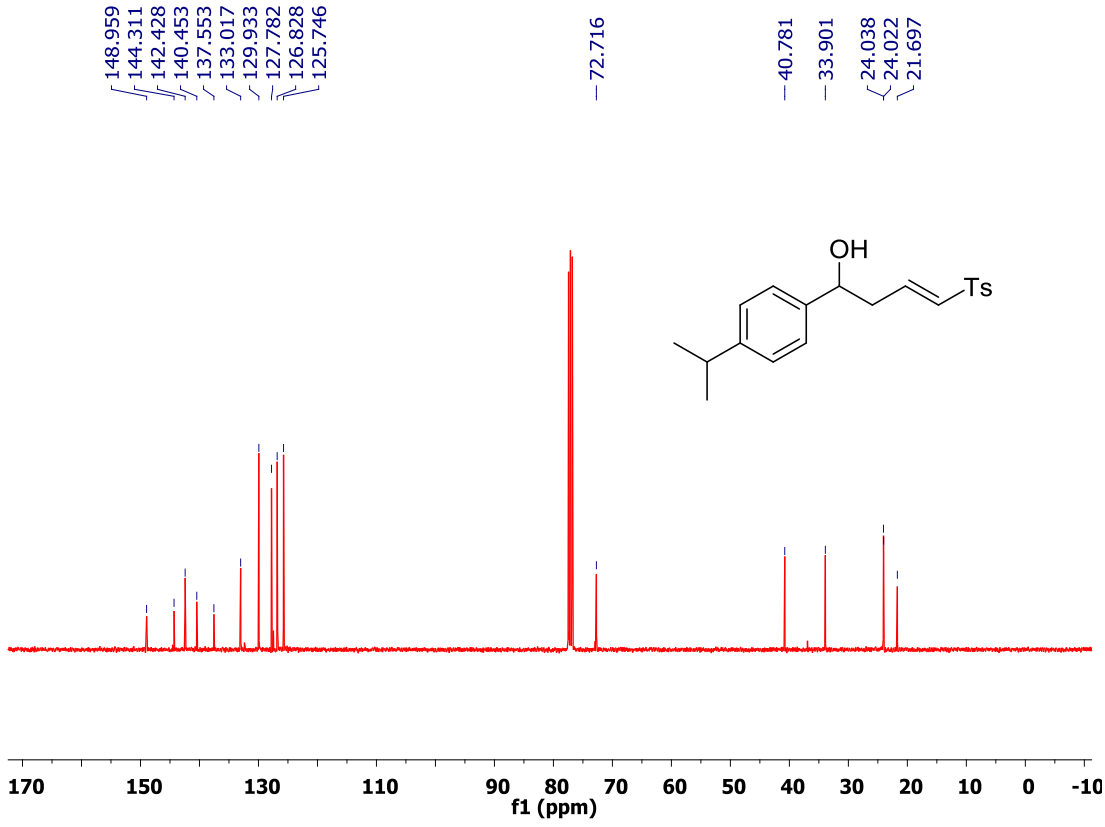
6.358
6.354
6.322
6.320
6.317
4.810
4.797
4.791
4.778
2.908
2.890
2.873
2.856
2.838
2.685
2.666
2.648
2.629
2.613
2.598
2.420
1.227
1.210
OH
Ts
1.96
2.24
4.22
0.97
1.13
1.01
1.06
2.02
3.00
3.15
2.82
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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127.782
126.828
125.746
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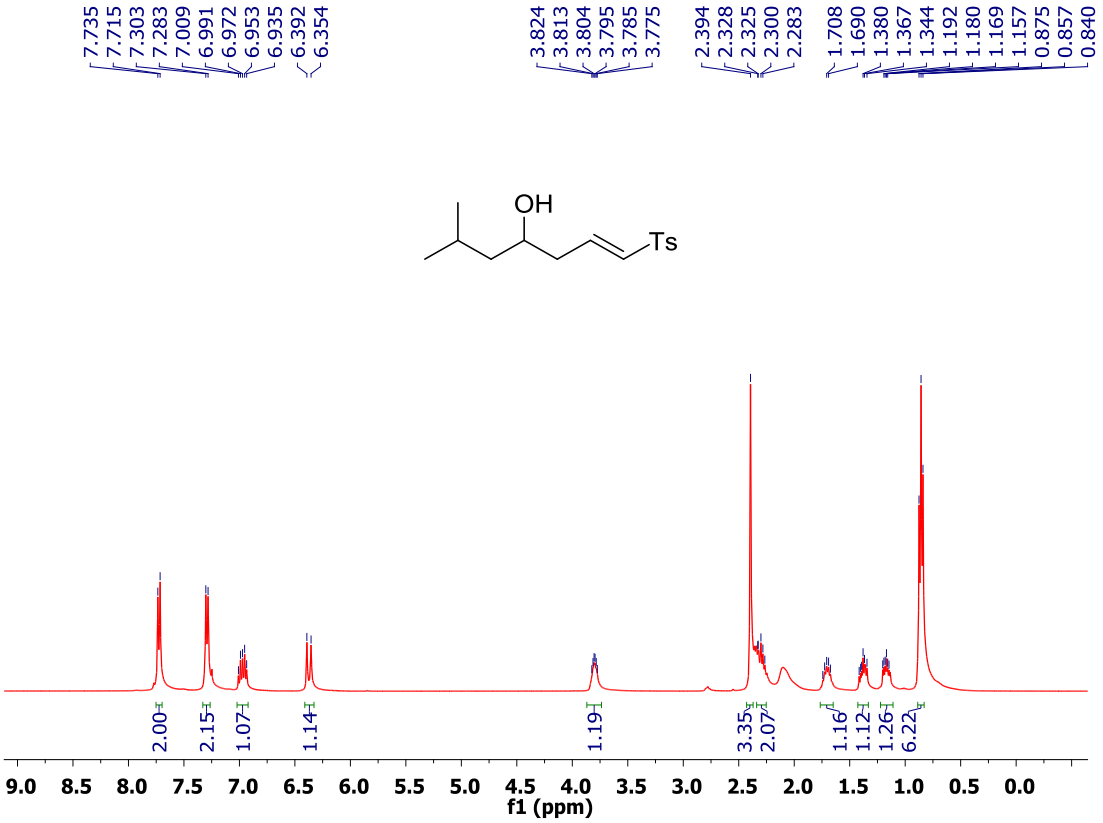
33.901
24.038
24.022
21.697
OH
Ts
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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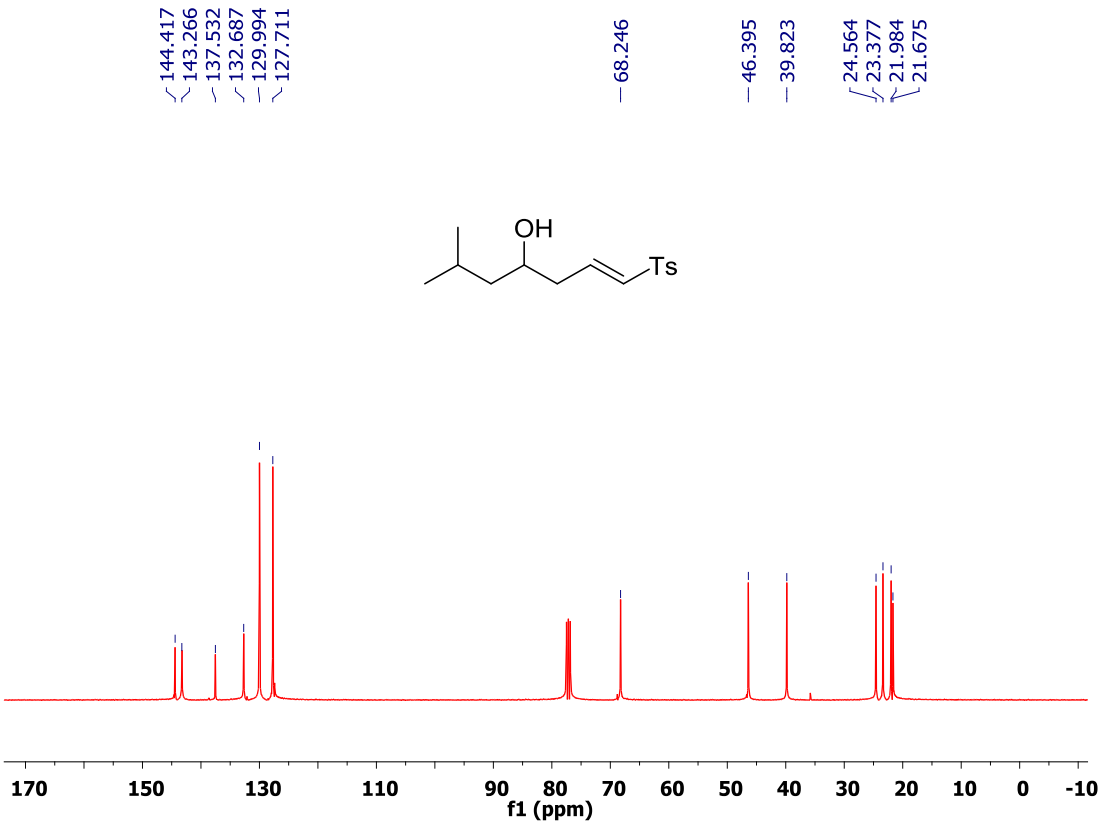
6.991
6.972
6.953
6.935
6.392
6.354
3.824
3.813
3.804
3.795
3.785
3.775
2.394
2.328
2.325
2.300
2.283
1.708
1.690
1.380
1.367
1.344
1.192
1.180
1.169
1.157
0.875
0.857
0.840
OH
Ts
2.00
2.15
1.07
1.14
1.19
3.35
2.07
1.16
1.12
1.26
6.22
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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23.377
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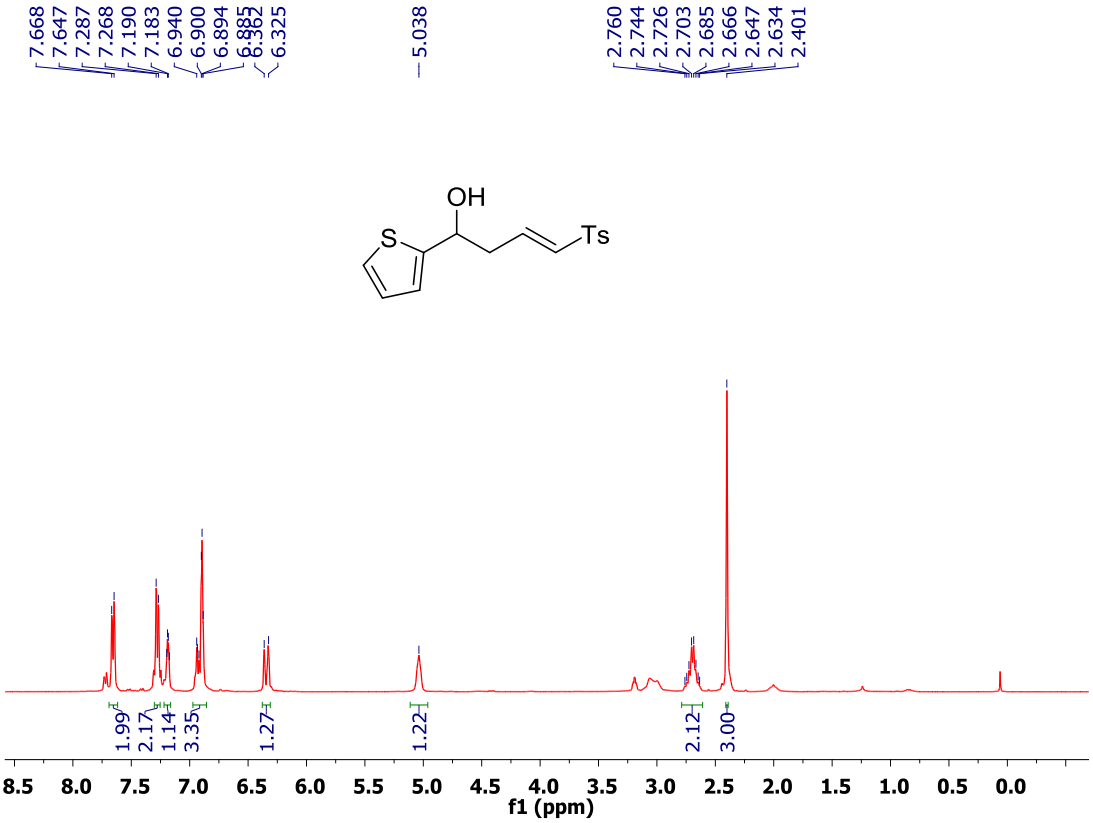
21.675
OH
Ts
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.668
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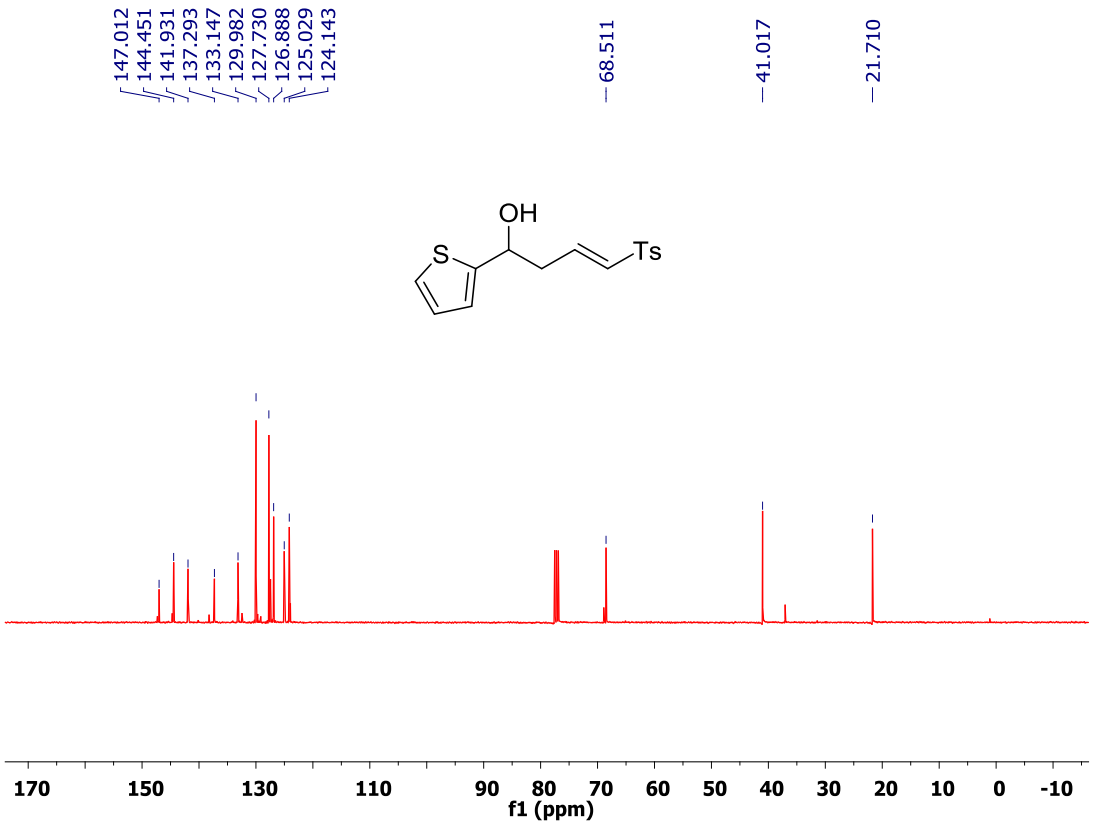
7.287
7.268
7.190
7.183
6.940
6.900
6.894
6.325
5.038
2.760
2.744
2.726
2.703
2.685
2.666
2.647
2.634
2.401
OH
S
Ts
1.99
2.17
1.14
3.35
1.27
1.22
2.12
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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133.147
129.982
127.730
126.888
125.029
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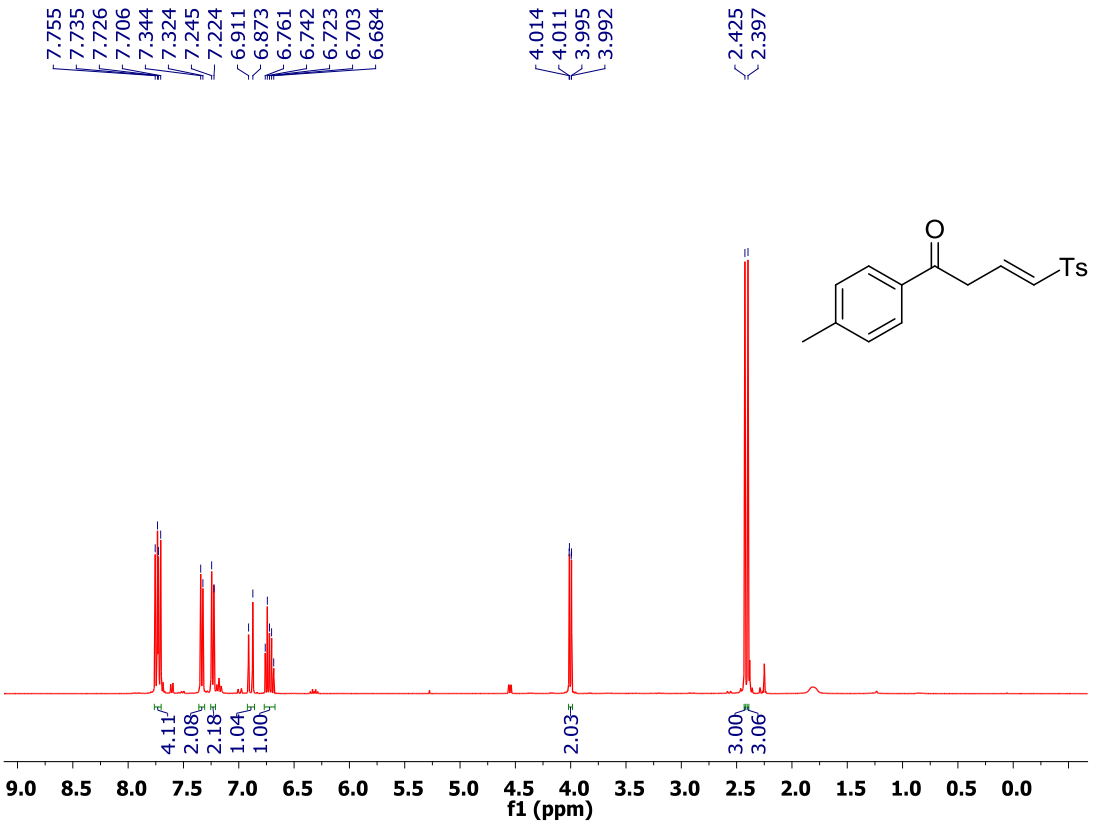
68.511
41.017
21.710
OH
S
Ts
170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.224
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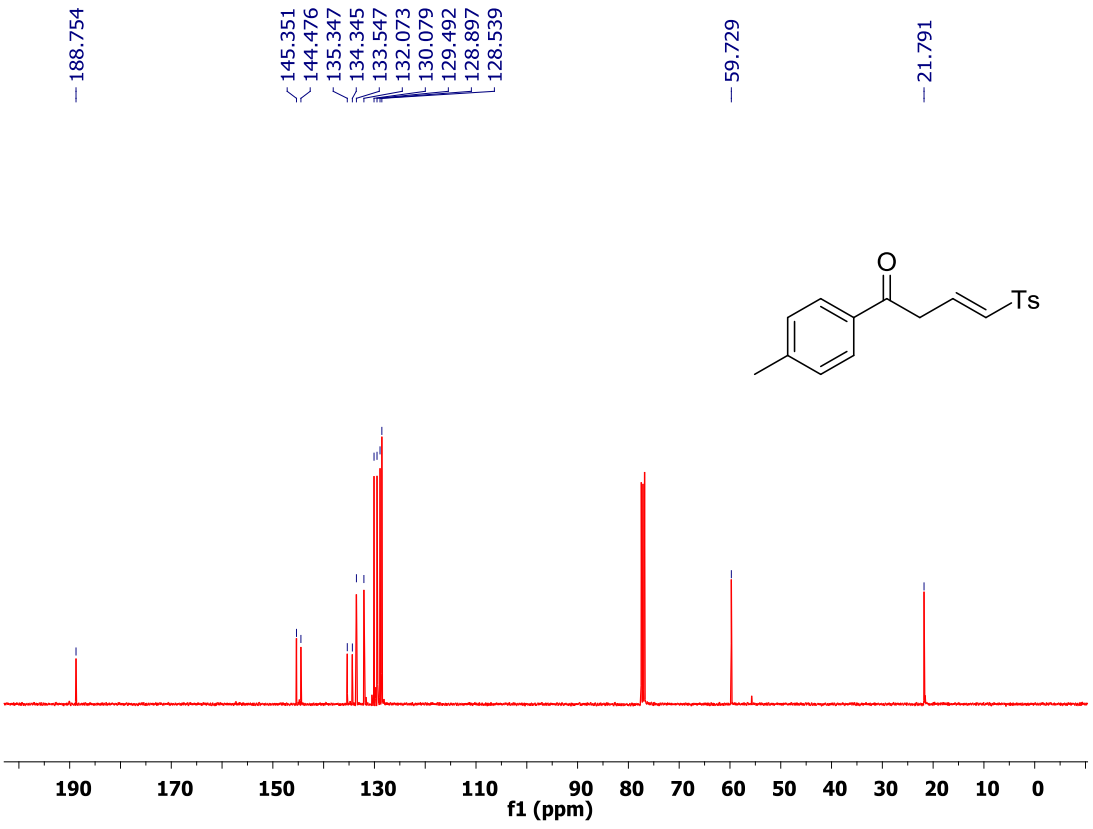
6.873
6.761
6.742
6.723
6.703
6.684
4.014
4.011
3.995
3.992
2.425
2.397
O
Ts
4.11
2.08
2.18
1.04
1.00
2.03
3.00
3.06
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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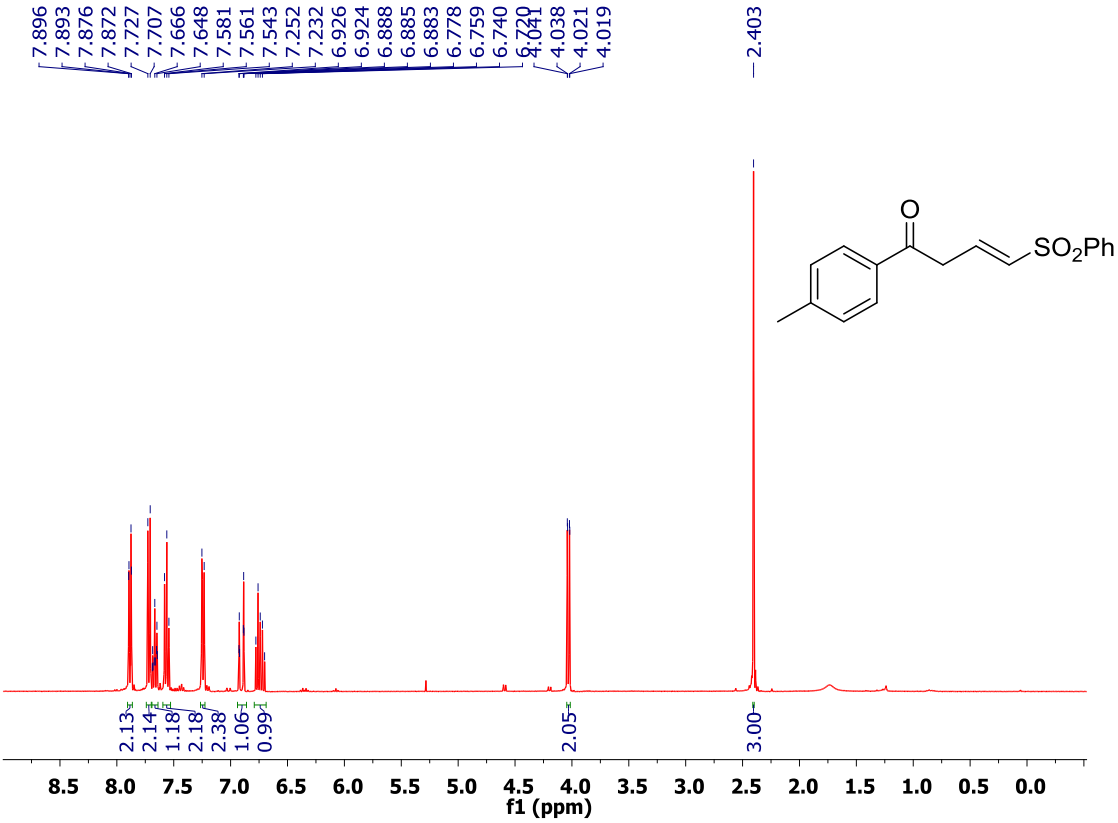
133.547
132.073
130.079
129.492
128.897
128.539
59.729
21.791
O
Ts
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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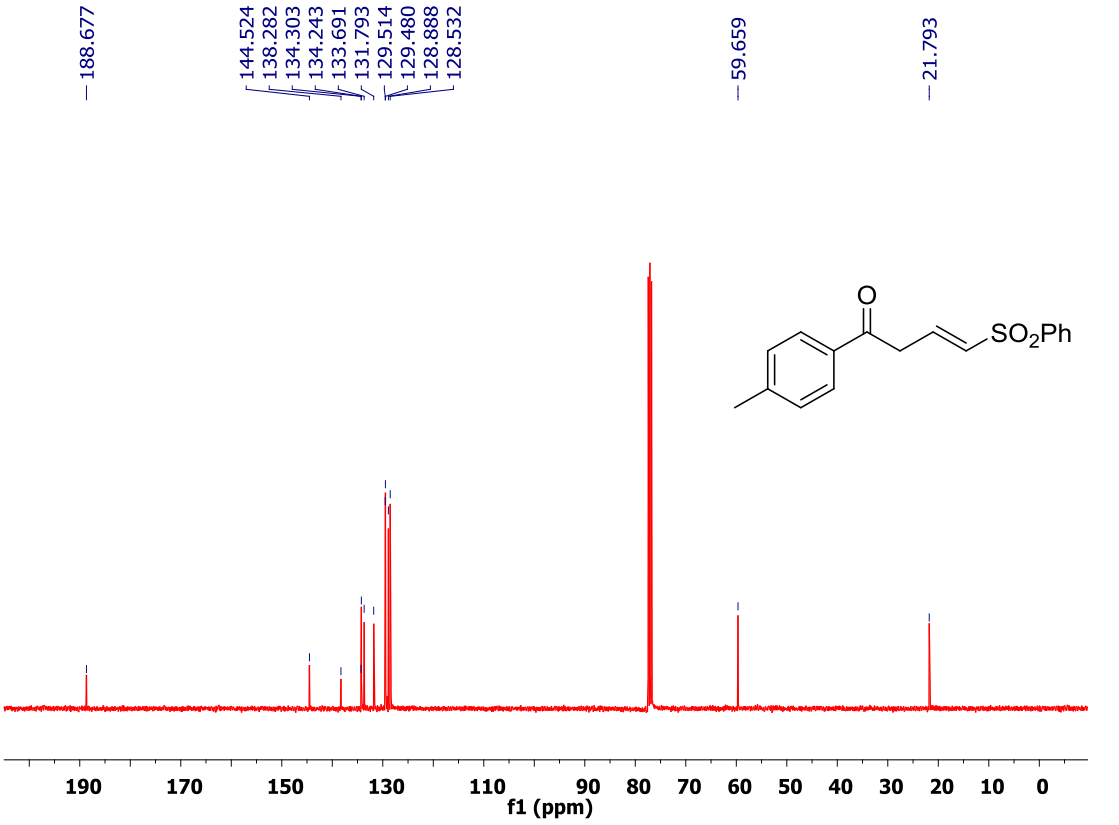
7.648
7.581
7.561
7.543
7.252
7.232
6.926
6.924
6.888
6.885
6.883
6.778
6.759
6.740
4.041
4.038
4.021
4.019
2.403
O
SO2Ph
2.13
2.14
1.18
2.18
2.38
1.06
0.99
2.05
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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21.793
O
SO2Ph
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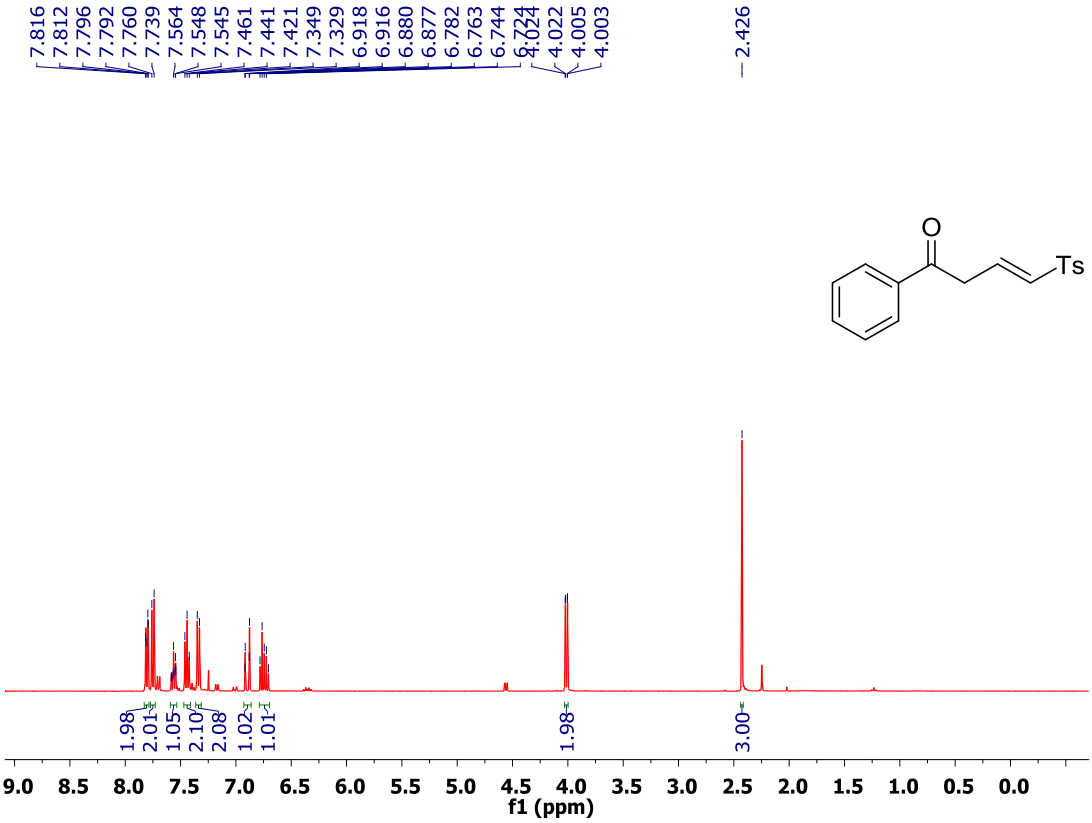
f1 (ppm)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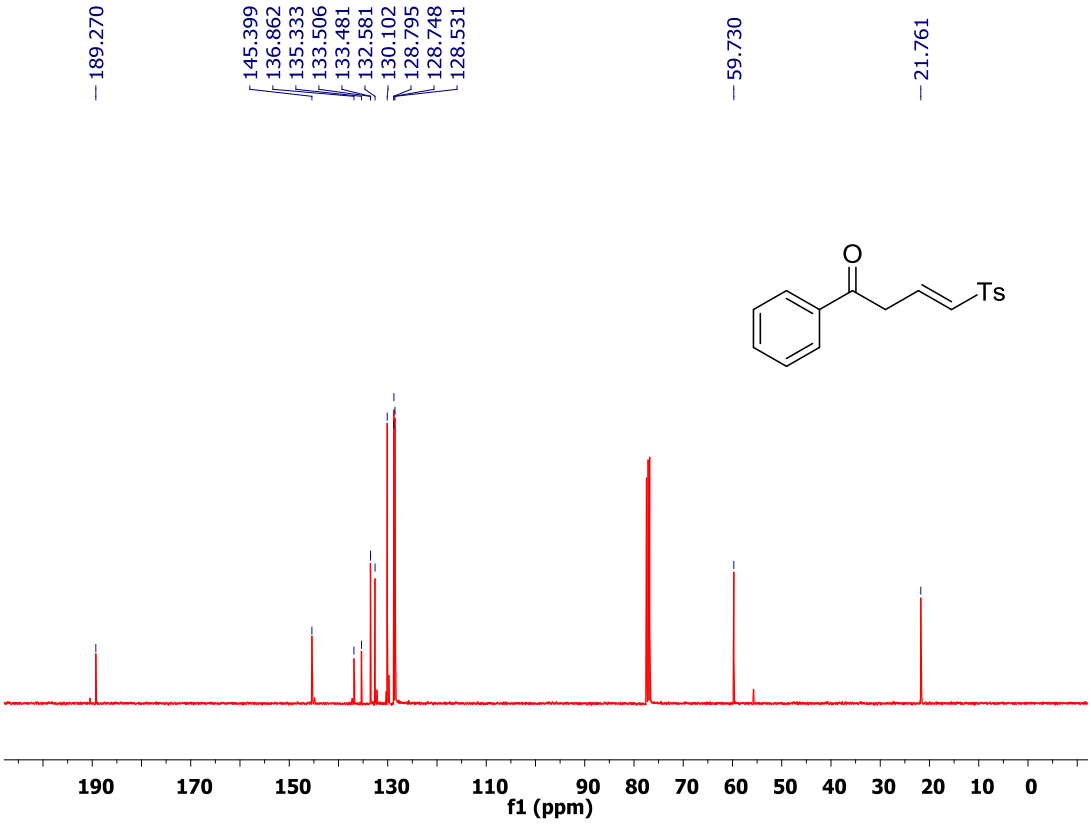
7.812
7.796
7.792
7.760
7.739
7.564
7.548
7.545
7.461
7.441
7.421
7.349
7.329
6.918
6.916
6.880
6.877
6.782
6.763
6.744
4.022
4.005
4.003
2.426
O
Ts
1.98
2.01
1.05
2.10
2.08
1.02
1.01
1.98
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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136.862
135.333
133.506
133.481
132.581
130.102
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128.531
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21.761
O
Ts
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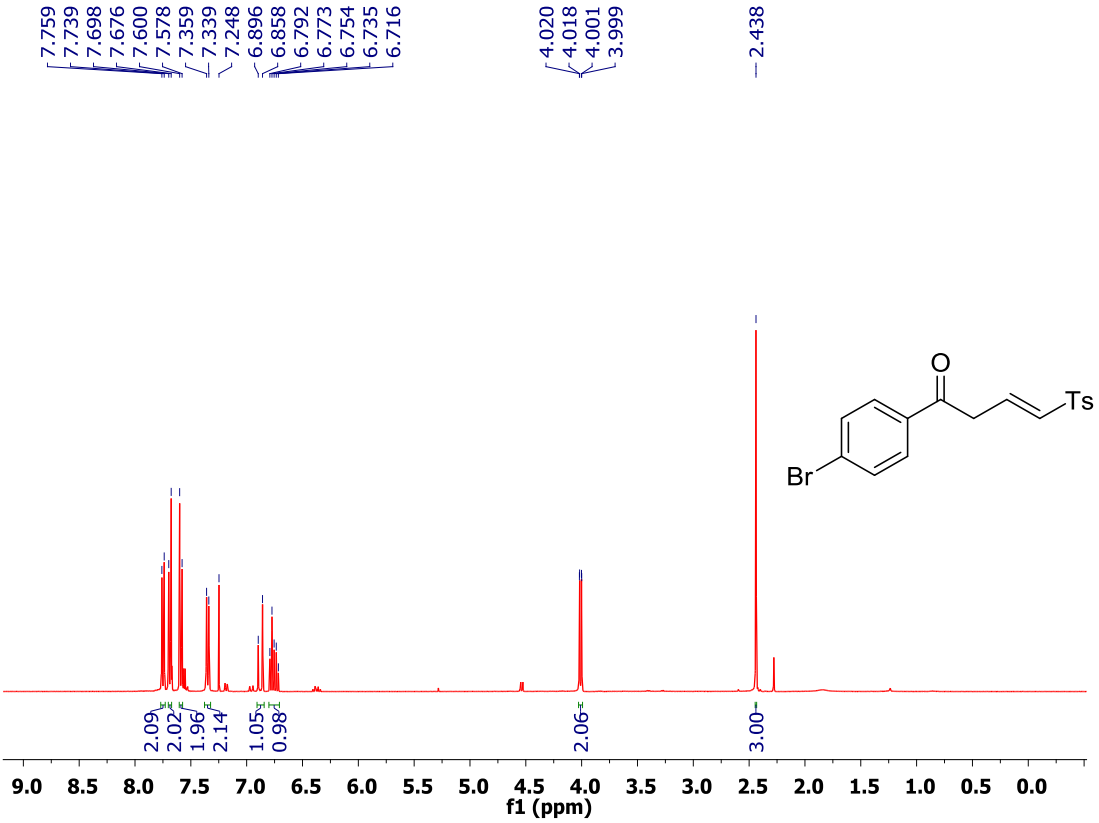
f1 (ppm)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7.739
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7.600
7.578
7.359
7.339
7.248
6.896
6.858
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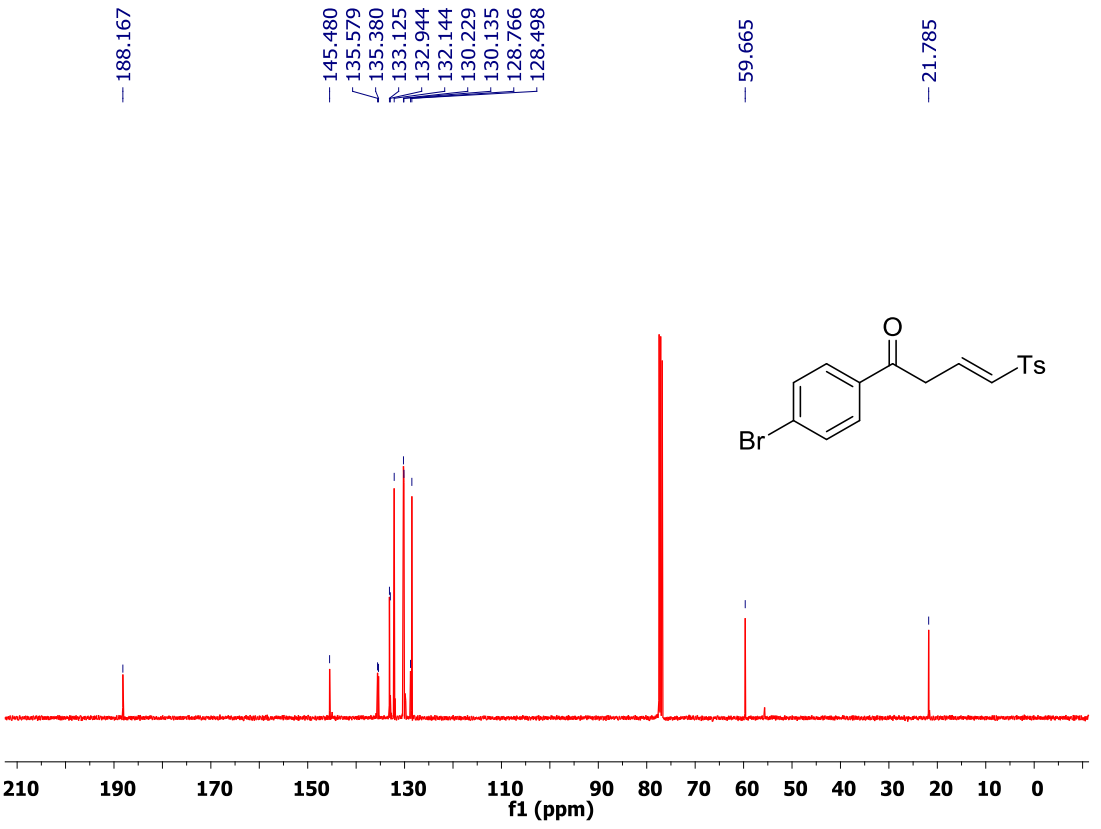
6.773
6.754
6.735
6.716
4.020
4.018
4.001
3.999
2.438
O
Ts
Br
2.09
2.02
1.96
2.14
1.05
0.98
2.06
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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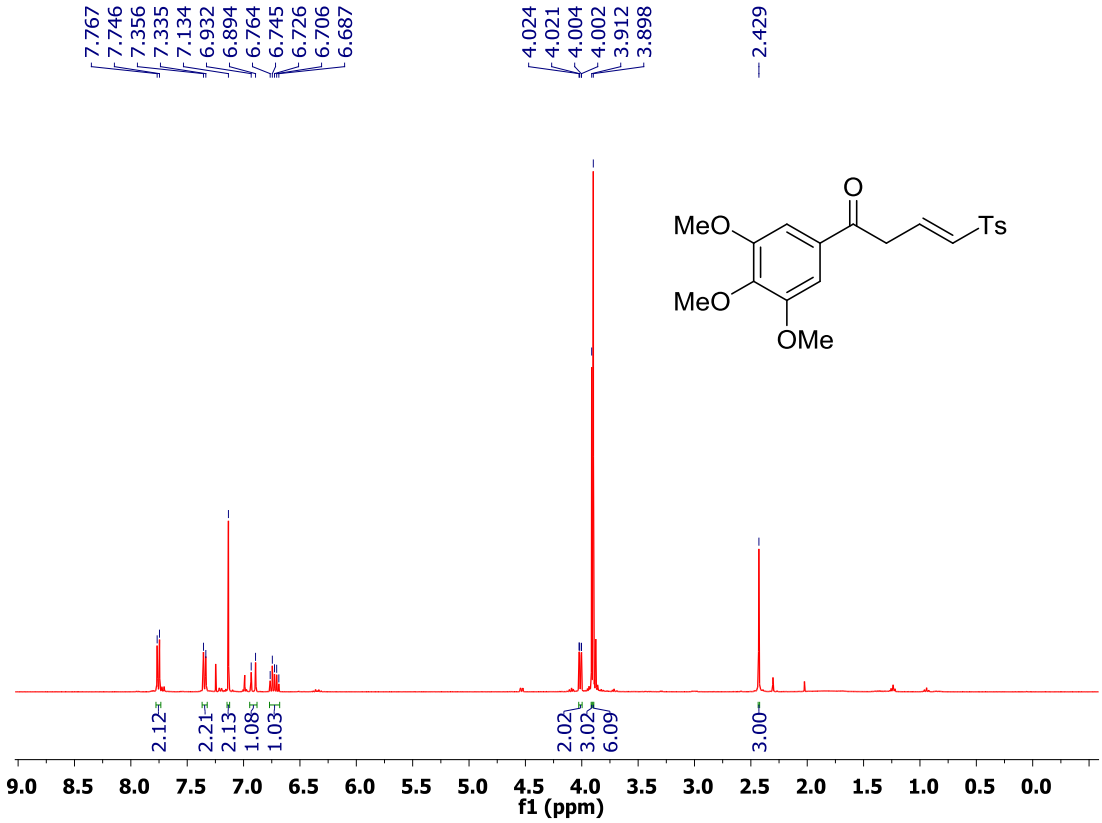
145.480
135.579
135.380
133.125
132.944
132.144
130.229
130.135
128.766
128.498
59.665
21.785
O
Ts
Br
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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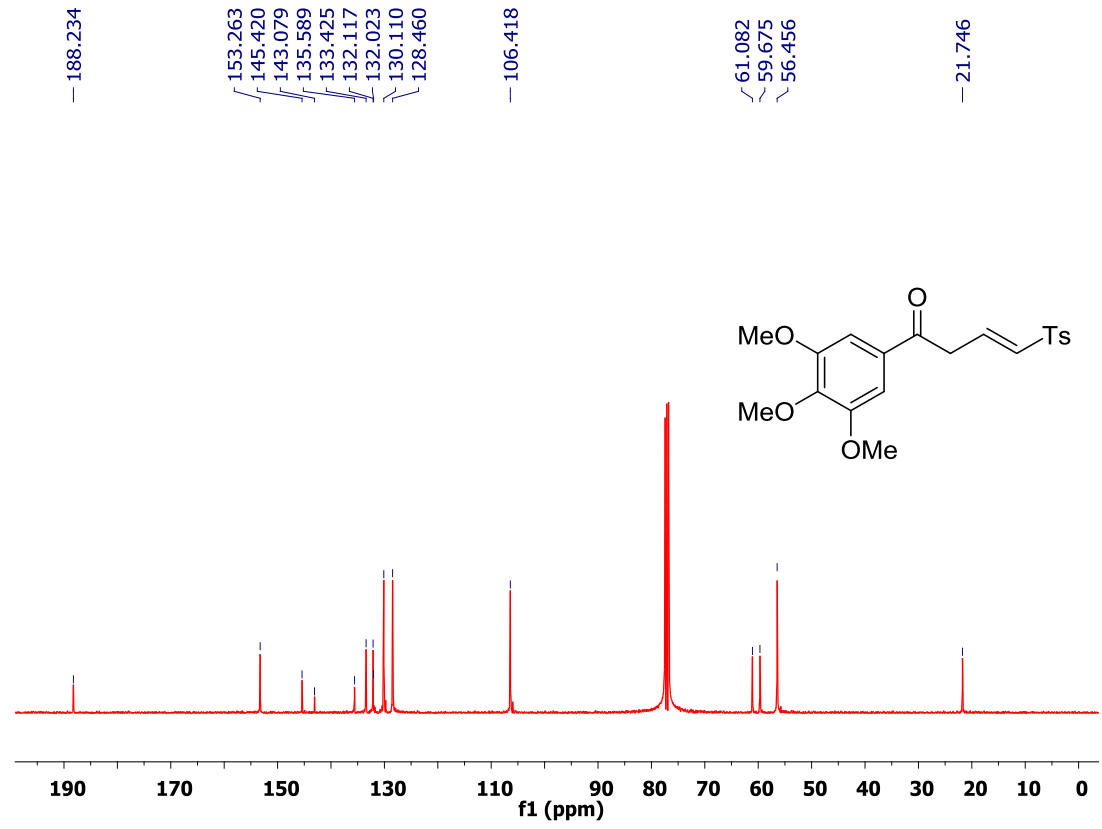
7.746
7.356
7.335
7.134
6.932
6.894
6.764
6.745
6.726
6.706
6.687
4.024
4.021
4.004
4.002
3.912
3.898
2.429
MeO
MeO
OMe
O
Ts
2.12
2.21
2.13
1.08
1.03
2.02
3.02
6.09
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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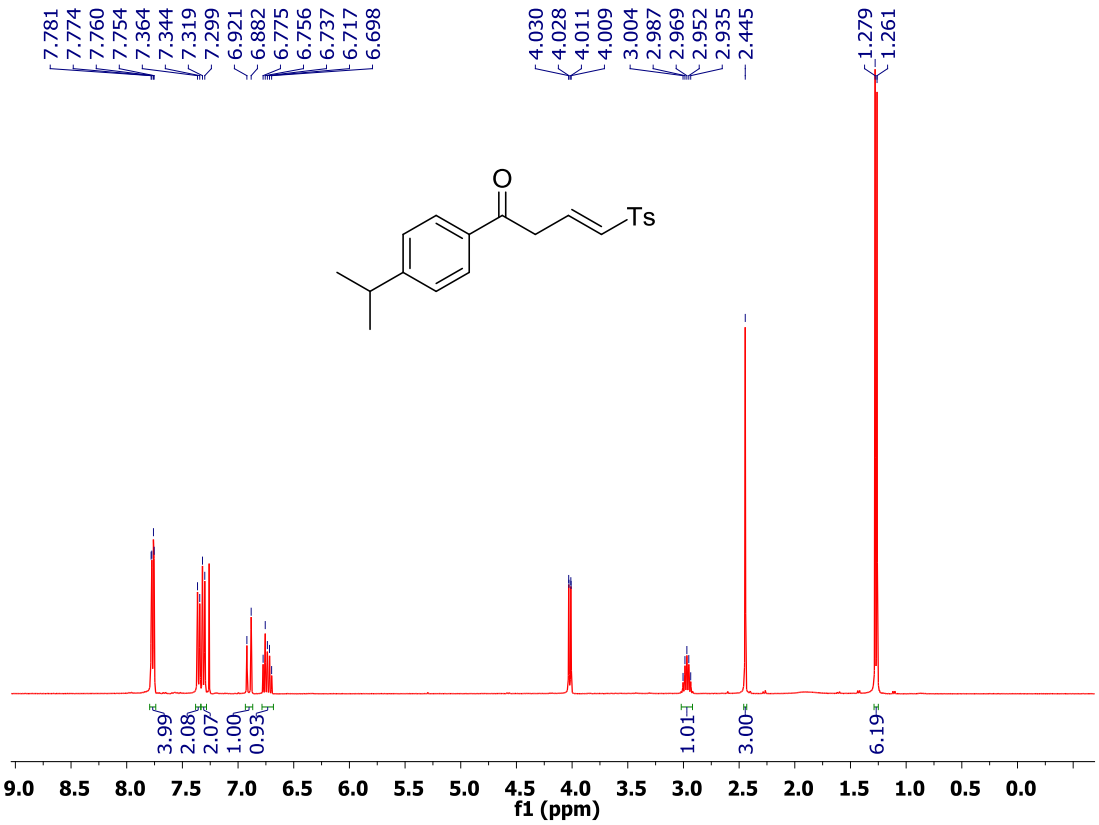
153.263
145.420
143.079
135.589
133.425
132.117
132.023
130.110
128.460
106.418
61.082
59.675
56.456
21.746
MeO
MeO
OMe
O
Ts
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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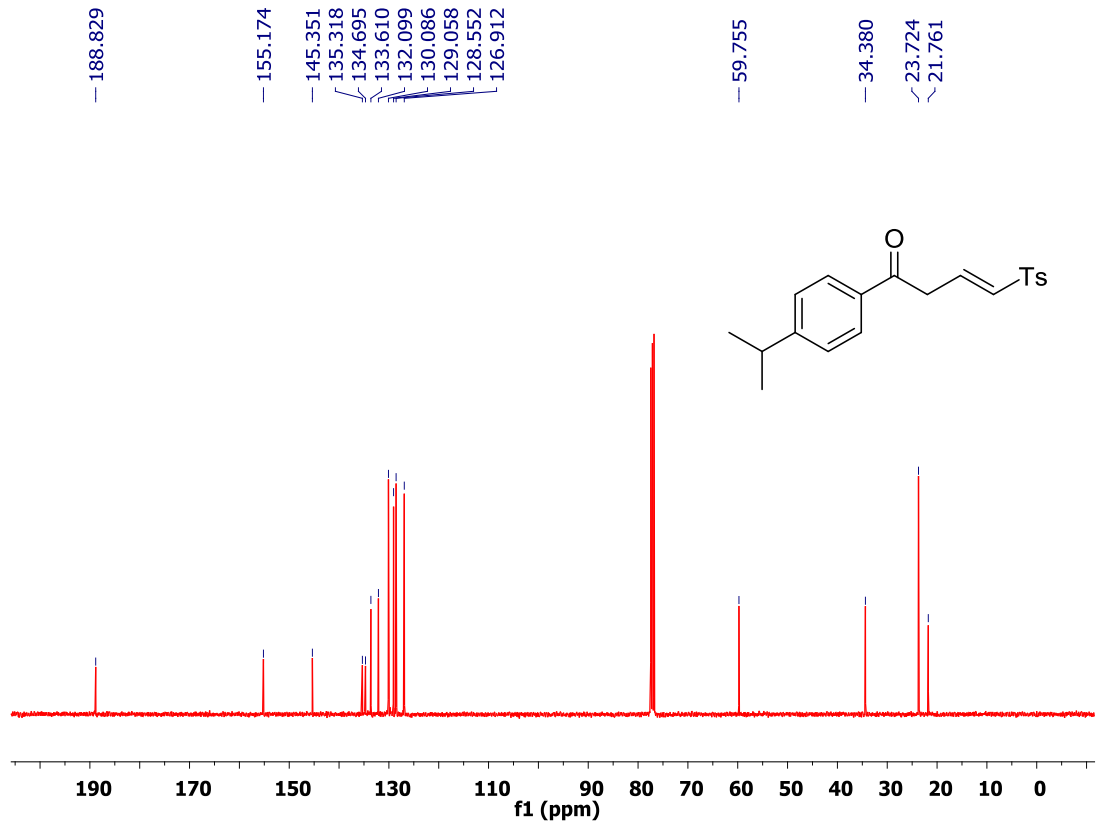
7.774
7.760
7.754
7.364
7.344
7.319
7.299
6.921
6.882
6.775
6.756
6.737
6.717
6.698
4.030
4.028
4.011
4.009
3.004
2.987
2.969
2.952
2.935
2.445
1.279
1.261
O
Ts
3.99
2.08
2.07
1.00
0.93
1.01
3.00
6.19
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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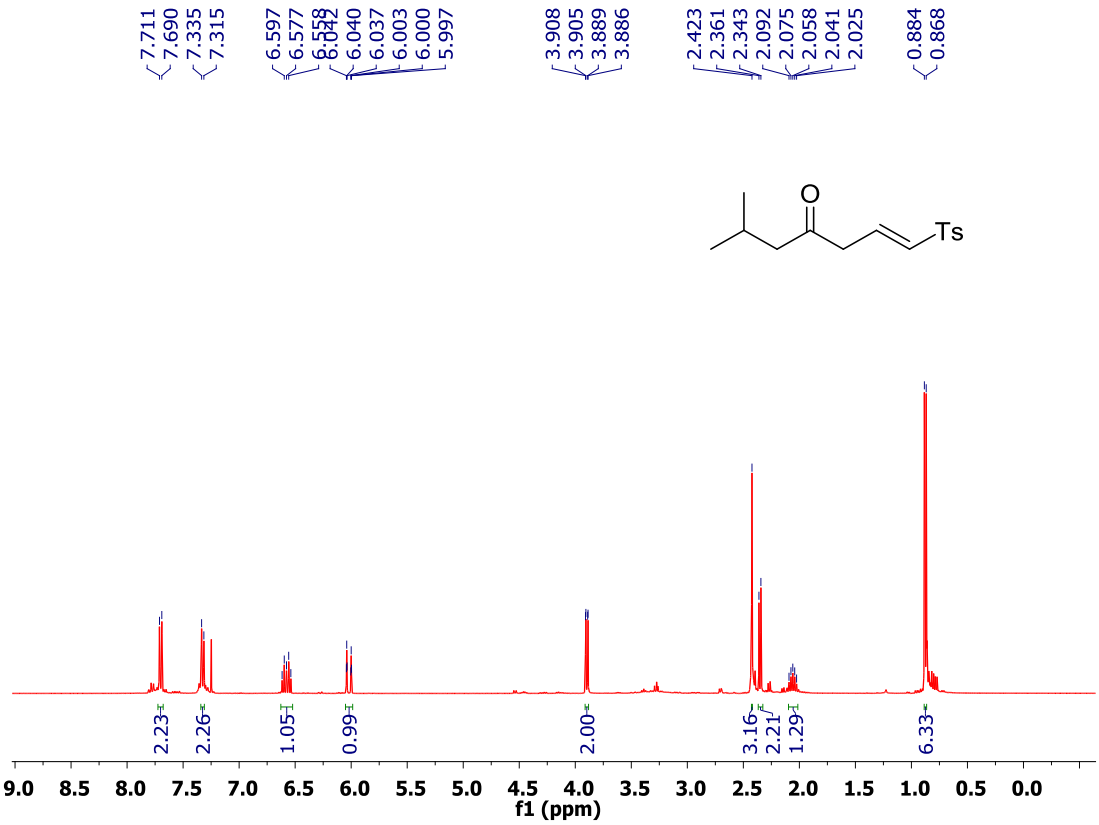
155.174
145.351
135.318
134.695
133.610
132.099
130.086
129.058
128.552
126.912
59.755
34.380
23.724
21.761
O
Ts
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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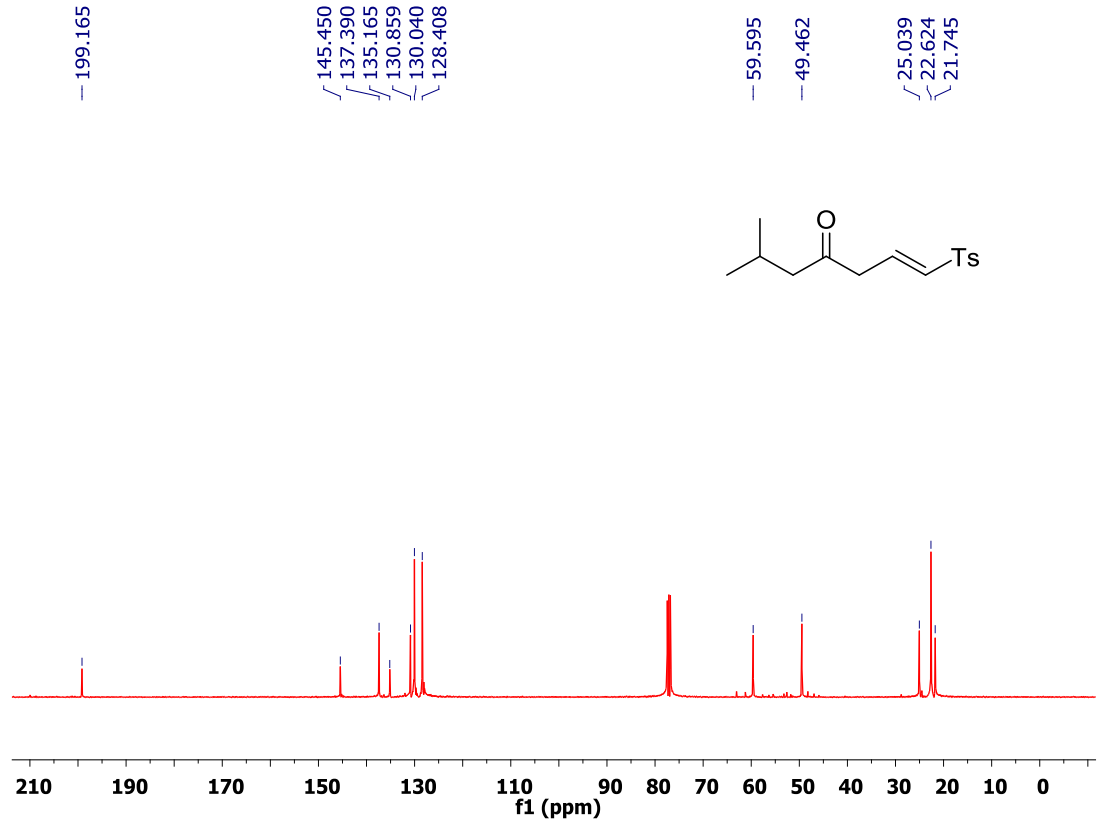
7.690
7.335
7.315
6.597
6.577
6.558
6.042
6.040
6.037
6.003
6.000
5.997
3.908
3.905
3.889
3.886
2.423
2.361
2.343
2.092
2.075
2.058
2.041
2.025
0.884
0.868
O
Ts
2.23
2.26
1.05
0.99
2.00
3.16
2.21
1.29
6.33
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


199.165
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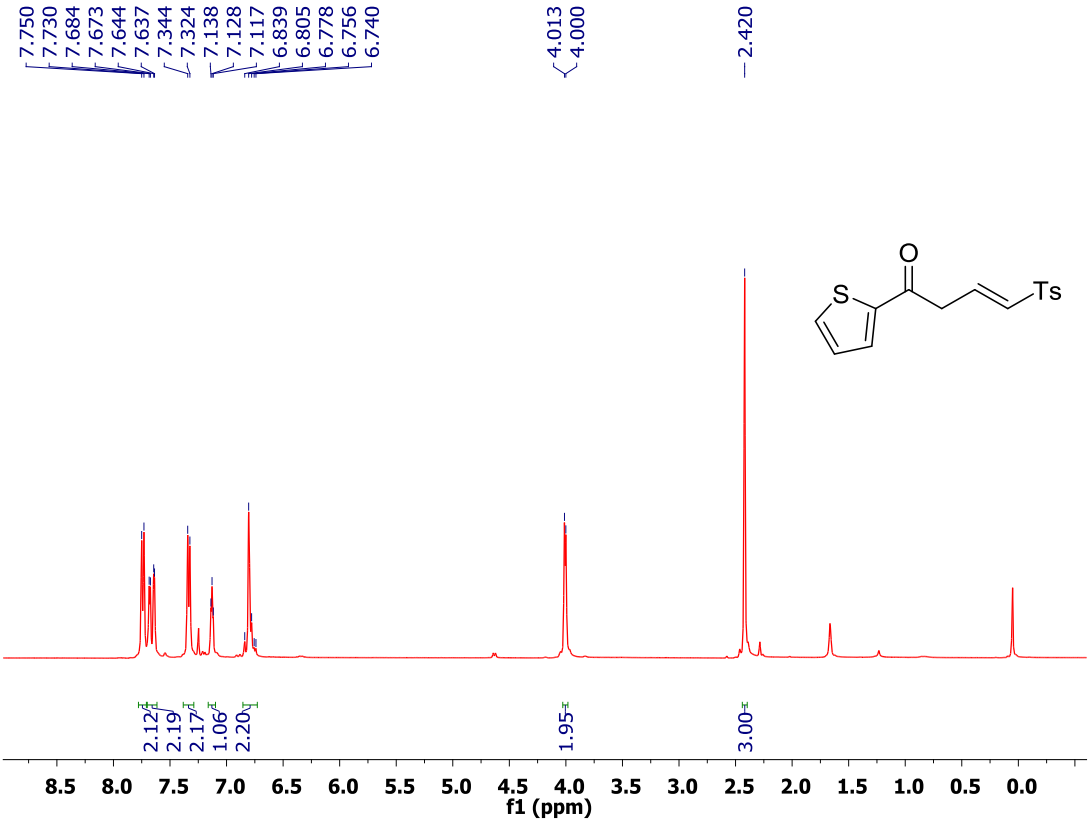
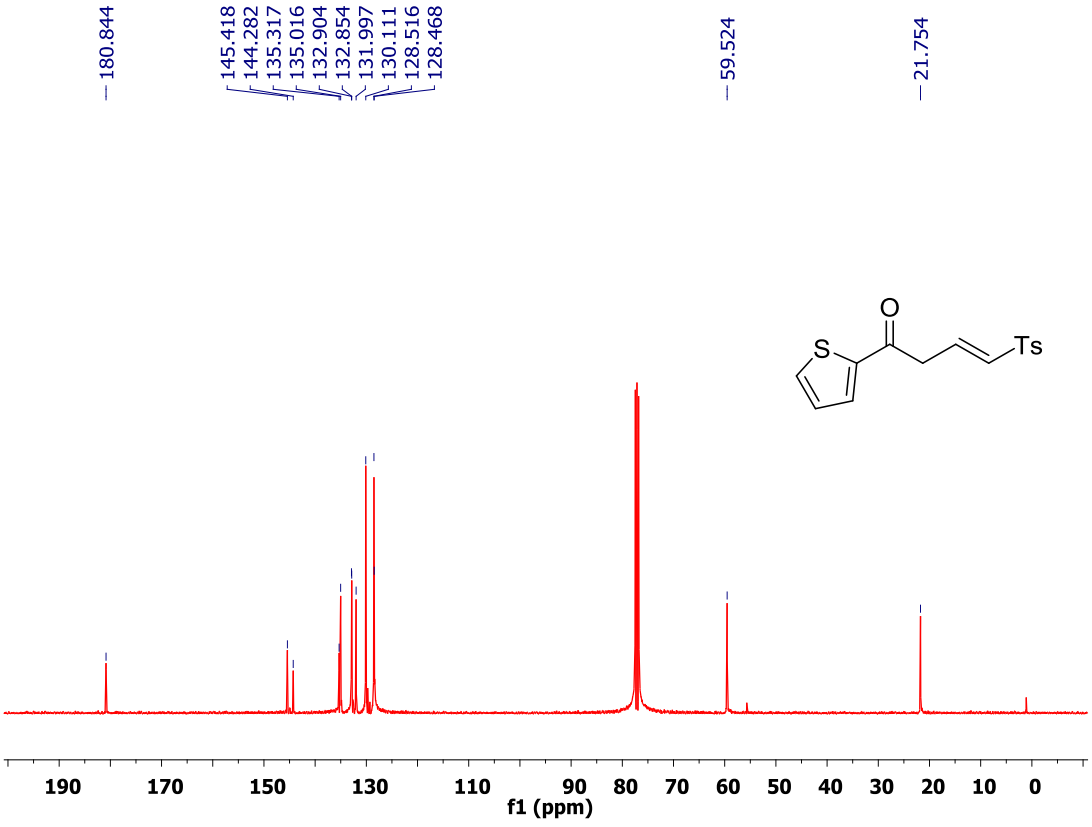
137.390
135.165
130.859
130.040
128.408
59.595
49.462
25.039
22.624
21.745
O
Ts
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.750
7.730
7.684
7.673
7.644
7.637
7.344
7.324
7.138
7.128
7.117
6.839
6.805
6.778
6.756
6.740
4.013
4.000
2.420
O
S
Ts
2.12
2.19
2.17
1.06
2.20
1.95
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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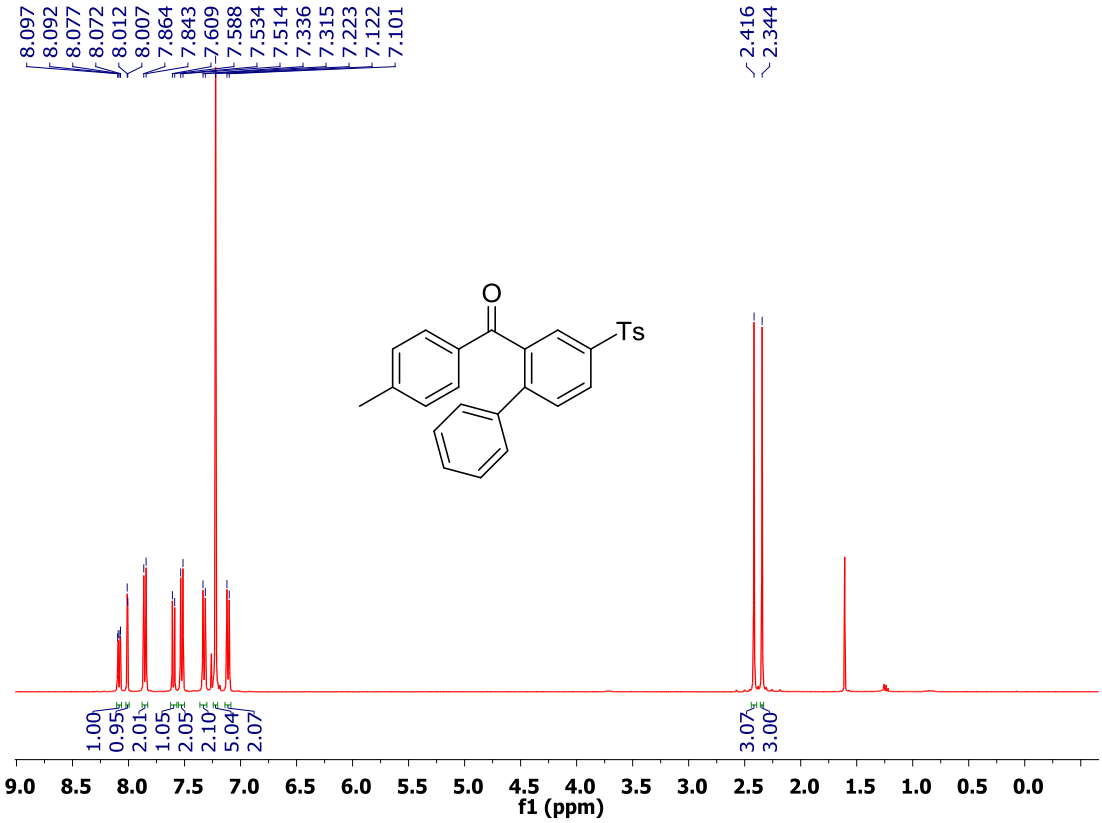
145.418
144.282
135.317
135.016
132.904
132.854
131.997
130.111
128.516
128.468
59.524
21.754
O
S
Ts
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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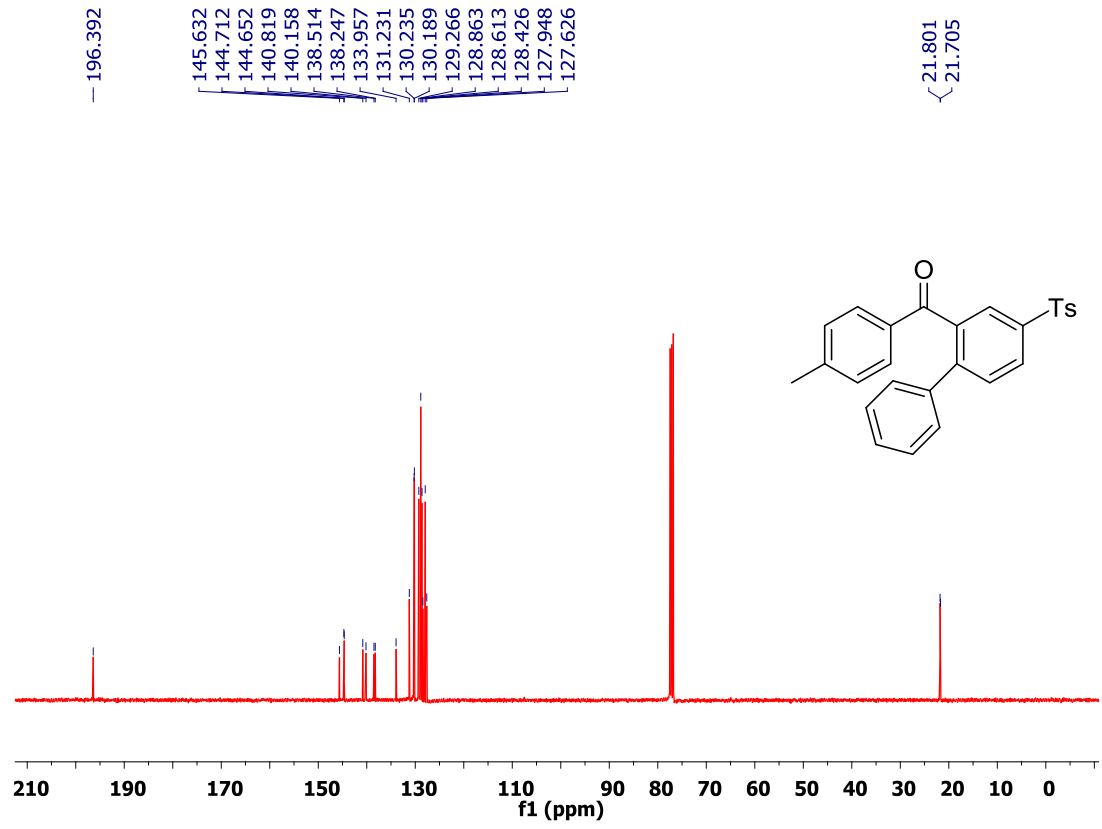
8.092
8.077
8.072
8.012
8.007
7.864
7.843
7.609
7.588
7.534
7.514
7.336
7.315
7.223
7.122
7.101
2.416
2.344
O
Ts
1.00
0.95
2.01
1.05
2.05
2.10
5.04
2.07
3.07
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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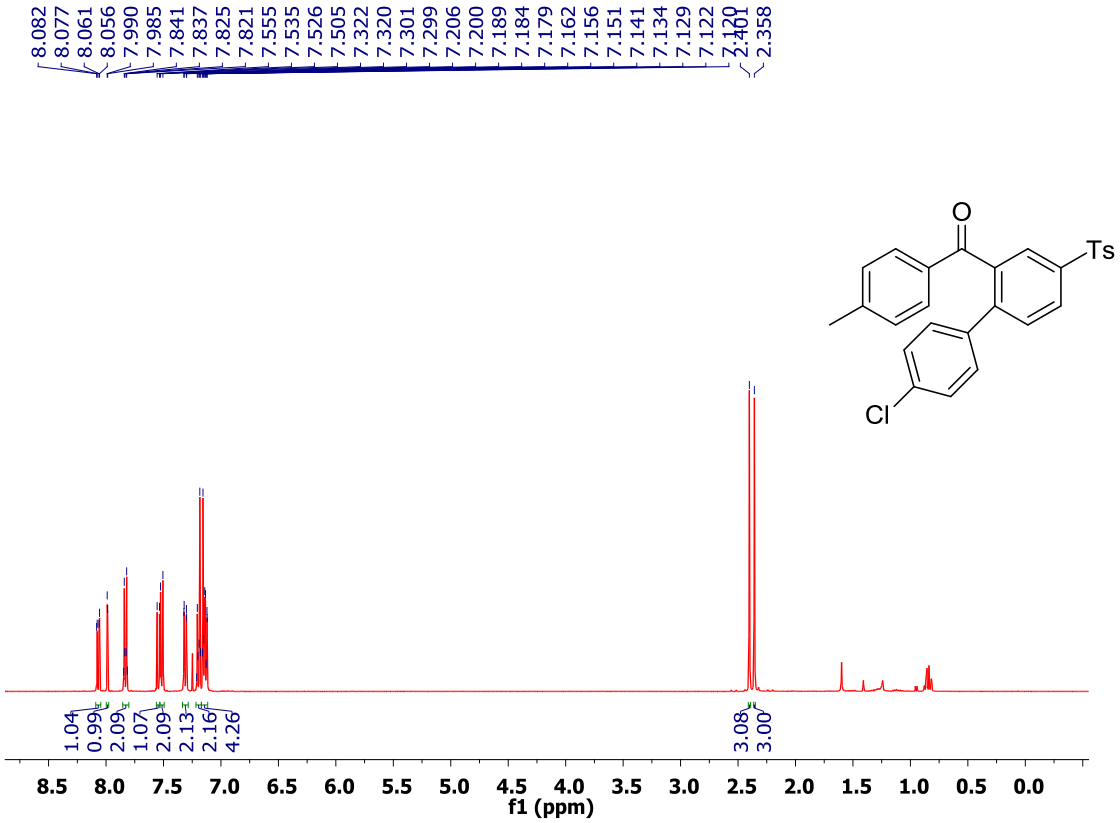
145.632
144.712
144.652
140.819
140.158
138.514
138.247
133.957
131.231
130.235
130.189
129.266
128.863
128.613
128.426
127.948
127.626
21.801
21.705
O
Ts
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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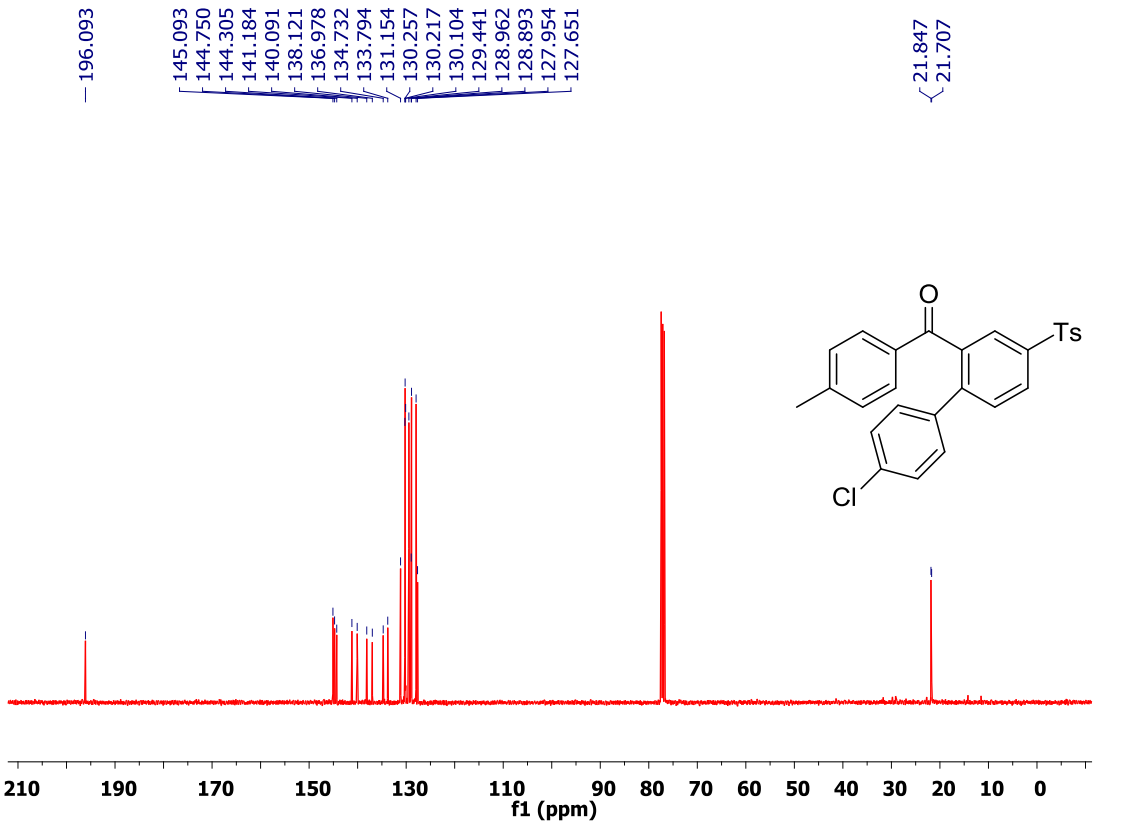
8.077
8.061
8.056
7.990
7.985
7.841
7.837
7.825
7.821
7.555
7.535
7.526
7.505
7.322
7.320
7.301
7.299
7.206
7.200
7.189
7.184
7.179
7.162
7.156
7.151
7.141
7.134
7.129
7.122
7.120
2.401
2.358
O
Ts
Cl
1.04
0.99
2.09
1.07
2.09
2.13
2.16
4.26
3.08
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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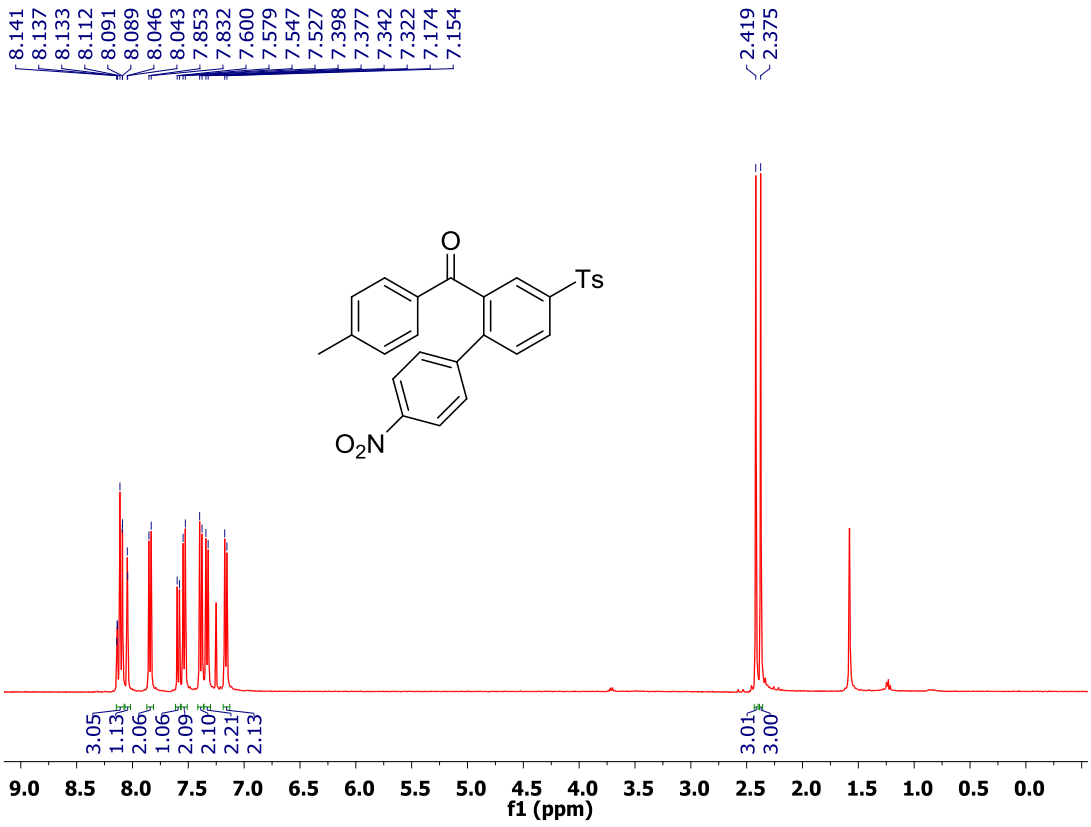
145.093
144.750
144.305
141.184
140.091
138.121
136.978
134.732
133.794
131.154
130.257
130.217
130.104
129.441
128.962
128.893
127.954
127.651
21.847
21.707
O
Ts
Cl
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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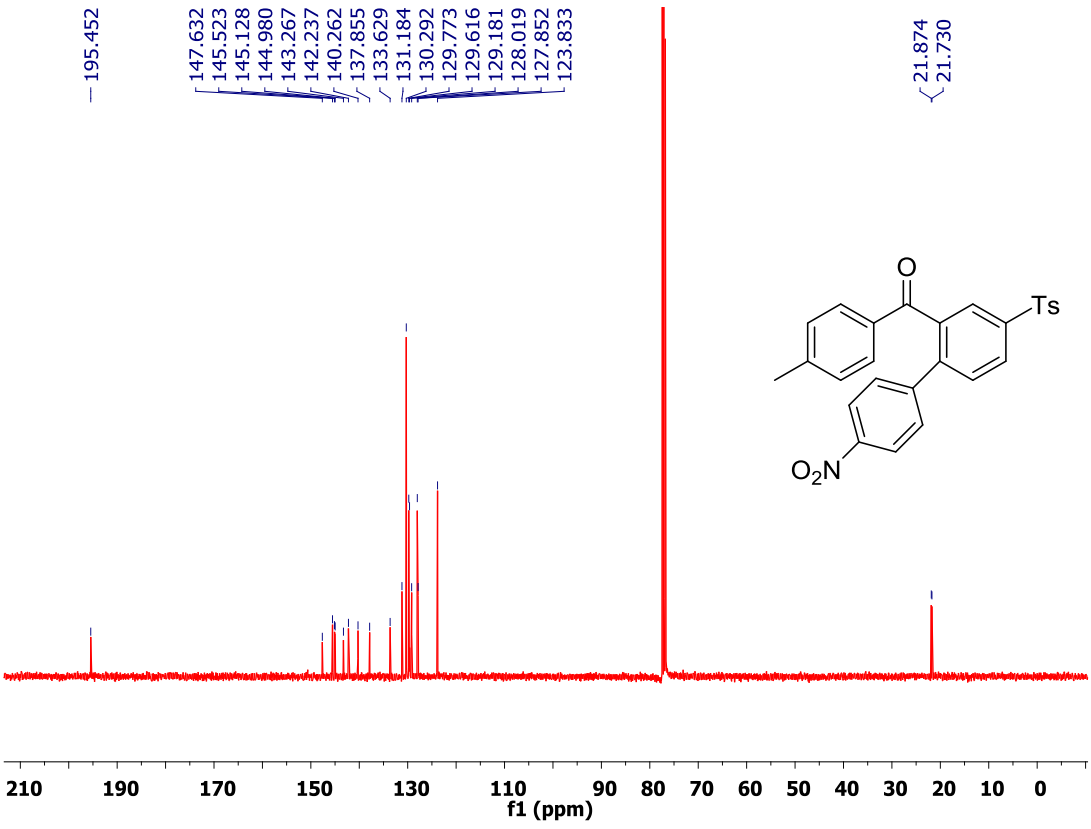
8.137
8.133
8.112
8.091
8.089
8.046
8.043
7.853
7.832
7.600
7.579
7.547
7.527
7.398
7.377
7.342
7.322
7.174
7.154
2.419
2.375
O
Ts
O2N
3.05
1.13
2.06
1.06
2.09
2.10
2.21
2.13
3.01
3.00
f1 (ppm)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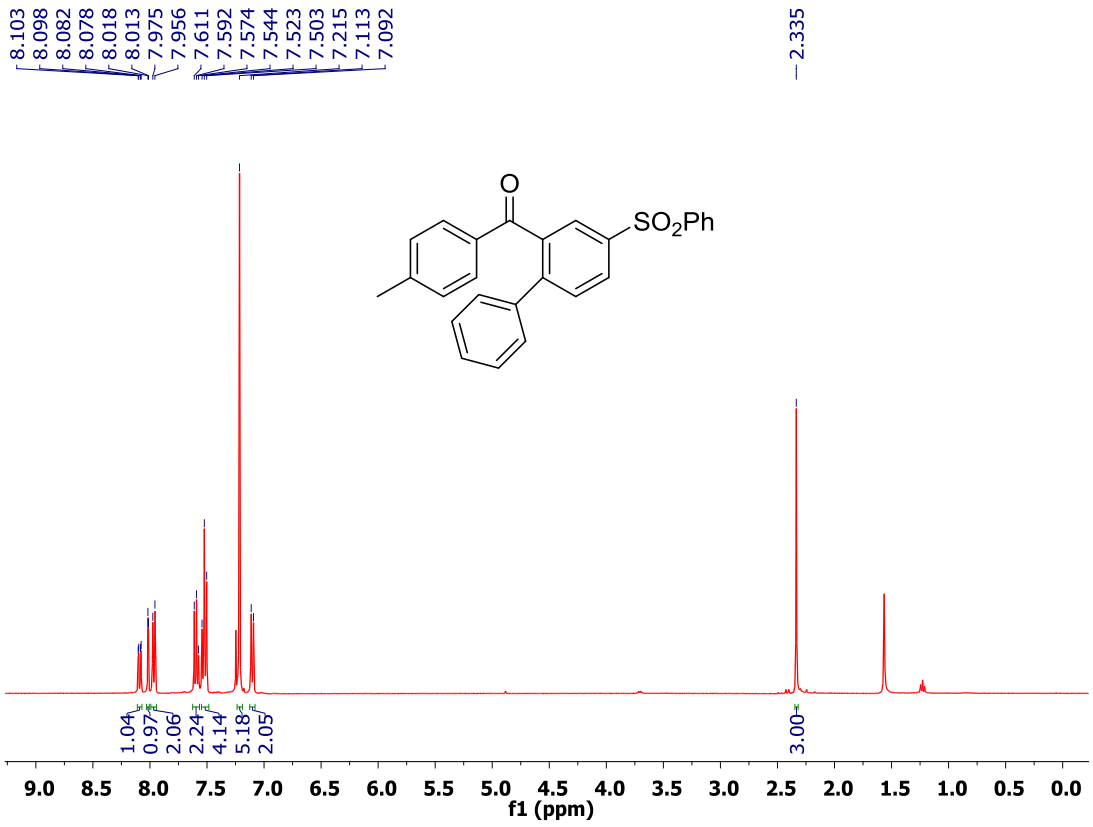
147.632
145.523
145.128
144.980
143.267
142.237
140.262
137.855
133.629
131.184
130.292
129.773
129.616
129.181
128.019
127.852
123.833
21.874
21.730
O
Ts
O2N
f1 (ppm)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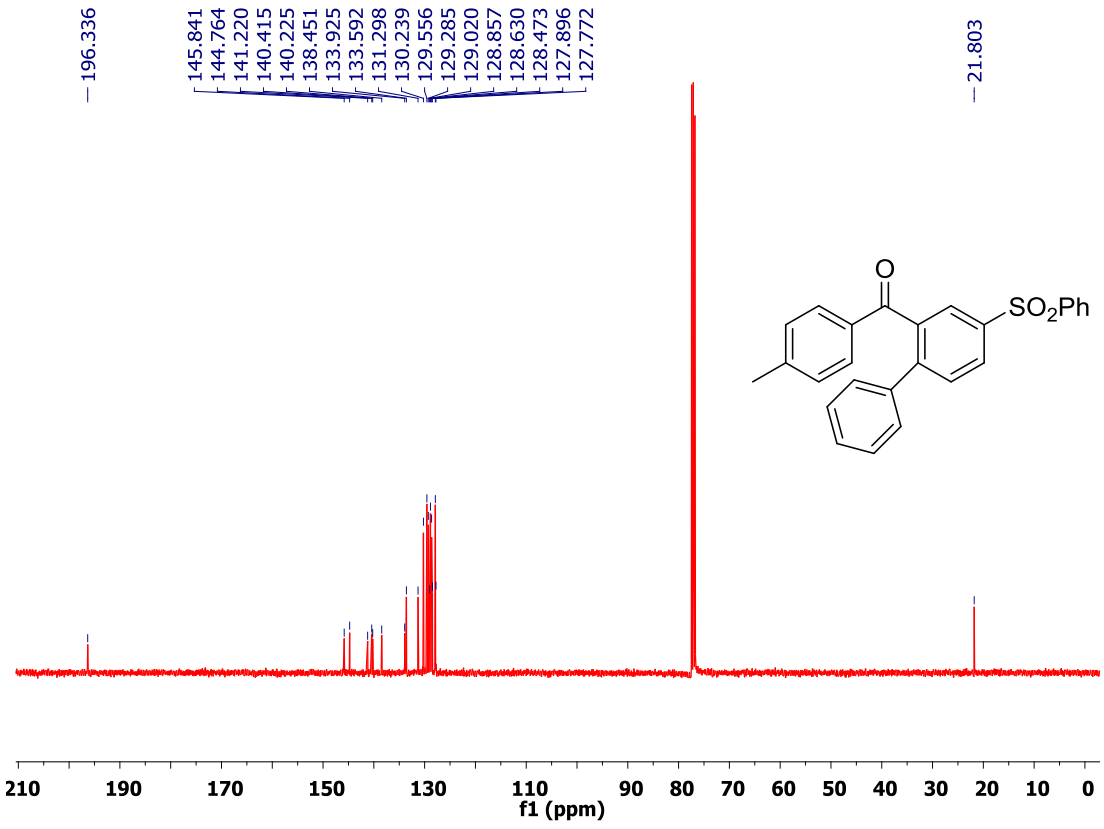
8.082
8.078
8.018
8.013
7.975
7.956
7.611
7.592
7.574
7.544
7.523
7.503
7.215
7.113
7.092
2.335
O
SO2Ph
1.04
0.97
2.06
2.24
4.14
5.18
2.05
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.556
129.285
129.020
128.857
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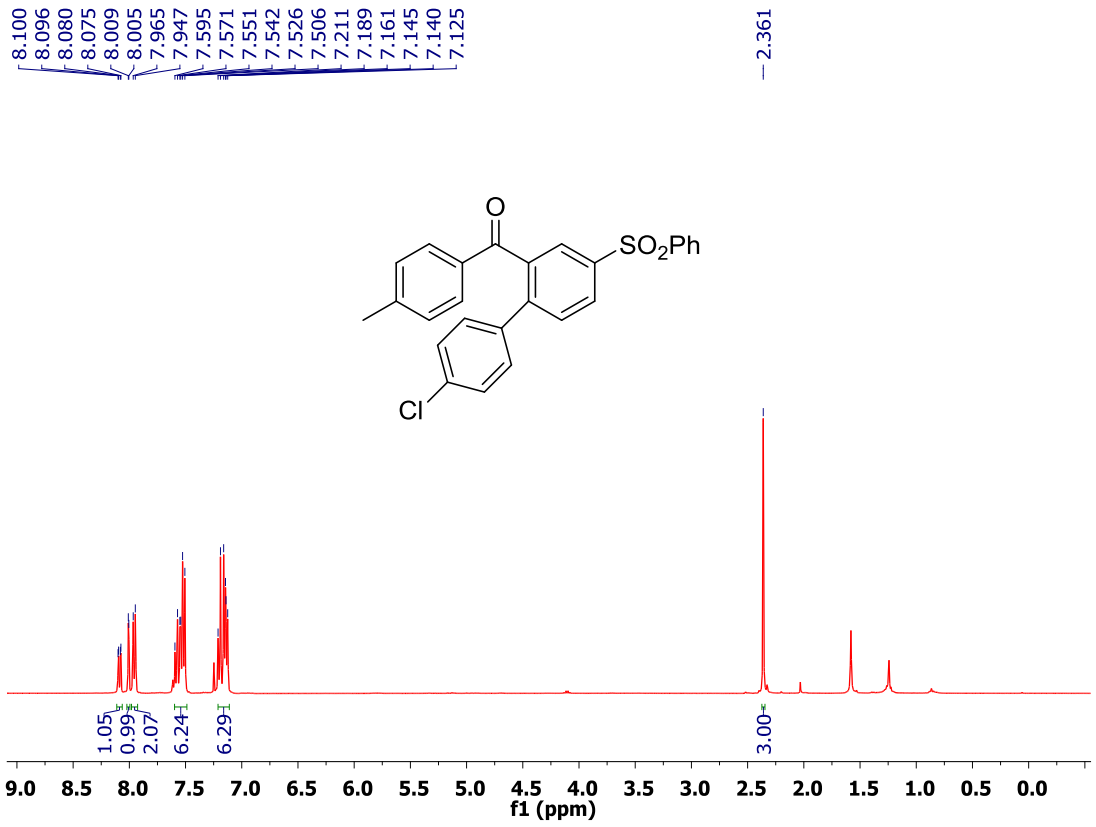
127.896
127.772
21.803
O
SO2Ph
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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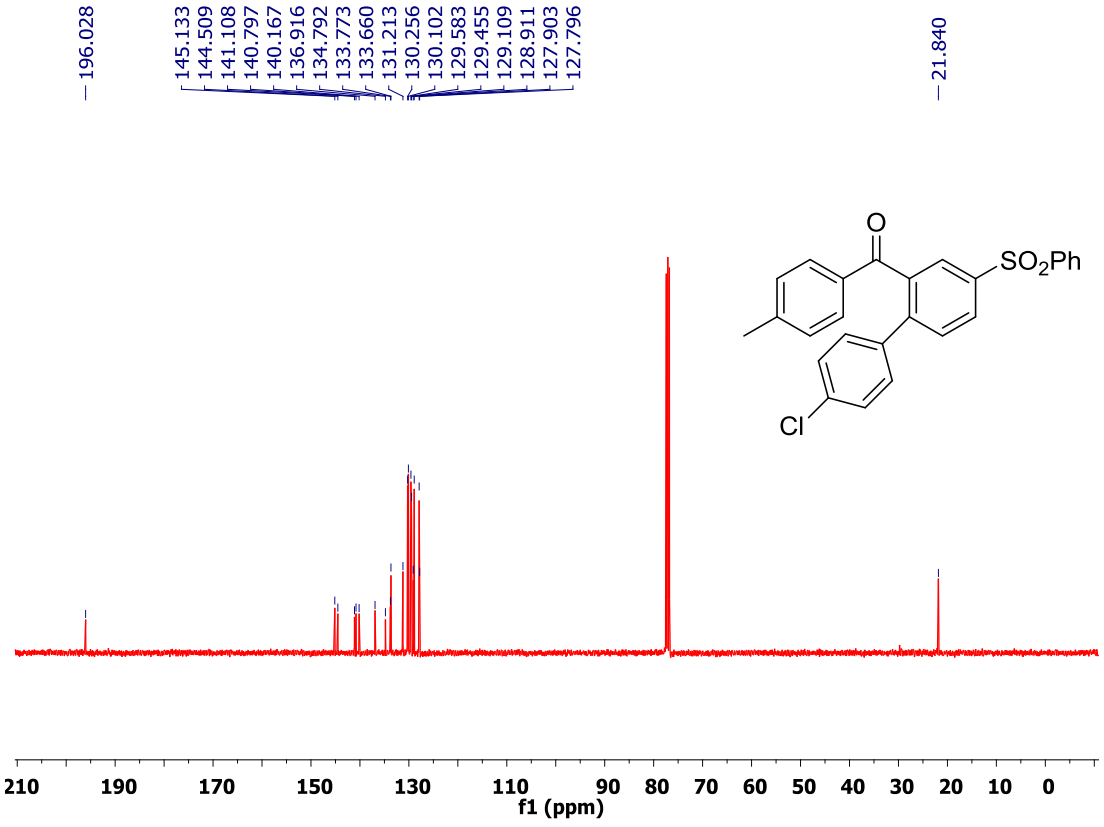
8.080
8.075
8.009
8.005
7.965
7.947
7.595
7.571
7.551
7.542
7.526
7.506
7.211
7.189
7.161
7.145
7.140
7.125
2.361
O
SO2Ph
Cl
1.05
0.99
2.07
6.24
6.29
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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140.797
140.167
136.916
134.792
133.773
133.660
131.213
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129.583
129.455
129.109
128.911
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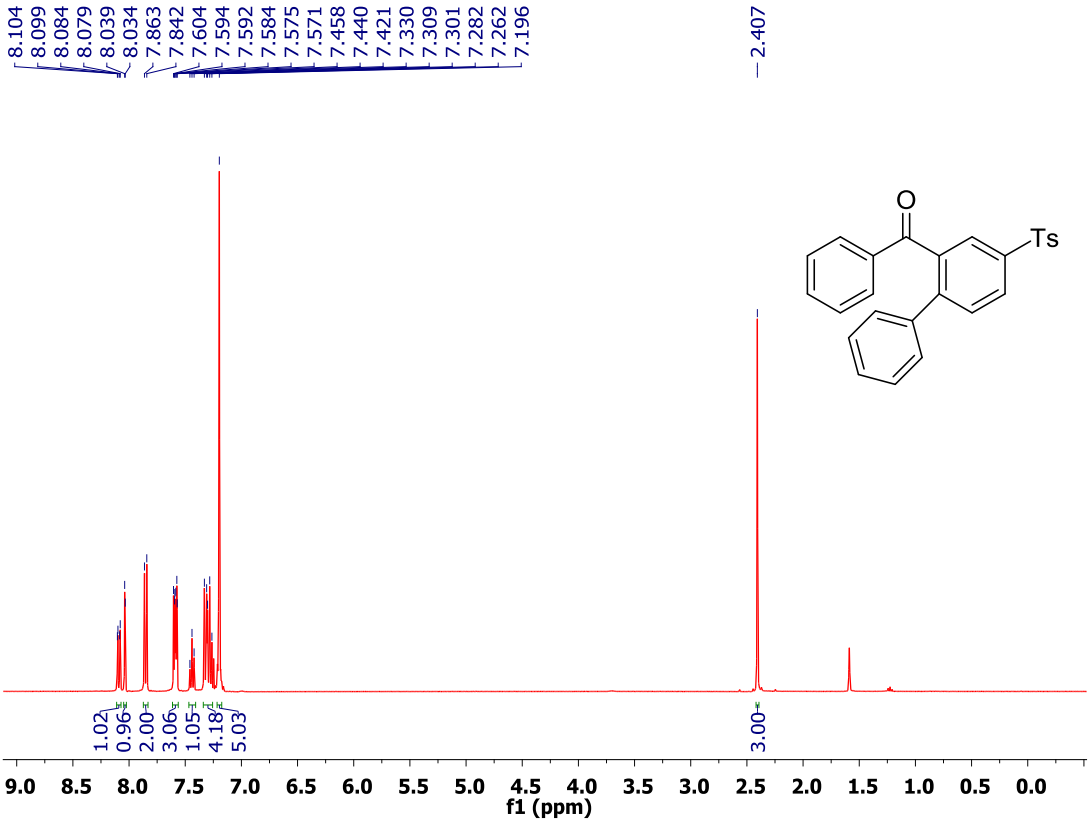
127.796
21.840
O
SO2Ph
Cl
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.034
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7.842
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7.594
7.592
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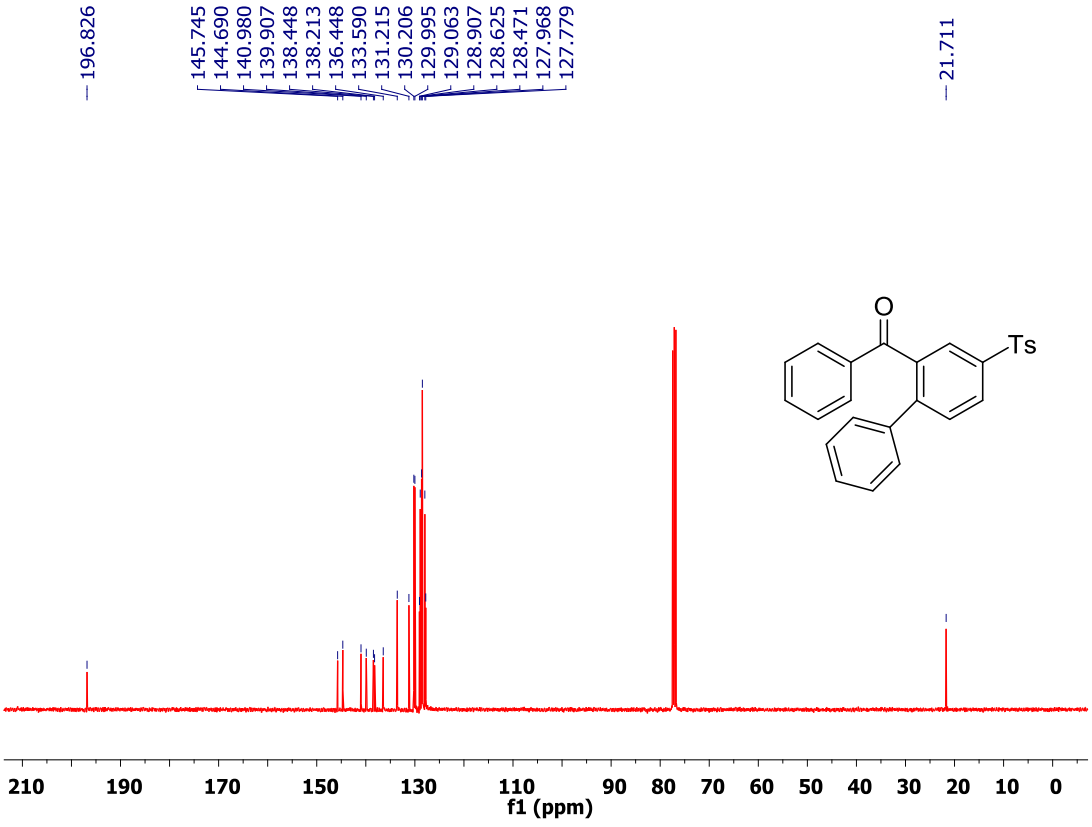
7.575
7.571
7.458
7.440
7.421
7.330
7.309
7.301
7.282
7.262
7.196
2.407
O
Ts
1.02
0.96
2.00
3.06
1.05
4.18
5.03
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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128.907
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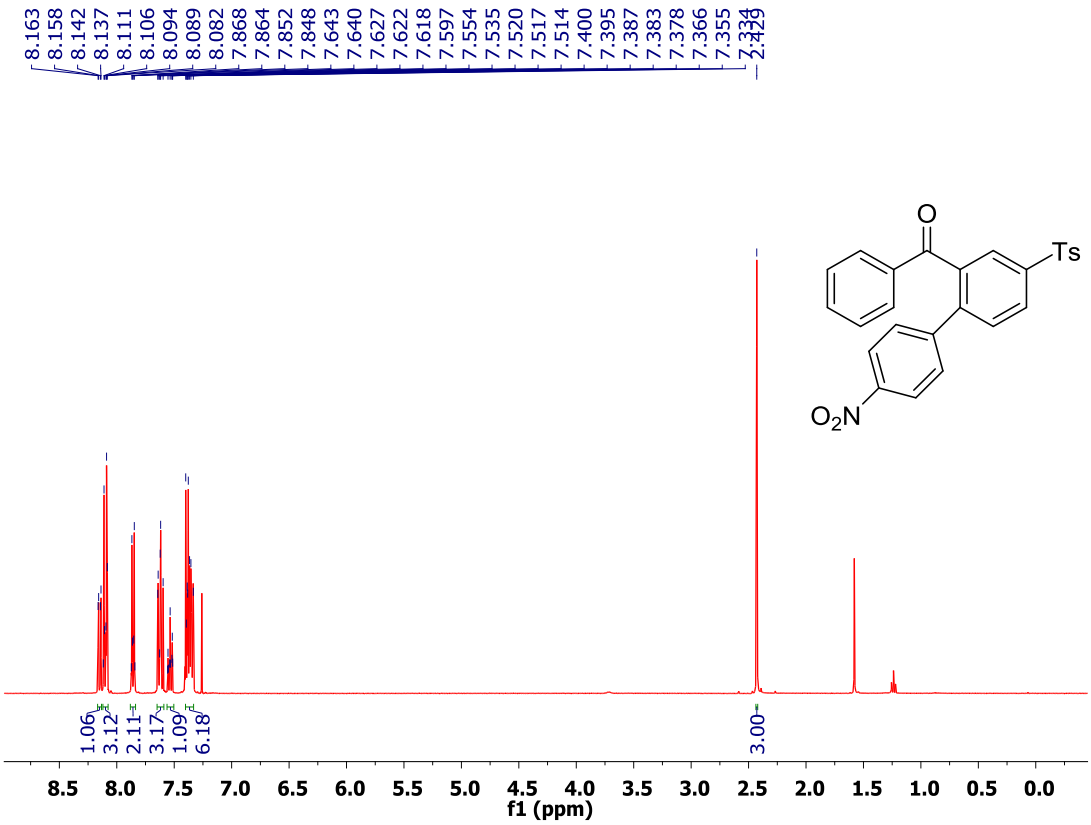
127.968
127.779
21.711
O
Ts
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.089
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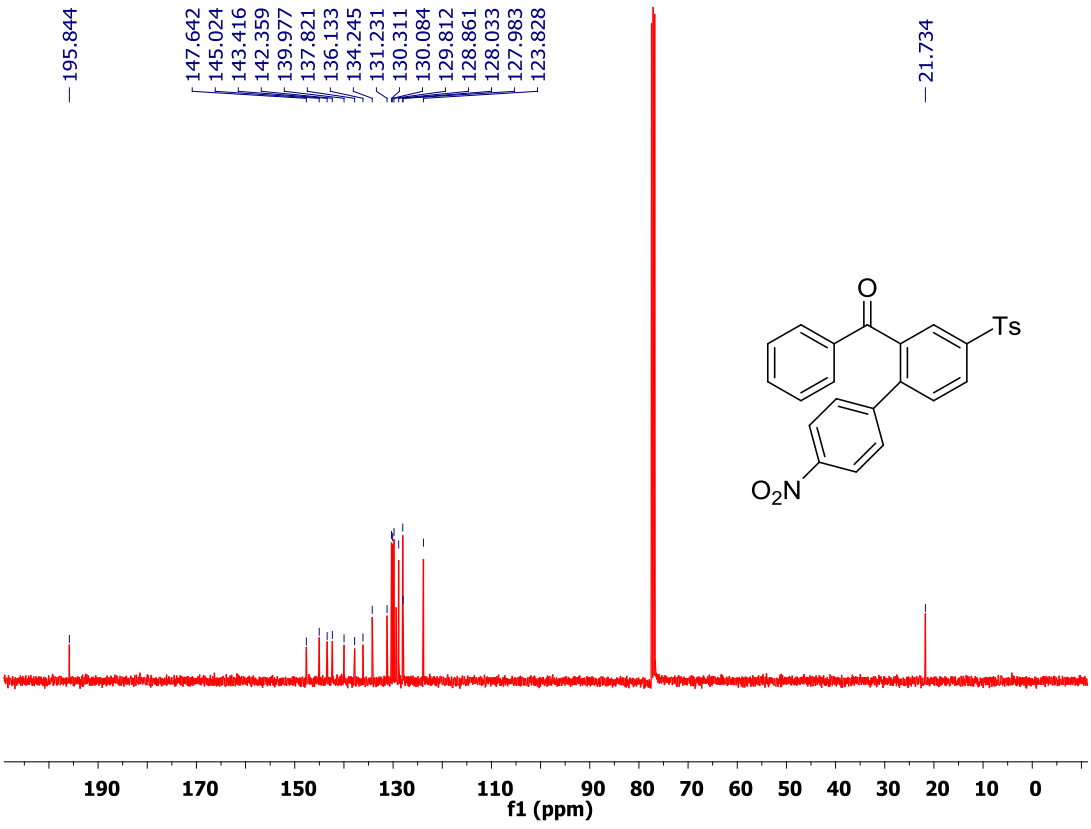
7.643
7.640
7.627
7.622
7.618
7.597
7.554
7.535
7.520
7.517
7.514
7.400
7.395
7.387
7.383
7.378
7.366
7.355
2.429
O
Ts
O2N
1.06
3.12
2.11
3.17
1.09
6.18
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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147.642
145.024
143.416
142.359
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136.133
134.245
131.231
130.311
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129.812
128.861
128.033
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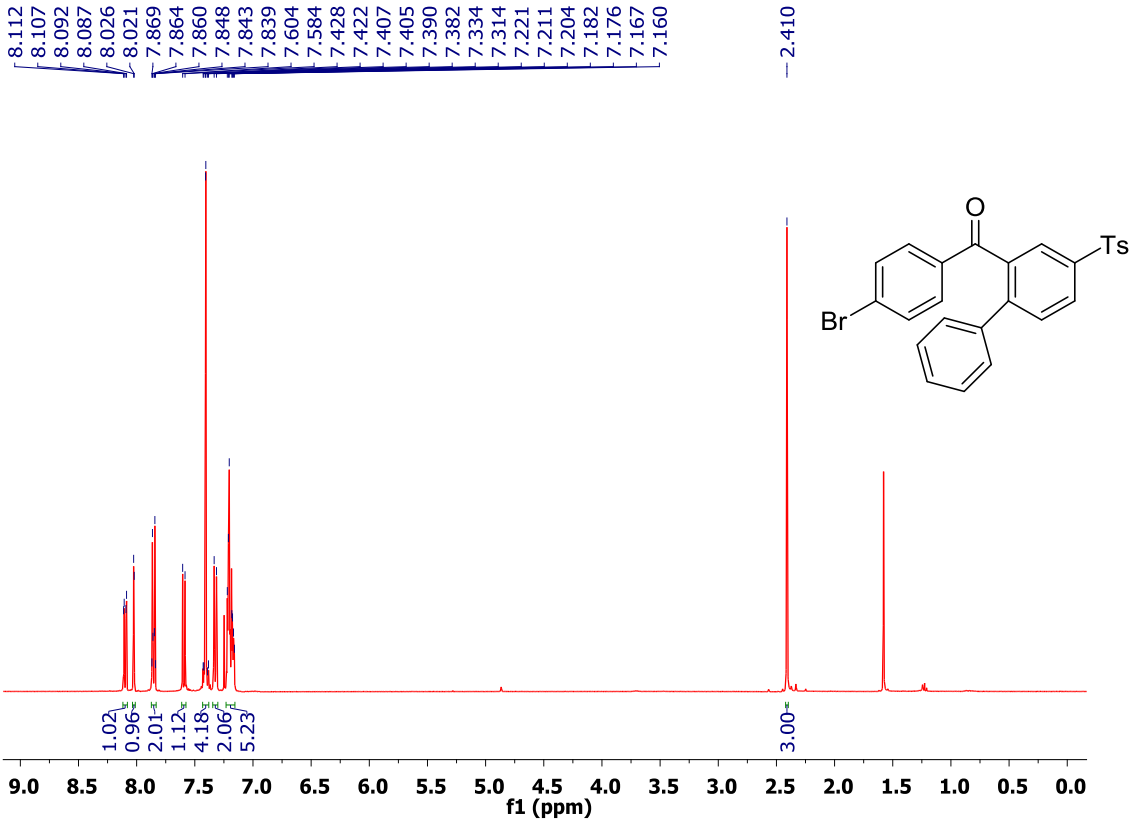
123.828
21.734
O
Ts
O2N
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.604
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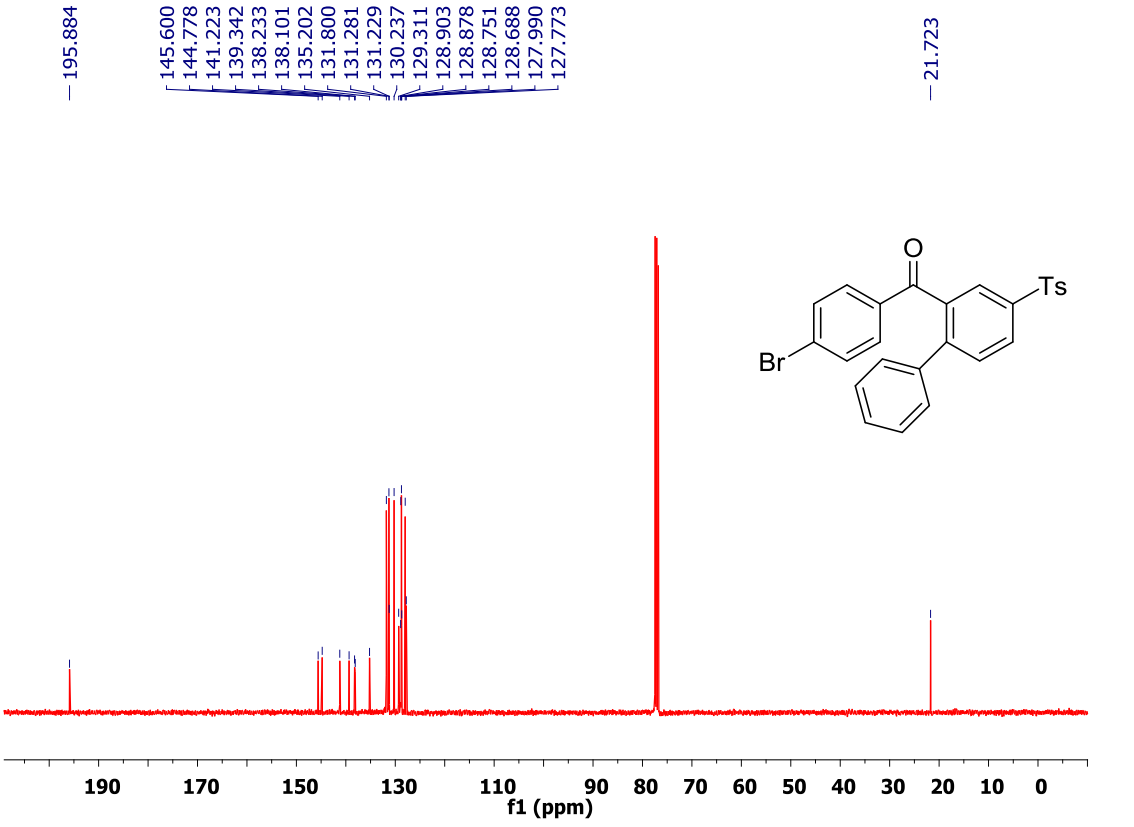
7.428
7.422
7.407
7.405
7.390
7.382
7.334
7.314
7.221
7.211
7.204
7.182
7.176
7.167
7.160
2.410
O
Ts
Br
1.02
0.96
2.01
1.12
4.18
2.06
5.23
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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131.229
130.237
129.311
128.903
128.878
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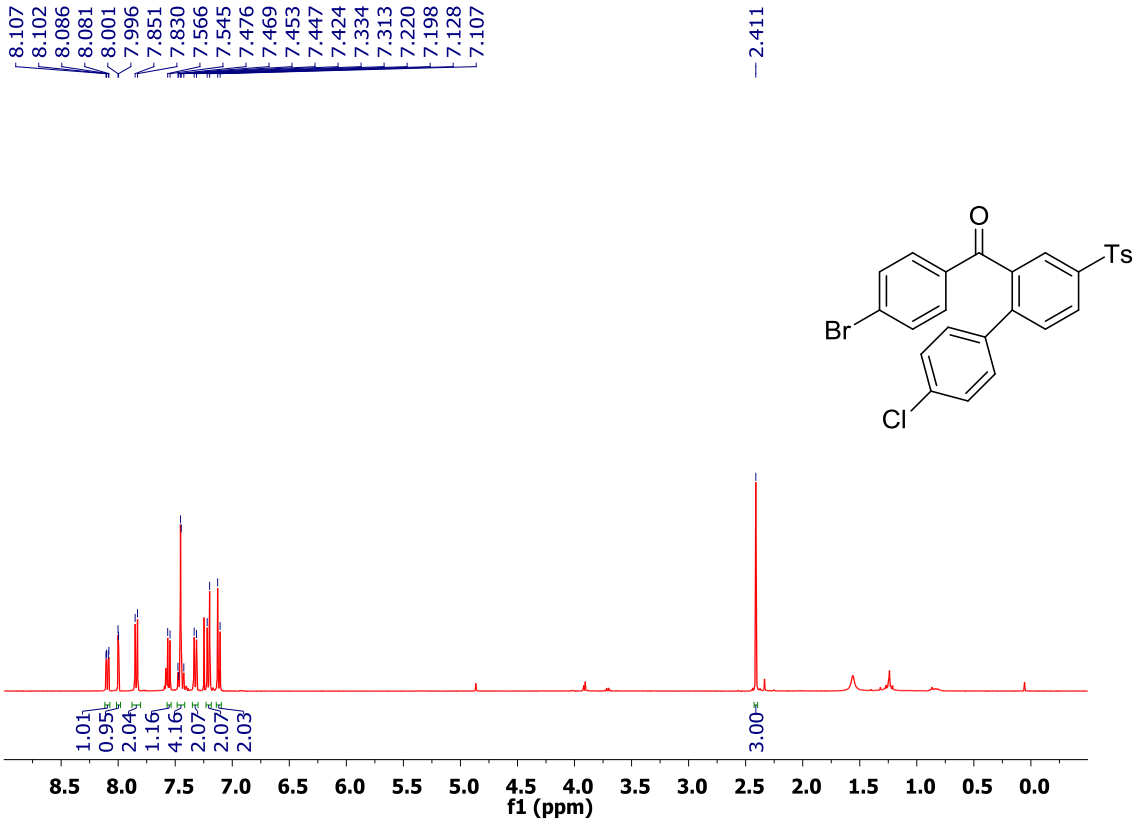
127.990
127.773
21.723
O
Ts
Br
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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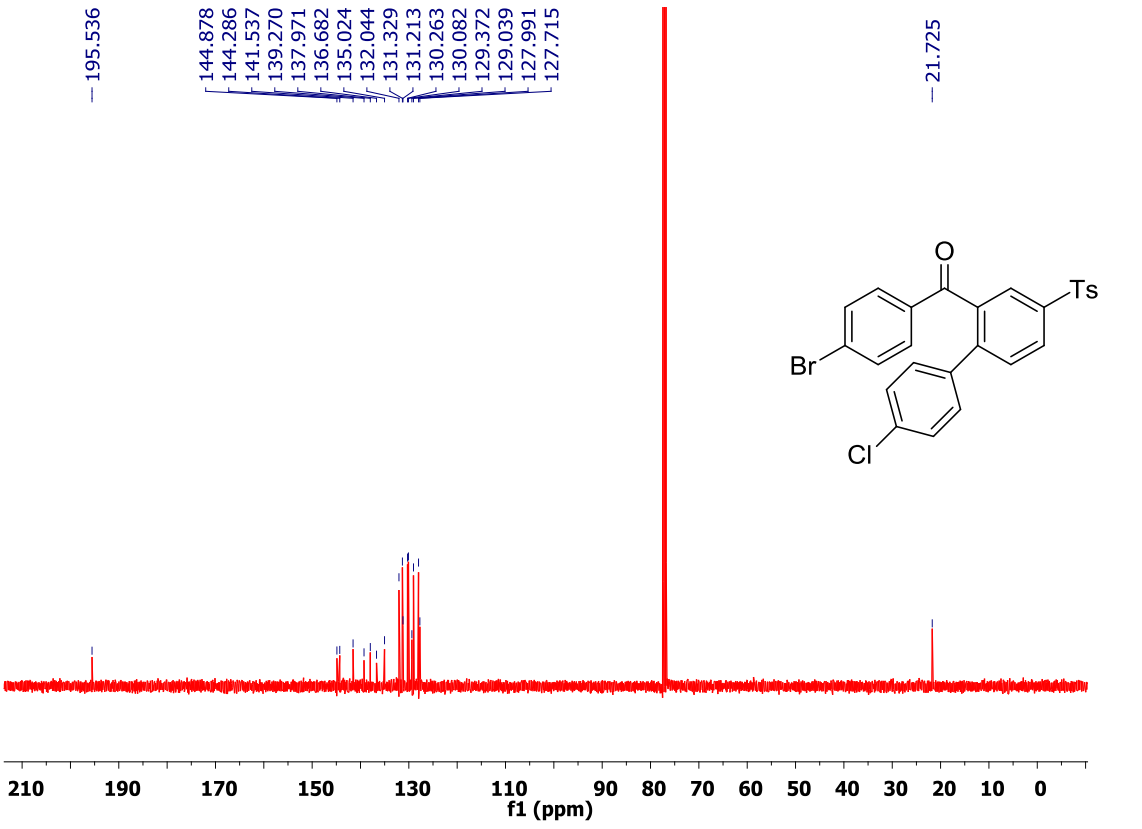
8.102
8.086
8.081
8.001
7.996
7.851
7.830
7.566
7.545
7.476
7.469
7.453
7.447
7.424
7.334
7.313
7.220
7.198
7.128
7.107
2.411
O
Ts
Br
Cl
1.01
0.95
2.04
1.16
4.16
2.07
2.07
2.03
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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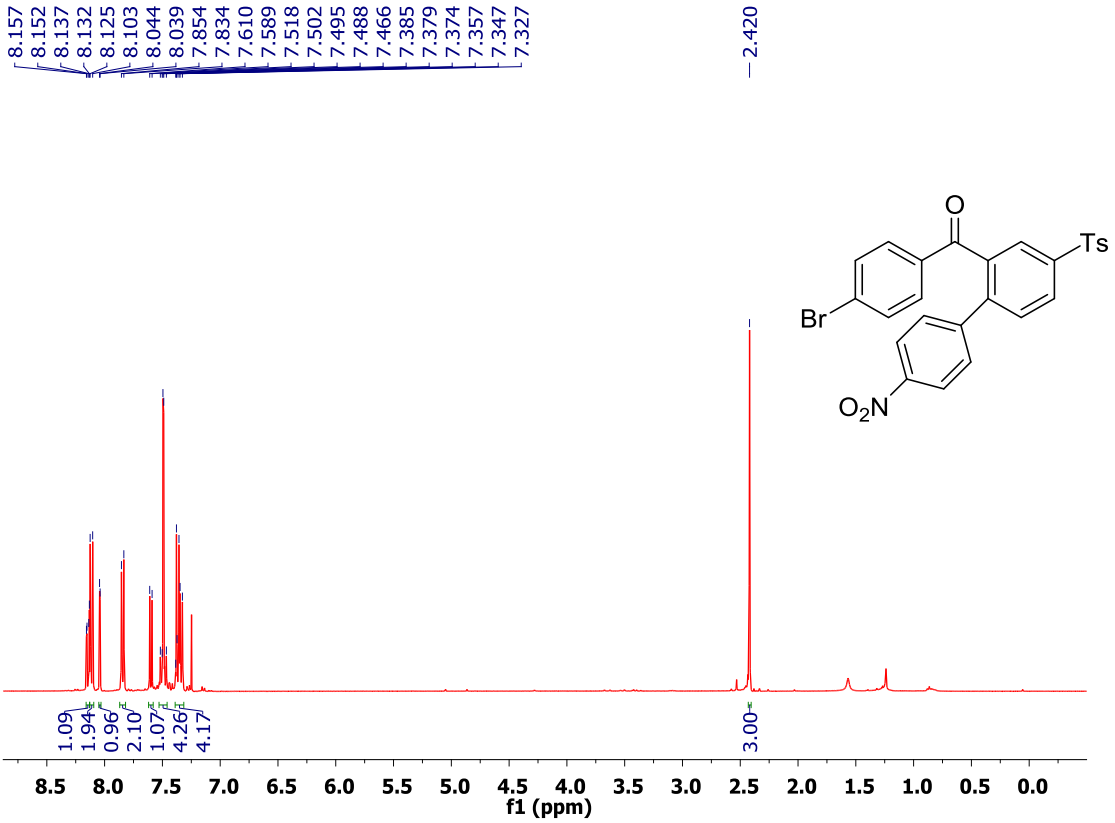
141.537
139.270
137.971
136.682
135.024
132.044
131.329
131.213
130.263
130.082
129.372
129.039
127.991
127.715
21.725
O
Ts
Br
Cl
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.152
8.137
8.132
8.125
8.103
8.044
8.039
7.854
7.834
7.610
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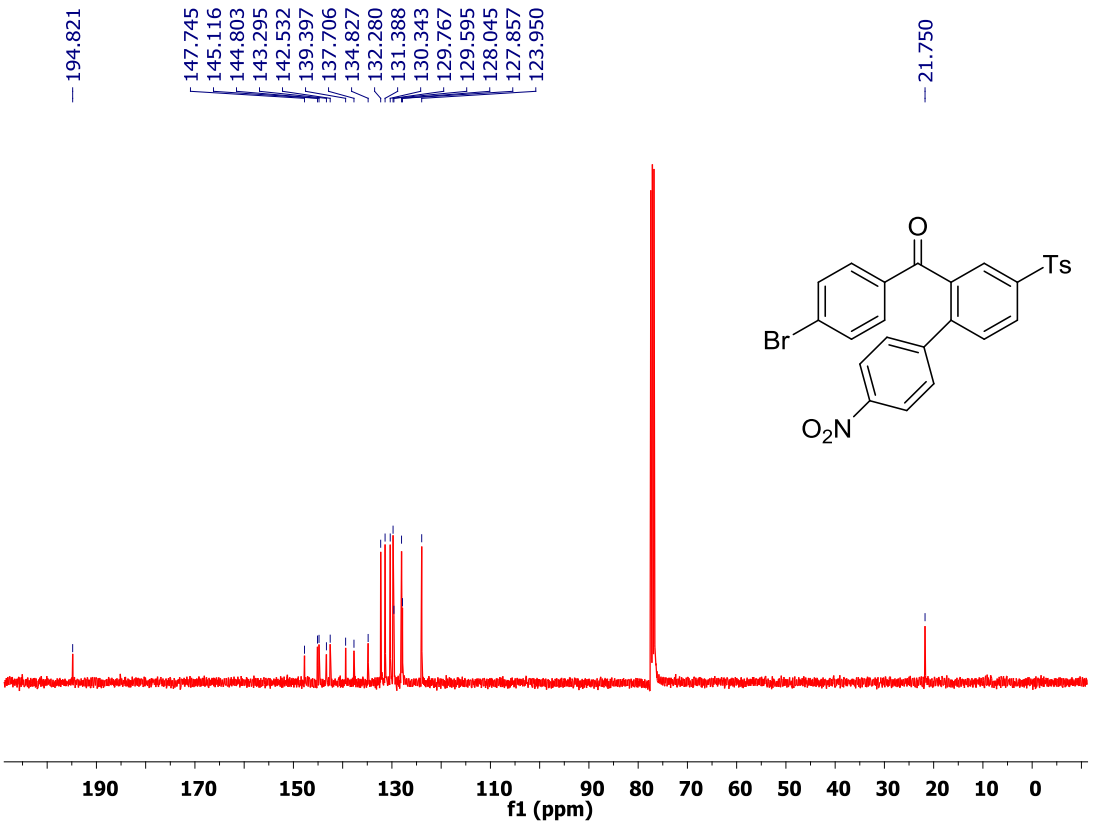
7.518
7.502
7.495
7.488
7.466
7.385
7.379
7.374
7.357
7.347
7.327
2.420
O
Ts
Br
O2N
1.09
1.94
0.96
2.10
1.07
4.26
4.17
3.00
f1 (ppm)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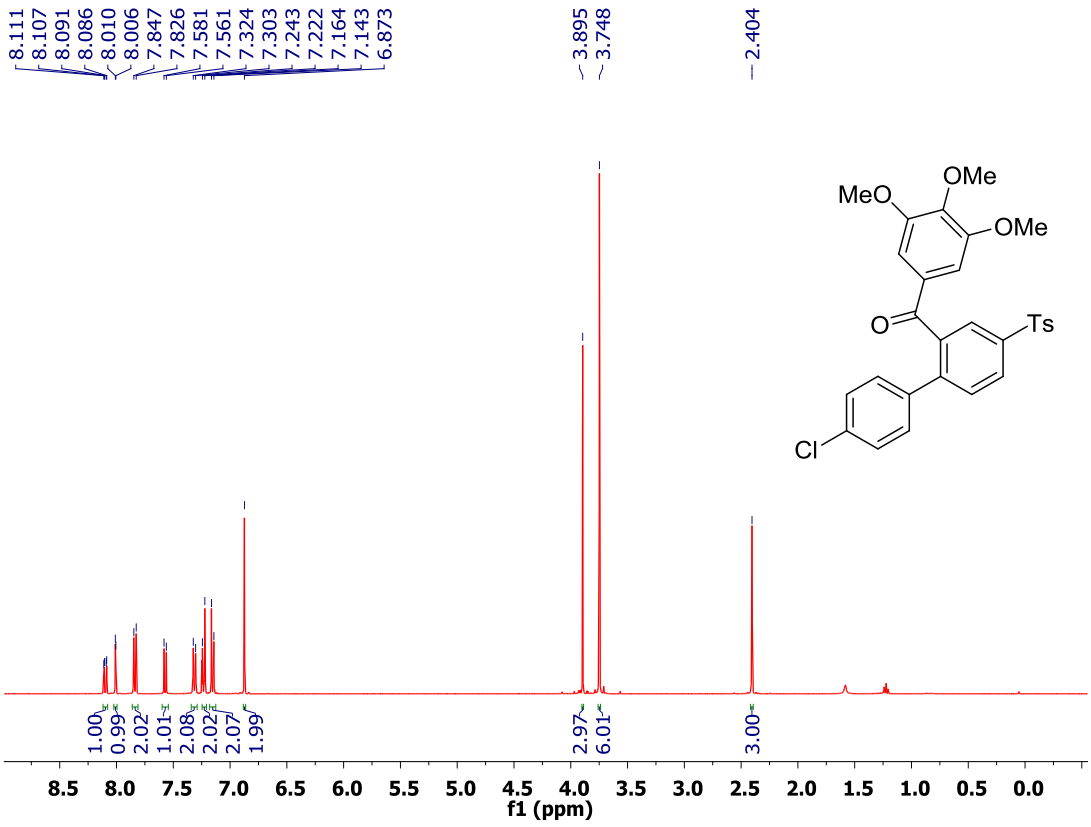
147.745
145.116
144.803
143.295
142.532
139.397
137.706
134.827
132.280
131.388
130.343
129.767
129.595
128.045
127.857
123.950
21.750
O
Ts
Br
O2N
f1 (ppm)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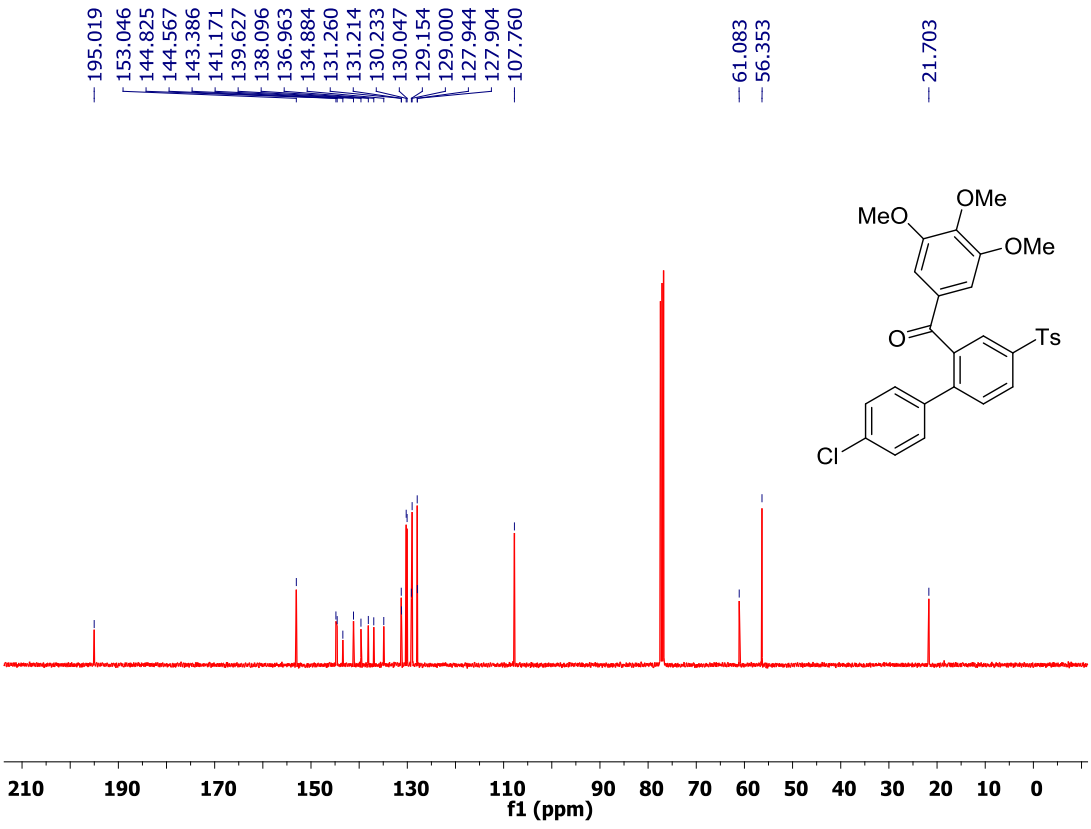
8.107
8.091
8.086
8.010
8.006
7.847
7.826
7.581
7.561
7.324
7.303
7.243
7.222
7.164
7.143
6.873
3.895
3.748
2.404
MeO
OMe
OMe
O
Ts
Cl
1.00
0.99
2.02
1.01
2.08
2.02
2.07
1.99
2.97
6.01
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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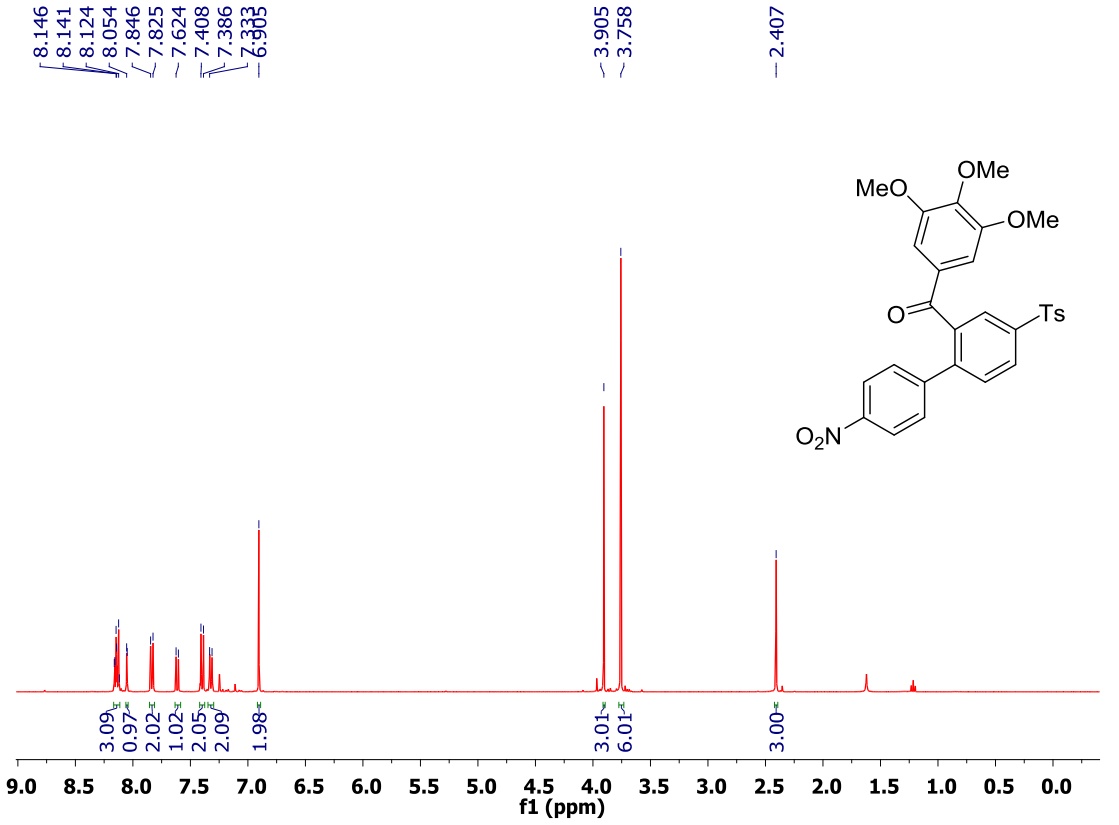
153.046
144.825
144.567
143.386
141.171
139.627
138.096
136.963
134.884
131.260
131.214
130.233
130.047
129.154
129.000
127.944
127.904
107.760
61.083
56.353
21.703
MeO
OMe
OMe
O
Ts
Cl
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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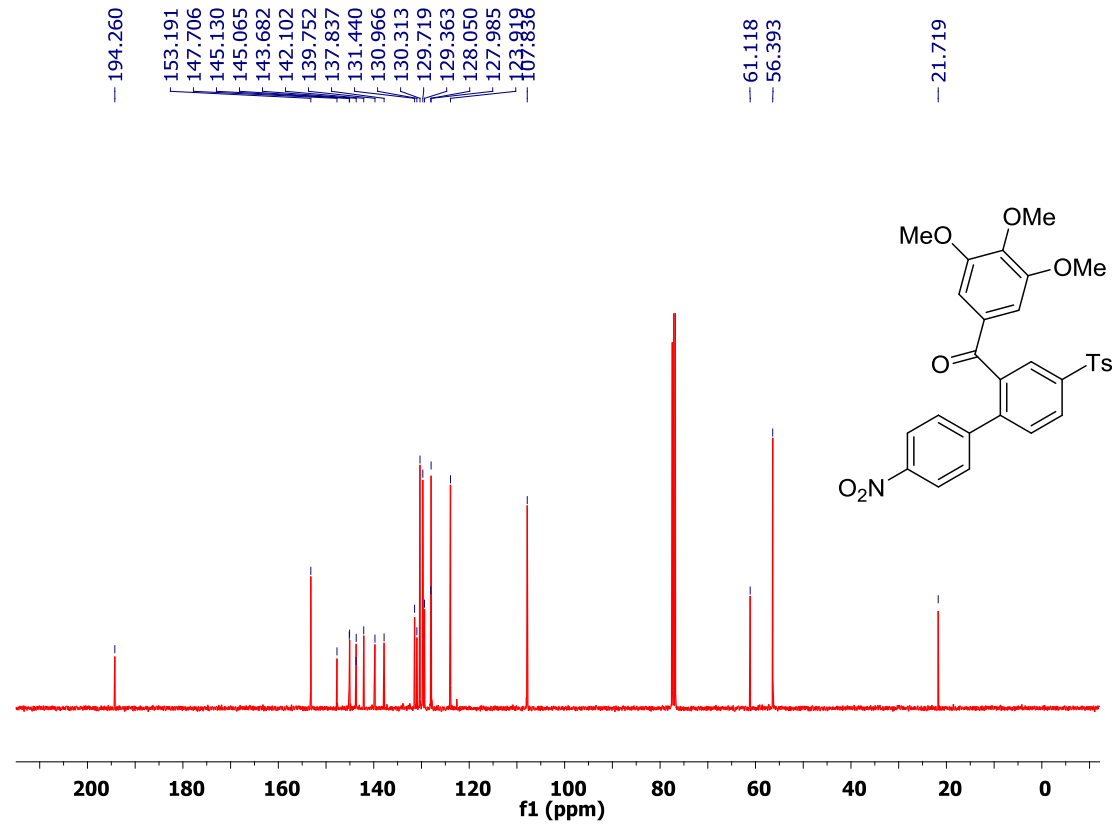
8.141
8.124
8.054
7.846
7.825
7.624
7.408
7.386
7.333
6.905
3.905
3.758
2.407
MeO
OMe
OMe
O
Ts
O2N
3.09
0.97
2.02
1.02
2.05
2.09
1.98
3.01
6.01
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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153.191
147.706
145.130
145.065
143.682
142.102
139.752
137.837
131.440
130.966
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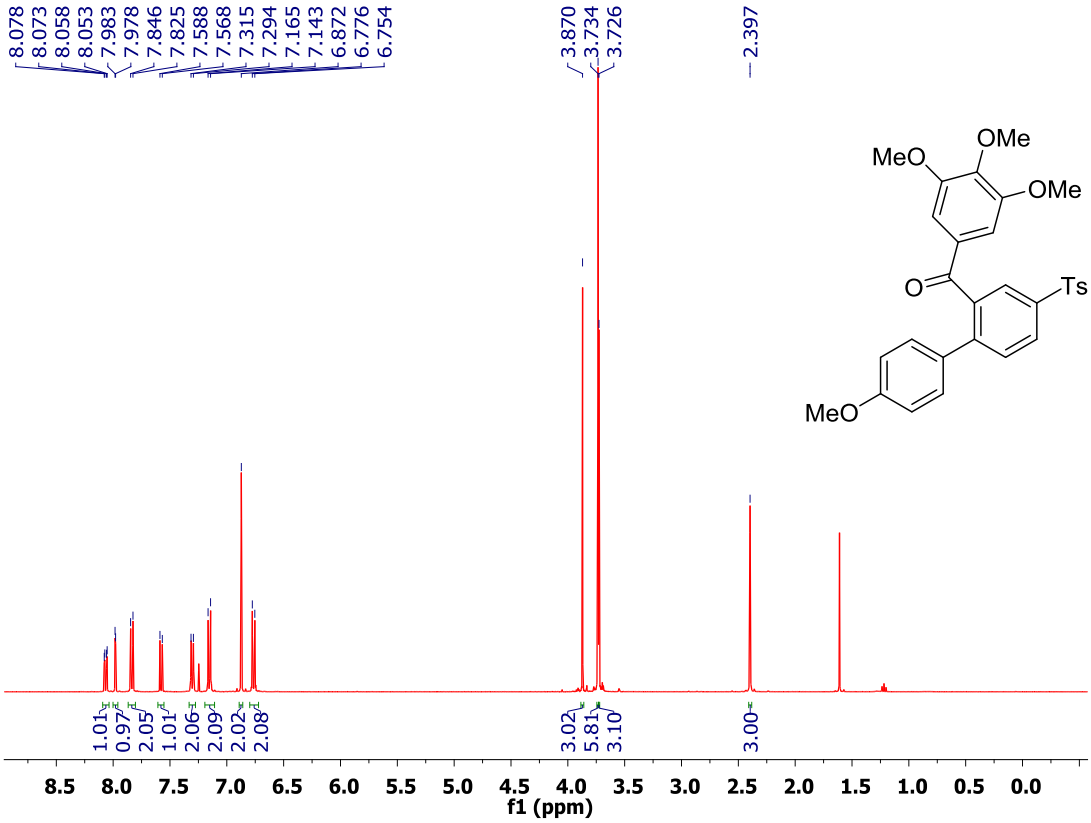
129.719
129.363
128.050
127.985
61.118
56.393
21.719
MeO
OMe
OMe
O
Ts
O2N
200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)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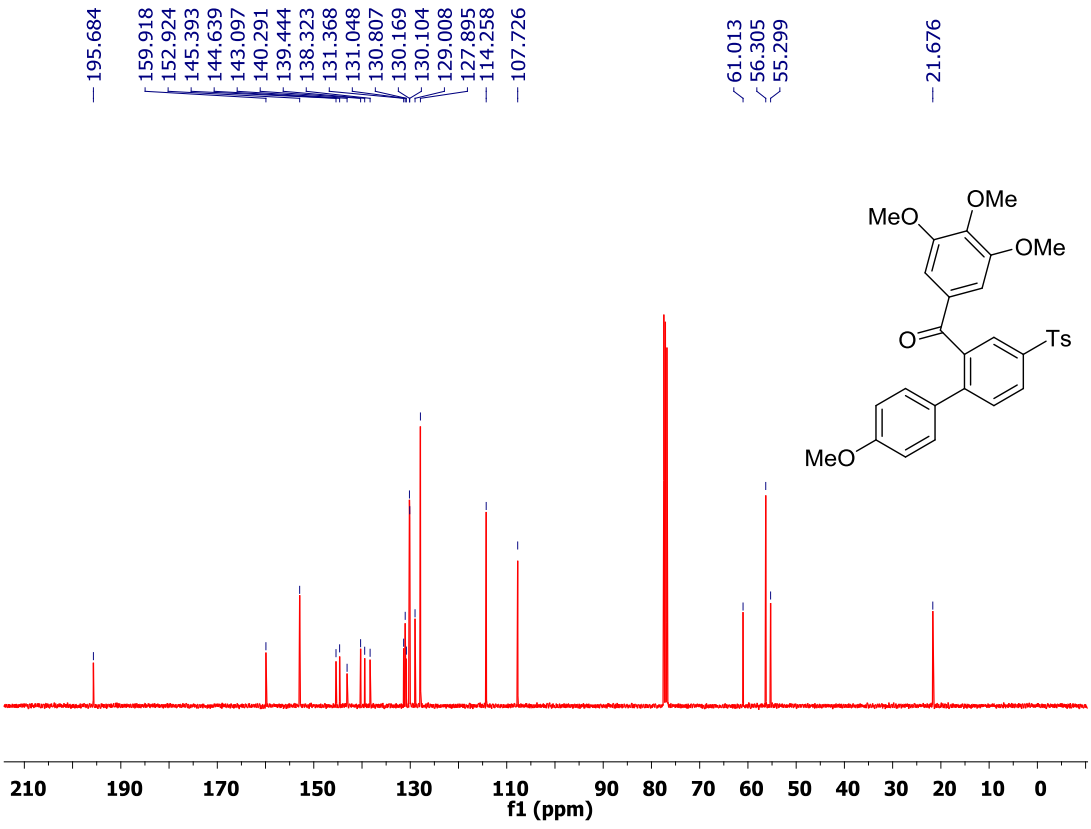
8.073
8.058
8.053
7.983
7.978
7.846
7.825
7.588
7.568
7.315
7.294
7.165
7.143
6.872
6.776
6.754
3.870
3.734
3.726
2.397
MeO
OMe
OMe
O
Ts
MeO
1.01
0.97
2.05
1.01
2.06
2.09
2.02
2.08
3.02
5.81
3.10
3.00
f1 (ppm)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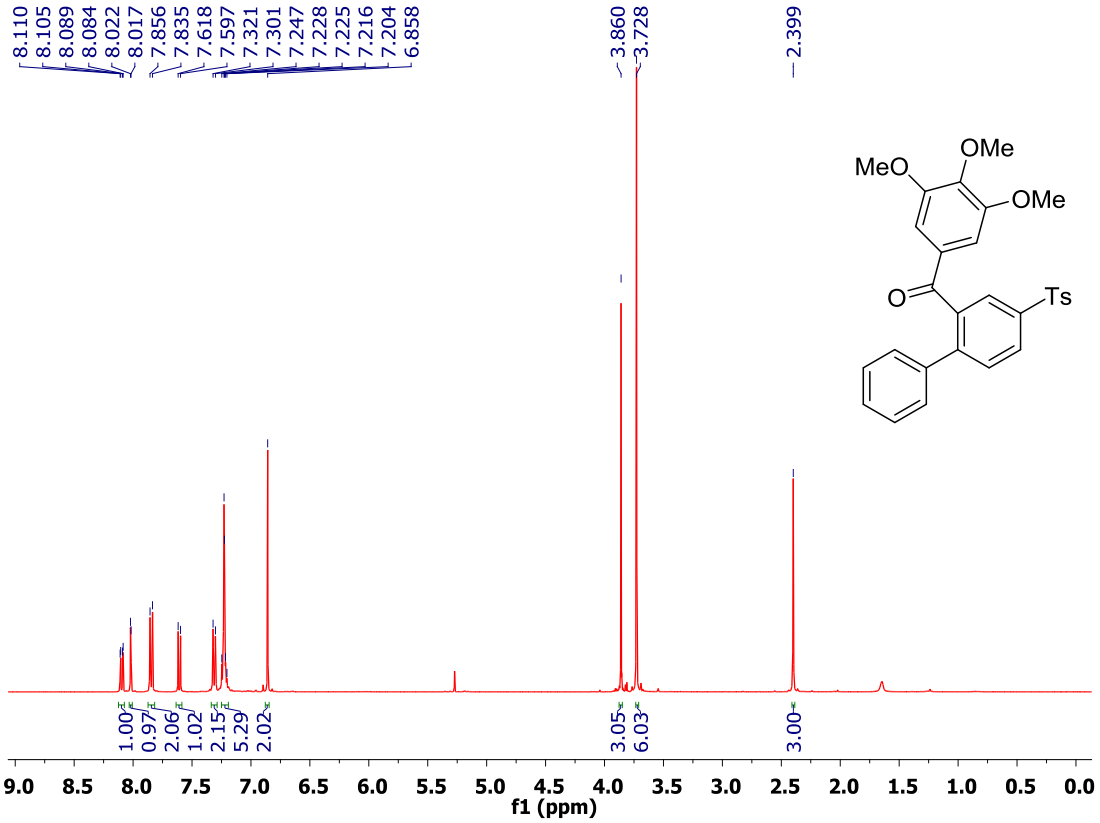
159.918
152.924
145.393
144.639
143.097
140.291
139.444
138.323
131.368
131.048
130.807
130.169
130.104
129.008
127.895
114.258
107.726
61.013
56.305
55.299
21.676
MeO
OMe
OMe
O
Ts
MeO
f1 (ppm)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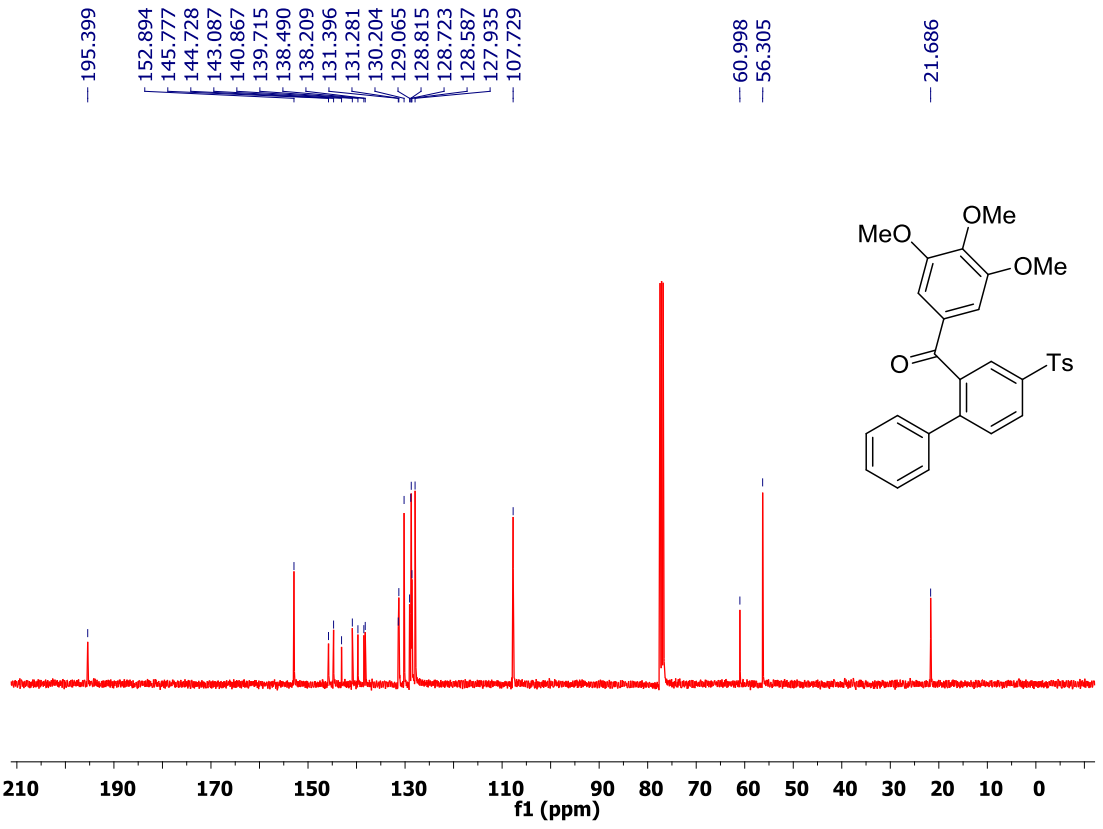
8.105
8.089
8.084
8.022
8.017
7.856
7.835
7.618
7.597
7.321
7.301
7.247
7.228
7.225
7.216
7.204
6.858
3.860
3.728
2.399
MeO
OMe
OMe
O
Ts
1.00
0.97
2.06
1.02
2.15
5.29
2.02
3.05
6.03
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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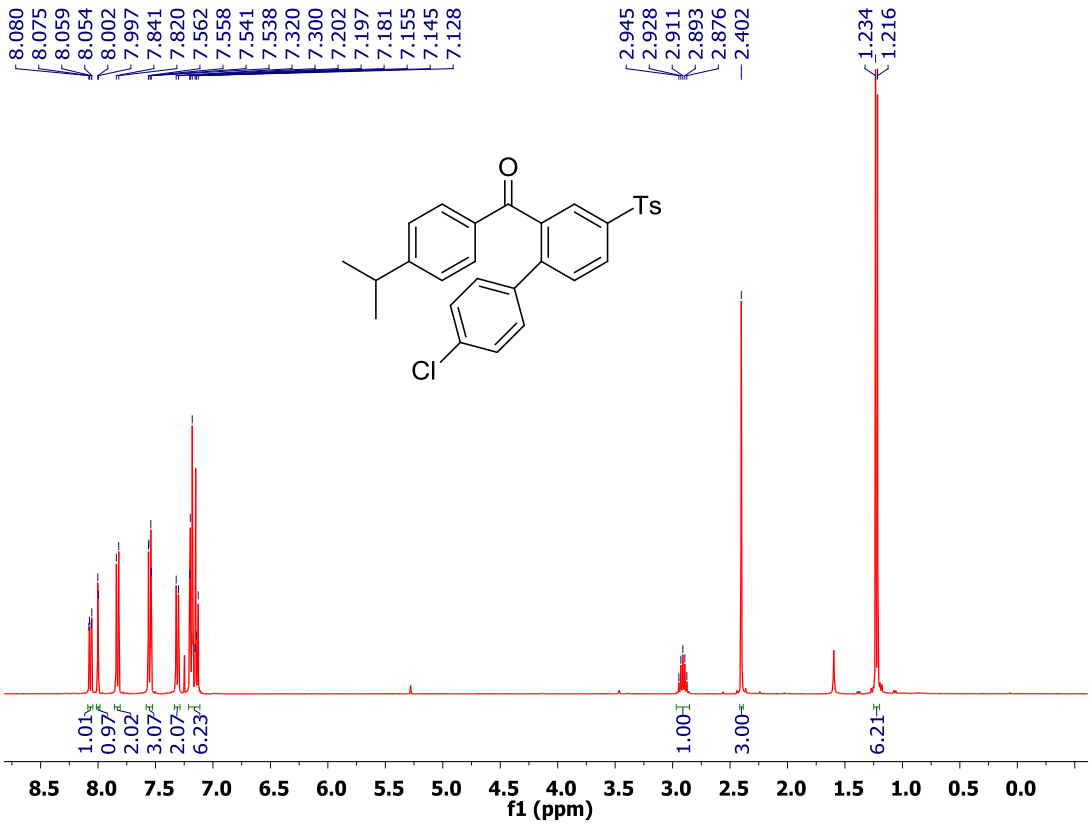
145.777
144.728
143.087
140.867
139.715
138.490
138.209
131.396
131.281
130.204
129.065
128.815
128.723
128.587
127.935
107.729
60.998
56.305
21.686
MeO
OMe
OMe
O
Ts
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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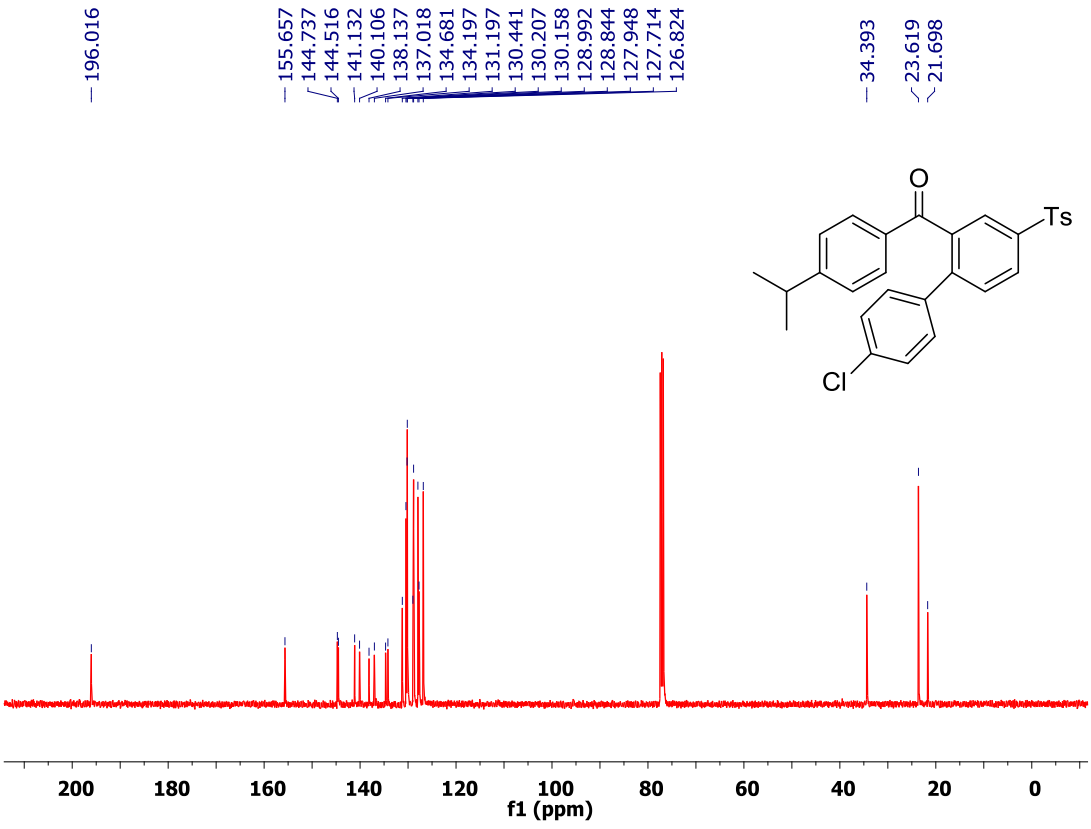
8.075
8.059
8.054
8.002
7.997
7.841
7.820
7.562
7.558
7.541
7.538
7.320
7.300
7.202
7.197
7.181
7.155
7.145
7.128
2.945
2.928
2.911
2.893
2.876
2.402
1.234
1.216
O
Ts
Cl
1.01
0.97
2.02
3.07
2.07
6.23
1.00
3.00
6.21
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.516
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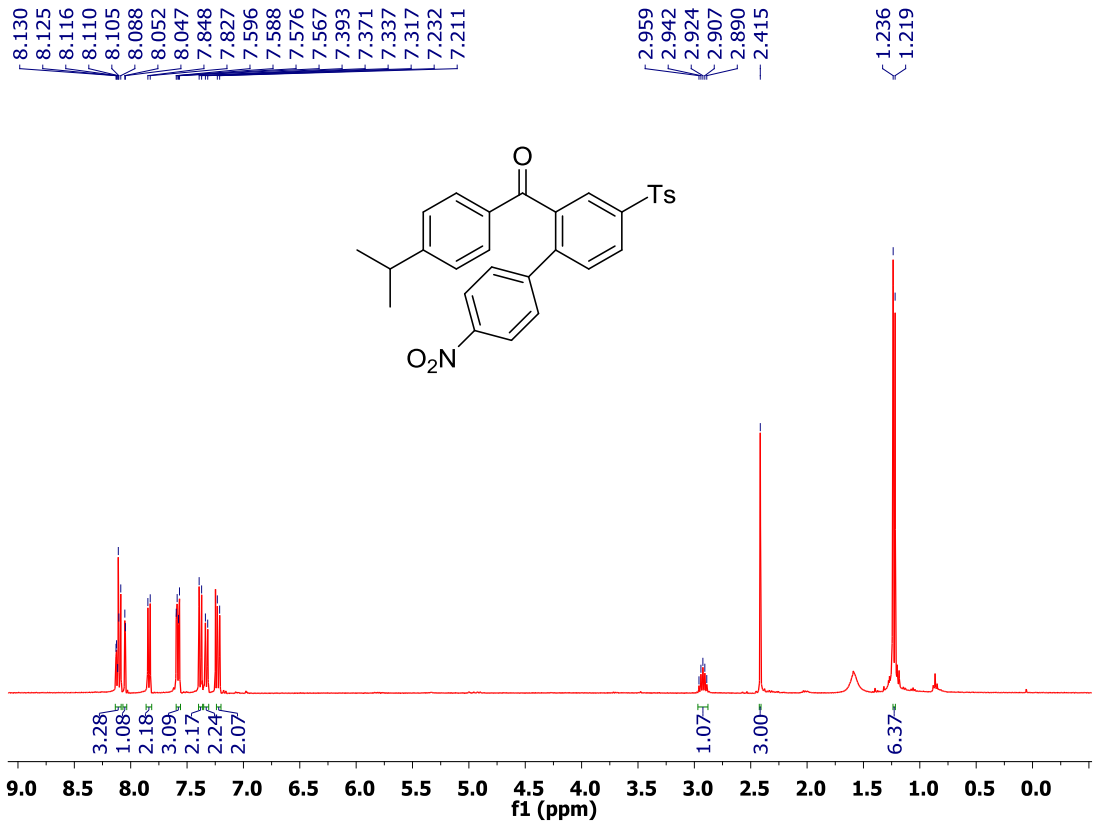
140.106
138.137
137.018
134.681
134.197
131.197
130.441
130.207
130.158
128.992
128.844
127.948
127.714
126.824
34.393
23.619
21.698
O
Ts
Cl
200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)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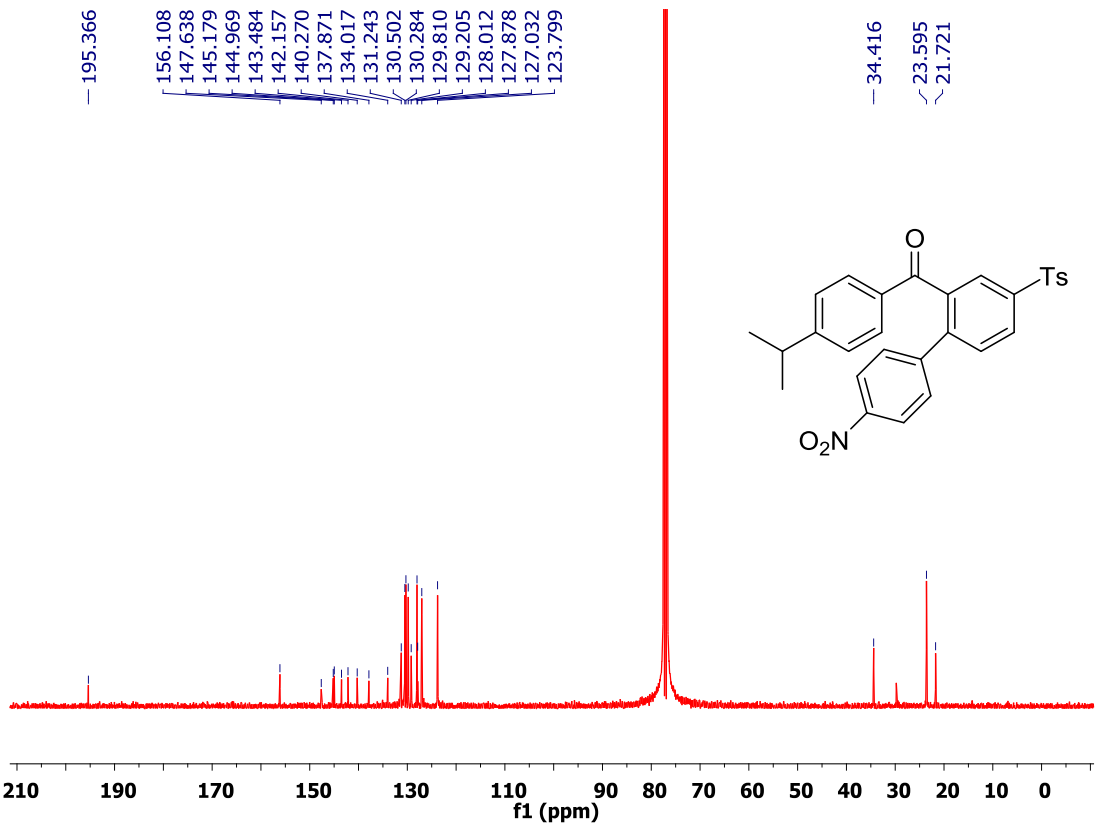
8.110
8.105
8.088
8.052
8.047
7.848
7.827
7.596
7.588
7.576
7.567
7.393
7.371
7.337
7.317
7.232
7.211
2.959
2.942
2.924
2.907
2.890
2.415
1.236
1.219
O
Ts
O2N
3.28
1.08
2.18
3.09
2.17
2.24
2.07
1.07
3.00
6.37
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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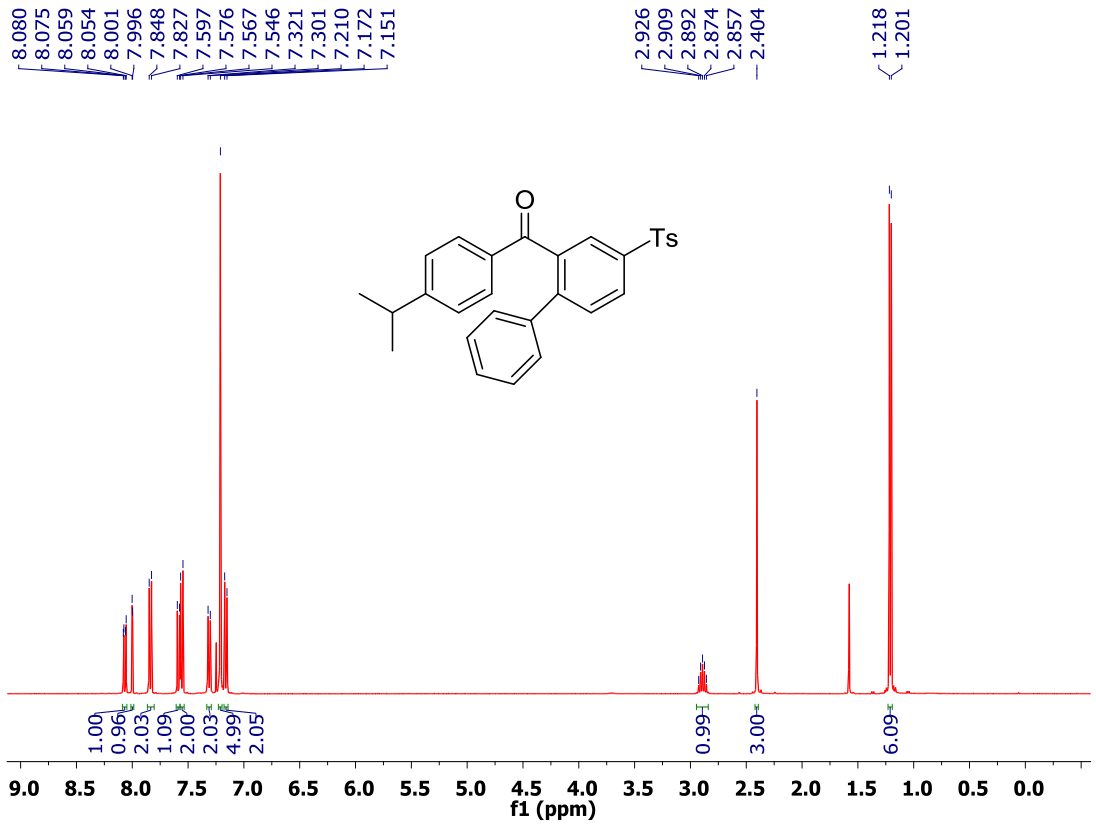
144.969
143.484
142.157
140.270
137.871
134.017
131.243
130.502
130.284
129.810
129.205
128.012
127.878
127.032
123.799
34.416
23.595
21.721
O
Ts
O2N
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.054
8.001
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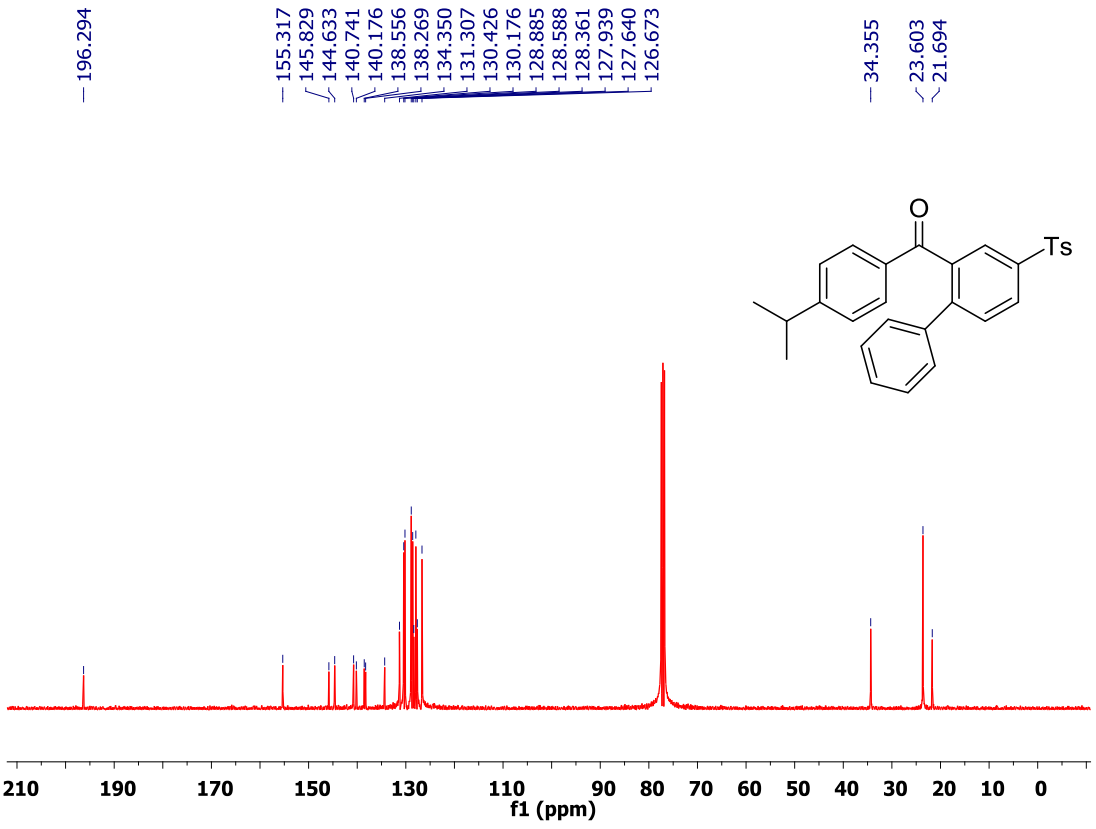
7.848
7.827
7.597
7.576
7.567
7.546
7.321
7.301
7.210
7.172
7.151
2.926
2.909
2.892
2.874
2.857
2.404
1.218
1.201
O
Ts
1.00
0.96
2.03
1.09
2.00
2.03
4.99
2.05
0.99
3.00
6.09
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.633
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140.176
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138.269
134.350
131.307
130.426
130.176
128.885
128.588
128.361
127.939
127.640
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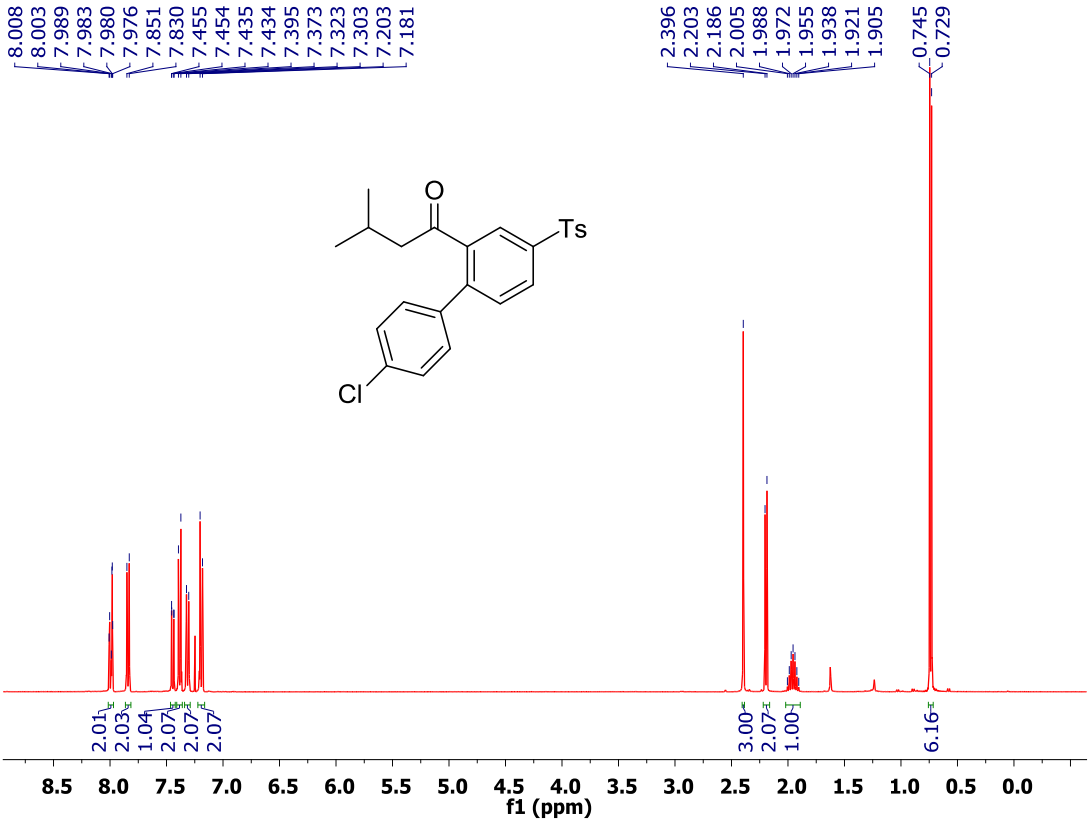
34.355
23.603
21.694
O
Ts
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.980
7.976
7.851
7.830
7.455
7.454
7.435
7.434
7.395
7.373
7.323
7.303
7.203
7.181
2.396
2.203
2.186
2.005
1.988
1.972
1.955
1.938
1.921
1.905
0.745
0.729
O
Ts
Cl
2.01
2.03
1.04
2.07
2.07
2.07
3.00
2.07
1.00
6.16
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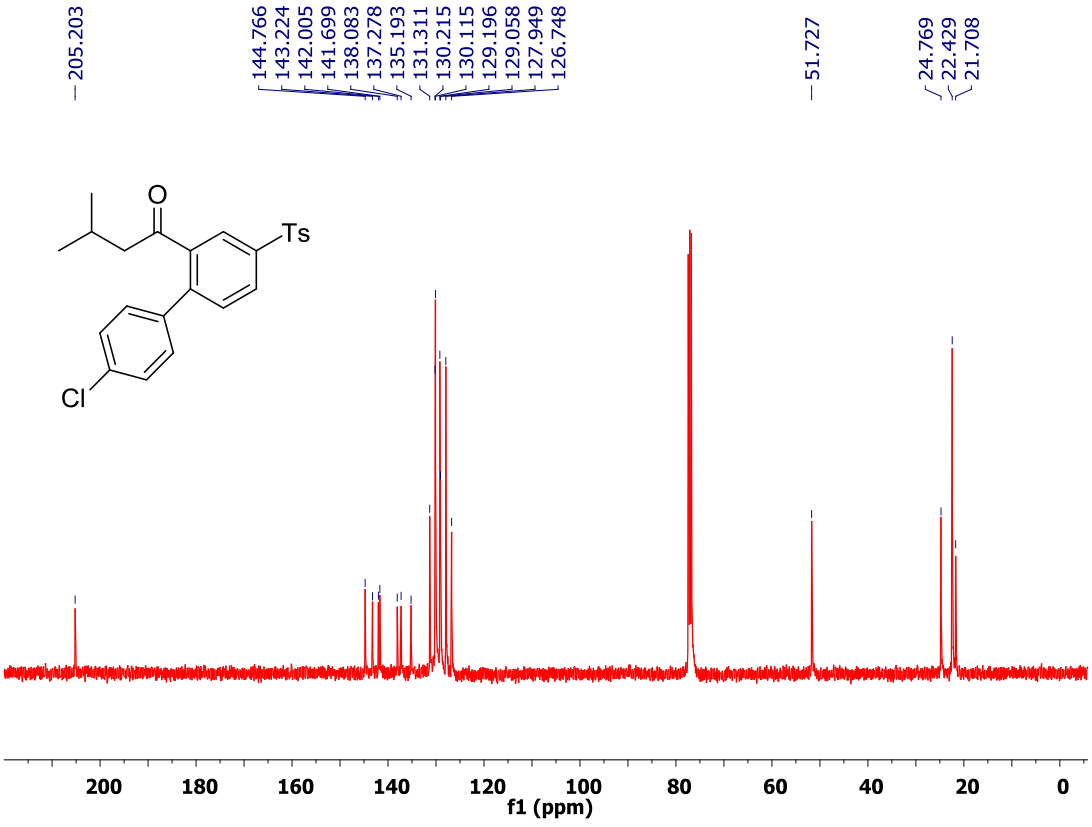
f1 (ppm)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135.193
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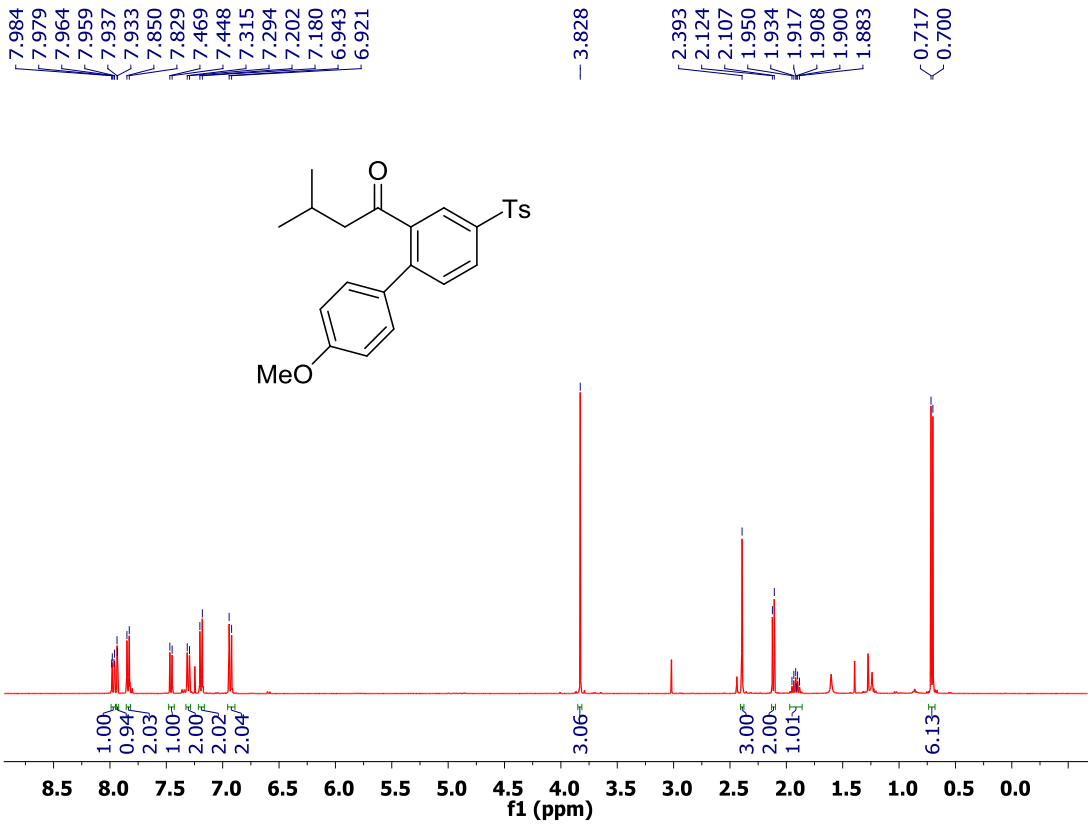
130.215
130.115
129.196
129.058
127.949
126.748
51.727
24.769
22.429
21.708
O
Ts
Cl
200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)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7.959
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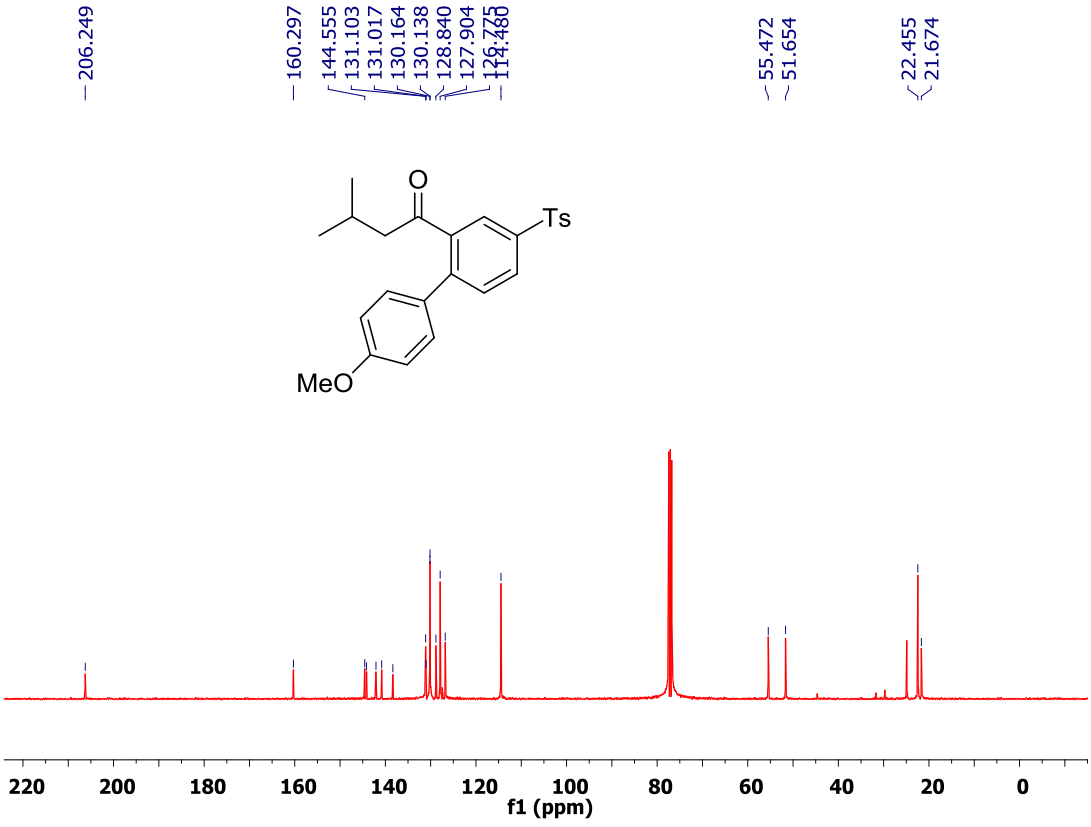
7.933
7.850
7.829
7.469
7.448
7.315
7.294
7.202
7.180
6.943
6.921
3.828
2.393
2.124
2.107
1.950
1.934
1.917
1.908
1.900
1.883
0.717
0.700
O
Ts
MeO
1.00
0.94
2.03
1.00
2.00
2.02
2.04
3.06
3.00
2.00
1.01
6.13
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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130.164
130.138
128.840
127.904
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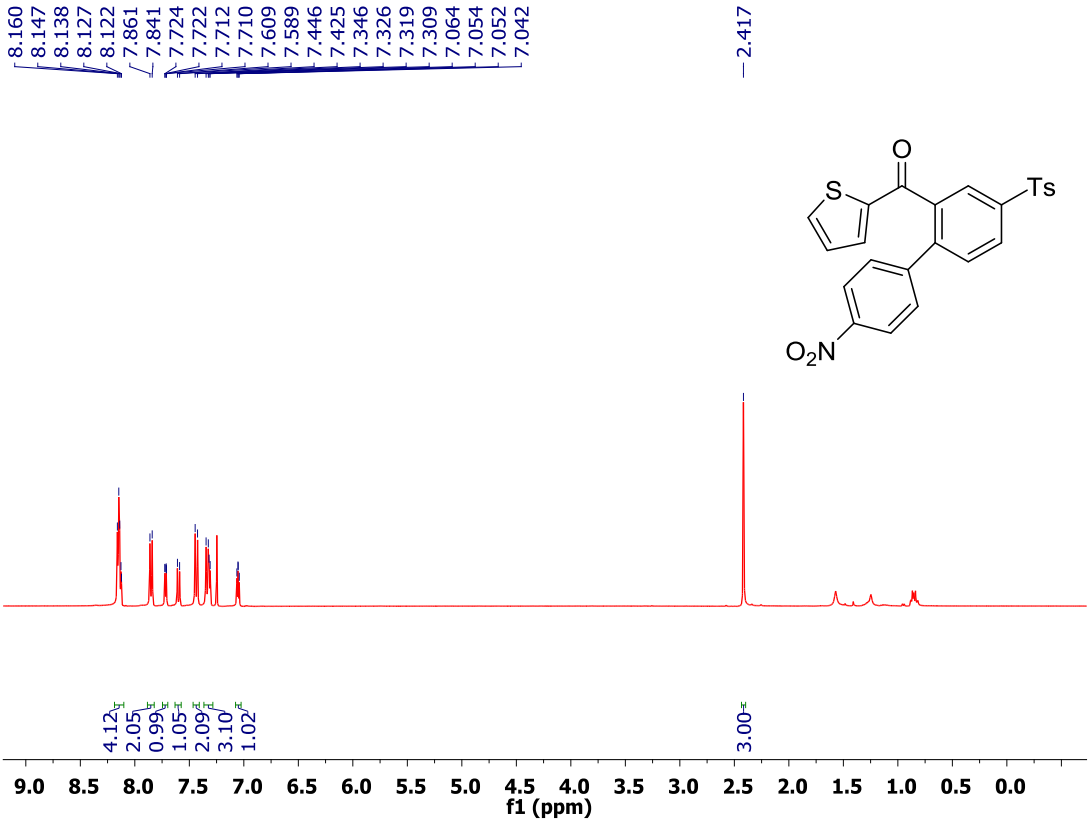
51.654
22.455
21.674
O
Ts
MeO
220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)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8.127
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7.724
7.722
7.712
7.710
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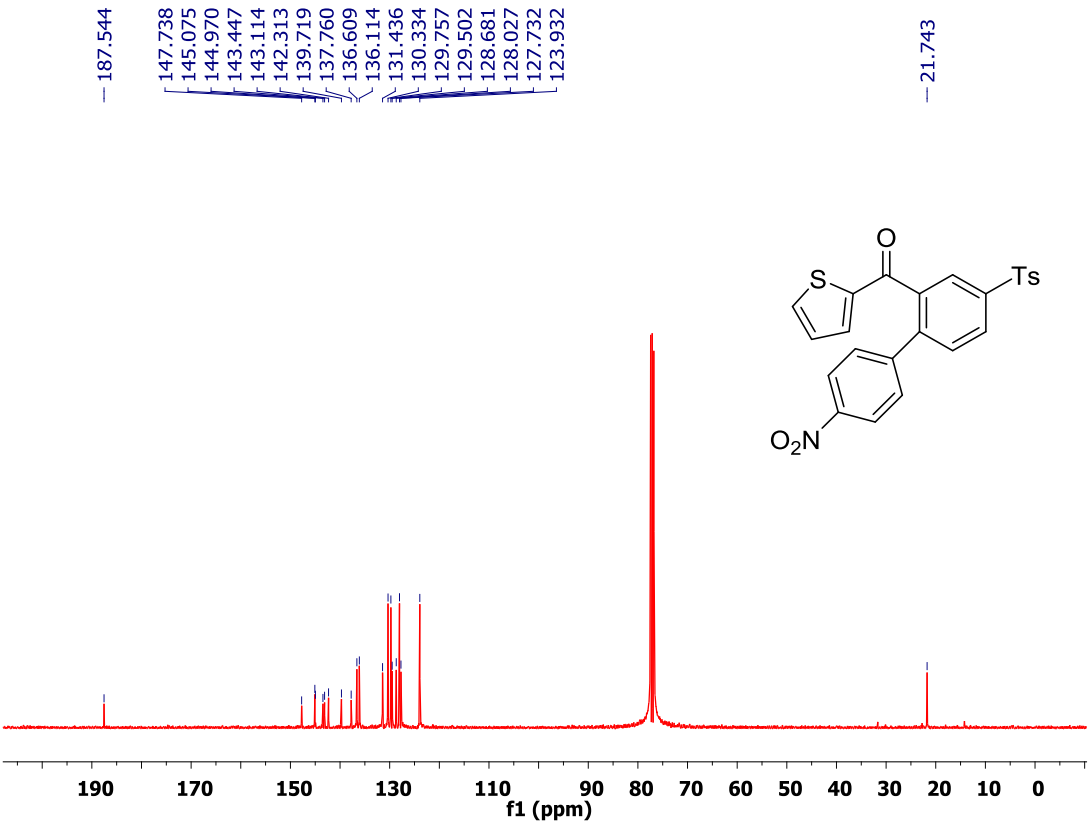
7.589
7.446
7.425
7.346
7.326
7.319
7.309
7.064
7.054
7.052
7.042
2.417
O
S
Ts
O_2N
4.12
2.05
0.99
1.05
2.09
3.10
1.02
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.970
143.447
143.114
142.313
139.719
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130.334
129.757
129.502
128.681
128.027
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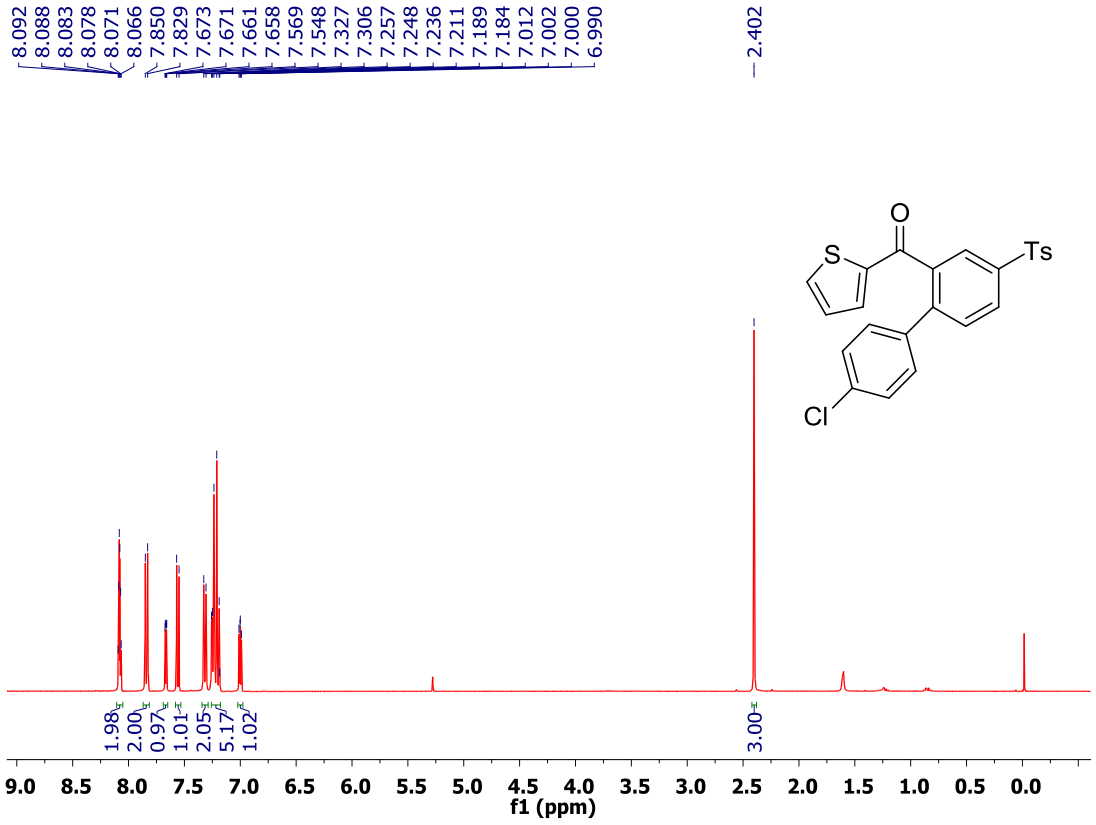
123.932
21.743
O
S
Ts
O_2N
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.066
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7.548
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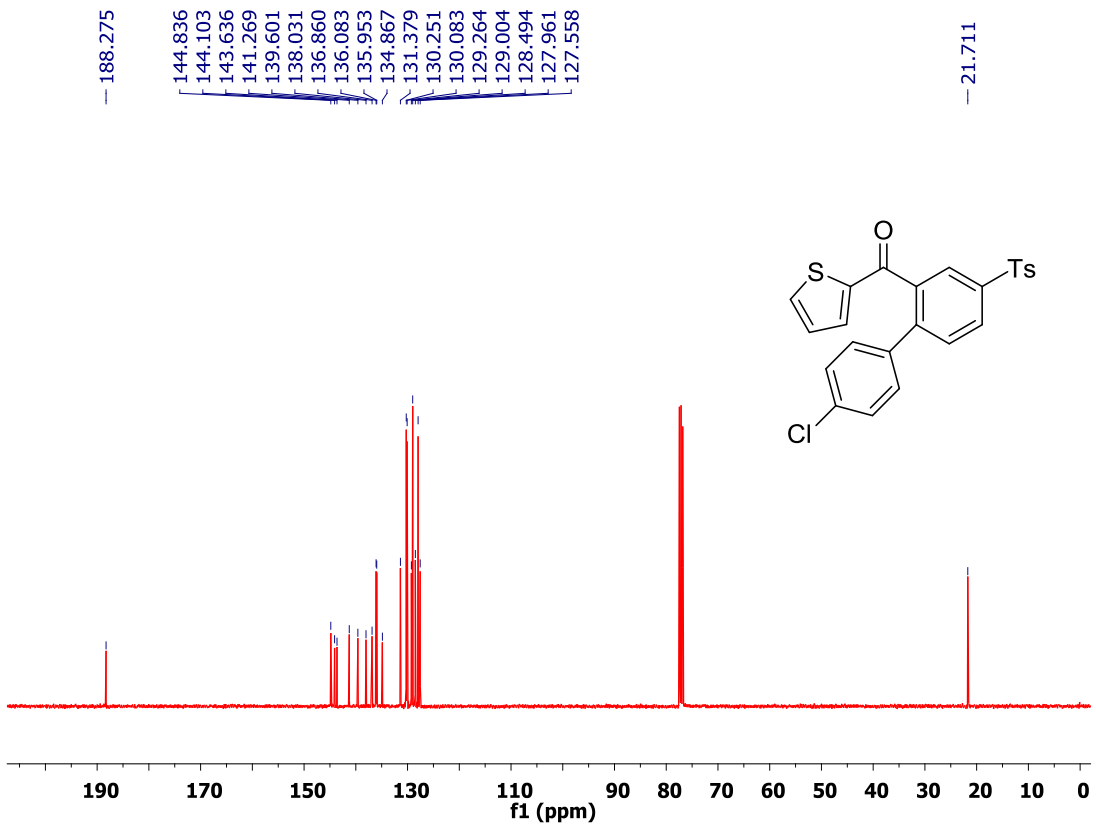
7.306
7.257
7.248
7.236
7.211
7.189
7.184
7.012
7.002
7.000
6.990
2.402
O
S
Ts
Cl
1.98
2.00
0.97
1.01
2.05
5.17
1.02
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.103
143.636
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130.083
129.264
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O
S
Ts
Cl
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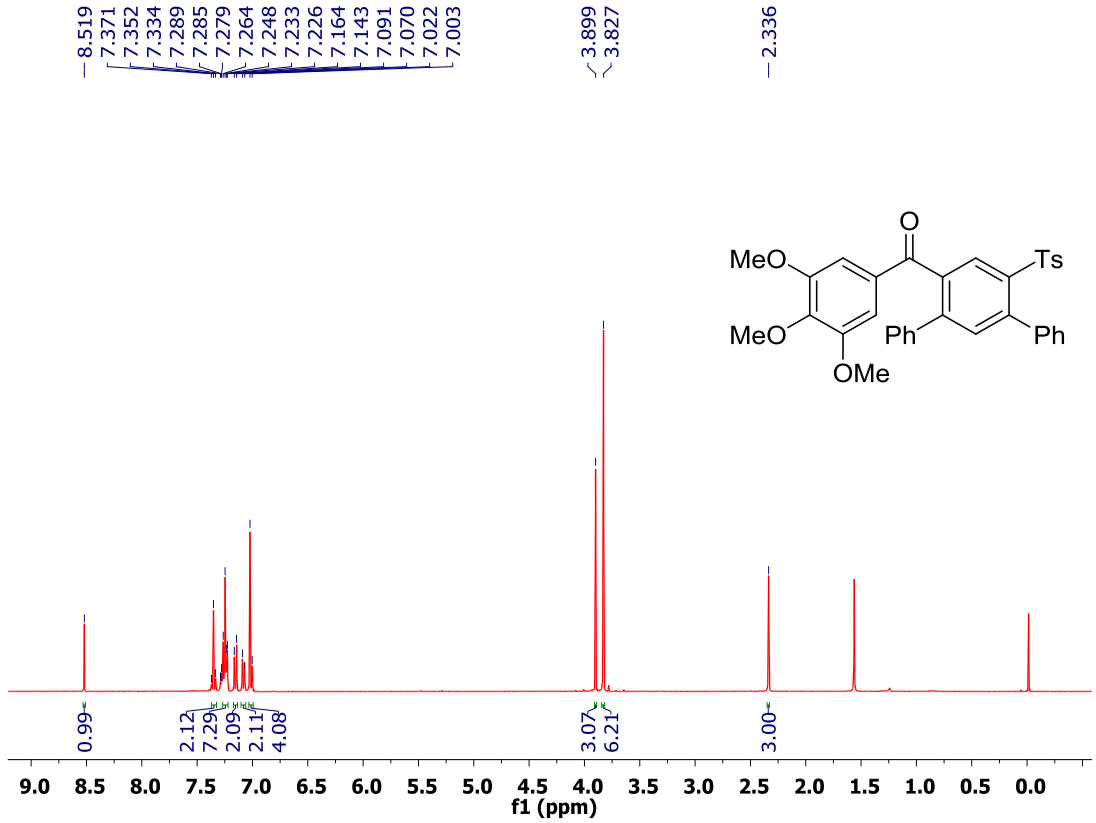
f1 (ppm)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7.289
7.285
7.279
7.264
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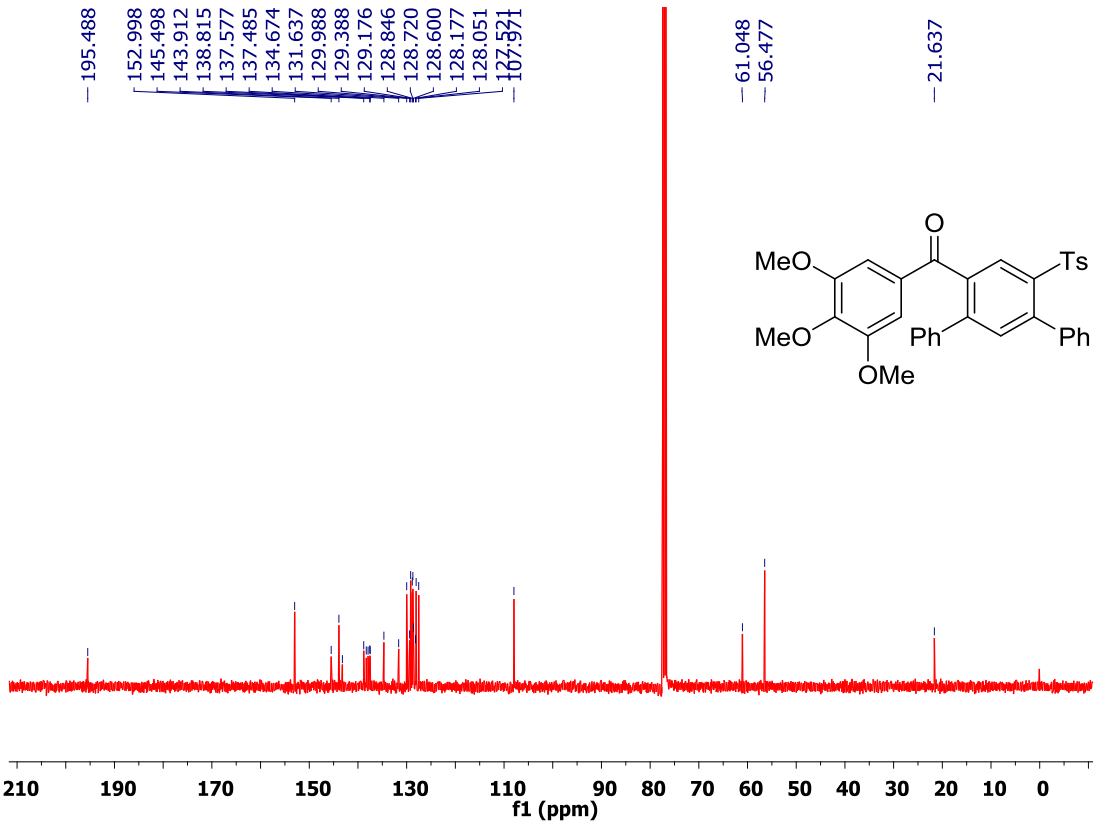
7.091
7.070
7.022
7.003
3.899
3.827
2.336
MeO
MeO
OMe
O
Ph
Ph
Ts
0.99
2.12
7.29
2.09
2.11
4.08
3.07
6.21
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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128.600
128.177
128.051
127.521
127.371
61.048
56.477
21.637
MeO
MeO
OMe
O
Ph
Ph
Ts
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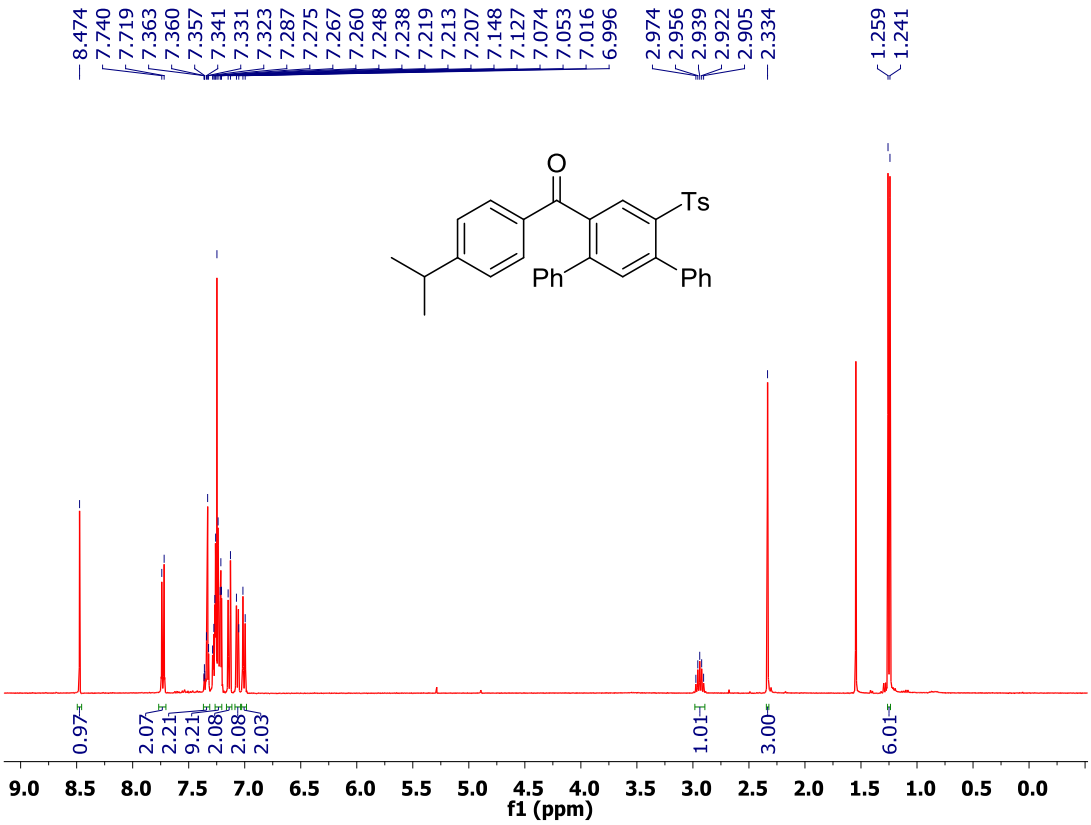
f1 (ppm)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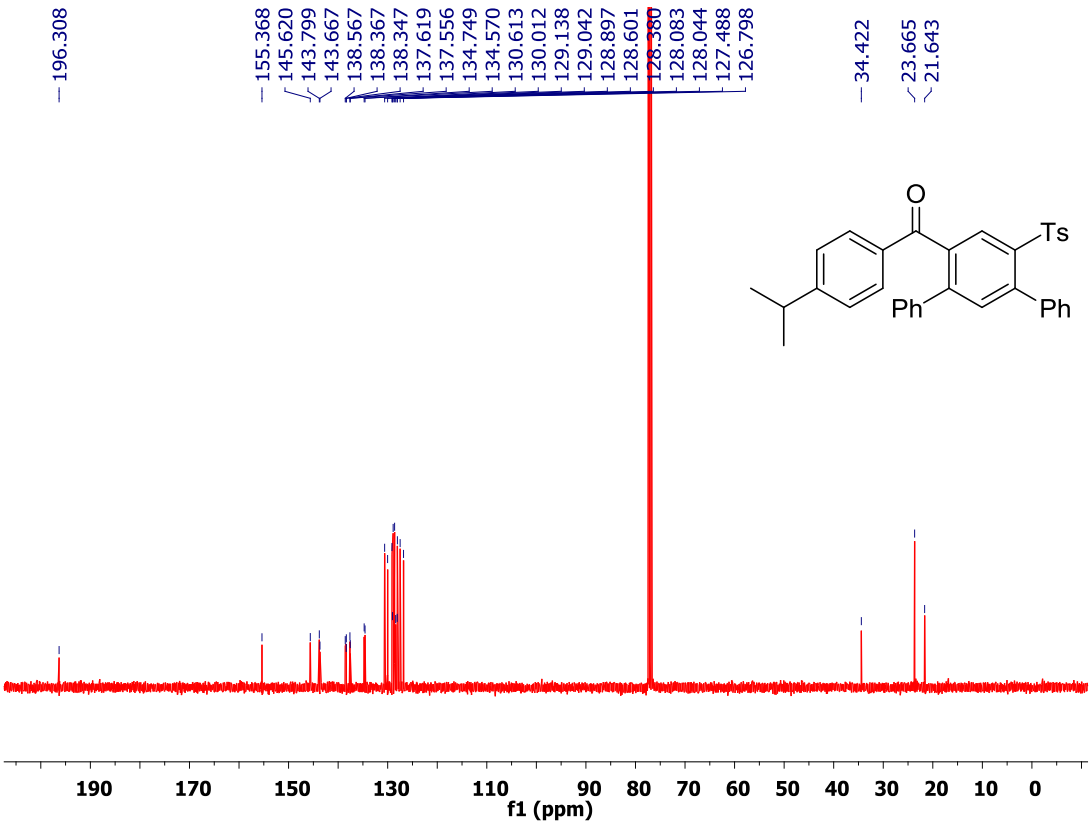
7.248
7.238
7.219
7.213
7.207
7.148
7.127
7.074
7.053
7.016
6.996
2.974
2.956
2.939
2.922
2.905
2.334
1.259
1.241
O
Ts
Ph
Ph
0.97
2.07
2.21
9.21
2.08
2.08
2.03
1.01
3.00
6.01
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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143.667
138.567
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130.613
130.012
129.138
129.042
128.897
128.601
128.380
128.083
128.044
127.488
126.798
34.422
23.665
21.643
O
Ts
Ph
Ph
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Chapter IV

Facile synthesis of sulfone-bearing indoles and related heterocycles via a sequential formal vinylic substitution and intramolecular Heck coupling reaction

4.1. Introduction

Indoles constitute one of the most abundant and important nitrogen heterocycles with a wide range of applications. The indole motif is present at the core of numerous natural products, drug molecules and agrochemicals.[1] A majority among the numerous structurally diverse, naturally occurring indole derivatives possess important pharmacological activites.[2] For example, vasoconstrictor hormone serotonin is an important monoamine neurotransmitter and reserpine is an indole-alkaloid used for the treatment of high blood pressure (Figure 1). Additionally, a variety of biological (such as cytotoxic, antiviral, antimicrobial, antiparasitic and anti-inflammatory) activities are exhibited by indole ring-bearing marine natural products.[3]

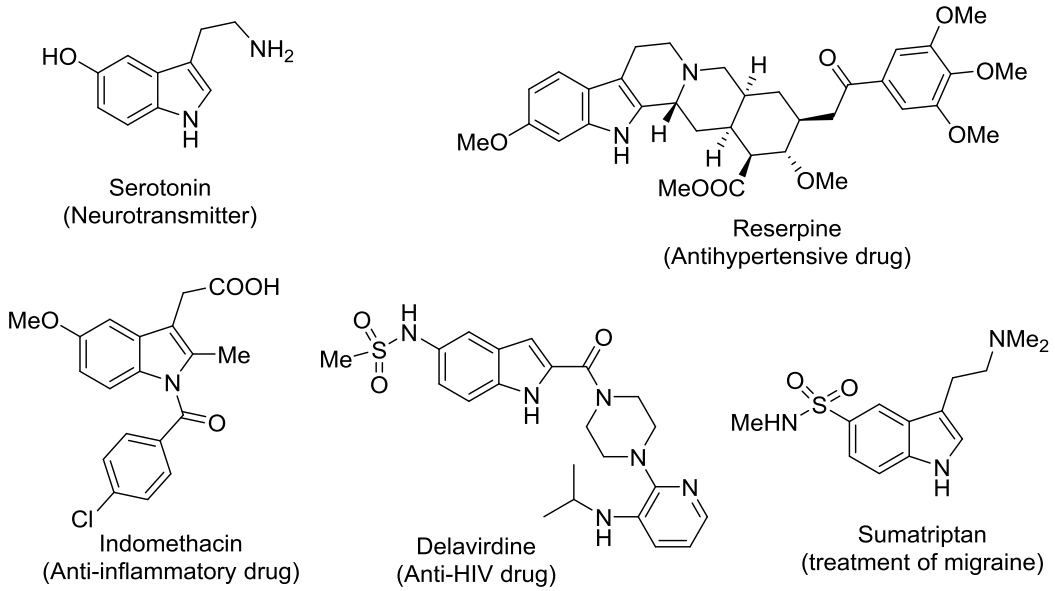


Figure 1: Some important biologically active natural and synthetic indole derivatives

Figure 1 shows some natural and synthetic indole derivatives that are bioactive or marketed as drugs. Indomethacin, for example, is a non-steroidal anti-inflammatory drug that works by inhibiting COX,[4] delavirdine is used for the treatment of human immunodeficiency virus type-1 (HIV-1),[5] and sumatriptan, (sold under the brand name imitrex) is a serotonin receptor agonist used for the treatment of migraine.[6]

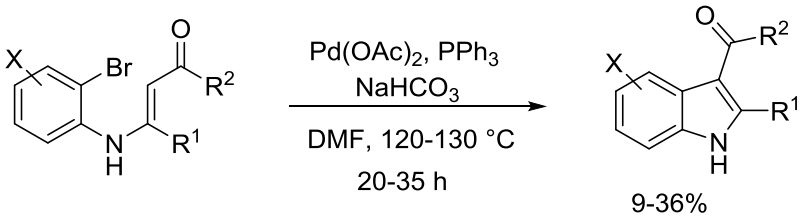
Owing to their importance and widespread applications, a variety of methods have been developed for indole synthesis. The most notable among them, Fischer indole synthesis introduced in 1883 constitutes one of the most powerful and popular method for indole synthesis.[7] In addition, other important classical methods include Madelung cyclisation of N-acyl-*o*-toluidines, Leimhruber-Batcho synthesis from *o*-nitrotoluene, Bischler-Möhlau synthesis from α-bromoacetophenone and aniline, Gassman indole synthesis and Bartoli synthesis.[8] Modern methods such as metal-catalyzed cyclization reactions of *o*-haloanilino enamines,[9] N-allyl-*o*-halo anilines,[10] *o*-halo-N-propargyl anilides,[11] *o*-vinyl anilines,[12] and *o*-allyl anilines[13] also afford convenient and efficient access to indoles.

The work described in this chapter focuses on a strategy for synthesis of indoles from *o*-haloanilino enamine derivatives *via* intramolecular Heck reaction (presented later in detail). In order to put the results in proper perspective, a brief overview of reported methods of indole construction from *o*-haloanilino enamines is presented below.

4.2. Synthesis of indoles from o-haloanilino enamines

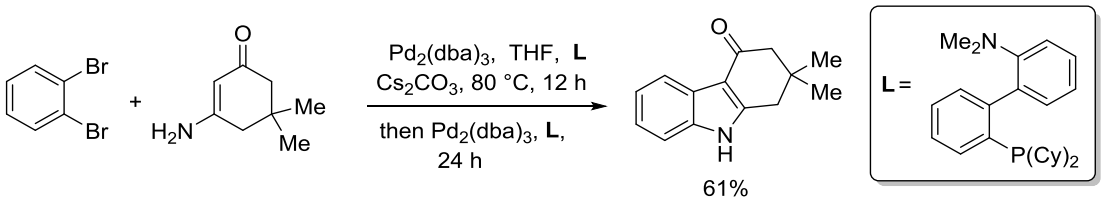
Kobayashi and co-workers reported in 1980 that *o*-haloaniline enamines conjugated to a carbonyl group can be converted to indole derivatives via intramolecular Heck reaction.

The enaminones were typically generated via the condensation of *o*-bromoaniline with 1,3-dicarbonyl compounds and the Pd-catalyzed Heck-cyclisation was carried out at high temperatures in DMF (Scheme 1).



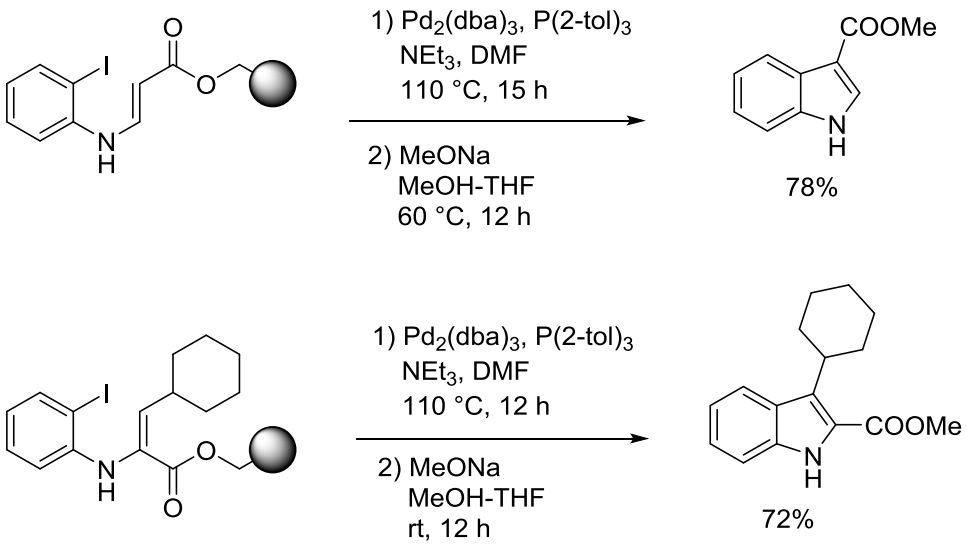
Scheme 1: Synthesis of indole derivatives via intramolecular Heck cyclisation

A domino Buchwald- Hartwig-Heck cyclisation for synthesis of 2,3-disubstituted indole derivatives has been reported. In this reaction, *o*-halo-enaminones generated by Buchwald-Hartwig coupling of vinylogous amides and dihaloarenes undergo an in situ Heck cyclization reaction to furnish indole derivatives (Scheme 2).



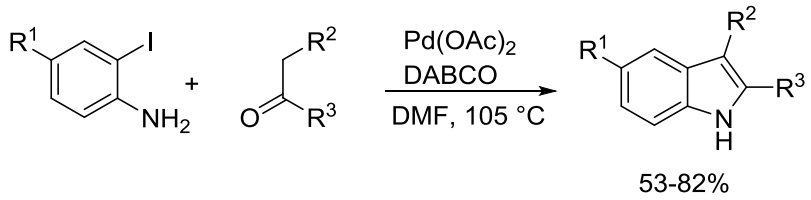
Scheme 2: Domino reaction for construction of 2,3-substituted indole derivatives

Haloanilino enamines conjugated to an ester group were also employed in study for preparation of indole derivatives. Kondo and co-workers developed a solid-phase synthesis of indole-3-carboxylates using similar substrates. Thus, the palladium-catalyzed cyclisation of immobilized enaminoesters followed by transesterification afforded indole-3-carboxylate derivatives as depicted in Scheme 3.



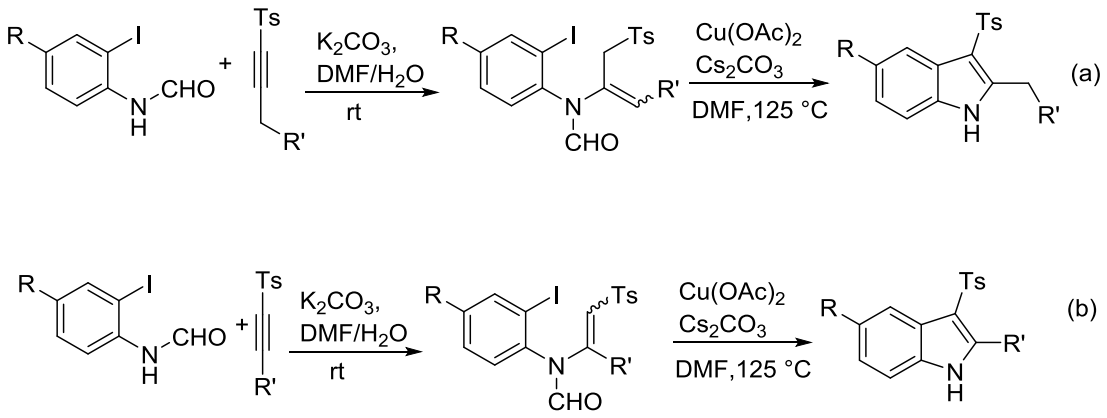
Scheme 3: Synthesis of indole-3-carboxylate and indole-2-carboxylate from o-iodoanilino enaminoesters

An efficient method for synthesis of indoles via annulation reaction between 2-iodoanilines and ketones was developed by Chen and co-workers. The reaction involved the generation of o-iodoanilino enamine followed by intramolecular Heck cyclisation to afford the corresponding indole derivative (Scheme 4).



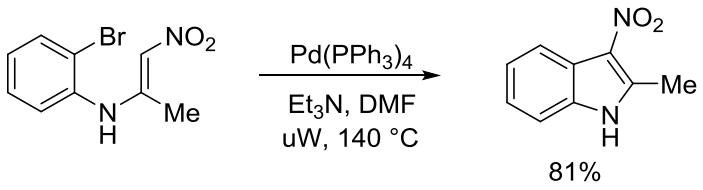
Scheme 4: Generation of enamine and subsequent Heck-cyclisation to afford indoles

The conjugate addition of o-iodoaniline derivatives to acetylenic sulfones containing γ-hydrogen afforded inseparable mixture of isomeric enamines (Scheme 5a). Similarly, terminal acetylenic sulfones reacted to afford enamines conjugated with sulfonyl group (Scheme 5b). Both classes of enamine derivatives underwent copper-catalyzed intramolecular coupling reaction to afford substituted 3-sulfonyl indole derivatives (Scheme 5).



Scheme 5: Cu-catalyzed synthesis of 3-sulfonyl indole derivatives

Kurth and co-workers have reported a microwave assisted construction of 3-nitroindoles from o-bromoanilino enamines via Pd-catalyzed intramolecular Heck-coupling reaction (Scheme 6).



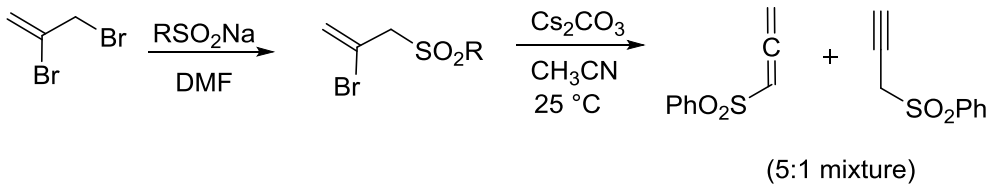
Scheme 6: Microwave assisted synthesis of 3-nitroindoles

4.3. Background to the present work

Allenyl sulfones are versatile building blocks in organic synthesis, however their potential remains largely underexploited.[14] Recent investigations form our laboratory have revealed novel reactivity patterns of allenyl sulfones and related specie for construction of various carbocycles and heterocycles. A short overview of these investigations that are particularly relevant for the work described in this chapter is given below.

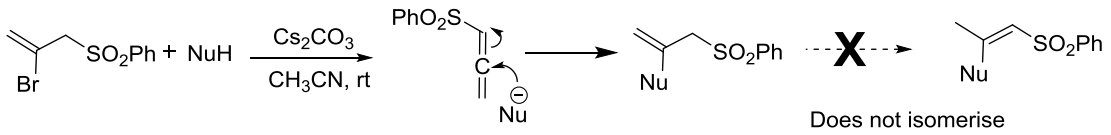
A key observation in this regard was that 2-bromoallyl sulfones could be transformed to allenyl sulfones by Cs_2CO_3 promoted dehydrohalogenation.[15] The 2-bromoallyl

sulfones are in turn, easily prepared from commercially available 2,3-dibromopropene and arylsulfinate salts (Scheme 7).



Scheme 7: Preparation of allenyl sulfone from 2-bromoallyl sulfone

Interestingly, isolation of the allenyl sulfone was not essential for its subsequent transformations. It was found that a variety of suitable nucleophiles underwent conjugate addition to *in-situ* generated allenyl sulfone and afforded functionalized allyl sulfones (Scheme 8). However, the overall reaction may be viewed as formal vinyl displacement reaction of 2-bromo allylsulfones.

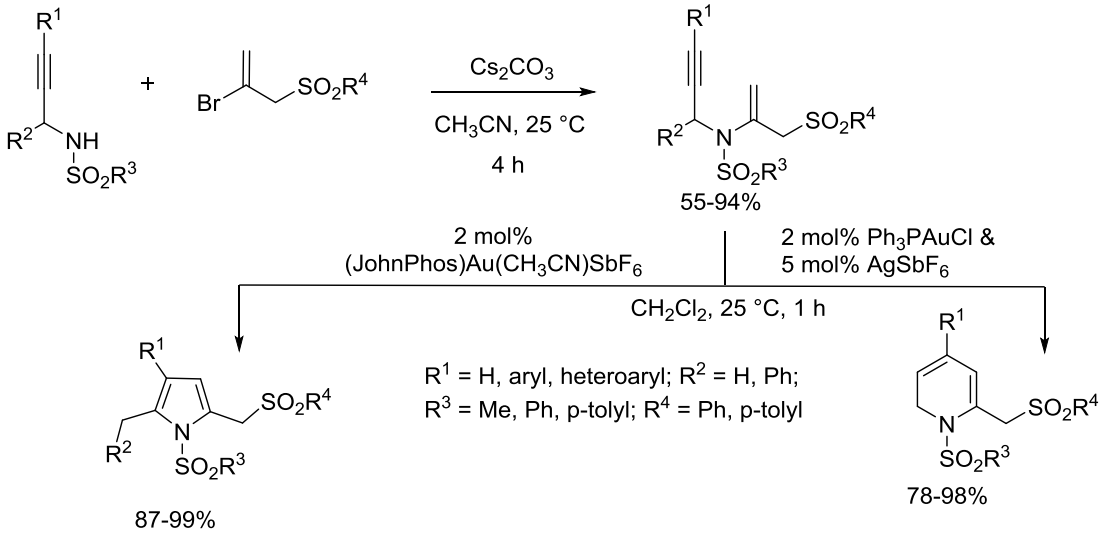


Scheme 8: Addition of nucleophile to in-situ generated allenyl sulfone

It may be noted that the double bond in the Michael adduct (Scheme 8) is not-conjugated to the sulfonyl group, despite being generated under basic conditions. This is presumably due to the well-known propensity of vinyl sulfones to undergo base-catalyzed isomerisation to produce allyl sulfones.[16] This feature allows for the development of further reactions of this reactive terminal alkene unit.

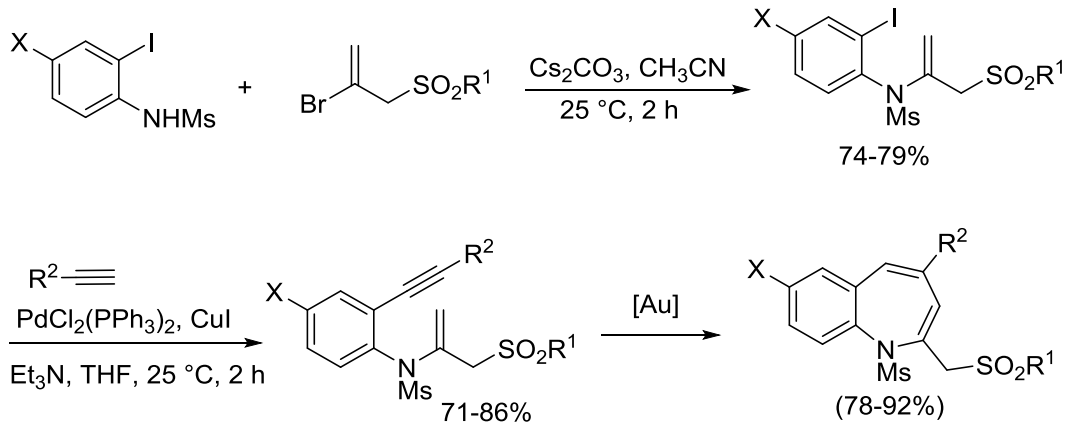
For example, the reaction of propargyl sulfonamides with 2-bromoallyl sulfone generated N-propargyl-N-vinyl sulfonamide adduct (aza-enynes) via the intermediacy

of allenyl sulfone. Subsequent gold-catalyzed cycloisomerisation of these aza-enynes proceeded in divergent pathways depending upon the choice of catalysts to afford substituted pyrroles or dihydropyridines (Scheme 9).[17] Echavarren's gold catalyst promoted the formation of pyrrole derivatives whereas a combination of gold and silver catalysts effected the formation of dihydropyridine derivatives.



Scheme 9: Conjugate addition of propargyl sulfonamide to allenyl sulfone and subsequent catalytic divergent cycloisomerisation

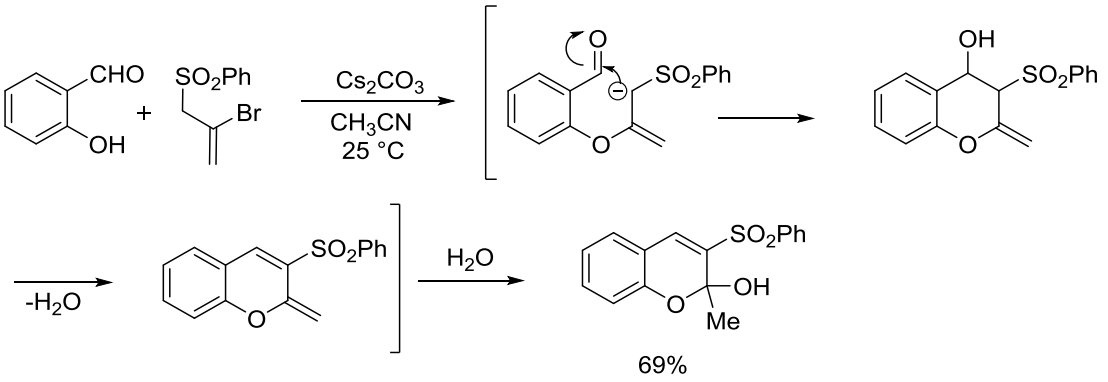
Other nitrogen heterocyclic compounds could also be produced by varying the position of alkyne unit or by incorporating extra carbon atoms in sulfonamide component. The formal vinylic displacement of bromo allylsulfone by 2-iodoaniline derivative, followed by Sonogashira coupling afforded an assortment of 3-aza-1,6-enynes. The regioselective cycloisomerization of latter catalyzed by a Au(I)-catalyst generated benzo-1-azepine derivatives (Scheme 10).[18]



R^1 = Ph, p-tolyl; R^2 = aryl, TMS; X = H, Cl;[Au] = $[JohnPhosAu(CH_3CN)]SbF_6$

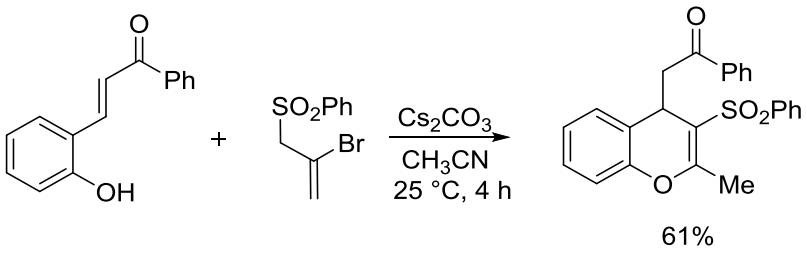
Scheme 10: Addition of o-iodoaniline derivative to allenyl sulfone and catalytic cycloisomerisation of 3-aza-1,6-enyne system

Similarly, oxygen nucleophiles such as phenols also underwent conjugate addition to allenyl sulfones. The cesium carbonate mediated cyclocondensation reaction of salicylaldehyde and 2-bromoallyl sulfone afforded 3-sulfonylchromene derivatives (Scheme 11).[15]



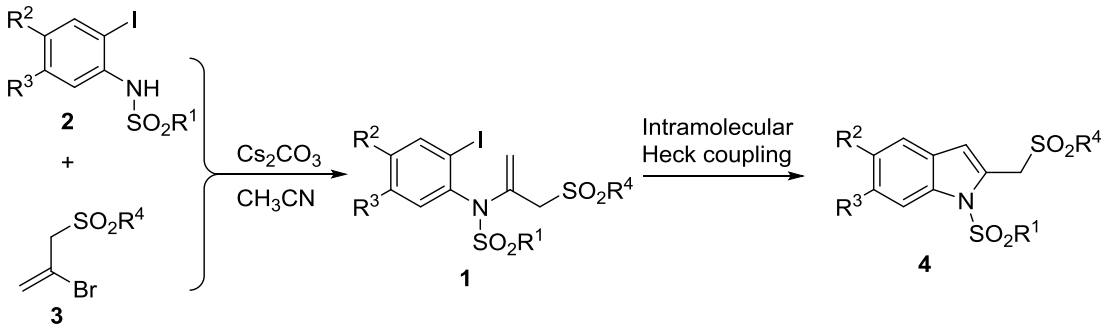
Scheme 11: Base promoted reaction of salicylaldehyde and allenyl sulfone

Additionally, the reaction of o-hydroxy chalcone and 2-bromoallyl sulfone furnished 3-sulfonyl-4*H*-chromene derivatives (Scheme 12). The base mediated reaction proceeds *via* oxa-Michael-Michael addition and isomerisation sequence.[19]



Scheme 12: Reaction of o-hydroxy chalcone with allenyl sulfone

It is clear from the foregoing discussion that the formal vinylic substitution reaction of allyl bromosulfones provides access to enamine-like and enol ether like products in a convenient manner. We surmised that these reactive product classes may further be elaborated to construct important heterocyclic derivatives. Therefore, we undertook investigations with a view to further explore synthetic utility of allenyl sulfones for the synthesis of sulfone containing heterocyclic compound *viz*., indole. It was envisaged that N-vinyl-o-halo sulfonamide/o-iodoanilino enamine **1** could be generated via the reaction of N-sulfonyl-o-iodoaniline **2** and 2-bromoallyl sulfone **3**. Subsequent intramolecular Heck coupling reaction was expected to lead to functionalized indole derivatives (Scheme 13).

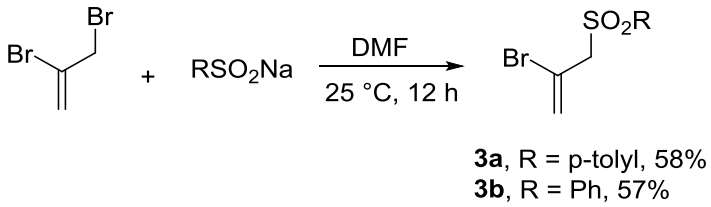


Scheme 13: Preparation and proposed reaction of N-vinyl-o-halo sulfonamide

4.4 Results and discussion

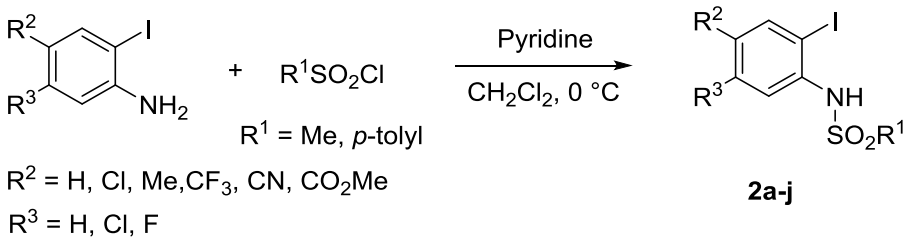
The proposed reaction sequence required access to 2-bromoallyl sulfones **3**. They were conveniently prepared as per the reported protocol starting from commercially available

1,3-dibromopropene.[15] A straightforward nucleophilic displacement reaction of the bromide in 2, 3-dibromopropene with arylsulfinate salts afforded the 2-bromoallyl sulfones **3a-b** in good yields (Scheme 14).



Scheme 14: Preparation of 2-bromoallyl sulfones **3a-b**

The required N-sulfonyl-o-iodoaniline derivatives **2** were then generated from the sulfonylation of corresponding anilines (Scheme 15). The sulfonamides **2a-j** were characterized by comparison of their physical and spectroscopic data with reported values.

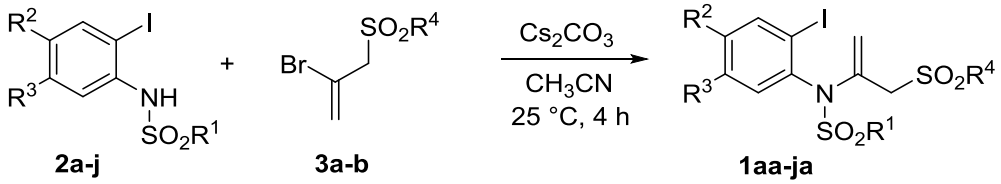


Scheme 15: Preparation of sulfonamides **2a-j**

The N-vinyl-o-halo sulfonamide precursors **(1aa-1ja)** were then prepared from 2-bromoallyl sulfones **(3a-b)** and N-sulfonyl-o-halo aniline **(2a-j)** *via* the formal vinylic substitution reaction. All the substrates reacted smoothly under the previously optimized conditions[17] to afford the corresponding N-vinyl-o-halo sulfonamides **1** in very good to high yields (Table 1). The products were characterized by standard spectroscopic analysis. The salient spectroscopic features of a representative product **1aa** are described below.

In ^{1}H NMR of **1aa**, two mutually coupled doublet signals at δ 5.53 (d, J = 1.2Hz, 1H) and δ 5.29 (d, J = 1.2Hz, 1H) were visible which were assigned to the terminal alkene protons. An AB quartet centered at δ 3.84 corresponded to the methylene unit adjacent to the sulfonyl group. Normally, this CH_2 group is expected to appear as a singlet. The fact that they appear as an AB quartet indicates that they form a very similar diastereotopic pair. A plausible reason for this could be the slow pyramidal inversion of sulfonamide nitrogen. In the ^{13}CNMR spectrum, this methylene resonated at δ 59.7. In addition, the peaks at δ 118.9 and 102.3 confirmed the presence of the alkene carbons. Other spectroscopic data were also in agreement with the structure **1aa** (see experimental section for details).

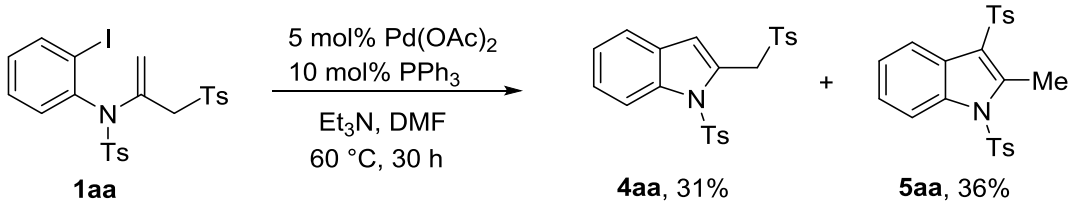
Table 1: Synthesis of N-vinyl-o-iodo sulfonamide *via* vinylic displacement reaction of 2-bromoallyl sulfones[a]



Entry	N-vinyl-o-iodo sulfonamide **(2)**	Bromoallyl sulfones **(3)**	Product (**1**)	Yield (%)[b]
1	**2a**, R^1 = p-tolyl; $R^2 = R^3$ = H	**3a**, R^4 = p-tolyl	**1aa**	79
2	**2a**	**3b**, R^4 = Ph	**1ab**	81
3	**2b**, R^1 = p-tolyl; R^2 = H, R^3 = Cl	**3a**, R^4 = p-tolyl	**1ba**	83
4	**2c**, R^1 = p-tolyl; R^2 = Cl, R^3 = H	**3a**, R^4 = p-tolyl	**1ca**	78
5	**2d**, R^1 = p-tolyl, $R^2 = CH_3$, R^3 = H	**3a**, R^4 = p-tolyl	**1da**	76
6	**2d**	**3b**, R^4 = Ph	**1db**	74
7	**2e**, R^1 = p-tolyl; R^2 = H, R^3 = F	**3a**, R^4 = p-tolyl	**1ea**	71
8	**2f**, $R^1 = CH_3$; $R^2 = R^3$ = H	**3a**, R^4 = p-tolyl	**1fa**	72
9	**2g**, $R^1 = CH_3$; R^2 = H, R^3 = Cl	**3b,** R^4 = Ph	**1gb**	78
10	**2h**, $R^1 = CH_3$; $R^2 = CF_3$, R^3 = H	**3b,** R^4 = Ph	**1hb**	68
11	**2i**, $R^1 = CH_3$; R^2 = CN, R_3 = H	**3a**, R^4 = p-tolyl	**1ia**	63
12	**2j**, $R^1 = CH_3$; $R^2 = CO_2Me$, R^3 = H	**3a**, R^4 = p-tolyl	**1ja**	69

[a]Reaction conditions: **2a-j** (1mmol), **3a-b** (1.5 mmol), Cs_2CO_3 (2.5mmol), acetonitrile (10 ml), 4h, 25 ˚C.
[b]Yields of products isolated after column chromatography

Following the synthesis of the precursors **1**, the conditions for implementing the proposed intramolecular Heck reaction were explored. To test our hypothesis, substrate **1aa** was subjected to the standard reaction conditions of intramolecular Heck coupling reaction.[20] A reaction was observed when **1aa** was treated with catalytic palladium acetate, triphenylphosphine and triethylamine in DMF at 60 °C. After standard work-up and chromatographic purification, two easily separable products were isolated from the reaction mixture (Scheme 16). They were identified as isomeric indoles **4aa** and **5aa** based on spectroscopic analysis.



Scheme 16: Intramolecular Heck coupling reaction of **1aa**

In ^{1}H NMR spectrum of **4aa** a singlet at δ 6.89 corresponding to one proton was assigned to the hydrogen at 3-position of indole. The singlet at δ 5.03 (2H) indicated the presence of methylene group in the product. Singlet resonances at δ 2.42 and δ 2.29 corresponding to three hydrogens each indicated that both the tosyl groups were intact. In the ^{13}C NMR spectrum, the signal at δ 55.1 confirmed the presence of the methylene unit. DEPT-135 spectrum of **4aa** confirmed that the signal at δ 55.1 is indeed a methylene group. Analysis of the mass spectrum clearly indicated that the iodine has been lost. Based on these observations, **4aa** was identified as the expected product of Heck coupling reaction, N-tosyl-2-tosylmethylindole. The isolated yield of **4aa** corresponded to a paltry 31%.

On the other hand, the ^{1}H NMR spectrum of the major product **5aa** showed three single resonances of three protons each at δ 2.97, 2.37 and 2.36. While the last two of these

singlets were clearly arising from the tosyl groups, the one at δ 2.97 indicated that a methyl group is present elsewhere in the molecule. The absence of any CH_2 resonance pointed to the fact that the double bond in **1aa** may have isomerised prior to the Heck coupling reaction. The signal at δ 13.1 in the ^{13}C NMR spectrum (methyl group) also supported this suggestion. DEPT-135 spectrum also showed that there are no methylene units in **5aa**. Based on all these **5aa** was assigned the structure 3-methyl-1,2-ditosylindole as depicted in Scheme 15. It may be noted that this product was obtained in 36% yield.

It may be recalled here that the base-mediated isomerisation of vinyl sulfones to allyl sulfones (and vice versa) is well documented. Therefore, it is reasonable to assume that the substrate **1aa** underwent isomerisation to the corresponding vinyl sulfonamide under the conditions of the Heck reaction. It is presumable that the coupling of the vinyl sulfone is more facile under these conditions.

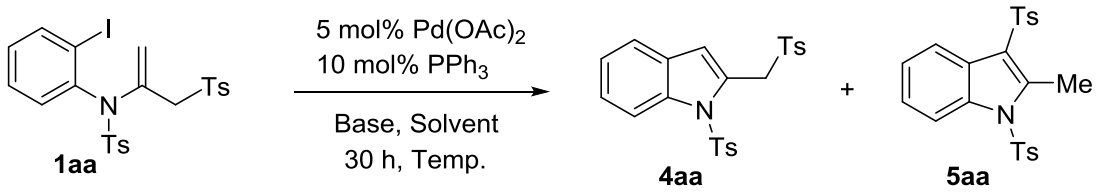
Although two products were formed in the Heck coupling reaction, their chromatographic separation was rather straightforward However, the Heck coupling reaction was further investigated with a view to improve the selectivity. The results of this optimization study are summarized in Table 2.

Initially, the effect of increasing the amount of base was explored. When reaction was tested with 3 equivalents of triethylamine, the yield of product **5aa** increased to 43% along with a reduction of the yield of **4aa** to 26% (entry 2). Increase in reaction temperature to 80 ˚C improved the selectivity for **5aa** (64%) over **4aa** (16%) further (entry 3). Indoles **4aa** and **5aa** were formed in lower yields (23% and 18 % respectively) when the reaction was carried out at 40˚C (entry 4). Interestingly, selective formation of indole derivative **5aa** was observed when either K_2CO_3 or Cs_2CO_3 was used as the base in DMF at 80 ˚C. Formation of monosubstituted indole **4aa** was not at all detected;

however, the isolated yields of **5aa** were only moderate under these conditions (46% and 52%; entries 5 and 6). The use of sodium bicarbonate as a base did not help in improving the yield or selectivity (entry 7). The performance of DBU as a base was also not satisfactory (entry 8). Similar results were obtained when the coupling reaction was carried out in acetonitrile in presence of various bases (entries 9-12).

Based on these results, the combination of $Pd(OAc)_2$, PPh_3 and Et_3N in DMF at 80 ˚C was selected as the optimum conditions for further investigations. It may be noted that the use of cesium carbonate in DMF afforded a single product (**5aa**) selectively. However, column chromatography was necessary in either case for the separation of products. Therefore, the reaction condition that afforded a higher yield and an additional product (without any added effort for separation) was selected for scope exploration.

Table 2: Optimisation of reaction conditions for intramolecular Heck coupling of **1aa**[a]

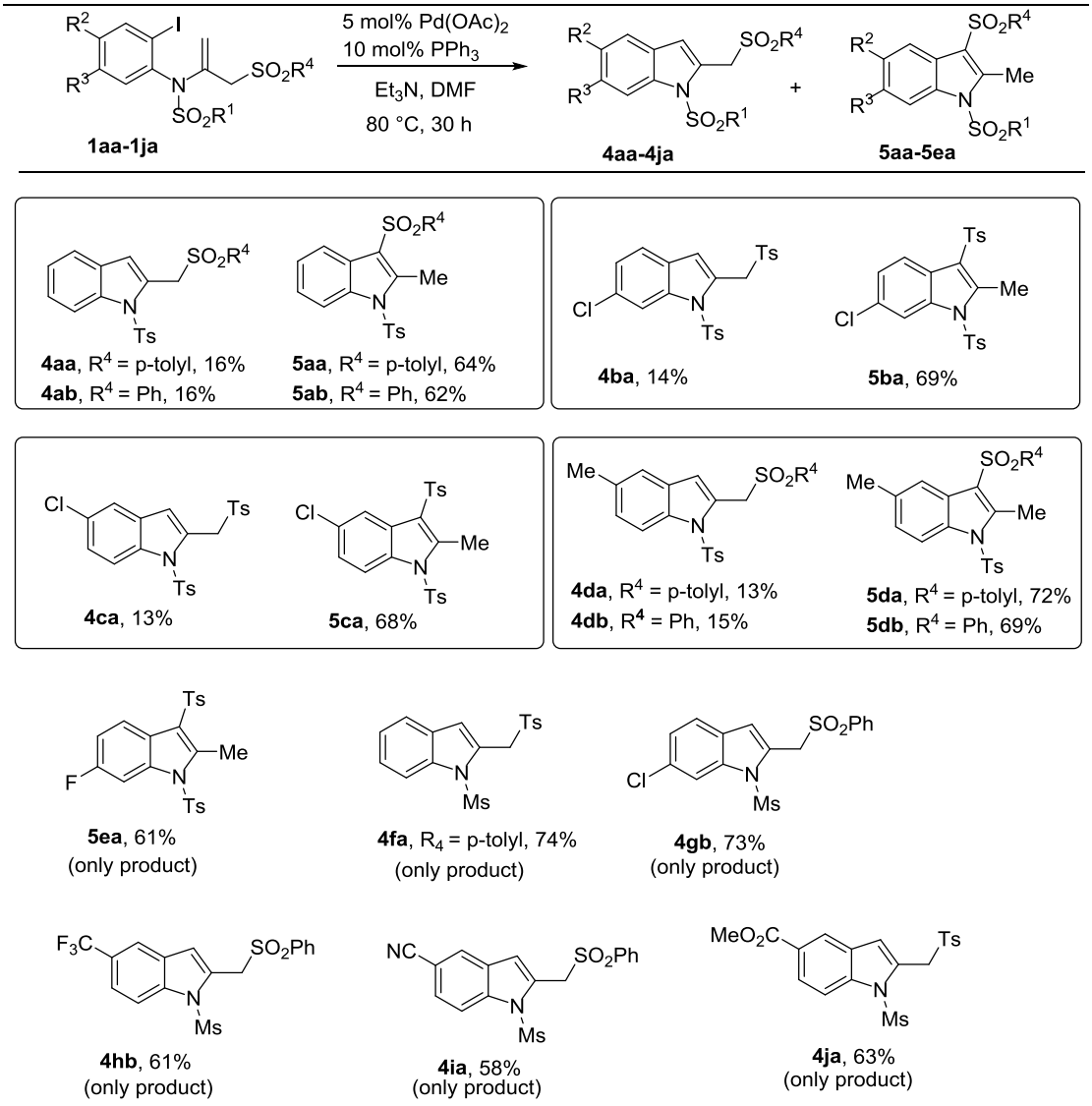


Entry	Solvent	Base	Temp.(˚C)	Yield of **4aa** (%)[b]	Yield of **5aa** (%)[b]
1[c]	DMF	Et_3N	60	31	36
2	DMF	Et_3N	60	26	43
3	**DMF**	**Et_3N**	**80**	**16**	**64**
4	DMF	Et_3N	40	23	18
5	DMF	K_2CO_3	80	-	46
6	**DMF**	**Cs_2CO_3**	**80**	**-**	**52**
7	DMF	$NaHCO_3$	80	19	31
8	DMF	DBU	80	Traces	23
9	MeCN	Et_3N	80	21	56
10	MeCN	Cs_2CO_3	80	18	41
11	MeCN	$NaHCO_3$	80	14	26
12	MeCN	K_2CO_3	80	15	37

[a]Reaction conditions: **1aa** (0.2mmol), $Pd(OAc)_2$ (5mol%), PPh_3 (10mol%), Et_3N (3 equiv), DMF (2ml). [b]Isolated yields of products. [c]2equiv of Et_3N was used.

As the method appeared suitable for the generation of two isomeric indoles from readily available precursors, its scope and generality were examined. Thus, the N-vinyl-o-halo sulfonamides **1aa-1ja** were subjected to the optimized conditions of the Heck coupling reaction. All of these substrates reacted smoothly to afford the indole derivatives **4** and **5**. The results are summarized in Table 3.

Table 3: Substrate scope of coupling reaction[a]



[a]Reaction conditions: **1aa-1ja** (0.4 mmol), $Pd(OAc)_2$ (5mol%), PPh_3 (10mol%), Et_3N (1.2 mmol), DMF (4ml).

The investigations revealed some very interesting features of this transformation. The most notable observation was that the reaction outcome is heavily dependent on the N-

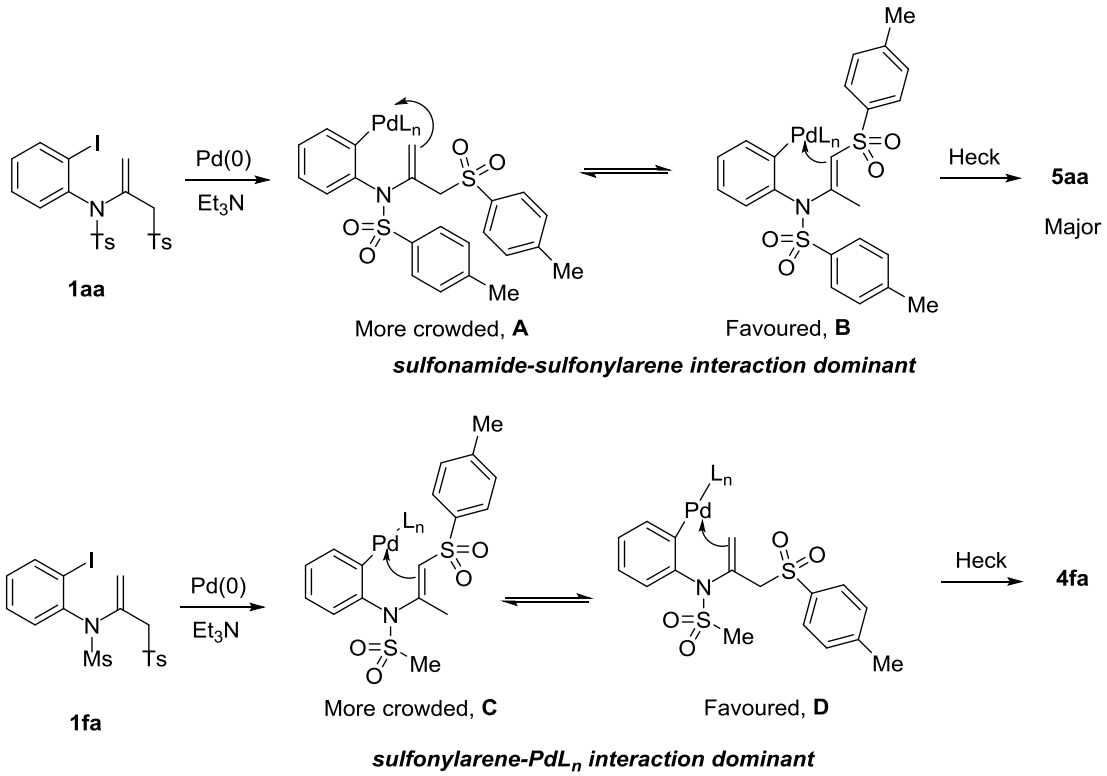
sulfonyl substituent. Substrates endowed with tosyl unit on the nitrogen (**1aa-1db**) generally reacted to afford both the indole products. The 2,3-disubstituted indoles **5aa-5db** were the major products in these cases. Minor amounts of corresponding 2-sulfonylmethyl indoles **4aa-4db** were also isolated in these reactions. Fluorine-bearing sulfonamide **1ea**, however, afforded a single product, the 2,3-disubstituted indole **5ea** in 61% yield.

Interestingly, all the substrates having N-methanesulfonyl groups (**1fa-1ja**) reacted under identical conditions to afford only the 2-sulfonylmethyl indoles **4fa-4ja** in good to high yields. In addition, the reaction showed a good level of functional group tolerance. Indole derivatives having halogens (Cl and F), trifluorormethyl, cyano and ester groups could be produced from corresponding precursors without trouble.

From the results depicted in table 3, it may be surmised that that it is possible to selectively access either of the indole derivatives (**4** or **5**) via this protocol. If the desired target is the 2-sulfonylmethyl indole **4**, the synthetic sequence may be initiated with N-mesylation of the iodoanilines **2**. On the other hand, 2,3-disubstituted indoles **5** may be selectively produced by using the N-tosyl derivatives.

The observed regioselectivity of Heck cyclisation presumably has steric origins. The organopalladium intermediate generated after oxidative addition of Pd(0) to **1aa** for example, may exist as two isomeric alkenes **A** and **B**. These isomeric alkenes can interact with palladium via either the α-sulfonyl or the γ-sulfonyl end. As both the sulfonyl groups (on nitrogen and carbon) are large in this case, the sterically favoured

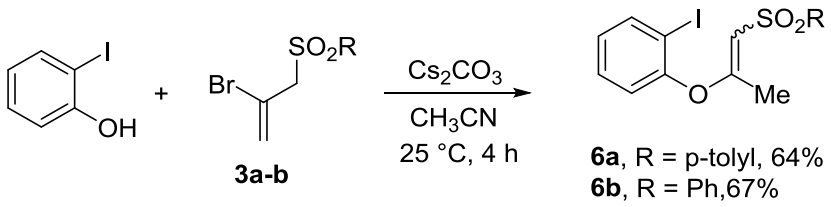
mode of cyclization may involve the reaction of the the α-sulfonyl end of the alkene **B**. This eventually leads to the formation of 2,3-substituted indole **5aa**. On the other hand, when the N-sulfonyl group is relatively smaller, as in the case of **1fa**, the major steric interaction becomes the one between N-sufonyl and the PdL_n unit. Therefore, out of the two depicted cyclisation intermediates **C** and **D**, the latter would be of less energy. It is clear that Heck cyclization via **D** would lead to the formation of the 3-substituted indole **4fa** (Scheme 17).



Scheme 17: Rationalisation of regioselectivity of Heck cyclisation based on minimisation of steric interactions

The successful development of the above-described indole synthesis method inspired further investigations to expand its scope towards the construction of other heterocyclic derivatives. It was conceivable that an analogous route starting from 2-iodophenols may

culminate in the generation of substituted benzofurans. In order to explore this possibility, the Cs_2CO_3-mediated reactions of 2-iodophenol and 2-bromoallyl sulfones **3a-b** were undertaken. It may be noted here that phenols have previously been successfully employed in similar formal vinylic substitution reactions developed in our laboratory (Scheme 11-12).[15,19] The reactions of o-iodophenol and **3a**-b, however, did not furnish the expected allyl sulfone products. Instead, the more substituted alkenes (vinyl sulfones) **6a-b** were obtained after standard workup and column chromatographic separation (Scheme 18).

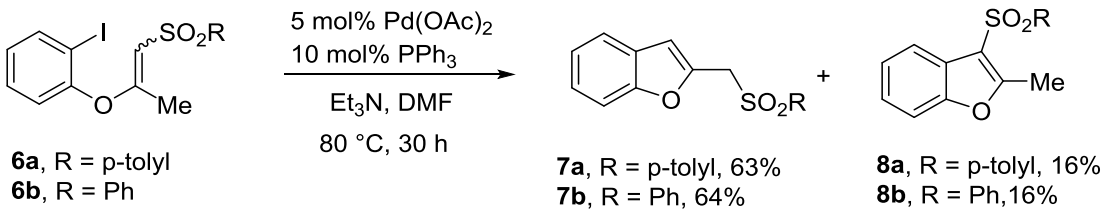


Scheme 18: Base-mediated reaction of 2-iodophenol and allylbromo sulfones **3a-b**

The products were identified via standard spectroscopic analysis. For example, the singlet absorptions at δ 5.96 (s, 1H) and 1.77 (s, 3H) in the ^{1}H NMR spectrum of **6b** clearly indicated the formation of the trisubstituted olefin unit. The stereochemistry of the double bond was not assigned at this stage as it was irrelevant in view of the planned intramolecular Heck reaction.

The two enol ethers **6a-b** were then subjected to the optimized conditions for the intramolecular Heck coupling reaction. In both the cases, two isomeric benzofurans were obtained after work-up and column chromatographic separation of the reaction mixtures. Spectroscopic analysis of the separated products revealed that the 2-

sulfonylmethyl benzofurans **7a-b** were the major product in both the cases. The 2,3-disubstituted benzofurans **8a-b** were isolated in lesser amounts (Scheme 19). It is notable that benzofurans constitute an important class of heterocycles owing to their widespread presence in nature, bioactive molecules and functional materials.[21]



6a, R = p-tolyl
6b, R = Ph

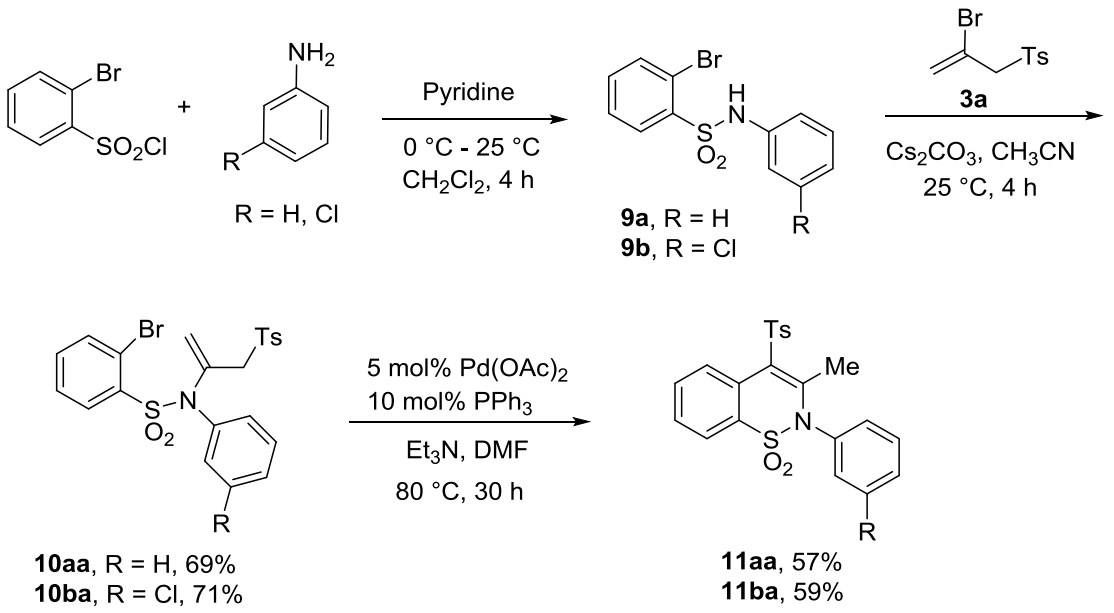
7a, R = p-tolyl, 63%
7b, R = Ph, 64%

8a, R = p-tolyl, 16%
8b, R = Ph,16%

Scheme 19: Intramolecular Heck reactions of 1-iodo-2-vinyloxy derivatives **6a-b**

It is intriguing that the regioselectivity of the benzofuran formation is opposite to that observed for the indole formation. Further studies may be required to gain an in-depth understanding of the factors that control the regioselectivity of these reactions.

The sequence of formal vinylic substitution-Heck coupling was also applicable to the construction of novel benzosultam derivatives. The sulfonamides **9a-b**[22] endowed with a bromine atom at the ortho-position was prepared from commercially available 2-bromobenzenesulfonyl chloride as shown in Scheme 19. The formal vinylic substitution reaction of the sulfonamides **9a-b** and 2-bromoallyl sulfone **3a** proceeded smoothly to afford the expected N-vinyl sulfonamides **10a-b** in good yields. The latter were then subjected to the previously established conditions of intramolecular Heck reaction. Disubstituted benzosultam derivatives were selectively formed in moderate yields after workup and chromatographic separation of the reaction mixture (Scheme 20). The products were characterised on the basis of standard spectroscopic analysis.



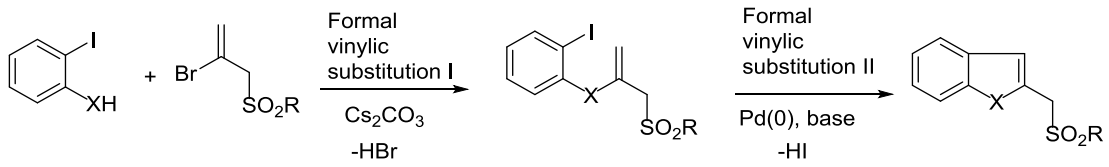
Scheme 20: Synthesis of benzosultam derivatives *via* formal vinylic substitution-Heck coupling sequence

The Heck cyclization afforded only single products in both the cases. The selectivity was similar to the one observed in N-tosyl indole formations. It may be presumed that the presence of the rather bulky N-sulfonylaryl group is responsible for the observed selectivity as seen in the case of N-tosyl indole formation (see Scheme 16). Incidentally, benzosultam derivatives are known to possess important biological activities, hence constitute much sought after synthetic targets.

4.5. Conclusion

In conclusion, a new strategy for synthesis of various important heterocyclic compounds, *viz*., indoles, benzofurans and benzosultams, has been developed. The sequence, in fact, involves two formal vinylic substitutions. The first one is mediated by cesium carbonate wherein the bromide of bromoallyl sulfone is displaced by either a nitrogen or oxygen nucleophile (sulfonamide or phenol). The second vinylic

substitution is an intramolecular Heck cyclization where in the aryl halide is substituted by the pendant alkene (Scheme 20).



Scheme 20: The method as a combination of two sequential vinylic substitutions

The intramolecular Heck coupling reaction exhibited interesting regioselective preferences. Both 2-sulfonylmethyl indoles and 2,3-disubstituted indoles could be selectively produced by choosing the right N-sulfonyl group. The vinylic substitution reaction of o-iodophenol and subsequent Heck cyclization showed selectivity that was different from corresponding aza analogues. A convenient synthesis of novel benzosultam derivatives were also developed using the same protocol. The heterocyclic motifs produced by this method are well known pharmacophores and valuable synthetic targets. Therefore, it is presumable that this method may find applications in the synthesis of designed molecules for development of therapeutics.

4.6. Experimental section

General information

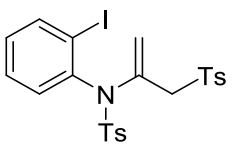
All ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solvent at ambient temperature, chemical shift δ are given in ppm on a scale downfield from TMS, and the coupling constant *J* are in Hz. The signal patterns are indicated as follows: s, Singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; brs = broad). FTIR spectra were recorded as neat. Melting points were recorded on an electrothermal apparatus and are uncorrected. All the reagents and solvents were used

without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh and 100- 200 mesh) packed in glass columns. All reactions were performed in oven-dried glassware with magnetic stirring. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining by $KMnO_4$. High-resolution mass spectra were recorded with q-TOF electrospray mass spectrometer. All purchased chemicals were used as received.

Synthesis of sulfonamide: General procedure

To a solution of the N-sulfonyl-o-iodo aniline **2** (1.0 mmol) and 2-bromoallyl sulfone **3** (1.5 mmol) in acetonitrile (10 mL), cesium carbonate (2.5 mmol) was added at room temperature and stirred the mixture for 4 hours. After completion of reaction, solvent was removed on a rotavapor and deionized water (20 mL) was added. The solution was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate and concentrated on a rotavapor. Column chromatography of the residue on silica gel using petroleum ether-ethyl acetate as eluent afforded analytically pure products.

Spectroscopic data for N-vinyl-o-iodo sulfonamides 1a-j



1aa, N-(2-iodophenyl)-4-methyl-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 448.29 mg, 79%

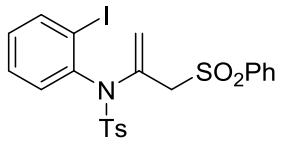
Melting point: 131-133 ˚C

IR (KBr) υ_{max}: 2922, 1620, 1595, 1460, 1346, 1311, 1157, 655, 586

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0, 1.2Hz, 1H), 7.72 (d, *J* = 8.4Hz, 2H), 7.56 (d, *J* = 8.4Hz, 2H), 7.34-7.21 (m, 4H), 7.22 (d, *J* = 8.0Hz, 2H), 7.05 (ddd, *J* = 8.0, 6.9, 2.2Hz, 1H), 5.53 (d, *J* = 1.2Hz, 1H), 5.29 (d, *J* = 1.2Hz, 1H), 3.84 (AB q, *J* = 15.2Hz , 2H), 2.45 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 144.5, 140.9, 140.0, 136.1, 135.1, 133.5, 132.5, 130.5, 129.7, 129.6, 129.2, 128.9, 128.7, 118.9, 102.3, 59.7, 21.7

HRMS calcd for $C_{23}H_{22}INO_4S_2$ (M+H) 568.0114 ; found 568.0116



1ab, N-(2-iodophenyl)-4-methyl-N-(3-(phenylsulfonyl)prop-1-en-2-yl)benzene sulfonamide

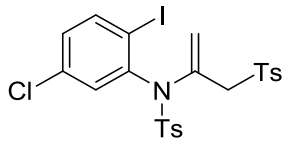
Colorless oil, 448.28 mg, 81%

IR (KBr) υ_{max}: 3062, 2924, 1591, 1496, 1315, 1153, 526

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0, 1.2Hz, 1H), 7.72–7.69 (m, 4H), 7.62-7.58 (m, 1H), 7.46 (t, *J* = 7.8Hz, 2H), 7.36–7.29 (m, 4H), 7.05 (ddd, *J* = 8.0, 6.8, 2.0Hz, 1H), 5.53, (d, *J* = 1.2Hz, 1H), 5.28 (d, *J* = 1.2Hz, 1H), 3.86 (AB q, *J* = 15.6Hz, 2H), 2.45 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 141.0, 139.9, 138.1, 136.1, 133.9, 133.3, 132.5, 130.6, 129.6, 129.2, 129.1, 128.9, 128.7, 118.8, 102.2, 59.7, 21.7

HRMS calcd for $C_{22}H_{20}INO_4S_2$ (M+H) 553.9957 ; found 553.9977



1ba, N-(5-chloro-2-iodophenyl)-4-methyl-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 499.57 mg, 83%

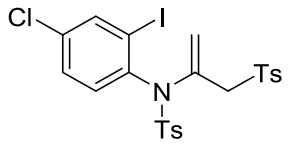
Melting point: 123-125 ˚C

IR (KBr) υ_{max}: 3244, 2924, 1620, 1595, 1448, 1309, 1157, 586, 516

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, J = 8.4Hz, 3H), 7.57 (d, J = 8.4Hz, 2H), 7.33 (d, J = 8.0Hz, 2H), 7.24 (d, J = 8.0Hz, 2H), 7.14 (d, J = 2.4Hz, 1H), 7.04 (dd, J = 8.4, 2.4Hz, 1H), 5.55 (d, J = 1.2Hz, 1H), 5.43 (d, J = 1.2Hz, 1H), 3.85 (AB q, J = 15.6Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.8, 141.3, 141.2, 135.7, 135.2, 134.9, 133.4, 132.2, 130.7, 129.8, 129.7, 128.9, 128.6, 119.7, 99.9, 59.9, 21.8, 21.7

HRMS calcd for $C_{23}H_{21}ClINO_4S_2$ (M+H) 601.9724; found 601.9737



1ca, N-(4-chloro-2-iodophenyl)-4-methyl-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 469.48 mg,78%

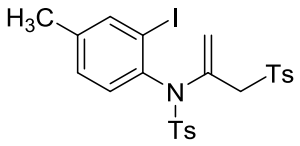
Melting point: 119-120 ˚C

IR (KBr) υ_{max}: 3091, 1597, 1577, 1463, 1334, 1163, 578

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.4Hz, 1H), 7.71 (d, J = 8.4Hz, 2H), 7.54 (d, J = 8.4Hz, 2H), 7.33–7.28 (m, 3H), 7.23-7.19 (m, 3H), 5.55 (d, J = 1.2Hz, 1H), 5.37 (d, J = 1.2Hz, 1H), 3.81 (s, 2H), 2.46 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.7, 140.2, 138.6, 135.9, 135.6, 134.9, 133.2, 132.7, 129.7, 129.6, 129.3, 128.9, 128.7, 120.0, 102.7, 59.6, 21.7

HRMS calcd for $C_{23}H_{21}ClINO_4S_2$ (M+H) 601.9724 ; found 601.9748



1da, N-(2-iodo-4-methylphenyl)-4-methyl-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 441.57 mg, 76%

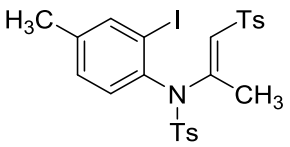
Melting point: 116-117 ˚C

IR (KBr) υ_{max}: 3041, 2924, 1624, 1595, 1477, 1319, 1159, 509

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4Hz, 2H), 7.64 (s, 1H), 7.55 (d, J = 8.0Hz, 2H), 7.31 (d, J = 8.0Hz, 2H), 7.22 (d, J = 8.4Hz, 2H), 7.16–7.10 (m, 2H), 5.52 (s, 1H), 5.25 (s, 1H), 3.82 (s, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 144.4, 141.3, 141.1, 137.2, 136.2, 135.1, 133.5, 131.9, 130.0, 129.6, 129.5, 128.9, 128.7, 118.6, 102.0, 59.6, 21.7, 20.7

HRMS calcd for $C_{24}H_{24}INO_4S_2$ (M+H) 582.0270 ; found 582.0284



1da', (E)-N-(2-iodo-4-methylphenyl)-4-methyl-N-(1-tosylprop-1-en-2yl)benzene sulfonamide

White solid

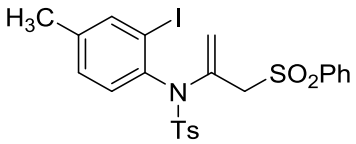
Melting point: 145-146 ˚C

IR (KBr) υ_{max}: 3035, 2922, 1581, 1473, 1365, 1292, 1130, 819, 661

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.68 (m, 4H), 7.27 (m, 4H), 7.20 (d, *J* = 8.4Hz, 1H), 7.14 (d, *J* = 8.0Hz, 1H), 6.09 (s, 1H), 2.43 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 145.2, 143.8, 141.8, 141.4, 139.9, 137.4, 136.2, 131.3, 130.0, 129.9, 129.7, 128.5, 127.0, 117.9, 101.7, 21.8, 21.7, 20.7, 17.3

HRMS calcd for $C_{24}H_{24}INO_4S_2$ (M+H) 582.0270 ; found 582.0271



1db,N-(2-iodo-4-methylphenyl)-4-methyl-N-(3-(phenylsulfonyl)prop-1-en-2-yl) benzenesulfonamide

Colorless oil, 419.29 mg, 74%

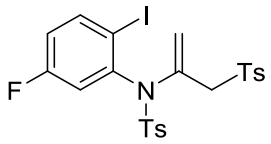
Melting point: 119-121 ˚C

IR (KBr) υ_{max}: 3040, 2922, 1620, 1585, 1440, 1307, 1153, 547

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 4H), 7.65 (d, *J* = 1.2Hz, 1H), 7.60 (t, *J* = 7.6Hz, 1H), 7.45 (t, *J* = 7.6Hz, 2H), 7.31 (d, *J* = 8.0Hz, 2H), 7.16 (d, *J* = 8.0Hz, 1H), 7.12 (d, *J* = 8.0, 1.6Hz, 1H), 5.52 (d, *J* = 1.2Hz, 1H), 5.24 (d, *J* = 1.2Hz, 1H), 3.85 (AB q, *J* = 15.2Hz, 2H), 2.45 (s, 3H), 2.31 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 141.4, 141.1, 138.1, 137.1, 136.2, 133.8, 133.4, 131.9, 130.0, 129.5, 129.0, 128.9, 128.8, 118.4, 101.9, 59.7, 21.7, 20.6

HRMS calcd for $C_{23}H_{22}INO_4S_2$ (M+H) 568.0114 ; found 568.0131



1ea, N-(5-fluoro-2-iodophenyl)-4-methyl-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 415.66 mg, 71%

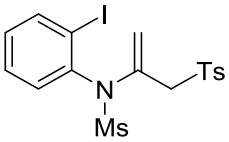
Melting point: 114-115 ˚C

IR (KBr) υ_{max}: 3099, 1589, 1460, 1354, 1292, 1159, 815, 580, 518

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.8, 6.0Hz, 1H), 7.73 (d, *J* = 8.4Hz, 2H), 7.57 (d, *J* = 8.4Hz, 2H), 7.33 (d, *J* = 8.0Hz, 2H), 7.24 (d, *J* = 8.0Hz, 2H), 6.99 (dd, *J* = 8.8, 3.2Hz, 1H), 6.85 (ddd, *J* = 8.8, 7.6, 3.2Hz, 1H), 5.53 (s, *J* = 1.6Hz, 1H), 5.35 (s, *J* = 1.6Hz, 1H), 3.84 (AB q, *J* = 15.6Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d), 144.9 (d), 141.4, 141.3 (d), 135.8, 135.1, 133.4, 129.8, 129.7, 128.9, 128.7, 119.8 (d), 119.3, 118.2 (d), 95.7 (d), 59.9, 21.8, 21.7

HRMS calcd for $C_{23}H_{21}FINO_4S_2$ (M+H) 586.0020 ; found 586.0026



1fa, N-(2-iodophenyl)-N-(3-tosylprop-1-en-2-yl)methanesulfonamide

White solid, 353.77 mg, 72%

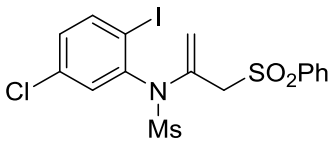
Melting point: 132-134 ˚C

IR (KBr) υ_{max}: 2922, 1629, 1595, 1462, 1334, 1309, 1286, 1147, 765, 516

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0Hz, 1H), 7.76 (d, *J* = 8.0Hz, 2H), 7.61 (d, *J* = 8.0Hz, 1H), 7.44 (t, *J* = 8.0Hz, 1H), 7.34 (d, *J* = 8.4Hz, 2H), 7.09 (t, *J* = 7.6Hz, 1H), 5.83 (s, 1H), 5.11 (s, 1H), 3.66 (AB q, *J* = 15.2Hz, 2H), 3.38 (s, 1H), 2.44 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 141.0, 139.6, 135.4, 132.7, 132.5, 130.8, 130.0, 129.6, 128.5, 116.9, 102.3, 59.7, 41.2, 21.7

HRMS calcd for $C_{17}H_{18}INO_4S_2$ (M+H) 491.9801; found 491.9811



1gb, N-(5-chloro-2-iodophenyl)-N-(3-(phenylsulfonyl)prop-1-en-2-yl)methane sulfonamide

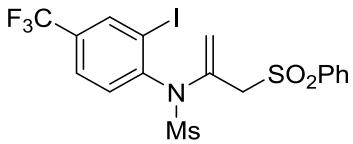
Pale yellow oil, 399.18 mg, 78%

Melting point: IR (KBr) υ_{max}: 2931, 1579, 1469, 1315, 1149, 746, 518

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.86 (m, 3H), 7.67 (t, J = 7.6Hz, 1H), 7.58–7.51 (m, 3H), 7.42-7.39 (m, 1H), 5.84 (s, 1H), 5.16 (s, 1H), 3.68 (AB q, J = 15.2Hz, 2H), 3.37 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.4, 138.3, 136.0, 134.3, 132.9, 132.4, 129.9, 129.5, 128.5, 117.5, 102.5, 59.6, 41.3

HRMS calcd for $C_{16}H_{15}ClINO_4S_2$ (M+H) 511.9255; found 511.9250



1hb, N-(2-iodo-4-(trifluoromethyl)phenyl)-N-(3-(phenylsulfonyl)prop-1-en-2 yl) methanesulfonamide

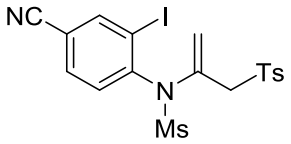
Reddish viscous oil, 370.82 mg, 68%

Melting point: IR (KBr) υ_{max}: 2933, 1600, 1446, 1315, 1126, 524

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.87 (d, J = 7.6Hz, 2H), 7.73–7.64 (m, 3H), 7.56 (t, J = 7.6Hz, 2H), 5.88 (s, 1H), 5.21 (s, 1H), 3.67 (AB q, J = 15.2Hz, 2H), 3.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.3, 137.9 (q), 134.4, 132.5 (q), 129.5, 128.4, 126.6, (q), 123.7, 121.0, 118.0, 102.3, 59.7, 41.5

HRMS calcd for $C_{17}H_{15}F_3INO_4S_2$ (M+H) 545.9518; found 545.9517



1 ia, N-(4-cyano-2-iodophenyl)-N-(3-tosylprop-1-en-2-yl)methanesulfonamide

Yellow solid, 325.31 mg, 63%

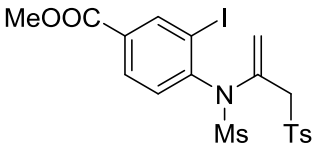
Melting point: 116-117 ˚C

IR (KBr) υ_{max}: 2924, 2233, 1629, 1595, 1469, 1315, 1149, 513

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.73-7.71 (m, 4H), 7.34 (d, J = 8.4Hz, 2H), 5.88 (s, 1H), 5.20 (s, 1H), 3.61 (AB q, J = 15.6Hz, 2H), 3.40 (s, 3H), 2.44 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 144.2, 144.0, 135.3, 133.0, 132.9, 132.1, 130.1, 128.4, 118.1, 116.2, 114.6, 102.6, 59.8, 41.5, 21.8

HRMS calcd for $C_{18}H_{17}IN_2O_4S_2$ (M+H) 516.9753; found 516.9764



1ja, methyl 3-iodo-4-(N-(3-tosylprop-1-en-2-yl)methylsulfonamido)benzoate

Pale yellow solid, 379.08 mg, 69%

Melting point: 132-134 ˚C

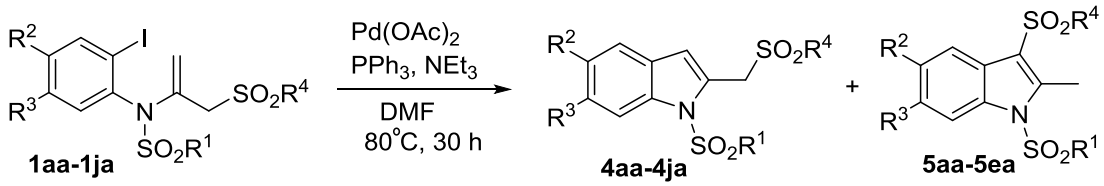
IR (KBr) υ_{max}: 2927, 1639, 1593, 1429, 1340, 1149, 509

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.08 (dt, J = 8.4, 1.6Hz, 1H), 7.74 (d, J = 8.0Hz, 2H), 7.66 (dd, J = 8.4, 1.6Hz, 1H), 7.34 (d, J = 8.0Hz, 2H), 5.88 (s, 1H), 5.20 (s, 1H), 3.94 (s, 3H), 3.65 (AB q, J = 15.6Hz, 2H), 3.41 (s, 3H), 2.44 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 145.4, 143.7, 142.0, 135.4, 132.3, 132.2, 132.1, 130.6, 130.0, 128.4, 117.6, 101.9, 59.7, 52.8, 21.7

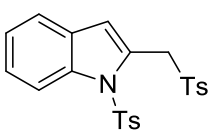
HRMS calcd for $C_{19}H_{20}INO_6S_2$ (M+H) 549.9856; found 549.9858

General procedure for indole synthesis



A mixture of N-vinyl-o-iodosulfonamide **1** (0.4mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and triethylamine (1.2 mmol) in DMF (4 ml) was stirred at 80 ˚C for 30 h. Upon completion of reaction, the reaction mixture was diluted with saturated NH_4Cl and product was extracted with ethyl acetate (3×15 ml). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated at rotavapour under reduced pressure. The residue was subjected to column charomatography on silica gel using petroleum ether-ethyl acetate as eluent to afford analytically pure sample of the product.

Spectroscopic data for products



4aa, 1-tosyl-2-(tosylmethyl)-1H-indole

White solid, 28.13 mg, 16%

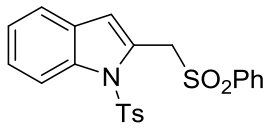
Melting point: 139-140 ˚C

IR (KBr) υ_{max}: 2935, 1593, 1490, 1446, 1367, 1309, 1147, 813, 651

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4Hz, 1H), 7.66 (d, *J* = 8.0Hz, 2H), 7.55 (d, *J* = 8.0Hz, 2H), 7.48 (d, *J* = 7.6Hz, 1H), 7.30–7.20 (m, 4H), 7.14 (d, *J* = 8.4Hz, 2H), 6.89 (s, 1H), 5.03 (s, 2H), 2.42 (s, 3H), 2.29 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 145.1, 137.3, 135.4, 135.1, 129.9, 129.7, 129.2, 128.8, 127.6, 126.5, 125.4, 124.1, 121.3, 116.1, 115.2, 55.1, 21.8, 21.6

HRMS calcd for $C_{23}H_{21}NO_4S_2$ (M+H) 440.0991; found 440.0990



4ab, 2-((phenylsulfonyl)methyl)-1-tosyl-1H-indole

White solid, 27.23 mg, 16%

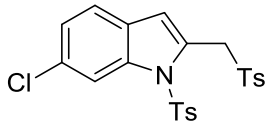
Melting point: 118-119 ˚C

IR (KBr) υ_{max}: 3014, 2947, 1565, 1448, 1361, 1300, 1145, 736, 538

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4Hz, 1H), 7.78 (d, *J* = 8.0Hz, 2H), 7.64 (t, *J* = 7.6Hz, 1H), 7.54 (d, *J* = 8.4Hz, 2H), 7.49–7.45 (m, 3H), 7.30–7.22 (m, 2H), 7.13 (d, *J* = 8.4Hz, 2H), 6.90 (s, 1H), 5.05 (s, 2H), 2.29 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 138.3, 137.3, 135.0, 134.1, 129.9, 129.2, 129.1, 128.8, 127.4, 126.5, 125.5, 124.1, 121.3, 116.3, 115.2, 55.2, 21.6

HRMS calcd for $C_{22}H_{19}NO_4S_2$ (M+H) 426.0834 ; found 426.0838



4ba, 6-chloro-1-tosyl-2-(tosylmethyl)-1H-indole

White solid, 26.54 mg, 14%

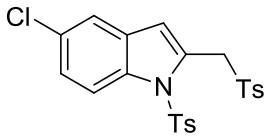
Melting point: 127-129 ˚C

IR (KBr) υ_{max}: 3107, 2924, 1563, 1452, 1369, 1317, 1153, 536

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.6Hz, 1H), 7.65 (d, *J* = 8.4Hz, 2H), 7.56 (d, *J* = 8.4Hz, 2H), 7.40 (d, *J* = 8.4Hz, 1H), 7.28 (d, *J* = 8.0Hz, 2H), 7.22 (dd, *J* = 8.4, 2.0Hz, 1H), 7.18 (d, *J* = 8.0Hz, 2H), 6.88 (s, 1H), 4.99 (s, 2H), 2.44 (s, 3H), 2.32 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 145.3, 137.6, 135.3, 134.9, 131.5, 130.0, 129.8, 128.7, 128.3, 127.6, 126.5, 124.8, 122.0, 115.4, 115.3, 55.0, 21.8, 21.6

HRMS calcd for $C_{23}H_{20}ClNO_4S_2$ (M+H) 474.0601; found 474.0610



4ca, 5-chloro-1-tosyl-2-(tosylmethyl)-1H-indole

White solid, 24.65 mg, 13%

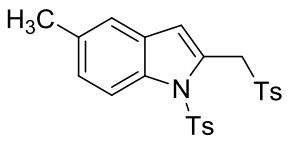
Melting point: 135-136 ˚C

IR (KBr) υ_{max}: 2922, 1595, 1442, 1371, 1317, 1155, 715, 536

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8Hz, 1H), 7.65 (d, *J* = 8.4Hz, 2H), 7.53 (d, *J* = 8.0HZ, 2H), 7.44 (d, *J* = 2.0Hz, 1H), 7.27 (d, *J* = 8.0Hz, 2H), 7.23 (dd, *J* = 8.8, 2.0HZ, 1H), 7.15 (d, *J* = 8.4Hz, 2H), 6.81 (s, 1H), 5.00 (s, 2H), 2.42 (s, 3H), 2.30 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 145.3, 135.6, 135.3, 134.9, 130.3, 130.0, 129.9, 129.8, 129.2, 128.8, 126.5, 125.7, 120.8, 116.2, 115.1, 55.0, 21.8, 21.6

HRMS calcd for $C_{23}H_{20}ClNO_4S_2$ (M+H) 474.0601; found 474.0616



4da, 5-methyl-1-tosyl-2-(tosylmethyl)-1H-indole

White solid, 23.58 mg, 13%

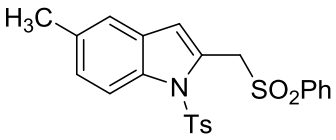
Melting point: 120-122 ˚C

IR (KBr) υ_{max}: 3035, 2922, 1581, 1435, 1365, 1292, 1130, 661

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4Hz, 1H), 7.66 (d, J = 8.0Hz, 2H), 7.53 (d, J = 8.0Hz, 2H), 7.27 (d, J = 8.0Hz, 2H), 7.14–7.09 (m, 3H), 6.83 (s, 3H), 5.02 (s, 2H), 2.43(s, 3H), 2.39 (s, 3H), 2.30 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 135.6, 135.4, 135.1, 133.8, 129.8, 129.7, 129.4, 128.8, 127.6, 126.9, 126.5, 121.1, 116.0, 114.9, 55.2, 21.8, 21.6, 21.2

HRMS calcd for $C_{24}H_{23}NO_4S_2$ (M+H) 454.1147 ; found 454.1149



4db, 5-methyl-2-((phenylsulfonyl)methyl)-1-tosyl-1H-indole

White solid, 26.37 mg, 15%

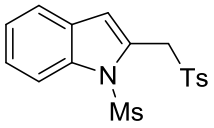
Melting point: 117-118 ˚C

IR (KBr) υ_{max}: 3010, 2941, 1585, 1450, 1359, 1298, 1170, 738, 578

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.8Hz, 1H), 7.77 (dd, J = 8.4, 1.2Hz, 2H), 7.66-7.11 (m, 1H), 7.52–7.45 (m, 4H), 7.25 (s, 1H), 7.13-7.09 (m, 3H), 6.83 (s, 1H), 5.03 (s, 2H), 2.38 (s, 3H), 2.29 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 138.2, 135.6, 135.0, 134.0, 133.8, 129.8, 129.4, 129.0, 128.9, 127.4, 127.0, 126.4, 121.1, 116.2, 114.9, 55.2, 21.6, 21.1

HRMS calcd for $C_{23}H_{21}NO_4S_2$ (M+H) 440.0991; found 440.1004



4fa, 1-(methylsulfonyl)-2-(tosylmethyl)-1H-indole

White solid, 107.58 mg, 74%

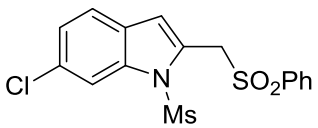
Melting point:

IR (KBr) υ_{max}: 3014, 2926, 1565, 1446, 1355, 1309, 1151, 536

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4Hz, 1H), 7.79 (d, J = 8.0Hz, 2H), 7.56 (d, J = 7.6Hz, 1H), 7.37–7.34 (m, 3H), 7.30 (d, J = 7.6Hz, 1H), 6.65 (s, 1H), 4.97 (s, 2H), 3.42 (s, 3H), 2.46 (, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 147.0, 135.9, 130.0, 128.5, 126.7, 125.6, 123.8, 121.5, 114.4, 114.0, 54.8, 41.2, 21.8

HRMS calcd for $C_{17}H_{17}NO_4S_2$ (M+H) 364.0678; found 364.0681



4gb, 6-chloro-1-(methylsulfonyl)-2-((phenylsulfonyl)methyl)-1H-indole

White solid, 112.09 mg, 73%

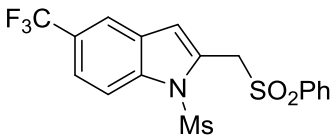
Melting point: 186-187 ˚C

IR (KBr) υ_{max}: 2953, 1583, 1444, 1361, 1309, 1161, 543

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6Hz, 2H), 7.87 (d, J = 8.8Hz, 1H), 7.70 (t, J = 7.6Hz, 1H), 7.59 (t, J = 7.6Hz, 2H), 7.53 (s, 1H), 7.34 (dd, J = 7.2, 1.6Hz, 1H), 6.58 (s, 1H), 4.98 (s, 2H), 3.43 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.3, 134.4, 129.7, 129.6, 129.5, 128.5, 127.9, 125.9, 121.0, 115.1, 113.7, 54.6, 41.5

HRMS calcd for $C_{16}H_{14}ClNO_4S_2$ (M+H) 384.0132; found 384.0149



4hb, 1-(methylsulfonyl)-2-((phenylsulfonyl)methyl)-5-(trifluoromethyl)-1H-indole

White solid, 101.85 mg, 61%

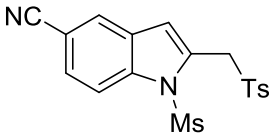
Melting point: 204-205 ˚C

IR (KBr) υ_{max}: 3008, 2953, 1620, 1448, 1356, 1313, 1159, 542

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8Hz, 1H), 7.93 (d, J = 8.4Hz, 2H), 7.86 (d, J = 0.8Hz, 1H), 7.73–7.69 (m, 1H), 7.63-7.58 (m, 3H), 6.71 (s, 1H), 5.02 (s, 2H), 3.49 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.4, 134.4, 129.5, 128.6, 128.5, 128.1, 126.2 (q), 123.0, 122.3(q), 119.0(q), 114.5, 114.2, 54.6, 41.8

HRMS calcd for $C_{17}H_{14}F_3NO_4S_2$ (M+H) 418.0395; found 418.0415



4ia, 1-(methylsulfonyl)-2-(tosylmethyl)-1H-indole-5-carbonitrile

White solid, 90.12 mg, 58%

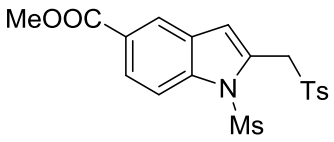
Melting point: 180-181 ˚C

IR (KBr) υ_{max}: 3020, 2926, 2223, 1595, 1456, 1363, 1303, 1138, 509

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4Hz, 1H), 7.91 (d, J = 1.6Hz, 1H), 7.80 (d, J = 8.0Hz, 2H), 7.63 (dd, J = 8.4, 1.6Hz, 1H), 7.39 (d, J = 8.0Hz, 2H), 6.69 (s, 1H), 4.98 (s, 2H), 3.53 (s, 3H), 2.48 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 138.6, 135.5, 130.2, 129.4, 128.5, 128.4, 128.3, 126.3, 119.0, 115.0, 113.5, 107.6, 54.6, 42.0, 21.8

HRMS calcd for $C_{18}H_{16}N_2O_4S_2$ (M+H) 389.0630; found 389.0631



4ja, methyl 1-(methylsulfonyl)-2-(tosylmethyl)-1H-indole-5-carboxylate

White solid, 106.21 mg, 63%

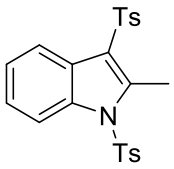
Melting point: 178-179 ˚C

IR (KBr) υ_{max}: 3014, 2958, 1716, 1606, 1438, 1354, 1136, 538

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.08 (d, J = 8.8Hz, 1H), 7.99 (d, J = 8.8Hz, 1H), 7.80 (d, J = 7.6Hz, 2H), 7.39 (d, J = 7.6Hz, 2H), 6.68 (s, 1H), 4.99 (s, 2H), 3.95 (s, 3H), 3.51 (s, 3H), 2.48 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 145.5, 139.4, 135.6, 130.1, 128.5, 128.3, 128.2, 126.6, 125.9, 123.7, 114.5, 113.8, 54.7, 52.3, 41.7, 21.8

HRMS calcd for $C_{19}H_{19}NO_6S_2$ (M+H) 422.0733; found 422.0749



5aa, 2-methyl-1,3-ditosyl-1H-indole

White solid, 112.52 mg, 64%

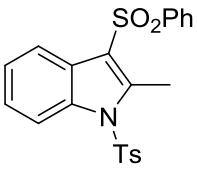
Melting point: 176-178 ˚C

IR (KBr) υ_{max}: 2922, 1593, 1543, 1442, 1371, 1153, 715, 534

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.19 (m, 1H), 8.11-8.09 (m, 1H), 7.80 (d, *J* = 8.0Hz, 2H), 7.69 m(d, *J* = 8.4Hz, 2H), 7.34-7.31 (m, 2H), 7.25 (d, *J* = 8.0Hz, 4H), 2.97 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 144.2, 142.3, 139.8, 135.6, 135.4, 130.3, 129.9, 126.7, 126.5, 125.5, 125.4, 124.8, 120.4, 119.9, 114.4, 21.7, 21.6, 13.1

HRMS calcd for $C_{23}H_{21}NO_4S_2$ (M+H) 440.0991 ; found 440.1000



5ab, 2-methyl-3-(phenylsulfonyl)-1-tosyl-1H-indole

White solid, 105.53 mg, 62%

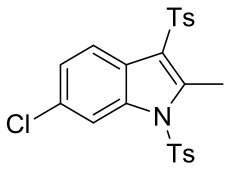
Melting point: 164-165 ˚C

IR (KBr) υ_{max}: 3057, 1544, 1442, 1373, 1313, 1182, 700, 542

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8Hz, 1H), 8.11 (d, *J* = 8.8Hz, 1H), 7.92 (d, *J* = 7.6Hz, 2H), 7.69 (d, *J* = 8.0Hz, 2H), 7.54 (t, *J* = 7.2Hz, 1H), 7.47 (t, *J* = 7.6Hz, 1H), 7.37–7.31 (m, 2H), 7.26 (d, *J* = 7.6Hz, 2H), 2.98 (s, 3H), 2.38 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 142.7, 142.6, 135.6, 135.4, 133.2, 130.4, 129.3, 126.7, 126.4, 125.6, 125.4, 124.9, 120.4, 119.5, 114.5, 21.7, 13.1

HRMS calcd for $C_{22}H_{19}NO_4S_2$ (M+H) 426.0834; found 426.0838



5ba, 6-chloro-2-methyl-1,3-ditosyl-1H-indole

White solid, 130.82 mg, 69%

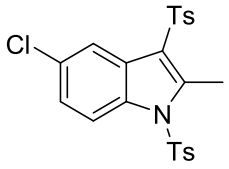
Melting point: 194-196 ˚C

IR (KBr) υ_{max}: 2922, 1544, 1417, 1373, 1311, 1151, 761, 535

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 1.6Hz, 1H), 8.02 (d, J = 8.8Hz, 1H), 7.77 (d, J = 8.4Hz, 2H), 7.68 (d, J = 8.4Hz, 2H), 7.31–7.24 (m, 5H), 2.92 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 144.4, 142.8, 139.5, 135.9, 135.1, 131.7, 130.5, 130.0, 126.7, 126.5, 125.5, 124.0, 121.2, 119.8, 114.6, 21.8, 21.6, 13.1

HRMS calcd for $C_{23}H_{20}ClNO_4S_2$ (M+H) 474.0601; found 474.0608



5ca, 5-chloro-2-methyl-1,3-ditosyl-1H-indole

White solid, 128.92 mg, 68%

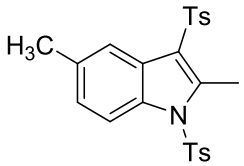
Melting point: 188-189 ˚C

IR (KBr) υ_{max}: 2924, 1541, 1436, 1373, 1315, 1149, 759, 532

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8Hz, 1H), 8.11 (d, J = 2.0Hz, 1H), 7.78 (d, J = 8.4Hz, 2H), 7.66 (d, J = 8.4Hz, 2H), 7.31–7.25 (m, 5H), 2.93 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 144.5, 143.5, 139.5, 135.1, 134.0, 130.8, 130.4, 130.0, 126.7, 126.5, 125.8, 120.0, 119.5, 115.5, 21.7, 21.6, 13.2

HRMS calcd for $C_{23}H_{20}ClNO_4S_2$ (M+H) 474.0601; found 474.0617



5da, 2,5-dimethyl-1,3-ditosyl-1H-indole

White solid, 130.62 mg, 72%

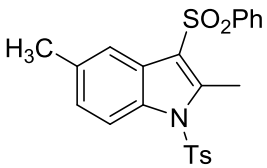
Melting point: 191-193 ˚C

IR (KBr) υ_{max}: 2924, 1591, 1544, 1456, 1369, 1315, 1145, 677, 534

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8Hz, 1H), 7.89 (d, J = 1.6Hz, 1H), 7.79 (d, J = 8.4Hz, 2H), 7.66 (d, J = 8.4Hz, 2H), 7.25–7.22 (m, 4H), 7.15 (dd, J = 8.8, 1.6Hz, 1H), 2.94 (s, 3H), 2.43 (s, 3H), 2.36 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 144.1, 142.3, 139.8, 135.4, 134.6, 133.8, 130.3, 129.9, 126.9, 126.6, 126.4, 125.6, 120.1, 119.6, 114.1, 21.7, 21.6, 21.5, 13.1

HRMS calcd for $C_{24}H_{23}NO_4S_2$ (M+H) 454.1147; found 454.1147



5db, 2,5-dimethyl-3-(phenylsulfonyl)-1-tosyl-1H-indole

White solid, 121.31 mg, 69%

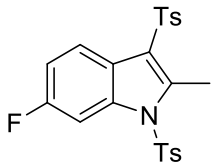
Melting point: 172-173 ˚C

IR (KBr) υ_{max}: 2924, 1593, 1544, 1444, 1373, 1313, 1147, 678, 538

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4Hz, 1H), 7.92-7.89 (m, 3H), 7.67 (d, J = 8.4Hz, 2H), 7.55-7.51 (m, 1H), 7.48–7.44 (m, 2H), 7.24 (d, J = 8.0Hz, 2H), 7.16 (dd, J = 8.8, 1.6Hz, 1H), 2.94 (s, 3H), 2.43 (s, 3H), 2.37 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 142.7, 142.6, 135.4, 134.7, 133.8, 133.2, 130.3, 129.2, 127.0, 126.6, 126.4, 125.6, 120.1, 119.2, 114.1, 21.7, 21.5, 13.1

HRMS calcd for $C_{23}H_{21}NO_4S_2$ (M+H) 440.0991; found 440.1005



5ea, 6-fluoro-2-methyl-1,3-ditosyl-1H-indole

White solid, 111.64 mg, 61%

Melting point: 187-188 ˚C

IR (KBr) υ_{max}: 2922, 1591, 1546, 1483, 1373, 1317, 1149, 806, 532

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.8, 5.6Hz, 1H), 7.96 (dd, J = 10.4, 2.0Hz, 1H), 7.78 (d, J = 8.0Hz, 2H), 7.69 (d, J = 8.0Hz, 2H), 7.27 (t, J = 8.4Hz, 4H), 7.09 (td, J = 8.8, 2.0Hz, 1H), 2.93 (s, 3H), 2.39 (s, 3H). 2.36 (s, 3H)

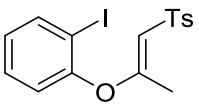
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (d), 146.4, 144.4, 142.6 (d), 139.6, 135.8 (d), 135.1, 130.5, 130.0, 126.7, 126.5, 121.7, 121.4 (d), 119.7, 113.2 (d), 102.0 (d), 21.7, 21.6, 13.1

HRMS calcd for $C_{23}H_{20}FNO_4S_2$ (M+H) 458.0897; found 458.0921

Synthesis of 1-iodo-2-vinyloxy benzene derivative 6

To a solution of the 2-iodophenol (1.0 mmol) and 2-bromoallyl sulfone **3** (1.5 mmol) in acetonitrile (10 mL) cesium carbonate (2.5 mmol) was added at room temperature and stirred the mixture for 4 hours. After completion of reaction, solvent was removed on a rotavapor and deionized water (20 mL) was added. The solution was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate and concentrated on a rotavapor. Column chromatography of the residue on silica gel using petroleum ether-ethyl acetate as eluent afforded analytically pure products.

Spectroscopic data



6a, (E)-1-iodo-2-((1-tosylprop-1-en-2-yl)oxy)benzene

White solid, 265.12 mg, 64%

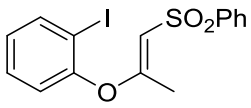
Melting point: 136-137 ˚C

IR (KBr) υ_{max}: 3068, 1627, 1462, 1284, 1130, 757

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4Hz, 2H), 7.76 (dd, J = 8.0, 1.6Hz, 1H), 7.30–7.25 (m, 3H), 6.92–6.88 (m, 1H), 6.85 (dd, J = 8.0, 1.2Hz, 1H), 5.95 (d, J = 0.8Hz, 1H), 2.39 (s, 3H), 1.75 (d, J = 0.8Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 153.5, 143.8, 139.8, 139.5, 129.8, 129.4, 128.3, 127.1, 121.0, 113.7, 89.4, 21.6, 19.1

HRMS calcd for $C_{16}H_{15}IO_3S$ (M+H) 414.9866; found 414.9887



6b, (E)-1-iodo-2-((1-(phenylsulfonyl)prop-1-en-2-yl)oxy)benzene

White solid, 268.15 mg, 67%

Melting point: 122-123 ˚C

IR (KBr) υ_{max}: 3070, 2924, 1627, 1458, 1436, 1286, 1126, 752, 567

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6Hz, 2H), 7.76 (d, *J* = 8.0Hz, 1H), 7.57–7.54 (m, 1H), 7.48 (t, *J* = 7.2Hz, 2H), 7.29 (t, *J* = 7.6Hz, 1H), 6.92 (t, *J* = 7.6Hz, 1H), 6.84 (d, *J* = 8.0Hz, 1H), 5.96 (s, 1H), 1.77 (s, 3H)

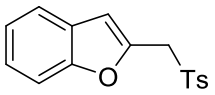
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 153.4, 142.4, 139.8, 132.9, 129.8, 128.8, 128.3, 127.3, 121.2, 113.0, 89.5, 19.2

HRMS calcd for $C_{15}H_{13}IO_3S$ (M+H) 400.9709; found 400.9711

Procedure for synthesis of benzofuran derivatives

A mixture of 1-iodo-2-vinyloxy benzene **6** (0.4mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and triethylamine (1.2 mmol) in DMF (4 ml) was stirred at 80 ˚C for 30 h. Upon completion of reaction, the reaction mixture was diluted with saturated NH_4Cl and product was extracted with ethyl acetate (3×15 ml). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated at rotavapour under reduced pressure. The residue was subjected to column charomatography on silica gel using petroleum ether-ethyl acetate as eluent to afford analytically pure sample of the product.

Spectroscopic data



7a, 2-(tosylmethyl)benzofuran

White solid, 72.16 mg, 63%

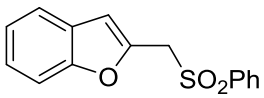
Melting point: 196-197 ˚C

IR (KBr) υ_{max}: 2987, 1591, 1448, 1303, 1286, 1145, 719, 520

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4Hz, 2H), 7.53–7.51 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.27 (m, 3H), 7.22 (td, J = 7.6, 1.2Hz, 1H), 6.67 (d, J = 0.8Hz, 1H), 4.53 (s, 2H), 2.43 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 145.3, 145.2, 135.3, 129.8, 128.6, 128.0, 125.0, 123.1, 121.3, 111.3, 108.9, 56.5, 21.7

HRMS calcd for $C_{16}H_{14}O_3S$ (M+H) 287.0743; found 287.0746



7b, 2-((phenylsulfonyl)methyl)benzofuran

White solid, 69.71 mg, 64%

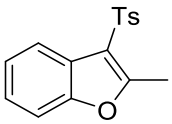
Melting point: 162-163 ˚C

IR (KBr) υ_{max}: 2880, 1581, 1448, 1305, 1141, 735, 569

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0Hz, 2H), 7.63 (t, J = 7.6Hz, 1H), 7.52–7.45 (m, 3H), 7.33 (d, J = 8.0Hz, 1H), 7.24–7.19 (m, 2H), 6.63 (s, 2H), 4.54 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 145.1, 138.2, 134.1, 129.2, 128.6, 127.9, 125.0, 123.2, 121.3, 111.3, 109.0, 56.5

HRMS calcd for $C_{15}H_{12}O_3S$ (M+H) 273.0586; found 273.0589



8a, 2-methyl-3-tosylbenzofuran

White solid, 18.32 mg, 16%

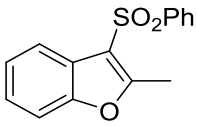
Melting point: 122-123 ˚C

IR (KBr) υ_{max}: 2922, 1583, 1446, 1296, 1143, 758, 580

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 3H), 7.42-7.39 (m, 1H), 7.31–7.28 (m, 4H), 2.80 (s, 3H), 2.38 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 153.2, 144.3, 139.7, 129.9, 126.7, 125.2, 124.4, 124.3, 120.3, 118.2, 111.2, 21.6, 13.6

HRMS calcd for $C_{16}H_{14}O_3S$ (M+H) 287.0743; found 287.0740



8b, 2-methyl-3-(phenylsulfonyl)benzofuran

White solid, 17.42 mg, 16%

Melting point: 106-107 ˚C

IR (KBr) υ_{max}: 3064, 2920, 1577, 1444, 1309, 1149, 750, 545

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4Hz, 2H), 7.88–7.86 (m, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.6 HZ, 2H), 7.42–7.39 (m, 1H), 7.31–7.28 (m, 2H), 2.80 (s, 3H)

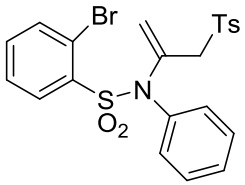
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 153.3, 142.5, 133.3, 129.3, 126.7, 125.3, 124.5, 124.4, 120.3, 117.9, 111.3, 13.7

HRMS calcd for $C_{15}H_{12}O_3S$ (M+H) 273.0586; found 273.0589

Procedure for synthesis 2-bromo-N-vinyl benzenesulfonamide 10

To a solution of the 2-bromobenzenesulfonamide **9** (1.0 mmol) and 2-bromoallyl sulfone **3** (1.5 mmol) in acetonitrile (10 mL) cesium carbonate (2.5 mmol) was added at room temperature and stirred the mixture for 4 hours. After completion of reaction, solvent was removed on a rotavapor and deionized water (20 mL) was added. The solution was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate and concentrated on a rotavapor. Column chromatography of the residue on silica gel using petroleum ether-ethyl acetate as eluent afforded analytically pure products.

Spectroscopic data



10aa, 2-bromo-N-phenyl-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 349.43 mg, 69%

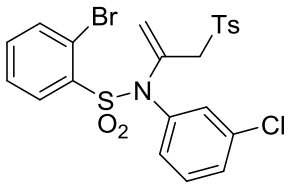
Melting point: 144-145 ˚C

IR (KBr) υ_{max}: 3062, 2924, 1593, 1489, 1448, 1317, 1149, 689, 513

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.2, 2.4Hz, 1H), 7.70 (dd, J = 7.6, 1.6Hz, 1H), 7.58 (d, J = 8.4Hz, 2H), 7.37–7.33 (m, 2H), 7.23–7.19 (m, 7H), 5.38 (s, 1H), 5.37 (s, 1H), 4.06 (s, 2H), 2.41 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 138.0, 137.9, 135.8, 135.4, 135.1, 134.3, 133.4, 130.0, 129.9, 129.8, 129.6, 129.2, 128.6, 128.5, 127.5, 121.0, 120.0, 60.5, 21.7

HRMS calcd for $C_{22}H_{20}BrNO_4S_2$ (M+H) 506.0095; found 506.0093



10ba, 2-bromo-N-(3-chlorophenyl)-N-(3-tosylprop-1-en-2-yl)benzenesulfonamide

White solid, 384.01 mg, 71%

Melting point: 151-152 ˚C

IR (KBr) υ_{max}: 3089, 2924, 1585, 1471, 1317, 1083, 684. 514

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 6.8, 2.4Hz, 1H), 7.73 (d, J = 6.8Hz, 1H), 7.58 (d, J = 8.0Hz, 2H), 7.40 (t, J = 4.4Hz, 2H), 7.26–7.23 (m, 3H), 7.17–7.13 (m, 3H), 5.50 (s, 1H), 5.35 (s, 1H), 4.08 (s, 2H), 2.43 (s, 3H)

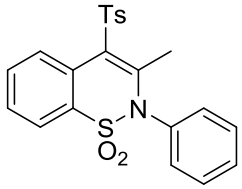
^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 139.1, 137.5, 135.9, 135.2, 134.9, 134.6, 134.5, 133.4, 130.0, 129.8, 129.3, 128.6, 128.4, 127.63, 127.61, 121.6, 120.9, 60.5, 21.8

HRMS calcd for $C_{22}H_{19}BrClNO_4S_2$ (M+H) 539.9706; found 539.9700

Procedure for synthesis of benzosultam derivative 11

A mixture of 2-bromo-N-vinylbenzenesulfonamide **10** (0.4mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and triethylamine (1.2 mmol) in DMF (4 ml) was stirred at 80 ˚C for 30 h. Upon completion of reaction, the reaction mixture was diluted with saturated NH_4Cl and product was extracted with ethyl acetate (3×15 ml). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated at rotavapour under reduced pressure. The residue was subjected to column charomatography on silica gel using petroleum ether-ethyl acetate as eluent to afford analytically pure sample of the product.

Spectroscopic data



11aa, 3-methyl-2-phenyl-4-tosyl-2H-benzo[e][1,2]thiazine 1,1-dioxide

White solid, 97.01 mg, 57%

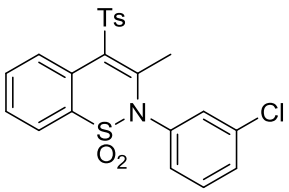
Melting point: 168-169 ˚C

IR (KBr) υ_{max}: 3064, 2924, 1570, 1541, 1492, 1346, 1282, 1139, 1083, 665. 565

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.4Hz, 1H), 7.74 (d, J = 8.0Hz, 3H), 7.59 (t, J = 4.0Hz, 1H), 7.47 (d, J = 7.6Hz, 1H), 7.44–7.39 (m, 3H), 7.24 (d, J = 8.0Hz, 2H), 7.14–7.12 (m, 2H), 2.41 (s, 3H), 2.35 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 144.2, 139.0, 134.9, 132.3, 132.2, 129.8, 129.7, 129.6, 128.8, 128.3, 127.6, 126.9, 123.1, 122.0, 21.6, 20.7

HRMS calcd for $C_{22}H_{19}NO_4S_2$ (M+H) 426.0834; found 426.0833



11ba, 2-(3-chlorophenyl)-3-methyl-4-tosyl-2H-benzo[e][1,2]thiazine 1,1-dioxide

White solid, 108.55 mg, 59%

Melting point: 184-185 ˚C

IR (KBr) υ_{max}: 2960, 1571, 1546, 1469, 1357, 1284, 1143, 1083, 671. 565

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.4Hz, 1H), 7.72 (d, J = 8.4Hz, 3H), 7.61–7.57 (m, 1H), 7.46 (td, J = 8.0, 0.8Hz, 1H), 7.38 (dt, J = 8.0, 1.6Hz, 1H), 7.32 (t, J = 8.0Hz, 1H), 7.23 (d, J = 8.0Hz, 2H), 7.11 (t, J = 2.0Hz, 1H), 7.05–7.02 (m, 1H), 2.41 (s, 3H), 2.34 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 144.3, 138.7, 135.9, 135.3, 132.4, 130.5, 129.8, 129.7, 129.4, 128.8, 128.6, 127.8, 127.0, 124.0, 122.1, 21.6, 20.7

HRMS calcd for $C_{22}H_{18}ClNO_4S_2$ (M+H) 460.0444; found 460.0436

4.7. References

1. (a) Ishikura, M.; Yamada, K. *Nat. Prod. Rep*. **2009**, *26*, 803. (b) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620. (c) Andreani, A.; Rambaldi, M. *J. Hetrocyclic. Chem.* **1988**, *25*, 1519.

2. (a) Crooke, S. T.; Bradner, W. T. *Cancer Treatment Reviews* **1976**, *3*, 121. (b) Berger, M.; Gray, J. A.; Roth, B. L. *Annu. Rev. Med*. **2009**. *60*, 355. (c) Chen, F.-E.; Huang, J. *Chem. Rev*. **2005**, *105*, 4671.

3. Gul, W.; Hamann, M. T. *Life Sciences* **2005**, *78*, 442.

4. Blobaum, A. L.; Uddin, M. J.; Felts, A. S.; Crews, B. C.; Rouzer, C. A.; Marnett, L. J. *ACS Medicinal Chemistry Letters* **2013**, *4*, *5*, 486.

5. Tran, J. Q.; Gerber, J. G.; Kerr, B. M. *Clin Pharmacokinet* **2001**, *40*, 207.

6. Plosker, G. L.; McTavish, D. *Drugs* **1994**, *47*, 622.

7. (a) Hughes, D. L.; *Org. Prep. Proced. Int.* **1993**, *25*, 607. (b) Robinson, B.; *Chem. Rev.* **1963**, *63*, 373.

8. (a) Gribble, G. W.; *J. Chem. Soc. Perkin. Trans*. **2000**, *1*, 1045. (b) Taber, B. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195.

9. (a) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980,** *45*, 2938. (b) Edmonson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000,** *2*, 1109. (c) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011. (d) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676. (e) Gao, D.; Parvez, M.; Back, T. G. *Chem. Eur. J*. **2010**, *16*, 14281. (f) Nguyen, H. H.; Kurth, M. J. *Org. Lett*. **2013**, *15*, 362.

10. (a) Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem*. **1997**, *62*, 1804. (b) Yun, W.; Mohan, R. *Tetrahedron Lett*. **1996**, *37*, 7189.

11. Brown, D.; Gribb, R.; Sridharan, V.; Tambyrajah, V.; Thornton-Pett, M. *Tetrahedron* **1998**, *54*, 2595.

12. Wu, M.; Yan. R. *Synlett* **2017**, *28*, 729.

13. Nallagonda, R.; Rehan, M.; Ghorai, P. *Org. Lett.* **2014,** *16*, 4786.

14. Yadav D.; Meon, R.S. *Org. Biomol. Chem.* **2020**, *18*, 365.

15. Kumar, A.; Thadkapally, S.; Menon, R. S. *J. Org. Chem*. **2015**, *80*, 11048.

16. (a) Hirata, T.; Sasada, Y.; Ohtani, T.; .Asada, T.; Kinoshita, H.; Senda, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 75. (b) Inomata, K.; Hirata, T.; Suhara, H.; Kinoshita, H.; Kotake, H.; Senda, H. *Chem. Lett.* **1988**, 2009.

17. Undeela, S.; Thadkapally, S.; Nanubolu, J. B.; Singarapu, K. K.; Menon, R. S. *Chem. Commun.* **2015**, *51*, 13748.

18. Undeela, S.; Ravikumar, G.; Nanubolu, J. B.; Singarapu, K. K.; Menon, R. S. *Chem. Commun.* **2016**, *52*, 4824.

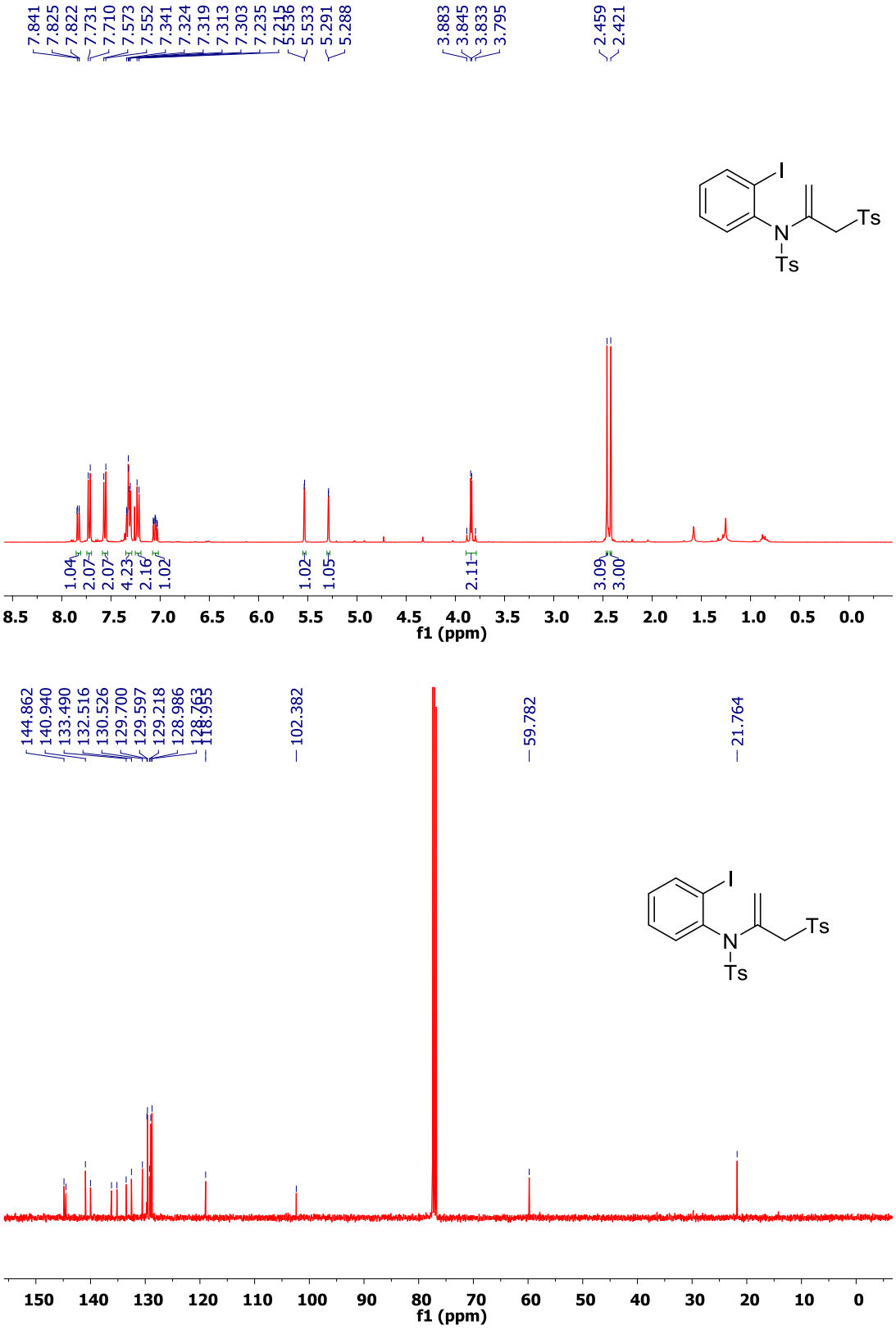
19. Thadkapally, S.; Kunjachan, A. C.; Menon, R. S. *Beilstein J. Org. Chem.* **2016,** *12*, 16.

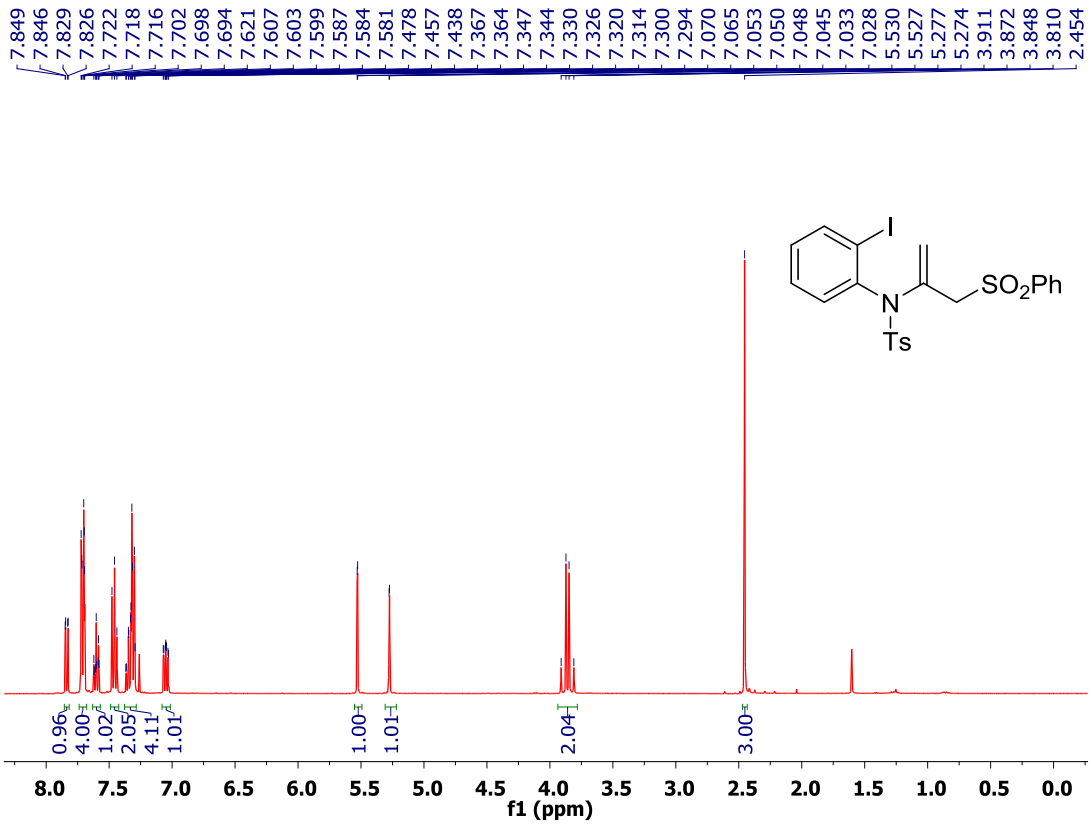
20. Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447.

21. (a) Miao, Yu-H.; Hu, Yu-H,; Yang, J.; Liu, T.; Sun, J.; Wang, X-J. *RSC Adv.* **2019**, *9*, 27510. (b) Khanam, H.; Shamsuzzaman. *Eur. J. of Med.Chem.***2015**, *97*, 483.

22. S. Debnath, S. Mondal, S. *J. Org. Chem*. **2015**, *80*, 3940.

4.8. NMR spectra of new compounds [^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$)]

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7.607
7.603
7.599
7.587
7.584
7.581
7.478
7.457
7.438
7.367
7.364
7.347
7.344
7.330
7.326
7.320
7.314
7.300
7.294
7.070
7.065
7.053
7.050
7.048
7.045
7.033
7.028
5.530
5.527
5.277
5.274
3.911
3.872
3.848
3.810
2.454
I
SO2Ph
N
Ts
0.96
4.00
1.02
2.05
4.11
1.01
1.00
1.01
2.04
3.00
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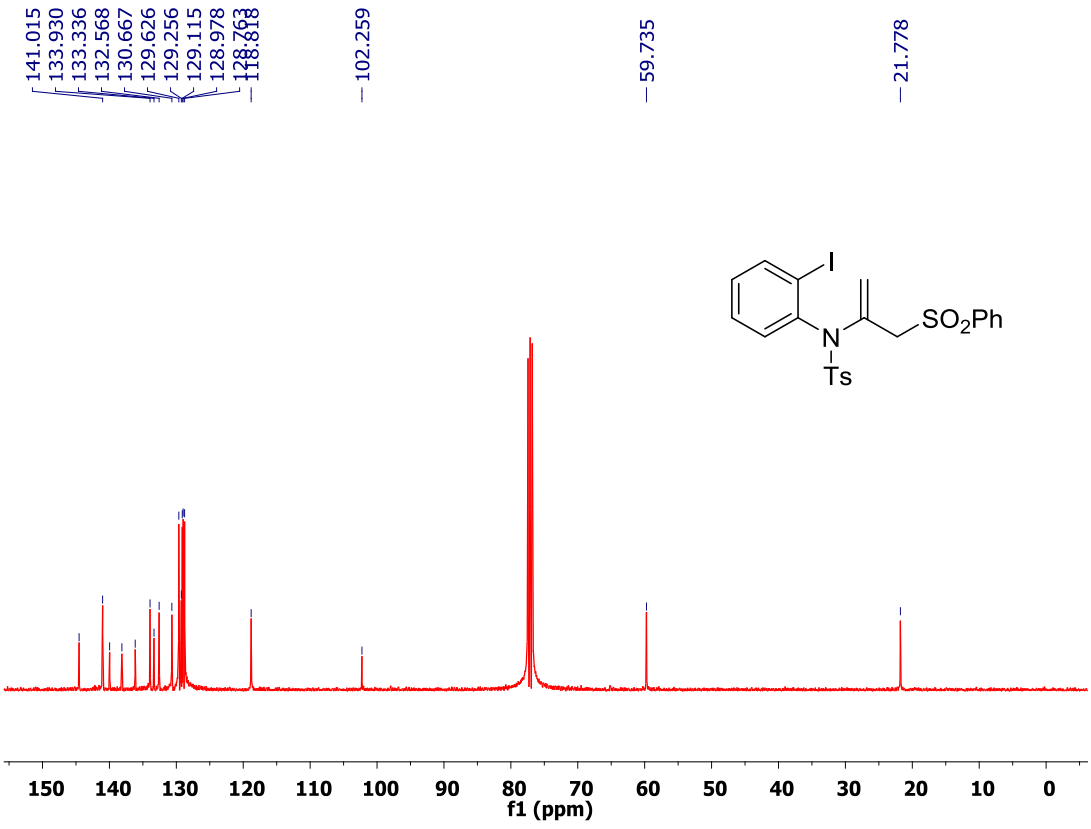
f1 (ppm)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133.930
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21.778
I
SO2Ph
N
Ts
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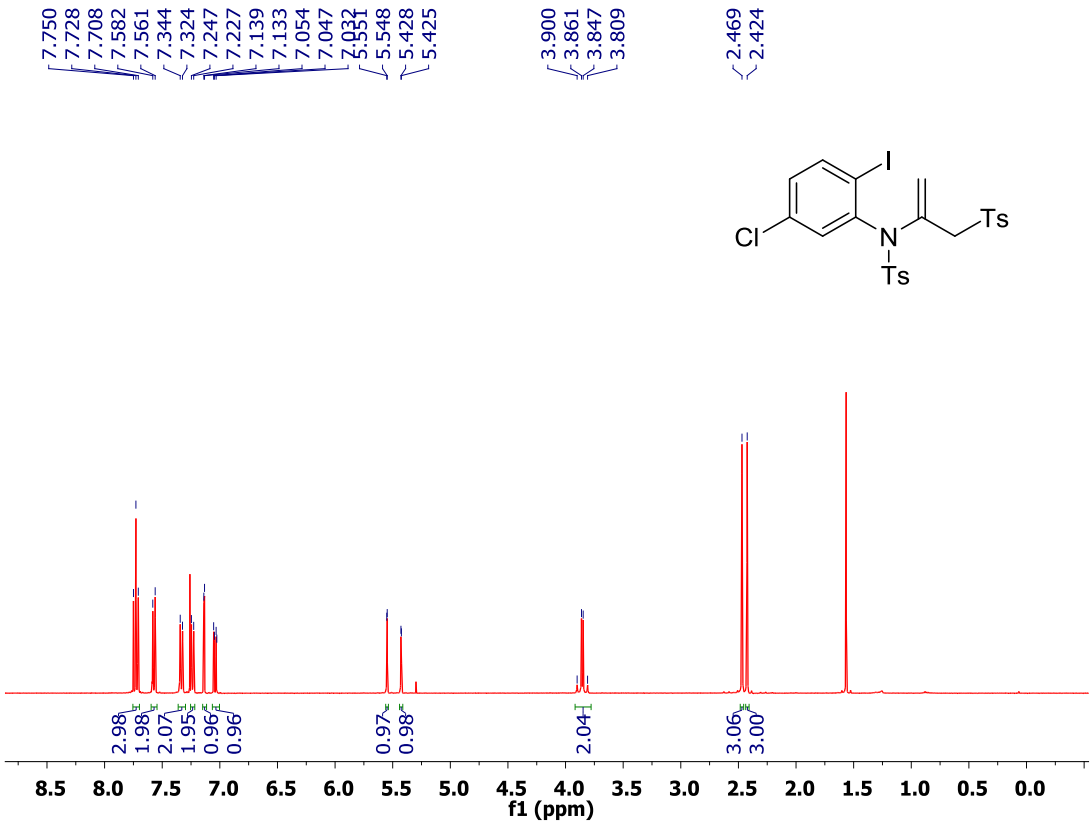
f1 (ppm)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7.708
7.582
7.561
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7.324
7.247
7.227
7.139
7.133
7.054
7.047
5.548
5.428
5.425
3.900
3.861
3.847
3.809
2.469
2.424
I
Cl
N
Ts
Ts
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1.98
2.07
1.95
0.96
0.96
0.97
0.98
2.04
3.06
3.00
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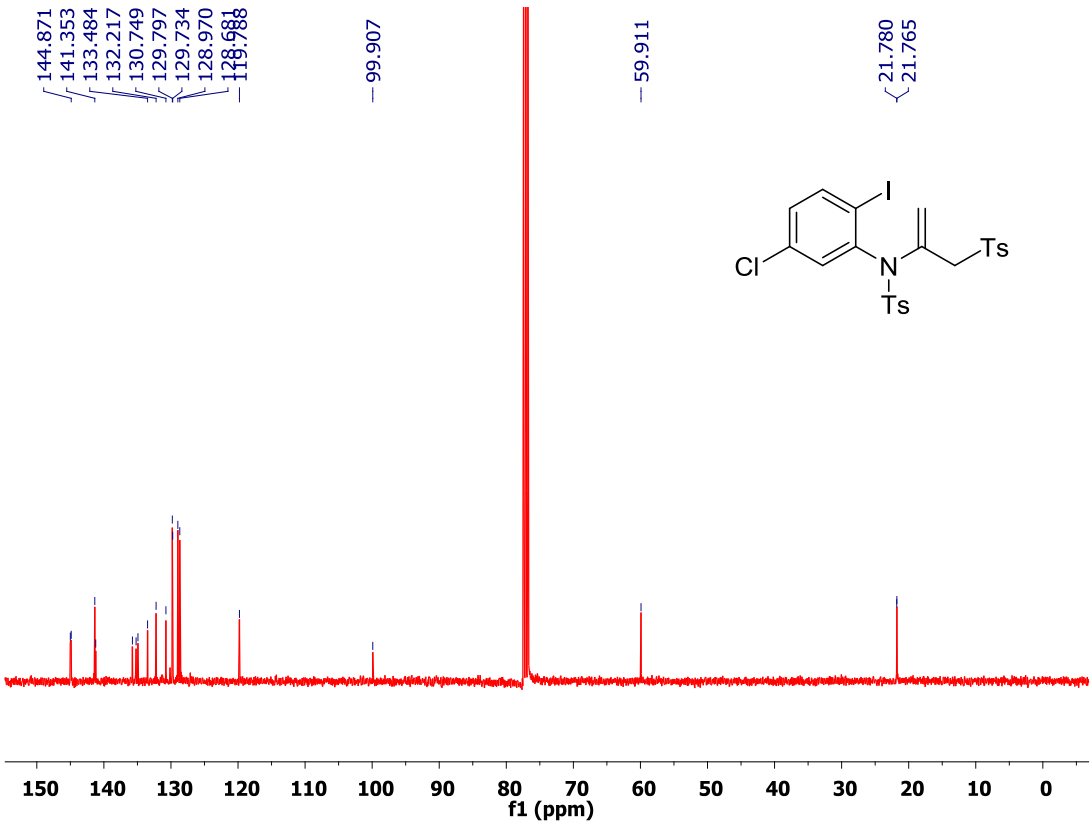
f1 (ppm)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Cl
N
Ts
Ts
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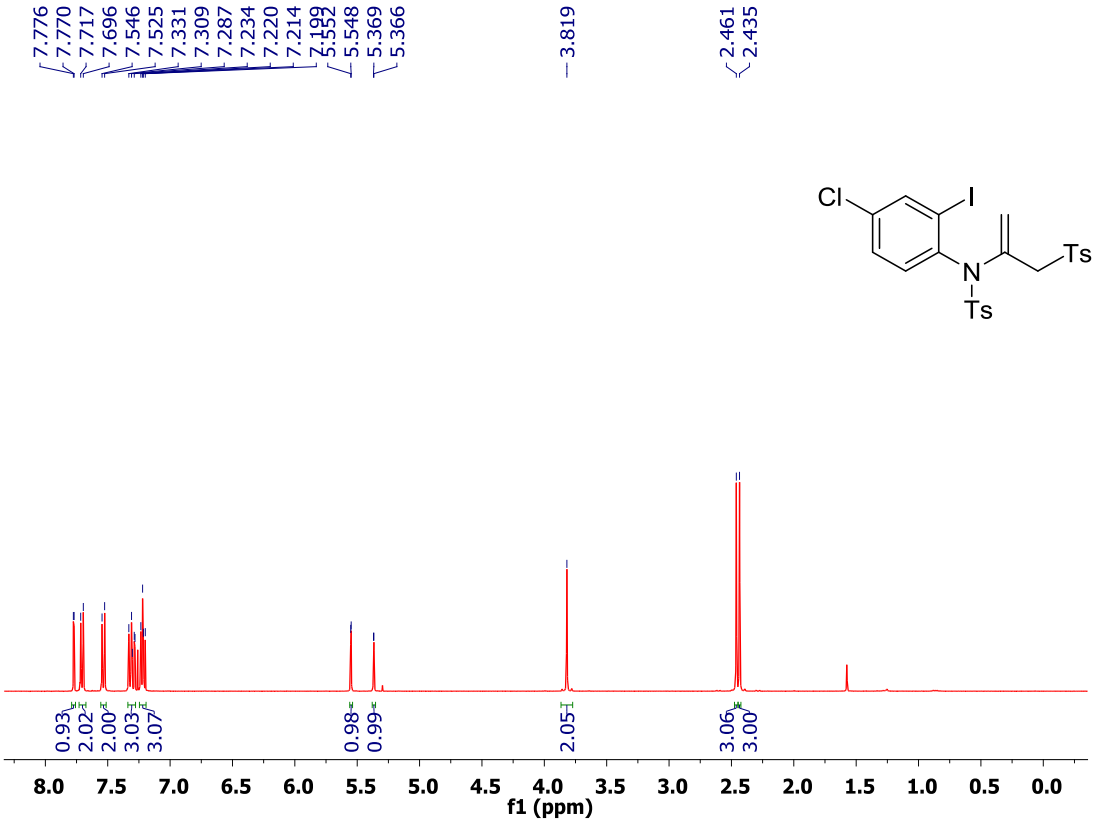
f1 (ppm)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7.192
5.548
5.369
5.366
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Cl
I
Ts
N
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2.05
3.06
3.00
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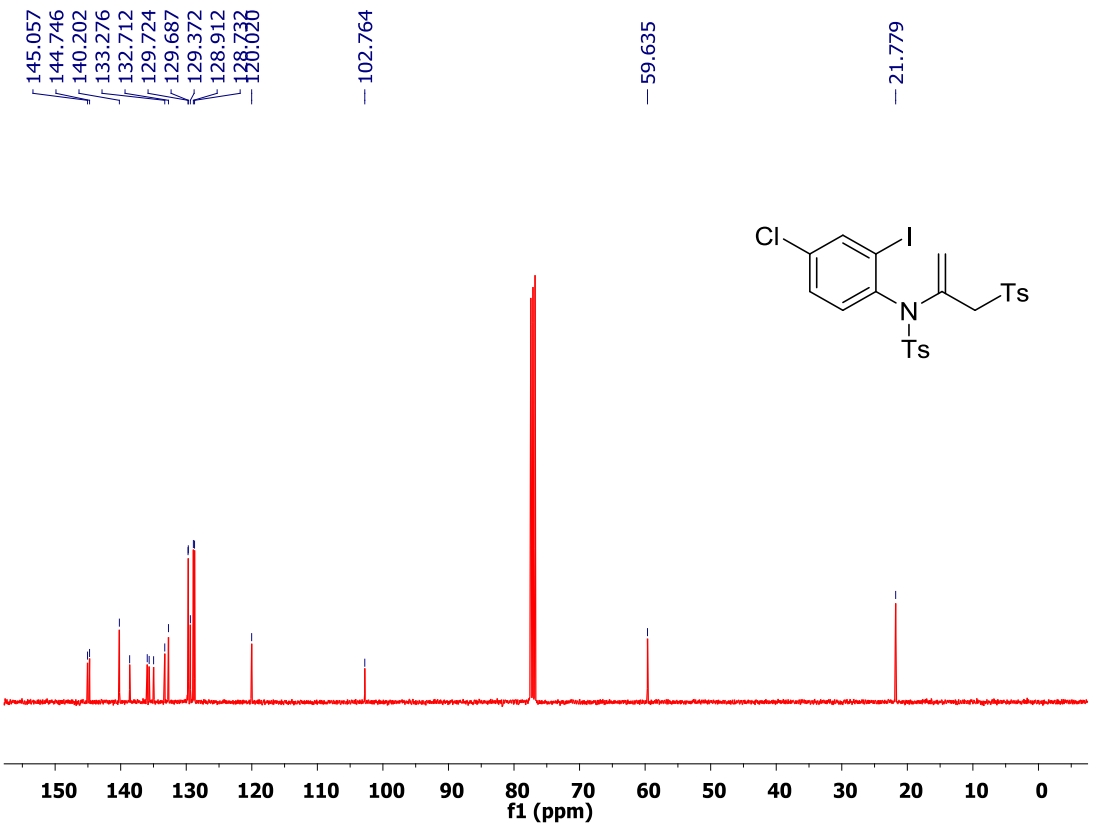
f1 (ppm)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I
Ts
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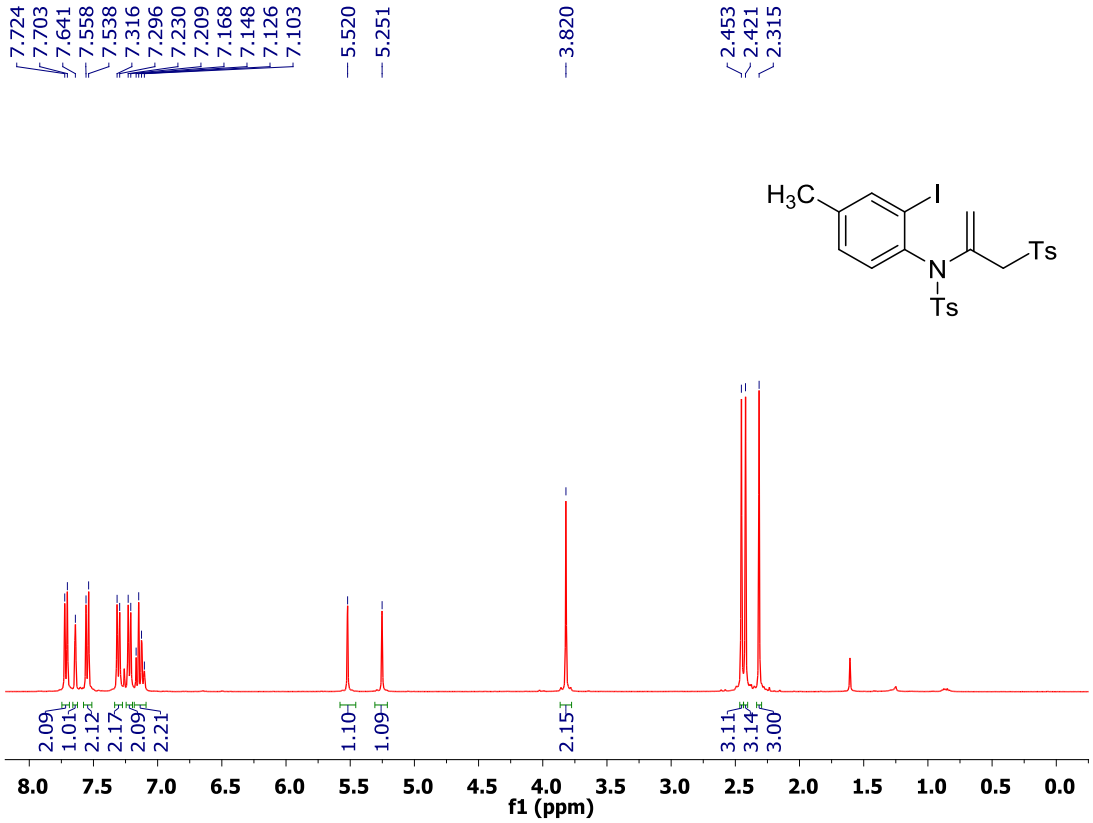
f1 (ppm)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2.12
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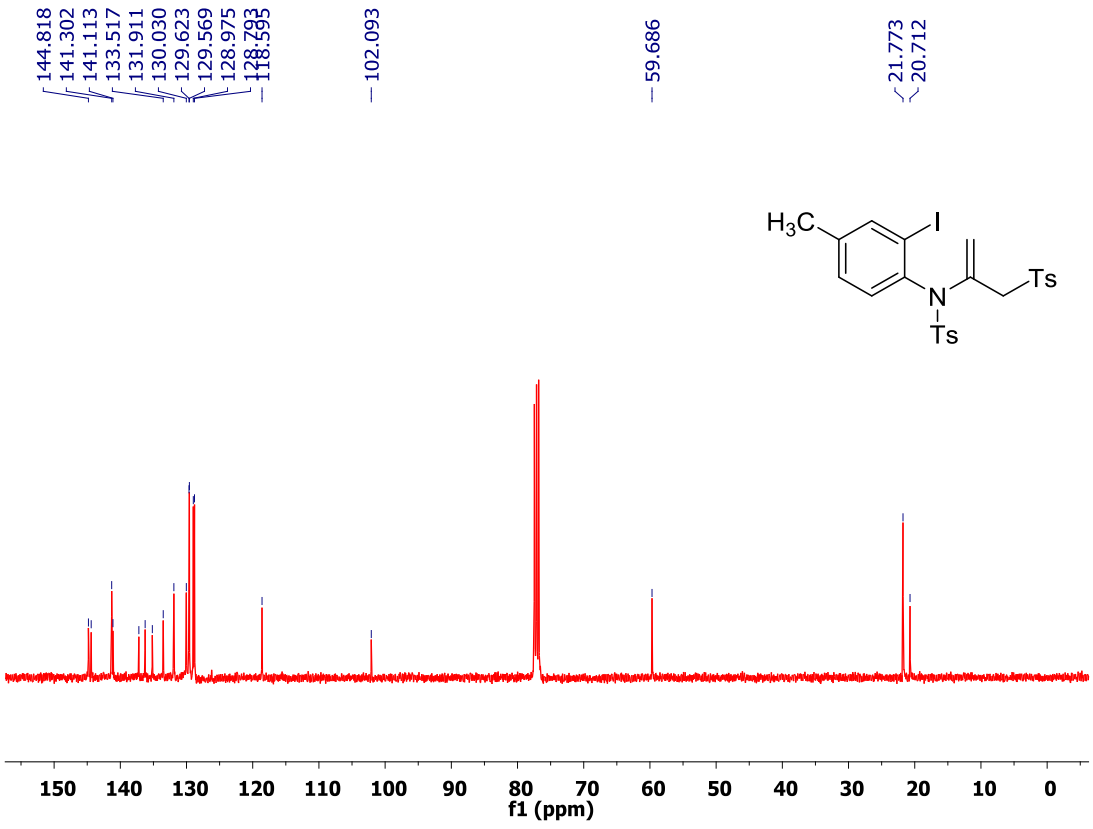
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I
Ts
N
Ts
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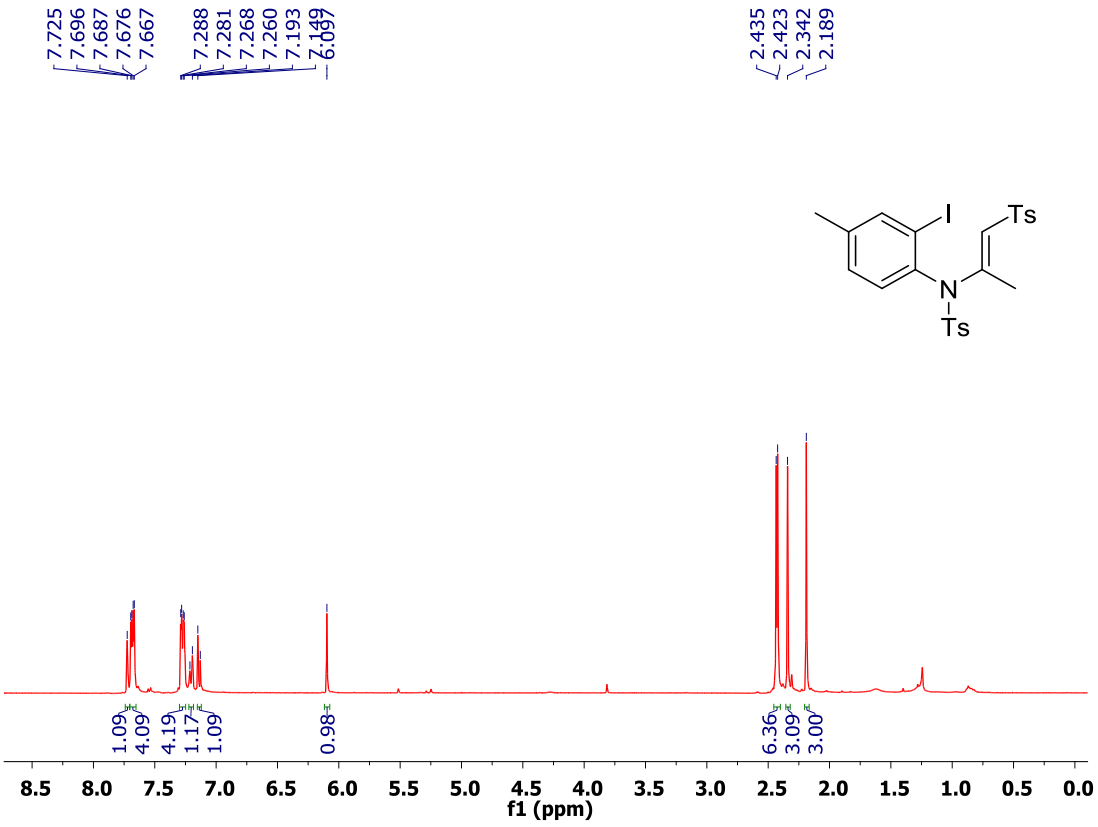
f1 (ppm)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2.423
2.342
2.189
I
Ts
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Ts
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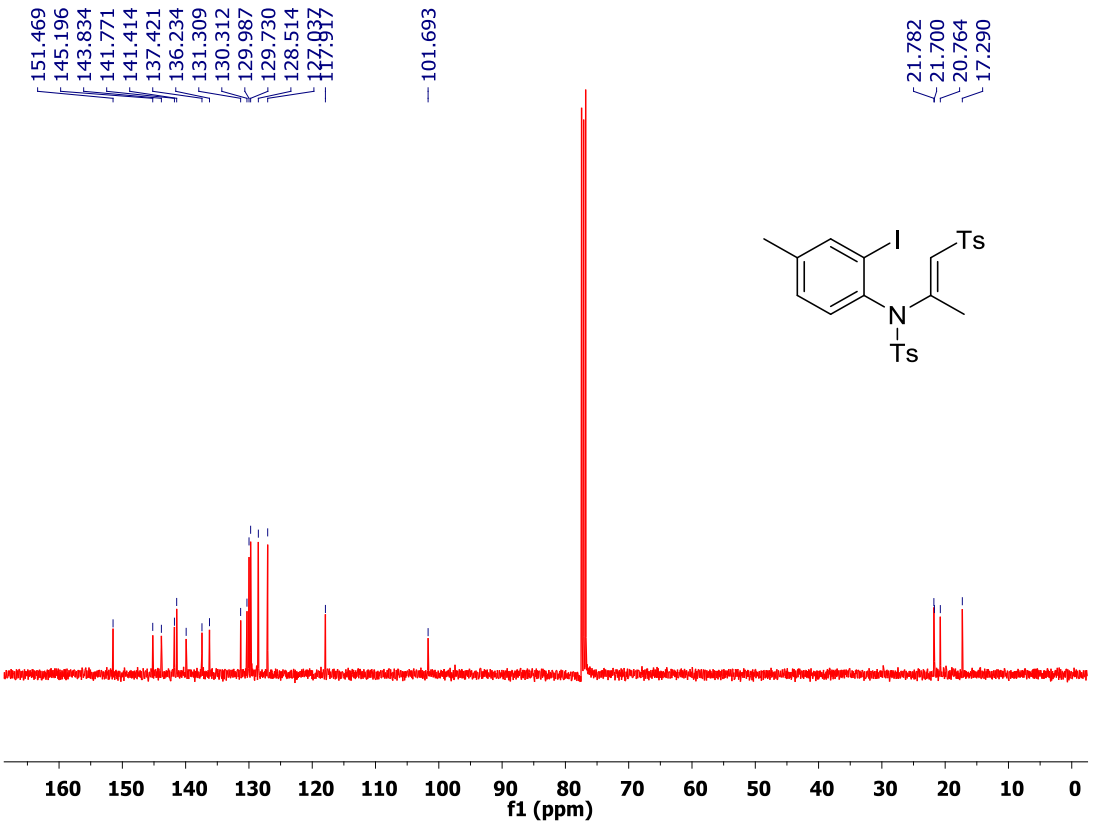
f1 (ppm)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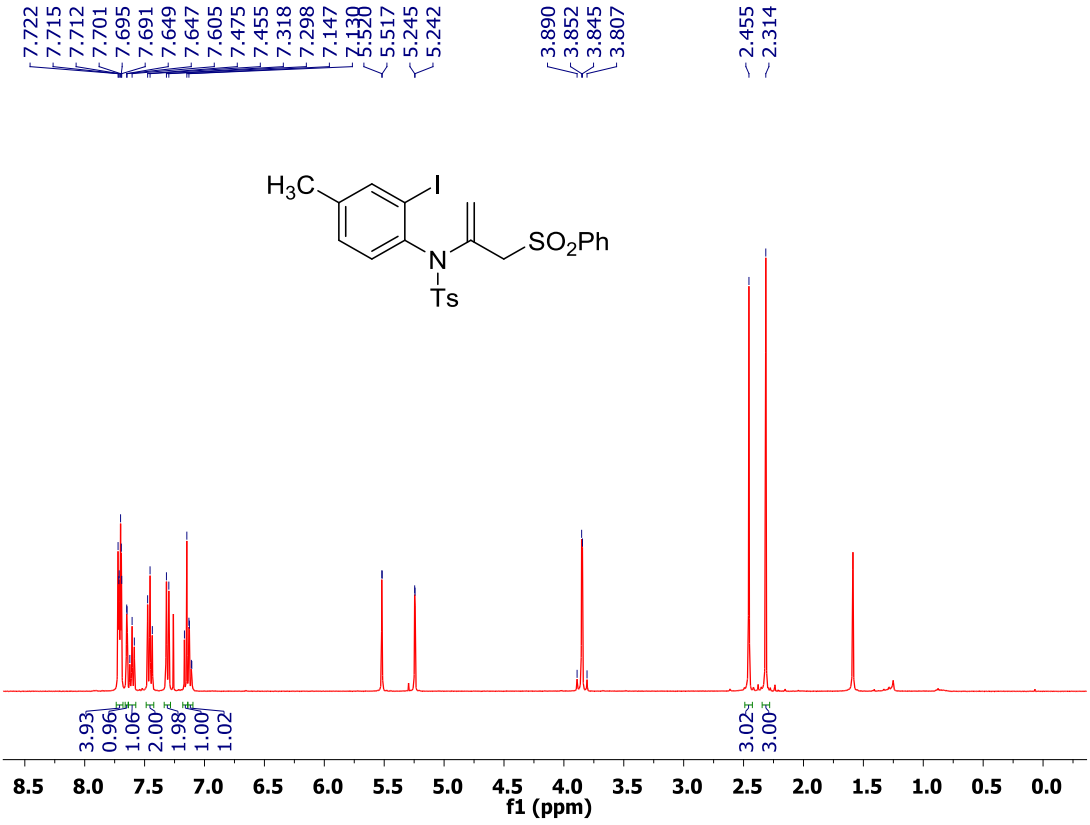
I
Ts
N
Ts
f1 (ppm)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7.147
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SO2Ph
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Ts
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1.06
2.00
1.98
1.00
1.02
3.02
3.00
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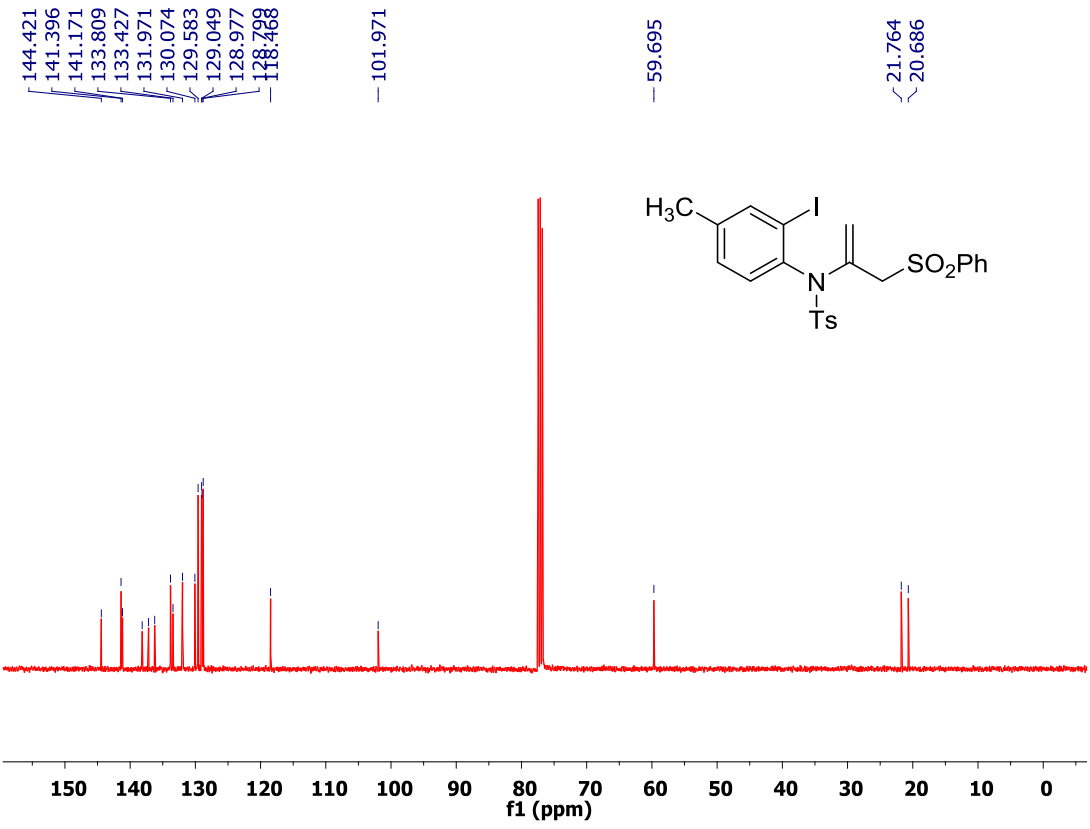
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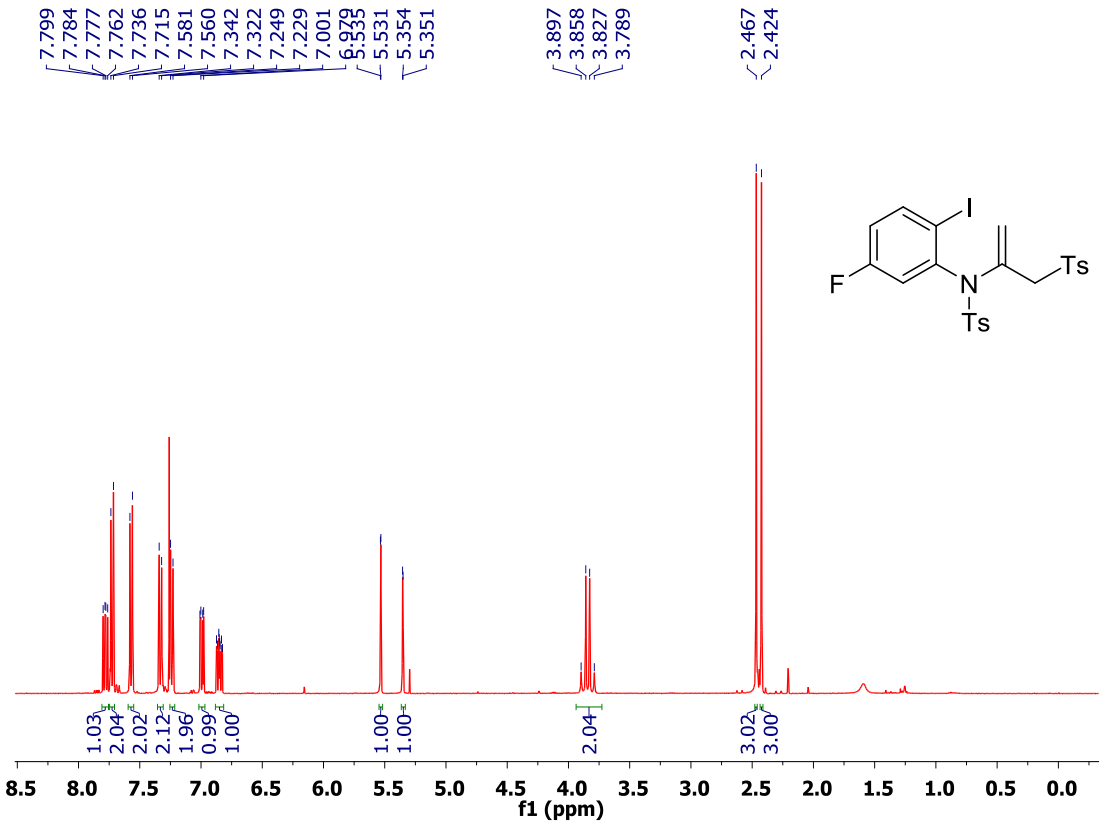
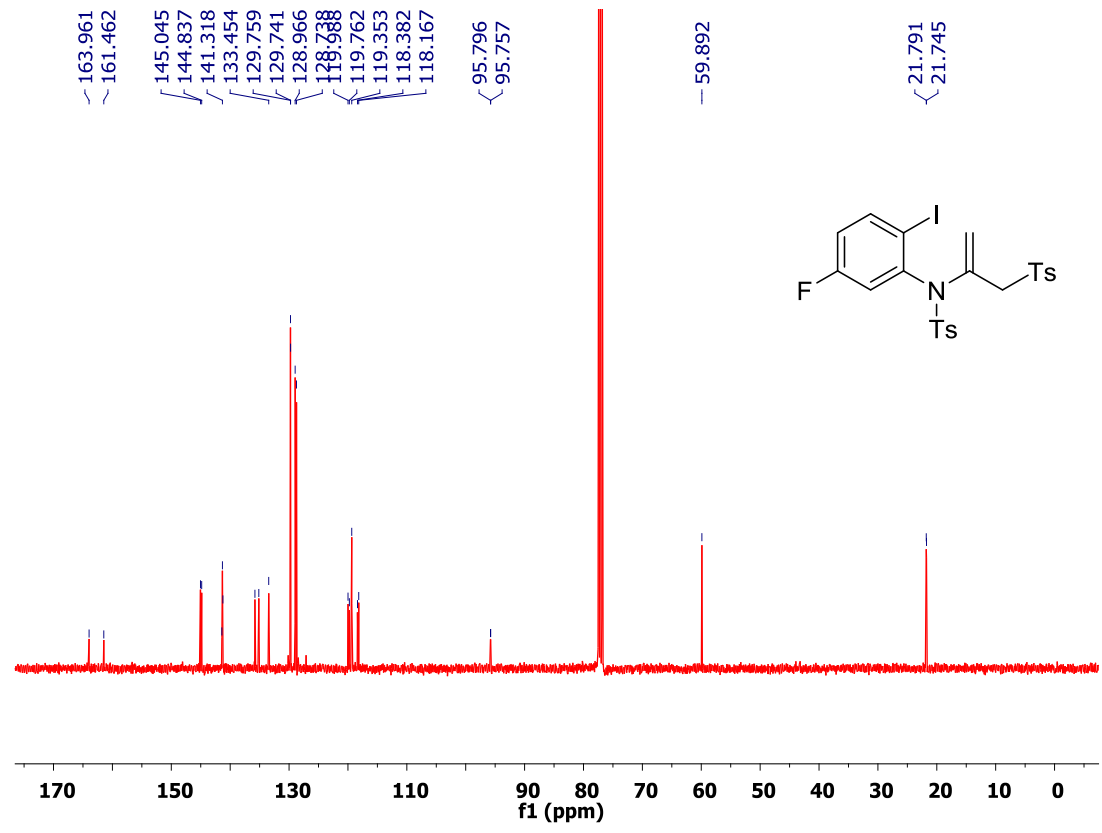
128.468
101.971
59.695
21.764
20.686
H3C
I
SO2Ph
N
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.799
7.784
7.777
7.762
7.736
7.715
7.581
7.560
7.342
7.322
7.249
7.229
7.001
6.979
6.935
5.531
5.354
5.351
3.897
3.858
3.827
3.789
2.467
2.424
I
F
N
Ts
Ts
1.03
2.04
2.02
2.12
1.96
0.99
1.00
1.00
1.00
2.04
3.02
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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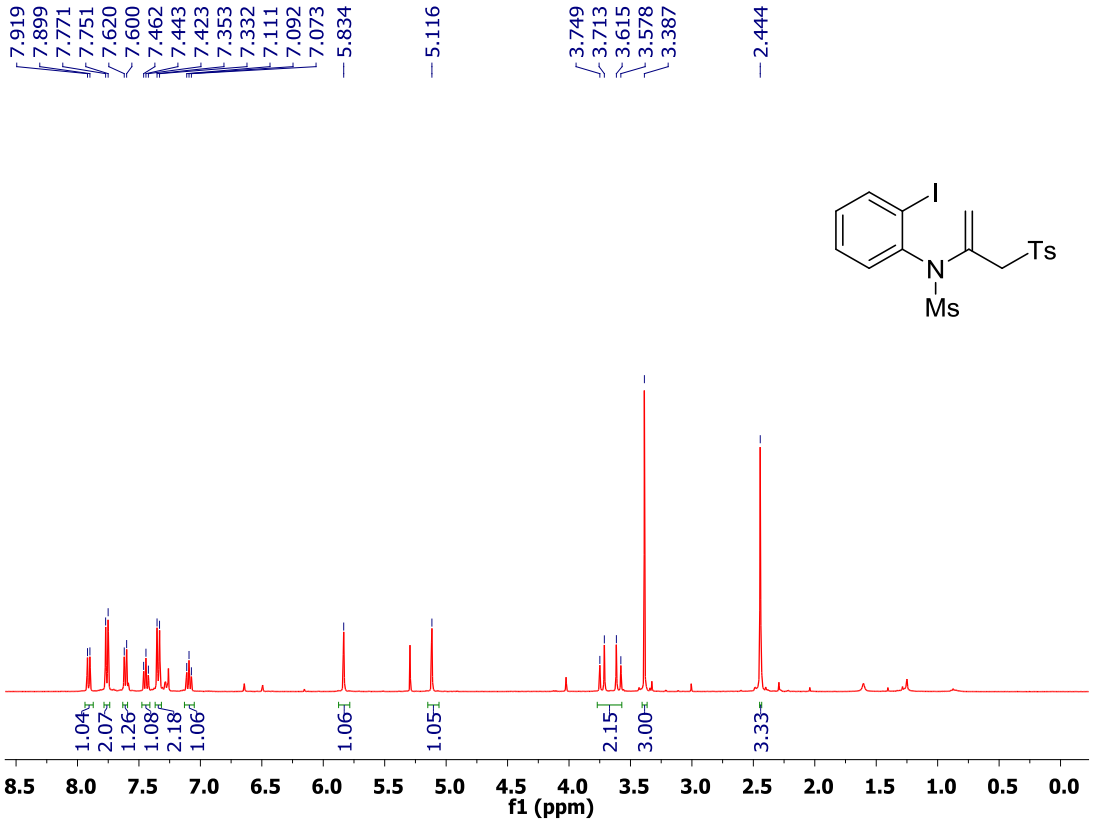
161.462
145.045
144.837
141.318
133.454
129.759
129.741
128.966
119.762
119.353
118.382
118.167
95.796
95.757
59.892
21.791
21.745
I
F
N
Ts
Ts
170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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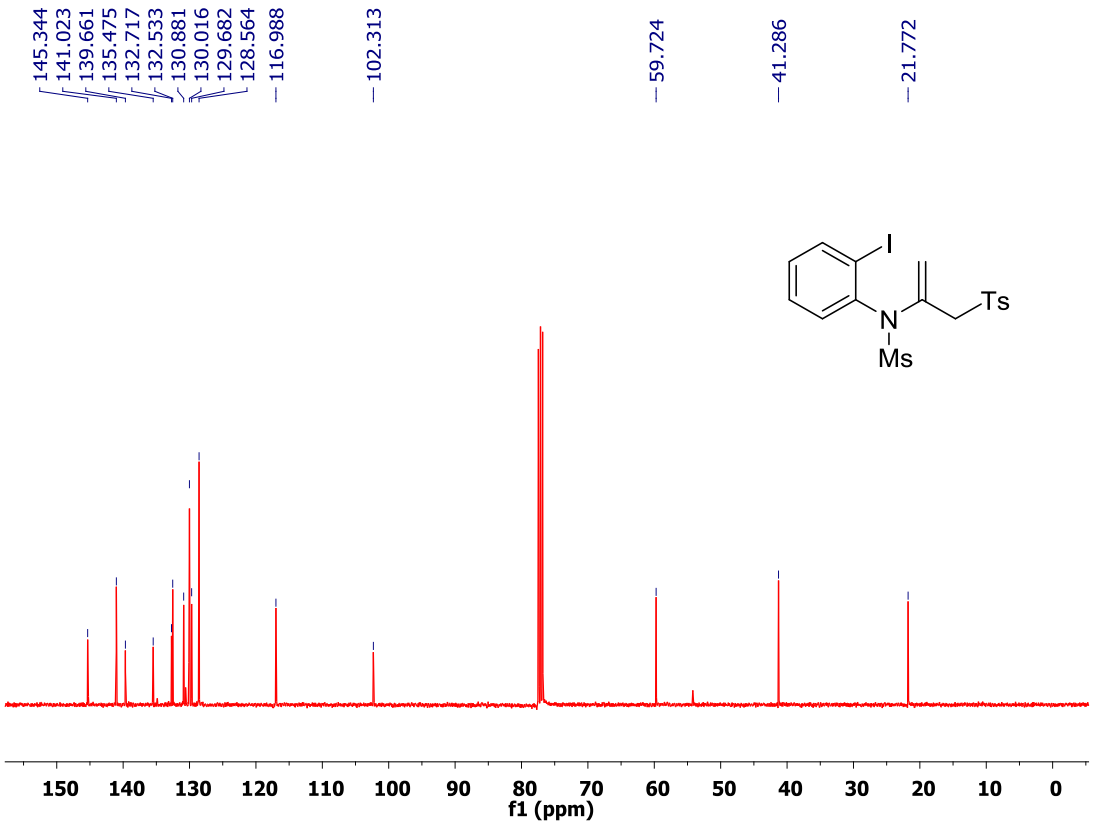
7.771
7.751
7.620
7.600
7.462
7.443
7.423
7.353
7.332
7.111
7.092
7.073
5.834
5.116
3.749
3.713
3.615
3.578
3.387
2.444
I
Ts
N
Ms
1.04
2.07
1.26
1.08
2.18
1.06
1.06
1.05
2.15
3.00
3.33
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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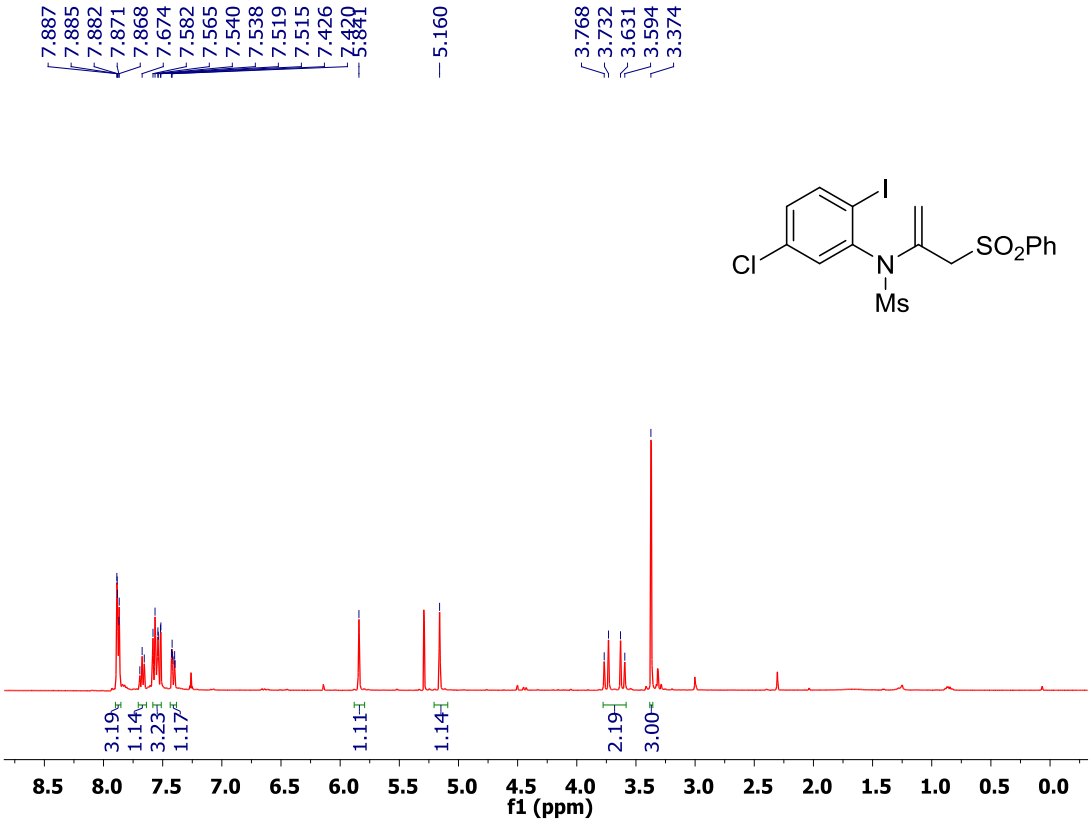
141.023
139.661
135.475
132.717
132.533
130.881
130.016
129.682
128.564
116.988
102.313
59.724
41.286
21.772
I
Ts
N
Ms
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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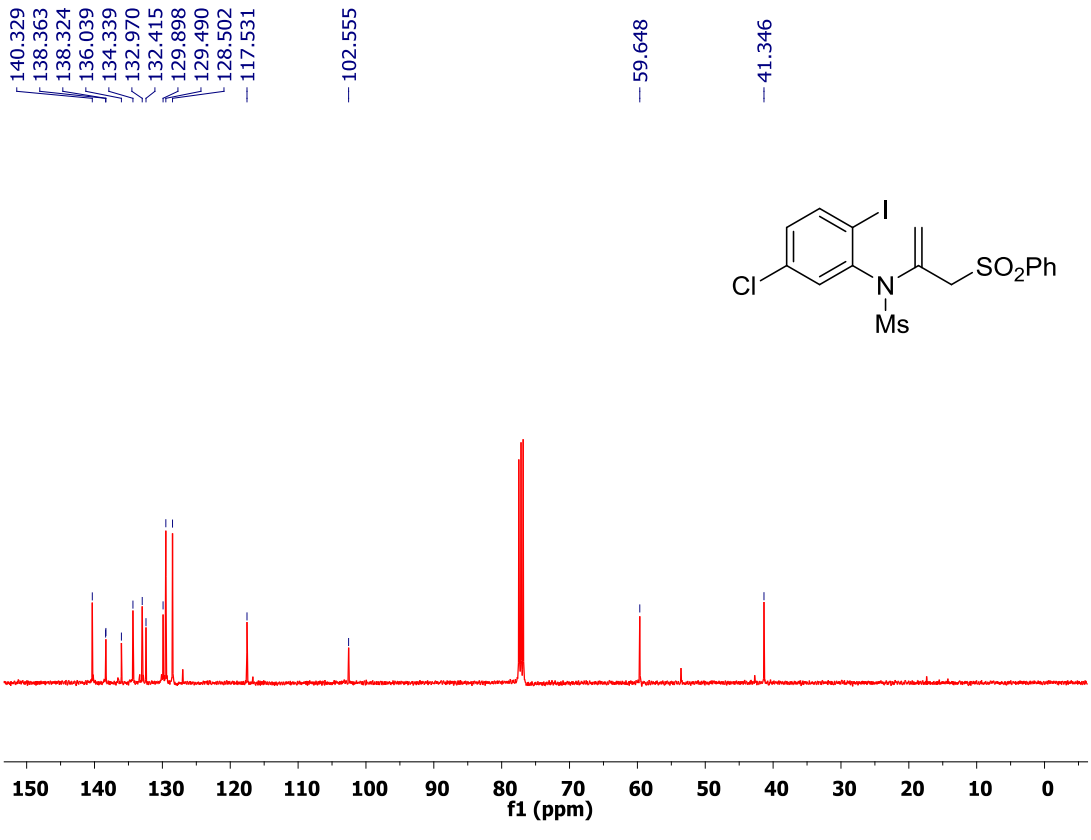
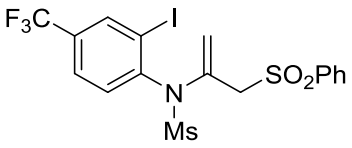
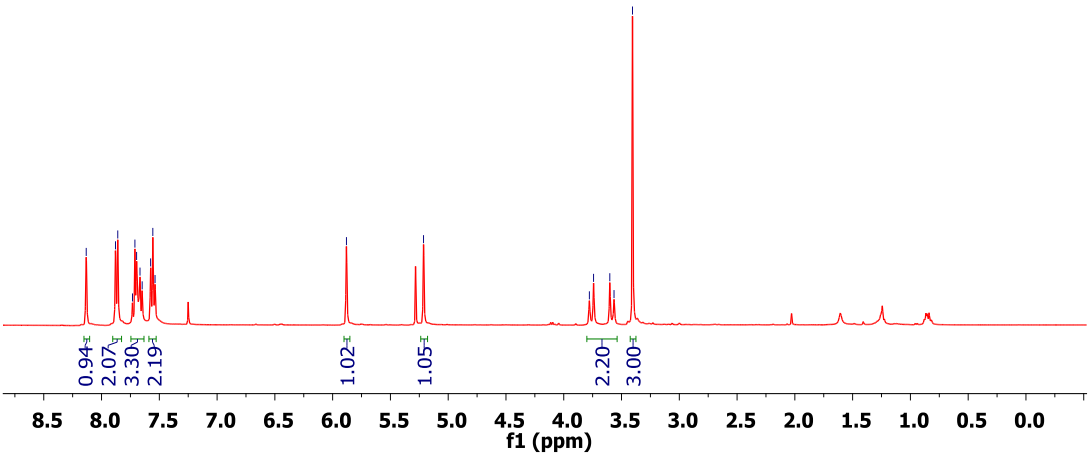
7.885
7.882
7.871
7.868
7.674
7.582
7.565
7.540
7.538
7.519
7.515
7.426
7.420
7.411
5.160
3.768
3.732
3.631
3.594
3.374
I
Cl
N
Ms
SO2Ph
3.19
1.14
3.23
1.17
1.11
1.14
2.19
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

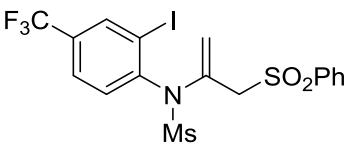

140.329
138.363
138.324
136.039
134.339
132.970
132.415
129.898
129.490
128.502
117.531
102.555
59.648
41.346
I
Cl
N
Ms
SO2Ph
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

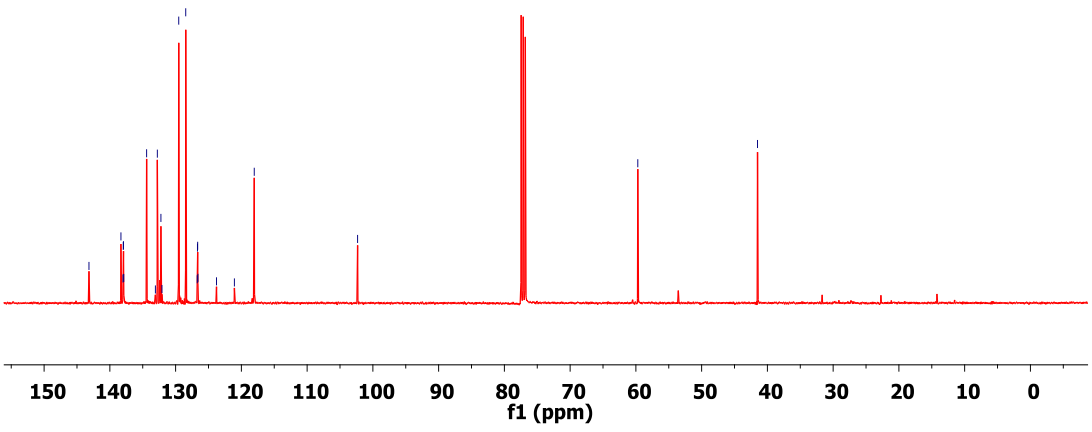

8.133
7.879
7.860
7.732
7.711
7.696
7.667
7.648
7.575
7.556
7.537
5.881
5.213
3.778
3.742
3.601
3.565
3.405

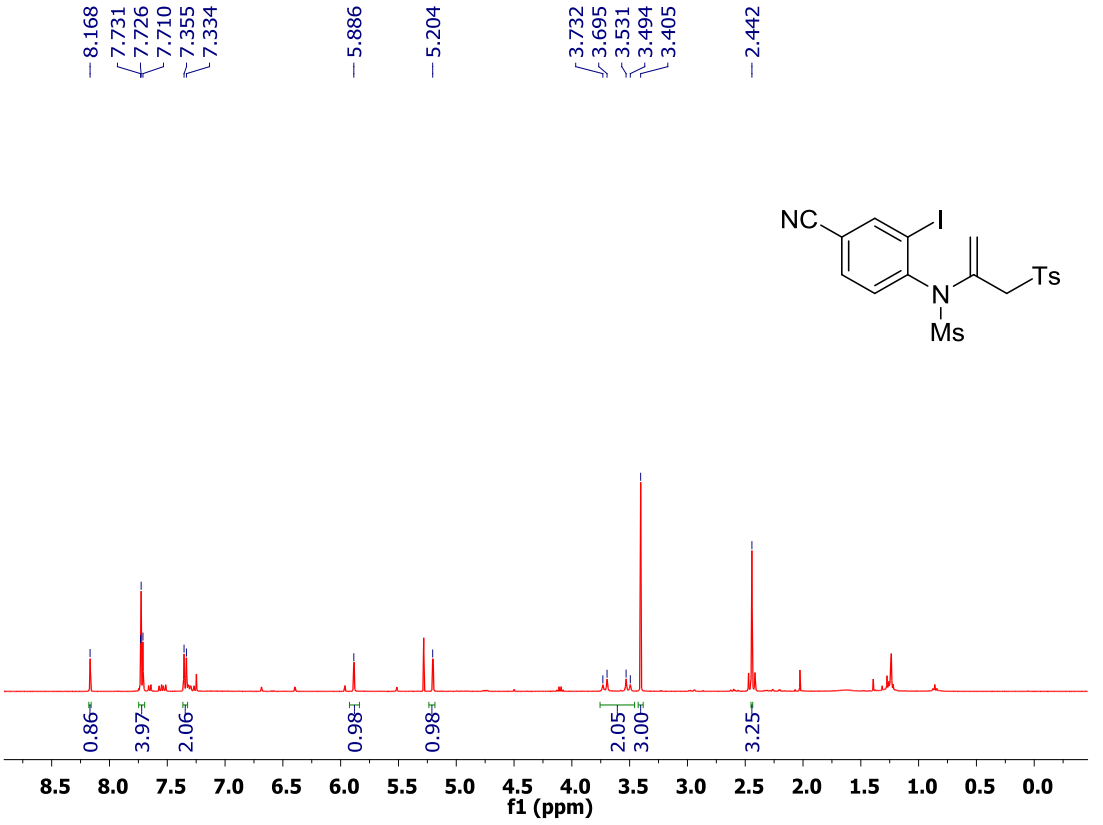

F3C
I
SO2Ph
N
Ms

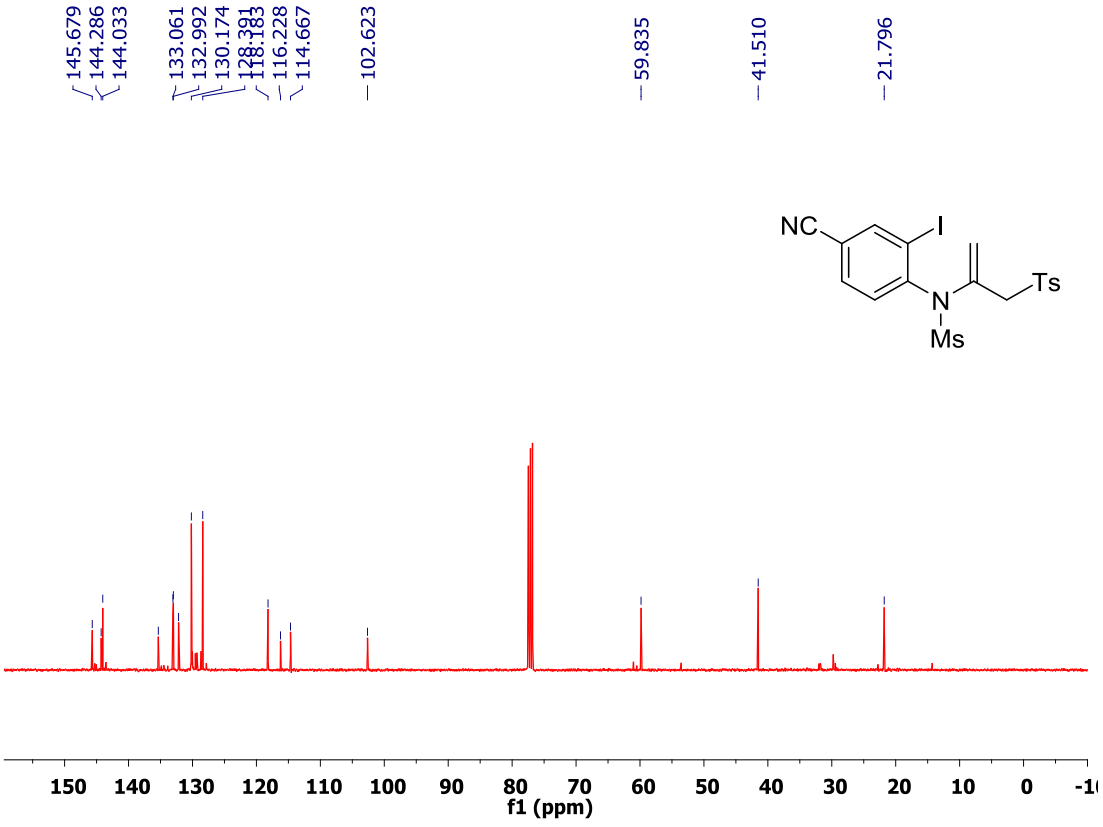

0.94
2.07
3.30
2.19
1.02
1.05
2.20
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

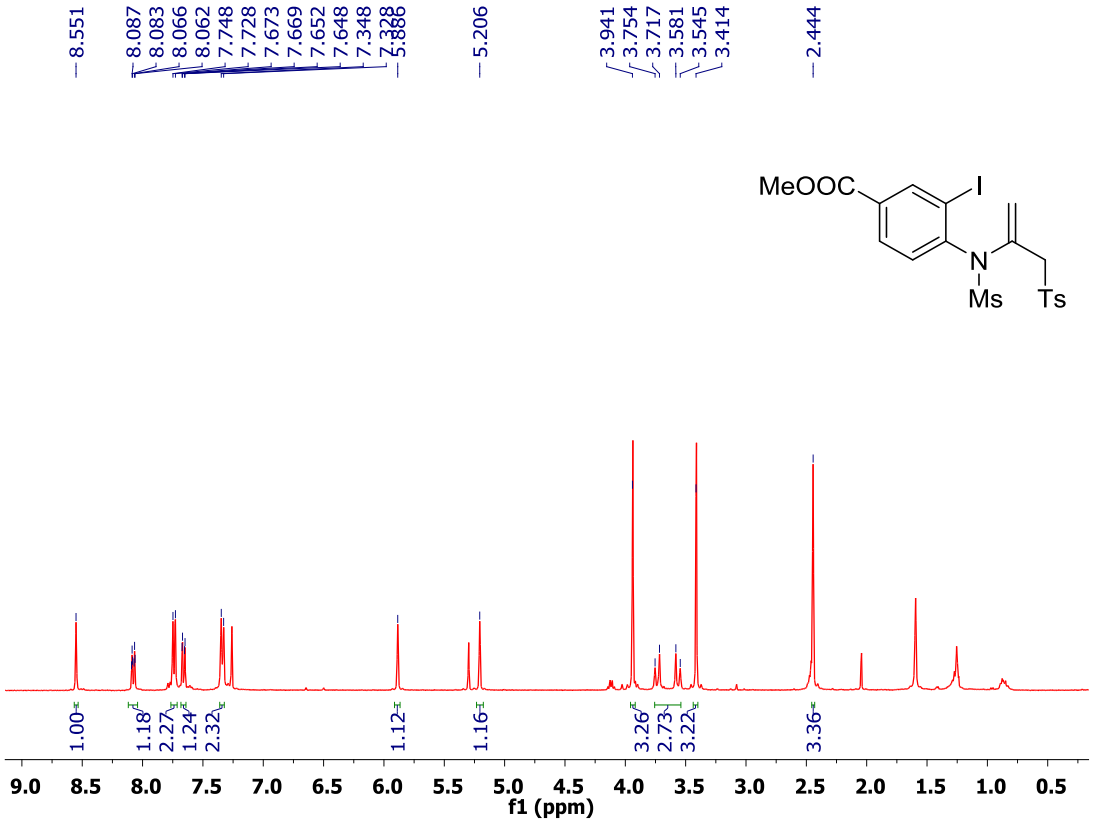

143.178
138.315
137.964
137.926
137.889
134.409
132.780
132.235
129.524
128.460
126.677
126.643
126.609
118.041
102.322
59.709
41.502

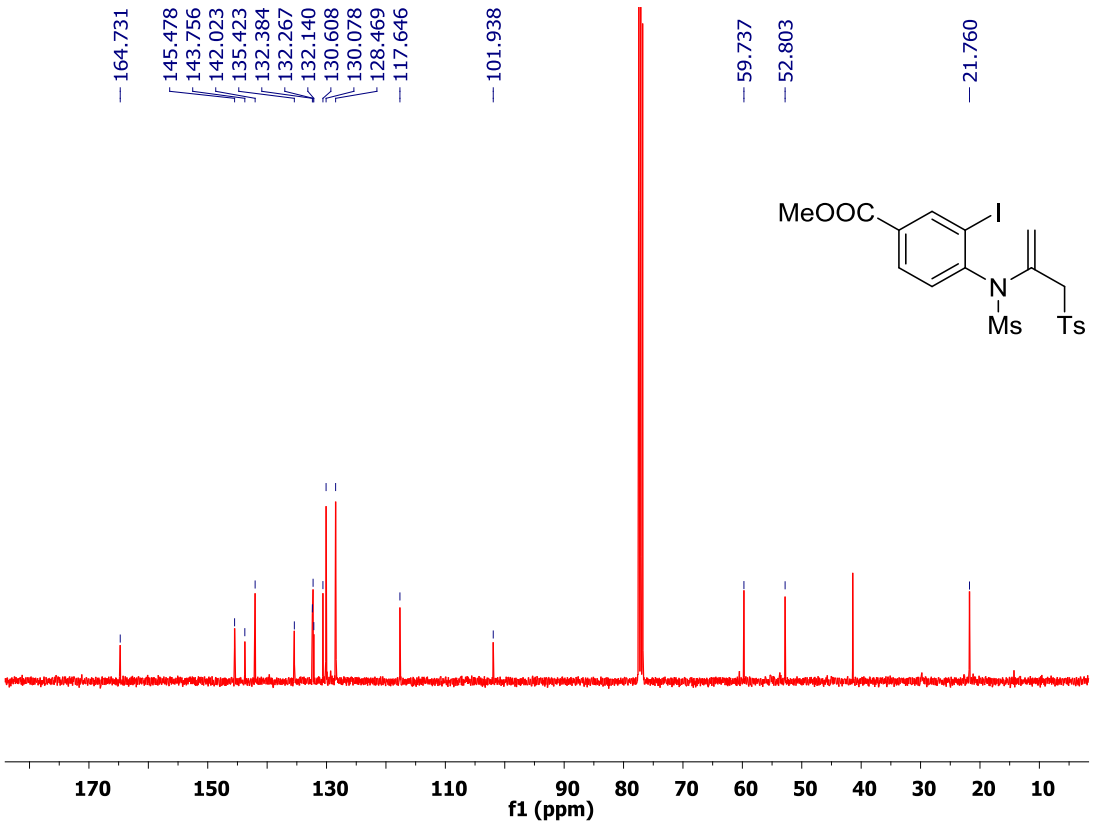

F3C
I
SO2Ph
N
Ms

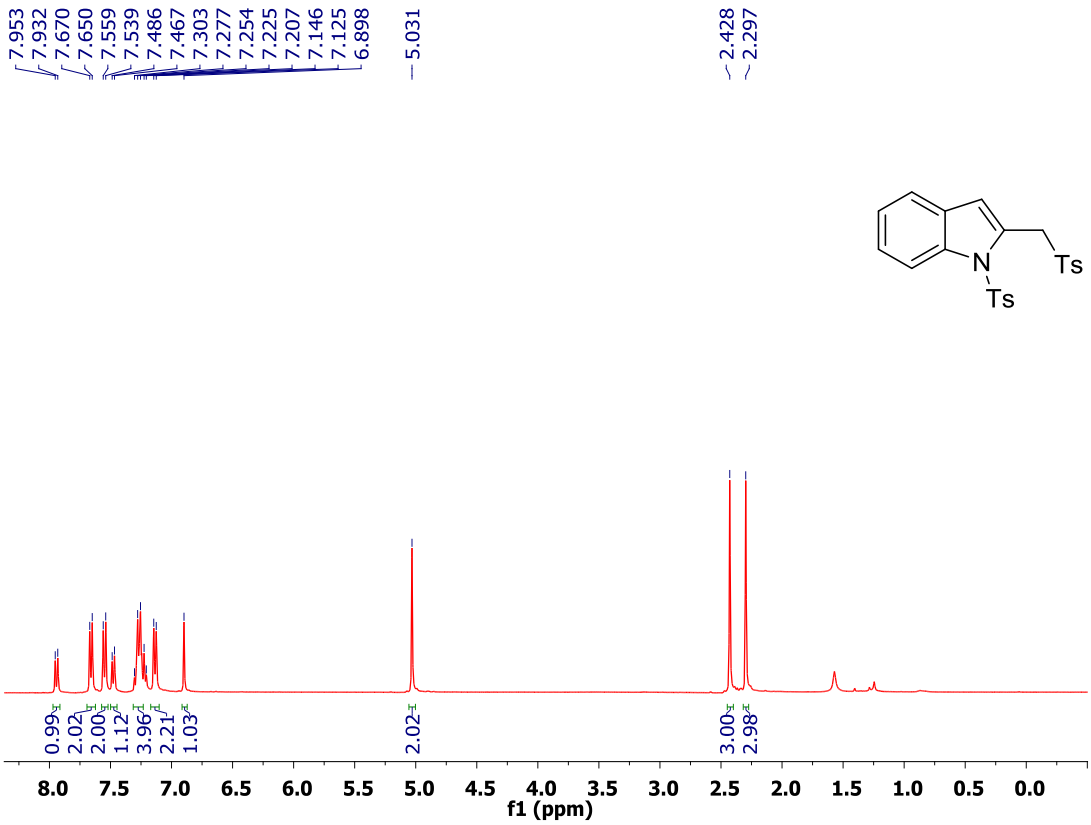

150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

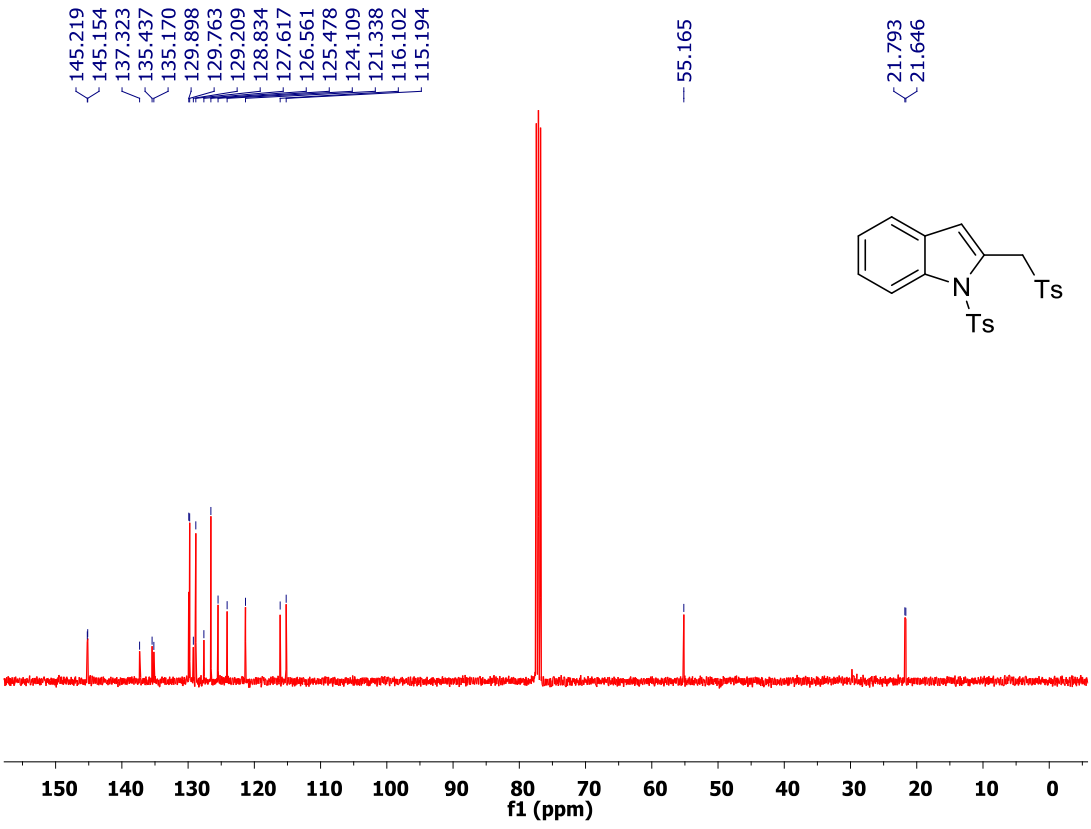

8.168
7.731
7.726
7.710
7.355
7.334
5.886
5.204
3.732
3.695
3.531
3.494
3.405
2.442
NC
I
Ts
N
Ms
0.86
3.97
2.06
0.98
0.98
2.05
3.00
3.25
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


145.679
144.286
144.033
133.061
132.992
130.174
128.391
118.183
116.228
114.667
102.623
59.835
41.510
21.796
NC
I
Ts
N
Ms
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.551
8.087
8.083
8.066
8.062
7.748
7.728
7.673
7.669
7.652
7.648
7.348
5.206
3.941
3.754
3.717
3.581
3.545
3.414
2.444
MeOOC
I
N
Ms
Ts
1.00
1.18
2.27
1.24
2.32
1.12
1.16
3.26
2.73
3.22
3.36
f1 (ppm)


164.731
145.478
143.756
142.023
135.423
132.384
132.267
132.140
130.608
130.078
128.469
117.646
101.938
59.737
52.803
21.760
MeOOC
I
N
Ms
Ts
f1 (ppm)


7.953
7.932
7.670
7.650
7.559
7.539
7.486
7.467
7.303
7.277
7.254
7.225
7.207
7.146
7.125
6.898
5.031
2.428
2.297
N
Ts
Ts
0.99
2.02
2.00
1.12
3.96
2.21
1.03
2.02
3.00
2.98
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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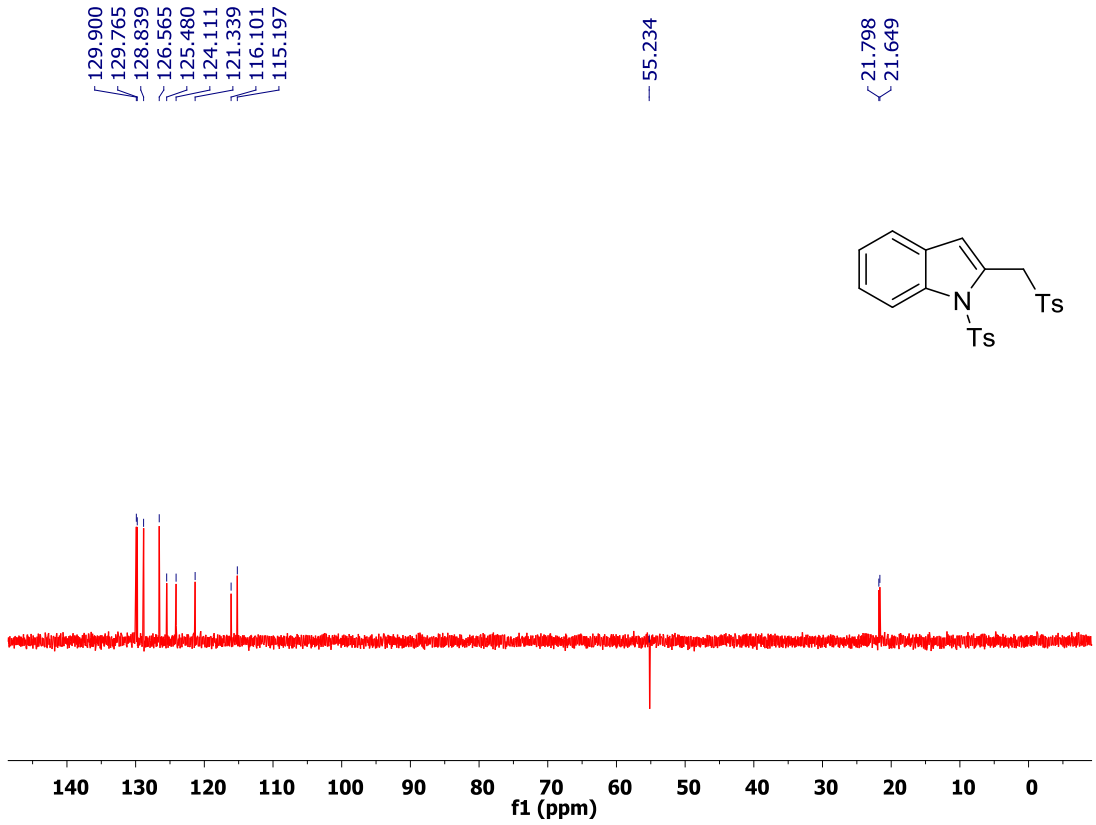
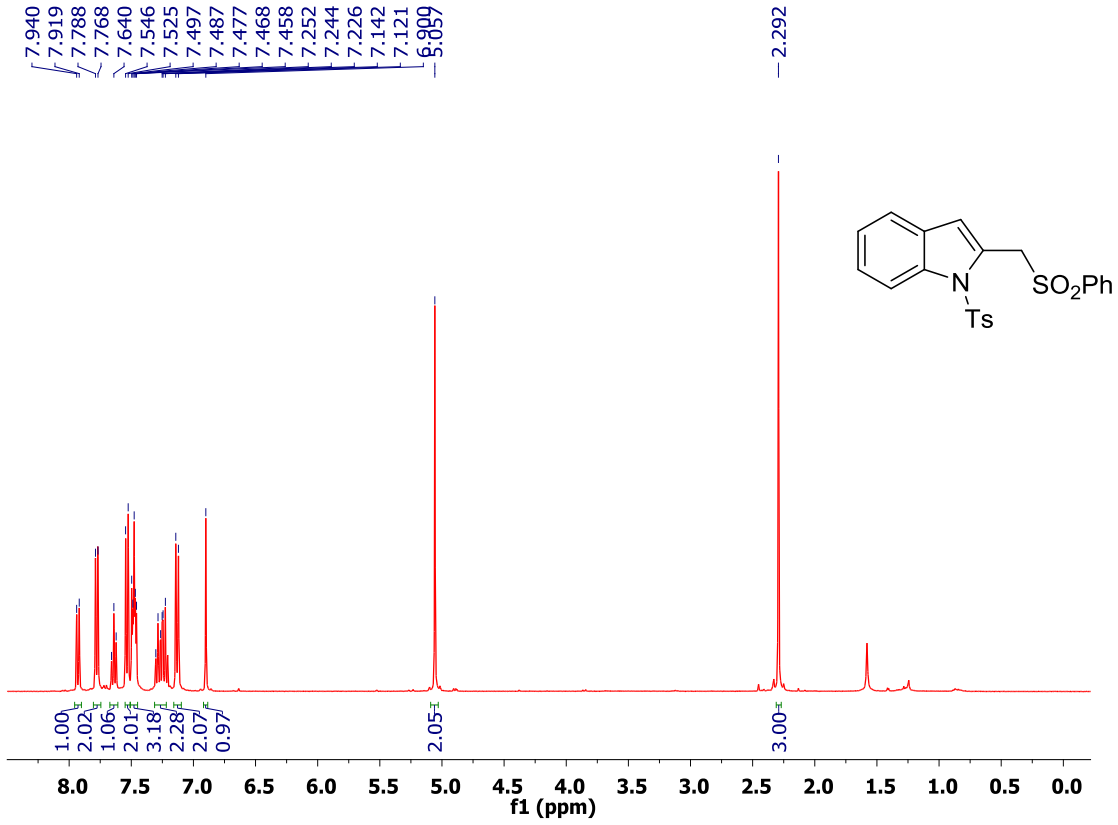
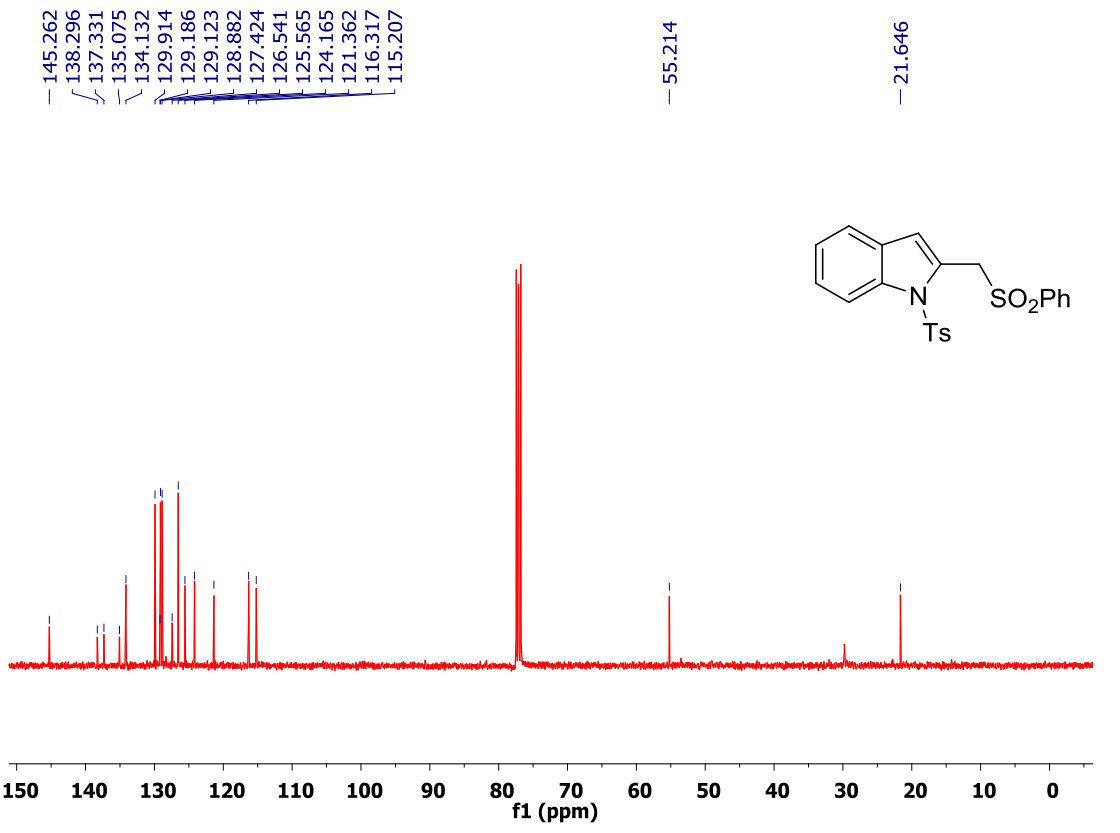
145.154
137.323
135.437
135.170
129.898
129.763
129.209
128.834
127.617
126.561
125.478
124.109
121.338
116.102
115.194
55.165
21.793
21.646
N
Ts
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

DEPT-135


129.900
129.765
128.839
126.565
125.480
124.111
121.339
116.101
115.197
55.234
21.798
21.649
N
Ts
Ts
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.940
7.919
7.788
7.768
7.640
7.546
7.525
7.497
7.487
7.477
7.468
7.458
7.252
7.244
7.226
7.142
7.121
6.899
5.057
2.292
1.00
2.02
1.06
2.01
3.18
2.28
2.07
0.97
2.05
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
N
Ts
SO2Ph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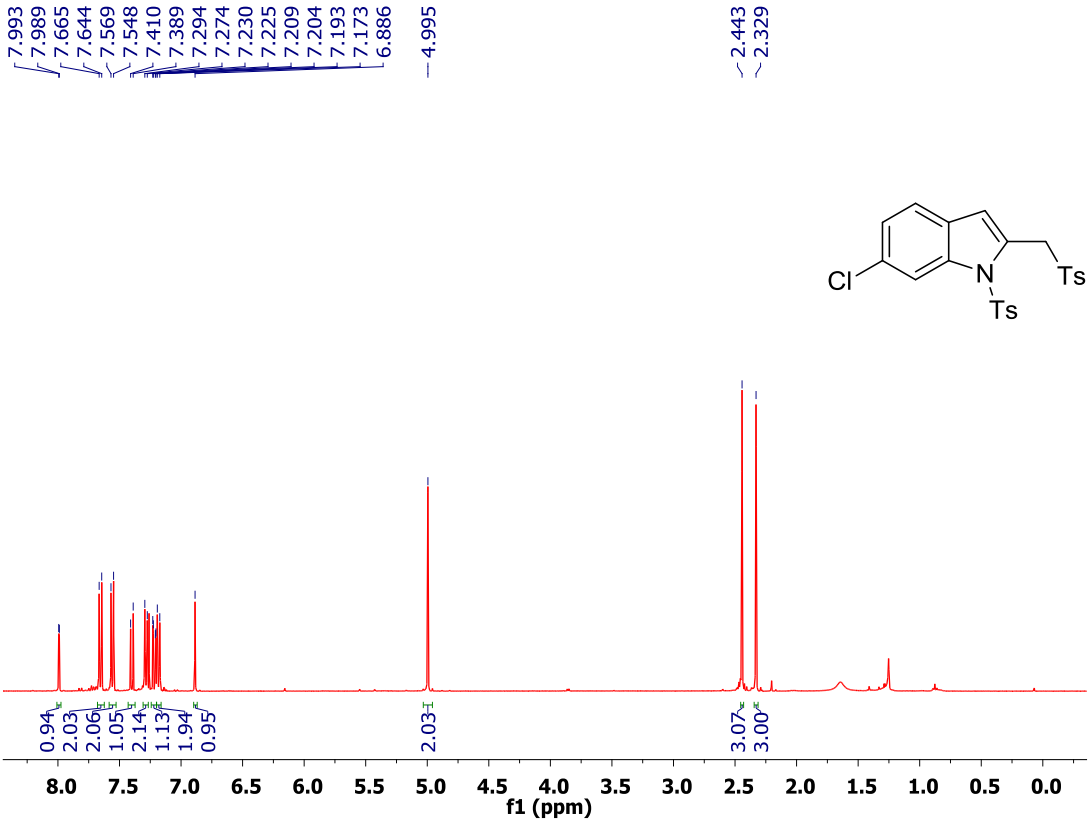
138.296
137.331
135.075
134.132
129.914
129.186
129.123
128.882
127.424
126.541
125.565
124.165
121.362
116.317
115.207
55.214
21.646
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
N
Ts
SO2Ph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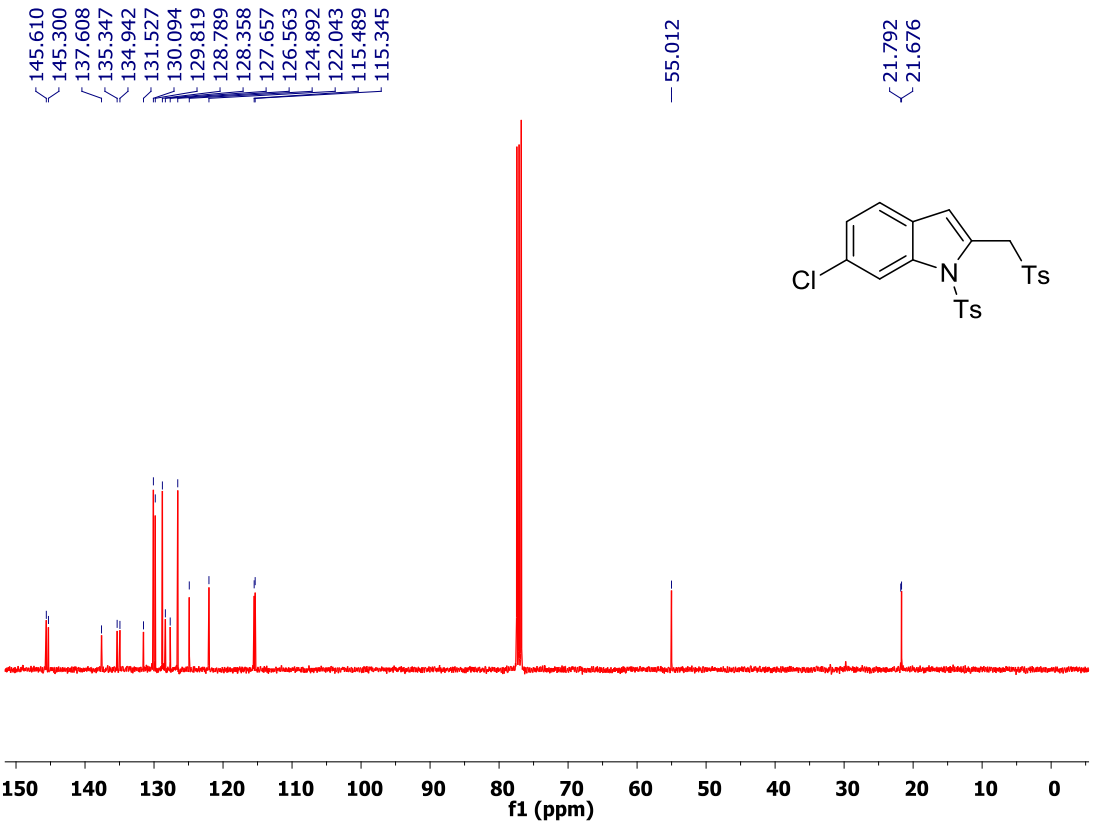
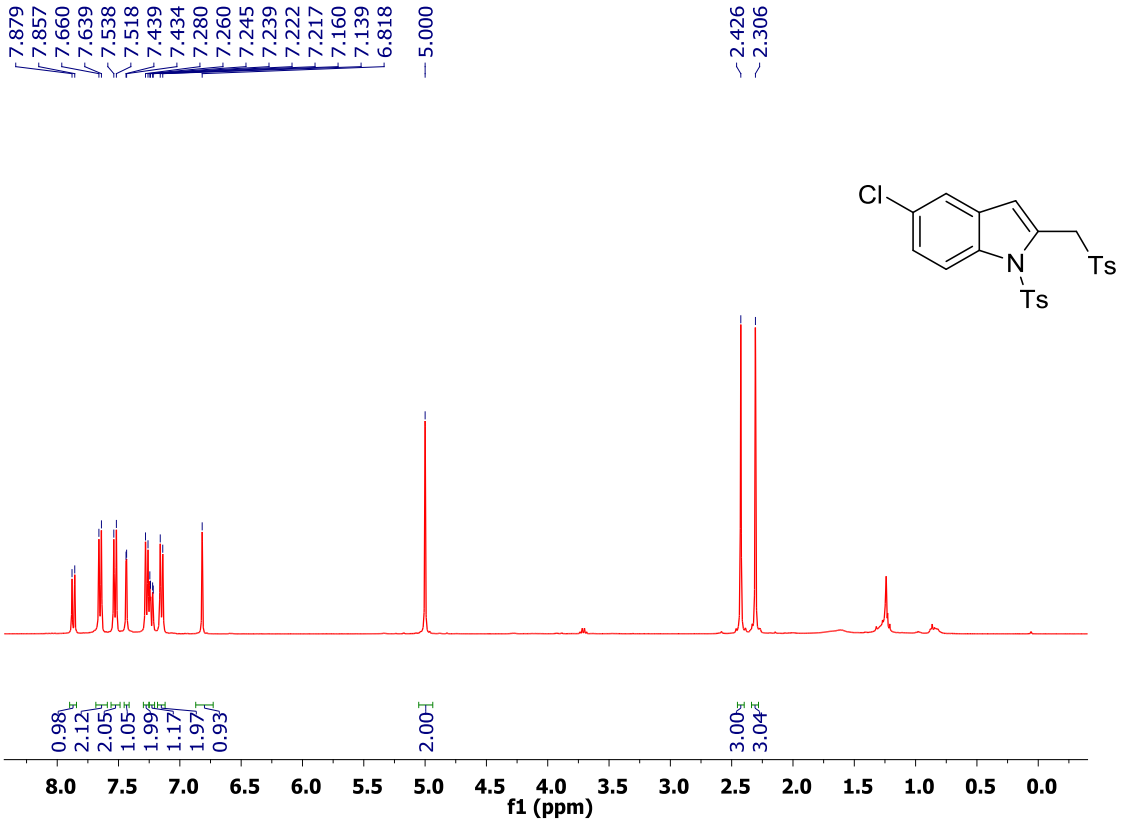
7.989
7.665
7.644
7.569
7.548
7.410
7.389
7.294
7.274
7.230
7.225
7.209
7.204
7.193
7.173
6.886
4.995
2.443
2.329
Cl
N
Ts
Ts
0.94
2.03
2.06
1.05
2.14
1.13
1.94
0.95
2.03
3.07
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


145.610
145.300
137.608
135.347
134.942
131.527
130.094
129.819
128.789
128.358
127.657
126.563
124.892
122.043
115.489
115.345
55.012
21.792
21.676
Cl
N
Ts
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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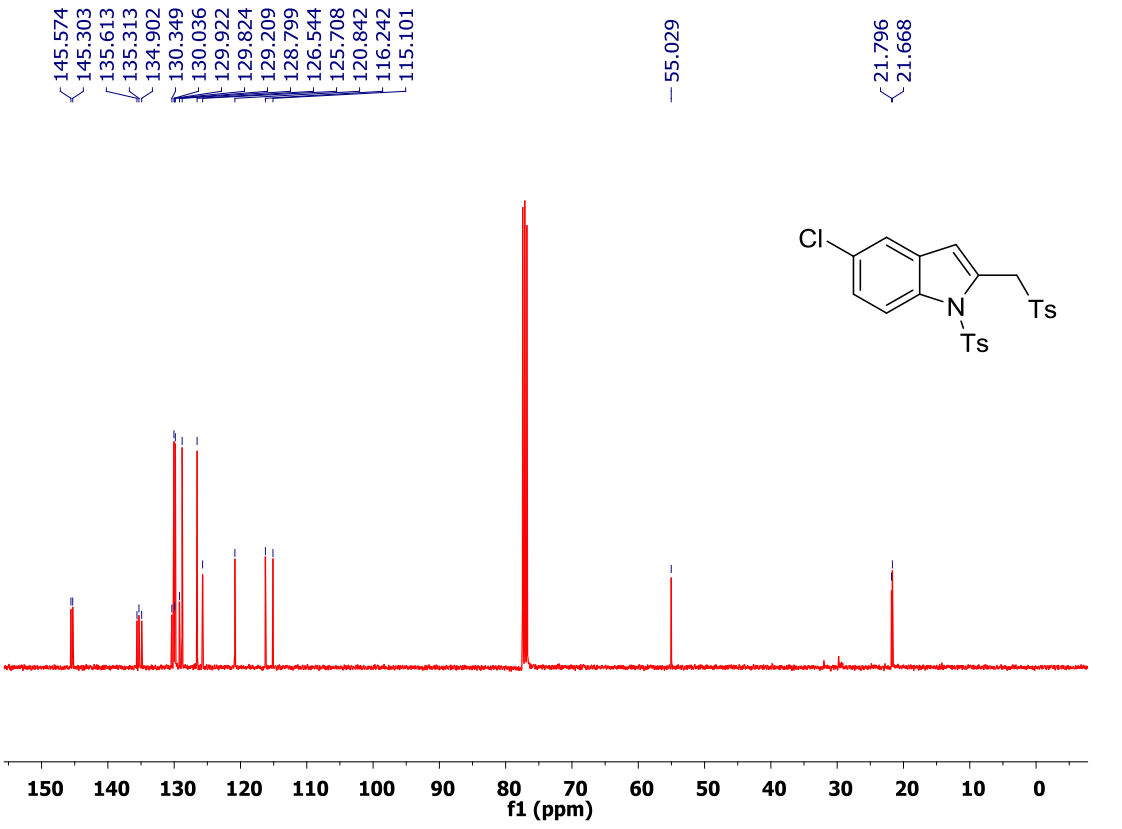
7.857
7.660
7.639
7.538
7.518
7.439
7.434
7.280
7.260
7.245
7.239
7.222
7.217
7.160
7.139
6.818
5.000
2.426
2.306
Cl
N
Ts
Ts
0.98
2.12
2.05
1.05
1.99
1.17
1.97
0.93
2.00
3.00
3.04
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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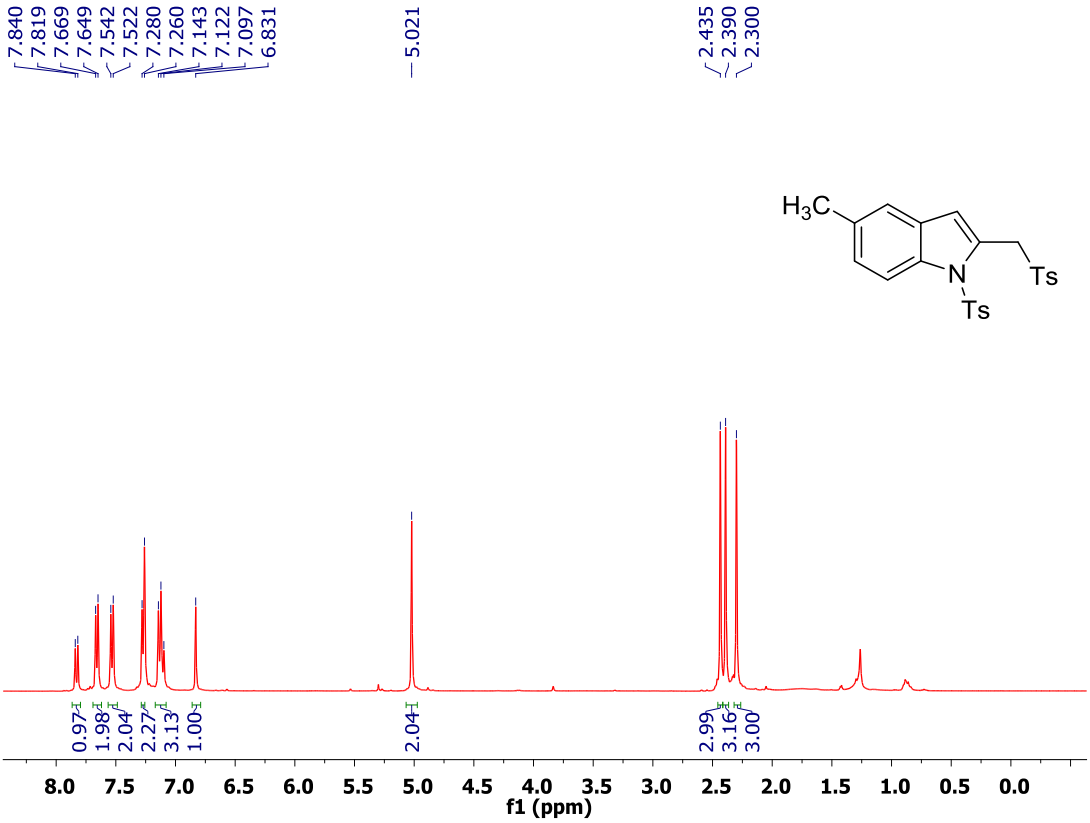
135.613
135.313
134.902
130.349
130.036
129.922
129.824
129.209
128.799
126.544
125.708
120.842
116.242
115.101
55.029
21.796
21.668
Cl
N
Ts
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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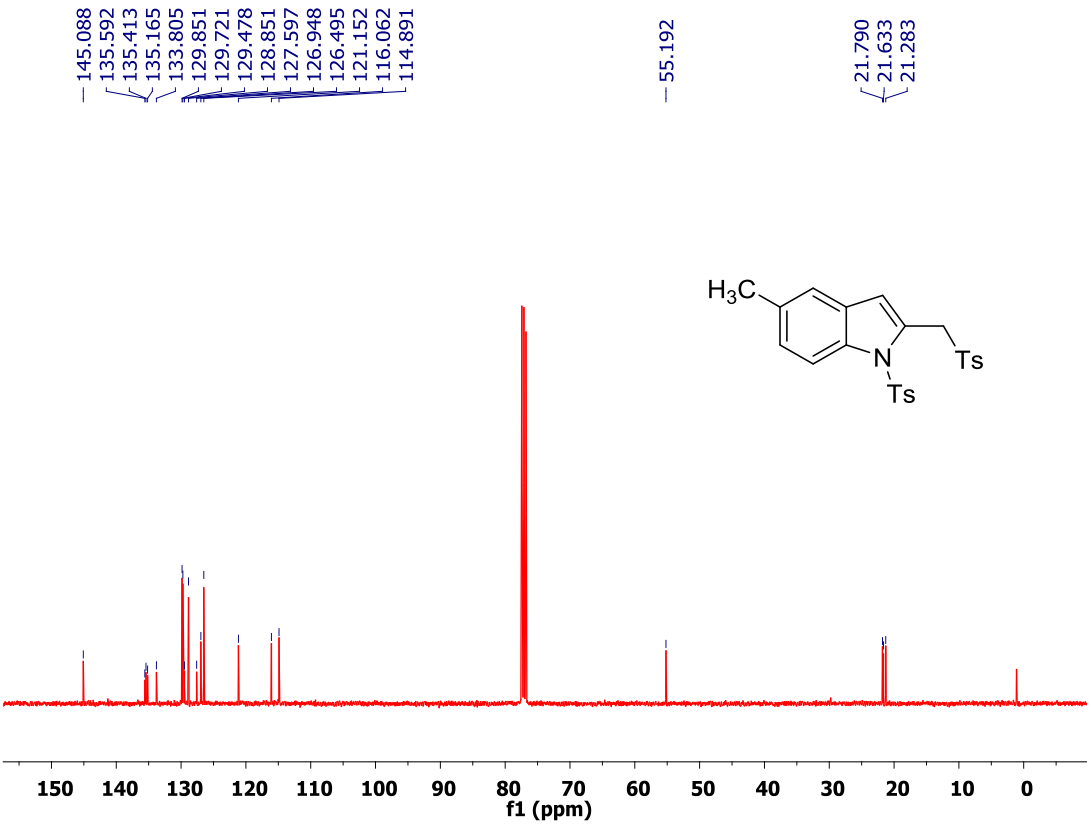
7.669
7.649
7.542
7.522
7.280
7.260
7.143
7.122
7.097
6.831
5.021
2.435
2.390
2.300
H3C
N
Ts
Ts
0.97
1.98
2.04
2.27
3.13
1.00
2.04
2.99
3.16
3.00
f1 (ppm)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135.592
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135.165
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129.851
129.721
129.478
128.851
127.597
126.948
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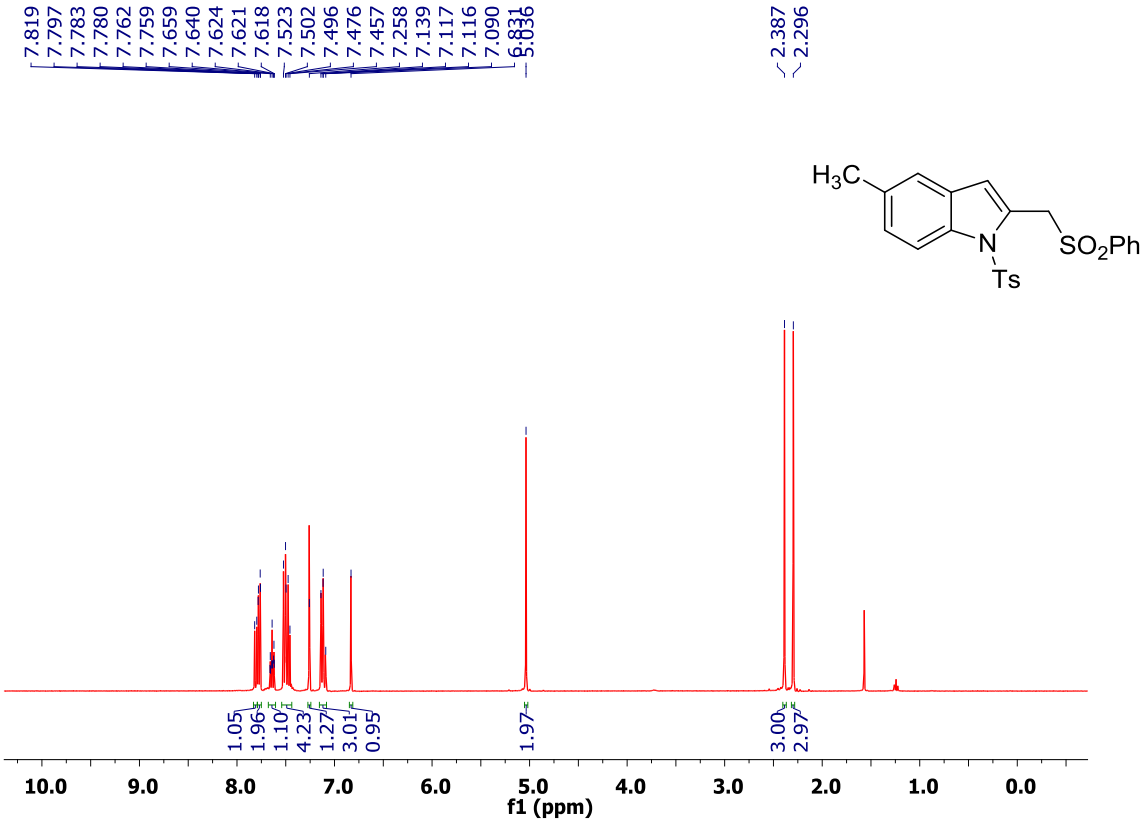
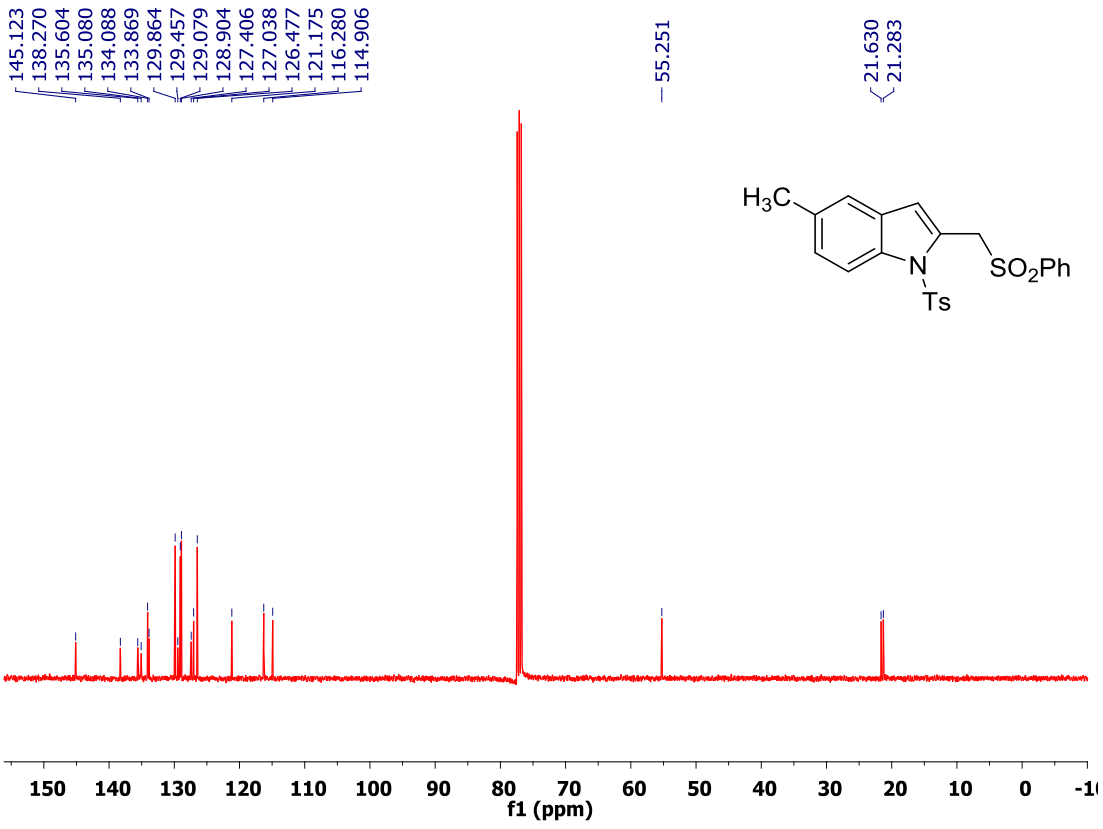
21.790
21.633
21.283
H3C
N
Ts
Ts
f1 (ppm)


7.819
7.797
7.783
7.780
7.762
7.759
7.659
7.640
7.624
7.621
7.618
7.523
7.502
7.496
7.476
7.457
7.258
7.139
7.117
7.116
7.090
6.831
6.830
2.387
2.296
H3C
N
Ts
SO2Ph
1.05
1.96
1.10
4.23
1.27
3.01
0.95
1.97
3.00
2.97
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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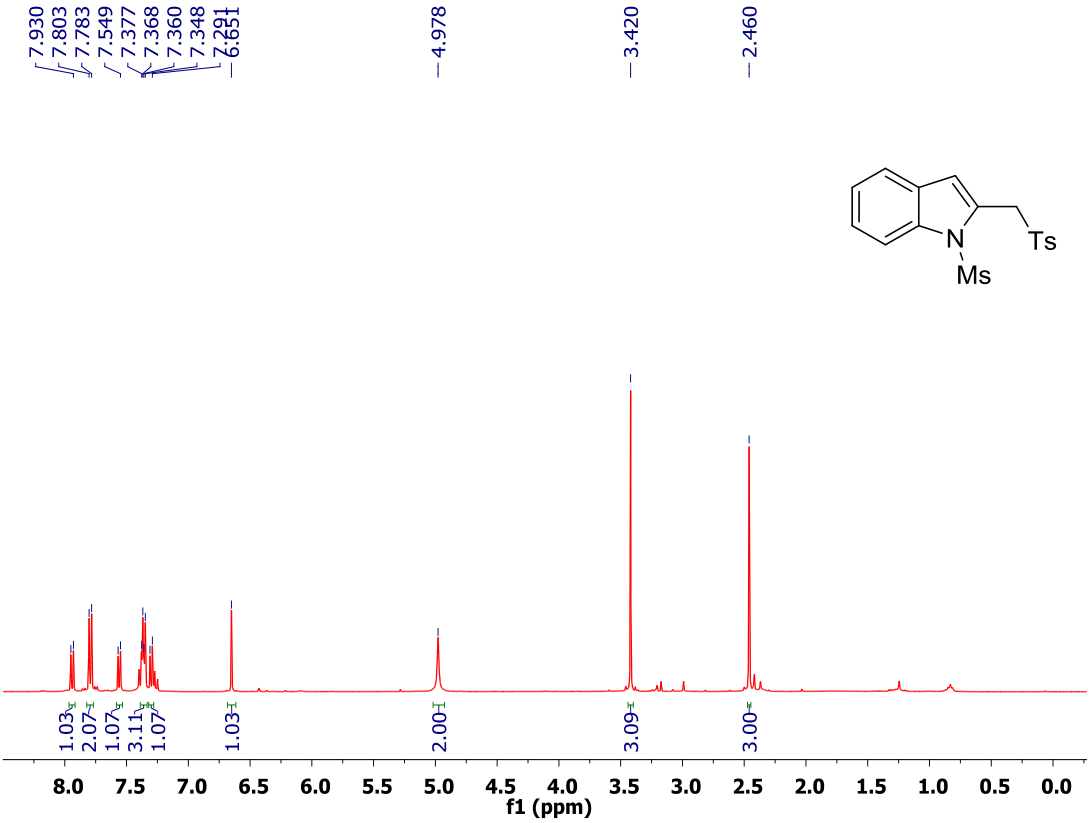
135.604
135.080
134.088
133.869
129.864
129.457
129.079
128.904
127.406
127.038
126.477
121.175
116.280
114.906
55.251
21.630
21.283
H3C
N
Ts
SO2Ph
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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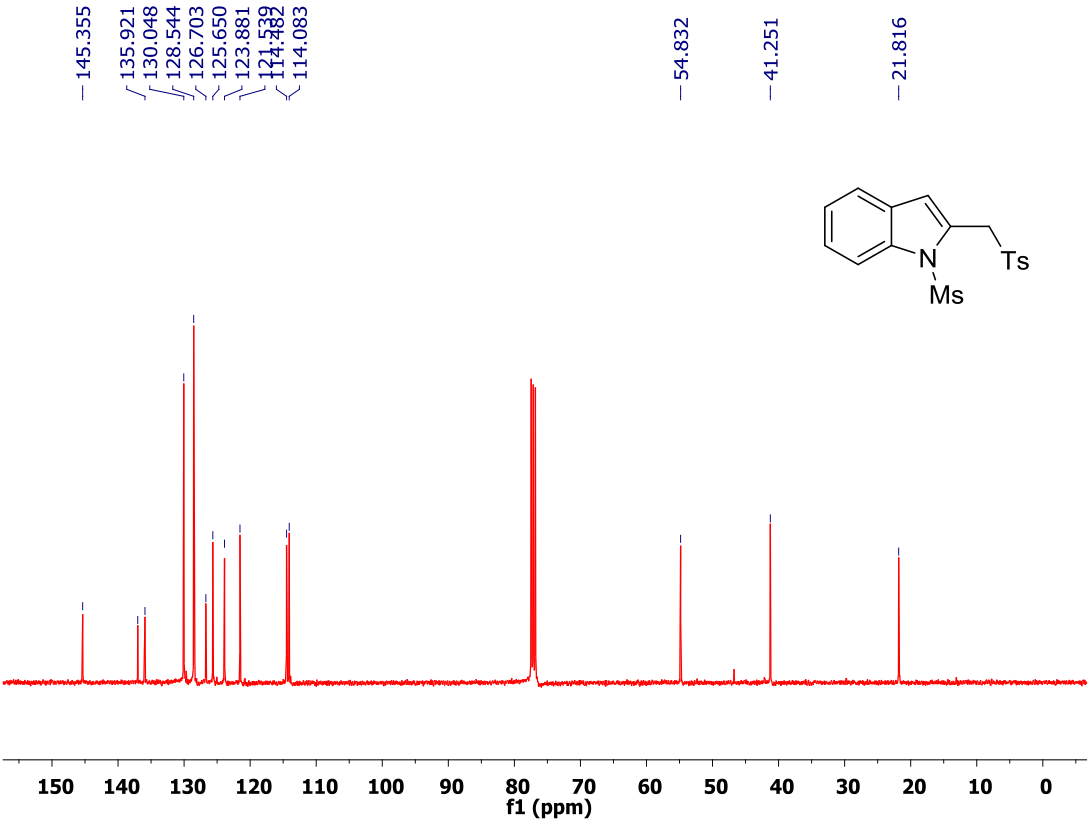
7.803
7.783
7.549
7.377
7.368
7.360
7.348
7.291
6.651
4.978
3.420
2.460
Ts
N
Ms
1.03
2.07
1.07
3.11
1.07
1.03
2.00
3.09
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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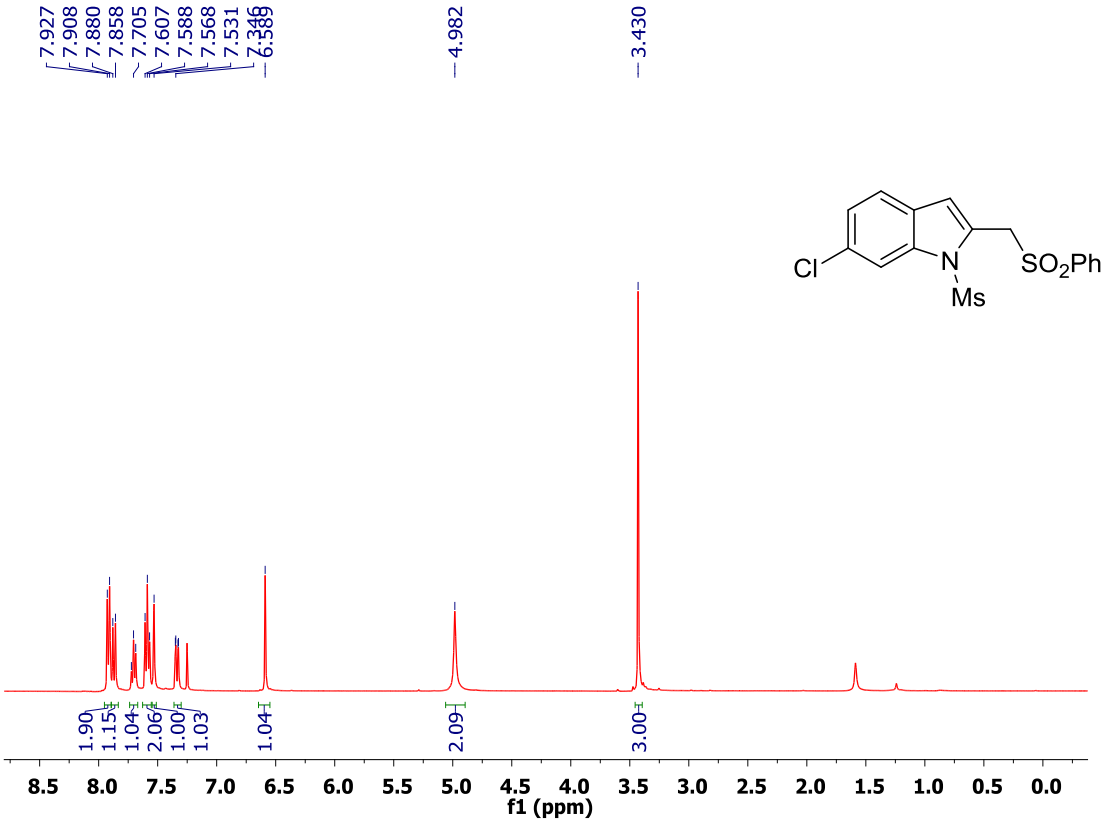
135.921
130.048
128.544
126.703
125.650
123.881
121.539
114.782
114.083
54.832
41.251
21.816
Ts
N
Ms
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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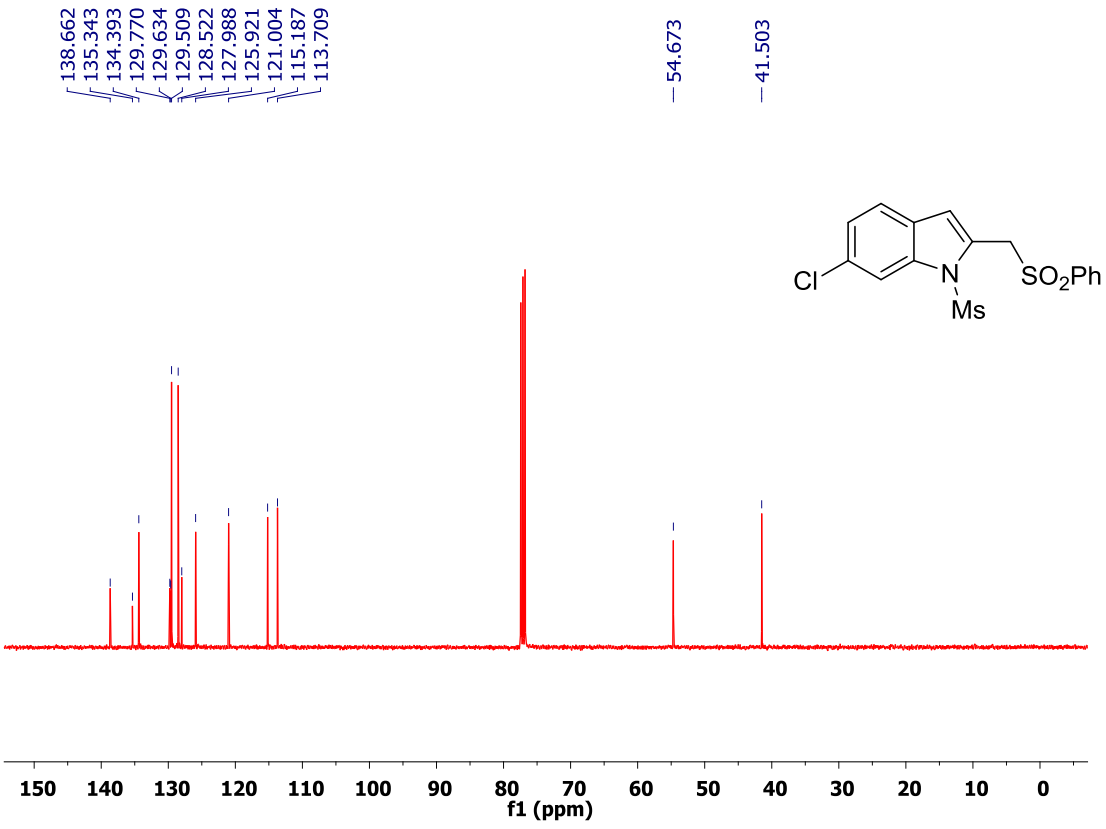
7.908
7.880
7.858
7.705
7.607
7.588
7.568
7.531
7.346
6.589
4.982
3.430
Cl
N
Ms
SO2Ph
1.90
1.15
1.04
2.06
1.00
1.03
1.04
2.09
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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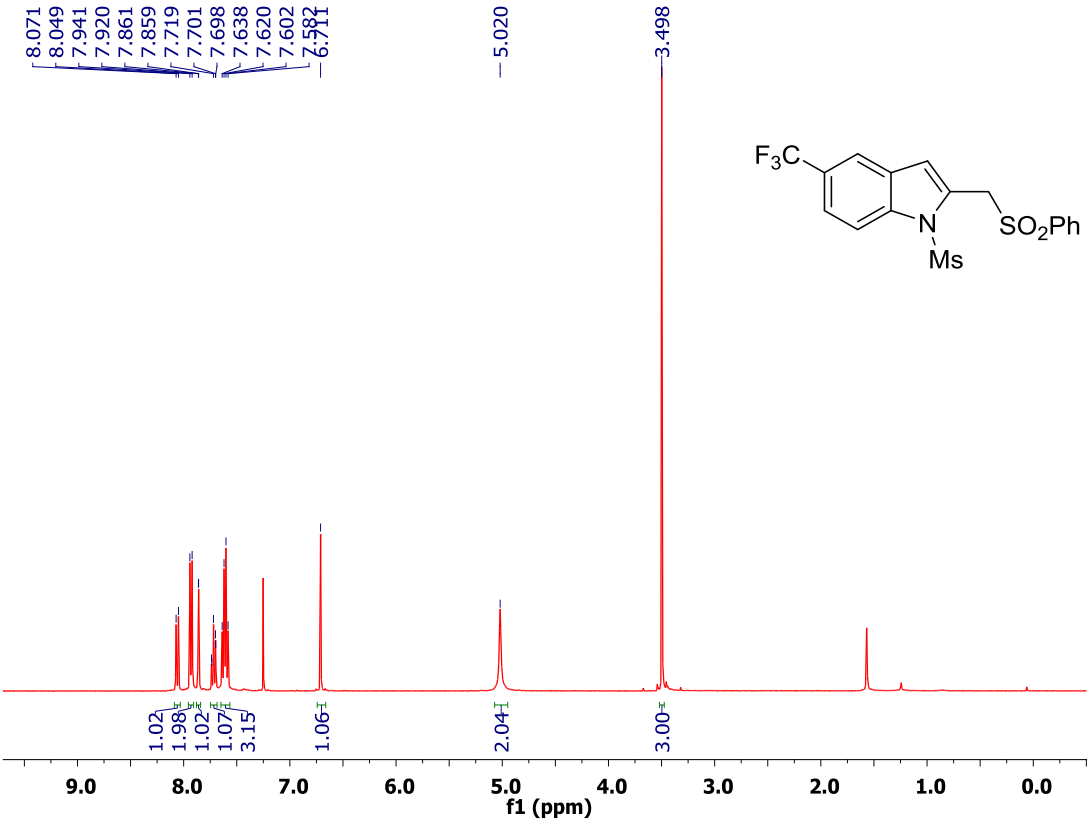
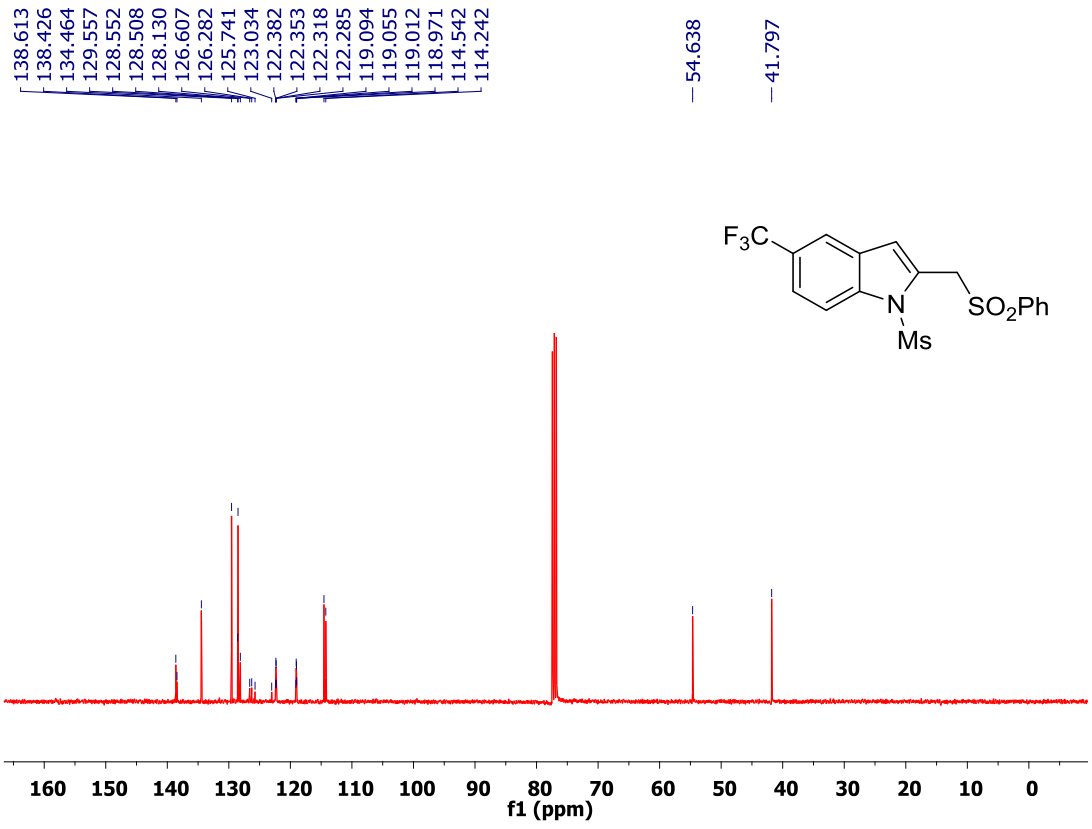
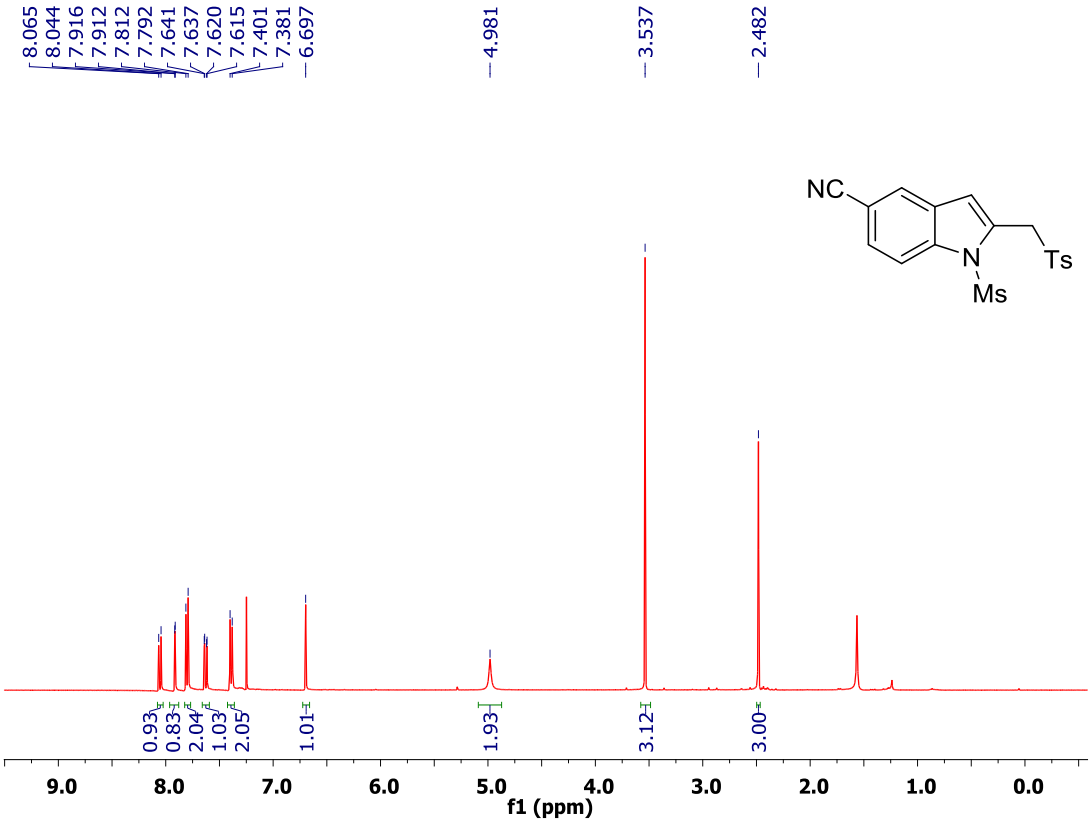
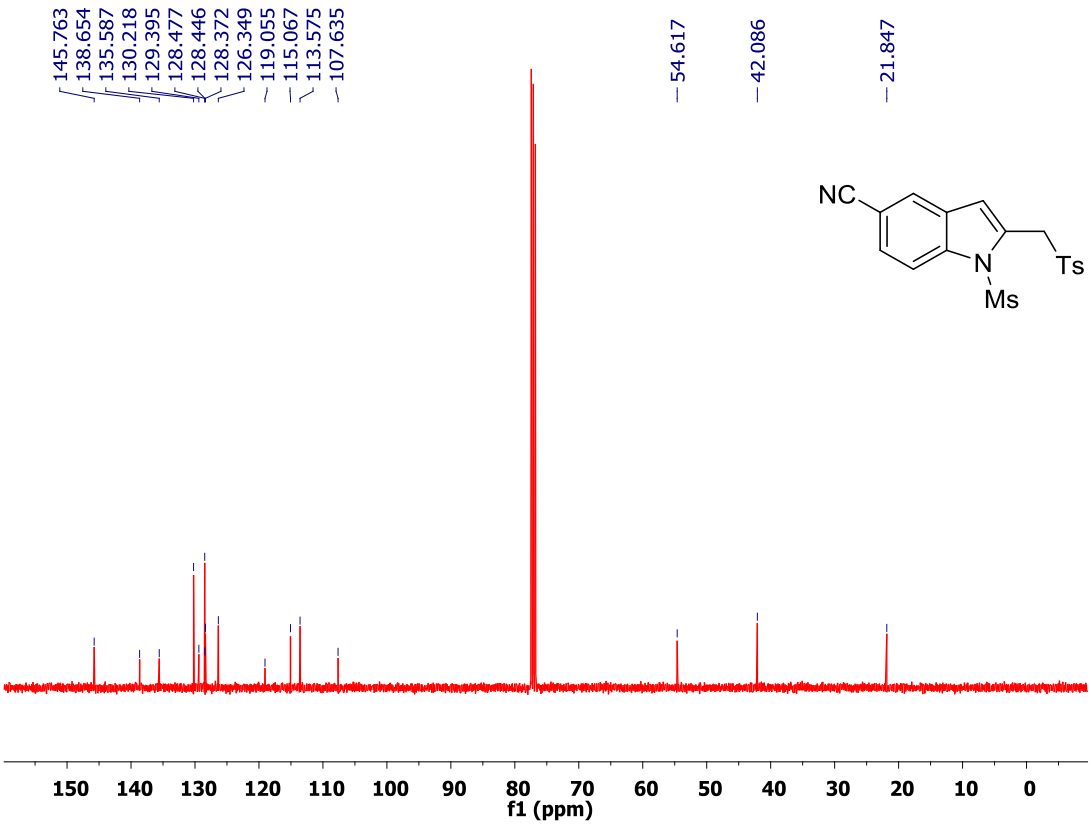
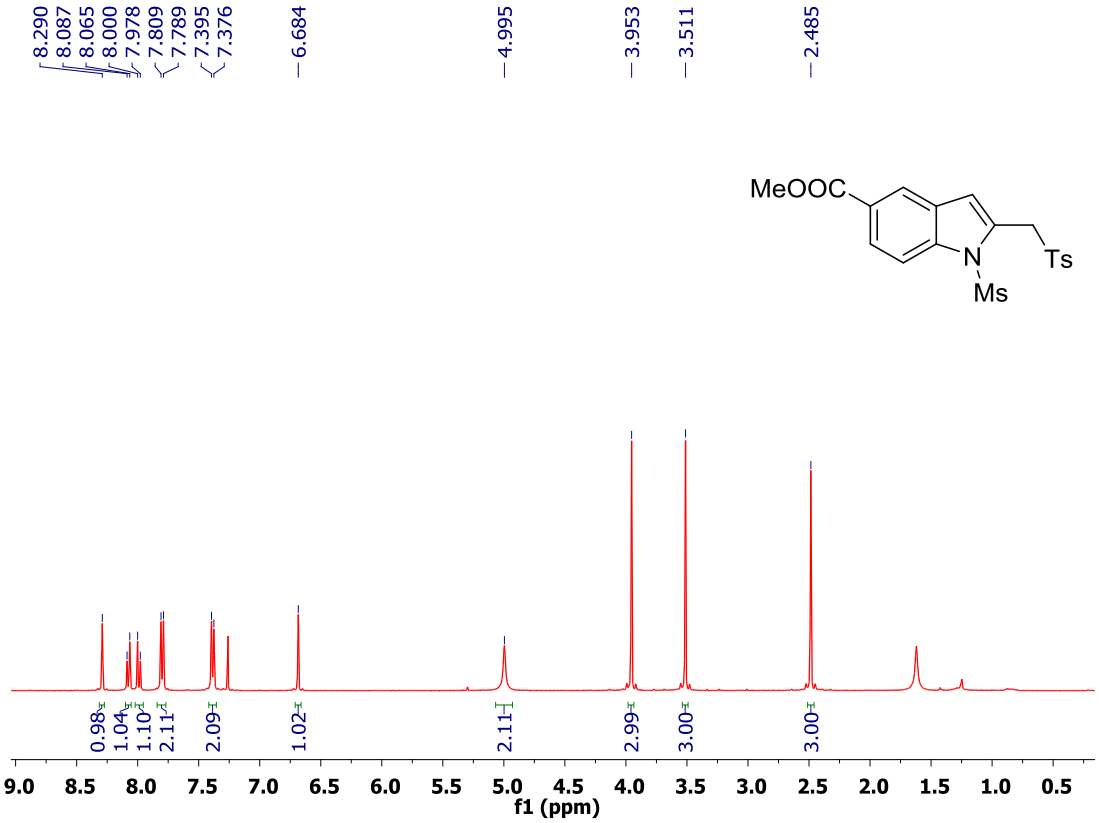
135.343
134.393
129.770
129.634
129.509
128.522
127.988
125.921
121.004
115.187
113.709
54.673
41.503
Cl
N
Ms
SO2Ph
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

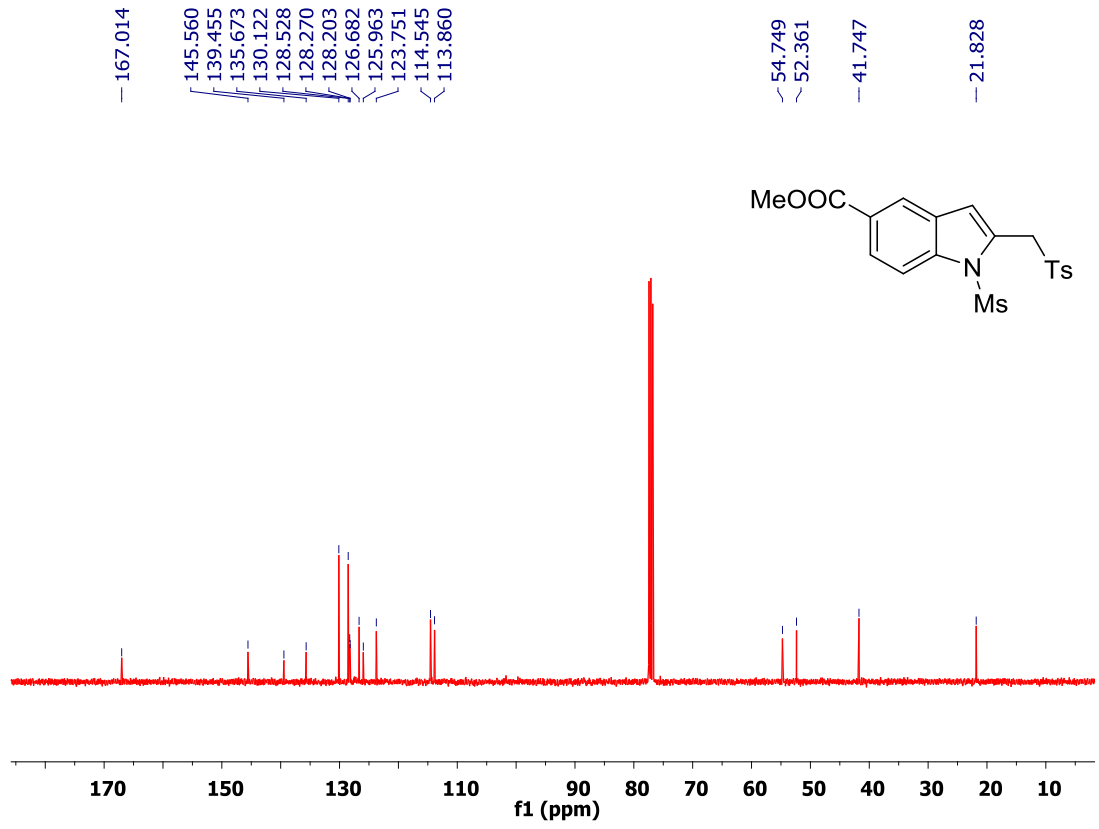

8.071
8.049
7.941
7.920
7.861
7.859
7.719
7.701
7.698
7.638
7.620
7.602
7.582
7.581
6.711
5.020
3.498
F3C
N
Ms
SO2Ph
1.02
1.98
1.02
1.07
3.15
1.06
2.04
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

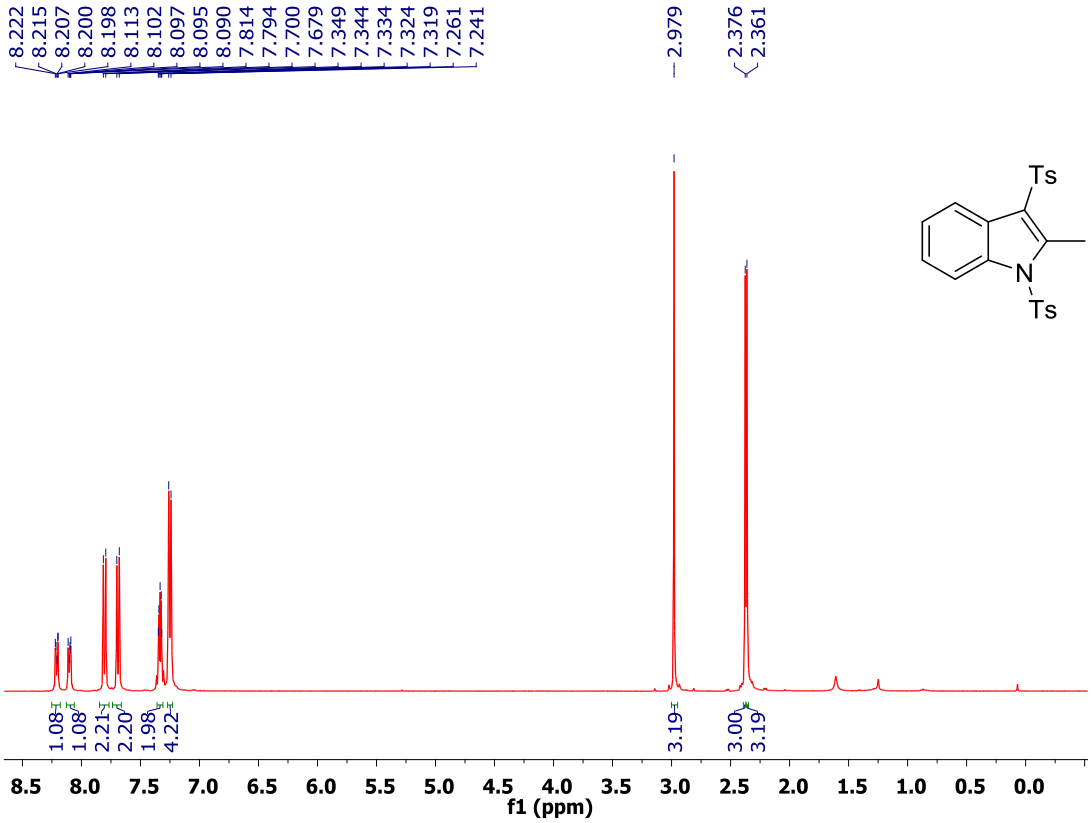

138.613
138.426
134.464
129.557
128.552
128.508
128.130
126.607
126.282
125.741
123.034
122.382
122.353
122.318
122.285
119.094
119.055
119.012
118.971
114.542
114.242
54.638
41.797
F3C
N
Ms
SO2Ph
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

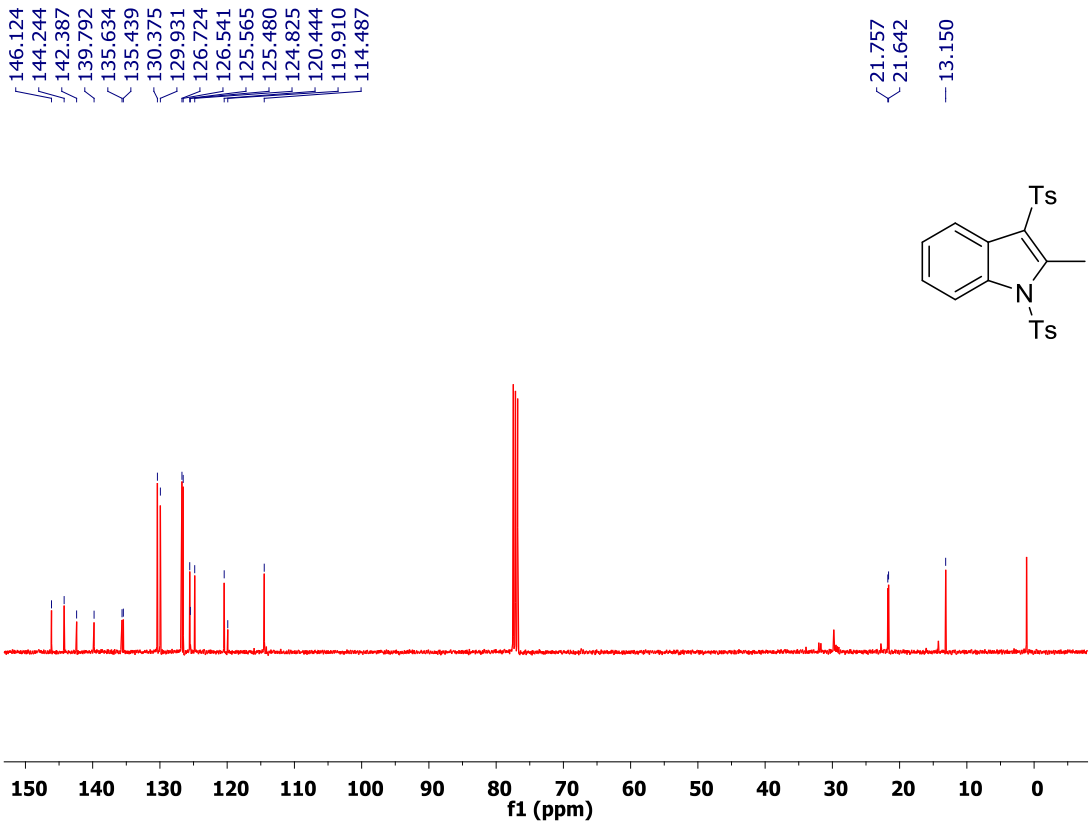

8.065
8.044
7.916
7.912
7.812
7.792
7.641
7.637
7.620
7.615
7.401
7.381
6.697
4.981
3.537
2.482
NC
N
Ts
Ms
0.93
0.83
2.04
1.03
2.05
1.01
1.93
3.12
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


145.763
138.654
135.587
130.218
129.395
128.477
128.446
128.372
126.349
119.055
115.067
113.575
107.635
54.617
42.086
21.847
NC
N
Ts
Ms
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

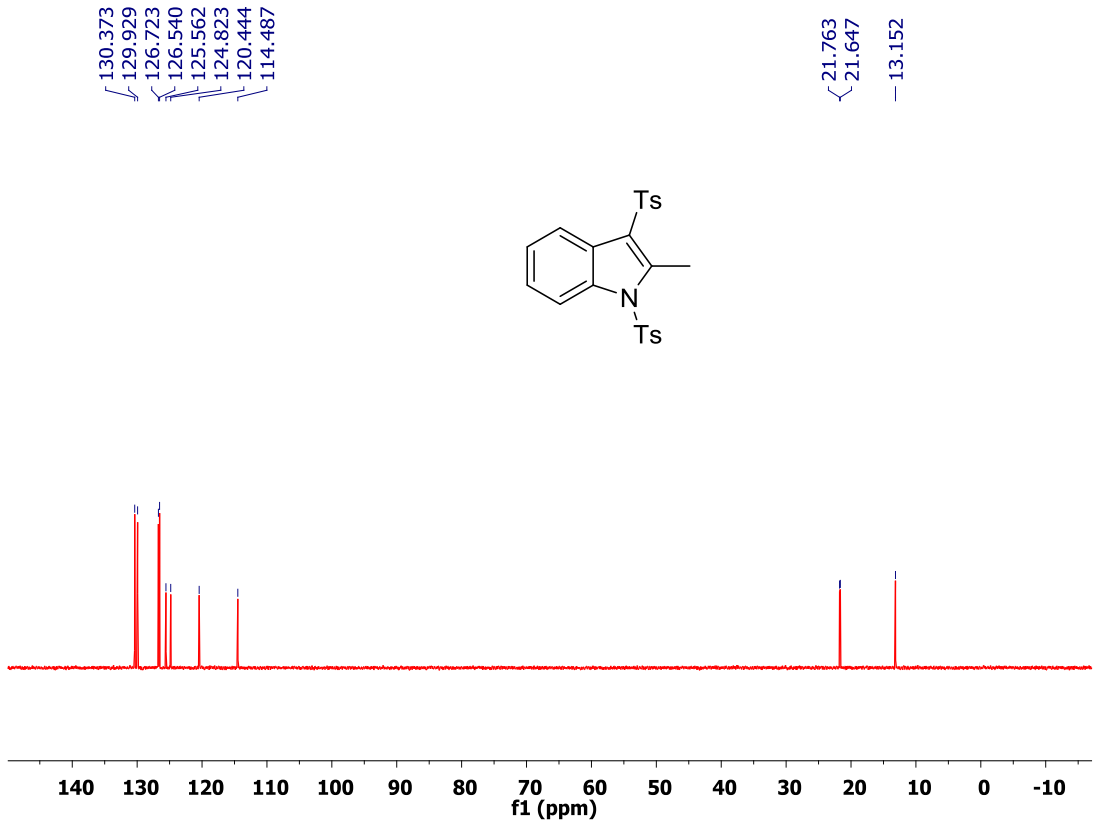

8.290
8.087
8.065
8.000
7.978
7.809
7.789
7.395
7.376
6.684
4.995
3.953
3.511
2.485
MeOOC
N
Ts
Ms
0.98
1.04
1.10
2.11
2.09
1.02
2.11
2.99
3.00
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

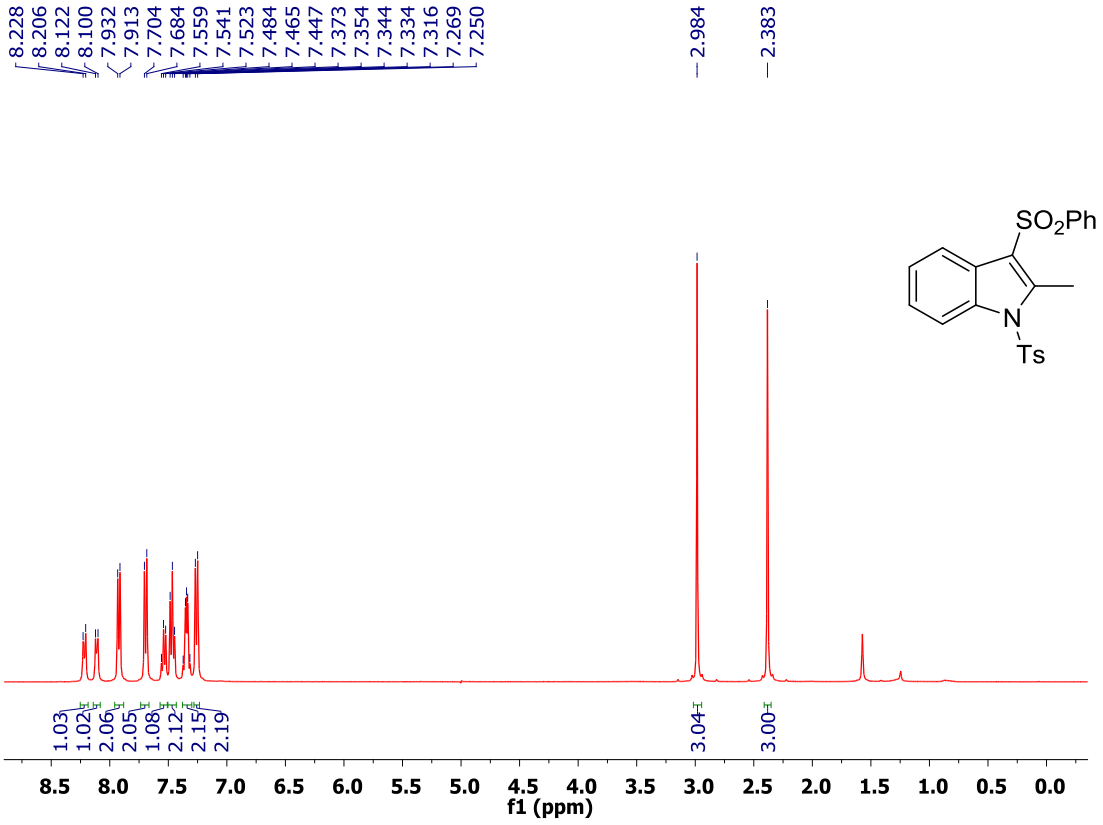

167.014
145.560
139.455
135.673
130.122
128.528
128.270
128.203
126.682
125.963
123.751
114.545
113.860
54.749
52.361
41.747
21.828
MeOOC
N
Ts
Ms
170 150 130 110 90 80 70 60 50 40 30 20 10
f1 (ppm)

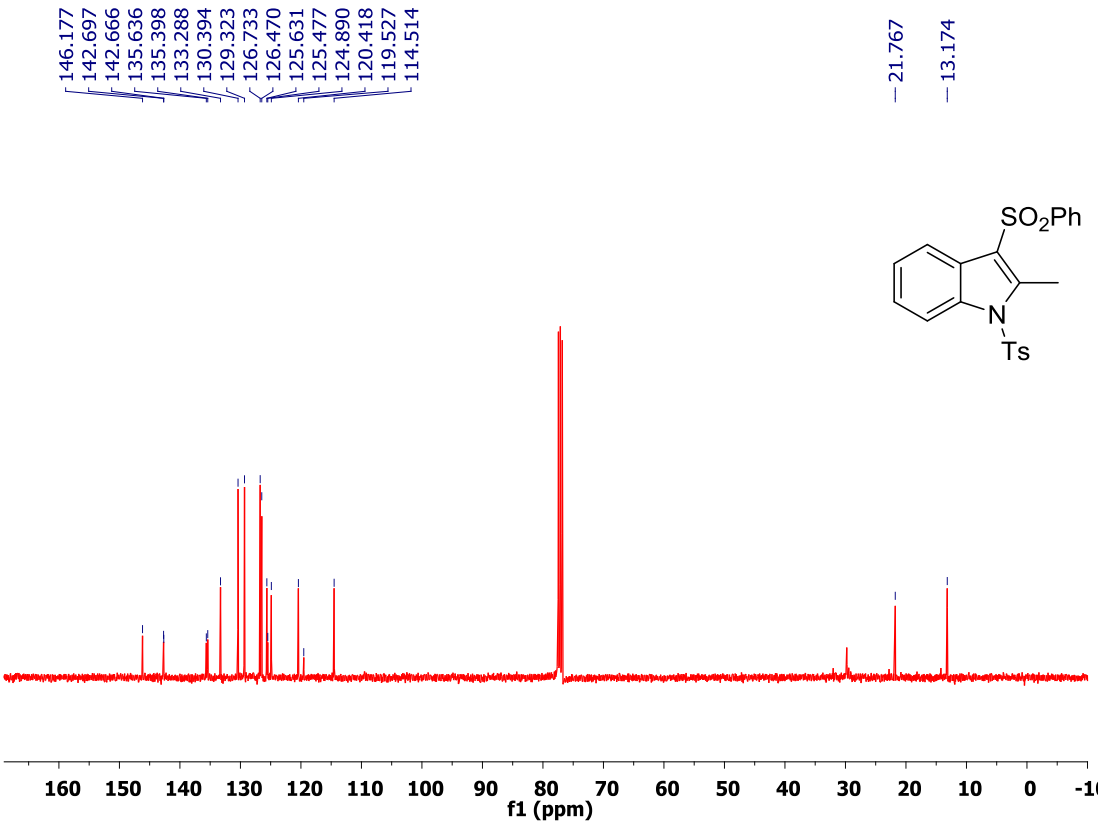

8.222
8.215
8.207
8.200
8.198
8.113
8.102
8.097
8.095
8.090
7.814
7.794
7.700
7.679
7.349
7.344
7.334
7.324
7.319
7.261
7.241
2.979
2.376
2.361
Ts
N
Ts
1.08
1.08
2.21
2.20
1.98
4.22
3.19
3.00
3.19
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

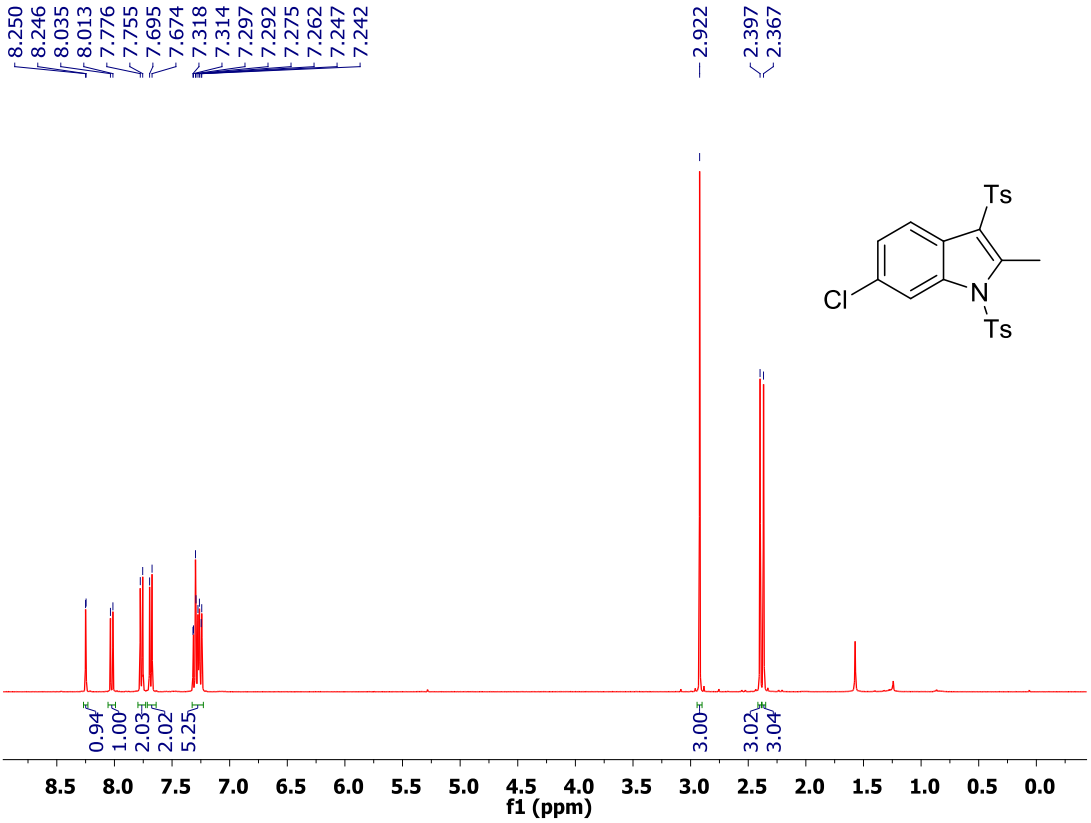

146.124
144.244
142.387
139.792
135.634
135.439
130.375
129.931
126.724
126.541
125.565
125.480
124.825
120.444
119.910
114.487
21.757
21.642
13.150
Ts
N
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

DEPT-135


130.373
129.929
126.723
126.540
125.562
124.823
120.444
114.487
21.763
21.647
13.152
Ts
N
Ts
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.228
8.206
8.122
8.100
7.932
7.913
7.704
7.684
7.559
7.541
7.523
7.484
7.465
7.447
7.373
7.354
7.344
7.334
7.316
7.269
7.250
2.984
2.383
SO2Ph
N
Ts
1.03
1.02
2.06
2.05
1.08
2.12
2.15
2.19
3.04
3.00
f1 (ppm)


146.177
142.697
142.666
135.636
135.398
133.288
130.394
129.323
126.733
126.470
125.631
125.477
124.890
120.418
119.527
114.514
21.767
13.174
SO2Ph
N
Ts
f1 (ppm)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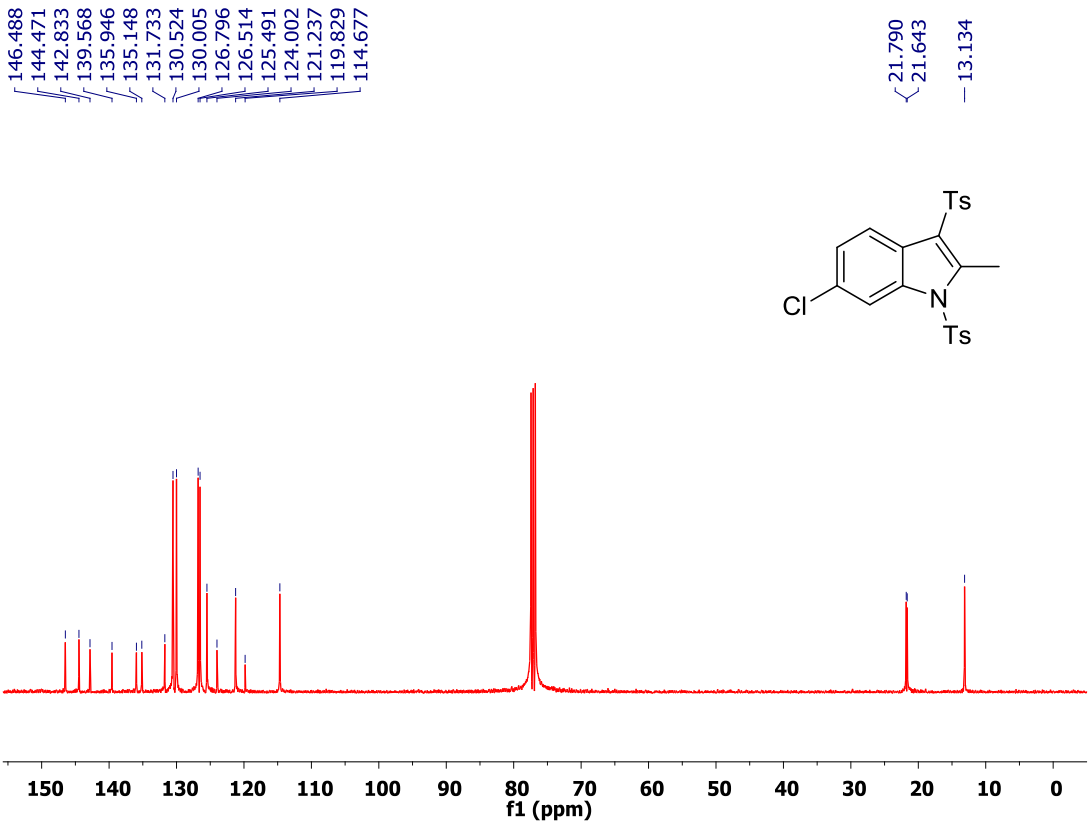
8.246
8.035
8.013
7.776
7.755
7.695
7.674
7.318
7.314
7.297
7.292
7.275
7.262
7.247
7.242
2.922
2.397
2.367
Ts
Cl
N
Ts
0.94
1.00
2.03
2.02
5.25
3.00
3.02
3.04
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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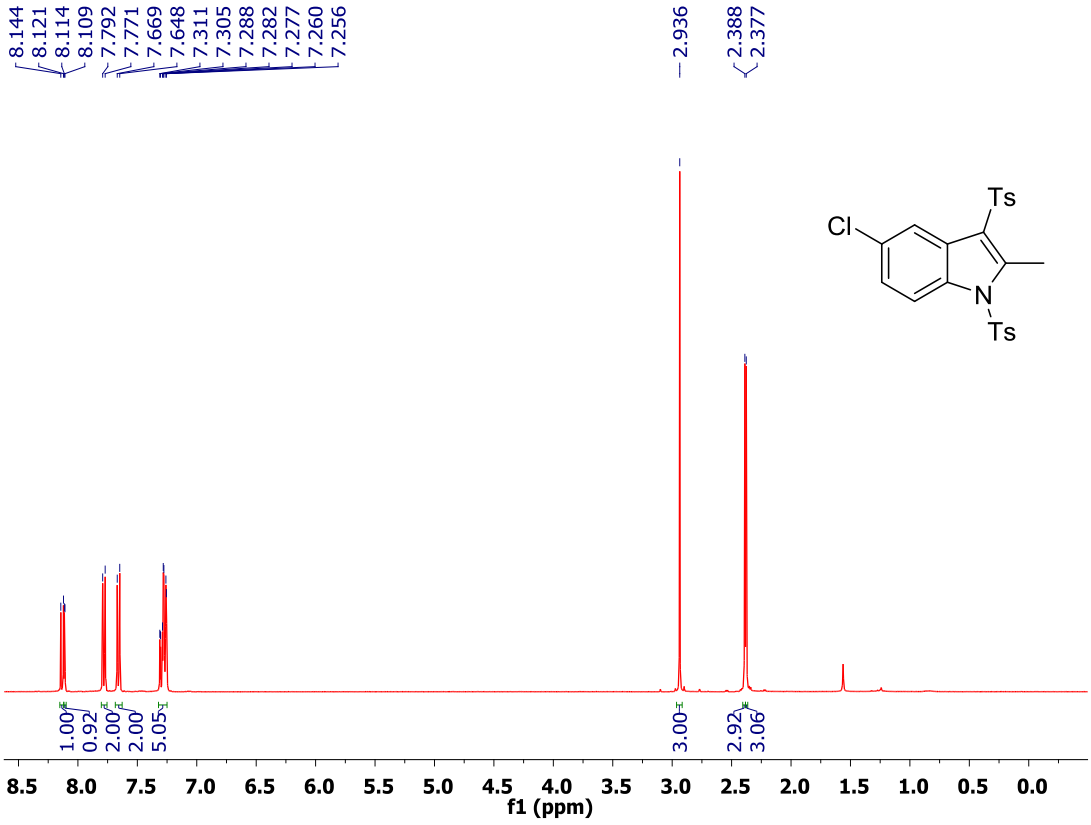
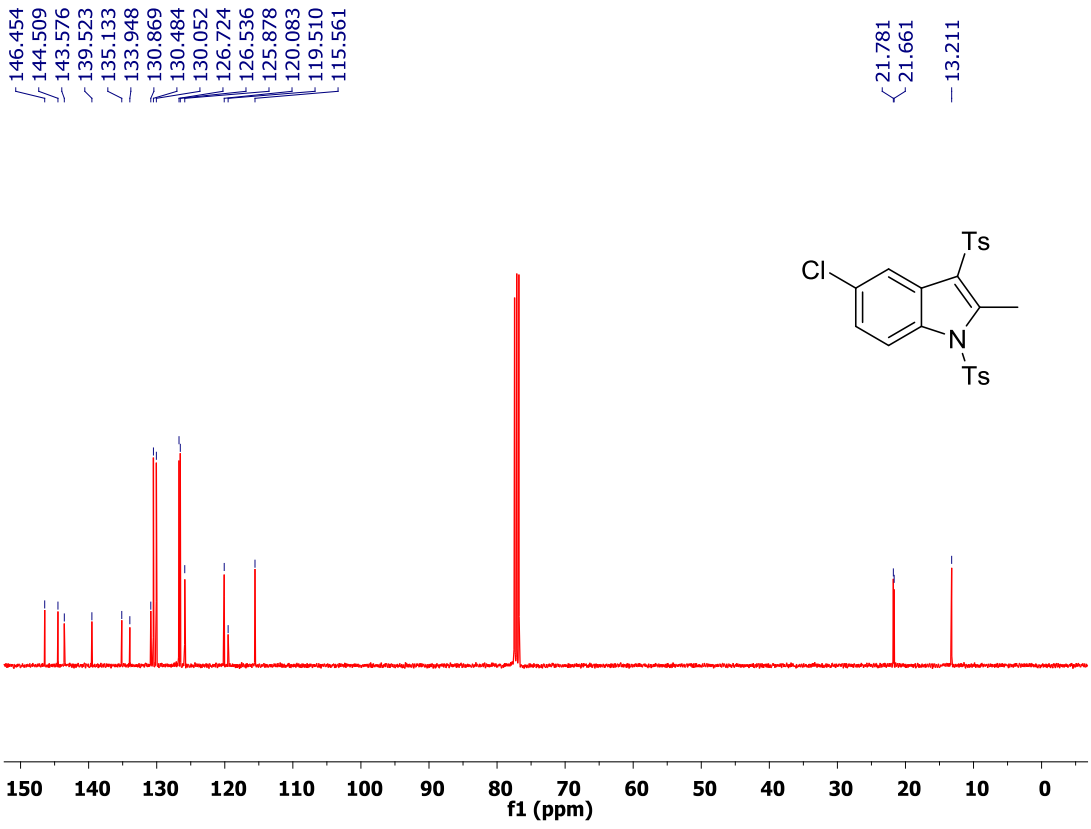
139.568
135.946
135.148
131.733
130.524
130.005
126.796
126.514
125.491
124.002
121.237
119.829
114.677
21.790
21.643
13.134
Ts
Cl
N
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.144
8.121
8.114
8.109
7.792
7.771
7.669
7.648
7.311
7.305
7.288
7.282
7.277
7.260
7.256
2.936
2.388
2.377
Cl
Ts
N
Ts
1.00
0.92
2.00
2.00
5.05
3.00
2.92
3.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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143.576
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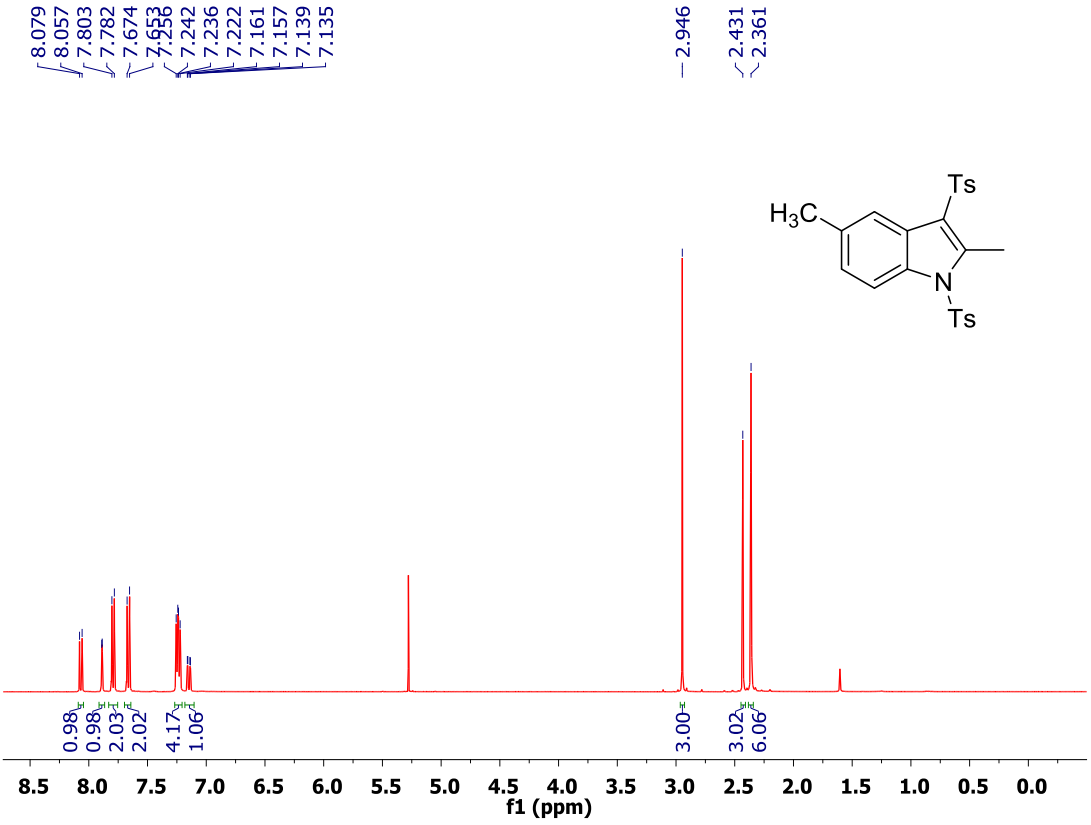
135.133
133.948
130.869
130.484
130.052
126.724
126.536
125.878
120.083
119.510
115.561
21.781
21.661
13.211
Cl
Ts
N
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.057
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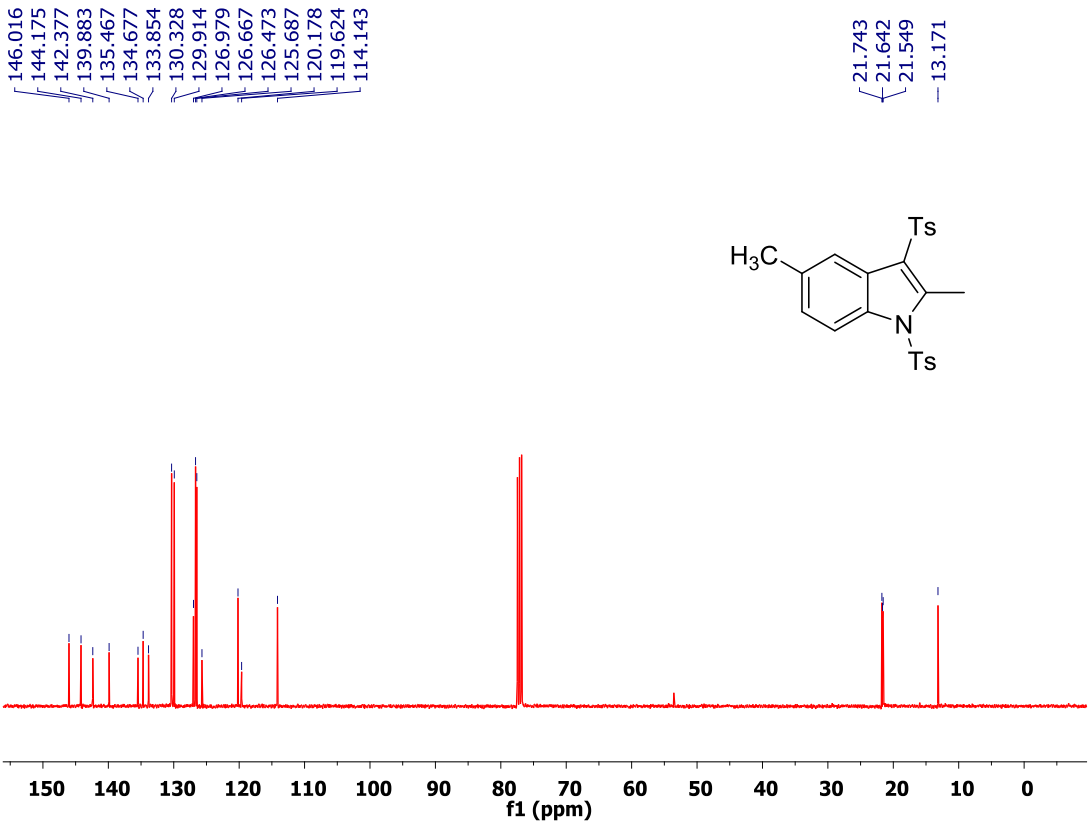
7.782
7.674
7.653
7.255
7.242
7.236
7.222
7.161
7.157
7.139
7.135
2.946
2.431
2.361
Ts
H3C
N
Ts
0.98
0.98
2.03
2.02
4.17
1.06
3.00
3.02
6.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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142.377
139.883
135.467
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130.328
129.914
126.979
126.667
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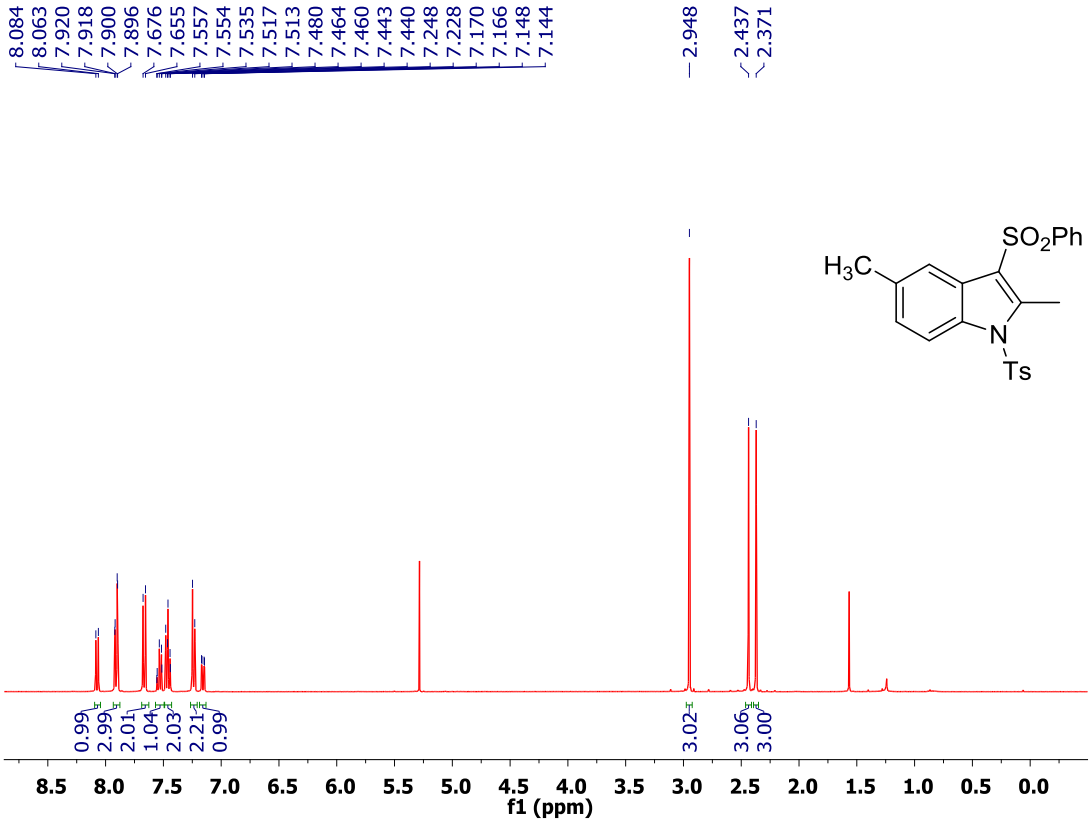
125.687
120.178
119.624
114.143
21.743
21.642
21.549
13.171
Ts
H3C
N
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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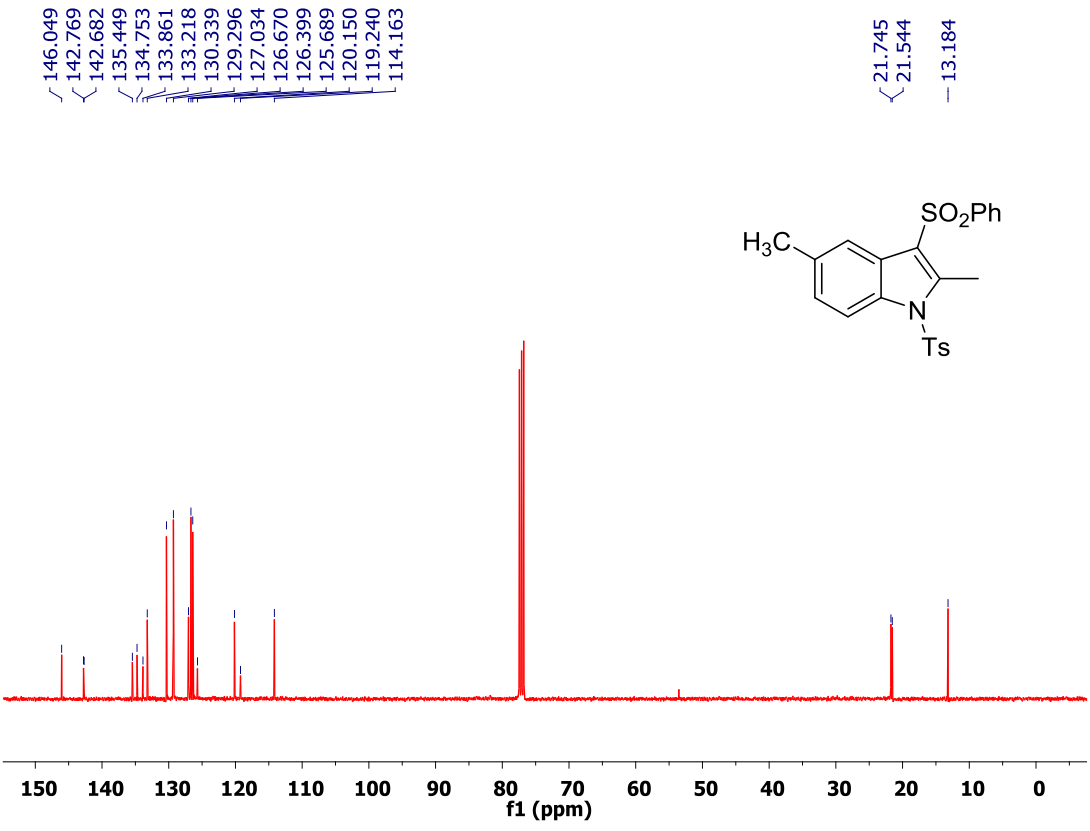
7.655
7.557
7.554
7.535
7.517
7.513
7.480
7.464
7.460
7.443
7.440
7.248
7.228
7.170
7.166
7.148
7.144
2.948
2.437
2.371
SO2Ph
H3C
N
Ts
0.99
2.99
2.01
1.04
2.03
2.21
0.99
3.02
3.06
3.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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133.861
133.218
130.339
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127.034
126.670
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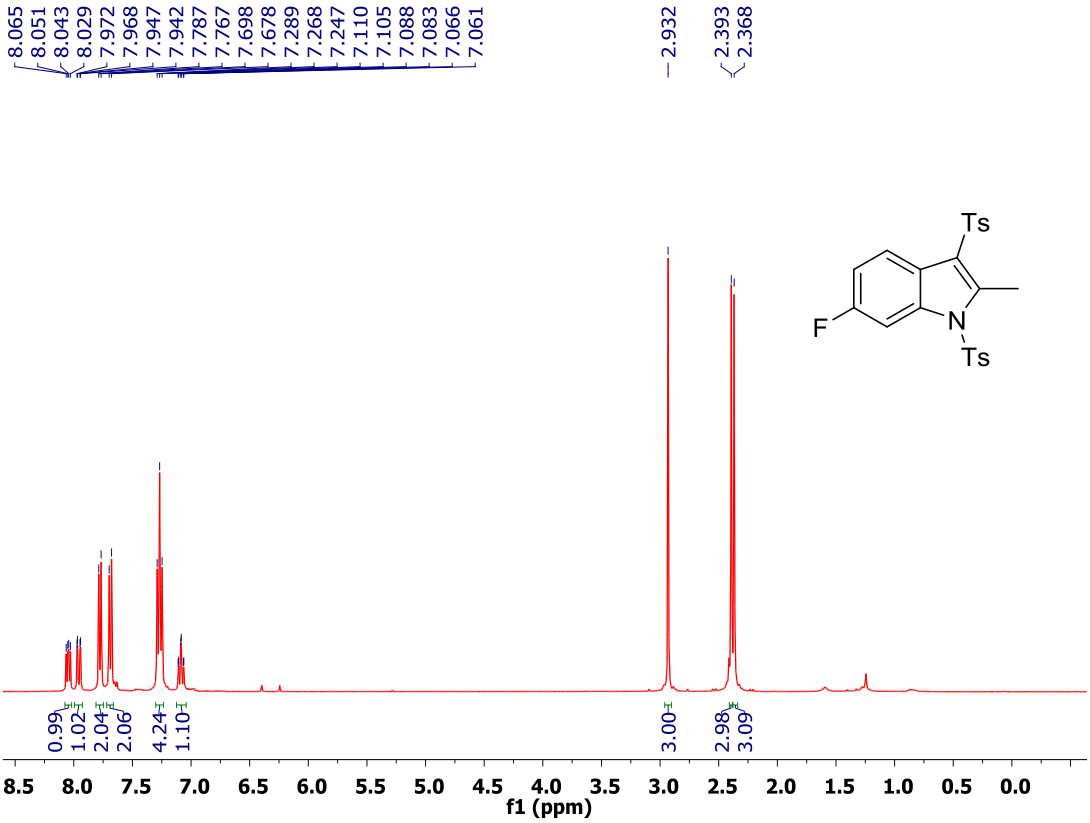
125.689
120.150
119.240
114.163
21.745
21.544
13.184
SO2Ph
H3C
N
Ts
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.043
8.029
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7.968
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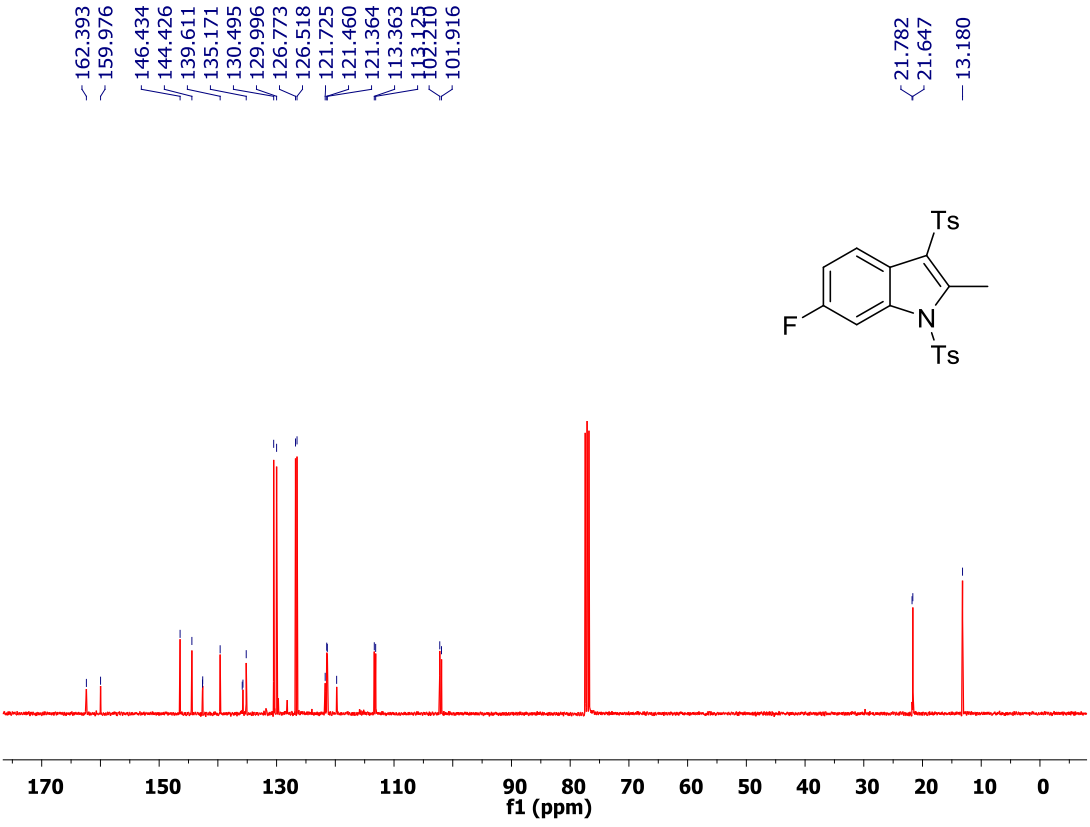
7.942
7.787
7.767
7.698
7.678
7.289
7.268
7.247
7.110
7.105
7.088
7.083
7.066
7.061
2.932
2.393
2.368
Ts
F
N
Ts
0.99
1.02
2.04
2.06
4.24
1.10
3.00
2.98
3.09
f1 (ppm)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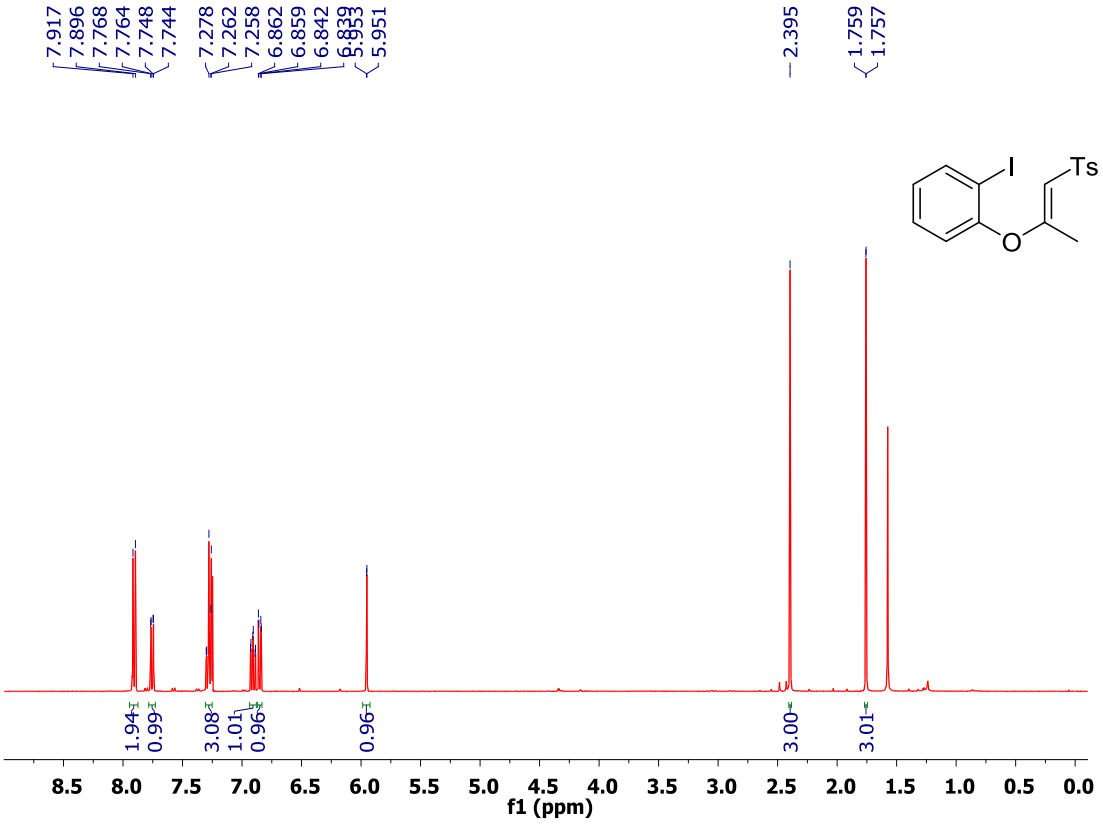
159.976
146.434
144.426
139.611
135.171
130.495
129.996
126.773
126.518
121.725
121.460
121.364
113.363
113.125
102.210
101.916
21.782
21.647
13.180
Ts
F
N
Ts
f1 (ppm)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7.768
7.764
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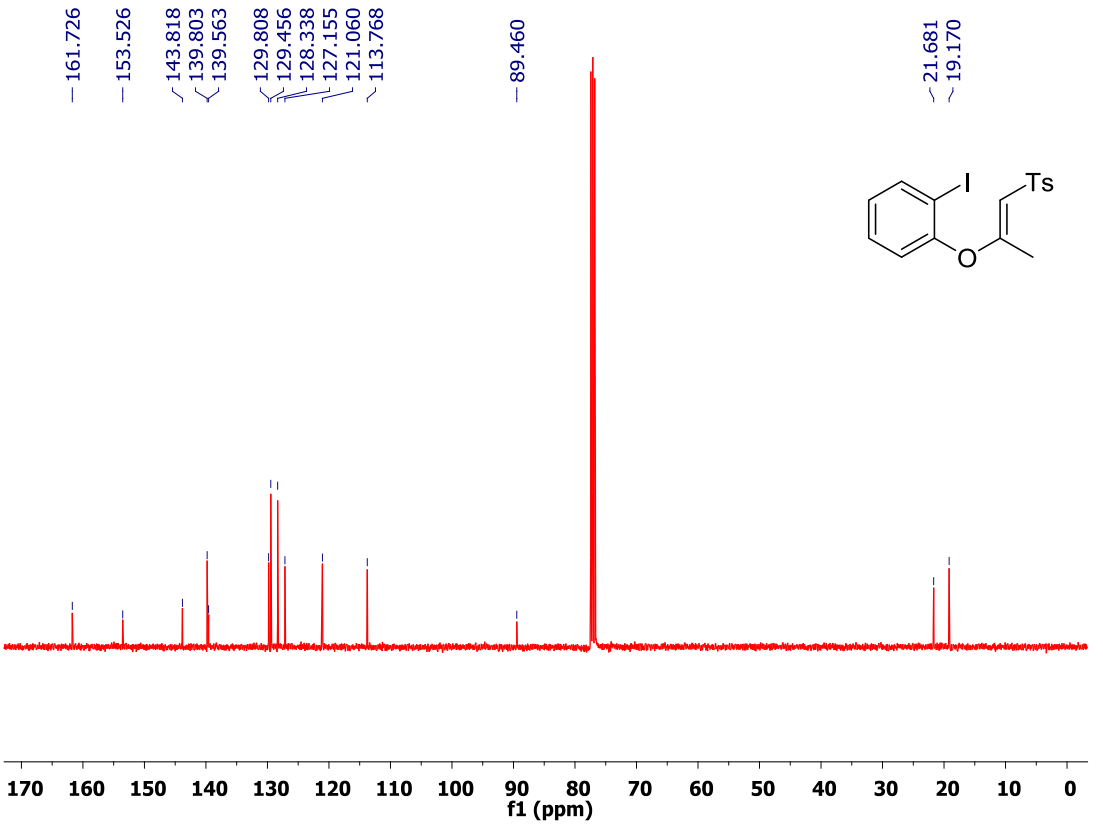
7.744
7.278
7.262
7.258
6.862
6.859
6.842
5.951
2.395
1.759
1.757
I
Ts
O
1.94
0.99
3.08
1.01
0.96
0.96
3.00
3.01
f1 (ppm)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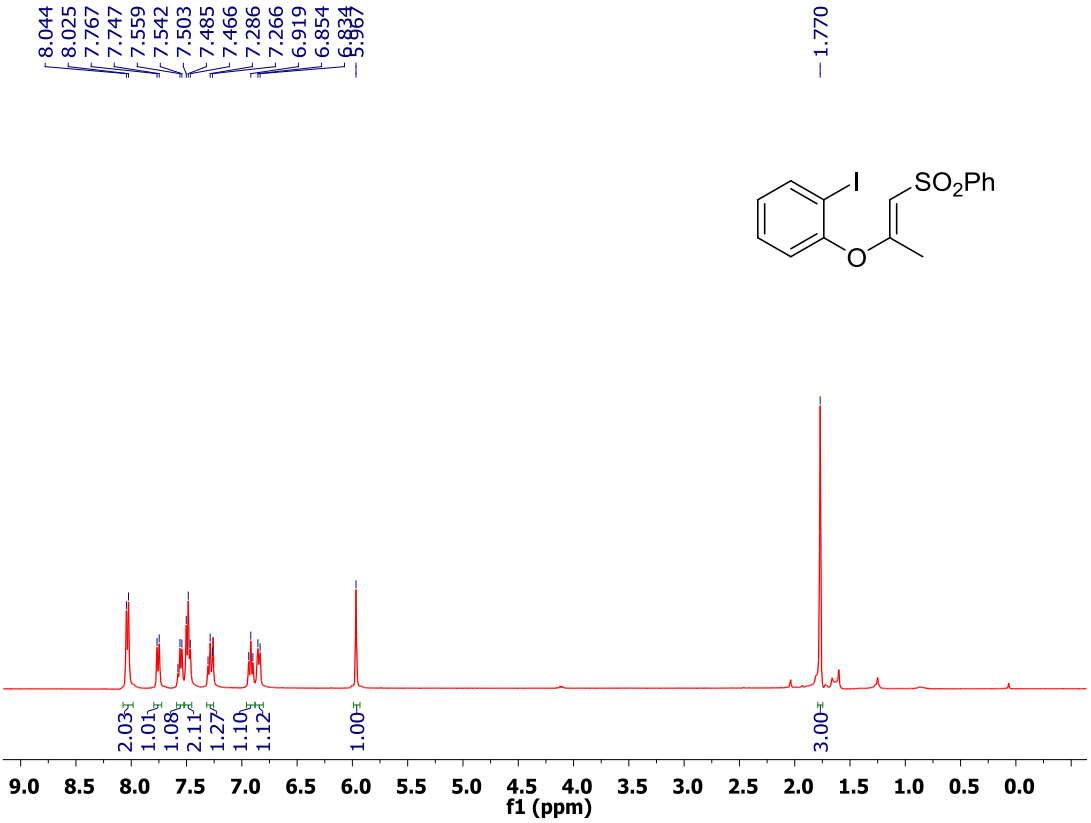
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O
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1.01
1.08
2.11
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1.10
1.12
1.00
3.00
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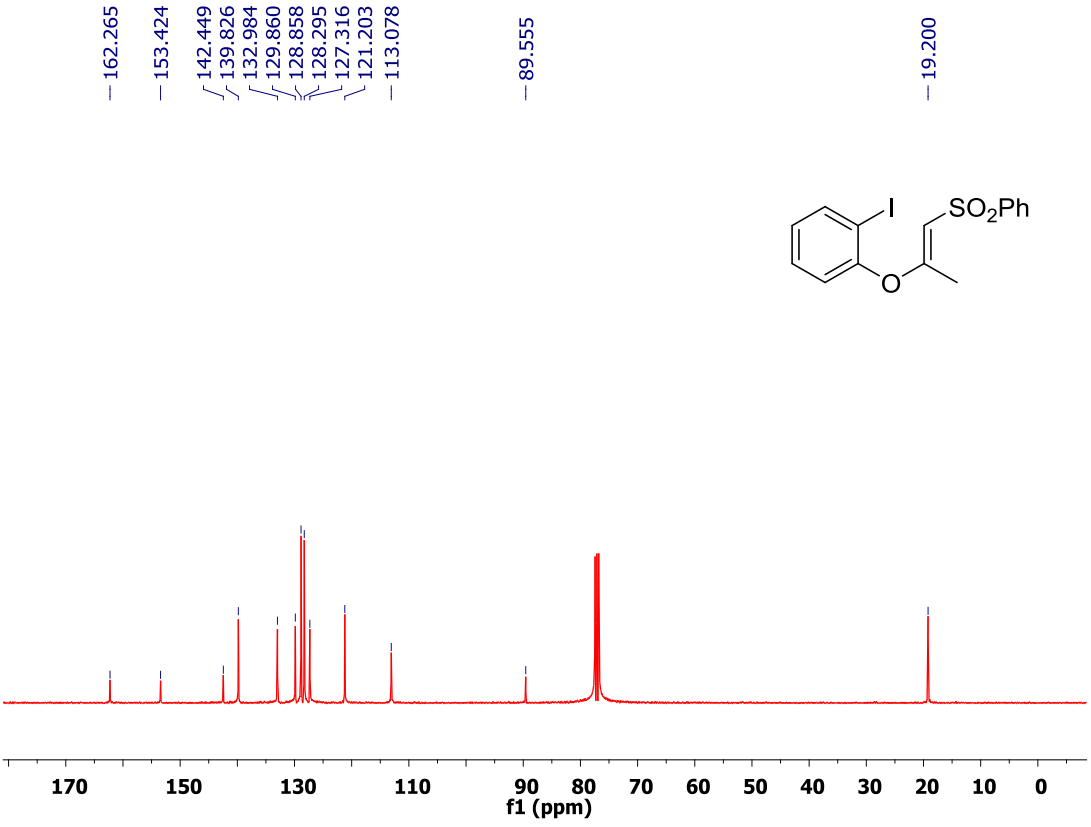
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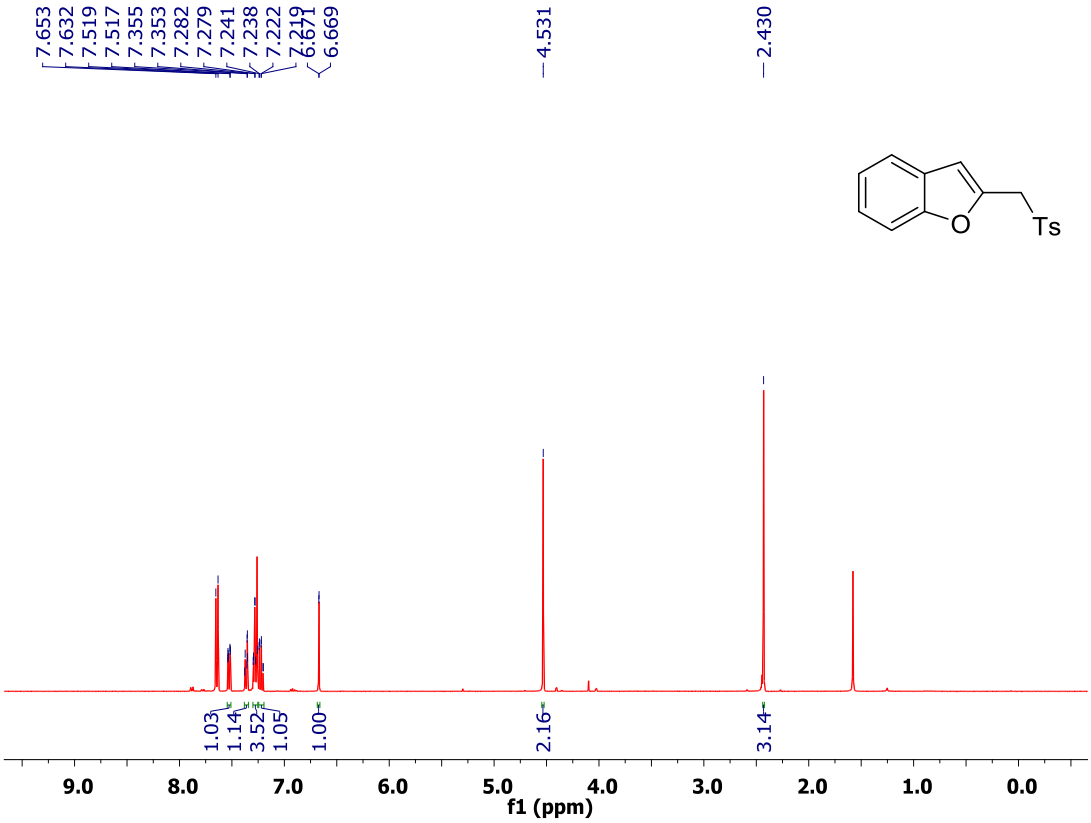
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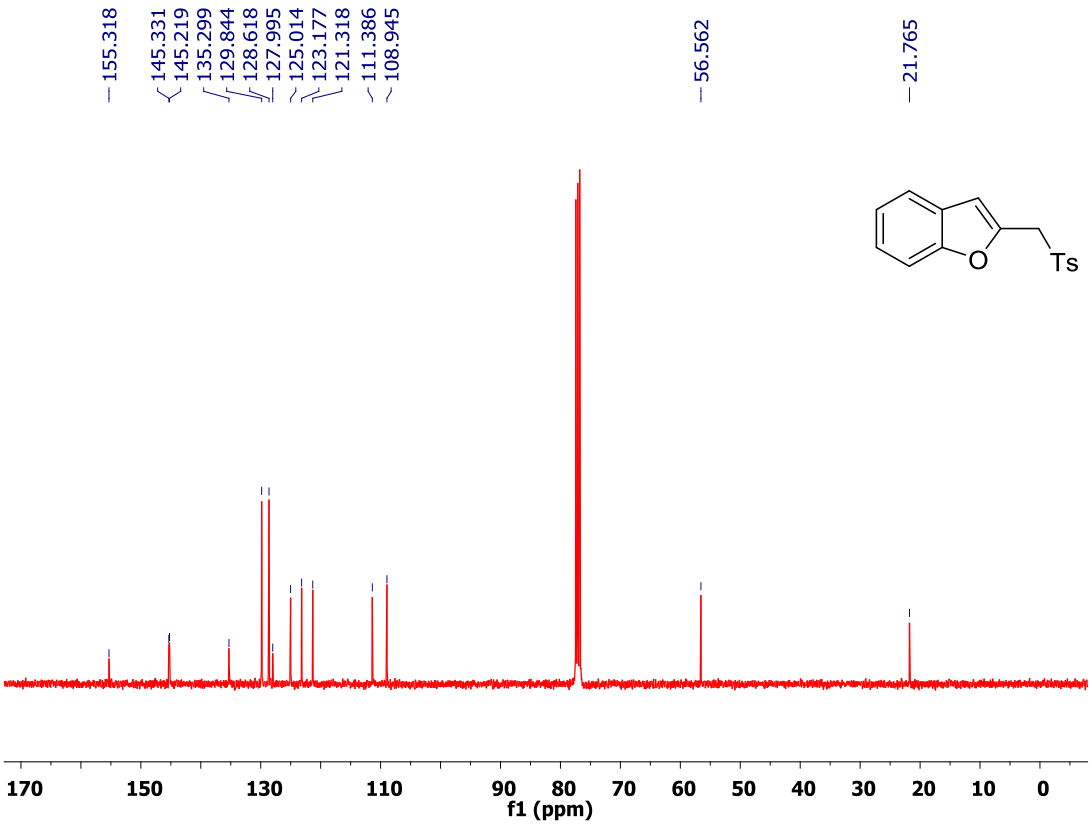
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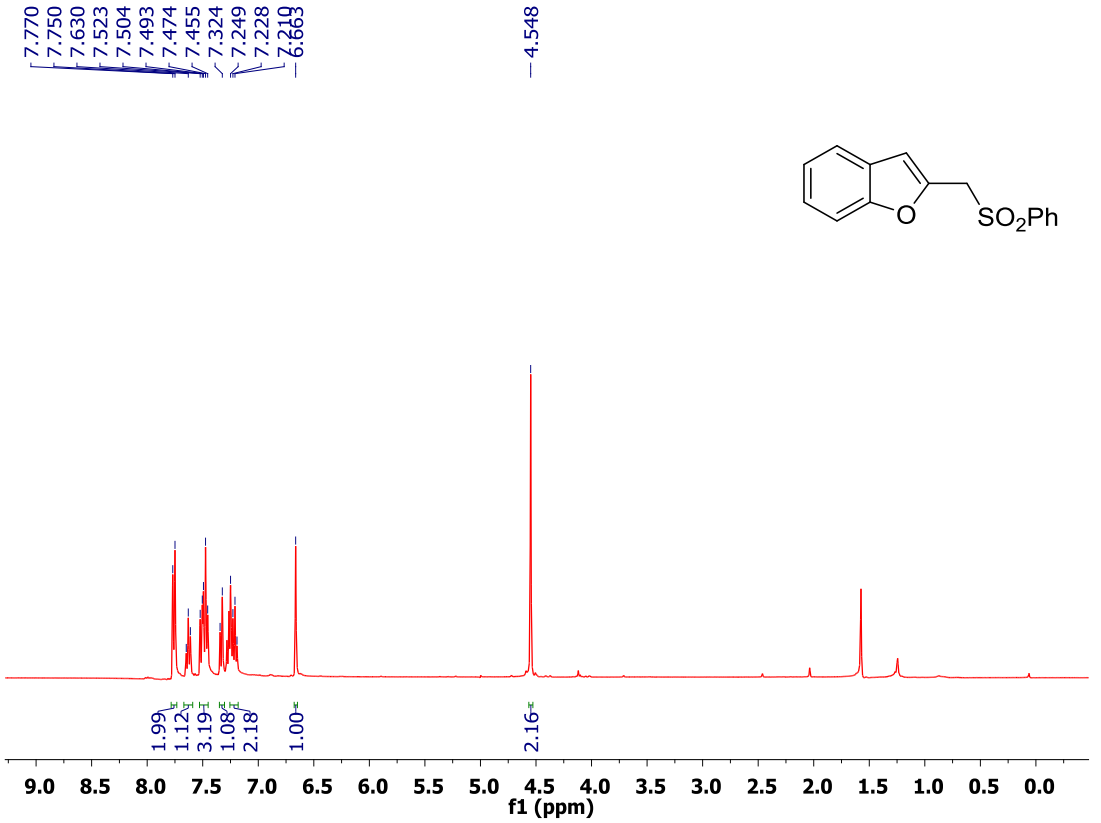
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2.18
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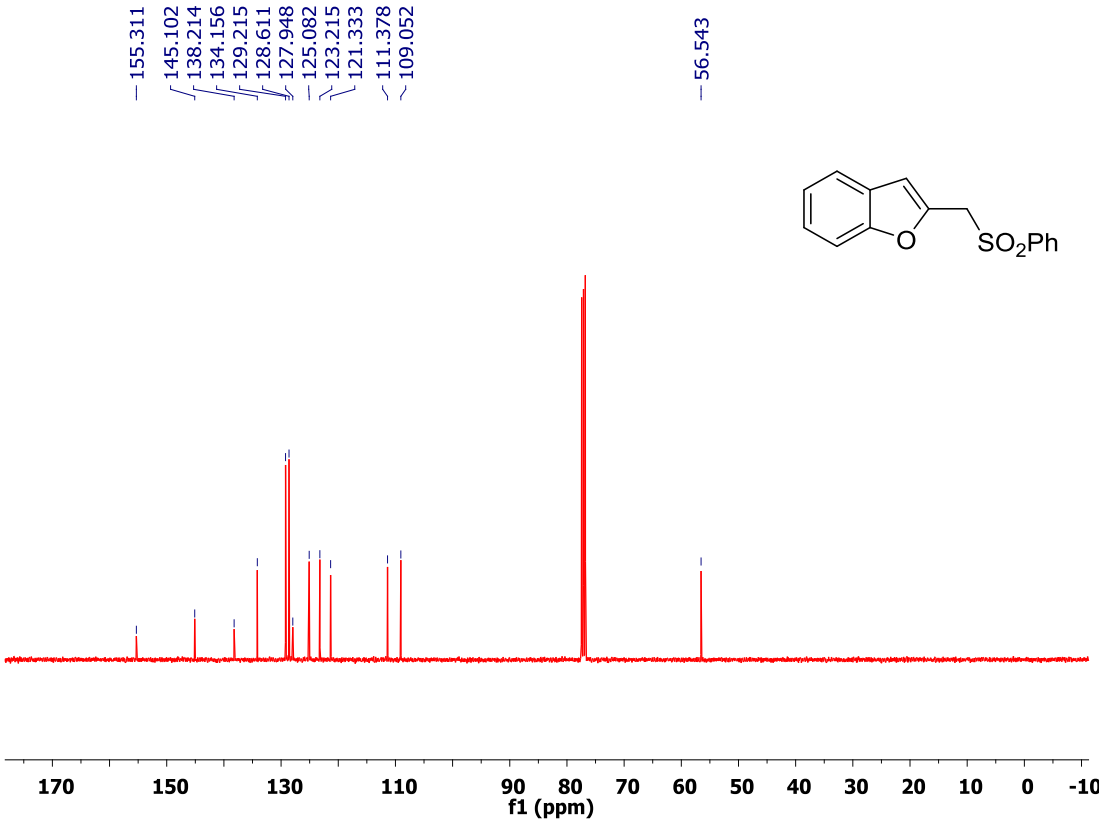
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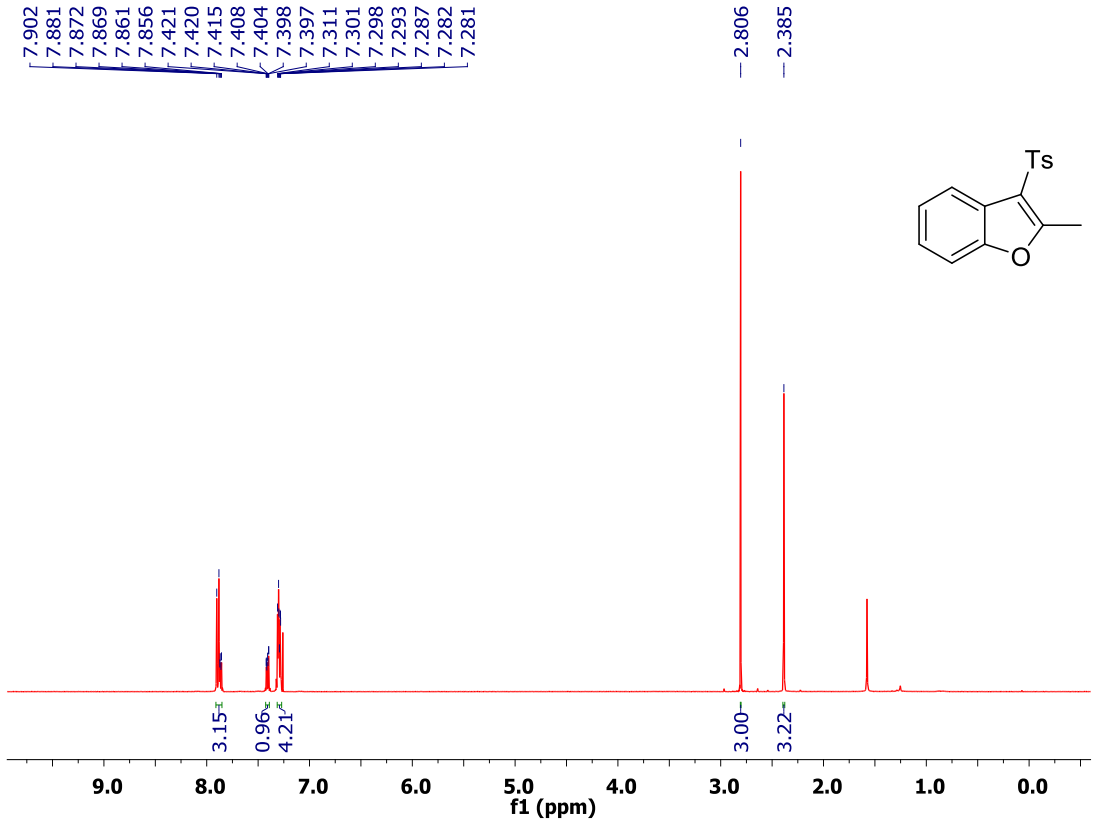
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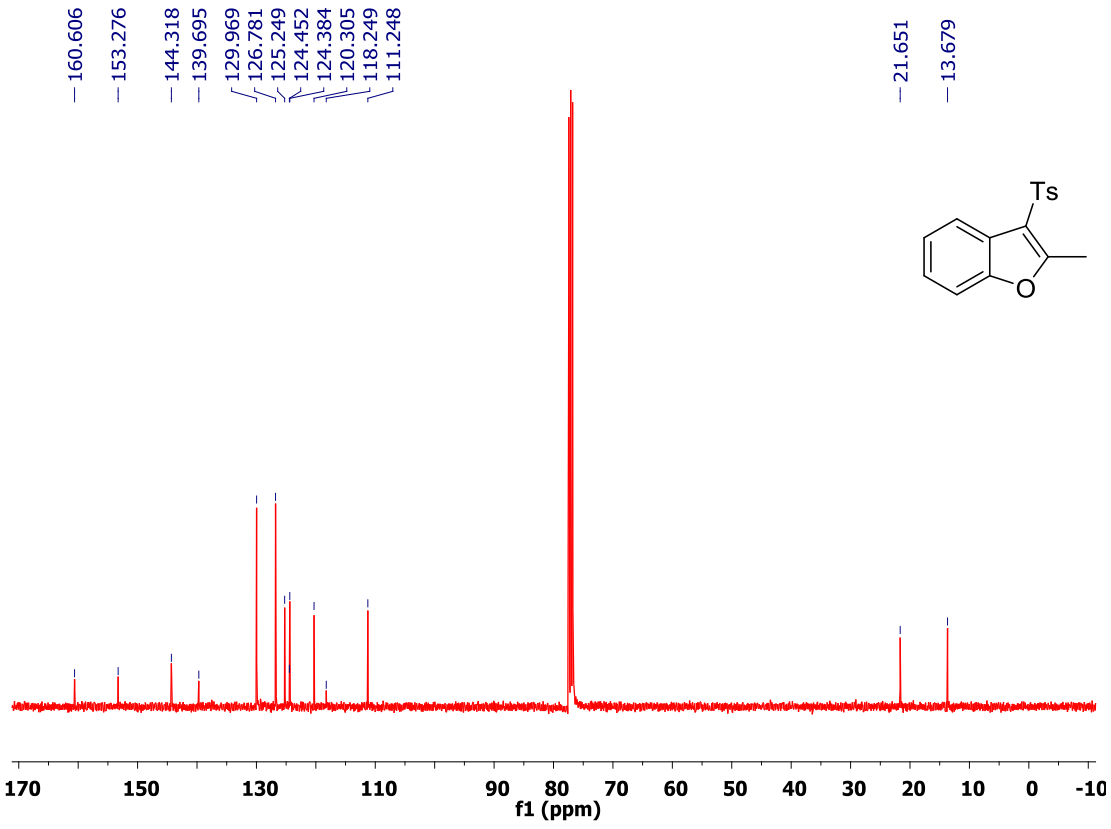
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40
30
20
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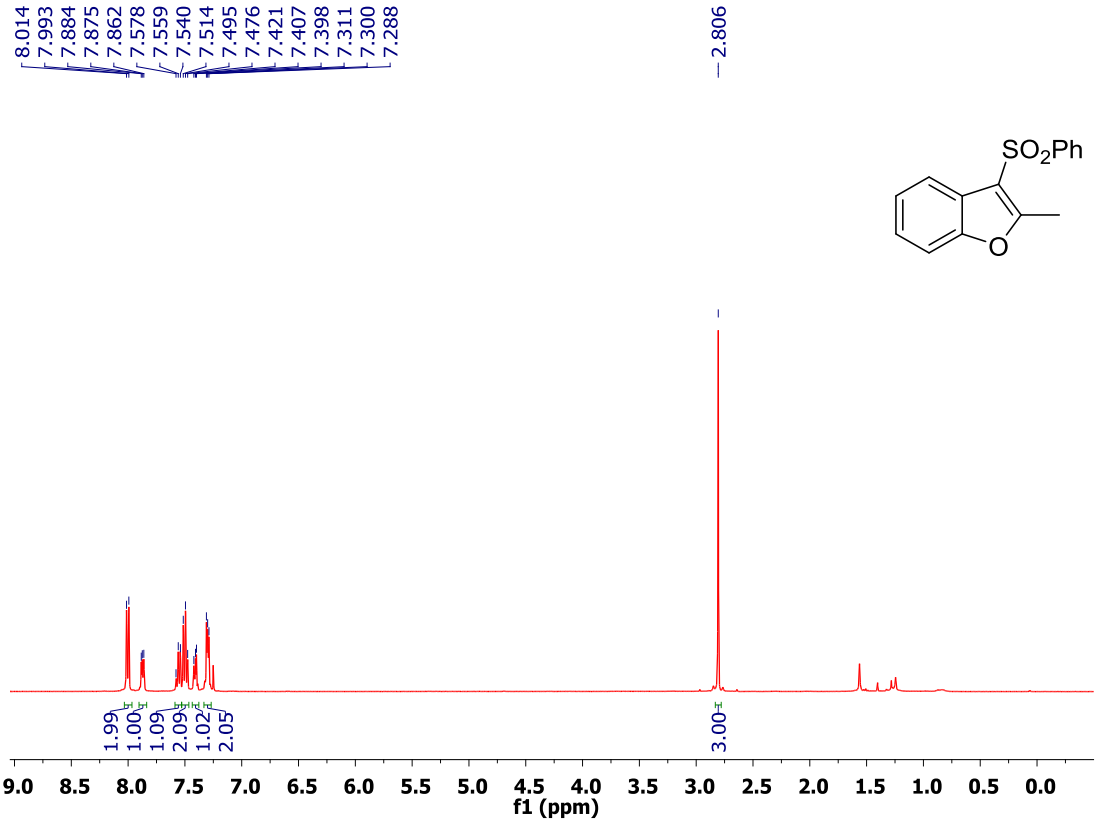
0
-10
f1 (ppm)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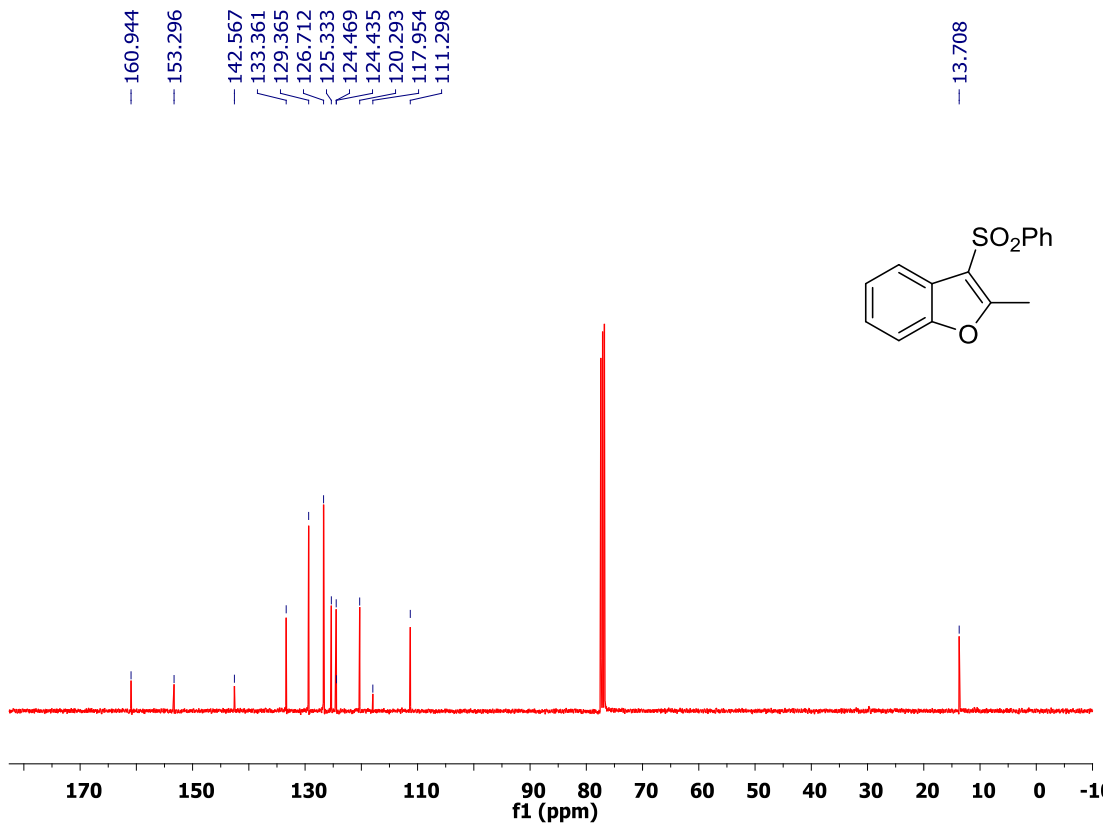
f1 (ppm)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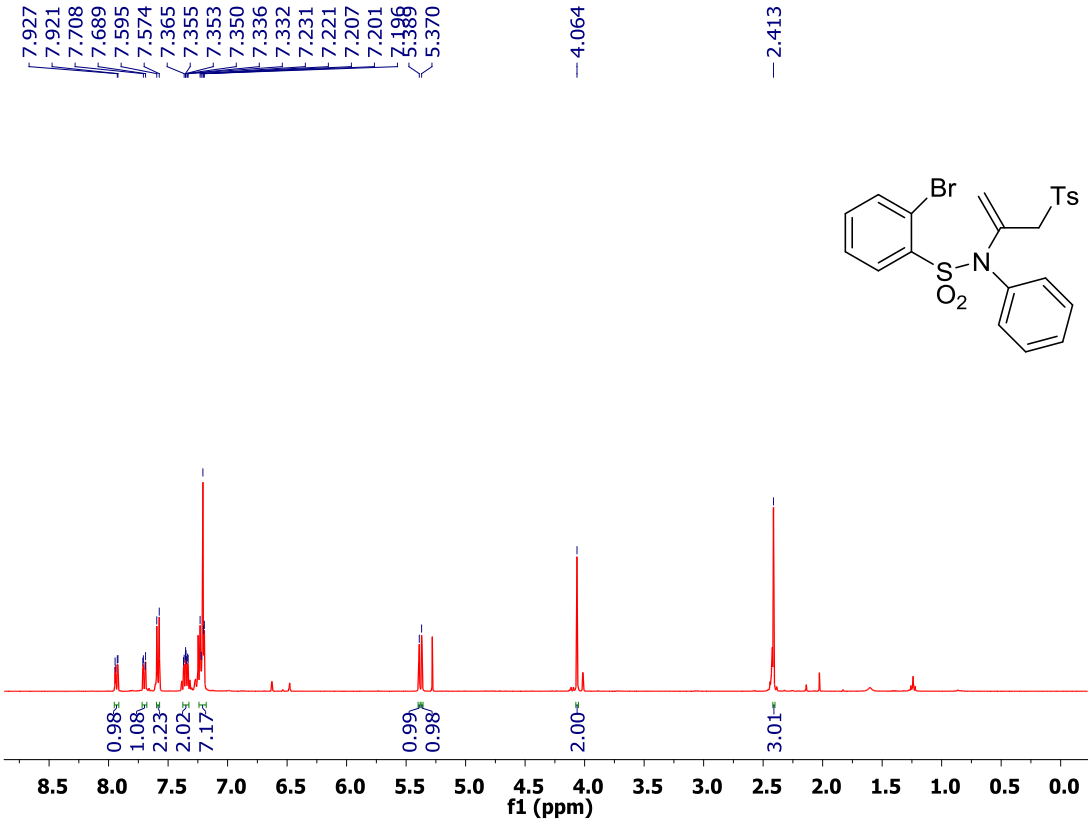
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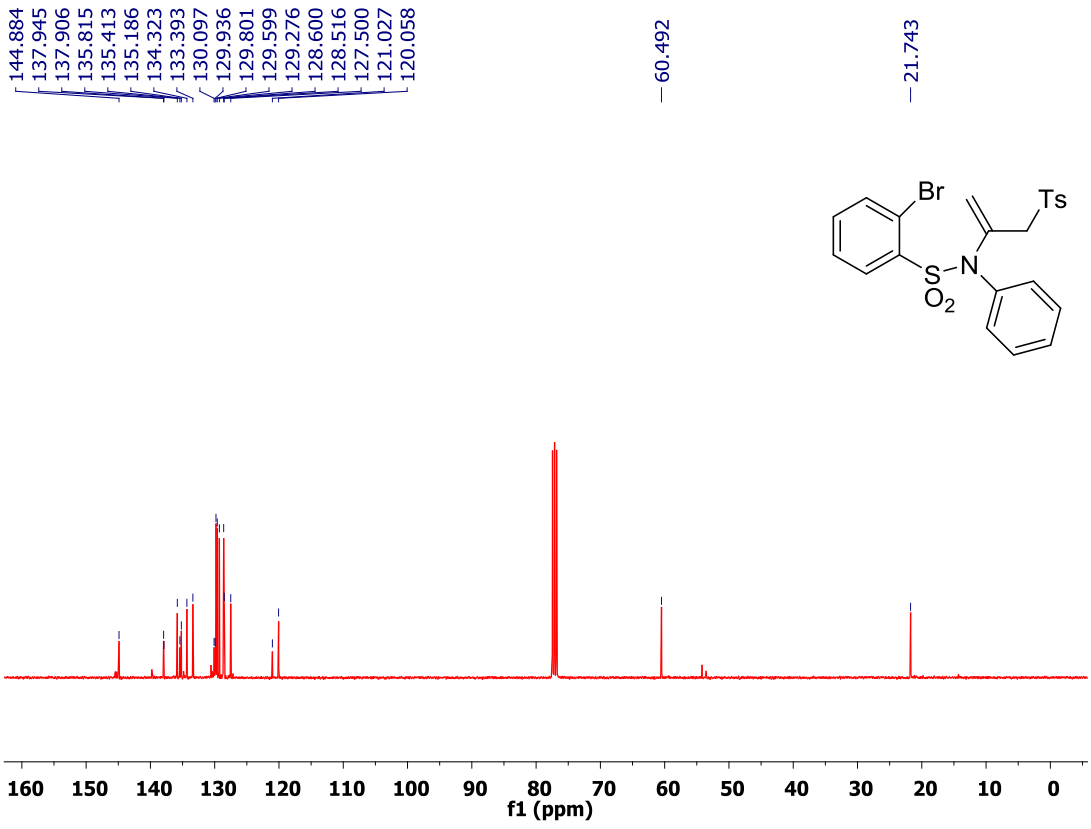
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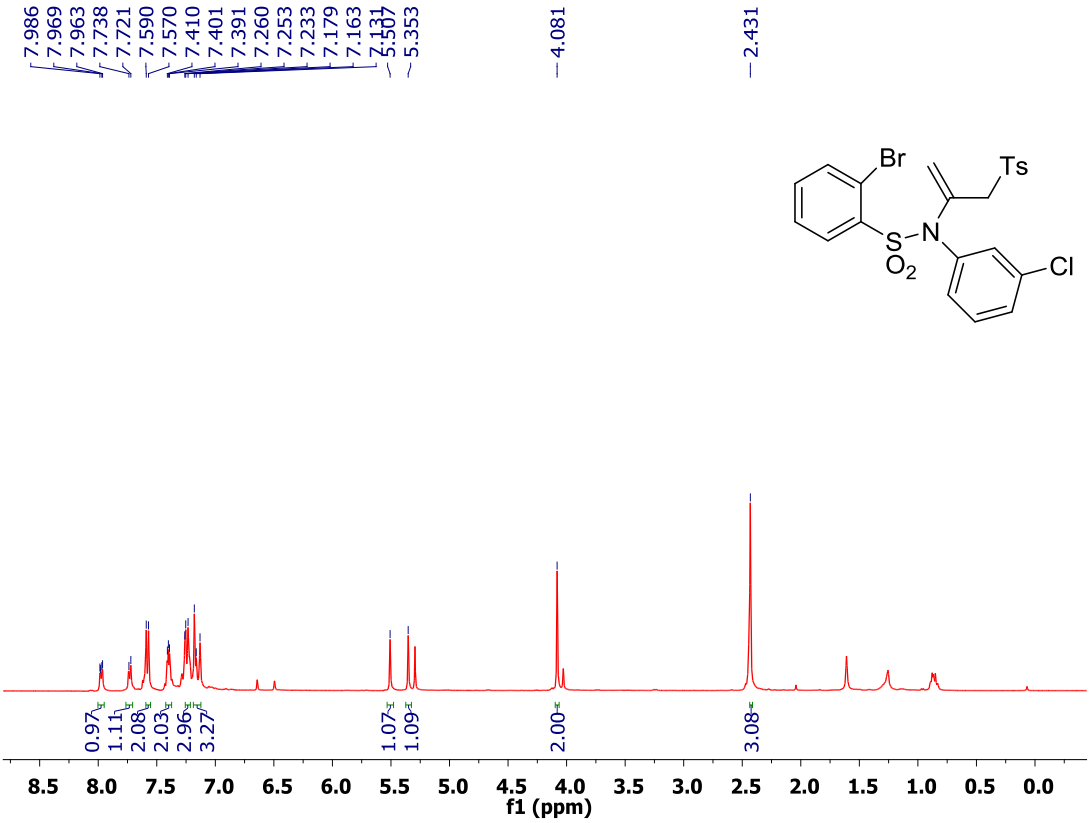
f1 (ppm)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O2
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1.09
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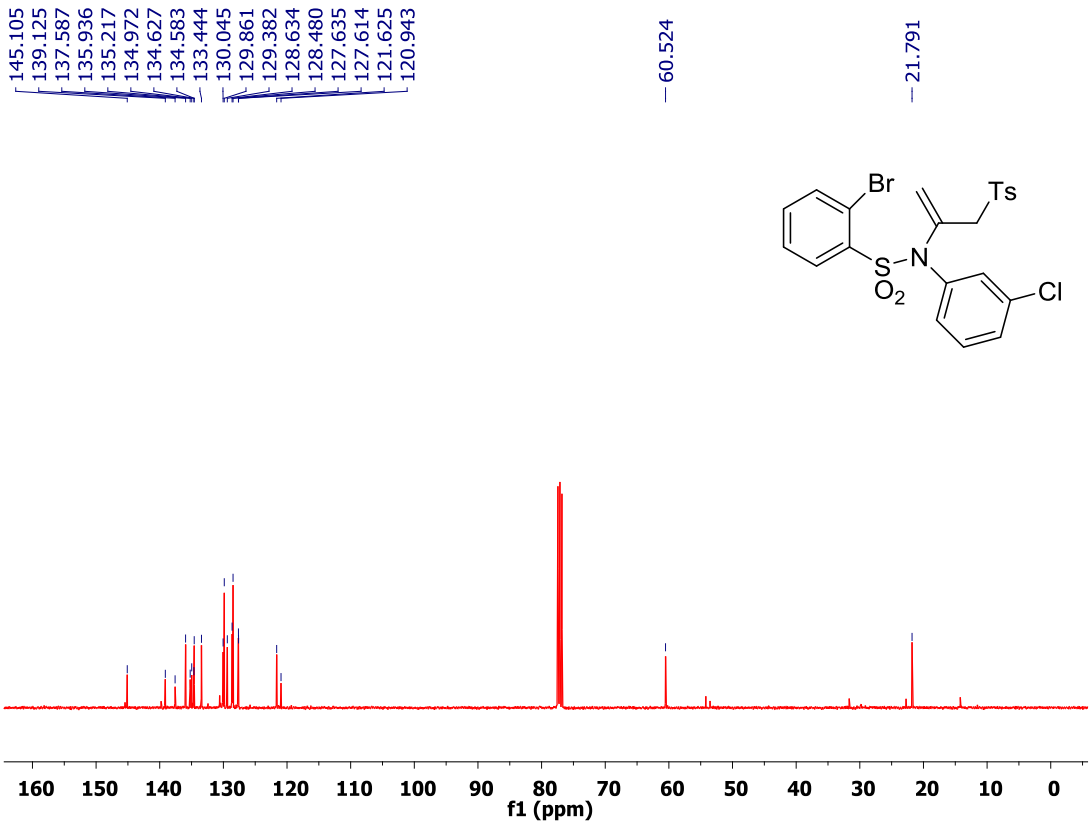
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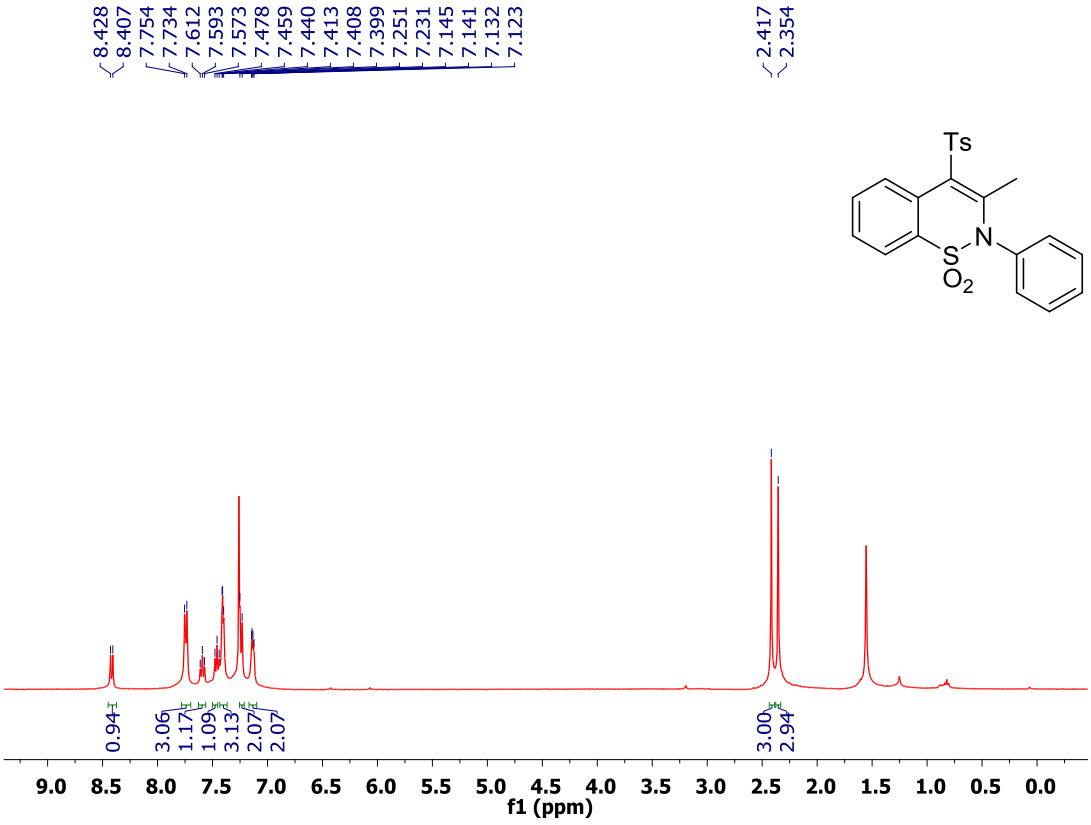
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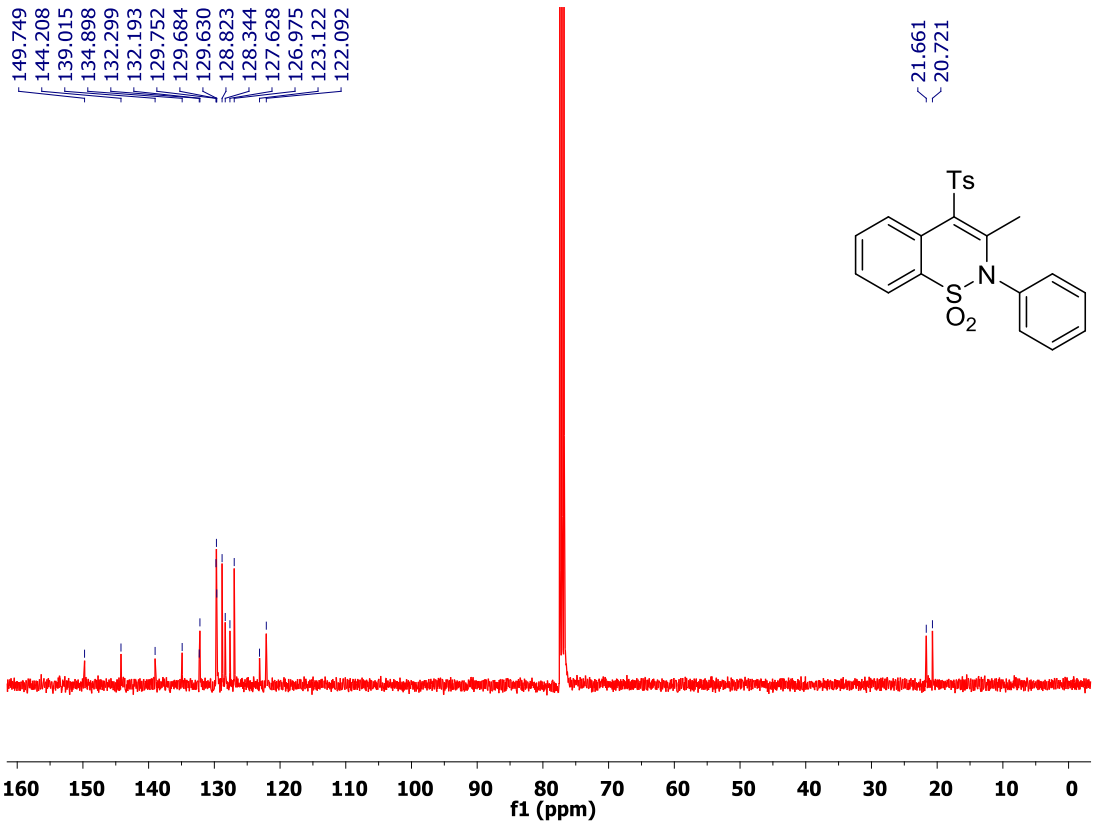
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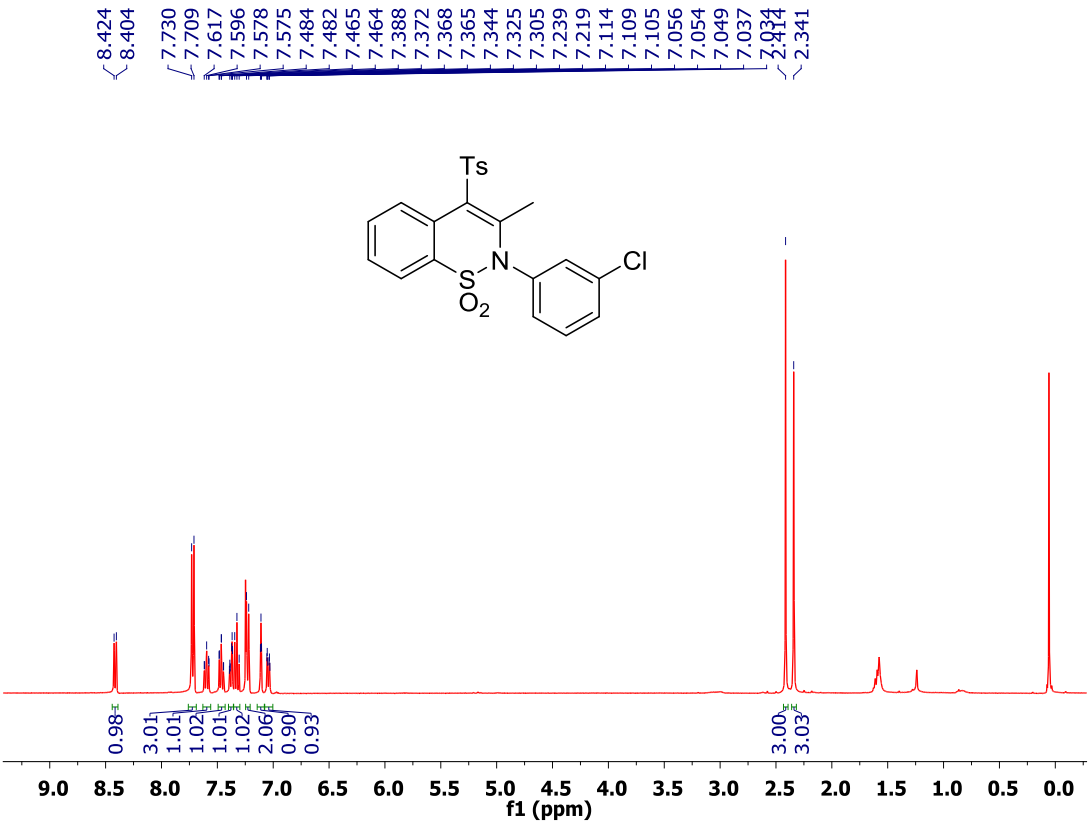
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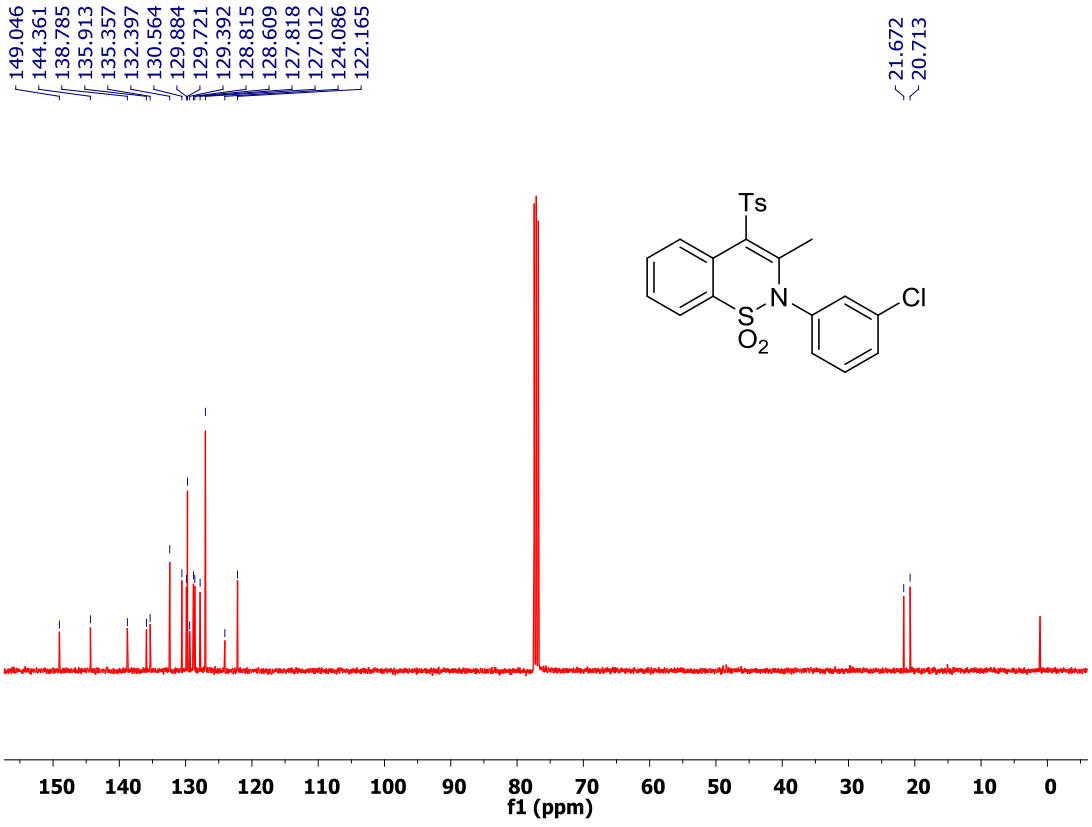
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127.012
124.086
122.165
21.672
20.713
Ts
N
S
O2
Cl
f1 (ppm)

Summary

The thesis entitled "**Unsaturated sulfones as versatile building blocks for carbocyclic and heterocyclic construction**" is divided into four chapters.

Chapter I

This chapter is divided into two parts *i.e.* Part-A and Part-B.

Part A of chapter I entitled "*Introduction and development of benzannulation chemistry*" provide an overview about the importance and methods of synthesis of substituted aromatic hydrocarbons. Substituted aromatic hydrocarbons find various applications in pharmaceuticals, agrochemicals, materials and synthesis. The transformations of quintessential aromatic hydrocarbon benzene into various other aromatic hydrocarbons and numerous aromatic substitution reactions on phenyl ring form a significant chunk in organic chemistry literature. As a consequence, organic chemists continue to develop new strategies for the construction of substituted aromatic hydrocarbons. Their construction conventionally relies on synthetic methods involving introduction of substituents on aromatic ring or by manipulating pre-installed functional groups. In this approach the control of regiochemistry is a major challenge hence the alternative strategy of *benzannulation*, a nonconventional approach becomes attractive. The various type benzannulation reactions are described in this chapter. In benzannulation reactions the union of simple and cheap acyclic precursors affords substituted arenes. In these reactions a variety of acyclic components are combined in various ways with excellent control of regiochemistry. Of late, this area has been growing continuously due its versatility, convenience, and economical viability.

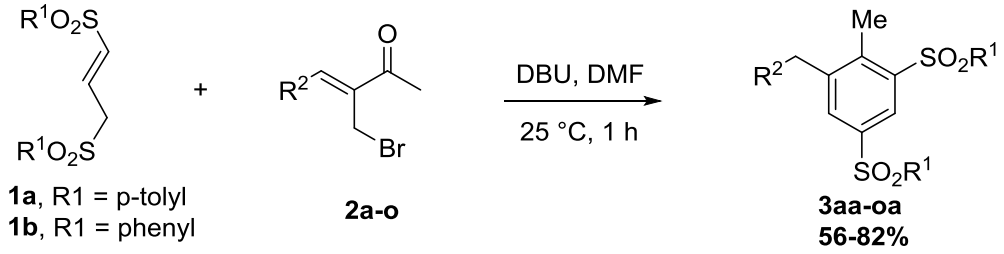
Part B entitled "*Introduction and synthetic applications of allenyl sulfones*" provides an account on electron deficient allenyl sulfones (or sulfonyl allene). The unusual features of sulfonyl, especially arylsulfonyl groups, such as tendency of vinyl sulfones undergo base-catalyzed isomerisation to allyl sulfones, leaving group capacity of sulfinate anions under both acidic and basic conditions influence the reactivity of allenyl framework and make it a special class of electron deficient allenes. Generally, the addition of nucleophiles to electron deficient allenes generates conjugated (vinyl) final products, however, in case of allenyl sulfones the nucleophilic addition afford allyl sulfones as final products. Other than addition of nucleophiles to the central atom of allene, allenyl sulfones also behave as dienophiles or dipolarophiles and readily engage in various cycloaddition reactions with dienes or dipoles. A variety of important transformation of allenyl sulfones are described in this chapter.

Chapter II: Base-mediated [3+3] benzannulation reactions of bis-sulfonyl propenes and Morita-Baylis-Hillman (MBH) bromides for the synthesis of highly substituted arenes

This chapter provides a brief overview about aryl sulfones. The construction of aryl sulfones is an important area of work due to their synthetic utility and favorable properties. The synthetic methods for construction of aryl sulfones are oxidation of aryl sulfides, sulfonylation of arenes and coupling of sulfinates with aryl halides or tosylates. Each of these methods is described in this chapter. The sulfonylation of pre-functionalised arene allows the synthesis of simple aryl sulfones, however, synthesis of more substituted aryl sulfones would be difficult by using these methods. Also, the already present functional group on arene will influence the regiochemistry and reactivity of sulfonylation reaction. *Benzannulation strategy*, in which an acyclic sulfone moiety can be converted

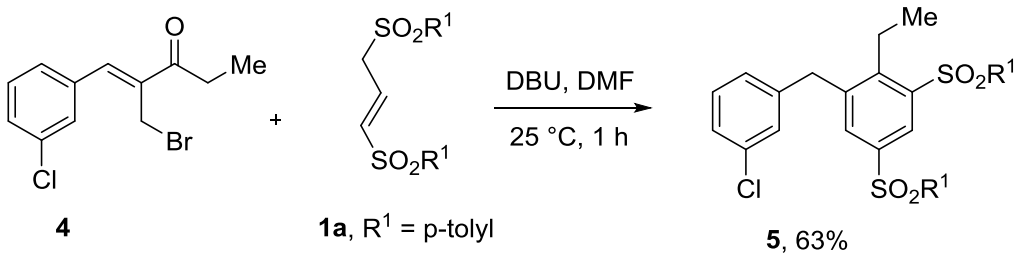
into arene (aryl sulfone) *via* annulation reaction with another suitable precursor, appears highly attractive. A highly substituted aryl sulfone with deactivating groups can be readily synthesized via benzannulation method, still this approach has been applied only rarely and the available examples are presented in this chapter.

The work presented in this chapter describes a [3+3] benzannulation for synthesis of highly substituted aryl sulfones. The building blocks of this benzannulation reaction are bis-sulfonyl propenes **1** and Morita-Baylis-Hillman (MBH) bromides **2** (Scheme 1). The reactions conditions involve the use of DBU as a base and DMF as the solvent. A variety of bis-sulfonyl propenes and MBH bromides afford highly substituted arene products **3.**



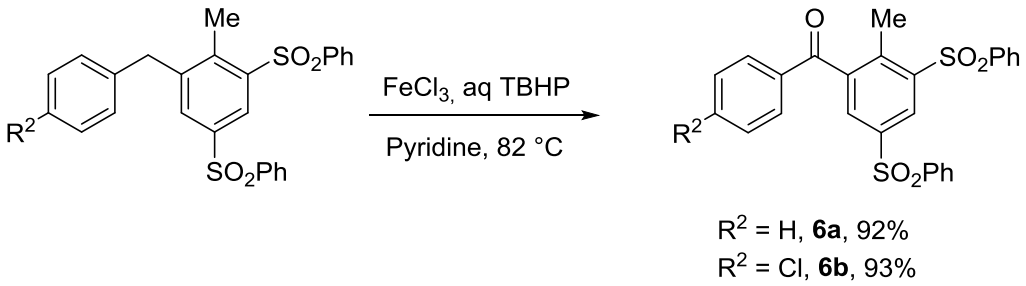
Scheme 1: [3+3] Benzannulation reaction of **1** and **2**

The benzannulation reaction of MBH bromide **4** derived from ethyl vinyl ketone with **1a** under the conditions of benzannulation reaction afforded ethyl-substituted bis-sulfonylarene **5** (Scheme 2).



Scheme 2: Benzannulation reaction with MBH bromide derived from ethyl vinyl ketone

The selective oxidation of methylene group of biarylmethane product by *tert*-butyl hydroperoxide (TBHP) and $FeCl_3$ afforded corresponding benzophenone derivatives **6** (Scheme 3).



Scheme 3: Site-selective oxidation of biarylmethanes

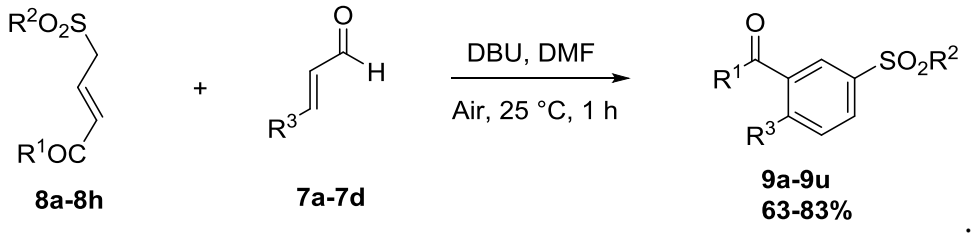
It is important to mention here that all the bis-sulfonylarene products are novel molecules. Also, the bis-sulfonylarene products may assume special importance in view of utility as pincer-type ligands.

Chapter III: Regioselective and oxidative [3+3] benzannulation reactions for the synthesis of highly Substituted benzophenone derivatives

Benzophenone is a privileged structural motif that is present in numerous biologically active natural products and pharmaceuticals. Many benzophenone containing naturally occurring molecules exhibits a wide range of biological activities. Additionally, benzophenone show a significant absorption of ultra-violet (UV) light and represents one of the important classes of compounds in photochemical applications. As a consequence, a number of synthetic methods have been developed for the construction of benzophenones and a brief discussion on the various methods for the synthesis of benzophenone derivatives is provided as an introduction.

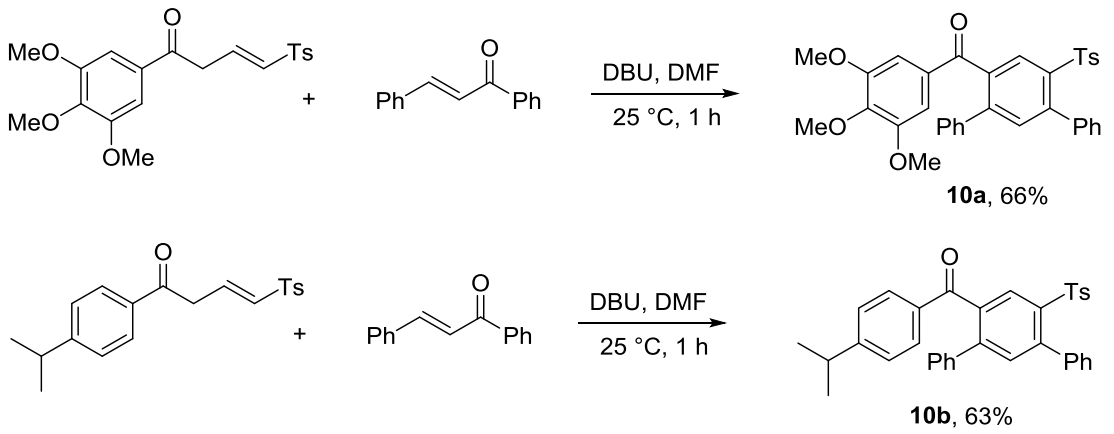
In this chapter, a novel regioselective and oxidative [3+3] benzannulation reaction for the synthesis of substituted benzophenone is described. In view of the successful

development of the [3+3] benzannulation reaction described in the previous chapter and a [3+3] benzannulation reaction of α,β-unsaturated carbonyl compounds with 4-sulfonyl crotonates developed by our group, it was of interest to explore the further application of benzannulation strategy in synthesis of highly substituted arenes. For this purpose we attempted a benzannulation reaction of α,β-unsaturated carbonyl compounds **7** with 1,3-bis-nucleophile **8**. Our investigation along this direction led to the discovery novel regioselective and oxidative [3+3] benzannulation reaction for the synthesis of arylsulfonyl containing benzophenone **9** (Scheme 4).



Scheme 4: [3+3] benzannulation reaction of α,β-unsaturated carbonyl compounds with 1,3-bis-nucleophile **8**

It is important to note that a heterocyclic residue can also be easily incorporated into final product **9** by using the corresponding 1,3-bis-nucleophile. Also, the reaction is not limited to aryl 1,3-bis-nucleophile. The alkyl ketone derivative of **8** reacted smoothly with various enals in the benzannulation reaction to generate the corresponding substituted isobutyl aryl ketones. The structure and regiochemistry of product was assigned on the basis of single crystal X-ray analysis of a crystalline derivative. Further benzannulation reaction of 1,3-bis-nucleophile with enones affords highly substituted benzophenone **10** (Scheme 5). The newly installed benzene ring is endowed with four substituents at well defined positions.

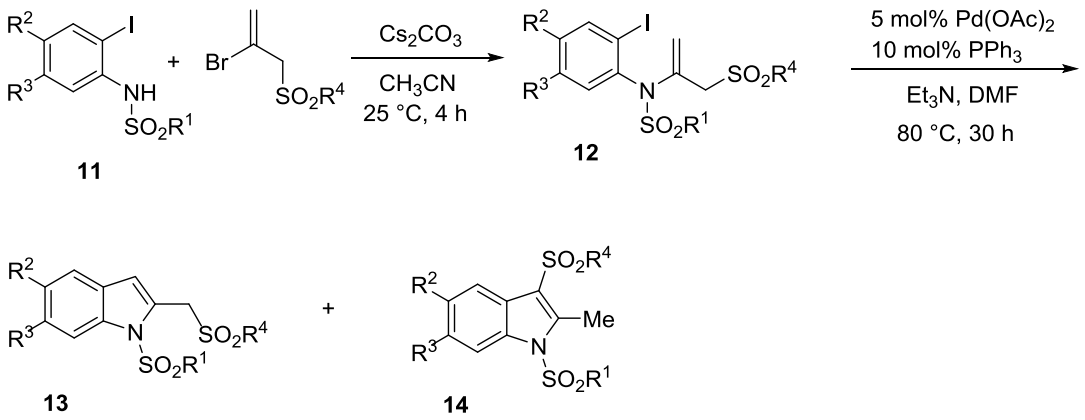


Scheme 5: Benzannulation reaction of trans-chalcone and enals

The regioselectivity is thought to arise from steric interactions that favor the bonding of carbonyl carrying carbon with the β-carbon of enal. The reaction is metal free, utilizes atmospheric oxygen for oxidation and proceeds at room temperature in an open flask, in presence of DBU under mild conditions. The benzannulation reaction described here afforded sulfonyl containing highly substituted benzophenone derivatives which are difficult to synthesize via conventional methods.

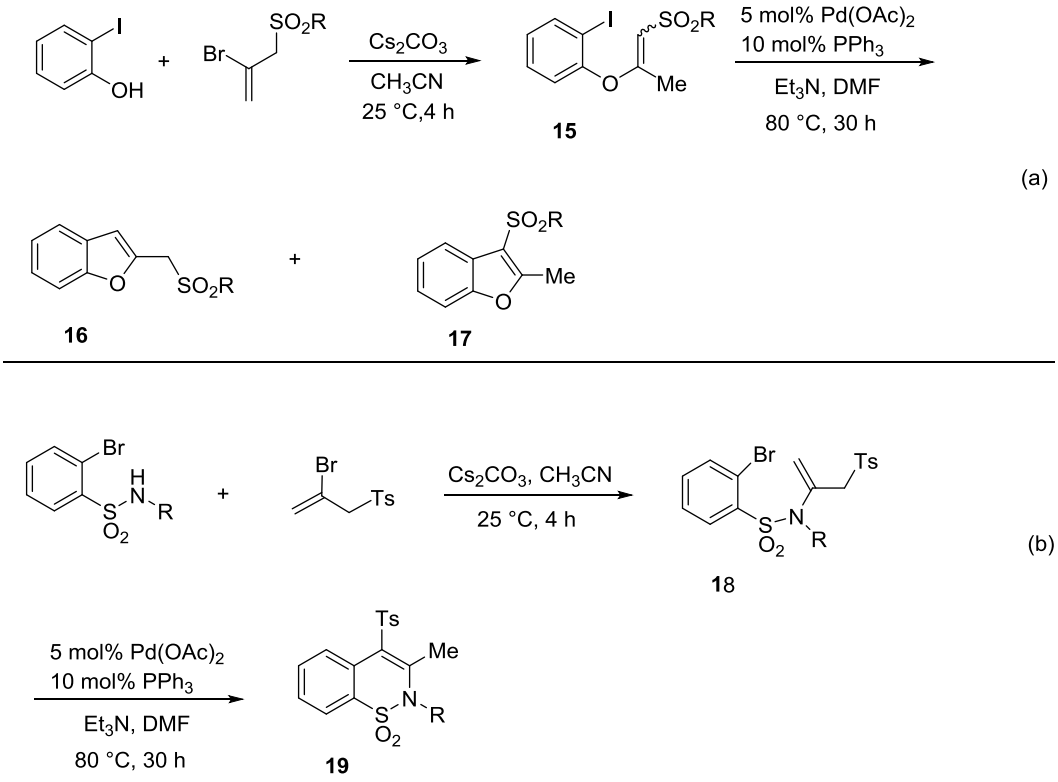
Chapter IV: Facile synthesis of sulfone-bearing indoles and related heterocycles via a sequential formal vinylic substitution and intramolecular Heck coupling reaction

Indole motif form core unit of valuable natural products, drug molecules and agrochemicals. A majority among the numerous naturally occurring indole derivatives exhibit important pharmacological activities. In this chapter a facile synthesis of arylsulfonyl group-bearing indoles is described. The reaction proceeds in two steps. Initially, ortho-halogenated sulfonamides **11** reacted with 2-bromoallyl sulfones in presence of cesium carbonate to furnish products **12** resulting from a formal vinylic substitution reaction. The intramolecular Heck cyclisation of these adducts furnished sulfonylated indoles **13** and **14** (Scheme 6).



Scheme 6: Synthesis and intramolecular Heck cyclisation of N-sulfonyl-N-vinyl-o-iodo sulfonamides **12**

Isomerisation of the double bond participating in the Heck reaction under basic conditions used in reaction led to the formation of two isomeric products of indole. It is important to mention here that conditions for selectively accessing each of the regioisomers were developed and the details are described in this chapter.



Scheme 7: (a) Synthesis of sulfonyl benzofurans **16** and **17** from *o*-iodophenol. (b) Synthesis of benzosultam derivatives **19** via regioselective Heck cyclization

We tested the applicability of this method for construction of other related hetrocycles. Our efforts along this direction led to the formation of benzofurans (Scheme 7a) and benzosultams (Scheme 7b) endowed with arylsulfonyl groups.

Benzosultams derivatives are well-known for their favorable biological activities. The reaction described here shows the synthetic utility of bromoallyl sulfones and afforded sulfonyl containing indoles, benzofurans and benzosultams derivatives.

Conclusion

In this section salient feature of newly developed reactions, their concise description and application are explained. The potential future applications of these methods and product classes are also described.