UNIVERSIDAD DE GUANAJUATO

DOCTORAL THESIS

"Iodine(III)-mediated Chlorination, Bromination and Nitration of Tosylanilines, Scope and Theoretical Studies of the Reaction Mechanism"

By

Dipak Bhatu Patil

under the guidance of

Prof. Dr. Cesar Rogelio Solorio Alvarado

Thesis Submitted in Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy in Chemical Sciences

in the

Campus Guanajuato

Department of Chemistry

Division of Natural and Exact Sciences

University of Guanajuato

February-2023

UNIVERSIDAD DE GUANAJUATO

Lascuráin de Retana No. 5,
Col. Centro C.P. 36000
Guanajuato, Gto., México
Tel: +52 (473) 732 00 06

February, 2023

CERTIFICATE

This is to certify that Dipak Bhatu Patil has been working under my supervision since August 2018, as a regular Ph.D. student in the Division of Natural and Exact Sciences of the University of Guanajuato, Campus Guanajuato, Mexico. I supervised the course, development and conclusion of this thesis entitled ***"Iodine(III)-mediated Chlorination, Bromination and Nitration of Tosylanilines, Scope and Theoretical Studies of the Reaction Mechanism"*** This thesis fully covered the requirements of quality in order the Philosophy of Doctor degree can be obtained under the rules of postgraduate department of chemistry the University of Guanajuato.

Prof. Dr. César Rogelio Solorio Alvarado
Director of Doctoral Thesis
Department of Chemistry
UNIVERSITY OF GUANAJUATO

Approval

Name: **Dipak Bhatu Patil**

Degree: **Doctor of Philosophy in Chemical Sciences**

Title: **"Iodine(III)-mediated Chlorination, Bromination and Nitration of Tosylanilines, scope and theoretical studies of the reaction mechanism"**

Examining Committee:

Dra. María del Rocío Gámez Montaño
President of the committee
Dept. of Chemistry, UG

Dr. José Oscar Carlos Jiménez Halla
Secretary of the committee
Dept. of Chemistry, UG

Dr. Luis Chacón García (External)
Member of the committee
Universidad Michoacana de San Nicolás de Hidalgo

Dr. Rafael Ortiz Alvarado (External)
Member of the committee
Universidad Michoacana de San Nicolás de Hidalgo

Dr. Gerardo González García
Member of the committee
Dept. of Chemistry, UG

Dr. Marco Antonio Ramírez Morales
Member of the committee (Reserve)
Dept. of Chemistry, UG

Date Defended/Approved: **February, 2023**

"No great mind has ever existed without a touch of madness"

- Aristotle

"Learn from yesterday, live for today, hope for tomorrow.
The important thing is not to stop questioning"

- Albert Einstein

Acknowledgment

At the end of my PhD period, my thesis provides me an opportunity to express my deepest gratitude to one and all who directly or indirectly involved in this journey of my Ph.D. at University of Guanajuato, Mexico.

First and foremost, it is my great privilege to express my deepest sense of gratitude to my Prof. and research supervisor **Dr. Cesar Rogelio Solorio Alvarado** for giving me an opportunity for doing my Ph.D. and for excellent guidance, constant encouragement, and motivation during my doctoral research. I consider extremely fortunate to have an advisor who not only educated me in chemistry but also taught me discipline and shown best ways to achieve my goals and also thankful to makes me good research student and helping me to increase writing and laboratory skills.

I would like to thank the **University of Guanajuato** and especially the national laboratory for the characterization of physicochemical properties and molecular structure. I would also like to thank the National Council of Science and Technology (**CONACyT**) for the financial support received during this doctoral work and special thanks to my friend and NMR lab technician **Daniel Ruiz Plaza** for all time support to me.

I would also like to thank all my colleagues and friends from the **CRSA** laboratory, Dr. Pradip Nahide, Dr. Yuvraj Satkar, Dr. Kevin, Narendra Mali, Edson, Beto, Karina, Jaime, Mauricio. All these people with their guidance and support made my time in the laboratory easy. Special thanks to Dr. Pradip Nahide, Dr. Yuvraj Satkar, Dr. Kevin, and Edson for unconditional support to me for everything.

I would like to thank to my comity members **Dra. María del Rocío Gámez Montaño** and **Dr. Marco Antonio Ramírez Morales** for guide me and giving me valuable suggestions about my PhD results. Special thanks to **Dra. María del Rocío Gámez Montaño** for teach me about Green chemistry and Multicomponents reactions and also thankful for provide me my project chemicals and project related materials.

I am very grateful to **Dr. José Oscar Carlos Jiménez Halla** for giving me opportunity to join his class and teach me computational chemistry. Prof. also giving me teaching and guidance about theoretical writing, theoretical concepts, and extra curriculum activity of chemistry.

I would like to thank to my senior friends Dr. Murali Venkata Basavanag Unnamatla, Dr. Shrikant Pharande, Dra. Lupita Aldaco, and Dr. Siddhant Kokate for support me throughout my PhD. Also, I would like to thank to my friends Angela and Cory Hogan (USA) for tremendous support to me and make my life is easy and enjoyable in Guanajuato.

I would like to thank my Mexican family members Rosalva Leal soto (Mother), Reyes Moises Medina Carrillo, Sinuhe Moisés Medina Leal, Gandhi Cuauhtemoc Medina Leal, Claudio Alejandro Medina Sanchez, Patricio Moisés Medina Sanchez, Hector Luciano Medina Sanchez. for lots of love, care, support, and help throughout my PhD.

Last but not the least, I am grateful to Indian Professors Dr. Nilesh Pawar Sir, Dr. Milind Thakare Sir, Dr. Vikas Patil Sir, Dr. Anant Kapdi Sir, Dr. Pankaj Khairnar Sir, Dr. Sagar Joshi, Jayshree Patil Ma'am, Dr. Pravin Patil Sir, Dr. Narendra Sonawane Sir, Dr. K. M. Borse Sir, Dr. Pramod Patil Sir for constant support, valuable suggestions, guidance and motivation.

Dipak Bhatu Patil

February 2023, Guanajuato, Mexico.

Dedicated

This thesis work dedicated to all my family members my father Bhatu Namdev Patil, my mother Naginbai Bhatu Patil, my elder brothers Ashok Patil, Ramesh shinde, Yogesh Bhamare, Kailas Patil, Ravsaheb shinde, and my younger brother Akshay Patil. My elder sisters Kokila walhe, Vandana Patil, my Sister's husband Parmeshvar walhe, Praful Patil, my sister-in-law Chetana Patil, My nephews Harshal Patil, Uday Patil, my nieces Harshada Patil, Priyanka Patil, son of brother my champ Swaroop Patil. I would like to thanks to all my family members for love, care, support, freedom, motivation, unconditional support and always standing with me. Words are not enough to express my gratitude towards my family.

I would like to dedicate this thesis to my friends Umesh Sattesa, Avinash Sapkale, Amol Jadhav, Dinesh Marathe, Pankaj Girase, Hitesh Sisode, Lalit Sisode, Samadhan Patil, Vipul Gavle. for all the love, support, and guidance for the past many years. Whenever I felt overwhelmed or didn't know how to handle the challenges that I have faced over the years, you guys were there to help, motivate, and push me to do my best. Without you guys, I could not have achieved whatever I achieved so far. Thank you so much!

Last but not the least I would like to dedicate this thesis to my schools and colleges Z. P. Marathi Shaala Pimprad, Maharashtra, India. Vikas Vidyalaya Nardana, Maharashtra, India. S.S.V.P.S college Shindkheda, Maharashtra, India. R.C. Patel Arts, Commerce and Science College, Shirpur, Maharashtra, India. Pratap College, Amalner, Maharashtra, India. Due to my schools, colleges and country (India) I am able to reach here in University of Guanajuato, Mexico for PhD.

Dipak Bhatu Patil

February 2023, Guanajuato, Mexico.

UNIVERSIDAD DE GUANAJUATO
Campus Guanajuato

LABORATORIO NACIONAL
DE CARACTERIZACIÓN DE PROPIEDADES
FISICOQUÍMICAS Y ESTRUCTURA MOLECULAR
UG-CONACYT

CONACYT
Consejo Nacional de Ciencia y Tecnología

Dirección de Apoyo
a la Investigación y al Posgrado

GUANAJUATO
Secretaría de Innovación,
Ciencia y Educación Superior

prodep
TIPO SUPERIOR

List of Publications

This thesis is based on the following publications. The contribution by the author to each publication is clarified in the copy of published articles in the Annex III.

I. **Iodine (III)-mediated, controlled Di-or monoiodination of phenols.**
Satkar, Y., Yera-Ledesma, L.F., Mali, N., **Patil, D.,** Navarro-Santos, P., Segura-Quezada, L.A., Ramírez-Morales, P.I. and Solorio-Alvarado, C.R.,* *The Journal of Organic Chemistry*, **2019**, *84*, 4149-4164.

II. **Iodine (III)/AlX_3-mediated electrophilic chlorination and bromination of arenes. Dual role of AlX_3 (X= Cl, Br) for (PhIO) n depolymerization and as the halogen source.**
Segura-Quezada, A., Satkar, Y., **Patil, D.,** Mali, N., Wrobel, K., González, G., Zárraga, R., Ortiz-Alvarado, R. and Solorio-Alvarado, C.R.,* *Tetrahedron Letters*, **2019**, *60*, 1551-1555.

III. **Oxidative Halogenation of Arenes, Olefins and Alkynes Mediated by Iodine (III) Reagents.**
Segura-Quezada, L.A., Torres-Carbajal, K.R., Satkar, Y., Juárez Ornelas, K.A., Mali, N., **Patil, D.B.,** Gámez-Montaño, R., Zapata-Morales, J.R., Lagunas-Rivera, S., Ortíz-Alvarado, R. and Solorio-Alvarado, C.R.,* *Mini-Reviews in Organic Chemistry*, **2021**, *18*, 159-172.

IV. **Gold (I)-Catalyzed Synthesis of 4 *H*-Benzo [*d*][1, 3] oxazines and Biological Evaluation of Activity in Breast Cancer Cells.**
Segura-Quezada, L.A., Torres-Carbajal, K.R., Mali, N., **Patil, D.B.**, Luna-Chagolla, M., Ortiz-Alvarado, R., Tapia-Juárez, M., Fraire-Soto, I., Araujo-Huitrado, J.G., Granados-López, A.J. Gutiérrez-Hernández, R., Reyes-Estrada, C. A., López-Hernández, Y., Adrián López, J.,* Chacón-García, L.,* and Solorio-Alvarado, C. R.* *ACS omega*, **2022**, *7*, 6944-6955.

V. **Iodine(III)-Mediated Electrophilic Chlorination and Catalytic Nitration of *N*-Tosyl Anilines Under a Common Strategy.**
Patil, **D.B.** Gámez-Montaño, R. Ordoñez, M. Solis-Santos, M. Jiménez-Halla, J.O.C.* and Solorio-Alvarado, C. R.*. *Eur, J. Org. Chem.* **2022**, *47*, e202201295.

Index

Prologue

This dissertation is divided into 5 sections: First section is the resume of the thesis. In the second section is chapter 1, explain short general introduction referring to the topics that were addressed in the work of investigation. The next three sections are chapters 2, 3, and the final section corresponds to annex. Each of them contains the same organization consisting of a small introduction regarding the subject, discussion of results and at the end of each chapter the conclusions.

1. In the first section, the resume talks about all the projects carried out in the doctoral thesis, which are briefly described in the chapters 2, 3 and annex A and B.

2. In the second section, chapter 1, the general introduction of the thesis contains a short overview about hypervalent iodine chemistry and gold chemistry about each of the projects that were investigated, and which will be discussed in chapters 2 and 3.

3. In the third section, chapter 2, described gold(I) catalyzed reaction which starting material tertiary aniline was inserted into gold(I) catalyst in dry-DCE as a solvent. In this reaction first cyclization was happened with indole formation and the benzyl group was migrate to 2 and 3 position of cyclized indole.

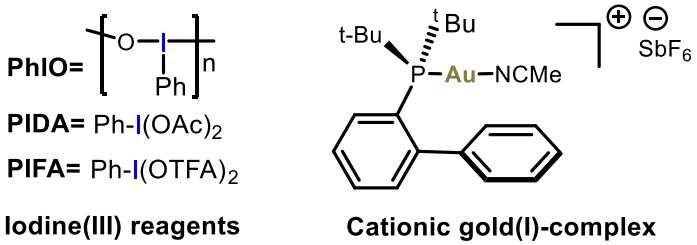
4. In the fourth section, the chapter 3, explain An efficient iodine(III)-based protocol for the chlorination and catalytic nitration of *N*-tosyl anilines as well as the proposed reaction mechanism is described. The synergistic combination of the commercially available [bis(trifluoroacetoxy)iodo]benzene (PIFA) with $AlCl_3$ and $(PhIO)_n$ with $Al(NO_3)_3$, allowed the electrophilic introduction of the chlorine and nitro group in the *N*-tosyl aniline core in non-acidic conditions under a common strategy. Our DFT theoretical calculations, performed for the chlorination process, indicate this occurs through a cationic pathway in which the $[Cl\text{-}PhI^{\oplus}\ominus OTFA\cdot AlCl_3]$ is the chlorinating species and is formed under neutral conditions.

5. In the last fifth section the annexes A are included the copies of **^{1}H, ^{13}C NMR** and **NOE** spectrums for all the synthesized compounds in the thesis. Also, in the annex B section, describes the theoretical calculations carried out under the guidance of Prof. Dr. Cesar Rogelio Solorio Alvarado, and Prof. Dr. J. Oscar C. Jiménez-Halla during PhD course work in the University of Guanajuato on Experimental Studies in The gold(I)-Catalyzed sequential indole formation-benzylic migration. At the end annex C included copy of published articles in PhD.

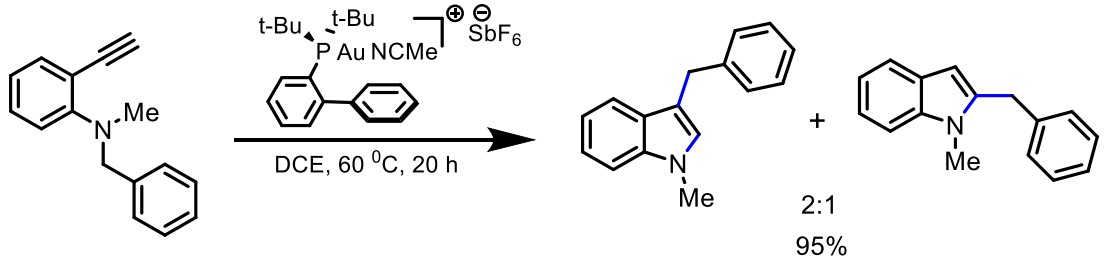
Resume

This dissertation contains one general introduction and two experimental chapters, which are outlined below.

1. In the **chapter 1**, general introduction, there are two topics discussed based on the research carried out in the doctoral thesis. In the first part, the background, general introduction, reactivity, and preparations of hypervalent iodine reagents, and their applications in organic synthesis specialy in C-X (X= -F, -Cl, -Br, -I) and C-N bond formation. In the second part, gold catalysts background, beginning history, reactivity of gold complexes and wide application in organic synthesis specialy in cycloisomerizations, cyclization, and migration reactions have been described.

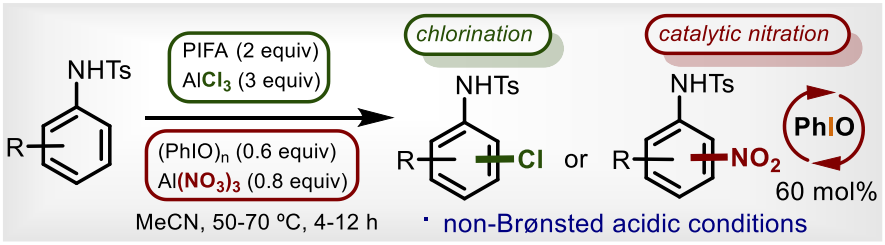


2. In the **chapter 2**, we have developed gold(I) catalyzed reaction which starting material tertiary aniline was inserted into gold(I) catalyst in dry-DCE as a solvent at 60 ^{0}C for 20 h. In this reaction first cyclization was happened with indole formation and the benzyl group was migrate to 2 and 3 position of cyclized indole. In this reaction we got two product as a major and minor with the ratio 2:1 as shown in the bellow scheme.



3. In the **chapter 3**, we have developed an efficient iodine(III)-based protocol for the chlorination and catalytic nitration of *N*-tosyl anilines as well as the proposed reaction mechanism is described. The synergistic combination of the commercially available [bis(trifluoroacetoxy)iodo]benzene (PIFA) with $AlCl_3$ and $(PhIO)_n$ with $Al(NO_3)_3$,

allowed the electrophilic introduction of the chlorine and nitro group in the *N*-tosyl aniline core in non-acidic conditions under a common strategy. Our DFT theoretical calculations, performed for the chlorination process, indicate this occurs through a cationic pathway in which the [Cl-PhI$^{\oplus}$$^{\ominus}$OTFA·$AlCl_3$] is the chlorinating species and is formed under neutral conditions.



Chapter 1.

Introduction and Background

1.1 Hypervalent Iodine Chemistry

1.1 Hypervalent Iodine Chemistry

1.1.1 Hypervalency

'Hypervalency' is the concept applied to polyvalent molecules and this concept introduced by Musher in 1969.[1] Based, on this concept hypervalent compounds are molecules or ions of the elements are belonged to periodic table groups V-VIII, having valence shell with more than eight electrons and this molecule is also called hypervalent molecules. This hypervalent molecule have two different types of chemical bonds by two identical monovalent ligands.

Iodine is a non-metal and one of the heaviest elements in the periodic table. But due to the large size of the iodine atom, it forms three-center-four-electron (3c-4e) bond (L-I-L) is formed by the overlapping of the 5p orbital on iodine atom with the orbitals on the two ligands L. This 3c-4e bond is commonly called as a "hypervalent bond" The presence of a weak, highly polarized hypervalent bond explains the special structural features and reactivity pattern of polyvalent iodine compounds. Compounds of iodine in higher oxidation states, which are known under common name of "hypervalent iodine compounds".[2,3,4]

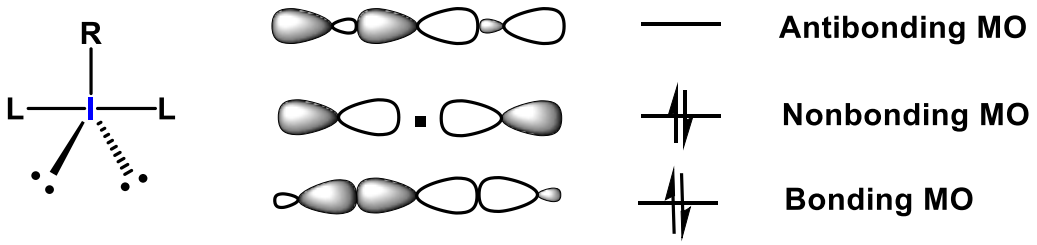


Figure 1. Molecular orbital description of the three-center-four-electron bond in hypervalent iodine(III) molecules RIL2.

Based on molecular orbital theory G. C. Pimentel[5] and R. E. Rundle[6] proposed the idea of a three-center-four electron (3c-4e) bond. The 3c-4e bond leads to a charge distribution of almost -0.5 charge on the ligands and about +1.0 charge on the central atom. These linear bonds are electron-rich, and the non-bonding molecular orbital becomes the highest occupied molecular orbital (HOMO). Therefore, in a 3c-4e bond, electrons are distributed to the ligands. The actual number of electron pairs in the valence shell of the central atom is less than four and the octet rule is not affected. Although there have been, and still are, discussions about whether one can use the expression "hypervalent" for these compounds.

1. Musher, J. I. *Angew. Chem. Int. Ed.* **1969**, *8*, 54-68.
2. Chemistry of Hypervalent Compounds; Akiba, K. y., Ed.; Wiley- VCH: New York, **1999**.
3. Zhdankin, V. V. Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Application of Polyvalent Iodine Compounds; John Wiley & Sons Ltd.: New York, **2014**.
4. Kaneko, N.; Kaiho, T. Iodine production from natural gas brine. In *Iodine Chemistry and Applications* John Wiley & Sons, Inc.: New York, **2015**, 231-241.
5. Pimentel, G. C. *J. Chem. Phys.* **1951**, *19*, 446-448.
6. Hach, R.J.; Rundle, R.E. *J. Am. Chem. Soc*, **1951**, *73*, 4321.

1.1.2 General Introduction to Hypervalent Iodine(III)

Iodine having atomic number 53, atomic weight 126.90 which comes in the fifth period , under Group VIIA , is a halogen element of the periodic table. Iodine was first extracted by a French industrial chemist Bernard Courtois in 1811 from the ash of a sea wood and it was subsequently named by J. L. Gay Lussac in 1813.[7]

Mostly iodine compounds are observed commonly in monovalent compounds with an oxidation state of -1, Iodine can form chemical compounds in oxidation states of 3^+, 5^+ and 7^+. Along with it also forms stable polycoordinate, multivalent compounds. because, of Iodine is the largest, most polarizable, and most electropositive of the group 17 elements, that's why it also forms stable polycoordinate, multivalent compounds.[2,3]

German chemist Willgerodt introduced the first member, $PhICl_2$ a l^3-iodanes in hypervalent iodine chemistry in the year 1886.[8] Subsequently , several hypervalent iodine compounds such as $PhI(OAc)_2$[9] and the first iodonium salt, $Ar_2I + HSO_4^-$,[10] were prepared. within the first report on polyvalent organoiodine species in 1914 by Willgerodt , there were nearly 500 hypervalent iodine compounds known.[2,3,11,12,13,14,15,]

Factors leading to resurgence of interest:
(1) The reactivity and chemical properties of iodine is like the heavy metal reagents such as Hg(III), Tl(III), Pb(IV) but except the toxicity and environmental issues.
(2) Iodine compounds require a mild reaction conditions and easy handling of hypervalent iodine compounds.
(3) The key precursors of hypervalent iodine compound are commercially available such as $PhI(OAc)_2$.

7. Gillespie, C. C. *Dictionary of Scientific Biography.* Charles Scribner's Sons: New York, **1971**.
8. Willgerodt, C.J. Prakt. *Chem.* **1886**, *33*, 154.
9. Willgerodt, C. *Chem. Ber.* **1892**, *25*, 3494-3502.
10. Hartmann, C.; Meyer, V. *Chem. Ber.* 1894, ***27,*** 426-432.
11. Wirth, T., Ed. Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. *Top. Curr. Chem.* **2003**, *224*, 1−248.
12. Varvoglis, A. The Organic Chemistry of Polycoordinate Iodine; VCH Publishers, Inc.: New York, **1992**.
13. Varvoglis, A. Hypervalent Iodine in Organic Synthesis; Academic Press: London, **1997**.
14. Koser, G. F. In Chemistry of Halides, Pseudo-Halides and Azides, Suppl. D2; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: Chichester, **1995**.
15. Ochiai, M. In Chemistry of Hypervalent Compounds; Akiba, K. y., Ed.; VCH Publishers: New York, **1999**.

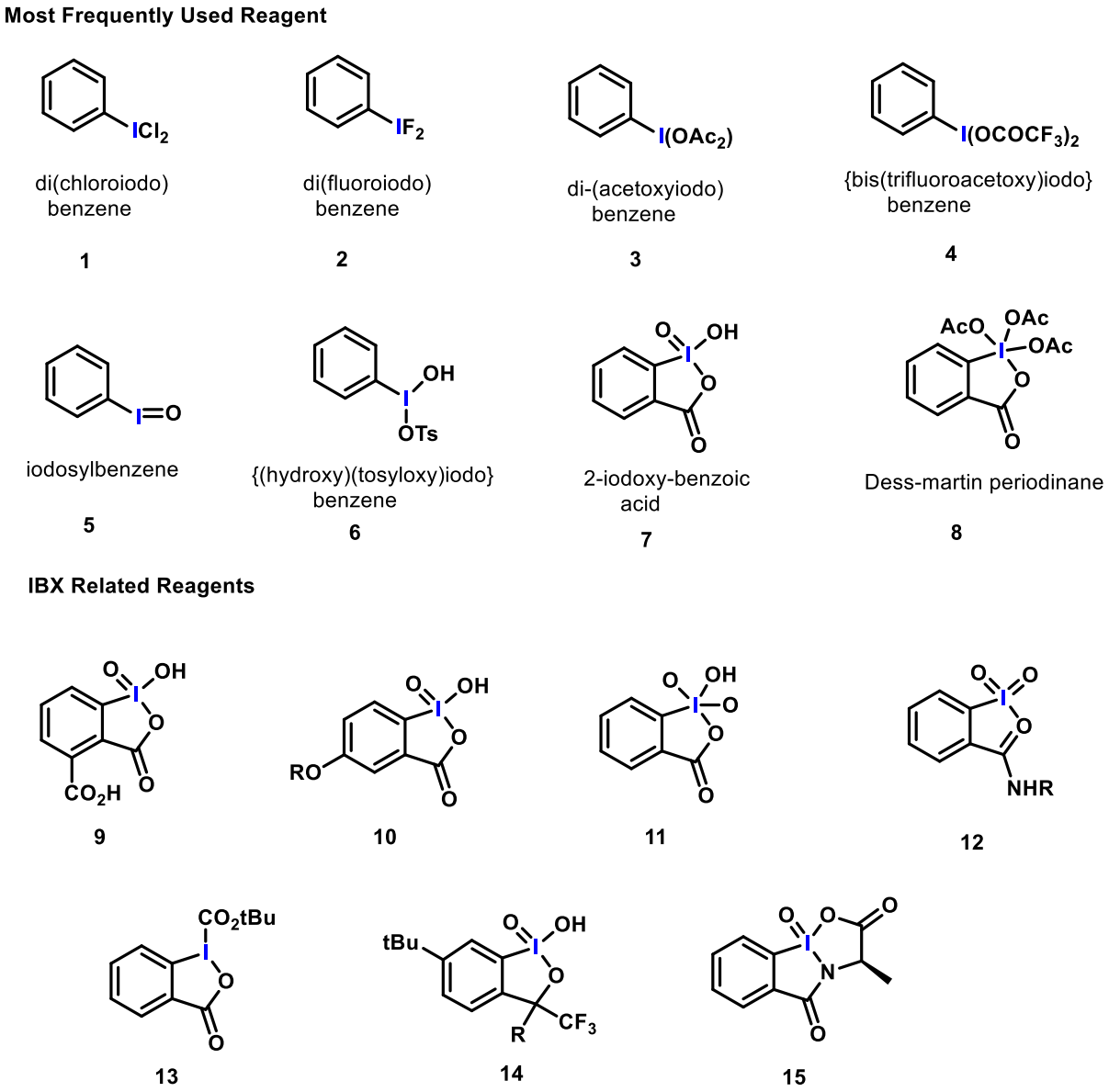


Figure 2. Main classes of organohypervalent iodine reagents.

Hypervalent iodine reagents (**1-15**) as shown in **figure 2**. The explosive development of Organohypervalent iodine compounds from the beginning twenty first century[16]. Organohypervalent iodine compounds shows very useful oxidizing properties which is very useful

[16] a) Grushin, V.V. Chem. Soc. Rev. **2000**, *29*, 315. b) Skulski, L. Molecules, **2000**, 5, 1331. c) Okuyama, T. *Acc. Chem. Res.* **2002**, *35*, 12. d) Ochiai, M. *J. Organomet. Chem.* **2000**, *611*, 494. e) Zhdankin, V.V.; Stang, P.J. *Chem Rev*. **2002**, *102*, 2523. f) Moreno, I.; Tellitu, I.; Herrero, M.T.; San Martin, R.; Dominguez, E. *Curr. Org. Chem.* **2002**, *6*, 1433-1452. g) Morales-Rojas, H.; Moss, R.A. *Chem. Rev*. **2002**, *102*, 2497. h) Stang, P.J. *J. Org. Chem*. **2003**, *68*, 2997.

in organic synthesis[17] and additionally these reagents are environment friendly, commercially available, and easy for handling. Since twenty first century Iodine(III) and Iodine(V) reagents[18] continuously used in oxidative transformation of complex organic molecules.[19]

[17] a) Feldman, K.S. *ARKIVOC*. **2003**, *6*, 179. b) French, A.N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev*. **2004**, *33*, 354. c) Muller, P. *Acc. Chem. Res*. **2004**, *37*, 243. d) Moriarty, R.M. *J. Org. Chem*. **2005**, *70*, 2893. e) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

[18] a) Zhdankin, V.V. *Curr. Org. Synth*. **2005**, *2*, 121. b) Kirmse, W. *Eur. J. Org. Chem*. **2005**, *2005*, 237. c) Richardson, R.D.; Wirth, T. *Angew. Chem. Int. Ed*. **2006**, *45*, 4402. d) Ochiai, M. *Chem. Rec*. **2007**, *7*, 12. e) Kita, Y.; Fujioka, H. *Pure Appl. Chem*. **2007**, *79*, 701. f) Zhdankin, V.V.; Stang, P.J. *Chem. Rev*. **2008**, *108*, 5299.

[19] a) Dohi, T.; Kita, Y. Chem. Commun. **2009**, *16*, 2073. b) Merritt, E.A.; Olofsson, B. *Angew. Chem. Int. Ed*. 2009, *48*, 9052. c) Zhdankin, V.V. *J. Org. Chem.* **2011**, *76*, 1185. d) Silva, J.L.F.; Olofsson, B. *Nat. Prod. Rep*. **2011**, *28*, 1722. e) Duschek, A.; Kirsch, S.F. *Angew. Chem. Int. Ed*. **2011**, *50*, 1524. f) Liang, H.; Ciufolini, M.A. *Angew. Chem. Int. Ed*. **2011**, *50*, 11849. g) Brand, J.P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.

1.1.3 General Reaction Mechanism

General reaction mechanism of hypervalent iodine compounds [Iodine(III) and Iodine(V)] based on exchange their ligands by nucleophile, are classified into three types:

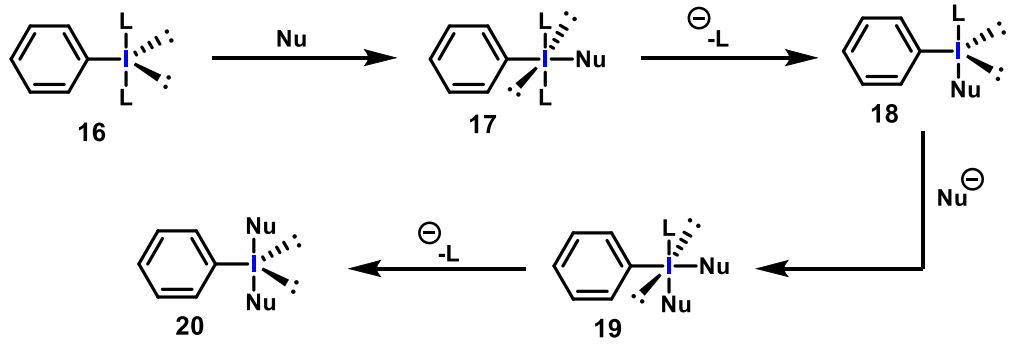
Ligand exchange
Reductive β-elimination
Reductive α-elimination with subsequent substitution

1.1.3.1 Ligand exchange

In ligand exchange reaction mechanism number of the heteroatom ligands and the number of carbon ligands control their reactivity pattern. Ligand exchange mechanism classified into two pathways.

1.1.3.1.1 Associative pathway

In Association reaction pathway firstly nucleophile attack on iodine **16** and formed tetracoordinate intermediate **17**. Once tetracoordinate intermediate is formed then elimination of ligand takes place. This procedure takes place two times on both ligands **18**, and **19**, generate new species **20** with two new ligands as shown in **scheme 1**.[20]

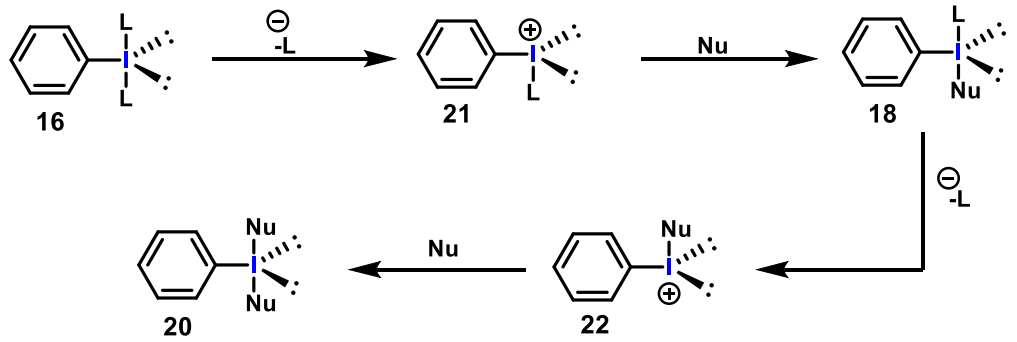


Scheme 1. Associative pathway in the ligand exchange.

1.1.3.1.2 Dissociative pathway

In dissociation reaction pathway firstly elimination of ligand takes place and formed high energy cationic iodonium species $PhI^{+}L$ **21**, followed by nucleophile attack on cationic iodonium species gives ArILNu **18**. This same process takes place again which gives intermediate **22**. later generate new species with two new ligands to generate $ArINu_2$ **20 (scheme 2)**. This mechanism required good electrophile for elimination of ligand.[20]

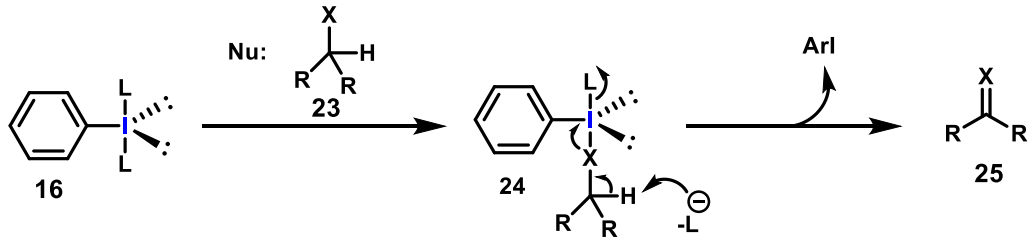
20. Wirth, T. Ed. *Hypervalent Iodine Chemistry, Top. Curr. Chem.* Springer: Heidelberg, **2003**.



Scheme 2. Dissociative pathway in the ligand exchange.

1.1.3.2 Reductive β- elimination

In reductive β-elimination concerted β-elimination take place in **24** (including 23), *syn* stereochemistry with the formation of oxidized product **25**. Here, hypervalent iodide **16**, is convert into the reduced iodoarene **25**, **(scheme 3)**. This method comprehensively used for the oxidation of sulphides, alcohols, and amines into the analogous sulphoxides, carbonyl compounds and imines.[21,22]

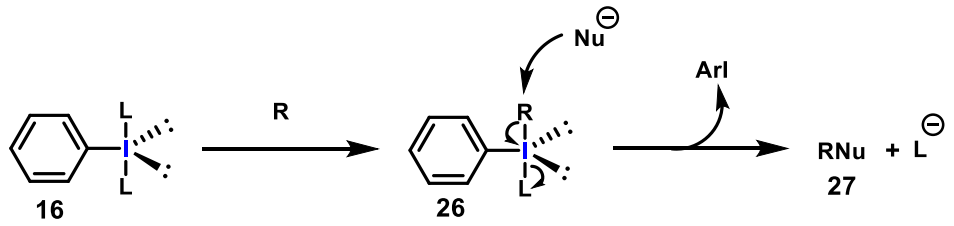


Scheme 3. Reductive β-elimination

1.1.3.3 Reductive α-elimination with subsequent substitution

In Reductive α-elimination with subsequent substitution reaction mechanism pathway is a low energy process in which elimination of heteroatom ligand in iodine(III) **16**, or iodine(V) with the help of outer nucleophile **26**, **(scheme 4)**.[21,22] The heteroatom ligand on iodine(III) has good leaving group ability and this is the key point of hypervalent iodine compounds. This mechanism leads to create reaction species like carbene **27**. Nitrenes, cations and arynes under mild conditions along with oxidize an extensive margin of functionalities. Here, good leaving group leads to reductive elimination with preferable energy for reduction to monovalent iodide.

21. Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100,* 4888.
22. a) Wirth, T.; Ochiai, M.; Varvgolis, A.; Zhdankin, V. V.; Koser, G. F.; Tohma, H.; Kita, Y.; Topics in Current Chemistry: Hypervalent Iodine Chemistry -/- Modern Developments in Organic Synthesis, 1-248, 224. Springer-Verlag, Berlin, **2002**. B) Varvoglis, A.; Hypervalent Iodine in Organic Synthesis, 1-223, Academic Press, London, **1997**. C) Stang, P.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123-1178.



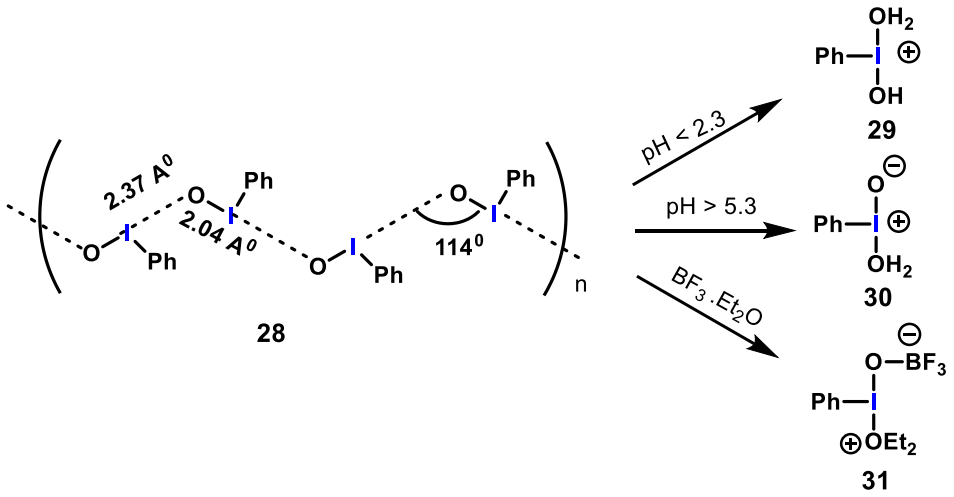
Scheme 4. General mechanism for the reductive elimination with substitution.

1.1.4 Physical Aspect of hypervalent Iodine(III)

The hypervalent iodine(III) reagents are solid (amorphous or crystalline) and are stable to atmospheric oxygen and moisture. Iodonium salts are less stable and should be generated *in situ*. A mild explosion will occur if heated in the absence of solvent for $PhI(OMe)_2$, $PhIO$, $PhIO_2$, $(PhI^+)_2O\ 2BF_4^-$ and o-iodylbenzoic acid.[23]

In the solid state:

The polymeric structures of Iodosylbenzene **28**, and (tosyliminoiodo)benzene are terminated by water: HO(PhIO)nH. Reactive solvent are generate a monomeric species like **29**, **30**, and **31**. In the results of polymeric structures secondary I-O bonds are also observed **(scheme 5)**.[23]

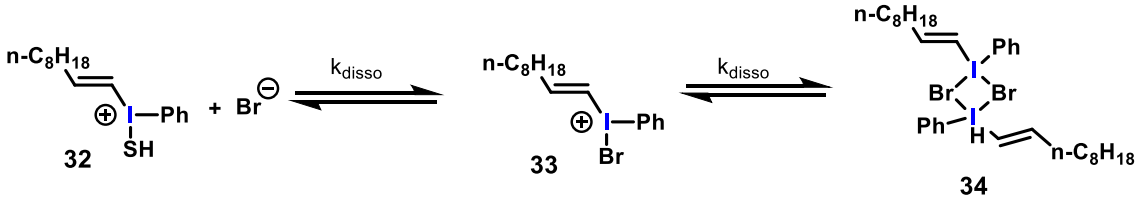


Scheme 5. Reactive solvent generate monomeric species from polymeric iodosylbenzene.

23. a) Stang, P.; Zhdankin, V. V. *Chem. Rev*. **1996**, *96*, 1123-1178. b) Wirth, T.; Ochiai, M.; Varvgolis, A.; Zhdankin, V. V.; Koser, G. F.; Tohma, H.; Kita, Y. Topics in Current Chemistry: Hypervalent Iodine Chemistry -/- Modern Developments in Organic Synthesis, 1-248, 224. Springer-Verlag, Berlin, **2002**. c) Varvoglis, A. Hypervalent Iodine in Organic Synthesis, 1-223, Academic Press, London, **1997**.

In solution:

Hypervalent iodine(III)-oxidant (Ar_2IL, where L = BF_4, Cl, Br, OAc) show extensive dissociation into solvated iodonium ions (Ar_2I^+S where S = H_2O, MeOH, and DMSO) in polar solvents. Alkenyl-iodine(III)exist in equilibrium as an iodonium ion **32**, **33**, and as a halogen-bridged dimeric and aggregate structures **34** (Eq. 1). [23]



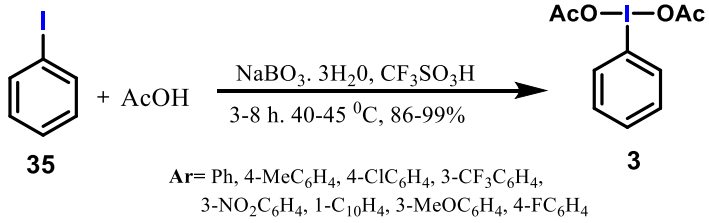
[1]

1.1.5 Preparation of Hypervalent Iodine(III) Reagents

Preparation of hypervalent iodine(III)reagents [Bis(acetoxy)iodo]arenes (PIDA), (Bis(trifluoroacetoxy)iodo)benzene (PIFA) and Iodosylbenzene (PhIO) method are as shown in bellow.

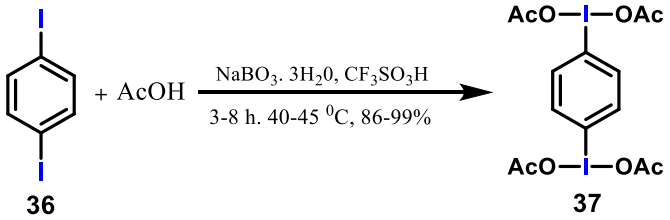
1.1.5.1 Preparation of PIDA

Preparation on PIDA **3**, from iodoarenes **35**, is achieved by using iodoarenes in the presence of sodium perborate in acetic acid with triflic acid at 40-45 ^{0}C (Eq. 2).[24] This method is easy, safe, and effective for the preparation of PIDA from iodoarenes. In this method trifluoromethanesulfonic acid (triflic acid) act as a promoter causes increase in the high yield of (diacetoxyiodo)arenes within short reaction time.



[2]

Based on the above we can prepare PIDA **37**, from 1,4-diiodobenzene **36**, *via* double oxidative diacetoxylation (Eq. 3).[52]

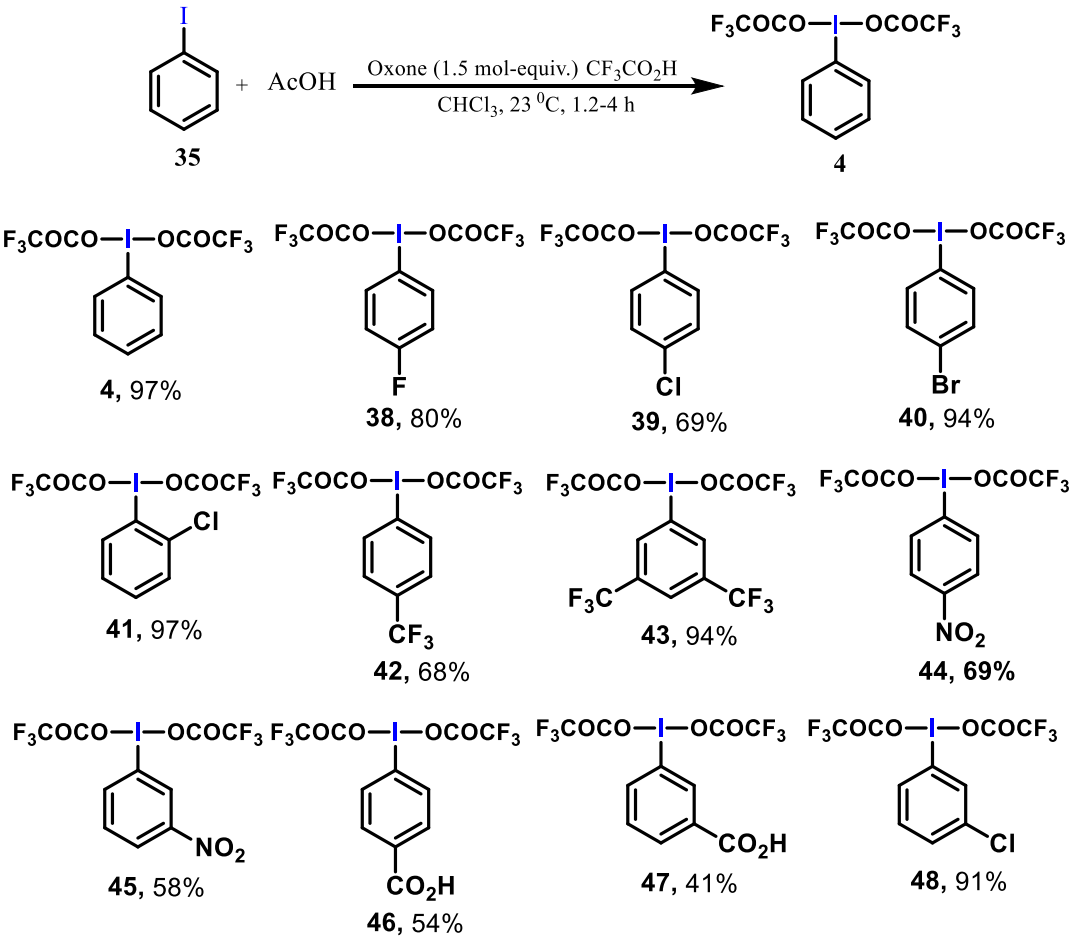


[3]

24. Hossain, M.D.; Kitamura, T. *J. Org. Chem.* **2005**, *70*, 6984-6986.

1.1.5.2 Preparation of PIFA

Preparation of PIFA **4**, from iodoarene achieved by using iodoarene **35**, in the presence of oxone as an oxidant in trifluoroacetic acid in $CHCl_3$ as a solvent at 23 ^{0}C **(scheme 6)**.[25] This is very simple, easy, and convenient method for the preparation of PIFA derivatives **38-48**.

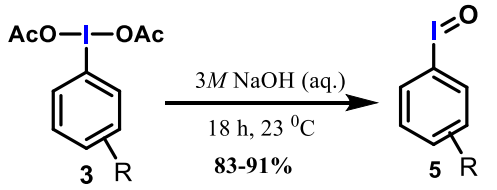


Scheme 6. Preparation of [Bis(trifluoroacetoxy)iodo]arenes.

25. Zagulyaeva, A.A.; Yusubov, M.S.; Zhdankin, V.V. *J. Org. Chem*. **2010**, *75*, 2119-2122.

1.1.5.3 Preparation of PhIO

Preparation of iodosylbenzene **5**, is from PIDA **3**, achieved by addition of PIDA into the basic media 3M NaOH solution and stir at room temperature for 12 hr. (Eq 4).[26] This is very simple and easy method for the preparation of iodosylbenzene.



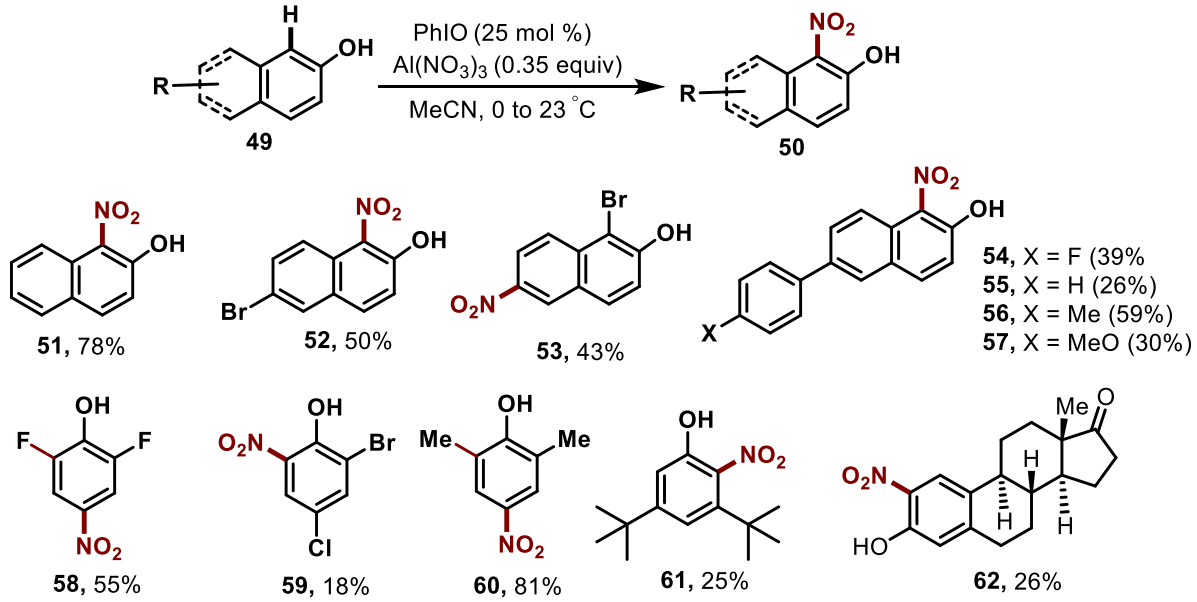
[4]

R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 3-$CF_3C_6H_4$,3-$NO_2C_6H_4$, 1-$C_{10}H_4$, 3-$MeOC_6H_4$, 4-FC_6H_4

1.1.6 Application of Organo-Hypervalent Iodine Reagents

1.1.6.1 Nitration

Recently, In 2019, Solorio-Alvarado and co-workers proposed the nitration of phenols **49**.[27] He developed first catalytic procedure of electrophilic nitration phenols with the help of Iodosylbenzene as an oxidant and aluminum nitrate play a role as a nitrating reagent. This nitration of phenols procedure carried out in mild and open flask reaction conditions and scope to get nitrated derivatives **50-62 (scheme 7)**.

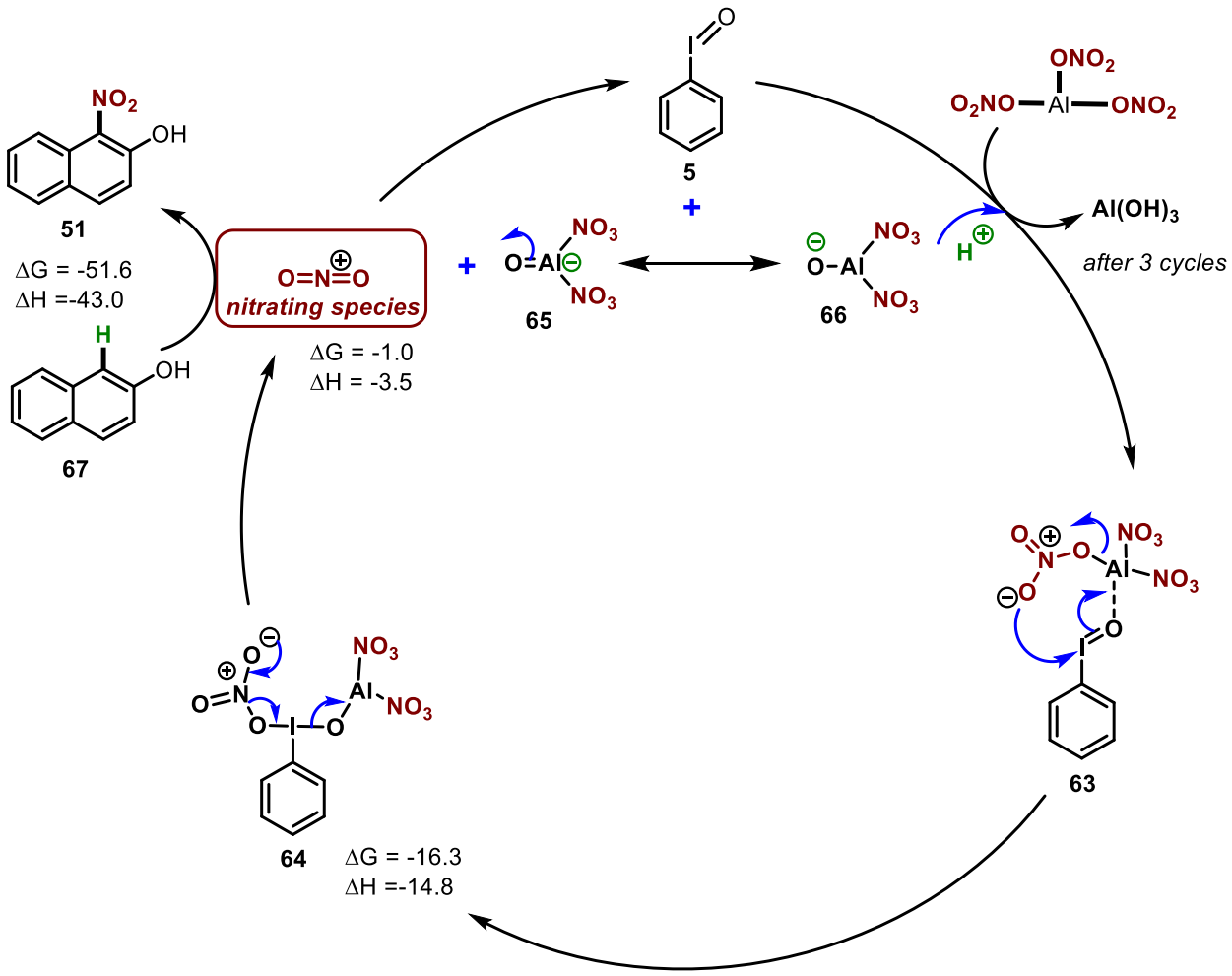


Scheme 7. Iodine(III)-mediated nitration of phenols.

---

26. a) Schardt, B. C.; Hill, C. L. Inorg. Chem. **1983**, *22*, 1563-1565. b) Ghosh, Subrata K.; Hu, Mengnan; Comito, Robert J. *Eur. J. Chem*. **2021**, *27*, 17601-17608.
27. Juárez-Ornelas, K.A.; Jiménez-Halla, J.O.C.; Kato, T.; Solorio-Alvarado, C.R.; Maruoka, K. *Org. lett*. **2019**, *21*, 1315-1319.

Now, Reaction mechanism proposal of nitration of phenols by using iodosylbenzene and aluminum nitrate, based on the theoretical DFT calculations with the help of (SMD:MeCN)Mo8-HX/(LANLo8+f,6-311+G*) level **(Scheme 8)**.

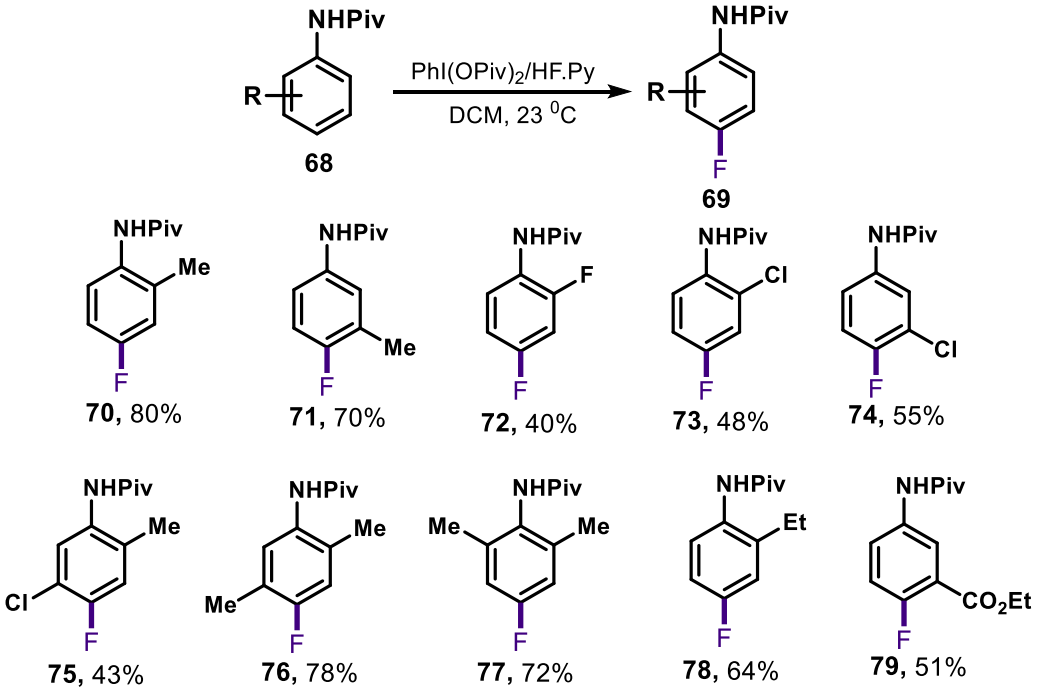


Scheme 8. The PhIO-catalyzed electrophilic nitration phenols and their reaction mechanism.

According to **scheme 8.** Reaction mechanism of nitration of phenols start from the iodosylbenzene (PhIO) and aluminum nitrate with their coordination gives **63,** followed by **63** in which [3,3] sigmatropic reaction take place and formed intermediate **64**. This intermediate **64** possess iodine(III)-nitrate bond undergo decomposition and generate nitrating species $\mathbf{NO_2^+}$. Then naphthol attack on $\mathbf{NO_2^+}$ species to give final nitrated product. In this mechanism bis(nitrooxy)aluminum oxide **65,** in resonance with **66**, and accompanying regeneration of iodosylbenzene.

1.1.6.2 Fluorination

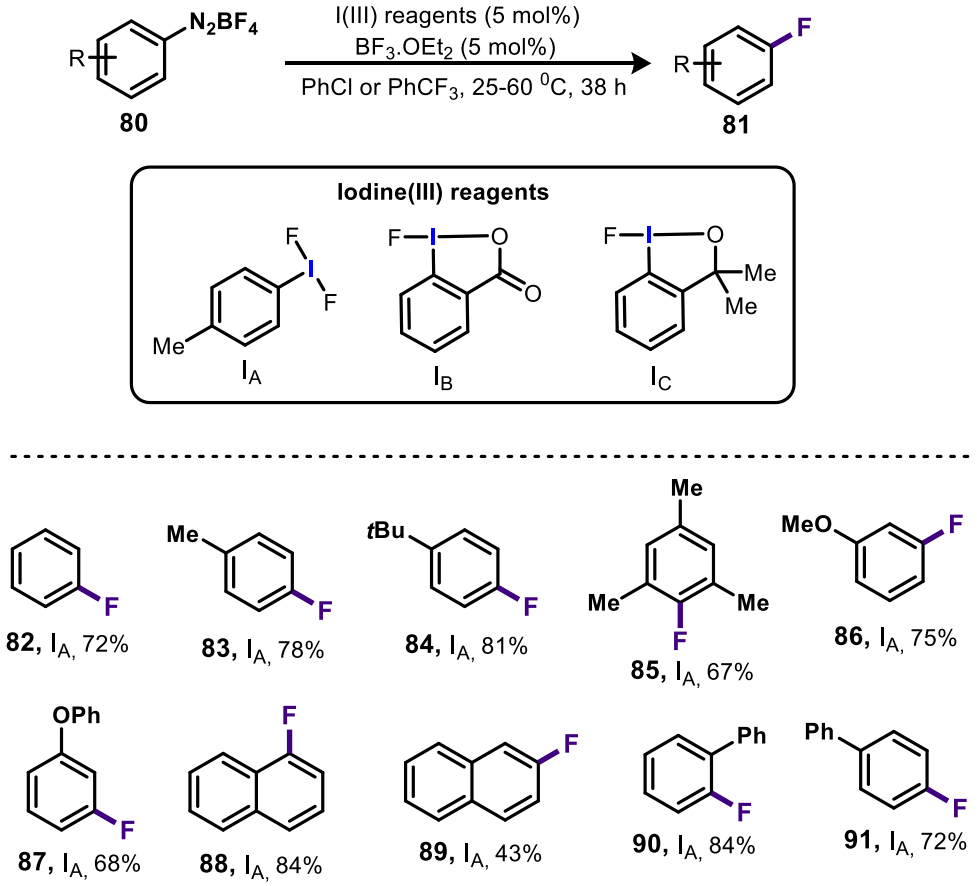
In 2013, Li and his co-workers developed the procedure of regioselective fluorination of anilides.[28] This metal-free fluorination of anilides **68**, is achieved from bis(tert-butylcarbonyloxy)-iodobenzene $PhI(OPiv)_2$ and hydrogen fluoride-pyridine and DCM as a solvent at room temperature. In this methodology obtained *para*-fluorinated derivates **69-79**, with moderate to good yields **(scheme 9)**.



Scheme 9. *para*-Fluorination of anilides using $PhI(OPiv)_2$/HF·Py system.

28. Tian, T.; Zhong, W.H.; Meng, S.; Meng, X.B.; Li, Z.J. *J. Org. Chem*. **2013**, *78*, 728−732.

In 2018, Hu and co-workers proposed the fluorination of arenes **81**[29] and this achieved by hypervalent iodine **(I_A, I_B, I_C)** catalyzed balz-schimann reaction. This fluorination reaction carried out in mild conditions and prepared variety of examples **82-91 (scheme 10)**.

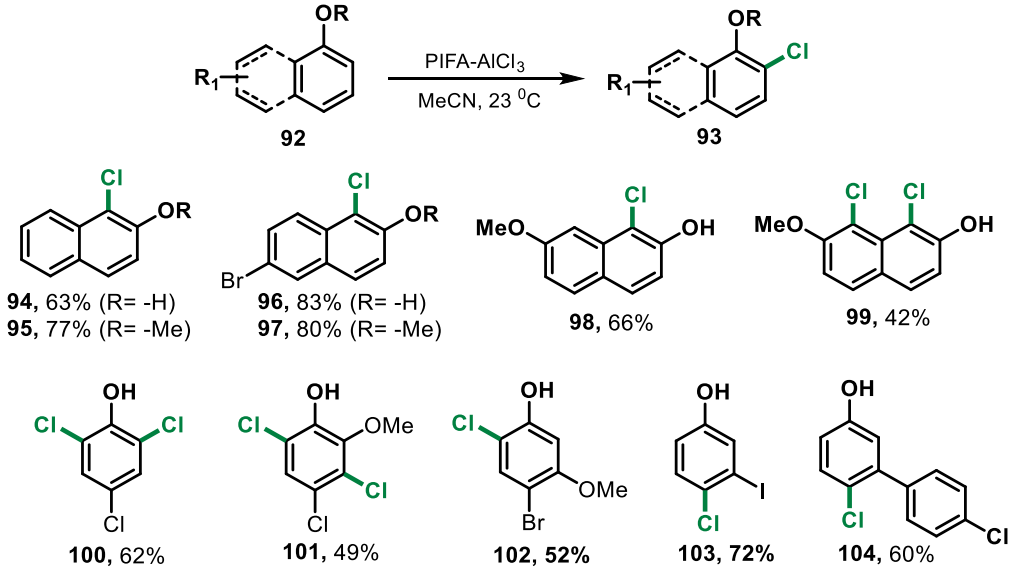


Scheme 10. Iodine(III)-catalyzed balz–schiemann fluorination of arenes.

29. Xing, B.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 9896 –9900.

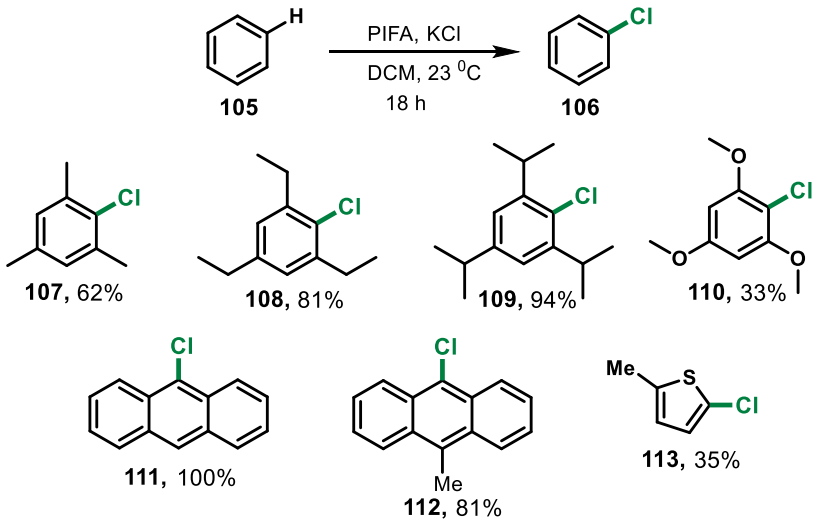
1.1.6.3 Chlorination

Recently, in 2018, Solorio-Alvarado and co-workers developed the procedure of chlorination of phenols, and phenol-ethers **92,**[30] from the PIFA-$AlCl_3$ system under mild reaction condition to get derivates **93-104 (scheme 11)**.



Scheme 11. Chlorination of phenol by PIDA–$AlBr_3$ system.

In 2019, Vallribera and co-workers developed the procedure of chlorination of arenes **105**,[31] with the help of PIFA-KCl system and DCM as a solvent at 23 ^{0}C to get derivatives **106-113 (scheme 12)**.

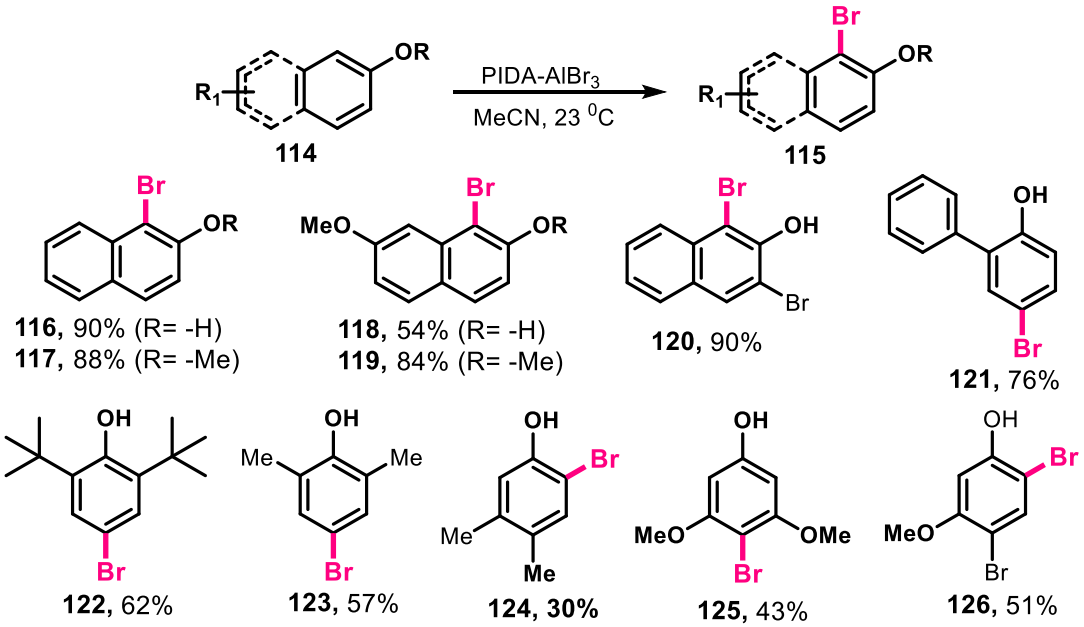


Scheme 12. Chlorination of arenes by using the PIFA-KCl system.

30. Nahide, P.D.; Ramadoss, V.; Juárez-Ornelas, K.A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J.M.; Alonso-Castro, Á.J.; Zapata-Morales, J.R.; Ramírez-Morales, M.A.; Ruiz-Padilla, A.J.; Deveze-Álvarez, M.A. *Eur. J. Org. Chem.* **2018**, *4*, 485-493.
31. Granados, A.; Jia, Z.; del Olmo, M.; Vallribera, A. *Eur. J. Org. Chem*. **2019**, *17*, 2812-2818.

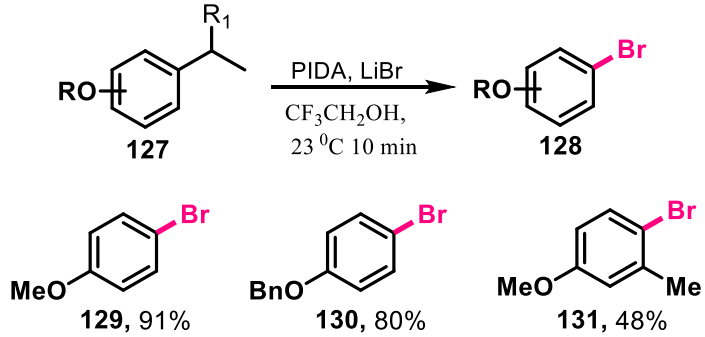
1.1.6.4 Bromination

Recently, in 2018, Solorio-Alvarado and co-workers developed the procedure of bromination of phenols and phenol-ether **115**,[32] from the PIDA-$AlBr_3$ system under mild reaction condition to get derivatives **115-126**. Bromination of phenols was possible by brominating reagent PhIOAcBr and this PhIOAcBr was generate from PIDA-$AlBr_3$ system **(scheme 13).**



Scheme 13. Bromination of phenol by using the PIDA–$AlBr_3$ system.

In 2018, Maegawa and co-workers proposed the alkoxybenzyl alcohol **127**, undergo bromination **128**,[33] take place with the help of Iodine(III)-reagent and lithium bromide in CF_3CH_2OH to formed brominated compounds **128-131**, *via* dehydroxymethyl bromination at 23 ^{0}C **(scheme 14).**

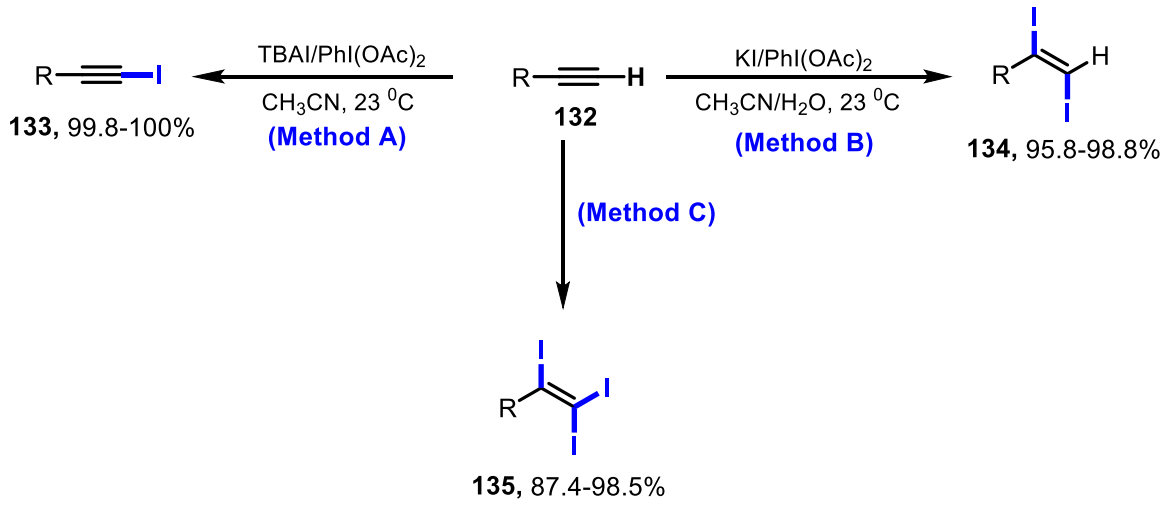


Scheme 14. Bromination of benzyl alcohols.

32. Satkar, Y.; Ramadoss, V.; Nahide, P.D.; García-Medina, E.; Juárez-Ornelas, K.A.; Alonso-Castro, A.J.; Chávez-Rivera, R.; Jiménez-Halla, J.O.C.; Solorio-Alvarado, C. R. *RSC Adv*., **2018**, *8*, 17806–17812.
33. Shibata, A.; Kitamoto, S.; Fujimura, K.; Hirose, Y.; Hamamoto, H.; Nakamura, A.; Miki, Y.; Maegawa, T. *Synlett,* **2018**, *29*, 2275–2278.

1.1.6.5 Iodination

In 2017, Maruoka and co-workers developed the procedure of chemoselective mono-**133**, di-**134**, and tri-iodination **135**, of alkynes by using hypervalent iodine(III) reagents.[34] In this procedure method A in which tetrabutylammonium iodide (TBAI)/ (diacetoxyiodo)benzene (PIDA) system is used for mono-iodination of alkyne, the method B KI/PIDA system is for di-iodination of alkynes and combination of method A TBAI/PIDA and method B KI/PIDA is used for tri-iodination of alkynes through one-pot reaction **(scheme 15)**.



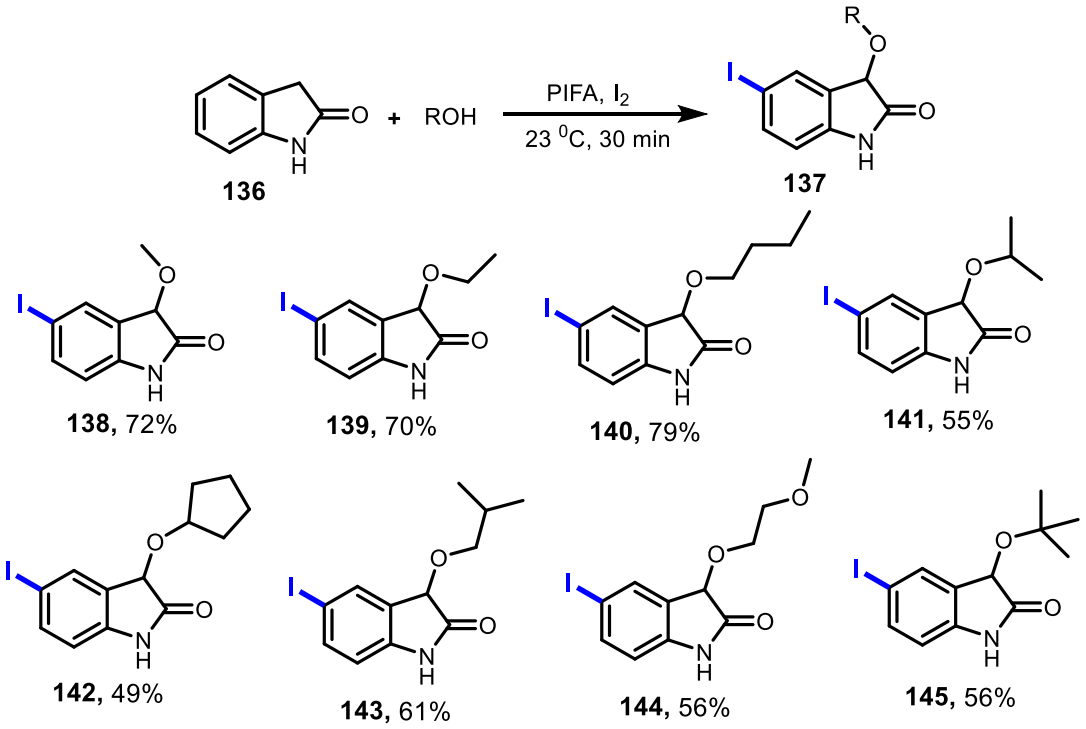
R= Ph, *p*-$MeOC_6H_4$, p-F-C_6H_4, *p*-CF_3-C_6H_4, *p*-$CH_3OCOC_6H_4$, CH_2CH_2OH, CH_2OAc.

Method A: Alkyne (1.0 equiv), TBAI (1.2 equiv), and PIDA (1.0 equiv) in MeCN, 23 ^{0}C, 2-24 h.
Method B: Alkyne (1.0 equiv), KI (2.5 equiv), and PIDA (1.0 equiv) in MeCN/H2O (1:3, v/v), 23 ^{0}C, 2-24 h.
Method C: (i) alkyne (1.0 equiv), TBAI (1.2 equiv), and PIDA (1.0 equiv) in MeCN, 23 ^{0}C, 3 h;
(ii) H_2O, KI (2.5 equiv), and PIDA (2.0 equiv), 3 h;
(iii) H_2O, KI (2.5 equiv), and PIDA (2.0 equiv), 12 h.

Scheme 15. Iodine(III)-mediated selective iodination of terminal alkynes.

In 2018, Kotagiri, and Adepu developed new, transition metal free, and one pot synthesis of 5-iodo-3,-mono alkoxyoxindole **137**, from the oxidative coupling between oxindole **136**, and alcohols generate alkoxylation and followed by iodination[35] take place by $PhI(OCOCF_3)_2/I_2$ system and this reaction carried out in mild conditions to get derivatives **137-145 (scheme 16).**

34. Liu, Y.; Huang, D.; Huang, J.; Maruoka, K. J. Org. Chem. **2017**, *82*, 11865−11871.
35. Kotagiri, R.; Adepu, R. *Eur. J. Org. Chem.* **2018**, *33*, 4556-4564.



Scheme 16. Iodo-monoalkylation of oxindoles.

1.2 Gold Chemistry

1.2 Gold Chemistry

1.2.1 General Introduction of Gold

Gold has tremendous importance and use in human life from beginning, because it's correlated with beauty and power. Due to the beauty of gold has captivated the people and rises his value from the biggening times in the history. Initially, from thousands of years ago gold is use as money purpose and from long time history proved that it has excellent durability and stability. Later, people tried to modified gold value and importance in other application like electrical devices, souvenir, jewelry, monetary exchange, and in dental medicine (**figure 3**). The broad application of gold proved the importance of gold in humans' life and shows excellent stability and inert reactivity. Since the Egyptian age and still widely used throughout in the world. Thus, metallic gold could be used in biocompatible area although ionic gold is toxic and not suitable.[36]

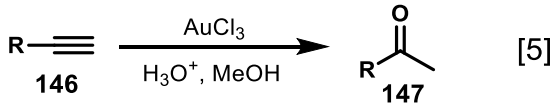
Figure 3. Importance of Gold

According to the chemistry point of view, gold is indicate by symbol-Au (from the Latin *aurum*, "shining dawn"), atomic number of gold is 79, and electronic configuration is $1S^2\ 2S^2\ 2P^6\ 3S^2\ 3P^6\ 3d^{10}\ 4S^2\ 4P^6\ 4d^{10}\ 5S^2\ 5P^6\ 4f^{14}\ 5d^{10}\ 6S^1$. gold is a transition metal belonging to the group 11 of the periodic table with three most common oxidation states: gold(0), gold(I) and gold(III). Gold is bright yellow metal, soft with several physical properties. Gold has one of the 81 nonradioactive elements should receive much attention in chemistry reactions as well.[36]

36. (a) Pyykkö, P. *Chem. Rev*. **1988**, *88*, 563-594. (b) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456. (c) Pitzer, K. S. *Acc. Chem. Res*. **1979**, *12*, 272-276. (d) Gorin, D. J.; Toste, F. D. *Nature*, **2007**, *446*, 395-403.

1.2.2 Beginning of Gold Chemistry

In 21st century until today gold chemistry achieved tremendous success in organic synthesis and from past records, we know gold for centuries. But here, we are discussing about beginning of gold in catalysis, there is not any single application reported in organic chemistry before 1976. The first application of gold in organic chemistry reported and developed by the hydration of alkynes **146** to get ketones **147**, by using gold(III) by Teles and coworkers (**Eq. 5**).[37]

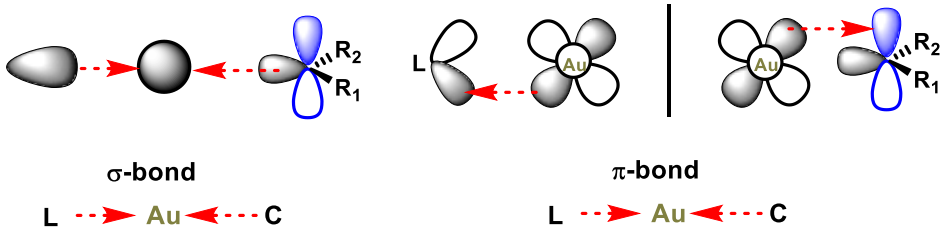


[5]

After some year in 1998,[38] Ito and Hayashi was developed the same hydration reaction under homogeneous reaction condition in the presence of gold(I) complexes. Later, in 2004,[39] Echavarren and coworkers developed the first application in gold catalysis for cyclization of 1,6-enynes with the help of same gold(I) complexes.

1.2.3 Gold Carbenes and Carbenoids

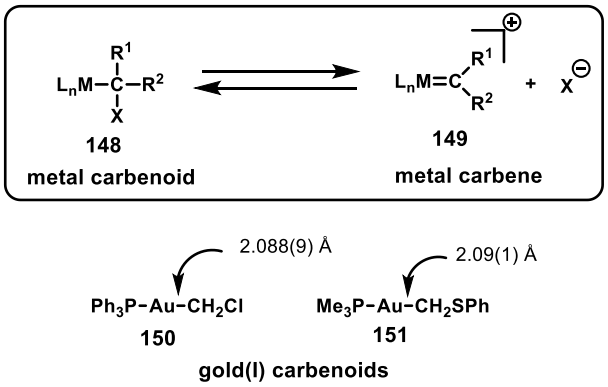
This basic explanation of the banding mode of gold carbene proposed by Toste and Goddard[40] in 2009. The basic concept of gold carbene is that the carbene and ligand L both formed a three-center four-electron bond by donate their paired electrons to gold. Beside that gold center can form two π-bonds by backdonation from two filled 5d orbitals to empty π-acceptors on the ligand and carbene **(Scheme 17)**.



Scheme 17. Schematic representation of the bonding of gold carbenes.

The basic difference between carbene and carbenoids are two different species and his difference related to the addition/elimination of X-group and the double bond character of the metal-carbon bond in the carbene **(scheme 18)**.[41]

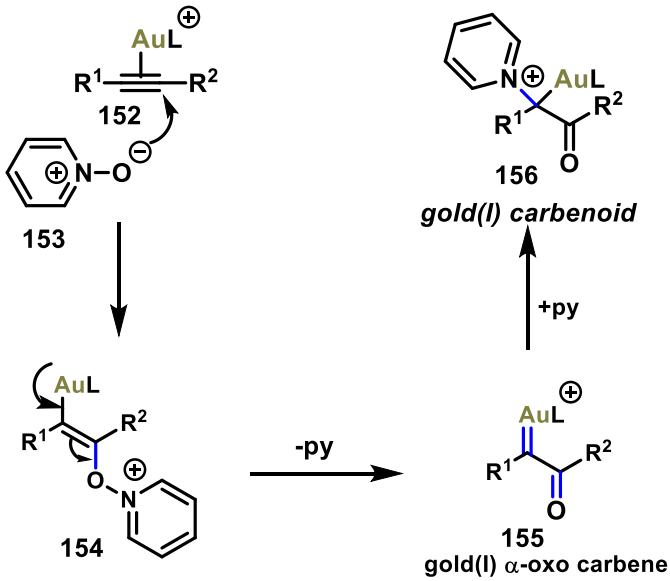
37. Nomran, R. O. C.; Parr, W. J. E.; Thomas, C. B. J. Chem. Soc., Perkin Trans. **1976**, 1983-1987.
38. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.
39. Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.
40. a) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482 –486. b) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, 21, 1 – 9.
41. a) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics*, **2000**, *19*, 5529 –5532. b) Nesmeyanov, A. N.; Perevalova, E. G.; Smyslova, E. I.; Dyadchenko, V. P.; Grandberg, K. I.; *Izv. Akad. Nauk SSSR Ser.*



Scheme 18. Carbenoid and carbene equilibrium and isolated gold(I) carbenoids.

Based on **scheme 18**, bond length of metal-carbon in these gold carbenoids (2.09 Å), is longer than in gold carbene.

At the end difference between gold(I) carbenes and carbenoids is helpful in mechanistic discussion point of view. In study of gas-phase was describe that the gold(I)-catalyzed oxidation of alkynes **152**, by pyridine *N*-oxides **153**, gives gold(I) carbenoids **156**, *via* vinylides gold(I) complex **154**, that evolves into a α-oxo carbenes **155**, **(scheme 19)**.[42]



Scheme 19. Generation of gold(I) carbenoids in the oxidation of alkynes with pyridine *N*-oxides.

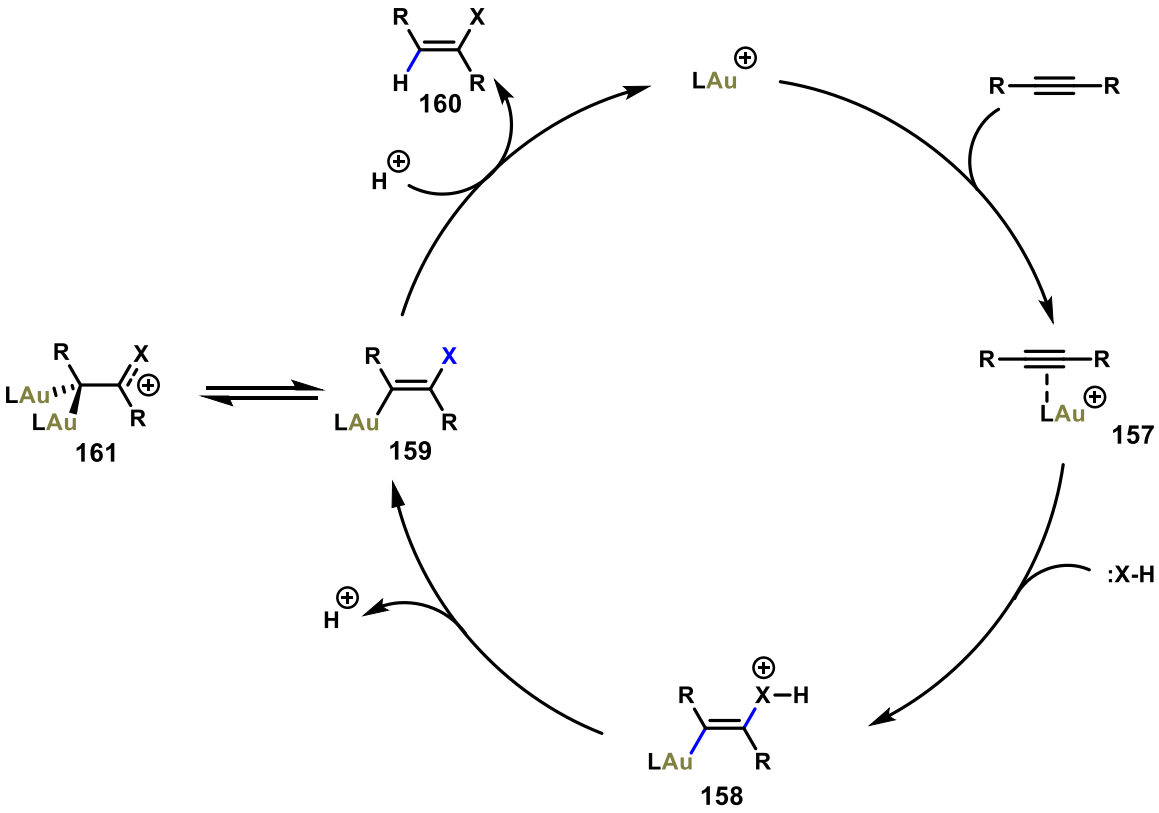
According to **scheme 19**, α-oxo carbene may be formed by elimination of pyridine from initial adduct, but it react instantly with pyridine to produce more stable gold(I) carbenoids.

Khim. **1977**, 2610– 2612; c) Steinborn, D.; Beckea, S.; Herzoga, R.; Gunther, M.; Kircheisen, R.; Stoeckli-Evans, H.; Bruhn, C. *Z. Anorg. Allg. Chem.* **1998**, *624*, 1303 –1307. d) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, 21, 1 – 9.

42. a) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, 21, 1 – 9 b) Schulz, J.; Jasikova, L.; Skriba, A.; Roithova, J. *J. Am. Chem. Soc.* **2014,** *136*, 11513– 11523.

1.2.4 Basic Principle of Gold(I)-Catalyzed Addition of Heteronucleophiles to Alkynes

The basic principle of gold(I)-catalyzed addition of heteronucleophile to alkynes, start from triple bond of alkyne activated by gold(I)-catalyst and generate π-complex **157**. Once complex **157**, is formed then nucleophile attack on **π**-complex **157,** in a stereoselective *trans* fashion which gives intermediate **158**. Intermediate **158** undergo loss of H^+ to give vinylidene gold(I) species **159**, followed by protodeauration to generate final product **160** and regeneration of catalyst. On the other hand, another possible pathway is the formation of *gem*-diaurated species **161**, this pathway might seriously compete with protodeauration.[43] The extraordinary catalytic activity of gold species can be explained in terms of basic principles in frontier orbitals, π-acidity, and relativistic effects **(scheme 20)**.



Scheme 20. Catalytic cycle for the gold-catalyzed *trans* addition of a protic nucleophile X-H to an alkyne substrate X=Heteroelement.

43. Seidel, G.; Lehmann, C. W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, 49, 8466-8470.

1.2.5 Gold(I) as a Soft Lewis Acid

The concept of Lewis acid-base theory is firstly introduced by G. N. Lewis in (1923).[44,45]According to these theory , an acid is a substance with an empty orbital have ability to accept a lone pair of electron is known as acid and the electron rich species have the ability to donate a lone pair of electron-to-electron deficient species like Lewis acid is known as Lewis base. Based on these theory, we will describing properly their electronic nature in terms of chemical bonds.

Basically, Lewis acid and base both are divide into hard and soft lewis acid and base (HSAB)[46] and this concept introduced by Pearson in 1963. According to Pearson soft lewis acid has a big atomic radius, low charge and strongly polarizable. While, hard Lewis acid has a small atomic radius, highly charges and weakly polarizable.[47,48]

Based on the concept of G.N Lewis and Pearson theories gold(I) and gold(III) are defined as soft Lewis acids as shown in bellow examples.

Examples of soft and hard Lewis acid.

Hard acids- H^{+}, Li^{+}, Na^{+}, K^{+},Ti^{4+}, Cr^{3+}, Cr^{6+}, Be^{2+}, Mg^{2+}, Ca^{2+}, $Sr^{2+,}$ Sn^{2+}, Al^{3+}, Si^{4+}.

Soft acid- Cu^{+}, Ag^{+}, Tl^{+}, Cs^{+}, I^{+}, Br^{+}, Hg^{2+}, Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, Tl^{3+}, **Au^{+}, Au^{3+}.**

44. Lewis, G. N. *J. Frank. Inst.* **1938**, *226*, 293-313.
45. Ebbing, D. D., Gammon, S. D. *General Chemistry* 8th ed. Boston, MA: Houghton Mifflin. **2005**.
46. Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539.
47. Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581-586.
48. Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 643-648.

1.2.6 Relativistic Effects in Gold

Relativistic effect shows by gold is due to it has high nuclear charge. Relativistic effects means irregular periodic behavior came from the internal shell electrons travelling with high velocity and almost close to the speed of light.[49,50] Based on the Schrodinger equation[51] and modified[52] heavy atoms with large atomic radius it shows relativistic effect.

Based on the documented[53,54,55]electronic structure and characteristics of gold shows strong relativistic effect. Relativistic effect of gold are demonstrated in A) the contraction of external 6s and 6p orbitals and B) expansion of the 5d orbitals (Figure 2) explain in bellow.

1.2.6.1 Contraction of external 6s and 6p orbitals

The π-bond activates and react on gold catalyst as a result of 6s and 6p orbital of gold was compressed, additionally cationic gold (I) exhibits superior Lewis acidity in comparison with cationic metals of group 11th. That incident time gold shows the most important peculiar characteristics relativistic effect then gold attract more electron density towards itself. Because the atom gold possess a high nuclear charge that is why it shows relativistic effect. In this incident gold shows interesting property with high electronegativity of 2.5[56] compared to 2.4 of carbon. That's mean in C-Au bond in which major bonding electron density is on gold, rather than carbon.

1.2.6.2 Expansion of 5d-orbitals

Simultaneously, after the compression of 6s and 6p orbital the small s-orbital of gold was shielded and the effect is that expansion of these orbitals in gold causes a diffuse electronic cloud, Posses electron-electron repulsions, resulting in a very high first ionization energy (9.22 eV).[57] Due to these electron-electron repulsion another important result caused by expansion of the 5d orbitals, is the gold-carbenoid behavior. Then diffuse of 5d electrons are delocalized into carbon-based orbitals of low enough energy, especially in the empty π-orbitals of the carbocation and back bonding take place and more electron density lost than it gains through back-donation.

49. Pitzer, K. S. *Acc. Chem. Res.* **1979**, *12*, 272-276.
50. McKelvey, D. R. *J. Chem. Educ.* **1983**, *60*, 112-116.
51. Schrödinger, E. *Phys. Rev.* **1926**, *26*, 1049-1070.
52. Dirac, P. A. M. *Proc. R. Soc.* **1928**, *117*, 610-624.
53. Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456.
54. Pyykkö, P. *Inorg. Chim. Acta.* **2005**, *358*, 4113-4130.
55. Gorin D.; Toste, F. D. *Nature* **2007**, *446*, 395-403.
56. Electronegativity is given in Pauling scale.
57. Neale, R. S. *J. Phys. Chem*. **1964**, *68*, 143–146.

This effect is relevant in catalysis because as a corollary of this relativist effect, the oxidative addition of gold(I) to form gold(III) is not a facile process and usually does not take place **(figure 4)**.[58]

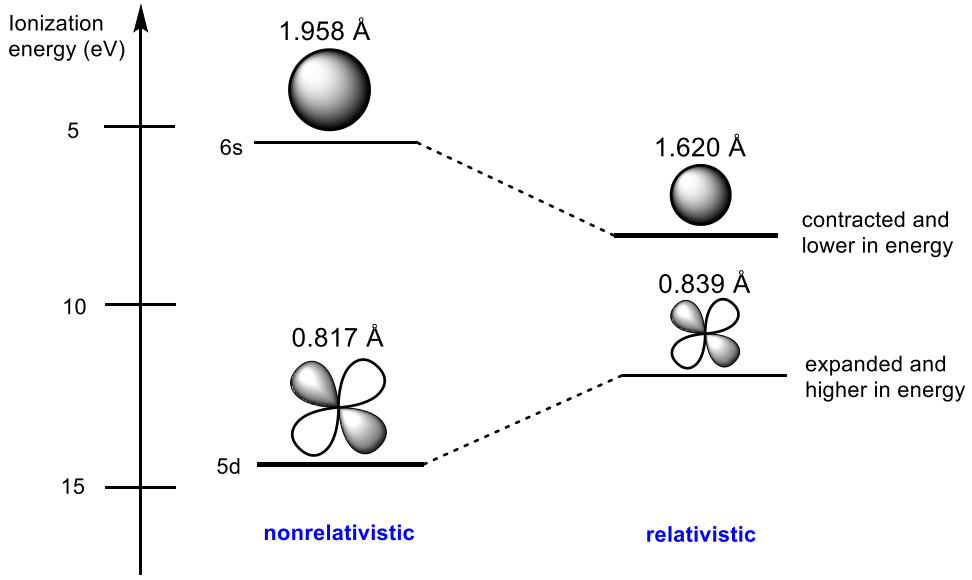


Figure 4. Relativistic effects on the energy for Au(I)

1.2.7 The π-Acidity of Gold(I) Complexes

The Gold(I) complexes shows important characteristic in catalysis, it shows more affinity with alkynes, allene and alkenes. Based on the activation of alkyne, allene and alkenes by gold(I) complexes several modification developed in organic chemistry **(Figure 5)**.

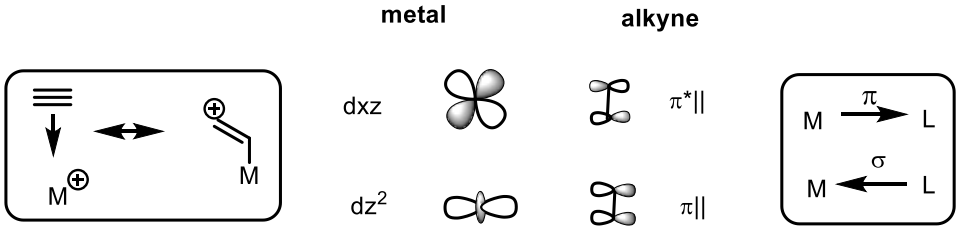


Figure 5. π–bond activation

π-acidity: Carbon-Carbon multiple bond of alkene or alkyne activate by reacting with gold(I) complexes followed by electron density of alkyne or alkene multiple bond disturbed and formed positive charge on the multiple bonds which is stabilized by metal ligand beck-bonding **(figure 5).**[59]

58. a) Shapiro, N. D.; Toste, F. D. *Synlett,* **2010**, *5*, 675-691. B) Peter Schwerdtfeger, Michael Dolg, W. H. Eugen Schwarz, Graham A. Bowmaker, and Peter D. W. Boyd *J. Chem. Phys.* **1989**, 91.
59. Fürstner, A.; Davies, W.P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449.

1.2.8 Bonding Models for Gold(I) Complexes

The most basic molecular orbital model of Dewar-Chatt-Duncanson (DCD) that explains the interaction between metals and π-bonded unsaturated ligands.

The importance of his model lies in the introduction of the metal-ligand orbital interactions concept. The model was first time described in 1951 by Dewar[60] with the help of perturbation theory[61,62] of quantum mechanics. Based on this Dewar model in 1953[63] Latter Chatt and Duncanson smartly described the interaction between metal-olefin complexes.

Based on the Dewar-Chatt-Duncanson (DCD) model describe gold(I)-alkyne interaction in bellow-

1. π-orbital of the alkyne interact with empty d orbital of the metal generate σ-donation.
2. Back-bonding from filled d-orbital of the metal to empty π–orbital of the alkyne.

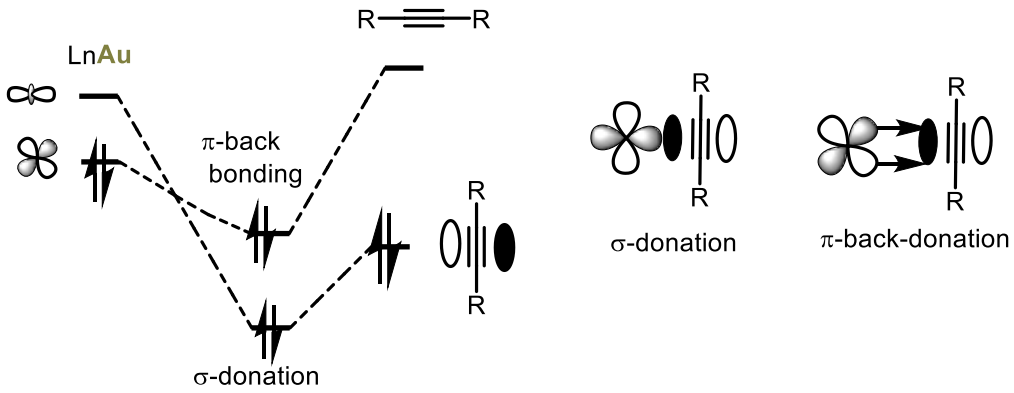


Figure 6. The Dewar-Chatt-Duncanson model showing the σ-donation and π-back-bonding in a gold-alkyne complex.

The electrophilicity of triple bond increases by σ-donation from the filled π-bond of alkyne to empty d-orbital of metal bonding interaction (56.6 Kcal/mol), which is support by Toste.[64] Toste did Density functional theory (DFT) calculations with the help of second order perturbative analysis of natural bond orbitals (NBO) and these DFT calculations he proves that the electrophilicity of triple bond increases by σ-donation.

The back-bonding from the filled metal orbital to the π* empty orbital of the alkyne, analyzed by frontier molecular orbitals. These back bonding is important from energy (13.3 Kcal/mol) point of view, shows back-bonding is possible due to LUMO. Overall, these bonding interaction

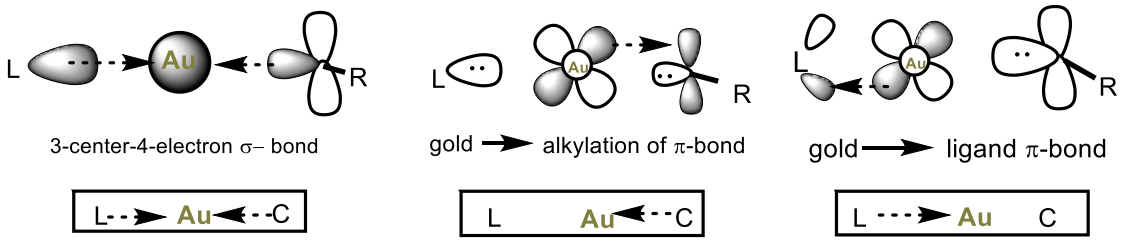
60. Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71.
61. Schrödinger, E. *Annalen der Physik,* **1926**, *80*, 437-490.
62. Fhelner, T. P. *J. Organomet. Chem.* **2001**, *635*, 92-99.
63. Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939-2947.
64. Shapiro, N. D.; Toste, F. D. *Proc. Nat. Acad. Sci. U.S.A.* **2008**, *105*, 2779-2782.

between Au(I)-complexes and alkyne proves that the Au(I) shows excellent Lewis acidity than other transition metals.[65]

From the above discussion strong σ-donation of alkyne π-bond (56.6 Kcal/mol) and the backdonation (13.3 Kcal/mol) support the π-acidity of gold(I) complexes with alkynes. Not only this but also complexes with different π- bond ligands and his study support the evidence of this strong π-affinity.[65]

Based on this σ-donation and backbonding is generate a three-center two bond system because, it decreases C-C bond order in alkyne, which leads to extent C-C distance regarding metallacyclopropene.[65]

On the other hand, Toste and Goddard developed bonding model for the ligand-gold-carbene (LGC) system model.[66] He described that the bond between gold and carbon consist of a π-bond and metal to carbene back bonding is tremendously depends on the substituent of carbene. In this model Toste and Goddard explain the LGC in three parts- 1) σ-bonding from carbene and ligand to metal, 2) π-bonding from metal to carbene and 3) π-bonding from metal to ligand (**Scheme 21**).



Scheme 21. Ligand-gold-carbene (LGC) system bonding model for gold(I)-carbene complexes.

The alkyne to ligand σ-bonding consist of three-center/four-electrons interaction between them and Back-bonding electron donation from two orthogonal d orbitals of gold to empty or π-acceptor orbitals of ligand and carbene. This model is explain that the effect of substituents on the carbene and influences in the reactivity will be noted. Overall, this model said that reactivity of gold(I)-carbene interaction is explained intermediate between metal-stabilized singlet carbene to a metal coordinated carbocation and the substituents on carbene and ancillary ligand will be determined important of each carbon. Some other model also explain the coordination between gold and alkyne.[67]

65. a) Elschenbroich, C. *Organometallics*, 3rd ed. Weinheim, Germany, WILEY-VCH Verlag GmbH & Co. KGaA, **2006**. b) Schmidbaur, H.; Schier, A. *Organometallics* **2010**, *29*, 2-23.

66. Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Godarr III, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482-486.

67. Salvi, N.; Belpassi, L.; Tarantelli, F. *Eur. J. Chem.* **2010**, *16*, 7231 – 7240.

1.2.10 Gold(I) complexes

Gold(I) complexes mostly exhibit a linear geometry[68] and possess a $[Xe]4f^{14}5d^{10}$ $6s^0$ configuration (d^{10}). Phosphines, phosphites and related donor ligands forms lineal L-Au-X complexes. The 14 electron complexes of the type **173-176**, **177**, and **178-181** (Figure), show a poor catalytic activity in comparison with cationic complexes **176, 162-169**, **170**, and **166-168** (**figure 7**). These cationic forms are generated by abstraction of the halogen, typically by using one equivalent of an Ag(I) salt with a non-coordinating anion.[69] Thus, complexes with the general formula [Au(S)(P)]X (P = phosphine ligand, S = solvent molecule, X = non-coordinating anion) are easily generated. These complexes have the advantage that they do not need to be activated, are soluble in the reaction media, and are stable in the solid state. To date various cationic gold(I) complexes have been synthesized. Among them, we can find complexes with bulky-biphenyl based phosphines as ligands, which were originally developed for Pd-catalyzed cross coupling.[70] The corresponding gold complexes are very active catalysts upon mixing with Ag(I) salts (**figure 7**, **162,163,173-176**).[71] Related complexes containing a labile bis(trifluoromethanesulfonyl)amide (NTf_2) as ligand have been reported showing similar properties.[72] The bulky bis-adamantyl phosphine ligand in complex **182,** has been synthesized for the use in hydroaminations of alkynes with dialkylamines.[73] Phosphite complex **177**[74] bearing tris(2,6-di-*tert*-butylphenyl)phosphite as the ligand, as well as its cationic counterpart **170**,[75] are particularly highly electrophilic Au(I) catalysts. Complexes strongly containing s-donating N-heterocyclic carbenes (NHC) **178-181** are

68. a) Carvajal, M.A.; Novoa, J.J.; Alvarez, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465-1477. b) For discussion about the choice of coordination number in d10 complexes of group 11 metals, see: Carvajal, M. A.; Novoa, J. J.; Álvareze, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465–1477.
69. (a) Nieto-Oberhuber, C; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E., Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693. (c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.
70. (a) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789-794. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871-1876. (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978-13980. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696. (e) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096-5101.
71. a) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz. J.; Echavarren. A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455 – 5459. (b) Partyka, D. V.; Robilotto, T. J.; Hunter, A. D.; Gray, T. G. *Organometallics* **2008**, *27*, 28-32.
72. Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
73. Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026–18029.
74. (a) López, S.; Herrero-Gómez, H.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032. (b) **X** structure was confirmed by X-Ray crystallography: Nieto- Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279.
75. Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730.

useful precatalysts.[76,77,78,79] NHC complexes **183-181** have been synthesized to study their π-acceptor properties.[80] Cationic NHC complexes **166-168** [78-81] and those bearing labile ligands such as NTf_2 **181-182** have also been described.[82]

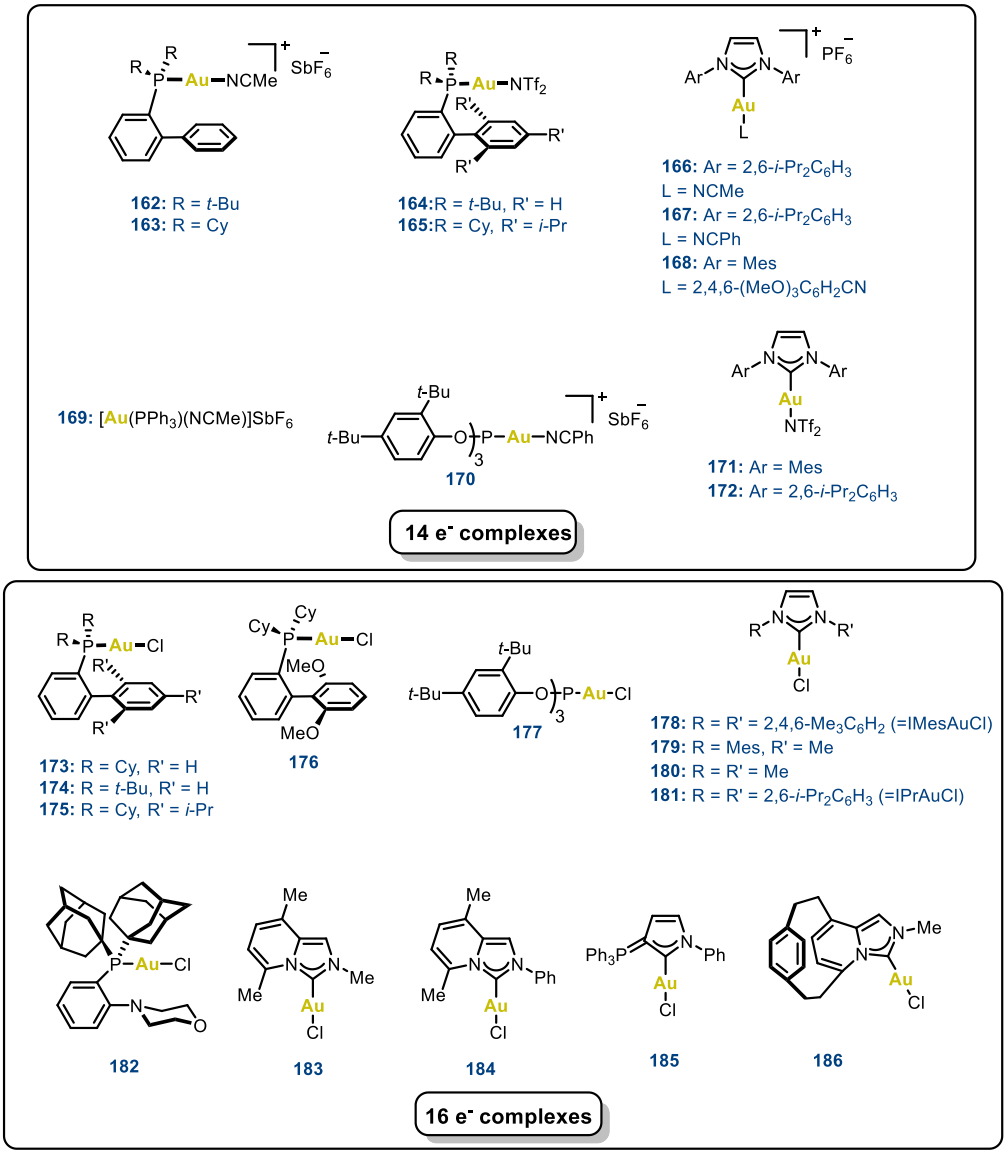


Figure 7. Representative neutral and cationic 14 e^- and 16 e^- gold(I) complexes.

76. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.
77. (a) Deetlefs, M.; Raubenheimer, H. G.; Esterhuysen, M. W. *Cat. Today.* **2002**, *72*, 29-41. (b) Schneider, S. K.; Herrmann, W. A.; Herdtrweck, E. Z. *Anorg. Allg. Chem.*, **2002**, *629*, 2363-2370.
78. de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411-2418.
79. For NHC-Au(III) complexes see: de Frémont, P.; Singh, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376-1385.
80. Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542-2546.
81. de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Diaz-Requejo, M. M.; Perez, P. J.; Nolan, S. P. *Chem Commun* **2006**, 2045-2047.
82. Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156-5159.

1.2.9 Gold(III) Complexes

Gold(III) complexes adopt a square planer geometry and their [Xe] $4f^{14}$ $5d^8$ $6s^0$ configuration (d^8). Gold(III) complexes has Lewis acid properties, and they also behave as oxidant. Most of gold(III) salts like $AuCl_3$ **187**, and $AuBr_3$ are commercially available. $AuCl_3$ **187**, or Au_2Cl_6 **188**, is very hygroscopic, light sensitive, and decompose at temperature above 160 ^{0}C.[83] Other gold(III) complexes based on tetrachloroaurate(III) anion ($AuCl_4^-$)[84,85] are obtained by the oxidation of gold(0) by *aqua regia*. Other sophisticated gold(III) complexes can be prepared by using stabilizing ligands, like pyridine, -NHC or chelating picolinate. Gold(III) complexes as shown in bellow **figure 8**.

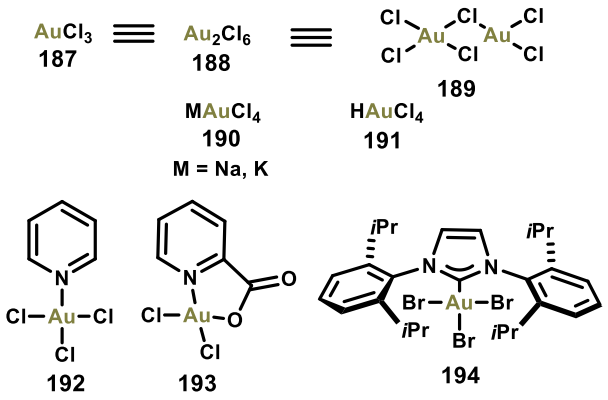


Figure 8. Described gold(III) salts and complexes.

Gold(III) complexes don't achieved success in organic transformation due to their lack of selectivity and limitations of modulabilty on the ligands. That's why gold(III) complexes is less interesting than gold(I) Complexes.

83. Wiber, E.; Wiber, N.; Holleman, A. F. Inorganic Chemistry 101 ed, Academic Press, **2001**, 1286-1287.
84. Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729-3733.
85. Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn*. **1991**, *56*, 3729-3733.

1.2.11 Cycloisomerization of Enynes

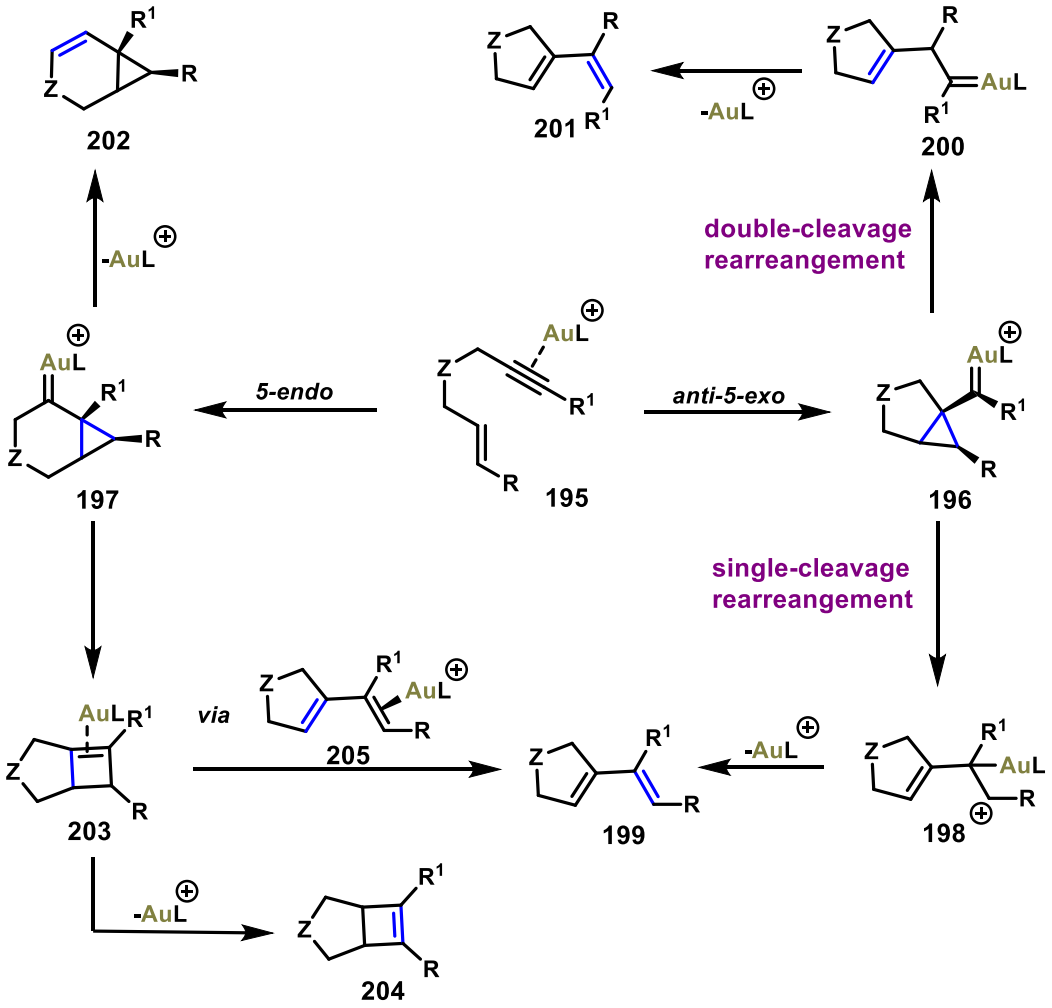
In 2004,[39] Echavarren and coworkers developed the first application in gold catalysis for cyclization of 1,6-enynes with the help of same gold(I) complexes. After this initiation in 2004, enynes Cycloisomerization reaction developed tremendously. Based on intramolecular process in enynes Cycloisomerization leads to prepared complex molecules.[86,87,88]

1.2.11.1 Cycloisomerization of 1,6-enynes

The Cycloisomerization of 1,6-enynes by activation of alkene with help of gold(I) catalyst to give (η^2-alkyne)metal complex **195,** then complex **195,** undergo nucleophilic attack *via* 5-*exo-dig* or 6-*endo-dig* **(scheme 22)**.[89,90,91] Firstly, activation of alkene take place which gives complex **195**, followed by complex **195,** undergo intramolecular two possible nucleophilic attack by 5-*exo-dig* and 6-*endo-dig* generate. Intermediate **196,** and **197,** respectively. Cyclopropyl gold(I) carbene **196** in which two types of skeletal rearrangements takes place to formed 1,3-dienes **199, and 201.** 1,3-dienes **199** is formed *via* single cleavage rearrangement by 1,3-migration from terminal carbon of the alkene to terminal carbon of alkynes and 1,3-dienes **201** is formed *via* double cleavage rearrangement.

Intermediate carbene **197,** leads to formed Bicyclic compounds **202,** and **204**. Product **202** is obtained from intermediate **197,** by elimination of proton take place in intermediate **197**,[92] which leads to formed **202**. Isomerization takes place in Intermediate **197**, to gives two possible product **204,** and **199.** Product **199**, obtained from Intermediate **197** via gold(I) complex **205**.[93] The kinetic data and DFT calculations report supported to both mechanism proposal (single and double cleavage rearrangements) **(scheme 22 and scheme 23)**.[93,94]

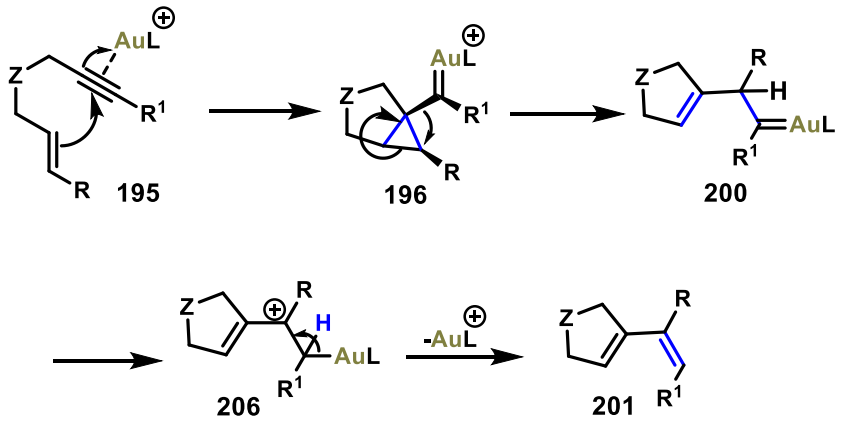
86. (a) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. (d) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378. (f) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208-3221. (g) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675-691. (h) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395-3442.
87. (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350. (c) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew.Chem. Int. Ed.* **2008**, *47*, 4268-4315.
88. (a) Obradors, C. Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16-28. (b) Obradors, C. Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902-912.
89. Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.
90. Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306- 6316.
91. Soriano, E.; J. Marco-Contelles, *Acc. Chem. Res.* **2009**, *42*, 1026-1036.
92. Chao, C. M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988-6990.
93. Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105-6111.
94. Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.



Scheme 22. Gold(I)-catalyzed cycloisomerization of 1,6-enynes.

Intermediate gold carbene **196**, the double cleavage takes place. In intermediate **196**, in which new gold carbene **200,** was formed by insertion of carbon of terminal alkene into the alkyne carbons. Gold carbene **200,** undergo dyotropic rearrangements[95] to formed **201 (scheme 23)**.[93,94]

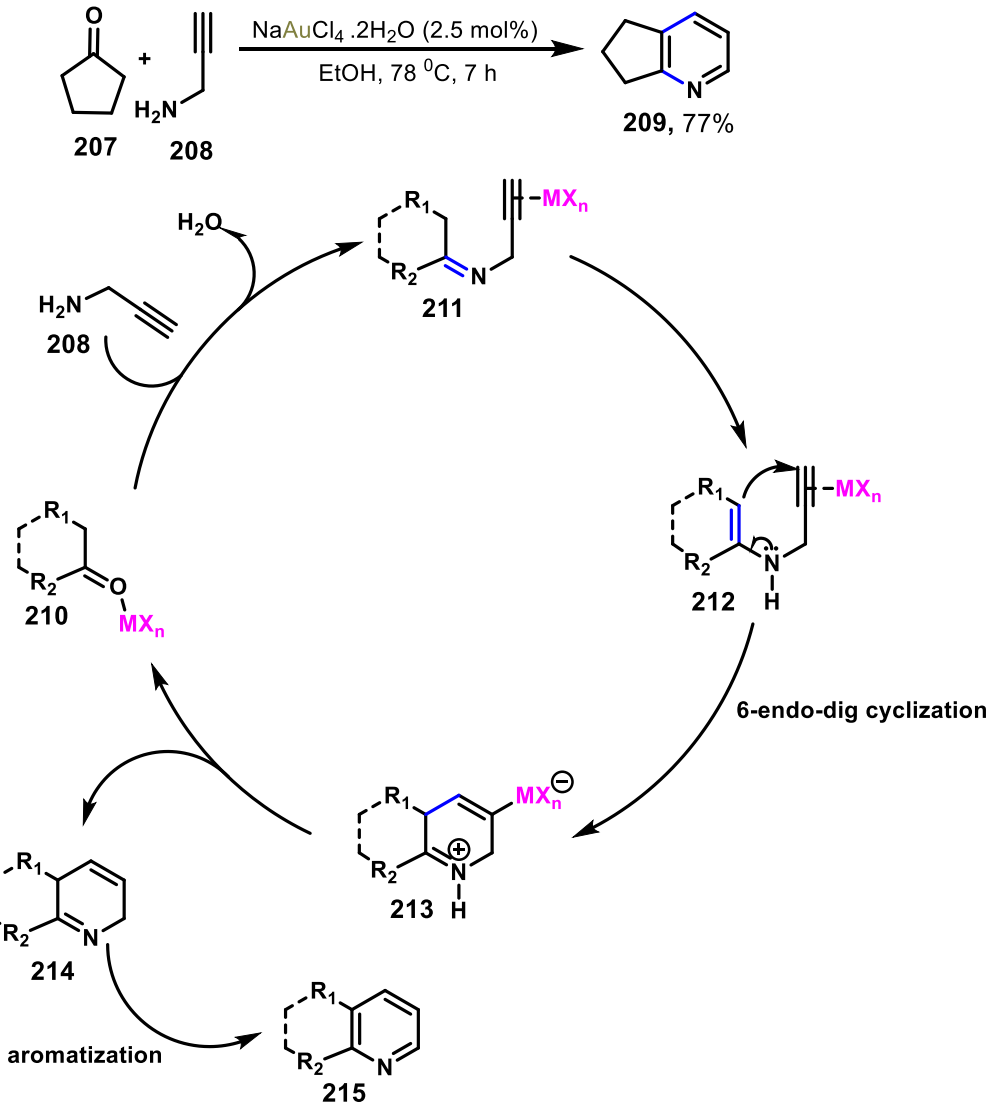
95. (a) Reetz, M. T. *Angew. Chem. Int. Ed.* **1972**, *11*, 129-130. (b) Reetz, M. T. *Angew. Chem. Int. Ed.* **1972**, *11*, 130-131.



Scheme 23. Double cleavage rearrangement.

1.2.11.2 Cycloisomerization of larger 1,5-enynes

Based on the firstly reported *endo* cyclization of 1,5-enynes strategy was try in novel One-pot synthesis of pyridines.[96] Synthesis of pyridines **209**, from ketone **207**, and propargylamine **208**, in the presence of gold(III) catalyst **165**. This reaction proceeds sequential amination of carbonyl compounds undergo imine-enamine isomerization followed by regioselective *6-endo-dig* cyclization of the *N*-propargylenamine (*N*-propargyldienamine) intermediate and at the end aromatization take place **(scheme 24).**

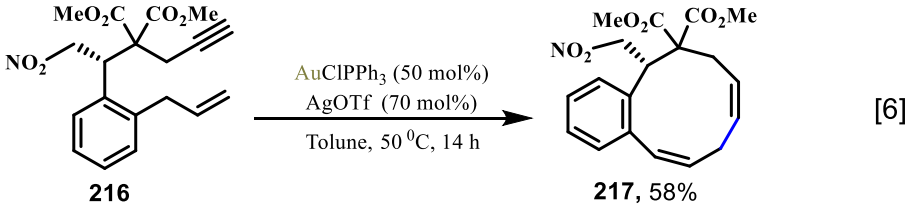


Scheme 24. Gold(III)-catalyzed synthesis of pyridines by cyclization of 1,5-enynes and their general reaction mechanism proposal.

96. Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959-6966.

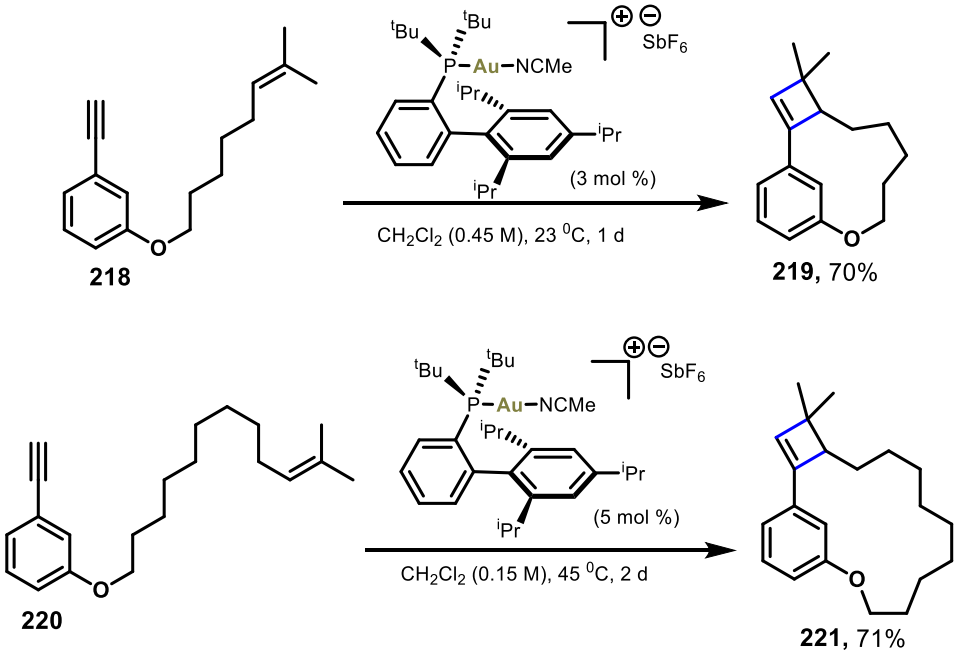
1.2.11.3 Cycloisomerization of larger 1,n-enynes (n>6)

The gold-catalyzed cycloisomerizations of 1,n enynes (n= 5-8) has been reported.[96,97,98, 99,100] Another gold-catalyzed cycloisomerizations reaction of 1,9-enyne to formed 10-membered ring **217**.[101] But this cyclization reaction need more gold(I) catalyst (50 mol %) and average yield of cyclized product (Eq. 6).



216 **217,** 58% [6]

In 2013, Echavarren and co-workers proposed the formation macrocycles containing a cyclobutene moiety **219** and **221**, by gold(I)-catalyzed cycloisomerization of larger 1,n-enynes (n= 10-16) **(scheme 25)**.[102]



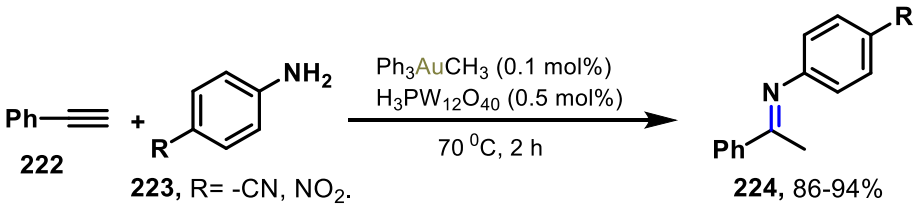
Scheme 25. Gold(I)-catalyzed cyclization of a 1,12 and 1,16-enyne to a *m*-cyclophane.

---

97. (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328–2334. (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal*. **2006**, *348*, 2271–2296. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev*. **2008**, *108*, 3326–3350. (e) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed*. **2008**, *47*, 4268–4315. (f) Ito, H., Ohmiya, H.; Sawamura, M. *Org. Lett.*, **2010**, *12*, 4380-4383.
98. Chao, C. M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988-6990.
99. Lee, S. I.; Kim, S. M.; Kim, S. Y.; Chung, Y. K. *Synlett* **2006**, *14*, 2256-2260.
100. Lee, Y. T.; Kang, Y. K.; Chung, Y. K. *J. Org. Chem.* **2009**, *74*, 7922-7934.
101. Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. Org. Lett. **2007**, 9, 2123–2126.
102. Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A.M. *Org. Lett.* **2013**, *15*, 1576-1579.

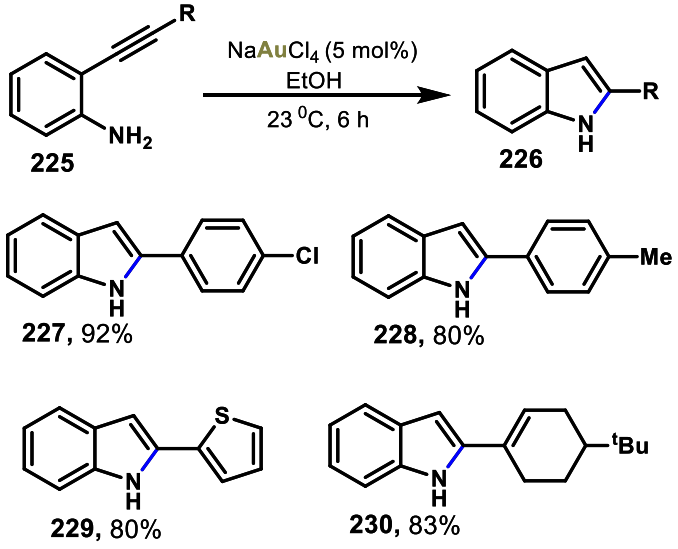
1.2.12 Hydroamination

In 2003, Tanaka and co-workers proposed the intermolecular hydroamination of alkynes with the help of gold(I) catalyst. In his proposal ketimines **224**, is formed by addition of aniline **223**, to aliphatic and aromatic alkynes **222**, in the presence of gold(I)-catalyst (**Eq. 7**).[103]



[7]

In 2004, Marinelli and co-workers describe the formation of indole derivatives by using environmentally friendly solvent, mild reaction condition, and without protection of -NH_2 . He proposed the formation of indole derivatives **226-230**, from gold(III)-catalyzed cyclization of 2-alkynylanilines **225**, in ethanol as a solvent under room temperature **(scheme 26)**.[104]

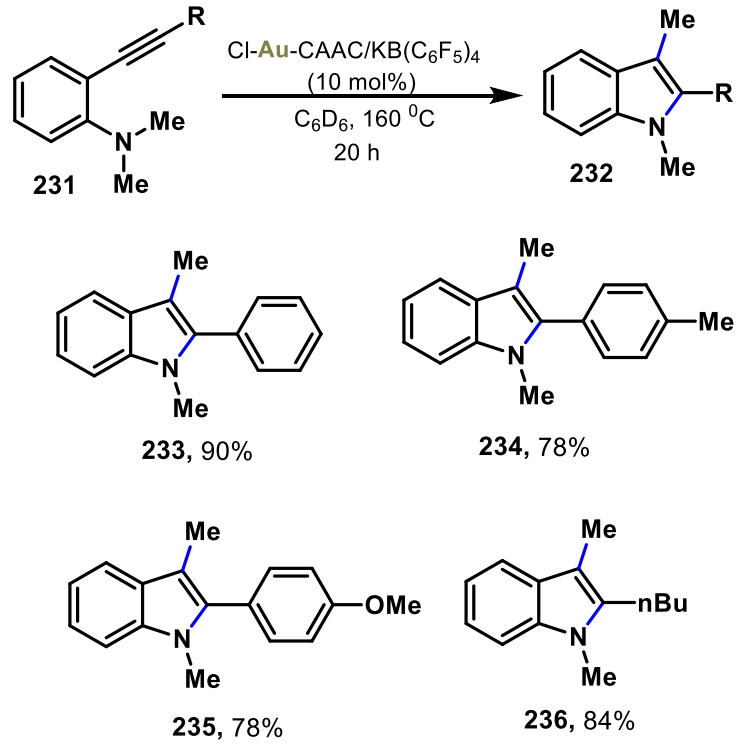


Scheme 26. Formation of indoles from 2-Alkynilanilines by gold(III)-catalyst.

In 2010, Bertrand and co-workers discovered first examples of catalytic intramolecular methylamination of alkynes. He proposed the formation 2,3-disubstituted indoles **232-236**, with excellent yields from 2-alkynyl-*N,N'*-dimethyl-benzenamines **231**, with the help of a 1:1 mixture of (CAAC)AuCl/ $KB(C_6F_5)_4$.[105] Here, the most important thing is that intramolecular

103.Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352.
104.Arcadi, A.; Bianchi, G.; Marinelli, F. Synthesis **2004**, *4*, 610–618.
105.Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem*. **2010**, *122*, 954 –957.

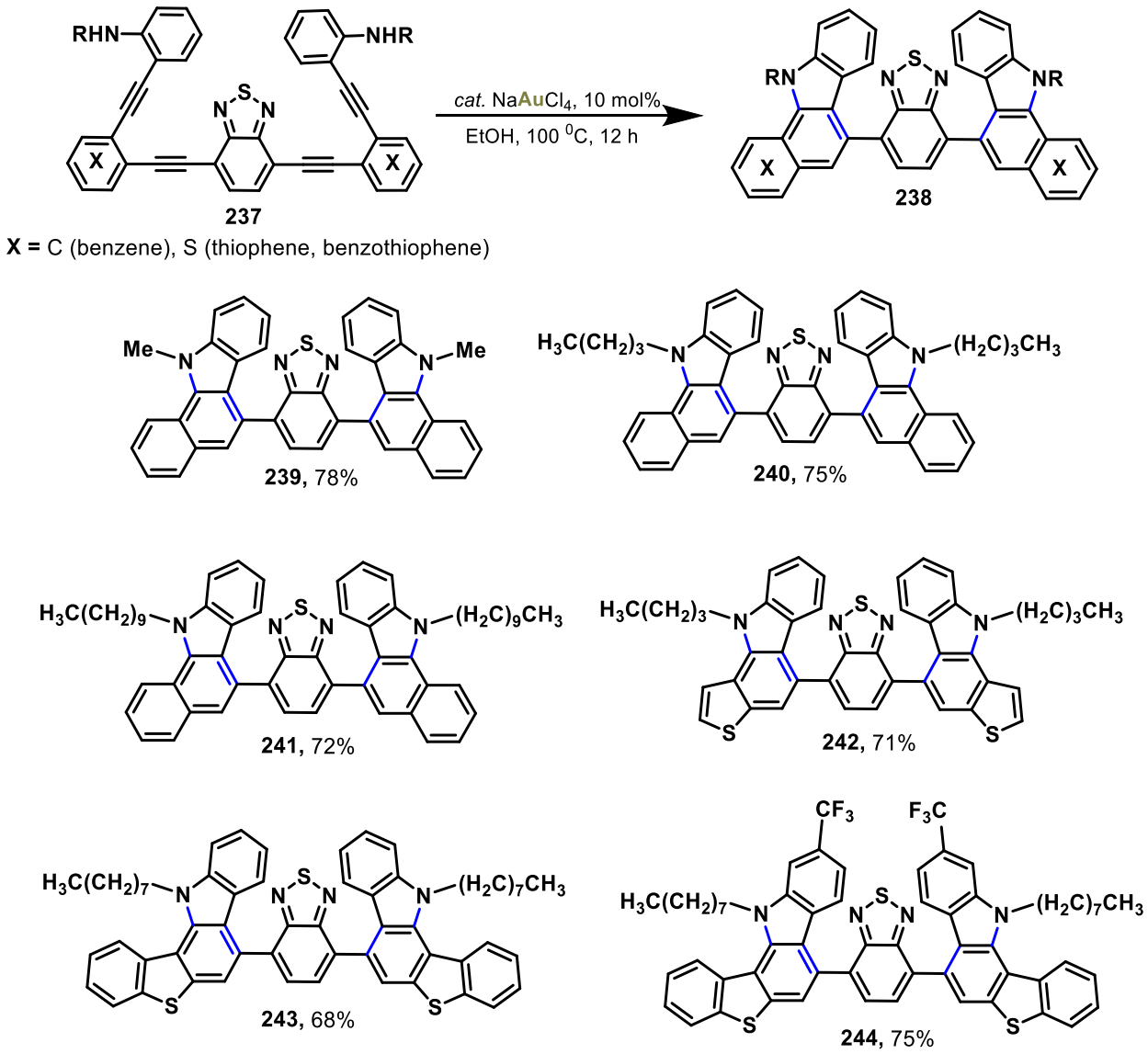
methylamination carried out by cationic gold(I) complexes supported by cyclic (alkyl)(amino)carbene(CAAC) ligands **(scheme 27)**.



Scheme 27. Gold(I)-catalyzed methylamination of alkyne.

1.2.13 Gold-Catalyzed Double Cascade Cyclization

In 2012, Yamamoto and co-workers proposed the formation of new symmetric π-conjugated donor–acceptor–donor (D–A–D) compounds **238-244**, *via* gold-catalyzed double cascade cyclization reaction. D-A-D compounds were synthesized from tetraynes **237**, (Tetraynes possess C-Benzene and S-thiophene, benzothiophene) with the help of $NaAuCl_4$-catalyst and double cascade cyclization in ethanol as a solvent **(scheme 28)**.[106]

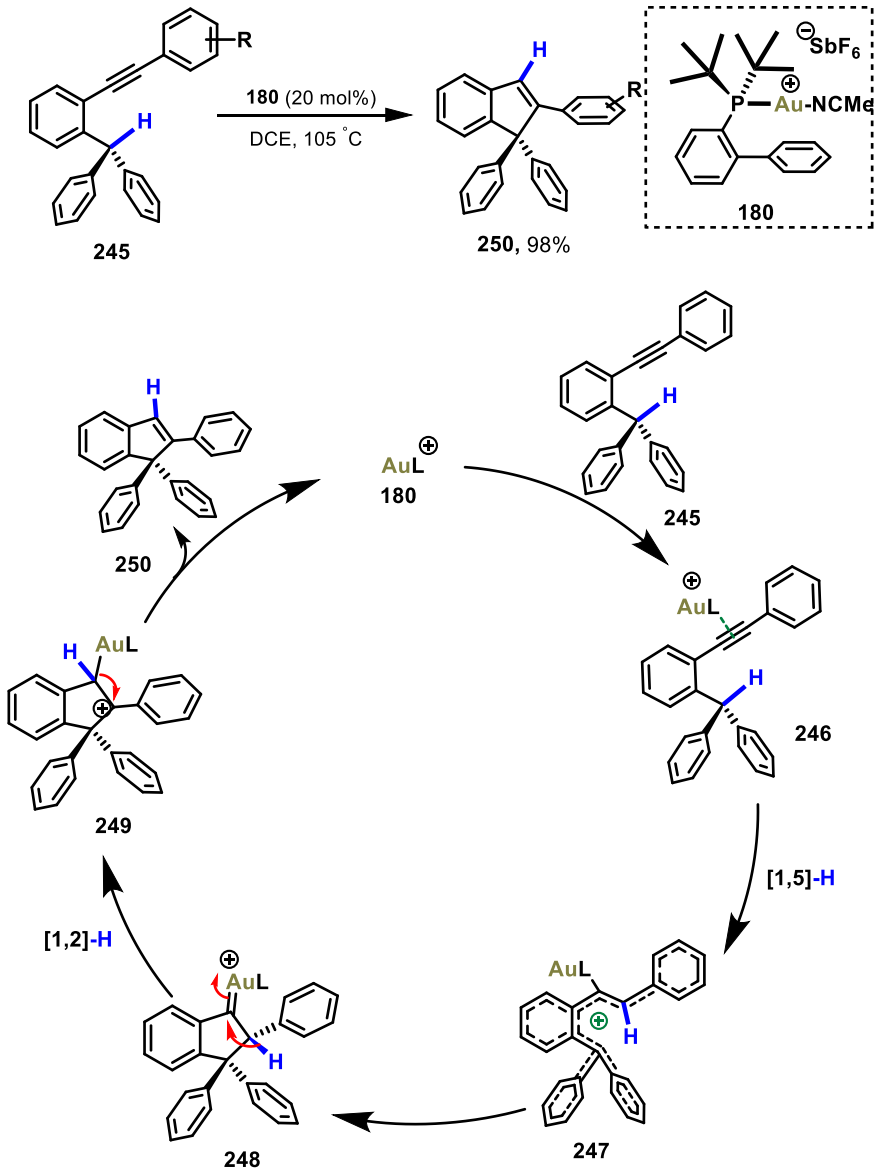


Scheme 28. Gold-catalyzed synthesis of D–A–D compounds from tetraynes.

106. Ferrara, G.; Jin, T.; Oniwa, K.; Zhao, J.; Asiri, A.M.; Yamamoto, Y. *Tetrahedron Lett. 53*, **2012**, *8*, 914–918.

1.2.14 Hydride-shift in Gold catalyzed reaction.

Recently, in 2018, Solorio-Alvarado and co-workers proposed the formation of indene's derivatives **250**, by direct Csp^3–H activation of **245**, by gold(I) catalyzed *via* 1,5-*H* shift fallowed by 1,2-*H* shift **(scheme 29)**.[107]

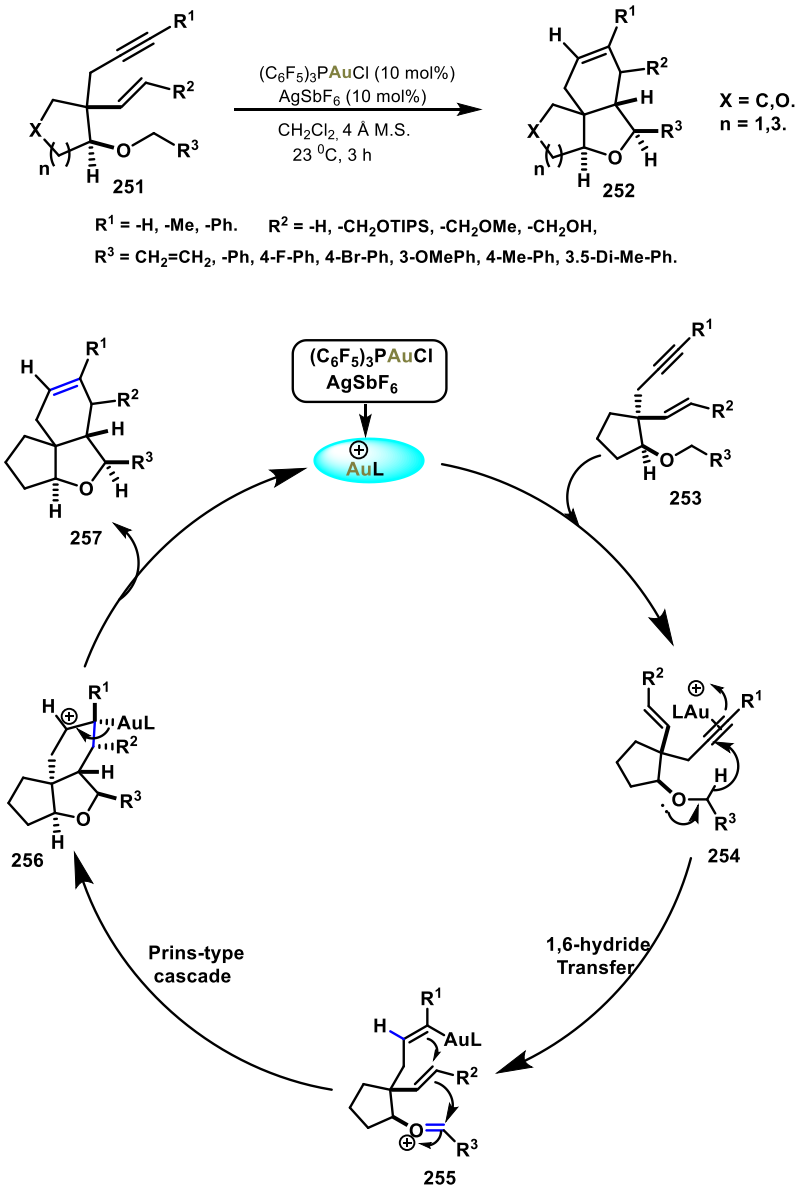


Scheme 29. Gold(I)-catalyzed synthesis of indenes and their reaction mechanism.

107. Nahide, P.D.; Jiménez-Halla, J.O.C.; Wrobel, K.; Solorio-Alvarado, C.R., Alvarado, R.O. and Yahuaca-Juárez, B., *Org. Biomol. Chem.,* **2018**, *16*, 7330–7335.

According to **scheme 29**, firstly started from the **180** gold(I) species coordinate with alkyne **245,** and gives **246,** followed Csp^3–H bond activation takes place via [1,5]-*H* shift and formed **247.** Species **247** is able to generate gold(I) carbene **248.** Carbene IV undergo [1,2]-*H* shift take place and formed **249**. and at the end, removal of the gold(I) complex and formed the indene **250** derivative with regeneration of catalyst.

In 2018, Wong and co-workers proposed the formation of fused polycyclic ring compounds **252**, by stereospecific, tandem gold-catalyzed reaction start by hydride shift with the help of $(C_6H_5)PAuCl/AgSbF_6$ catalyst. This tandem gold-catalyzed reaction gives quick support to formation of diverse fused polycyclic compound **252 (scheme 30)**.[108]



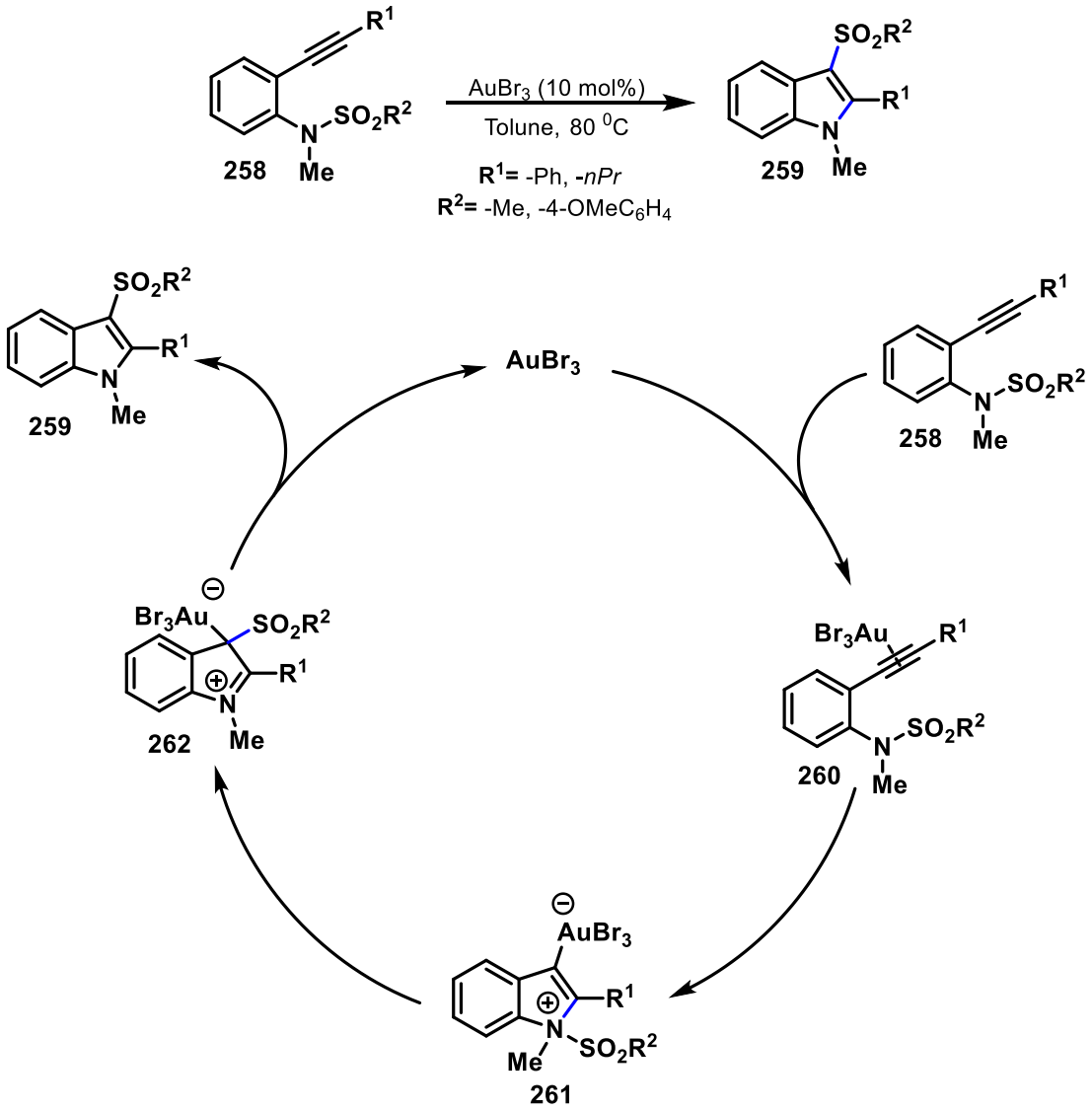
Scheme 30. Reaction mechanism of gold(I)-catalyzed cycloisomerization by hydride transfer.

108. Lu, X.L.; Lyu, M.Y.; Peng, X.S.; Wong, H.N. Angew. Chem. **2018**, *130*, 11535–11538.

According to **Scheme 30**, This reaction initiated from gold catalyst activate the triple bond of **253**, generate **254,** followed by 1,6-hydride shift under **254,** to formed oxonium ion **255**. Then, vinyl-gold makes intramolecular nucleophilic attack on double bond in **255**, also interact with admissible cationic species which leads to form intermediate carbocation **256,** like prince type reaction mechanism**.** At the end elimination of gold(I)-catalyst takes place and carbocation **256,** is convert into final product polycyclic species **257**.

1.2.15 Gold-Catalyzed Sequential Reactions *via* Cyclization/Migration

In 2007, Nakamura and co-workers proposed gold(III)-catalyzed formation of 3-sulfonylindoles **259**, from *ortho*-Alkynyl-N sulfonylanilines **258**, by cyclization and 1,3-migration of sulfonyl group and their mechanism **(scheme 31)**.[109]

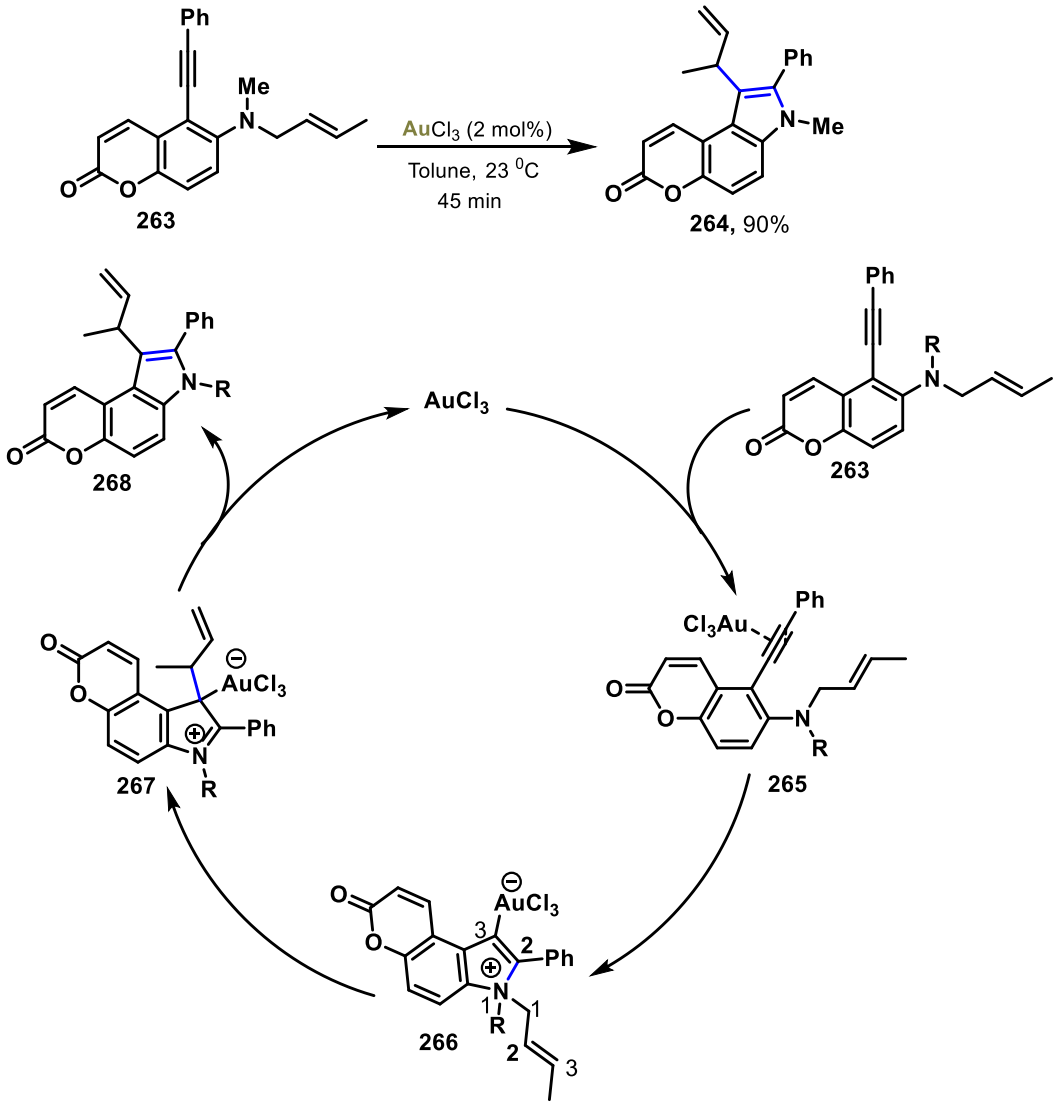


Scheme 31. $AuBr_3$-catalyzed cyclization and their reaction mechanism.

109. Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2284 –2287.

According to **Scheme 31**, reaction mechanism start from the activation of triple of **258**, by $AuBr_3$ to give π-complex **260**. Complex **260** undergo cyclization take place by intramolecular nucleophilic attack of Nitrogen atom on activated alkyne generate intermediate **261**, followed by intramolecular migration of sulfonyl group to 3-position of indole to give **262,** and at the end intermediate **262** in which elimination of $AuBr_3$ take place and finally formed 3-sulfonylindole **259**.

In 2011, Roy and co-workers proposed the formation of highly substituted indoles **264**, from 6-(allyl(methyl)amino)-5-(phenylethynyl)-2Hchromen-2-one **263**, and their derivatives by gold-catalyst *via* cyclization followed by [3,3]-migration of the allyl and their mechanism **(scheme 32)**.[110]



Scheme 32. $AuCl_3$-catalyzed cyclization and their proposed reaction mechanism.

110. Majumdar, K.C.; Hazra, S.; Roy, B. *Tetrahedron Lett.* **2011**, *52*, 6697–6701.

Reaction mechanism as shown in **scheme 32**. Reaction mechanism start from the activation of triple of **263**, by $AuCl_3$ to give **π**-complex **265**. Complex **265** undergo cyclization take place by intramolecular nucleophilic attack of Nitrogen atom on activated alkyne generate intermediate **266.**[73] Intermediate **266,** undergo migration of the allyl group *via* [3,3]-sigmatropic rearrangement which gives intermediate **267**. Finally, intermediate **267,** in which elimination of $AuCl_3$ take place and formed product **268**.

Chapter 2.

"Experimental Studies in The Gold(I)-Catalyzed Sequential Indole Formation-Benzylic Migration"

2.1 Introduction

The benzo[*b*]carbazols are an important class of heteroaromatic compounds.[111] The relevance of these derivatives have been demonstrated by its presence in organic light emitting diodes (OLEDs)[112] and in general they are relevant blocks in materials science.[113]
Importance of carbazols, benzo[*b*]carbazols, and their derivatives as shown in **figure 9**. According to figure 1. benzo[*b*]carbazols compound **269,** has more importance because pharmacological and biological active alkaloids possess this component and compound **270,** shows antitumor activity[114] and due to their structure, it's also used to developed and preparation of antineoplastic agents.[115] Compound of carbazole **271**, shows cytostatic activity against leukemia type L 1210 cell culture,[116] and benzo[*b*]carbazols derivative **272,** play variety of role in organic light-emitting diodes (OLEDs)[117] and derivative **273,** is used in the form of intercalating agent as a bifunctional nucleic acid.[118]

Benzo[*b*]carbazols derivative **274,** shows activeness in vitro anticancer activity[119] and derivative **275,** in which indole in on C-6 position was observed in Aβ1−40 aggregation inhibitor, that's why it will be or may be beneficial for the cure progressive neurodegenerative diseases.[120] TCTA(**279**) possess three carbazole units and CBP6(**276**) possess two carbazole units has high energy with very well hole conductivity and for this reason it's useful in organic light-emitting diodes (OLEDs) for host material.[121] Midostaurin **277**, is an FDA approved drug is useful for the treatment of acute myeloid leukemia Mutations[122] and 4CzlPN **278**, shows photoelectronic activity and its applicable in photochemical reaction carried out in visible-light.[123]
Some synthesis for this heterocycle are to date described.[124] However, one of main disadvantages of these procedures is the costly and low-yielding aspects form which they lack.

111. Zhang, Y.; Peng, F.; He, R.; Ying, L.; Yang, W.; Cao, Y. *New J. Chem.* 2018, *42*, 2750-2757.
112. Keruckienė, R.; Volyniuk, D.; Bezvikonnyi, O.; Masimukku, N.; Ivaniuk, K.; Stakhira, P.; Gražulevičius, J.V. *Dyes Pigm*. **2018**, *154*, 145-154.
113. Ravichandran, P.; Santhosh Kumar, P.; Vasanth Kumar, S. *J. Saudi. Chem. Soc*. **2017**, *21*, 35-41.
114. Miller, C. M.; McCarthy, F. O. *RSC Adv*. **2012**, *2*, 8883 and references cited therein.
115. Asche, C.; Frank, W.; Albert, A.; Kucklaender, U. *Bioorg. Med. Chem*. **2005**, 819.
116. Gribble, G. W.; Saulnier, M. *J. Chem. Soc., Chem. Commun.* 1984, 168.
117. A few selected examples: (a) Levick, M. T.; Coote, S. C.; Grace, I.; Lambert, C.; Turner, M. L.; Procter, D. J. *Org. Lett*. **2012**, *14*, 5744. (b) Balandier, J.-Y.; Henry, N.; Arlin, J.-B.; Sanguinet, L.; Lemaur, V.; Niebel, C.; Chattopadhyay, B.; Kennedy, A. R.; Leriche, P.; Blanchard, P.; Cornil, J.; Geerts, Y. H. *Org. Lett*. **2013**, *15*, 302. (c) Hu, N.-X.; Xie, S.; Popovic, Z.; Ong, B.; Hor, A.-M. *J. Am. Chem. Soc*. **1999**, *121*, 5097.
118. Pindur, U.; Haber, M.; Sattler, K. *J. Chem. Educ.* **1993**, *70*, 263.
119. Asche, C.; Frank, W.; Albert, A.; Kucklaender, U. *Bioorg. Med. Chem.* **2005**, *13*, 819.
120. Carter, M. D.; Weaver, D. F.; Jacobo, S. M. H. *WO058402 A1*. **2008**.
121. (a) Thelakkat, M.; Schmitz, C.; Hohle, C.; Strohriegl, P.; Schmidt, H.-W.; Hofmann, U.; Schloter, S.; Haarer, D. *Phys. Chem. Chem. Phys. 1*, 1693-1698. (b) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. K.; Tester, J. W. *Org. Biomol. Chem.* **2005**, *3*, 3767−3781.
122. Gallogly, M. M.; Lazarus, H. M.; Cooper, B. W. *Ther. Adv. Hematol.* **2017**, *8*, 245−261.
123. (a) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873−877. (b) Liu, Y.; Chen, X.-L.; Li, X.-Y.; Zhu, S.-S.; Li, S.-J.; Song, Y.; Qu, L.-B.; Yu, B. *J. Am. Chem. Soc.* **2021**, *143*, 964−972.
124. Mandal, A.; Mondal, S.K.; Jana, A.; Manna, S. K.; Ali, S.A.; Samanta, S. *J. Heterocycl. Chem*. **2017**, *54*, 2529-2535.

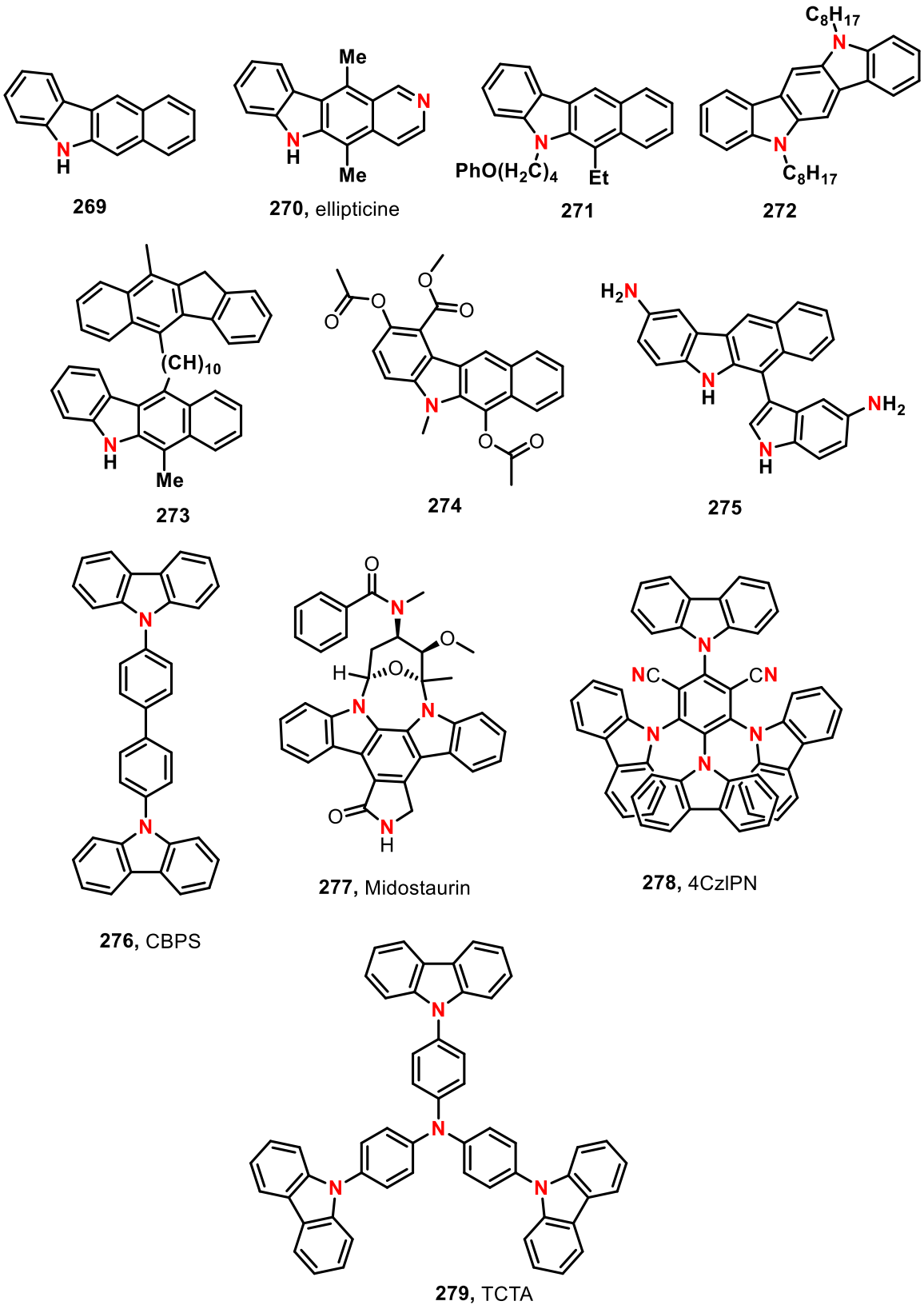
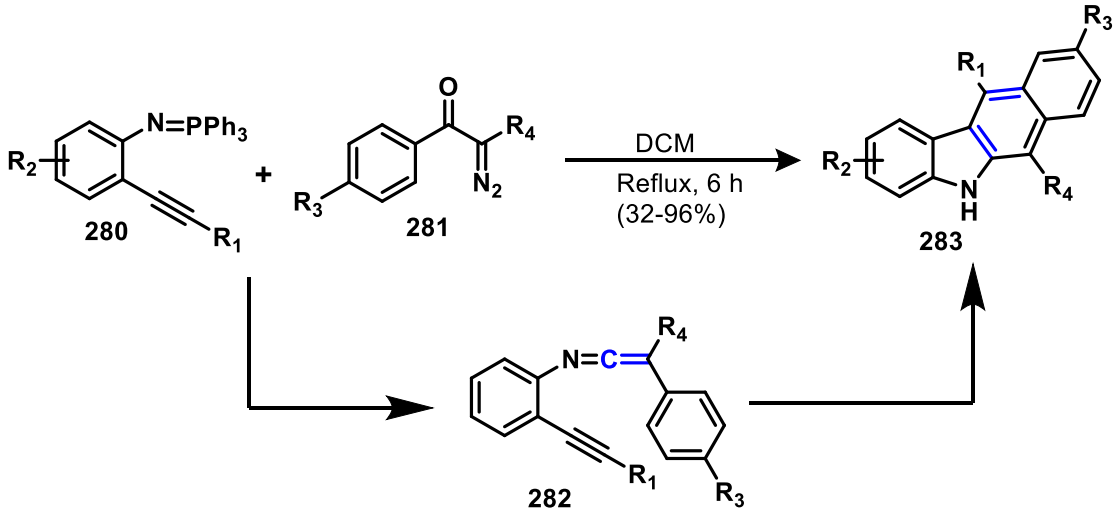


Figure 9. Importance of carbazoles, benzo[*b*]carbazols and their derivatives.

2.2 Previous work

Synthesis of benzo(*b*)carbazoles, with the help of different catalyst or different routes are as discuss bellow.

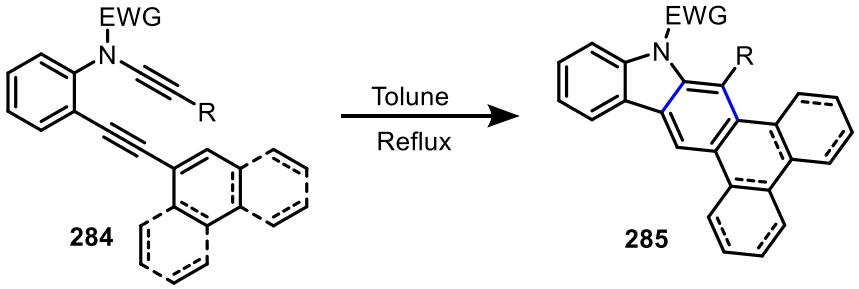
In 1998, Wang and co-worker proposed the formation of 5*H*-Benzo[*b*]carbazoles **283**, from aza-Wittig reaction between **280**, and diphenyl ketene **281**, generate ketenimine Intermediate **282,** undergo cycloaromatization give biradical species which is responsible for the formation of 5*H*-Benzo[*b*]carbazoles **283**, under reflux condition **(scheme 33)**.[125]



R_1= C_6H_5, *p*-MeC_6H_5, *p*-ClC_6H_4, *n*-C_5H_{11} **R_2=** H, -Me, -Cl
R_3= -H, -Me, -OMe, -F, -Br. **R_4=** -H, -Ph, -CH_3CO

Scheme 33. Synthesis of 5*H*-Benzo[*b*]carbazoles **283**, from *N*-[2-(1-Alkynyl)phenyl]ketenimines

In 2005, Saa´ and co-workers used reported intramolecular dehydro Diels-Alder reactions of ynamides and new approach to carbazoles and benzannulated carbazoles. Based on the new approach he describe the formation of carbazoles and benzo[*b*]-, tetrahydrobenzo[*b*]-, naphtho[1,2-*b*]-, naphtho[2,1-*b*]-, and dibenzo[*a,c*]carbazoles **285**, from starting material **284**, *via* intramolecular dehydro Diels-Alder reactions under reflux condition (Eq. 8).[126]

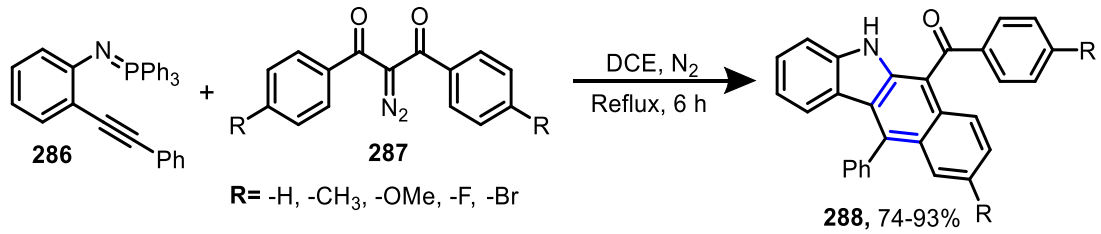


[8]

EWG= -Ts, -CO_2Me. R= -H, -TMS, -Ar

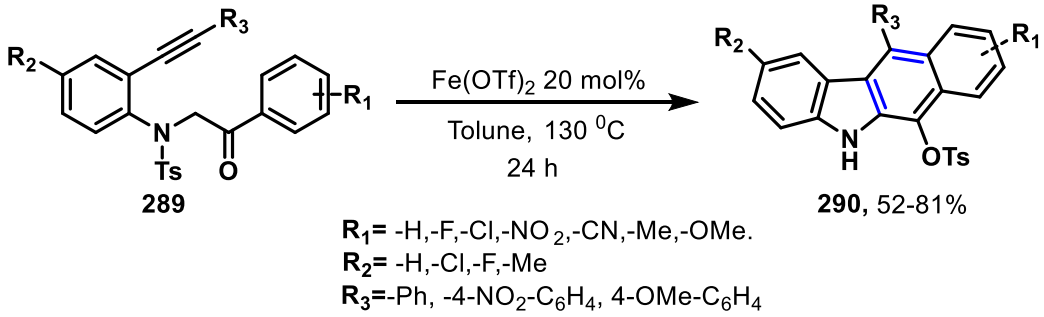
125. Shi, C.; Wang, K. K. *J. Org. Chem*. **1998**, *63*, 3517-3520.
126. Martínez-Esperón, M.F.; Rodríguez, D.; Castedo, L.; Saá, C. *Org. lett.* **2005**. *7*, 2213-2216.

In 2013, Wang and co-workers developed the formation of benzo[*b*]carbazoles and their derivatives **288**, from 2-ethynyl-N-triphenylphosphoranylidene anilines **286**, and a-diazoketones **287**, *via* ketenimine under reflux condition (Eq. 9).[127]



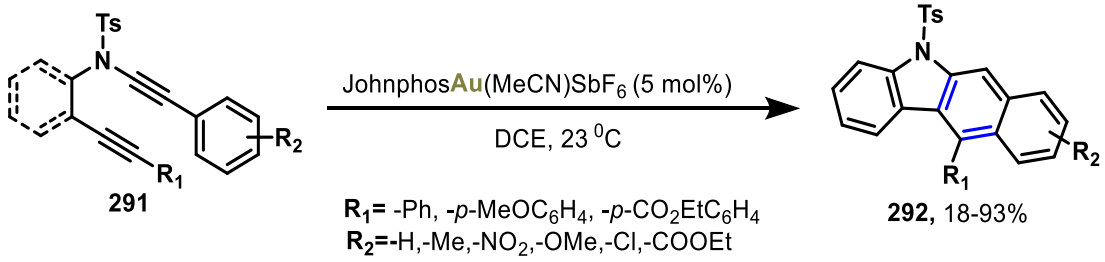
[9]

In 2015, Wang and co-workers developed the formation of benzo[*b*]carbazoles derivatives **290**, from starting material **289,** in the presence of iron catalyst *via* cascade reaction pathway and 1,4-sulfonyl migration as shown in (Eq. 10).[128]



[10]

In 2018, Liu and co-workers proposed the formation of benzo[*b*]carbazoles derivatives **292**, from cycloisomerization of ynamides-ynes **291**, with the help of gold(I)-catalyst *via* dehydro-Diels-Alder-reaction as shown in (Eq. 11).[129]

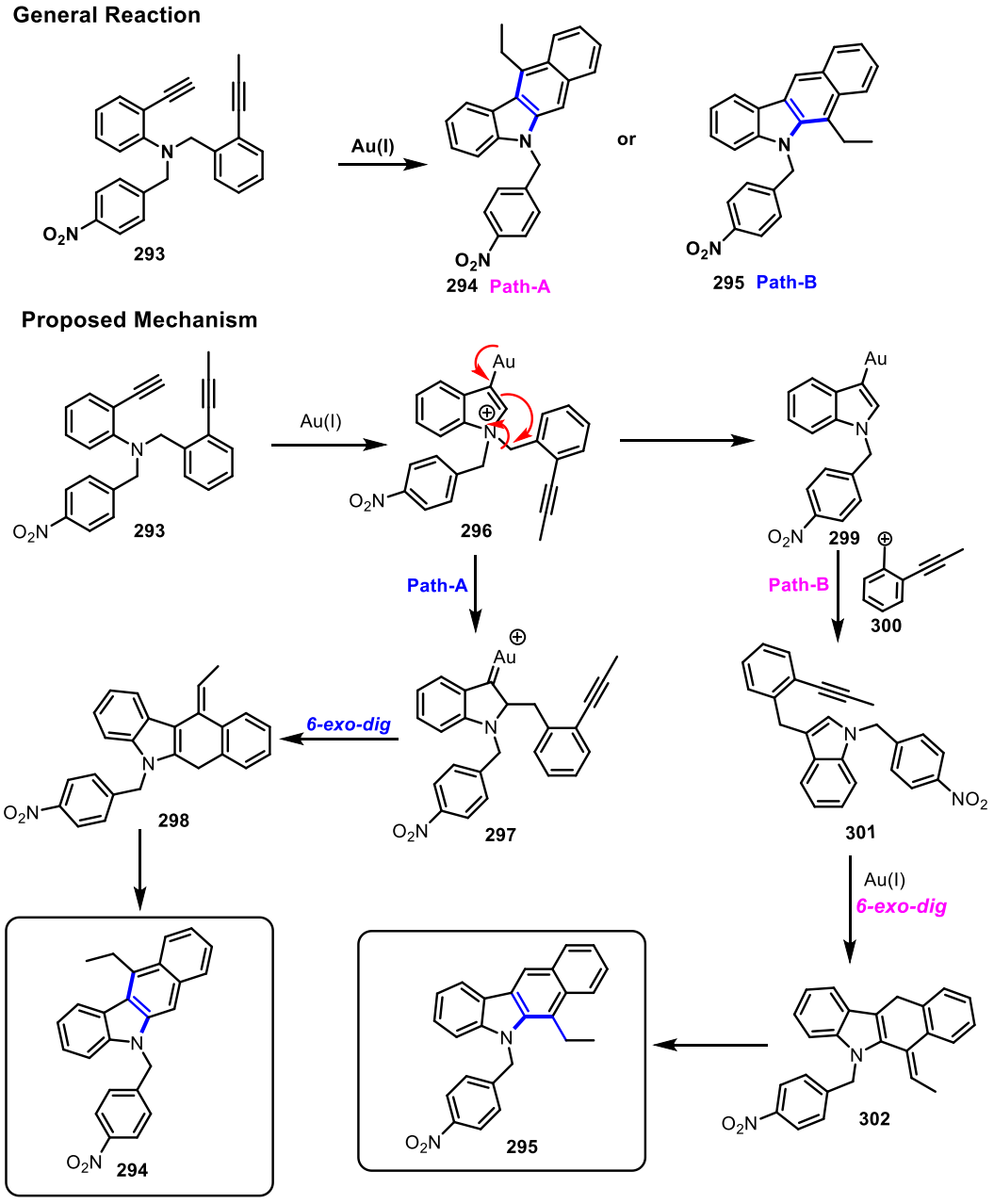


[11]

127. Xing, Y.; Hu, B.; Yao, Q.; Lu, P.; Wang, Y. *Eur. J. Chem.* **2013**, *19*, 12788-12793.
128. Boominathan, S. S. K.; Senadi, G. C.; Vandavasi, J. K.; Chen, J. Y. F.; Wang, J. J. *Eur. J. Chem*. **2015**. *21*, 3193-3197.
129. Xu, W.; Wang, G.; Xie, X.; Liu, Y. *Org. lett.* **2018**. *20*, 3273-3277.

2.3 Our Proposal

Herein we propose a novel alternative bases upon the Au(I) chemistry that has been demonstrated to be an excellent high-yielding alternative to the common Pd- or Cu catalyzed processes. Our strategy implicates the novel propargyl migration, which has as precedent the allyl migration[130] in this class of cycloisomerization reaction (**scheme 34**).



Scheme 34. Our proposed synthesis of benzo[*b*]carbazols.

130. Uemura, M; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc*. **2009**, *131*, 3464-3465.

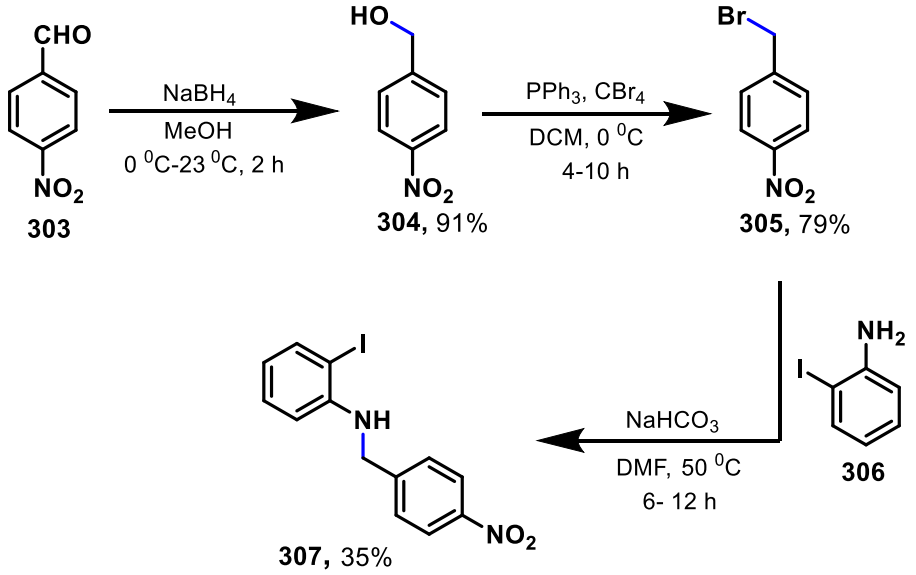
Our proposal starts with the tertiary aniline **293**, which is submitted in gold catalysis. First step is the cyloisomerization to yield the corresponding indol-3-carbene **296**, that can follows two pathways. In Pathway **A** the benzyl group migrates to position 2 of indole, further cycloisomerization and aromatization gives the corresponding 11- methylbenzo[*b*]carbazole **294**. On the other hand, in pathway **B**, the benzylgroup migrates to the position 3, the following cycloisomerization and aromatization yields the corresponding 6-methylbenzo[*b*]carbazole **295**.

2.4 Objectives

- Firstly, Based on our proposal, we will synthesized tertiary aniline as a starting material.
- We will check migratory aptitude of benzyl group. Based on electron donating (-OMe, -Me) and withdrawing substituents (-F, -NO_2) on benzyl group.
- We will developed methodology based on tandem process *via* cyclization/migration/ cyclization.

2.5 Experimental Results and discussion

Initially, we start to prepare starting material based on proposal. Firstly, we prepared 4-nitrobenzyl bromide **305**, from 4-nitrobenzaldehyde **303**, based on documented procedure. Benzaldehyde reduction by $NaBH_4$ to give alcohol **304**, followed by alcohol **304**, is convert into 4-nitro benzylbromide **305**, by using PPh_3 and CBr_4. Then, we prepared *N*-(4-Nitrobenzyl)-2-iodoaniline **307,** from 2-iodo aniline **306,** and 4-nitro benzylbromide **305**, in the presence of $NaHCO_3$-(2 equi) **(scheme 35)**, and this procedure is also documented.[131]



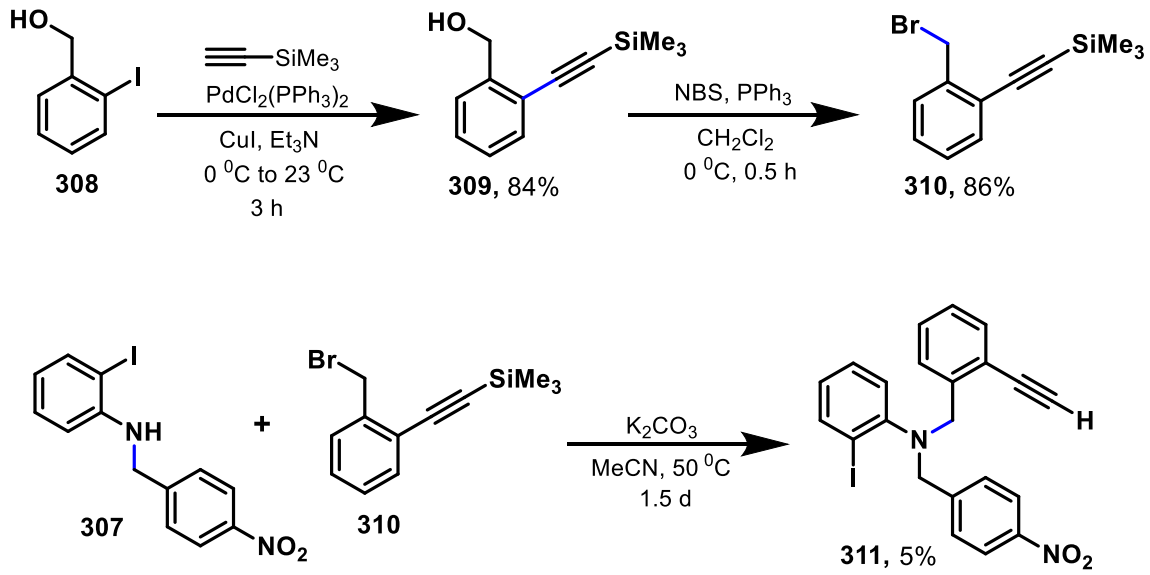
Scheme 35. Synthesis of *N*-(4-Nitrobenzyl)-2-iodoaniline.

After the preparation of *N*-(4-Nitrobenzyl)-2-iodoaniline **307,** we start to prepare ((Trimethylsilyl)-ethynyl)benzyl bromide **310**, from 2-Iodo benzyl alcohol **308**, by sonogashira reaction using trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, and triethyl amine gives compound **309,**

131.Chen, Z.; Li, H.; Cao, G.; Xu, J.; Miao, M.; Ren, H. *Synlett*, **2017**, *28*, 504-508.

and compound **309**, alcohol is convert into, ((Trimethylsilyl)ethynyl)benzyl bromide **310**, with the help of NBS and PPh_3 as per the documented procedure.[132]

Once we prepared ((Trimethylsilyl)ethynyl)benzyl bromide **310**, at the end we use ((Trimethylsilyl)ethynyl)benzyl bromide **310**, for the benzylation on *N*-(4-Nitrobenzyl)-2-iodoaniline **307,** by using K_2CO_3 to form TMS-deprotected tertiary aniline **311, (scheme 36)**. Due to the deprotection of TMS, we failed to prepare tertiary aniline starting material as per our proposal.



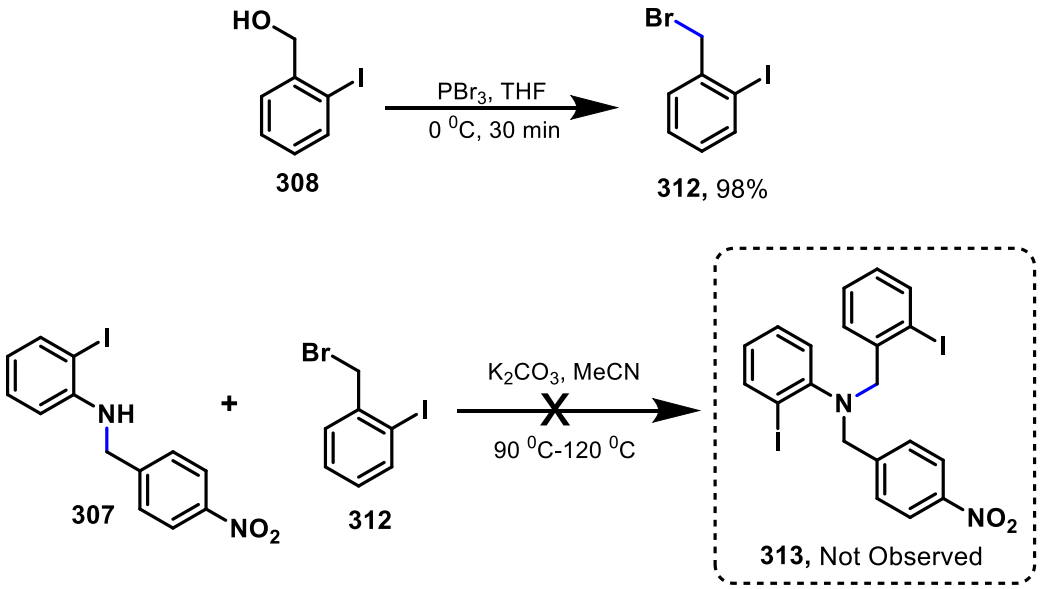
Scheme 36. Synthesis of tertiary aniline **311,** from **307,** and **310.** .

After the deprotection of TMS in tertiary aniline **311**, we change strategy and prepared 2-iodo benzylbromide **312**, from 2-iodo benzyl alcohol **308**, with the help PBr_3 based on documented procedure.[133]

We use this 2-iodo benzylbromide **312**, for benzylation on *N*-(4-Nitrobenzyl)-2-iodoaniline **307,** by using K_2CO_3 **(scheme 37)**. But unfortunately, we don't get tertiary aniline product from this reaction, and we conclude that due to the -NO_2 Substituent on *N*-(4-Nitrobenzyl)-2-iodoaniline **307,** disfavor for benzylation.

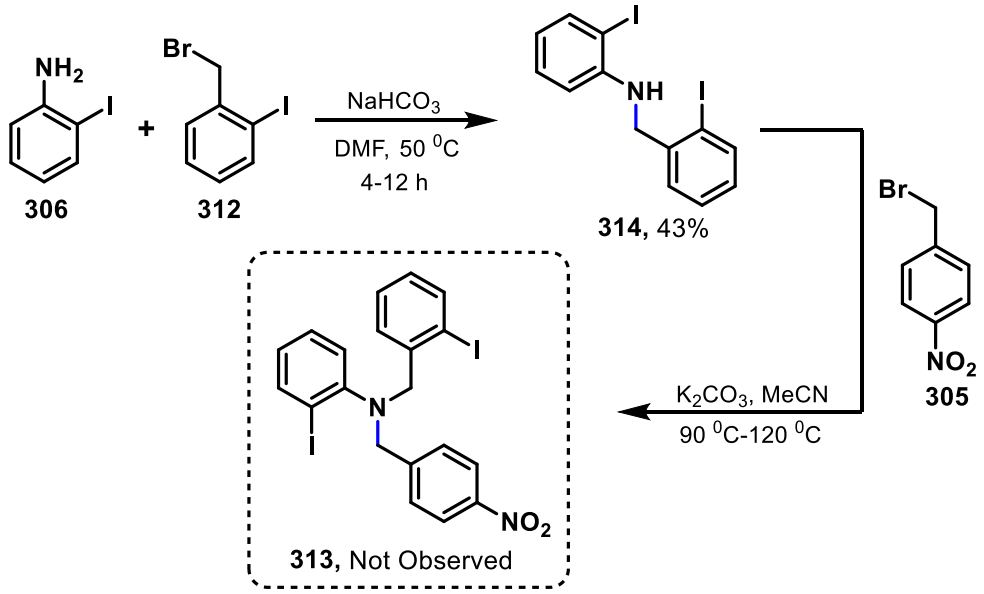
132. a) Albano, G., Morelli, M. and Aronica, L.A. *Eur. J. Org. Chem*. **2017**, *2017*, 3473-3480. b) Ichikawa, Y., Nishimura, T. and Hayashi, T. *Organometallics*, 2011 *30*, 2342-2348.

133. Landge, K.P.; Jang, K.S.; Lee, S.Y.; Chi, D.Y. *J. Org. Chem*. **2012**, *77,* 5705-5713.



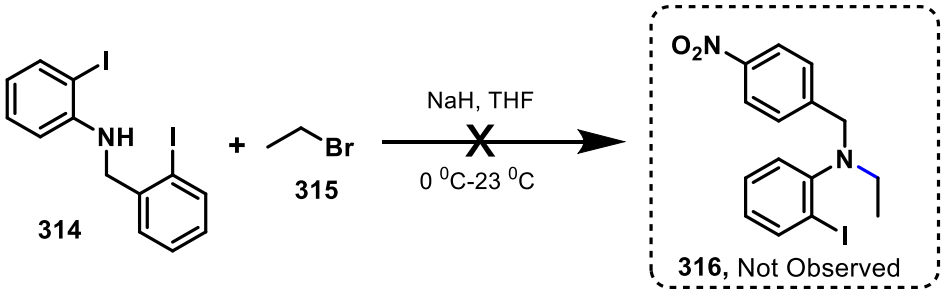
Scheme 37. Synthesis of tertiary aniline **313,** from **307**, and **312**.

Based on the above experiment and conclusion again we change the strategy. Based on the previous procedure[131] we prepared benzylated compound **314**, from 2-iodoaniline **306,** and 2-iodo benzylbromide **312,** with help of $NaHCO_3$. Once we get benzylated compound **314**, we use 4-nitro benzylbromide **305**, for benzylation on compound **314**, by using base K_2CO_3 **(scheme 38)**. But this time also we don't get tertiary aniline compound as a starting material based on our proposal. In this experiment we conclude may be bulky benzylbromide group with electron withdrawing NO_2-substituent disfavor for bis-benzylation.



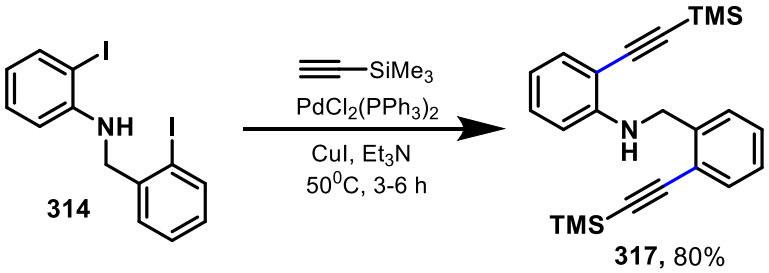
Scheme 38. Synthesis of tertiary aniline **313,** from **314**, and **305**.

According to above pathway and conclusion we use ethyl bromide **315**, for ethylation on benzylated compound **314**, with the help of strong base Sodium hydride **(NaH)**. But this time also we don't get tertiary aniline product. Again, we conclude steric hindrance in benzylated compound **314**, due to iodine substituents interfere and create steric hindrance in compound **314** (Eq. 12).



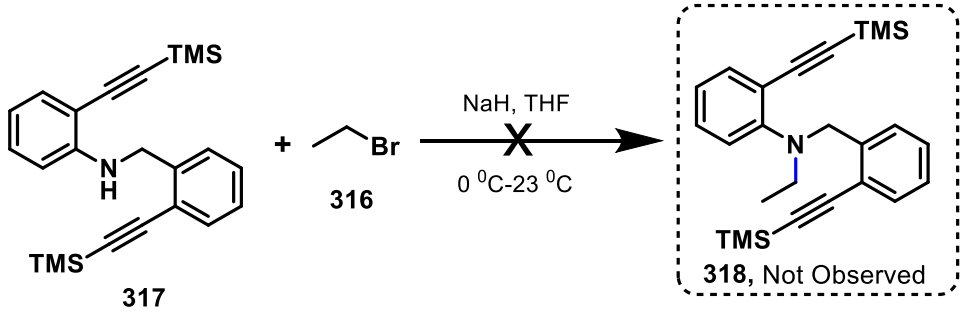
[12]

As per the above conclusion and experience we decided to apply sonogashira reaction on compound **314**, by using trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, and triethyl amine as per the above procedure to give compound **317** (Eq. 13).



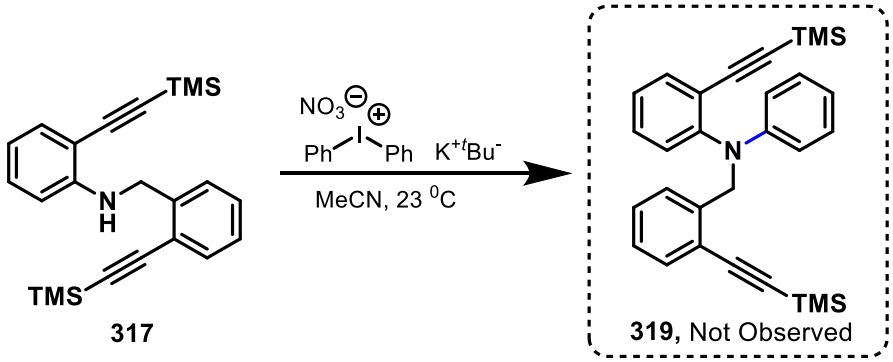
[13]

Once we get compound **317**, we use ethylbromide for ethylation on compound **317**, with the help of strong base sodium hydride **(NaH).** But this time also we don't get tertiary aniline as a starting material (Eq. 14).



[14]

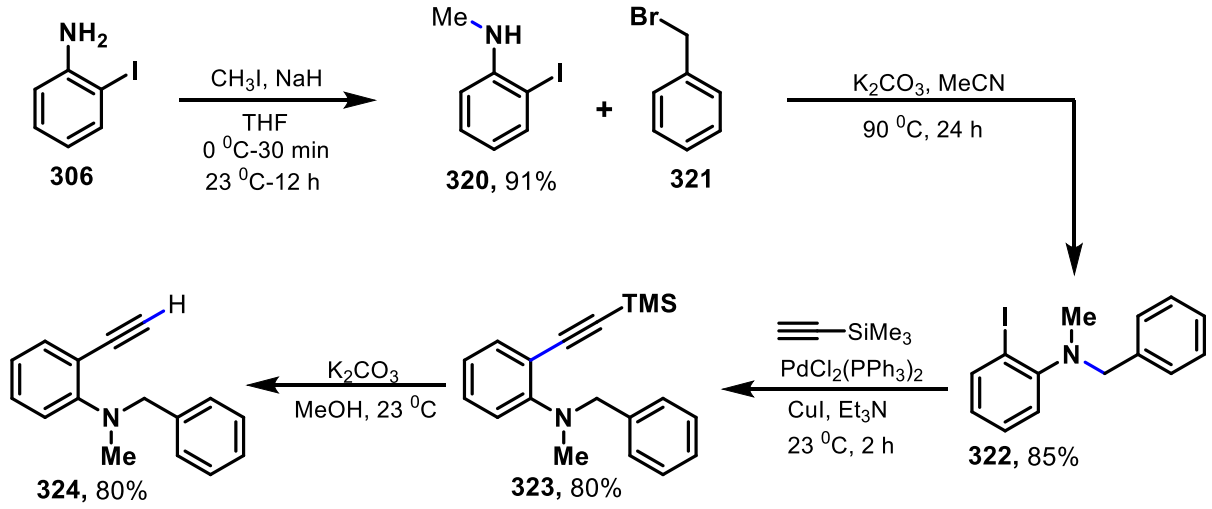
We also use diaryliodonium salt for arylation on compound **317**, with the help of base potassium tertiary butoxide, but here also we don't get tertiary aniline product (Eq. 15).



[15]

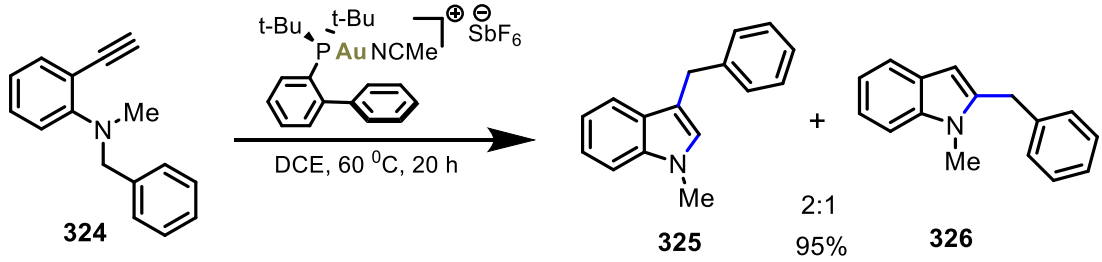
After the above experimental and many pathway trials we make strategy to prepare tertiary aniline **324**, to check cyclization and migration. Based on this strategy we get tertiary aniline **324**, as a starting material different from our proposal as in bellow **(scheme 39)**.

Starting Material Preparation



Scheme 39. Synthesis of tertiary-aniline **324**.

According to above **scheme 39**. Tertiary aniline **324**, preparation start from 2-iodoaniline **306**, in which methylation[134] take place with the help of methyl bromide and sodium hydride as a strong base to give compound **320**. Compound **320**, undergo benzylation[135] by benzylbromide **321**, to give compound **322**. Then, Sonogashira reaction by using trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, and triethyl amine on compound **322**, to generate compound **323**, followed by deprotection[136] of TMS takes place in compound **323**, by K_2CO_3 to formed tertiary aniline **324**, as a starting material for gold-catalyzed reaction as shown in **scheme 40**. This starting material preparation procedure of each step has been almost documented.

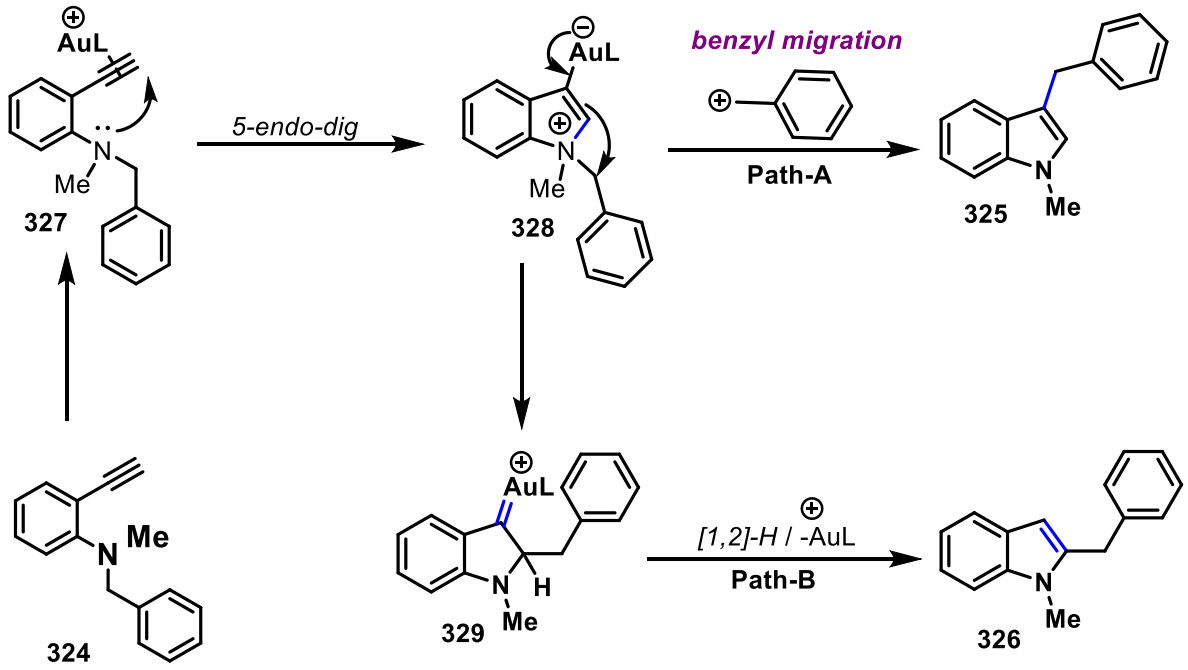


Scheme 40. Gold(I)-catalyzed sequential indole formation-benzyl migration.

134. Chung, H.; Kim, J.; González-Montiel, G.A.; Ha-Yeon Cheong, P.; Lee, H.G. *Org. Lett*. **2021**, *23,* 1096-1102.
135. Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *Organometallics*, **2004**, *23*, 1438-1447.
136. Chen, D.F., Han, Z.Y., He, Y.P., Yu, J. and Gong, L.Z., *Angew. Chem. Int. Ed.,* **2012**. *51*, 12307-12310.

Initial optimization with Tertiary Aniline **324**, with 5mol% of (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate as Gold(I)-catalyst, in Dry-DCM or Dry-DCE at 23 ^{0}C. But unfortunately, we do not get result.

According to Gold catalyzed reaction which shown in above **scheme 40**. Starting material tertiary aniline **325,** was inserted into Gold(I) catalyst (10 mol%) in Dry-DCE as a solvent at 60 °C for 20-hour. In this reaction first cyclization was happened with indole formation and the benzyl group was migrate to 2 and 3 position of cyclized indole. Benzyl group migrate on 3-position **325,** is major product than that of migrate on 2-position **326,** and we get 2:1 as a ratio of two compound with 95% yield which is confirmed by **^{1}H, ^{13}C** and **NOE** spectrum. The migratory aptitude of benzyl group is more than methyl group.

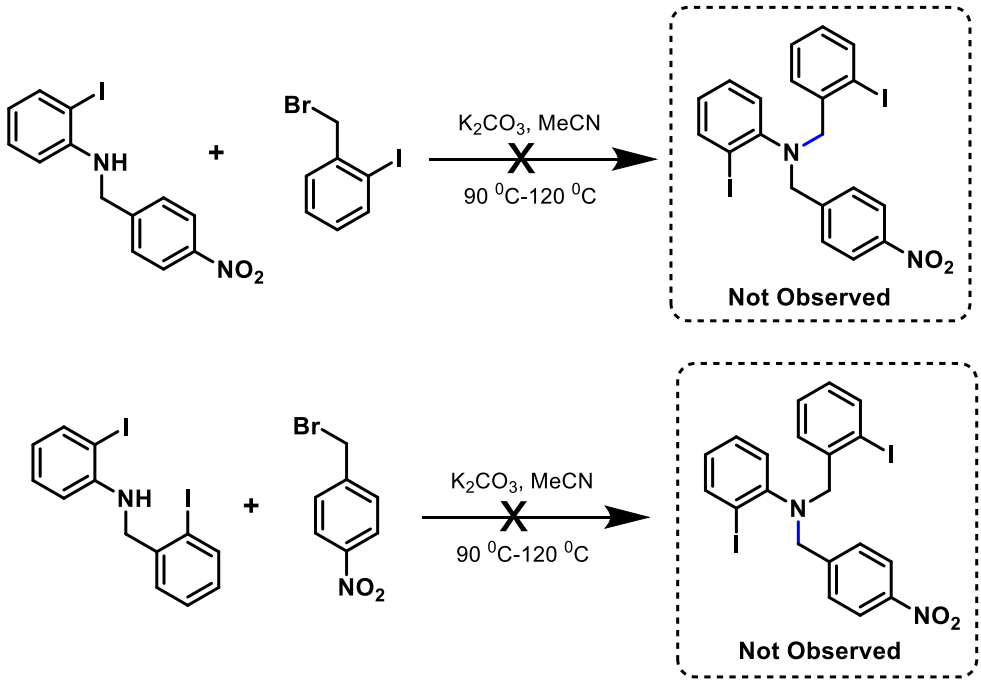


Scheme 41. Plausible reaction mechanism.

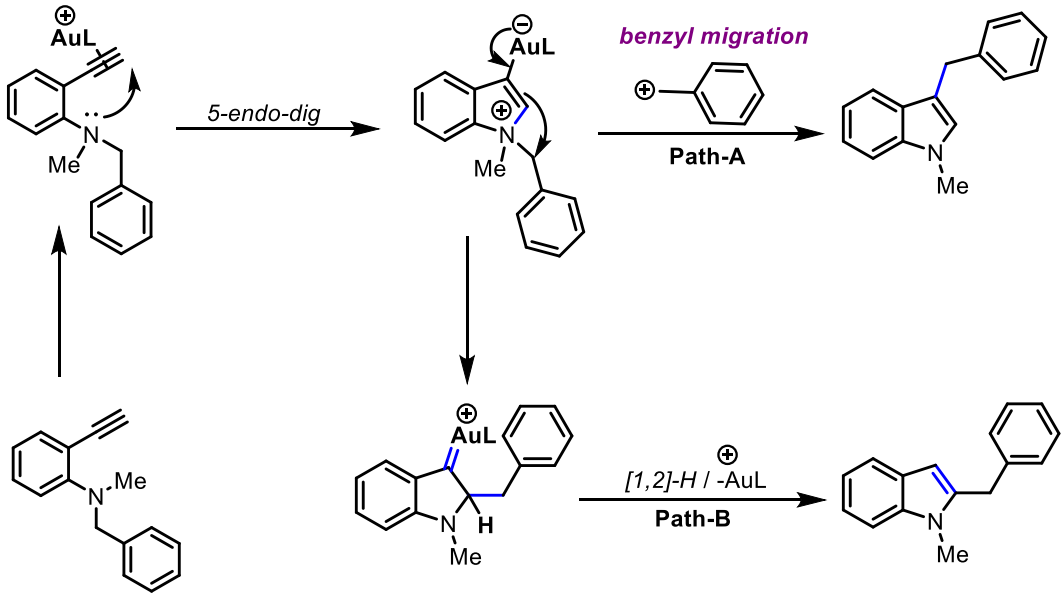
Based on plausible reaction mechanism in **scheme 41**. Initially, gold(I)-catalyst activate the triple bond of tertiary aniline **324**, to give complex **327,** in which cyclization take place to give intermediate **328**. Intermediate **328**, undergo two types of migration of benzyl group take place. Intermediate **328**, undergo benzyl migration on third position of indole generate product **325, (Path-A)**, and benzyl migration on second position on indole leads to afford intermediate **328**, followed by 1,2-*H* shift takes place in intermediate **329**, to formed product **326, (Path-B)**.

2.6 Conclusion

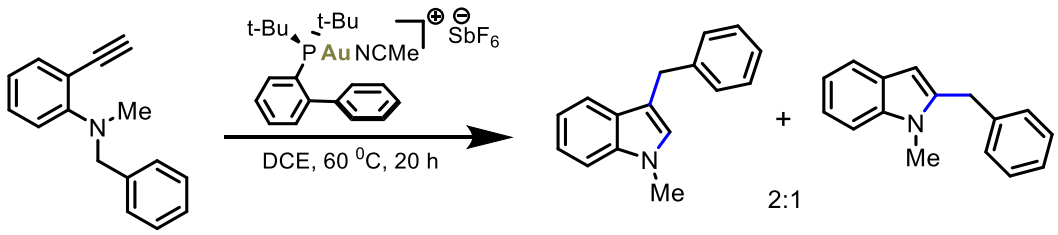
i) Bis alkylation on 2-iodo aniline with two different substituted benzyl moiety is difficult.



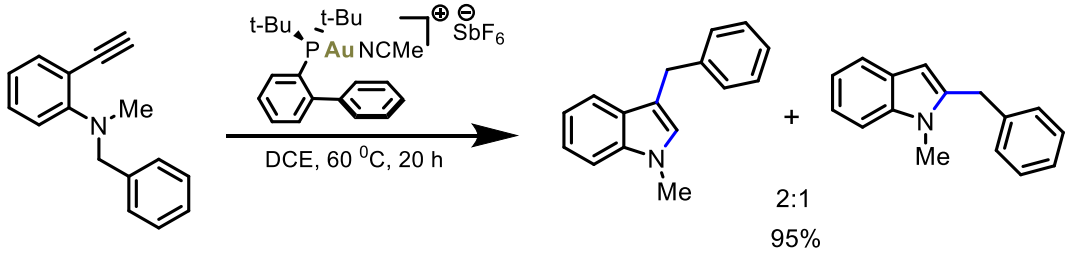
ii) Migratory aptitude of benzyl group is more as compared to methyl group.



iii) Cyclization and migration were take place in same reaction and condition.

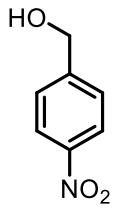


iv) We get first intramolecular cyclized product of benzyl substituted indole with excellent yield.



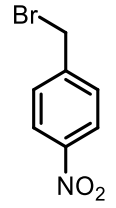
2.7 Experimental Section

(4-nitrophenyl)methanol (304)



Add sodium borohydride (2 equiv.) slowly to the solution of 4-nitro benzaldehyde **303**, in methanol with continuous stirring at 0°C. Stir the resulting mixture in an ice bath for 30 minutes and 23 ^{0}C for 2 hr. Quenched the reaction with cold water and extracted with ethyl acetate and water. The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (10% - 20% EtOAc: hexane) system to give (4-nitrophenyl)methanol **304**, (1.39g, 91%) as a yellowish solid. Spectral data were identical to those previously reported.[137] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 9.0 Hz, 2H), 4.83 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 147.4, 127.1, 123.8, 64.1.

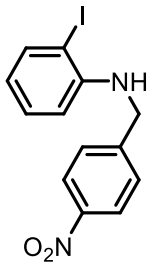
1-(bromomethyl)-4-nitrobenzene (305)



Cool a solution of triphenylphosphine (1.2 equiv.) dissolved in dry CH2Cl2 to 0 °C. Add CBr4 (1.2 equiv.) slowly over 5 minutes. Dissolve *p*-nitrobenzyl alcohol (1.2 equiv.) in dry CH_2Cl_2 and added to the reaction mixture. Bring the reaction mixture to room temperature. Stir the reaction mixture for 24 hours. After 24 hours, indicate TLC analysis complete consumption of the starting material. Concentrate the reaction mixture in vacuo. Add water (20 mL) to the mixture. Extract the aqueous layer with EtOAc (3 × 30 mL). Wash the combined organic extracts with water (3 × 30 mL), brine (2 × 30 mL). Dry the combined organic extracts (Na_2SO_4). Concentrate the combined organic extracts in vacuo. Purify the product by silica gel column chromatography (10% EtOAc: hexane) to give 1-(bromomethyl)-4-nitrobenzene **305,** (1.11g, 79%)**.** Spectral data were identical to those previously reported.[137] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 4.52 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 144.9, 130.0, 124.2, 31.0.

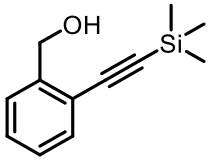
[137] Champagne, P.A., Benhassine, Y., Desroches, J. and Paquin, J.F., *Angew. Chem. Int. Ed*., **2014**. *53*, 13835-13839.

2-iodo-*N*-(4-nitrobenzyl)aniline (307)



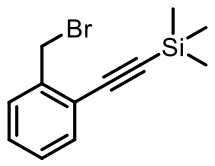
An oven-dried flask was charged with 2-iodoaniline **306** (1 equiv.), the 4-nitrobenzyl bromide (1.2 equiv.), $NaHCO_3$ (2 equiv.), and DMF. The mixture was stirred at 50 °C under air for 6-12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature and 15 mL water was added to the mixture, then extracted by EtOAc for 3 times (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel to afford pure product 2-iodo-*N*-(4-nitrobenzyl)aniline **307**. Spectral data were identical to those previously reported.[131] Yield: 35%; light yellow solid; m.p = 122-124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.9 Hz, 2H), 7.70 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J*= 8.5 Hz, 1H), 6.48 (td, *J* = 7.5, 1.3 Hz, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 4.80 (s, 1H), 4.55 (d, *J* = 5.9 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 146.6, 146.4, 139.3, 129.6, 127.6, 124.1, 119.7, 111.0, 85.6, 47.8.

(2-((trimethylsilyl)ethynyl)phenyl)methanol (309)



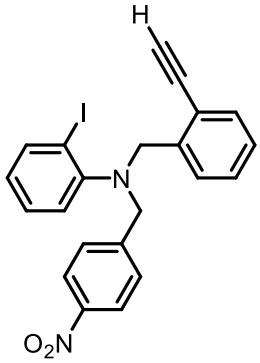
In a 100 mL three-necked round bottom flask, equipped with reflux condenser and mechanical stirrer, 3.36 g (14.4 mmol) of (2-iodophenyl)methanol (**308**) and 30 mL of distilled Et_3N were mixed together, then 2.6 mL (18.8 mmol) of trimethylsilylacetylene, 500 mg (0.71 mmol) of $PdCl_2(PPh_3)_2$ and 270 mg (1.42 mmol) of CuI were added to the solution at 0 °C. The resulting mixture was left under stirring for 3 h at room temperature, then it was hydrolyzed with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified through column chromatography (SiO2, CH_2Cl_2) to give **309,** as a yellowish oil (2.47 g, yield 84%), Spectral data were identical to those previously reported.[132a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.33 (td, *J* = 7.5, 1.3 Hz, 1H), 7.24 (td, *J* = 7.6, 1.5 Hz, 1H), 4.82 (d, *J* = 6.2 Hz, 2H), 0.27 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 132.5, 129.0, 127.4, 127.3, 121.3, 102.7, 99.7, 64.2, 0.0.

((2-(bromomethyl)phenyl)ethynyl)trimethylsilane (310)



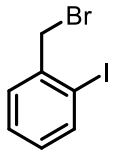
To a solution of 2-(trimethylsilylethynyl)benzyl alcohol **309** (10.0 g, 48.9 mmol) in CH_2Cl_2 (200 mL) were added successively PPh_3 (13.9 g, 53.0 mmol) and NBS (9.30 g, 52.3 mmol) at 0 °C. After stirring for 30 min, the mixture was quenched with brine and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vaccum. The crude product was chromatographed on silica gel with hexane to give **310** (11.3 g, 42.3 mmol, 86%) as colorless oil. Spectral data were identical to those previously reported.[132b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.9 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.30 (td, *J* = 7.6, 1.5 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.4 Hz, 1H), 4.67 (s, 2H), 0.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 132.8, 129.7, 129.1, 128.4, 123.1, 102.0, 100.8, 31.9, 0.00.

***N*-(2-ethynylbenzyl)-2-iodo-*N*-(4-nitrobenzyl)aniline (311)**



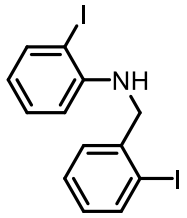
An oven-dried flask was charged with 2-iodo-*N*-(4-nitrobenzyl)aniline **307**, (1 equiv.), the ((2-(bromomethyl)phenyl)ethynyl)trimethylsilane **310**, (1.2 equiv.), K_2CO_3 (2 equiv.), and MeCN. The mixture was stirred at 50 °C under air for 1.5 day. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature and 15 mL water was added to the mixture, then extracted by EtOAc for 3 times (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel to afford pure product *N*-(2-ethynylbenzyl)-2-iodo-*N*-(4-nitrobenzyl)aniline **311,** (7mg, 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.88 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 6.1 Hz, 1H), 7.31 (t, J= 6.1 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 2H), 6.96 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.80 (td, *J* = 7.6, 1.5 Hz, 1H), 4.38 (s, 2H), 4.28 (s, 2H), 3.22 (s, 1H).

1-(bromomethyl)-2-iodobenzene (312)



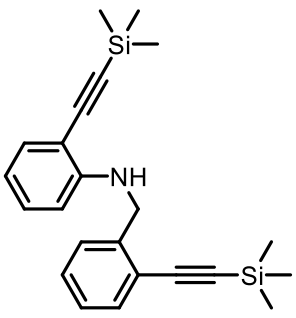
A stirred sample of commercially available 2-iodobenzyl alcohol **308**, (5.00 g, 21.4 mmol) in THF (25 mL) at 0 °C under Ar was treated with PBr_3 (1.2 mL, 12.8 mmol). The reaction mixture was stirred at 0 °C for 30 min. Quenched the reaction by Adding cold water (20 mL) to the mixture. Extract the aqueous layer with EtOAc (3 × 30 mL). Wash the combined organic extracts with water (3 × 30 mL), brine (2 × 30 mL). Dry the combined organic extracts (Na_2SO_4). Concentrate the combined organic extracts in vacuo. concentrated under reduced pressure to provide the crude product. Flash column chromatography (SiO2, 30% EtOAc/hexanes) afforded **312** (6.50 g, 98%) as a yellow solid: mp 56−60 °C; Spectral data were identical to those previously reported.[133] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.97 (td, *J* = 7.7, 1.7 Hz, 1H), 4.60 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 140.2, 130.6, 130.2, 129.0, 100.1, 38.9.

2-iodo-*N*-(2-iodobenzyl)aniline (314)



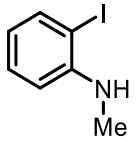
An oven-dried flask was charged with 2-iodoaniline (1 equiv.), the 2-iodobenzyl bromide **312** (1.2 equiv.), $NaHCO_3$ (2 equiv.), and DMF. The mixture was stirred at 50 °C under air for 4-12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature and 15 mL water was added to the mixture, then extracted by EtOAc for 3 times (3 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel to afford pure product 2-iodo-*N*-(2-iodobenzyl) aniline **314** (85mg mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.30 (d, *J* = 4.2 Hz, 2H), 7.14 (td, *J*= 7.5, 1.5, 1H), 6.98 (m, 1H), 6.44 (m, 2H), 4.78 (s, 1H), 4.38 (d, *J* = 5.6 Hz, 2H).

2-((trimethylsilyl)ethynyl)-*N*-(2-((trimethylsilyl)ethynyl)benzyl)aniline (317)



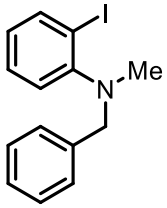
In 25ml Round bottom flask equipped with reflux condenser and mechanical stirrer 2-iodo-*N*-(2-iodobenzyl) aniline **314** (1 equiv.) and distilled Et_3N were mixed together, then (2.4 equiv.) of trimethylsilyl acetylene, (0.10 equiv.) of $PdCl_2(PPh_3)_2$ and (0.6 equiv.) of CuI were added to the solution at 23 °C. The resulting mixture was left under stirring for 3-6 h at 50 ^{0}C, then it was hydrolyzed with a sat-urated solution of NH_4Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified through column chromatography to give **317** (138mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.30 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.13 (td, J= 7.8, 1.7 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 5.12 (s, 1H), 4.58 (s, 2H), 0.24 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 141.2, 132.5, 132.2, 130.3, 129.0, 126.9, 126.8, 121.8, 116.5, 109.9, 107.5, 102.5, 102.1, 100.5, 100.2, 46.3, 0.27, 0.1.

2-iodo-*N*-methylaniline (320)



A round-bottom flask equipped with a magnetic stirrer bar was charged with 2-iodoaniline **306** (12.0 mmol) and NaH (60% in mineral oil, 40.0 mmol) dissolved in THF (30 mL). The resulting mixture was stirred at 0 °C for 30 min. Then iodomethane (10.0 mmol) was added dropwise for 10 min and left the reaction for 12 h at 23 ^{0}C. The reaction mixture was quenched with water and the organic layer was extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give product 2-iodo-*N*-methylaniline 2.12 g (91%) **320**. Colorless oil. Spectral data were identical to those previously reported.[134] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.26 (dd, *J* = 15.4, 1.7 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 6.47 (t, *J* = 7.4 Hz, 1H), 4.22 (s, 1H), 2.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 138.9, 129.5, 118.5, 110.1, 85.2, 31.0.

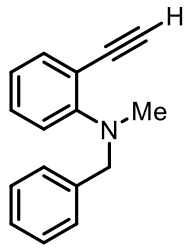
***N*-benzyl-2-iodo-*N*-methylaniline (322)**



To a solution of 2-iodo-N-methylaniline (0.7 g, 3.0 mmol) **320**, in acetonitrile (50 mL) were added benzyl bromide (1.43 mL, 12.0 mmol), K_2CO_3 (3.32 g, 24.0 mmol), and the mixture was heated at reflux for 24 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and water. The organic extracts were dried and concentrated, and the residue was purified by chromatography (SiO2, from hexane to 1:1 hexane-EtOAc) to give aniline **322**, as an oil. Yield: 858 mg, 85%. Spectral data were identical to those previously reported.[135] ^{1}H NMR (500 MHz,

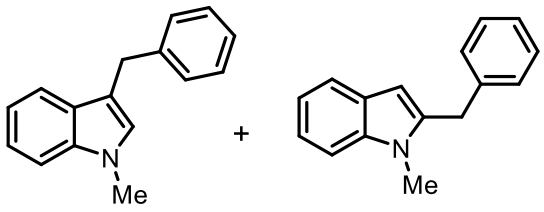
$CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.30 (m, 4H), 7.10 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.81 (td, *J* = 7.5, 1.5 Hz, 1H), 4.12 (s, 2H), 2.62 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 140.2, 138.3, 129.1, 128.8, 128.3, 127.2, 125.6, 122.4, 98.7, 61.2, 41.7.

_N_-benzyl-2-ethynyl-_N_-methylaniline (324)



To a solution of **323** (1 equiv.) in MeOH was added K_2CO_3 (2 equiv.). After being stirred at room temperature for 12 h, the mixture was concentrated to the minimum volume and diluted with dichloromethane, washed with brine, dried, filtered and concentrated in vacuo. The residue was purified through flash column chromatography (hexane and ethyl acetate) to afford, after concentration and high vacuum-drying, the final product **324**.(180mg, 80% yield), light yellow oil. Spectral data were identical to those previously reported.[136] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.18 (m, 2H), 6.83 (m, 2H), 4.42 (s, 2H), 3.28 (s, 1H), 2.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 138.8, 135.1, 129.8, 128.4, 128.3, 127.1, 120.9, 118.4, 114.7, 82.9, 82.8, 60.3, 39.4.

3-benzyl-1-methyl-1*H*-indole and **2-benzyl-1-methyl-1*H*-indole (325 & 326)**



2:1

To a solution of *N*-benzyl-2-ethynyl-*N*-methylaniline **324** , in Dry-DCE added gold(I)-catalyst (10 mol%) at 60 °C for 20-hour. the mixture was concentrated to the minimum volume and diluted with dichloromethane, washed with brine, dried, filtered and concentrated in vacuo. The residue was purified through flash column chromatography (2% hexane and ethyl acetate system) to afford **325** and **326**. 47.5mg, 95% yield, Pale yellow oil. Product **325** NMR data matches to Spectral data were identical to those previously reported.[138] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 17.1, 7.9 Hz, 2H), 7.26 (m, 9H), 7.16 (m, 5H), 7.05 (m, 2H), 6.73 (s, 1H), 6.27 (s, 1H), 4.13 (s, 1H), 4.09 (s, 2H), 3.71 (s, 3H), 3.54 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 139.2, 138.5, 137.8,

[138] Porcheddu, A., Mura, M.G., De Luca, L., Pizzetti, M. and Taddei, M., *Org. lett.,* **2012**. *14*, 6112-6115.

130.4, 128.8, 128.7, 128.4, 127.9, 127.9, 127.2, 126.6, 126.6, 125.9, 125.7, 121.7, 121.0, 120.3, 120.1, 119.5, 119.4, 119.3, 118.9, 114.4, 109.4, 109.2, 108.9, 101.3, 33.5, 32.7, 31.6, 29.8.

Chapter 3.

"Iodine(III)-Mediated Electrophilic Chlorination and Catalytic Nitration of N-Tosyl Anilines Under a Common Strategy"

3.1 Introduction

Chlorinated[139] and nitrated anilines[140] are an important class of organic compounds. In one side, chloroanilines are present in *N*-glucosides plant metabolites,[141] dyes, cosmetics, pharmaceuticals and herbicides;[142] they also display biological activities such as antiprotozoal,[143] receptor tyrosine kinase (RTK) inhibitors,[144] and as useful building blocks in organic synthesis.[145] On the other hand, nitroanilines are important in materials science as a highly relevant push-pull molecules in non-linear optics,[146] photoluminescence,[147] synthesis of dyes[148] and explosives.[149] The nitroaniline core serves as a building block in the pharmaceutical industry,[150] as reagents for diazotization in assays of proteases,[151] as prodrug-type in neuramidase-triggered activation,[152] metabolic products of PhEBfx against *T. cruzi,*[153] and slow releasers of the endothelial relaxer nitric oxide (NO).[154]

Concerning their synthesis, to date, some procedures have been described for the introduction of the chlorine and nitro groups into the functionalized aniline moiety as anilide or benzenesulfonamide. For the case of chlorination, several metal-free procedures involving the use of NCS[155] (in combination with TMSCl[156] or thioureas[157]), alkyl ammonium chlorides in acid

---

[139] (a) K. Naumann. *Pest Manag Sci*. **2000**, *56*, 3-21. (b) M. Z. Hernandes, S. M. T. Cavalcanti, D. R. M. Moreira, *Curr. Drug Targets*. **2010**, *11*, 303-314.

[140] (a) N. Ono, *The Nitro Group in Organic Synthesis;* Wiley-VCH: New York, **2001**. (b) K.-S. Ju, R. E. Parales, *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 250-272. (c) K. J. Indest, J. O. Eberly, D. E. Hancock, *J. Gen. Appl. Microbiol.* **2015**, *61*, 217-223. (d) J. C. Spain, *Annu. Rev. Microbiol.* **1995**, *49*, 523-555.

[141] R. Winkler, H. Sandermann, *J. Agric. Food Chem.* **1992**, *40*, 2008-2012.

[142] A.S. Vangnai, W. Petchkroh, *FEMS Microbiol. Let*. **2007**, *268*, 209-216.

[143] C. Eberle, J. A. Burkhard, B. Stump, M. Kaiser, R. Brun, R. L. Krauth-Siegel, F. Diederich, *ChemMedChem*. **2009**, *4*, 2034-2044.

[144] A. Gangjee, S. Kurup, M. A. Ihnat, J. E. Thorpe, S. S. Shenoy, *Bioorg. Med. Chem*. **2010**, *18*, 3575-3587.

[145] Y. Zou, J. E. Melvin, S. S. Gonzales, M. J. Spafford, A. B. Smith III, *J. Am. Chem. Soc.* **2015**, *137*, 7095-7098.

[146] (a) C. C. Teng, A. F. Garito, *Phys. Rev*. **1983**, *28,* 6766. (b) D. M. Bishop, B. Champagne, B. Kirtman, *J. Chem. Phys*. **1998**, *109*, 9987-9994. (c) H. Reis, M. G. Papadopoulos, P. Calaminici, K. Jug, A. M. Koster, *Chem. Phys*. **2000**, *561*, 359-371.

[147] (a) C. J. Seliskar, O. S. Khalil, S. P. McGlynn, *Excited States*, **1974**, *1*, 231-294. (b) M. M. Szostak, B. Kozankiewicz, J. Lipinski, *Acta A Mol. Biomol. Spectrosc. SPECTROCHIM ACTA A.* **2007**, *67*, 1412-1416.

[148] (a) C. J. Agudelo-Morales, O. F. Silva, R. E. Galian, J. Perez-Prieto, *ChemPhysChem*, **2012**, *13*, 4195-4201. (b) L. Hermosilla, M. C. Rezende, V. G. Machado, R. I. Stock, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. **2017**, *173*, 556-561.

[149] (a) P. R. Lee, J. A. Zukas, W. P. Walters, **2002**, 23-45. (b) R. P. Schwar-zenbach, P. M. Gschwend, D. M. Imboden, *Environmental Organic Chemistry*; *Wiley-VCH: New York*, **2002**.

[150] (a) A. Bhattacharya, V. C. Purohit, V. Suarez, R. Tichkule, G. Parmer.; F. Rinaldi, *Tetrahedron Lett*. **2006**, *47*, 1861-1864. (b) A. N. Gritsenko, Z. I. Ermakova, S. V. Zhuravlev, *Chem. Heterocycl. Compd.* **1970**, *6*, 1245-1246. (c) S. Radl, P. Hezky, J. Proska, I. Krejci, *Arch. Pharm. Pharm. Med. Chem*. **1999**, *332*, 13-18. (d) Gerald Booth. *Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VHC.* **2007**.

[151] M. J. Lee, J. H. Anstee, *Anal. Biochem.***1994**, *218*, 480-482.

[152] T. Matsushita, M. N. Danyel, T. Koyama, K. Hatano, K. Matsuoka, *Bioorg. Med. Chem. Lett*. **2020**, *30*, 126883.

[153] M. Boiani, A. Merlino, A. Gerpe, W. Porcal, F. Croce, S. Depaula, M. A. Rodríguez, H. Cerecetto, M. González, *Xenobioteca*. **2009**, *39,* 236-248.

[154] (a) P. Chauhan, N. Yan, *Carbohydr. Polym*. **2017**, *174*, 1106-1113. (b) A. R. Badour, J. A. Wisniewski, D. K. Mohanty, P. J. Squattrito, *Acta Crystallogr. C*. **2016**, *72*, 405-410.

[155] R. S. Neale, R. G. Schepers, M. R. Walsh, *J. Org. Chem*. **1964**, *29*, 3390-3393.

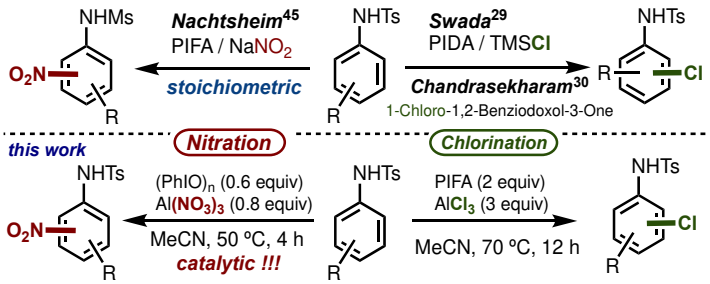
[156] T. Maibunkaew, C. Thongsornkleeb, J. Tummatorn, A. Bunrit, S. Ruchirawat, *Synlett*. **2014**, *25*, 1769-1775.

[157] A. N. Dinh, S. M. Maddox, S. D. Vaidya, M. A. Saputra, C. J. Nalbandian, J. L. Gustafson, *J. Org. Chem.* **2020***, 85,* 13895-13905.

media,[158] oxidation of the chloride anion (with Oxone®[159] or *m*-CPBA[160]) and *N*-chloro sulfonamide-based reagents (CFBS[161] or CMOBSA[162]) have been reported. The metal-catalyzed chlorination has been mainly described with Cu,[163] Pd[164] or Fe[165]. In this work, only two protocols using iodine(III)-based reagents[166] have been described by Swada,[167] and Chandrasekharam.[168] For the nitration of anilides or benzenesulfonamides, different metal-free protocols involving the use of nitrocyclohexadienones,[169] ionic liquids [Msim]NO_3,[170] montmorillonite clay,[171] urea nitrate[172] or via the formation of the aniline nitric salts-H_2SO_4 are found in the literature.[173] Also, nitration of anilides or benzenesulfonamides using the nitrite group present in $^tBuONO_2$[174] and pyridinium salts,[175] or by oxidizing the $NaNO_2$ with Oxone®,[176] or under photocatalytic conditions with RFTA (riboflavin tetraacetate) at 455 nm,[177] are the most representative protocols. Other metal-catalyzed nitration procedures imply the use of Cu,[178] Fe,[179] Bi,[180] Ag,[181] and Ni.[182] Regarding this report, the nitration of benzenesulfonamides using iodine(III) reagents is restricted to a single report by Nachtsheim[183] using stoichiometric amounts of PIFA (**Scheme 42**).

---

[158] (a) X. Bao, J. Yao, H. Zhou, G. Xu, *Org. Lett*. **2017**, *19*, 5780-5782. (b) X. Xiong, Y. Y. Yeung, *Angew. Chem. Int. Ed. Engl*. **2016**, *55*, 16101-16105.
[159] V. M. Lakshmireddy, Y. Naga Veera, T. J. Reddy, V. J. Rao, B. China Raju, *Asian J. Org. Chem.* **2019**, *8*, 1380-1384.
[160] C. Y. Chen, G. C. Senadi, M. C. Liu, J. J. Wang, *ChemistrySelect*. **2016**, *1*, 2207-2211.
[161] Z. Lu, Q. Li, M. Tang, P. Jiang, H. Zheng, X. Yang, *Chem Commun*. **2015**, *51*, 14852-14855.
[162] X. Pu, Q. Li, Z. Lu, X. Yang, *Eur. J. Org. Chem*. **2016**, *2016*, 5937-5940.
[163] (a) B. Urones, A. M. Martínez, N. Rodríguez, R. G. Arrayas, J. C. Carretero, *Chem. Commun*. **2013**, *49*, 11044-11046. (b) H. Wang, K. Wen, N. Nurahmat, Y. Shao, H. Zhang, C. Wei, Y. Li, Y. Shen, Z. Sun, *Beilstein J. Org. Chem*. **2012**, *8*, 744-748.
[164] a) H. Shi, P. Wang, S. Suzuki, M. E. Farmer, J. Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14876-14879. b) S. Xiuyun, S. Gang, S. Yonghui, R. Yu, *Angew. Chem. Int. Ed*. **2013**, *52*, 4440-4444.
[165] M. A. Mostafa, R. M. Bowley, D. T. Racys, M. C. Henry, A. Sutherland, *J. Org. Chem.* **2017***, 82,* 7529-7537.
[166] M. Wang, Y. Zhang, T. Wang, C. Wang.; D. Xue, J. Xiao, *Org. Lett*. **2016**, *18*, 1976-1979.
[167] K. Yamamoto, S. Kamino, D. Sawada, *Tetrahedron Lett*. **2017**, *58*, 3936-3938.
[168] B. Vinayak, P. V. Ravindrakumar, D. V. Ramana, M. Chandrasekharam, *New J. Chem*. **2018**, *42*, 8953-8959.
[169] M. Lemaire, A. Guy, P. Boutin, J. P. Guette, *Synthesis*, **1989**, *1989*, 761-763.
[170] M. A. Zolfigol, A. Khazaei, A. R. Moosavi-Zare, A. Zare, H. G. Kruger, Z. Asgari, V. Khakyzadeh, M. Kazem-Rostami, *J. Org. Chem.* **2012**, *77*, 3640-3645.
[171] S. K. Bharadwaj, P. K. Boruah, P. K. Gogoi, *Catal. Commun*. **2014**, *57*, 124-128.
[172] T. P. Sura, M. M. V. Ramana, N. A. Kudav, *Synth. Commun*. **1988**, *18*, 2161-2165.
[173] P. Zhang, M. Cedilote, T. P. Cleary, M. E. Pierce, *Tetrahedron Lett*. **2007**, *48*, 8659-8664.
[174] (a) B. Kilpatrick, M. Heller, S. Arns, *Chem. Commun*. **2013**, *49*, 514-516. (b) P. Chaudhari, S. Gupta, N. Sabieh, J. Kandasamy, *J. Org. Chem.* **2018**, *84*, 104-119.
[175] P. Natarajan, R. Chaudhary, N. Rani, P. Venugopalan, *Tetrahedron Lett*. **2020**, *61*, 151529.
[176] Y. X. Li, L. H. Li, Y. F. Yang, H. L. Hua, X. B. Yan, L. B. Zhao, J. B. Zhang, F. J. Ji, Y. M. Liang, *Chem. Commun*. **2014**, *50*, 9936-9938.
[177] S. J. Düsel, B. König, *J. Org. Chem*. **2018**, *83*, 2802-2807.
[178] (a) E. Hernando, R. R. Castillo, N. Rodríguez, R. Gómez Arrayás, J. C. Carretero, *Chem. Eur. J.* **2014**, *20*, 13854-13859. (b) P. Sadhu, S. K. Alla, T. Punniyamurthy, *J. Org. Chem*. ***2015***, *80*, 8245-8253. (c) B. Vinayak, M. Chandrasekharam, *Org. Lett*. **2017**, *19*, 3528-3531.
[179] (a) V. Botla, D. V. Ramana, B. Chiranjeevi, M. Chandrasekharam, *ChemistrySelect*. **2016**, *1*, 3974-3978. (b) Y. Gao, Y. Mao, B. Zhang, I. Zhan, Y. Huo, *Org. Biomol. Chem*. ***2018***, *16*, 3881-3884.
[180] Y. Lu, Y. Li, R. Zhang, K. Jin, C. Duan, *Tetrahedron*, **2013**, *69*, 9422-9427.
[181] N. Iranpoor, H. Firouzabadi, N. Nowrouzi, D. Firouzabadi, *Tetrahedron Lett*. **2006**, *47*, 6879-6881.
[182] Tasneem, M. M. Ali, K. C. Rajanna, P. K. Saiparakash, *Synth. Commun*. **2001**, *31*, 1123-1127.
[183] U. Kloeckner, B. J. Nachtsheim, *Chem. Commun*. **2014**, *50*, 10485-10487.



Scheme 42. Known procedures for the chlorination and nitration of *N*-aryl sulfonamides using iodine(III) reagents.

As part of our research on iodine(III) chemistry[184] we focused our work in the oxidative functionalization[185] of aromatic derivatives[186] to get compounds mainly with biological importance.[187] Thus, considering the relevance of chloroaniline as well as the nitroaniline core, the design of procedures that avoid the harsh conditions described for the synthesis of both nuclei, especially the acidic nitration, is currently an interesting challenge to complete. In this regard, we envisioned the development of a mild and non-Brønsted-acidic protocol for the chlorination and nitration of *N*-tosyl anilines. We based our strategy in the application of our recent methods which use commercially available iodine(III) reagents[188] in synergistic combination with different aluminum salts.[189] By employing an aluminum salt as a common strategy, we showed that the formation of an ionic pair enabled the introduction of chlorine as the functional group.

---

[184] (c) L. A. Segura-Quezada, K. R. Torres-Carbajal, Y. Satkar, K. A. Juarez-Ornelas, N. Mali, D. B. Patil, R. Gámez-Montaño, J. R. Zapata-Morales, S. Lagunas-Rivera, R. Ortiz-Alvarado, C. R. Solorio-Alvarado, *Mini-Rev. Org. Chem*. **2021**, *18*, 159-172. (d) L. A. Segura-Quezada, K. R. Torres-Carbajal, K. A. Juarez-Ornelas, R. Ortiz-Alvarado, A. J. Alonso-Castro, T. Dohi, C. R. Solorio-Alvarado, *Org. Biomol. Chem*. **2022**, *20*, 5009-5034.

[185] B. Yahuaca-Juárez, G. González, M. A. Ramírez-Morales, C. Alba-Betancourt, M. A. Deveze-Álvarez, C. L. Mendoza-Macías, R. Ortiz-Alvarado, K. A. Juárez-Ornelas, C. R. Solorio-Alvarado, and K. Maruoka, *Synth. Commun.*, **2020**. *50*, 539-548.

[186] a) Y. Satkar, K. Wrobel, D. E. trujillo-González, R. Ortíz-Alvarado, J. O. C. Jiménez-Halla, and C. R. Solorio-Alvarado. *Front. Chem.* **2020**, *8*, 563470. b) P. D. Nahide and C. R. Solorio-Alvarado. *Tetrahedron Lett.,* **2017***, 58, 279–284.*

[187] a) P. D. Nahide, C. Alba-Betancourt, R. Chávez-Rivera, P. Romo-Rodríguez, M. Solís-Hernández, L. A. Segura-Quezada, K. R. Torres-Carbajal, R. Gámez-Montaño, M. A. Deveze-Álvarez, M. A. Ramírez-Morales, A. J. Alonso-Castro, J. R. Zapata-Morales, A. J. Ruiz-Padilla, C. L. Mendoza-Macías, V. Meza-Carmen, C. J. Cortés-García, A. R. Corrales-Escobosa, R. E. Núñez-Anita, R. Ortíz-Alvarado, L. Chacón-García, C. R. Solorio-Alvarado. *Bioorg. Med. Chem. Lett.*, **2022**, *63*, 128649. b) L. A. Segura-Quezada, K. R. Torres-Carbajal, N. Mali, D. B. Patil, M. Luna-Chagolla, R. Ortiz-Alvarado, M. Tapia-Juárez, I. Fraire-Soto, J. G. Araujo-Huitrado, A. J. Granados-López, R. Gutiérrez-Hernández, C. A. Reyes-Estrada, Y. López-Hernández, J. Adrián López, L. Chacón-García, and C. R. Solorio-Alvarado**.** *ACS Omega*, **2022**, *7*, 6944-6955. c) V. Ramadoss, R. Gámez-Montaño, J. R. Zapata-Morales, Á. J. Alosno-Castro and C. R. Solorio-Alvarado. *Med. Chem. Res.* **2019**, *28*, 473-484. d) V. Ramadoss, Á. J. Alonso-Castro, N. Campos-Xolalpa, R. Ortiz-Alvarado, B. Yahuaca-Juárez and C. R. Solorio-Alvarado. *RSC Adv.* **2018**, *8*, 30761-30776. e) V. Ramadoss, Á. J. Alonso-Castro, N. Campos-Xolalpa and C. R. Solorio-Alvarado. *J. Org. Chem.* **2018**, *83*,10627-10635.

[188] (a) P. J. Sarang, V. V. Zhdankin, *Chem. Rev*. **1996**, *96*, 1123-1178. (b) V. V. Zhdankin, P. J. Sarang, *Chem. Rev*. **2002**, *102*, 2523-2584.

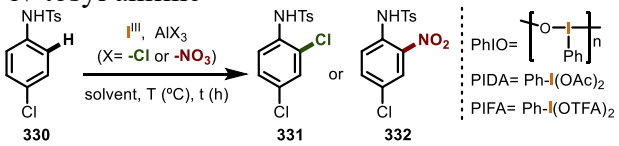
[189] (a) P. D. Nahide, V. Ramadoss, K. A. Juarez-Ornelas, Y. Satkar, R. Ortiz-Alvarado, J. M. Cervera-Villanueva, A. J. Alonso-Castro, J. R. Zapata-Morales, A. J. Ruiz-Padilla, M. A. Deveze-Alvarez, C. R. Solorio-Alvarado, *Eur. J. Org. Chem*.; **2018**, *2018*, 485-493. (b) Y. Satkar, V. Ramadoss, P. D. Nahide, E. García-Medina, K. A. Juarez-Ornelas, A. J. Alonso-Castro, R. Chavez-Rivera, J. O. C. Jiménez-Halla, C. R. Solorio-Alvarado, *RSC. Adv*. **2018**, *8*, 17806-17812. (c) K. A. Juarez-Ornelas, J. O. C. Jiménez-Halla, T. Kato, C. R. Solorio-Alvarado, K. Maruoka, *Org. Lett*. **2019**, *21*, 1315-1319. (d) Y. Satkar, L. F. Yeara-Ledesma, N. Mali, D. Patil, P. Navarro-Santos, L. A. Segura-Quezada, P. I.

In this work, we present our results using the PIFA/$AlCl_3$ and $(PhIO)_n/Al(NO_3)_3$ systems which allowed us the oxidative electrophilic chlorination and to the best of our knowledge, the first catalytic nitration of several *N*-tosyl anilines.

3.2 Results and Discussion

We initially sought validation of our hypothesis using 4-chloro-*N*-tosyl aniline (Table 1).

Table 1. Optimization of the Iodine(III)-mediated the electrophilic chlorination and the catalytic nitration of 4-chloro-*N*-tosyl aniline[a,b]



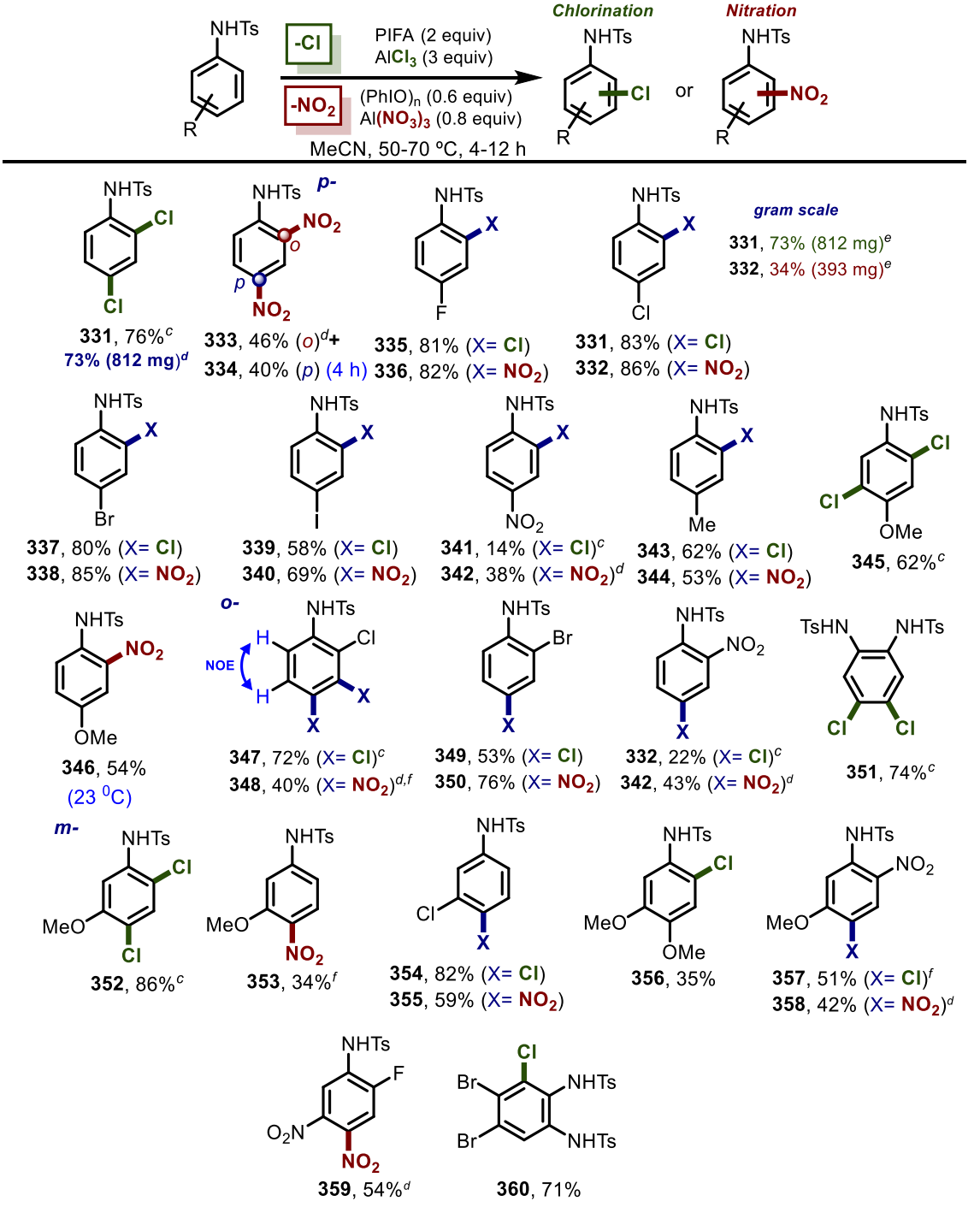
Entry	I^{III} source (equiv)	AlX_3 source (equiv)	Solvent	T (°C)	t (h)	Yield (%)[c] 2 / 3
1	PIFA (1.2)	$AlCl_3$ (2.4)	MeCN	23	12	n.r. / - -
2	PIFA (1.2)	$AlCl_3$ (2.4)	MeCN	50	12	n.r. / - -
3	PIDA (1.2)	$AlCl_3$ (2.4)	MeCN	70	12	65 / - -
4	PIFA (1.5)	$AlCl_3$ (2.4)	MeCN	70	12	68 / - -
5	PIFA (1.5)	$AlCl_3$ (3.0)	MeCN	70	12	74 / - -
6	***PIFA (2.0)***	***$AlCl_3$ (3.0)***	***MeCN***	***70***	***12***	***83 / - -***
7	PIFA (2.0)	$AlCl_3$ (3.0)	DCE	70	12	c.r.m. / - -
8	PIFA (2.0)	$AlCl_3$ (3.0)	THF	70	12	c.r.m. / - -
9	PIFA (2.0)	- -	MeCN	70	12	c.r.m. / - -
10	- -	$AlCl_3$ (3.0)	MeCN	70	12	0 / - -
11[d,e]	PhIO (0.3)	$Al(NO_3)_3$ (0.4)	MeCN	23	4	- - / 35
12[d]	PhIO (0.3)	$Al(NO_3)_3$ (0.4)	MeCN	50	4	- - / 60
13[d]	***PhIO (0.6)***	***$Al(NO_3)_3$ (0.8)***	***MeCN***	***50***	***4***	***- - / 86***
14[d]	PhIO (1.2)	$Al(NO_3)_3$ (1.0)	MeCN	50	4	- - / 40
15[d]	PIDA (0.6)	$Al(NO_3)_3$ (0.8)	MeCN	50	4	- - / 34
16	PhIO (0.6)	--	MeCN	50	4	- - / n.r.
17[d]	--	$Al(NO_3)_3$ (0.8)	MeCN	50	4	- - / 0

Ramírez-Morales, C. R. Solorio-Alvarado, *J. Org. Chem*. **2019**, *84*, 4149-4164. (e) A. Segura-Quezada, Y. Satkar, D. Patil, N. Mali, K. Wrobel, G. González, R. Zarraga, R. Ortiz-Alvarado, C. R. Solorio-Alvarado, *Tetrahedron Lett*. **2019**, *60*, 1551-1555.

[a] Reaction conditions: 4-chloro-*N*-tosyl aniline (0.5 mmol), solvent (0.3 *M*), 50 or 70 ºC, no inert atmosphere. [b] The Ac-, Piv- and $(PhO)_2P(O)$- groups at the *N*- of aniline were tested, however no reaction was found. [c] Isolated yields. [d] $Al(NO_3)_3 \cdot 9H_2O$ was used. [e] 50% of starting material recovered. c.r.m. = complex reaction mixture. n.r. = no reaction observed.

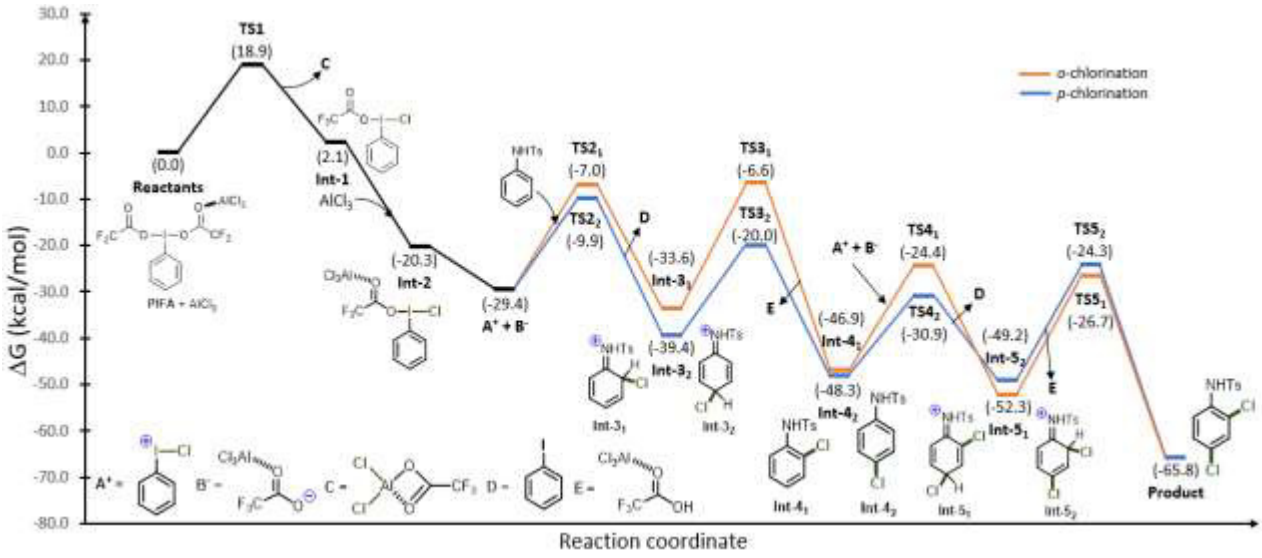
Initial attempts to induce the chlorination were carried out using the simple *N*-tosyl aniline. However, a mixture of *o*- and *p*-chlorination was obtained. Therefore, to determine the optimum stoichiometry, we started with 4-chloro-*N*-tosyl aniline **330**, as the model system. Based on our previous chlorination protocol,[189a] 1.2 equivalents of PIFA and 2.4 equivalents of aluminum trichloride did not give the expected product **331**, at 23 or 50 °C (entries 1 and 2). By heating at 70 °C, product **331**, in 65% yield was isolated (entry 3). The use of 1.5 equivalents of oxidant and 3 equivalents of the aluminum salt increased the yield to 74% (entries 4 and 5). However, the best result was obtained with 2 equivalents of PIFA and 3 equivalents of aluminum trichloride at 70 °C in 12 hrs, to get 83% yield (entry 6). Under these conditions, other solvents (entries 7 and 8), including the control experiments (entries 9 and 10), did not afford the desired chlorination. Concerning the nitration, our previous report on catalytic nitration[189c] provided the starting conditions. Thereby, sub-stoichiometric amounts of the oxidant and the aluminum salt, consisted in 0.3 equivalents of polymeric iodosylbenzene $(PhIO)_n$ and 0.4 equivalents of aluminum nitrate nonahydrate, produced the desired nitrated product in 34% yield at 23 °C. The starting material was not fully consumed in 12 hrs (entry 11). Nevertheless, at 50 °C, the nitroaniline **332**, was obtained in 60% yield (entry 12). The use of a double amount of each reagent, still in sub-stoichiometric quantities, gave the best result with a 78% of isolated yield (entry 13). To our delight, these results indicated the nitration process occurred as expected, in catalytic conditions and water tolerant. Increasing the amount of both reagents, or changes of the iodine(III) oxidant (entries 14 and 15), or in the control experiments (entries 16 and 17) did not improve the yield. The use of aluminum tribromide was also attempted and gave the corresponding brominated product. However, large excesses of the oxidant and salt were necessary. In consequence, this proposal was ruled out. Thus, with the optimal conditions for chlorination and nitration, we proceeded to explore the scope of the reaction (**Scheme 43**).

Scheme 43. Scope of the PIFA/$AlCl_3$-mediated electrophilic chlorination and $(PhIO)_n$/$Al(NO_3)_3$-catalyzed nitration of *N*-tosyl anilines[a,b]



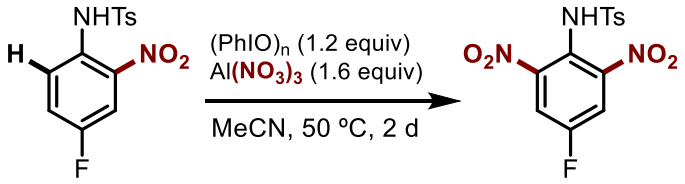
[a] Reaction conditions: substituted *N*-tosyl aniline (0.5 mmol), solvent (0.3 *M*), 50-70 °C, 4-12 h, no inert atmosphere, $Al(NO_3)_3 \cdot 9H_2O$ was used for nitration reactions. [b] Isolated yields. [c] PIFA (3 equiv) / $AlCl_3$ (5.5 equiv) were used for 1-2 days. [d] $(PhIO)_n$ (1.2 equiv) / $Al(NO_3)_3 \cdot 9H_2O$ (1.6 equiv) were used for 2 days. [e] Gram scale reaction. [f] Regioselectivity was confirmed by NOESY.

Scheme 44. Energy profile for the chlorination mechanism of *N*-tosyl aniline using the PIFA/$AlCl_3$ system calculated at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level.



Chlorination of simple *N*-tosyl aniline produced bis-chlorinated **331**, in 76% yield. The nitration gave a separable mixture of *o*- **333**, and *p*-nitro-*N*-tosyl aniline **334**, in 46 and 40% yield, respectively (grey shadow). Several *para*-substituted *N*-tosyl anilines containing the complete halogen family and the strong electro-attracting nitro group **335-342**, were successfully chlorinated, and nitrated in yields ranging from 14 to 85%. The *p*-iodo- and *p*-nitro derivatives gave from modest to low yields, presumably due to the steric hindrance of the iodine atom and to the deactivation by the nitro group. The gram scale chlorination for **331**, gave 73% yield while the nitration for **332**, proceeded with a 34% yield. Other donating groups, such as *p*-methyl, gave rise to chlorinated **343**, and nitrated **344**, in good yields (62 and 53%). With electron-rich *N*-tosyl anilines containing a *p*-methoxy group, the mono-chlorinated compound could not be obtained as the sole product. Instead, bis-chlorinated **345**, was obtained in 58% yield using an excess of reagents, and the single nitration to get **346**, was achieved in 54% yield (green shadow). The *ortho*-chloro, -bromo and -nitro substituted *N*-tosyl anilines led to the formation of the corresponding chlorinated and nitrated products **332**, **342**, and **347-350**, in good to excellent yields (40-76%) with exception of *o*-nitro-*N*-tosyl aniline that gave lower yields for **332**, and **342**, (22 and 43%). An interesting 3,4-dichlorination and -nitration had place to get **348**, and **349**, which was confirmed by NOESY. The *o*-*N*Ts- derivative also gave the bis-chlorinated compound **351**, in good yield (74%). The corresponding nitration gave a complex reaction mixture. This poor performance could be the result of several nucleophilic centres that compete for the formed electrophile (blue shadow). In the assays, with *meta*-substituted *N*-tosyl anilines, again, those containing the *m*-methoxy group gave the bis-chlorination product **352**, in 86% yield and led to the single nitration product **353**, in 34% yield. The *m*-chloro *N*-tosyl aniline gave the chlorinated and nitrated substrates **354**, and **355**, in 82 and 59% yield (brown shadow). Disubstituted *N*-tosyl anilines, containing the methoxy and nitro groups, gave rise to chlorination and nitration products **356-358** in modest to good yields (35-51%). Strongly deactivated *N*-tosyl anilines substituted with the nitro and fluor groups did not react under these chlorination conditions. However, nitration of this compound gave **359**, in 54% yield using an excess of reagents. Chlorination of tetra-substituted anilines, possessing 1,2-di-*N*Ts groups, formed **360**, in 71% yield, while the nitration gave a complex reaction mixture as previously observed for this class of substrate (beige shadow).

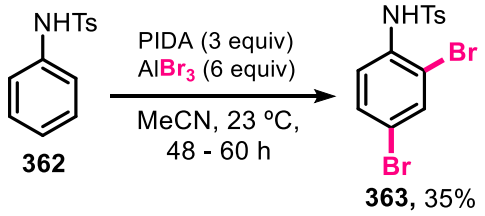
To demonstrate the utility of our protocol, starting from **336**, we synthesized the highly deactivated bis-nitrated derivative **361**, in 49% yield. This compound would be difficult to get by other electrophilic aromatic substitution procedures **(Eq. 16)**



336 **361**, 49% [**16**]

Finally, the reaction pathway for the developed chlorination process was elucidated. Our theoretical calculations at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level allowed us to propose a reaction mechanism. It starts with the coordination of one of the trifluoroacetate groups of PIFA to $AlCl_3$. Then, the acetate group dissociates as one of the chloride ions is transferred to the iodine simultaneously *via* transition state **TS1** ($\Delta G_1^{\ddagger}$ = 18.9 kcal/mol) to give **Int-1** which is +2.1 kcal/mol from the reactants (the acetate group evolves into species C). **Int-1** coordinates to a second $AlCl_3$ unit, which lowers the energy for -22.4 kcal/mol (**Int-2**). This spontaneously dissociates into the ion pair $\mathbf{A}^+$ and $\mathbf{B}^-$ releasing 9.1 kcal/mol, which is the active form of the catalyst. At this point, the stage of the reaction with *N*-tosyl aniline can proceed by attacking the *ortho*- or the *para*- position of aniline. We calculated both transition states: **TS2₁** (*o*-chlorination route) and **TS2₂** (*p*-chlorination route) for the transfer of a chloronium cation from $\mathbf{A}^+$ to each position of the aromatic ring, resulting in energy barriers of 22.4 and 19.5 kcal/mol, respectively. This energy difference of $\Delta\Delta G_2^{\ddagger}$ = 2.9 kcal/mol is even more notable when comparing intermediate **Int-3₁** and **Int-3₂** ($\Delta\Delta G_3$ = 5.8 kcal/mol), despite this reaction step is exergonic for both cases (-4.2 and -10.0 kcal/mol, respectively). Moreover, species $\mathbf{B}^-$ deprotonated *via* either **TS3₁** ($\Delta G_3^{\ddagger}$ = 27.0 kcal/mol) or **TS3₂** ($\Delta G_2^{\ddagger}$ = 19.4 kcal/mol) which is the largest energy difference between both routes ($\Delta\Delta G_3^{\ddagger}$ = 13.4 kcal/mol). Preliminarily, we can conclude that the *p*-chlorination process is much faster than the *o*-chlorination reaction. The monochlorination products **Int-4₁** and **Int-4₂** are only 1.4 kcal/mol distant. In the second chlorination reaction of aniline, there is an inversion of the stabilities when transferring the chloronium cation from $\mathbf{A}^+$ being **Int-5₁** 3.1 kcal/mol more stable than **Int-5₂**. Despite **TS4₂** is notably faster ($\Delta\Delta G_4^{\ddagger}$ = 6.5 kcal/mol) than **TS41** in this step, we can notice that the next and last deprotonation step, **TS5₁** becomes lower in energy ($\Delta\Delta G_5^{\ddagger}$ = 2.4 kcal/mol) than **TS5₂** to reach the bi-chlorinated product. When comparing **Int-4₁**→ **TS-4₁** ($\Delta G^{\ddagger}$ = 22.5 kcal/mol, now attacking on the *para* position) and **Int-4₂**→**TS5₂** ($\Delta G^{\ddagger}$ = 24.0 kcal/mol, now attacking on *ortho* position), we can observe that, again, the attack on the *para* position is faster. However, this selectivity is decided from the first chlorination on the aniline ring.

Also, we determined that after the chlorination and nitration reactions were working, the chemical obvious way for accessing to a broad scope is use the aluminum tribromide to get the corresponding brominated anilines. Thus, the reaction was explored (**Eq. 17**), and the optimizations is as follow **(Table 2).**



362 **363,** 35% [17]

Table 2. Optimization of the Iodine(III)-mediated bromination of *N*-tosyl aniline (**362**)

Entry	PIDA (equiv)	$AlBr_3$ source (equiv)	Solvent	T (ºC)	t (h)	Yield (%)
1.	3	6	MeCN	23 ºC	48-60	35%
2.	3	6	MeCN	40 ºC	12-18	crm
3.	3	6	MeCN	60 ºC	12-18	crm
4.	3	4	MeCN	70 ºC	12-14	crm
5.	3	4	DCE	70 ºC	12-14	crm

crm= complex reaction mixture.

As can be observed in the optimization of bromination reaction **(Table 2)**, large amounts of oxidant as well as aluminum salts were necessary to get reasonable chemical yields. Therefore, we conclude that under these conditions there is not a synthetic useful procedure, and we ruled out to expand the scope of our protocol to the bromination of anilines.

3.3 Conclusions

In summary, we have developed an efficient and mild iodine(III)-mediated electrophilic chlorination protocol and the first catalytic nitration method of *N*-tosyl anilines which uses polymeric iodosylbenzene **$(PhIO)_n$** as catalyst and was conducted in neutral and non-Brønsted-acidic conditions. Under a common strategy, the use of an aluminum salt provided the functional group in its ionic pair, which is oxidized by the iodine(III) reagent and finally reacted with the aromatic ring. Our DFT calculations allowed us the elucidation of the chlorination reaction pathway and indicate that [Cl-PhI$^{\oplus}$$^{\ominus}$OTFA·$AlCl_3$] is the chlorinating species which is operative in a cationic route.

3.4 Experimental Section

General Method. All moisture and oxygen sensitive reactions were carried out in flame-dried round bottom flask or using Schlenk techniques under an inert atmosphere of nitrogen, unless otherwise specified. NMR spectra were measured on ^1H and $^{13}C\{^1H\}$NMR spectra were acquired on Bruker Advance III (500 MHz) and JEOL JNM-ECA500 (500 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sep= septet, dd = doublet-doublet. m = multiplet, b = broad), coupling constants (Hz), and assignment. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet Is5 spectrometer. High resolution mass spectra (HRMS) were performed on Bruker microTOF and Thermo Exactive plus. YMC syringe pump (model number: YSP-101) was used when slow addition of a solution of a solution was conducted. The products were purified by flash column chromatography (silica gel 60, Merch and Sigma aldrich, 230-400 mesh) or preparative thin layer chromatography silica gel (PLC 60 F254. 0.5mm). Commercially available reagents were purchased from Wako, Aldrich, TCI and Alfa-aesar chemicals and used as received. Anhydrous solvents were purchased from Sigma Aldrich in SureSealR bottles. Thin layer chromatography was performed with TLC Silica gel 60 F256 plates, and visualization was affected with short wavelength UV light (254 nm).

Compounds were characterized using ^{1}H NMR, $^{13}C\{^{1}H\}$NMR, melting point, IR (ATR) and Mass spectroscopy and copies of spectra are provided in the supporting information for all new compounds. Data of known compounds were compared with existing literature characterization data and the references are given.

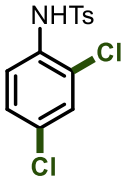
Synthesis of Iodosylbenzene $(PhIO)_n$. In a 250 ml round bottom flask was suspended (diacetoxyiodo)benzene (PIDA) (5g, 15.52 mmol, 1equiv) in 75 mL of a 3 *M* NaOH solution. The reaction was strongly stirred to room temperature during 12 h and precipitate was formed. After filtered off and neutralized with cold water until neutral pH this solid was washed (3 X 10 mL) with $CHCl_3$ to remove impurities of PIDA. The obtained solid was dried at high vacuum without heating to yield **$(PhIO)_n$** (3.1 g, 91%) as a yellowish solid. ***Caution!*** **$(PhIO)_n$** is explosive upon drying at 110 ^{0}C in vacuum conditions.

General procedure for *N*-tosyl aniline synthesis. To a solution of the aniline (4.05 mmol, 1 equiv) in pyridine (20.25 mL, 0.2 *M*) was added *p*-toluenesulfonyl chloride (4.45 mmol, 1.1 equiv) at 0 ^{0}C and then warm at 25 ^{0}C. After being stirred at 25 ^{0}C or 90 ^{0}C for 2-12 hours, the reaction mixture was poured into water. The product was extracted with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel to give the corresponding *N*-tosyl anilines.

General Procedure for Chlorination. A 25 mL oven-dried round bottom flask equipped with a magnetic stirrer bas was charged with PIFA bis(trifluoroacetoxy)iodo benzene (2.0 equiv) and acetonitrile (0.3 *M*) at 25 ^{0}C. After dissolving and obtaining homogeneous mixture, $AlCl_3$ (3.0 equiv) was added and stirred for 10 min. Then, the corresponding *N*-tosyl aniline (1.0 equiv) was added and stirred at 70 ^{0}C until fully consumption of the starting material (usually 5 to 18 h). To quench the reaction, EtOAc (5 mL) was added and concentrated to *vacuo*. Purification was carried out by column chromatography with EtOAc-Hexane system to give the desired product.

General Procedure for Nitration. In a 25 mL oven-dried round bottom flask was suspended polymeric **$(PhIO)_n$** (0.6 equiv) in acetonitrile at 23 ^{0}C. Then, $Al(NO_3)_3$ (0.8 equiv) was added and stirred for 10 min. Then, the corresponding *N*-tosyl aniline (1.0 equiv) was incorporated in one portion. The reaction was stirred at 23 or 50 ^{0}C for a period 1- 4 h until the starting *N*-tosylaniline was fully consumed judging its advance by TLC. To quench the reaction, EtOAc (5 mL) was added and concentrated to *vacuo*. Purification was carried out by column chromatography with EtOAc-Hexane system to give the desired product.

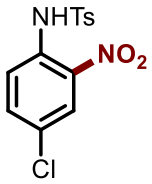
N-(2,4-dichlorophenyl)-4-methylbenzenesulfonamide (**331**).[160]



The following compound was obtained according to the general procedure for chlorination starting from 4-methyl-*N*-phenylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **331,**

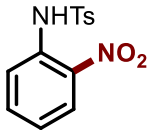
(29.1 mg, 76%). From 4-chloro-*N*-tosyl aniline (28 mg, 83%) gram scale (812 mg, 73%) as a white solid. m.p. = 118-120 ^{0}C. IR (neat) v/cm^{-1} = 3252, 1469, 1330, 1160, 810, 666. ^{1}H ($CDCl_3$, 500 MHz) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.26 (s, 1H), 7.23 (d, *J* = 6.1 Hz, 2H), 7.21 (dd, *J* = 9.5, 2.3 Hz, 1H) 6.89 (s, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 144.6, 135.7, 132.4, 130.9, 129.9, 129.2, 128.3, 127.4, 125.9, 123.4, 27.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}Cl_2NO_2S$ $[M+H]^+$= 315.9966, found 315.9966.

N-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide (**332**).[174,176]



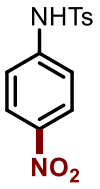
The following compound was obtained according to the general procedure for nitration starting from *N*-(4-chlorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **332,** (30 mg, 86%), gram scale (393 mg, 34%). From 2-nitro-*N*-tosyl aniline (25 mg, 22%) as a yellow solid. m.p. = 98-102 ^{0}C. IR (neat) *v*/cm^{-1}= 3306, 3085, 2925, 1345, 1168, 1086, 814. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.7 (s, 1H), 8.09 (d, *J* = 2.4, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.53 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.2, 137.3, 136.0, 135.5, 132.7, 130.2, 129.4, 127.4, 125.3, 122.5, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{11}ClN_2O_4S$ $[M+Na]^+$= 349.0026, found 349.0034.

4-methyl-*N*-(2-nitrophenyl)benzenesulfonamide (**333**).[176]



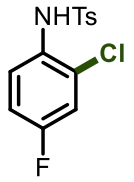
The following compound was obtained according to the general procedure for nitration starting from 4-methyl-*N*-phenylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **333,** (54.4 mg, 46%), as a yellow solid. m.p. = 98-99 ^{0}C. IR (neat) *v*/cm^{-1}= 3272, 1479, 1334, 1160, 910, 810, 650. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.02 (dd, *J*= 8.4, 1.5 Hz, 1H), 7.76 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.50 (td, *J* = 7.9, 1.5 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.07 (td, *J* = 7.8 Hz, 1.3 Hz, 1H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.9, 136.0, 134.12, 130.1, 129.6, 129.5, 127.3, 126.3, 123.3, 121.1, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{13}N_2O_4S$ $[M+H]^+$= 293.0596, found 293.0524.

4-methyl-*N*-(4-nitrophenyl)benzenesulfonamide (**334**). [176]



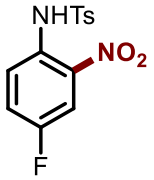
The following compound was obtained according to the general procedure for nitration starting from 4-methyl-*N*-phenylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (6-10% EtOAc/Hexane) to afford the product **334,** (47.3 mg, 40%), as a yellow solid. m.p. = 186-187 ^{0}C. IR (neat) ν/cm^{-1}= 3327, 1515, 1334, 1151, 900, 656. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 9.1 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 9.1 Hz, 2H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.6, 143.6, 143.5, 136.0, 130.0, 127.2, 125.3, 118.2, 21.6. HRMS (ESI+) m/z: calcd. for $C_{13}H_{13}N_2O_4S$ $[M+H]^+$= 293.0596, found 293.0597.

N-(2-chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (**335**).[160]



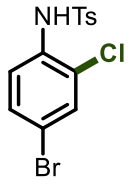
The following compound was obtained according to the general procedure for chlorination starting from *N*-(4-fluorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **335,** (27.4 mg, 81%), as a white solid. m.p. = 109-111 ^{0}C. IR (neat) ν/cm^{-1}= 3242, 1484, 1334, 1160, 806, 671. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.65 (dd, J = 8.8, 5.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.98 (m, 2H), 6.80 (s, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) d 159.8 (d, J= 249.3 Hz), 144.5, 135.8, 129.9 (d, J= 3.6 Hz), 129.8, 127.4, 127.0 (d, J= 10.9 Hz), 125.1 (d, J= 9.1 Hz), 116.8 (d, J= 25.9 Hz), 115.2 (d, J= 22.3 Hz), 21.7. ^{19}F NMR (500 MHz, $CDCl_3$) d/ppm: -114.22. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}ClFNO_2S$ $[M+H]^+$= 300.0261, found 300.0266.

N-(4-fluoro-2-nitrophenyl)-4-methylbenzenesulfonamide (**336**).



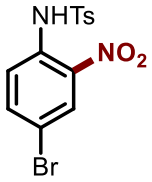
The following compound was obtained according to the general procedure for nitration starting from *N*-(4-fluorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2–4% EtOAc/Hexane) to afford the product **336,** (28.7 mg, 82 %), as a yellow solid. m.p. = 116-118 ^{0}C. IR (neat) ν/cm^{-1} = 3257, 1490, 1160, 881, 806, 650. ^{1}H NMR (500 MHz, $CDCl_3$) d 9.51 (s, 1H), 7.88 (dd, J = 9.2, 4.9 Hz, 1H), 7.78 (dd, J = 8.6, 3.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.34 (td, J = 7.9 Hz, 3.0 Hz, 1H), 7.24 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) d 157.9 (d, J= 249.7 Hz), 145.1, 138.0 (d, J= 8.2 Hz), 135.5, 130.2, 127.3, 124.0 (d, J= 8.2 Hz), 123.6 (d, J= 22.3 Hz), 113.0, 112.8, 21.7. ^{19}F NMR (500 MHz, $CDCl_3$) d/ppm: -114.67. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}FN_2O_4S$ $[M+H]^+$ 311.0502; found, 311.0471.

N-(4-bromo-2-chlorophenyl)-4-methylbenzenesulfonamide (**337**).[160]



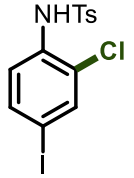
The following compound was obtained according to the general procedure for chlorination starting from *N*-(4-bromophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4 % EtOAc/Hexane) to afford the product **337**, (26.5 mg, 80%), as a white solid. m.p. = 115-117 ^{0}C. IR (neat) ν/cm^{-1}= 3257, 1469, 1330, 810, 746, 671. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 9.0, 2.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.95 (s, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.6, 135.7, 132.9, 132.0, 131.1, 129.9, 127.3, 126.3, 123.6, 118.1, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}BrClNO_2S$ $[M+H]^+$= 359.9461, found 359.9499.

N-(4-bromo-2-nitrophenyl)-4-methylbenzenesulfonamide (**338**).[176]



The following compound was obtained according to the general procedure for nitration starting from *N*-(4-bromophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4 % EtOAc/Hexane) to afford the product **338,** (29 mg, 85%), as a yellow solid. m.p. = 101-102 ^{0}C. IR (neat) ν/cm^{-1} = 3298, 1477, 1340, 1164, 1082, 816, 650. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.23 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.66 (dd, J = 9.0, 2.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.3, 138.8, 137.4, 135.5, 133.2, 130.3, 128.8, 127.4, 122.5, 116.2, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}BrN_2O_4S$ $[M+H]^+$= 370.9701, found 370.9765.

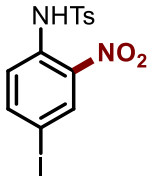
N-(2-chloro-4-iodophenyl)-4-methylbenzenesulfonamide (**339**).[160]



The following compound was obtained according to the general procedure for chlorination starting from *N*-(4-iodophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **339** (19 mg, 58%), as a white solid. m.p. = 118-120 ^{0}C. IR (neat) ν/cm^{-1} = 3232, 1469, 1330, 1160, 806, 666. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.57 (s, 1H), 7.52

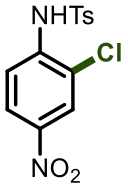
(d, J = 8.5, 1H), 7.39 (d, J = 8.7, 1H), 7.23 (d, J = 8.3 Hz, 2H), 6.94 (s, 1H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.6, 137.6, 137.0, 135.7, 133.6, 129.9, 127.4, 125.8, 123.5, 88.2, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}ClINO_2S$ $[M+H]^+$= 407.9322, found 407.9310.

N-(4-iodo-2-nitrophenyl)-4-methylbenzenesulfonamide (**340**).[174]



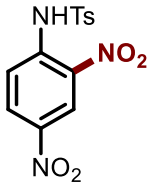
The following compound was obtained according to the general procedure for chlorination starting from *N*-(4-iodophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **340,** (43 mg, 39%), as yellow solid. m.p. = 157-159 ^{0}C. IR (neat) ν/cm^{-1} = 3257, 1469, 1334, 1160, 810, 656. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.8, 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 7.8, 2H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.2, 144.5, 137.2, 135.5, 134.6, 133.8, 130.2, 127.3, 122.4, 85.5, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}IN_2O_4S$ $[M+H]^+$= 418.9562, found 418.9622.

N-(2-chloro-4-nitrophenyl)-4-methylbenzenesulfonamide (**341**).[176]



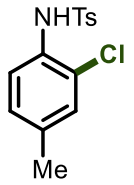
The following compound was obtained according to the general procedure for chlorination starting from 4-methyl-*N*-(4-nitrophenyl)benzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4 % EtOAc/Hexane) to afford the product **341,** (16 mg, 14%), as a white solid. m.p. = 157-158 ^{0}C. IR (neat) ν/cm^{-1} = 3287, 1510, 1334, 1160, 810, 656. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 2.6 Hz, 1H), 8.08 (dd, J = 9.4, 2.6 Hz, 1H), 7.76 (m, 3H), 7.45 (s, 1H), 7.29 (d, J = 8.2, 2H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.4, 143.6, 139.6, 135.3, 130.3, 127.4, 125.3, 123.6, 123.3, 118.8, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}ClN_2O_4S$ $[M+H]^+$= 327.0206, found 327.0229.

N-(2,4-dinitrophenyl)-4-methylbenzenesulfonamide (**342**).[174]



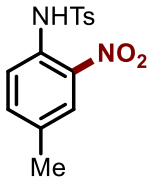
The following compound was obtained according to the general procedure for chlorination starting from 4-methyl-*N*-(4-nitrophenyl)benzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (4-8 % EtOAc/Hexane) to afford the product **13** (22 mg, 38%). From 4-methyl-*N*-(2-nitrophenyl)benzenesulfonamide (25.0 mg, 43%) as a light-yellowish white solid. m.p. = 154-156 ^{0}C. IR (neat) ν/cm^{-1} = 3251, 2922, 1620, 1348, 1169, 886. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 9.06 (d, J = 2.7 Hz, 1H), 8.39 (dd, J = 9.3, 2.7 Hz, 1H), 8.0 (d, J = 9.3 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.42 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 146.0, 141.9, 139.4, 135.1, 134.8, 130.5, 130.2, 127.6, 122.8, 119.6, 21.8. HRMS (ESI+) m/z: calcd. for $C_{13}H_{11}N_3O_6S$ $[M+Na]^+$= 360.0267, found 360.0259.

N-(2-chloro-4-methylphenyl)-4-methylbenzenesulfonamide (**343**).[160]



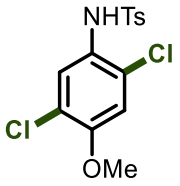
The following compound was obtained according to the general procedure for chlorination starting from 4-methyl-*N*-(*p*-tolyl)benzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **343** (35 mg, 62%), as a white solid. m.p. = 93-95 ^{0}C. IR (neat) ν/cm^{-1} = 3242, 1490, 1330, 1160, 806, 661. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.03 (m, 2H), 6.81 (s, 1H), 2.37 (s, 3H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.2, 136.5, 136.1, 130.9, 129.8, 129.8, 128.7, 127.4, 125.4, 123.0, 21.7, 20.8. HRMS (ESI+) m/z: calcd. for $C_{14}H_{15}ClNO_2S$ $[M+H]^+$= 296.0512, found 296.0545.

4-methyl-*N*-(4-methyl-2-nitrophenyl)benzenesulfonamide (**344**).[176]



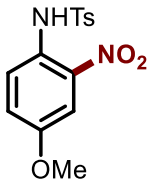
The following compound was obtained according to the general procedure for nitration starting from 4-methyl-*N*-(*p*-tolyl)benzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4% EtOAc/Hexane) to afford the product **344,** (31 mg, 53%), as a yellow solid. m.p. = 148-149 ^{0}C. IR (neat) ν/cm^{-1} = 3277, 1525, 1160, 881, 810, 650. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.87 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.39 (dd, J = 8.5, 2.1 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 2.37 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.7, 137.4, 136.8, 135.8, 134.6, 131.4, 130.0, 127.3, 126.0, 121.7, 21.7, 20.6. HRMS (ESI+) m/z: calcd. for $C_{14}H_{15}N_2O_4S$ $[M+H]^+$= 307.0753, found 307.0717.

N-(2,5-dichloro-4-methoxyphenyl)-4-methylbenzenesulfonamide (**345**).



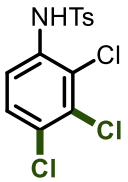
The following compound was obtained according to the general procedure for chlorination starting from *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4 % EtOAc/Hexane) to afford the product **345,** (36 mg, 58%), as a white solid. m.p. = 132-134 ^{0}C. IR (neat) ν/cm^{-1} = 3252, 1490, 1330, 1165, 1080, 810, 666. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.78 (s, 1H), 6.64 (s, 1H), 3.82 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.2, 144.4, 135.8, 129.8, 127.4, 126.8, 125.9, 125.4, 122.1, 112.6, 56.7, 21.7. HRMS (ESI+) m/z: calcd. for $C_{14}H_{14}Cl_2NO_3S$ $[M+H]^+$= 346.0071, found 346.0093.

N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide (**346**).[176]



The following compound was obtained according to the general procedure for nitration starting from *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-4 % EtOAc/Hexane) to afford the product **346,** (63 mg, 54%), as a yellow solid. m.p. = 101-102 ^{0}C. IR (neat) ν/cm^{-1} = 3252, 1490, 1275, 1155, 885, 646. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.79 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 3.0 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.18 (dd, J = 9.1, 3.0 Hz, 1H), 3.81 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.3, 144.7, 139.1, 135.6, 130.0, 127.2, 126.7, 124.9, 123.2, 109.1, 56.0, 21.7. HRMS (ESI+) m/z: calcd. for $C_{14}H_{15}N_2O_5S$ $[M+H]^+$= 323.0702, found 323.0676.

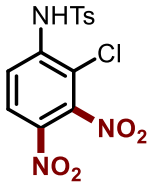
4-methyl-*N*-(2,3,4-trichlorophenyl)benzenesulfonamide (**347**).



The following compound was obtained according to the general procedure for chlorination starting from *N*-(2-chlorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (1-2% EtOAc/Hexane) to afford the product **347,** (22 mg, 72%), as white-solid. m.p. = 121-123 ^{0}C. IR (neat) ν/cm^{-1} = 3257, 1450, 1165, 941, 806, 661. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 9.0 Hz,

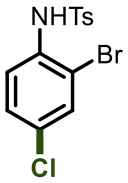
1H), 7.33 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.9, 135.6, 133.8, 132.0, 130.1, 130.0, 128.8, 127.3, 125.0, 120.0, 217. HRMS (ESI+) m/z: calcd for $C_{13}H_{11}Cl_3NO_2S$ $[M+H]^+$= 349.9576, found 349.9551.

N-(2-chloro-3,4-dinitrophenyl)-4-methylbenzenesulfonamide (**348**).



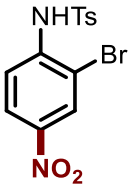
The following compound was obtained according to the general procedure for nitration starting from *N*-(2-chlorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (6-10% EtOAc/Hexane) to afford the product **348** (23 mg, 40%), as white-solid. m.p. = 114-118 ^{0}C. IR (neat) ν/cm^{-1} = 3226, 1593, 1330, 1162, 1088, 943, 825. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.66 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.11 (dd, J = 8.9, 2.4 Hz, 1H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.4, 143.3, 141.6, 135.2, 130.4, 129.4, 127.6, 127.4, 121.1, 116.9, 21.8. HRMS (ESI+) m/z: calcd. for $C_{13}H_{10}ClN_3O_6S$ $[M+Na]^+$ = 393.9877, found 393.9871.

N-(2-bromo-4-chlorophenyl)-4-methylbenzenesulfonamide (**349**).[190]



The following compound was obtained according to the general procedure for chlorination starting from *N*-(2-bromophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-6% EtOAc/Hexane) to afford the product **349,** (29.5 mg, 53%), as white-solid. m.p. = 119-120 ^{0}C. IR (neat) ν/cm^{-1} = 3252, 1465, 1330, 1160, 1085, 806, 656. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 3H), 7.40 (d, J = 2.3 Hz, 1H), 7.23 (m, 3H), 6.91 (s, 1H), 2.38 (s, 3H).). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.6, 135.7, 133.6, 132.2, 131.1, 129.9, 128.8, 127.4, 123.5, 116.2, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}BrClNO_2S$ $[M+H]^+$= 359.9461, found 359.9493.

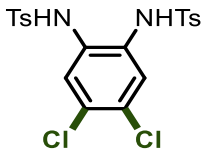
N-(2-bromo-4-nitrophenyl)-4-methylbenzenesulfonamide (**350**).[176]



[190] M. E. Krolski, A. F. Renaldo, D. E. Rudisill, J. K. Stille, *J. Org. Chem.* **1998**, *53*, 1170-1176.

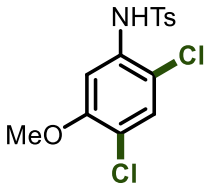
The following compound was obtained according to the general procedure for nitration starting from *N*-(2-bromophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2-6% EtOAc/Hexane) to afford the product **350,** (24 mg, 76%), as a yellowish brown solid. m.p. = 133-134 ^{0}C. IR (neat) ν/cm^{-1} = 3287, 2918, 1479, 1155, 1085, 895, 656. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 9.1, 2.4 Hz, 1H), 7.75 (m, 3H), 7.42 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.4, 143.8, 140.8, 135.3, 130.2, 128.5, 127.5, 124.2, 118.2, 113.8, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}BrN_2O_4S$ $[M+H]^+$= 370.9701, found 370.9689.

N,N′-(4,5-dichloro-1,2-phenylene)bis(4 methylbenzenesulfonamide) (**351**).



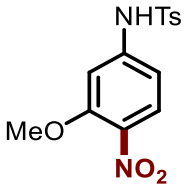
The following compound was obtained according to the general procedure for chlorination starting from *N,N′*-(1,2-phenylene)bis(4-methylbenzenesulfonamide). The crude material was purified by flash column chromatography over silica gel with the system (12-18% EtOAc/Hexane) to afford the product **351,** (42 mg, 72%), as a white solid. m.p. = 196-197 ^{0}C. IR (neat) ν/cm^{-1} = 3247, 3213, 1475, 1320, 1155, 1085, 800, 716. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 4H), 7.27 (d, J = 8.2 Hz, 4H), 7.06 (s, 2H), 6.87 (s, 2H), 2.42 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.9, 135.0, 131.0, 130.2, 129.9, 127.6, 127.1, 21.7. HRMS (ESI+) m/z: calcd. for $C_{20}H_{19}Cl_2N_2O_4S_2$ $[M+H]^+$= 485.0163, found 485.0188.

N-(2,4-dichloro-5-methoxyphenyl)-4 methylbenzenesulfonamide (**352**).



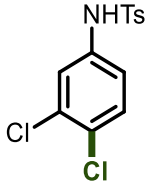
The following compound was obtained according to the general procedure for chlorination starting from *N*-(3-methoxyphenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (6-10% EtOAc/Hexane) to afford the product **352,** (54 mg, 86%), as a white solid. m.p. = 192-195 ^{0}C. IR (neat) ν/cm^{-1} = 3263, 1479, 1330, 1155, 1080, 870, 661. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.23 (m, 3H), 6.88 (s, 1H), 3.90 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.6, 144.7, 135.6, 133.0, 129.96, 129.94, 127.3, 119.4, 116.3, 106.4, 56.7, 21.7. HRMS (ESI+) m/z: calcd. for $C_{14}H_{14}Cl_2NO_3S$ $[M+H]^+$= 346.0071, found 346.0051.

N-(3-methoxy-4-nitrophenyl)-4-methylbenzenesulfonamide (**353**).[178]



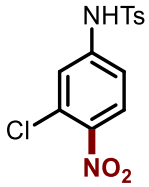
The following compound was obtained according to the general procedure for nitration starting from *N*-(3-methoxyphenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (4-8% EtOAc/Hexane) to afford the product **353,** (20 mg, 34%), as a light-yellow solid. m.p. = 133-135 ^{0}C. IR (neat) ν/cm^{-1} = 3245, 2923, 1582, 1278, 1085, 816, 648. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.10 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.27 (m, 3H), 6.59 (dd, J = 9.4, 2.6 Hz, 1H), 3.87 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.4, 145.0, 136.9, 135.8, 130.1(x2), 128.6, 127.5, 110.6, 103.5, 56.2, 21.7. HRMS (ESI+) m/z: calcd. for $C_{14}H_{15}N_2O_5S$ $[M+H]^+$ 323.0702, found 323.0695.

N-(3,4-dichlorophenyl)-4-methylbenzenesulfonamide (**354**).



The following compound was obtained according to the general procedure for chlorination starting from *N*-(3-chlorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2–4% EtOAc/Hexane) to afford the product **354,** (46 mg, 82%), as a white solid. m.p. = 114-116 ^{0}C. IR (neat) ν/cm^{-1} = 3257, 1475, 1335, 1167, 1090, 813, 768. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.21 (m, 4H), 6.90 (s, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.6, 135.7, 132.4, 130.9, 129.9, 129.2, 128.3, 127.3, 125.9, 123.4, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}Cl_2NO_2S$ $[M+H]^+$ = 315.9966, found 315.9965.

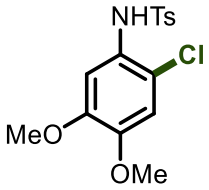
N-(3-chloro-4-nitrophenyl)-4-methylbenzenesulfonamide (**355**).[176]



The following compound was obtained according to the general procedure for nitration starting from *N*-(3-chlorophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2–6% EtOAc/Hexane) to afford the product **355,** (27 mg, 59%), as aa yellowish-brown solid. m.p. = 165-168 ^{0}C. IR (neat) ν/cm^{-1} = 3342, 3078, 1590, 1469, 1334, 1160, 1035, 810, 656. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 2.5 Hz, 1H), 8.08 (dd, J = 9.1, 2.6 Hz, 1H), 7.76 (m, 3H), 7.44 (s, 1H), 7.29 (d, J = 8.3 Hz, 2H),

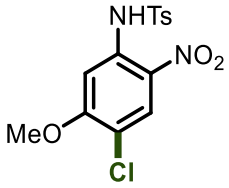
2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 145.4, 143.6, 138.6, 135.4, 130.2, 127.4, 125.3, 123.6, 123.3, 118.8, 21.7. HRMS (ESI+) m/z: calcd. for $C_{13}H_{12}ClN_2O_4S$ $[M+H]^+$ = 327.0206, found 327.0290.

N-(2-chloro-4,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (**356**).



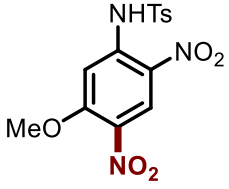
The following compound was obtained according to the general procedure for chlorination starting from *N*-(3,4-dimethoxyphenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (4–8% EtOAc/Hexane) to afford the product **356,** (12 mg, 35%), as a whitish-brown solid. m.p. = 195-198 ^{0}C. IR (neat) ν / cm^{-1} = 3252, 2932, 1504, 1334, 1155, 985, 806, 666. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.23 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 6.67 (s, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 148.5, 147.4, 144.2, 135.8, 129.7, 127.4, 126.2. 117.6, 111.7, 108.0, 56.4, 56.3, 21.7. HRMS (ESI+) m/z: calcd. for $C_{15}H_{17}ClNO_4S$ $[M+H]^+$ = 342.0567, found 342.0598.

N-(4-chloro-5-methoxy-2-nitrophenyl)-4 methylbenzenesulfonamide (**357**).



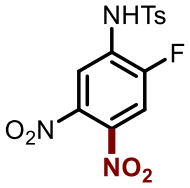
The following compound was obtained according to the general procedure for chlorination starting from *N*-(5-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2–4% EtOAc/Hexane) to afford the product **357,** (22 mg, 51%), as a yellow-solid. m.p. = 196-198 ^{0}C. IR (neat) ν/cm^{-1} = 3252, 2917, 2850, 1567, 1245, 1156, 818, 724. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.17 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 7.28 (d, J = 8.2 Hz, 2H), 3.98 (s, 3H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 160.7, 145.3, 135.6, 135.4, 130.2, 129.7, 127.8, 127.4, 118.1, 102.3, 57.2, 21.7. HRMS (ESI+) m/z: calcd. for $C_{14}H_{13}ClN_2O_5S$ $[M+Na]^+$= 379.0132, found 379.0124.

N-(5-methoxy-2,4-dinitrophenyl)-4-methylbenzenesulfonamide (**358**).[178]



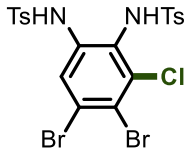
The following compound was obtained according to the general procedure for nitration starting from *N*-(5-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2–6% EtOAc/Hexane) to afford the product **358,** (22 mg, 42%), as white-solid. m.p. 161-163 ^{0}C. IR (neat) ν/cm^{-1}= 3250, 2924, 2854, 1588, 1273, 1177, 828, 745. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.86 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.74 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.04 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.4, 146.1, 139.9, 135.2, 133.4, 130.5, 128.7, 127.5, 126.0, 102.2, 57.6, 21.8. HRMS (ESI+) m/z: calcd. for $C_{14}H_{13}N_3O_7S$ $[M+Na]^+$= 390.0372, found 390.0365.

N-(2-fluoro-4,5-dinitrophenyl)-4-methylbenzenesulfonamide (**359**).



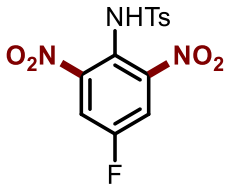
The following compound was obtained according to the general procedure for nitration starting from *N*-(2-fluoro-5-nitrophenyl)-4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (2–6% EtOAc/Hexane) to afford the product **359,** (28 mg, 54%), as a white solid. m.p. = 198-201 ^{0}C. IR (neat) ν/cm^{-1} = 3263, 2922, 1510, 1341, 1157, 1089, 868, 745. ^{1}H NMR (500 MHz, CD_3CN) d 8.12 (d, *J* = 6.8 Hz, 1H), 7.84 (d, *J* = 9.6 Hz, 1H), 7.79 (d, *J* = 8.4, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CD_3CN) d 154. (d, *J*= 257.5 Hz), 146.5, 136.7, 132.4 (d, *J*= 13.6 Hz), 131.1, 130.5, 128.0, 127.2, 117.5 (d, *J*= 3.1 Hz), 115.0 (d, *J*= 26.8 Hz), 21.5. ^{19}F NMR (500 MHz, CD_3CN) d/ppm: -117.14. HRMS (ESI+) m/z: calcd. for $C_{13}H_{10}FN_3O_6S$ $[M+Na]^+$= 378.0172, found 378.0167.

N,N′-(4,5-dibromo-3-chloro-1,2-phenylene)bis(4 methylbenzenesulfonamide) (**360**).



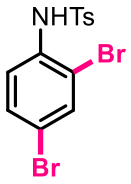
The following compound was obtained according to the general procedure for nitration starting from *N,N′*-(4,5-dibromo-1,2-phenylene)bis(4-methylbenzenesulfonamide. The crude material was purified by flash column chromatography over silica gel with the system (12–18% EtOAc/Hexane) to afford the product **360,** (38 mg, 71%), as a light brown-solid. m.p. = 174-176 ^{0}C. IR (neat) ν/cm^{-1} = 3222, 2922, 1444, 1555, 1085, 808, 658. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.96 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.02 (s, 1H), 2.41 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.6, 144.6, 136.24, 135.9, 134.2, 133.9, 130.0, 129.9, 127.8, 127.6, 125.9, 125.8, 124.6, 121.5, 21.8, 21.7. HRMS (ESI+) m/z: calcd. for $C_{20}H_{18}Br_2ClN_2O_4S_2$ $[M+H]^+$= 606.8763, found 606.8746.

N-(4-fluoro-2,6-dinitrophenyl)-4-methylbenzenesulfonamide (**361**).



The following compound was obtained according to the general procedure for nitration starting from *N*-(4-fluoro-2-nitrophenyl)-4-methylbenzenesulfonamide **7**. The crude material was purified by flash column chromatography over silica gel with the system (6–10 % EtOAc/Hexane) to afford the product **361,** (17 mg, 49%), as a white solid. m.p. = 165-167 ^{0}C. IR (neat) ν/cm^{-1} = 3238, 3082, 2913, 1535, 1334, 1160, 810, 675. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (s, 1H), 7.89 (d, J = 6.9 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.25 (d, J= 8.3 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.9 (d, J= 258.4 Hz), 147.5, 145.8, 134.2, 130.5, 127.2, 122.0 (d, J= 4.5 Hz), 117.9 (d, J= 26.8 Hz), 21.8. HRMS (ESI+) m/z: calcd. for $C_{13}H_{11}FN_3O_6S$ $[M+H]^+$= 356.0353, found 356.0340.

N-(2,4-dibromophenyl)-4-methylbenzenesulfonamide (**363**).[160]



A 25 mL oven-dried round bottom flask equipped with a magnetic stirrer bas was charged with PIDA (Diacetoxyiodo)benzene (3.0 equiv) and acetonitrile (0.3 *M*) at 25 ^{0}C. After dissolving and obtaining homogeneous mixture, $AlBr_3$ (6.0 equiv) was added and stirred for 10 min. Then, the corresponding *N*-tosyl aniline (1.0 equiv) was added and stirred at 25 ^{0}C until fully consumption of the starting material (usually 48 to 60 h). To quench the reaction, EtOAc (5 mL) was added and concentrated to *vacuo*. Purification was carried out by column chromatography to give the desired product **363**. The crude material was purified by flash column chromatography over silica gel with the system (0-2 % EtOAc/Hexane) to afford the product **363** (57 mg, 35%), as a white solid. Spectral data were identical to those previously reported.[160]
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 2H), 7.55 (m, 2H), 7.39 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 6.92 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 135.7, 134.9, 134.1, 131.8, 129.9, 127.4, 123.7, 118.4, 116.3, 21.7.

Computational Techniques. All the gas-phase theoretical calculations were performed using the Gaussian09 program.[191] First, carried out geometry optimizations, with no restrictions, using the range-divided ωB97X-D[192] density functional in combination with the Aldrich's basis set def2-svpp.[193] A subsequent harmonic frequency calculation, for each optimized geometry, was done to corroborate the character of each critical point in the potential energy surface (PES): reactants, intermediates and products must present all the frequencies as positive whereas transition state must have one and just one negative frequency. Thermal and entropy corrections to the total energy were taken from the thermochemistry analysis in the output file at 298K and 1 atm. Also, we performed calculations for including the solvent effect through the PCM model[194] using the SMD parameters[195] according to the Truhlars model using acetonitrile (ε = 35.688) as solvent. These calculations were performed as single points of the optimized geometry at the level of theory mentioned above. Other single-point calculations were run using a more robust basis set, def2-tzvpd, to improve the accuracy of the calculated electronic energies. The obtained energies were added to the gas-phase calculations and were reported as our final values.

[191] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B. and Fox, D. J. Gaussian 16, Revision C.01, Gaussian, Inc., Wallingford CT, 2019.

[192] Chai, J.-D. and Head–Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615-6620.

[193] Weigend F. and Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305.

[194] a) Barone, V. and Cossi, M. *J. Phys. Chem. A.* **1998**, *102*, 1995-2001. b) Cossi, M.; Barone, V.; Mennucci, B. and Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253-260. c) Barone, V.; Cossi, M. and Tomasi, J. *J. Comp. Chem.* **1998**, *19*, 404-417. d) Tomasi, J.; Mennucci, B. and Cammi, R. *Chem. Rev.* **2005**, *105*, 2999-3094.

[195] Marenich, A. V.; Cramer, C. J. and Truhlar, D. G.. *J. Phys. Chem. B,* **2009**, *113*, 6378-6396.

DFT Calculations for chlorination reaction

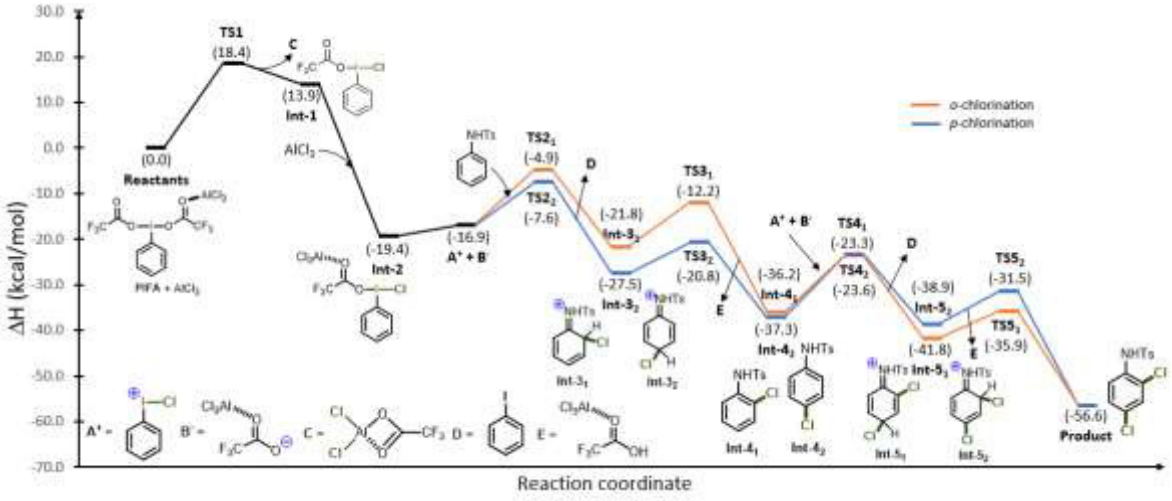


Figure S1. Energy profile (enthalpy scale) for the chlorination reaction calculated at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level.

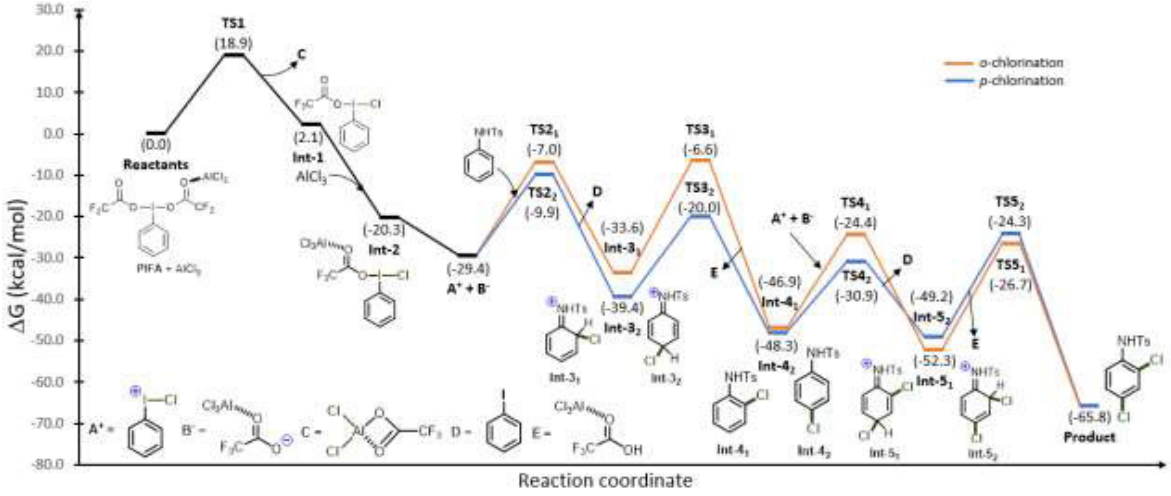


Figure S2. Energy profile (Gibbs free energy scale) for the chlorination reaction calculated at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level.

Table S1. Cartesian coordinates (in x-y-z format) of all the optimized structures involved in the reaction mechanisms calculated at the ωB97X-D/def2-svpp level.

Chlorination mechanism

PIFA_$AlCl_3$

E(scf) = −3203.17089354 a.u.

I	-0.682430	-0.139318	-0.571435
C	-1.071509	1.602396	0.528278
C	-1.798373	2.639602	-0.053397
C	-0.547573	1.663672	1.819214
C	-2.009564	3.788353	0.707316
H	-2.205296	2.552426	-1.062501
C	-0.769866	2.826243	2.555976
H	0.025921	0.833099	2.242411
C	-1.497226	3.880481	2.002440
H	-2.579519	4.616874	0.279097
H	-0.369927	2.901947	3.570273
H	-1.667419	4.787667	2.588435
O	-2.511366	-0.976293	-0.051374
O	1.254527	0.992378	-1.046015
C	-3.588421	-0.481893	-0.624925
C	2.431027	0.847764	-0.661901
O	-3.640636	0.430770	-1.398670
O	2.934397	-0.080208	-0.002461
C	3.369978	2.027261	-1.020033
C	-4.844903	-1.250813	-0.145131
Al	2.661533	-1.834515	0.560771
Cl	4.568456	-2.660962	0.889294
Cl	1.584576	-2.634587	-1.126411
Cl	1.418483	-1.596072	2.288371
F	-4.977845	-1.122004	1.170711
F	-5.924708	-0.768743	-0.732193
F	-4.734159	-2.540447	-0.439523
F	4.636629	1.698430	-0.861740
F	3.173224	2.407506	-2.273503
F	3.083804	3.048202	-0.213961

TS1

E(scf) = −3203.13626369 a.u.

ν_{min} = −62.4 cm^{-1}

I	-0.644631	0.392073	0.601788
C	-1.590109	2.121773	-0.113893
C	-1.783156	2.234212	-1.494338
C	-1.975541	3.128540	0.775759
C	-2.384727	3.389631	-1.988230
H	-1.478460	1.430588	-2.170047
C	-2.574875	4.276405	0.262350
H	-1.812605	3.025332	1.851767
C	-2.777773	4.403782	-1.113240
H	-2.546401	3.495925	-3.063959
H	-2.883486	5.075590	0.941190
H	-3.248388	5.307949	-1.508986
O	-2.409098	-0.574462	0.902120
O	1.913331	1.501788	0.440240
C	-2.979902	-1.096067	-0.180083
C	2.952174	0.879555	0.311992
O	-2.615212	-0.979683	-1.307973
O	3.113172	-0.366812	0.086989
C	4.298774	1.633584	0.433828
C	-4.250850	-1.876938	0.241550
Al	2.348661	-1.842620	-0.570152
Cl	3.650633	-3.475076	-0.540267
Cl	1.260507	-1.317527	-2.302134
Cl	0.491660	-2.246350	1.264735
F	-5.112198	-1.044939	0.820066
F	-4.819670	-2.410523	-0.821247
F	-3.940157	-2.836555	1.098659
F	5.001080	1.480133	-0.684700
F	4.105945	2.925620	0.639664
F	5.001996	1.140430	1.447821

$AlCl_3$

E(scf) = −1622.72010132 a.u.

Al	-0.000088	-0.000020	-0.000004
Cl	0.993808	1.828144	0.000001
Cl	-2.080107	-0.053433	0.000001
Cl	1.086366	-1.774696	0.000001

Tolylaniline

E(scf) = −1105.63523265 a.u.

C	3.034003	-2.506001	0.074328
C	2.277732	-2.339113	-1.085290
C	1.723631	-1.096614	-1.386688
C	1.947992	-0.003803	-0.542347
C	2.719850	-0.165112	0.613642
C	3.246441	-1.417381	0.921601
H	3.461129	-3.483106	0.316258
H	2.104026	-3.185060	-1.756397
H	3.845334	-1.538503	1.828793
N	1.391259	1.262894	-0.852715
H	1.148729	1.407167	-1.829775
S	0.223445	1.955840	0.139701
O	-0.231348	3.121577	-0.593236
O	0.784291	2.041782	1.473417
C	-1.093670	0.759264	0.178172
C	-1.035909	-0.301413	1.081976
C	-2.135380	0.863861	-0.741952
C	-2.033589	-1.271145	1.049330
H	-0.218716	-0.361408	1.804567
C	-3.127610	-0.112550	-0.755444
H	-2.169901	1.712293	-1.430113
C	-3.092408	-1.193587	0.135075
H	-1.988787	-2.107274	1.753929
H	-3.950329	-0.030311	-1.472524
C	-4.186267	-2.229889	0.135869
H	-4.977949	-1.957014	0.857134
H	-4.658357	-2.319885	-0.856011
H	-3.801474	-3.221034	0.427107
H	2.893483	0.695559	1.261459
H	1.106425	-0.971095	-2.281731

C

E(scf) = −1688.32437511 a.u.

O	-0.205966	-0.011157	1.066004
C	-0.848090	-0.012765	-0.018136
O	-0.195039	-0.009431	-1.092954
C	-2.386043	-0.004718	-0.004635
Al	1.391688	-0.000539	0.000960
Cl	2.394140	-1.826191	0.001260
Cl	2.365753	1.840634	0.001840
F	-2.864028	-0.101259	-1.228813
F	-2.821818	-1.023787	0.719209
F	-2.802740	1.128499	0.541497

Int1

E(scf) = −1514.80979013 a.u.

I	-0.766507	-1.191259	-0.078650
C	-1.300678	0.851445	-0.048933
C	-2.125708	1.325786	-1.065141
C	-0.838071	1.652696	0.990128
C	-2.492758	2.669928	-1.037299
H	-2.490655	0.668507	-1.857663
C	-1.215045	2.996652	0.992262
H	-0.182329	1.250934	1.765574
C	-2.037092	3.502181	-0.013819
H	-3.138723	3.065980	-1.825279
H	-0.860608	3.647955	1.795491
H	-2.328243	4.555932	-0.000503
O	1.268491	-0.543189	-0.593573
C	2.042482	-0.147262	0.364763
O	1.768803	-0.002509	1.531753
C	3.465977	0.158973	-0.165306
F	4.263708	0.552112	0.815048
F	3.996612	-0.924616	-0.730366
F	3.418630	1.126094	-1.081064
Cl	-3.104594	-1.795984	0.332523

Int2

E(scf) = −3137.59762171 a.u.

I	-1.168454	-1.006857	-0.687468
C	-2.447087	0.326102	0.319468
C	-3.615607	0.761443	-0.299798
C	-2.061068	0.734284	1.593741
C	-4.432772	1.648011	0.399594
H	-3.893971	0.421350	-1.300094
C	-2.890569	1.629235	2.269091
H	-1.135948	0.371443	2.051997
C	-4.069490	2.081084	1.675892
H	-5.356739	2.005588	-0.062225
H	-2.609477	1.968332	3.269399
H	-4.714669	2.780124	2.214679
O	0.084445	1.012079	-0.881649
C	1.206529	1.432312	-0.572548
O	2.165204	0.823593	-0.043591
C	1.460081	2.940798	-0.817675
Al	2.578578	-0.876610	0.552789

A^+

E(scf) = −988.884234671 a.u.

I	-1.123771	-0.588120	0.001253
C	0.910888	-0.158102	0.000382
C	1.561149	-0.031426	-1.234027
C	1.561049	-0.025483	1.234206
C	2.927250	0.231740	-1.217079
H	1.029180	-0.132970	-2.183270
C	2.927144	0.237636	1.216088
H	1.029010	-0.122510	2.183881
C	3.602903	0.365315	-0.000782
H	3.465914	0.334032	-2.162374
H	3.465726	0.344538	2.160921
H	4.676086	0.573509	-0.001227
Cl	-2.061667	1.556216	-0.003356

B^-

E(scf) = −2148.55209093 a.u.

O	-1.345897	-1.740760	0.000192

Cl	4.636153	-0.901087	0.997129
Cl	1.988606	-2.103006	-1.125332
Cl	1.249412	-1.131258	2.220651
F	2.710498	3.158022	-1.188007
F	0.648098	3.415471	-1.748910
F	1.229179	3.594787	0.320401
Cl	-2.701812	-2.823883	-0.526579
C	-1.362357	-0.537077	0.000315
O	-0.380987	0.297198	0.000299
C	-2.717222	0.215679	0.000032
Al	1.414564	0.048494	0.000014
Cl	2.226130	2.044016	-0.000612
Cl	1.965752	-1.006141	-1.791061
Cl	1.966624	-1.005305	1.791274
F	-2.836533	0.996536	-1.078934
F	-3.747939	-0.627496	0.000065
F	-2.836796	0.996823	1.078933

TS21

E(scf) = −2094.55305028 a.u.

ν_{min} = −178.6 cm^{-1}

C	0.780807	-3.783938	0.185001
C	0.172303	-3.013265	1.126139
C	0.425696	-1.593571	1.180016
C	1.446776	-1.019214	0.306573
C	2.021921	-1.845302	-0.693658
C	1.695365	-3.178528	-0.732138
H	0.579648	-4.855130	0.120112
H	-0.538297	-3.435550	1.840634
H	2.159898	-3.805255	-1.499133
N	1.783162	0.261963	0.498603
H	1.294372	0.795691	1.216422
S	2.761839	1.319106	-0.510330
O	2.391545	2.606665	0.023435
O	2.518050	0.916684	-1.874967
C	4.404035	0.900805	-0.042183
C	5.199797	0.159292	-0.915243
C	4.892837	1.356921	1.185370
C	6.502010	-0.149362	-0.533573
H	4.815015	-0.151474	-1.889587
C	6.193660	1.033267	1.546249
H	4.269605	1.969126	1.842185
C	7.018525	0.277032	0.697244
H	7.134509	-0.726110	-1.214280
H	6.585194	1.385470	2.504907
C	8.438639	-0.028446	1.087128
H	9.093153	0.825184	0.834420
H	8.529402	-0.203852	2.171190
H	8.824359	-0.912541	0.555747

TS22

E(scf) = −2094.55536044 a.u.

ν_{min} = −186.0 cm^{-1}

C	-0.135005	1.452148	-1.033173
C	0.245944	0.713526	-2.215704
C	1.297746	-0.147411	-2.193349
C	2.075729	-0.315675	-0.997028
C	1.745193	0.441650	0.174286
C	0.691752	1.303955	0.142753
H	-0.707700	2.375753	-1.156381
H	-0.339601	0.844567	-3.129297
H	0.438187	1.885001	1.033220
N	3.098254	-1.178528	-1.029134
H	3.268096	-1.704404	-1.885807
S	4.214032	-1.669281	0.242022
O	4.817717	-2.825482	-0.371215
O	3.441152	-1.716429	1.460038
C	5.354380	-0.331901	0.302699
C	5.301934	0.568833	1.366351
C	6.320436	-0.222564	-0.701903
C	6.222417	1.611901	1.404895
H	4.568899	0.441799	2.166588
C	7.225552	0.828419	-0.644332
H	6.374007	-0.958645	-1.508166
C	7.193106	1.761235	0.405426
H	6.192249	2.319006	2.238648
H	7.985469	0.921904	-1.425472
C	8.208863	2.868387	0.472426
H	9.150054	2.493285	0.913251
H	8.447006	3.256593	-0.531034
H	7.858062	3.704528	1.097329

H	2.720638	-1.425825	-1.415280	H	2.319024	0.304626	1.089224
H	0.205818	-1.066620	2.113871	H	1.565653	-0.720282	-3.084999
I	-3.560632	0.370834	-1.364167	I	-4.209627	-1.269310	0.458074
C	-4.858212	0.429417	0.290488	C	-5.582592	0.306396	0.214460
C	-5.653863	-0.683043	0.567444	C	-5.817530	1.171862	1.283416
C	-4.905734	1.583914	1.073036	C	-6.238165	0.451446	-1.008668
C	-6.517519	-0.630378	1.661061	C	-6.734631	2.208886	1.114575
H	-5.611283	-1.578631	-0.057004	H	-5.301561	1.044235	2.238040
C	-5.776368	1.616878	2.161966	C	-7.151901	1.494470	-1.157709
H	-4.281891	2.450557	0.841403	H	-6.049166	-0.236235	-1.836425
C	-6.579216	0.514464	2.456100	C	-7.399823	2.370821	-0.100962
H	-7.150016	-1.492902	1.887334	H	-6.931312	2.891771	1.945388
H	-5.827688	2.516642	2.780836	H	-7.675786	1.616958	-2.109438
H	-7.261745	0.549399	3.309234	H	-8.120039	3.183834	-0.224330
Cl	-1.304957	-0.782370	0.011943	Cl	-1.885588	0.216724	-0.379884

Int31

E(scf) = −1565.40484274 a.u.

C	-3.742449	-2.192938	-0.349800
C	-3.812487	-1.359427	0.703348
C	-2.701451	-0.407383	0.997860
C	-1.700157	-0.188486	-0.118511
C	-1.638633	-1.159999	-1.161048
C	-2.625263	-2.100909	-1.261048
H	-4.523798	-2.933424	-0.533423
H	-4.633069	-1.397929	1.425218
H	-2.586467	-2.800404	-2.102079
N	-0.897817	0.844465	-0.017924
H	-1.102774	1.533702	0.712565
S	0.482091	1.370862	-1.060889
O	0.542032	2.762591	-0.706547
O	0.164221	0.879142	-2.377160
C	1.811955	0.476450	-0.358526
C	2.233444	-0.713544	-0.957039
C	2.440739	0.992436	0.779470
C	3.294988	-1.404411	-0.384449
H	1.758712	-1.080589	-1.870053
C	3.497397	0.281600	1.332476
H	2.121217	1.943658	1.212803
C	3.941939	-0.923490	0.764157
H	3.639008	-2.332823	-0.848749
H	3.999494	0.677446	2.219729

Int32

E(scf) = −1565.40863258 a.u.

C	-3.643146	1.242686	-0.273997
C	-3.422733	0.393572	-1.476663
C	-2.364986	-0.428391	-1.591978
C	-1.394196	-0.540594	-0.516210
C	-1.582900	0.226237	0.699554
C	-2.643275	1.048695	0.811806
Cl	-5.292766	0.935625	0.377546
H	-4.158546	0.468552	-2.283170
H	-2.801896	1.615390	1.734496
N	-0.366857	-1.343575	-0.688373
H	-0.304471	-1.876642	-1.558059
S	0.990211	-1.796997	0.425506
O	1.442883	-2.992660	-0.232509
O	0.415590	-1.761343	1.745727
C	2.113128	-0.475706	0.192266
C	2.187971	0.539617	1.148933
C	2.941849	-0.488493	-0.934799
C	3.098372	1.571547	0.952137
H	1.566595	0.510066	2.047153
C	3.839838	0.555505	-1.109166
H	2.898870	-1.311171	-1.653151
C	3.934499	1.599689	-0.174092
H	3.171552	2.367084	1.698856
H	4.494609	0.554577	-1.985108

C	5.116097	-1.656820	1.349533	C	4.944240	2.697896	-0.356322
H	6.056709	-1.256209	0.929984	H	5.920967	2.382304	0.053095
H	5.164176	-1.534290	2.443219	H	5.094386	2.934951	-1.421629
H	5.080289	-2.732568	1.116654	H	4.644407	3.617245	0.170451
H	-0.873150	-1.074422	-1.931443	H	-0.887958	0.096098	1.528115
Cl	-3.281159	1.120735	1.716862	H	-2.223335	-1.034344	-2.491083
H	-2.096116	-0.902016	1.789762	H	-3.633283	2.305708	-0.582274

TS31

E(scf) = −3714.07461184 a.u.

ν_{min} = −1565.1 cm^{-1}

C	-0.486461	-3.373273	-0.864952	C	0.347650	3.386236	-0.038273
C	-1.264585	-3.311048	0.264415	C	1.379447	3.400195	0.961739
C	-2.187994	-2.231678	0.432961	C	2.397524	2.491689	0.912702
C	-2.442173	-1.317882	-0.652951	C	2.499764	1.572832	-0.174294
C	-1.633830	-1.434465	-1.805247	C	1.569867	1.650590	-1.243977
C	-0.676519	-2.424897	-1.892283	C	0.562486	2.580858	-1.206183
H	0.281440	-4.142112	-0.964057	Cl	-0.686175	4.805000	-0.176987
H	-1.153325	-4.029587	1.079438	H	1.287749	4.091966	1.802824
H	-0.044212	-2.466057	-2.782145	H	-0.164282	2.632716	-2.020775
N	-3.390463	-0.349133	-0.504191	N	3.488018	0.646944	-0.131801
H	-3.999544	-0.405659	0.309502	H	4.121257	0.654986	0.663694
S	-3.357924	1.227469	-1.183425	S	3.679025	-0.798290	-1.071076
O	-4.507136	1.844253	-0.559543	O	4.964139	-1.271415	-0.608550
O	-3.227771	1.082934	-2.616564	O	3.417832	-0.443725	-2.447494
C	-1.866184	1.922832	-0.534019	C	2.388867	-1.822908	-0.452884
C	-0.758037	2.084480	-1.364304	C	1.171019	-1.892551	-1.130855
C	-1.834914	2.319947	0.803904	C	2.594394	-2.501445	0.749807
C	0.398058	2.650988	-0.838331	C	0.137460	-2.633221	-0.570789
H	-0.794913	1.771909	-2.409434	H	1.024184	-1.383626	-2.085533
C	-0.665472	2.875241	1.311593	C	1.542280	-3.226402	1.296466
H	-2.717832	2.209144	1.438734	H	3.565481	-2.460354	1.249480
C	0.467275	3.051174	0.501747	C	0.295613	-3.290198	0.657728
H	1.271246	2.766284	-1.485184	H	-0.816971	-2.704202	-1.098603
H	-0.632860	3.185294	2.359598	H	1.690589	-3.752488	2.243939
C	1.742433	3.634978	1.047022	C	-0.865823	-4.018312	1.273952
H	2.042083	4.525065	0.467978	H	-1.329628	-4.709241	0.551041
H	1.637799	3.927651	2.103103	H	-0.562452	-4.587996	2.166613
H	2.563705	2.900981	0.972825	H	-1.646143	-3.294518	1.565452
H	-1.789239	-0.735956	-2.627575	H	1.675616	0.997982	-2.109758
Cl	-3.283891	-2.254953	1.795407	H	3.131721	2.447198	1.721140
H	-1.006106	-1.176267	0.733260	H	-0.447205	2.503204	0.506334

TS32

E(scf) = −3714.09257564 a.u.

ν_{min} = −819.6 cm^{-1}

O	0.314302	-0.558410	0.334531	O	-1.419980	1.605909	0.774991
C	1.161121	-0.086167	1.102636	C	-1.336670	0.448589	1.204119
O	2.314078	0.254767	0.751795	O	-2.013771	-0.530155	0.813054
C	0.850387	0.034888	2.610702	C	-0.292885	0.143998	2.303613
Al	3.154459	-0.392114	-0.810070	Al	-3.086170	-0.563775	-0.733821
Cl	5.031017	0.585311	-0.740508	Cl	-3.589673	-2.627605	-0.905535
Cl	1.987872	0.101505	-2.541412	Cl	-1.702966	0.061687	-2.266833
Cl	3.116850	-2.503057	-0.448307	Cl	-4.714781	0.745703	-0.401559
F	1.287894	1.176887	3.111938	F	0.892344	-0.084813	1.722487
F	-0.464752	-0.050050	2.824572	F	-0.147791	1.192673	3.108336
F	1.437523	-0.968786	3.249249	F	-0.614645	-0.911022	3.024281

Int41

E(scf) = −1565.09200251 a.u.

C	-2.907862	2.241768	0.930347	C	3.280795	0.422856	0.123438
C	-2.126768	2.324879	-0.219828	C	2.502914	0.649606	1.257046
C	-1.598604	1.163004	-0.776481	C	1.387261	-0.149840	1.490238
C	-1.864274	-0.097180	-0.217051	C	1.062824	-1.191465	0.614942
C	-2.664539	-0.162613	0.929326	C	1.862216	-1.419892	-0.510601
C	-3.170353	0.998248	1.505996	C	2.961738	-0.605378	-0.763304
H	-3.315155	3.154293	1.373656	Cl	4.665979	1.431901	-0.186717
H	-1.910025	3.288374	-0.686026	H	2.760149	1.458306	1.944381
H	-3.788590	0.928058	2.404791	H	3.585257	-0.778245	-1.643202
N	-1.328597	-1.277469	-0.774623	N	-0.071549	-2.004095	0.855501
H	-1.068645	-1.201538	-1.756362	H	-0.396352	-2.032951	1.818771
S	-0.136439	-2.126149	0.068791	S	-1.384082	-1.972400	-0.200134
O	0.310162	-3.145831	-0.858707	O	-2.403179	-2.760323	0.464556
O	-0.681833	-2.440720	1.374400	O	-0.879839	-2.296848	-1.519663
C	1.164138	-0.933208	0.285144	C	-1.895690	-0.268486	-0.214046
C	1.111809	-0.047449	1.360319	C	-1.273931	0.630315	-1.080460
C	2.172161	-0.844474	-0.673667	C	-2.865506	0.158872	0.691513
C	2.080164	0.947580	1.462155	C	-1.626274	1.975506	-1.024548
H	0.321422	-0.140431	2.108887	H	-0.526173	0.275515	-1.793556
C	3.135288	0.151342	-0.550672	C	-3.208905	1.507391	0.728713
H	2.198431	-1.555337	-1.503272	H	-3.353024	-0.565068	1.349524
C	3.103121	1.063684	0.512807	C	-2.595707	2.435316	-0.123563
H	2.039536	1.648803	2.301236	H	-1.137257	2.684186	-1.699906
H	3.929992	0.223395	-1.299650	H	-3.974153	1.845879	1.434098
C	4.166098	2.122813	0.648043	C	-2.994605	3.888009	-0.098950
H	5.044056	1.724180	1.188148	H	-3.791730	4.082932	-0.839187
H	4.514836	2.471014	-0.338075	H	-3.380795	4.184358	0.889849
H	3.797388	2.994937	1.212059	H	-2.144095	4.543153	-0.349069

Int42

E(scf) = −1565.08965897 a.u.

H	-2.869598	-1.144305	1.358917	H	1.607960	-2.236368	-1.188220
Cl	-0.590550	1.275957	-2.196868	H	0.756083	0.043548	2.362691

TS41

E(scf) = −2554.00523729 a.u.

ν_{min} = −192.3 cm^{-1}

C	-0.233536	1.281143	-1.148226	C	-0.775258	3.425802	0.151031
C	0.154332	0.245598	-2.073398	C	-0.172024	2.682628	1.118740
C	1.197873	-0.579932	-1.793466	C	-0.400019	1.263645	1.174129
C	1.974764	-0.411147	-0.582374	C	-1.405999	0.661633	0.305519
C	1.628098	0.652792	0.311689	C	-1.972402	1.466562	-0.723527
C	0.579894	1.474085	0.028128	C	-1.665934	2.798705	-0.782439
H	-0.807345	2.127859	-1.535161	Cl	-0.500488	5.119937	0.010892
H	-0.414171	0.112335	-2.996508	H	0.515707	3.134207	1.836337
H	0.320624	2.283137	0.715522	H	-2.114388	3.417333	-1.564385
N	2.985645	-1.247684	-0.351642	N	-1.744369	-0.612872	0.518643
H	3.149846	-1.993030	-1.031501	H	-1.269658	-1.128992	1.258741
S	4.103172	-1.341946	1.009870	S	-2.706039	-1.697455	-0.486835
O	4.679452	-2.643115	0.788182	O	-2.321510	-2.972501	0.065144
O	3.337820	-0.990337	2.181904	O	-2.454795	-1.304276	-1.852632
C	5.263772	-0.075147	0.639467	C	-4.354223	-1.292234	-0.032727
C	5.224070	1.124805	1.349816	C	-5.148590	-0.556529	-0.912406
C	6.228745	-0.313005	-0.343891	C	-4.848343	-1.750303	1.192122
C	6.158343	2.110709	1.047487	C	-6.455088	-0.255783	-0.539864
H	4.490772	1.276865	2.145322	H	-4.760092	-0.244765	-1.884951
C	7.147742	0.687193	-0.630417	C	-6.153654	-1.434466	1.543507
H	6.269665	-1.272318	-0.866177	H	-4.225974	-2.358017	1.853906
C	7.129401	1.912159	0.056682	C	-6.977315	-0.684117	0.688105
H	6.139032	3.052062	1.603830	H	-7.086633	0.316066	-1.225536
H	7.906995	0.510413	-1.397619	H	-6.549540	-1.788206	2.499777
C	8.159531	2.967219	-0.239095	C	-8.401802	-0.386892	1.067698
H	9.094143	2.748259	0.308124	H	-9.049913	-1.242763	0.806158
H	8.406065	2.998498	-1.312648	H	-8.502210	-0.216352	2.151640
H	7.817973	3.967058	0.071362	H	-8.787469	0.497359	0.536576
H	2.192761	0.774266	1.234545	H	-2.652134	1.027841	-1.451926
Cl	1.632919	-1.855782	-2.880968	H	-0.167377	0.748537	2.111160
I	-4.310862	-0.920857	1.033795	I	3.591992	-0.691382	-1.367737
C	-5.722169	0.377887	0.169629	C	4.880320	-0.712442	0.294503
C	-6.062727	1.552126	0.842183	C	5.643583	0.421805	0.574648
C	-6.297380	0.036030	-1.054909	C	4.953762	-1.864217	1.079169
C	-7.005520	2.402639	0.265500	C	6.500958	0.394115	1.674066
H	-5.608694	1.805504	1.803151	H	5.580717	1.315071	-0.051417

TS42

E(scf) = −2554.00190972 a.u.

ν_{min} = −180.0 cm^{-1}

C	-7.238372	0.899643	-1.614941	C	5.817865	-1.871948	2.173691
H	-6.025833	-0.889137	-1.568863	H	4.355072	-2.747742	0.844956
C	-7.591652	2.078840	-0.958433	C	6.588448	-0.747598	2.471261
H	-7.284845	3.323969	0.783512	H	7.108197	1.273854	1.903198
H	-7.700342	0.642182	-2.571772	H	5.889624	-2.769072	2.794349
H	-8.332571	2.748895	-1.402247	H	7.266022	-0.762727	3.328912
Cl	-1.985747	0.286331	-0.169602	Cl	1.316160	0.438006	-0.005128

Int51

E(scf) = −2024.85688786 a.u.

C	3.446040	1.438303	0.424407
C	3.273183	0.165549	1.175276
C	2.232114	-0.657433	0.960681
C	1.221186	-0.341869	-0.056446
C	1.370107	0.874503	-0.831356
C	2.414418	1.695053	-0.615331
Cl	5.074177	1.453202	-0.344858
H	4.026457	-0.084046	1.927909
H	2.534825	2.600296	-1.218116
N	0.221344	-1.169512	-0.223944
H	0.214250	-2.017648	0.352325
S	-1.175650	-1.156377	-1.390345
O	-1.501503	-2.555645	-1.384996
O	-0.690620	-0.437443	-2.540109
C	-2.357332	-0.220159	-0.506623
C	-2.518811	1.136650	-0.800144
C	-3.135519	-0.863880	0.461471
C	-3.469416	1.859579	-0.089767
H	-1.931785	1.613886	-1.588427
C	-4.076074	-0.117462	1.158133
H	-3.020073	-1.933759	0.652881
C	-4.259819	1.250407	0.897241
H	-3.611340	2.919940	-0.316284
H	-4.692766	-0.610288	1.914909
C	-5.313325	2.032742	1.629656
H	-6.284452	1.930983	1.112064
H	-5.447661	1.663643	2.658794
H	-5.068746	3.105743	1.668840
H	0.646662	1.082831	-1.618850
Cl	2.045043	-2.125436	1.855415
H	3.445339	2.277812	1.145266

TS51

Int52

E(scf) = −2024.85117113 a.u.

C	3.638858	1.071506	0.018005
C	3.447891	0.138394	0.968612
C	2.121455	-0.529980	1.112246
C	1.164043	-0.376828	-0.052198
C	1.399190	0.692702	-0.971836
C	2.583893	1.364725	-0.934096
Cl	5.115282	1.940387	-0.131246
H	4.213482	-0.097158	1.712049
H	2.774237	2.144719	-1.677528
N	0.136313	-1.185525	-0.105638
H	0.127090	-1.978353	0.544651
S	-1.270285	-1.251299	-1.255122
O	-1.623556	-2.638274	-1.130874
O	-0.784264	-0.639113	-2.464858
C	-2.425170	-0.221414	-0.442180
C	-2.535730	1.119731	-0.820041
C	-3.230205	-0.775241	0.558779
C	-3.462562	1.919044	-0.162363
H	-1.927597	1.526197	-1.631654
C	-4.147475	0.046211	1.200578
H	-3.153956	-1.834659	0.816591
C	-4.280224	1.400755	0.854297
H	-3.564345	2.967941	-0.454443
H	-4.785999	-0.376519	1.981282
C	-5.308768	2.265129	1.527631
H	-6.272400	2.188336	0.992011
H	-5.483314	1.949589	2.568381
H	-5.011851	3.325644	1.525520
H	0.679505	0.890348	-1.765529
Cl	2.275534	-2.226096	1.654205
H	1.603038	0.001125	1.941054

TS52

E(scf) = –4173.53099530 a.u.

ν_{min} = –1422.6 cm^{-1}

C	1.340326	3.085827	-0.439051
C	2.415325	2.760720	0.455017
C	3.001158	1.528063	0.400721
C	2.614658	0.558614	-0.585972
C	1.605233	0.913360	-1.516624
C	1.023090	2.155630	-1.482238
Cl	0.920577	4.775214	-0.644885
H	2.722657	3.487281	1.209937
H	0.237053	2.410587	-2.197349
N	3.207702	-0.651481	-0.568796
H	3.924760	-0.816259	0.135877
S	2.777286	-2.105884	-1.415164
O	3.880918	-2.970574	-1.067633
O	2.470625	-1.724651	-2.774942
C	1.313707	-2.602777	-0.577973
C	0.066780	-2.332539	-1.147205
C	1.433878	-3.203866	0.674392
C	-1.075330	-2.652402	-0.423698
H	-0.019996	-1.888389	-2.138641
C	0.277921	-3.501272	1.385252
H	2.419297	-3.434781	1.091750
C	-0.990772	-3.213894	0.860745
H	-2.058112	-2.455684	-0.859526
H	0.356440	-3.953642	2.377957
C	-2.253325	-3.493220	1.629573
H	-2.844498	-4.308435	1.120054
H	-2.014625	-3.810250	2.680919
H	-2.899387	-2.567536	1.646479
H	1.309345	0.201486	-2.286213
Cl	4.229714	1.104818	1.552598
H	0.234999	2.543275	0.355298
O	-1.131901	1.991476	0.688928
C	-1.322821	0.875739	1.185200
O	-2.297203	0.128374	0.943057
C	-0.266556	0.312170	2.163667
Al	-3.461974	0.339960	-0.519608
Cl	-4.578592	-1.473169	-0.494710
Cl	-2.079047	0.429672	-2.177093
Cl	-4.594972	2.097854	-0.197759
F	0.702067	-0.282234	1.452630

E(scf) = –4173.52527525 a.u.

ν_{min} = –1612.3 cm^{-1}

C	-2.023639	-3.150230	-0.491302
C	-2.635699	-2.624665	0.618808
C	-2.840124	-1.210569	0.705989
C	-2.604749	-0.363088	-0.435333
C	-1.968984	-0.958016	-1.551443
C	-1.681200	-2.304514	-1.569673
Cl	-1.669053	-4.838637	-0.580643
H	-2.905895	-3.250160	1.471349
H	-1.174890	-2.729476	-2.438680
N	-2.951410	0.946733	-0.366945
H	-3.472452	1.256632	0.451080
S	-2.502837	2.253161	-1.397466
O	-3.397917	3.298112	-0.956008
O	-2.501048	1.737211	-2.748482
C	-0.853863	2.626853	-0.902359
C	0.222108	2.000991	-1.535407
C	-0.657509	3.544838	0.129836
C	1.510689	2.284351	-1.099242
H	0.068841	1.302885	-2.360347
C	0.640752	3.812179	0.549443
H	-1.511415	4.042358	0.595302
C	1.741202	3.179527	-0.044447
H	2.359144	1.797353	-1.587558
H	0.802712	4.521819	1.365633
C	3.142421	3.415791	0.443827
H	3.798554	3.738836	-0.381711
H	3.174262	4.177952	1.238227
H	3.565508	2.475303	0.836527
H	-1.743036	-0.344454	-2.422314
Cl	-3.786687	-0.590082	2.038706
H	-1.277805	-0.988414	1.038758
O	0.208791	-1.173753	0.839026
C	0.994517	-0.321676	1.287932
O	2.181734	-0.179375	0.933082
C	0.486525	0.596771	2.422900
Al	3.097735	-1.105726	-0.434646
Cl	3.569659	-2.982968	0.425984
Cl	4.727428	0.208189	-0.826560
Cl	1.729794	-1.204843	-2.090937
F	1.296678	1.602734	2.667515

F	0.298322	1.297039	2.856465
F	-0.777328	-0.569823	3.000667

Product

E(scf) = −2024.54528099 a.u.

C	3.213319	0.332500	-0.210190
C	2.417536	0.679410	0.878409
C	1.299900	-0.097380	1.169164
C	0.979596	-1.234607	0.410792
C	1.809899	-1.567061	-0.665459
C	2.913002	-0.785191	-0.988053
Cl	4.599533	1.309038	-0.595455
H	2.652713	1.553656	1.486900
H	3.550733	-1.049848	-1.833732
N	-0.157631	-2.016257	0.696516
H	-0.498963	-1.935478	1.652625
S	-1.459572	-2.004818	-0.383534
O	-2.505354	-2.737287	0.300519
O	-0.937896	-2.404589	-1.675384
C	-1.917110	-0.289803	-0.477543
C	-1.255006	0.549123	-1.372999
C	-2.870019	0.209869	0.408722
C	-1.547368	1.909996	-1.364301
H	-0.521768	0.137075	-2.070338
C	-3.154317	1.571437	0.397032
H	-3.384140	-0.467220	1.095378
C	-2.496949	2.442052	-0.482758
H	-1.025762	2.572998	-2.061262
H	-3.903399	1.967927	1.089305
C	-2.829983	3.911135	-0.503795
H	-3.661062	4.109653	-1.204747
H	-3.143631	4.267512	0.490961
H	-1.968362	4.515042	-0.831941
H	1.562920	-2.451227	-1.254929
Cl	0.280954	0.356664	2.507662
F	-0.721188	1.078559	2.094333
F	0.343914	-0.124729	3.529566

D

E(scf) = −529.162648764 a.u.

I	1.551544	0.000000	-0.000005
C	0.556068	-0.000001	-0.000011
C	1.245859	1.213292	0.000026
C	1.245860	-1.213293	0.000026
C	2.641162	1.206228	0.000025
H	0.702667	2.161507	0.000088
C	2.641164	-1.206227	0.000025
H	0.702669	-2.161509	0.000088
C	3.340977	0.000001	-0.000074
H	3.182751	2.156552	0.000069
H	3.182753	-2.156551	0.000069
H	4.434455	0.000001	-0.000148

E

E(scf) = −2149.01306956 a.u.

O	-1.358076	-1.626064	-0.001586
C	-1.323114	-0.346858	0.004287
O	-0.319605	0.360956	0.006001
C	-2.722109	0.310564	0.002999
Al	1.587330	0.117444	0.000131
Cl	2.188099	0.972862	-1.821315
Cl	1.604315	-2.065206	-0.010800
Cl	2.197609	0.954829	1.826788
F	-3.357332	-0.035281	-1.106355
F	-3.406051	-0.120580	1.050936
F	-2.608677	1.618553	0.057168
H	-0.424343	-2.014610	-0.005927

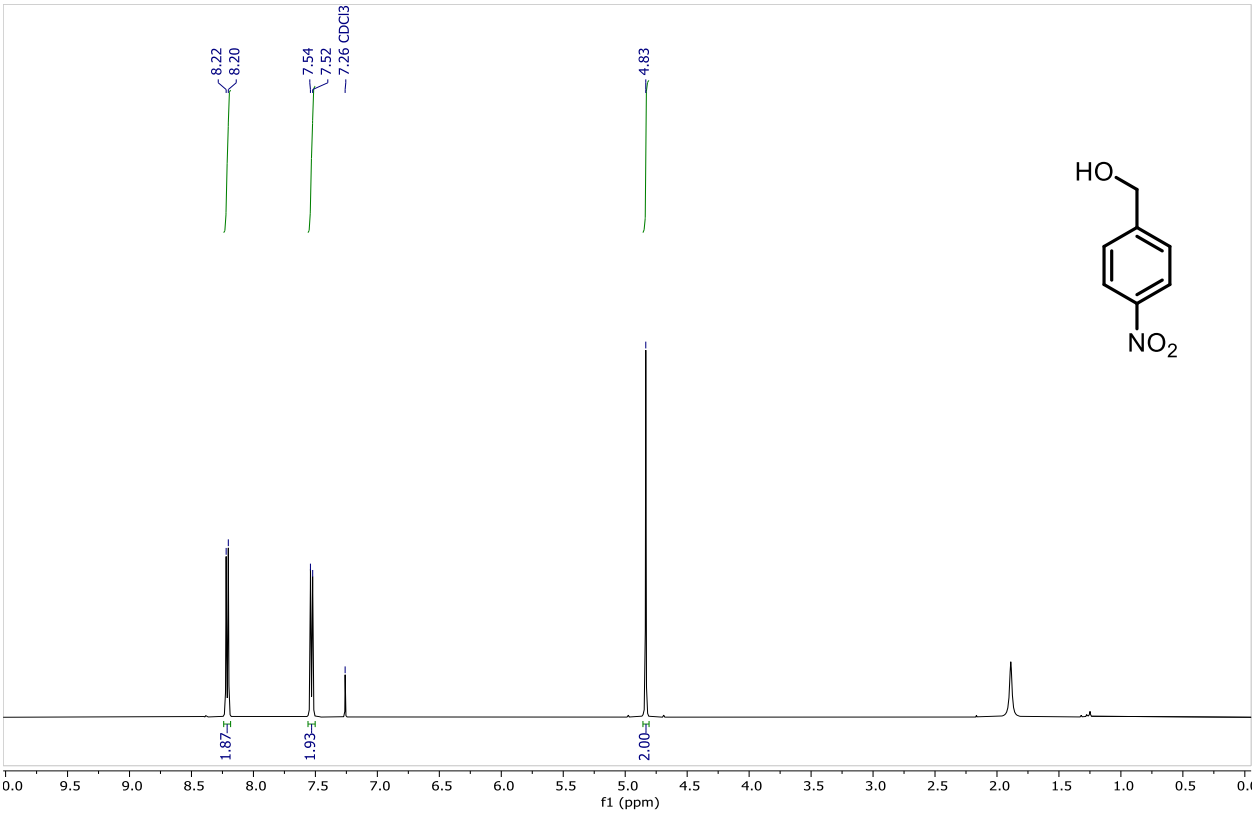
ANNEXES

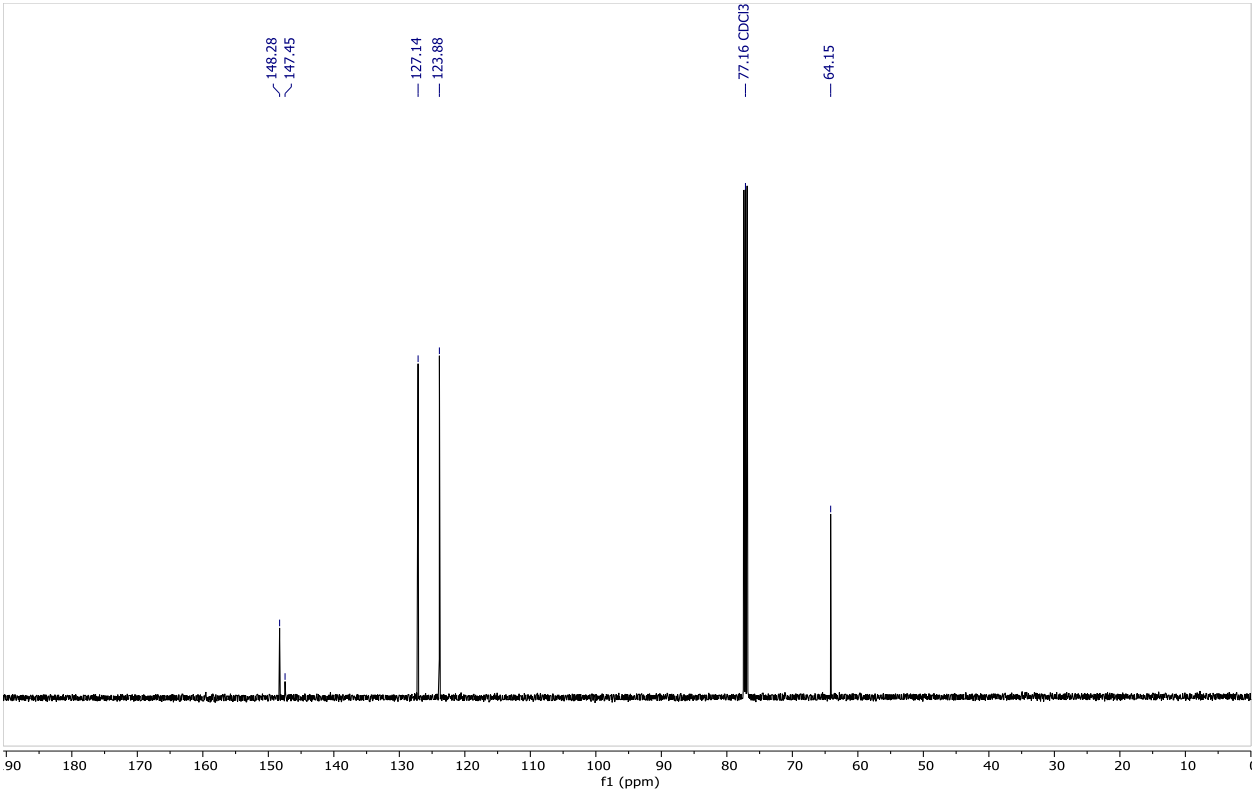
Annex A.

^{1}H and ^{13}C NMR spectrums of Chapter 2 and 3

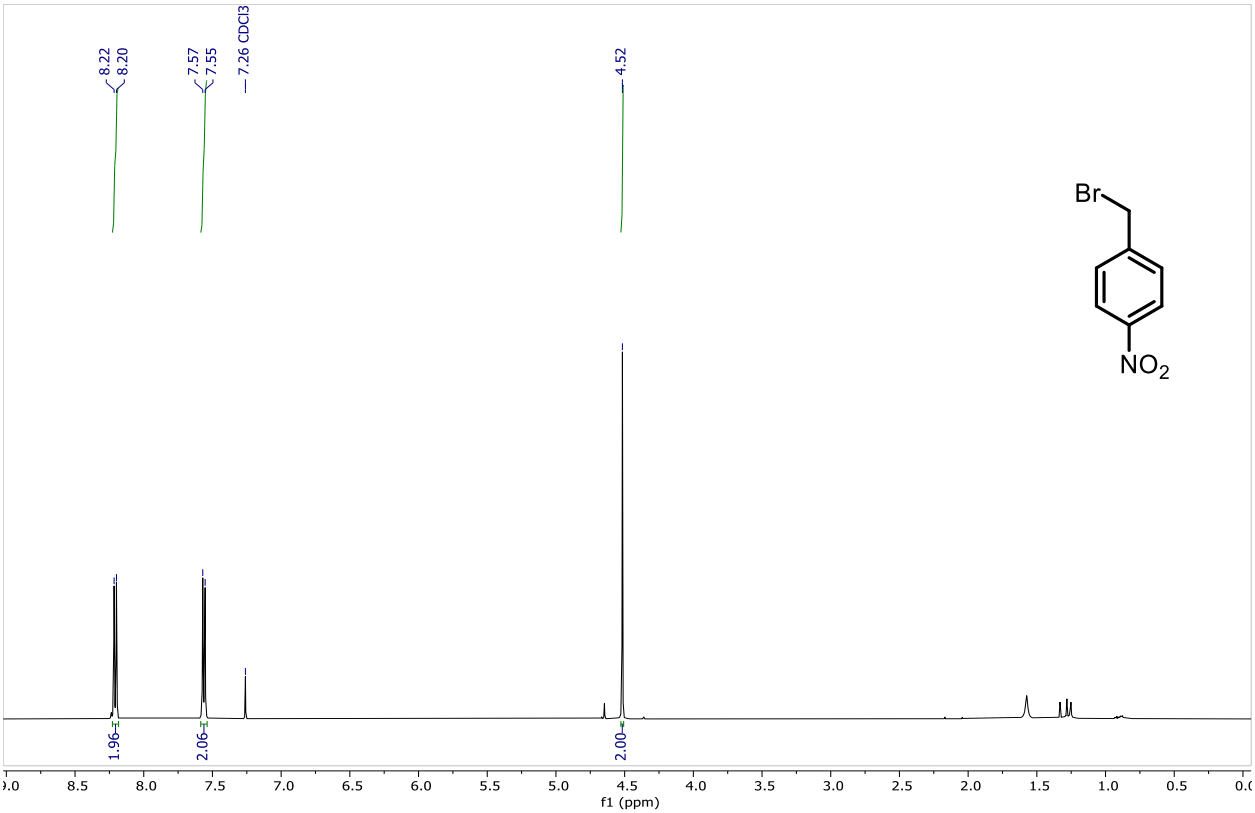
^{1}H and ^{13}C NMR spectrums of chapter 2

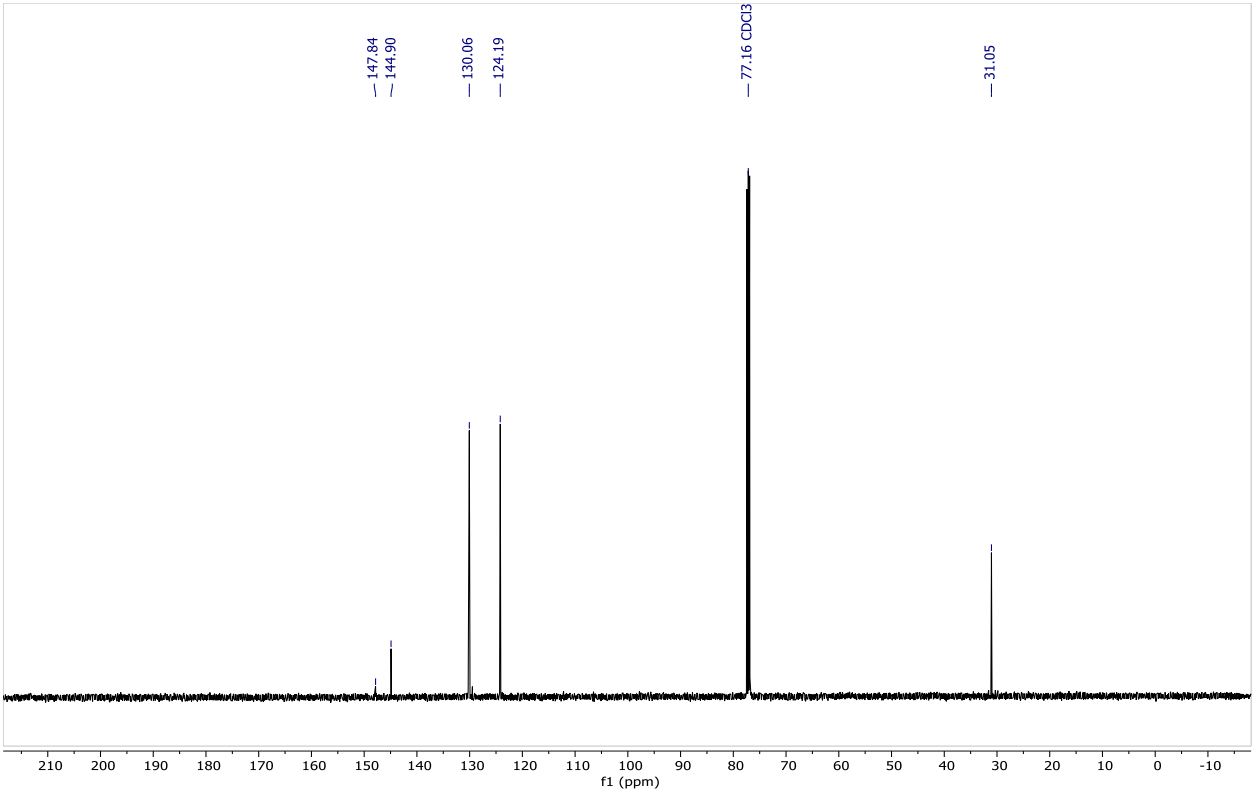
(4-nitrophenyl)methanol **(304)**



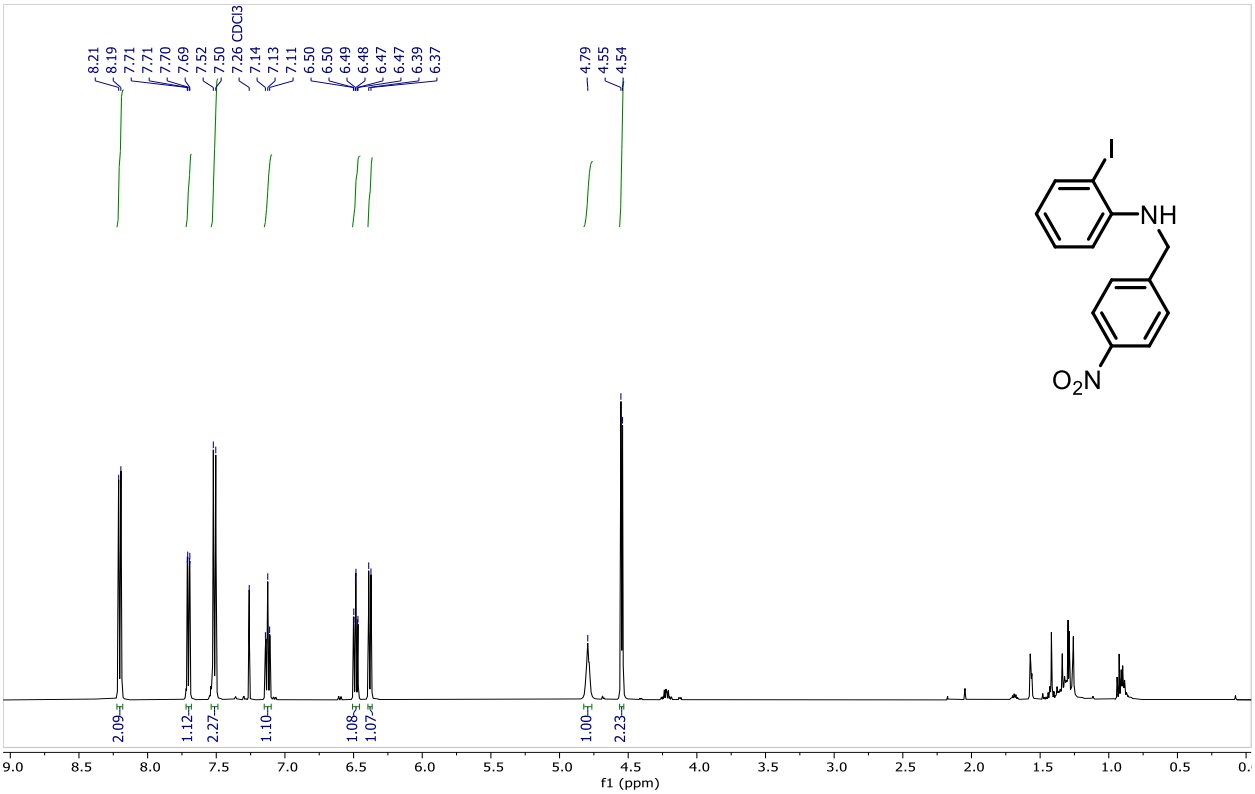


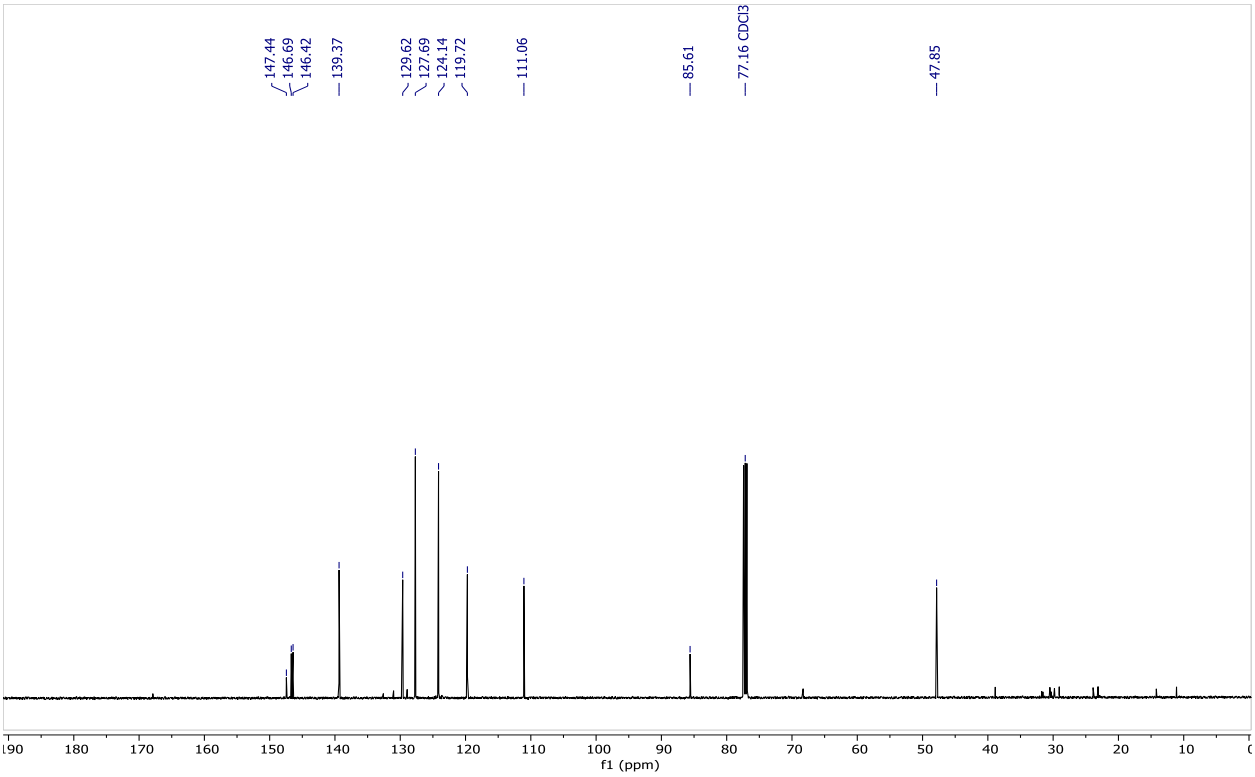
1-(bromomethyl)-4-nitrobenzene **(305)**



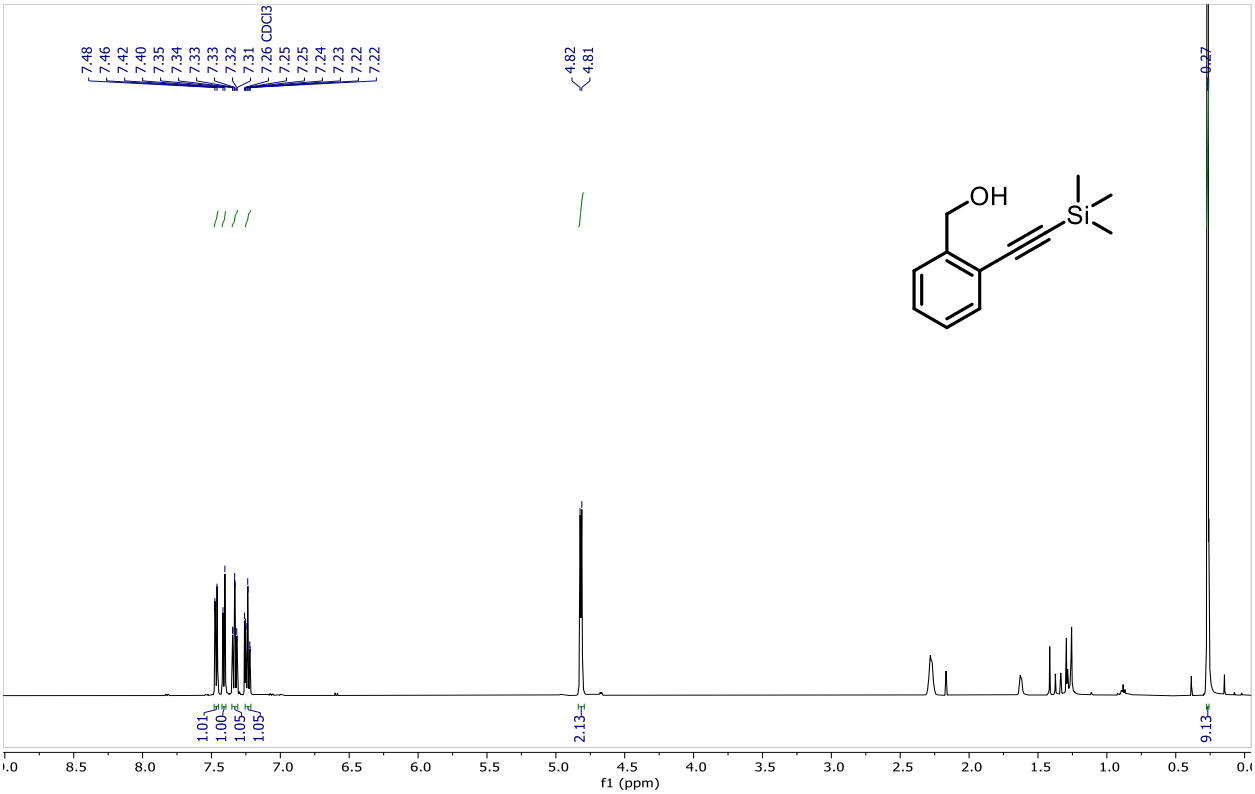


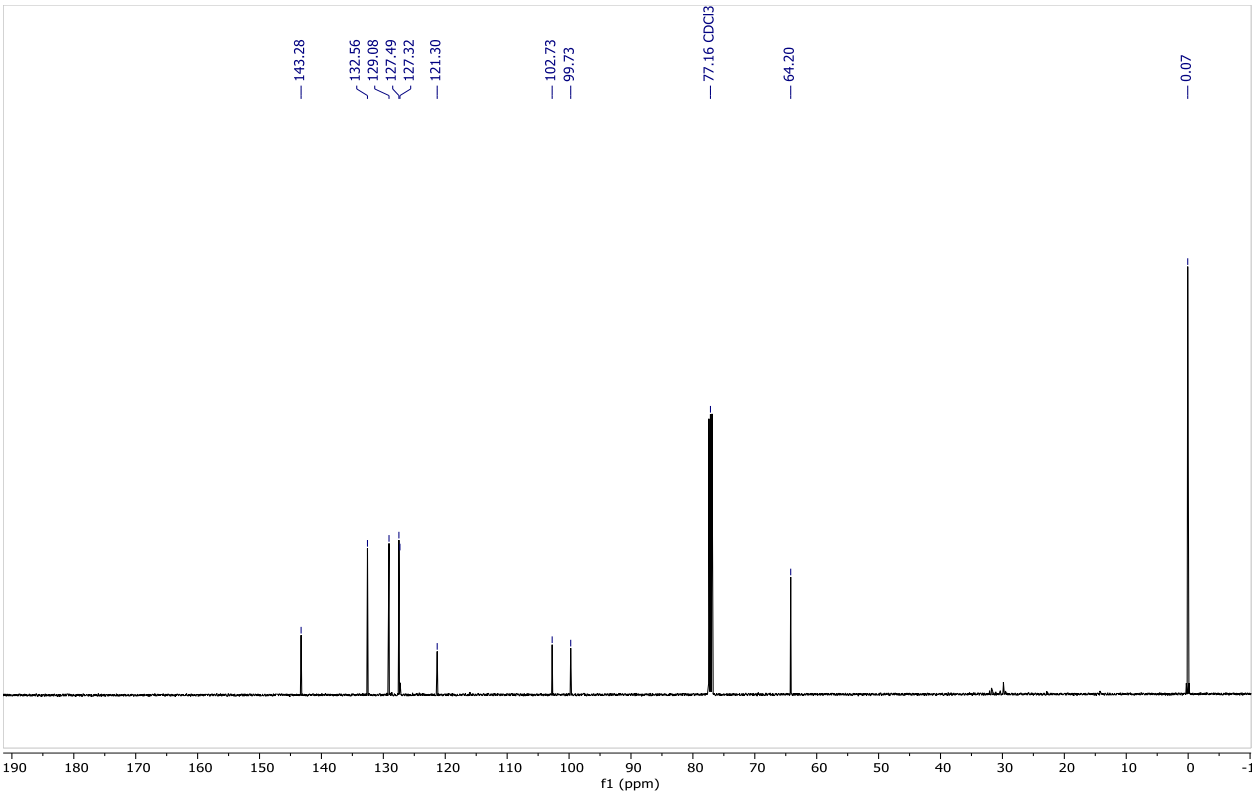
2-iodo-*N*-(4-nitrobenzyl)aniline **(307)**



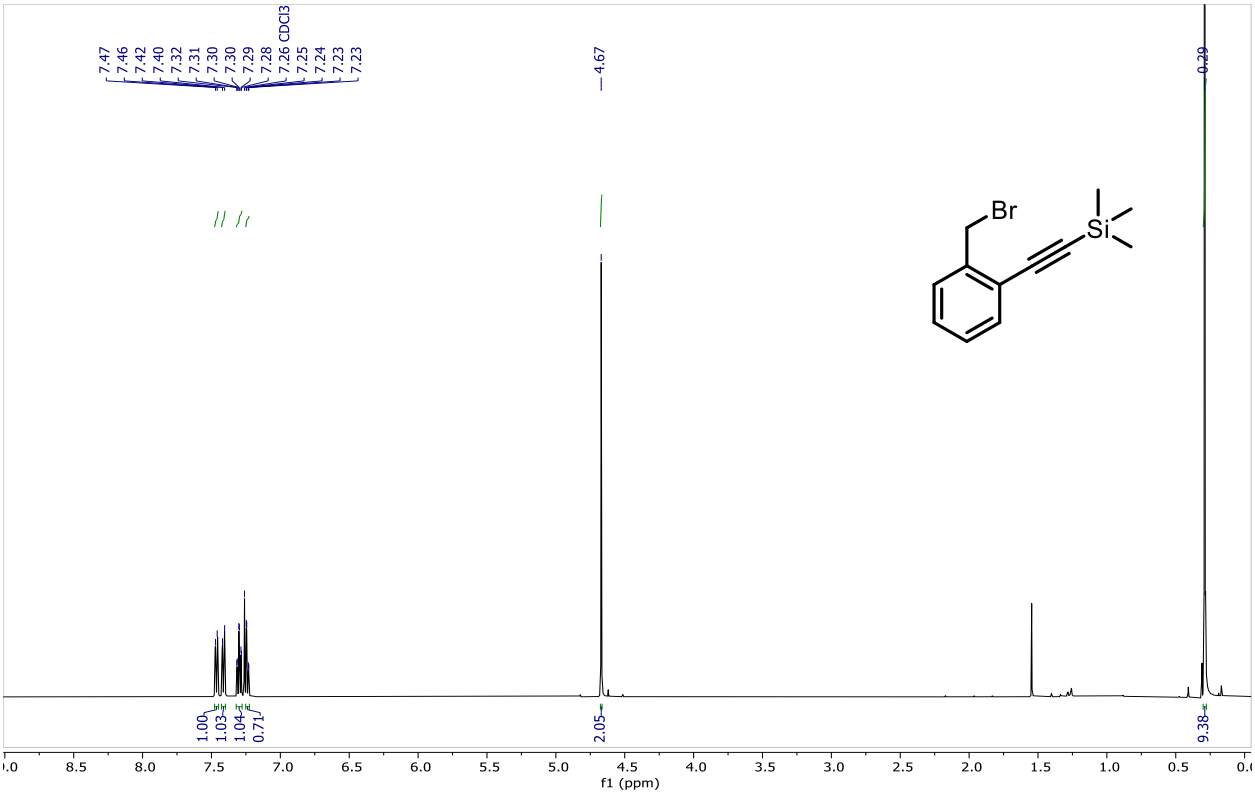


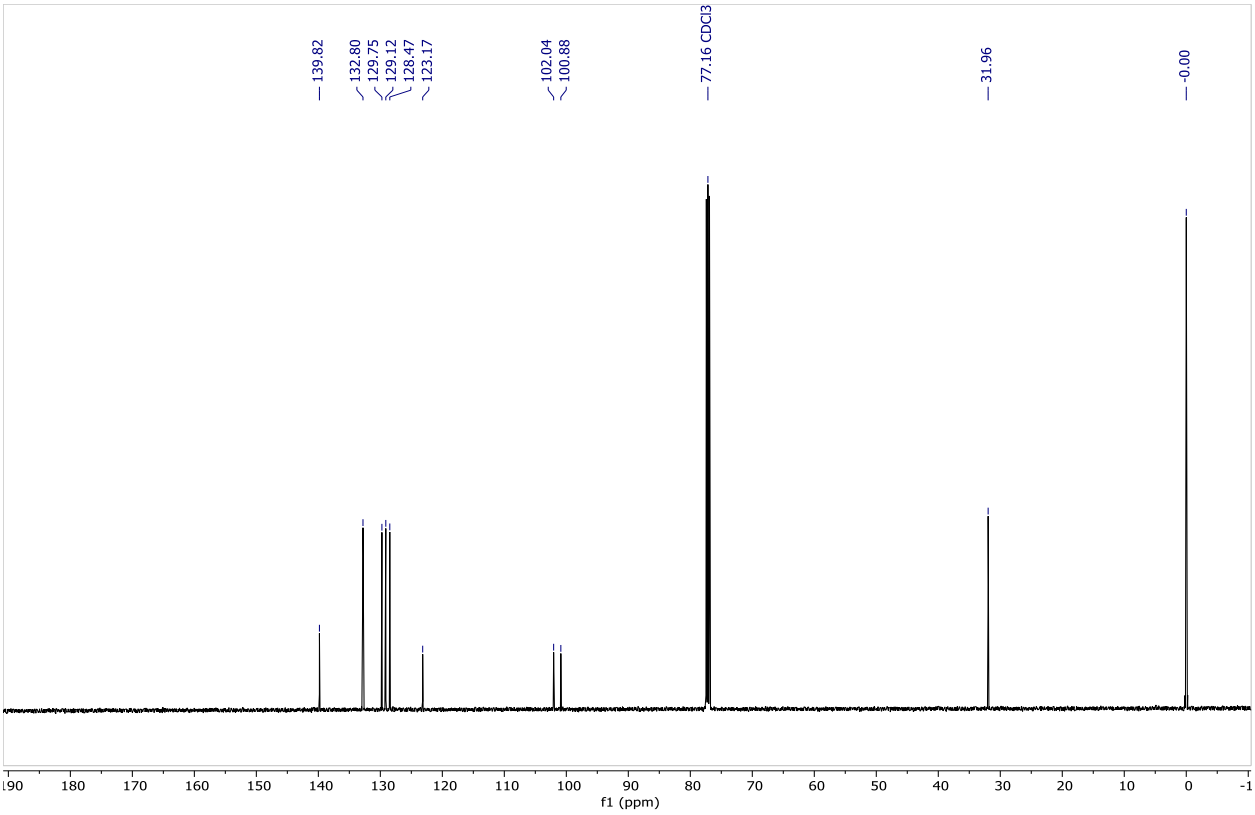
(2-((trimethylsilyl)ethynyl)phenyl)methanol **(309)**



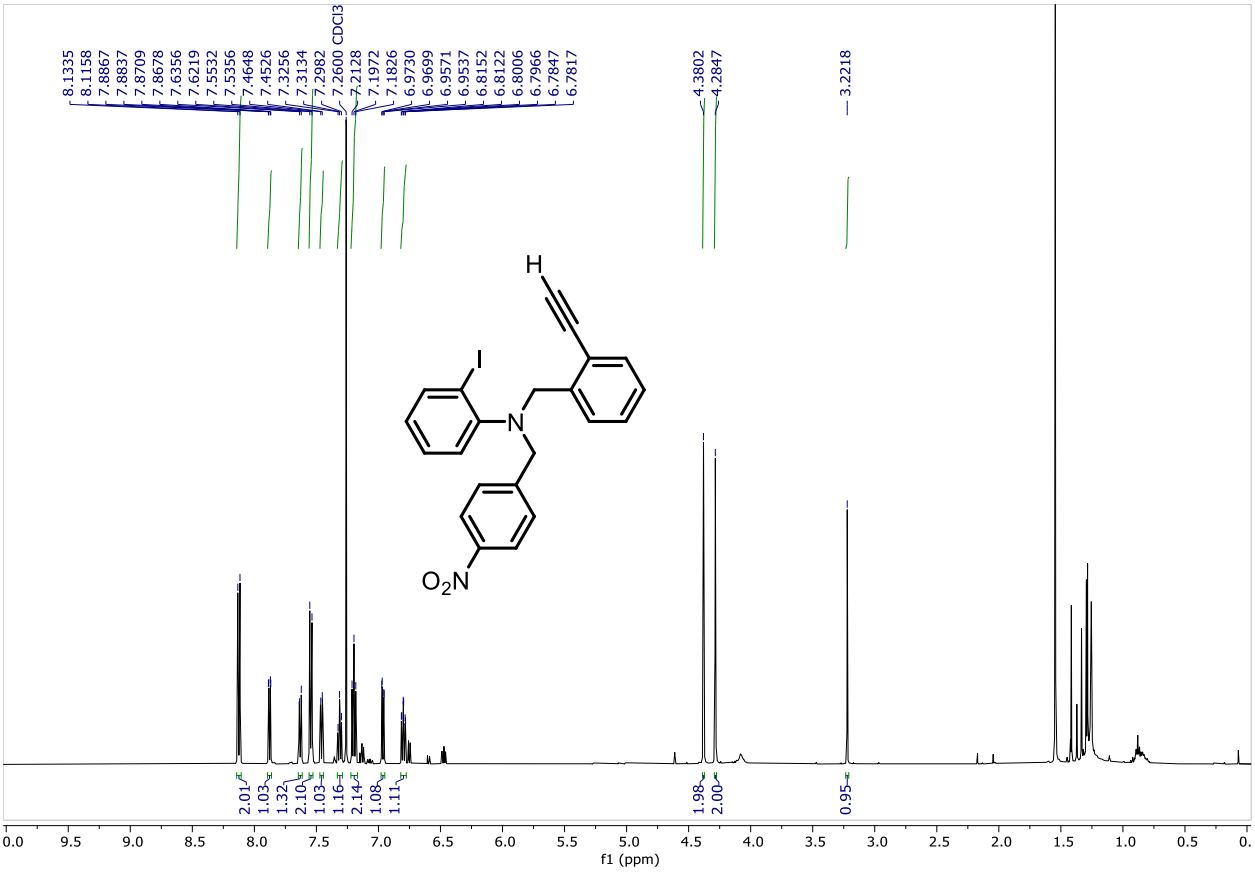


((2-(bromomethyl)phenyl)ethynyl)trimethylsilane **(310)**

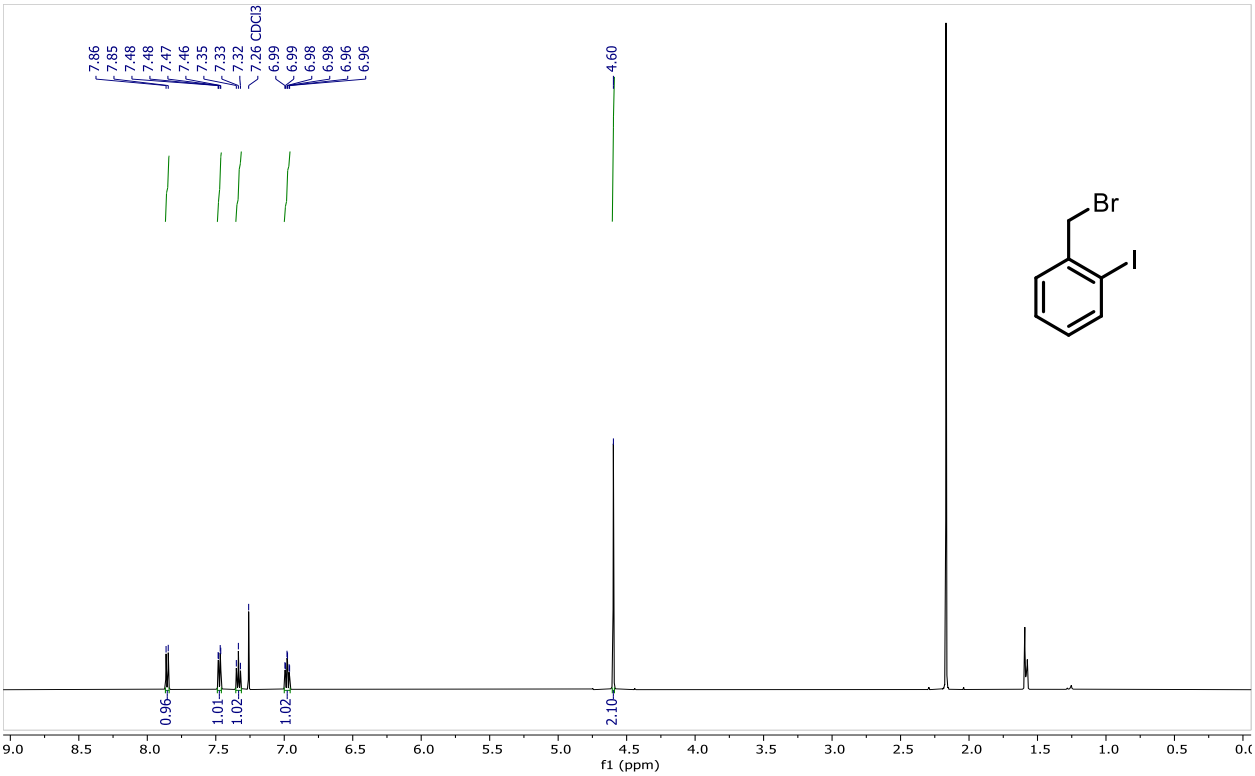


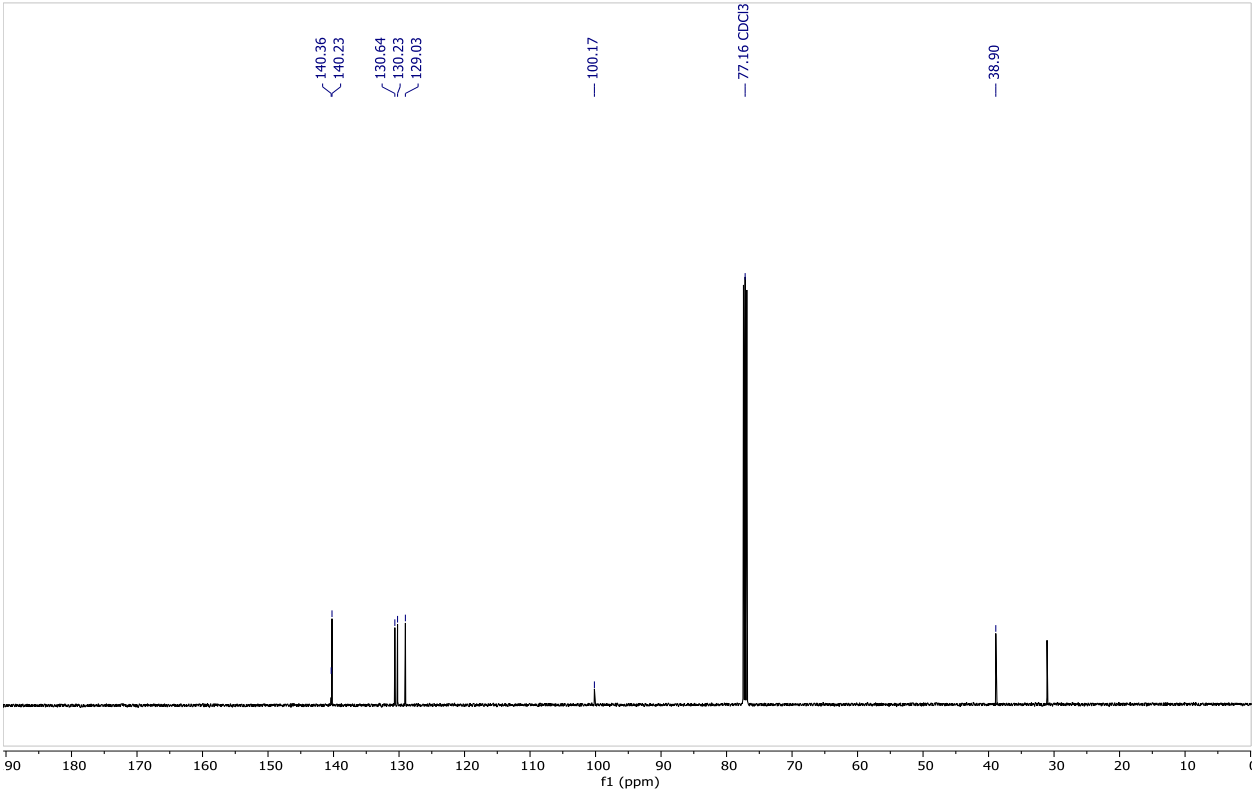


N-(2-ethynylbenzyl)-2-iodo-*N*-(4-nitrobenzyl)aniline **(311)**

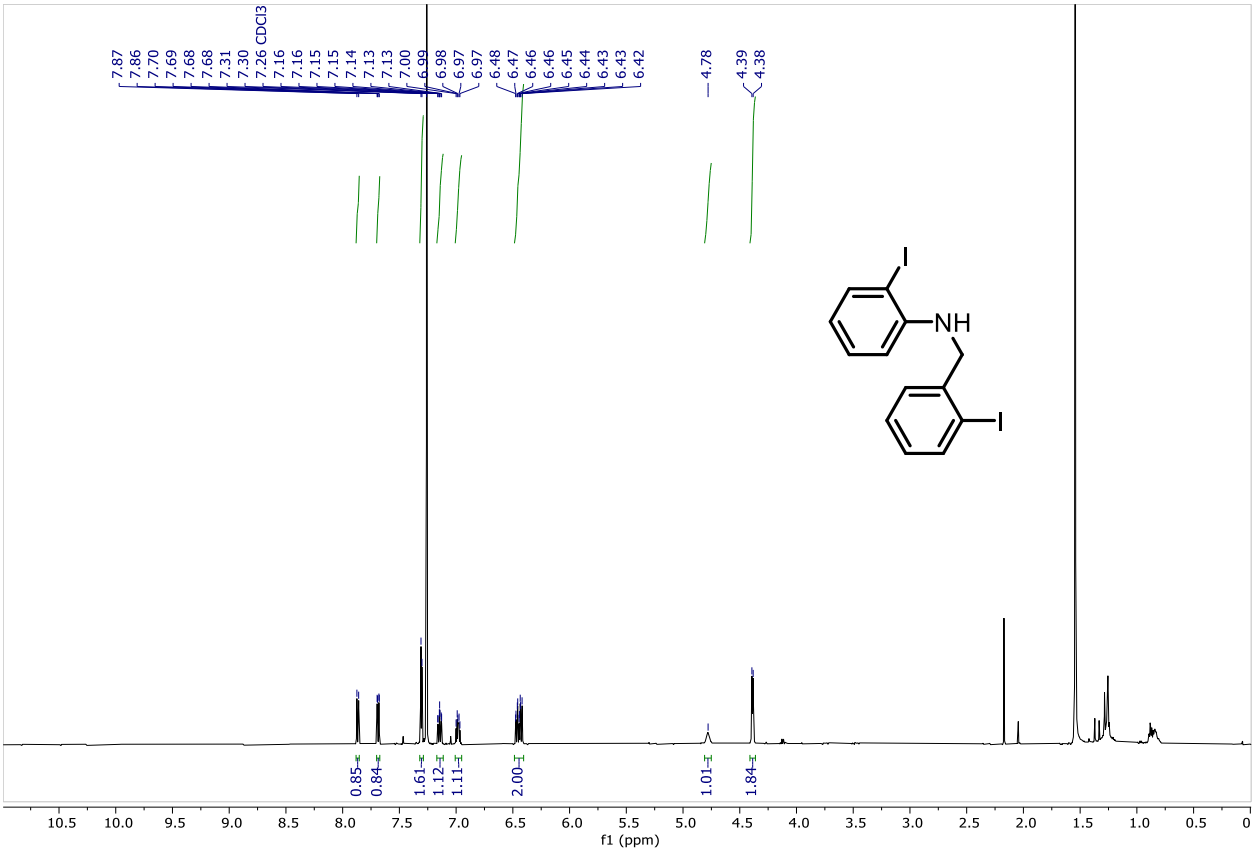


1-(bromomethyl)-2-iodobenzene **(312)**

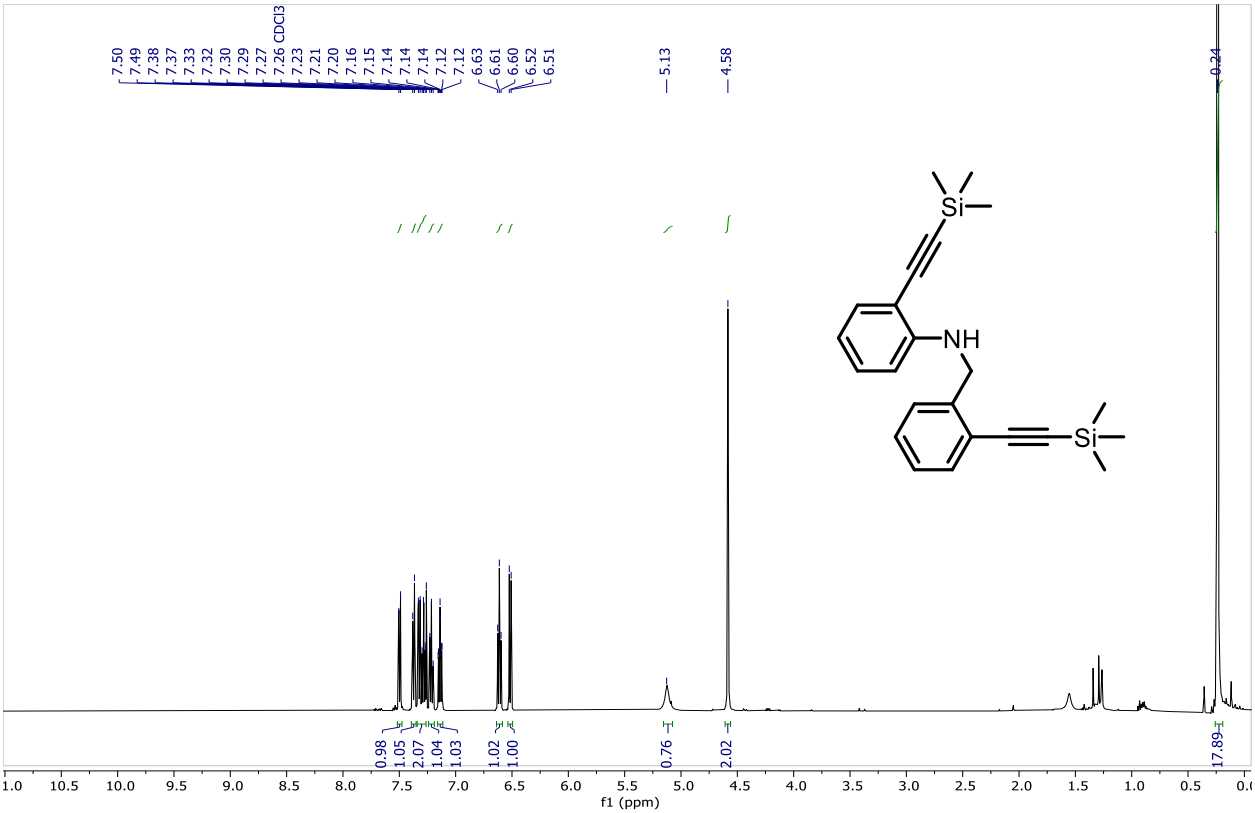


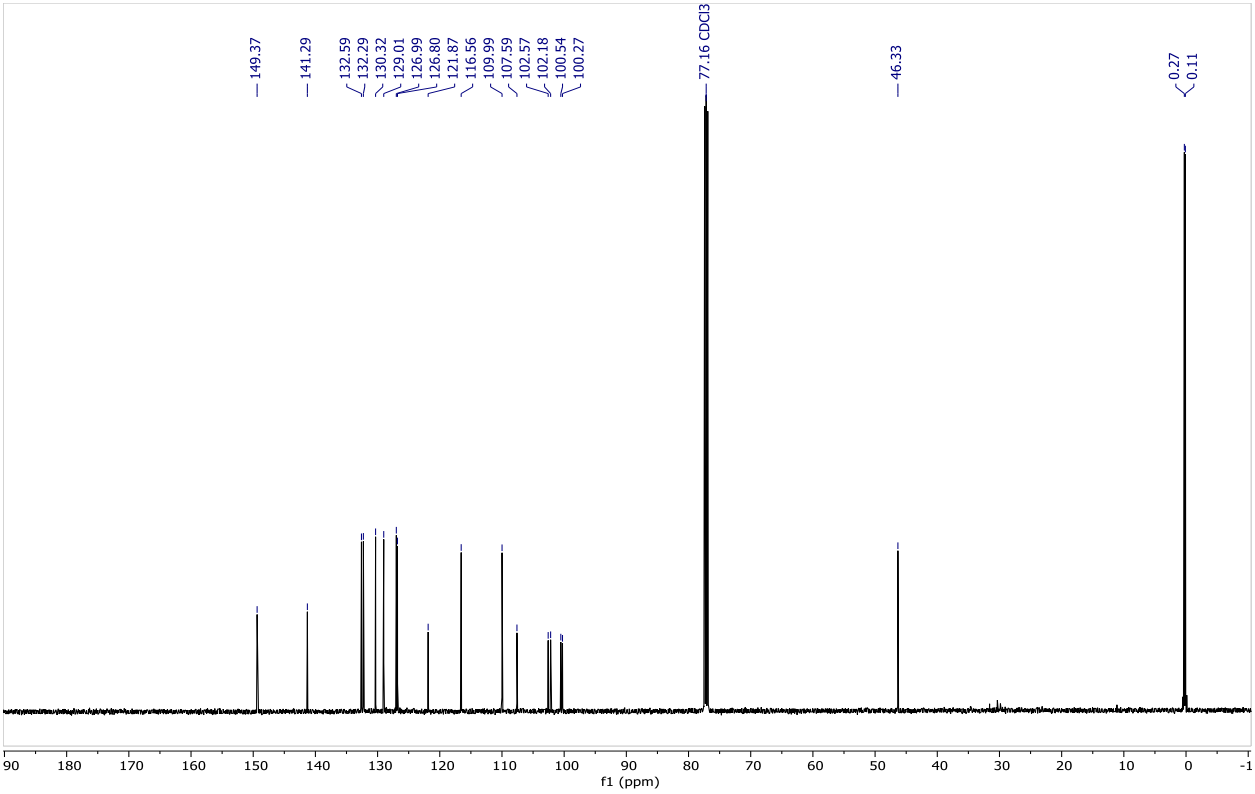


2-iodo-N-(2-iodobenzyl)aniline **(314)**

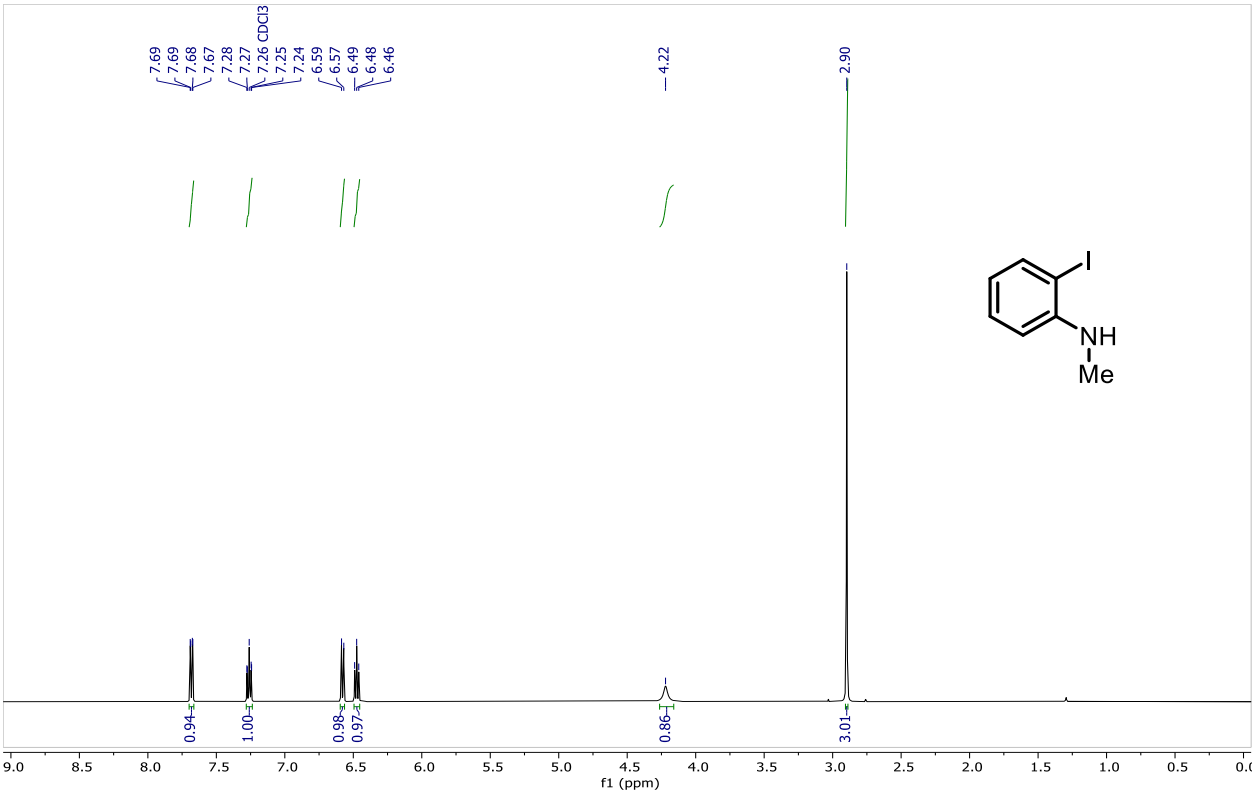


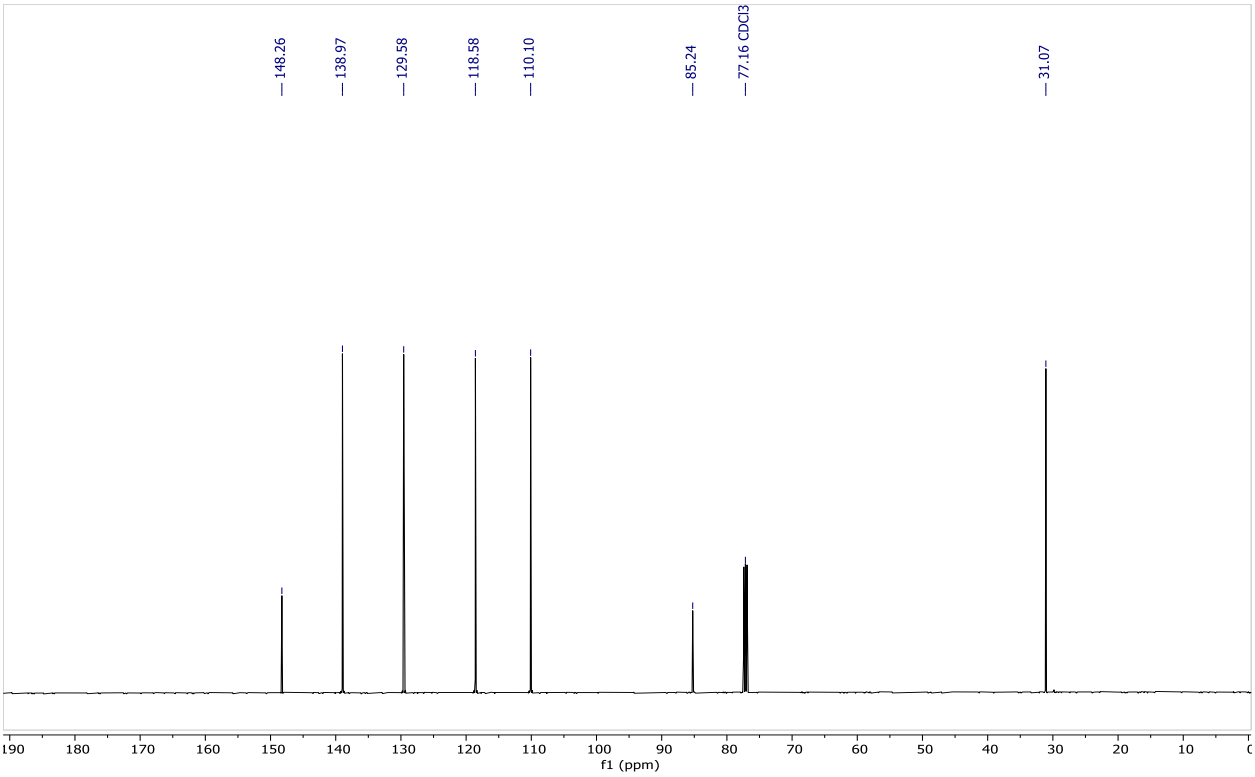
2-((trimethylsilyl)ethynyl)-*N*-(2-((trimethylsilyl)ethynyl)benzyl)aniline **(317)**



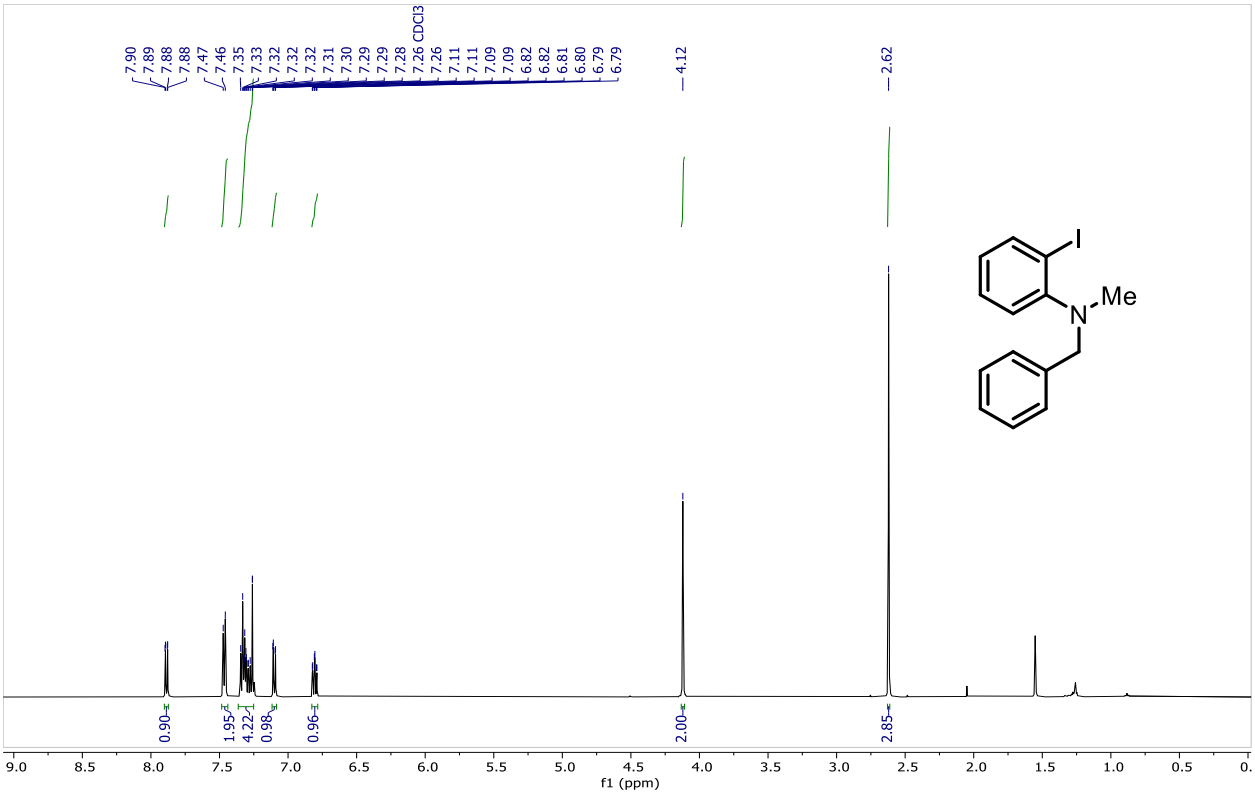


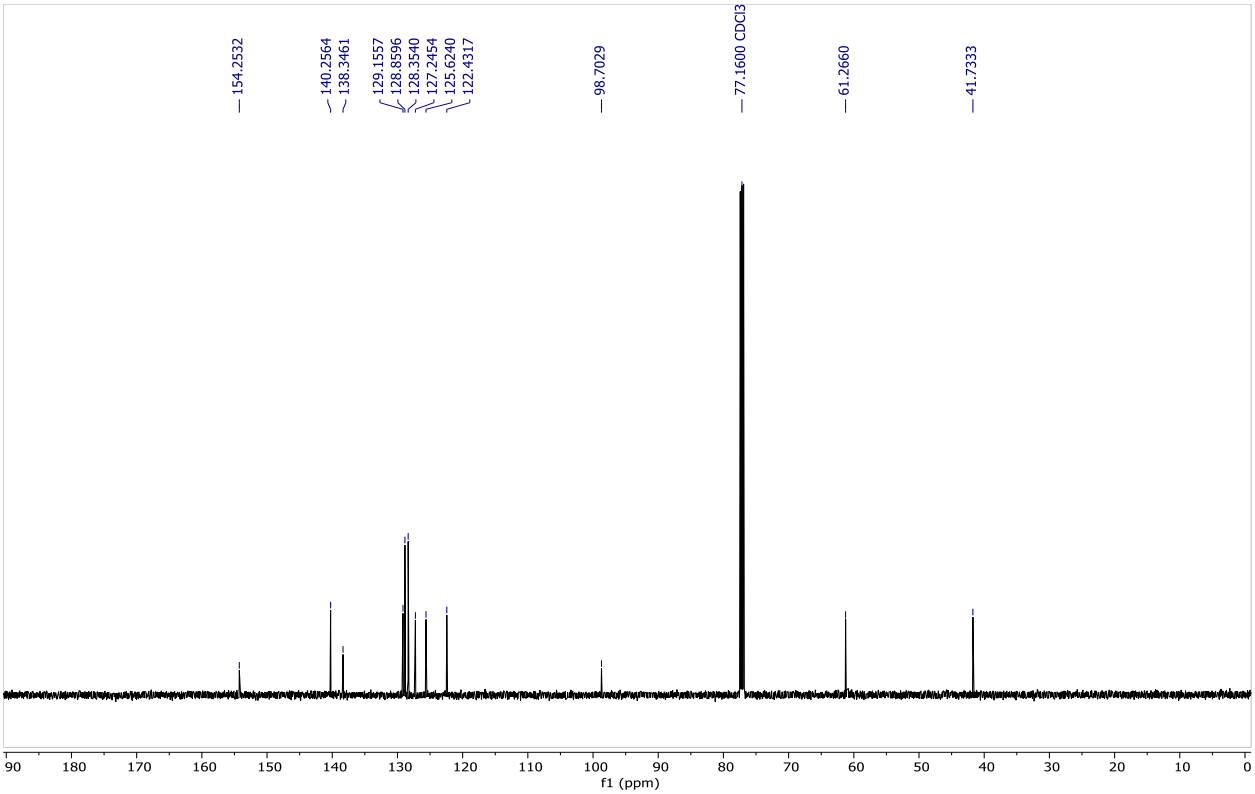
2-iodo-*N*-methylaniline **(320)**



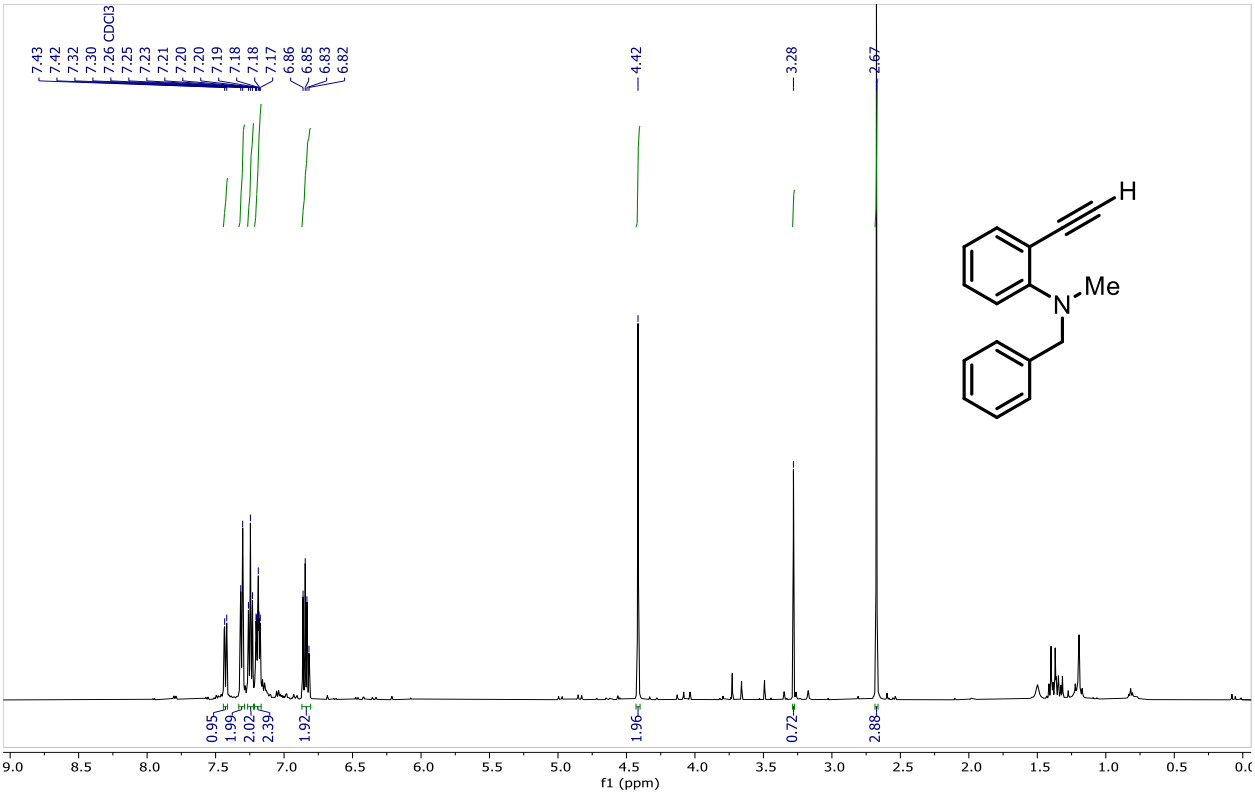


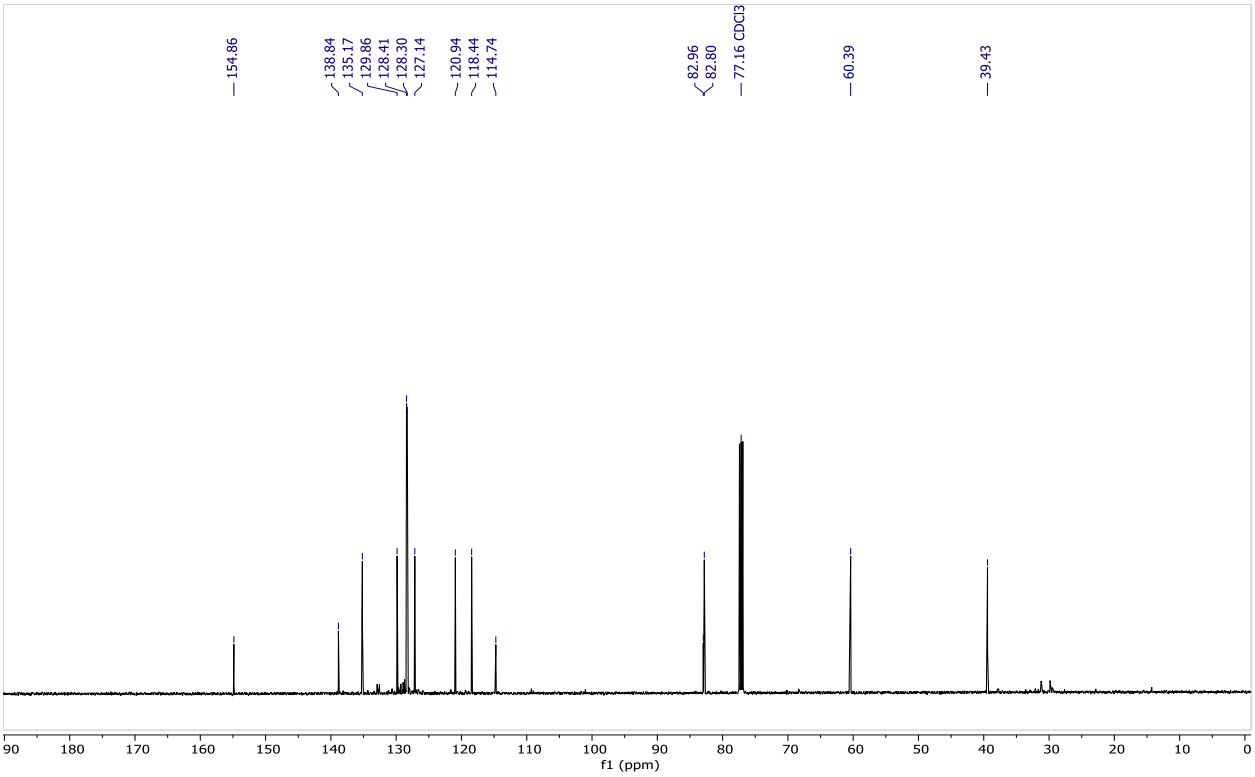
N-benzyl-2-iodo-*N*-methylaniline **(322)**



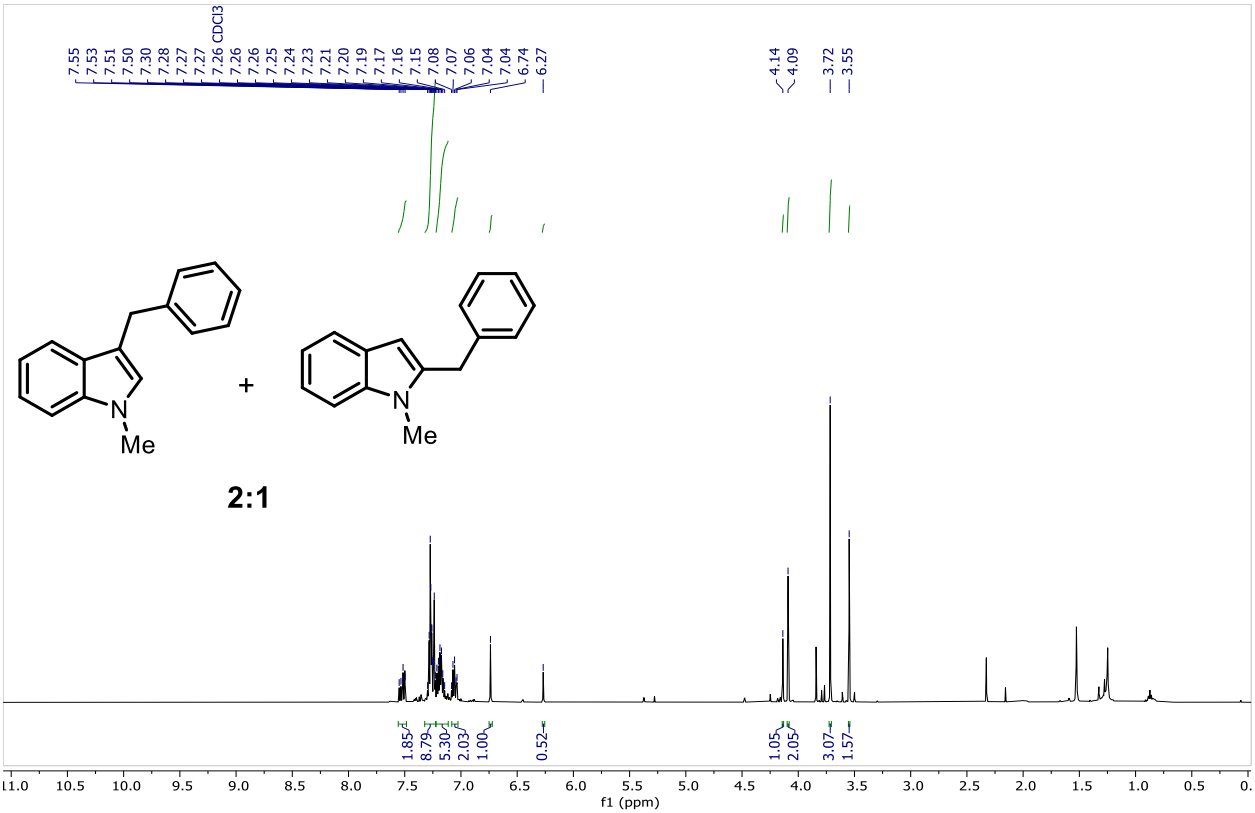


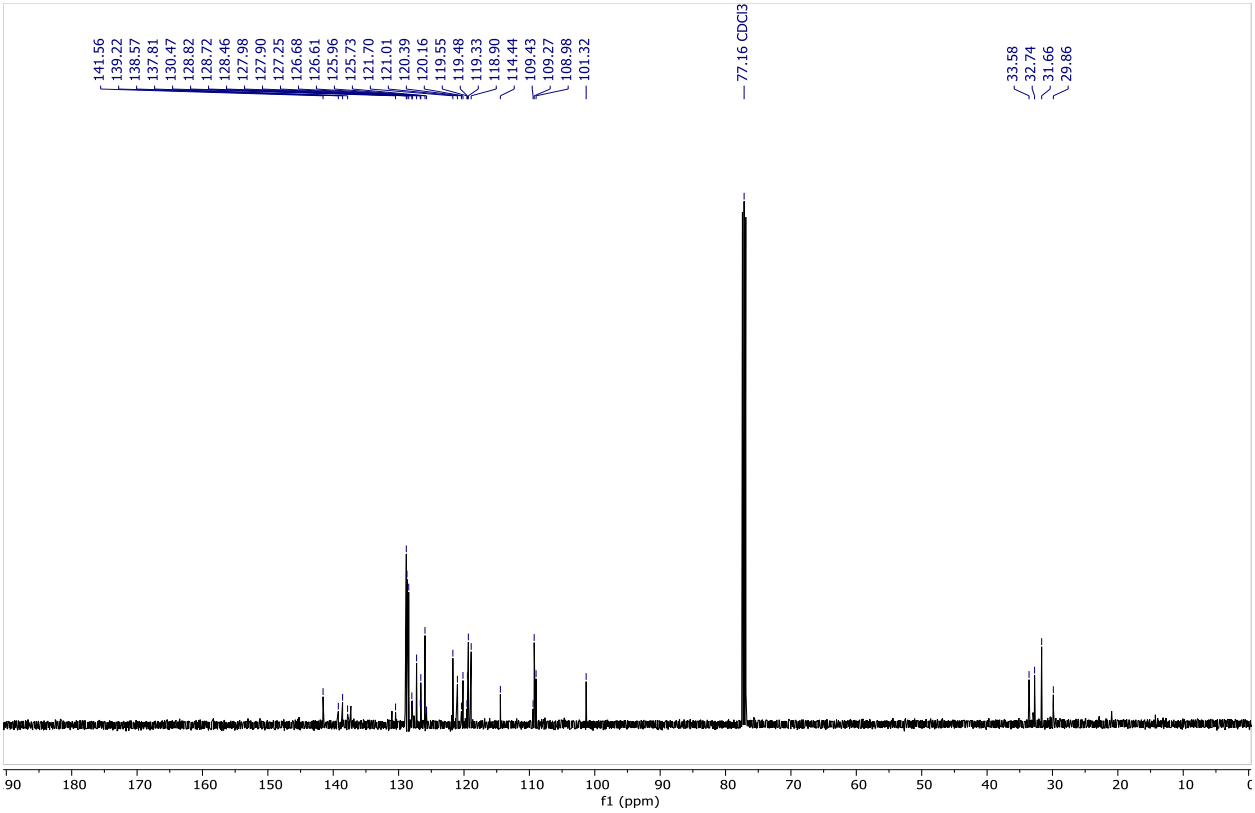
N-benzyl-2-ethynyl-*N*-methylaniline **(324)**





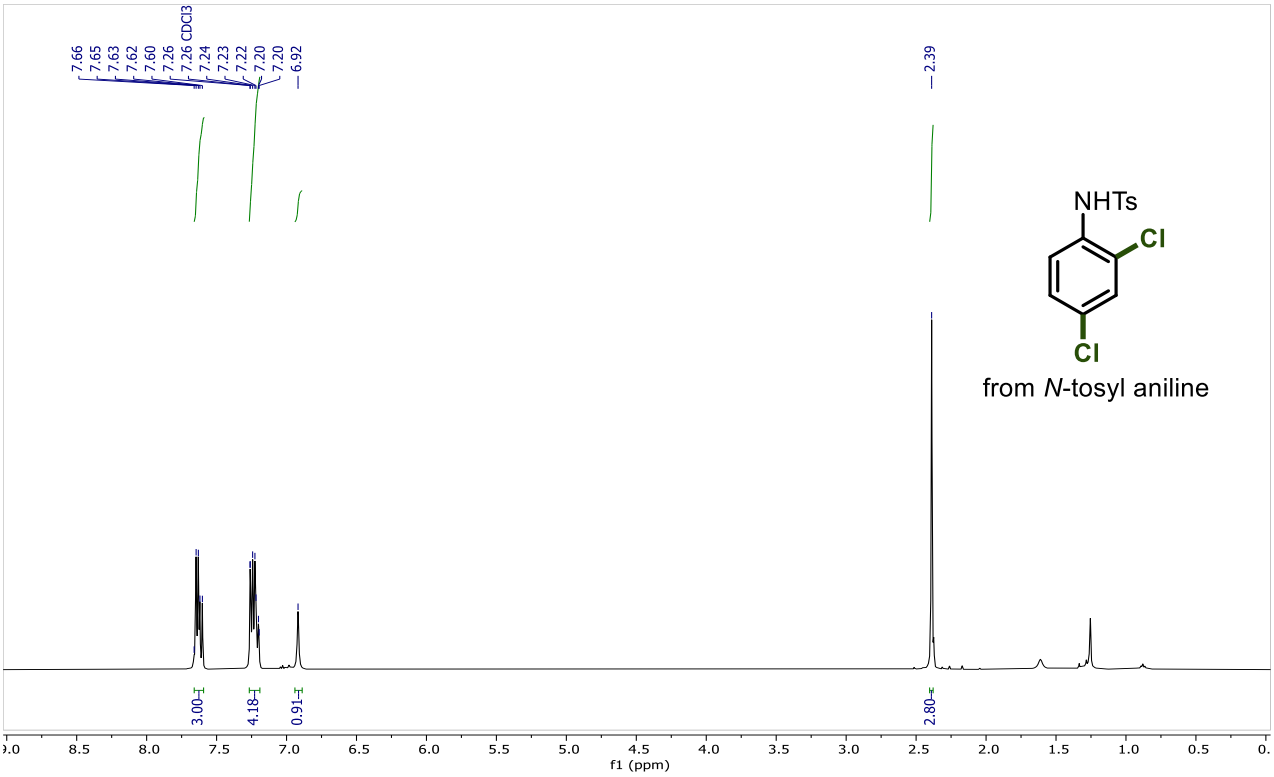
3-benzyl-1-methyl-1*H*-indole **(325)** and 2-benzyl-1-methyl-1*H*-indole **(326)**

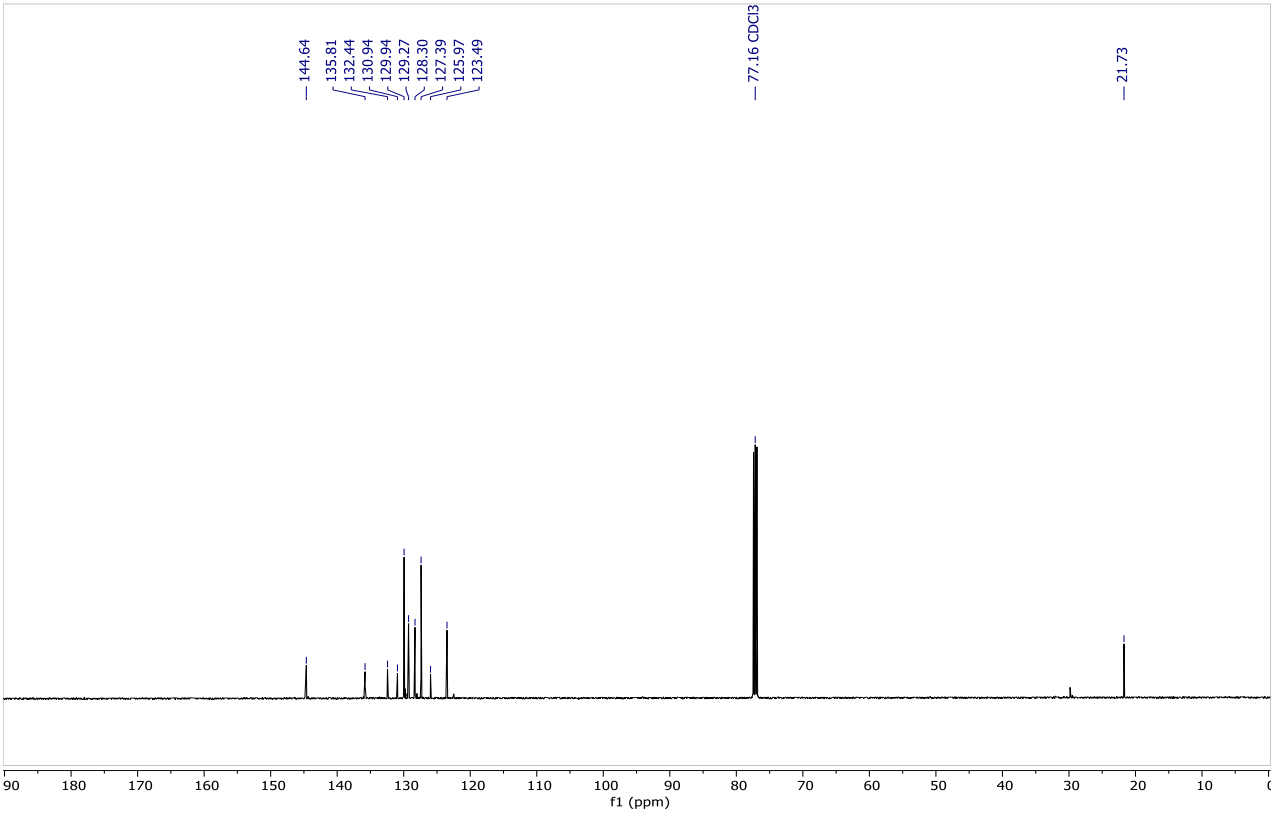




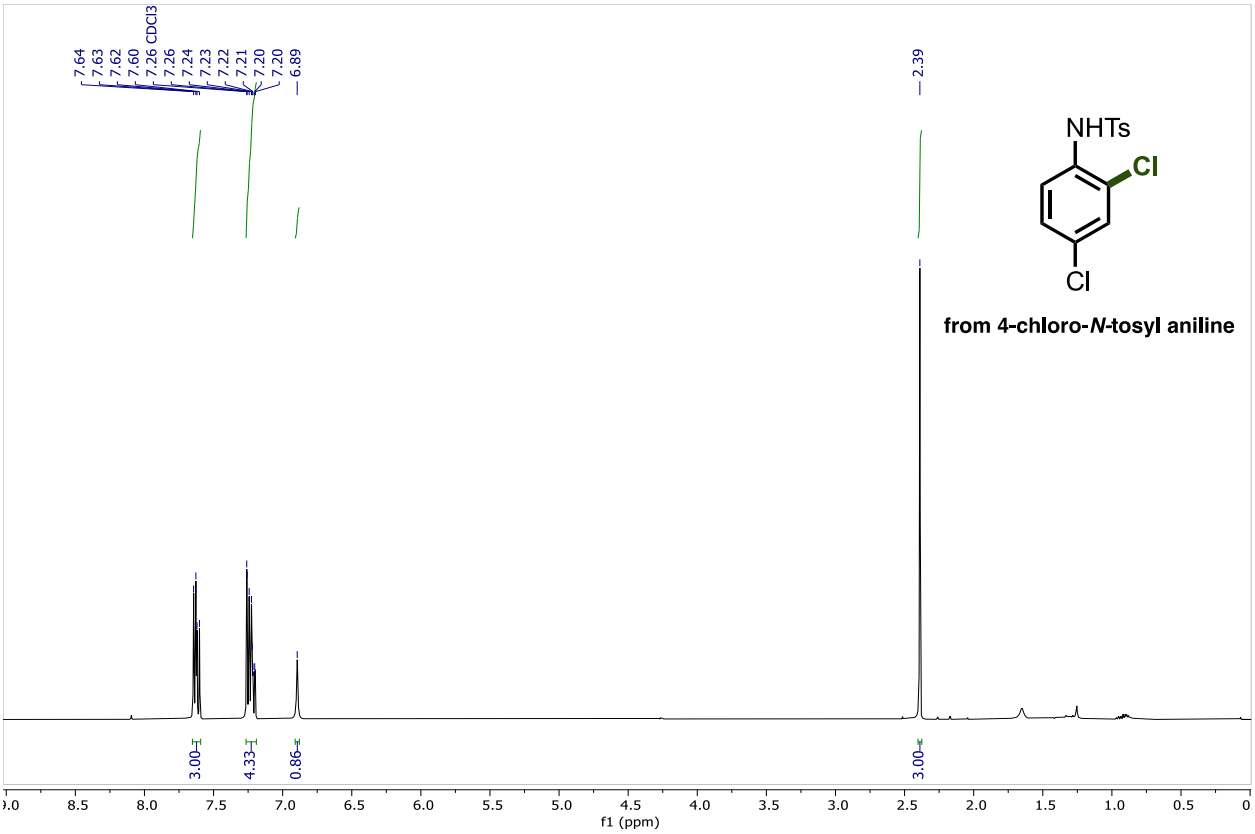
^{1}H, ^{13}C, ^{19}F, and NOE NMR spectrums of Chapter 3

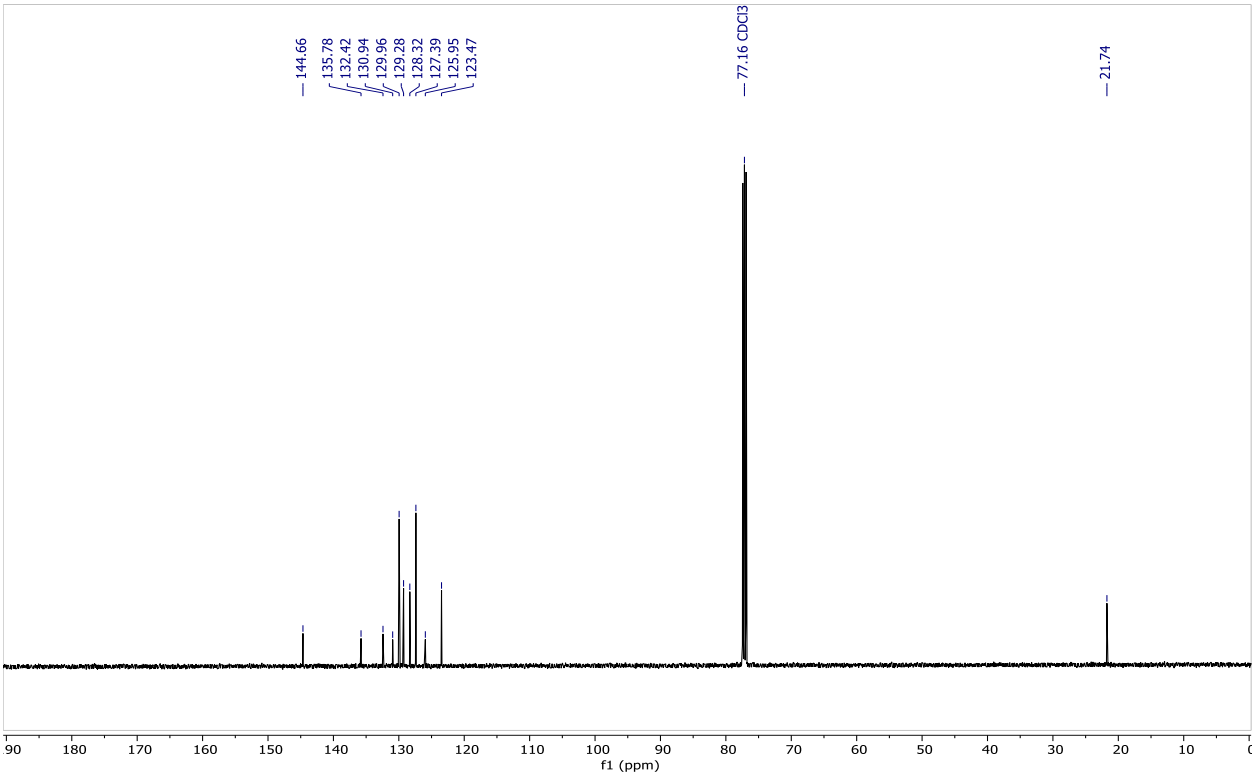
N-(2,4-dichlorophenyl)-4-methylbenzenesulfonamide (**331**)



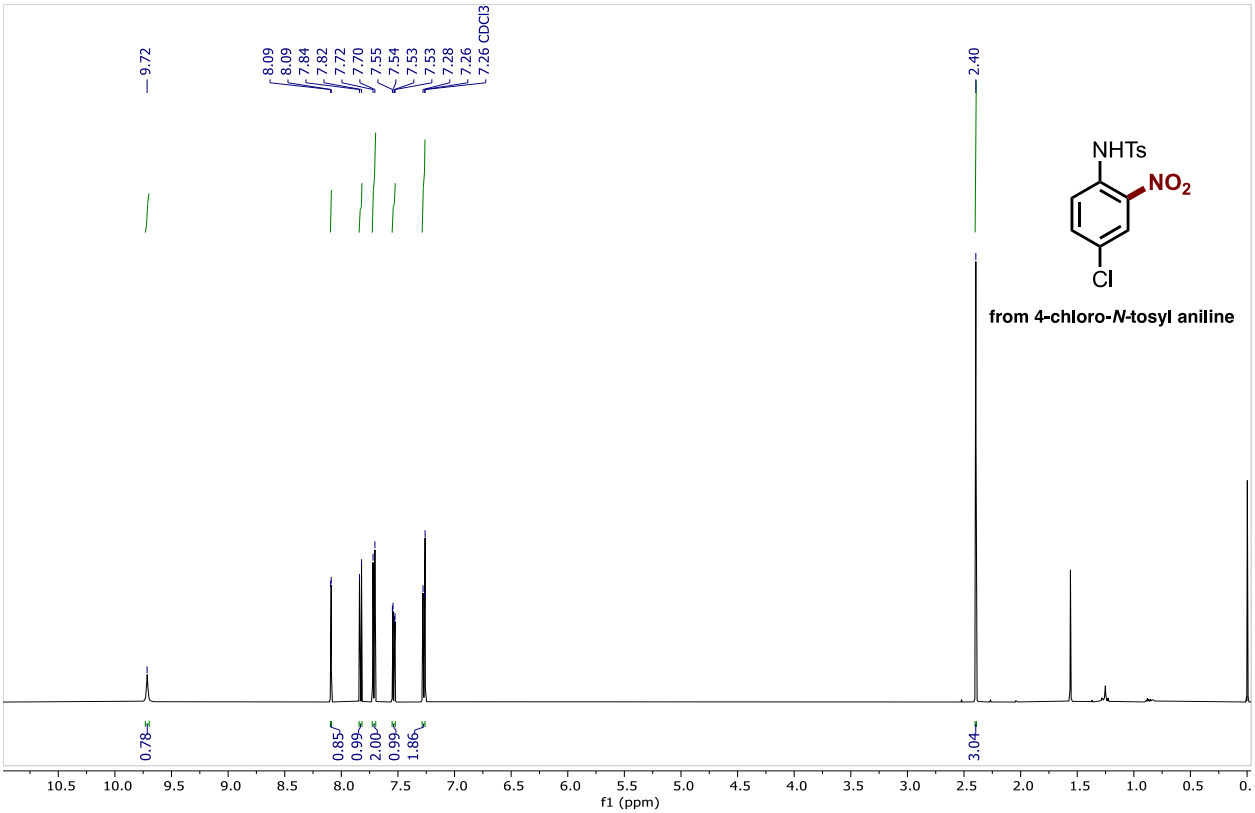


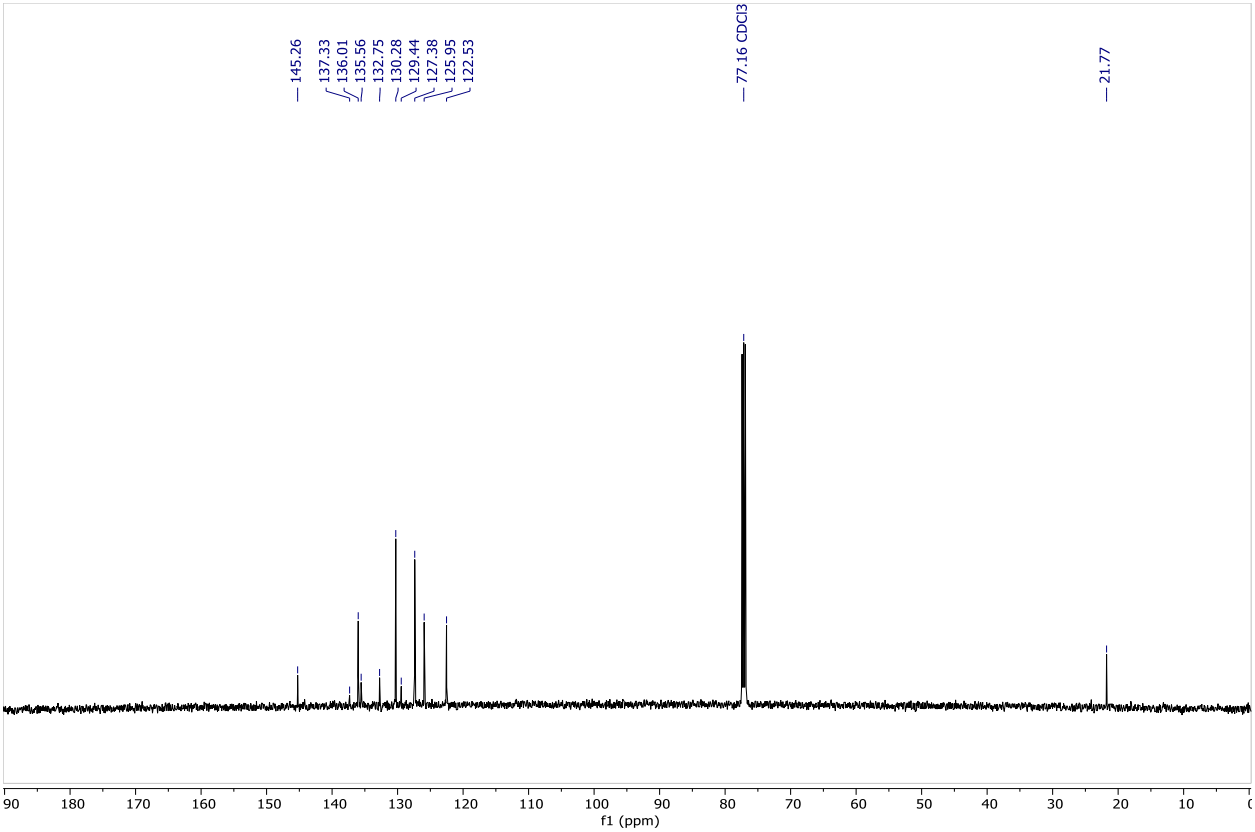
N-(2,4-dichlorophenyl)-4-methylbenzenesulfonamide (**331**)



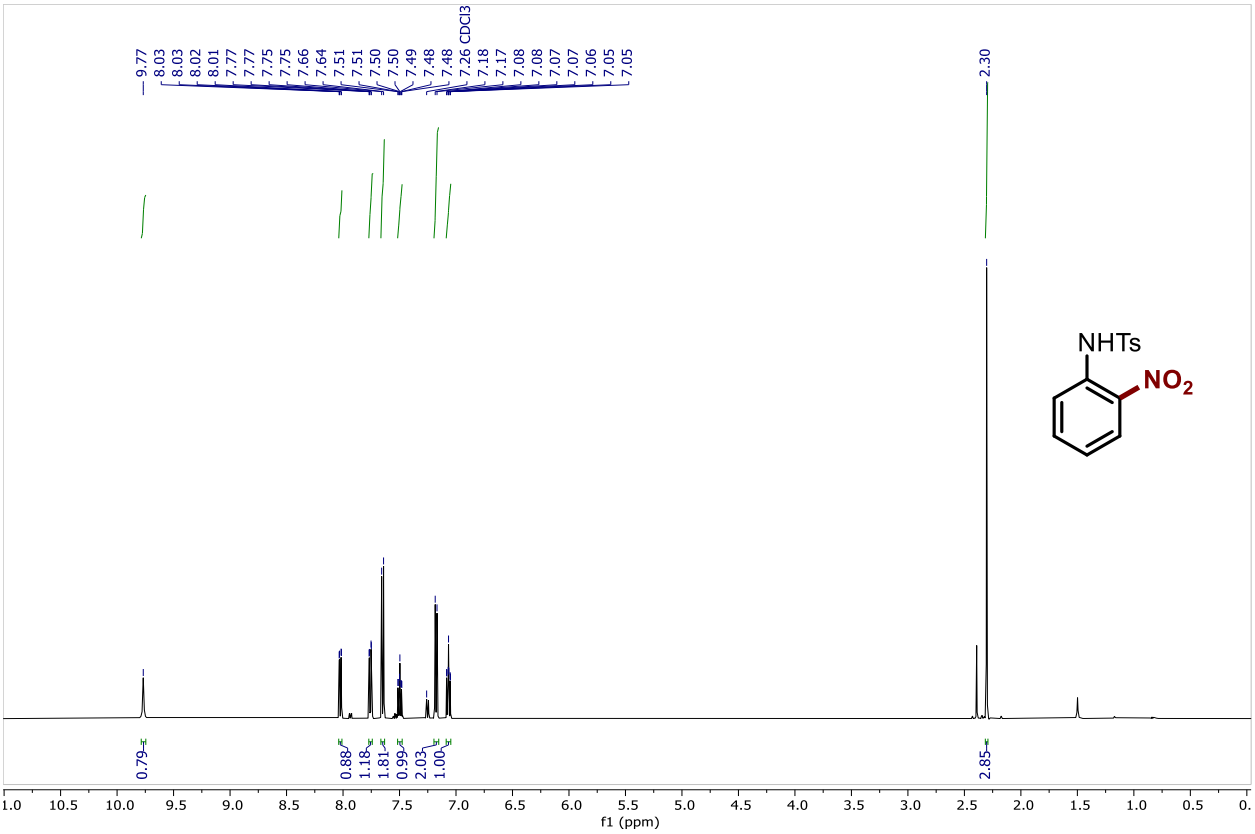


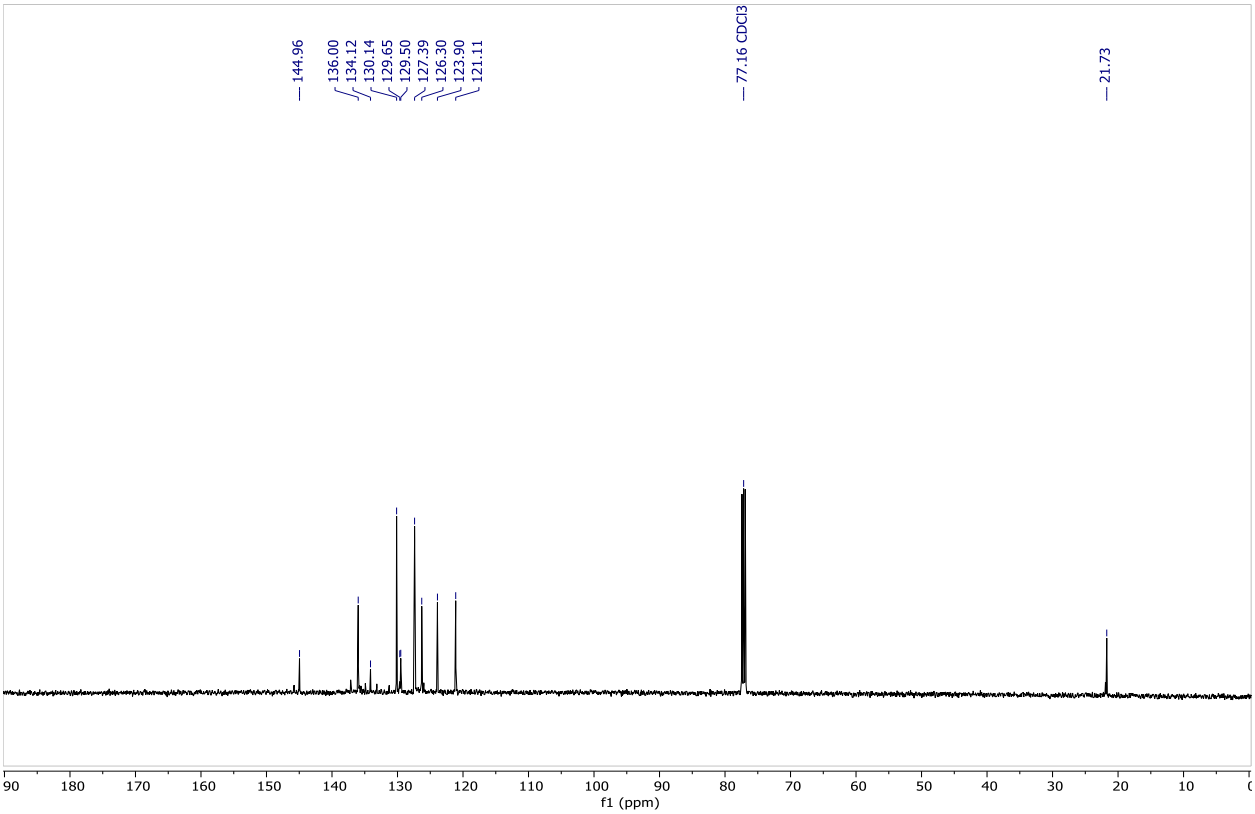
N-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide (**332**).



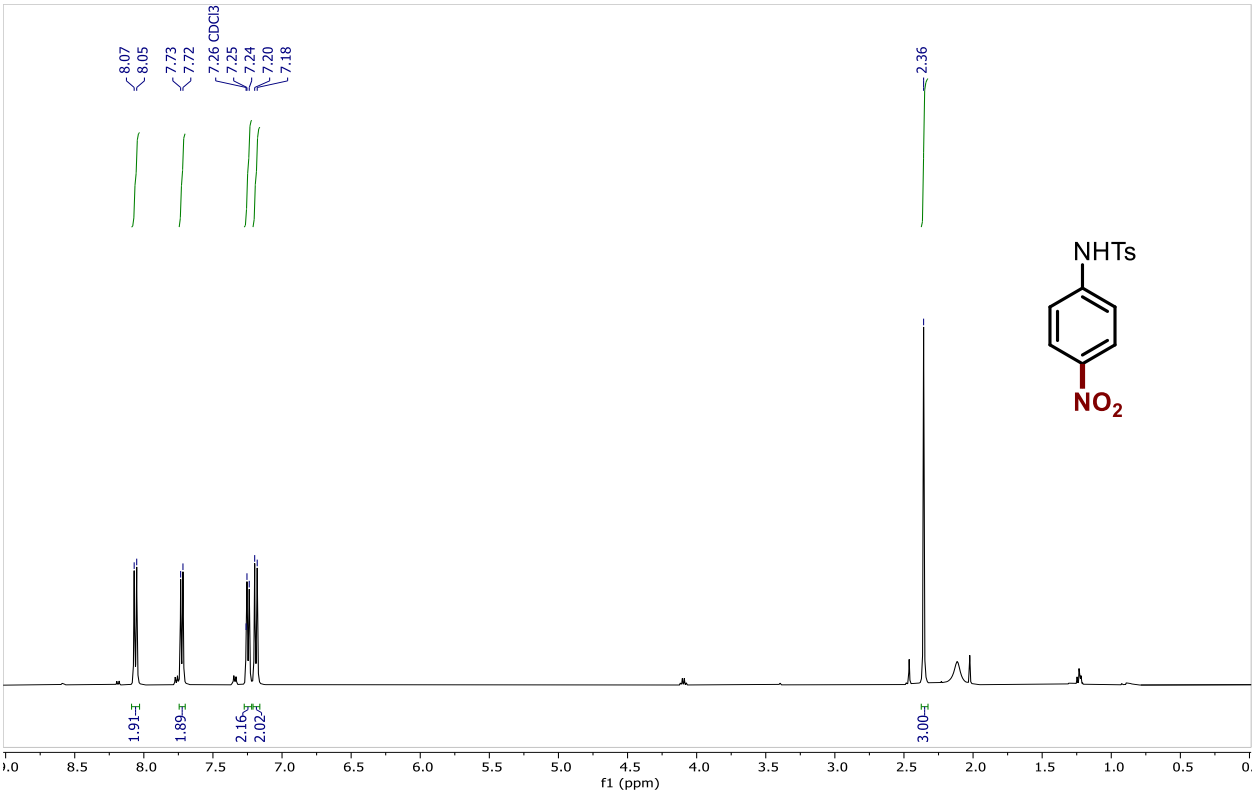


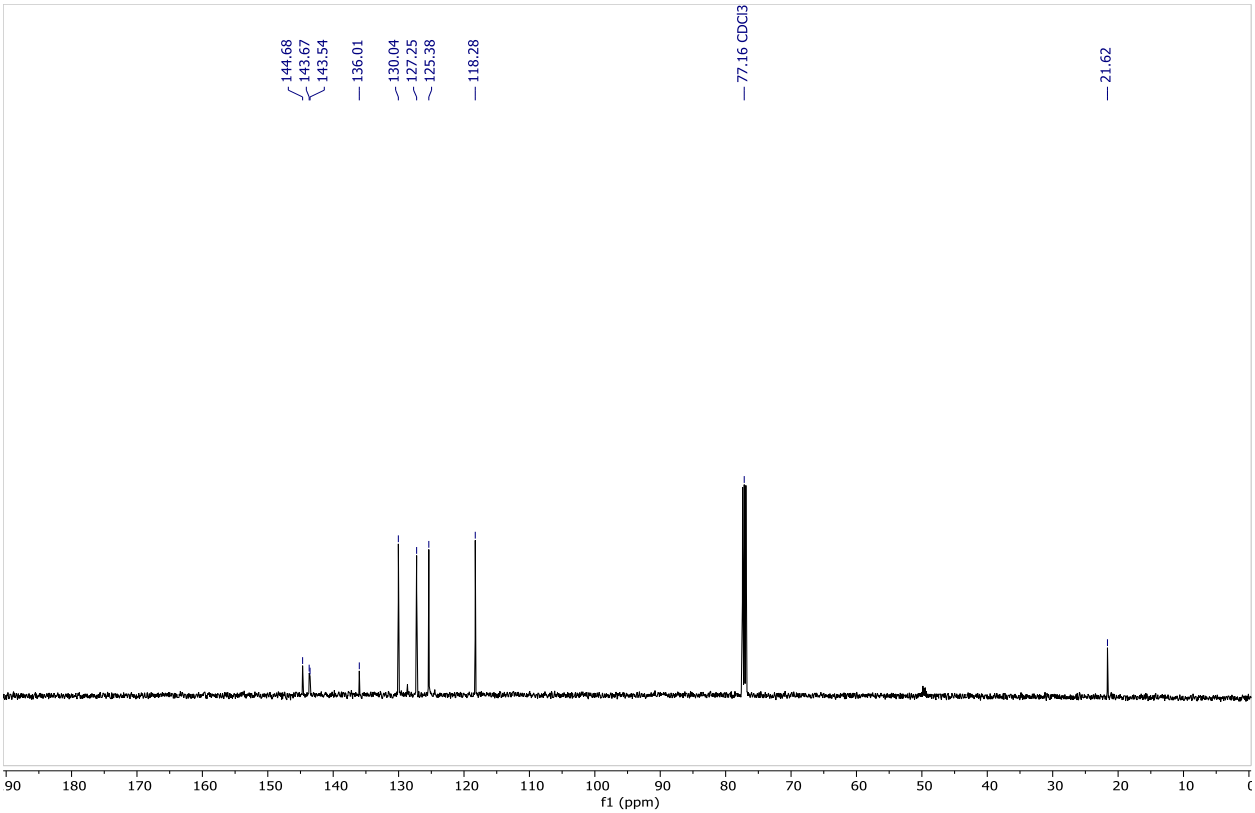
4-methyl-*N*-(2-nitrophenyl)benzenesulfonamide (**333**)



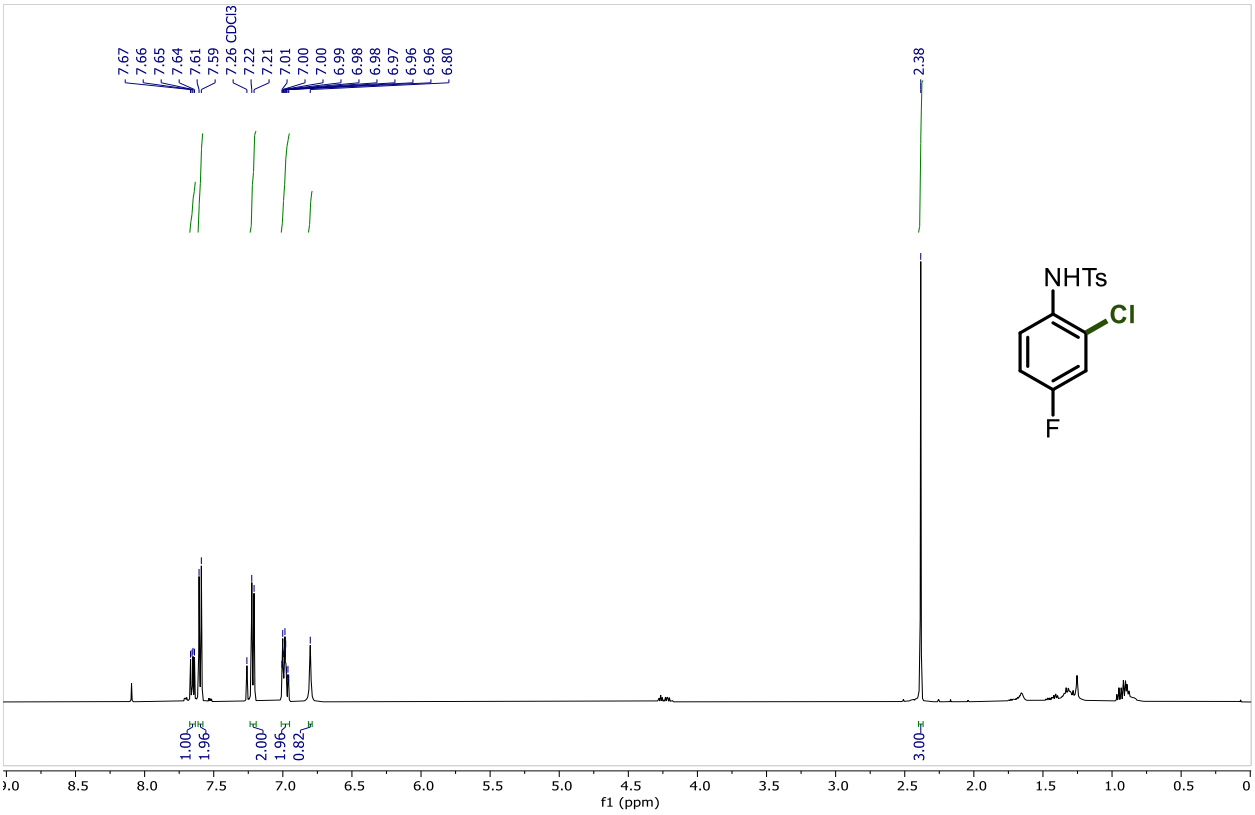


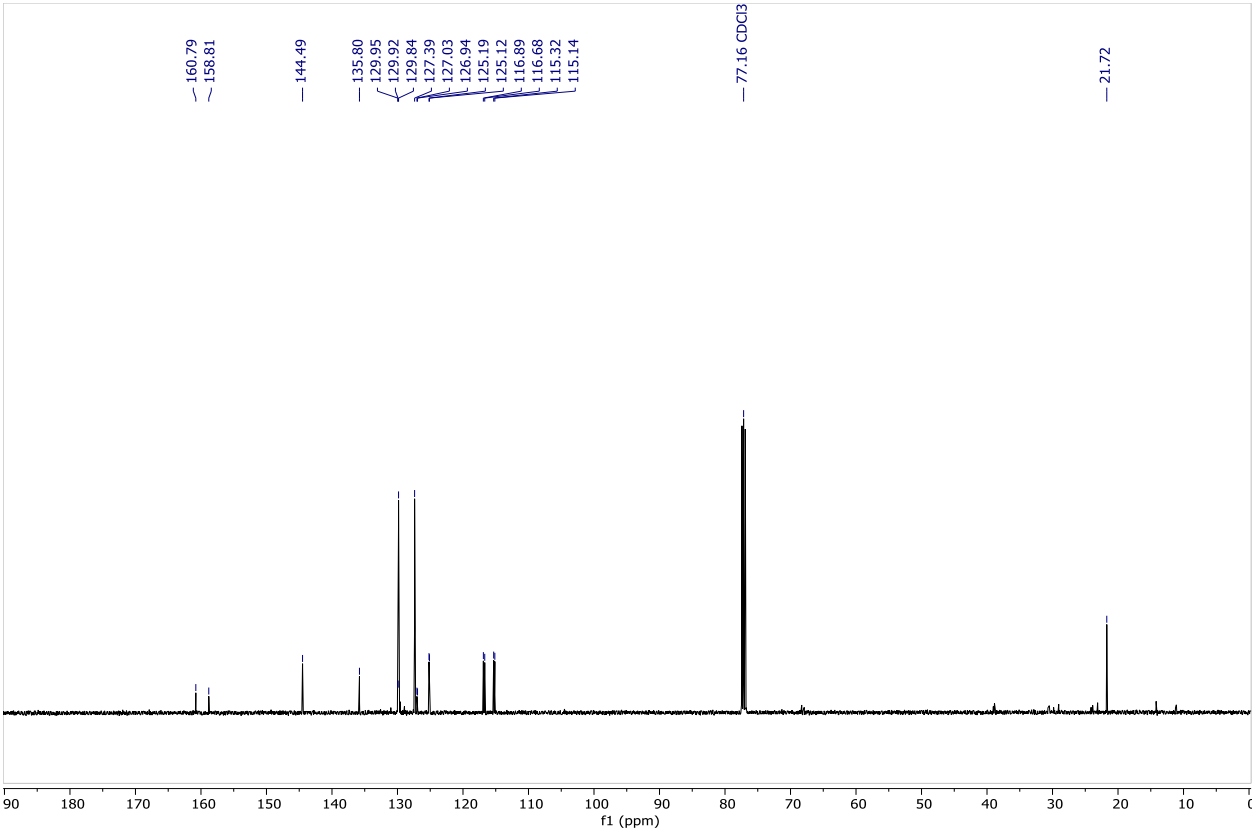
4-methyl-*N*-(4-nitrophenyl)benzenesulfonamide (**334**)

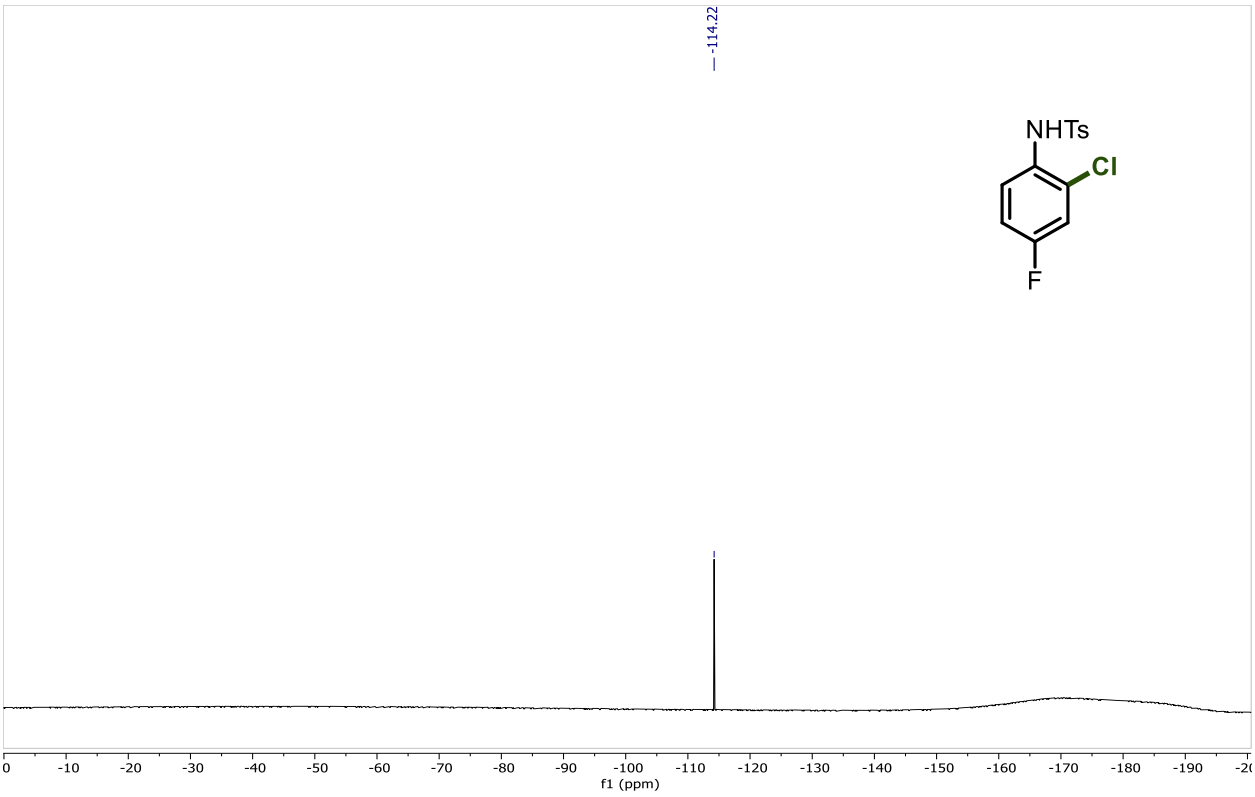




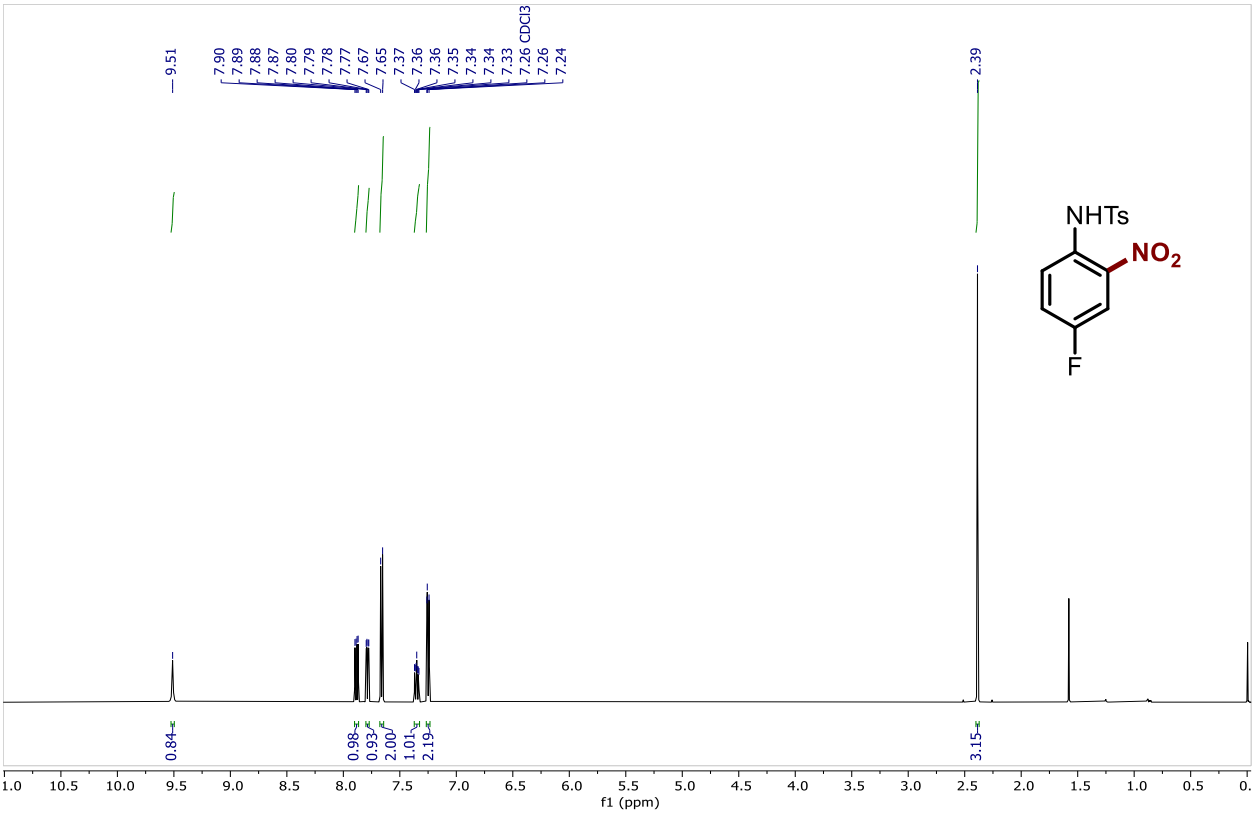
N-(2-chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (**335**)

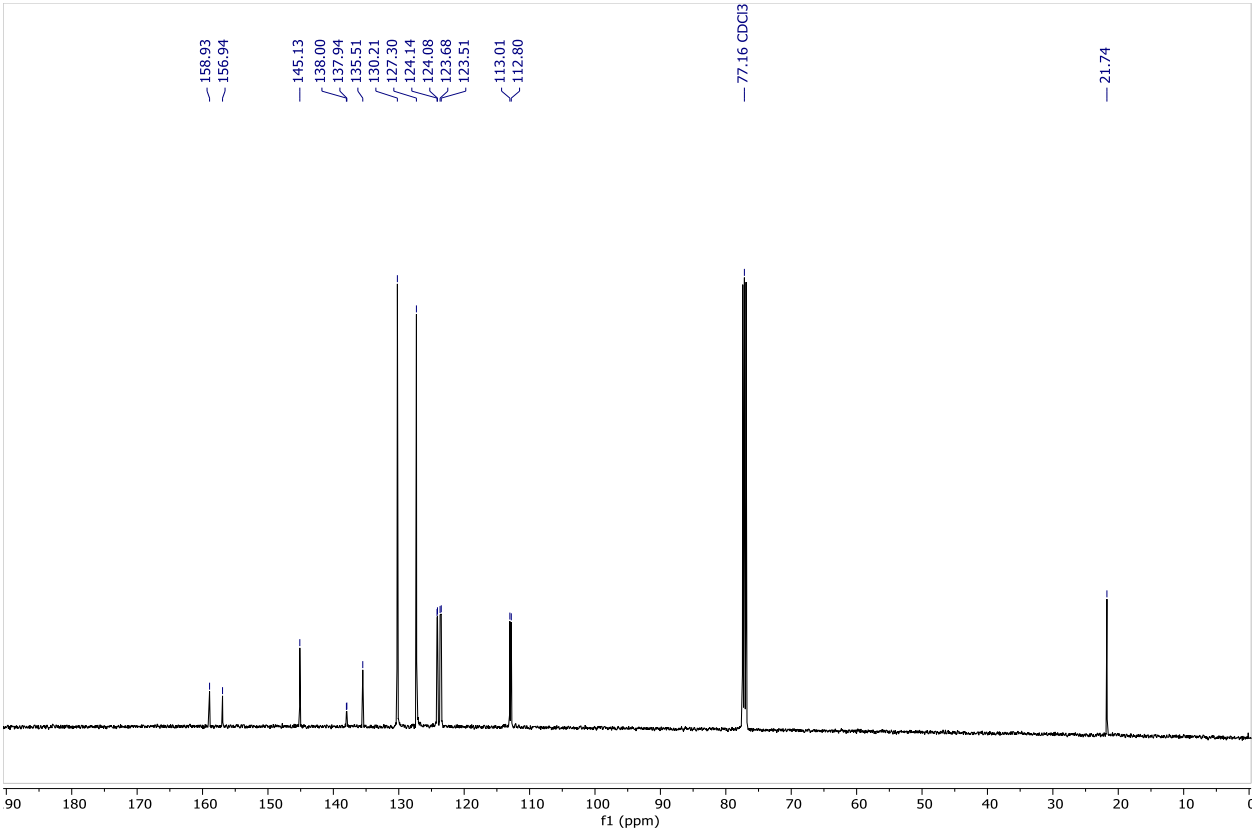


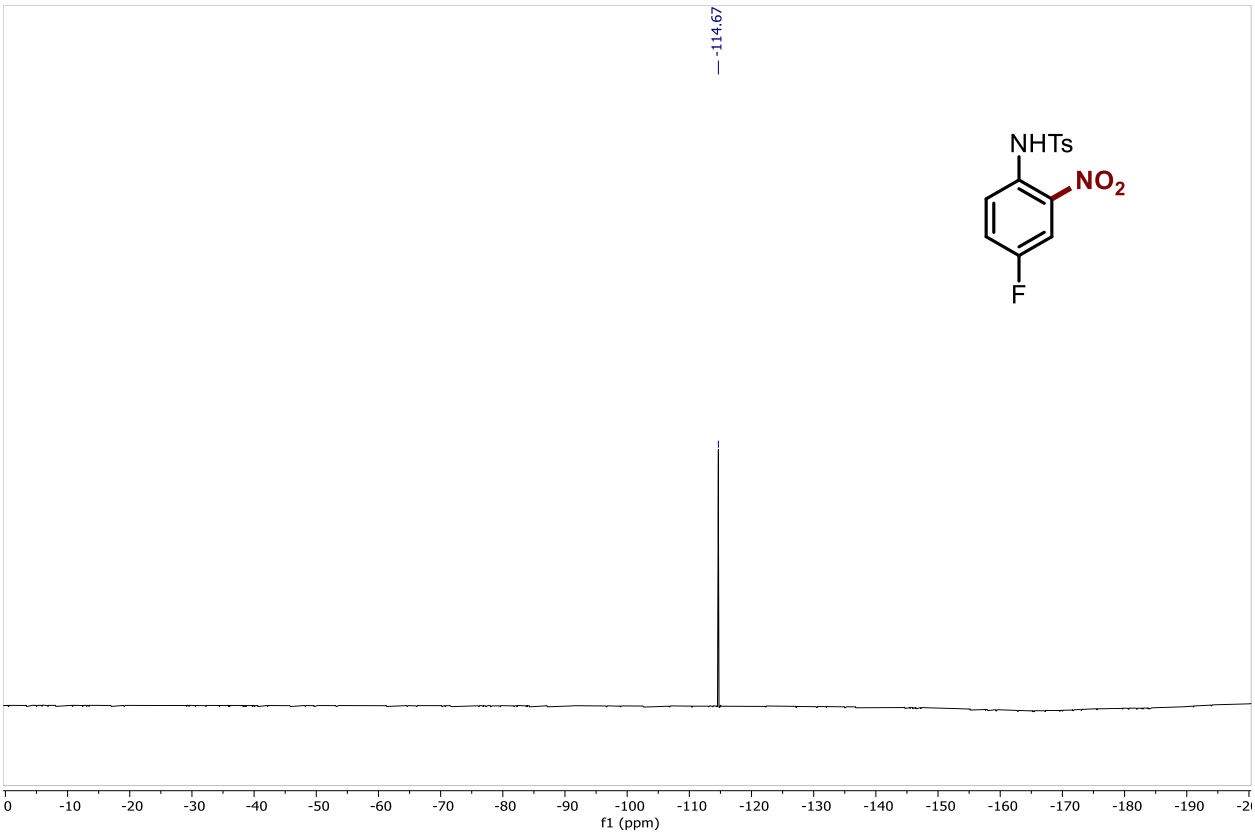



-114.22
NHTs
Cl
F
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

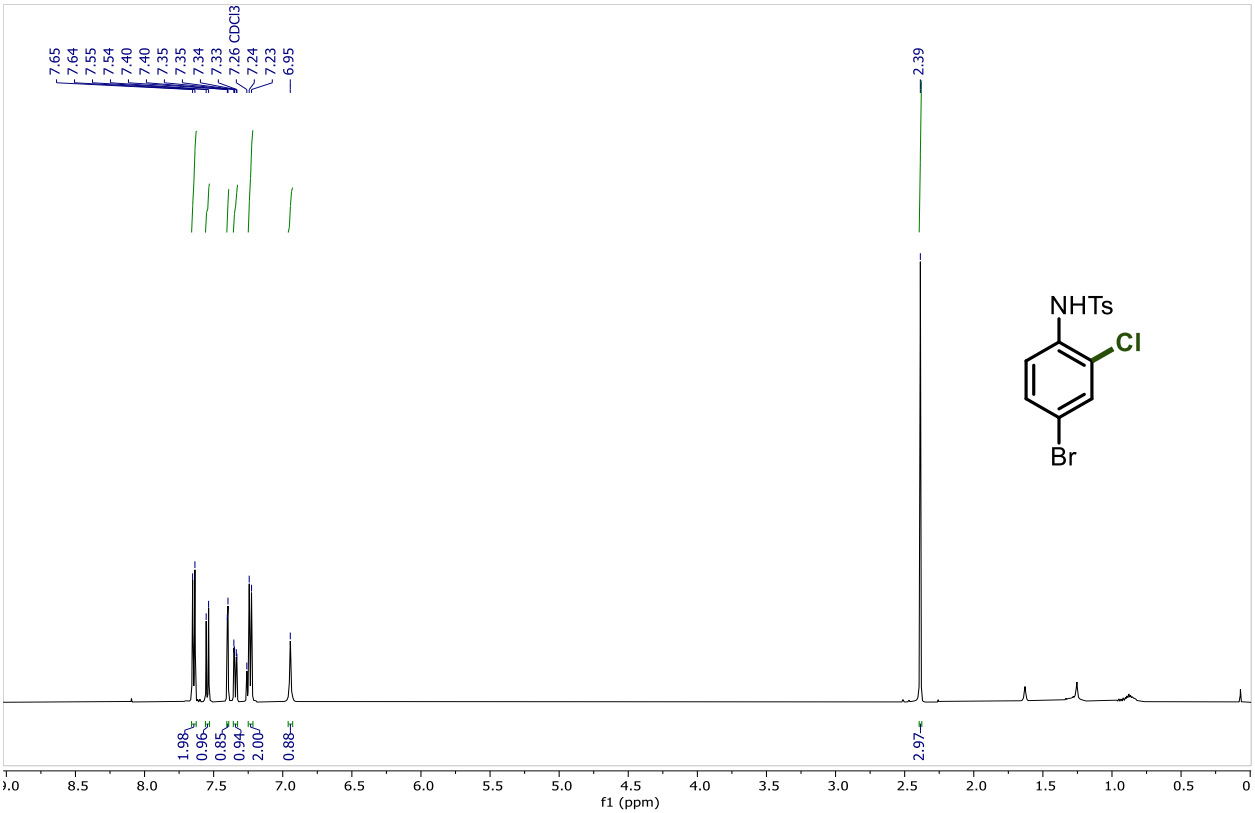
N-(4-fluoro-2-nitrophenyl)-4-methylbenzenesulfonamide (**336**)

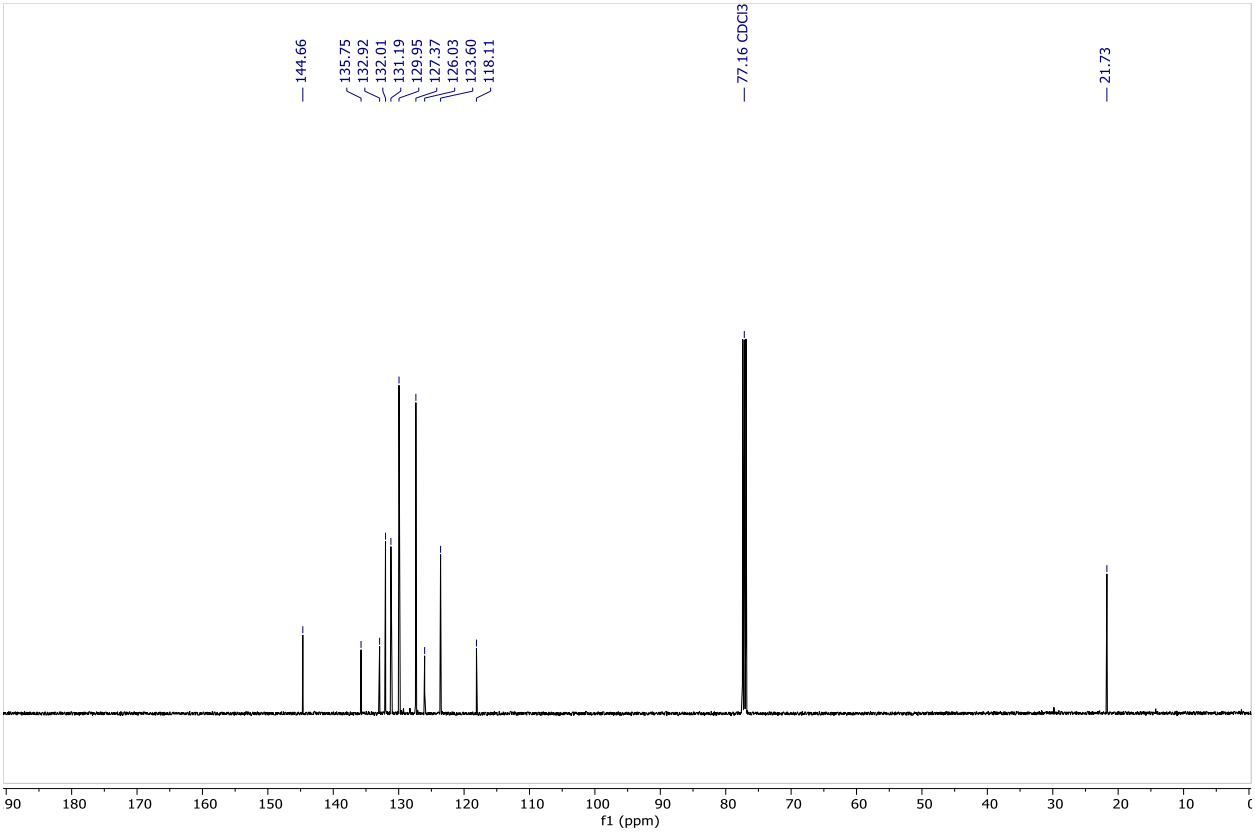




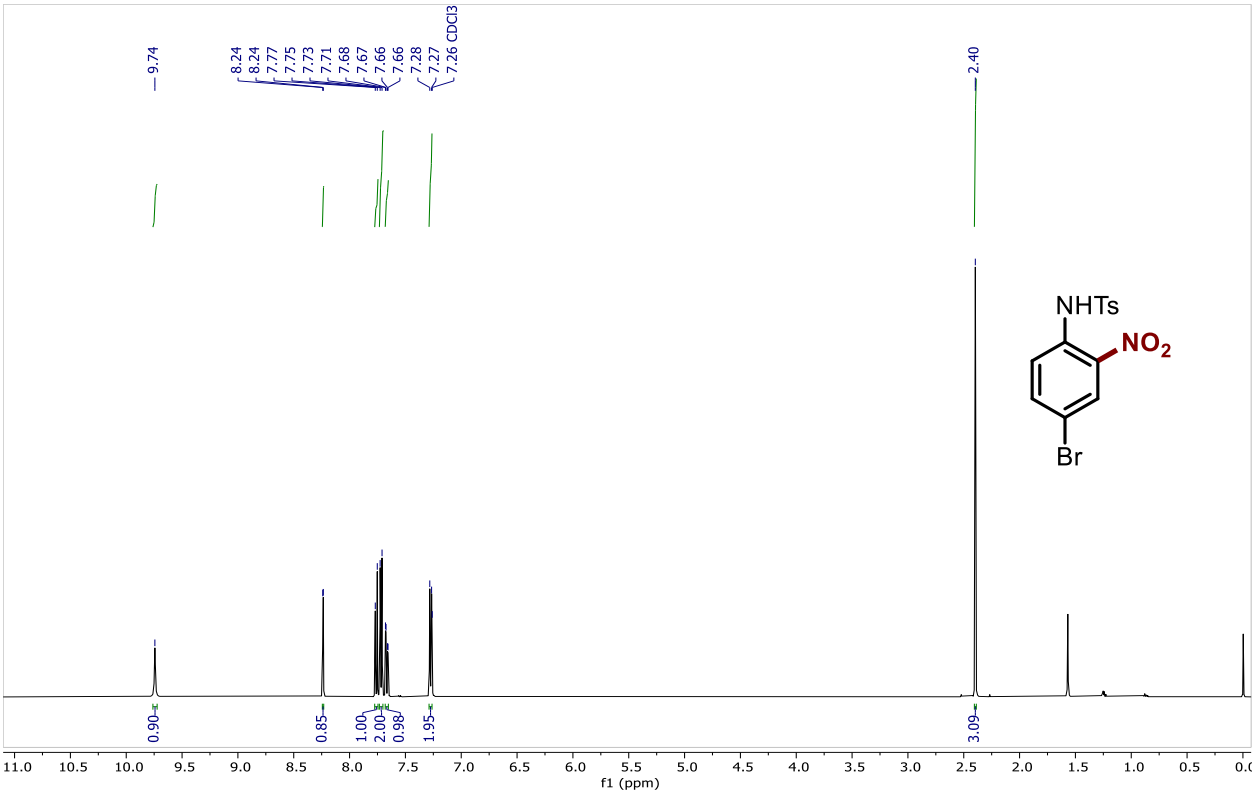

-114.67
NHTs
NO2
F
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

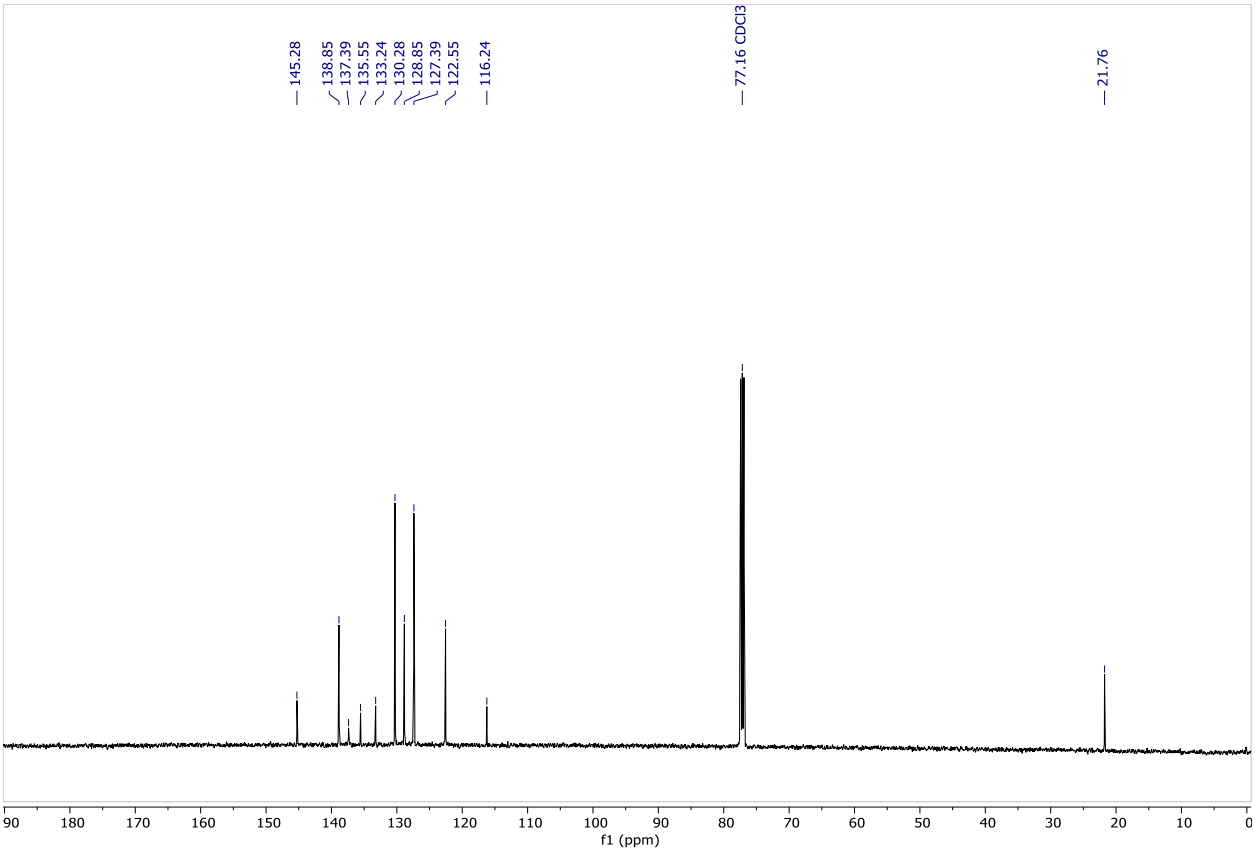
N-(4-bromo-2-chlorophenyl)-4-methylbenzenesulfonamide (**337**)



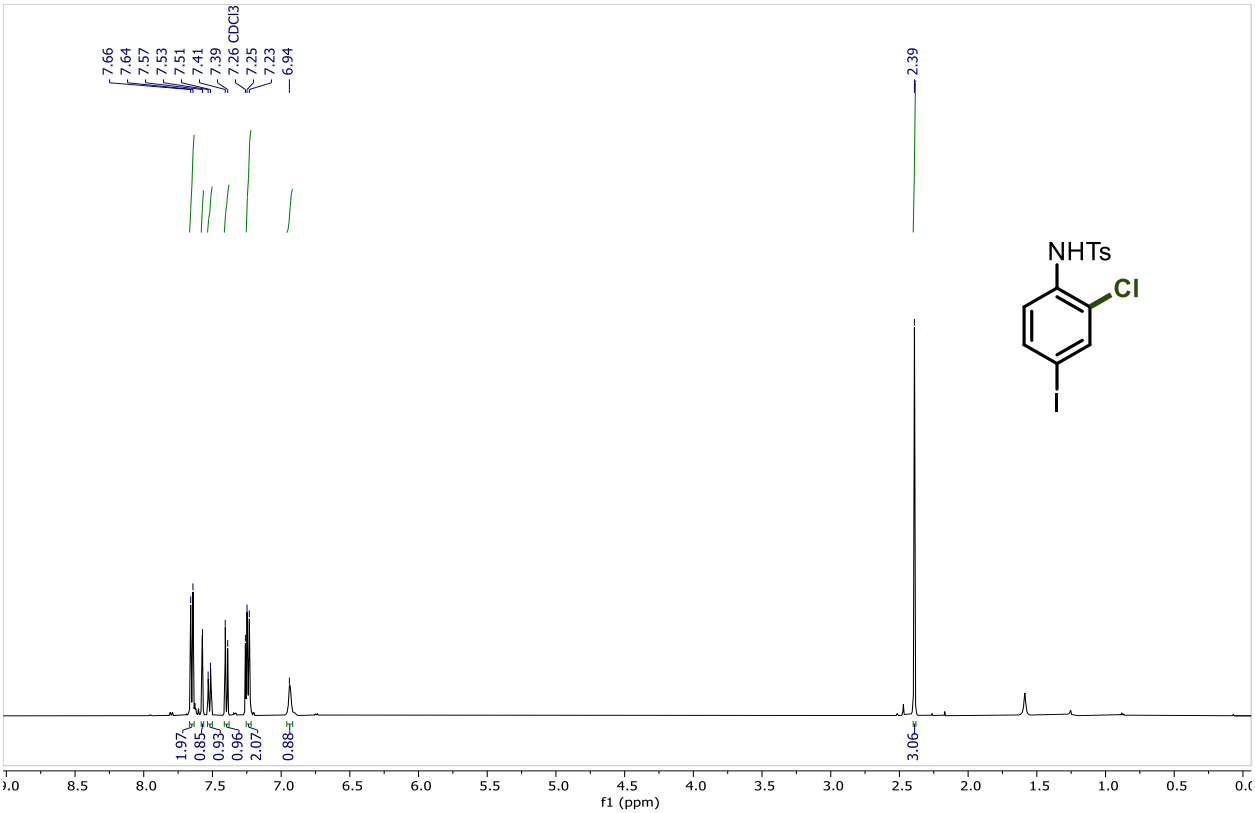


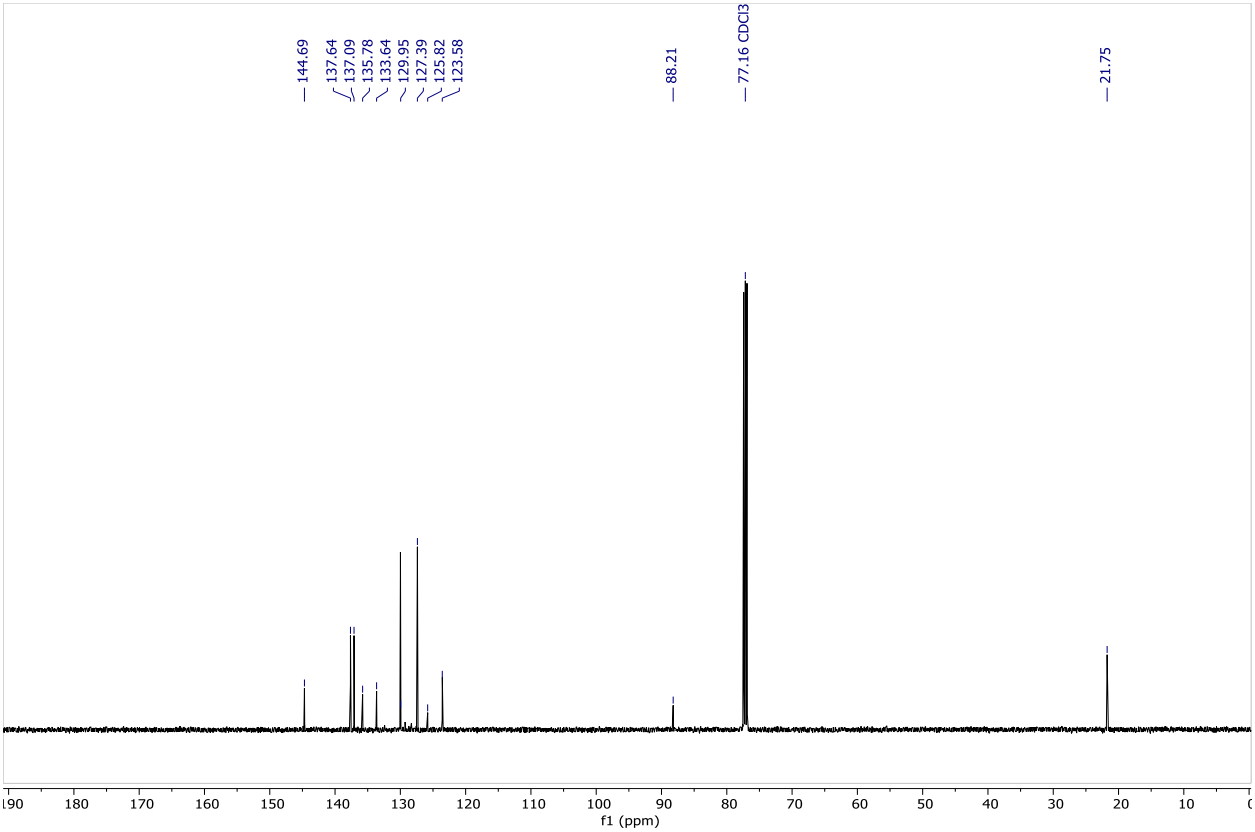
N-(4-bromo-2-nitrophenyl)-4-methylbenzenesulfonamide (**338**)



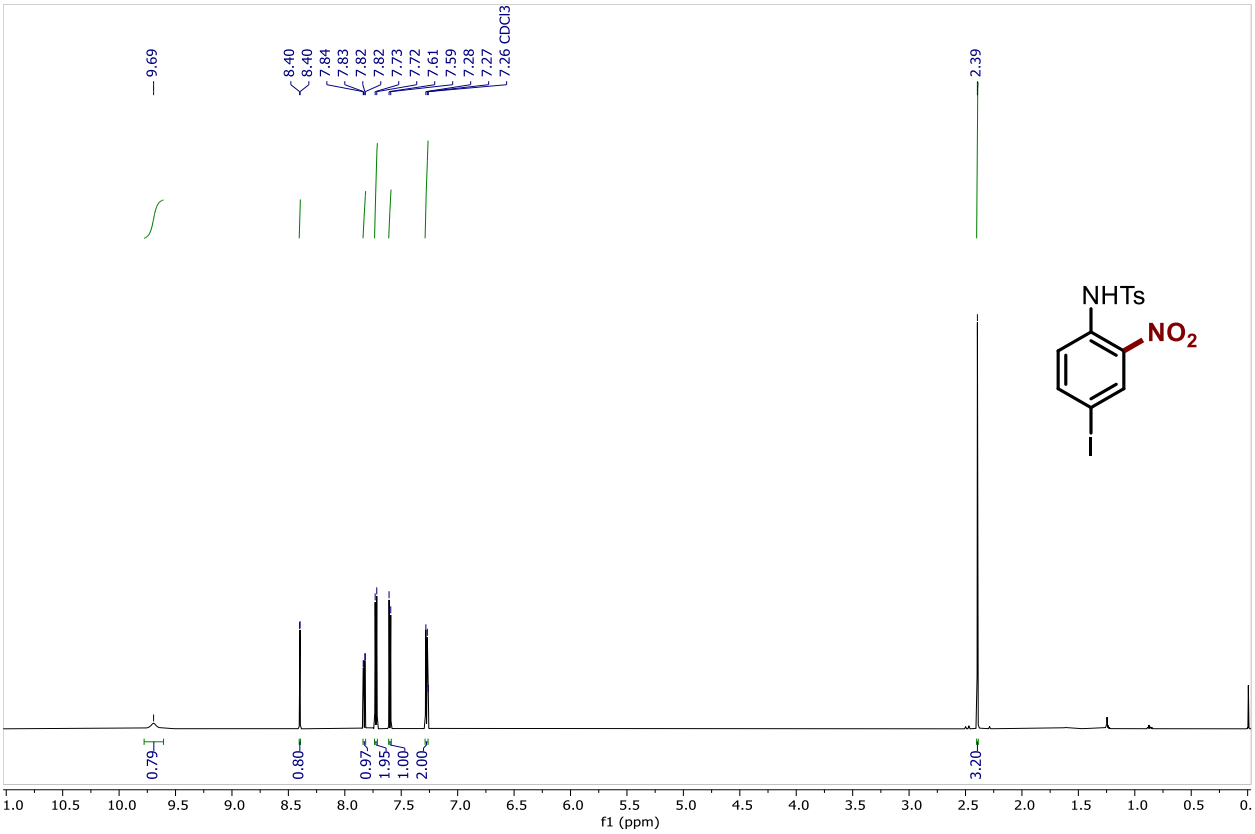


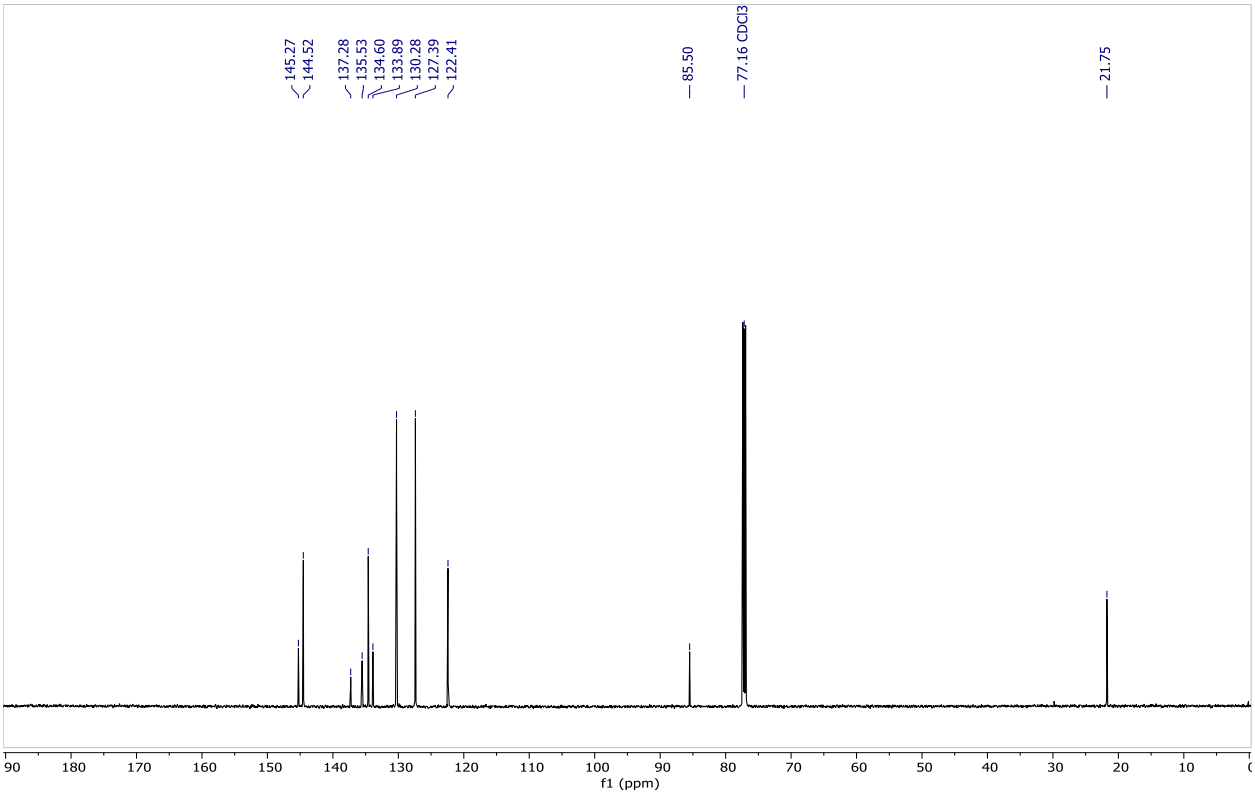
N-(2-chloro-4-iodophenyl)-4-methylbenzenesulfonamide (**339**)



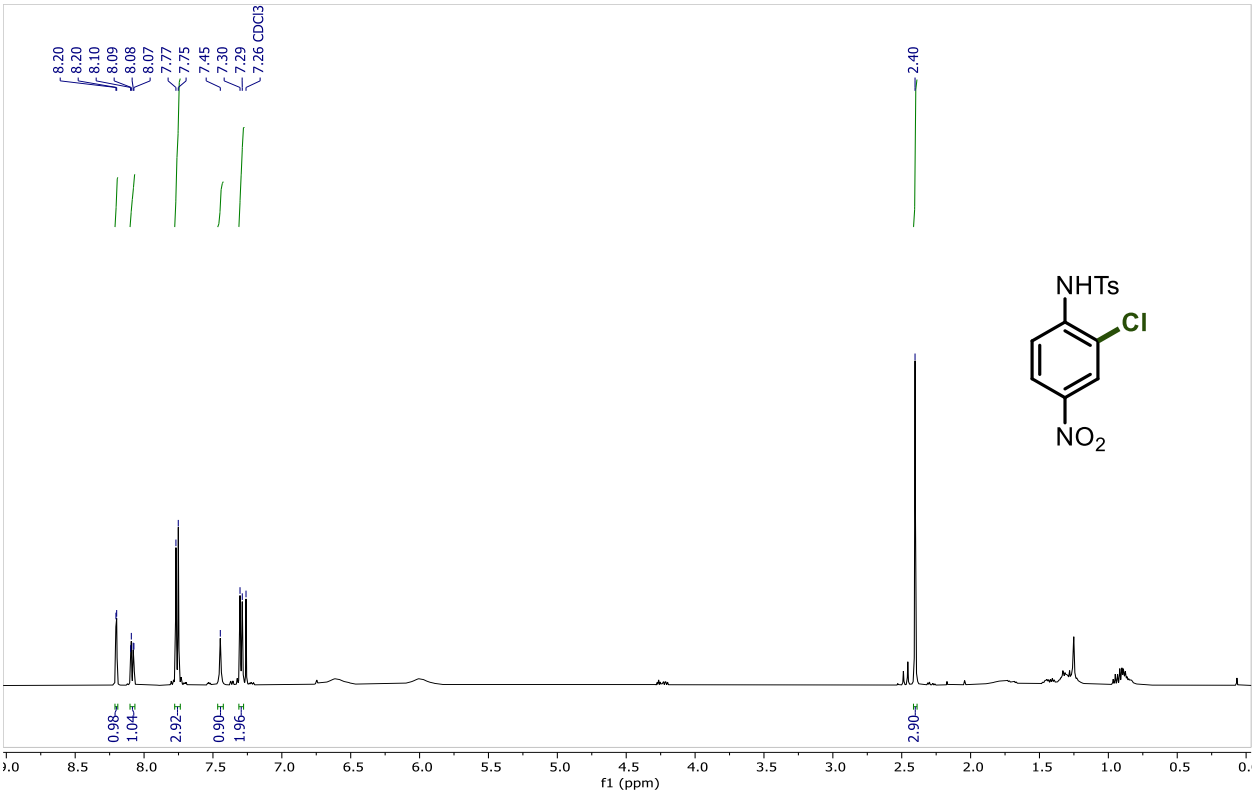


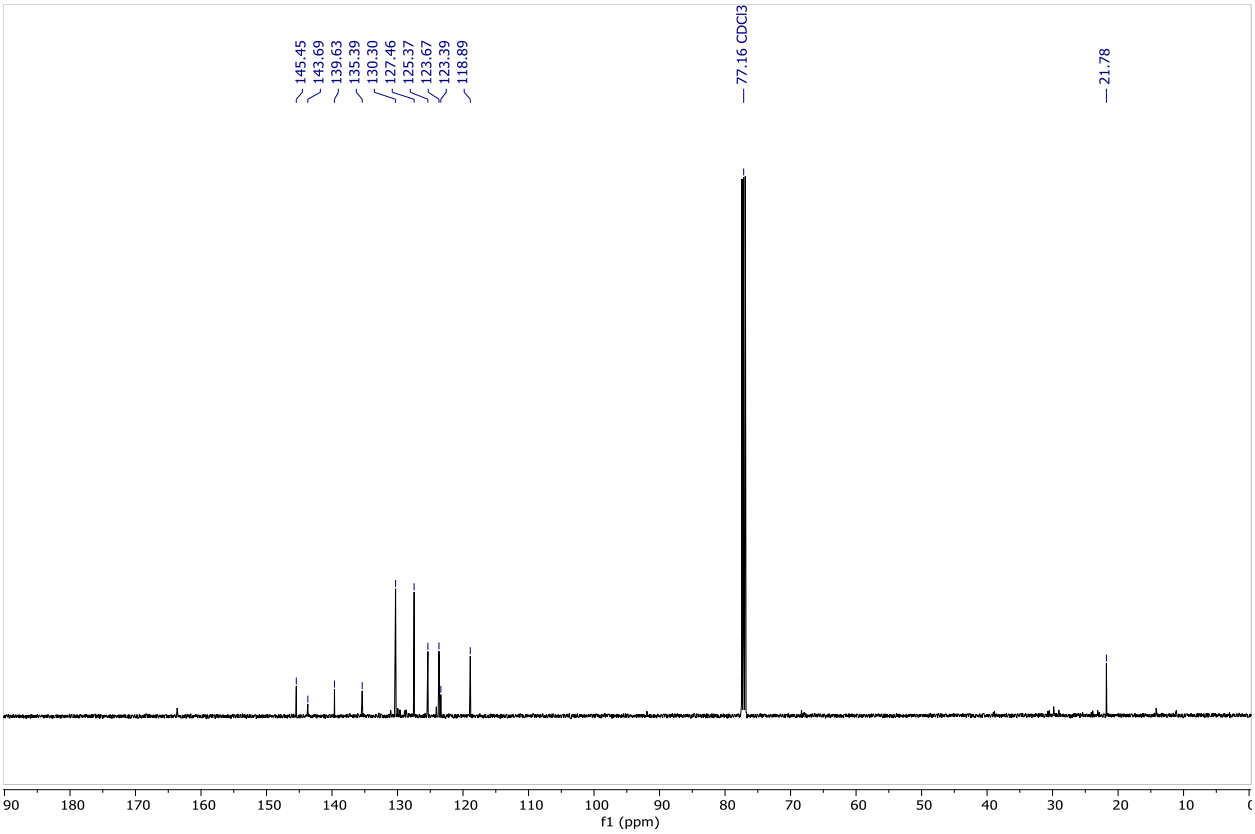
N-(4-iodo-2-nitrophenyl)-4-methylbenzenesulfonamide (**340**)



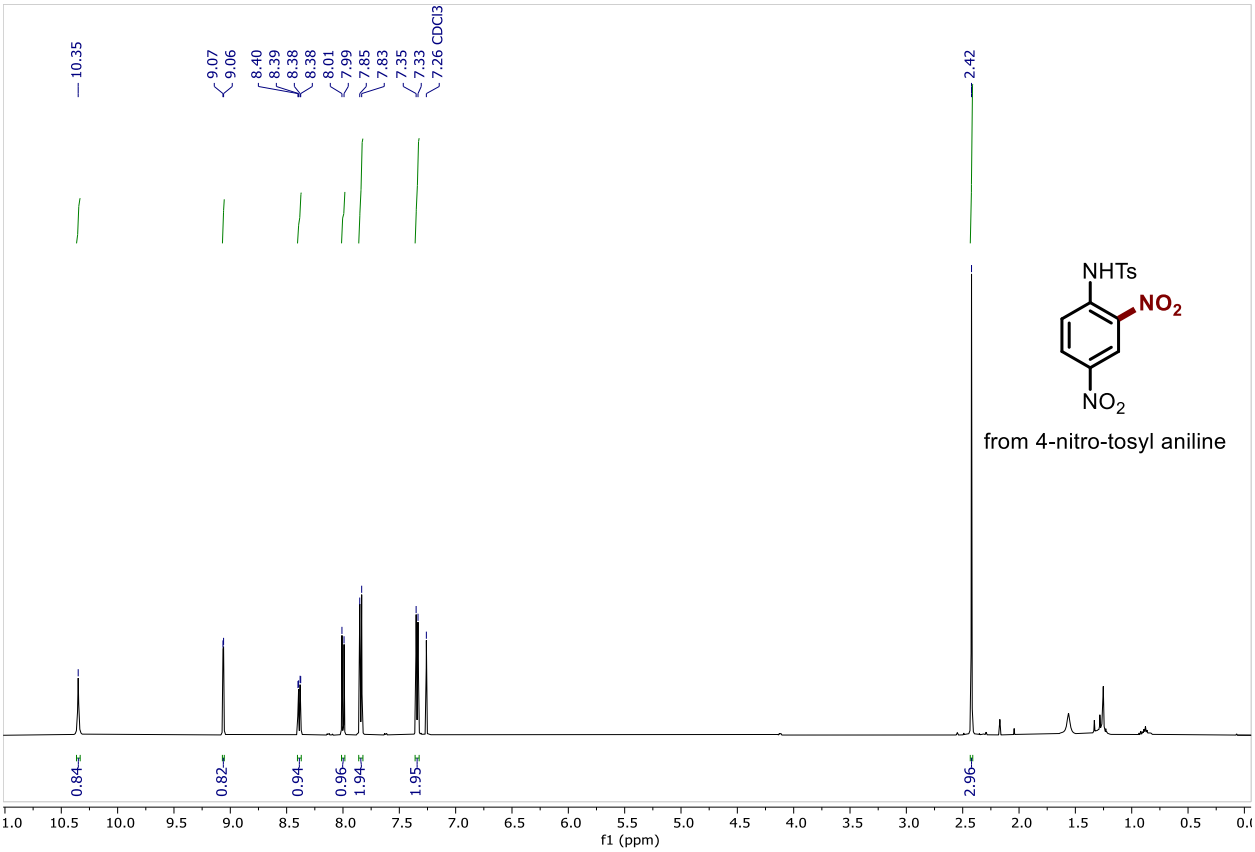


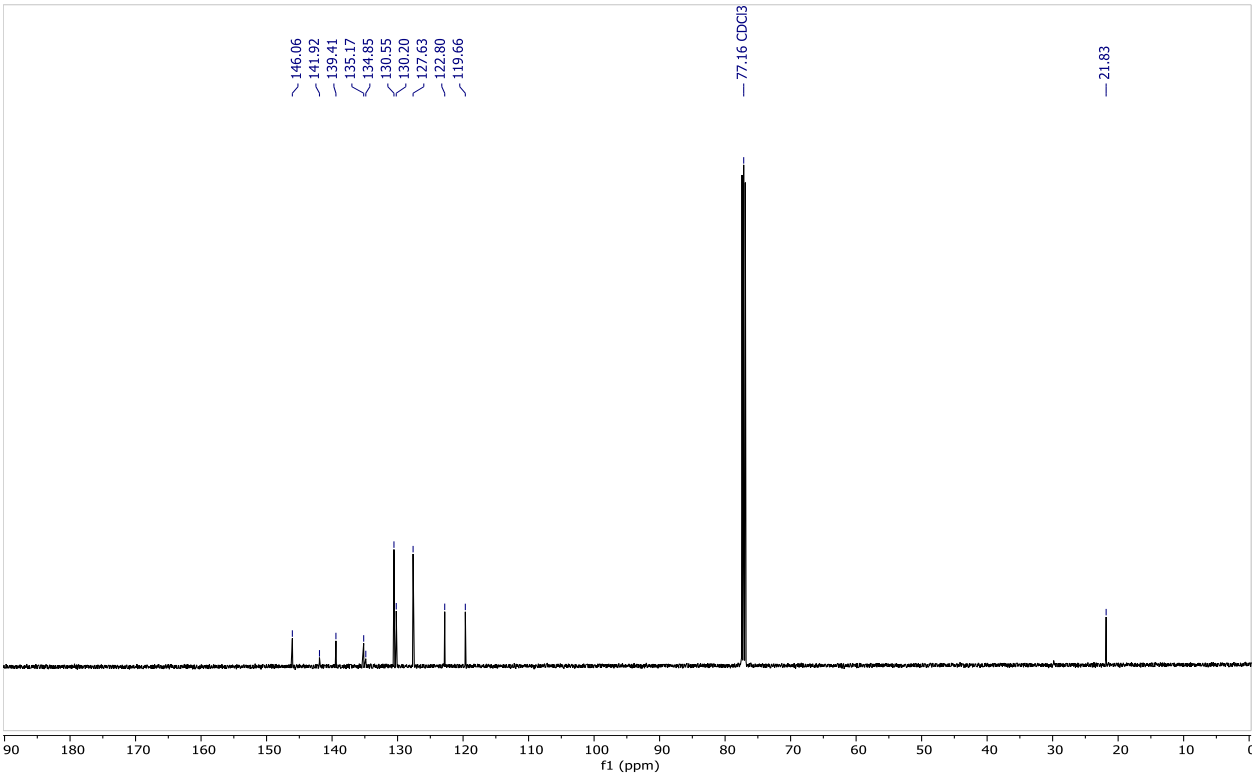
N-(2-chloro-4-nitrophenyl)-4-methylbenzenesulfonamide (**341**)



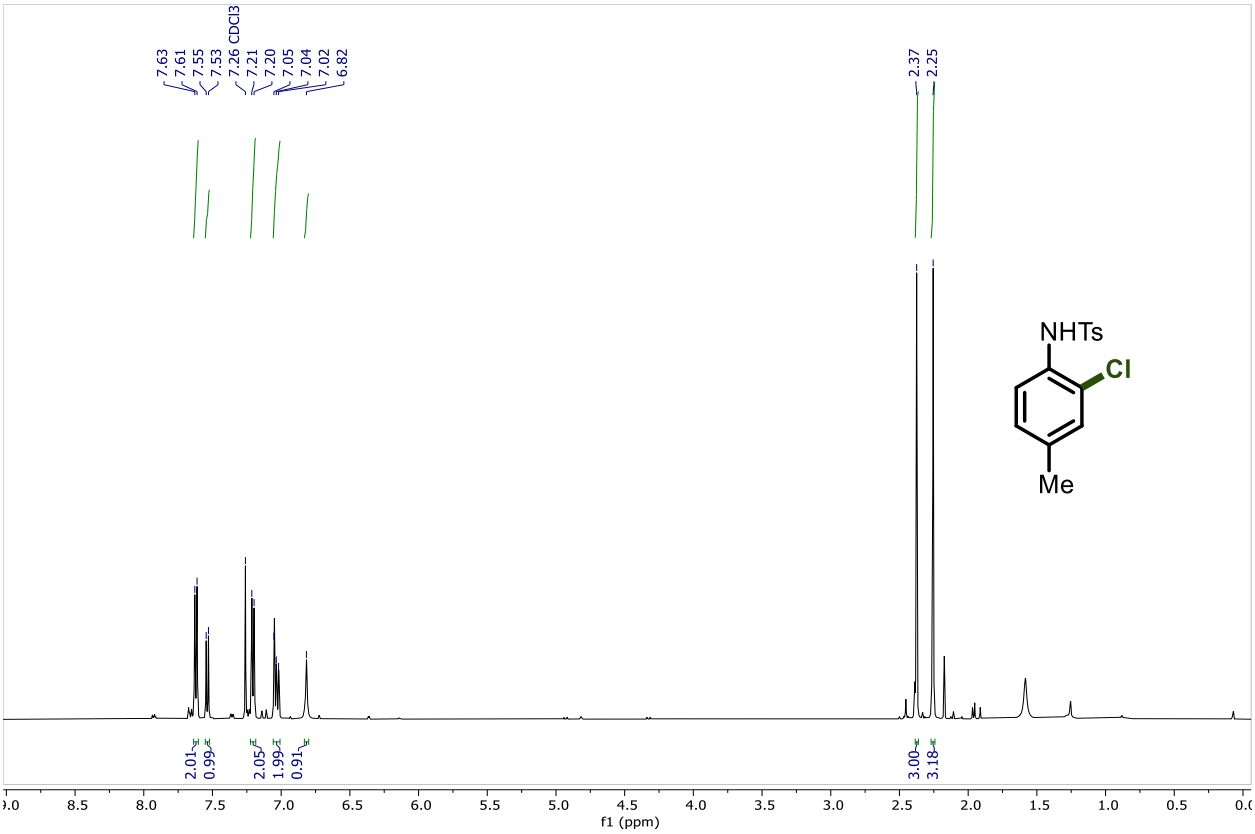


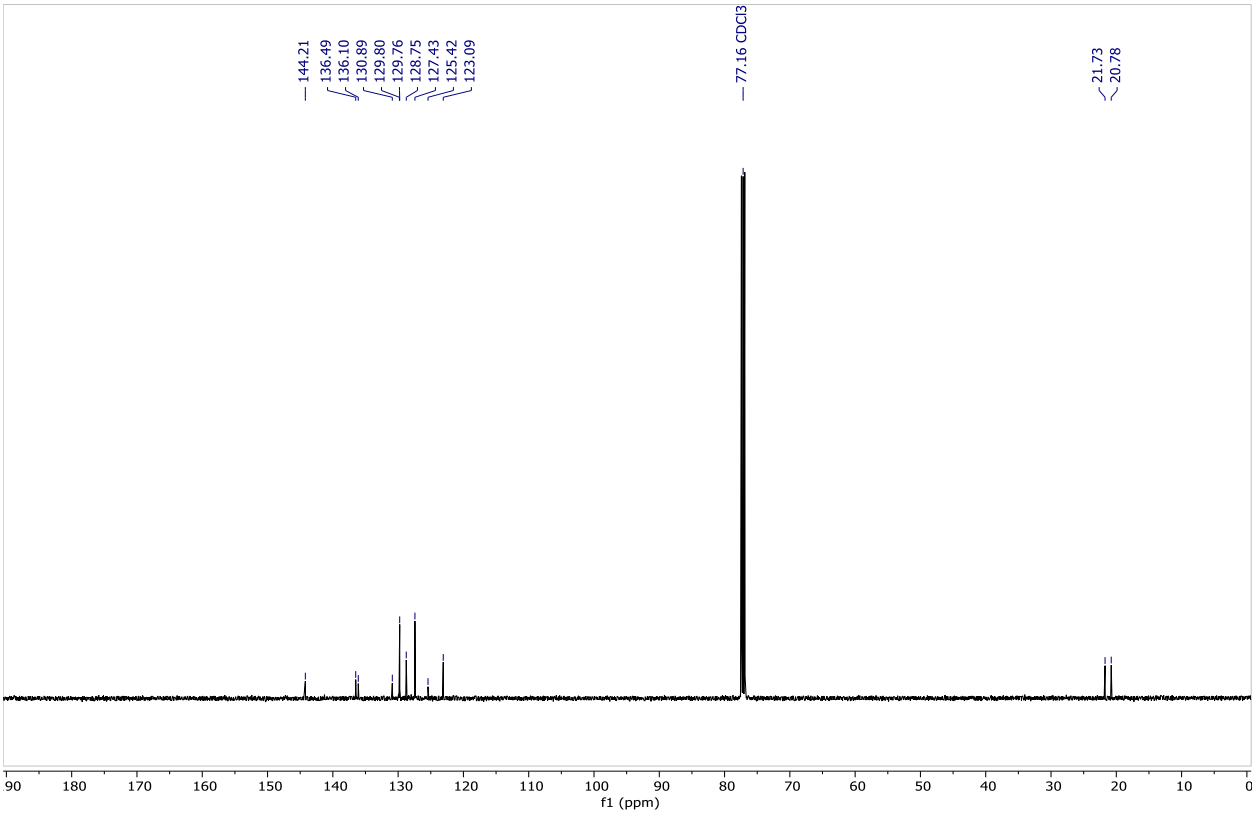
N-(2,4-dinitrophenyl)-4-methylbenzenesulfonamide (**342**)



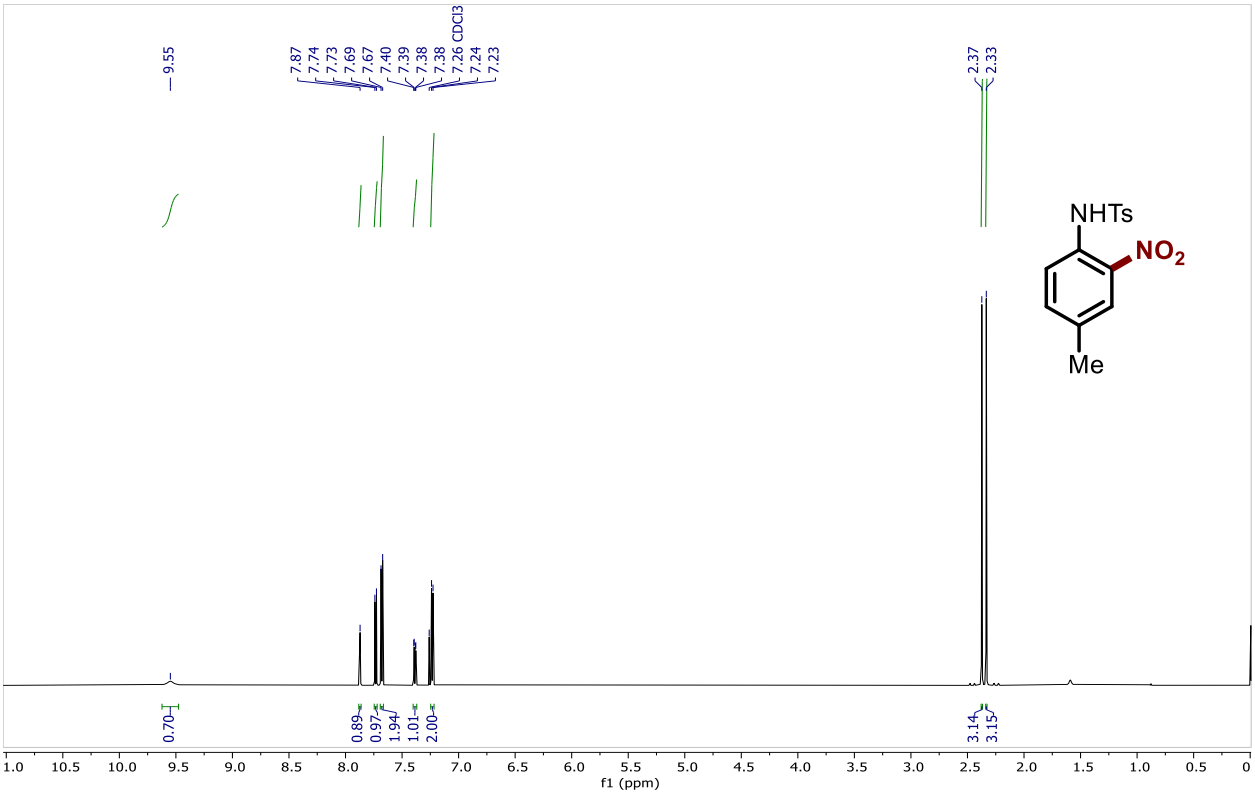


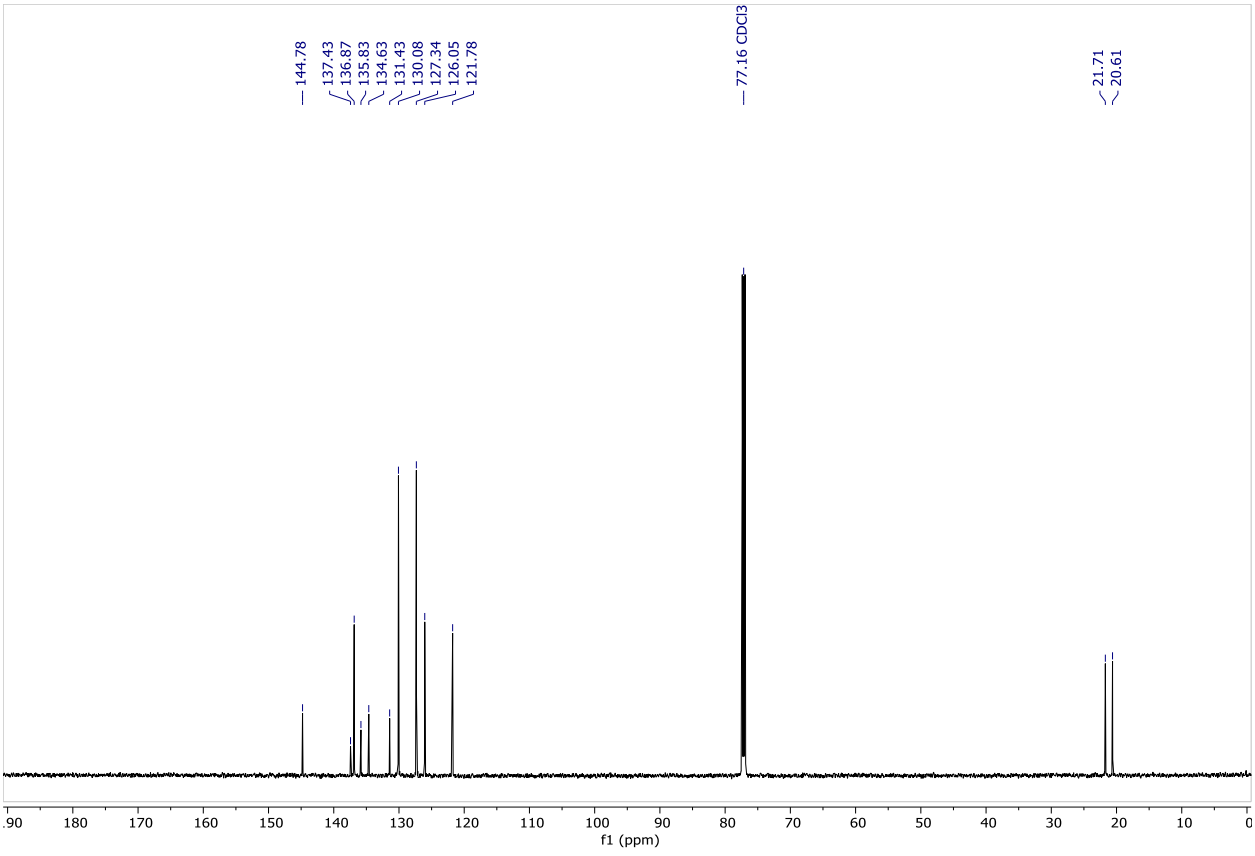
N-(2-chloro-4-methylphenyl)-4-methylbenzenesulfonamide (**343**).



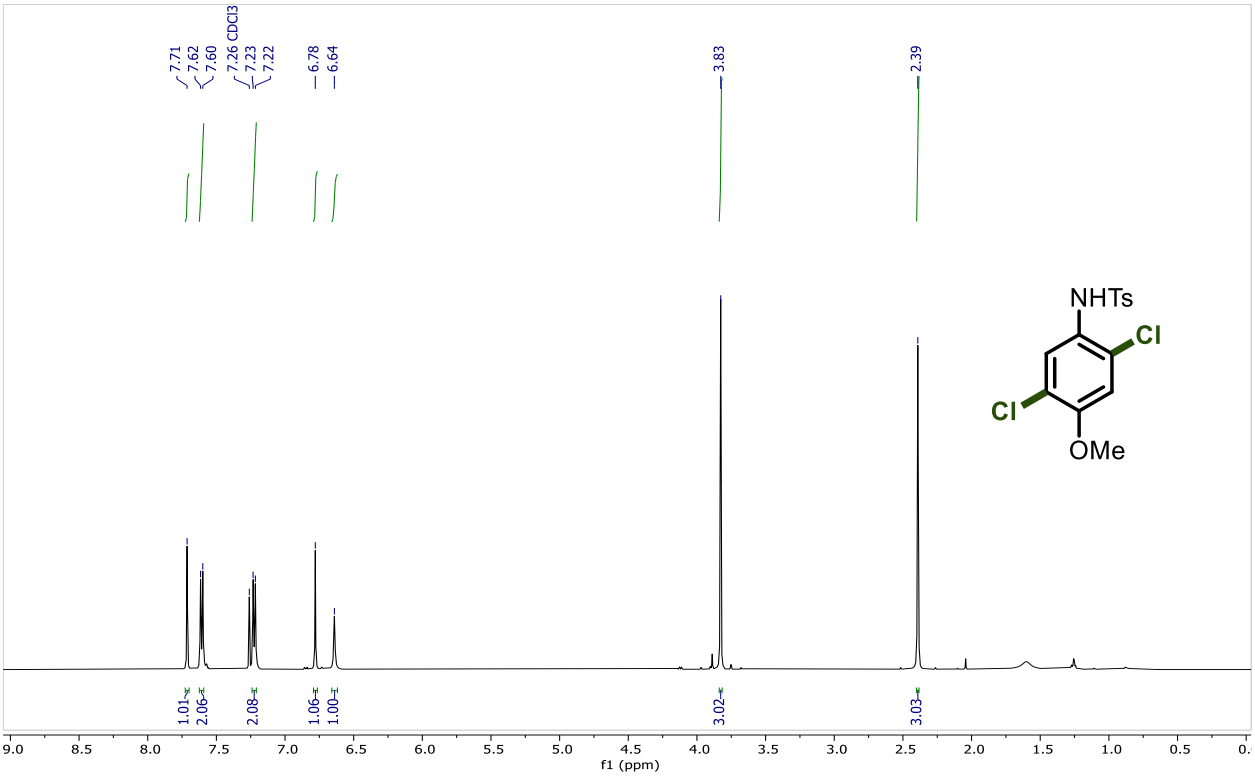


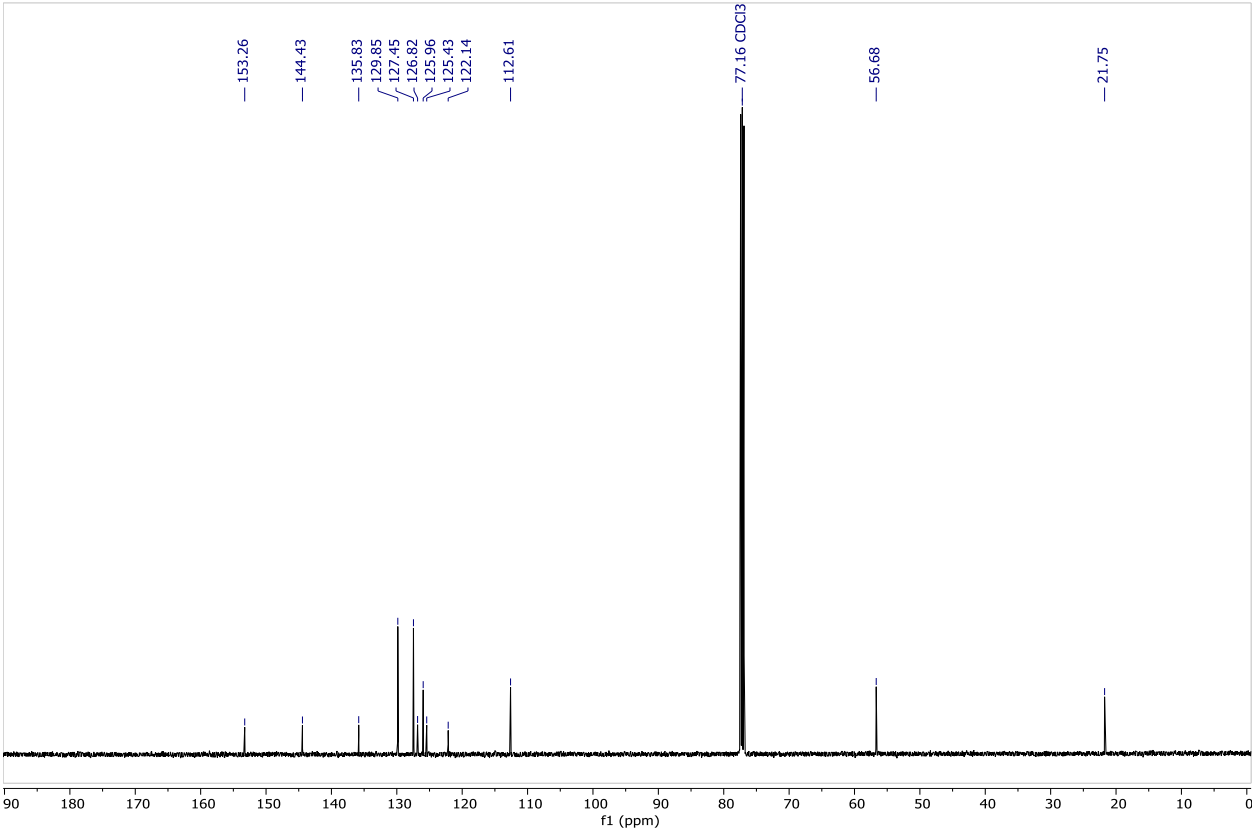
4-methyl-*N*-(4-methyl-2-nitrophenyl)benzenesulfonamide (**344**)



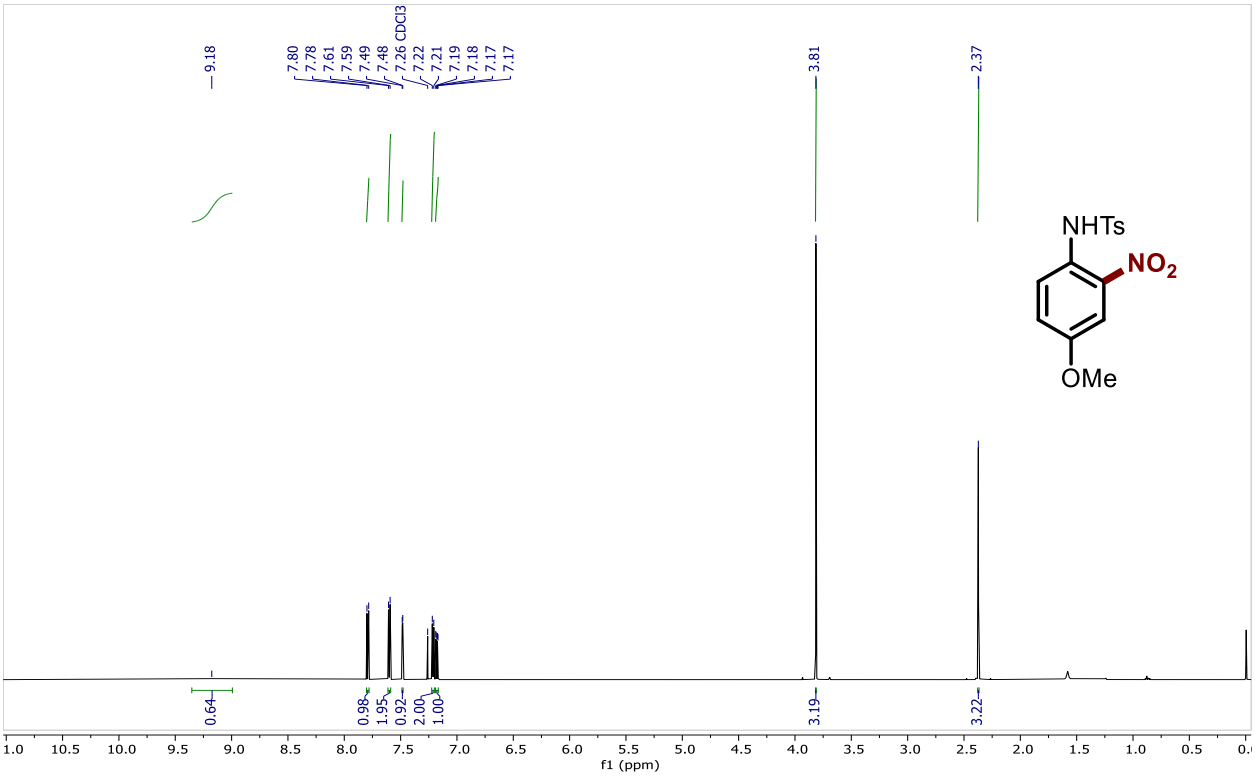


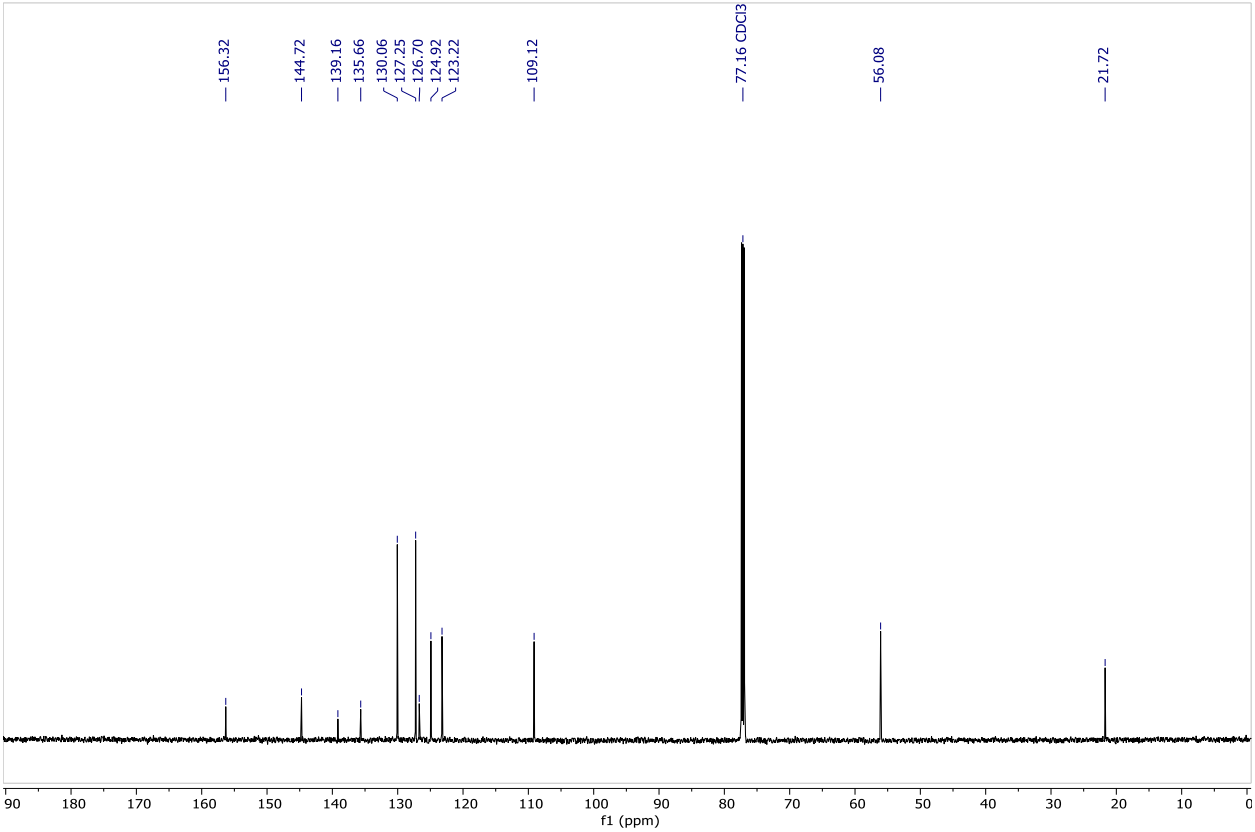
N-(2,5-dichloro-4-methoxyphenyl)-4-methylbenzenesulfonamide (**345**)



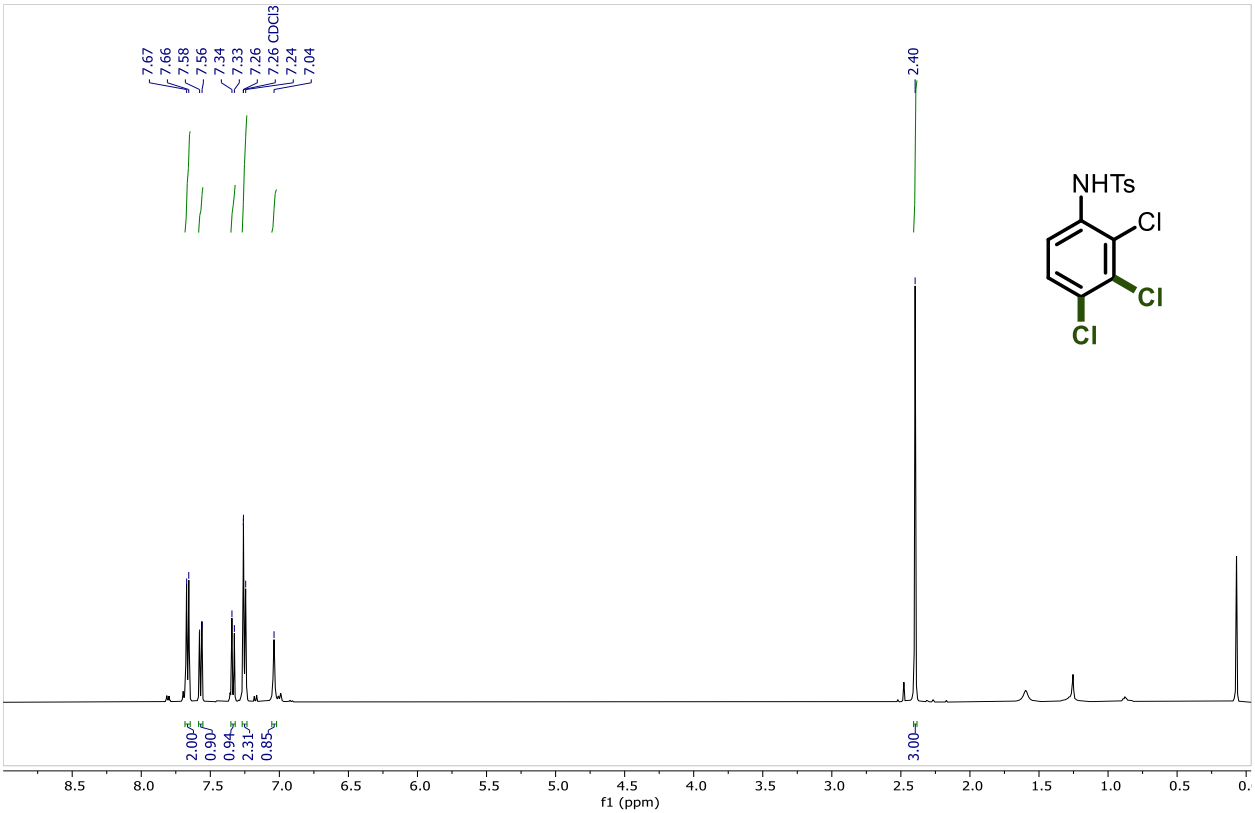


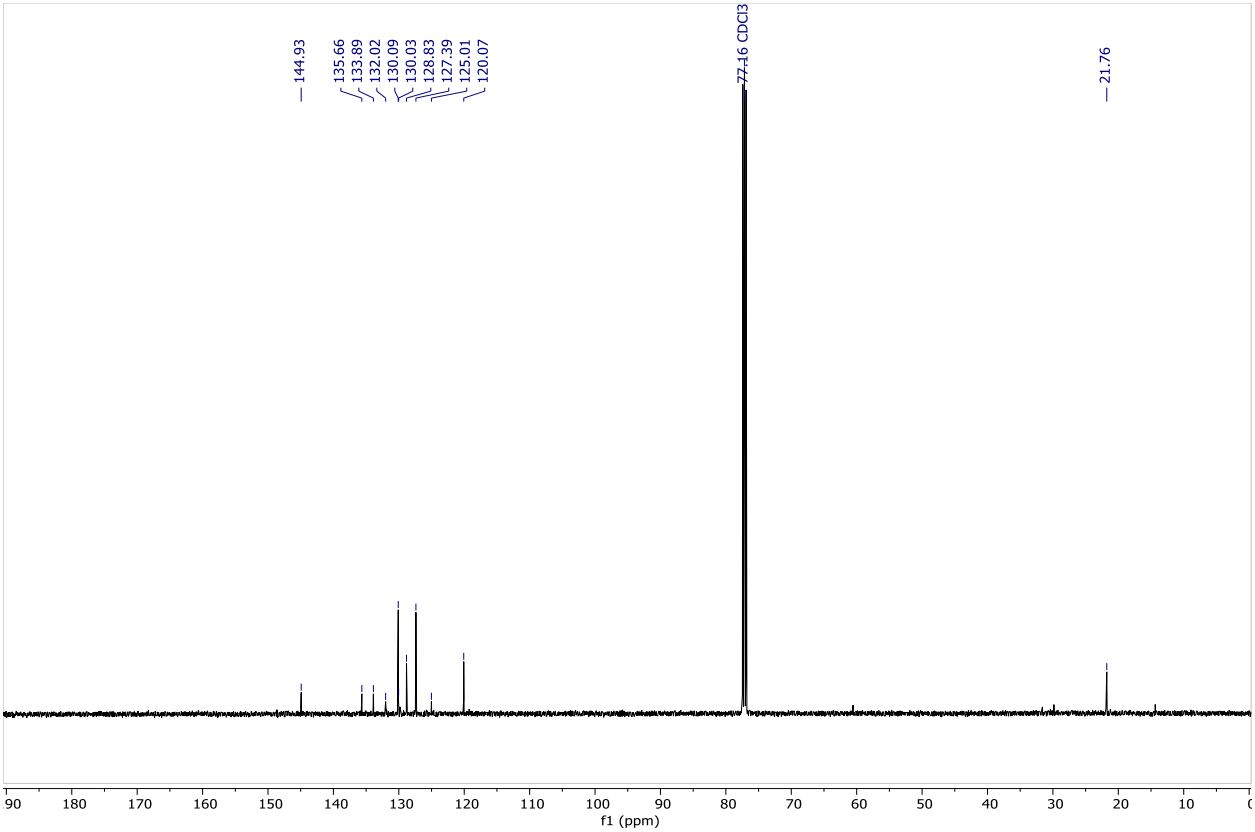
N-(4-methoxy-2-nitrophenyl)-4-methylbenzenesulfonamide (**346**)



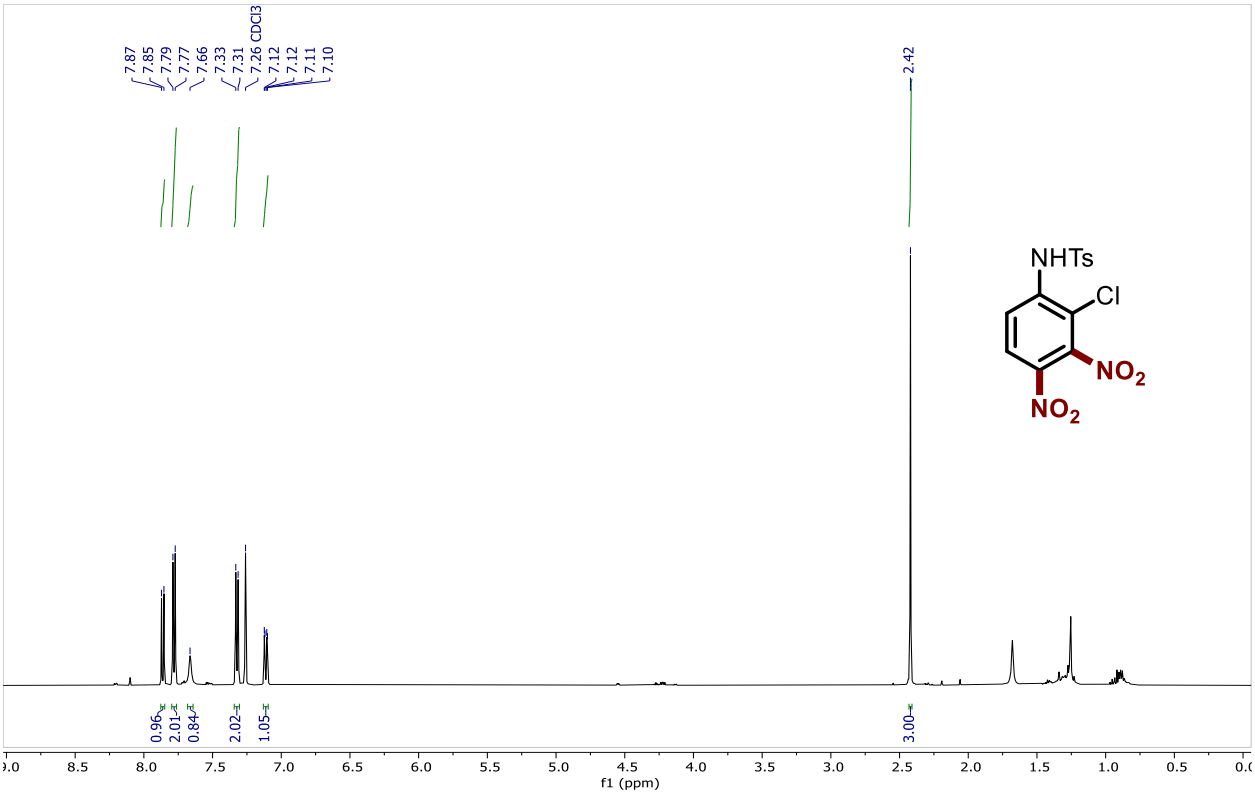


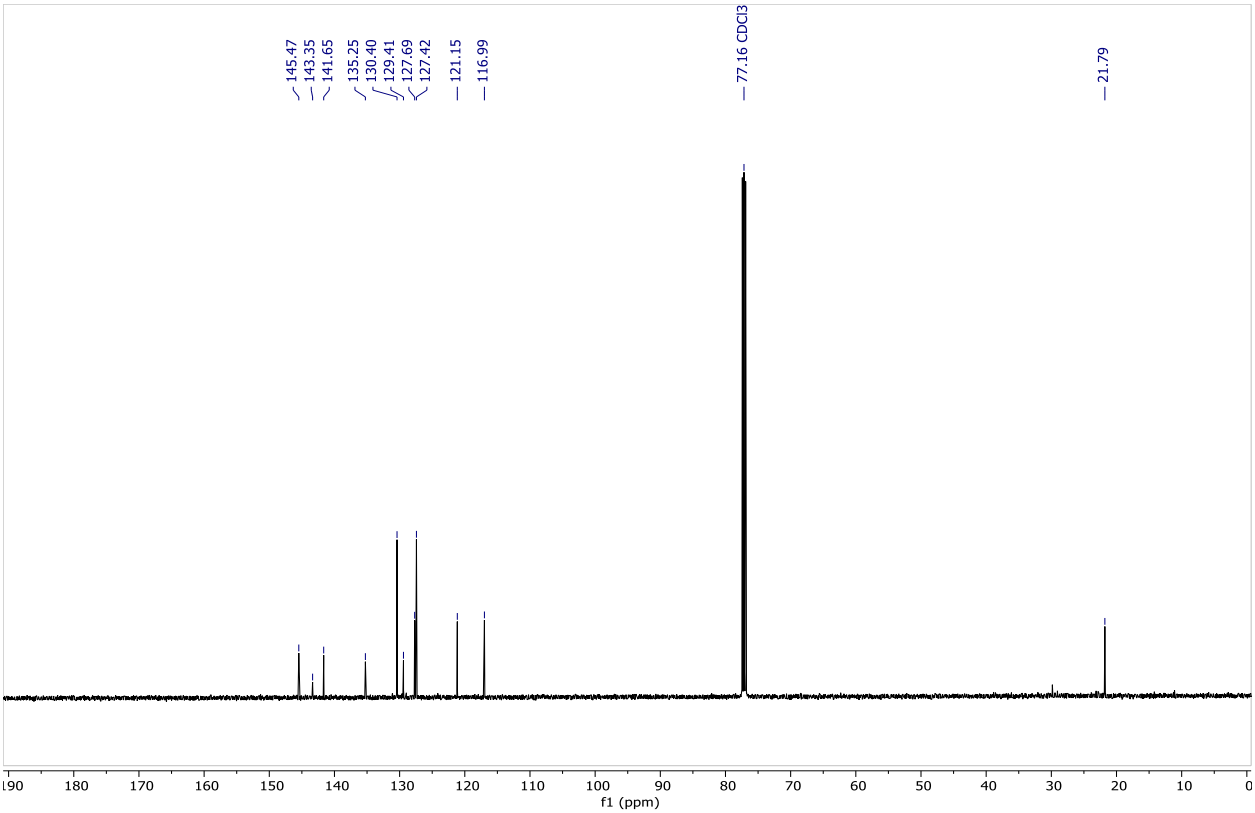
4-methyl-*N*-(2,3,4-trichlorophenyl)benzenesulfonamide (**347**)

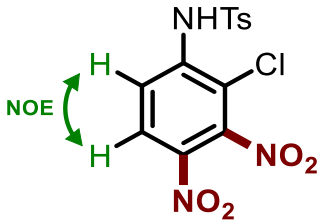




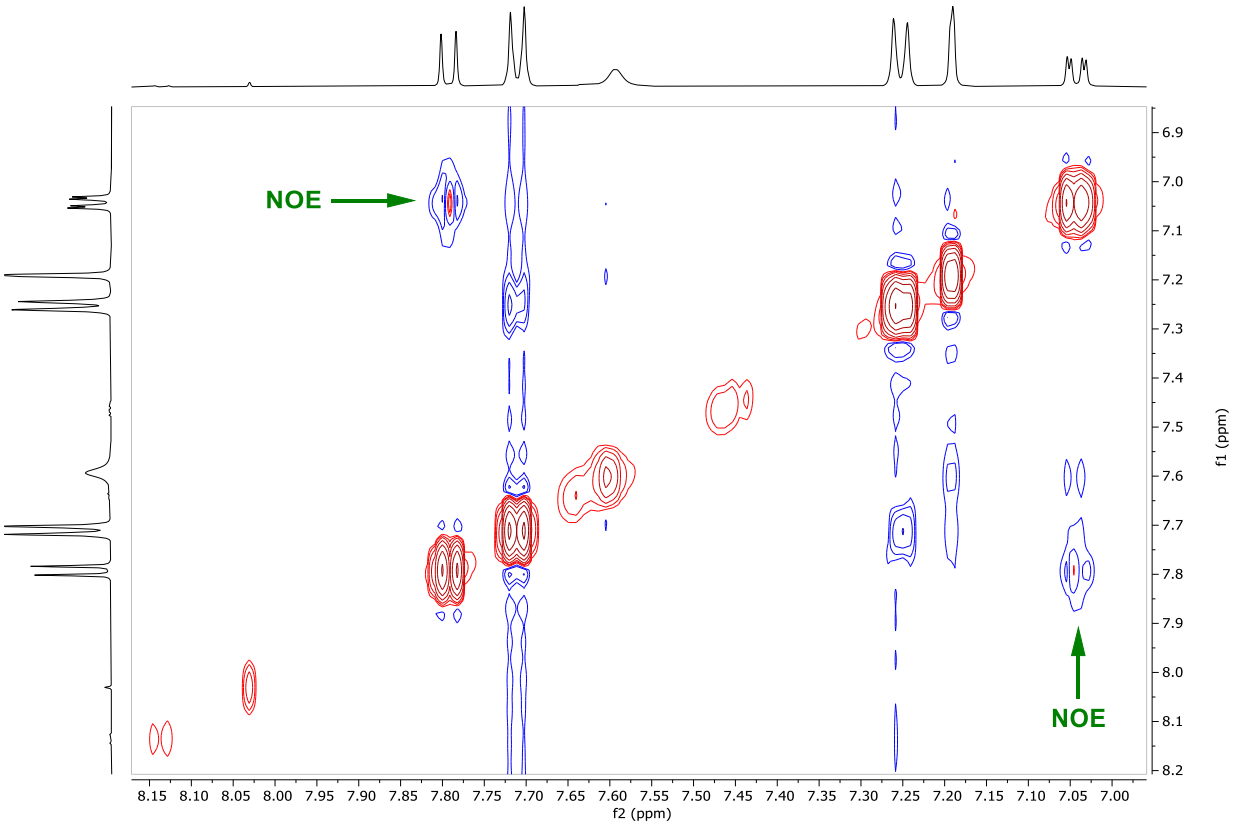
N-(2-chloro-3,4-dinitrophenyl)-4-methylbenzenesulfonamide (**348**)



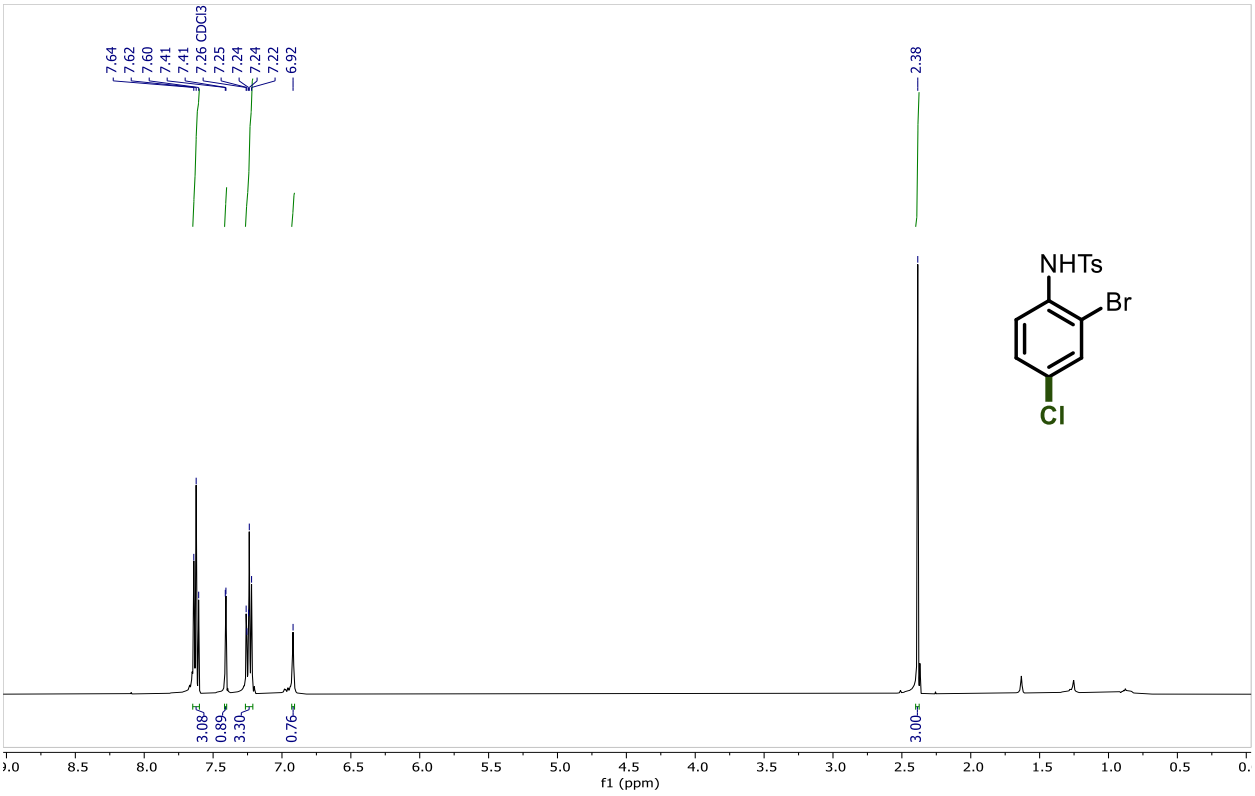


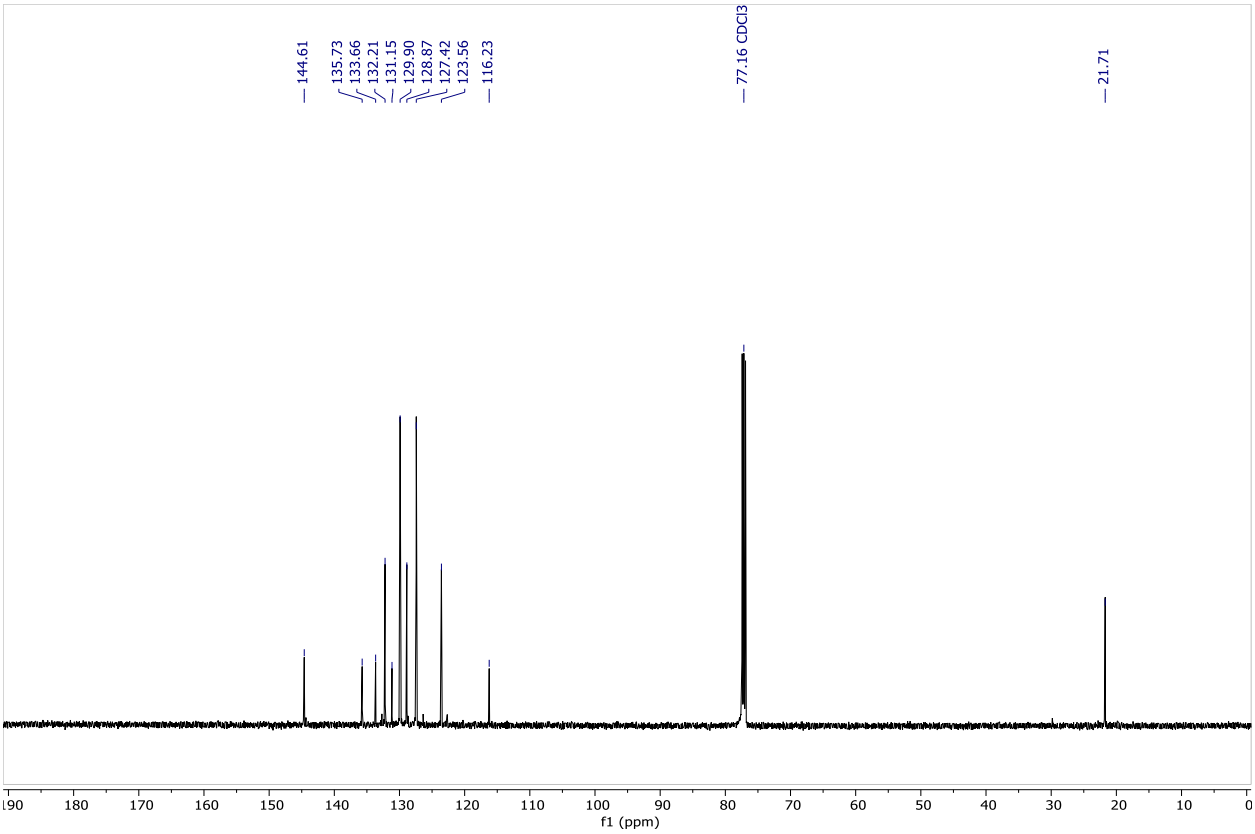

NHTs
H
Cl
NOE
H
NO2
NO2

348

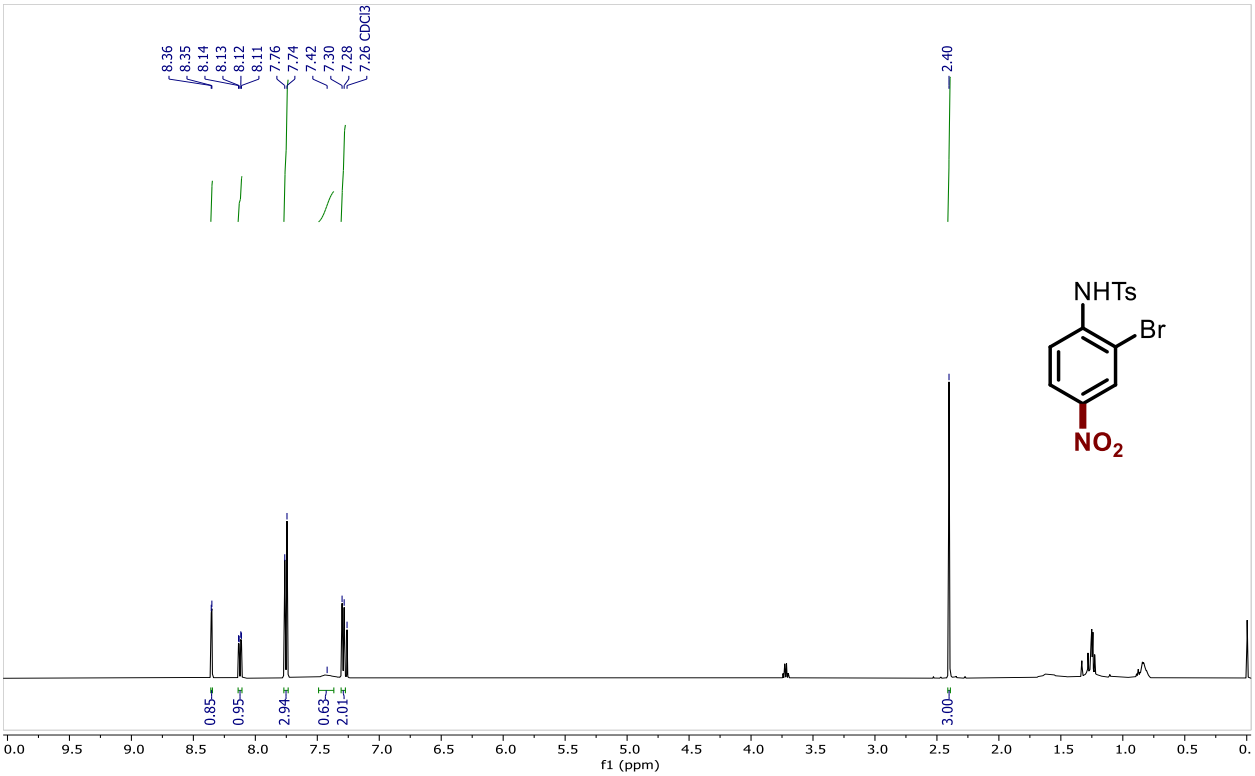

NOE
NOE
8.15 8.10 8.05 8.00 7.95 7.90 7.85 7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00
f2 (ppm)
6.9 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9 8.0 8.1 8.2
f1 (ppm)

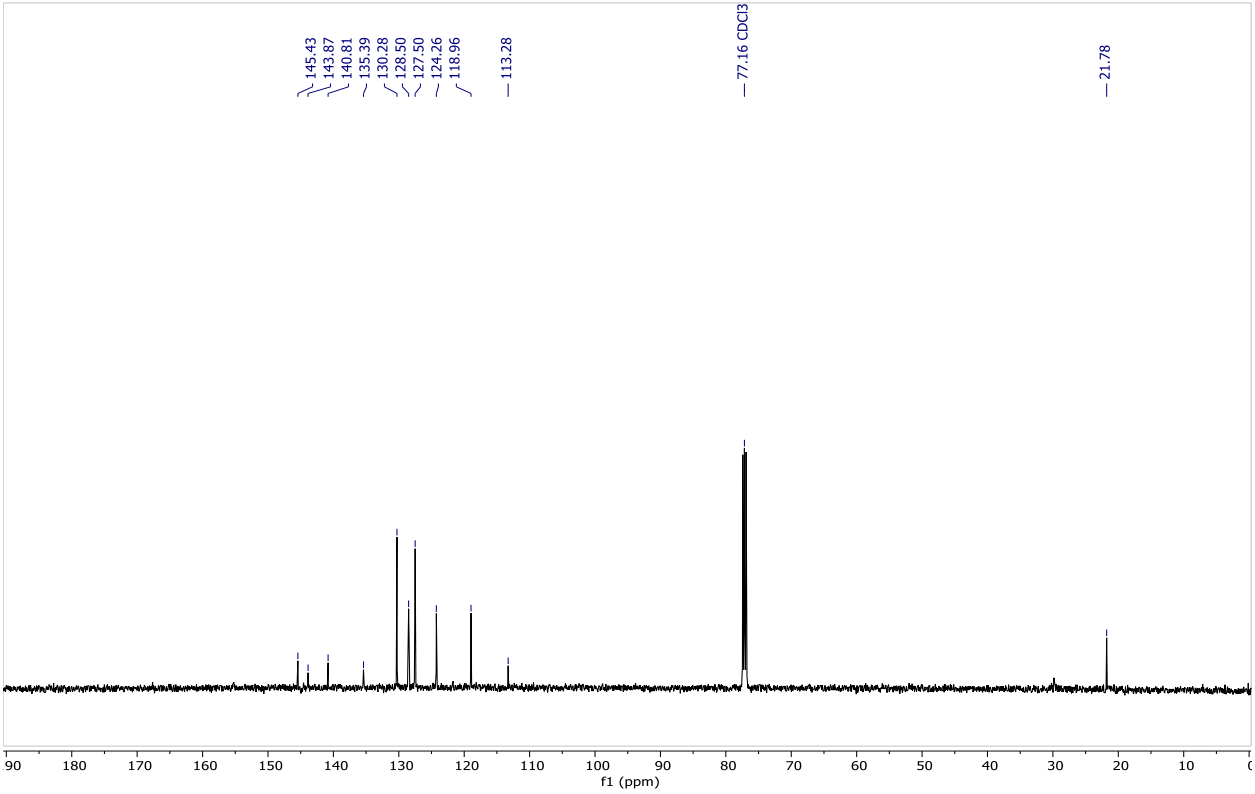
N-(2-bromo-4-chlorophenyl)-4-methylbenzenesulfonamide (**349**)



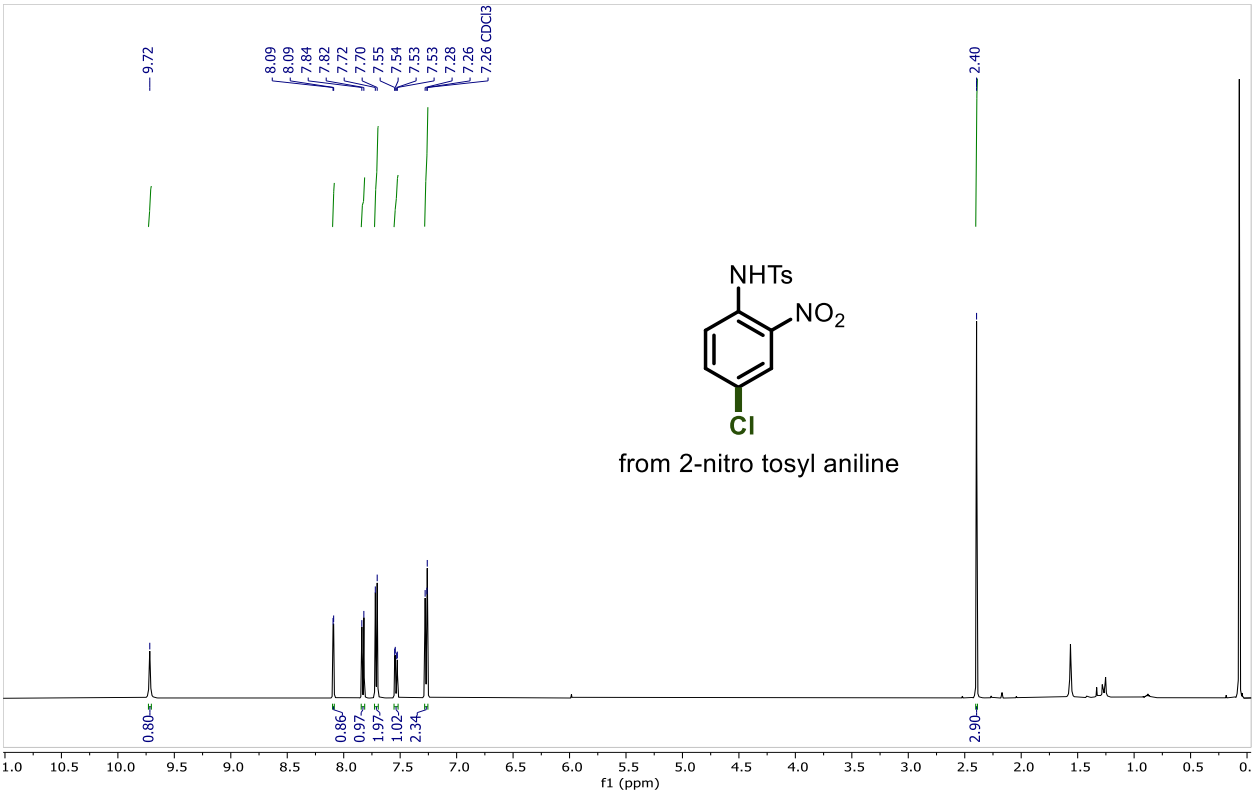


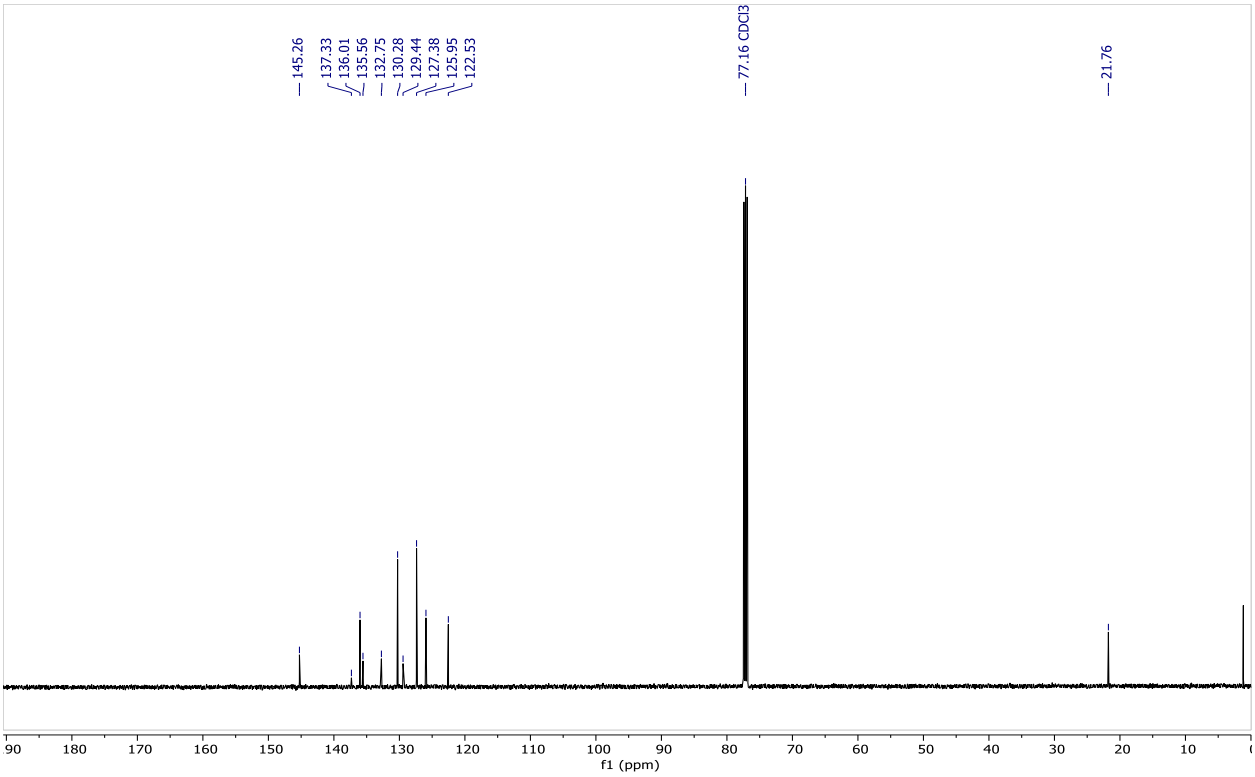
N-(2-bromo-4-nitrophenyl)-4-methylbenzenesulfonamide (**350**)



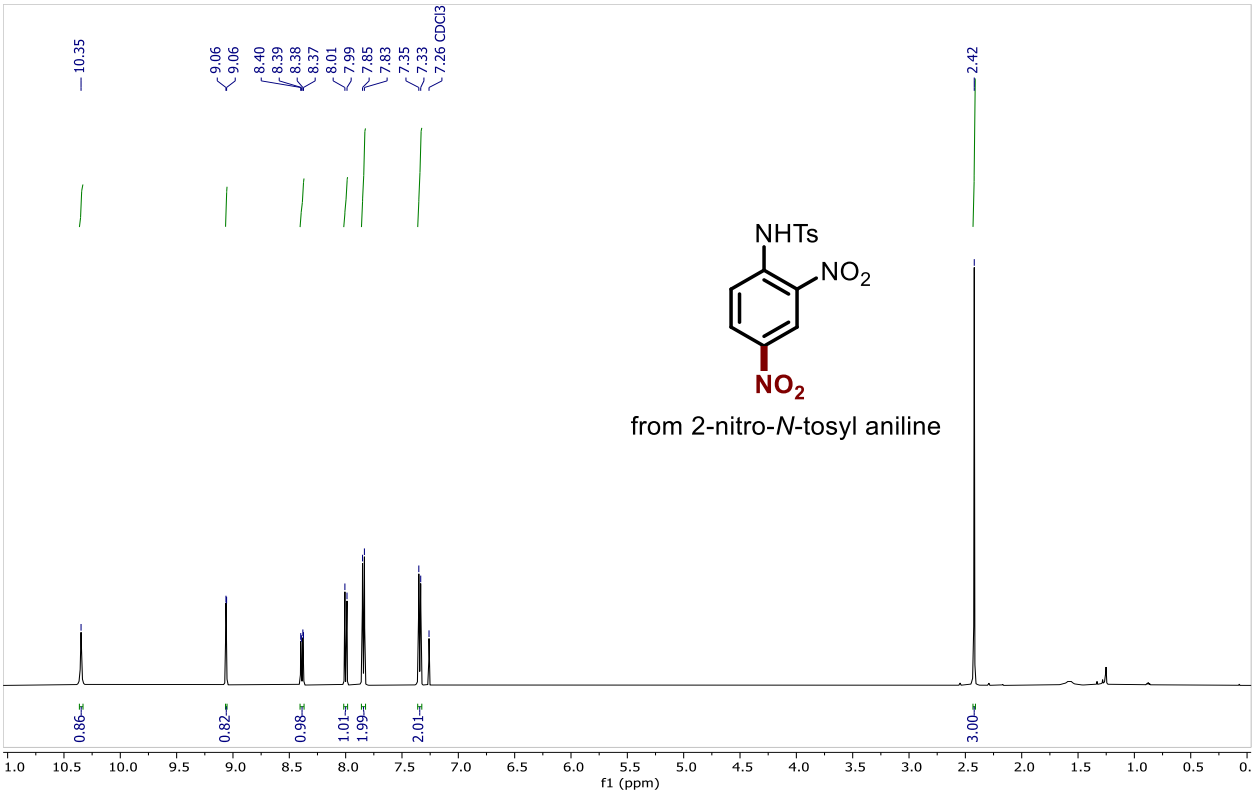


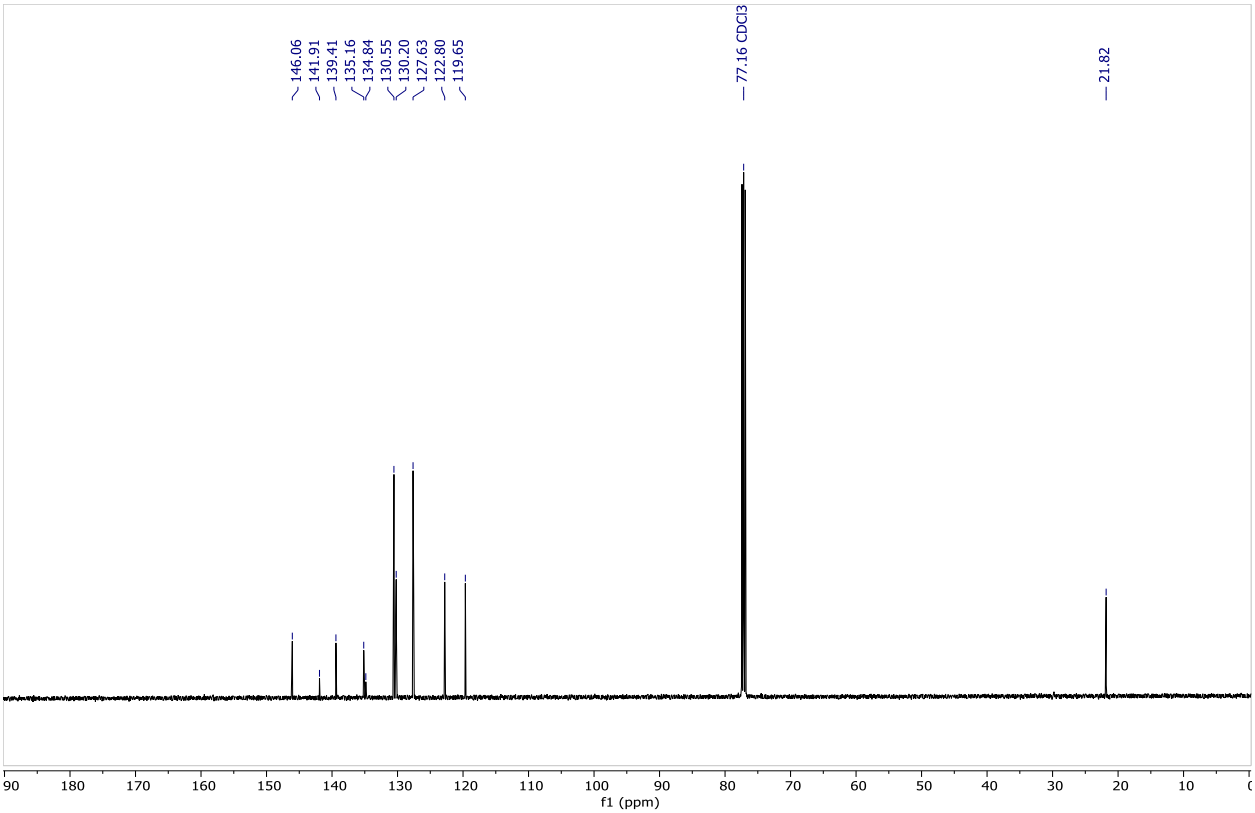
N-(4-chloro-2-nitrophenyl)-4-methylbenzenesulfonamide (**332**).



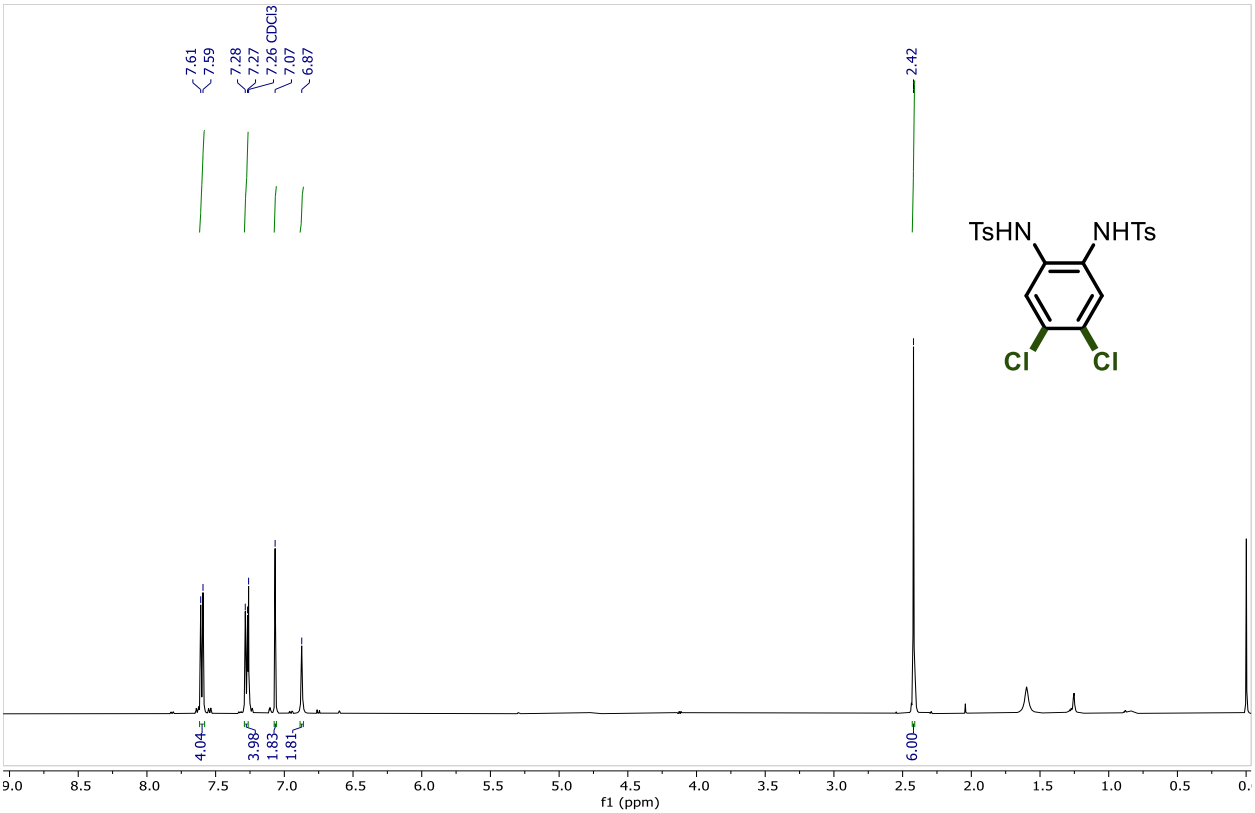


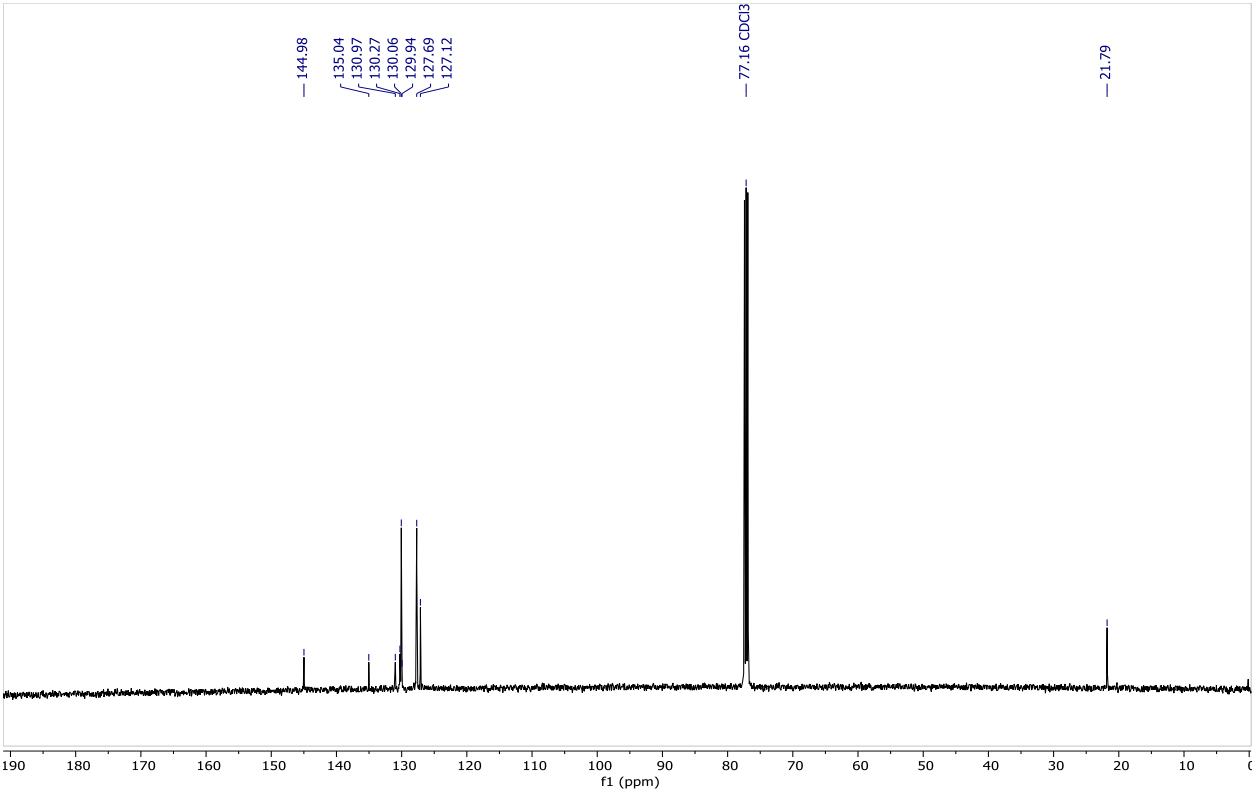
N-(2,4-dinitrophenyl)-4-methylbenzenesulfonamide (**342**)



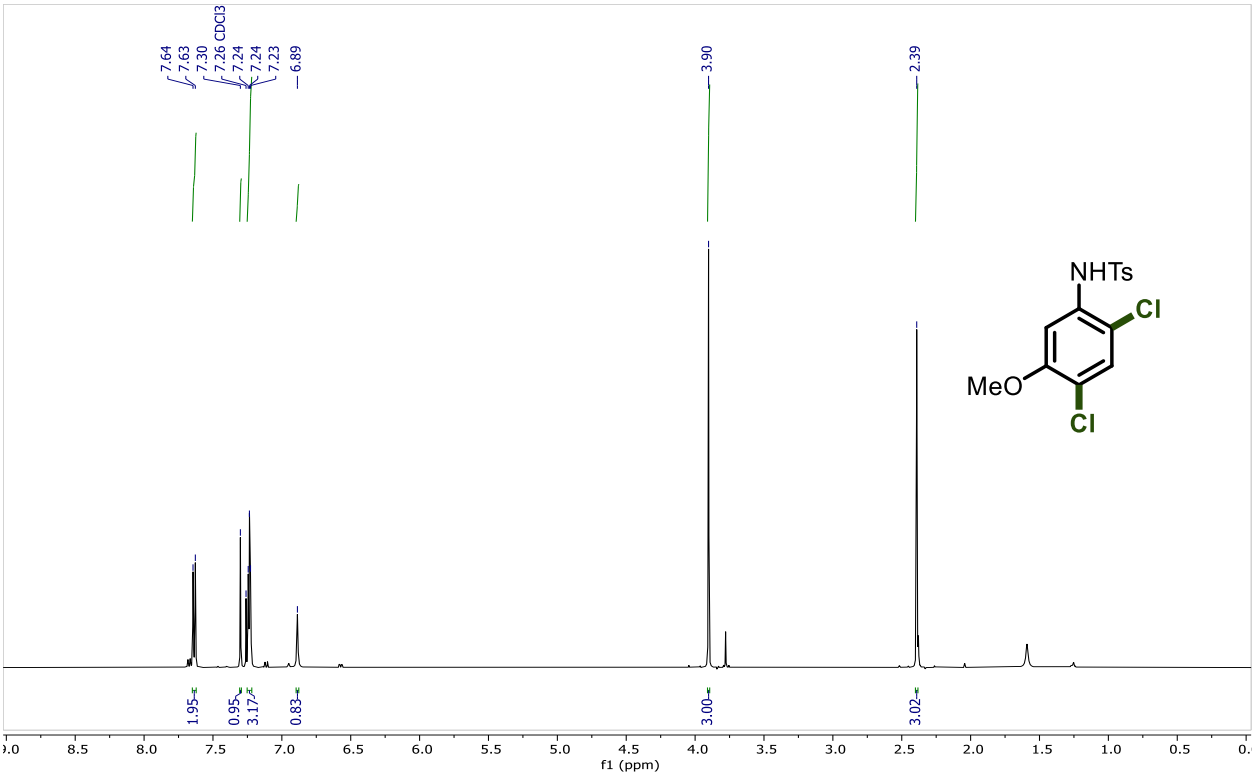


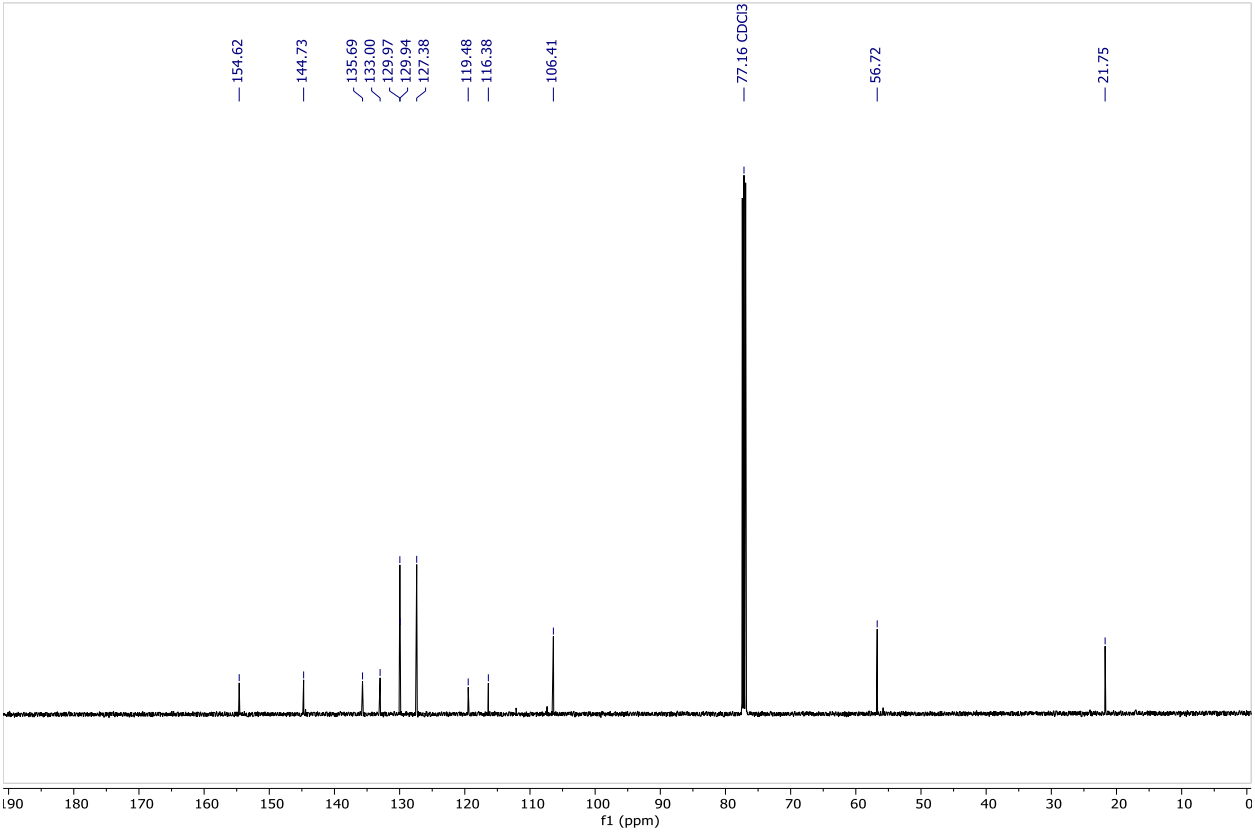
N,N′-(4,5-dichloro-1,2-phenylene)bis(4 methylbenzenesulfonamide) (**351**)



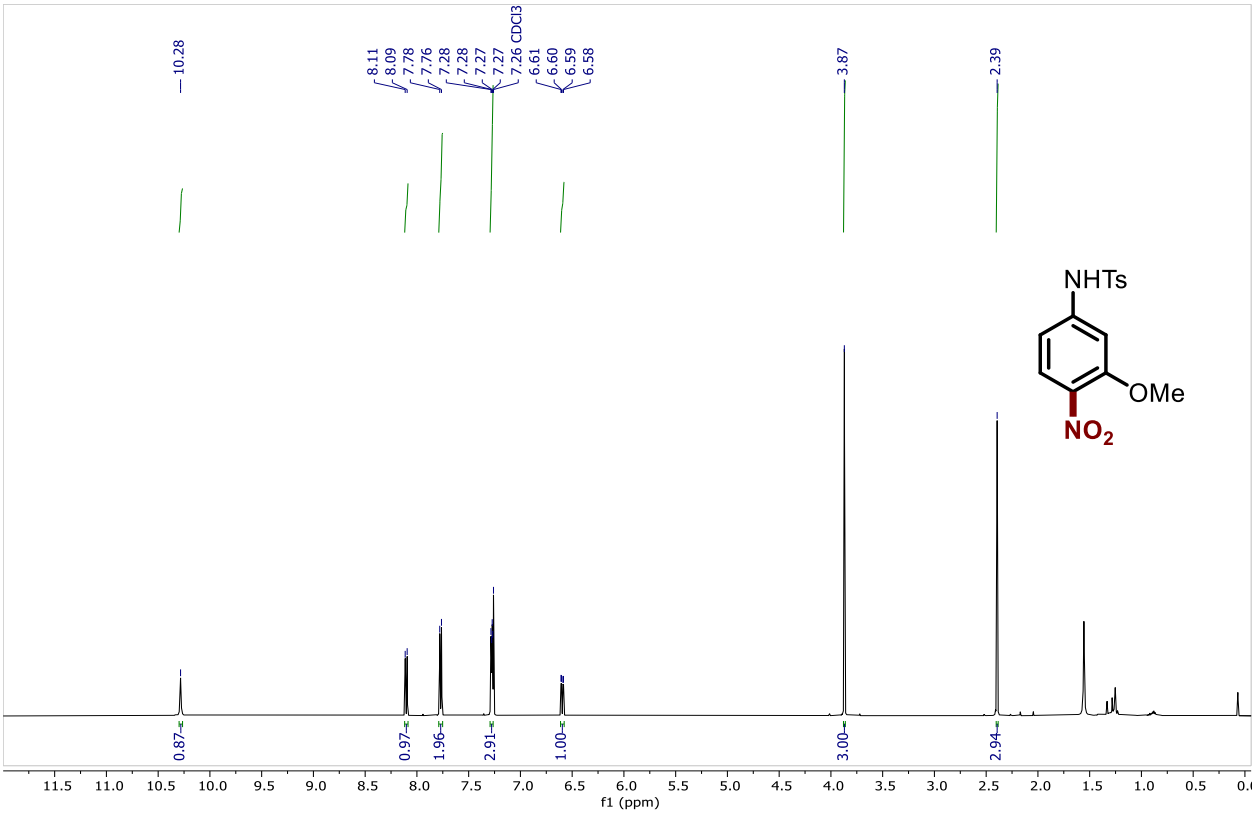


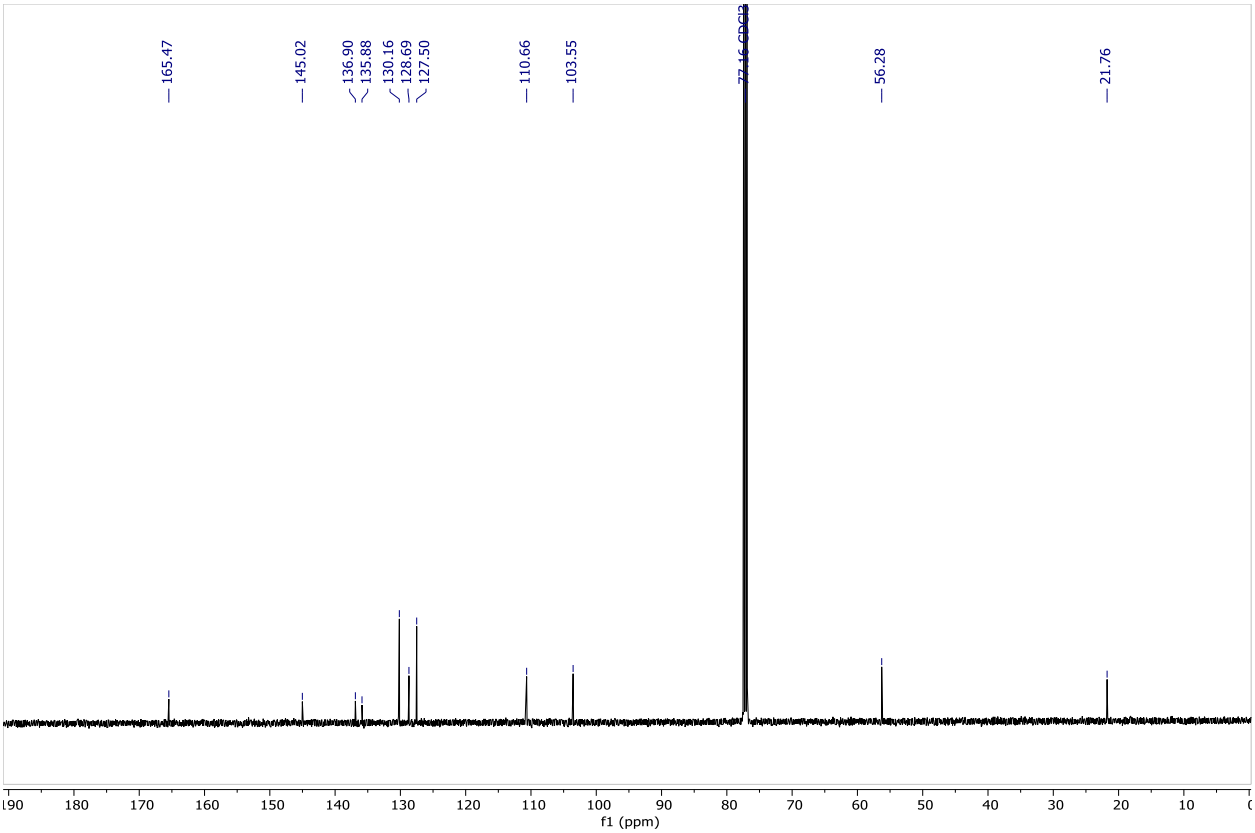
N-(2,4-dichloro-5-methoxyphenyl)-4 methylbenzenesulfonamide (**352**)

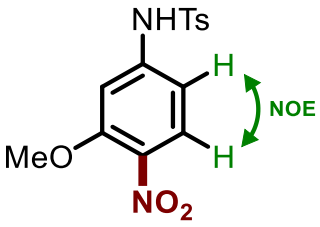




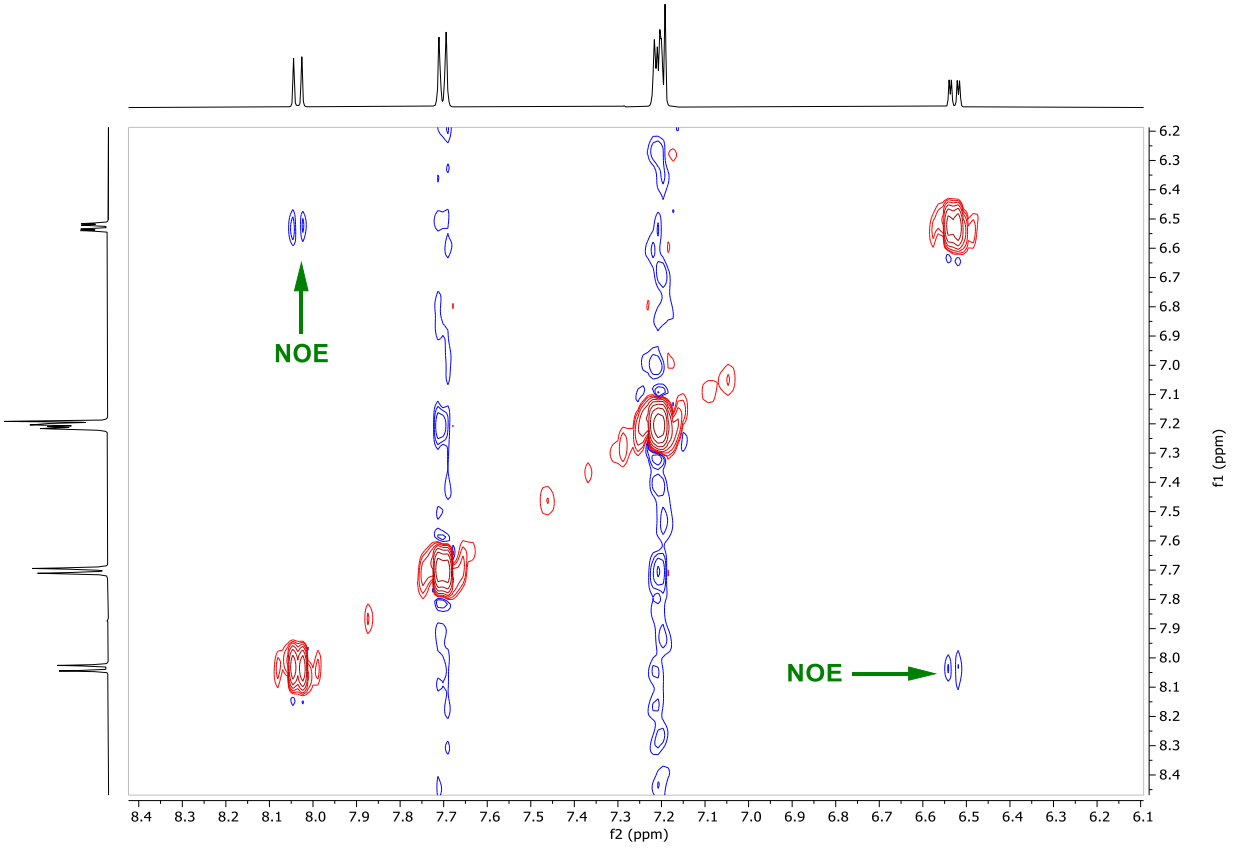
N-(3-methoxy-4-nitrophenyl)-4-methylbenzenesulfonamide (**353**)



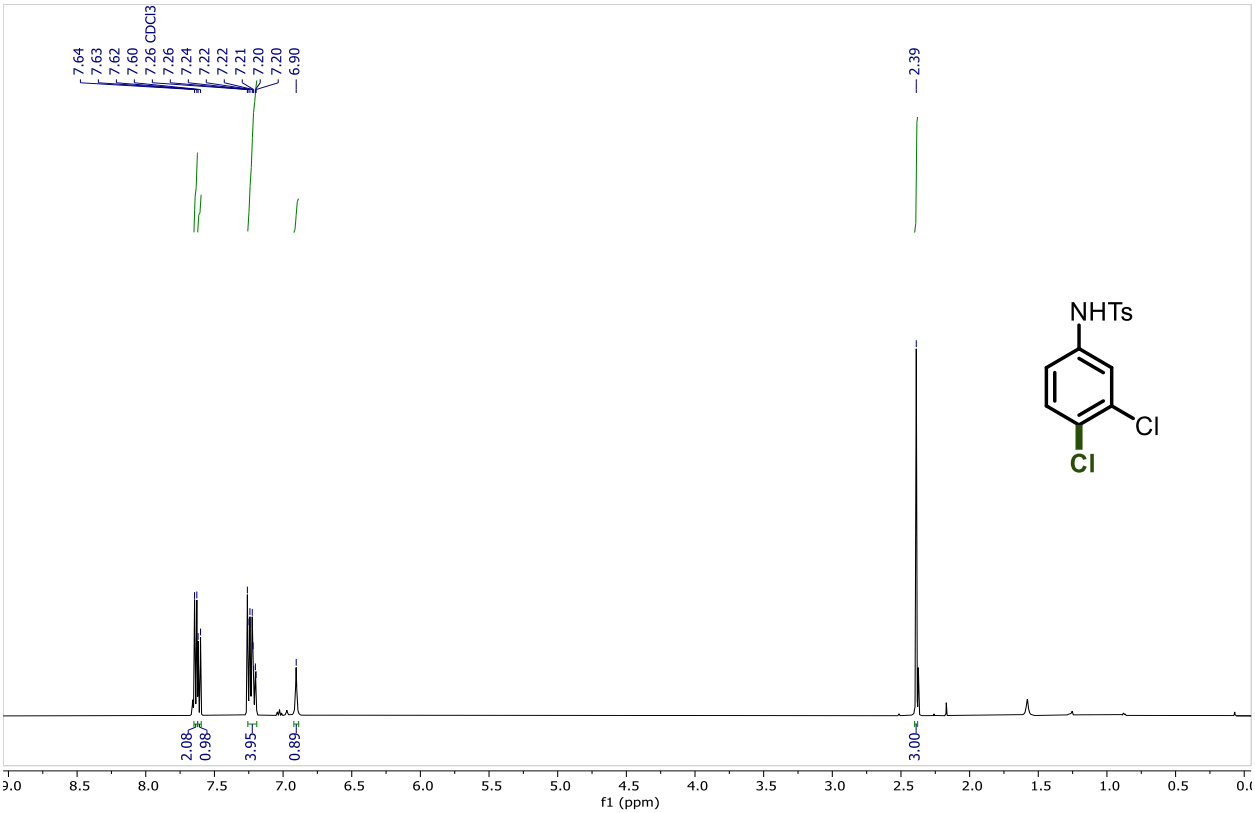


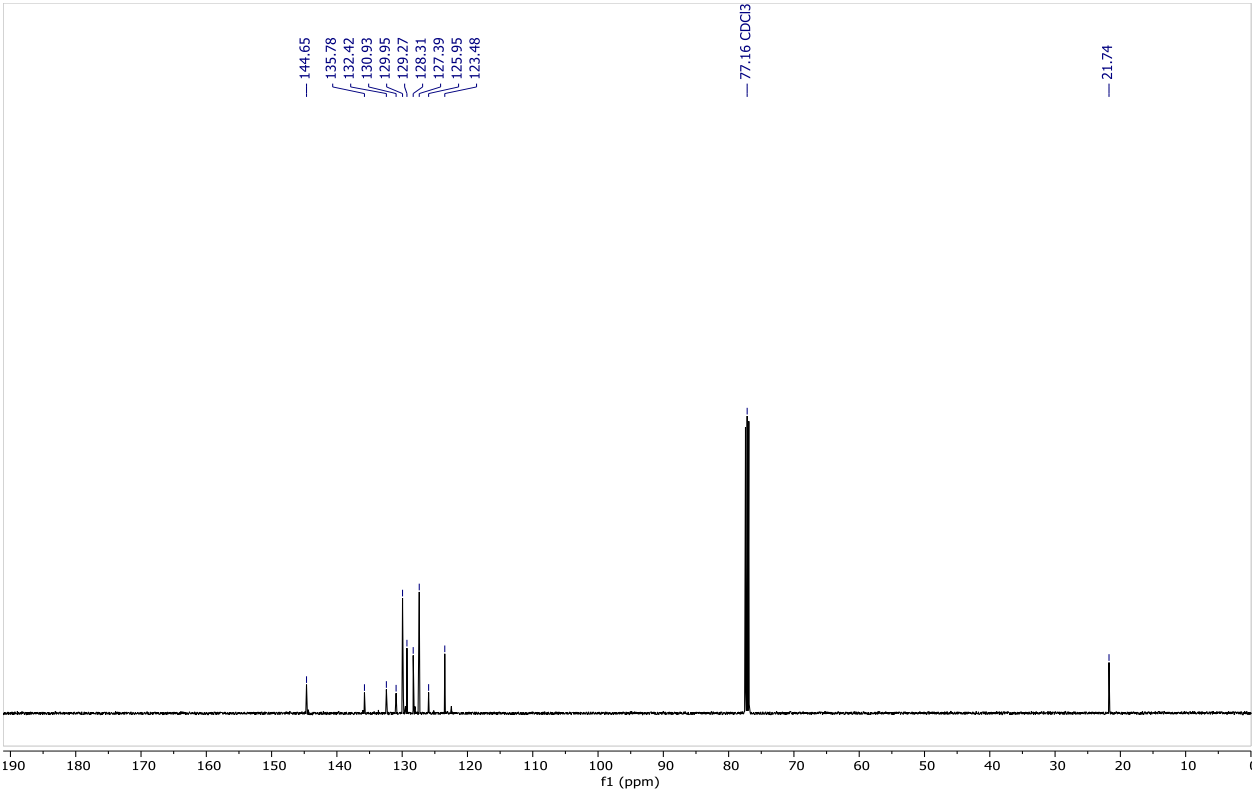


353

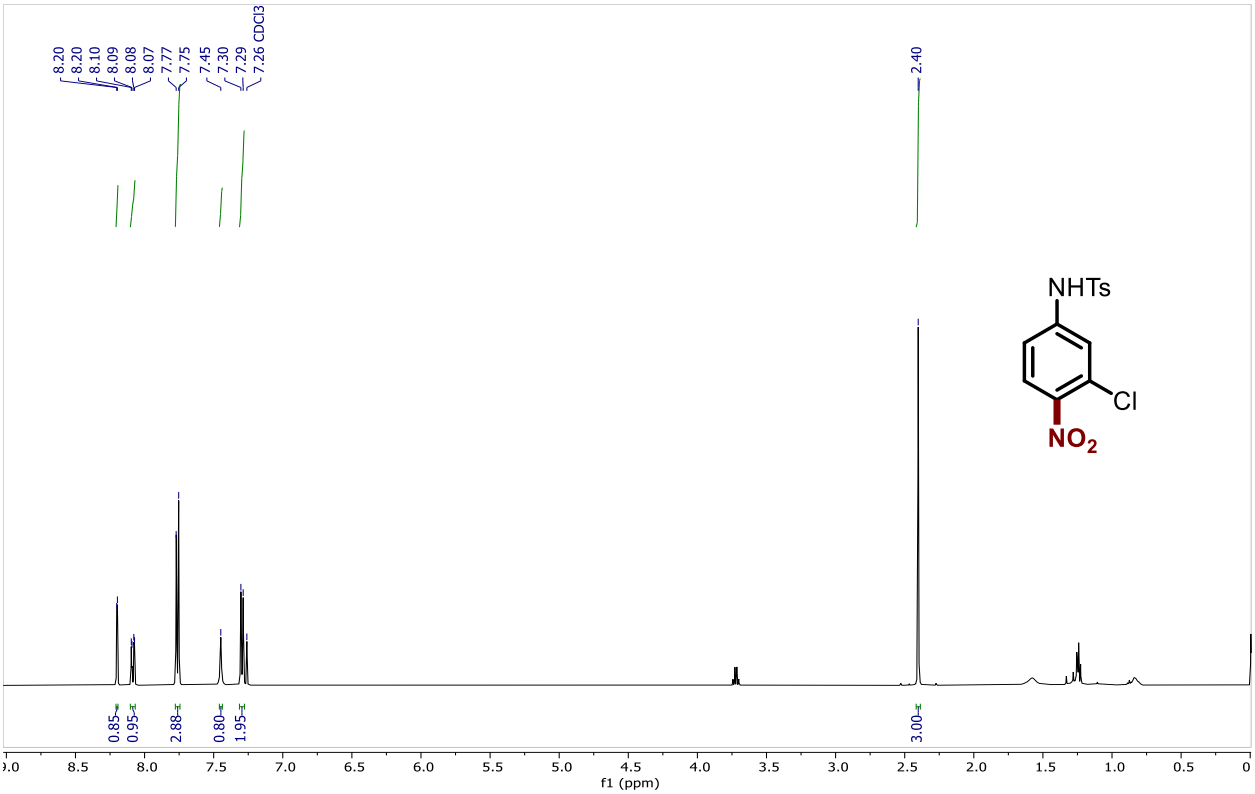


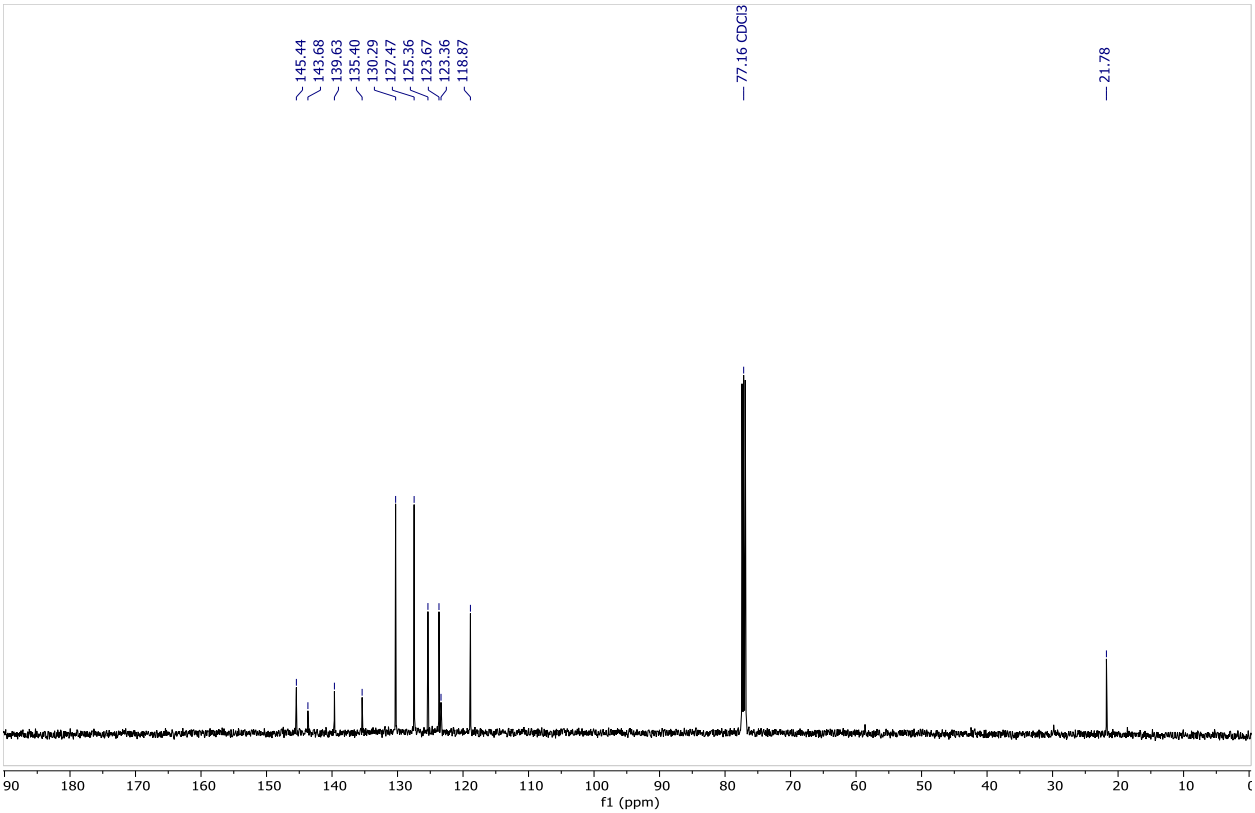
N-(3,4-dichlorophenyl)-4-methylbenzenesulfonamide (**354**)



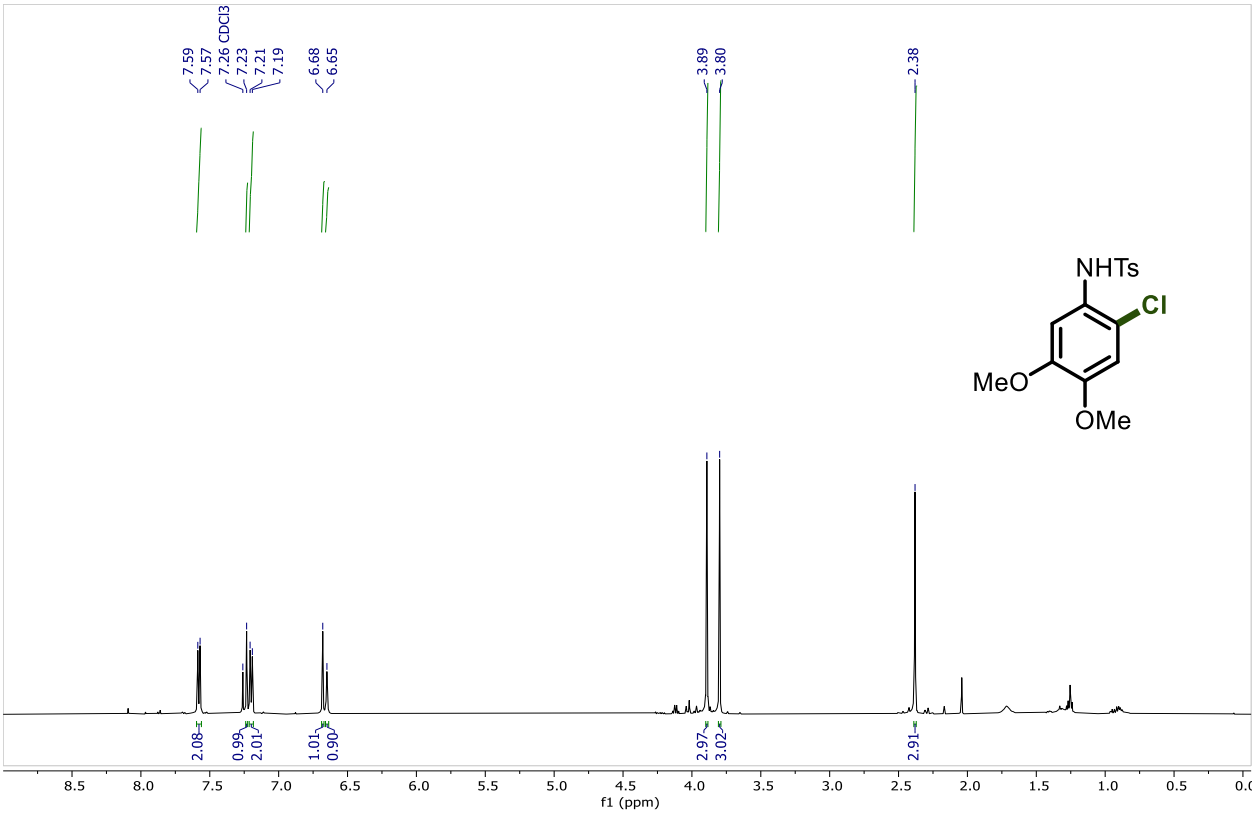


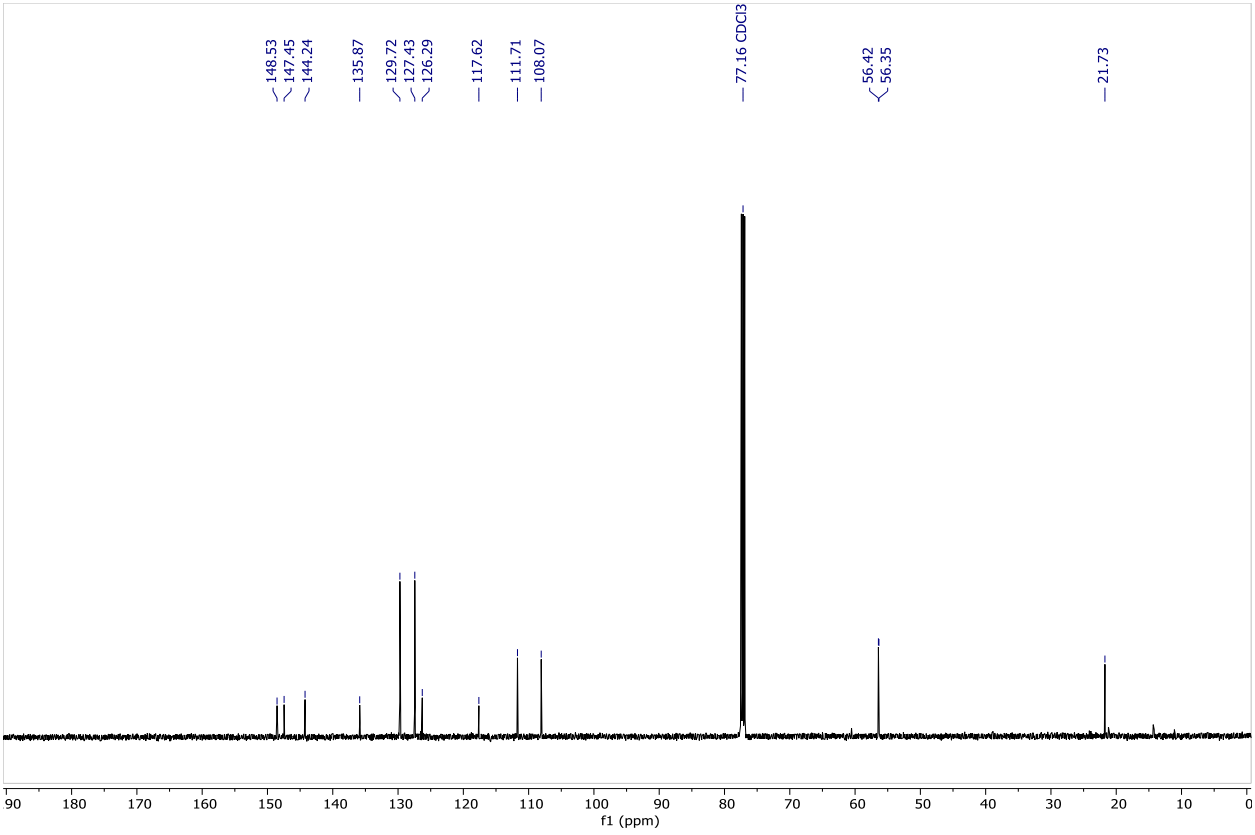
N-(3-chloro-4-nitrophenyl)-4-methylbenzenesulfonamide (**355**)



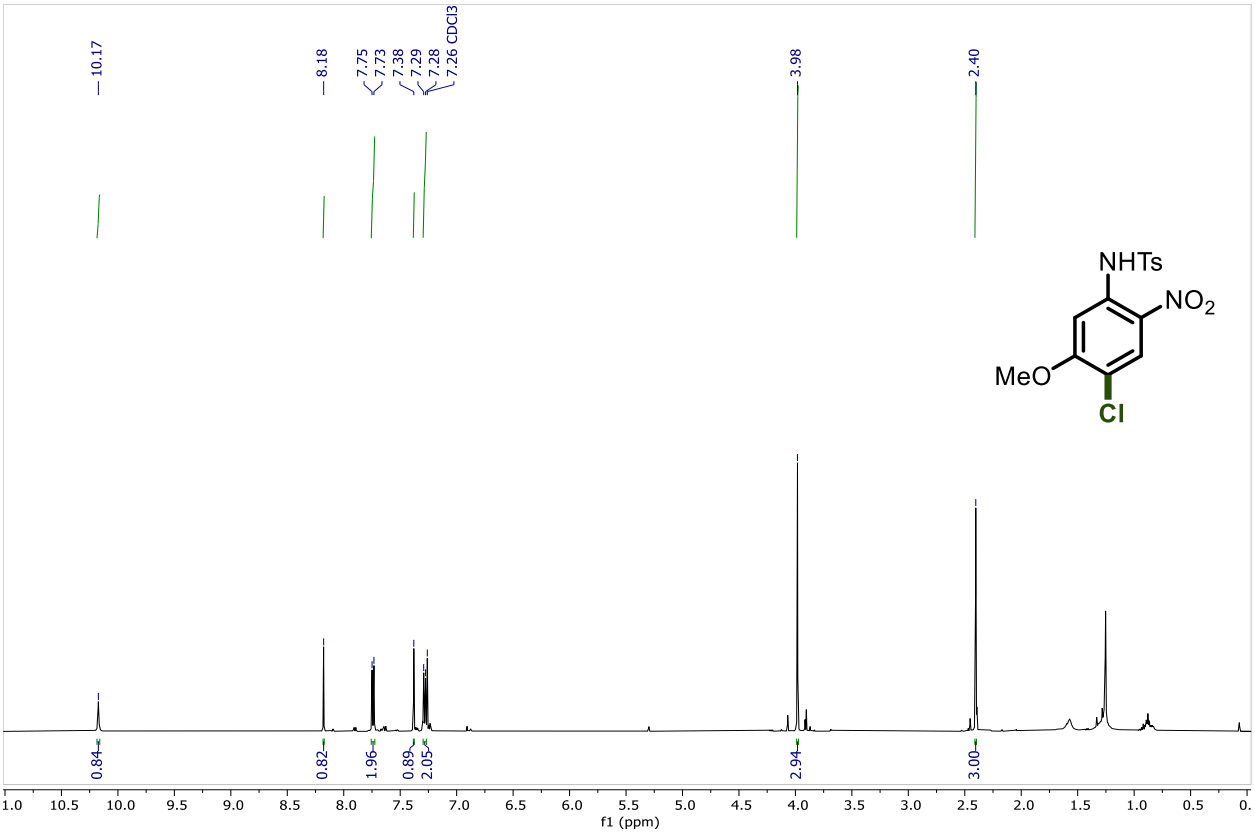


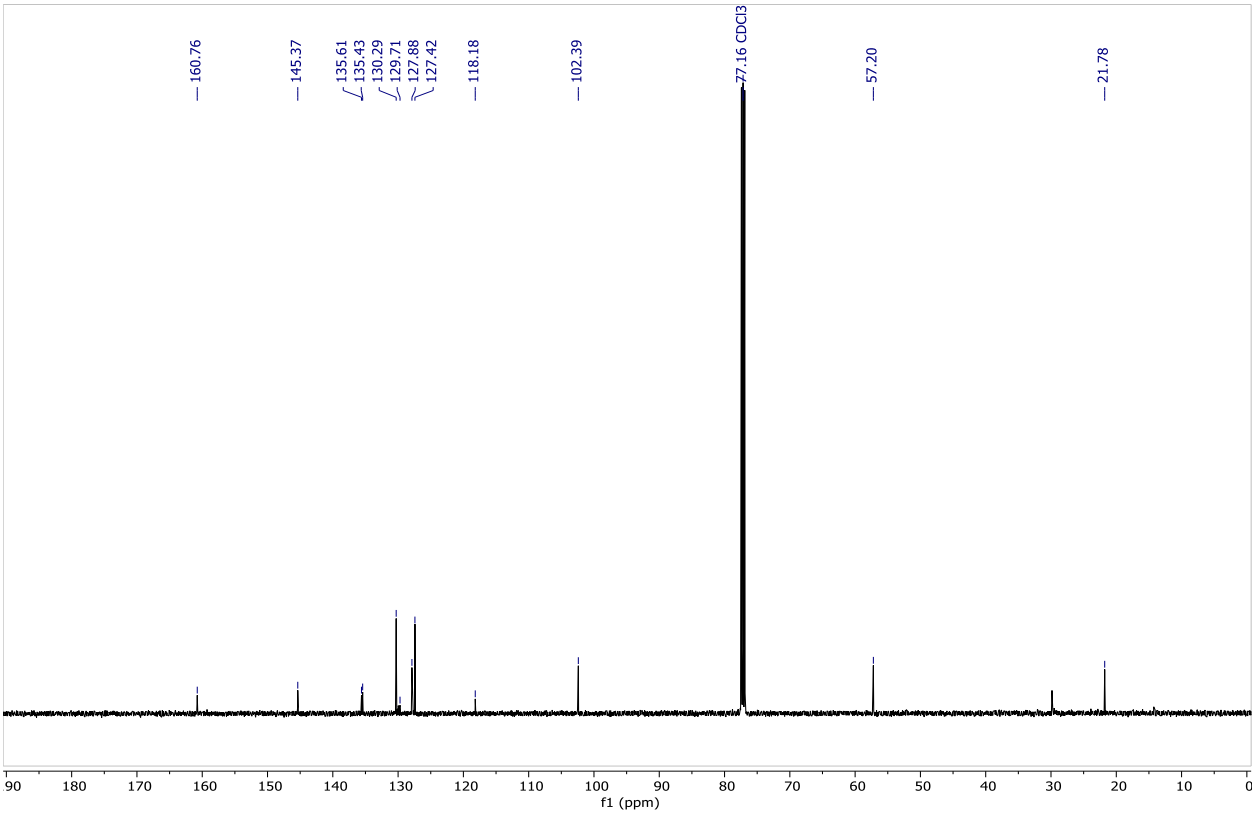
N-(2-chloro-4,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (**356**)

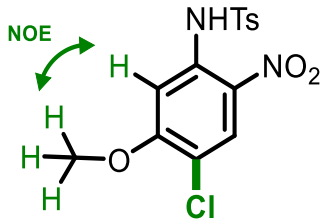




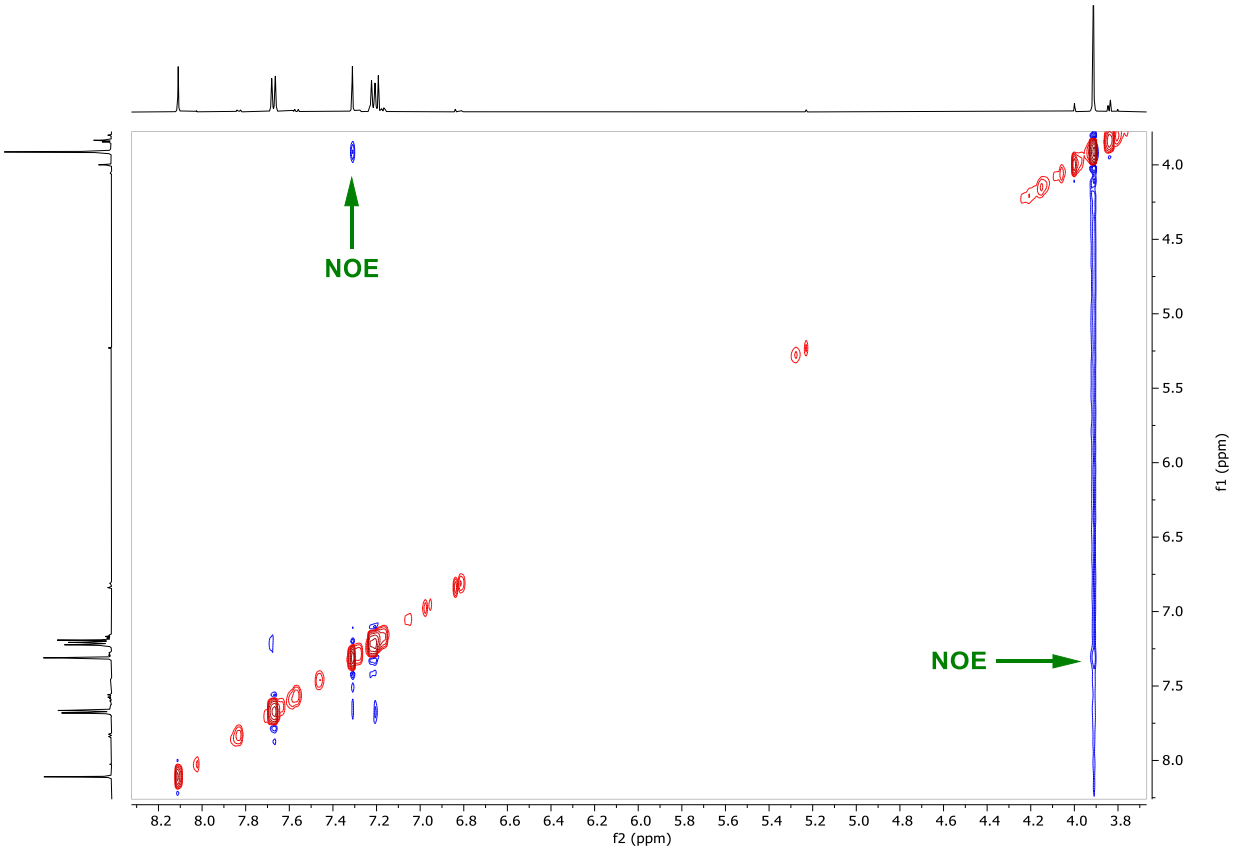
N-(4-chloro-5-methoxy-2-nitrophenyl)-4 methylbenzenesulfonamide (**357**)



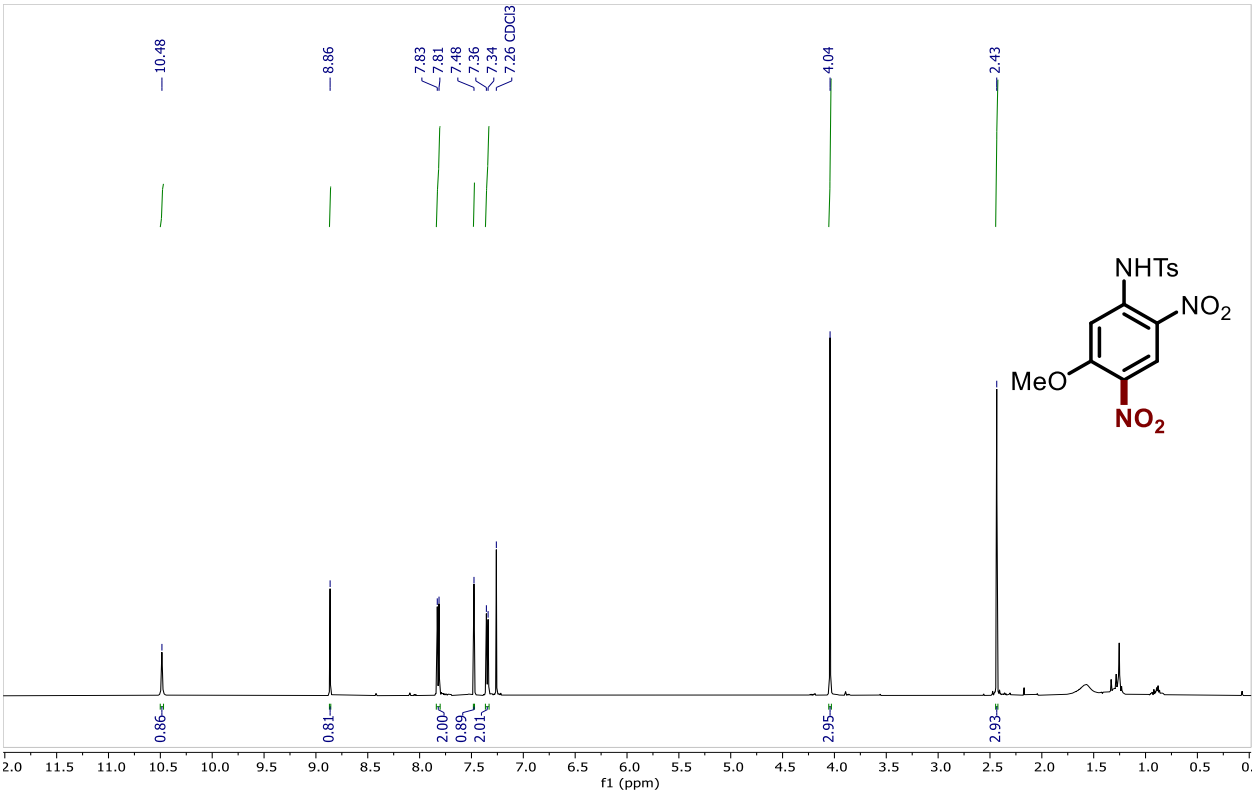


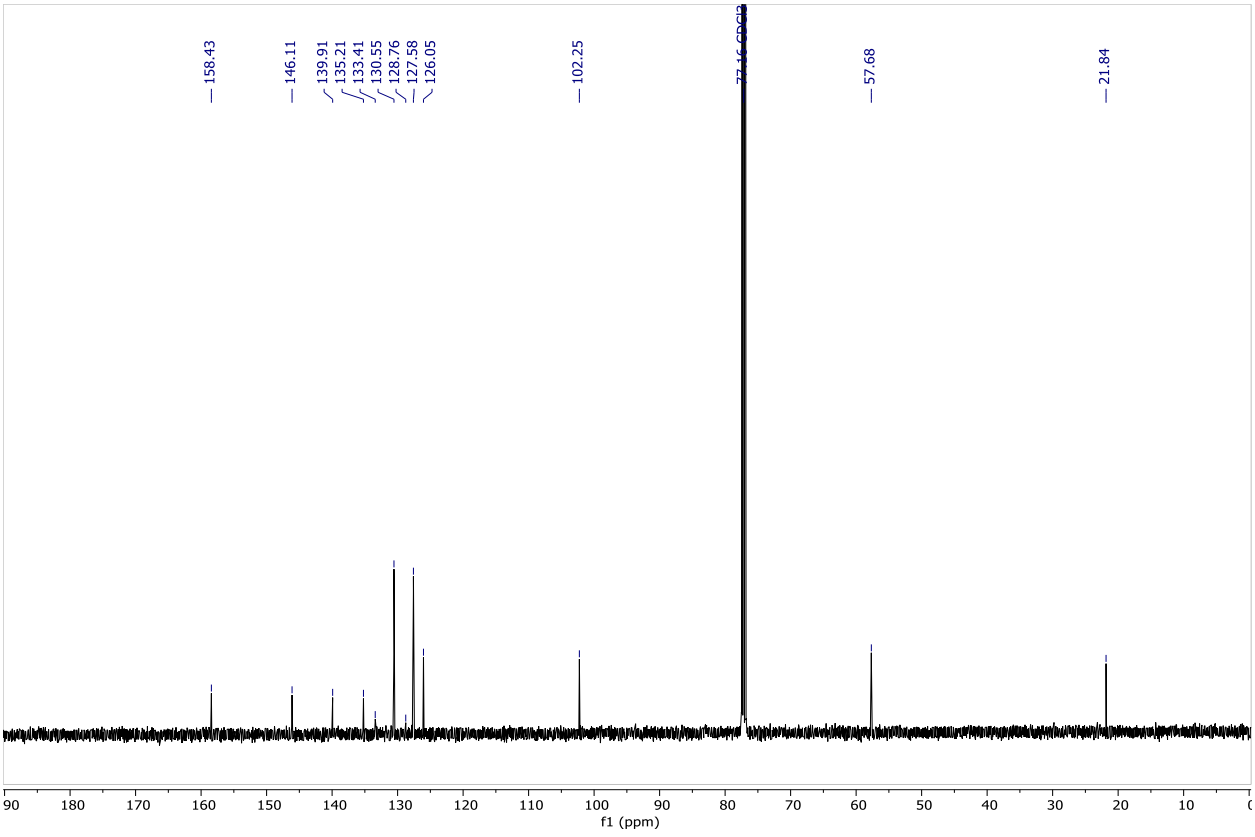

NOE
NHTs
H
NO2
H
H
O
H
Cl

357

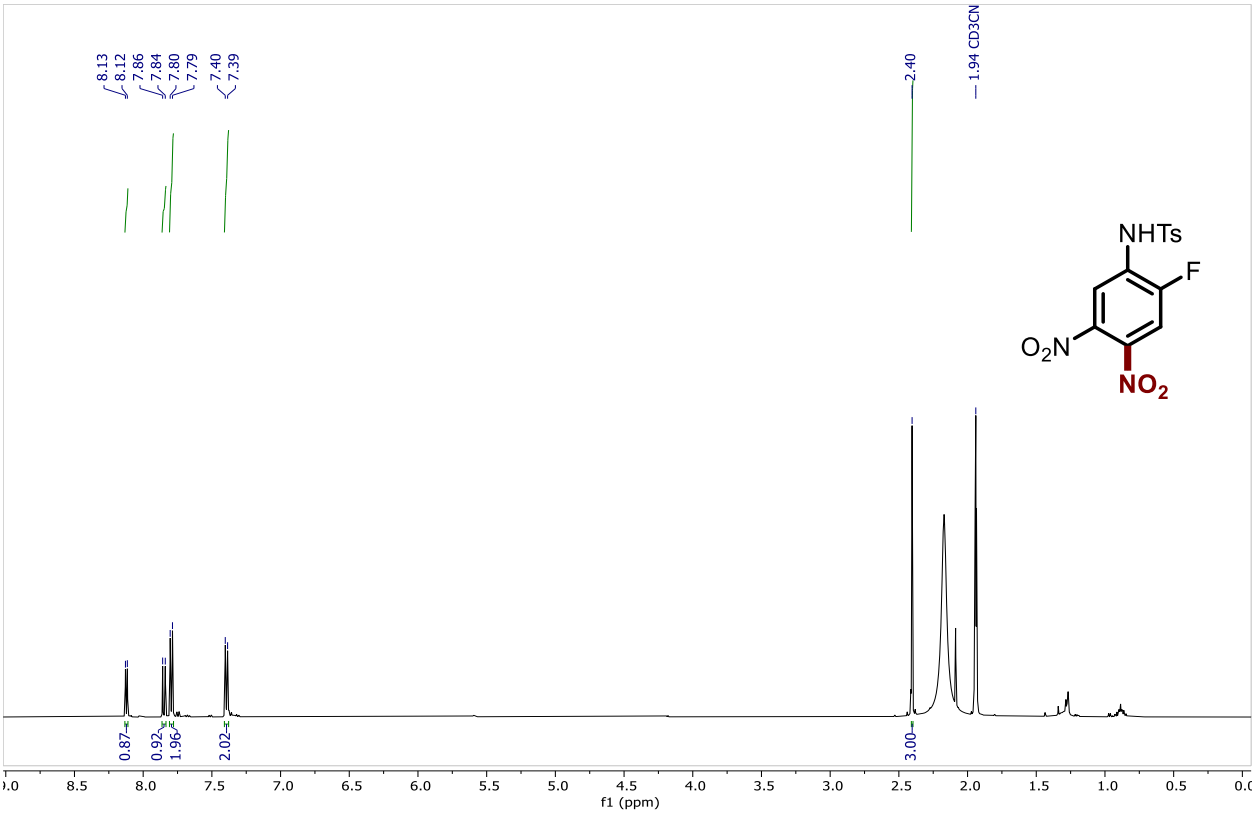

NOE
NOE
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
f2 (ppm)
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)

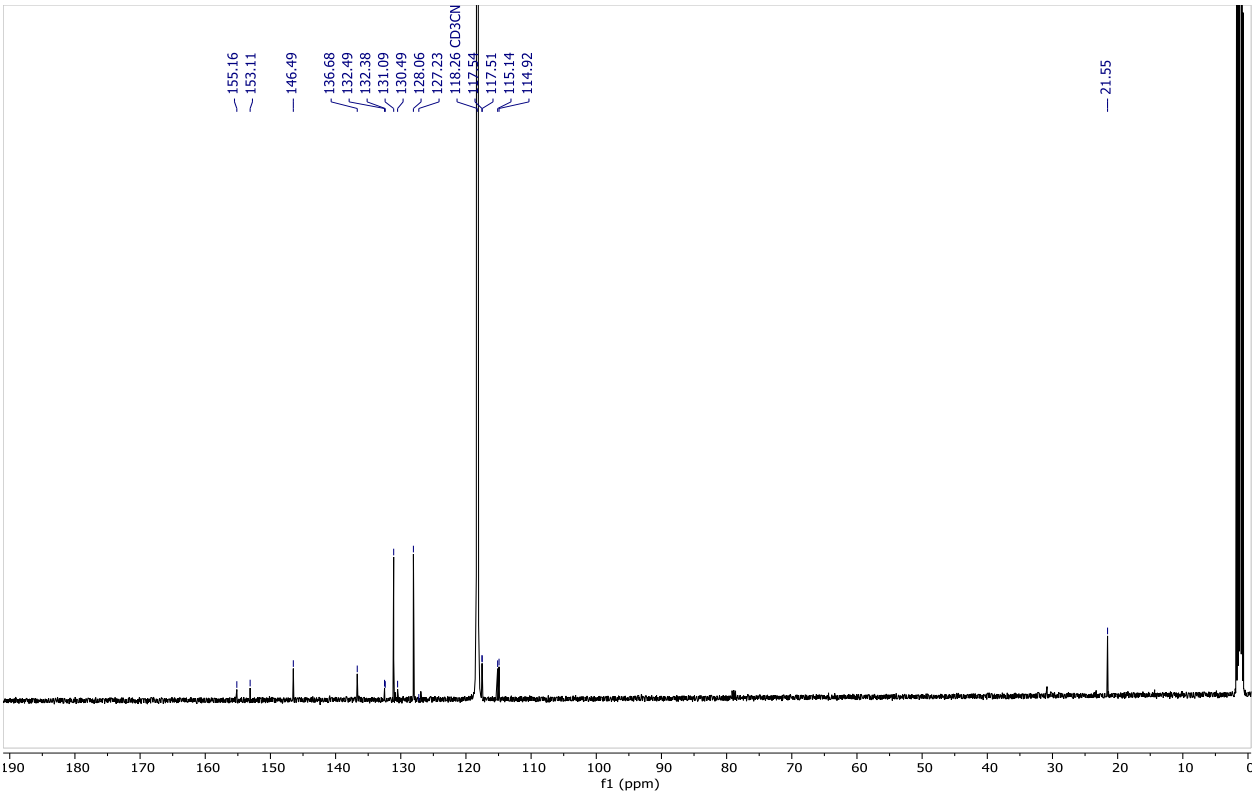
N-(5-methoxy-2,4-dinitrophenyl)-4-methylbenzenesulfonamide (**358**)

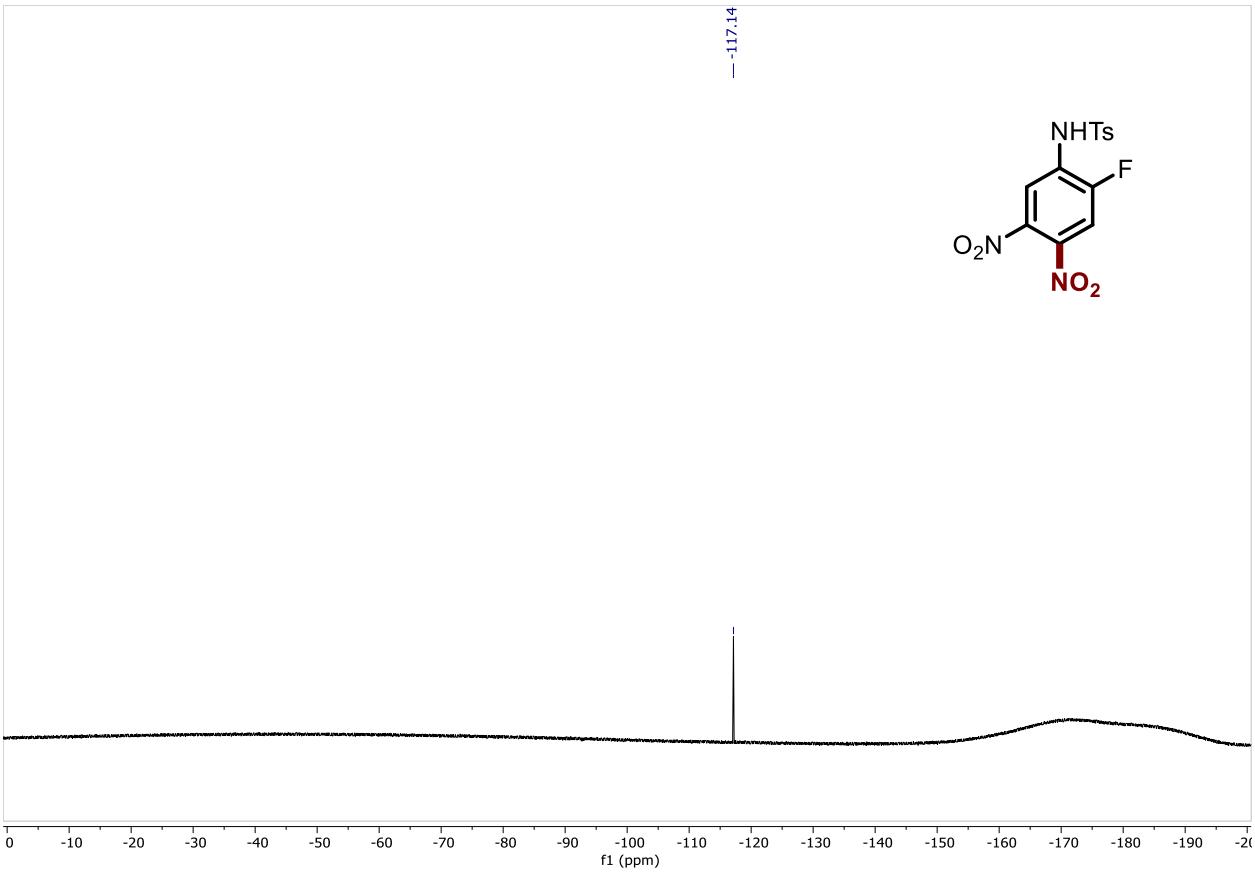




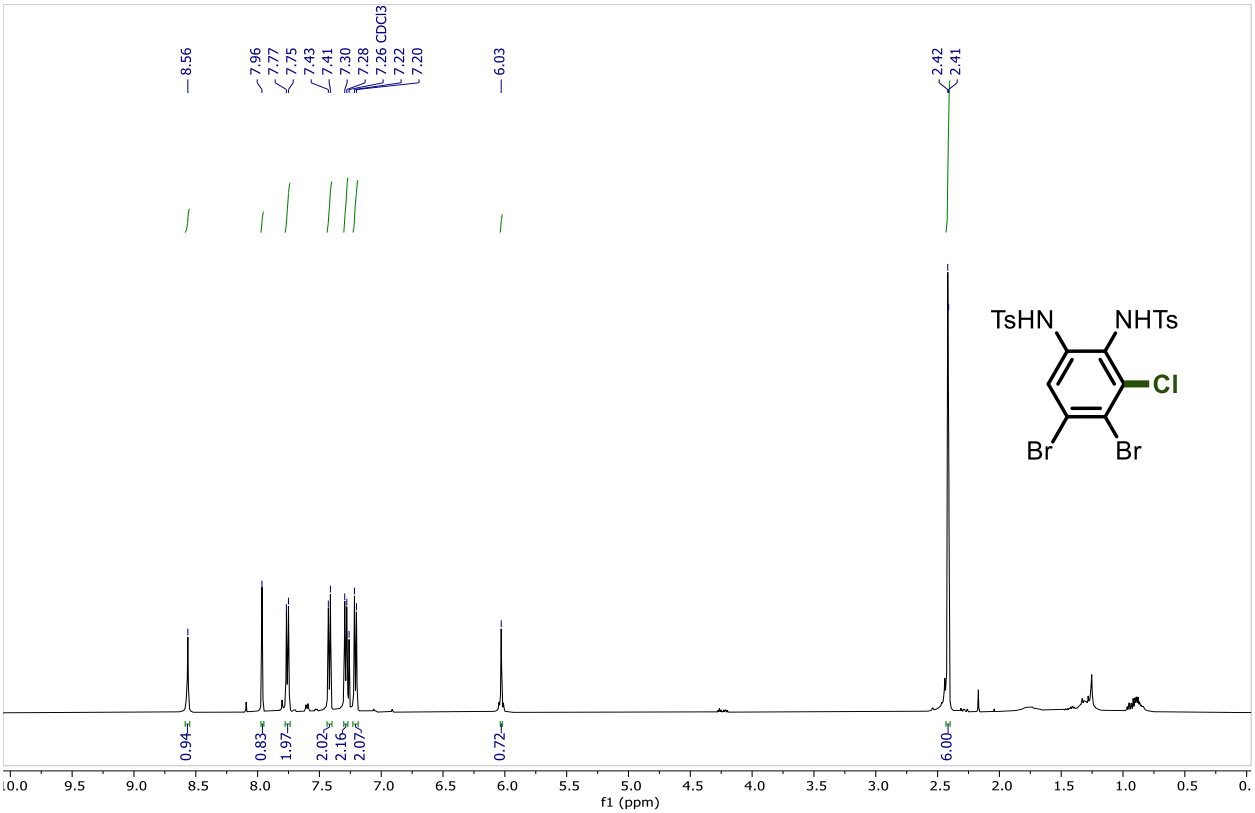
N-(2-fluoro-4,5-dinitrophenyl)-4-methylbenzenesulfonamide (**359**)

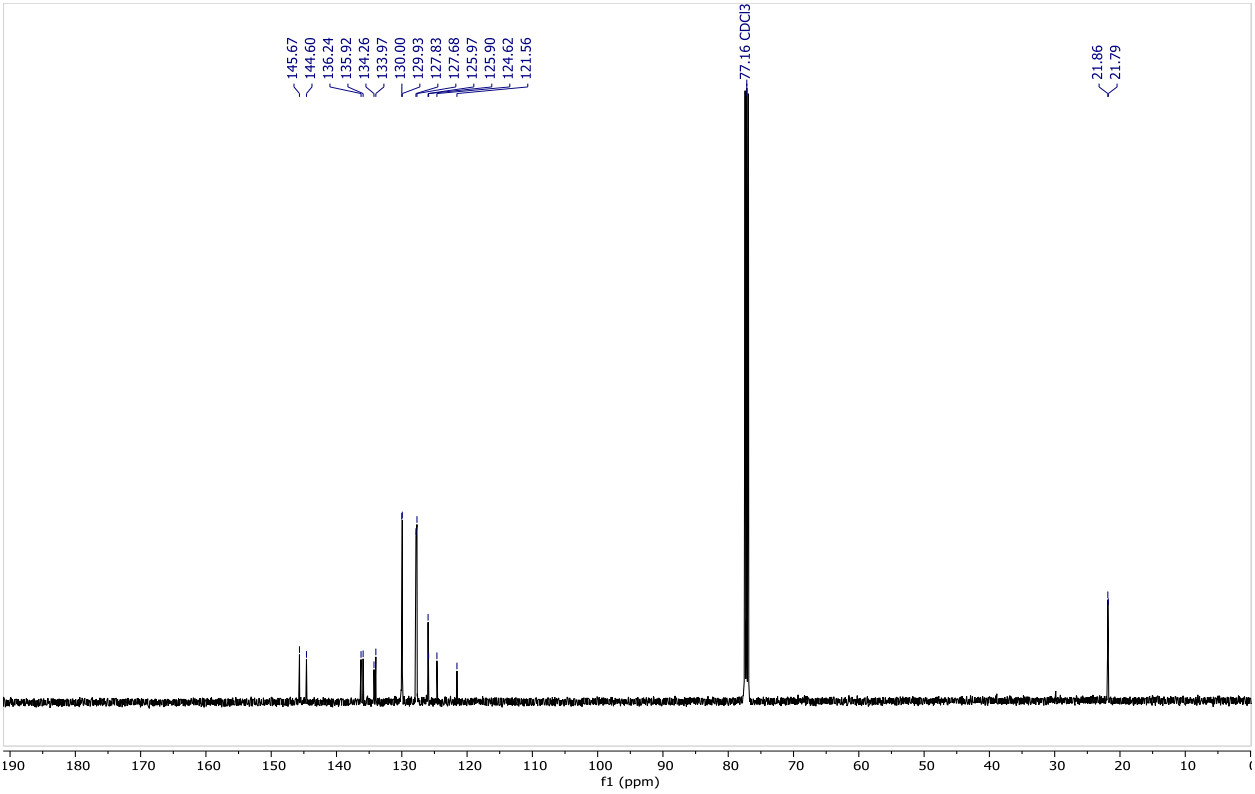




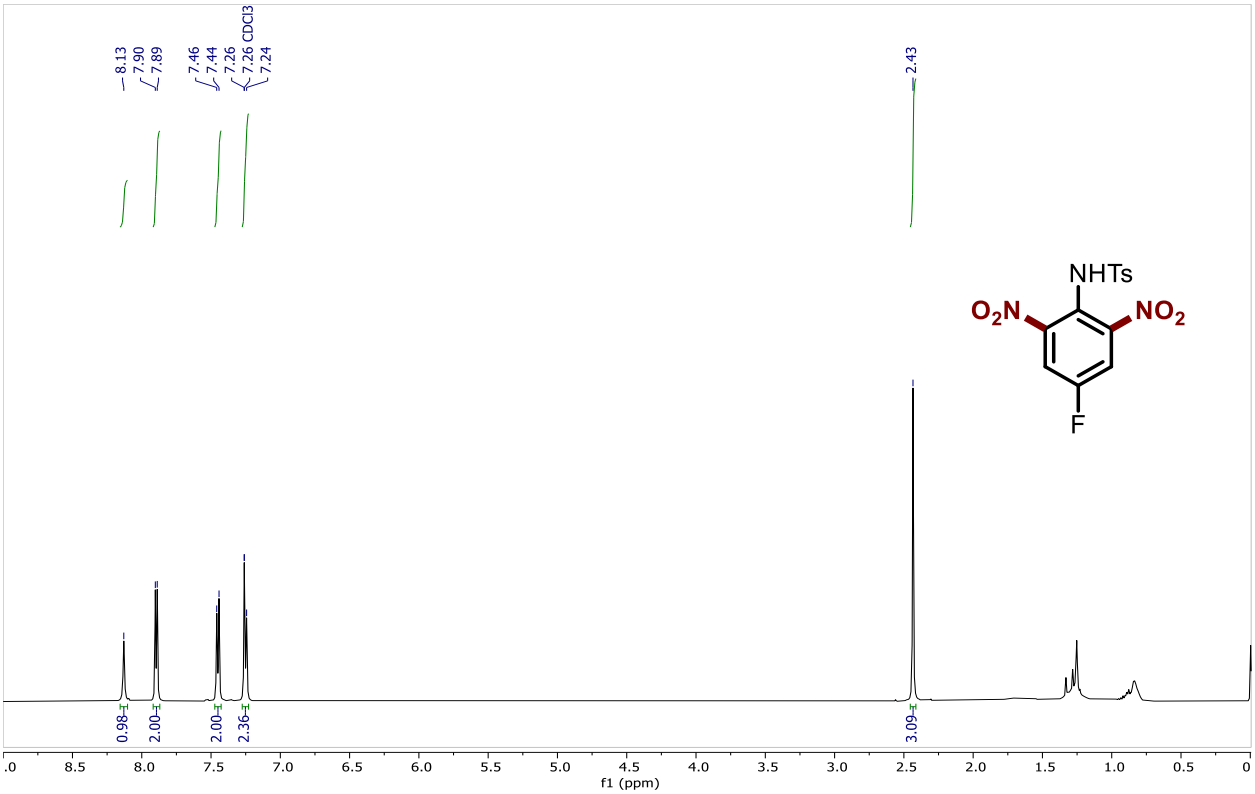

-117.14
NHTs
F
O2N
NO2
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

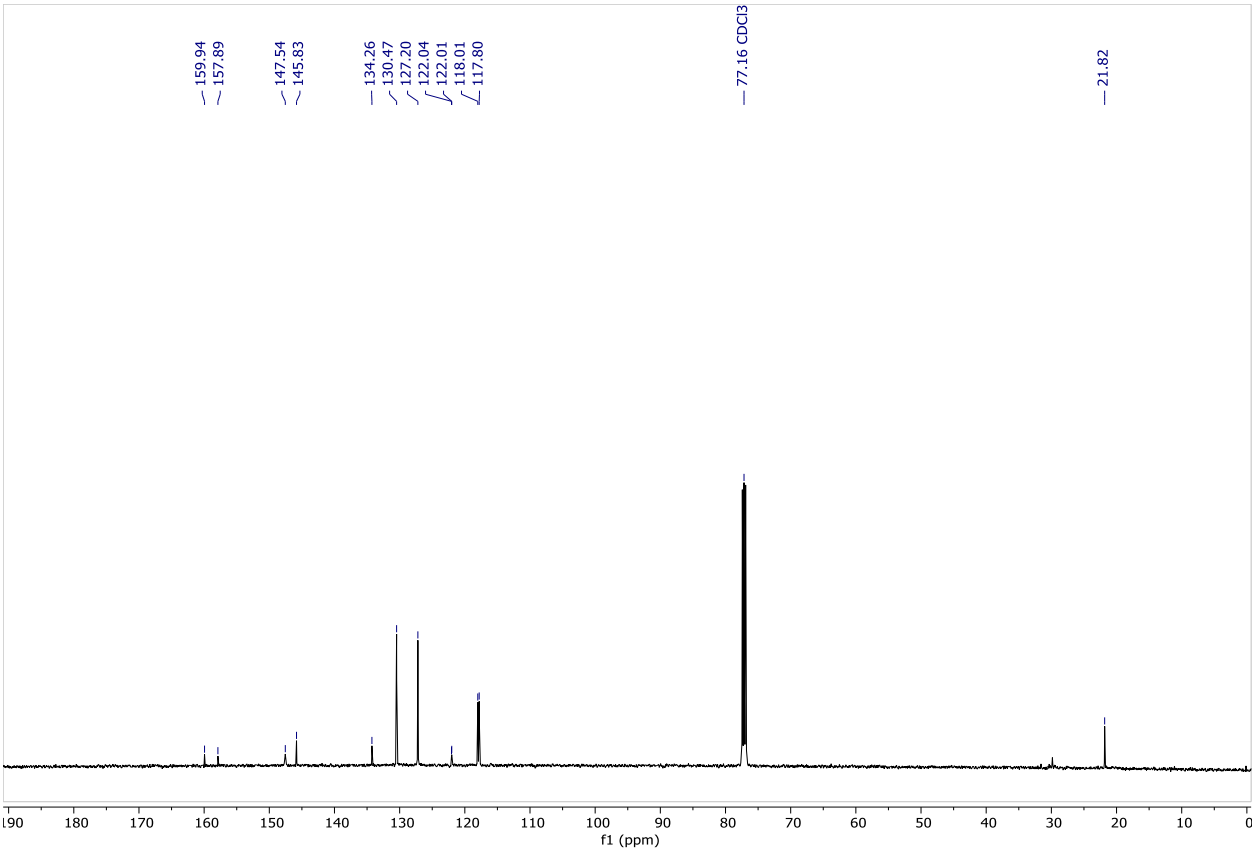
N,N'-(4,5-dibromo-3-chloro-1,2-phenylene)bis(4 methylbenzenesulfonamide) (**360**)



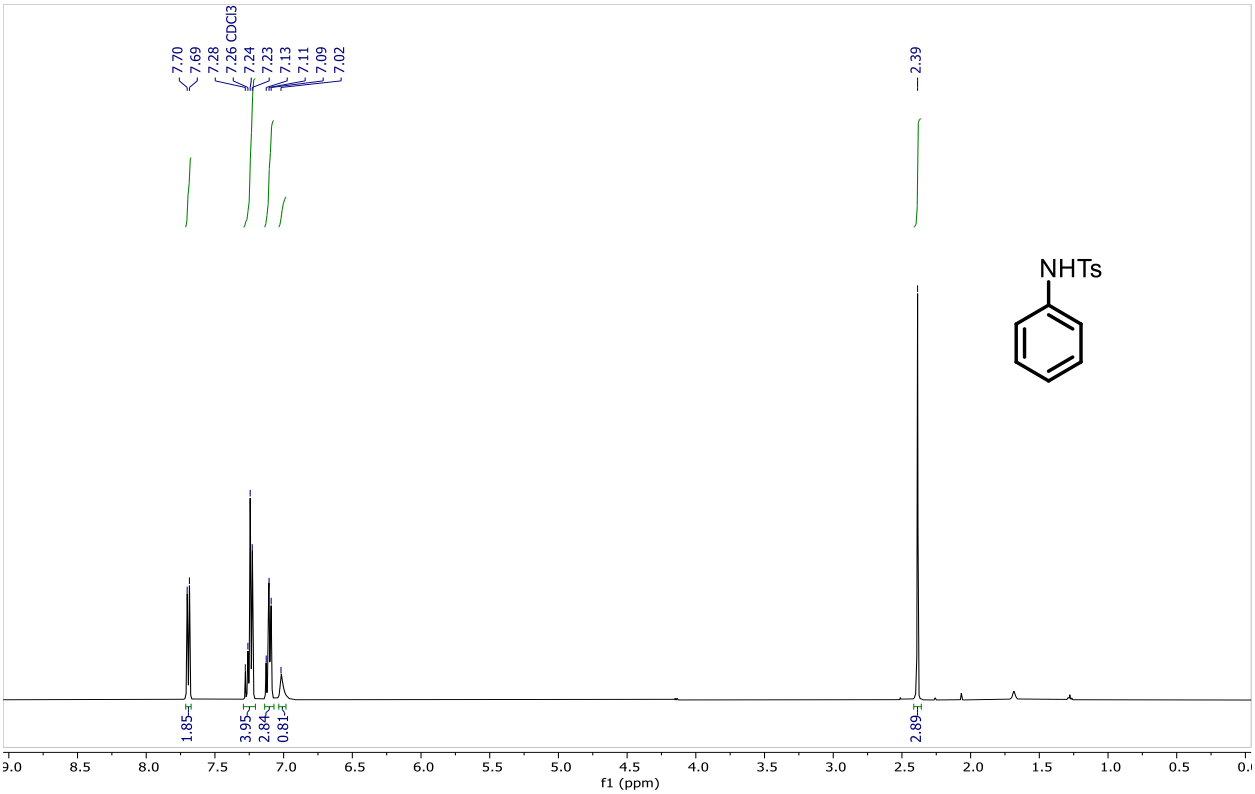


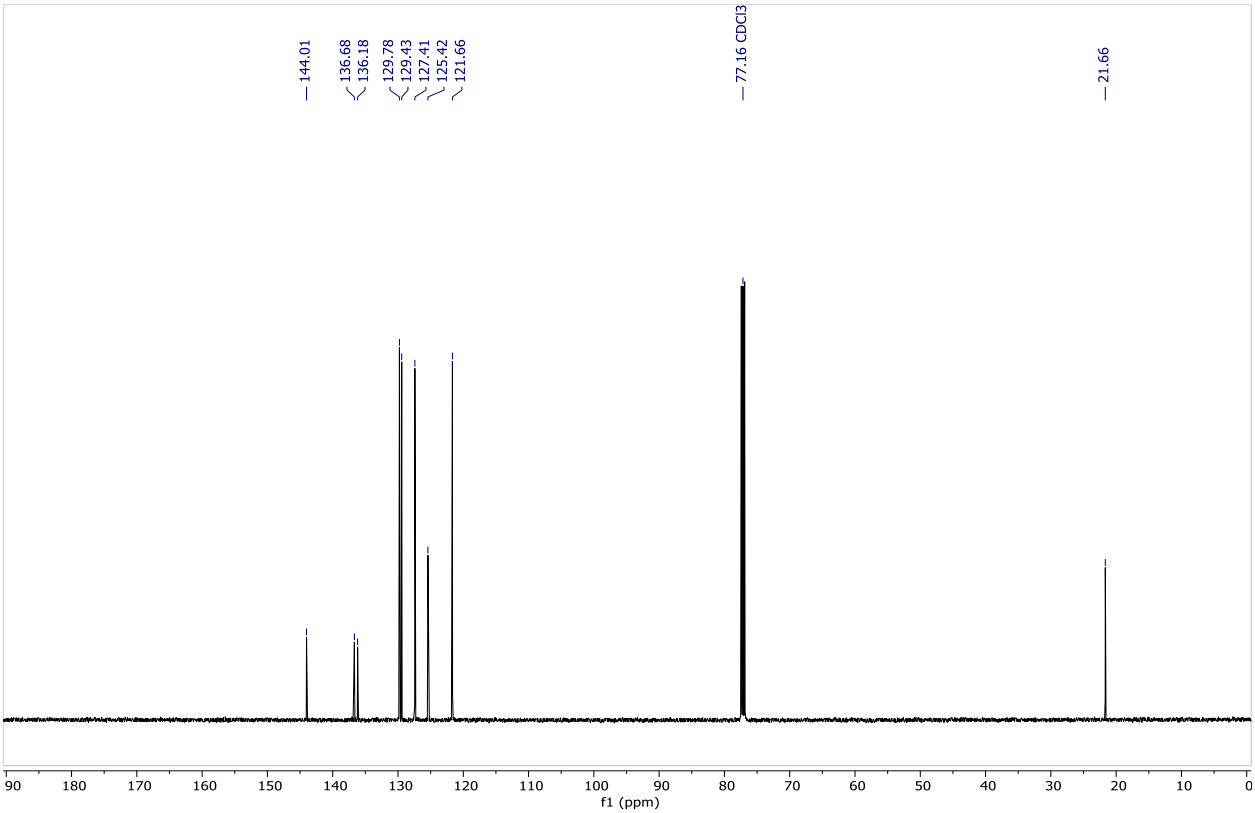
N-(4-fluoro-2,6-dinitrophenyl)-4-methylbenzenesulfonamide (**361**)



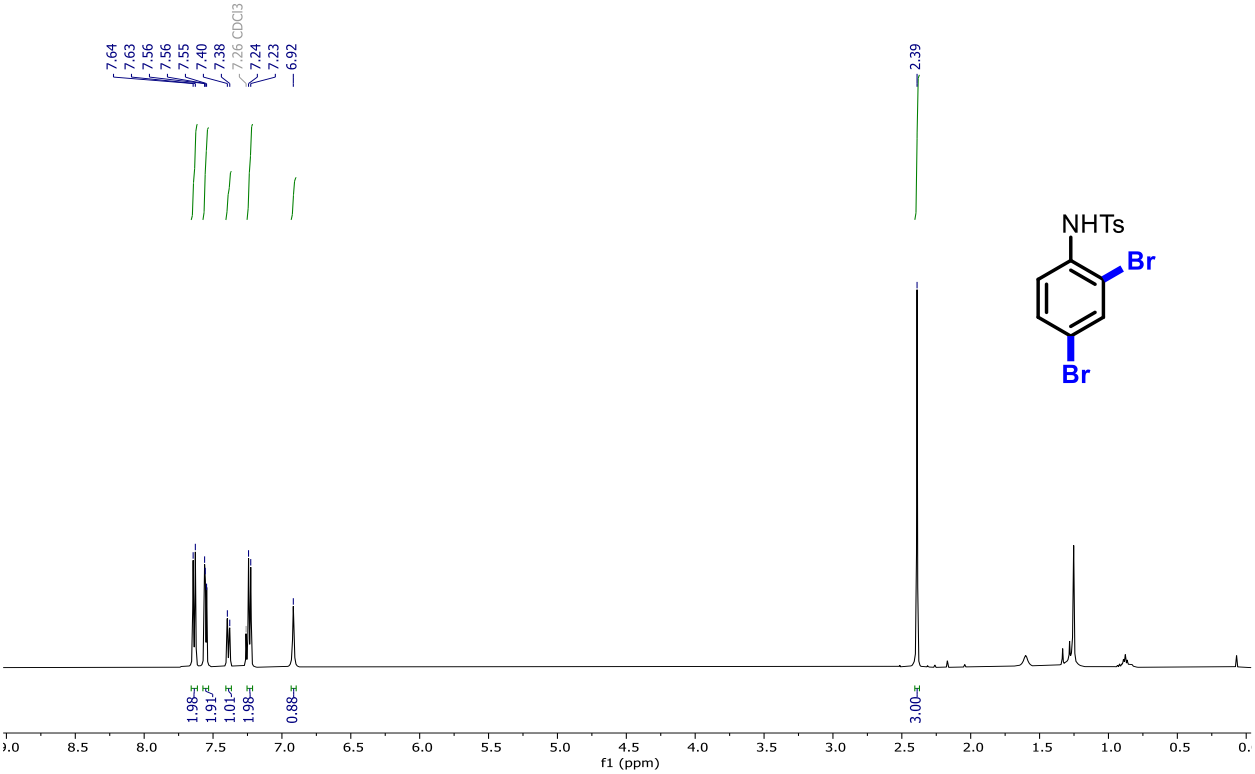


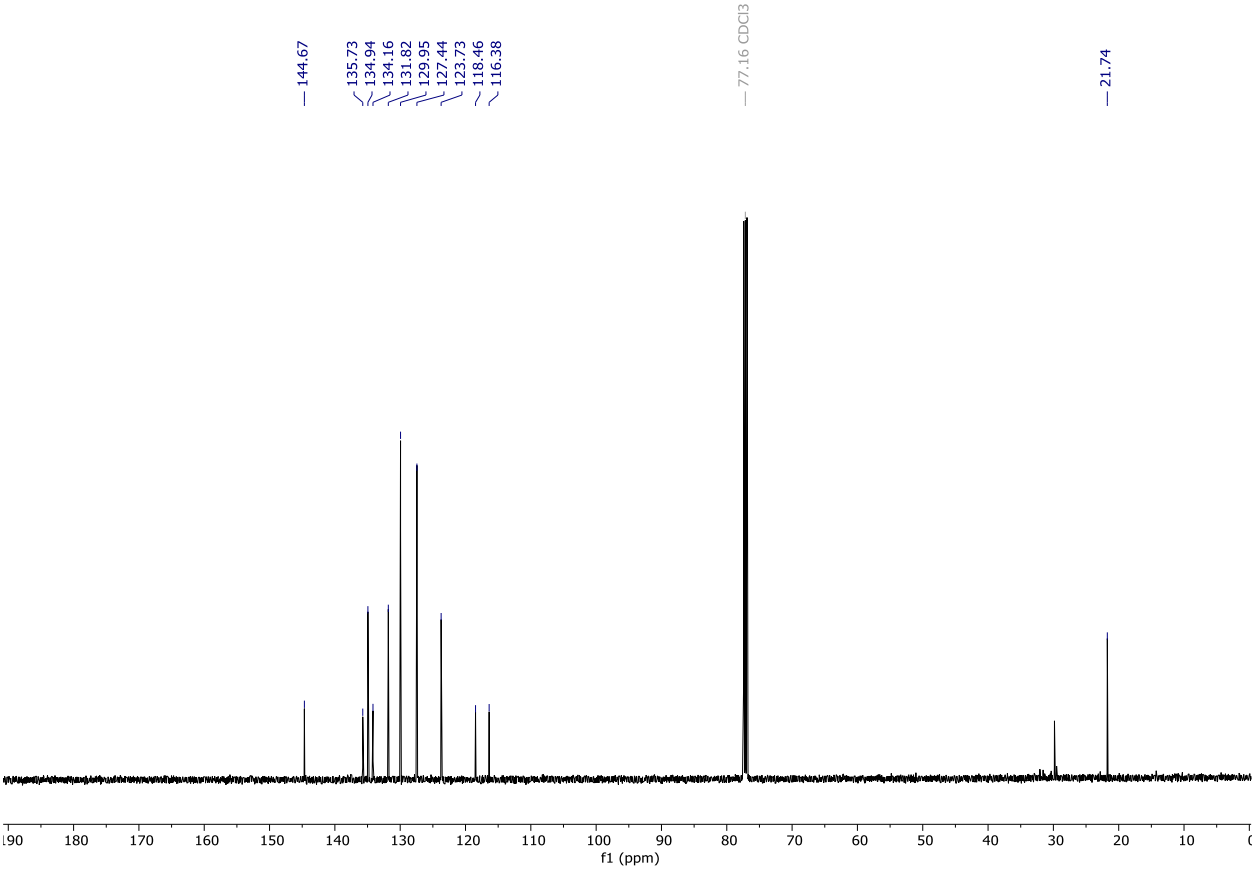
4-methyl-*N*-phenylbenzenesulfonamide (**362**)

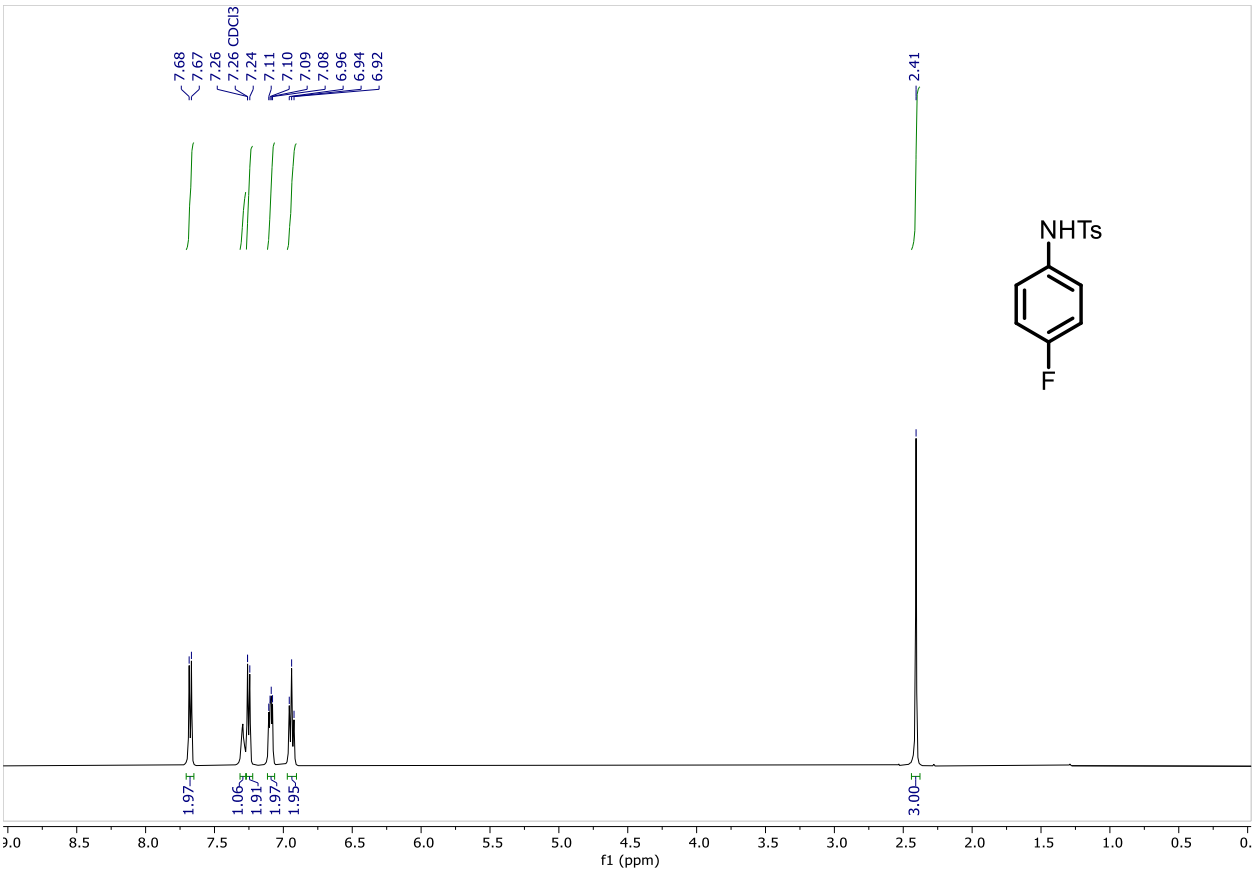


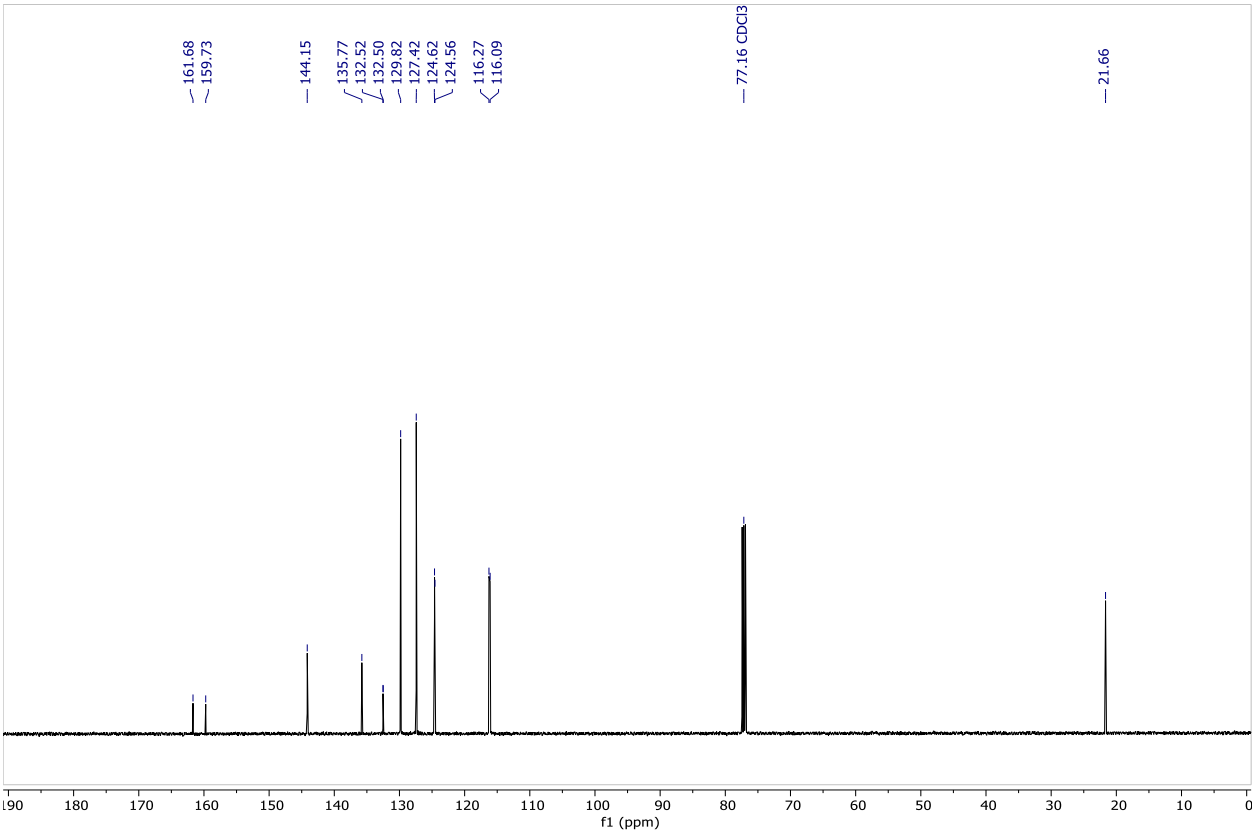


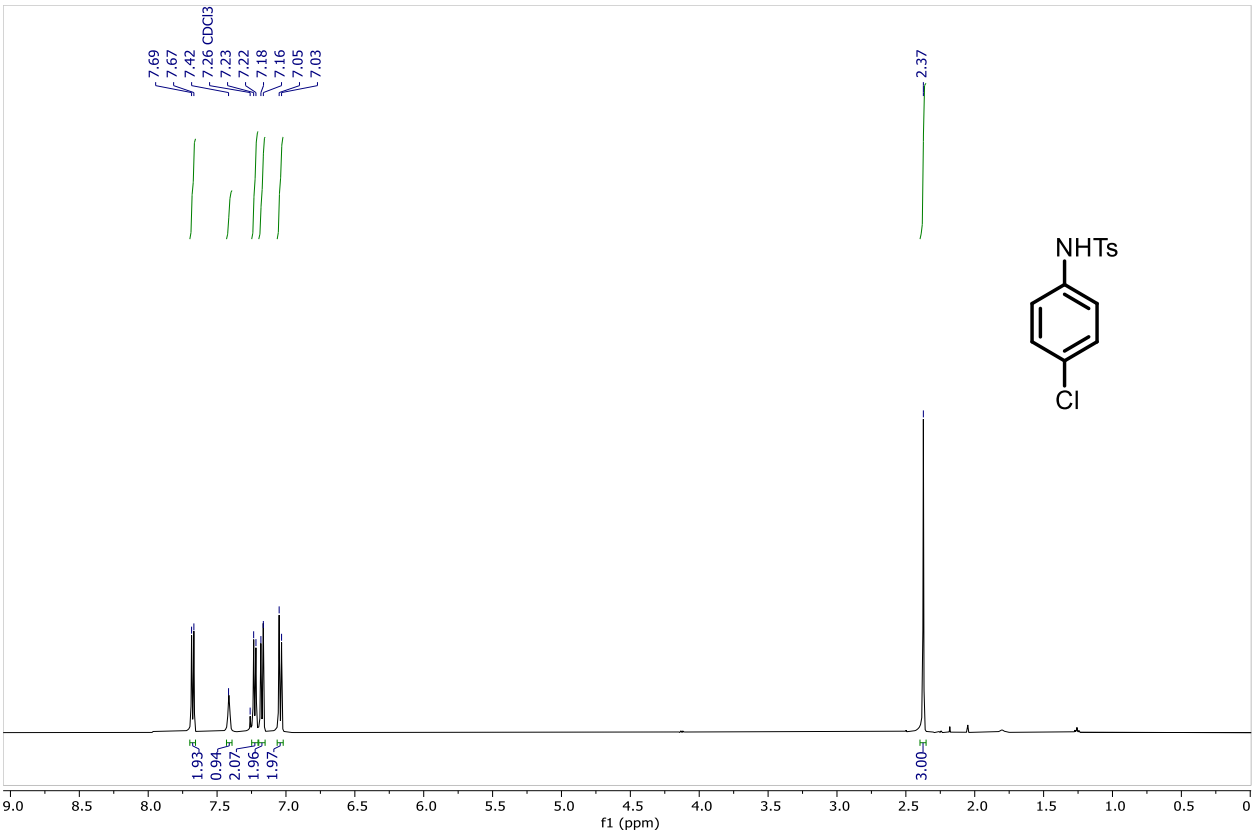
N-(2,4-dibromophenyl)-4-methylbenzenesulfonamide (**363**)

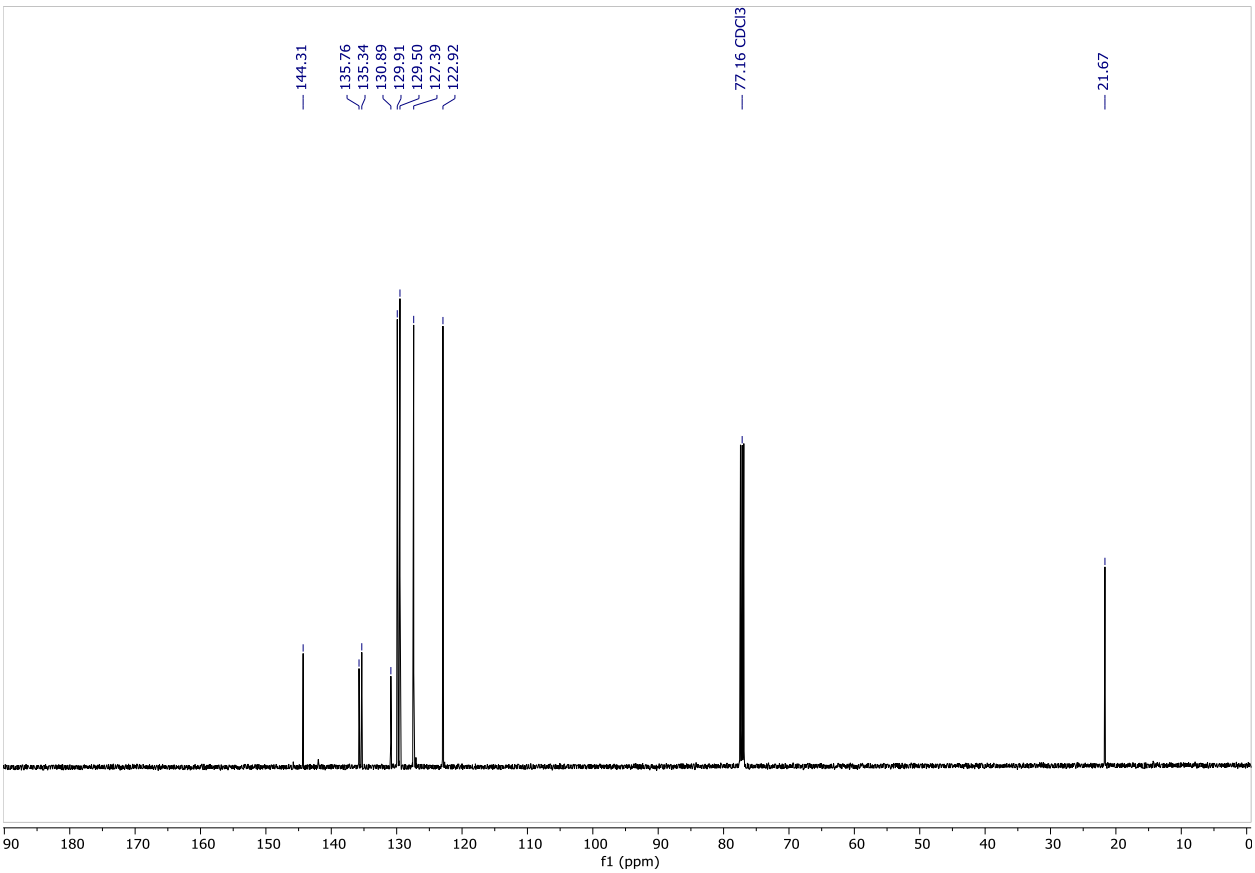


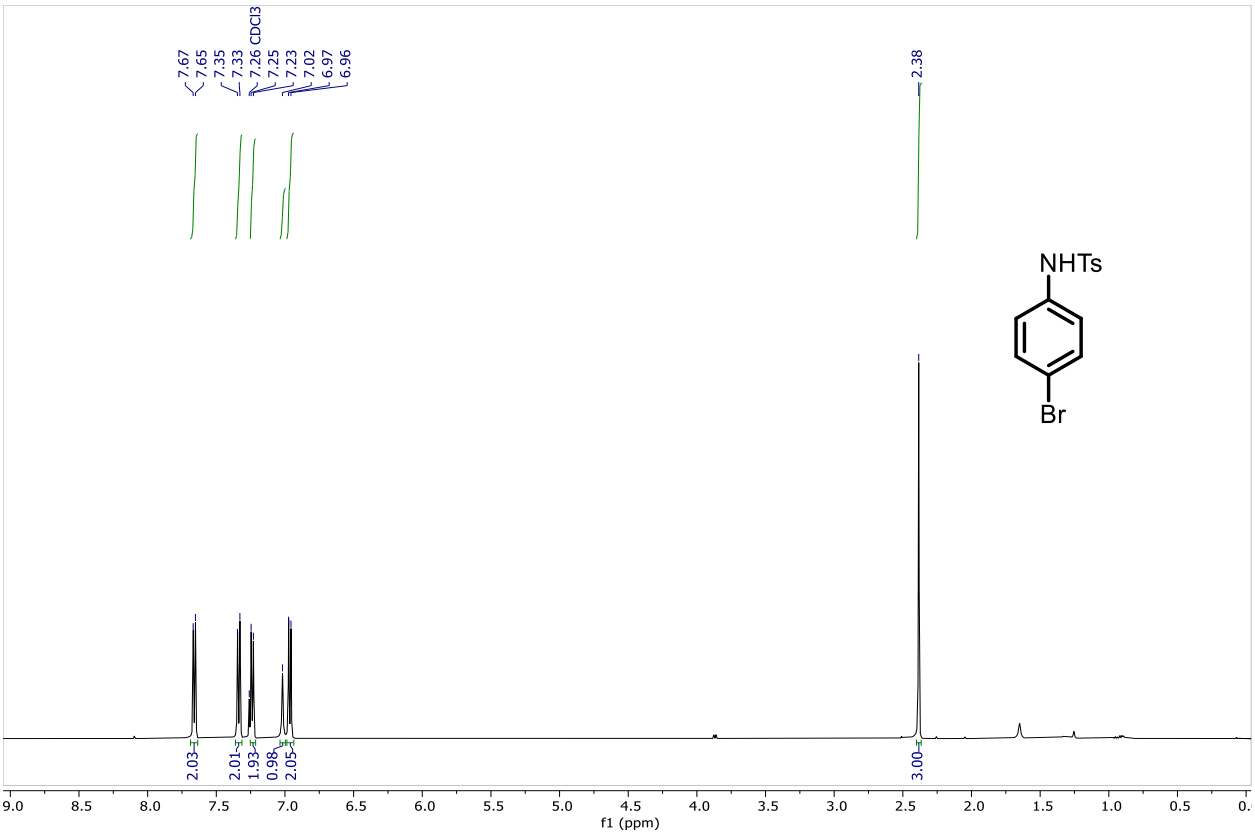


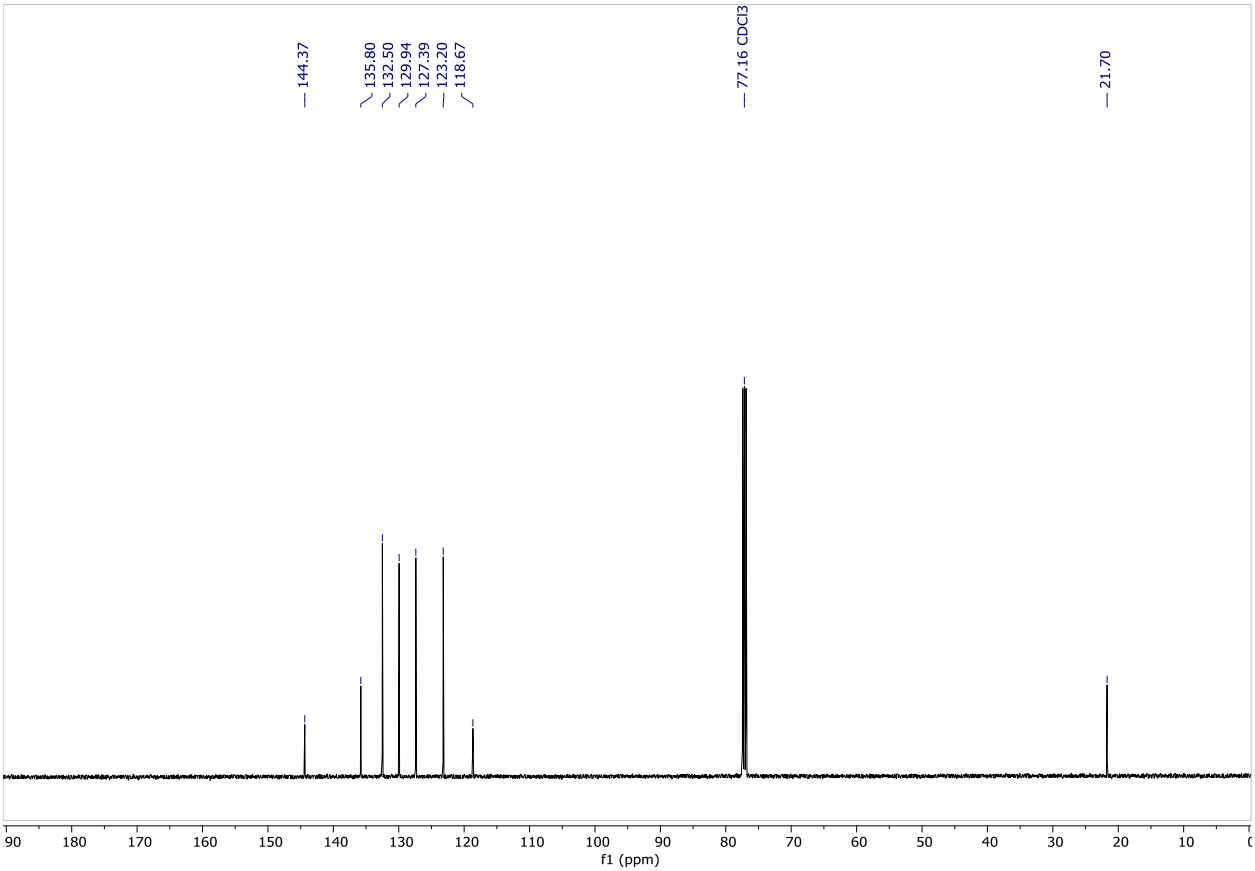

7.68
7.67
7.26
7.26 CDCl3
7.24
7.11
7.10
7.09
7.08
6.96
6.94
6.92
2.41
NHTs
F
1.97
1.06
1.91
1.97
1.95
3.00
f1 (ppm)

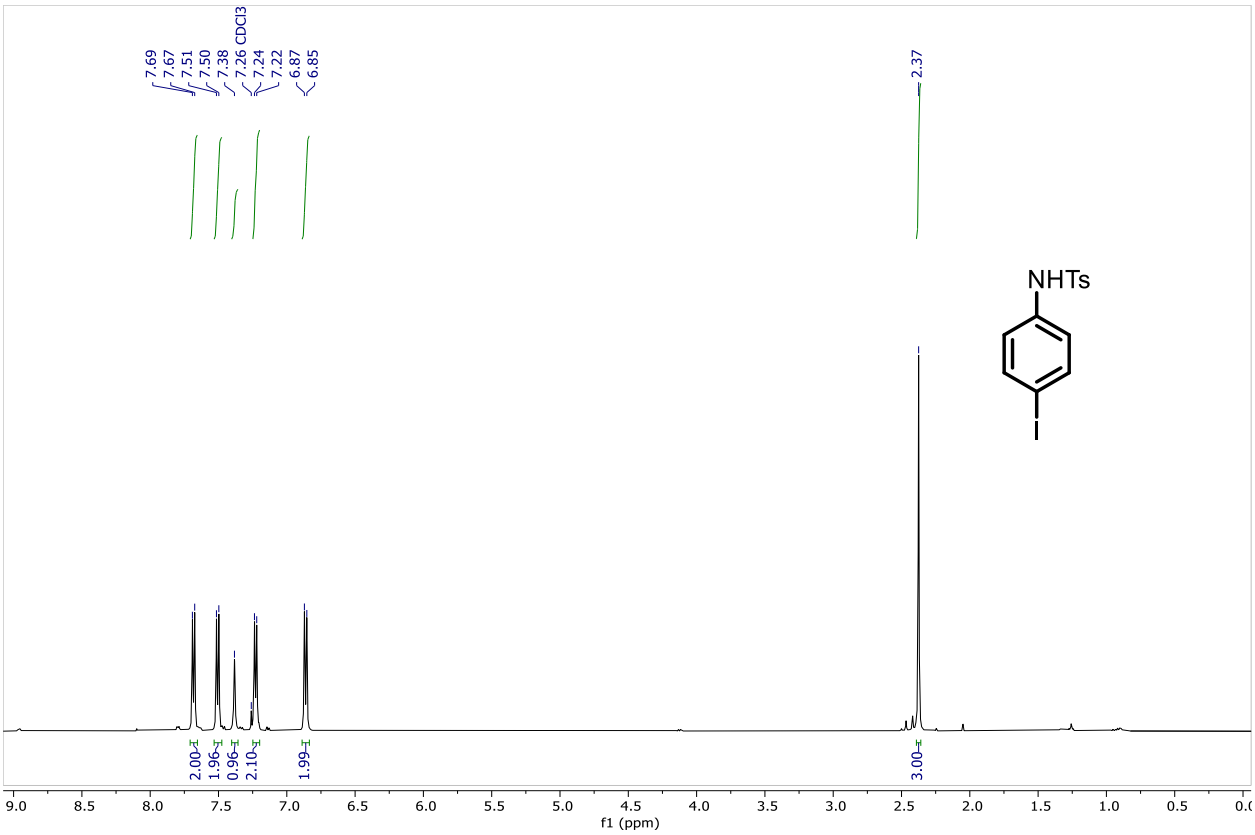

161.68
159.73
144.15
135.77
132.52
132.50
129.82
127.42
124.62
124.56
116.27
116.09
77.16 CDCl3
21.66
f1 (ppm)

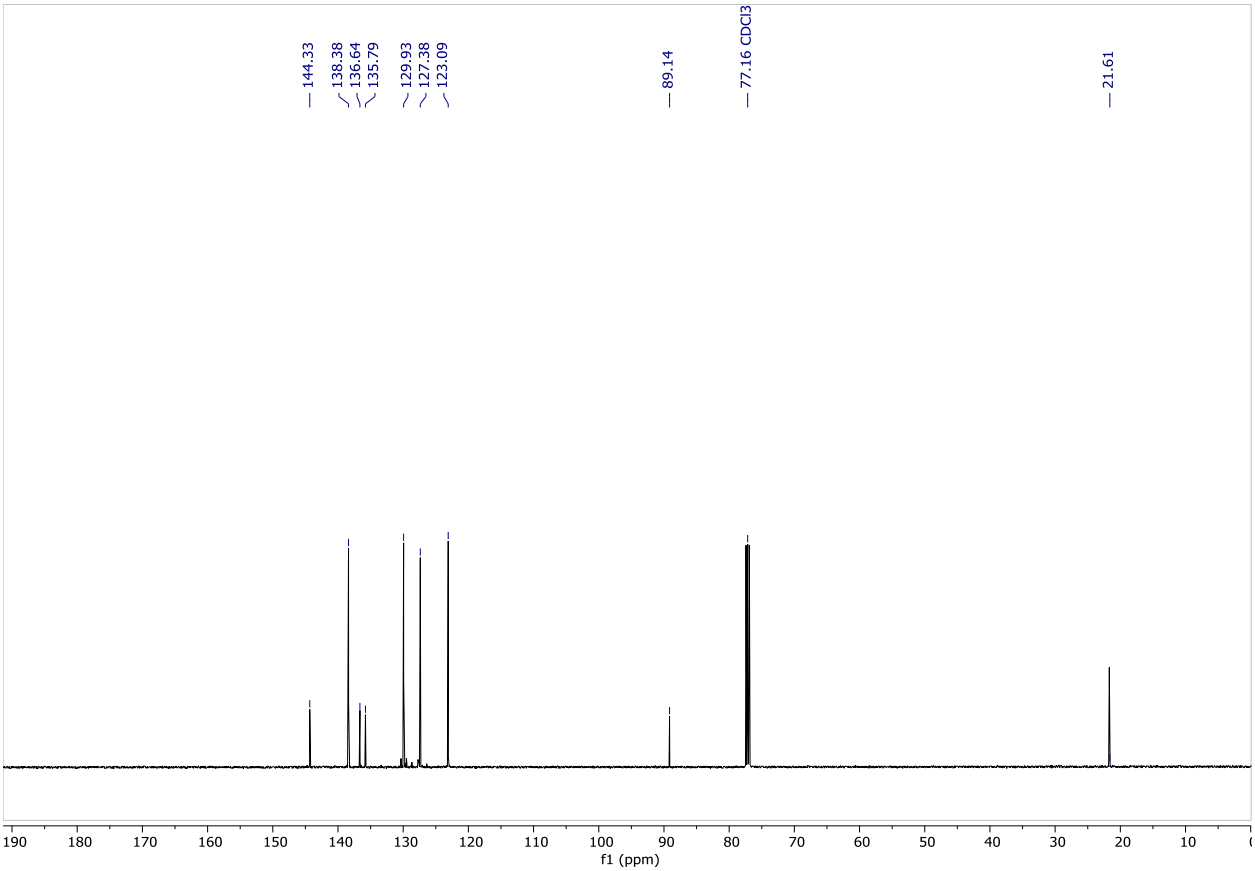

7.69
7.67
7.42
7.26 CDCl3
7.23
7.22
7.18
7.16
7.05
7.03
2.37
NHTs
Cl
1.93
0.94
2.07
1.96
1.97
3.00
f1 (ppm)

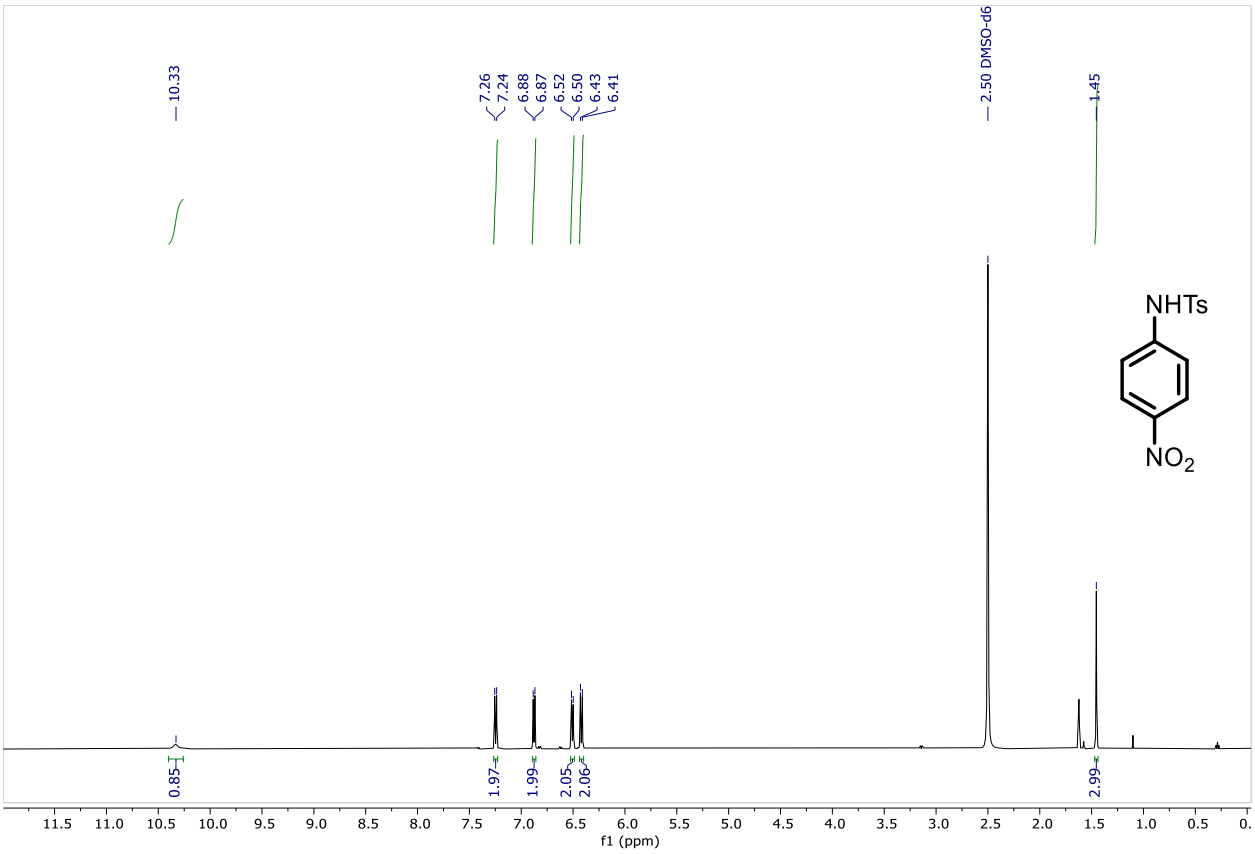

144.31
135.76
135.34
130.89
129.91
129.50
127.39
122.92
77.16 CDCl3
21.67
f1 (ppm)

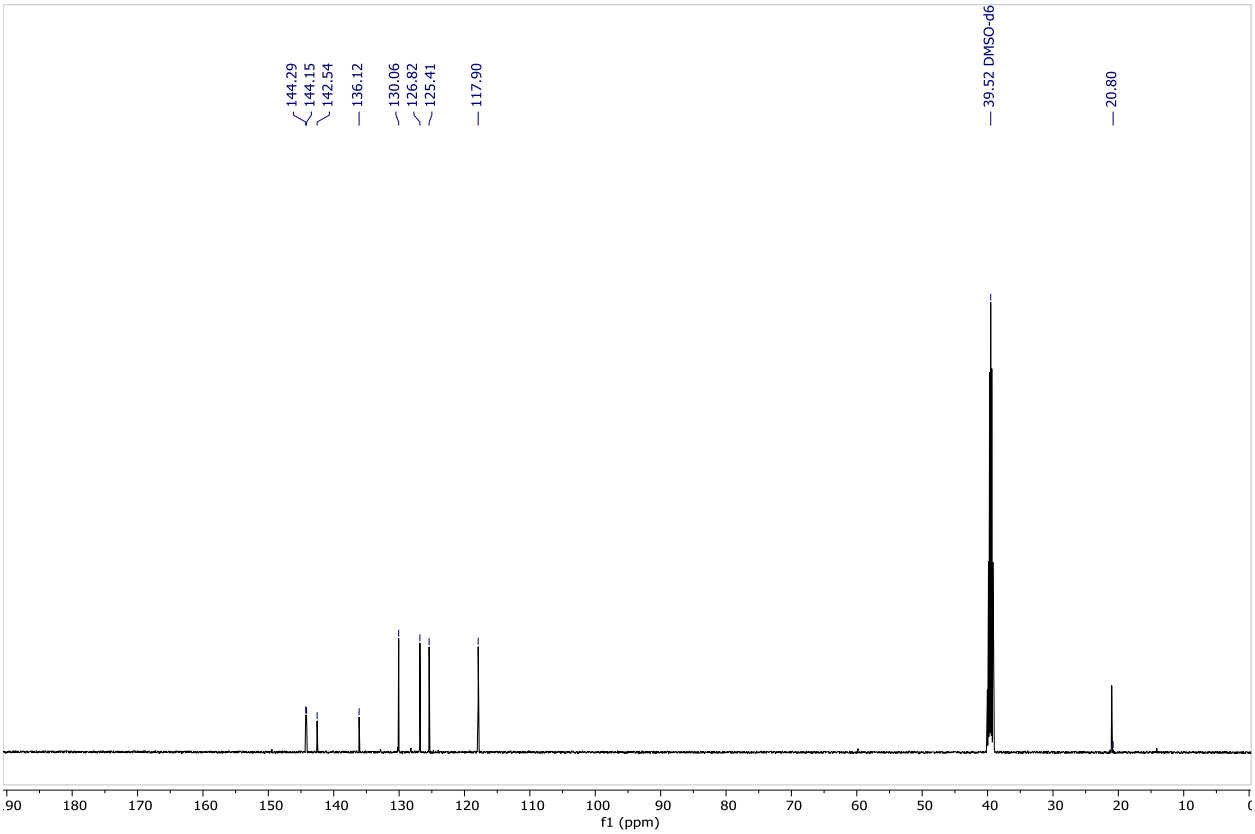

7.67
7.65
7.35
7.33
7.26 CDCl3
7.25
7.23
7.02
6.97
6.96
2.38
NHTs
Br
2.03
2.01
1.93
0.98
2.05
3.00
f1 (ppm)

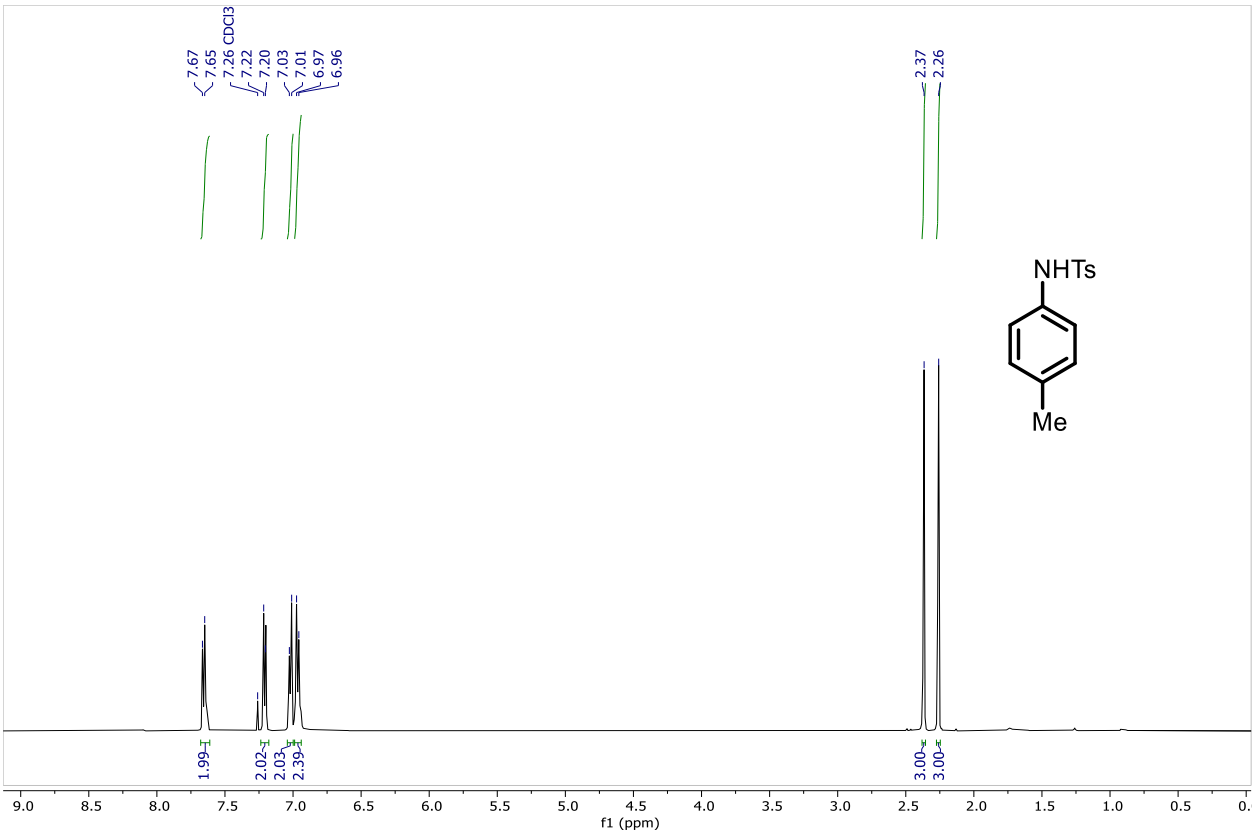

144.37
135.80
132.50
129.94
127.39
123.20
118.67
77.16 CDCl3
21.70
f1 (ppm)

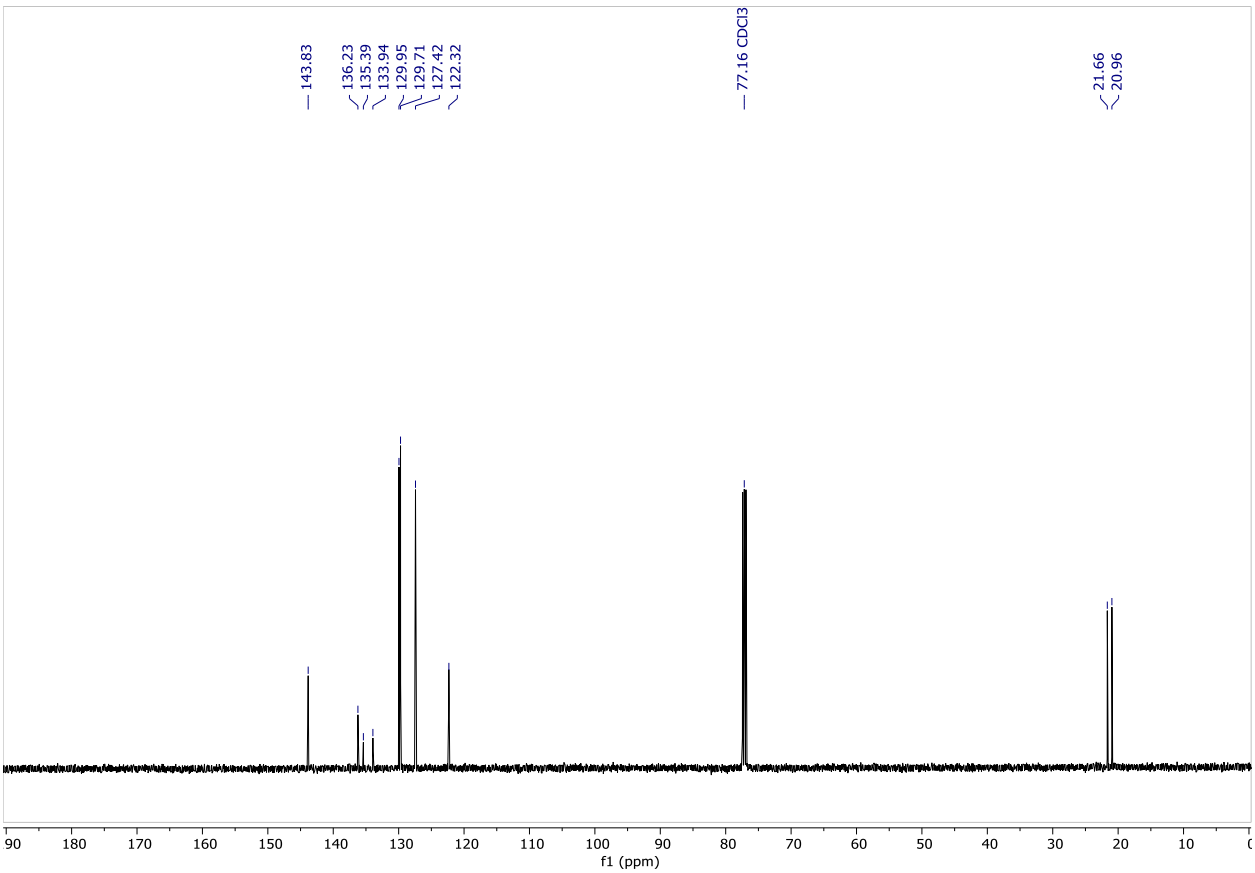

7.69
7.67
7.51
7.50
7.38
7.26 CDCl3
7.24
7.22
6.87
6.85
2.37
NHTs
2.00
1.96
0.96
2.10
1.99
3.00
f1 (ppm)

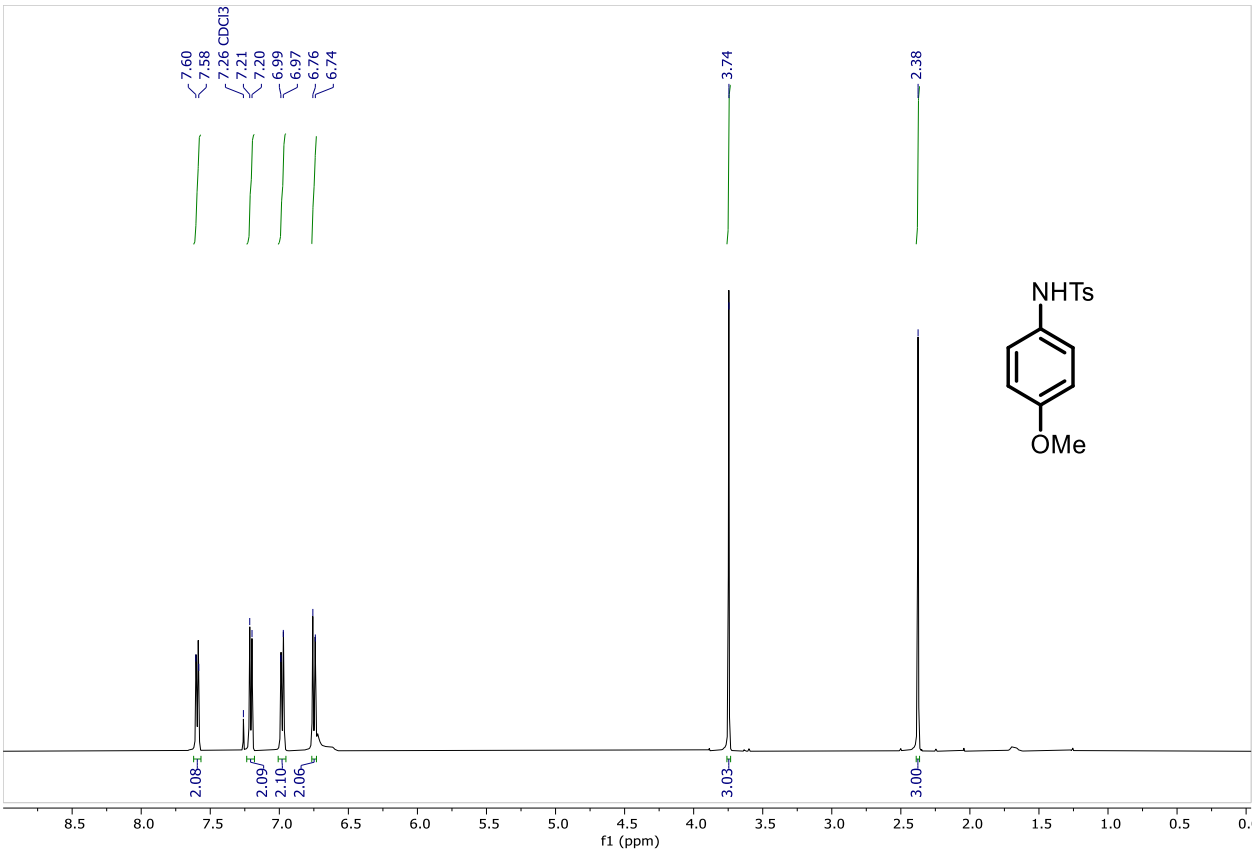

144.33
138.38
136.64
135.79
129.93
127.38
123.09
89.14
77.16 CDCl3
21.61
f1 (ppm)

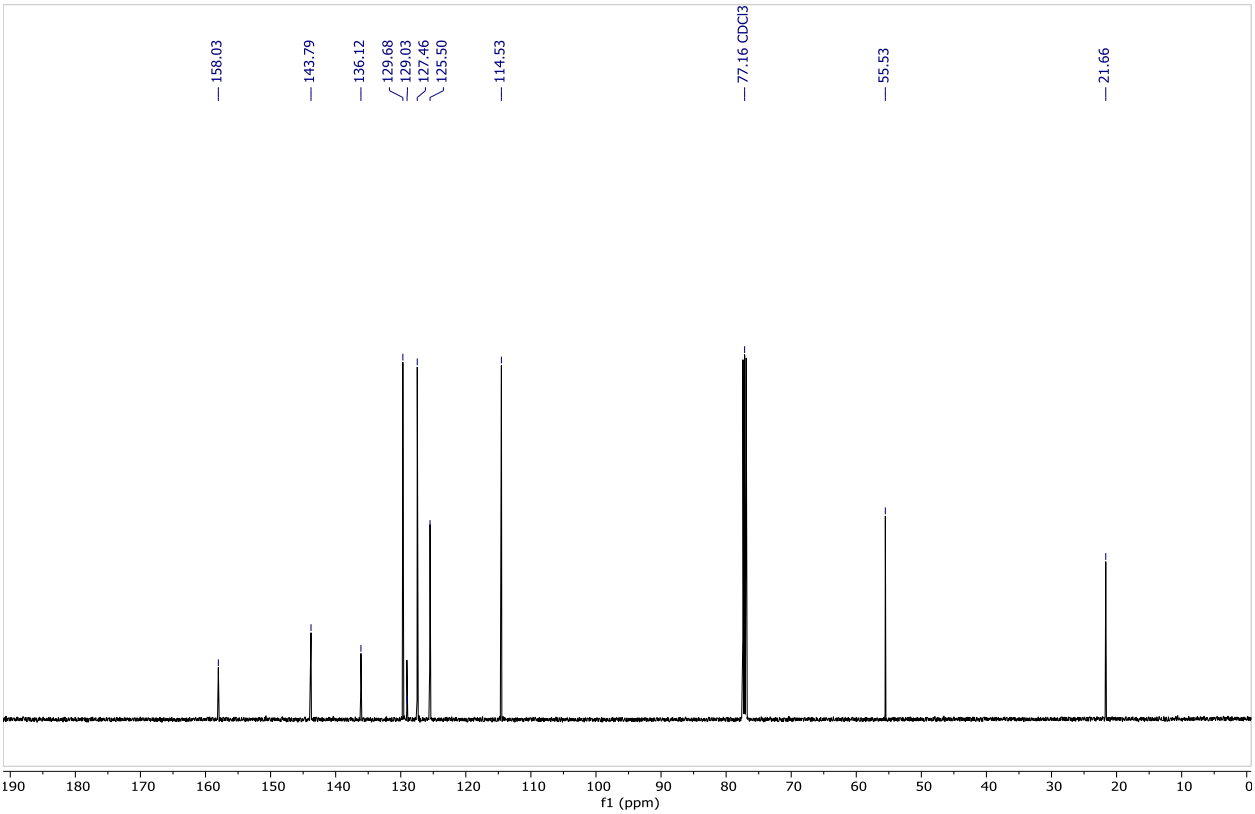

10.33
7.26
7.24
6.88
6.87
6.52
6.50
6.43
6.41
2.50 DMSO-d6
1.45
NHTs
NO2
0.85
1.97
1.99
2.05
2.06
2.99
f1 (ppm)

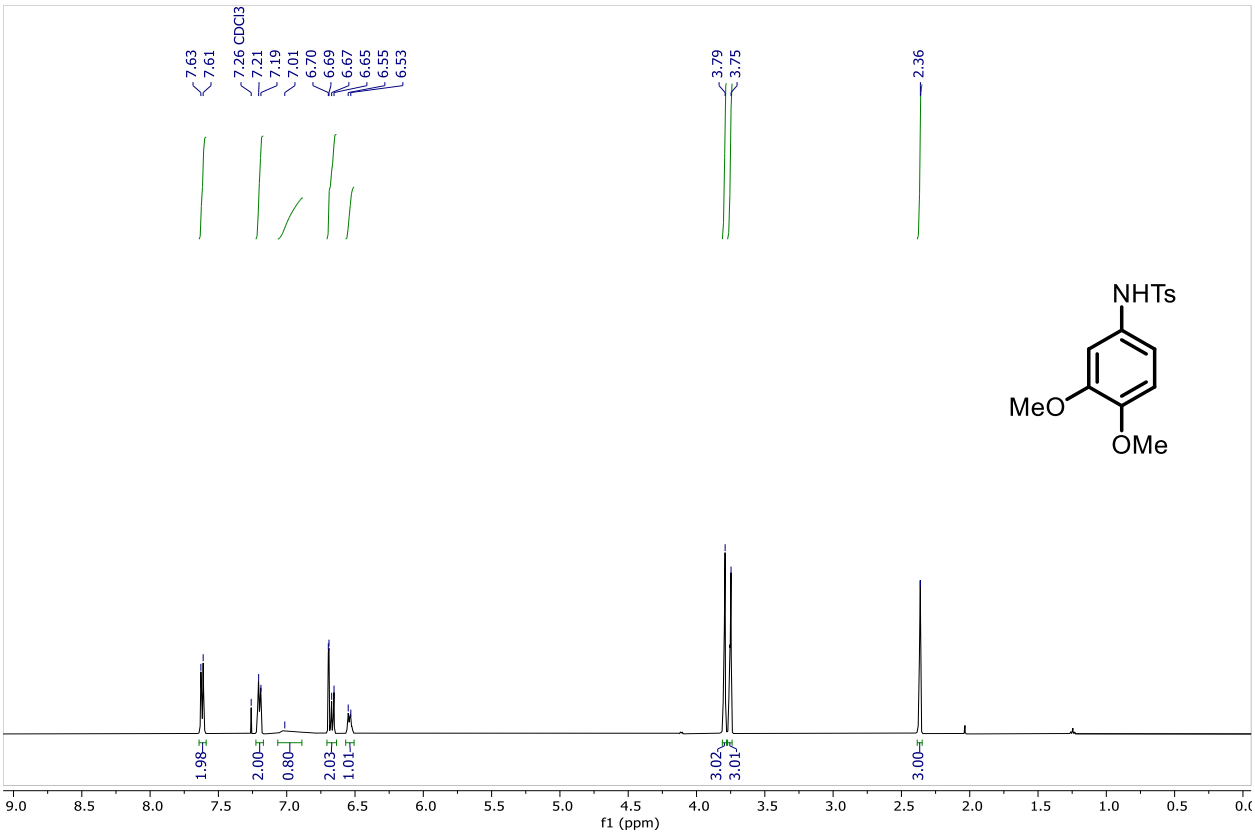

144.29
144.15
142.54
136.12
130.06
126.82
125.41
117.90
39.52 DMSO-d6
20.80
f1 (ppm)

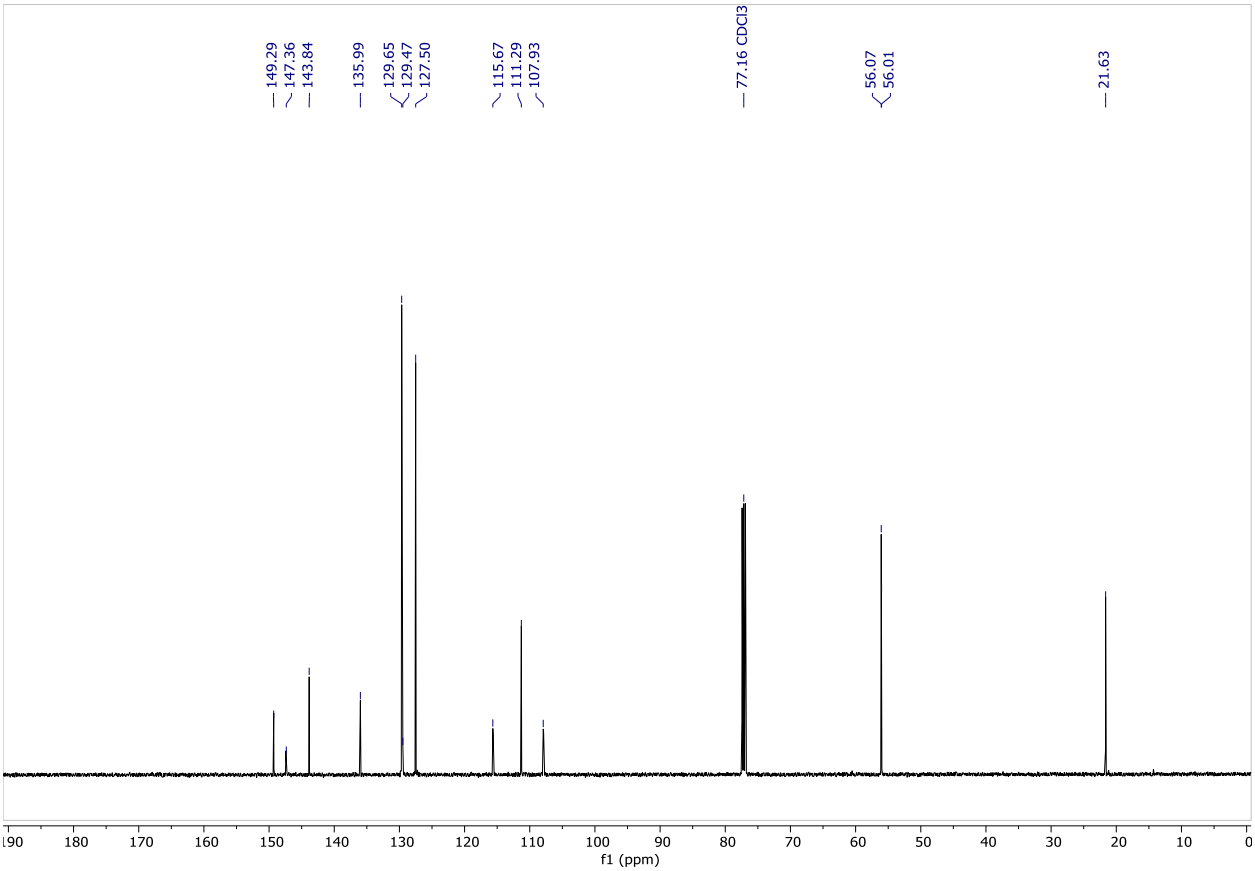

7.67
7.65
7.26 CDCl3
7.22
7.20
7.03
7.01
6.97
6.96
2.37
2.26
NHTs
Me
1.99
2.02
2.03
2.39
3.00
3.00
f1 (ppm)

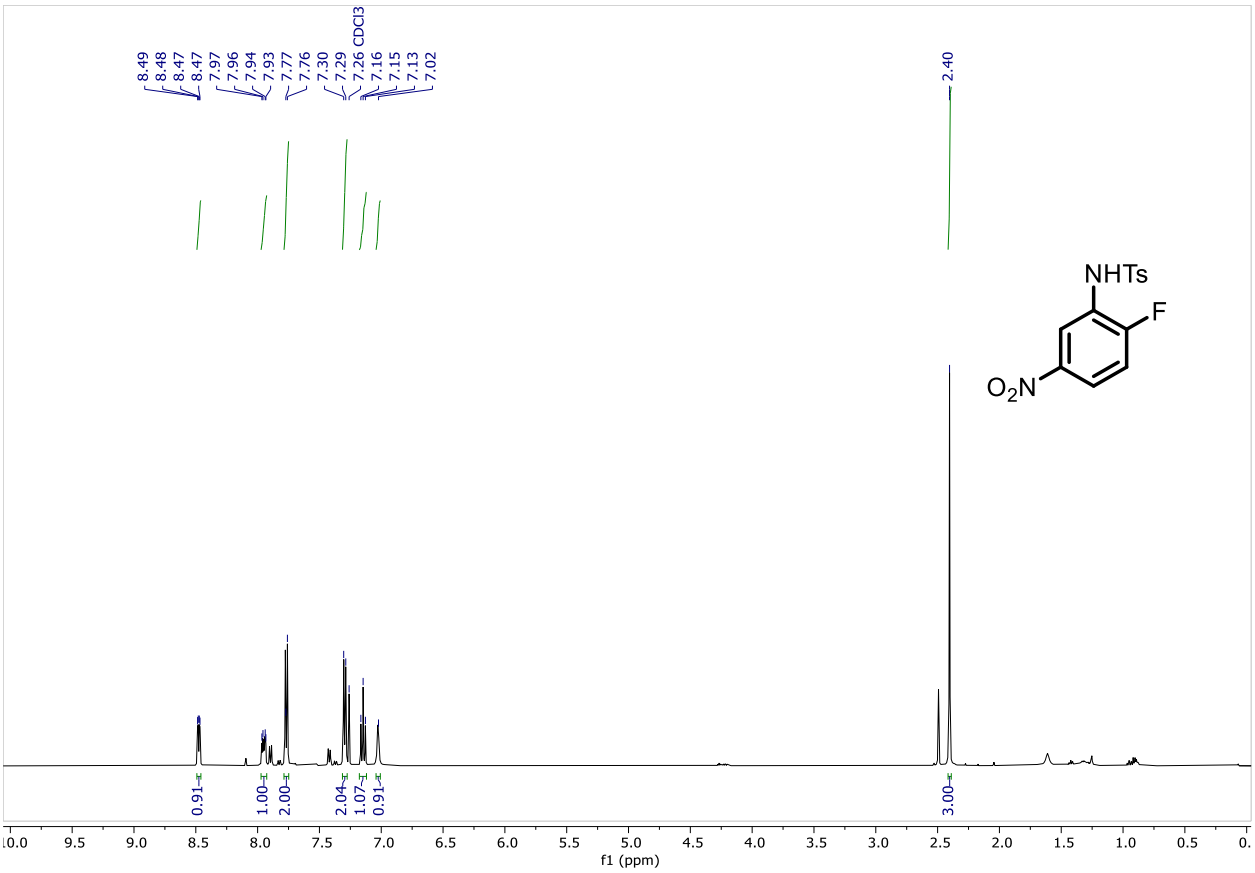

143.83
136.23
135.39
133.94
129.95
129.71
127.42
122.32
77.16 CDCl3
21.66
20.96
f1 (ppm)

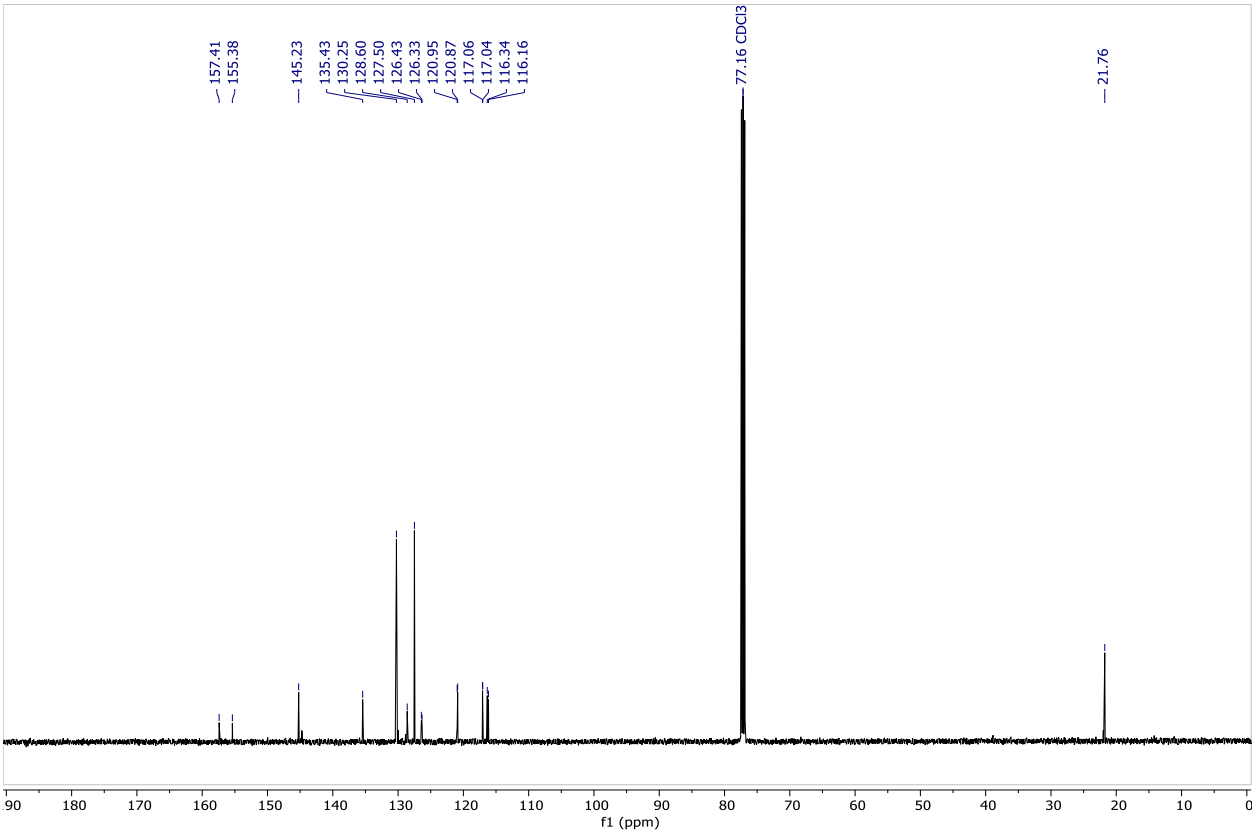

7.60
7.58
7.26 CDCl3
7.21
7.20
6.99
6.97
6.76
6.74
3.74
2.38
NHTs
OMe
2.08
2.09
2.10
2.06
3.03
3.00
f1 (ppm)

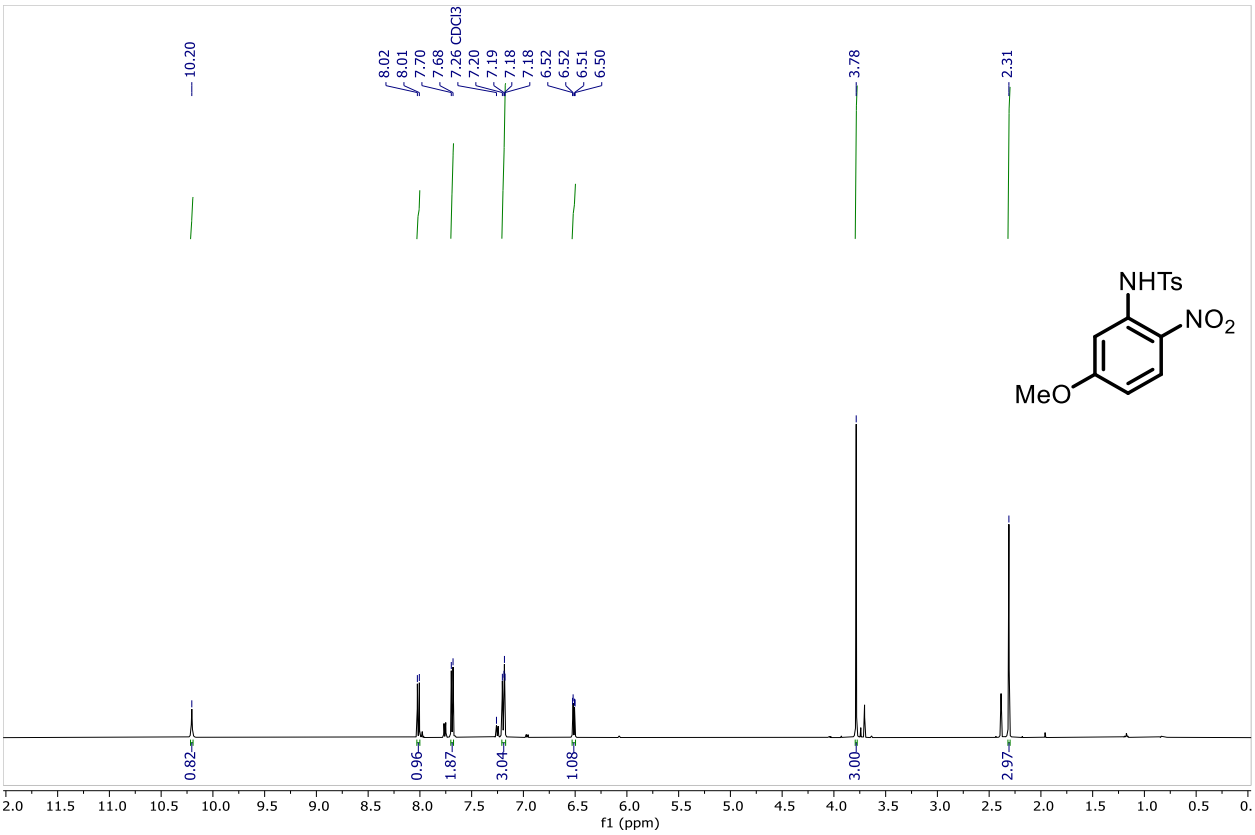

158.03
143.79
136.12
129.68
129.03
127.46
125.50
114.53
77.16 CDCl3
55.53
21.66
f1 (ppm)

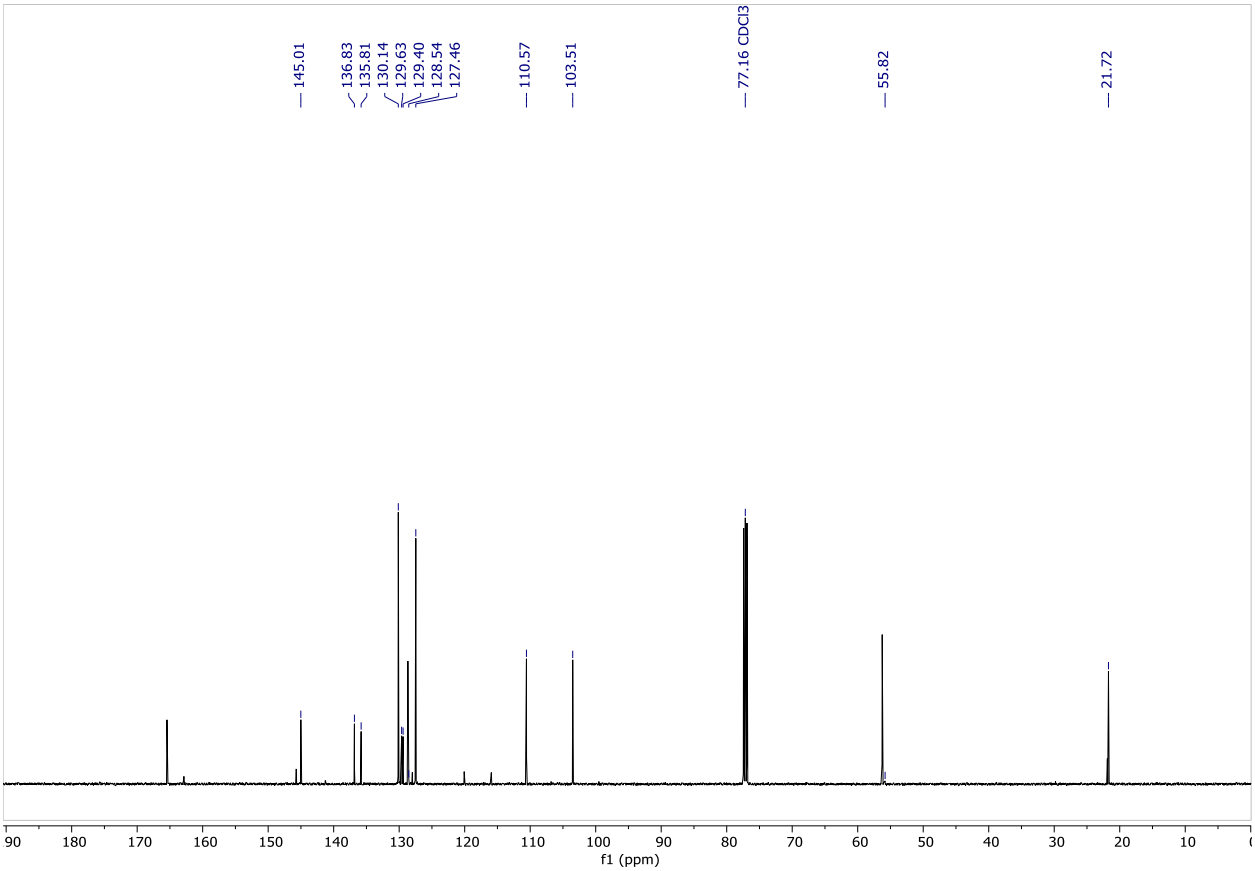

7.63
7.61
7.26 CDCl3
7.21
7.19
7.01
6.70
6.69
6.67
6.65
6.55
6.53
3.79
3.75
2.36
NHTs
MeO
OMe
1.98
2.00
0.80
2.03
1.01
3.02
3.01
3.00
f1 (ppm)

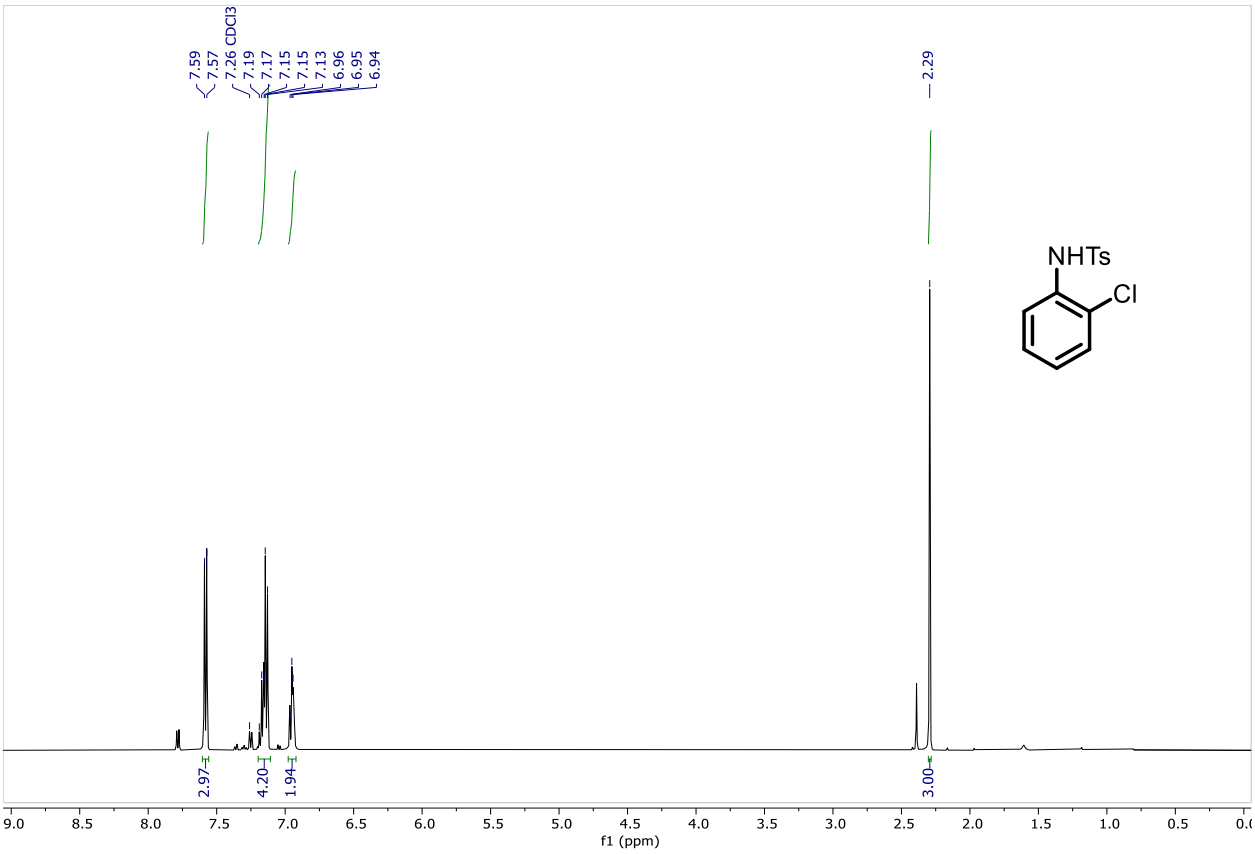

149.29
147.36
143.84
135.99
129.65
129.47
127.50
115.67
111.29
107.93
77.16 CDCl3
56.07
56.01
21.63
f1 (ppm)

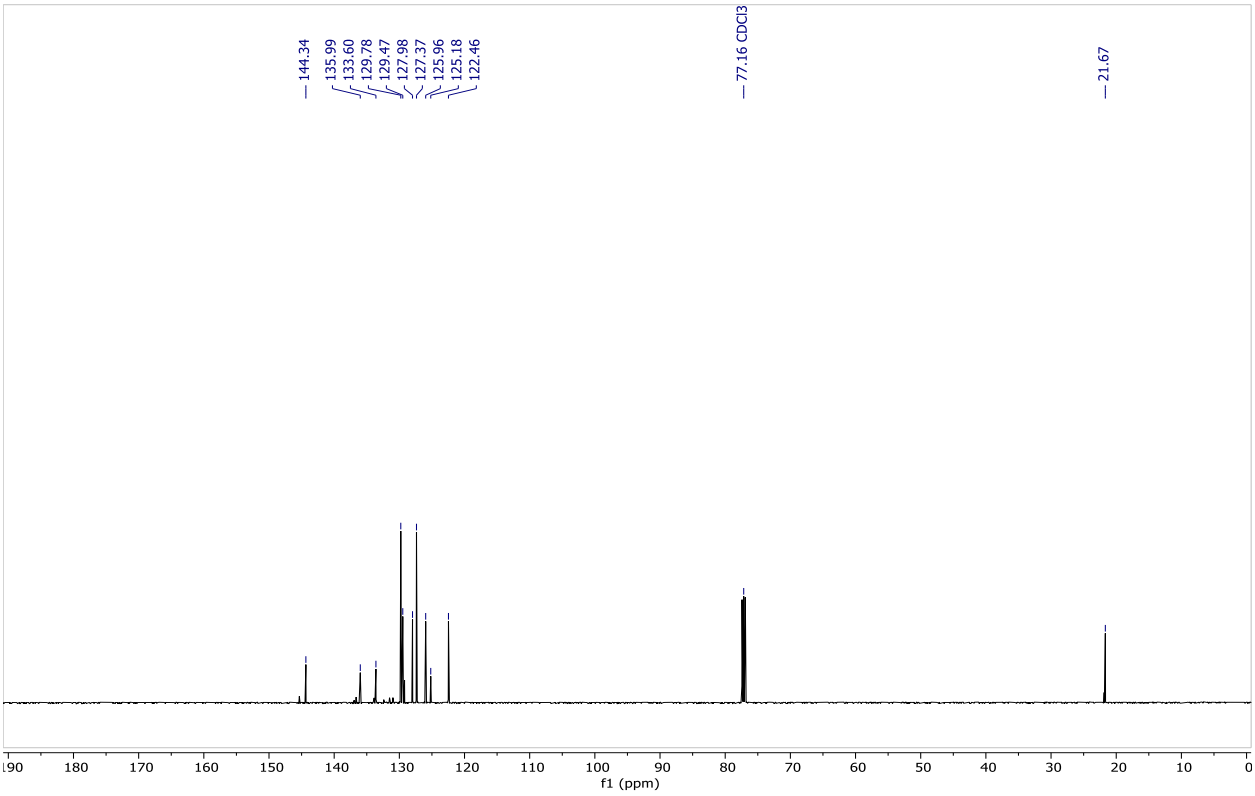

8.49
8.48
8.47
8.47
7.97
7.96
7.94
7.93
7.77
7.76
7.30
7.29
7.26 CDCl3
7.16
7.15
7.13
7.02
2.40
NHTs
F
O2N
0.91
1.00
2.00
2.04
1.07
0.91
3.00
f1 (ppm)

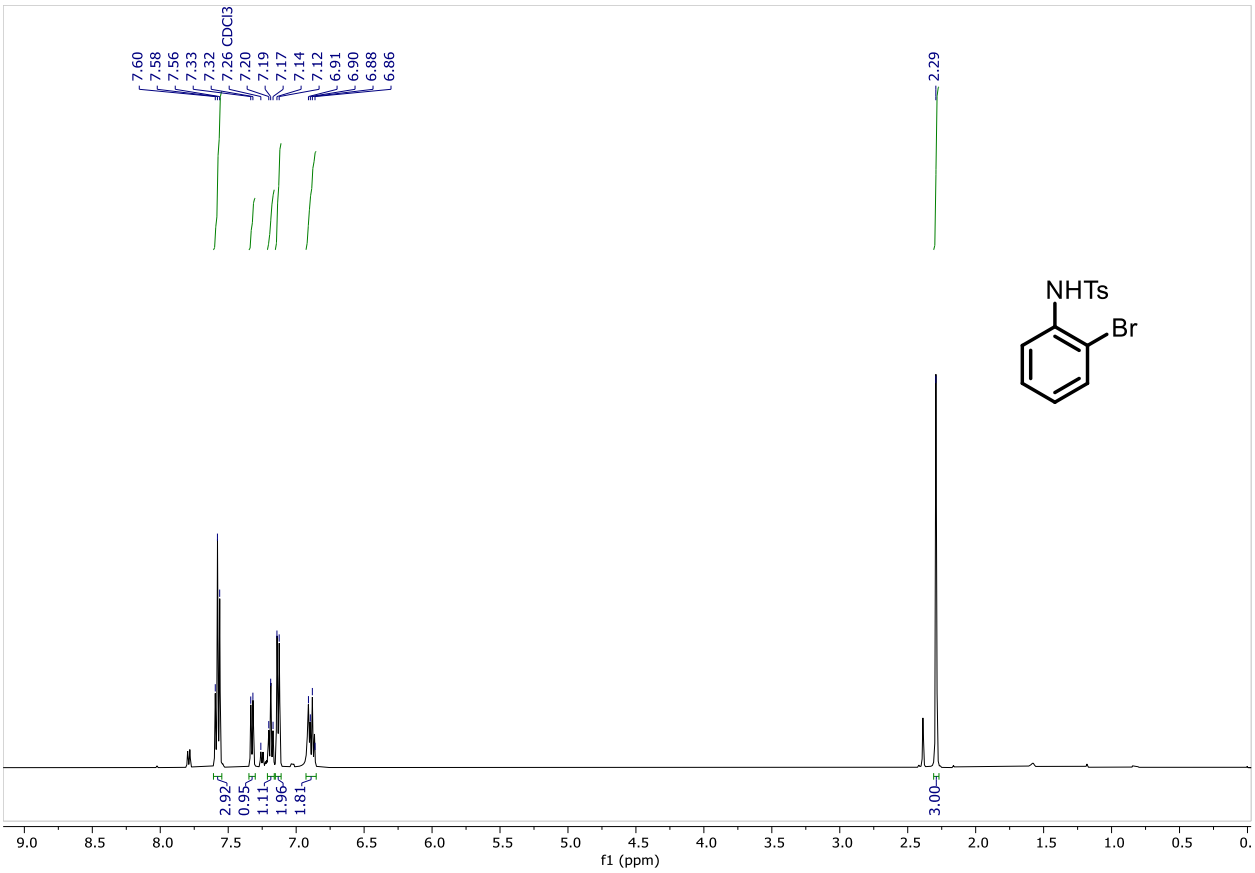

157.41
155.38
145.23
135.43
130.25
128.60
127.50
126.43
126.33
120.95
120.87
117.06
117.04
116.34
116.16
77.16 CDCl3
21.76
f1 (ppm)

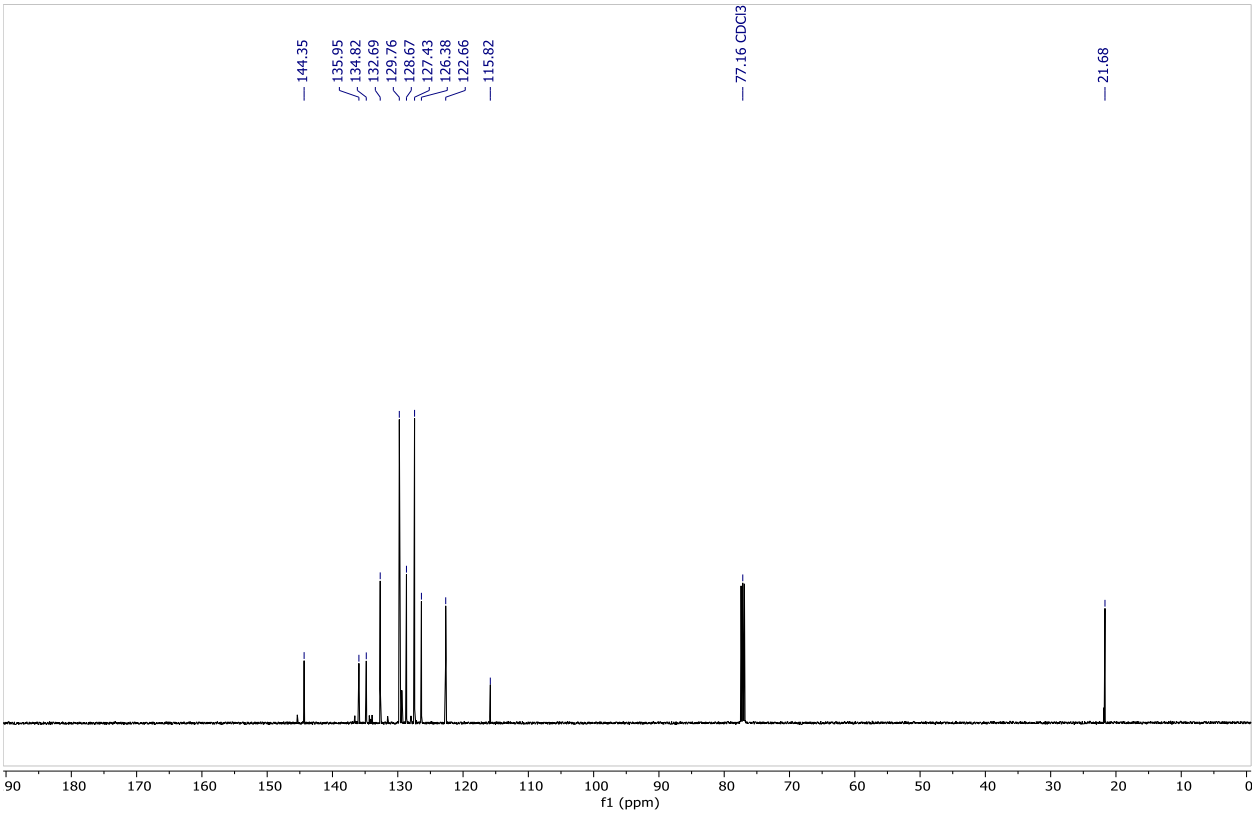

10.20
8.02
8.01
7.70
7.68
7.26 CDCl3
7.20
7.19
7.18
7.18
6.52
6.52
6.51
6.50
3.78
2.31
NHTs
NO2
MeO
0.82
0.96
1.87
3.04
1.08
3.00
2.97
f1 (ppm)

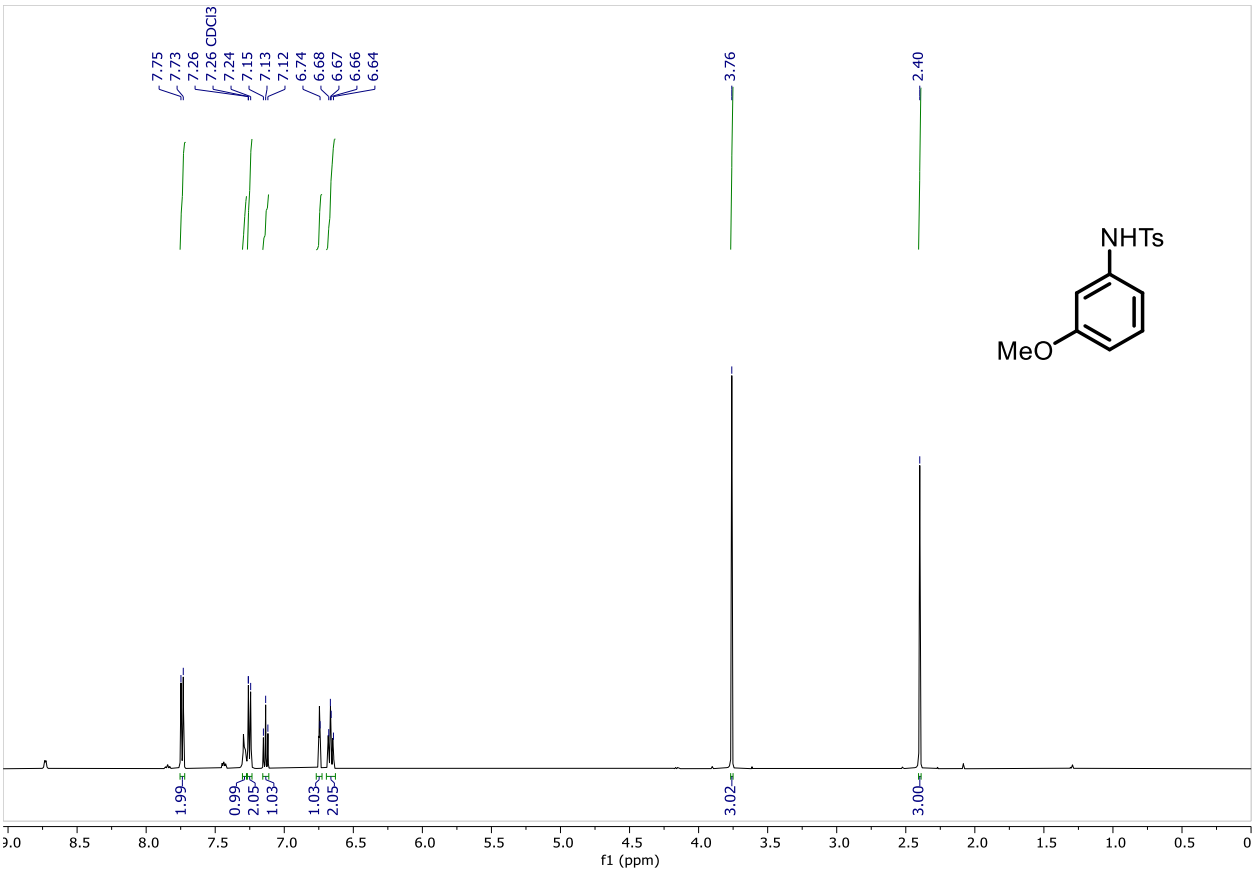

145.01
136.83
135.81
130.14
129.63
129.40
128.54
127.46
110.57
103.51
77.16 CDCl3
55.82
21.72
f1 (ppm)

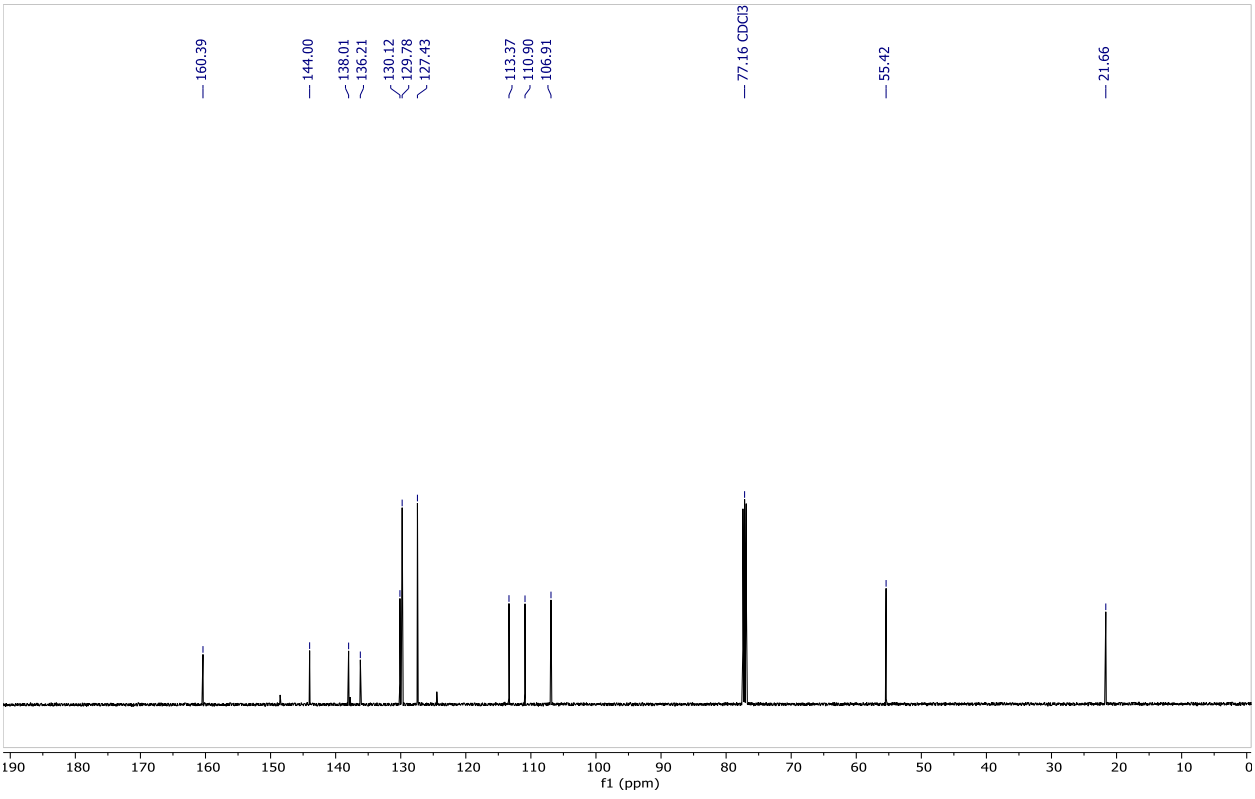

7.59
7.57
7.26 CDCl3
7.19
7.17
7.15
7.15
7.13
6.96
6.95
6.94
2.29
NHTs
Cl
2.97
4.20
1.94
3.00
f1 (ppm)

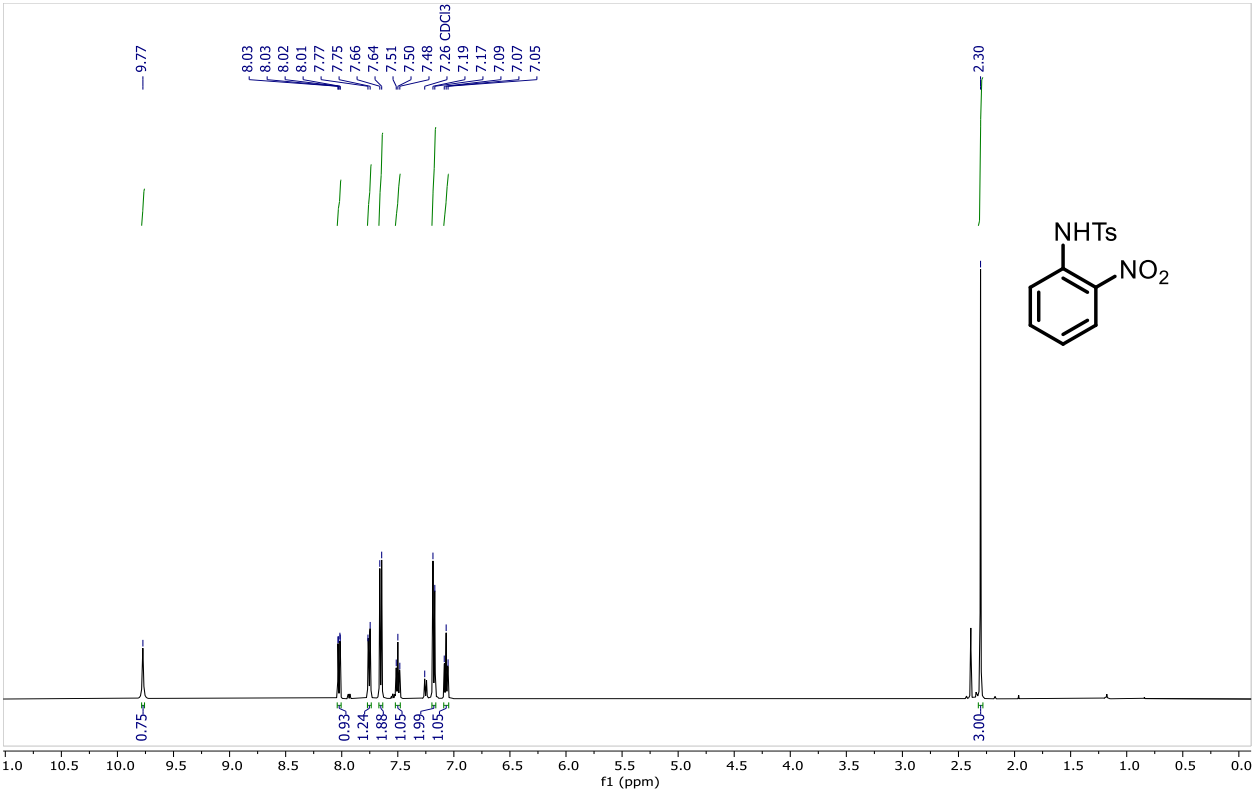

144.34
135.99
133.60
129.78
129.47
127.98
127.37
125.96
125.18
122.46
77.16 CDCl3
21.67
f1 (ppm)

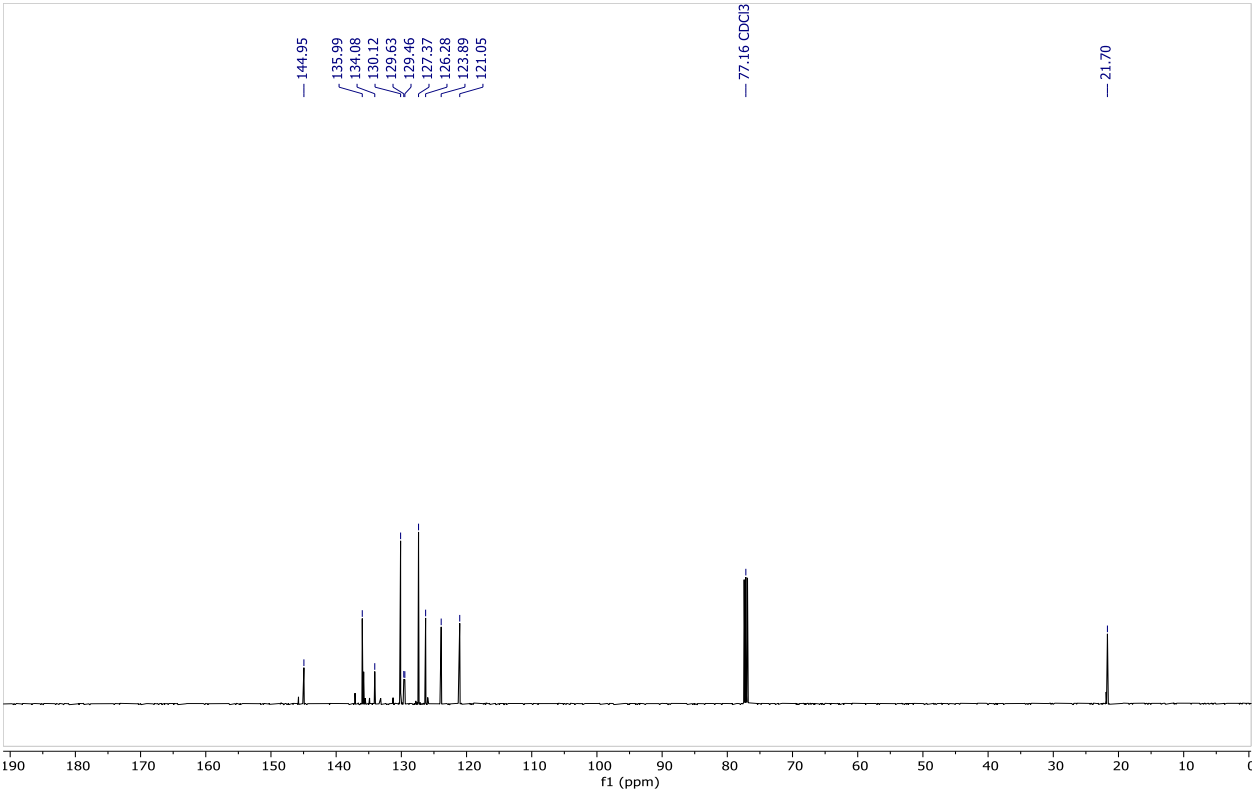

7.60
7.58
7.56
7.33
7.32
7.26 CDCl3
7.20
7.19
7.17
7.14
7.12
6.91
6.90
6.88
6.86
2.29
NHTs
Br
2.92
0.95
1.11
1.96
1.81
3.00
f1 (ppm)

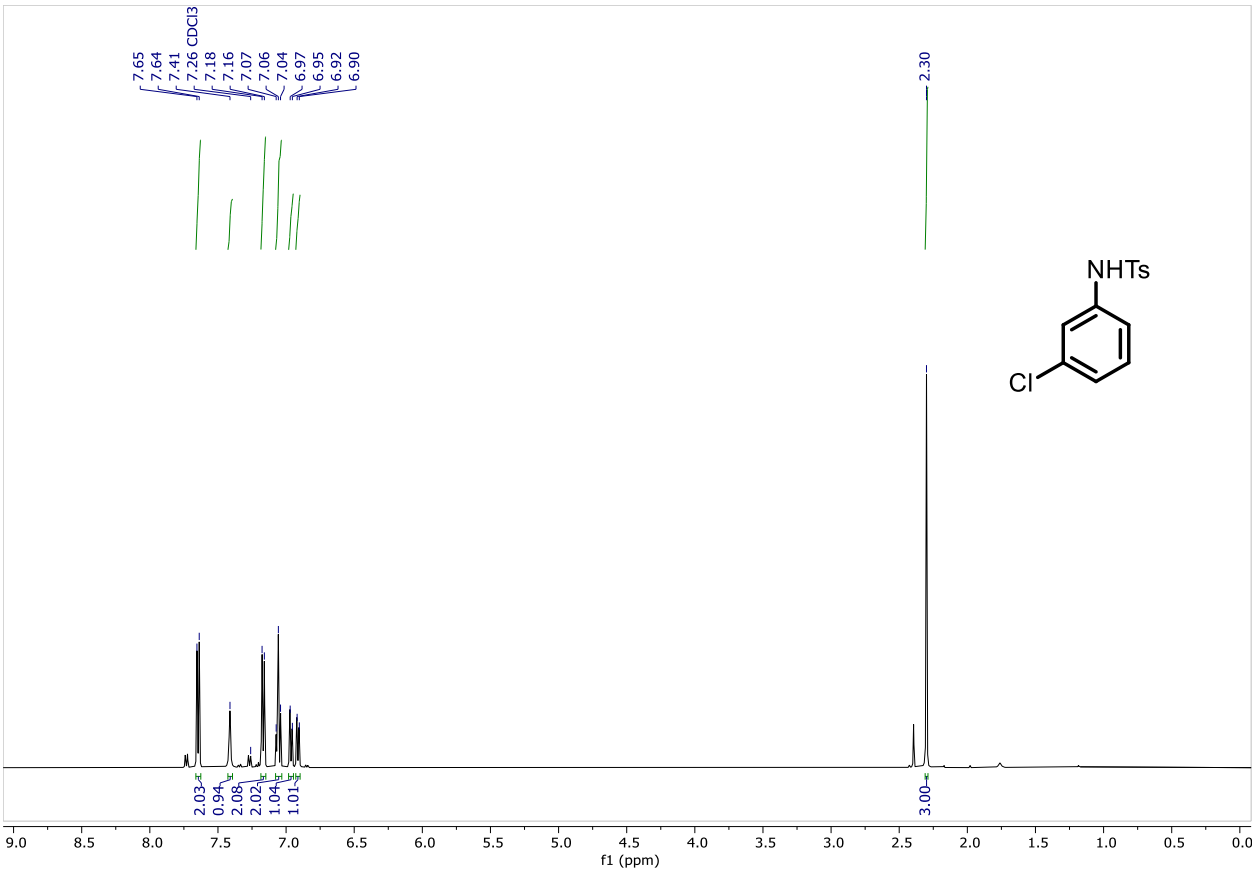

144.35
135.95
134.82
132.69
129.76
128.67
127.43
126.38
122.66
115.82
77.16 CDCl3
21.68
f1 (ppm)

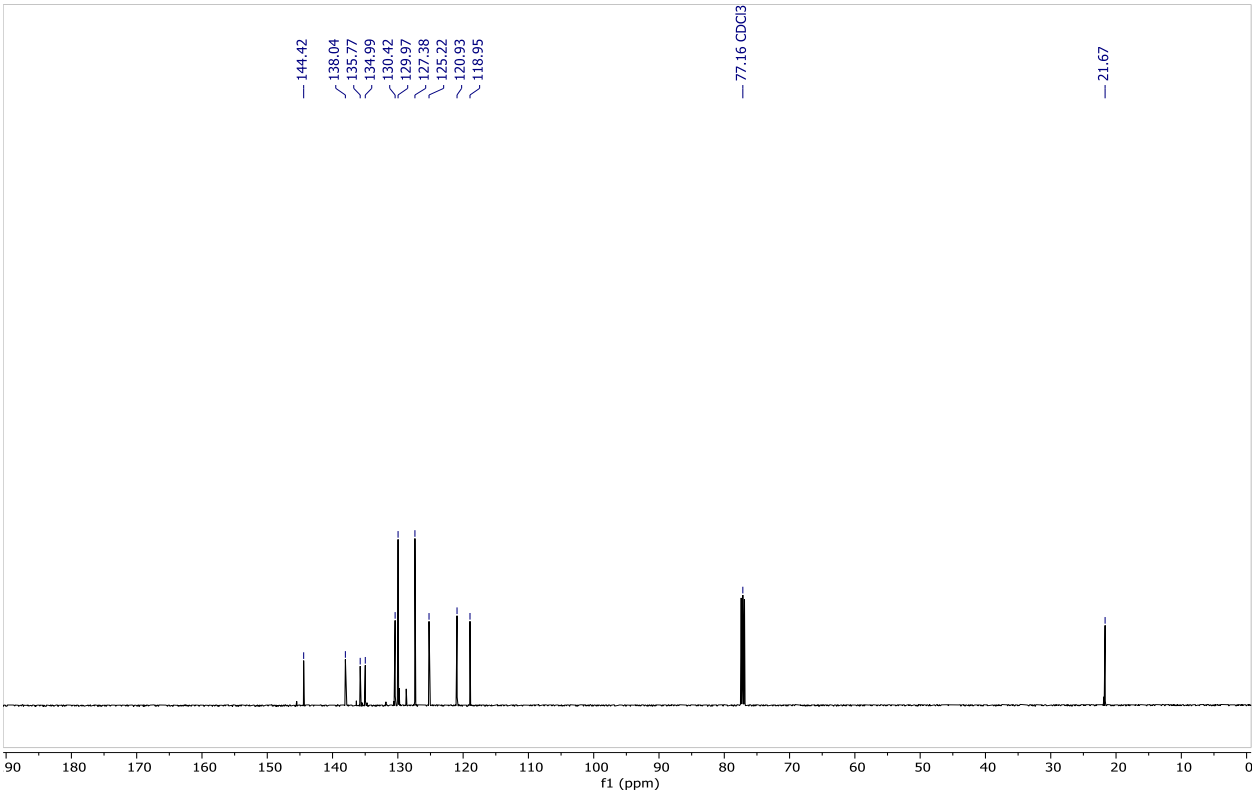

7.75
7.73
7.26
7.26 CDCl3
7.24
7.15
7.13
7.12
6.74
6.68
6.67
6.66
6.64
3.76
2.40
NHTs
MeO
1.99
0.99
2.05
1.03
1.03
2.05
3.02
3.00
f1 (ppm)

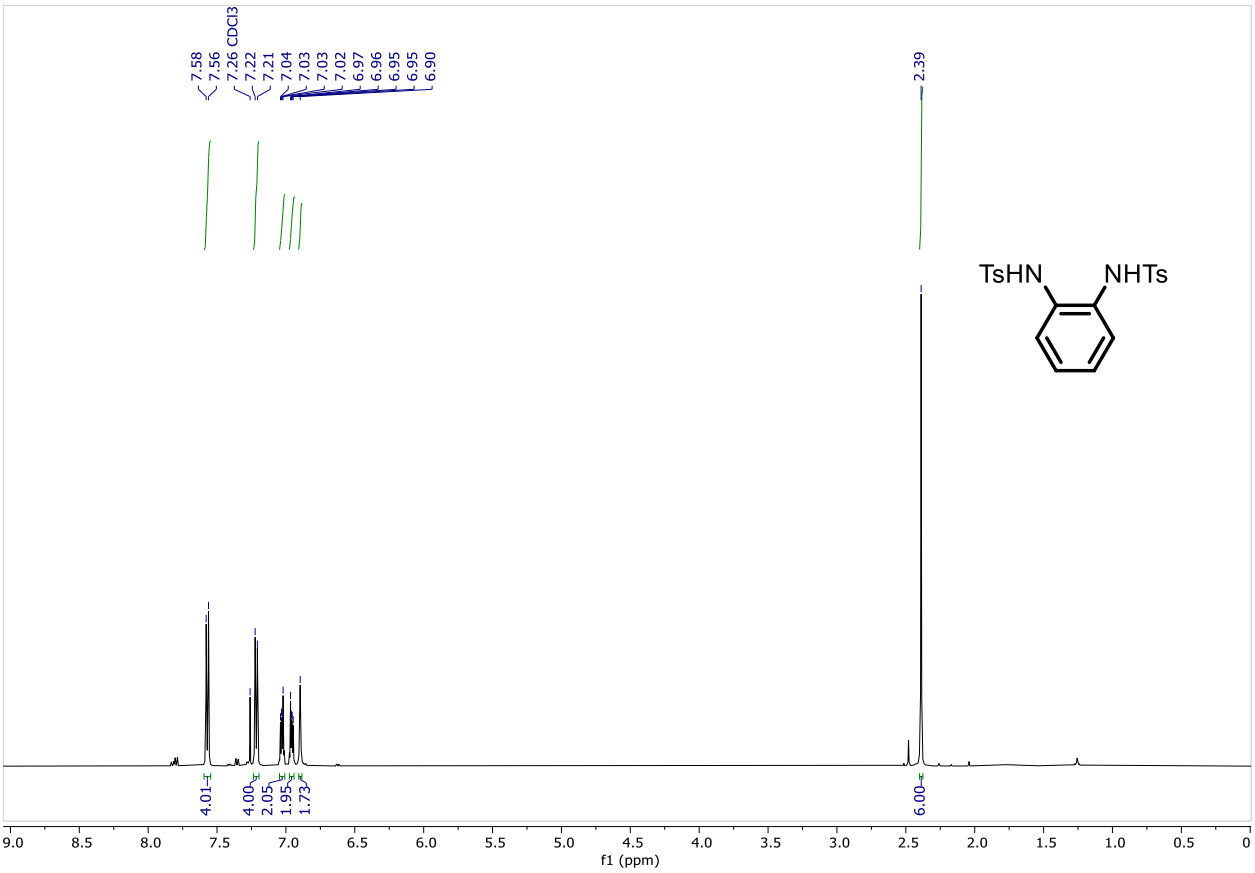

160.39
144.00
138.01
136.21
130.12
129.78
127.43
113.37
110.90
106.91
77.16 CDCl3
55.42
21.66
f1 (ppm)

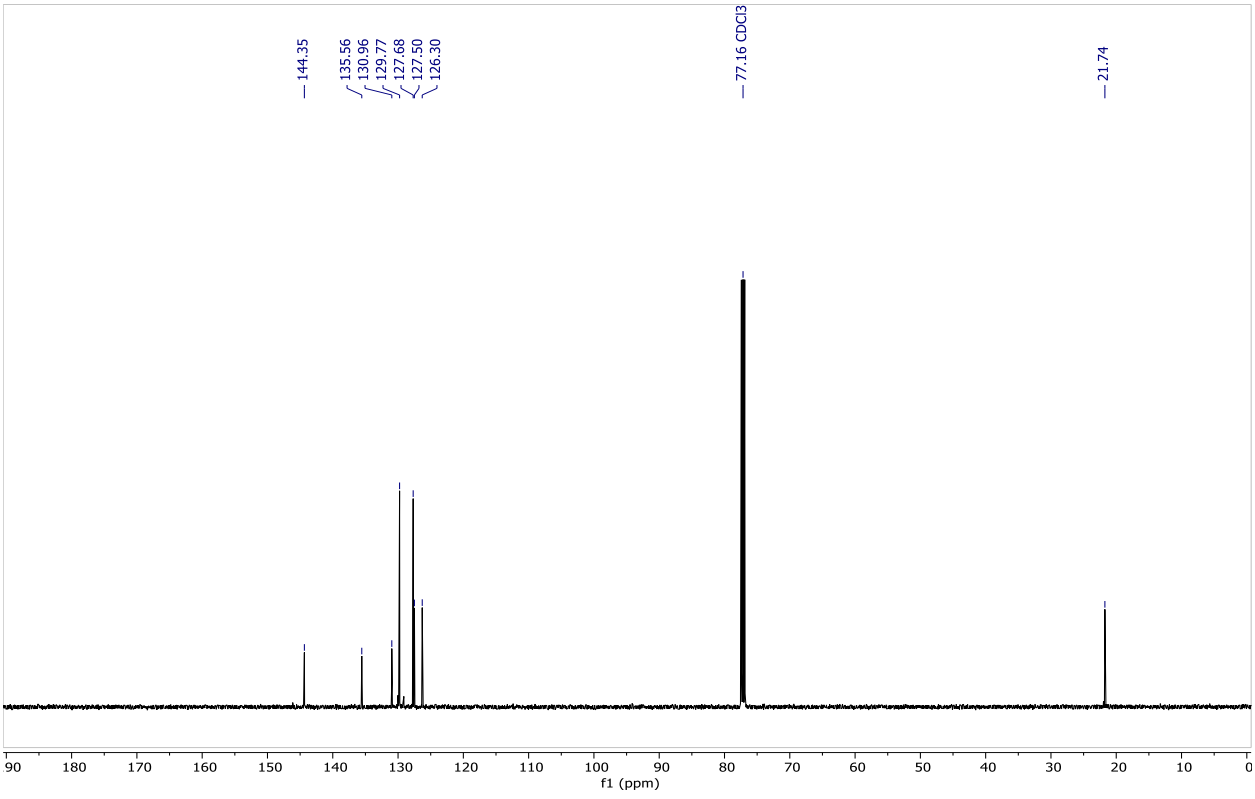

9.77
8.03
8.03
8.02
8.01
7.77
7.75
7.66
7.64
7.51
7.50
7.48
7.26 CDCl3
7.19
7.17
7.09
7.07
7.05
2.30
NHTs
NO2
0.75
0.93
1.24
1.88
1.05
1.99
1.05
3.00
f1 (ppm)

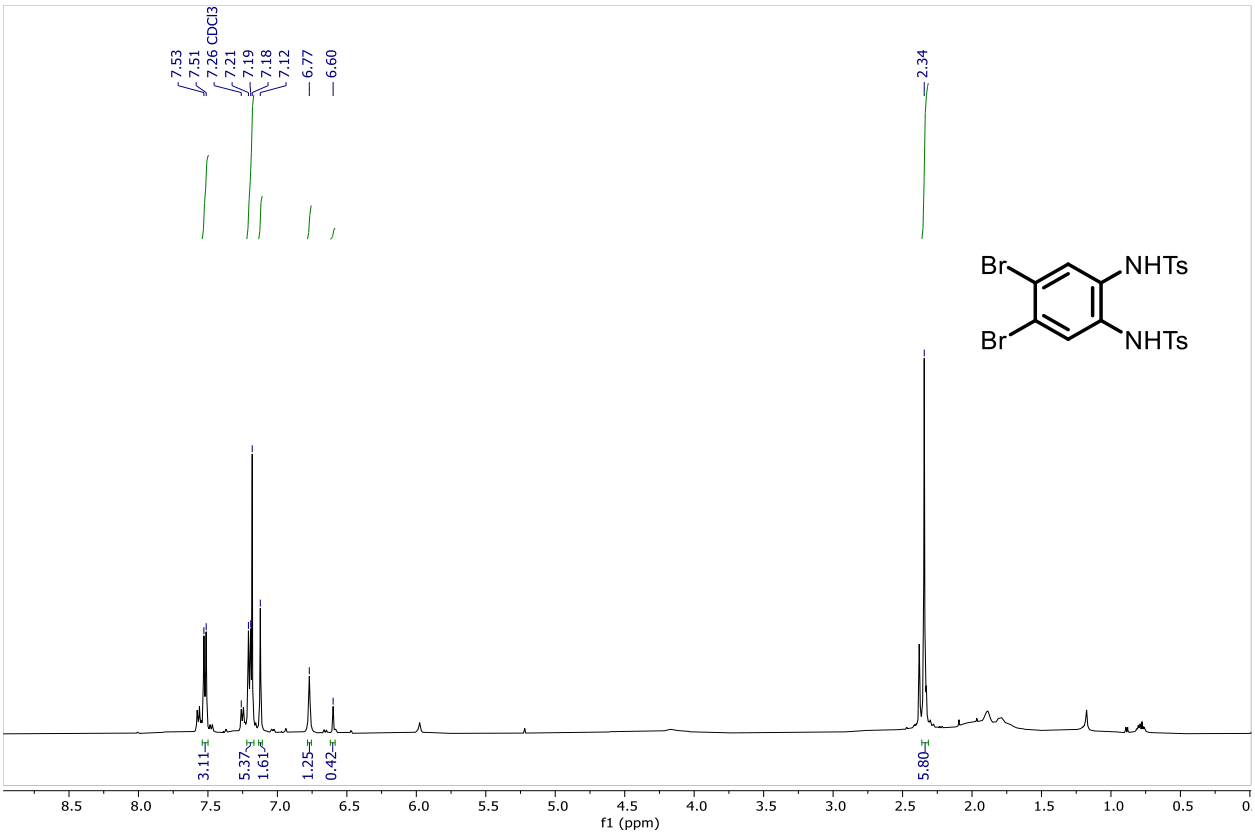

144.95
135.99
134.08
130.12
129.63
129.46
127.37
126.28
123.89
121.05
77.16 CDCl3
21.70
f1 (ppm)

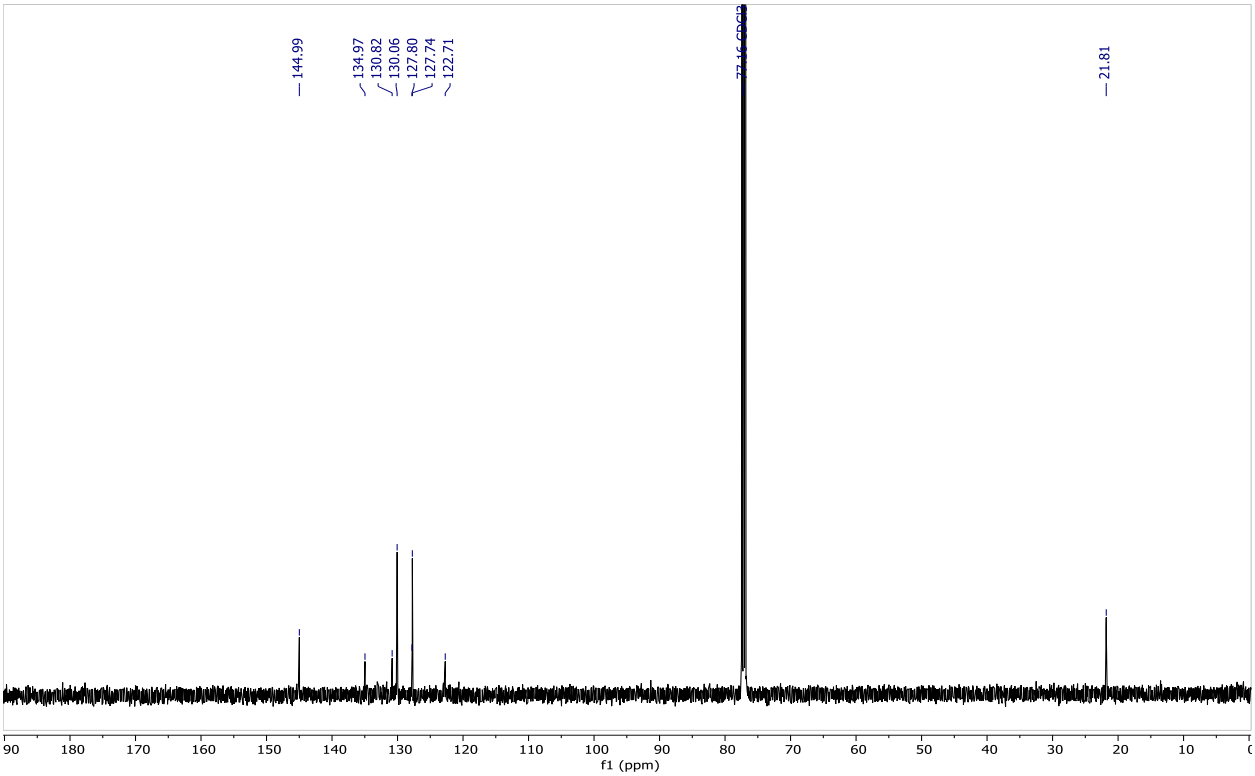

7.65
7.64
7.41
7.26 CDCl3
7.18
7.16
7.07
7.06
7.04
6.97
6.95
6.92
6.90
2.30
NHTs
Cl
2.03
0.94
2.08
2.02
1.04
1.01
3.00
f1 (ppm)


144.42
138.04
135.77
134.99
130.42
129.97
127.38
125.22
120.93
118.95
77.16 CDCl3
21.67
f1 (ppm)


7.58
7.56
7.26 CDCl3
7.22
7.21
7.04
7.03
7.03
7.02
6.97
6.96
6.95
6.95
6.90
2.39
TsHN
NHTs
4.01
4.00
2.05
1.95
1.73
6.00
f1 (ppm)


144.35
135.56
130.96
129.77
127.68
127.50
126.30
77.16 CDCl3
21.74
f1 (ppm)


7.53
7.51
7.26 CDCl3
7.21
7.19
7.18
7.12
6.77
6.60
2.34
Br
NHTs
Br
NHTs
3.11
5.37
1.61
1.25
0.42
5.80
f1 (ppm)


144.99
134.97
130.82
130.06
127.80
127.74
122.71
77.16 CDCl3
21.81
f1 (ppm)

ANNEX B

Theoretical Studies on Gold(I)-Catalyzed Sequential Indole Formation-Benzylic Migration.

(Under the guidance of Prof. Dr. Cesar Rogelio Solorio Alvarado and Prof. Dr. Jose Oscar Carlos Jimenez Halla, at Universidad de Guanajuato, Mexico.)

1. Theoretical Results and discussion-

We started DFT-study based on ωb97xd/3-21g* level for fukui-functions and chemical shift of ^{1}H, ^{13}C NMR-calculation for Comparative study of Experimental and theoretical discussion is as shown in below-

A. Fukui-function calculation- for Tertiary-aniline:-

DFT-study based on ωb97xd/3-21g* level of fukui-functions calculation for tertiary-aniline **324**, to check the reactivity pattern and confirmation about cyclization by gold(I)-catalyst. In this fukui function calculation, we calculate the NBO-Charges and fukui-function value is as shown in bellow table-

Table 1. NBO-charges and Fukui-function values calculations of tertiary-aniline **324**.

Atom no.	Atom	NBO Charges (Neutral)	NBO Charges (Cation)	NBO Charges (Anion)	f+	f-	f0
1	C	-0.12523	-0.073112	-0.168685	0.052118	0.043455	0.0477865
2	C	0.346441	0.332116	0.302259	-0.014325	0.044182	0.0149285
3	C	-0.217884	-0.173519	-0.236299	0.044365	0.018415	0.03139
4	C	-0.21764	-0.204903	-0.282554	0.012737	0.064914	0.0388255
5	C	-0.224256	-0.181533	-0.229107	0.042723	0.004851	0.023787
6	C	-0.201176	-0.184691	-0.23982	0.016485	0.038644	0.0275645
7	H	0.21871	0.273837	0.141161	0.055127	0.077549	0.066338
8	H	0.221345	0.288591	0.119879	0.067246	0.101466	0.084356
9	H	0.219135	0.2955	0.135655	0.076365	0.08348	0.0799225
10	H	0.227837	0.287787	0.146173	0.05995	0.081664	0.070807
11	N	-0.717549	-0.609283	-0.7165	0.108266	-0.001049	0.0536085
12	C	-0.435301	-0.490949	-0.407384	-0.055648	-0.027917	-0.0417825
13	H	0.248291	0.316973	0.20527	0.068682	0.043021	0.0558515
14	H	0.194605	0.279206	0.160356	0.084601	0.034249	0.059425
15	H	0.230057	0.286122	0.211277	0.056065	0.01878	0.0374225
16	C	-0.267013	-0.313952	-0.251665	-0.046939	-0.015348	-0.0311435
17	H	0.272815	0.308842	0.283657	0.036027	-0.010842	0.0125925
18	H	0.210951	0.288666	0.168915	0.077715	0.042036	0.0598755
19	C	-0.012367	-0.022256	-0.007511	-0.009889	-0.004856	-0.0073725
20	C	-0.20411	-0.216027	-0.191797	-0.011917	-0.012313	-0.012115
21	C	-0.227376	-0.220226	-0.230569	0.00715	0.003193	0.0051715
22	C	-0.221705	-0.212066	-0.226507	0.009639	0.004802	0.0072205
23	H	0.239109	0.220374	0.258951	-0.018735	-0.019842	-0.0192885
24	C	-0.217275	-0.208623	-0.223365	0.008652	0.00609	0.007371
25	H	0.209438	0.232341	0.189733	0.022903	0.019705	0.021304
26	C	-0.222927	-0.212549	-0.231045	0.010378	0.008118	0.009248
27	H	0.217691	0.249021	0.19506	0.03133	0.022631	0.0269805
28	H	0.217058	0.254874	0.184605	0.037816	0.032453	0.0351345
29	H	0.216628	0.255576	0.183293	0.038948	0.033335	0.0361415
30	C	0.091315	0.070796	0.063919	-0.020519	0.027396	0.0034385
31	C	-0.366496	-0.268478	-0.516199	**0.098018**	**0.149703**	0.1238605
32	H	0.296876	0.351547	0.208842	0.054671	0.088034	0.0713525

f = Fukui function

a. **b.** **c.**

Figure 1. Structures related to tertiary aniline **a.** Structure of tertiary-aniline**. b.** Structure of tertiary-aniline with numbering to the atom. **c.** Structure of tertiary-aniline with Fukui-function values.

According to **Table 1**. and **figure 2. (a.b.c.)** and their results shows the Fukui-functions value for the indications of reactivity pattern of tertiary-aniline **324**. this fukui-functions value gives the concrete proof and support to the cyclization with the formation five member *N*-containing ring was happened in tertiary aniline by gold(I)-catalyzed reaction. The tertiary-aniline fukui function value for all atom is in the **Table 1**. and selective fukui-function value for the indication of cyclization in tertiary aniline with the reactive site of nitrogen and terminal carbon of acetylene is as shown in **figure 2. (a.b.c.).**

B. Chemical-shift calculations of ^{1}H and ^{13}C-spectrum

The chemical-shift values calculations of ^{1}H and ^{13}C- spectrum of Tertiary-aniline **1** and Substituted-indole **2**, by DFT-study based on ωb97xd/3-21g* level for chemical shift of ^{1}H, ^{13}C NMR-calculations for comparative study of experimental and theoretical spectrum with their data.

a. Tertiary aniline 324, chemical shift values of H^{1}, C^{13}-Spectrum calculations

i. **ii.**

Figure 2. Structures related to Tertiary aniline. **i.** structure of tertiary-aniline. **ii.** Structure of aniline with numbering to the atom.

Table 2. ^{1}H-Chemical shift calculation of Tertiary aniline **324,** in Gas-phase and THF-Phase.

	TMS (GP)(IV)	TMS-THF (IV)	Hn	Aniline (GP)(IV)	Hn	Aniline-THF (IV)	Chemical-shift-Aniline (GP)	Chemical-shift-Aniline-THF
C-Atom	201.8241	202.7277	H-7	26.4314	H-7	26.027	6.3116	6.649
H-Atom	32.743	32.676	H-8	25.9201	H-8	25.5322	6.8229	7.1438
			H-9	26.3647	H-9	26.0451	6.3783	6.6309
			H-10	25.6915	H-10	25.4279	7.0515	7.2481
			H-13	30.0641	H-13	30.1041	2.6789	2.5719
			H-14	30.4061	H-14	30.1236	2.3369	2.5524
			H-15	30.3179	H-15	30.1474	2.4251	2.5286
			H-17	27.6159	H-17	27.6386	5.1271	5.0374
			H-18	29.3551	H-18	28.9913	3.3879	3.6847
			H-23	24.5794	H-23	24.5803	8.1636	8.0957
			H-25	25.9512	H-25	25.5687	6.7918	7.1073
			H-27	25.6609	H-27	25.3581	7.0821	7.3179
			H-28	25.7812	H-28	25.4341	6.9618	7.2419
			H-29	25.7587	H-29	25.4367	6.9843	7.2393
			H-32	29.7808	H-32	29.2971	2.9622	3.3789

TMS = Tetramethylsilane. **GP** = Gas Phase. **THF** = Tetrahydrofuran solvent Phase. **Aniline** = Tertiary aniline. **Cn** = Numbering to carbon atom in aniline. **Hn** = Numbering to hydrogen atom in aniline, **δ** = Chemical shift value.

Table 3. ^{13}C-Chemical shift calculation of Tertiary aniline **324,** in Gas-phase and THF-Phase.

	TMS (GP)(IV)	TMS-THF (IV)	Cn	Aniline (GP)(IV)	Cn	Aniline-THF (IV)	Chemical-shift Aniline (GP)	Chemical-shift-Aniline-THF
C-Atom	201.8241	202.7277	C-1	104.3368	C-1	105.7009	97.4873	97.0268
H-Atom	32.743	32.676	C-2	68.0364	C-2	67.4919	133.7877	135.2358
			C-3	101.2636	C-3	100.5492	100.5605	102.1785
			C-4	90.5995	C-4	89.4183	111.2246	113.3094
			C-5	99.9484	C-5	99.9144	101.8757	102.8133
			C-6	85.0725	C-6	85.1051	116.7516	117.6226
			C-12	173.032	C-12	173.3516	28.7921	29.3761
			C-16	152.104	C-16	152.4743	49.7201	50.2534
			C-19	80.628	C-19	79.474	121.1961	123.2537
			C-20	90.3088	C-20	90.734	111.5153	111.9937
			C-21	92.3104	C-21	91.8087	109.5137	110.919
			C-22	91.895	C-22	91.7152	109.9291	111.0125
			C-24	92.3706	C-24	91.6962	109.4535	111.0315
			C-26	92.8633	C-26	92.6526	108.9608	110.0751
			C-30	133.5442	C-30	132.9856	68.2799	69.7421
			C-31	126.7677	C-31	126.3533	75.0564	76.3744

TMS = Tetramethylsilane. **GP** = Gas Phase. **THF** = Tetrahydrofuran Solvent Phase. **Aniline** = Tertiary aniline **324**. **Cn** = Numbering to carbon atom in aniline. **Hn** = Numbering to hydrogen atom in aniline, **δ** = Chemical shift value.

Experimental Data of Tertiary aniline (324) :-

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.29 – 7.16 (m, 4H), 7.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.73 (td, *J* = 7.5, 1.5 Hz, 1H), 4.05 (s, 2H), 2.55 (s, 3H), 1.48 (s, 1H).

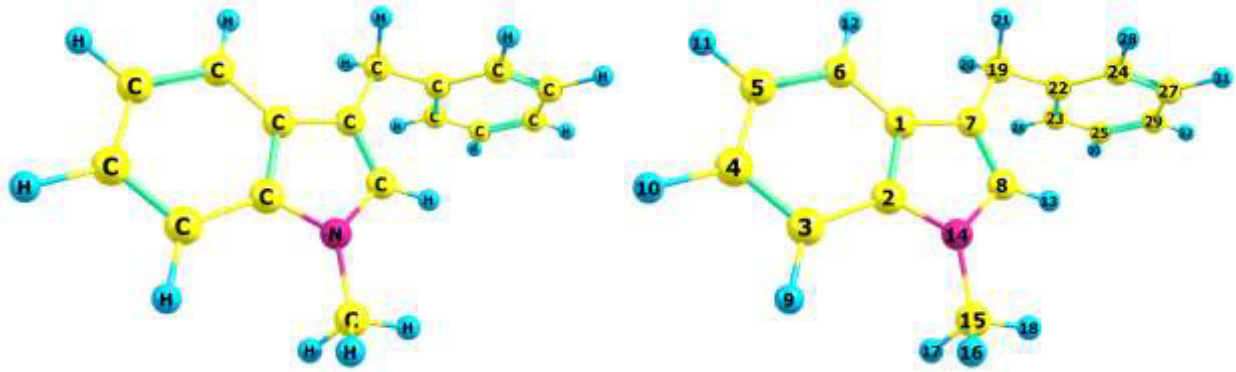
^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.25, 140.26, 138.35, 129.16, 128.86, 128.35, 127.25, 125.62, 122.43, 98.70, 61.27, 41.73.

Table 4. Tertiary aniline **324,** comparative δ-value with experimental and calculated (Gas-phase and THF-solvent Phase) ^{1}H, ^{13}C-spectra.

Cn	Exp. δ–value	Aniline GP-δ–value	Aniline THF-δ–value	Hn	Exp. δ–value	Aniline GP-δ–value	Aniline THF-δ–value
C-1	140	97.4873	97.0268	H-7	7.3	6.3	6.649
C-2	154	133.7877	135.2358	H-8	7.4-7.3	6.8229	7.1438
C-3	128.3	100.5605	102.1785	H-9	7.4-7.3	6.3783	6.6309
C-4	129	111.2246	113.3094	H-10	7.81	7.0515	7.2481
C-5	128.8	101.8757	102.8133	H-13	2.55	2.6789	2.5719
C-6	128	116.7516	117.6226	H-14	2.55	2.3369	2.5524
C-12	41	28.7921	29.3761	H-15	2.55	2.4251	2.5286
C-16	61	49.7201	50.2534	H-17	4.2	5.1271	5.0374
C-19	138	121.1961	123.2537	H-18	4.2	3.3879	3.6847
C-20	127	111.5153	111.9937	H-23	7.29-7.16	8.1636	8.0957
C-21	127	109.5137	110.919	H-25	6.73	6.7918	7.1073
C-22	127	109.9291	111.0125	H-27	7.29-7.16	7.0821	7.3179
C-24	127	109.4535	111.0315	H-28	7.29-7.16	6.9618	7.2419
C-26	122	108.9608	110.0751	H-29	7.29-7.16	6.9843	7.2393
C-30	125	68.2799	69.7421	H-32	1.48	2.9622	3.3789
C-31	98	75.0564	76.3744				

TMS = Tetramethylsilane. **GP** = Gas Phase. **THF** = Tetrahydrofuran solvent phase. **Aniline** = Tertiary aniline. **Cn** = Numbering to carbon atom in aniline. **Hn** = Numbering to hydrogen atom in aniline. **Exp** = Experimental Chemical shift value. **δ** = Chemical shift value.

b. Substituted-indole 325, chemical shift values of ^{1}H, ^{13}C-Spectrum calculations-



i. **ii.**

Figure 3. Structures related to Substituted indole. **i.** structure of Substituted-indole. **ii.** Structure of Substituted-indole with numbering to the atom.

Table 5. ^{1}H-Chemical shift calculation of 3-Benzyl-1-methyl-1*H*-indole **325,** in Gas-phase and THF-Phase.

	TMS (GP)(IV)	TMS-THF (IV)	Hn	Indole (GP)(IV)	Hn	Indole-THF (IV)	Chemical-shift-indole (GP)	Chemical-shift-indole-THF
C-Atom	201.8241	202.7277	H-9	26.2236	H-9	25.7561	6.5194	6.9199
H-Atom	32.743	32.676	H-10	25.9035	H-10	25.5998	6.8395	7.0762
			H-11	25.9964	H-11	25.725	6.7466	6.951
			H-12	25.6208	H-12	25.294	7.1222	7.382
			H-13	27.666	H-13	27.3179	5.077	5.3581
			H-16	29.3468	H-16	29.1403	3.3962	3.5357
			H-17	29.3468	H-17	29.1403	3.3962	3.5357
			H-18	29.6463	H-18	29.2479	3.0967	3.4281
			H-20	29.1511	H-20	28.9568	3.5919	3.7192
			H-21	29.1511	H-21	28.9568	3.5919	3.7192
			H-26	25.7098	H-26	25.4248	7.0332	7.2512
			H-28	25.7098	H-28	25.4248	7.0332	7.2512
			H-30	25.7424	H-30	25.4082	7.0006	7.2678
			H-31	25.7424	H-31	25.4082	7.0006	7.2678
			H-32	25.8053	H-32	25.4725	6.9377	7.2035

TMS = Tetramethylsilane. **GP** = Gas Phase. **THF** = Tetrahydrofuran solvent phase. **Indole** = 3-Benzyl-1-methyl-1*H*-indole **Cn** = Numbering to carbon atom in Indole. **Hn** = Numbering to hydrogen atom in Indole. **Exp** = Experimental Chemical shift value. **δ** = Chemical shift value.

Table 6. ^{13}C-Chemical shift calculation of 3-Benzyl-1-methyl-1*H*-indole **325,** in Gas-phase and THF-Phase.

	TMS (GP)(IV)	TMS-THF (IV)	Cn	Indole (GP)(IV)	Cn	Indole-THF (IV)	Chemical-shift Indole (GP)	Chemical-shift-Indole-THF
C-Atom	201.8241	202.7277	C-1	91.9216	C-1	92.9679	109.9025	109.7598
H-Atom	32.743	32.676	C-2	85.3562	C-2	85.4278	116.4679	117.2999
			C-3	108.7586	C-3	107.6856	93.0655	95.0421
			C-4	97.0911	C-4	97.1603	104.733	105.5674
			C-5	99.4799	C-5	99.8223	102.3442	102.9054
			C-6	99.0845	C-6	99.0496	102.7396	103.6781
			C-7	100.5131	C-7	101.0417	101.311	101.686
			C-8	89.861	C-8	88.9286	111.9631	113.7991
			C-15	175.9563	C-15	176.269	25.8678	26.4587
			C-19	175.1324	C-19	175.9396	26.6917	26.7881
			C-22	80.3038	C-22	79.6592	121.5203	123.0685
			C-23	89.8969	C-23	89.6599	111.9272	113.0678
			C-24	89.8969	C-24	89.6599	111.9272	113.0678
			C-25	91.7282	C-25	91.2224	110.0959	111.5053
			C-27	91.7282	C-27	91.2224	110.0959	111.5053
			C-29	93.737	C-29	93.29	108.0871	109.4377

TMS = Tetramethylsilane. **GP** = Gas Phase. **THF** = Tetrahydrofuran solvent phase. **Indole** = 3-Benzyl-1-methyl-1*H*-indole **Cn** = Numbering to carbon atom in Indole. **Hn** = Numbering to hydrogen atom in Indole. **Exp** =Experimental Chemical shift value. **δ** = Chemical shift value.

Experimental Data of 3-Benzyl-1-methyl-1*H*-indole :-

^{1}H NMR (300 MHz, $CDCl_3$) d 7.63 (d, *J*) 7.9 Hz, 1H), 7.45-7.24 (m, 7H), 7.18 (m, 1H), 6.83 (s, 1H), 4.21 (s, 2H), 3.79 (s, 3H).

^{13}C NMR (75 MHz, CDCl3) d 141.4, 137.1, 128.6, 128.3, 127.8, 127.1, 125.8, 121.5, 119.2, 118.7, 114.3, 109.1, 32.5, 31.5

Table 7. 3-Benzyl-1-methyl-1*H*-indole **325,** comparative d-value with experimental and calculated (Gas-phase and THF-solvent Phase) ^{1}H, ^{13}C-spectra.

Cn	Exp. δ-value	indole GP-δ-value	indole THF-δ-value	Hn	Exp. δ-value	indole GP-δ-value	indole THF-δ-value
C-1	128.6	109.9025	109.7598	H-9	7.63	6.5194	6.9199
C-2	141.4	116.4679	117.2999	H-10	7.45-7.24	6.8395	7.0762
C-3	127.8	93.0655	95.0421	H-11	7.45-7.24	6.7466	6.951
C-4	129	104.733	105.5674	H-12	7.18	7.1222	7.382
C-5	128.8	102.3442	102.9054	H-13	6.83	5.077	5.3581
C-6	128	102.7396	103.6781	H-16	3.79	3.3962	3.5357
C-7	128.3	101.311	101.686	H-17	3.79	3.3962	3.5357
C-8	137.1	111.9631	113.7991	H-18	3.79	3.0967	3.4218
C-15	31.5	25.8678	26.4587	H-20	4.21	3.5917	3.7192
C-19	32.5	26.6917	26.7881	H-21	4.21	3.5919	3.7192
C-22	118.7	121.5203	123.0685	H-26	7.45-7.24	7.0332	7.2512
C-23	119.2	111.9272	113.0678	H-28	7.45-7.24	7.0332	7.2512
C-24	119.2	111.9272	113.0678	H-30	7.45-7.24	7.0006	7.2678
C-25	119.2	110.0959	111.5053	H-31	7.45-7.24	7.0006	7.2678
C-27	119.2	110.0959	111.5053	H-32	7.45-7.24	6.9377	7.2035
C-29	109.1	108.0871	109.4377				

TMS = Tetramethylsilane. **GP** = Gas Phase. **THF**= Tetrahydrofuran solvent phase. **Indole** = 3-Benzyl-1-methyl-1*H*-indole **Cn** = Numbering to carbon atom in Indole. **Hn** = Numbering to hydrogen atom in Indole. **Exp** = Experimental Chemical shift value. **δ** = Chemical shift value.

According to the above results and discussion Fukui-function calculation support the cyclization reaction and **^{1}H**, **^{13}C** NMR calculation shows slightly different results than experimental.

Conclusion-

i. Fukui-function calculations also support the reactivity and cyclization was happened in experimentally.
ii. ^{1}**H** and ^{13}**C** chemical shift calculation shows the slightly difference chemical shift value than experimental based on ωb97xd/3-21g* Level.
iii. We need to try ^{1}**H** and ^{13}**C** chemical shift calculation based on higher level of basis set.

Annex C.

Copies of the published articles

EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202201295

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Iodine(III)-Mediated Electrophilic Chlorination and Catalytic Nitration of *N*-Tosyl Anilines

Dipak B. Patil,[a] Rocío Gámez-Montaño,[a] Mario Ordoñez,[b] Melchor Solis-Santos,[b] J. Oscar C. Jiménez-Halla,*[a] and César R. Solorio-Alvarado*[a]

In the memory of Kevin.

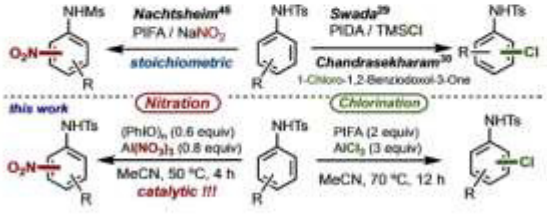
An efficient iodine(III)-based protocol for the chlorination and catalytic nitration of *N*-tosyl anilines as well as the proposed reaction mechanism is described. The synergistic combination of the commercially available [bis(trifluoroacetoxy)iodo]benzene (PIFA) with $AlCl_3$, or $(PhIO)_n$ with $Al(NO_3)_3$, allowed the electrophilic introduction of chlorine and nitro group in the *N*-tosyl aniline core in non-acidic conditions. Our DFT calculations, performed for the chlorination process, indicate that this occurs through a cationic pathway in which the [Cl-PhI⊕ ⊖OTFA-$AlCl_3$] is the chlorinating species and is formed under neutral conditions.

Introduction

Chlorinated[1] and nitrated anilines[2] are an important class of organic compounds. In one side, chloroanilines are present in *N*-glucosides plant metabolites,[3] dyes, cosmetics, pharmaceuticals and herbicides;[4] they also display biological activities such as antiprotozoal,[5] receptor tyrosine kinase (RTK) inhibitors,[6] and as useful building blocks in organic synthesis.[7] On the other hand, nitroanilines are important in materials science as a highly relevant push-pull molecules in non-linear optics,[8] photoluminescence,[9] synthesis of dyes[10] and explosives.[11] The nitroaniline core serves as a building block in the pharmaceutical industry,[12] as reagents for diazotization in assays of proteases,[13] as prodrug-type in neuramidase-triggered activation,[14] metabolic products of PhEBfx against *T. cruzi*,[15] and slow releasers of the endothelial relaxer nitric oxide (NO).[16]

Concerning their synthesis, to date, some procedures have been described for the introduction of the chlorine and nitro groups into the functionalized aniline moiety as anilide or benzenesulfonamide. For the case of chlorination, several metal-free procedures involving the use of NCS[17] (in combination with TMSCl[18] or thioureas[19]), alkyl ammonium chlorides in acid media,[20] oxidation of the chloride anion (with Oxone®[21] or *m*-CPBA[22]) and *N*-chloro sulfonamide-based reagents (CFBS[23] or CMOBSA[24]) have been reported. The metal-catalyzed chlorination has been mainly described with Cu,[25] Pd[26] or Fe.[27] In this work, only two protocols using iodine(III)-based reagents[28] have been described by Swada,[29] and Chandrasekharam.[30] For the nitration of anilides or benzenesulfonamides, different metal-free protocols involving the use of nitrocyclohexadienones,[31] ionic liquids $[Msim]NO_3$,[32] montmorillonite clay,[33] urea nitrate[34] or via the formation of the aniline nitric salts-H_2SO_4 are found in the literature.[35] Also, nitration of anilides or benzenesulfonamides using the nitrite group present in $^tBuONO_2$[36] and pyridinium salts,[37] or by oxidizing the $NaNO_2$ with Oxone®,[38] or under photocatalytic conditions with RFTA (riboflavin tetraacetate) at 455 nm,[39] are the most representative protocols. Other metal-catalyzed nitration procedures imply the use of Cu,[40] Fe,[41] Bi,[42] Ag,[43] and Ni.[44] Regarding this report, the nitration of benzenesulfonamides using iodine(III) reagents is restricted to a single report by Nachtsheim[45] using stoichiometric amounts of PIFA (Scheme 1).

As part of our research on iodine(III) chemistry[46] we focused our work in the oxidative functionalization[47] of aromatic derivatives[48] to get compounds mainly with biological importance.[49] Thus, considering the relevance of chloroaniline as well as the nitroaniline core, the design of procedures that avoid the harsh conditions described for the synthesis of both



Scheme 1. Known procedures for the chlorination and nitration of *N*-aryl sulfonamides using iodine(III) reagents.

[a] D. B. Patil,+ R. Gámez-Montaño, Dr. J. O. C. Jiménez-Halla, Dr. C. R. Solorio-Alvarado
Guanajuato University, Department of Chemistry
Noria Alta S/N, Guanajuato., Gto. México 36050
E-mail: jjimenez@ugto.mx
csolorio@ugto.mx
https://cesarrogelio.wixsite.com/crsa
[b] Dr. M. Ordoñez, Dr. M. Solis-Santos
Centro de Investigaciones Químicas-IICBA
Universidad Autónoma del Estado de Morelos
Av. Universidad 1001, 62209Cuernavaca, Morelos (México)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202201295

nuclei, especially the acidic nitration, is currently an interesting challenge to complete. In this regard, we envisioned the development of a mild and non-Brønsted-acidic protocol for the chlorination and nitration of *N*-tosyl anilines. We based our strategy in the application of our recent methods which use commercially available iodine(III) reagents[50] in synergistic combination with different aluminum salts.[51] By employing an aluminum salt as a common strategy, we showed that the formation of an ionic pair enabled the introduction of chlorine as the functional group.

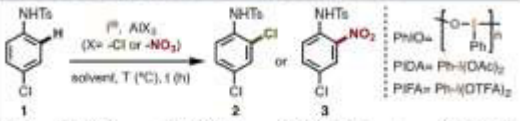
In this work, we present our results using the PIFA/$AlCl_3$ and $(PhIO)_n$/$Al(NO_3)_3$ systems which allowed us the oxidative electrophilic chlorination and to the best of our knowledge, the first catalytic nitration of several *N*-tosyl anilines.

Results and Discussion

We initially sought validation of our hypothesis using 4-chloro-*N*-tosyl aniline (Table 1).

Initial attempts to induce the chlorination were carried out using the simple *N*-tosyl aniline. However, a mixture of *o*- and *p*-chlorination was obtained. Therefore, to determine the optimum stoichiometry, we started with 4-chloro-*N*-tosyl aniline **1** as the model system. Based on our previous chlorination protocol,[51a] 1.2 equivalents of PIFA and 2.4 equivalents of aluminum trichloride did not give the expected product **2** at 23 or 50 °C (entries 1 and 2). By heating at 70 °C, product **2** in 65% yield was isolated (entry 3). The use of 1.5 equivalents of oxidant and 3 equivalents of the aluminum salt increased the yield to 74% (entries 4 and 5). However, the best result was obtained with 2 equivalents of PIFA and 3 equivalents of aluminum trichloride at 70 °C in 12 h, to get 83% yield (entry 6). Under these conditions, other solvents (entries 7 and 8), including the control experiments (entries 9 and 10), did not afford the desired chlorination. Concerning the nitration, our previous report on catalytic nitration[51c] provided the starting conditions. Thereby, sub-stoichiometric amounts of the oxidant and the aluminum salt, consisted in 0.3 equivalents of polymeric iodosylbenzene $(PhIO)_n$ and 0.4 equivalents of aluminum nitrate nonahydrate, produced the desired nitrated product in 34% yield at 23 °C. The starting material was not fully consumed in 12 h (entry 11). Nevertheless, at 50 °C, the nitroaniline **3** was obtained in 60% yield (entry 12). The use of a double amount of each reagent, still in sub-stoichiometric quantities, gave the best result with a 78% of isolated yield (entry 13). To our delight, these results indicated the nitration process occurred as expected, in catalytic conditions and water tolerant. Increasing the amount of both reagents, or changes of the iodine(III) oxidant (entries 14 and 15), or in the control experiments (entries 16 and 17) did not improve the yield. The use of aluminum tribromide was also attempted and gave the corresponding brominated product. However, large excesses of the oxidant and salt were necessary. In consequence, this proposal was ruled out. Thus, with the optimal conditions for chlorination and nitration, we proceeded to explore the scope of the reaction (Scheme 2).

Table 1. Optimization of the Iodine(III)-mediated the electrophilic chlorination and the catalytic nitration of 4-chloro-*N*-tosyl aniline.[a,b]

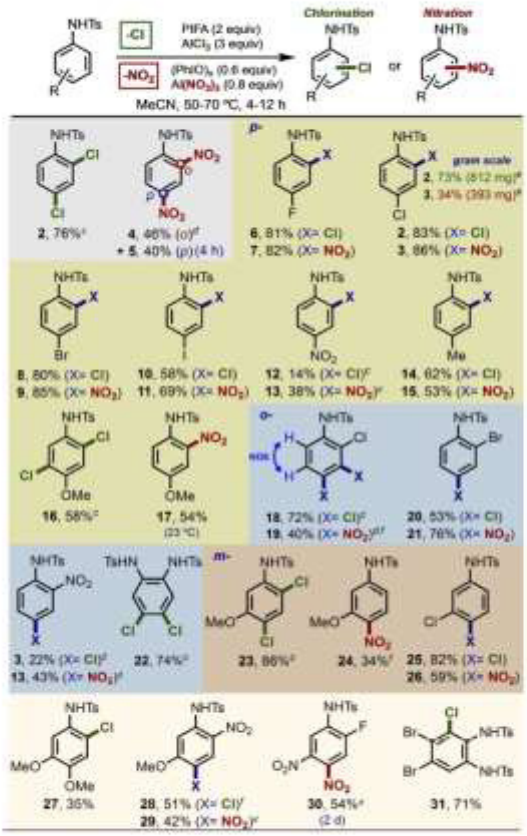


Entry	I^{III} source (equiv.)	AlX_3 source (equiv.)	Solvent	T [°C]	t [h]	Yield [%][c] 2/3
1	PIFA (1.2)	$AlCl_3$ (2.4)	MeCN	23	12	n.r./- -
2	PIFA (1.2)	$AlCl_3$ (2.4)	MeCN	50	12	n.r./- -
3	PIDA (1.2)	$AlCl_3$ (2.4)	MeCN	70	12	65/- -
4	PIFA (1.5)	$AlCl_3$ (2.4)	MeCN	70	12	68/- -
5	PIFA (1.5)	$AlCl_3$ (3.0)	MeCN	70	12	74/- -
6	**PIFA (2.0)**	**$AlCl_3$ (3.0)**	**MeCN**	**70**	**12**	**83/- -**
7	PIFA (2.0)	$AlCl_3$ (3.0)	DCE	70	12	c.r.m./- -
8	PIFA (2.0)	$AlCl_3$ (3.0)	THF	70	12	c.r.m./- -
9	PIFA (2.0)	- -	MeCN	70	12	c.r.m./- -
10	- -	$AlCl_3$ (3.0)	MeCN	70	12	0/- -
11[d,e]	PhIO (0.3)	$Al(NO_3)_3$ (0.4)	MeCN	23	4	- -/35
12[d]	PhIO (0.3)	$Al(NO_3)_3$ (0.4)	MeCN	50	4	- -/60
13[d]	**PhIO (0.6)**	**$Al(NO_3)_3$ (0.8)**	**MeCN**	**50**	**4**	**- -/86**
14[d]	PhIO (1.2)	$Al(NO_3)_3$ (1.0)	MeCN	50	4	- -/40
15[d]	PIDA (0.6)	$Al(NO_3)_3$ (0.8)	MeCN	50	4	- -/34
16	PhIO (0.6)	–	MeCN	50	4	- -/n.r.
17[d]	–	$Al(NO_3)_3$ (0.8)	MeCN	50	4	- -/0

[a] Reaction conditions: 4-chloro-*N*-tosyl aniline (0.5 mmol), solvent (0.3 *M*), 50 or 70 °C, no inert atmosphere. [b] The Ac-, Piv- and $(PhO)_2P(O)$-groups at the *N*- of aniline were tested, however no reaction was found. [c] Isolated yields. [d] $Al(NO_3)_3 \cdot 9H_2O$ was used. [e] 50% of starting material recovered. c.r.m. = complex reaction mixture. n.r. = no reaction observed.

Chlorination of simple *N*-tosyl aniline produced bis-chlorinated **2** in 76% yield. The nitration gave a separable mixture of *o*-**4** and *p*-nitro-*N*-tosyl aniline **5** in 46 and 40% yield, respectively (grey shadow). Several *para*-substituted *N*-tosyl anilines containing the complete halogen family and the strong electro-attracting nitro group **6**–**13** were successfully chlorinated and nitrated in yields ranging from 14 to 85%. The *p*-iodo- and *p*-nitro derivatives gave from modest to low yields, presumably due to the steric hindrance of the iodine atom and to the deactivation by the nitro group. The gram scale chlorination for **2** gave 73% yield while the nitration for **3** proceeded with a 34% yield. Other donating groups, such as *p*-methyl, gave rise to chlorinated **14** and nitrated **15** in good yields (62 and 53%). With electron-rich *N*-tosyl anilines containing a *p*-methoxy group, the mono-chlorinated compound could not be obtained as the sole product. Instead, bis-chlorinated **16** was obtained in 58% yield using an excess of reagents, and the single nitration to get **17** was achieved in 54% yield (green shadow). The *ortho*-chloro, -bromo and -nitro substituted *N*-tosyl anilines led to the formation of the corresponding chlorinated and nitrated products **3**, **13**, and **18**–**21** in good to excellent yields (40–76%) with exception of *o*-nitro-*N*-tosyl aniline that gave lower yields for **3** and **13** (22 and 43%). An interesting 3,4-dichlorination and -dinitration had place to get **18** and **19**, which was confirmed by NOESY. This result could be explained through the initial reaction at *para* position of the aniline core, followed by the reaction at the C-3 which presumably is directed by the chlorine atom in C-2. This regiochemistry is observed with chlorine and not with bromine

Research Article
doi.org/10.1002/ejoc.202201295



Scheme 2. Scope of the PIFA/$AlCl_3$-mediated electrophilic chlorination and $(PhIO)_n$/$Al(NO_3)_3$-catalyzed nitration of *N*-tosyl anilines.[a,b] [a] Reaction conditions: substituted *N*-tosyl aniline (0.5 mmol), solvent (0.3 *M*), 50–70 °C, 4–12 h, no inert atmosphere, $Al(NO_3)_3 \cdot 9H_2O$ was used for nitration reactions. [b] Isolated yields. [c] PIFA (3 equiv)/$AlCl_3$ (5.5 equiv.) were used. [d] $(PhIO)_n$ (1.2 equiv.)/$Al(NO_3)_3 \cdot 9H_2O$ (1.6 equiv) were used. [e] Gram scale reaction. [f] Regioselectivity was confirmed by NOESY.

atom due to its higher electronegativity and in consequence the ability to make stronger interactions with the chlorinating and nitrating species. The *o*-NTs- derivative also gave the bis-chlorinated compound **22** in good yield (74%). The corresponding nitration gave a complex reaction mixture. This poor performance could be the result of several nucleophilic centres that compete for the formed electrophile (blue shadow). In the assays, with *meta*-substituted *N*-tosyl anilines, again, those containing the *m*-methoxy group gave the bis-chlorination product **23** in 86% yield and led to the single nitration product **24** in 34% yield. The *m*-chloro *N*-tosyl aniline gave the chlorinated and nitrated substrates **25** and **26** in 82 and 59% yield (brown shadow). Disubstituted *N*-tosyl anilines, containing the methoxy and nitro groups, gave rise to chlorination and nitration products **27–29** in modest to good yields (35–51%). Strongly deactivated *N*-tosyl anilines substituted with the nitro and fluor groups did not react under these chlorination conditions. However, nitration of this compound gave **30** in 54% yield using an excess of reagents. Chlorination of tetra-substituted anilines, possessing 1,2-di-NTs groups, formed **31** in 71% yield, while the nitration gave a complex reaction mixture as previously observed for this class of substrate (beige shadow).

To demonstrate the utility of our protocol, starting from **7**, we synthesized the highly deactivated bis-nitrated derivative **32** in 49% yield. This compound would be difficult to get by other electrophilic aromatic substitution procedures (Figure 1).

Dear Editors Pleaase insert here figure 1.

Finally, the reaction pathway for the developed chlorination process was elucidated. Our theoretical calculations at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X–D/def2-svpp level allowed us to propose a reaction mechanism (Scheme 3).

It starts with the coordination of one of the trifluoroacetate groups of PIFA to $AlCl_3$. Then, the acetate group dissociates as one of the chloride ions is transferred to the iodine simultaneously via transition state **TS1** ($\Delta G_1^{\ddagger} = 18.9$ kcal/mol) to give **Int-1** which is + 2.1 kcal/mol from the reactants (the acetate group evolves into species C). **Int-1** coordinates to a second $AlCl_3$ unit, which lowers the energy for −22.4 kcal/mol (**Int-2**). This spontaneously dissociates into the ion pair A^+ and B^- releasing 9.1 kcal/mol, which is the active form of the catalyst. At this point, the stage of the reaction with *N*-tosyl aniline can proceed by attacking the *ortho*- or the *para*- position of aniline. We calculated both transition states: $TS2_1$ (*o*-chlorination route) and $TS2_2$ (*p*-chlorination route) for the transfer of a chloronium cation from A^+ to each position of the aromatic ring, resulting in energy barriers of 22.4 and 19.5 kcal/mol, respectively. This energy difference of $\Delta\Delta G_2^{\ddagger} = 2.9$ kcal/mol is even more notable when comparing intermediate $Int\text{-}3_1$ and $Int\text{-}3_2$ ($\Delta\Delta G_3 = 5.8$ kcal/mol), despite this reaction step is exergonic for both cases (−4.2 and −10.0 kcal/mol, respectively). Moreover, species B^- deprotonated via either $TS3_1$ ($\Delta G_3^{\ddagger} = 27.0$ kcal/mol) or $TS3_2$ ($\Delta G_3^{\ddagger} = 19.4$ kcal/mol) which is the largest energy difference between both routes ($\Delta\Delta G_3^{\ddagger} = 13.4$ kcal/mol). Preliminarily, we can conclude that the *p*-chlorination process is much faster than the *o*-chlorination reaction. The monochlorination products $Int\text{-}4_1$ and $Int\text{-}4_2$ are only 1.4 kcal/mol distant. In the second chlorination reaction of aniline, there is an inversion of the stabilities when transferring the chloronium cation from A^+ being $Int\text{-}5_1$ 3.1 kcal/mol more stable than $Int\text{-}5_2$. Despite $TS4_2$ is notably faster ($\Delta\Delta G_4^{\ddagger} = 6.5$ kcal/mol) than **TS41** in this step, we can notice that the next and last deprotonation step, $TS5_1$ becomes lower in energy ($\Delta\Delta G_5^{\ddagger} = 2.4$ kcal/mol) than $TS5_2$ to reach the bi-chlorinated product. When comparing $Int\text{-}4_1 \rightarrow$ TS-

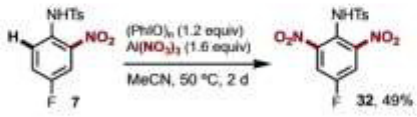
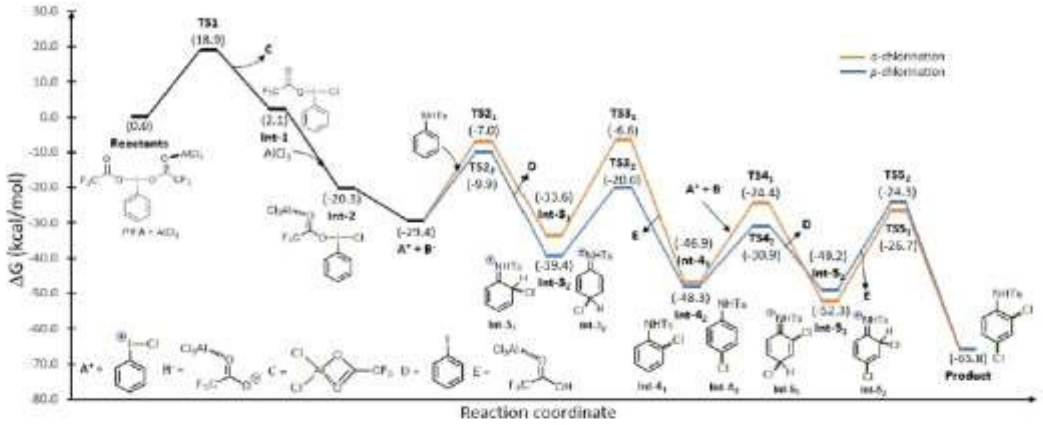


Figure 1. Synthetic utility of the developed procedure.



Scheme 3. Energy profile for the chlorination mechanism of *N*-tosyl aniline using the PIFA/$AlCl_3$ system calculated at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level.

$\mathbf{4}_1$ ($\Delta G^{\ddagger} = 22.5$ kcal/mol, now attacking on the *para* position) and **Int-4**$_2$→**TS5**$_2$ ($\Delta G^{\ddagger} = 24.0$ kcal/mol, now attacking on *ortho* position), we can observe that, again, the attack on the *para* position is faster. However, this selectivity is decided from the first chlorination on the aniline ring.

Conclusions

In summary, we have developed an efficient and mild iodine(III)-mediated electrophilic chlorination protocol and the first catalytic nitration method of *N*-tosyl anilines which uses polymeric iodosylbenzene $(PhIO)_n$ as catalyst and was conducted in neutral and non-Brønsted-acidic conditions. Under a common strategy, the use of an aluminum salt provided the functional group in its ionic pair, which is oxidized by the iodine(III) reagent and finally reacted with the aromatic ring. Our DFT calculations allowed us the elucidation of the chlorination reaction pathway and indicate that [Cl-PhI-⊕ ⊖OTFA·$AlCl_3$] is the chlorinating species which is operative in a cationic route.

Experimental Section

General Methods: All moisture and oxygen sensitive reactions were carried out in flame-dried round bottom flask or using Schlenk techniques under an inert atmosphere of nitrogen, unless otherwise specified. NMR spectra were measured on ^{1}H and ^{13}C{^{1}H}NMR spectra were acquired on Bruker Advance III (500 MHz) and JEOL JNM-ECA500 (500 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sep = septet, dd = doublet-doublet. m = multiplet, b = broad), coupling constants (Hz), and assignment. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet Is5 spectrometer. High resolution mass spectra (HRMS) were performed on Bruker microTOF and Thermo Exactive plus. YMC syringe pump (model number: YSP-101) was used when slow addition of a solution of a solution was conducted. The products were purified by flash column chromatography (silica gel 60, Merch and Sigma Aldrich, 230–400 mesh) or preparative thin layer chromatography silica gel (PLC 60 F254. 0.5 mm). Commercially available reagents were purchased from Wako, Aldrich, TCI and Alfa Aesar chemicals and used as received. Anhydrous solvents were purchased from Sigma Aldrich in Sure-SealR bottles. Thin layer chromatography was performed with TLC Silica gel 60 F256 plates, and visualization was affected with short wavelength UV light (254 nm). Compounds were characterized using ^{1}H NMR, ^{13}C{^{1}H}NMR, melting point, IR (ATR) and Mass spectroscopy and copies of spectra are provided in the Supporting Information for all new compounds. Data of known compounds were compared with existing literature characterization data and the references are given.

Computational Techniques: All the gas-phase theoretical calculations were performed using the Gaussian09 program.[52] First, carried out geometry optimizations, with no restrictions, using the range-divided ωB97X-D[53] density functional in combination with the Aldrich's basis set def2-svpp.[54] A subsequent harmonic frequency calculation, for each optimized geometry, was done to corroborate the character of each critical point in the potential energy surface (PES): reactants, intermediates and products must present all the frequencies as positive whereas transition state must have one and just one negative frequency. Thermal and entropy corrections to the total energy were taken from the thermochemistry analysis in the output file at 298 K and 1 atm. Also, we performed calculations for including the solvent effect through the PCM model[55] using the SMD parameters[56] according to the Truhlars model using acetonitrile (ε = 35.688) as solvent. These calculations were performed as single points of the optimized geometry at the level of theory mentioned above. Other single-point calculations were run using a more robust basis set, def2-tzvpd, to improve the accuracy of the calculated electronic energies. The obtained energies were added to the gas-phase calculations and were reported as our final values.

Synthesis of Iodosylbenzene $(PhIO)_n$: In a 250 ml round bottom flask was suspended (diacetoxyiodo)benzene (PIDA) (5 g,

15.52 mmol, 1 equiv.) in 75 mL of a 3 *M* NaOH solution. The reaction was strongly stirred to room temperature during 12 h and precipitate was formed. After filtered off and neutralized with cold water until neutral pH this solid was washed (3 X 10 mL) with $CHCl_3$ to remove impurities of PIDA. The obtained solid was dried at high vacuum without heating to yield $(PhIO)_n$ (3.1 g, 91%) as a yellowish solid. ***Caution!*** $(PhIO)_n$ is explosive upon drying at 110 °C in vacuum conditions.

General procedure for *N*-tosyl aniline synthesis: To a solution of the aniline (4.05 mmol, 1 equiv.) in pyridine (20.25 mL, 0.2 *M*) was added *p*-toluenesulfonyl chloride (4.45 mmol, 1.1 equiv.) at 0 °C and then warm at 25 °C. After being stirred at 25 °C or 90 °C for 2–12 h, the reaction mixture was poured into water. The product was extracted with CH_2Cl_2 (3×20 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel to give the corresponding *N*-tosyl anilines.

General Procedure for Chlorination: A 25 mL oven-dried round bottom flask equipped with a magnetic stirrer bas was charged with PIFA bis(trifluoroacetoxy)iodo benzene (2.0 equiv.) and acetonitrile (0.3 *M*) at 25 °C. After dissolving and obtaining homogeneous mixture, $AlCl_3$ (3.0 equiv.) was added and stirred for 10 min. Then, the corresponding *N*-tosyl aniline (1.0 equiv.) was added and stirred at 70 °C until fully consumption of the starting material (usually 5 to 18 h). To quench the reaction, EtOAc (5 mL) was added and concentrated to *vacuo*. Purification was carried out by column chromatography with EtOAc-Hexane system to give the desired product.

General Procedure for Nitration: In a 25 mL oven-dried round bottom flask was suspended polymeric $(PhIO)_n$ (0.6 equiv.) in acetonitrile at 23 °C. Then, $Al(NO_3)_3$ (0.8 equiv.) was added and stirred for 10 min. Then, the corresponding *N*-tosyl aniline (1.0 equiv.) was incorporated in one portion. The reaction was stirred at 23 or 50 °C for a period 1–4 h until the starting *N*-tosylaniline was fully consumed judging its advance by TLC. To quench the reaction, EtOAc (5 mL) was added and concentrated to *vacuo*. Purification was carried out by column chromatography with EtOAc-Hexane system to give the desired product.

Acknowledgements

This work was supported by CONACyT (FORDECYT-PRONACES/610286/2020). We acknowledge the facilities of the DCNyE, the Chemistry Department, the National Laboratory UG-CONACyT (LACAPFEM) at the University of Guanajuato. We also thank CONACyT for a fellowship to D.B.P.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: catalytic nitration · electrophilic chlorination · iodosylbenzene · *N*-Tosyl anilines · PIFA

[1] a) K. Naumann, *Pest Manag Sci.* **2000**, *56*, 3–21; b) M. Z. Hernandes, S. M. T. Cavalcanti, D. R. M. Moreira, *Curr. Drug Targets.* **2010**, *11*, 303–314.
[2] a) N. Ono, *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, **2001**; b) K.-S. Ju, R. E. Parales, *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 250–272; c) K. J. Indest, J. O. Eberly, D. E. Hancock, *J. Gen. Appl. Microbiol.* **2015**, *61*, 217–223; d) J. C. Spain, *Annu. Rev. Microbiol.* **1995**, *49*, 523–555.
[3] R. Winkler, H. Sandermann, *J. Agric. Food Chem.* **1992**, *40*, 2008–2012.
[4] A. S. Vangnai, W. Petchkroh, *FEMS Microbiol. Let.* **2007**, *268*, 209–216.
[5] C. Eberle, J. A. Burkhard, B. Stump, M. Kaiser, R. Brun, R. L. Krauth-Siegel, F. Diederich, *ChemMedChem* **2009**, *4*, 2034–2044.
[6] A. Gangjee, S. Kurup, M. A. Ihnat, J. E. Thorpe, S. S. Shenoy, *Bioorg. Med. Chem.* **2010**, *18*, 3575–3587.
[7] Y. Zou, J. E. Melvin, S. S. Gonzales, M. J. Spafford, A. B. Smith III, *J. Am. Chem. Soc.* **2015**, *137*, 7095–7098.
[8] a) C. C. Teng, A. F. Garito, *Phys. Rev.* **1983**, *28*, 6766; b) D. M. Bishop, B. Champagne, B. Kirtman, *J. Chem. Phys.* **1998**, *109*, 9987–9994; c) H. Reis, M. G. Papadopoulos, P. Calaminici, K. Jug, A. M. Koster, *Chem. Phys.* **2000**, *561*, 359–371.
[9] a) C. J. Seliskar, O. S. Khalil, S. P. McGlynn, *Excited States.* **1974**, *1*, 231–294; b) M. M. Szostak, B. Kozankiewicz, J. Lipinski, *Acta A Mol. Biomol. Spectrosc. Spectrochim. Acta A.* **2007**, *67*, 1412–1416.
[10] a) C. J. Agudelo-Morales, O. F. Silva, R. E. Galian, J. Perez-Prieto, *ChemPhysChem.* **2012**, *13*, 4195–4201; b) L. Hermosilla, M. C. Rezende, V. G. Machado, R. I. Stock, *Spectrochim. Acta Part A.* **2017**, *173*, 556–561.
[11] a) P. R. Lee, J. A. Zukas, W. P. Walters, *Explosive effects and Aapplications*, Springer Science New York, **2003**; b) R. P. Schwarzenbach, P. M. Gschwend, D. M. Imboden, *Environmental Organic Chemistry*, Wiley-VCH: New York, **2002**.
[12] a) A. Bhattacharya, V. C. Purohit, V. Suarez, R. Tichkule, G. Parmer, F. Rinaldi, *Tetrahedron Lett.* **2006**, *47*, 1861–1864; b) A. N. Gritsenko, Z. I. Ermakova, S. V. Zhuravlev, *Chem. Heterocycl. Compd.* **1970**, *6*, 1245–1246; c) S. Radl, P. Hezky, J. Proska, I. Krejci, *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 13–18; d) G. Booth, *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim: Wiley-VHC, **2007**.
[13] M. J. Lee, J. H. Anstee, *Anal. Biochem.* **1994**, *218*, 480–482.
[14] T. Matsushita, M. N. Danyel, T. Koyama, K. Hatano, K. Matsuoka, *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126883.
[15] M. Boiani, A. Merlino, A. Gerpe, W. Porcal, F. Croce, S. Depaula, M. A. Rodriguez, H. Cerecetto, M. González, *Xenobioteca.* **2009**, *39*, 236–248.
[16] a) P. Chauhan, N. Yan, *Carbohydr. Polym.* **2017**, *174*, 1106–1113; b) A. R. Badour, J. A. Wisniewski, D. K. Mohanty, P. J. Squattrito, *Acta Crystallogr. Sect. C* **2016**, *72*, 405–410.
[17] R. S. Neale, R. G. Schepers, M. R. Walsh, *J. Org. Chem.* **1964**, *29*, 3390–3393.
[18] T. Maibunkaew, C. Thongsomkleeb, J. Tummatorn, A. Bunrit, S. Ruchirawat, *Synlett* **2014**, *25*, 1769–1775.
[19] A. N. Dinh, S. M. Maddox, S. D. Vaidya, M. A. Saputra, C. J. Nalbandian, J. L. Gustafson, *J. Org. Chem.* **2020**, *85*, 13895–13905.
[20] a) X. Bao, J. Yao, H. Zhou, G. Xu, *Org. Lett.* **2017**, *19*, 5780–5782; b) X. Xiong, Y. Y. Yeung, *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 16101–16105.
[21] V. M. Lakshmireddy, Y. Naga Veera, T. J. Reddy, V. J. Rao, B. China Raju, *Asian J. Org. Chem.* **2019**, *8*, 1380–1384.
[22] C. Y. Chen, G. C. Senadi, M. C. Liu, J. J. Wang, *ChemistrySelect* **2016**, *1*, 2207–2211.
[23] Z. Lu, Q. Li, M. Tang, P. Jiang, H. Zheng, X. Yang, *Chem. Commun.* **2015**, *51*, 14852–14855.
[24] X. Pu, Q. Li, Z. Lu, X. Yang, *Eur. J. Org. Chem.* **2016**, *2016*, 5937–5940.
[25] a) B. Urones, A. M. Martínez, N. Rodríguez, R. G. Arrayas, J. C. Carretero, *Chem. Commun.* **2013**, *49*, 11044–11046; b) H. Wang, K. Wen, N. Nurahmat, Y. Shao, H. Zhang, C. Wei, Y. Li, Y. Shen, Z. Sun, *Beilstein J. Org. Chem.* **2012**, *8*, 744–748.
[26] a) H. Shi, P. Wang, S. Suzuki, M. E. Farmer, J. Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14876–14879; b) S. Xiuyun, S. Gang, S. Yonghui, R. Yu, *Angew. Chem. Int. Ed.* **2013**, *52*, 4440–4444.
[27] M. A. Mostafa, R. M. Bowley, D. T. Racys, M. C. Henry, A. Sutherland, *J. Org. Chem.* **2017**, *82*, 7529–7537.
[28] M. Wang, Y. Zhang, T. Wang, C. Wang, D. Xue, J. Xiao, *Org. Lett.* **2016**, *18*, 1976–1979.
[29] K. Yamamoto, S. Kamino, D. Sawada, *Tetrahedron Lett.* **2017**, *58*, 3936–3938.
[30] B. Vinayak, P. V. Ravindrakumar, D. V. Ramana, M. Chandrasekharam, *New J. Chem.* **2018**, *42*, 8953–8959.

[31] M. Lemaire, A. Guy, P. Boutin, J. P. Guette, *Synthesis* **1989**, *1989*, 761–763.
[32] M. A. Zolfigol, A. Khazaei, A. R. Moosavi-Zare, A. Zare, H. G. Kruger, Z. Asgari, V. Khakyzadeh, M. Kazem-Rostami, *J. Org. Chem.* **2012**, *77*, 3640–3645.
[33] S. K. Bharadwaj, P. K. Boruah, P. K. Gogoi, *Catal. Commun.* **2014**, *57*, 124–128.
[34] T. P. Sura, M. M. V. Ramana, N. A. Kudav, *Synth. Commun.* **1988**, *18*, 2161–2165.
[35] P. Zhang, M. Cedilote, T. P. Cleary, M. E. Pierce, *Tetrahedron Lett.* **2007**, *48*, 8659–8664.
[36] a) B. Kilpatrick, M. Heller, S. Arns, *Chem. Commun.* **2013**, *49*, 514–516; b) P. Chaudhari, S. Gupta, N. Sabieh, J. Kandasamy, *J. Org. Chem.* **2018**, *84*, 104–119.
[37] P. Natarajan, R. Chaudhary, N. Rani, P. Venugopalan, *Tetrahedron Lett.* **2020**, *61*, 151529.
[38] Y. X. Li, L. H. Li, Y. F. Yang, H. L. Hua, X. B. Yan, L. B. Zhao, J. B. Zhang, F. J. Ji, Y. M. Liang, *Chem. Commun.* **2014**, *50*, 9936–9938.
[39] S. J. Düsel, B. König, *J. Org. Chem.* **2018**, *83*, 2802–2807.
[40] a) E. Hernando, R. R. Castillo, N. Rodríguez, R. Gómez Arrayás, J. C. Carretero, *Chem. Eur. J.* **2014**, *20*, 13854–13859; b) P. Sadhu, S. K. Alla, T. Punniyamurthy, *J. Org. Chem.* **2015**, *80*, 8245–8253; c) B. Vinayak, M. Chandrasekharam, *Org. Lett.* **2017**, *19*, 3528–3531.
[41] a) V. Botla, D. V. Ramana, B. Chiranjeevi, M. Chandrasekharam, *ChemistrySelect* **2016**, *1*, 3974–3978; b) Y. Gao, Y. Mao, B. Zhang, L. Zhan, Y. Huo, *Org. Biomol. Chem.* **2018**, *16*, 3881–3884.
[42] Y. Lu, Y. Li, R. Zhang, K. Jin, C. Duan, *Tetrahedron* **2013**, *69*, 9422–9427.
[43] N. Iranpoor, H. Firouzabadi, N. Nowrouzi, D. Firouzabadi, *Tetrahedron Lett.* **2006**, *47*, 6879–6881.
[44] Tasneem, M. M. Ali, K. C. Rajanna, P. K. Saiparakash, *Synth. Commun.* **2001**, *31*, 1123–1127.
[45] U. Kloeckner, B. J. Nachtsheim, *Chem. Commun.* **2014**, *50*, 10485–10487.
[46] a) L. A. Segura-Quezada, K. R. Torres-Carbajal, Y. Satkar, K. A. Juarez-Ornelas, N. Mali, D. B. Patil, R. Gámez-Montaño, J. R. Zapata-Morales, S. Lagunas-Rivera, R. Ortiz-Alvarado, C. R. Solorio-Alvarado, *Mini-Rev. Org. Chem.* **2021**, *18*, 159–172; b) L. A. Segura-Quezada, K. R. Torres-Carbajal, K. A. Juarez-Ornelas, R. Ortiz-Alvarado, A. J. Alonso-Castro, T. Dohi, C. R. Solorio-Alvarado, *Org. Biomol. Chem.* **2022**, *20*, 5009–5034.
[47] B. Yahuaca-Juárez, G. González, M. A. Ramírez-Morales, C. Alba-Betancourt, M. A. Deveze-Álvarez, C. L. Mendoza-Macías, R. Ortiz-Alvarado, K. A. Juárez-Ornelas, C. R. Solorio-Alvarado, K. Maruoka, *Synth. Commun.* **2020**, *50*, 539–548.
[48] a) Y. Satkar, K. Wrobel, D. E. Trujillo-González, R. Ortiz-Alvarado, J. O. C. Jiménez-Halla, C. R. Solorio-Alvarado, *Front. Chem.* **2020**, *8*, 563470; b) P. D. Nahide, C. R. Solorio-Alvarado, *Tetrahedron Lett.* **2017**, *58*, 279–284.
[49] a) P. D. Nahide, C. Alba-Betancourt, R. Chávez-Rivera, P. Romo-Rodríguez, M. Solís-Hernández, L. A. Segura-Quezada, K. R. Torres-Carbajal, R. Gámez-Montaño, M. A. Deveze-Álvarez, M. A. Ramírez-Morales, A. J. Alonso-Castro, J. R. Zapata-Morales, A. J. Ruiz-Padilla, C. L. Mendoza-Macías, V. Meza-Carmen, C. J. Cortés-García, A. R. Corrales-Escobosa, R. E. Núñez-Anita, R. Ortiz-Alvarado, L. Chacón-García, C. R. Solorio-Alvarado, *Bioorg. Med. Chem. Lett.* **2022**, *63*, 128649; b) L. A. Segura-Quezada, K. R. Torres-Carbajal, N. Mali, D. B. Patil, M. Luna-Chagolla, R. Ortiz-Alvarado, M. Tapia-Juárez, I. Fraire-Soto, J. G. Araujo-Huitrado, A. J. Granados-López, R. Gutiérrez-Hernández, C. A. Reyes-Estrada, Y. López-Hernández, J. Adrián López, L. Chacón-García, C. R. Solorio-Alvarado, *ACS Omega* **2022**, *7*, 6944–6955; c) V. Ramadoss, R. Gámez-Montaño, J. R. Zapata-Morales, A. J. Alosno-Castro, C. R. Solorio-Alvarado, *Med. Chem. Res.* **2019**, *28*, 473–484; d) V. Ramadoss, A. J. Alonso-Castro, N. Campos-Xolalpa, R. Ortiz-Alvarado, B. Yahuaca-Juárez, C. R. Solorio-Alvarado, *RSC Adv.* **2018**, *8*, 30761–30776; e) V. Ramadoss, A. J. Alonso-Castro, N. Campos-Xolalpa, C. R. Solorio-Alvarado, *J. Org. Chem.* **2018**, *83*,10627–10635.
[50] a) P. J. Sarang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123–1178; b) V. V. Zhdankin, P. J. Sarang, *Chem. Rev.* **2002**, *102*, 2523–2584.
[51] a) P. D. Nahide, V. Ramadoss, K. A. Juarez-Ornelas, Y. Satkar, R. Ortiz-Alvarado, J. M. Cervera-Villanueva, A. J. Alonso-Castro, J. R. Zapata-Morales, A. J. Ruiz-Padilla, M. A. Deveze-Alvarez, C. R. Solorio-Alvarado, *Eur. J. Org. Chem.* **2018**, *2018*, 485–493; b) Y. Satkar, V. Ramadoss, P. D. Nahide, E. García-Medina, K. A. Juarez-Ornelas, A. J. Alonso-Castro, R. Chavez-Rivera, J. O. C. Jiménez-Halla, C. R. Solorio-Alvarado, *RSC Adv.* **2018**, *8*, 17806–17812; c) K. A. Juarez-Ornelas, J. O. C. Jiménez-Halla, T. Kato, C. R. Solorio-Alvarado, K. Maruoka, *Org. Lett.* **2019**, *21*, 1315–1319; d) Y. Satkar, L. F. Yeara-Ledesma, N. Mali, D. Patil, P. Navarro-Santos, L. A. Segura-Quezada, P. I. Ramírez-Morales, C. R. Solorio-Alvarado, *J. Org. Chem.* **2019**, *84*, 4149–4164; e) A. Segura-Quezada, Y. Satkar, D. Patil, N. Mali, K. Wrobel, G. González, R. Zarraga, R. Ortiz-Alvarado, C. R. Solorio-Alvarado, *Tetrahedron Lett.* **2019**, *60*, 1551–1555.
[52] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian 16, Revision C.01, Gaussian, Inc., Wallingford CT, **2019**.
[53] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
[54] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.
[55] a) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995–2001; b) M. Cossi, V. Barone, B. Mennucci, J. Tomasi, *Chem. Phys. Lett.* **1998**, *286*, 253–260; c) V. Barone, M. Cossi, J. Tomasi, *J. Comb. Chem.* **1998**, *19*, 404–417; d) J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999–3094.
[56] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

Manuscript received: November 3, 2022
Revised manuscript received: November 17, 2022
Accepted manuscript online: November 21, 2022

JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. 2019, 84, 4149−4164 Article pubs.acs.org/joc

Iodine(III)-Mediated, Controlled Di- or Monoiodination of Phenols

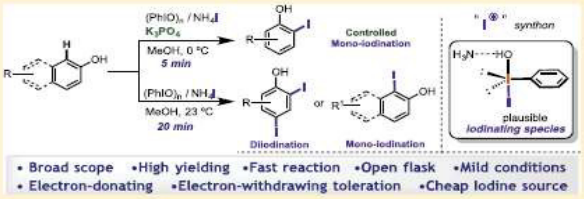
Yuvraj Satkar,[†,§] Luisa F. Yera-Ledesma,[†,§] Narendra Mali,[†] Dipak Patil,[†] Pedro Navarro-Santos,[‡] Luis A. Segura-Quezada,[†] Perla I. Ramírez-Morales,[†] and César R. Solorio-Alvarado*[,†]

[†]Universidad de Guanajuato, Campus Guanajuato, División de Ciencias Naturales y Exactas, Departamento de Química, Noria Alta S/N, 36050, Guanajuato, Guanajuato, México

[‡]Universidad Michoacana de San Nicolás de Hidalgo, Instituto de Ciencias Químico Biológicas, Av. Universidad S/N, 58000, Morelia, Michoacán, México

Supporting Information

ABSTRACT: An oxidative procedure for the electrophilic iodination of phenols was developed by using iodosylbenzene as a nontoxic iodine(III)-based oxidant and ammonium iodide as a cheap iodine atom source. A totally controlled monoiodination was achieved by buffering the reaction medium with K_3PO_4. This protocol proceeds with short reaction times, at mild temperatures, in an open flask, and generally with high yields. Gram-scale reactions, as well as the scope of this protocol, were explored with electron-rich and electron-poor phenols as well as heterocycles. Quantum chemistry calculations revealed PhI(OH)·NH_3 to be the most plausible iodinating active species as a reactive "I^+" synthon. In light of the relevance of the iodoarene moiety, we present herein a practical, efficient, and simple procedure with a broad functional group scope that allows access to the iodoarene core unit.



INTRODUCTION

Iodinated arenes and heteroarenes including indophenols are an important class of organic structures.[1] They are ubiquitous in marine natural products such as the terpenes or prostanoids isolated from sponges *Topsentia sp.*[2] or from corals of genus *Clavularia viridis*.[3] In the field of medical research, iodoarenes are found in pharmacologically active drugs,[4] in nonsteroidal hormones L-thyroxine (T_4) and Liothyronine (T_3),[5] or in antifungal[6] or bactericidal compounds.[7] In chemistry, iodoarenes are found as starting materials in the synthesis of hypervalent I(V)[8] or iodine(III)[9] derivatives. They have also been found to be the best electrophiles in the Suzuki and Stille cross-coupling reactions, as well as the Sonogashira alkynylation and the Mizoroki−Heck olefination (Figure 1).[10]

Due to the high relevance of the iodophenol moiety, several procedures have been developed to date for its synthesis. Among the most significant iodination strategies are those involving transition metals such as Ru,[11] In,[12] Pd,[13] Mo,[14] Hg,[15] Fe,[16] Ce,[17] Yb,[18] or Ag.[19] A number of transition-metal-free iodination procedures have also been described using I_2 in combination with 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate,[20] DMSO,[21] HIO_3,[22] urea-H_2O_2,[23] or NO_2.[24] An additional strategy consists of the oxidation of iodide salts using the systems NH_4I/H_2O_2,[25] $NaI/NaClO_2$,[26] or $NaClO_2$/NaI/HCl.[27] On the other hand, iodination reactions based on the use of (I^+) synthons are frequently carried out with ICl,[28] *N*-iodosaccharin,[29] IPy_2BF_4,[30] and NIS in harsh acidic media such as TFA,[31] TfOH,[32] and HFIP.[33] Additionally, radical iodination using I_2/TBHP[34] has recently been developed. Finally, a much less well exploited strategy for the oxidative iodination of arenes and phenols involves the use of hypervalent iodine(V)[35] or iodine(III) reagents. The few procedures using iodine(III)[36] have a common strategy involving the synthesis of a diaryliodonium salt as an intermediate, which then reacts with a metallic iodide, typically NaI. This intermediate undergoes a thermally promoted reductive elimination, allowing the formation of two different aryl iodides[37] from the iodonium salt at high temperatures (Scheme 1).

In general, iodination methods of phenols require expensive transition metals or are based on oxidative procedures using strong oxidants, leading to poor functional group compatibility. To overcome this problem, hypervalent reagents appear to be an excellent alternative. With respect to the known hyper-

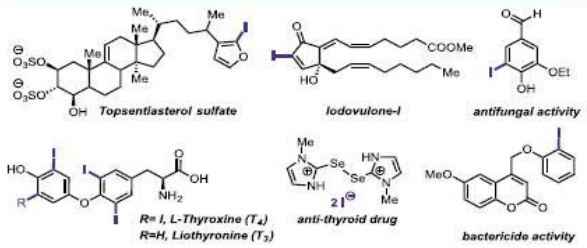
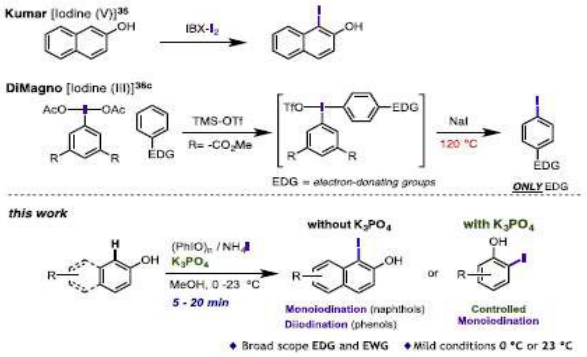


Figure 1. Relevance of the iodoarene moiety.

Received: January 16, 2019
Published: March 12, 2019

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

Scheme 1. Hypervalent Iodine Strategies for the Iodination of Arenes and Phenols



valent-based iodination procedures of phenols, the very few of them that are available are synthetically restricted in several ways, the most significant being low selectivity,[35] polyhalogenation, expensive starting materials,[36] more than one preparation step, limitation to electron-rich arenes, very narrow scope, and the requirement for high temperatures, strong Lewis acids, and/or long reaction times. All of the aforementioned aspects make an efficient iodine(III)-based iodination procedure elusive. Therefore, we were interested in developing a new and systematic alternative iodination of phenols by using the hypervalent iodine(III) reagent iodosylbenzene (PhIO) in combination with NH_4I, an inexpensive source of iodine atoms. The scope and advantages of our new method are detailed herein, and theoretical calculations supporting the plausible operation of PhII(OH)·NH_3 as the iodinating species are provided.

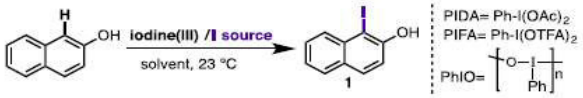
RESULTS

Our initial optimization of the iodination reaction used 2-naphthol as a model system, the results of which are tabulated in Table 1.

The starting conditions were based on our previous chlorination[38] and bromination[39] procedures. Thus, 1.2 equiv of PIDA or PIFA was used, along with 2.4 equiv of AlI_3 in acetonitrile at room temperature (Table 1, entries 1 and 2). Unfortunately, only molecular iodine was obtained as product in this trial. Different conditions were explored by changing the iodine(III) reagent from PIDA/PIFA to iodosylbenzene (PhIO). Iodide salts were also considered as the iodine atom source. In line with the results of Kita and co-workers, both PIFA and PIDA are prone to generate radicals when mixed with halogen salts having cations different to ammonium.[40] The topic about radical generation is outside of this work scope; hence PhIO was chosen as the iodine(III) reagent. Initial trials used potassium iodide in methanol to solubilize both PhIO and KI. In this way, **1** was isolated in a 17% yield (entry 3). The reaction in water as solvent showed poor conversion (<5%) and large quantities of unreacted starting material (entry 4). The use of 5 mol % of sulfuric acid as additive significantly increased the yield to 86% in methanol (entry 5) and 25% in water (entry 6). The (1:1) solvent combination of methanol and water did not improve the yield (entry 7); however, it demonstrated that the reaction is water tolerant. As acidic media gave considerably better yields, another protic iodide salt was explored. Surprisingly, use of 1.2 equiv of PhIO and 2.4 equiv of ammonium iodide in methanol at 23 °C provided 1-iodo-2-naphthol in nearly quantitative yield (98%) within 20 min (entry 8). This result highlighted several aspects of the process, such as the fast and high-yield reactions as well as its economical iodine atom source. Additionally, we avoid the possibility of the radical generation in the process since the ammonium cation is used. Changing the solvent to acetonitrile lowered the yield to 70% (entry 9). Decreasing the amount of PhIO (to 1.0 and 0.5 equiv) provided yields of only 80% and 40%, respectively (entries 10 and 11). On the other hand, the yield was not improved by decreasing the ammonium iodide loading to 1.5 equiv (entry 12). At this point, the possibility of the iodide anion oxidation generating molecular iodine was considered, which could be the iodinating active species in the process. To test this mechanistic hypothesis, experiments using molecular iodine in the absence of an iodine(III) reagent were carried out, using the conditions found to be best in the initial optimizations (entry 8). Thus, the reaction was tested with 1.0, 1.5, and 2.0 equiv of molecular iodine at 23 °C in methanol (entries 13–15) or trifluoroethanol (entry 16). Interestingly, the desired iodination was achieved with yields of 58%, 52%, 46%, and 57%, respectively. However, the yields remain far below that obtained in entry 8; thus molecular iodine was ruled out as the iodinating species. Control experiments were then carried out in order to complete the optimization. The use of PhIO in the absence of ammonium salt led to no reaction (entry 17). Similarly, the use of ammonium iodide without the iodine(III) reagent failed to produce **1**.

This set of experiments allowed reliable determination of the optimal iodination conditions; thus we proceeded to explore

Table 1. Optimization of the Iodine(III)-Mediated Electrophilic Iodination of 2-Naphthol[a]



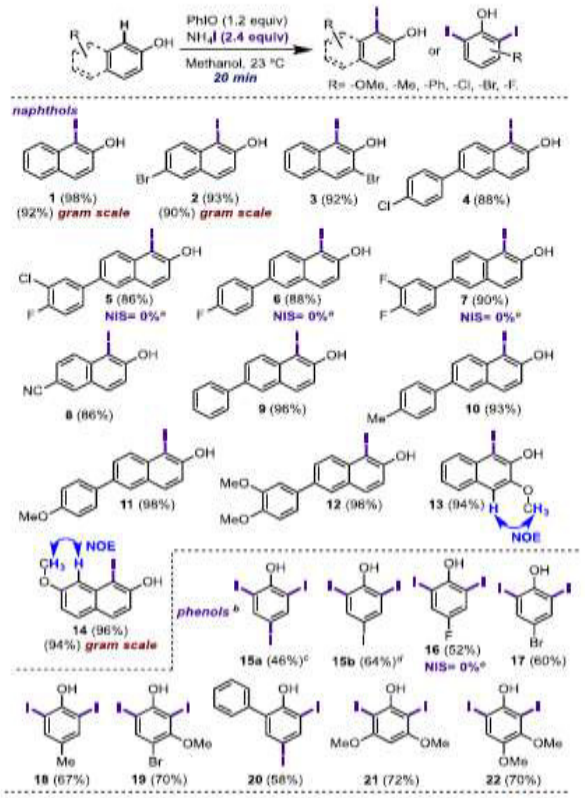
entry	iodine(III) (equiv)	I source (equiv)	solvent	yield (%)[b]
1	PIDA (1.2)	AlI_3 (2.4)	MeCN	[c]
2	PIFA (1.2)	AlI_3 (2.4)	MeCN	[c]
3	PhIO (1.2)	KI (2.4)	MeOH	17
4	PhIO (1.2)	KI (2.4)	H2O	<5
5	PhIO (1.2)	KI (2.4)	MeOH	86[d]
6	PhIO (1.2)	KI (2.4)	H_2O	25[d]
7	PhIO (1.2)	KI (2.4)	MeOH/H_2O	38
8	***PhIO (1.2)***	***NH_4I (2.4)***	***MeOH***	***98***[e]
9	PhIO (1.2)	NH_4I (2.4)	MeCN	70
10	PhIO (1.0)	NH_4I (2.4)	MeOH	80
11	PhIO (0.5)	NH_4I (2.4)	MeOH	40
12	PhIO (1.2)	NH_4I (1.5)	MeOH	68
13		I_2 (1.0)	MeOH	58
14		I_2 (1.5)	MeOH	52
15		I_2 (2.0)	MeOH	46
16		I_2 (1.0)	TFE	57
17	PhIO (1.2)		MeOH	n.r.
18		NH_4I (2.4)	MeOH	n.r.

[a]Reaction conditions: 2-naphthol (0.5 mmol), solvent (0.15 M), open flask. [b]Yields as average of two runs. [c]I_2 was obtained. [d]5 mol % of H_2SO_4 used as additive. [e]Yields as average of three runs. n.r. = no reaction observed.

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

the scope of the new procedure with respect to changes in the aryl unit (Scheme 2).

Scheme 2. Phenol Ring Scope in the PhIO/NH_4I-Mediated Iodination of Phenols[a]

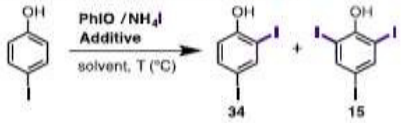


[a]Reaction conditions: 2-naphthol (0.5 mmol), methanol (0.15 M), open flask. [b]PhIO (2.4 equiv)/NH_4I (4.8 equiv) were used. [c]Synthesized from phenol. [d]Synthesized from 4-iodophenol. [e]Reaction conditions: phenol (0.5 mmol), NIS (1.2 equiv), TFA (10 mol %), MeCN (0.15 M) at 23 °C by 12 h.

Several monoannular phenols and naphthols were submitted to our optimized iodination conditions. We observed that the reaction shows great tolerance toward naphthols containing the electron-withdrawing groups bromine (**2** and **3**), chlorine (**4** and **5**), fluorine (**6** and **7**), or nitrile (**8**), as well as the electron-donating groups phenyl (**9**), tolyl (**10**), and methoxyl (**11** and **12**). The reaction took place regioselectively at the *ortho* position with respect to the hydroxyl group, in no more than 20 min and with good yields ranging from 86% to 98%. The NOESY correlation of methoxyl protons in **13** and **14** with the *ortho* protons at C4 and C8 demonstrated the observed regiochemistry (Scheme 2). Moreover, the scalability was illustrated by the gram-scale preparation of **1**, **2**, and **14** in excellent yields (93−98%). On the other hand, when the procedure was applied to the iodination of monoannular phenols, a mixture of unreacted starting material, mono- and diiodinated derivatives was obtained, in which case an additional amount of PhIO/NH_4I was necessary to complete the reaction. Under these conditions, a range of phenols bearing electron-attracting fluorine, bromine, or iodine groups (**15**−**17**), as well as electron-rich phenols bearing methyl, methoxyl, and phenyl groups (**18**−**22**), were diiodinated in moderate to good yields (46−72%). Although it was expected to obtain the monoiodination products, the synthesized derivatives **15**−**22** are also important building blocks in synthetic chemistry.[8−10] On the other hand, the reactivity of our system was compared against the commonly used reagent NIS. Different phenols containing strong electron-withdrawing groups (**5**−**7** and **16**), which usually show great difficulties to react, undergo iodination reaction with moderate (52%) to excellent yields (86−90%) by using our system.

From this initial scope exploration, it is possible to conclude that the optimized conditions allow the controlled monoiodination of naphthols, while phenols are diiodinated. Inspired by these results, we were interested in developing controlled monoiodination reactions; thus a new optimization was initiated using 4-iodophenol as the model system (Table 2).

Table 2. Optimization of the PhIO/NH_4I-Mediated, Controlled Monoiodination of Phenols[a]



entry	PhIO (equiv)	NH_4I (equiv)	additive (equiv)	solvent	T (°C)	yield (%) 34/15
1	1.2	2.4		MeOH	23	--/64
2	1.2	2.0		MeOH	23	--/56
3	1	1.5		MeOH	23	--/60
4	1.2	2.4		MeCN	23	n.r.
5	1.2	2.4		H_2O	23	n.r.
6	1.2	2.4		MeOH	0	25/36
7	1.2	2.4	K_3PO_4 (1.5)	MeOH	0	80/5
8	***1.2***	***2.4***	***K_3PO_4 (1.0)***	***MeOH***	***0***	***88***/--
9[b]	1.2	2.4	H_2SO_4	MeOH	23	--/55
10[b]	1.2	2.4	H_2SO4	MeOH	0	10/28

[a]Reaction conditions: 4-iodophenol (0.5 mmol), solvent (0.15 M), open flask. [b]5 mol % of additive was used. n.r. = no reaction observed.

The optimal previous conditions afforded the diiodinated phenol **15** in 64% yield at 23 °C (Table 2, entry 1). By reducing the NH_4I loading to 2.0 or 1.5 equiv, and the PhIO loading to 1.0 equiv, **15** was systematically obtained in lower yields (entries 2 and 3). Changing the solvent to acetonitrile or water did not yield any product (entries 4 and 5). However, when the reaction was carried at 0 °C in methanol, a mixture of mono- and diiodinated phenols was observed, but the starting material was not fully consumed (entry 6). This result highlights the important role of the temperature in controlling the reaction. At this point, we hypothesized that a slightly acidic media could be influencing the outcome due to the inherently acidic nature of NH_4I, as well as the release of H^+ after the aromatization process. This could be eroding the control over the monoiodination process, since it is well-known that acidic media accelerate the iodination process, leading to unwanted polyhalogenation.[22,27,31−33] In consequence, we decided to buffer the reaction pH by using tribasic

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

potassium phosphate as an additive.[41] To our delight, the use of 1.5 equiv of K_3PO_4 at 0 °C gave rise to the monoiodination product **34** in 80% yield in *only 5 min of reaction*, in addition to a small amount (5%) of the diiodination product **15** (entry 7). Upon decreasing the phosphate salt loading to 1.0 equiv, the yield of **34** increased to 88% and the diiodination derivative **15** was not observed. These reaction conditions finally facilitated the totally ***controlled monoiodination*** of the 4-iodophenol. To validate if the acidic medium is responsible for the observed diiodination in the reaction, we performed the reaction with 5 mol % of sulfuric acid as additive. Under these conditions (at 23 °C), the complete consumption of the starting material was observed, but with only a 55% yield to the diiodination product **15**, in a complex reaction mixture (entry 9). When the reaction was carried at 0 °C, a mixture of **34** and **35** was obtained (entry 10). These results strongly point toward the diiodination being promoted by acidic medium.

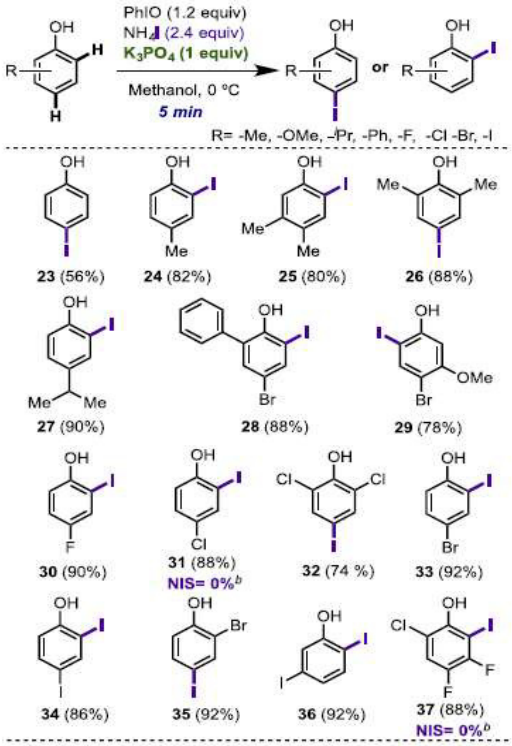
After this analysis and determination of the optimal conditions, we explored the scope of the controlled monoiodination of phenols (Scheme 3).

A number of monoannular phenols bearing groups with different electronic nature were tested in the controlled monoiodination reaction. The exploration started with the simplest phenol (hydroxybenzene), leading to the monoiodinated product **23** in 56% yield in only 5 min. Neither the *ortho* regioisomer nor the diiodinated product was observed. Other monoiodinated phenols bearing alkyl groups, such as one (**24**) or two methyl groups (**25** and **26**) or an isopropyl (**27**), were successfully obtained in good yields ranging from 80% to 90%. Phenols containing electron-rich groups such as phenyl or methoxyl (**28** and **29**) afforded excellent monoiodination yields (88% and 78%). Additional examples involving phenols with the electron-attracting fluoride (**30**), chloride (**31** and **32**), bromide (**33** and **35**), or iodide (**34** and **36**) groups were tolerated very well, leading to the totally controlled introduction of a single iodine atom in high to excellent yields (86−92%). Even the strongly deactivated 2-chloro-4,5-difluorophenol led to the monoiodinated **37** in 88% yield. This starting phenol as well as the 4-chlorophenol did not react under the typically iodination conditions with NIS.

This set of monoiodinated phenols obtained demonstrated the scope and the excellent applicability of this methodology, allowing the use of both electron-rich and electron-poor monoannular phenols. The short reaction times (ca. 5 min.), good yields, and mild and open-flask reaction conditions are important aspects to be highlighted. To the best of our knowledge, this is the first report describing a totally controlled monoiodination of phenols using a buffered system.

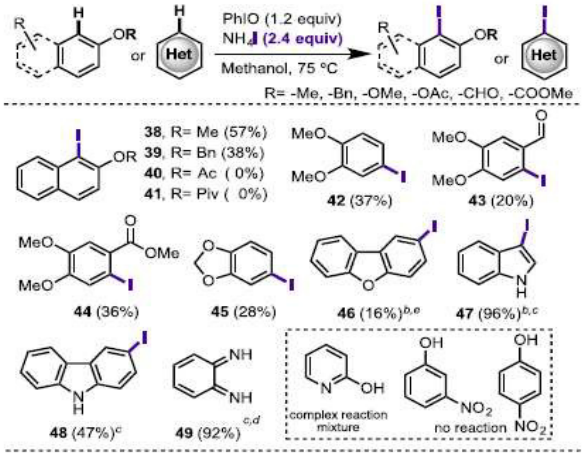
The following set of trials was devised to determine the tolerance of our procedure in the presence of (1) different functional groups at the phenolic oxygen, (2) functionalized phenols with more than one functional group, (3) functionalities other than phenol present in the aryl moiety, and (4) heterocycles (Scheme 4).

Scheme 3. Scope of the PhIO/NH_4I-Mediated, Controlled Monoiodination of Phenols[a]



[a]Reaction conditions: phenol (0.5 mmol), methanol (0.15 M), open flask. [b]Reaction conditions: phenol (0.5 mmol), NIS (1.2 equiv), TFA (10 mol %), MeCN (0.15 M) at 23 °C by 12 h.

Scheme 4. Functional Group Scope in the PhIO/NH_4I-Mediated Iodination of Arenes and Heteroarenes[a]



[a]Reaction conditions: arene (0.5 mmol), methanol (0.15 M), open flask. [b]One equivalent of NH_4I was used. [c]Reaction carried out at 23 °C. [d]*o*-Phenylenediamine was the starting material. [e]Combined yield of the mono- and diiodination at the 2,8 positions in a (1.5:1) ratio.

The first attempts to carry out the iodination reaction were evaluated using 2-methoxynaphthalene as the model system. However, no reaction was observed when the standard conditions (PhIO 1.2 equiv/NH_4I 2.4 equiv, 23 °C) were applied, suggesting the importance of the hydroxyl group. By heating this reaction to 75 °C, using the same stoichiometry, the iodination provided a 57% yield of **38**. By increasing the

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

size of the alkyl group through the use of a benzyl-substituted substrate, iodide **39** was obtained in only 38% yield. When the acetyl **40** and pivaloyl **41** derivatives were submitted to the same reaction conditions, no product was formed. Functionalities at the aryl moiety other than phenol, such as phenol-ether (**42**), aldehyde (**43**), or ester (**44**), could only be iodinated in moderate to low yields (20−37%). Moreover, oxyheterocycles as well as nitrogenated heterocycles were tested. In these cases, the iodination of a 1,3-benzodioxole, dibenzofuran, as well as free N-H indoles and carbazoles (**45**−**48**) was achieved in low to excellent yields (16−96%) by using only 1 equiv of NH_4I. It is important to mention that dibenzofuran gave rise to a (1.5:1) ratio of mono- and diiodinated products. Finally, *o*-phenylenediamine gave rise to the 1,2-diimine oxidation product **51** in 91% yield rather than the expected iodination product. Other substrates such as pyridine-2-ol, as well as 3-nitro- and 4-nitrophneo, showed complex reaction mixtures or did not react even by heating at 75 °C for a period of 24 h.

A complementary scope exploration was considered in order to determine if different halogens can be introduced by changing the anion in the ammonium salt, thereby a range of phenols were examined (Scheme 5).

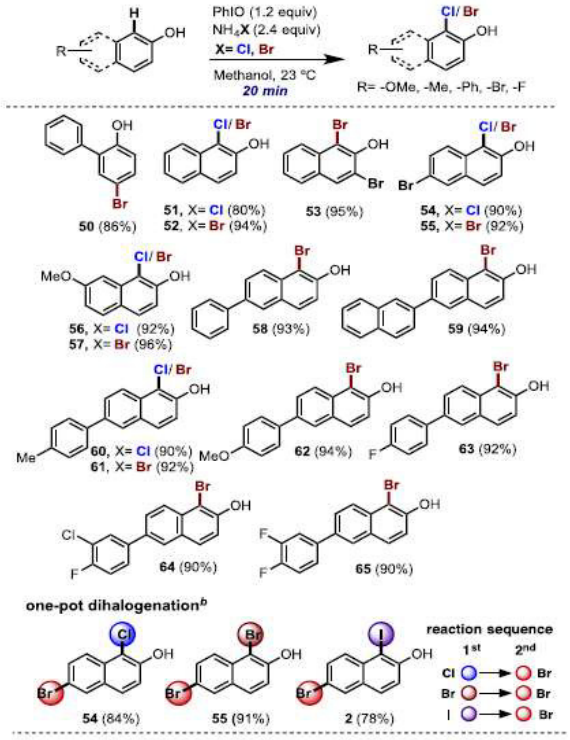
The ammonium chloride and bromide were mainly employed under the optimized standard conditions (Scheme 5) in order to introduce these halides into a range of phenols. In this way, 2-phenylphenol was brominated in 86% yield, giving rise to **50**. The chlorination and bromination of 2-naphthol, 6-bromo-2-naphthol, 7-methoxy-2-naphthol, and 6-(*p*-tolyl)-2-naphthol also produced their corresponding chlorinated and brominated derivatives **51** and **52**, **54**−**57**, **60**, and **61**, respectively, in 80−96% yields. A number of additional brominated phenols containing electron-withdrawing (**53**, **62**−**65**) and electron-donating groups (**58** and **59**) were isolated in high yields (90−95%), which demonstrated the excellent efficiency of our protocol. In fact, these described conditions resulted in a general improvement of our previous iodine(III)-mediated chlorination[38] and bromination[39] procedures. It is also important to mention that a very complex reaction mixture was observed when NH_4F was used, presumably due to formation of a strongly oxidizing reagent that degraded the starting material. To conclude the exploration of the scope of the halide salt, a one-pot two-halogenation reaction sequence was attempted. Thus, starting from 2-naphthol, the one-pot chlorination-bromination sequence afforded **54** in an 84% overall yield. Similarly, tandem bromination-bromination and iodination-bromination sequences gave rise to **55** and **2** in 91% and 78% yields, respectively.

In addition to its broad scope, these tests demonstrated the exciting and varied possibilities of this reaction method, including high-yielding bis-iodination, fully controlled mono-iodination, and chlorination or bromination of phenols possessing a free hydroxyl group.

To conclude the experimental part of this study, a series of reactions were devised to showcase the synthetic utility of the reaction (Scheme 6).

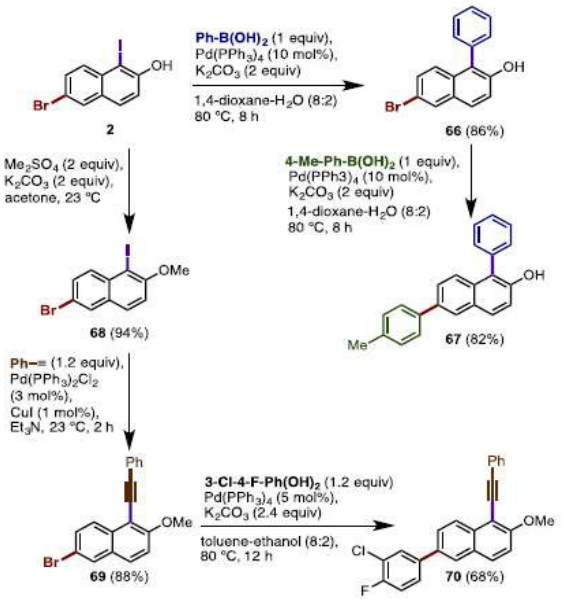
The synthetic applicability of the derivatives obtained through our procedure was illustrated with the compound 6-bromo-1-iodo-2-naphthol (**2**) which possesses two halide

Scheme 5. Scope of the NH_4X Salt in the PhIO/NH_4X-Mediated Chlorination and Bromination of Phenols[a]



[a]Reaction conditions: phenol (0.5 mmol), methanol (0.15 M), open flask. [b]Overall yield for the one-pot dihalogenation reaction using 2-naphthol as starting material.

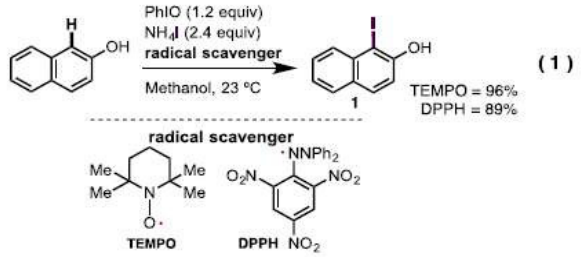
Scheme 6. Synthetic Utility of the Synthesized Halogenated Derivatives



DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

groups with different reactivities. We considered the synthesis of **2** as an excellent opportunity to carry out two distinct orthogonal reaction sequences: sequential double Suzuki cross-coupling, and Sonogashira alkynylation/Suzuki cross-coupling. In the first sequence, regioselective Suzuki cross-coupling at the C1 atom of **2** with phenyl boronic acid led to the formation of the 6-bromo-1-phenyl-2-naphthol **66** in 86% yield. The second Suzuki cross-coupling with 4-methylboronic acid introduced the *p*-tolyl fragment exclusively at the C6 position, affording the diarylated naphthol **67** in 82% yield. The second sequence started with the *O*-methylation of **2**, producing **68** in 94% yield. This compound was submitted to Sonogashira alkynylation conditions, giving rise to **69** in 88% yield with regioselective functionalization at the C1 position. The methylated alkynyl naphthol underwent subsequent Suzuki cross-coupling with (3-chloro-4-fluorophenyl)boronic acid, leading to the formation of **70** in 68% yield with the regioselective functionalization at C6 of the naphthol.

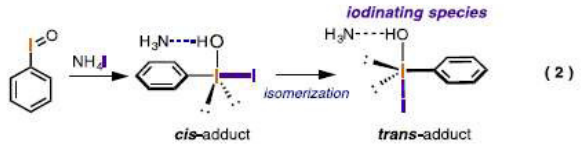
Finally, in order to gain more insight into the reaction mechanism, we decided to carry out the iodination of 2-naphthol in the presence of the radical scavengers TEMPO[42] (tetramethylpiperidine *N*-oxide) and DPPH (2,2-diphenyl-1-picrylhydrazyl) in order to determine if a radical or cationic pathway was operating (eq 1).



(1)

The presence of 1 equiv of TEMPO or DPPH did not affect the reaction, and **1** was isolated in 96% and 89% yield, respectively. This experiment ruled out a radical mechanism in the process, suggesting a cationic iodination as the more feasible pathway.

To provide a preliminary determination of the iodinating active species involved in this process, a DFT computational study was performed at the B3LYP/DGDZVP level[43] (eq 2).



(2)

The enthalpy and Gibbs free energy of the reaction between PhIO and NH_4I were calculated to evaluate the energetic stability of the obtained product. The resulting values strongly suggested the formation of the *trans*-adduct PhII(OH)·NH_3 as the most plausible active iodinating species. This hypervalent iodine(III) derivative is obtained after the isomerization of its corresponding *cis*-adduct which is formed initially as the kinetic product, while the aforementioned *trans*-PhII(OH)·NH_3 is the thermodynamic compound (see Supporting Information (SI) for full details).[44] We verified that the optimized geometry of the iodinating active species corresponds to a minimum on the potential energy surface by performing harmonic frequency calculations at 298 K and 1 atm (selected bond lengths and angles are included; see SI).

On the other hand, the electrophilic nature of the plausible iodinating species was analyzed by using the Fukui functions as the covalent descriptor[45,46] (Figure 2).

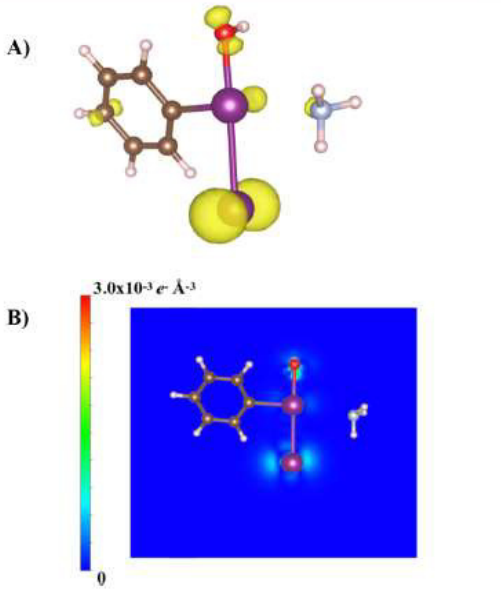


Figure 2. (a) The Fukui function for electrophilic attack of the plausible iodinating active species and (b) its 2D projection. Color code for atoms in brackets: C (brown), O (red), I (purple), (N) light blue, and H (pink).

The highest values of the calculated Fukui function (Figure 2a) showed the most electrophilic site[47] at the terminal iodine atom as an electrophilic center[48] which is identified with the isosurface in yellow color. It is clearly observed that the terminal iodine is the most electrophilic atom of the adduct PhII(OH)·NH_3, which is in agreement with our proposed cationic iodination mechanism. A 2D projection of the electrophilic form of the Fukui function (Figure 2b) is illustrated to evaluate the reactivity and susceptibility of the iodinating adduct toward electrophilic attacks. The full results of this mechanic study will be published separately.

■ CONCLUSIONS

In summary, we have developed a new hypervalent iodine(III)-based iodination procedure of phenols by using iodosylbenzene (PhIO) and ammonium iodide (NH_4I) as an inexpensive source of iodine atoms. This protocol was applied to a wide range of different arenes including aromatic and heteroaromatic derivatives. The best yields were obtained with phenols having at least one free hydroxyl group, and total control over the di- or monoiodination was achieved by buffering the reaction with tribasic potassium phosphate (K_3PO_4). This novel procedure takes place under mild, open-flask, one-step, and operationally simple reaction conditions with short reaction times (5−20 min) and high yields. Initial mechanistic investigations showed PhII(OH)·NH_3 to be the most plausible iodinating species in the process.

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

EXPERIMENTAL SECTION

Organic Synthesis. General Information. All moisture- and oxygen-sensitive reactions were carried out in flame-dried round-bottom flasks under an inert atmosphere of nitrogen. Unless otherwise specified, all commercial materials were used as received without further purification. Anhydrous solvents were purchased from Sigma-Aldrich in SureSeal bottles. Column chromatography was performed using silica gel of sizes 100−200 and 230−400 mesh (Sigma-Aldrich). Thin layer chromatography was performed with TLC silica gel 60 F256 plates, and visualization was effected with short wavelength UV light (254 nm). Compounds were characterized using ^{1}H NMR and ^{13}C NMR. (Copies of ^{1}H NMR and ^{13}C NMR spectra are provided for all the compounds in the SI.) Data of known compounds were compared with existing literature characterization data, and the references are given. ^{1}H and ^{13}C NMR spectra were recorded with 500 MHz and Bruker advance 400 MHz instruments using deuterated solvents purchased from Sigma-Aldrich like $CDCl_3$. ^{1}H spectra were referenced with tetramethyl silane (TMS, 0.0 ppm) or chloroform ($CDCl_3$, 7.26 ppm) and are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (δ = 77.16 ppm). All the starting materials were synthesized according to reported procedures in the literature. High-resolution mass (HRMS) analyses were obtained under the following procedure: Samples were introduced by direct infusion at 3 μL min^{-1} to the electrospray ionization (ESI) source of a quadrupole time-of-flight mass spectrometer (Bruker Daltonics ESI-QTOF-MS maXis impact), equipped with Data Analysis 4.1. ESI was operated in positive mode with ion spray voltage 4 500 V, nitrogen dry gas 4 L min^{-1}, drying temperature 180 °C, and gas pressure 0.4 bar. Mass calibration was accomplished based on sodium formate clusters. Chemical nomenclature was generated using Chemdraw. Infrared (IR) spectra were recorded using a PerkinElmer system 2000 FT-IR spectrometer. Melting points of solids were measured using a Fisher-Johns melting point apparatus.

Synthesis of Iodosylbenzene $(PhIO)_n$. In a 250 mL round-bottom flask was suspended bis(acetoxy)iodobenzene (PIDA) (10 g, 31.04 mmol, 1 equiv) in 150 mL of a 3 M NaOH solution. The reaction was strongly stirred to room temperature during 12 h. Then, a precipitate was formed which was filtered off and washed with cold water until pH of water was neutral. Then the solid was washed (3 × 10 mL) with $CHCl_3$ to remove impurities of PIDA. The obtained solid was dried at high vacuum without heating to yield $(PhIO)_n$ (6.2 g, 91%) as a yellowish solid. ***Caution!*** *$(PhIO)_n$ is explosive upon drying at 110 °C in vacuum conditions.*

General Procedure A. A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with the corresponding phenol (0.5 mmol, 1 equiv) and methanol (0.15 M) at 25 °C. After dissolving and obtaining a homogeneous mixture, NH_4X (1.2 mmol, 2.4 equiv) (X = Cl, Br, or I) was added and stirred for 2 min. Then iodosylbenzene (0.6 mmol, 1.2 equiv) was added and stirred at 25 °C until full consumption of the starting material (usually 5−20 min). To quench the reaction, AcOEt (5 mL) was added and concentrated in vacuo. Purification was carried out by column chromatography with the EtOAc-Hexanes system to give the desired product.

General Procedure B. A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with the corresponding phenol (0.5 mmol, 1 equiv) and methanol (0.15 M) at 0 °C. After dissolving and obtaining a homogeneous mixture, NH_4I (1.2 mmol, 2.4 equiv) was added and stirred for 2 min. Then K_3PO_4 (1 equiv) and iodosylbenzene (0.6 mmol, 1.2 equiv) were added and stirred at 25 °C until full consumption of the starting material (usually 5 min). To quench the reaction, AcOEt (5 mL) was added and concentrated in vacuo. Purification was carried out by column chromatography with the EtOAc-Hexanes system to give the desired product.

Suzuki−Miyaura Cross-Coupling Procedure. The starting materials of the examples **4**−**12**[68−70] and **58**−**65**[68−70] were synthesized by Suzuki−Miyaura cross-coupling according to the following procedure. A 50 mL round-bottom flask with a stir bar was fitted with a rubber septum and flame-dried under high vacuum. The flask was purged with argon and charged with $Pd(PPh_3)_4$ (155.5 mg, 0.1 mmol), K_2CO_3 (580.5 mg, 4.2 mmol), 6-bromonaphthalen-2-ol (443.9 mg, 2.0 mmol), boronic acid (4.0 mmol), 10.0 mL of 1,4-dioxane, and 2 mL of distilled water. The following boronic acids were purchased from Sigma-Aldrich and used as such without additional purification: 4-chlorophenylbronic acid for compound **4**; 3-chloro-4-fluorophenylboronic acid for compounds **5** and **64**; 4-fluorophenylboronic acid for compounds **6** and **63**; 3,4-difluorophenylboronic acid for compounds **7** and **65**; 4-cyanophenylboronic acid for compound **8**; phenylboronic acid for compounds **9** and **58**; 4-methylboronic acid for compounds **10**, **60**, and **61**; 4-methoxyphenyl boronic acid for compounds **11** and **62**; 3,4-dimethoxyphenylboronic acid for compound **12**; and 2-naphthylboronic acid for compound **59**. The reaction mixture was then heated at 80 °C for 8 h. After the reaction was cooled down to room temperature, the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The crude products were purified by flash chromatography on silica gel.

Examples in Scheme 2. *1-Iodonaphthalen-2-ol (1).*[21] The following compound was obtained according to the general procedure A, by using 2-naphthol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **1** (92 mg, 98%), gram scale (1.72 g, 92%), as a white solid. m.p. = 89−91 °C. R_f = 0.5 (5% EtOAc/Hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 1H), 7.76 (dd, J = 8.4, 3.3 Hz, 2H), 7.58 (t, 1H), 7.42 (t, 1H), 7.28 (d, J = 2.1 Hz, 1H), 5.79 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.9, 134.9, 130.7, 130.4, 129.8, 128.4, 128.4, 124.3, 116.9, 86.7. HRMS (ESI+): m/z calculated for $C_{10}H_8IO$ $[M + H]^+$ = 270.9620, found 270.9616.

6-Bromo-1-iodonaphthalen-2-ol (2).[49] The following compound was obtained according to the general procedure A, by using 6-bromonaphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **2** (73 mg, 93%), gram scale (1.41 g, 90%), as a white solid. m.p. = 85−87 °C. R_f = 0.2 (8% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3439, 3228, 2921, 1589. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 9.9 Hz, 1H), 7.82 (dd, J = 8.9, 5.2 Hz, 1H), 7.56 (dd, J = 8.7, 5.4 Hz, 2H), 7.27 (dd, J = 2.6 Hz, 1H), 5.81 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.1, 133.4, 132.1, 131.3, 130.4, 130.0, 129.6, 118.6, 117.5, 85.9. HRMS (ESI+): m/z calculated for $C_{10}H_7BrIO$ $[M + H]^+$ = 348.8725, found 348.8705.

3-Bromo-1-iodonaphthalen-2-ol (3). The following compound was obtained according to the general procedure A, by using 3-bromonaphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **3** (72 mg, 92%) as a white solid. m.p. = 67−69 °C. R_f = 0.14 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3390, 3023, 1560, 1429. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 6.22 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.7, 134.7, 132.5, 130.8, 129.9, 128.6, 127.4, 125.1, 109.6, 84.7. HRMS (EI): m/z calculated for $C_{10}H_6BrIO$ $[M]^+$ = 347.8647, found 347.8639.

1-Iodo-3-methoxynaphthalen-2-ol (4). The following compound was obtained according to the general procedure A, by using 3-methoxynaphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **4** (81 mg, 94%) as a white solid. m.p. = 73−75 °C. R_f = 0.5 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3328, 3012, 1620, 1478, 1439. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.12 (s, 1H), 6.58 (s, 1H), 4.04 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 146.6, 146.9, 130.8, 129.6, 127.7, 126.1, 126.3, 124.8, 106.6, 82.7,

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

56.9. HRMS (EI): m/z calculated for $C_{11}H_9IO2$ $[M]^+$ = 299.9647, found 299.9641.

1-Iodo-7-methoxynaphthalen-2-ol (5). The following compound was obtained according to the general procedure A, by using 7-methoxynaphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (6% EtOAc/Hexane) to afford the product **5** (83 mg, 96%), gram scale (1.62 g, 94%), as a white solid m.p. = 79−81 °C. R_f = 0.15 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3428, 3018, 1630, 1380, 1409. ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.7, 5.7 Hz, 2H), 7.28 (s, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 5.84 (s, 1H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.9, 154.4, 136.5, 130.6, 130.2, 124.9, 116.5, 114.3, 109.8, 85.6, 55.6. HRMS (ESI+): m/z calculated for $C_{11}H_{10}IO_2$ $[M + H]^+$ = 300.9725, found 300.9715.

1-Iodo-6-phenylnaphthalen-2-ol (6).[50] The following compound was obtained according to the general procedure A, by using 6-phenylnaphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **6** (66 mg, 96%) as a white solid. m.p. = 138−140 °C. R_f = 0.42 (8% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3410, 3020, 1585, 1472, 1430. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.7 Hz, 1H), 7.92 (s, 1H), 7.77 (t, J = 8.2 Hz, 2H), 7.68 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 3.3 Hz, 1H), 5.79 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.8, 140.4, 136.9, 134.5, 130.8, 130.8, 129.8, 128.9, 127.7, 127.4, 127.8, 126.1, 116.8, 85.9. HRMS (EI): m/z calculated for $C_{16}H_{11}IO$ $[M]^+$ = 345.9855, found 345.9847.

1-Iodo-6-(p-tolyl)naphthalen-2-ol (7).[50] The following compound was obtained according to the general procedure A, by using 6-(*p*-tolyl)naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (6% EtOAc/Hexane) to afford the product **7** (62 mg, 93%) as a white solid. m.p. = 132−134 °C. R_f = 0.55 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3210, 3040, 1680, 1600, 1530, 1482, 1454. ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.7 Hz, 1H), 7.88 (s, 1H), 7.77 (t, J = 8.2 Hz, 2H), 7.56 (d, J = 7.7 Hz, 2H), 7.24 (d, J = 4.1 Hz, 1H), 7.21 (s, 1H), 5.74 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 137.6, 137.4, 137.2, 134.0, 130.9, 130.9, 129.8, 127.8, 127.3, 125.8, 116.9, 86.8, 21.9. HRMS (EI): m/z calculated for $C_{17}H_{13}IO$ $[M]^+$ = 360.0011, found 360.0006.

1-Iodo-6-(4-methoxyphenyl)naphthalen-2-ol (8). The following compound was obtained according to the general procedure A, by using 6-(4-methoxyphenyl)naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (8% EtOAc/Hexane) to afford the product **8** (74 mg, 98%) as a white solid. m.p. = 140−142 °C. R_f = 0.12 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3398, 3040, 1598, 1498, 1440. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.7 Hz, 1H), 7.88 (s, 1H), 7.75 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 3.7 Hz, 1H), 7.01 (d, J = 8.3 Hz, 2H), 5.79 (s, 1H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.8, 153.7, 136.8, 133.8, 132.9, 130.8, 130.8, 130.4, 128.4, 127.8, 125.6, 116.9, 114.5, 86.8, 55.5. HRMS (EI): m/z calculated for $C_{17}H_{13}IO_2$ $[M]^+$ = 375.9960, found 375.9955.

6-(3,4-Dimethoxyphenyl)-1-iodonaphthalen-2-ol (9). The following compound was obtained according to the general procedure A, by using 6-(3,4-dimethoxyphenyl)-naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **9** (70 mg, 96%) as a white solid. m.p. = 132−134 °C. R_f = 0.15 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3330, 3020, 1610, 1491, 1425. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 9.6 Hz, 1H), 7.80−7.75 (m, 2H), 7.27 (d, J = 9.2 Hz, 2H), 7.21 (d, J = 1.7 Hz, 1H), 6.99 (d, J = 8.1, 4.2 Hz, 1H), 5.79 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.7, 149.4, 148.8, 136.8, 133.9, 133.9, 130.8, 130.7, 129.8, 127.6, 125.5, 119.6, 116.8, 111.6, 110.5, 85.9, 56.0. HRMS (EI): m/z calculated for $C_{18}H_{15}IO_3$ $[M]^+$ = 406.0066, found 406.0063.

6-(4-Chlorophenyl)-1-iodonaphthalen-2-ol (10). The following compound was obtained according to the general procedure A, by using 6-(4-chlorophenyl)naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (8% EtOAc/Hexane) to afford the product **10** (65 mg, 88%) as a white solid. m.p. = 160−162 °C. R_f = 0.20 (8% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3330, 3045, 1580, 1486, 1460. 1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 1.5 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 8.7, 1.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.44−7.40 (m, 2H), 7.24 (d, J = 6.7 Hz, 1H), 5.79 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.4, 138.8, 135.7, 134.9, 133.7, 131.2, 130.8, 129.8, 129.9, 128.8, 127.6, 126.2, 117.5, 85.8. HRMS (EI): m/z calculated for $C_{16}H_{10}ClIO$ $[M]^+$ = 379.9465, found 379.9460.

6-(4-Fluorophenyl)-1-iodonaphthalen-2-ol (11). The following compound was obtained according to the general procedure A, by using 6-(4-fluorophenyl)naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (12% EtOAc/Hexane) to afford the product **11** (67 mg, 88%) as a light yellowish solid. m.p. = 136−138 °C. R_f = 0.14 (20% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3035, 1580, 1485, 1454. ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 1.4 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.75 (dd, J = 8.7, 1.7 Hz, 1H), 7.67−7.63 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 7.17 (t, J = 8.7 Hz, 2H), 5.80 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.74 (d, J = 247.0 Hz), 154.8, 136.7 (d, J = 3.3 Hz), 136.9, 134.8 (d, J = 3.1 Hz), 131.2 (d, J = 17.9 Hz), 130.1, 128.9 (d, J = 8.0 Hz), 127.7, 126.1, 117.1, 115.9 (d, J = 21.5 Hz), 86.4. HRMS (EI): m/z calculated for $C_{16}H_{10}FIO$ $[M]^+$ = 363.9760, found 363.9753.

6-(4-Chloro-3-fluorophenyl)-1-iodonaphthalen-2-ol (12). The following compound was obtained according to the general procedure A, by using 6-(4-chloro-3-fluorophenyl)naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **12** (63 mg, 86%) as a light yellowish solid. m.p. = 142−144 °C. R_f = 0.55 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3440, 3140, 1680, 1498, 1420. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.7 Hz, 1H), 7.84 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.67 (t, J = 7.2 Hz, 2H), 7.53−7.47 (m, 1H), 7.22 (dd, J = 16.8, 9.0 Hz, 2H), 5.80 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.9 (d, J = 249.5 Hz), 154.3, 137.8 (d, J = 4.1 Hz), 134.8, 134.4, 131.8, 130.9, 129.8, 129.7, 127.4, 127.2 (d, J = 7.1 Hz), 126.7, 121.6 (d, J = 18.0 Hz), 117.7 (d, J = 13.7 Hz), 117.5, 86.1. HRMS (ESI−): m/z calculated for $C_{16}H_8ClFIO$ $[M - H]^-$ = 396.9298, found 396.9290.

6-(3,4-Difluorophenyl)-1-iodonaphthalen-2-ol (13). The following compound was obtained according to the general procedure A, by using 6-(3,4-difluorophenyl)naphthalen-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford the product **13** (67 mg, 90%) as a light yellowish solid. m.p. = 122−124 °C. R_f = 0.55 (20% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3040, 1600, 1498, 1445. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.74 (dd, J = 8.8, 1.7 Hz, 1H), 7.69−7.65 (m, 1H), 7.49−7.42 (m, 1H), 7.39−7.33 (m, 1H), 7.26−7.19 (m, 2H), 5.80 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.9, 151.9−150.9 (m), 150.6−148.8 (m), 137.7 (dd, J = 5.6, 3.9 Hz), 135.0, 134.4, 131.2, 130.9, 129.8, 127.2, 126.4, 123.7 (dd, J = 6.0, 3.3 Hz), 117.8 (d, J = 17.3 Hz), 117.3, 116.5 (d, J = 17.7 Hz), 86.0. HRMS (EI): m/z calculated for $C_{16}H_9F_2IO$ $[M]^+$ = 381.9666, found 381.9662.

6-Hydroxy-5-iodo-2-naphthonitrile (14).[50] The following compound was obtained according to the general procedure A, by using phenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **14** (75 mg, 86%) as a yellow solid. From 6-hydroxy-2-naphthonitrile. R_f = 0.55 (15% EtOAc/Hexane). ^1H NMR (500 MHz, DMSO) δ 8.43 (d, J = 1.1 Hz, 1H),

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

8.04 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.78 (dd, J = 8.8, 1.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO) δ 158.9, 137.6, 135.6, 131.6, 131.8, 128.9, 127.9, 119.6, 119.6, 105.9, 84.7.

*2,4,6-Triiodophenol (**15**).*[35] The following compound was obtained according to the general procedure A, by using phenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **15a** (116 mg, 46%) as a white solid. From 4-iodophenol, **15b** (160 mg, 64%). m.p. = 137−139 °C. R_f = 0.46 (4% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 2H), 5.69 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.8, 146.4, 83.9, 83.5. HRMS (ESI+): m/z calculated for $C_6H_4I_3O$ $[M + H]^+$ = 472.7396, found 472.7391.

*4-Fluoro-2,6-diiodophenol (**16**).* The following compound was obtained according to the general procedure A, by using 4-fluorophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **16** (65 mg, 52%) as a white solid. m.p. = 64−66 °C. R_f = 0.15 (6% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 290, 1580, 1498, 1465. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, 2H), 5.49 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.9 (d, J = 248.5 Hz), 150.8 (d, J = 3.0 Hz), 125.9 (d, J = 24.6 Hz), 80.6 (d, J = 8.5 Hz). HRMS (ESI−): m/z calculated for $C_6H_2FI_2O$ $[M - H]^-$ = 362.8179, found 362.8175.

*4-Bromo-2,6-diiodophenol (**17**).*[51] The following compound was obtained according to the general procedure A, by using 4-bromophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **17** (85 mg, 60%) as a white solid. m.p. = 115−117 °C. R_f = 0.4 (4% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 2H), 5.65 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.7, 140.9, 113.6, 82.6.

*2,6-Diiodo-4-methylphenol (**18**).*[51] The following compound was obtained according to the general procedure A, by using 4-methylphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **18** (100 mg, 67%) as a white solid. m.p. = 49−51 °C. R_f = 0.55 (6% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 2H), 5.59 (s, 1H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.4, 139.6, 133.8, 82.5, 19.7. HRMS (ESI+): m/z calculated for $C_7H_7I_2O$ $[M + H]^+$ = 360.8586, found 360.8577.

*4-Bromo-2,6-diiodo-3-methoxyphenol (**19**).* The following compound was obtained according to the general procedure A, by using 4-bromo-3-methoxyphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **19** (79 mg, 70%) as a white solid. m.p. = 64−68 °C. IR (neat) ν/cm^{-1} = 3382, 3060, 1613, 1485, 1454. R_f = 0.2 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 5.84 (s, 1H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.8, 154.6, 141.5, 107.4, 82.3, 76.4, 60.8. HRMS (EI): m/z calculated for $C_7H_5BrI_2O_2$ $[M]^+$ = 453.7562, found 453.7559.

*3,5-Diiodo-[1,1′-biphenyl]-2-ol (**20**).* The following compound was obtained according to the general procedure A, by using [1,1′-biphenyl]-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **20** (81 mg, 58%) as a colorless oil. R_f = 0.14 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3480, 3010, 1485, 1470, 1430. ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 1.7 Hz, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.51−7.37 (m, 5H), 5.58 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.9, 145.2, 139.5, 135.9, 130.7, 129.2, 128.6, 87.1, 83.7. HRMS (ESI−): m/z calculated for $C_{12}H_7I_2O$ $[M - H]^-$ = 420.8292, found 420.8263.

*2,6-Diiodo-3,5-dimethoxyphenol (**21**).*[52] The following compound was obtained according to the general procedure A, by using 3,5-dimethoxyphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **21** (190 mg, 72%) as a white solid. m.p. = 149−141 °C. R_f = 0.55 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3430, 2920, 1810, 1488, 1428. ^1H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.92 (s, 1H), 3.83 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.4, 154.9, 88.4, 64.5, 56.8. HRMS (ESI+): m/z calculated for $C_8H_9I_2O_3$ $[M + H]^+$ = 406.8641, found 406.8638.

*2,6-Diiodo-3,4-dimethoxyphenol (**22**).* The following compound was obtained according to the general procedure A, by using 3,4-dimethoxyphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (6% EtOAc/Hexane) to afford the product **22** (186 mg, 70%) as a white solid. m.p. = 150−152 °C. R_f = 0.5 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3030, 1595, 1492, 1430. ^1H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.92 (s, 1H), 3.83 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.3, 154.9, 130.8, 128.8, 88.4, 68.7, 64.5, 56.8. HRMS (EI): m/z calculated for $C_8H_8I_2O_3$ $[M]^+$ = 405.8563, found 405.8558.

Examples in Scheme 3. *4-Iodophenol (**23**).*[21] The following compound was obtained according to the general procedure B, by using phenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **23** (133 mg, 56%) as a white solid. m.p. = 80−82 °C. R_f = 0.5 (6% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.7 Hz, 2H), 6.55 (d, J = 7.6 Hz, 2H), 4.91 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.8, 138.9, 117.9, 82.8.

*2-Iodo-4-methylphenol (**24**).*[21] The following compound was obtained according to the general procedure B, by using 4-methylphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **24** (178 mg, 82%) as a white solid. m.p. = 96−98 °C. R_f = 0.55 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 1.4 Hz, 1H), 7.04 (dd, J = 8.2, 1.6 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 5.15 (s, 1H), 2.25 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.9, 138.4, 132.1, 130.9, 114.8, 85.5 20.8.

*2-Iodo-4,5-dimethylphenol (**25**).*[53] The following compound was obtained according to the general procedure B, by using 4,5-dimethylphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **25** (176 mg, 80%) as a white solid. m.p. = 50−52 °C. R_f = 0.12 (8% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.79 (s, 1H), 5.04 (s, 1H), 2.18 (s, 3H), 2.15 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.80, 139.6, 138.6, 130.9, 116.4, 81.7, 19.9, 18.9.

*4-Iodo-2,6-dimethylphenol (**26**).*[51] The following compound was obtained according to the general procedure B, by using 2,6-dimethylphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (6% EtOAc/Hexane) to afford the product **26** (178 mg, 88%) as a white solid. m.p. = 96−98 °C. R_f = 0.2 (10% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 2H), 4.62 (s, 1H), 2.19 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.8, 137.1, 125.7, 82.3, 15.5.

*2-Iodo-4-isopropylphenol (**27**).*[54] The following compound was obtained according to the general procedure B, by using 4-isopropylphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **27** (174 mg, 90%) as a colorless liquid. R_f = 0.55 (8% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.41 (m, 1H), 7.02 (dd, J = 8.3, 2.0 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 5.05 (s, 1H), 2.72 (hept, J = 13.7, 6.9 Hz, 1H), 1.13 (d, J = 6.0 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.8, 143.3, 135.8, 128.3, 114.8, 85.6, 32.9, 24.6.

*5-Bromo-3-iodo-[1,1′-biphenyl]-2-ol (**28**).* The following compound was obtained according to the general procedure B, by using 5-bromo-[1,1′-biphenyl]-2-ol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **28** (66 mg, 88%) as a yellowish liquid. R_f = 0.55 (10% EtOAc/Hexane). IR

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

(neat) ν/cm^{-1} = 3360, 3080, 1540, 1486, 1480. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.51−7.36 (m, 6H), 5.57 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.4, 139.5, 135.9, 133.5, 129.9, 128.9, 128.9, 128.5, 113.3, 86.6. HRMS (ESI−): m/z calculated for $C_{12}H_7BrIO$ $[M - H]^-$ = 372.8730, found 372.8727.

4-Bromo-2-iodo-5-methoxyphenol (29).[55] The following compound was obtained according to the general procedure B, by using 4-bromo-5-methoxyphenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **29** (66 mg, 78%) as a yellow liquid. R_f = 0.55 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.62 (s, 1H), 5.26 (s, 1H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.6, 155.4, 139.9, 103.9, 99.4, 73.8, 56.6. HRMS (ESI+): m/z calculated for $C_7H_7BrIO_2$ $[M + H]^+$ = 328.8674, found 328.8661.

4-Fluoro-2-iodophenol (30).[56] The following compound was obtained according to the general procedure B, by using 4-fluorophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **30** (96 mg, 90%) as a white solid. m.p. = 118−120 °C. R_f = 0.55 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.6, 2.9 Hz, 1H), 7.02−6.96 (m, 1H), 6.93 (dd, J = 9.0, 4.9 Hz, 1H), 5.11 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.6 (d, J = 243.4 Hz), 151.6 (d, J = 2.5 Hz), 124.5 (d, J = 25.4 Hz), 117.1 (d, J = 23.1 Hz), 115.5 (d, J = 7.8 Hz), 84.6.

4-Chloro-2-iodophenol (31).[17] The following compound was obtained according to the general procedure B, by using 4-chlorophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **31** (87 mg, 88%) as a white solid. m.p. = 76−78 °C. R_f = 0.4 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.7, 2.4 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 5.29 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.9, 137.3, 130.9, 126.5, 115.8, 85.6.

2,6-Dicholoro-4-iodophenol (32).[71] The following compound was obtained according to the general procedure B, by using 2,6-dichlorophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **32** (65 mg, 74%) as a white solid. R_f = 0.22 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 5.83 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.7, 136.6, 122.5, 80.5.

4-Bromo-2-iodophenol (33).[17] The following compound was obtained according to the general procedure B, by using 4-bromophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **33** (79 mg, 92%) as a white solid. m.p. = 70−72 °C. R_f = 0.22 (8% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.7, 2.3 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.28 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.3, 139.8, 133.7, 116.3, 113.6, 86.1.

2,4-Diiodophenol (34).[51] The following compound was obtained according to the general procedure B, by using 4-iodophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **34** (68 mg, 86%) as a colorless needle. m.p. = 72−74 °C. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 2.3 Hz, 1H), 7.51 (dd, J = 8.5, 2.3 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.32 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.3, 145.7, 139.4, 117.9, 87.9, 82.9.

2-Bromo-4-iodophenol (35).[57] The following compound was obtained according to the general procedure B, by using 2-bromophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **35** (79 mg, 92%) as a white solid. m.p. = 52−54 °C. R_f = 0.14 (8% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 1.5 Hz, 1H), 7.51 (dd, J = 8.4, 2.3 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 5.52 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.5, 139.7, 138.7, 118.3, 111.6, 82.6.

2,5-Diiodophenol (36). The following compound was obtained according to the general procedure B, by using 3-iodophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **36** (73 mg, 92%) as a white solid. m.p. = 68−70 °C. R_f = 0.14 (5% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3390, 3023, 1580, 1450, 1429. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, J = 4.8, 3.4 Hz, 2H), 7.00 (dd, J = 8.3, 1.3 Hz, 1H), 5.29 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.0, 139.2, 131.0, 124.5, 94.4, 85.3. HRMS (ESI−): m/z calculated for $C_6H_4I_2O$ $[M - H]^-$ = 345.8352, found 345.8350.

6-Chloro-3,4-difluoro-2-iodophenol (37). The following compound was obtained according to the general procedure B, by using 6-chloro-3,4-difluorophenol as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **37** (92 mg, 98%) as a white solid. m.p. = 80−82 °C. R_f = 0.5 (5% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3385, 3080, 1590, 1486, 1427. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, J = 8.5 Hz, 1H), 5.86 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.6 (d, J = 14.5 Hz), 149.8−149.1 (m), 144.1 (dd, J = 249.2, 15.8 Hz), 120.1 (d, J = 21.0 Hz), 101.8 (dd, J = 7.7, 4.2 Hz), 73.3 (d, J = 25.7 Hz). HRMS (EI): m/z calculated for $C_6H_2ClF_2IO$ $[M]^+$ = 289.8807, found 289.8803.

Examples in Scheme 4. The starting materials for the examples **38**−**41**[39,67] were synthesized according to the previously described procedures.

2-Methoxynaphthalene.[39,67] A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-naphthol (2 mmol), dimethyl sulfate (2 mmol), and 3 mL of a solution (2 M) of Na_2CO_3. After dissolving in 8 mL of acetonitrile, the mixture was stirred at 25 °C overnight. After this period, the starting material was fully consumed judging by TLC. To quench the reaction, AcOEt (5 mL) was added and concentrated in vacuo. Purification was carried out by column chromatography with the EtOAc-Hexanes system to give the desired product.

2-Benzyloxynaphthalene.[39,67] A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-naphthol (2 mmol), benzyl bromide (2 mmol), and 3 mL of a solution (2 M) of Na_2CO_3. After dissolving in 8 mL of acetonitrile, the mixture was stirred at 25 °C overnight. After this period, the starting material was fully consumed judging by TLC. To quench the reaction, AcOEt (5 mL) was added and concentrated in vacuo. Purification was carried out by column chromatography with the EtOAc-Hexanes system to give the desired product.

2-Acetylnaphthalene.[39,67] A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-naphthol (2 mmol), acetyl chloride (2 mmol), and triethylamine (2 mmol). After dissolving in 8 mL of dichloromethane, the mixture was stirred at 25 °C overnight. After this period, the starting material was fully consumed judging by TLC. To quench the reaction, AcOEt (5 mL) was added and concentrated in vacuo. Purification was carried out by column chromatography with the EtOAc-Hexanes system to give the desired product.

Naphthalene-2-yl Pivalate.[39,67] A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-naphthol (2 mmol), pivaloyl chloride (2 mmol), and triethylamine (2 mmol). After dissolving in 8 mL of dichloromethane, the mixture was stirred at 25 °C overnight. After this period, the starting material was fully consumed judging by TLC. To quench the reaction, AcOEt (5 mL) was added and concentrated in vacuo. Purification was carried out by column chromatography with the EtOAc-Hexanes system to give the desired product.

1-Iodo-2-methoxynaphthalene (38).[21] The following compound was obtained according to a modified general procedure A, by using 2-methoxynaphthalene as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **38** (52 mg, 57%) as a white solid. m.p. = 86−88 °C. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.1 Hz,

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

1H), 7.54 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.03 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.6, 135.6, 131.2, 130.7, 129.9, 128.9, 128.2, 124.6, 112.9, 87.7, 57.4.

*2-(Benzyloxy)-1-iodonaphthalene (**39**).*[58] The following compound was obtained according to a modified general procedure A, by using 2-(benzyloxy)naphthalene as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **39** (30 mg, 38%) as a white solid. m.p. = 84−86 °C. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.56 (t, J = 10.2 Hz, 3H), 7.40 (q, J = 7.5 Hz, 3H), 7.33 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 5.32 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.8, 136.6, 135.7, 131.6, 130.3, 130.1, 128.6, 128.9, 128.9, 127.9, 127.4, 124.6, 114.7, 89.5, 71.9.

*4-Iodo-1,2-dimethoxybenzene (**42**).*[54] The following compound was obtained according to a modified general procedure A, by using 1,2-dimethoxybenzene as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **42** (71 mg, 37%) as a yellow liquid. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, J = 11.1, 4.6 Hz, 1H), 7.09 (s, 1H), 6.77 (d, J = 9.8, 4.9 Hz, 1H), 4.01 (s, 3H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.8, 149.2, 129.7, 120.8, 113.8, 111.3, 82.3, 55.9, 55.8.

*2-Iodo-4,5-dimethoxybenzaldehyde (**43**).*[33] The following compound was obtained according to a modified general procedure A, by using 4,5-dimethoxybenzaldehyde as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **43** (36 mg, 20%) as a white solid. R_f = 0.5 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.37 (s, 1H), 7.21 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 194.9, 154.5, 149.9, 128.4, 121.8, 111.2, 92.7, 56.9, 56.8.

*Methyl 2-Iodo-4,5-dimethoxybenzoate (**44**).*[59] The following compound was obtained according to a modified general procedure A, by using methyl 3,4-dimethoxybenzoate as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **44** (59 mg, 36%) as a white solid. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39 (s, 1H), 3.91 (s, 6H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 166.5, 152.7, 148.8, 126.9, 123.8, 113.9, 84.8, 56.4, 56.8, 52.4.

*5-Iodobenzo[d][1,3]dioxole (**45**).*[54] The following compound was obtained according to a modified general procedure A, by using benzo[d][1,3]dioxole as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **45** (58 mg, 28%) as a liquid. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 5.3 Hz, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.07 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.8, 147.9, 130.7, 117.9, 110.6, 101.5, 82.5.

*2-Iododibenzo[b,d]furan (**46**).*[72] The following compound was obtained according to a modified general procedure A, by using dibenzo[b,d]furan as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **46** (58 mg, 16%) as a white solid in a 1.5:1 mixture with its corresponding 2,8-diiododibenzo[b,d]furane. R_f = 0.15 (4% EtOAc/Hexane). Signals for monoiodinated derivative. ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.74 (t, J = 12.0, 8.6, 1.8 Hz, 2H), 7.57 (d, J = 8.3 Hz, 1H), 7.51−7.46 (m, 1H), 7.36 (dt, J = 8.6, 3.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.3, 155.6, 136.4, 135.6, 129.8, 129.6, 127.9, 123.1, 120.8, 113.8, 113.7, 111.8, 85.7.

*3-Iodo-1H-indole (**47**).*[60] The following compound was obtained according to a modified general procedure A, by using 1*H*-indole as starting material and NH_4I (iodosylbenzene and ammonium iodide were used in 1 equiv each). The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford the product **47** (99.5 mg, 96%) as a white solid. R_f = 0.54 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.22−7.10 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 135.6, 129.8, 128.4, 123.2, 121.3, 120.8, 111.7, 57.6.

*3-Iodo-9H-carbazole (**48**).*[61,64] The following compound was obtained according to a modified general procedure A, by using 9*H*-carbazole as starting material and NH_4I (reaction was in reflux overnight). The crude material was purified by flash column chromatography over silica gel with the system (3% EtOAc/Hexane) to afford the product **48** (58 mg, 47%) as a liquid. R_f = 0.5 (5% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 1.5 Hz, 1H), 8.08 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.66 (dd, J = 8.5, 1.7 Hz, 1H), 7.47−7.41 (m, 2H), 7.26−7.24 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 139.6, 138.9, 134.2, 129.9, 126.7, 126.7, 122.5, 120.6, 120.1, 112.7, 110.8, 82.3.

*Cyclohexa-3,5-diene-1,2-diimine (**49**).*[62] The following compound was obtained according to the general procedure A, by using *o*-phenylendiamine as starting material and NH_4I. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford the product **49** (56 mg, 38%) as a white solid. m.p. = 64−66 °C. R_f = 0.4 (6% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3045, 1600, 1495, 1450, 1265. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 1H), 5.74−5.70 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.6, 114.6, 106.2. HRMS (ESI+): m/z calculated for $C_6H_7N_2$ $[M + H]^+$ = 107.0609, found 107.0602.

Examples in Scheme 5. *5-Bromo-[1,1′-biphenyl]-2-ol (**50**).*[39] The following compound was obtained according to the general procedure A, by using [1,1′-biphenyl]-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **50** (63 mg, 86%) as a yellow oil. R_f = 0.12 (8% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (t, J = 8.0 Hz, 2H), 7.43 (d, J = 8.1 Hz, 3H), 7.37−7.34 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 5.22 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.7, 135.8, 132.7, 131.9, 130.2, 129.6, 129.0, 128.5, 117.7, 112.9.

*1-Chloronaphthalen-2-ol (**51**).*[38] The following compound was obtained according to the general procedure A, by using 2-napthol as starting material and NH_4Cl. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **51** (49 mg, 80%) as a white solid. R_f = 0.2 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.59 (t, J = 8.8 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.27 (s, 1H), 5.90 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 149.3, 131.0, 129.4, 128.4, 128.1, 127.5, 124.1, 122.7, 117.2, 113.3.

*1-Bromonaphthalen-2-ol (**52**).*[39] The following compound was obtained according to the general procedure A, by using 2-naphthol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **52** (69 g, 94%) as a white solid. R_f = 0.55 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.14 (s, 1H), 5.83 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 150.6, 132.4, 129.8, 129.4, 128.3, 127.9, 125.4, 124.2, 117.2, 106.2.

*1,3-Dibromonaphthalen-2-ol (**53**).*[39] The following compound was obtained according to the general procedure A, by using 3-bromonaphthalen-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **53** (65 mg, 95%) as a white solid. R_f = 0.10 (15% EtOAc/Hexane). ^1H NMR (500 MHz) δ 8.04 (d, J = 7.2 Hz, 2H), 7.70 (s, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 6.21 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.3, 131.9, 131.6, 129.9, 128.3, 127.4, 125.9, 125.2, 110.8. 106.5.

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

*6-Bromo-1-chloronaphthalen-2-ol (**54**).*[38] The following compound was obtained according to the general procedure A, by using 6-bromonaphthalen-2-ol as starting material and NH_4Cl. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **54** (65 mg, 90%) as a white solid. R_f = 0.2 (15% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 9.9 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 7.4 Hz, 1H), 5.84 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.7, 130.9, 130.5, 130.2, 129.7, 127.6, 124.7, 118.5, 118.1, 113.6.

*1,6-Dibromonaphthalen-2-ol (**55**).*[39] The following compound was obtained according to the general procedure A, by using 6-bromonaphthalen-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **55** (63 mg, 92%) as a white solid. R_f = 0.49 (10% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.58–7.51 (m, 2H), 7.19 (d, J = 8.7 Hz, 1H), 5.85 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.0, 131.8, 131.1, 130.7, 130.2, 128.5, 127.3, 118.4, 118.1, 106.2.

*1-Chloro-7-methoxynaphthalen-2-ol (**56**).*[38] The following compound was obtained according to the general procedure A, by using 1-chloro-7-methoxynaphthalen-2-ol as starting material. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **56** (55 mg, 92%) as a white solid. R_f = 0.55 (15% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 7.11 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.9 Hz, 1H), 5.90 (s, 1H), 3.97 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.4, 150.0, 132.6, 130.0, 128.2, 124.8, 116.7, 114.6, 112.6, 101.7, 55.5.

*1-Bromo-7-methoxynaphthalen-2-ol (**57**).*[39] The following compound was obtained according to the general procedure A, by using 7-methoxynaphthalen-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (8% EtOAc/Hexane) to afford the product **57** (66 mg, 96%) as a white solid. R_f = 0.55 (15% EtOAc/Hexane). ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 9.2 Hz, 2H), 7.26 (d, J = 2.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 6.98 (dd, J = 8.9, 2.5 Hz, 1H), 5.89 (s, 1H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.6, 150.9, 133.8, 129.9, 129.1, 124.9, 116.4, 114.5, 105.3, 104.4, 55.4.

*1-Bromo-6-phenylnaphthalen-2-ol (**58**).*[63] The following compound was obtained according to the general procedure A, by using 2-naphthol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product **58** (73 mg, 93%) as a white solid. m.p. =138–140 °C. R_f = 0.12 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3390, 3026, 1598, 1485, 1415. ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.84 (dd, J = 8.7, 1.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.73–7.68 (m, 2H), 7.49 (t, J = 7.7 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 150.8, 140.9, 137.1, 131.5, 129.9, 129.9, 128.9, 127.5, 127.3, 127.7, 126.5, 125.9, 117.6, 106.3. HRMS (EI): m/z calculated for $C_{16}H_{11}BrO$ $[M]^+$ = 297.9993, found 297.9988.

*5-Bromo-[2,2′-binaphthalen]-6-ol (**59**).* The following compound was obtained according to the general procedure A, by using 5-bromo-[2,2′-binaphthalen]-6-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **59** (69 mg, 94%) as a white solid. m.p. = 144–146 °C. R_f = 0.55 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3386, 1717, 1600, 1450, 1258. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.12 (d, J = 5.7 Hz, 1H), 7.90 (ddd, J = 28.0, 19.6, 9.1 Hz, 5H), 7.57–7.48 (m, 2H), 7.31 (d, J = 8.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.7, 137.7, 136.8, 133.7, 132.8, 131.6, 130.2, 129.6, 128.6, 128.2, 127.7, 127.6, 126.4, 126.5, 126.9, 126.6, 125.9, 125.2, 117.7, 106.9. HRMS (EI): m/z calculated for $C_{20}H_{13}BrO$ $[M]^+$ = 348.0150, found 348.0145.

*1-Chloro-6-(p-tolyl)naphthalen-2-ol (**60**).* The following compound was obtained according to the general procedure A, by using 6-(*p*-tolyl)naphthalen-2-ol as starting material and NH_4Cl. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **60** (52 mg, 90%) as a white solid. m.p. = 146–148 °C. R_f = 0.22 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3398, 3032, 1600, 1498, 1429. 1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.7 Hz, 1H), 7.90 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.51 (t, J = 13.2 Hz, 2H), 7.21 (dd, J = 14.3, 5.6 Hz, 3H), 5.82 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.9, 137.6, 137.8, 136.9, 130.1, 129.9, 129.7, 128.6, 127.9, 127.1, 125.7, 123.6, 117.6, 113.3, 21.6. HRMS (EI): m/z calculated for $C_{17}H_{13}ClO$ $[M]^+$ = 268.0655, found 268.0649.

*1-Bromo-6-(p-tolyl)naphthalen-2-ol (**61**).* The following compound was obtained according to the general procedure A, by using 6-(*p*-tolyl)naphthalen-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (8% EtOAc/Hexane) to afford the product **61** (62 mg, 92%) as a white solid. m.p. = 150–152 °C. R_f = 0.46 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3043, 1603, 1490, 1450, 1260. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H), 7.79–7.68 (m, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.20 (dd, J = 14.5, 5.9 Hz, 4H), 5.84 (s, 1H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 150.8, 137.7, 137.4, 137.7, 131.5, 130.5, 129.8, 129.8, 127.6, 127.4, 126.3, 125.8, 117.8, 106.8, 21.8. HRMS (EI): m/z calculated for $C_{17}H_{13}BrO$ $[M]^+$ = 312.0150, found 312.0148.

*1-Bromo-6-(4-methoxyphenyl)naphthalen-2-ol (**62**).*[65] The following compound was obtained according to the general procedure A, by using 6-(4-methoxyphenyl)naphthalen-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **62** (62 mg, 94%) as a white solid. m.p. = 156–158 °C. R_f = 0.28 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3033, 1590, 1495, 1429. ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.75–7.68 (m, 2H), 7.59–7.53 (m, 2H), 7.19 (d, J = 3.6 Hz, 1H), 6.97–6.91 (m, 2H), 5.83 (s, 1H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.3, 150.5, 136.6, 132.9, 131.8, 130.5, 129.4, 128.8, 127.9, 125.8, 125.3, 117.5, 114.4, 106.4, 55.9. HRMS (EI): m/z calculated for $C_{17}H_{13}BrO_2$ $[M]^+$ = 328.0099, found 328.0091.

*1-Bromo-6-(4-fluorophenyl)naphthalen-2-ol (**63**).* The following compound was obtained according to the general procedure A, by using 6-(4-fluorophenyl)naphthalen-2-ol and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **63** (61 mg, 92%) as a white solid. m.p. = 124–126 °C. R_f = 0.45 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3045, 2225, 1600, 1485, 1450. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.8 Hz, 1H), 7.93 (s, 1H), 7.85–7.70 (m, 2H), 7.68–7.62 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.17 (t, J = 8.7 Hz, 2H), 5.95 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.6 (d, J = 246.7 Hz), 150.7, 136.8, 136.0, 131.4, 129.9, 129.54, 128.8 (d, J = 8.1 Hz), 127.7, 126.07, 125.9, 117.7, 115.8 (d, J = 21.5 Hz), 106.3. HRMS (EI): m/z calculated for $C_{16}H_{10}BrFO$ $[M]^+$ = 315.9899, found 315.9895.

*1-Bromo-6-(3-chloro-4-fluorophenyl)naphthalen-2-ol (**64**).* The following compound was obtained according to the general procedure A, by using 6-(3-chloro-4-fluorophenyl)naphthalen-2-ol as starting material and NH_4Br. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **64** (61 mg, 90%) as a white solid. m.p. = 136–138 °C. R_f = 0.45 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3395, 3060, 1660, 1540, 1427. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.87 (s, 1H), 7.80–7.63 (m, 3H), 7.49 (s, 1H), 7.22 (d, J = 13.2 Hz, 2H), 5.92 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.9 (d, J = 254 HZ), 151.1, 137.9, 134.8, 131.9, 130.0, 129.7, 129.5, 127.1, 127.0, 126.4, 126.2, 121.6 (d, J = 60 Hz), 118.1, 117.1 (d, J = 85 Hz), 106.2. HRMS (ESI+): m/z calculated for $C_{16}H_{10}BrClFO$ $[M + H]^+$ = 350.9588, found 350.9580.

*1-Bromo-6-(3,4-difluorophenyl)naphthalen-2-ol (**65**).* The following compound was obtained according to the general procedure A, by using 6-(3,4-difluorophenyl)naphthalen-2-ol and NH_4Br. The

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149–4164

crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford the product **67** (88 mg, 90%) as a white solid. m.p. = 124−126 °C. R_f = 0.14 (20% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3395, 3032, 1600, 1496, 1427. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.66 (dd, J = 8.8, 1.6 Hz, 1H), 7.42 (ddd, J = 11.3, 7.6, 2.1 Hz, 1H), 7.35−7.30 (m, 1H), 7.25−7.17 (m, 2H), 5.91 (d, J = 4.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.5 (dd, J = 256 Hz), 151.0, 149.1 (dd, J = 256 Hz), 137.6 (dd, J = 24 Hz), 134.9, 131.7, 129.8, 129.6, 126.9, 126.3, 126.1, 123.1 (dd, J = 24 Hz), 117.9, 117.7 (d, J = 68 Hz), 116.1 (d, J = 68 Hz), 106.0. HRMS (EI): m/z calculated for $C_{16}H_9BrF_2O$ [M]$^+$ = 333.9805, found 333.9801.

One-Pot Dihalogenations. *One-Pot Synthesis of **54**.* This compound was synthesized by two consecutive halogenations (chlorination-bromination) which were carried out in the same flask with only single purification after the second reaction. Starting from 2-naphthol and NH_4Cl, the general procedure A was used to obtain 1-chloro-2-naphthol **51** (58 mg) as a dark solid. The ^{1}H and ^{13}C{^{1}H} of this derivative match perfectly with the previous obtained compound. Then, without purification, this dark solid was submitted to the second halogenation reaction using the general procedure A and NH_4Br to yield the compound **56** (71 mg, 84%) after column chromatography as a withe solid. The ^{1}H and ^{13}C{^{1}H} of this compound match perfectly with the previously obtained.

*One-Pot Synthesis of **55**.* This compound was synthesized by two consecutive halogenations (bromination-bromination) which were carried out in the same flask with only single purification after the second reaction. Starting from 2-naphthol and NH_4Br, the general procedure A was used to obtain 1-bromo-2-naphthol **52** (72 mg) as a dark-yellow solid. The ^{1}H and ^{13}C{^{1}H} of this derivative match perfectly with the previously obtained compound. Then, without purification, this dark-yellow solid was submitted to the second halogenation reaction using the general procedure A and NH_4Br to yield the compound **57** (89 mg, 91%) after column chromatography as a withe solid. The ^{1}H and ^{13}C of this compound match perfectly with the previously obtained.

*One-Pot Synthesis of **2**.* This compound was synthesized by two consecutive halogenations (iodination-bromination) which were carried out in the same flask with only single purification after the second reaction. Starting from 2-naphthol and NH_4I, the general procedure A was used to obtain 1-iodo-2-naphthol **1** (88 mg) as a gray solid. The ^{1}H and^{13}C{^{1}H} of this derivative match perfectly with the previous obtained compound. Then, without purification, this gray solid was submitted to the second halogenation reaction using the general procedure A and NH_4I to yield the compound **2** (89 mg, 78%) after column chromatography as a withe solid. The ^{1}H and ^{13}C of this compound match perfectly with the previously obtained.

Sequences Followed in Scheme 6. *6-Bromo-1-phenylnaphthalen-2-ol (**66**).*[66] The following substrate was prepared by Suzuki−Miyaura cross-coupling reactions between 6-bromo-1-iodonaphthalen-2-ol and phenylboronic acid. A 50 mL round-bottom flask with a stir bar was fitted with a rubber septum and flame-dried under high vacuum. The flask was purged with argon and charged with $Pd(PPh_3)_4$ (173.1 mg, 0.1 mmol), K_2CO_3 (445.2 mg, 4.2 mmol), 6-bromo-1-iodonaphthalen-2-ol (667.9 mg, 2.0 mmol), phenylboronic acid (4.0 mmol), 10.0 mL of 1,4-dioxene, and 2 mL of distiled water. The reaction mixture was then heated at 80 °C for 12 h. Afterward, the reaction was cooled down to room temperature, the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The crude products were purified by flash chromatography on silica gel (5% EtOAc/Hexane) to afford the product 6-bromo-1-phenylnaphthalen-2-ol (420.1 mg, 86%) as a white solid. m.p. = 96−98 °C. R_f = 0.2 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3386, 3034, 1720, 1600, 1450, 1260. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.7 Hz, 1H), 7.94 (s, 1H), 7.83−7.75 (m, 2H), 7.62 (d, J = 7.9 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 5.95 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.8, 138.9, 135.7, 133.8, 131.6, 129.8, 129.9, 129.8, 128.8, 127.8, 126.5, 125.9, 117.8, 106.4. HRMS (EI): m/z calculated for $C_{16}H_{11}BrO$ [M]$^+$ = 297.9993, found 297.9985.

*1-Phenyl-6-(p-tolyl)naphthalen-2-ol (**67**).* The following substrate was prepared by Suzuki−Miyaura cross-coupling reactions between 6-bromo-1-phenylnaphthalen-2-ol (**66**) obtained in the previous reaction and *p*-tolylboronic acid. A 50 mL round-bottom flask with a stir bar was fitted with a rubber septum and flame-dried under high vacuum. The flask was purged with argon and charged with $Pd(PPh_3)_4$ (106.24 mg, 0.1 mmol), K_2CO_3 (445.2 mg, 4.2 mmol), 6-bromo-1-phenylnaphthalen-2-ol (**66**) (410 mg, 2.0 mmol), *p*-tolylboronic acid (4.0 mmol), 10.0 mL of 1,4-dioxene, and 2 mL of distiled water. The reaction mixture was then heated at 80 °C for 12 h. After the reaction was cooled down to room temperature, the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The crude products were purified by flash chromatography on silica gel (10% EtOAc/Hexane) to afford the product 1-phenyl-6-(*p*-tolyl)naphthalen-2-ol (**67**) (349 mg, 82%) as a yellowish solid. m.p. =138−140 °C. R_f = 0.2 (10% EtOAc/Hexane). mp = 92−94 °C. R_f = 0.2 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3040, 2222, 1600, 1482, 1454. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.63 (dd, J = 14.4, 6.8 Hz, 5H), 7.56 (t, J = 7.4 Hz, 1H), 7.49 (d, J = 6.2 Hz, 3H), 7.31 (dd, J = 13.6, 7.0 Hz, 3H), 5.20 (s, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.8, 138.4, 136.9, 136.5, 134.3, 132.2, 131.8, 129.7, 129.7, 129.7, 129.2, 128.6, 127.6, 126.1, 125.6, 125.4, 120.9, 117.8, 21.2. HRMS (EI): m/z calculated for $C_{23}H_{18}O$ [M]$^+$ = 310.1358, found 310.1355.

*6-Bromo-1-iodo-2-methoxynaphthalene (**68**).*[50] To a solution of **2** (0.434 mg, 1.25 mmol) in acetone (5 mL) were added K_2CO_3 (0.345 mg, 10.0 mmol) and dimethyl sulfate (0.2 mL, 10.0 mmol). The solution was heated to reflux for 4 h, at which time TLC indicated complete consumption of the naphthol. The reaction mixture was cooled to room temperature, Et_3N (5.0 mL) was added, and the reaction was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude material, which was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product 6-bromo-1-iodo-2-methoxynaphthalene **68** (0.413 mg, 94%) as a yellowish solid. R_f = 0.15 (8% EtOAc/Hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 9.1 Hz, 1H), 7.91 (s, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 4.02 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.9, 134.3, 133.2, 131.8, 130.6, 129.9, 129.4, 118.2, 113.7, 87.7, 57.2.

*6-Bromo-2-methoxy-1-(phenylethynyl)naphthalene (**69**).* A 50 mL round-bottom flask with a stir bar was fitted with a rubber septum and flame-dried under high vacuum. The flask was purged with nitrogen and sequentially charged with 6-bromo-1-iodo-2-methoxynaphthalene (**68**) (361.8 mg, 1.00 mmol), and Et_3N (2 mL), phenylacetylene (1.1 mmol), $PdCl_2(PPh_3)_2$ (0.1 mmol), and CuI (0.25 mmol) were added. The mixture was stirred at 60 °C for 6 h until full consumption of **68** by judging on TLC development. Then the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure to afford the crude material which was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) giving rise to the product 6-bromo-2-methoxy-1-(phenylethynyl)-naphthalene (**69**) (0.296 mg, 88%) as a yellow liquid. R_f = 0.44 (5% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3400, 3360,3033, 1590, 1495, 1460. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.9 Hz, 1H), 7.93 (s, 1H), 7.71 (d, J = 9.1 Hz, 1H), 7.66 (d, J = 6.8 Hz, 2H), 7.60 (d, J = 8.9 Hz, 1H), 7.42−7.35 (m, 3H), 7.27 (d, J = 9.4 Hz, 1H), 4.04 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.1, 133.9, 131.9, 130.6, 130.0, 129.9, 129.1, 128.9, 128.7, 127.2, 123.7, 117.9, 113.7, 106.8, 99.4, 83.5, 56.7. HRMS (ESI+): m/z calculated for $C_{19}H_{13}BrO$ [M + H]$^+$ = 337.0228, found 337.0237.

*6-(3-Chloro-4-fluorophenyl)-2-methoxy-1-(phenylethynyl)naphthalene (**70**).* The following substrate was prepared by Suzuki−Miyaura cross-coupling reactions between 6-bromo-2-methoxy-1-

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

(phenylethynyl)naphthalene (**69**) obtained in the previous reaction and (3-choloro-4-fluorophenyl)boronic acid. A 50 mL round-bottom flask with a stir bar was fitted with a rubber septum and flame-dried under high vacuum. The flask was purged with argon and charged with $Pd(PPh_3)_4$ (0.1 mmol), K_2CO_3 (4.2 mmol), 6-bromo-2-methoxy-1-(phenylethynyl)naphthalene (**69**) (56 mg, 2.0 mmol), (3-choloro-4-fluorophenyl)boronic acid (4 mmol), 1,4-dioxene (10.0 mL), and distilled water (2 mL). The reaction mixture was then heated at 80 °C for 12 h. Afterward, the reaction was cooled down to room temperature, the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The crude products were purified by flash chromatography on silica gel (5% EtOAc/Hexane) to afford the product 6-(3-chloro-4-fluorophenyl)-2-methoxy-1-(phenylethynyl)naphthalene (**70**) (45 mg, 68%) as a white solid. m.p. = 96−98 °C. R_f = 0.55 (8% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3460, 3320,2933, 1560, 1510, 1440. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 8.7 Hz, 1H), 7.93 (s, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.74 (s, 1H), 7.73 (t, J = 2.4 Hz, 1H), 7.69 (dt, J = 3.4, 1.9 Hz, 2H), 7.56 (t, J = 8.5, 4.5, 2.3 Hz, 1H), 7.43−7.35 (m, 3H), 7.33 (d, J = 9.1 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 4.09 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.4, 158.6, 156.6 (d, J = 1.1 Hz), 138.2 (d, J = 5.1 Hz), 134.9, 133.9, 131.9, 130.4, 129.3, 128.6, 128.3 (d, J = 11.6 Hz), 126.8 (d, J = 6.9 Hz), 126.5−125.9 (m), 123.6, 121.46, 121.3 (d, J = 1.3 Hz), 117.02, 116.85, 113.4, 106.3, 99.1, 83.6, 56.7. HRMS (EI): m/z calculated for $C_{25}H_{16}ClFO$ $[M]^+$ = 386.0874, found 386.0866.

Computational Details. The enthalpy and Gibbs free energy calculations for the adduct PhII(OH)·NH_3 were computed as the energy difference between the adduct and the sum of the energies of the optimized PhIO and the NH_4I at the gas phase employing the Gaussian 16 software package.

Fukui Function Calculations for PhII(OH)·NH_3. The reactivity of the iodinating species was analyzed by exploring a very useful covalent reactivity descriptor: the Fukui or frontier function, which is usually a reliable predictor of the regioselectivity of soft molecules.[44−46] Fukui functions are defined as the response of the electron density when the number of electrons (N) suffers an infinitesimal change, providing us information about the reactive sites of a molecular system.[47] Particularly to indicate how the electron density is redistributed when molecules react, thus, molecular regions suffering more charge rearrangements are the most reactive sites. The Fukui functions are obtained calculating the electron density of the PhII(OH)·NH_3 with N, $N-1$, and $N+1$ electrons, respectively, at the ground state. The positive ($f^+(r)$) and negative ($f^-(r)$) forms of the Fukui functions are useful descriptors to evaluate nucleophilic or electrophilic attacks, respectively.[48]

The transition state search for the PhII(OH)·NH_3 adduct was obtained by using the DL-FIND library[73] implemented in Terachem 1.9.3[74,75] employing the nudged elastic band method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00161.

Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**−**70** as well as computational details related to the energetic profile formation, MEP, and general details regarding PhII(OH)·NH_3 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: csolorio@ugto.mx.

ORCID

Yuvraj Satkar: 0000-0002-7545-6884
Luisa F. Yera-Ledesma: 0000-0002-1992-2828
Narendra Mali: 0000-0003-4976-7600
Dipak Patil: 0000-0003-2010-5822
Pedro Navarro-Santos: 0000-0001-8370-1651
Luis A. Segura-Quezada: 0000-0003-2179-9678
Perla I. Ramírez-Morales: 0000-0001-7096-9683
César R. Solorio-Alvarado: 0000-0001-6082-988X

Author Contributions

§Y. Satkar and L. F. Yera-Ledesma contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by CONACyT (CB-2013/220836). We acknowledge the facilities of the DCNyE, the Chemistry Department, and the National Laboratory UG-CONACyT (LACAPFEM) at the University of Guanajuato, for full characterization. We thank CONACyT for Ph.D. fellowships to Y.S., N.M., and D.P. We also thank M. C. Kevin Juárez for preliminary optimization assays.

■ DEDICATION

Dedicated to Professor Keiji Maruoka on the occasion of his 66th birthday.

■ REFERENCES

(1) Organic Bromine and Iodine compounds. *Handbook of Environmental Chemsitry*; Neilson, A. H., Ed.; Springer: Heidelberg, 2003.

(2) Guzii, A. G.; Makarieva, T. N.; Denisenko, V. A.; Dmitrenok, P. S.; Burtseva, Y. V.; Krasokhin, V. B.; Stonik, V. A. Topsentiasterol Sulfates with Novel Iodinated and Chlorinated side Chains from the Marine Songe *Topsentia sp. Tetrahedron Lett.* **2008**, *49*, 7191−7193.

(3) (a) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. Bromovulone I and Iodovulone I, Unprecedent Brominated and Iodinated Marine Prostanoids with Antitumor Activity Isolated from the Japanese Stolonifer *Clavularia viridis* Quoy and Gaimard. *J. Chem. Soc., Chem. Commun.* **1986**, 981−982.

(4) Roy, G.; Nethaji, M.; Mugesh, G. Interaction of Anti-Thyroid Drugs with Iodine: The Isolation of Two Unusual Ionic Compounds Derived from Se-Methimazole. *Org. Biomol. Chem.* **2006**, *4*, 2883−2887.

(5) (a) Larsen, P. R. Thyroidal Triiodothyronine and Thyroxine in Gravés Disease: Correlation with Presurgical Treatment, Thyroid Status and Iodine Content. *J. Clin. Endocrinol. Metab.* **1975**, *41*, 1098−1104.

(6) Ihssen, J.; Schubert, M.; Thöny-Meyer, L.; Richter, M. Lacasse Catalyzed Synthesis of Iodinated Phenolic Compounds with Antifungal Activity. *PLoS One* **2014**, *9*, No. e89924.

(7) Antimicrobial Agents. *Advances in Structure and Activity Relationship of Cumarin Derivatives*; Penta, S., Ed.; Academic Press, 2016.

(8) (a) Silva, L. F., Jr.; Olofsson, B. Hypervalent Iodine Reagents in The Total Synthesis of Natural Products. *Nat. Prod. Rep.* **2011**, *28*, 1722−1754. (b) Skulski, L. Organic Iodine (I, III and V) Chemistry: 10 Years of Development at the Medical University of Warsaw. *Molecules* **2000**, *5*, 1331−1371.

(9) Merritt, E. A.; Olofsson, B. Diaryliodoniumsalts-A Journey from Obscurity to Fame. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070.

(10) Sampson, P. Metal Catalyzed Cross-Coupling Reactions *J. J. Am. Chem. Soc.* **1998**, *120*, 11836−11837.

(11) Wang, L.; Ackermann, L. Ruthenium-catalyzed ortho-C−H halogenations of benzamides. *Chem. Commun.* **2014**, *50*, 1083−1085.

(12) Zhou, C.; Li, J.; Peddibhotla, S.; Romo, D. Mild Arming and Derivatization of Natural Products via an In(OTf)$_3$-Catalyzed Arene Iodination. *Org. Lett.* **2010**, *12*, 2104−2107.

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

(13) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. A Simple Catalytic Method for the Regioselective Halogenation of Arenes. *Org. Lett.* **2006**, *8*, 2523−2526.
(14) Branytska, O. V.; Neumann, R. An Efficient, Catalytic, Aerobic, Oxidative Iodination of Arenes Using the $H_5PV_2Mo_{10}O_{40}$ Polyoxometalate as Catalyst. *J. Org. Chem.* **2003**, *68*, 9510−9512.
(15) Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. Iodination of Alkyl Aryl Ethers by Mercury(II) Oxide-Iodine Reagent in Dichloromethane. *Synthesis* **1995**, 1273−1277.
(16) Racys, D. T.; Warrilow, C. E.; Pimlott, S. L.; Sutherland, A. Highly Regioselective Iodination of Arenes via Iron(III)-Catalyzed Activation of N-Iodosuccinimide. *Org. Lett.* **2015**, *17*, 4782−4785.
(17) Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V. S. A mild and simple regioselective iodination of activated aromatics with iodine and catalytic ceric ammonium nitrate. *Tetrahedron Lett.* **2007**, *48*, 81−83.
(18) Janjetovic, M.; Ekebergh, A.; Träff, A. M.; Hilmersson, G. Catalytic Iodination of the Aliphatic C-F Bond by $YbI_3(THF)_3$: Mechanistic Insight and Synthetic Utility. *Org. Lett.* **2016**, *18*, 2804−2807.
(19) Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. Silver(I)-Catalyzed Iodination of Arenes: Tuning the Lewis Acidity of N-Iodosuccinimide Activation. *J. Org. Chem.* **2016**, *81*, 772−780.
(20) Badri, R.; Gorjizadeh, M. A mild, efficient and selective iodination of aromatic compounds using iodine and 1,4-bis-(triphenylphosphonium)-2-butene peroxodisulfate. *Chin. Chem. Lett.* **2009**, *20*, 1439−1443.
(21) Patil, A. M.; Kamble, D. A.; Lokhande, P. D. A Metal-Free Iodination of Aryl Ethers and Phenols Using I_2. *ChemistrySelect* **2017**, *2*, 8418−8422.
(22) Vibhute, A.; Mokle, S.; Karamunge, K.; Gurav, V.; Vibhute, Y. A simple and efficient method for solvent-free iodination of hydroxylated aromatic aldehydes and ketones using iodine and iodic acid by grinding method. *Chin. Chem. Lett.* **2010**, *21*, 914−918.
(23) Pavlinac, J.; Zupan, M.; Stavber, S. Solvent-free iodination of organic molecules using the I_2/urea-H_2O_2 reagent system. *Org. Biomol. Chem.* **2007**, *5*, 699−707.
(24) Noda, Y.; Kashima, M. An Efficient and Regioselective Direct Aromatic Iodination Using Iodine and Nitrogen Dioxide. *Tetrahedron Lett.* **1997**, *38*, 6225−6228.
(25) Narender, N.; Reddy, K. S. K.; Mohan, K. V. V. K.; Kulkarni, S. J. Eco-friendly oxyiodination of aromatic compounds using ammonium iodide and hydrogen peroxide. *Tetrahedron Lett.* **2007**, *48*, 6124−6128.
(26) Edgar, K. J.; Falling, S. N. An Efficient and Selective Method for the Preparation of Iodophenols. *J. Org. Chem.* **1990**, *55*, 5287−5291.
(27) Lista, L.; Pezzella, A.; Napolitano, A.; d'Ischia, M. Mild and efficient iodination of aromatic and heterocyclic compounds with the $NaClO_2$/NaI/HCl system. *Tetrahedron* **2008**, *64*, 234−239.
(28) Hubig, S. M.; Jung, W.; Kochi, J. K. Cation Radicals as Intermediates in Aromatic Halogenation with Iodine Monochloride: Solvent and Salt Effects on the Competition between Chlorination and Iodination. *J. Org. Chem.* **1994**, *59*, 6233−6244.
(29) Bailey, L.; Handy, S. T. Aromatic iodination using N-iodosaccharin in room temperature ionic liquids. *Tetrahedron Lett.* **2011**, *52*, 2413−2414.
(30) Barluenga, J.; Gonzalez, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asensio, G. Acid-mediated reaction of bis(pyridine)iodonium(I) tetrafluoroborate with aromatic compounds. A selective and general iodination method. *J. Org. Chem.* **1993**, *58*, 2058−2060.
(31) Castanet, A. S.; Colobert, F.; Broutin, P. E. Mild and regioselective iodination of electron-rich aromatics with *N*-iodosuccinimide and catalytic trifluoroacetic acid. *Tetrahedron Lett.* **2002**, *43*, 5047−5048.
(32) Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. Synthetic methods and reactions. 181. Iodination of deactivated aromatics with N-iodosuccinimide in trifluoromethanesulfonic acid (NIS-CF_3SO_3H) via in situ generated superelectrophilic iodine(I) trifluoromethanesulfonate. *J. Org. Chem.* **1993**, *58*, 3194−3195.
(33) Tang, R.-J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83*, 930−938.
(34) Sun, K.; Lv, Y.; Wang, J.; Sun, J.; Liu, L.; Jia, M.; Liu, X.; Li, Z.; Wang, X. Regioselective, Molecular Iodine-Mediated C3 Iodination of Quinolines. *Org. Lett.* **2015**, *17*, 4408−4411.
(35) Moorthy, J. N.; Senapati, K.; Kumar, S. IBX-I_2 Redox Couple for Facile Generation of IOH and I^+: Expedient Protocol for Iodohydroxylation of Olefins and Iodination of Aromatics. *J. Org. Chem.* **2009**, *74*, 6287−6290.
(36) (a) Spyroudis, S.; Tarantili, P. Phenyliodoniophenolates from 1,3-Dihydroxybenzene Derivatives. *Tetrahedron* **1994**, *50*, 11541−11552. (b) Prakash, O.; Sharma, V.; Tanwar, M. P. Hypervalent iodine oxidation of α -substituted 2,4-dihydroxyacetophenones: synthesis of novel o-iodophenoxy ethers via rearrangement of iodonium ylides. *Can. J. Chem.* **1999**, *77*, 1191−1195. (c) Hu, B.; Miller, W. H.; Neumann, K. D.; Linstad, E. J.; DiMagno, S. G. An Alternative to the Sandmeyer Approach to Aryl Iodides. *Chem. - Eur. J.* **2015**, *21*, 6394−6398. (d) Daub, K. S.; Habermann, B.; Hahn, T.; Teich, L.; Eger, K. Synthesis of 3-Aryloxy-2-iodoemodines by Oxidation of Emodin with (Diacetoxyiodo)arenes. *Eur. J. Org. Chem.* **2004**, *2004*, 894−898. For activation modes of iodine(III) reagents: (e) Shu, S.; Li, Y.; Jiang, J.; Ke, Z.; Liu, Y. Mechanism of Hypervalent Iodine Promoted Fluorocyclization of Unsaturated Alcohols: Metathesis via Double Acids Activation. *J. Org. Chem.* **2019**, *84*, 458−462.
(37) Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. Regiospecific Reductive Elimination from Diaryliodonium Salts. *Angew. Chem., Int. Ed.* **2010**, *49*, 4079−4083.
(38) Nahide, P. D.; Ramadoss, V.; Juárez-Ornelas, K. A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J. M. J.; Alonso-Castro, A. J.; Zapata-Morales, J. R.; Ramírez-Morales, M. A.; Ruiz-Padilla, A. J.; Deveze-Álvarez, M. A.; Solorio-Alvarado, C. R. In Situ Formed iodine(III)-Based Reagent for the Electrophilic *ortho*-Chlorination of Phenols and Phenol-Ethers: The Use of PIFA-$AlCl_3$ System. *Eur. J. Org. Chem.* **2018**, *2018*, 485−493.
(39) Satkar, Y.; Ramadoss, V.; Nahide, P. D.; García-Medina, E.; Juárez-Ornelas, K. A.; Alonso-Castro, A. J.; Chávez-Rivera, R.; Jiménez-Halla, J. O. C.; Solorio-Alvarado, C. R. Practical, Mild and Efficient Electrophilic Bromination of Phenols by a New I(III)-based Reagent: The PIDA-$AlBr_3$ System. *RSC Adv.* **2018**, *8*, 17806−17812.
(40) (a) Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. Direct Lactone Formation by Using Hypervalent Iodine(III) Reagents with KBr via Selective Abstraction Protocol. *Org. Lett.* **2007**, *9*, 3129−3132. (b) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007−2010.
(41) Beitia, J. L. L. Tripotassium Phosphate: From Buffers to Organic Synthesis. *Synlett* **2011**, *2011*, 139−140.
(42) Carroll, M. A.; Nairne, J.; Smith, G.; Widdowson, D. A. Radical Scavengers: A Practical solution to the reproducibility issue in the fluoridation of diaryliodonium salts. *J. Fluorine Chem.* **2007**, *128*, 127−132.
(43) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. *Gaussian 16*, Revision A.03; Gaussian Inc.: Wallingford, CT, 2016.
(44) For an excellent discussion about *cis* and *trans* geometries in hypervalent iodine(III) derivatives, see: Sajith, P. K.; Suresh, C. H. Trans and Cis Influences in Hypervalent Iodine(III) Complexes: A DFT Study. *Inorg. Chem.* **2013**, *52*, 6046−6065.
(45) (a) Ayers, P. W.; Parr, R. G.; Pearson, R. G. Elucidating the hard/soft acid/base principle: A perspective based on half-reactions. *J. Chem. Phys.* **2006**, *124*, 194107. (b) Gazquez, J. L.; Mendez, F. The hard and soft acids and bases principle: an atoms in molecules viewpoint. *J. Phys. Chem.* **1994**, *98*, 4591−4593.
(46) Mendez, F.; Gazquez, J. L. Chemical-Reactivity of Enolate Ions - The Local Hard and Soft Acids and Bases Principle Viewpoint. *J. Am. Chem. Soc.* **1994**, *116*, 9298−9301.

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

(47) Ayers, P. W.; Parr, R. G. Variational Principles for Describing Chemical Reactions: The Fukui Function and Chemical Hardness Revisited. *J. Am. Chem. Soc.* **2000**, *122*, 2010−2018.
(48) Johnson, P. A.; Bartolotti, L. J.; Ayers, P. W.; Fievez, T.; Geerlings, P. Charge Density and Chemical Reactions: A Unified View from Conceptual DFT. In *Modern Charge-Density Analysis*; Gatti, C., Macchi, P., Eds.; Springer Netherlands: Dordrecht, 2012; pp 715−764.
(49) Crittall, M. R.; Fairhurst, N. W. G.; Carbery, D. R. Point-to-helical chirality transfer for a scalable and resolution-free synthesis of a helicenoidal DMAP organocatalyst. *Chem. Commun.* **2012**, *48*, 11181−11183.
(50) Zhao, C.; Guo, D.; Munkerup, K.; Huang, K.-W.; Li, F.; Wang, J. Enantioselective [3 + 3] atroposelective annulation catalyzed by *N*-heterocyclic carbenes. *Nat. Commun.* **2018**, *9*, 611.
(51) Mbatia, H. W.; Ulloa, O. A.; Kennedy, D. P.; Incarvito, C. D.; Burdette, S. C. Iodination of anilines and phenols with 18-crown-6 supported ICl_2^-. *Org. Biomol. Chem.* **2011**, *9*, 2987−2991.
(52) Kauch, M.; Hoppe, D. Synthesis of Halogenated Phenols by Directed *ortho*-Lithiation and *ipso*-Iododesilylation Reactions of *O*-Aryl *N*-Isopropylcarbamates. *Synthesis* **2006**, *2006*, 1578−1589.
(53) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. Iodination of Phenols by Use of Benzyltrimethylammonium Dichloroiodate (I-). *Chem. Lett.* **1987**, *16*, 2109−2112.
(54) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. S. R.; Basak, A. K.; Narsaiah, A. V. Efficient Halogenation of Aromatic Systems Using *N*-Halosuccinimides in Ionic Liquids. *Adv. Synth. Catal.* **2004**, *346*, 77−82.
(55) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. Synthesis of many different types of organic small molecules using one automated process. *Science* **2015**, *347*, 1221−1226.
(56) Yoshida, S.; Nagai, A.; Uchida, K.; Hosoya, T. Enhancing the Synthetic Utility of 3-Haloaryne Intermediates by Their Efficient Generation from Readily Synthesizable *ortho*-Iodoaryl Triflate-type Precursors. *Chem. Lett.* **2017**, *46*, 733−736.
(57) Kiran, Y. B.; Konakahara, T.; Sakai, N. A Green Reagent for the Iodination of Phenols. *Synthesis* **2008**, *2008*, 2327−2332.
(58) Yang, Y.; Zhang, L.; Deng, G.-J.; Gong, H. Simple, Efficient and Controllable Synthesis of Iodo/Di-iodoarenes via Ipsoiododecarboxylation/ Consecutive Iodination Strategy. *Sci. Rep.* **2017**, *7*, 40430−40439.
(59) Miles, K. C.; Le, C. C.; Stambuli, J. P. Direct Carbocyclizations of Benzoic Acids: Catalyst-Controlled Synthesis of Cyclic Ketones and the Development of Tandem aHH (acyl Heck−Heck) Reactions. *Chem. - Eur. J.* **2014**, *20*, 11336−11339.
(60) Sun, L.; Zhang, X.; Li, Z.; Ma, J.; Zeng, Z.; Jiang, H. A Versatile C−H Halogenation Strategy for Indole Derivatives under Electrochemical Catalyst- and Oxidant-Free Conditions. *Eur. J. Org. Chem.* **2018**, *2018*, 4949−4952.
(61) Naykode, M. S.; Humne, V. T.; Lokhande, P. D. A One-Pot Direct Iodination of the Fischer−Borsche Ring Using Molecular Iodine and Its Utility in the Synthesis of 6 Oxygenated Carbazole Alkaloids. *J. Org. Chem.* **2015**, *80*, 2392−2396.
(62) Wang, X.; Qin, W. Tetra(*p*-tolyl)borate-Functionalized Solvent Polymeric Membrane: A Facile and Sensitive Sensing Platform for Peroxidase and Peroxidase Mimetics. *Chem. - Eur. J.* **2013**, *19*, 9979−9986.
(63) Pan, C.; Zhu, Z.; Zhang, M.; Gu, Z. Palladium-Catalyzed Enantioselective Synthesis of 2-Aryl Cyclohex-2-enone Atropisomers: Platform Molecules for the Divergent Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2017**, *56*, 4777−4781.
(64) Naykode, M. S.; Humne, V. T.; Lokhande, P. D. A One-Pot Direct Iodination of the Fischer−Borsche Ring Using Molecular Iodine and Its Utility in the Synthesis of 6 Oxygenated Carbazole Alkaloids. *J. Org. Chem.* **2015**, *80*, 2392−2396.
(65) Ishikawa, S.; Manabe, K. DHTP Ligands for the Highly Ortho-Selective, Palladium-Catalyzed Cross-Coupling of Dihaloarenes with Grignard Reagents: A Conformational Approach for Catalyst Improvement. *Angew. Chem., Int. Ed.* **2010**, *49*, 772−775.
(66) Qian, X.; Han, J.; Wang, L. Copper-catalyzed selective ortho-arylations of 2-naphthol and phenol derivatives with diaryliodonium salts. *Tetrahedron Lett.* **2016**, *57*, 607−610.
(67) Guardado-Cruz, S. T.; Ortiz-Alvarado, R.; de León, C.; Solorio-Alvarado, C. R. Unprecedent and Scalable Copper (I)-Catalyzed Oxidation of the Csp^2-H bond on 2-phenylnaphthalene-1,3-diol with Atmospheric Oxygen: Synthesis of 2-hydroxy-3-phenyl-1,4-naphthoquinone via direct Csp^2-O bond formation. *Acta Univ.* **2017**, *27*, 62−68.
(68) Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. Atroposelective Synthesis of Axially Chiral Biaryldiols via Organocatalytic Arylation of 2-Naphthols. *J. Am. Chem. Soc.* **2015**, *137* (48), 15062−15065.
(69) Park, Y. H.; Ahn, H. R.; Canturk, B.; Jeon, S. I.; Lee, S.; Kang, H.; Molander, G. A.; Ham, J. A Facile One-Pot Preparation of Potassium Hydroxyaryl- and (Hydroxyalkyl)aryltrifluoroborates. *Org. Lett.* **2008**, *10* (6), 1215−1218.
(70) Kamal, A.; Reddy, M. K.; Ramaiah, M. J.; Srikanth, Y. V. V.; Rajender; Reddy, V. S.; Kumar, G. B.; Pushpavalli, S. N. C. V. L.; Bag, I.; Juvekar, A.; Sen, S.; Zingde, S. M.; Pal-Bhadra, M. Synthesis of Aryl-Substituted Naphthalene-Linked Pyrrolobenzodiazepine Conjugates as Potential Anticancer Agents with Apoptosis-Inducing Ability. *ChemMedChem* **2011**, *6* (9), 1665−1679.
(71) Georgiades, S. N.; Clardy, J. Preparation of a Psammaplysene-Based Library. *Org. Lett.* **2006**, *8*, 4251−4254.
(72) Wang, Y.; Gevorgyan, V. Synthesis of Active Hexafluoroisopropyl Benzoates through a Hydrogen-Bond-Enabled Palladium(II)-Catalyzed C-H Alkoxycarbonylation Reaction. *Angew. Chem., Int. Ed.* **2017**, *56*, 3191−3195.
(73) Kästner, J.; Carr, J. M.; Keal, T. W.; Thiel, W.; Wander, A.; Sherwood, P. DL-FIND: An Open- Source Geometry Optimizer for Atomistic Simulations. *J. Phys. Chem. A* **2009**, *113*, 11856.
(74) Ufimtsev, I. S.; Martínez, T. J. Quantum Chemistry on Graphical Processing Units. 3. Analytical Energy Gradients and First Principles Molecular Dynamics. *J. Chem. Theory Comput.* **2009**, *5*, 2619.
(75) Titov, A. V.; Ufimtsev, I. S.; Luehr, N.; Martínez, T. J. Generating Efficient Quantum Chemistry Codes for Novel Architectures. *J. Chem. Theory Comput.* **2013**, *9*, 213.

DOI: 10.1021/acs.joc.9b00161
J. Org. Chem. 2019, 84, 4149−4164

Tetrahedron Letters 60 (2019) 1551–1555

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iodine(III)/AlX_3-mediated electrophilic chlorination and bromination of arenes. Dual role of AlX_3 (X = Cl, Br) for $(PhIO)_n$ depolymerization and as the halogen source

Alberto Segura-Quezada [a,1], Yuvraj Satkar [a,1], Dipak Patil [a], Narendra Mali [a], Kazimirez Wrobel [a], Gerardo González [a], Ramón Zárraga [a], Rafael Ortiz-Alvarado [b], César R. Solorio-Alvarado [a,*]

[a] Universidad de Guanajuato, Campus Guanajuato, División de Ciencias Naturales y Exactas, Departamento de Química, Noria Alta S/N, 36050 Guanajuato, Gto, Mexico
[b] Universidad Michoacana de San Nicolás de Hidalgo, Facultad de Químicofarmacobiología, Tzintzuntzan 173, Col. Matamoros, Morelia, Mich, Mexico

ARTICLE INFO

Article history:
Received 14 March 2019
Revised 4 May 2019
Accepted 9 May 2019
Available online 10 May 2019

Keywords:
Chlorination and bromination of arenes
Iodosylbenzene $(PhIO)_n$
Chloronium and bromonium synthons
Depolymerization of $(PhIO)_n$

ABSTRACT

An efficient chlorination and bromination of arenes mediated by *in situ*-formed PhI(X)OAlX$_2$ (X = -Cl, -Br), which is proposed as a plausible halogenating species, is described. The proposed dual role displayed by AlX_3, enables the Iodosylbenzene [$(PhIO)_n$] depolymerization while also acting as the halogen source by transferring the chlorine or bromine atoms to the iodine(III) center. This process allowed the chlorination and bromination of different arenes and heteroarenes under mild and open flask conditions. To the best of our knowledge, this is the first report describing a dual role of aluminum salts applied to the direct C-H chlorination and bromination of arenes.

Introduction

Aromatic chlorides and bromides [1] are an important class of structures in organic synthesis. They are found in naturally occurring compounds [2], agrochemicals [3] and in material sciences [4]. They are also broadly used as building blocks in the pharmaceutical industry [5] as well as starting materials in metal-catalyzed cross-coupling reactions such as Suzuki [6], Stille [7], Negishi [8], the Sonogashira alkynylation [9] and the Mizoroki-Heck [10] olefination (Fig. 1).

To date, the introduction of chlorine and bromine atoms to aromatic moieties has been described extensively. However, few of these procedures are broad enough to allow the functionalization with more than one different halogen, therefore they are restricted to a single type of halogen (Cl or Br or I) connection. Regarding the methods which allow direct C-H chlorination and bromination, two common strategies have been used. The oxidation of chloride and bromide salts and the activation of NCS [11] or NBS [12]. These strategies can be categorized as metal-catalyzed procedures using Rh [13], Pd [14], Cu [15] or Zr [16]. Also, metal-free-mediated methods activating chloro- or bromosuccinimides were described using TMSCl [17], Ph_3PS [18] and under ball milling conditions [19]. Finally in the context of this work, different iodine(III)-mediated chlorination and bromination methods have been reported. These protocols utilise pre-synthesized reagents (Zupan [20], Zhdankin [21], Xue [22], Karade [23]) or *in situ*-formed reagents (Bradock [24], Zhou [25], Evans [26] and ours [27,28]) as chlorinating and brominating active species (Scheme 1).

All of the aforementioned protocols display significant advantages in terms of chemical reactivity and chemical-economy [15,17]. Nevertheless serious synthetic issues such as the use of strong acids (TFA[13] or TfOH[14a]), aggressive oxidants ($Na_2S_2O_8$) [14b], high temperatures [15], the necessity for using directing groups [12] and the insolubility of the pre-synthesized reagents [20–23] can be limiting for an optimal protocol that proceeds under mild reaction conditions. Herein, we present an efficient procedure which allows the chlorination and bromination of a broad range of naphthol derivatives in good to excellent yields at room temperature with *in situ* formation of the halogenating reagent [PhI(Cl)OAlCl$_2$ or PhI(Br)OAlBr$_2$]. This feature avoids the synthesis of a chlorinating or brominating reagent, thus diminishing the cost of the process. Additionally, the *in situ* preparation is enabled by the dual role of the aluminum salt ($AlCl_3$ or $AlBr_3$) which depolymerizes the iodosylbenzene $(PhIO)_n$ [29] and is also the source of chlorine and bromine atoms.

* Corresponding author.
E-mail address: csolorio@ugto.mx (C.R. Solorio-Alvarado).
[1] A.Seugra-Quezada and Y. Satkar contributed equally to this work.

https://doi.org/10.1016/j.tetlet.2019.05.019
0040-4039/

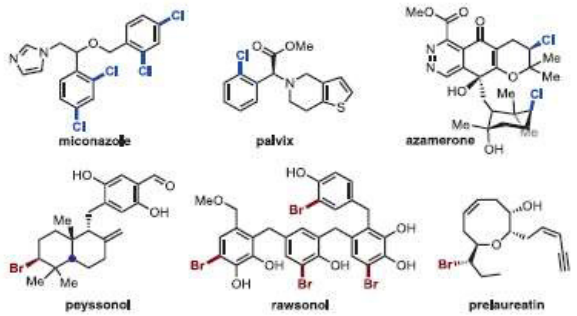
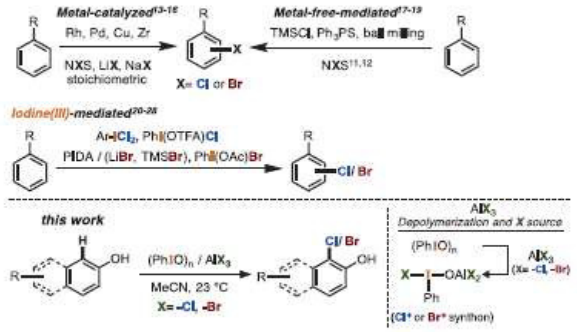


Fig. 1. Relevance of the aromatic chloride and bromide core.

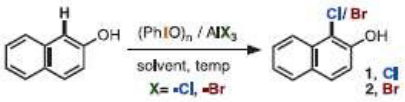


Scheme 1. Representative methods for the chlorination and bromination of arenes.

Encouraged by our recent results regarding the nitration of phenols catalyzed by PhIO [30], we envisioned the possibility of extending our procedure to the bromination and chlorination of these aromatic systems. Hence, we could develop a broad and robust protocol simply by changing the halogen of the aluminum salt. In this way, we started an optimization of the reaction conditions using the $(PhIO)_n/AlX_3$ (X = Cl, Br) system (Table 1).

The optimization started using 1.1 equiv. of iodosylbenzene and 1.2 equiv. of aluminum trichloride or tribromide (AlX_3; X = Cl or Br) in acetonitrile at room temperature, which gave chlorinated (**1**) and brominated 2-naphthol (**2**) in 58% and 47% yield, respectively (Entries 1 and 9). These experiments validated our hypothesis and confirmed that the use of polymeric $(PhIO)_n$ was able to introduce chlorine or bromine atoms to 2-naphthol. Mechanistic investigation regarding the active iodine(III) species reacting with chlorine or bromine atoms from the aluminum salts to form a plausible halogenating species in the process, will be further described. The optimization continued with a slight increase to 1.2 equiv. of $(PhIO)_n$ and 1.5 equiv. of AlX_3; giving 71% and 65% yield for **1** and **2**, respectively (Entries 2 and 10). It was observed that the yield increased with the amount of the aluminum salt. We also used 2.4 equiv. of AlX_3 with additional heating at 40 °C retaining the Iodosylbenzene stoichiometry. In these reactions 69% and 61% yield for **1** and **2**, respectively, were attained (Entries 3 and 11). The observed lower yields were attributed to the heating. Thus, the same conditions (1.2 equiv. $(PhIO)_n$ and 2.4 equiv. of AlX_3) at room temperature were used, and to our delight an excellent 94% and 98% yield for 1-chloro-2-naphthol (**1**) and 1-bromo-2-naphthol (**2**), respectively, was achieved in 20–25 min (Entries 4 and 12). The following solvent optimization gave rise to lower yields (Entries 6 and 13), complex reaction mixtures (Entry 7) or no reaction (Entry 5). To complete the optimization, a number of

Table 1
Optimization of the $(PhIO)_n/AlX_3$-mediated chlorination and bromination of 2-naphthol (X = Cl, Br).[a]



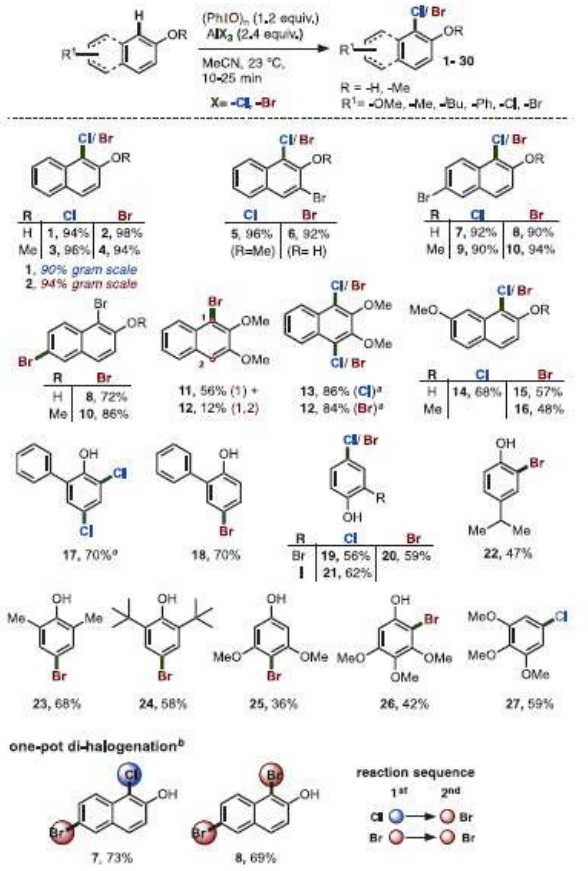
Entry	$(PhIO)_n$ (equiv.)	AlX_3 (equiv.)	Solvent, Temp (°C)	Yield (%)[b]
1	1.1	$AlCl_3$ (1.2)	MeCN, 23	58
2	1.2	$AlCl_3$ (1.5)	MeCN, 23	71
3	1.2	$AlCl_3$ (2.4)	MeCN, 40	69
4	***1.2***	***$AlCl_3$ (2.4)***	***MeCN, 23***	***94***
5	1.2	$AlCl_3$ (2.4)	MeOH, 23	n. r.
6	1.2	$AlCl_3$ (2.4)	THF, 23	48
7	1.2	$AlCl_3$ (2.4)	DCM, 23	c. m.
8	- -	$AlCl_3$ (2.4)	MeCN, 23	n. r.
9	1.1	$AlBr_3$ (1.2)	MeCN, 23	47
10	1.2	$AlBr_3$ (1.5)	MeCN, 23	65
11	1.2	$AlBr_3$ (2.4)	MeCN, 40	61
12	***1.2***	***$AlBr_3$ (2.4)***	***MeCN, 23***	***98***
13	1.2	$AlBr_3$ (2.4)	THF, 23	54
14	- -	$AlBr_3$ (2.4)	MeCN, 23	n. r.

[a] Reagents and conditions: 2-naphthol (0.5 mmol), solvent (0.3 *M*).
[b] Isolated yield. n. r. = no reaction was observed. c. m. = complex reaction mixture.

control experiments were carried out for the chlorination and bromination reactions. In the absence of $(PhIO)_n$ using only the AlX_3 salts, no reaction was identified (Entries 8 and 14). These experiments ruled out the AlX_3 salts as the halogenating species.

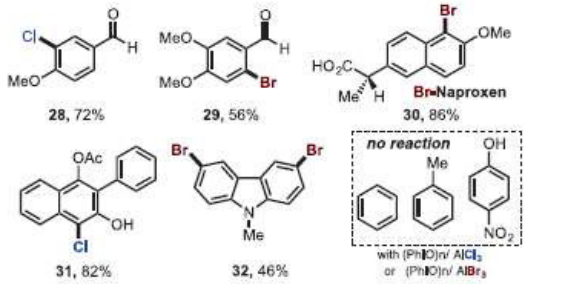
With the optimal chlorination and bromination conditions in hand, we proceeded to explore the scope of this protocol (Scheme 2).

Several mono- and bis-annular naphthols and their corresponding ethers were chlorinated and brominated under the optimized conditions. 2-Naphthol was chlorinated (**1**) and brominated (**2**) in 94% and 98% yield, respectively, on milligram scales. Remarkably, the gram scale reactions proceeded in excellent yields: 90% for 1-chloro-2-naphthol and 94% for 1-bromo-2-naphthol. The chlorination of 3-bromo-2-menthoxynaphthalene gave **5** in 96% yield, while bromination of the corresponding naphthol gave **6** in 92% yield. On the other hand, 6-bromo-2-naphthol was chlorinated and brominated to give **7** and **8** in 92% and 90% yield, respectively. Also, their methyl-ethers lead to the formation of **9** and **10** in 90% and 94% yield, respectively. Similarly, the bromination of 1-bromo-2-naphthol gave **8** in 72% yield as well as 86% yield for its methyl-ether (**10**). These lower yields compared with the previous reactions can be explained by considering that the first position is more reactive than the sixth position in the naphthalene fragment. The bromination of 2,3-dimethoxynaphthalene gave a mixture of mono- (**11**) and bis-bromination (**12**) products in 56% and 12% yield, respectively. This was the only example of polyhalogenation in the naphthalenes tested. Considering these results, a double amount of the reagent was used to complete the bis-chlorination and bromination reactions. Thus, 1,4-dichloro- (**13**) and 1,4-dibromo-2,3-dimethoxynaphthalene (**12**) were obtained in 86% and 84% yield, respectively. These experiments demonstrate that it is possible to expand our protocol to di-halogenation. To complete the study with the naphthalene core, 7-methoxy-2-naphthol was regioselectively chlorinated and brominated in the first position to give **14** and **15** in 68% and 57% yield, respectively. Also, 1,7-dimethoxynaphthalene was brominated producing **16** in 48% yield. These moderate results were attributed to complex reaction mixtures, which resulted in difficult purification. It is important to note that for this example, dihalogenation products were not iden-



Scheme 2. Scope of the (PhIO)n/AlX_3-mediated chlorination and bromination of phenols and phenol-ethers (X = Cl, Br). Reagents and conditions: phenol (0.5 mmol), (PhIO)n (1.2 equiv.), AlX_3 (2.4 equiv.), MeCN, 23 °C, open flask. a (PhIO)n (2.4 equiv.), AlX_3 (4.8 equiv.) were used. b Overall yield for the one-pot dihalogenation reaction starting from 2-naphthol.

tified, at least within the ^{1}H NMR detection limits. Selected monoannular phenols were examined. The chlorination [31] and bromination of 2-phenylphenol both gave **17** and **18** in 70% yield. The halogenation of 2-bromophenol produced chlorinated **19** and brominated **20** in 56% and 59% yield, respectively. Also, 2-iodophenol was chlorinated leading to the formation of **21** in 62% yield. The bromination of moderately activated phenols (**23**), with bulky substituents (**22** and **24**) or containing two (**25**) or three (**26**) methoxy groups was achieved in 36–68% yield. Additionally, 1,2,3-trimethoxybenzene was chlorinated to give **27** in 59% yield. Finally, to complete the initial scope exploration we carried out a one-pot dihalogenation sequence starting from 2-phenol. Thus, the one-pot, chloro-bromine and bromine-bromine reactions produced **7**, and **8** in 73% and 69% overall yield, respectively, after a single column chromatography purification. In all of the halogenation reactions, the regioselectivity observed obeyed the known reactivity for naphthalenes with initial reaction at the first position of the ring followed by the sixth position. For phenols, the *ortho*- and/or *para*-regioselectivity observed is dictated by the more electron-donating group. Also, it is important to note that both electron-rich (**1–4**, **11–18** and **22–27**) phenols and those containing electron-attracting groups (**5–10** and **19–21**) were successfully chlorinated and brominated.



Scheme 3. Functional group tolerance for the (PhIO)n /AlX_3-mediated chlorination and bromination of phenols-ethers and carbazole (X = Cl, Br).

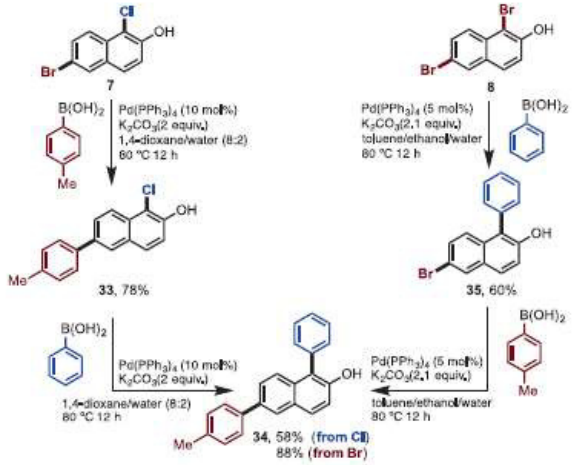
Next, various functional groups were explored to determine the tolerance of the reaction (Scheme 3).

The chlorination of formyl aromatic derivatives was explored with *p*-anisaldehyde which gave **28** in 72% yield, while the bromination of veratraldehyde led to the formation of **29** in 56% yield. The carboxylic acid group was evaluated with the bromination of naproxen giving **30** in 86% yield. Additionally, naphthols containing the ester functionality reacted under our chlorination conditions to give **31** in 82% yield. The bis-bromination of 1-methyl-1*H*-carbazole gave **32** in 46% yield. Other substrates such as benzene, toluene or 4-nitrophenol did not react under our halogenating conditions.

After evaluating the functional group scope, it was decided to demonstrate the synthetic utility of our procedure (Scheme 4).

It was decided to use products **7** and **8** obtained using our developed method to demonstrate its synthetic utility and obtain **34** *via* two sequential cross-coupling reactions. We started with a regioselective Suzuki cross-coupling using **7** and *p*-tolylboronic acid giving **33** in 78% yield. The second cross-coupling led to the formation of **34** in 58% yield. On the other hand, compound **8** was submitted to a two-consecutive cross-coupling sequence starting with selective reaction at the first position using phenylboronic acid, to give **35** in 60% yield. The second Suzuki reaction gave **34** in 88% yield.

Finally, to gain insight into the reaction mechanism, we analyzed the reaction of $(PhIO)_n$ with $AlCl_3$ and $AlBr_3$. The literature



Scheme 4. Synthetic utility of the (PhIO)n /AlX_3-mediated chlorination and bromination of phenols (X = Cl, Br).

describes that polymeric Iodosylbenzene is prone to depolymerize releasing its monomeric sub-unit PhIO when dissolved in methanol [32], upon treatment with (18-C-6/ HBF_4·Me_2O) [33], or in presence of Lewis acids such as BF_3 [34]. Based upon these precedents, it was hypothesized that the reaction of $(PhIO)_n$ with aluminum salts could depolymerize it releasing monomeric PhIO (Fig. 2).

To our delight after the reaction of $(PhIO)_n$ with aluminum chloride in acetonitrile at room temperature, the monomeric PhIO was identified by HRMS ESI(+) analysis (Fig. 3).

Fig. 2 unequivocally shows the depolymerization of $(PhIO)_n$ promoted by $AlCl_3$. It was possible to detect the protonated formed adduct of the monomeric PhIO $[PhIOH]^+$. This mass analysis demonstrated that monomeric PhIO was released after the reaction with the chlorine aluminum salt. Also is important to note that other possible species which could act as chlorinating or brominating reagents such as $PhICl_2$ or $PhIBr_2$ were not identified.

This short mechanistic experiment allowed us to rationalize that the aluminum salts display a dual role: promoting the $(PhIO)_n$ depolymerization (as supported by HRMS) while acting as a chlorine or bromine atom source. To the best of our knowledge this is the first report describing the aforementioned dual role of such AlX_3 (X = Cl, Br) salts.

With the experimental evidence obtained and the known chemistry [35] of iodine(III) the following reaction mechanism was proposed (Scheme 5).

The mechanism starts with AlX_3 coordination to $(PhIO)_n$ to give the adduct $(PhIO)_n$-AlX_3. Then the longer bond in $(PhIO)_n$ is broken while a halogen (X) is transferred to the iodine(III) center forming a plausible halogenating species. The latter reacts with the corresponding phenol or phenol-ether *via* electrophilic aromatic substitution which promotes reductive elimination from the I^{III} to the I^{I} center, releasing iodobenzene, -$OAlX_2$ and gives rise to the non-aromatic intermediate **I**. Finally, the aromatization of **I** assisted by -$OAlX_2$ leads to formation of the chlorinated or brominated phenol.

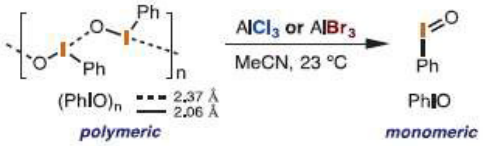


Fig. 2. Proposed depolymerization of (PhIO)n using AlX_3 (X = Cl, Br).

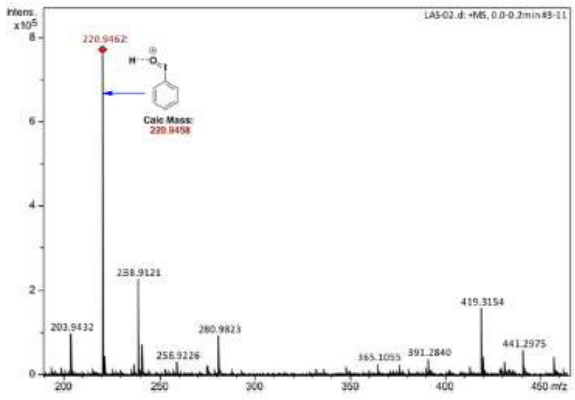
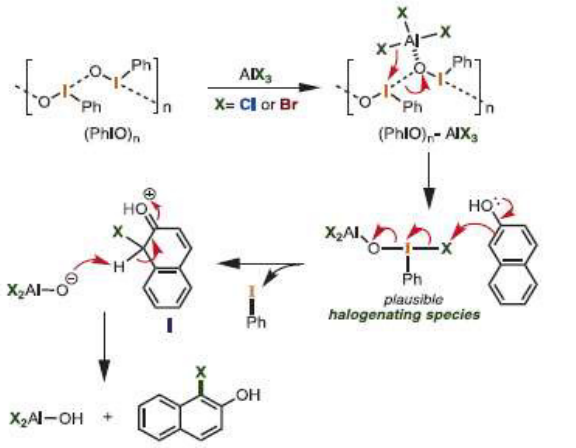


Fig. 3. Identification of monomeric PhIO after the AlX_3 promoted depolymerization of (PhIO)n.



Scheme 5. Mechanistic proposal for the (PhIO)n /AlX_3-mediated chlorination and bromination of phenols and phenol-ethers (X = Cl, Br).

In summary, we have developed an efficient and mild chlorination and bromination of mono- and bis-annular phenols using polymeric Iodosylbenzene and aluminum chloride and bromide salts as starting materials. The reaction takes place at room temperature and under open flask conditions allowing the chlorination and bromination of a broad range of phenols containing electron-donating as well as electron-attracting groups. The proposed reaction mechanism involves $(PhIO)_n$ depolymerization promoted by AlX_3 salts (X = Cl, Br) and concomitant chlorine or bromine transfer to the iodine(III) center. This process forms the plausible chlorinating $[PhI(Cl)OAlCl_2]$ or brominating $[PhI(Br)OAlBr_2]$ active species *in situ* which carries out the halogenation reaction in the phenol *via* electrophilic aromatic substitution. The AlX_3-mediated Iodosylbenzene depolymerization was supported by HRMS. To the best of our knowledge, this is the first report describing the dual role of aluminum chloride and bromide salts in the depolymerization, and as halogen source by transfer from the aluminum to the iodine(III) center. Additional mechanistic studies as well as a full computational study of this reaction are currently ongoing in our laboratory.

Acknowledgments

This work was supported by CONACyT (CB-2013/220836). We acknowledge the facilities of the DCNyE, the Chemistry Department, and the National Laboratory UG-CONACyT (LACAPFEM) at the University of Guanajuato, for full characterization. We thank CONACyT for PhD fellowships to Y.S., N.M. and D.B. We also thank Dra. Claudia de León for discussion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.05.019.

References

[1] A.H. Nelson (Ed.), Organic Bromine and Iodine Compounds, The Handbook of Environmental Chemistry, Springer, Berlin, 2003.
[2] (a) In regard to miconazole see: G.L. Regina, F.D. Dauria, A. Tafi, F. Piscitelli, S. Olla, F. Caporuscio, L. Nencioni, R. Cirrilli, F. La Torre, N.D. De Mello, S.L. Kelly, D.C. Lamb, M. Artico, M. Botta, A.T. Palamara, R. Silvestri J. Med. Chem. 51 (2008) 3841–3855;

(b) For palvix see:N. McGrath, M. Brichacek, J.T.J. Njardarson, Chem. 87 (2010) 1348–1349;
(c) For azamerone and peyssonol isolation see:K. Shiomi H. Nakamura, H. Iinuma, H. Naganawa, T. Takeuchi, H. Umezawa, Y. Iitaka, J. Antibiot. 40 (1987) 1213–1219;
(d) For rawsonol and prelaureatin isolation see:G.W. Gribble, Chem. Soc. Rev. 28 (1999) 335–346.
[3] (a) For aromatic chlorides in agrochemicals see: R. Krieger, Hayes' Handbook of Pesticide Toxicology, Elsevier, London, 1991;
(b) For aromatic chlorides in agrochemicals see:C.S. Neuman, D.G. Fujimori, C.T. Walsh, Chem. Biol. 15 (2008) 99–109.
[4] L.M. Tang, Z. Bao, Chem. Mater. 23 (2011) 446–455.
[5] A. Jain, L.S. Duvvuri, S. Farah, N. Beyth, A.J. Domb, W. Khan, Adv. Healthcare Mater. 3 (2014) 1969–1985.
[6] N. Miyaura, A. Suzuki, Chem. Rev. 95 (1995) 2457–2483.
[7] P. Espinet, A.M. Echavarren, Angew. Chem. Int. Ed. 43 (2004) 4707–4734.
[8] E. Negishi, Acc. Chem. Res. 15 (1982) 340–348.
[9] R. Chinchilla, C. Nájera, Chem. Rev. 107 (2007) 874–922.
[10] C.B. Ziegler, R.F. Heck, J. Org. Chem. 34 (1978) 2941–2946.
[11] (a) Chlorination of arenes with *N*-chloro compounds. Using N-chlorosaccharin: S.P.L. Souza, J.F.M. Silva, M.C.S. Mattos J. Braz. Chem. Soc. 14 (2003) 832–835;
(b) Using-N-chloro-2,10-camphorsultam:Z. Fan, H. Lu, Z. Cheng, A. Zhang, Chem. Commun. 54 (2018) 6008–6011;
(c) Using $(DHQD)_2PHAL$-NCP:X.-W. Liang, C. Zheng, S.-L. You, Adv. Synth. Catal. 358 (2016) 2066–2071;
(d) For a mechanistic study of chlorination using hydantoins:A. Akdag, S.D. Worley, O. Acevedo, M.L.J. McKee, Theory Comput. 3 (2007) 2282–2289.
[12] (a) Bromination of arenes with *N*-bromo compounds. R. Ghorbani-Vaghei, H. Jalili Synthesis (2005) 1099–1102;
(b) R. Ghorbani-Vaghei, Tetrahedron Lett. 44 (2003) 7529–7532;
(c) Using DBDMH and DBH:J. Auerbach, S.A. Weissman, T.J. Blacklock, M.R. Angeles, K. Hoogsteen, Tetrahedron Lett. 34 (1993) 931–934;
(d) C. Chassaing, A. Hauderchy, Y. Langlois, Tetrahedron Lett. 38 (1997) 4415–4416;
(e) For an excellent review regarding *N*-halo derivatives in the chlorination, bromination and iodination of various substrates see:H. Veisi, R. Ghorbani-Vaghei, M.A. Zolfigol, Org. Prep. Proced. Int. 43 (2011) 489–540.
[13] P. Zhang, L. Hong, G. Li, R. Wang, Adv. Synth. Catal. 357 (2015) 345–349.
[14] a) X. Sun, G. Shan, Y. Sun, Y. Rao, Angew. Chem. Int. Ed. 52 (2013) 4440–4444;
b) D. Sarkar, F.S. Melkonyan, A.V. Gulevich, V. Gevorgyan, Angew. Chem. Int. Ed. 52 (2013) 10800–10804.
[15] L. Yang, Z. Lu, S. Sthal, Chem. Commun. (2009) 6460–6462.
[16] Y. Zhang, K. Shibatomi, H. Yamamoto, Synlett 18 (2005) 2837–2842.
[17] T. Maibunkaew, C. Thongsornkleeb, J. Tummatorn, A. Bunrit, S. Ruchirawat, Synlett 25 (2014) 1769–1775.
[18] M.S. Maddox, C.J. Nalbandian, D.E. Smith, J.L. Gustafson, Org. Lett. 17 (2015) 1042–1045.
[19] A. Bose, P. Mal, Tetrahedron Lett. 55 (2014) 2154–2156.
[20] B. Sket, M. Zupan, P. Zupet, Tetrahedron 40 (1984) 1603–1606.
[21] J.M. Chen, X.M. Zeng, K. Middleton, V.V. Zhdankin, Tetrahedron Lett. 52 (2011) 1952–1955.
[22] M. Wang, Y. Zhang, T. Wang, C. Wang, D. Xue, J. Xiao, Org. Lett. 18 (2016) 1976–1979.
[23] P.B. Thorat, B.Y. Bhong, N.N. Karade, Synlett 24 (2013) 2061–2066.
[24] D.C. Braddock, G. Cansell, S.A. Hermitage, Synlett 3 (2004) 461–464.
[25] Z. Zhou, H. He, Synthesis 2 (2011) 207–209.
[26] P.A. Evans, T.A. Brandt, J. Org. Chem. 62 (1997) 5321–5326.
[27] P.D. Nahide, V. Ramadoss, K.A. Juárez-Ornelas, Y. Satkar, R. Ortíz-Alvarado, J.M. J. Cervera-Villanueva, A.J. Alonso-Castro, J.R. Zapata-Morales, M.A. Ramírez-Morales, M.A. Deveze-Álvarez, C.R. Solorio-Alvarado, Eur. J. Org. Chem. (2018) 485–493.
[28] Y. Satkar, V. Ramadoss, P.D. Nahide, E. García-Medina, K.A. Juárez-Ornelas, A.J. Alonso-Castro, R. Chávez-Rivera, J.O.C. Jiménez-Halla, C.R. Solorio-Alvarado, RSC Adv. 8 (2018) 17806–17812.
[29] A.S. Ivanov, L.A. Popov, A.I. Boldyrev, V.V. Zhdankin, Iodosylbenzene or iodozobenzene $(PhIO)_n$ is known to be a polymeric compound, Angew. Chem. Int. Ed. 53 (2014) 9617–9621.
[30] K.A. Juárez-Ornelas, J.O.C. Jiménez-Halla, T. Kato, C.R. Solorio-Alvarado, K. Maruoka, Org. Lett. (2019) ASAP.
[31] Due to a mixture of mono- and bis-chlorination products a double amount of reagent was used: (PhIO)n (2.4 equiv.)/AlCl3 (4.8 equiv).
[32] B.C. Schardt, C.L. Hill, Inorg. Chem. 22 (1983) 1563–1565.
[33] M. Ochia, K. Miyamoto, M. Shiro, T. Ozawa, K. Yamaguchi, J. Am. Chem. Soc. 125 (2003) 13006–13007.
[34] R.M. Moritary, M.P. Duncan, O. Prakash, J. Chem. Soc. Perkin Trans. 1 (1987) 1781–1784.
[35] (a) V.V. Zhdankin, ARKIVOC i (2009) 1–62;
(b) V.V. Zhdankin, P.J. Stang, Chem. Rev. 102 (2002) 2523–2584.

Send Orders for Reprints to reprints@benthamscience.net

Mini-Reviews in Organic Chemistry, 2021, *18*, 1-14

REVIEW ARTICLE

Oxidative Halogenation of Arenes, Olefins and Alkynes Mediated by Iodine(III) Reagents

Luis A. Segura-Quezada[1], Karina R. Torres-Carbajal[1], Yuvraj Satkar[1], Kevin A. Juárez Ornelas[1], Narendra Mali[1], Dipak B. Patil[1], Rocío Gámez-Montaño[1], Juan R. Zapata-Morales[2], Selene Lagunas-Rivera[1,*], Rafael Ortíz-Alvarado[3,*] and César R. Solorio-Alvarado[1,*]

[1]*Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, 36050 Guanajuato, Gto., México;* [2]*Departamento de Farmacia, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, 36050 Guanajuato, Gto., México;* [3]*Facultad de Químico Farmacobiología. Universidad Michoacana de San Nicolás de Hidalgo, Tzintzuntzan 173, Matamoros, Morelia, Mich., México*

ARTICLE HISTORY

Received: March 04, 2020
Revised: April 10, 2020
Accepted: April 10, 2020

DOI:
10.2174/1570193X17999200504095803

Abstract: Iodine(III)-based reagents have been broadly used in oxidative reactions for structural functionalization with several functional groups. Among the more relevant and useful synthetic transformations using these hypervalent λ^3-reagents, the fluorination, chlorination, bromination, as well as the iodination protocols, can be found. Herein, we present some of the most representative oxidative halogenation procedures of arenes, olefins and alkynes dating from the oldest to the more recent advances in the area, highlighting the discovery and application of new iodine(III)-based halogenating species.

Keywords: Bromination, chlorination, fluorination, iodination, iodine(III)-based reagent, oxidative halogenation.

1. INTRODUCTION

Halogenated aryls, olefins and alkynes are highly relevant and synthetically useful building blocks in several areas of the chemistry. Many specialized reviews on synthetic applications of specific classes of hypervalent iodine compounds have been published [1-5]. In this regard, the hypervalent iodine(III)-based reagents focused on the oxidative introduction of the full family of the halogens, have been extensively used for the fluorination, chlorination bromination and iodination of different arenes, heteroarenes, alkenes and alkynes. This review addresses the most relevant oxidative halogenations described in a summarized fashion during the period between 1966 to 2018.

2. OXIDATIVE FLUORINATION OF ARENES MEDIATED BY λ^3-IODANES

The fluorination of organic molecules is a field of synthesis that poses great challenges despite the progress made in recent decades. It is not surprising that fluorinated compounds play a role as templates of bioactive molecules. For example, 20% of compounds in the pharmaceutical industry include a molecule with a fluorine atom. In some cases, the replacement of hydrogen by its isostere fluorine increases the hydrophobicity leading to a delay in metabolism [6]. From the chemical and especially pharmaceutical point of view, adding fluorine at specific sites in substituted aromatic rings is an important task. The method of Balz [7], which has been used since the 1960s, many times requires diazotization with explosive diazofluoroborates. Therefore, alternatives have been designed for the synthesis of fluorinated aromatic compounds [8]. Fluorinated hypervalent iodine(III) reagents (HIR) represented initially by the difluoroiodobenzene, are promising replacements to the highly toxic heavy metal oxidants, since they possess characteristics such as broad availability, low toxicity, high stability against oxygen and moisture and their reactions usually proceed under mild conditions releasing iodobenzene in a safe manner. Thus, their versatility as synthetic tools in organic chemistry is currently increasing for chemical fluorination [9] (Fig. 1).

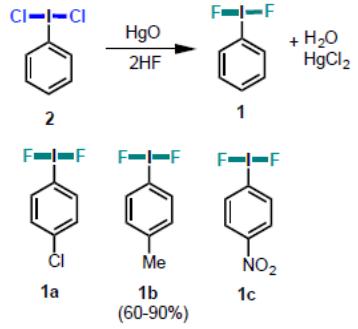
1

Fig. (1). Structure of the hypervalent iodine(III) reagent difluoroidobenzene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

*Address correspondence to these authors at the Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, 36050 Guanajuato, Gto., México;
Tel/Fax: +52-473-732-0006, ext. 1418;
E-mails: csolorio@ugto.mx; s.lagunas@ugto.mx; rafael.ortiz@umich.mx

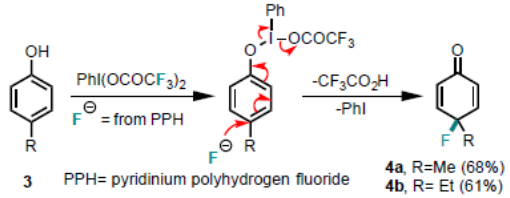
1570-193X/21 $65.00+.00

One of the initial methods for the one-step preparation of difluoroiodobenzene derivatives using HIR (**2**) was described by Carpenter in 1966 [10]. In this protocol, fluorine sources such as F_2, SF_4 or XeF_4 were avoided. The synthesis of 4-iodotoluene difluoride and derivatives **1a-c** was achieved in good yields (60-90%) (Scheme **1**).



Scheme 1. Synthesis of difluoroaryl-λ^3-iodanes **1a-c**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

With this background, Jacquesy *et al.* [11] described a new method for incorporating fluorine in aromatic compounds such as 4-substituted phenols (**3**), using the combination of PIFA [bis(trifluoroacetoxy)iodobenzene] and PPHF [12] (pyridinium polyhydrogen fluoride) to obtain mono- and polycyclic 4-fluorocyclohexa-2,5-dienes (**4**) in fairly good yields (61-77%) (Scheme **2**).

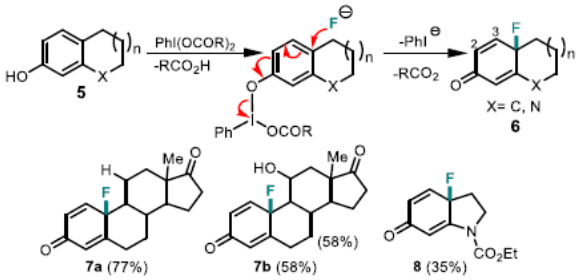


Scheme 2. Putative fluorination of aromatic phenols **4a-b** using PIFA and PPHF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

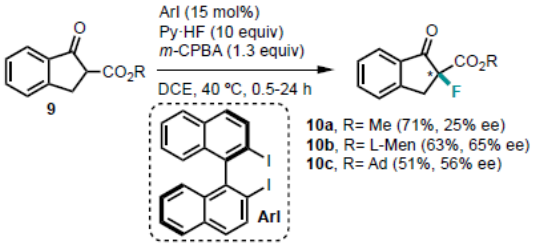
In 2004, Karam *et al.* [13] reported a fluorination procedure using phenols of type **5**. The combination of PPHF with PIDA diacetoxyiodo(benzene) gave rise to the fluorination of angular fluorocyclohexenones in low to moderate yields. The procedure was also applied to the *ipso*-fluorination of estrogen steroids (**7a-b**) within moderates yields (58-77%) as well as to the hydroindole **8** in moderate yield (35%) (Scheme **3**).

Later, Kita and Shibata [14] described enantioselective fluorination of indenones (**9**) catalyzed by the (*R*)-binaphthyldiiodide (**ArI**) which is oxidized *in situ* to the corresponding λ^3-iodane. This protocol proceeded in mild and effective reaction conditions (Scheme **4**).

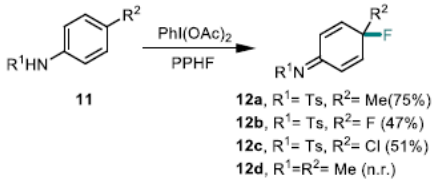
Afterward, Jouannetaud *et al.* [15] carried out the reaction of *para*-substituted anilines (**11**) in the presence of PIDA and PPHF, giving easy access to new 4-fluorinated cyclohexa-2,5-dienimines (**12**). These fluorinated derivatives **12** were obtained in low to moderate yields (18-75%). The protecting group on the aniline nitrogen atom and the substitution of the aromatic moiety have a crucial role in the success of the reaction (Scheme **5**).



Scheme 3. Preparation of substituted fluorocyclohexenones using PIFA. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 4. Enantioselective a-fluorination of 1,3-dicarbonyl-indenones, catalyzed by hypervalent iodine(III) reagents and Py·HF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



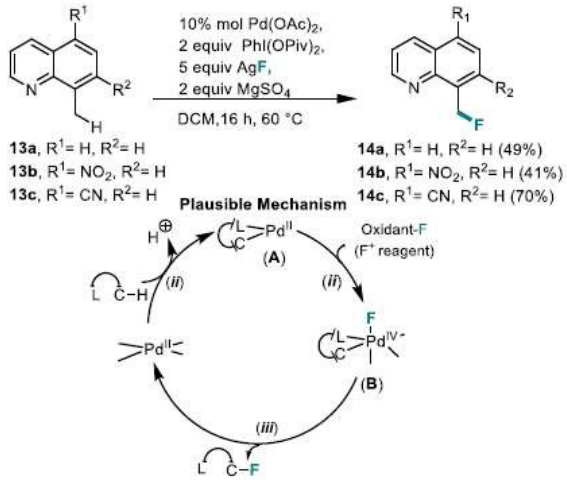
Scheme 5. Synthesis of 4-halo-4-alkylcyclohexa-2,5-dienimines (**12**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Following the timeline, the group of Sanford [16] described an example of palladium-catalyzed C-H fluorination for a variety of 8-mehtylquinoline derivatives **13**, using AgF as fluoride source in mixture with $PhI(OPiv)_2$ bis(*tert*-butylcarbonyloxy)-iodobenzene. The reaction proceeded in modest yields (41-59%) giving rise to the corresponding benzylic fluorination products **14**.

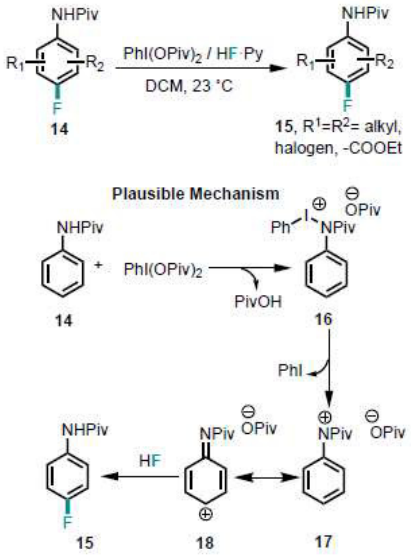
Interestingly, in the proposed catalytic cycle, the fluoride atom is the oxidizing agent (Pd^{II} to Pd^{IV}) and the source of the fluorine atom (Scheme **6**).

In 2013, Meng and Li [17] used several aromatic anilides **14** and developed regioselective *para*-fluorination obtaining the anilides **15**. The reaction took place in the presence of $PhI(OPiv)_2$ and pyridine-hydrogen fluoride (Py·HF). They obtained moderate to good yields (40-80%). Scheme **7** outlines a plausible mechanism. Herein the intermediate **16** was

obtained through the nucleophilic attack from the anilide **14** to $PhI(OPiv)_2$ following reductive elimination at the iodine atom with the concomitant generation of nitrenium ion **17**. Finally, the intermediate **18** was trapped by HF to give the corresponding fluorinated derivatives **15** (Scheme 7).

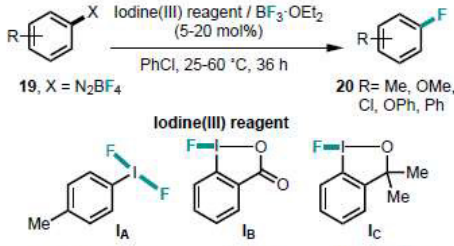


Scheme 6. Palladium-catalyzed C-H fluorination of 8-methylquinoline derivatives **13a-c** using $PhI(OPiv)_2$ as oxidant. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



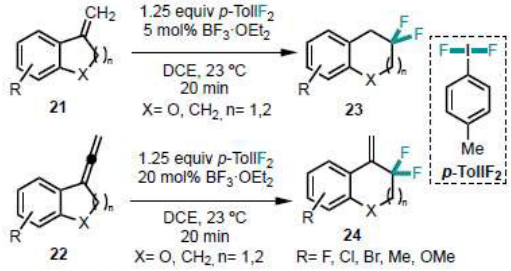
Scheme 7. Regioselective *para*-fluorination of anilides **14** mediated by $PhI(OPiv)_2$ / Py·HF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Subsequently, Hu *et al.* [18] established an efficient iodine(III)-mediated method as a safe alternative to the potentially explosive Balz-Schiemann procedure. Compounds **20** were obtained in moderate to good yields (48-83%). The reaction took place under mild conditions allowing a wide range of functional groups (Scheme **8**).



Scheme 8. Iodine(III)-catalyzed Balz–Schiemann fluorination of arenes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Recently, Murphy *et al.* [19] described a novel chemoselective fluorinative ring expansion of the alkenylbenzofuranes **21** and **22** using (p-$TolIF_2$). The procedure supports a great variety of functional groups, including carbo- and heterocycles **23-24** with moderate to good yields (49-78%) (Scheme **9**).

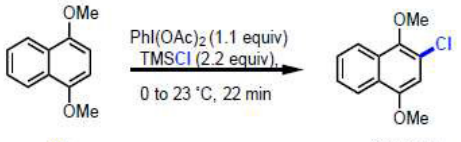


Scheme 9. Difluorinative ring expansions of 3-alkenyl- and 3-allenyl-benzofuranes using p-(difluoroiodo)toluene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3. OXIDATIVE CHLORINATION OF ARENES MEDIATED BY λ^3-IODANES

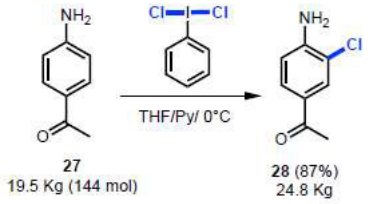
Another class of relevant compounds is the chloroarenes. Herein we describe some representative procedures for the chlorination of these compounds using novel hypervalent iodine(III) reagents as oxidants.

Evans *et al.* [20] described a method for the chlorination of 1,4-dimethoxynaphthalene by combining PIDA and trimethylsilyl chloride (TMS-Cl). 2-chloro-1,4-dimethoxynaphthalene (**26**) was obtained in 83% yield (Scheme **10**).



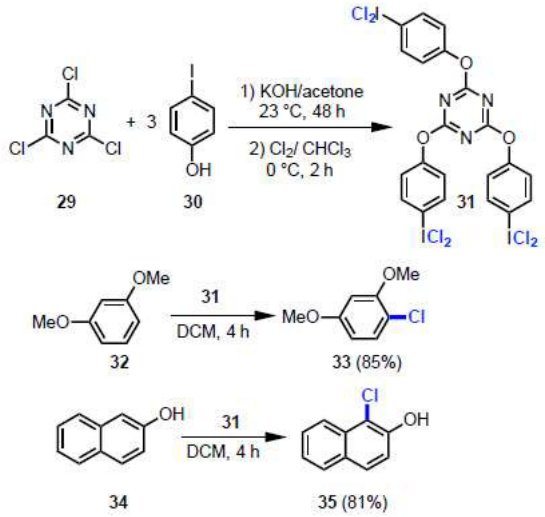
Scheme 10. Chlorination of 1,4-dimethoxynaphthalene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

On the other side, in 1998, Zanka *et al.* [21] carried out large-scale monochlorination of 4-aminoacetophenone (**27**) (144 mol) using iodobenzene dichloride. The final process was scaled up to afford 24.8 kg (87% yield) with 94% purity (Scheme **11**).



Scheme 11. Monochlorination of 4-aminoacetophenone mediated by $PhICl_2$. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

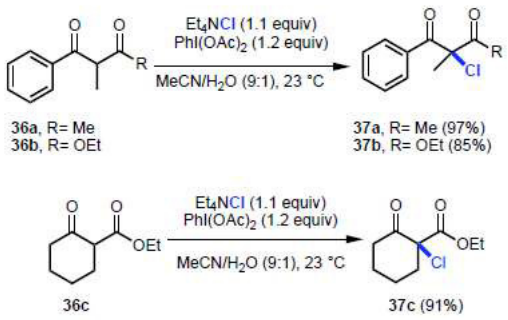
Interestingly, Karade *et al.* [22] described a method for the preparation of the recyclable hypervalent iodine(III) **31**. The iodine reagent was synthesized from 4-iodophenol **30** and 2,4,6-trichloro-1,3,5-triazine **29** to form 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine **31** as a recyclable analog non-polymeric of (dichloroiodo)benzene. This compound was used with various arenes (**32**, **34**) obtaining good to excellent yields (81-100%) of the corresponding chlorinated derivatives (**33**, **35**). The products were separated by simple filtration and recycling the iodide reagent (Scheme **12**).



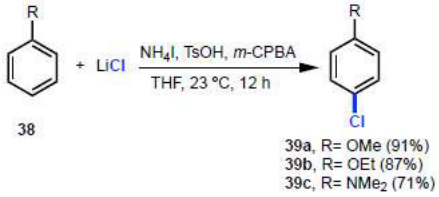
Scheme 12. Preparation of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine (**31**) and use in the chlorination of some arenes (**33**, **35**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

On the other hand, in 2014, Ibrahim *et al.* [23] set precedent for the use of ammonium salts, a source of halogens in the hypervalent iodine chemistry applied to the α-chlorination of 1,3-dicarbonyl compounds **36**. This protocol gave excellent yields (80% to 97%) under mild reaction conditions (Scheme **13**).

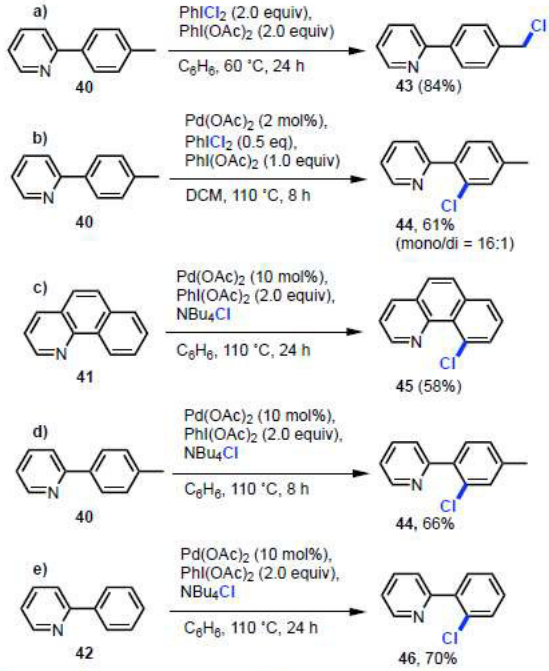
Regarding the catalytic reactions using hypervalent iodine reagents, Min *et al.* [24] developed regioselective chlorination of electron-rich aromatic compounds **38**. The protocol uses NH_4I, *m*-CPBA and LiCl to form *in situ*, the hypervalent iodane intermediate. In this way, the monochlorinated compounds **39** are obtained in moderate to good yields (71-91%) (Scheme **14**).



Scheme 13. α-Halogenation of 1,3-Dicarbonyl compounds using the Et_4NCl /PIDA system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 14. Catalytic *p*-chlorination of electron-rich arenes using the NH_4I/TsOH/*m*-CPBA/LiCl system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

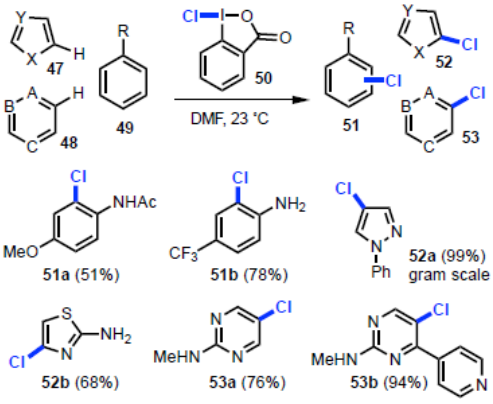


Scheme 15. Some examples of Pd-catalyzed C-H chlorination by *in situ*-generation of PhI(OAc)Cl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another chlorination protocol was developed by Kim *et al.* [25]. This procedure provides chemo- and regioselective C-H chlorination reaction at the benzylic or the aromatic position of *p*-tolylpyridine **40** if a stoichiometric or sub-stoichiometric amount of $PhICl_2$ is used (Scheme **15a-b**).

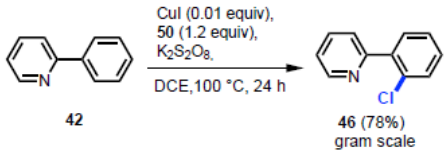
On the other hand, the palladium-catalyzed chlorination of benzo[*h*]quinoline and the *p*-tolylpyridine derivatives **40**-**42** by using $Pd(OAc)_2$, $PhI(OAc)_2$ and ammonium chloride as a chlorine source, produced the corresponding halogenated derivatives **44**-**46** in moderate to good yields (58-70%) (Scheme **15c**-**d**).

Subsequently, another chlorination method for arenes and heteroarenes (**47**-**49**) was developed by Xue [26]. Here, the use of the known iodine(III)-based chlorinating reagent 1-chloro-1,2-benziodoxol-3-one (**50**) allowed the access to several chlorinated carbo- and heterocycles (**51**-**53**) in moderate to good yields (62-82%) (Scheme **16**).



Scheme 16. Scope of chlorination by 1-chloro-1,2-benziodoxol-3-one (old-age reagent) in arenes and heteroarenes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

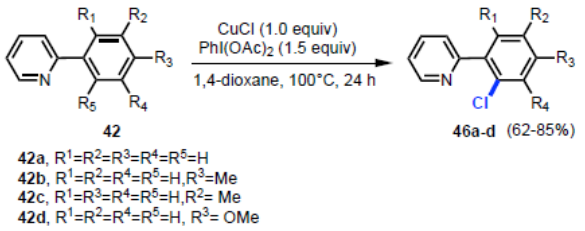
A regioselective copper-catalyzed method to successfully obtain chlorinated aryl heterocycles (**46**) was described by Parvathaneni [27]. This protocol combines **50** with copper iodide and $K_2S_2O_8$ as additive. Also, the procedure takes place in a gram scale within good yields (78%) (Scheme **17**).



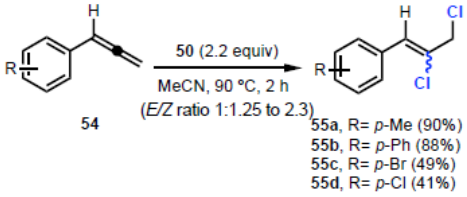
Scheme 17. Copper-catalyzed *orto*-chlorination of aryl pyridines. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The same group of Parvathaneni [28] explored the reaction with CuCl and $PhI(OAc)_2$ in several 2-arylpyridines **42**. Different chlorinated derivatives **46** were obtained in *ortho*-selective fashion with moderate to excellent yields (62-85%) (Scheme **18**).

In 2018, Murphy and Zhao [29] reported bis-chlorination of phenylallene derivatives **54** using the chlorinating hypervalent iodine(III)-based reagent **50**. This reaction allowed access to vicinal bis-chlorides **55** showing broad group tolerance and scope, in moderate to excellent yields (30- 93%) (Scheme **19**).

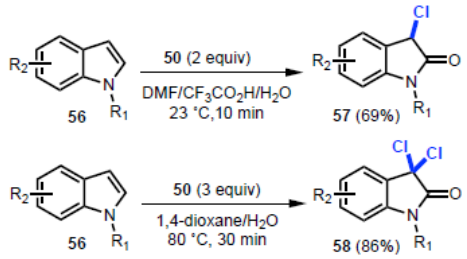


Scheme 18. *ortho*-chlorination of an aromatic compound using PIDA and CuCl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 19. Iodine(III)-mediated chlorination of phenylallene derivatives **54**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

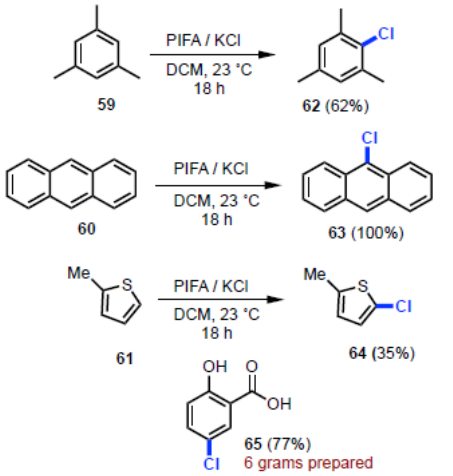
Later, in 2019, Yu *et al.* [30] described the transformation of a wide range of indoles **56** into 3-chloro-2-oxindoles (**57**-**58**). The reaction proceeds *via* the selective oxidation of C-2 with concomitant mono- or bis-chlorination at C-3. This iodine(III)-promoted chloro-oxidation is a one-pot transformation which takes place in moderate to high yields (65-99%) with excellent functional group compatibility (Scheme **20**).



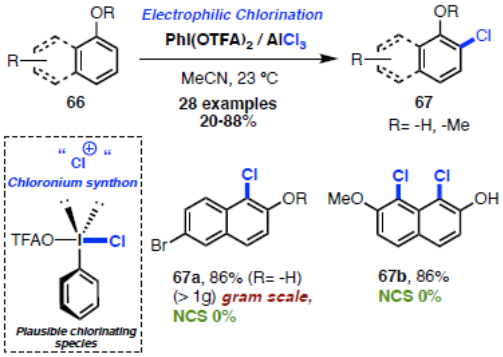
Scheme 20. Synthesis of 3-chlorooxindoles mediated by 1-chloro-1,2-benziodoxol-3-one **50**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another chlorination protocol was described by Vallribera *et al.* [31]. Herein several arenes (**59**-**61**) were chlorinated using the mixture of PIFA and KCl, yielding the halogenated derivatives (**62**-**65**). Remarkably, this new methodology was successfully tested on a multigram scale to obtain 4-chloro salicylic acid **65** (6g, 77%) (Scheme **21**).

Recently, the group of Solorio-Alvarado [32] described electrophilic chlorination of different phenols and phenol-ethers (**66**) using the PIFA/$AlCl_3$ system. The procedure that allowed access to a wide range of chlorinated naphthols (**67**), is gram-scalable and the proposed chlorinating species resulted as even more reactive than common commercially available reagents such as NCS (Scheme **22**).



Scheme 21. Chlorination of arenes by using the PIFA-KCl system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



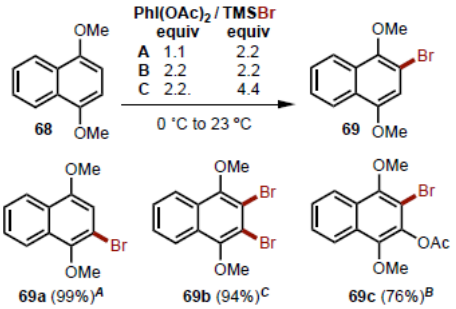
Scheme 22. Chlorination of arenes mediated by the PIFA/$AlCl_3$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. OXIDATIVE BROMINATION OF ARENES MEDIATED BY λ^3-IODANES

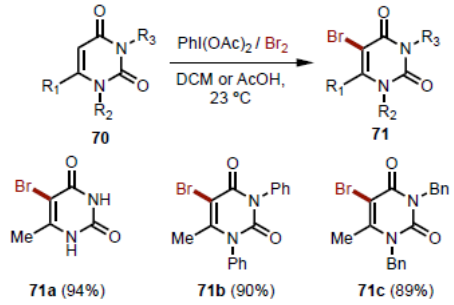
Concerning the brominated derivatives, due to their high relevance in organic synthesis, there is an increasing interest in accessing such important core. Herein we review some relevant protocols of bromination mediated by iodine(III) reagents.

In 1996, Evans *et al.* [20] reported novel haloacetoxylation of the 1,4-dimethoxynapthalene **68** using PIDA as an oxidant in the presence of TMS-Br as halogen source. The varied molar ratio of PIDA and TMS-Br gives rise to the mono- or bis-brominated or the bromoacetoxylated product **69**. The mechanism of this arene oxidation plausibly involves the formal addition of the acetoxyl anion to benzyne formed in 1,4-dimethoxynaphthalene (Scheme **23**).

In 2002, Chen *et al.* [33] described the bromination of methyluracil derivatives **70** using diacetoxyiodo(benzene) and molecular bromine. The method leads to the formation of the desired brominated methyluracils **71**, in yields usually higher than 90% (Scheme **24**).



Scheme 23. Bromination and acetoxylation of 1,4-dimethoxynaphthalene using PIDA and TMS-Br. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 24. Bromination of methyluracil mediated by the PIDA/Br_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

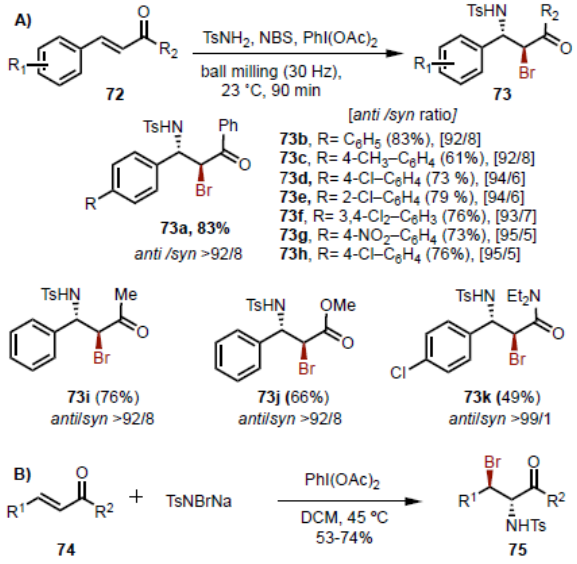
Later, Wang *et al.* [34] reported an oxidative iodine(III)-based procedure for the aminobromination of α, β-unsaturated ketones, esters, and amides **72**. The protocol displayed excellent diastereoselectivities under mechanical ball milling conditions, using $TsNH_2$ and NBS as the nitrogen and bromine sources respectively and (diacetoxyiodo)benzene as oxidant. The electron-donating olefins showed reversed regioselectivity and the corresponding bromoamine **73** was isolated with 77% of yield exclusively with *anti*-configuration (Scheme **25A**).

The same group in 2008 reported a procedure using bromamine-T as the nitrogen and bromine source for the aminobromination of electron-deficient olefins **74**. Excellent stereoselectivities were found for the corresponding reaction products **75** (Scheme **25B**) [35].

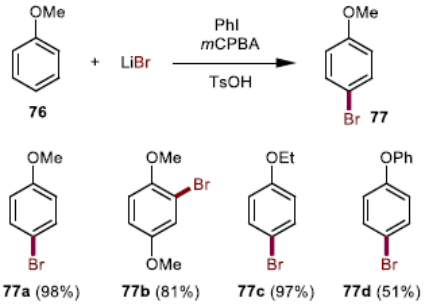
Another iodine(III)-catalyzed protocol for the regioselective monobromination of electron-rich arenes **76** was reported by Zhou *et al.* [36]. The procedure allowed the bromination of different phenols-ethers and heterocycles in excellent yields. The mechanism proposes the formation *in situ* of the Koser's type reagent [PhI(OTs)Br] following the electrophilic aromatic substitution. In this way, different brominated arenes **77** were obtained (Scheme **26**).

On the other hand, Hangirgekar *et al.* [37] developed a procedure for the facile regio- and stereoselective methoxybromination of olefins **78** using PIDA as oxidant and trimethyphenylammonium tribromide (PTAB) as a halogenating

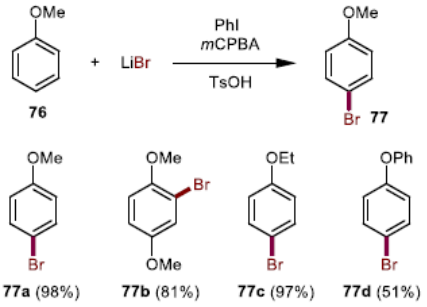
source. The mechanism of this reaction involves an S_N2 ring-opening reaction which explains the high *anti*-stereoselectivity of the brominated products **79**. Additionally, this methodology is characterized by high yields, short reaction times and easy workup procedure (Scheme **27**).



Scheme 25. Aminobromination of olefins promoted by $PhI(OAc)_2$. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

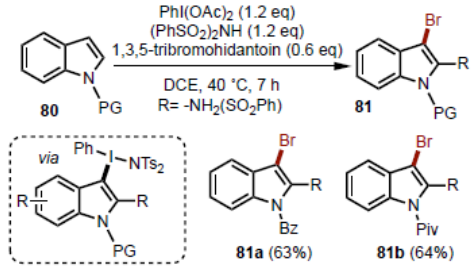


Scheme 26. Iodine(III)-catalyzed bromination of electron-rich arenes using PhI(OTs)Br. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



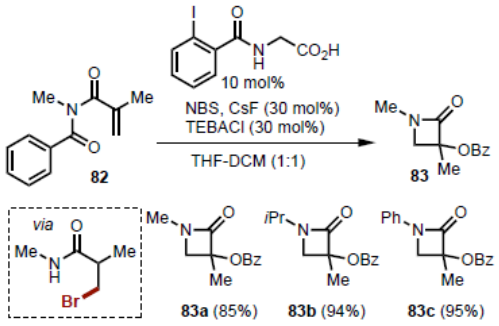
Scheme 27. Synthesis of vicinal methoxy-bromides from olefins using PIDA and PTAB. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another bromination procedure was described by Moriyama and Togo [38]. They developed a metal-free synthesis of 2-bis(sulfonyl)amino-3-bromo-indoles *via* the 1,3-migration of imide groups on indolyl(phenyl)iodonium imide. This protocol allowed the regioselective C_{sp}^2–H bromination of indoles in a two-step one-pot process (Scheme **28**).



Scheme 28. Regioselective C_{sp}^2–H bromo-amination of indoles mediated by PIDA and $(PhSO_2)NH$. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

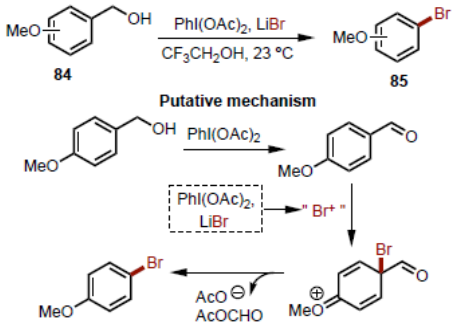
Also, the Gulder group [39] reported a one-pot synthesis of β-lactams under iodine(III)-catalyzed conditions. This cascade of reaction involves the bromination/rearrangement/cyclization sequence with excellent yields. In general, this three-step one-pot reaction gave direct access to isoserine derivatives from simple imines (Scheme **29**).



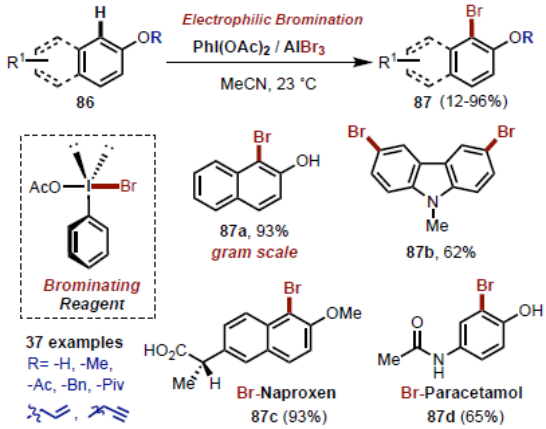
Scheme 29. Iodine(III)-catalyzed triple cascade reaction to obtain β-lactams. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Besides, Maegawa *et al.* [40] reported the first study about the dehydroxymethylbromination of methoxy-substituted benzyl alcohol derivatives **84** using (PIDA) and lithium bromide. This protocol involves the initial alcohol oxidation followed by the *ipso* attack of bromide to the arene with concomitant acetyl formate loss. The mono- or bis-brominated arenes **85** can be obtained by controlling the molar ratio of the hypervalent iodine(III) reagent and the lithium bromide (Scheme **30**).

Another relevant procedure to obtain brominated arenes was reported by Solorio-Alvarado [41]. The protocol described an efficient electrophilic bromination of several phenols and heterocycles **86**, with a broad scope of functional groups using the $PIDA/AlBr_3$ system. The gram-scale reaction proceeded with excellent yields and was applied to a wide range of different compounds including analgesics such as naproxen or paracetamol **87** (Scheme **31**).



Scheme 30. Conversion of benzylic alcohols into arene bromides. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

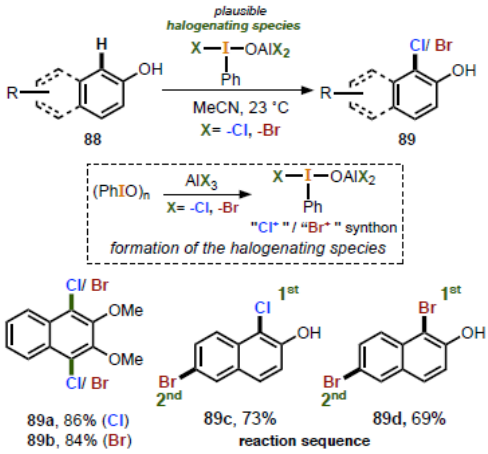


Scheme 31. Bromination of arenes mediated by the PIDA/$AlBr_3$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Moreover, a variant of the previous protocols of chlorination (PIFA/$AlCl_3$) [30] and bromination (PIDA/$AlBr_3$) [41] was described by the same group, using polymeric iodosylbenzene $(PhIO)_n$ [42] and the corresponding aluminum salt which carry a dual role in the depolymerization of iodosylbenzene and as halogen source (AlX_3; X= Cl, Br). The protocol was applied to a wide range of phenols and phenol-ethers **88** and some heterocycles obtaining different chlorinated and brominated arenes **89**. Additionally, the sequential bis-halogenation to obtain the chlorine-bromine and bromine-bromine phenols was achieved (Scheme **32**).

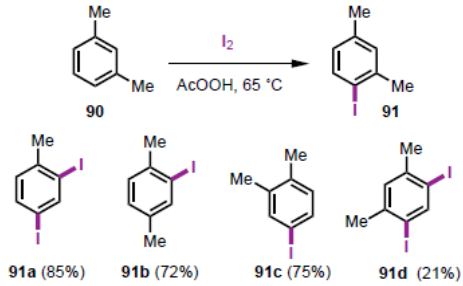
5. OXIDATIVE IODINATION OF ARENES MEDIATED BY λ^3-IODANES

The iodine derivatives including aryl-, alkyl, alkenyl- or alkynyl iodides are a very important class of organic halides, especially in organic synthesis. They are the best electrophilic partners in the cross-coupling reactions and they are used as organic building blocks for several transformations. Along with the most relevant strategies for accessing these derivatives, hypervalent iodine chemistry has been used due to the low toxicity and generally easy handling. Herein we present a brief overview of some of the most representative iodination procedures which used hypervalent iodine reagents.



Scheme 32. Chlorination and bromination of arenes mediated by the $(PhIO)_n/AlX_3$ (X= Cl, Br) system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The very initial examples of iodination with hypervalent iodine reagents were reported in 1968 by Aoki *et al.* [43]. Herein, the relative rate of the iodination reaction was measured of some aromatic compounds **90** using molecular iodine in peracetic acid as solvent. A rate law was found which can be expressed as $I = k[I_2][CH_3CO_3H]$ where the electron-withdrawing substituents accelerated the rate of reaction. Representative aryliodides **91** obtained are outlined (Scheme **33**).

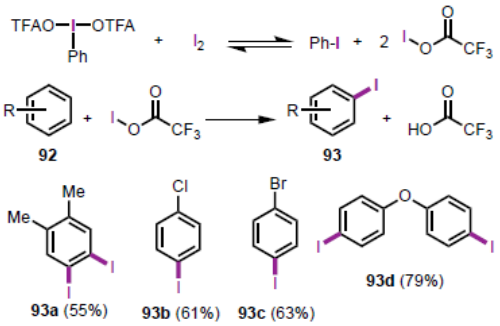


Scheme 33. Kinetic study and development of the iodination procedure of arenes using I_2/AcO_3H. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

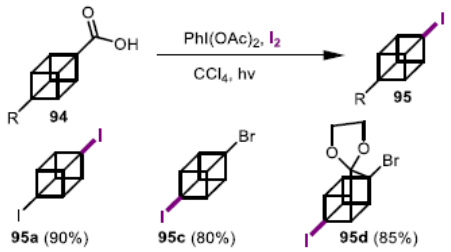
Initial examples of iodination with hypervalent iodines were reported in 1979 by Merkushev *et al.* [44]. They described the iodination of xylenes **92** in the presence of PIFA or iodosobenzene and molecular iodine using chloroform as solvent. The iodination procedure was fast and proceeded smoothly, with high yields at room temperature (Scheme **34**).

Subsequently, in 1988, Moriarty *et al.* [45] reported the decarboxylative-iodination of some cubane derivatives **94**. These homocubyl and cubyl carboxylic acids were treated with the PIDA/I_2 system in CCl_4 under irradiation condition giving rise to the corresponding iodinated products in excellent yields (80-90%). Also, the mechanism probably involves the hypervalent iodine(III) reagent prone to ligand exchange in one or two of the carboxylic acid groups to generate the

cubyl-acyloxy-hypervalent type system which upon irradiation generates the radical that is iodinated with molecular iodine (Scheme **35**).

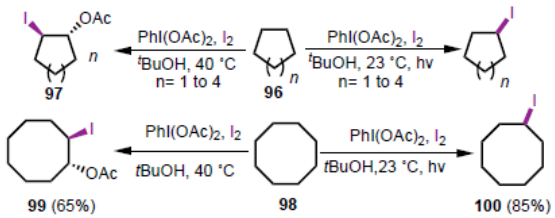


Scheme 34. Iodination of different arenes using PIFA/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



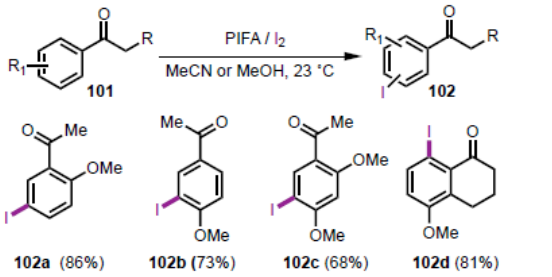
Scheme 35. Hypervalent iodine(III) mediated decarboxylative-iodination of homocubyl and cubyl carboxylic acids. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

On the other hand, C-H activation is an important and challenging concept in organic synthesis. In this regard, Barluenga *et al.* [46] developed a new protocol for the C-H iodination using hypervalent iodine(III) reagents. In this approach, the single as well as the double formal C-H bond activation occurs either in iodoalkanes or 1-acetoxy-2-iodocycloalkanes respectively **96-98**. The reaction proceeds by treating the alkanes with PIDA and I_2 in *tert*-butylalcohol under photochemical or thermal conditions, giving rise to the iodinated products **99-100**. The authors suggested that the reaction proceeded through a radical pathway to initially generate species of hypoiodite nature such as ^{t}**BuOI**. This approach shows different diastereoselectivities under thermal and photochemical conditions (Scheme **36**).



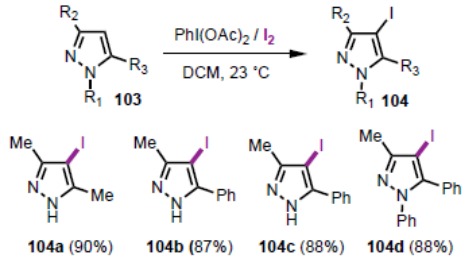
Scheme 36. Photochemical and thermal iodination of hydrocarbons with PhI(OAc)$_2$/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

A slight variant was reported in 2003 by Tingoli *et al.* [47]. Herein the iodination of aryl ketones **101** using PIFA and molecular iodine took place in acetonitrile or methanol to produce de-iodinated aromatic derivatives **102** (Scheme **37**).



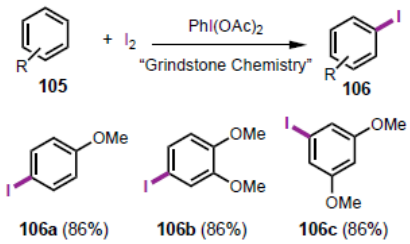
Scheme 37. Electrophilic aromatic-iodination of alkyl- and aryl ketones mediated by the PIFA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Also, Chen *et al.* [48] reported the iodination of pyrazoles **103** mediated by the broadly used PIDA/I_2 system. The reaction proceeded in dichloromethane at room temperature to yield the corresponding 4-iodopyrazole derivatives **104** generally in high yields (Scheme **38**).



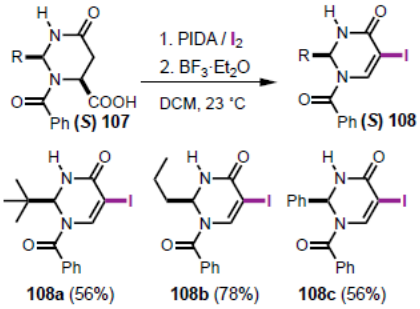
Scheme 38. Iodination of pyrazole derivatives mediated by PIDA/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

An additional use of the PIDA/I_2 system was developed by Karade *et al.* [49] using the "Grindstone Chemistry" approach. This new approach allowed the mild, regioselective, and easy to handle iodination of different arenes **105** with a broad substrate scope, for accessing some iodoarene derivatives **106**. Improved yields and higher purities of the products were observed compared with those from established methods (Scheme **39**).



Scheme 39. Iodination of arenes with the PIDA/I_2 system under the grindstone chemistry approach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

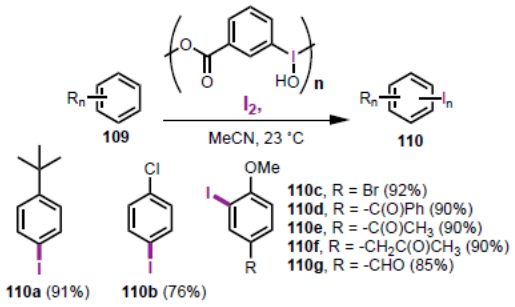
In 2007, Juaristi *et al.* [50] developed an iodination procedure for the synthesis of α-substituted β-aminoacids, using the PIDA/I_2 system. The reaction proceeded with perhydropyrimidinone-6-carboxylic acids **107** in DCM at room temperature to afford the expected mixture of the reduced enones and iodoenones. The addition of $BF_3{\cdot}Et_2O$ drives the reaction to the complete conversion into iodoenone **108** (Scheme **40**).



Scheme 40. Preparation of enantiopure iodoenones using the PIDA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Subsequently, Kirschning *et al.* [51] reported in 2007, a new approach for the iodination of arenes and heterocyclic compounds using a polymeric hypervalent iodine(III) reagent. In this approach, *m*-iodosylbenzoic acid performed the iodination of arenes **109** in the presence of molecular iodine, at room temperature, in acetonitrile, obtaining good yields of the corresponding iodinated arenes **110**.

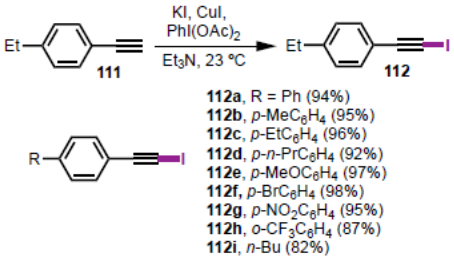
The *m*-iodobenzoic acid can easily be removed by simple acidification or by resin extraction (Scheme **41**).



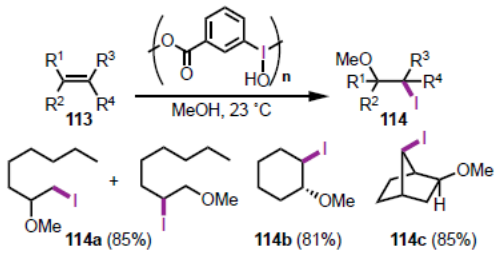
Scheme 41. Mono-iodination of arenes with *m*-iodosylbenzoic acid and molecular iodine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The iodination mediated by hypervalent iodine(III) reagents has also been applied to alkynes. In 2007, Yan *et al.* [52] reported the iodination of terminal alkynes **111** using PIDA, potassium iodide and copper(I). The protocol afforded 1-iodoalkynes **112** in good to excellent yields under mild conditions (Scheme **42**).

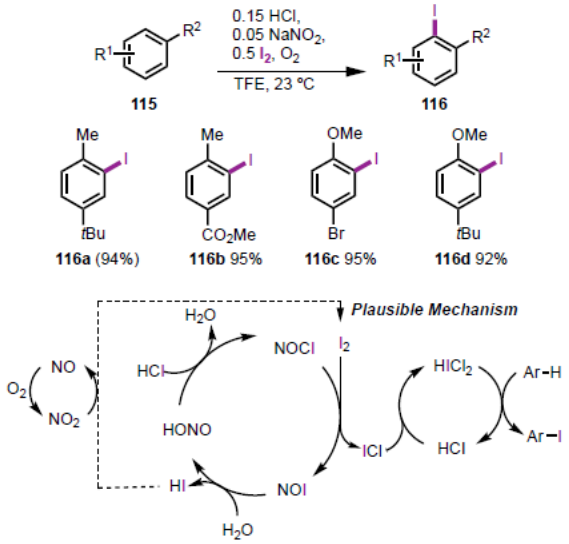
Yusubov *et al.* [53] developed another approach using *m*-iodosylbenzoic acid and molecular iodine for the iodination of alkenes and alkynes **113**. This efficient and facile method afforded the iodinated products **114** in good yields under mild conditions. The final purification of *m*-iodosylbenzoic acid by acidification or extraction by resins allowed easy isolation of the obtained products (Scheme **43**).



Scheme 42. Iodination of arenes mediated by PIDA/KI/CuI. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

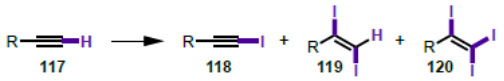


Scheme 43. Iodomethoxylations of alkenes using hypervalent *m*-iodosylbenzoic and molecular iodine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 44. Nitrite-mediated aerobic iodination of arenes by *in situ* generation of ICl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Later, Iskra *et al.* [54] reported an electrophilic aromatic iodination catalyzed by nitrous acid generated *in situ*. Different arenes are converted to the corresponding iodinated products *via* oxidative treatment at room temperature with catalytic quantities of iodine and nitrous acid in trifluoroethanol as the solvent. Dichloroiodic acid is proposed as the hypervalent iodinating reagent. A plausible mechanism for

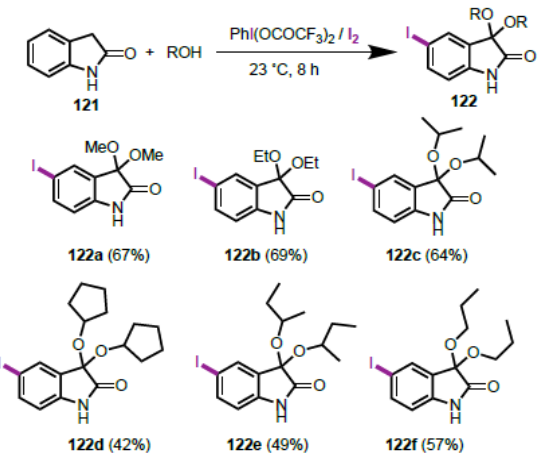


alkyne	method	mayor product	%yield (2:3:4)
R= *p*-tolyl	A	**2a**	99 (100:0:0)
	B	**3a**	99 (0.8:98.8:0.4)
	C	**4a**	93(3.7:3.2:93.1)
R= Ph	A	**2b**	93(100:0:0)
	B	**3b**	97(0.2:97.6:2.2)
	C	**4b**	91(0.8:0.7:98.5)
R= *m*-tolyl	A	**2c**	98(100:0:0)
	B	**3c**	98(0.9:98.1:1.0)

Method A: TBAI / $PhI(OAc)_2$ **Method B**: KI / $PhI(OAc)_2$

Method C: 1. TBAI / $PhI(OAc)_2$, 2. KI / $PhI(OAc)_2$, 3. KI / $PhI(OAc)_2$

Scheme 45. Iodination of alkynes mediated by PIDA/TBAI or PIDA/KI. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



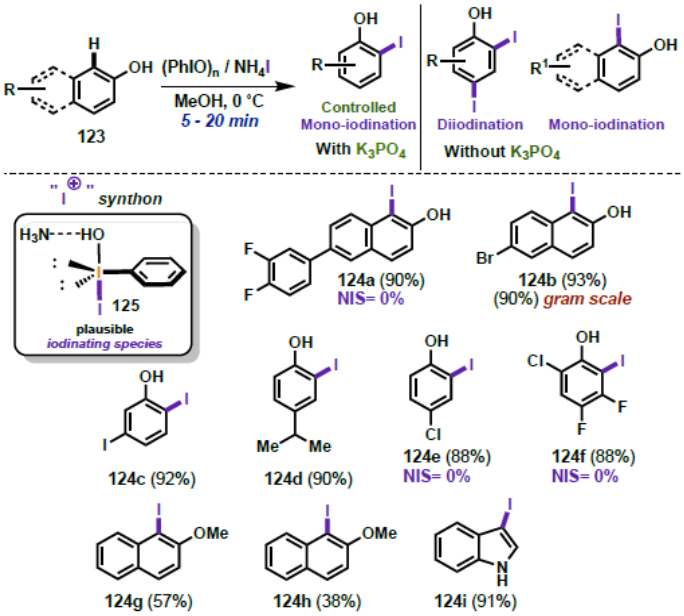
Scheme 46. Iodoalkoxylation of arenes mediated by the PIFA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

this reaction involves the interaction of sodium nitrate and hydrochloric acid to produce nitrosyl chloride. This reacts with molecular iodine to generate iodine chloride through a process that likely liberates nitrosyl iodide as a by-product. Iodine chloride reacts with arenes to produce iodinated product (Scheme **44**).

In 2017, Maruoka and Liu [55] developed a new practical approach for the chemoselective mono-, di-, and tri-iodination of alkynes using hypervalent iodine(III) reagents. The PIDA/TBAI (tetrabutylammonium iodide) system is selectively applied for mono-iodination, while the PIDA/KI system results in di-iodination. Combining the TBAI/PIDA and PIDA/KI systems in a one-pot protocol provided the corresponding tri-iodination products efficiently (Scheme **45**).

Kotagiri *et al.* [56] reported metal-free iodoalkoxylation of oxindoles **121** using the PIFA/I_2 system. In the first instance, the ketal formation at the benzylic carbon takes place, followed by the oxidative iodination leading to the formation of the observed functionalized compounds **122** (Scheme **46**).

Recently, another procedure for the electrophilic iodination of phenols **123** and phenol-ethers has been described in 2018 by Solorio-Alvarado [57]. The protocol is gram-scalable and in many cases more efficient than com-



Scheme 47. Controlled di- or monoiodination of arenes mediated by the $(PhIO)_n/NH_4I$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

mon procedures using iodinating reagents such as NIS. Additionally, the di-iodination of mono-annular phenols is a typical issue difficult to control. In this report, the mono-iodination of several phenols was exclusively obtained by buffering the reaction with K_3PO_4, while the reaction in the absence of this salt, usually produced di-iodinated derivatives. Additional computational studies revealed **125** as the most plausible iodinating species (Scheme **47**).

CONCLUSION

In summary, some of the most representative protocols for the halogenation of arenes, olefins and alkynes mediated by different types of iodine(III)-based reagents were described. Remarkably, every year there is a notable increased interest and demand for the use of iodine(III) chemistry positioned as one of the main tools in organic synthesis. There are several competitive advantages for using hypervalent iodine(III)-based reagents for the functional groups introduction, specifically concerning the full family of halogens in different aryls, heteroaryls, alkenes and alkynes, compared with the transition-metal transformation strategy. This oxidative approach for the functionalization of aromatic derivatives resulted generally in the fast, efficient, non-toxic and easy to handle reactions with the final introduction of the fluorine, chlorine, bromine and iodine atoms.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We acknowledge the Guanajuato University and the National Laboratory UG-CONACyT (LACAPFEM) at the UG. We thank CONACyT for providing fellowship to YS, L. A. S-Q, K. R. T-C., K. A. J-O., N. M. and D. B. P.

REFERENCES

[1] Lee, J.H.; Choi, S.; Hong, K.B. Alkene Difunctionalization Using Hypervalent Iodine Reagents: Progress and Developments in the Past Ten Years. *Molecules,* **2019**, *24*(14), 2634. http://dx.doi.org/10.3390/molecules24142634 PMID: 31331092

[2] Li, X.; Chen, P.; Liu, G. Recent advances in hypervalent iodine(III)-catalyzed functionalization of alkenes. *Beilstein J. Org. Chem.*, **2018**, *14*, 1813-1825. http://dx.doi.org/10.3762/bjoc.14.154 PMID: 30112085

[3] Zhdankin, V.V. Hypervalent iodine(III) reagents in organic synthesis. *ARKIVOC,* **2009**, *i*, 1-62.

[4] Yoshimura, A.; Zhdankin, V.V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.,* **2016**, *116*(5), 3328-3435. http://dx.doi.org/10.1021/acs.chemrev.5b00547 PMID: 26861673

[5] Peilleron, L.; Grayfer, T.D.; Dubois, J.; Dodd, R.H.; Cariou, K. Iodine(III)-mediated halogenations of acyclic monoterpenoids. *Beilstein J. Org. Chem.*, **2018**, *14*, 1103-1111. http://dx.doi.org/10.3762/bjoc.14.96 PMID: 29977382

[6] Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D.M.; Santi, C.; Ruzziconi, R.; Soloshonok, V.A. Fluorine-containing drugs approved by the FDA in 2018. *Chemistry,* **2019**, *25*(51), 11797-11819. http://dx.doi.org/10.1002/chem.201901840 PMID: 31099931

[7] Balz, G.; Schiemann, G. *Eur. J. Inorg. Chem.,* **1927**, *60*, 1186-1190.

[8] Tellitu, I. Explorando nuevas aplicaciones del reactive de yodo hipervalentes PIFA [bis(trifluoroacetoxi)yodobenceno] en la construcción de heterocíclos pirrolidínicos. *An. Quim.,* **2013**, *109*, 5-10.

[9] Kohlhepp, S.V.; Gulder, T. Hypervalent iodine(III) fluorinations of alkenes and diazo compounds: new opportunities in fluorination chemistry. *Chem. Soc. Rev.,* **2016**, *45*(22), 6270-6288. http://dx.doi.org/10.1039/C6CS00361C PMID: 27417189

[10] Carpenter, W. *J. Org. Chem.,* **1966**, *31*, 2688-2689. http://dx.doi.org/10.1021/jo01346a512

[11] Karam, O.; Jacquesy, J.C.; Jouannetaud, M.P. Nucleophilic *para*-fluorination of 4-alkylphenols by hypervalent iodine reagent and pyridinium polyhydrogen fluoride (PPHF), a novel route to 4-fluorocyclohexa-2,5-Dienones. *Tetrahedron Lett.,* **1994**, *35*, 2541-2544. http://dx.doi.org/10.1016/S0040-4039(00)77165-6

[12] Olah, G.A.; Shih, J.G.; Prakash, G.K.S. Fluorine-containing reagents in organic synthesis. *J. Fluor. Chem.,* **1986**, *33*, 377-396. http://dx.doi.org/10.1016/S0022-1139(00)85282-3

[13] Karam, O.; Martin-Mingot, A.; Jouannetaud, M.P.; Jacquesy, J.C.; Cousson, A. Efficient oxidative *ipso*-fluorination of *para*-substituted phenols using pyridinium polyhydrogen fluoride in combination with hypervalent iodine(III) reagents. *Tetrahedron,* **2004**, *60*, 6629-6638. http://dx.doi.org/10.1016/j.tet.2004.05.083

[14] Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, K.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. Iodoarene-catalyzed fluorination and aminofluorination by an Ar-I/HF·Pyridine/*m*CPBA system. *Chem. Sci. (Camb.),* **2014**, 2754-2760. http://dx.doi.org/10.1039/C3SC53107D

[15] Basset, L.; Martin-Mingot, A.; Jouannetaud, M.P.; Jacquesy, J.C. Access to new 4-fluorocyclohexa-2,5-dienimines using hypervalent iodine and pyridinium polyhydrogen fluoride. *Tetrahedron Lett.,* **2008**, *49*, 1551-1554. http://dx.doi.org/10.1016/j.tetlet.2007.12.082

[16] McMurtrey, K.B.; Racowski, J.M.; Sanford, M.S. Pd-catalyzed C-H fluorination with nucleophilic fluoride. *Org. Lett.,* **2012**, *14*(16), 4094-4097. http://dx.doi.org/10.1021/ol301739f PMID: 22844875

[17] Tian, T.; Zhong, W.H.; Meng, S.; Meng, X.B.; Li, Z.J. Hypervalent iodine mediated para-selective fluorination of anilides. *J. Org. Chem.,* **2013**, *78*(2), 728-732. http://dx.doi.org/10.1021/jo302099d PMID: 23228030

[18] Xing, B.; Ni, C.; Hu, J. Hypervalent iodine(III)-catalyzed Balz-Schiemann fluorination under mild conditions. *Angew. Chem. Int. Ed. Engl.,* **2018**, *57*(31), 9896-9900. http://dx.doi.org/10.1002/anie.201802466 PMID: 29932480

[19] Zhao, Z.; To, A.J.; Murphy, G.K. Difluorinative ring expansions of benzo-fused carbocycles and heterocycles are achieved with p-(difluoroiodo)toluene. *Chem. Commun. (Camb.),* **2019**, *55*(98), 14821-14824. http://dx.doi.org/10.1039/C9CC08310C PMID: 31763650

[20] Evans, P.A.; Brandt, T.A. Novel Haloacetoxylation of 1,4-dimethoxynaphthalenes using hypervalent iodine chemistry. *Tetrahedron Lett.,* **1996**, *37*, 6443-6446. http://dx.doi.org/10.1016/0040-4039(96)01427-X

[21] Zanka, A.; Takeuchi, H.; Kubota, A. Large-Scale Preparation of iodobenzene dichloride and efficient monochlorination of 4-Aminoacetophenone. *Org. Process Res. Dev.,* **1998**, *2*, 270-273. http://dx.doi.org/10.1021/op980024e

[22] Thorat, P.B.; Bhong, B.Y.; Karade, N.Y. 2,4,6-Tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine as a new recyclable hyperva-

lent iodine(III) reagent for chlorination and oxidation Reactions. *Synlett,* **2013**, *24*, 2061-2066.
http://dx.doi.org/10.1055/s-0033-1339495

[23] Galligan, M.J.; Akula, R.; Ibrahim, H. Unified strategy for iodine(III)-mediated halogenation and azidation of 1,3-dicarbonyl compounds. *Org. Lett.,* **2014**, *16*(2), 600-603.
http://dx.doi.org/10.1021/ol403504z PMID: 24372311

[24] Min, Z.; Ying-Guo, F. An efficient monochlorination of electron-rich aromatic compounds catalyzed by ammonium iodide. *J. Chem. Res.,* **2014**, *38*, 197-199.
http://dx.doi.org/10.3184/174751914X13929076043809

[25] Kang, K.; Lee, S.; Kim, H. Radical chlorination with hypervalent iodine(III) generated by ligand exchange: revisiting palladium(II)-catalyzed directed C-H chlorination. *Asian J. Org. Chem.,* **2015**, *4*, 137-140.
http://dx.doi.org/10.1002/ajoc.201402284

[26] Wang, M.; Zhang, Y.; Wang, T.; Wang, C.; Xue, D.; Xiao, J. Story of an age-old reagent: an electrophilic chlorination of arenes and heterocycles by 1-Chloro-1,2-Benziodoxol-3-One. *Org. Lett.,* **2016**, *18*(9), 1976-1979.
http://dx.doi.org/10.1021/acs.orglett.6b00547 PMID: 27074528

[27] Parvathaneni, S.P.; Perumgani, P.C. Regioselective chlorination of aryl C–H bonds with the hypervalent iodine(III) reagent 1-Chloro-1,2-Benziodoxol-3-One. *Asian J. Org. Chem.,* **2018**, *7*, 324-327.
http://dx.doi.org/10.1002/ajoc.201700620

[28] Perumgani, P.C.; Parvathaneni, S.P.; Surendra Babu, G.V.; Srinivas, K.; Mandapati, M.R. Copper(I) halide for regioselective *ortho*-halogenation of directed arenes. *Catal. Lett.,* **2018**, *148*, 1067-1072.
http://dx.doi.org/10.1007/s10562-018-2324-5

[29] Zhao, Z.; Murphy, G.K. Chlorination of phenylallene derivatives with 1-chloro-1,2-benziodoxol-3-one: synthesis of *vicinal*-dichlorides and chlorodienes. *Beilstein J. Org. Chem.,* **2018**, *14*, 796-802.
http://dx.doi.org/10.3762/bjoc.14.67 PMID: 29719576

[30] Jiang, X.; Yang, L.; Yang, W.; Zhu, Y.; Fang, L.; Yu, C. Controllable synthesis of 3-chloro- and 3,3-dichloro-2-oxindoles *via* hypervalent iodine-mediated chlorooxidation. *Org. Biomol. Chem.,* **2019**, *17*(28), 6920-6924.
http://dx.doi.org/10.1039/C9OB01173K PMID: 31282524

[31] Granados, A.; Jia, Z.; del Olmo, M.; Vallribera, A. *In-situ* generation of hypervalent iodine reagents for the electrophilic chlorination of arenes. *Eur. J. Org. Chem.,* **2019**, 2812-2818.
http://dx.doi.org/10.1002/ejoc.201900237

[32] Nahide, P.D.; Ramadoss, V.; Juárez-Ornelas, K.A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J.M.J.; Alonso-Castro, A.J.; Zapata-Morales, J.R.; Ramírez-Morales, M.A.; Ruiz-Padilla, A.J.; Deveze-Álvarez, M.A.; Solorio-Alvarado, C.R. *In Situ* formed I^{III}-based reagent for electrophilic *ortho*-chlorination of phenols and phenol-ethers: the use of PIFA/$AlCl_3$ system. *Eur. J. Org. Chem.,* **2018**, 485-493.
http://dx.doi.org/10.1002/ejoc.201701399

[33] Cheng, D.; Chen, Z.; Zheng, Q. Hypervalent iodine in synthesis 91: a mild and efficient method for the halogenation of 6-methyluracil derivatives. *J. Chem. Res.,* **2002**, 624-625.
http://dx.doi.org/10.3184/030823402103171032

[34] Wu, X-L.; Xia, J-J.; Wang, G-W. Aminobromination of olefins with $TsNH_{(2)}$ and NBS as the nitrogen and bromine sources mediated by hypervalent iodine in a ball mill. *Org. Biomol. Chem.,* **2008**, *6*(3), 548-553.
http://dx.doi.org/10.1039/B717333D PMID: 18219426

[35] Xia, J-J.; Wu, X-L.; Wang, G-W. Hypervalent iodine-promoted aminobromination of electron-deficient olefins with bromamine-T. *ARKIVOC,* **2008**, *16*, 22-28.

[36] Zhou, Z.; He, X. An Efficient and Regioselective Monobromination of electron-rich aromatic compounds using catalytic hypervalent iodine(III) reagent. *Synthesis,* **2011**, *2*, 207-209.
http://dx.doi.org/10.1055/s-0030-1258350

[37] Shirodkar, S.G.; Hangirgekar, S.P. A Regioselective and stereoselective methoxy bromination of olefins using diacetoxyiodobenzene and phenyltrimethyl ammoniumtribromide. *Orient. J. Chem.,* **2011**, *27*, 179-184.

[38] Moriyama, K.; Ishida, K.; Togo, H. Regioselective $C(_{sp}{}^2)$-H dual functionalization of indoles using hypervalent iodine(III): bromoamination *via* 1,3-migration of imides on indolyl(phenyl)iodonium imides. *Chem. Commun. (Camb.),* **2015**, *51*(12), 2273-2276.
http://dx.doi.org/10.1039/C4CC09077B PMID: 25556519

[39] Patzelt, C.; Pöthig, A.; Gulder, T. Iodine(III)-catalyzed cascade reactions enabling a direct access to β-lactams and α-hydroxy-β-amino acids. *Org. Lett.,* **2016**, *18*(14), 3466-3469.
http://dx.doi.org/10.1021/acs.orglett.6b01658 PMID: 27380445

[40] Shibata, A.; Kitamoto, S.; Fujimura, K.; Hirose, Y.; Hamamoto, H.; Nakamura, A.; Miki, Y.; Maegawa, T. Dehydroxymethyl bromination of alkoxybenzyl alcohols by using a hypervalent iodine reagent and lithium bromide. *Synlett,* **2018**, *29*, 2275-2278.
http://dx.doi.org/10.1055/s-0037-1610980

[41] Satkar, Y.; Ramadoss, V.; Nahide, P.D.; García-Medina, E.; Juárez-Ornelas, K.A.; Alonso-Castro, A.J.; Chávez-Rivera, R.; Jiménez-Halla, J.O.C.; Solorio-Alvarado, C.R. Practical, mild and efficient electrophilic bromination of phenols by a new I(III)-based reagent: the PIDA–$AlBr_3$ system. *RSC Advances,* **2018**, *8*, 17806-17812.
http://dx.doi.org/10.1039/C8RA02982B

[42] Segura-Quezada, A.; Satkar, Y.; Patil, D.; Mali, N.; Wrobel, K.; González, G.; Zárraga, R.; Ortiz-Alvarado, R.; Solorio-Alvarado, C.R. Iodine (III)/AlX_3-mediate electrophilic chlorination and brominating of arenes. The Dual Role of AlX_3 (X=Cl, Br) in the $(PhIO)_n$ depolymerization and halogen Source. *Tetrahedron Lett.,***2019**, *60*, 1551-1555. Other relevant functional groups introduced using iodine(III) and aluminums salts. (a) For nitration of arenes using $(PhIO)_n$/$Al(NO_3)_3$ see: Juárez-Ornelas, K. A.; Jiménez-Halla, J. O. C.; Kato, T.; Solorio-Alvarado, C. R.; Maruoka, K. Iodine(III)-catalyzed electrophilic nitration of phenols *via* non-brönsted acidic NO_2^+ generation. *Org. Lett.***2019**, *21*, 315-1319. (b) For benzylic oxidation $(PhIO)_n$/$Al(NO_3)_3$ see: Yahuaca-Juárez, B.; González, G.; Ramírez-Morales, M. A.; Alba-Betancourt, C.; Deveze-Álvarez, M. A.; Mendoza-Macías, C. L.; Ortiz-Alvarado, R.; Juárez-Ornelas, K. A.; Solorio-Alvarado, C. R.; Maruoka, K. Iodine(III)-catalyzed benzylic oxidation by using the $(PhIO)_n$/$Al(NO_3)$ system. *Synth. Commun.,* **2020**, *50*, 539-548.

[43] Ogata, Y.; Aoki, K. Iodination of aromatic compounds with a mixture of iodine and peracetic acid. 111. Autocatalysis and relative rates. . *J. Am. Chem. Soc.,* **1968**, *90*, 6187-6191.
http://dx.doi.org/10.1021/ja01024a043

[44] Merkushev, E.B.; Simakhina, N.D.; Koveshnikova, G.M. A new convenient iodination method of aromatic compunds. *Syntheis,* **1980**, *80*, 486-487.
http://dx.doi.org/10.1055/s-1980-29066

[45] Moriarty, R.M.; Khosrowshahi, J.S.; Dalecki, T.M. Hypervalent iodine iodinative decarboxylation of cubyl and homocubyl carboxylic acids. *J. Chem. Soc. Chem. Commun.,* **1987**, *9*, 675-676.
http://dx.doi.org/10.1039/c39870000675

[46] Barluenga, J.; González-Bobes, F.; González, J.M. Activation of alkanes upon reaction with $PhI(OAc)_2$-I_2. *Angew. Chem. Int. Ed. Engl.,* **2002**, *41*(14), 2556-2558.
http://dx.doi.org/10.1002/1521-3773(20020715)41:14<2556::AID-ANIE2556>3.0.CO;2-C PMID: 12203532

[47] Panunzi, B.; Rotiroti, L.; Tingoli, M. Solvent directed electrophilic iodination and phenylselenenylation of activated alkyl aryl ketones. *Tetrahedron Lett.,* **2003**, *44*, 8753-8756.
http://dx.doi.org/10.1016/j.tetlet.2003.10.037

[48] Cheng, D-P.; Chen, Z-C.; Zheng, Q-G. Hypervalent iodine in synthesis. 90. A mild and efficient method for the iodination of pyrazoles. *Synth. Commun.,* **2003**, *33*, 2671-2676.
http://dx.doi.org/10.1081/SCC-120021987

[49] Karade, N.N.; Tiwari, G.B.; Huple, D.B.; Siddiqui, T.A.J. Grindstone chemistry: (diacetoxyiodo)benzene-mediated oxidative nuclear halogenation of arenes using NaCl, NaBr or I_2. *J. Chem. Res.,* **2006**, 366-368.
http://dx.doi.org/10.3184/030823406777946761

[50] Díaz-Sánchez, B.R.; Iglesias-Arteaga, M.A.; Melgar-Fernández, R.; Juaristi, E. Synthesis of 2-substituted-5-halo-2,3-dihydro-4(*H*)-pyrimidin-4-ones and their derivatization utilizing the Sonogashira coupling reaction in the enantioselective synthesis of α-substituted β-amino acids. *J. Org. Chem.,* **2007**, *72*(13), 4822-4825.
http://dx.doi.org/10.1021/jo0705115 PMID: 17523668

[51] Kirschning, A.; Yusubov, M.S.; Yusubova, R.Y.; Chi, K-W.; Park, J.Y. *m*-Iodosylbenzoic acid - a convenient recyclable reagent for

highly efficient aromatic iodinations. *Beilstein J. Org. Chem.*, **2007**, *3*(19), 19.
http://dx.doi.org/10.1186/1860-5397-3-19 PMID: 17543133

[52] Li, J.; Cheng, D.; Yan, J. Novel and efficient synthesis of 1-iodoalkynes. *Synlett*, **2007**, *15*, 2442-2444.

[53] Yusubov, M.S.; Yusubova, R.Y.; Kirschning, A.; Park, J.Y.; Chi, K-W. *m*-Iodosylbenzoic acid, a tagged hypervalent iodine reagent for the iodo-functionalization of alkenes and alkynes. *Tetrahedron Lett.*, **2008**, *49*, 1506-1509.
http://dx.doi.org/10.1016/j.tetlet.2007.12.120

[54] Iskra, J.; Murphree, S.S. Rapid aerobic iodination of arenes mediated by hypervalent iodine in fluorinated solvents. *Tetrahedron Lett.*, **2017**, *58*, 645-648.
http://dx.doi.org/10.1016/j.tetlet.2017.01.003

[55] Liu, Y.; Huang, D.; Huang, J.; Maruoka, K. Hypervalent iodine mediated chemoselective iodination of alkynes. *J. Org. Chem.*, **2017**, *82*(22), 11865-11871.
http://dx.doi.org/10.1021/acs.joc.7b01555 PMID: 28803465

[56] Kotagiri, R.; Adepu, R. Alkoxylation followed by iodination of oxindole with alcohols mediated by hypervalent iodine reagent in the presence of iodine. *Eur. J. Org. Chem.*, **2018**, *33*, 4556-4564.
http://dx.doi.org/10.1002/ejoc.201800723

[57] Satkar, Y.; Yera-Ledesma, L.F.; Mali, N.; Patil, D.; Navarro-Santos, P.; Segura-Quezada, L.A.; Ramírez-Morales, P.I.; Solorio-Alvarado, C.R. Iodine (III)-mediated, controlled di- or monoiodination of Phenols. *J. Org. Chem.*, **2019**, *84*(7), 4149-4164.
http://dx.doi.org/10.1021/acs.joc.9b00161 PMID: 30888169

ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

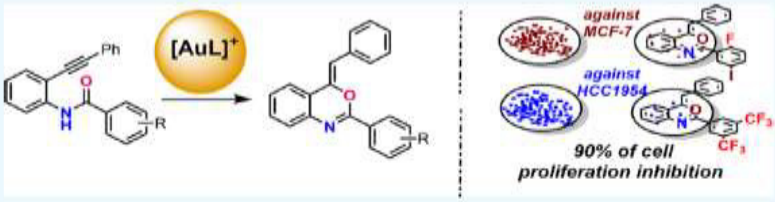
Gold(I)-Catalyzed Synthesis of 4*H*-Benzo[*d*][1,3]oxazines and Biological Evaluation of Activity in Breast Cancer Cells

Luis A. Segura-Quezada, Karina R. Torres-Carbajal, Narendra Mali, Dipak B. Patil, Mauricio Luna-Chagolla, Rafael Ortiz-Alvarado, Melissa Tapia-Juárez, Ixamail Fraire-Soto, Jorge Gustavo Araujo-Huitrado, Angelica Judith Granados-López, Rosalinda Gutiérrez-Hernández, Claudia Araceli Reyes-Estrada, Yamilé López-Hernández, Jesús Adrián López,* Luis Chacón-García,* and César R. Solorio-Alvarado*

Cite This: *ACS Omega* 2022, 7, 6944−6955

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: The first gold(I)-catalyzed cycloisomerization procedure applied to the synthesis of substituted 4*H*-benzo[*d*][1,3]-oxazines has been developed starting from *N*-(2-alkynyl)aryl benzamides. The chemoselective oxygen cyclization via the 6-*exo*-dig pathway yielded the observed heterocycles in modest to good chemical yields under very mild reaction conditions. The obtained oxazines were assayed on the breast cancer (BC)-derived cell lines MCF-7 and HCC1954 with differential biological activity. The newly synthesized 4*H*-benzo[*d*][1,3]oxazine compounds showed several degrees of cell proliferation inhibition with a remarkable effect for those compounds having a substituted aryl at C-2 of the molecules. The 4*H*-benzo[*d*][1,3]oxazines showed an IC_{50} ranking from 3.1 to 95 μM in MCF-7 and HCC1954 cells. These compounds represent potential drug candidates for BC treatment. However, additional assays are needed to elucidate their complete effect over the cellular and molecular hallmarks of cancer.

INTRODUCTION

Oxazines[1] are a class of heterocyclic compounds broadly studied in chemistry. In specific, 4*H*-benzo[*d*][1,3]oxazines have been extensively used in different fields. Their importance can be found in a broad applicability since this core can be found in heat-resistant and electronic materials,[2] naturally occurring active compounds,[3] and biologically important molecules[4] such as pharmaceuticals, agrochemicals,[5] anxiolytics, anticonvulsants,[6] fungicides, or anti-inflammatories[7] among others. Representative examples of the benzo[*d*][1,3]oxazine nucleus is established by etifoxine, a potent GABA receptor inhibitor, or by efavirenz, which is an efficient inhibitor of reverse transcriptase against HIV-1 mutant strain[8] (Figure 1).

Regarding diseases that cause great mortality, 4*H*-benzo[*d*]-[1,3]oxazines were successfully used as human leucocyte elastase and C1r serine protease inhibitors.[9] Finally, in the context of this work, they have been used as progesterone receptor agonist and DNA-binding antitumor agents.[10] We strongly considered this antitumor activity to design, postulate, and explore a family of highly substituted 4*H*-benzo[*d*][1,3]-oxazines in the biological assays of activity against MCF7 and HCC1954 breast cancer (BC) cell lines, which have been previously used as models for several compounds testing for cancer treatment.[11,12] BC is one of the most frequent and deathly pathologies worldwide, women from 45 to 55 years old being the most vulnerable population. In 2020, 684,996 deaths were registered.[11,13,14] Notably, there is a great difference in 5 year overall survival between developed and underdeveloped countries with 80% of the population versus 40%, respectively.[15] MCF7 cells have been used as a model for BC[16,17] since 1973,[18] and several compounds have been used to evaluate their potential in cancer treatment.[19,20]

Regarding the synthesis of the new 4*H*-benzo[*d*][1,3]-oxazines, several procedures have been developed for accessing this core (Figure 2).

Some of the more representatives include metal-catalyzed procedures with Pd,[21−23] Cu,[24] and Fe;[25] also, different metal-

Received: November 23, 2021
Accepted: February 1, 2022
Published: February 15, 2022

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

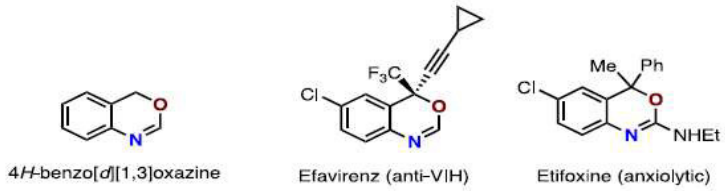


Figure 1. 4*H*-Benzo[*d*][1,3]oxazine core and examples of relevance.

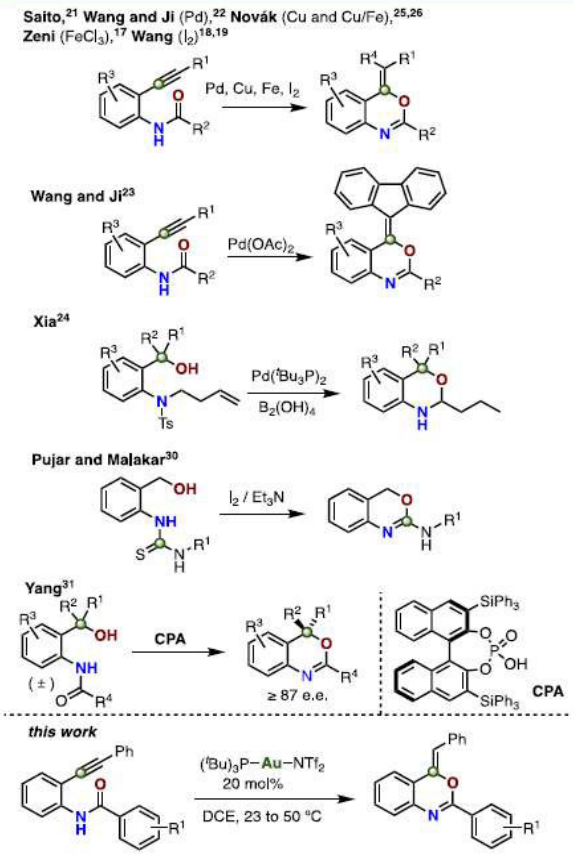


Figure 2. Described procedures for the synthesis of 4*H*-benzo[*d*]-[1,3]oxazines and our developed protocol.

free-catalyzed protocols using I_2[26,27] or chiral phosphoric acids[28] have been reported. All the aforementioned methods involve the use of high temperatures, potentially toxic reagents or starting materials, and general nonmild conditions. According to our research group interest,[29] herein, we present our gold(I)-catalyzed approach of 4*H*-benzo[*d*][1,3]oxazines using very mild reaction conditions. To the best of our knowledge, this is the first procedure using gold(I) catalysis applied to the synthesis of benzo[*d*][1,3]oxazines[30] (Figure 2).

RESULTS AND DISCUSSION

Organic Synthesis. The starting material synthesis of the *N*-(2-alkynyl)aryl benzamides **5**−**15** had taken place by two different routes (A and B) using the amide formation bond and the Sonogashira alkynylation as main tools (Figure 3).

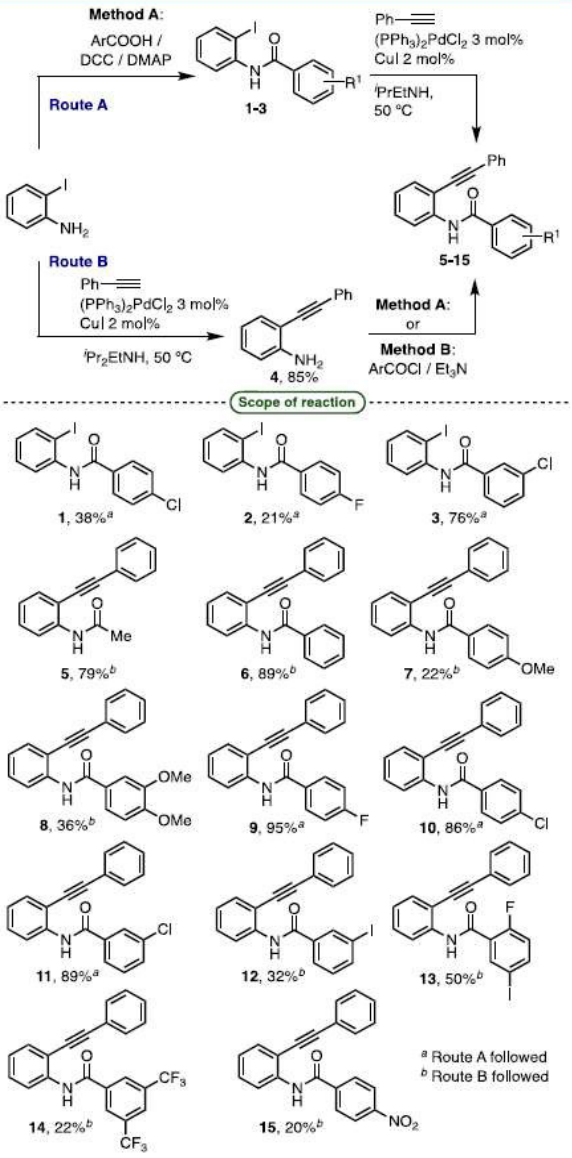


Figure 3. Routes for the synthesis of *N*-(2-alkynyl)aryl benzamides **5**−**15**.

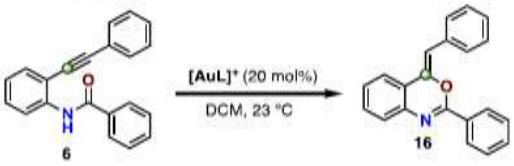
In the *N*-(2-alkynyl)aryl benzamide synthesis, route A started with the amide formation on 2-iodoaniline. The use of different substituted benzoic acids in the presence of dimethyl amino-pyridine (DMAP) and dicyclohexyl carbodiimide (DCC)

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

(method A) produced 2-iodobenzamides **1**−**3** in low to good yields (21−76%). The following Sonogashira alkynylation using phenyl acetylene under catalytic conditions of $(Ph_3P)_2PdCl_2$ and CuI led to the formation of *N*-(2-alkynyl)aryl benzamides **5**−**15**. On the other hand, route B started with the Sonogashira alkynylation on 2-iodoaniline with phenyl acetylene to yield **4** in 85%. Next, amide formation using method A or the corresponding benzoyl chloride derivatives in the presence of triethylamine (method B) gave rise to the desired benzamide in modest to good yields (20−95%). The electron-donating (**5**−**8**) and electron-attracting groups (**9**−**15**) were perfectly tolerated in the procedure, generating a great variety of precursors to be assayed in gold(I) catalysis.

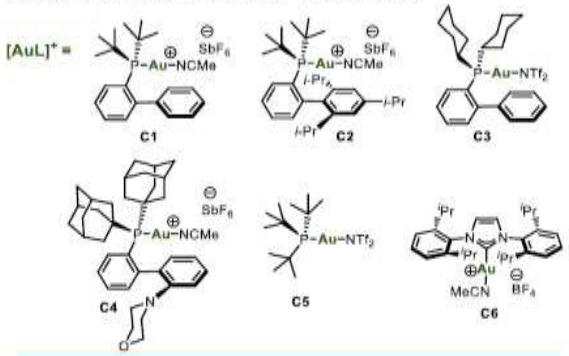
After having the *N*-(2-alkynyl)aryl benzamides produced, we proceeded to test and optimize our hypothesis on the gold(I)-catalyzed synthesis of 4*H*-benzo[*d*][1,3]oxazines. Accordingly, several cationic gold(I) complexes were assayed to determine the best yield (Table 1).

Table 1. Optimization of the Gold(I)-Catalyzed Synthesis of 4*H*-Benzo[*d*][1,3]oxazine 16[a]



entry	catalyst	time (h)	yield (%)[b]
1	**C1**	24	92[c]
2	**C2**	20	66
3	**C3**	17	61
4	**C4**	23	60
5	**C5**	24	95
6	**C6**	21	90

[a]Reaction conditions: all the reactions were carried out using 0.1 mmol of **6** and 20 mol % gold(I) catalyst at 23 °C in DCM (0.1 M), without a nitrogen atmosphere. [b]Yields were determined using mesitylene as an internal standard. [c]Isolated yields.

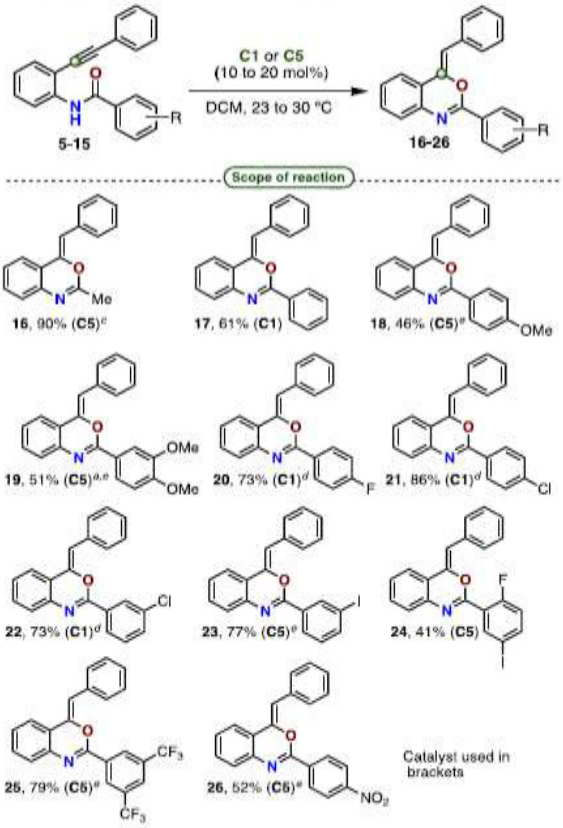


The optimization was carried out using *N*-(2-alkynyl)aryl benzamide **6** as a model. In such a way, we started by testing the cationic catalyst **C1** (Echavarren's catalyst)[31] using increasing amounts of the catalyst starting from 5 to 15 mol %; however, the full consumption of the starting material was achieved with 20 mol % catalytic charge obtaining the desired benzoxazine **16** in an excellent yield of 92% (entry 1). Accordingly, we decided to test **C2**−**C5** in this catalytic amount. Next, the ^{t}BuXPhos-based[32] gold(I) catalyst **C2** was tested, obtaining a moderate 66% yield of the desired product (entry 2). The following catalyst tested which contained the cyclohexyl JohnPhos-based[33] gold(I) catalyst **C3** yielded the expected compound in 61%. On the other hand, cationic gold(I) catalyst **C3** containing MorDalphos[34] as phosphine gave a similar 60% yield. Also, the use of gold(I) complex **C5** containing Fu's[35] phosphine gave rise to **16** in an excellent 95% yield. Finally, cationic carbene IPr-based[36] gold(I) catalyst **C6** led to the formation of the desired 4*H*-benzo[*d*][1,3]oxazine **16** in good 90% yield. After this optimization, the catalysts **C1** and **C5** turned out to be the most efficient and were used in the following cycloisomerization reactions.

With the optimized conditions, we proceeded to carry out the gold(I)-catalyzed cycloisomerization reaction to test the scope of this protocol (Table 2).

According to our optimization table, catalysts **C1** and **C5** were the most efficient; thereby, we decided to test both when a cyclization reaction showed a complex profile. The obtained

Table 2. Scope of the Gold(I)-Catalyzed Synthesis of a Family of Highly Substituted 4*H*-Benzo[*d*][1,3]oxazines[a,b]



[a]Reaction conditions: unless otherwise indicated, all the reactions were carried out using 20 mol % gold(I) catalyst at 23 °C in DCM (0.1 M), without a nitrogen atmosphere. [b]Isolated yields reported. [c]3 mol % catalyst used. [d]10 mol % catalyst used. [e]Reaction heated at 30 °C.

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

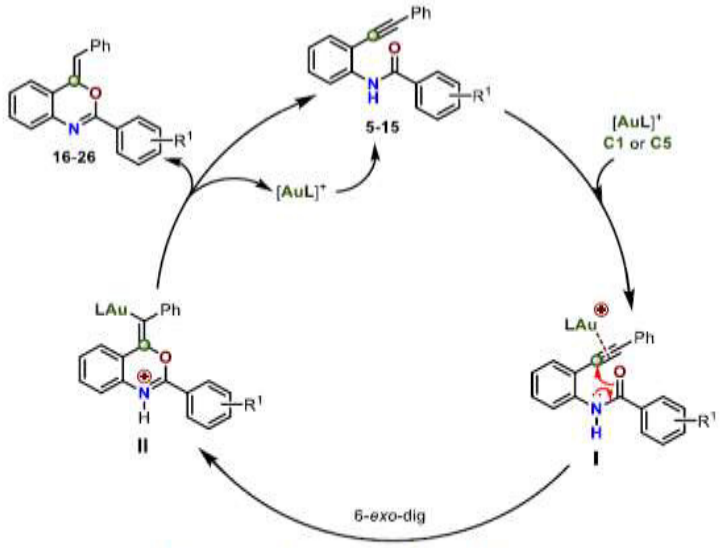


Figure 4. Plausible reaction mechanism of the gold(I)-catalyzed synthesis of 4*H*-benzo[*d*][1,3]oxazines.

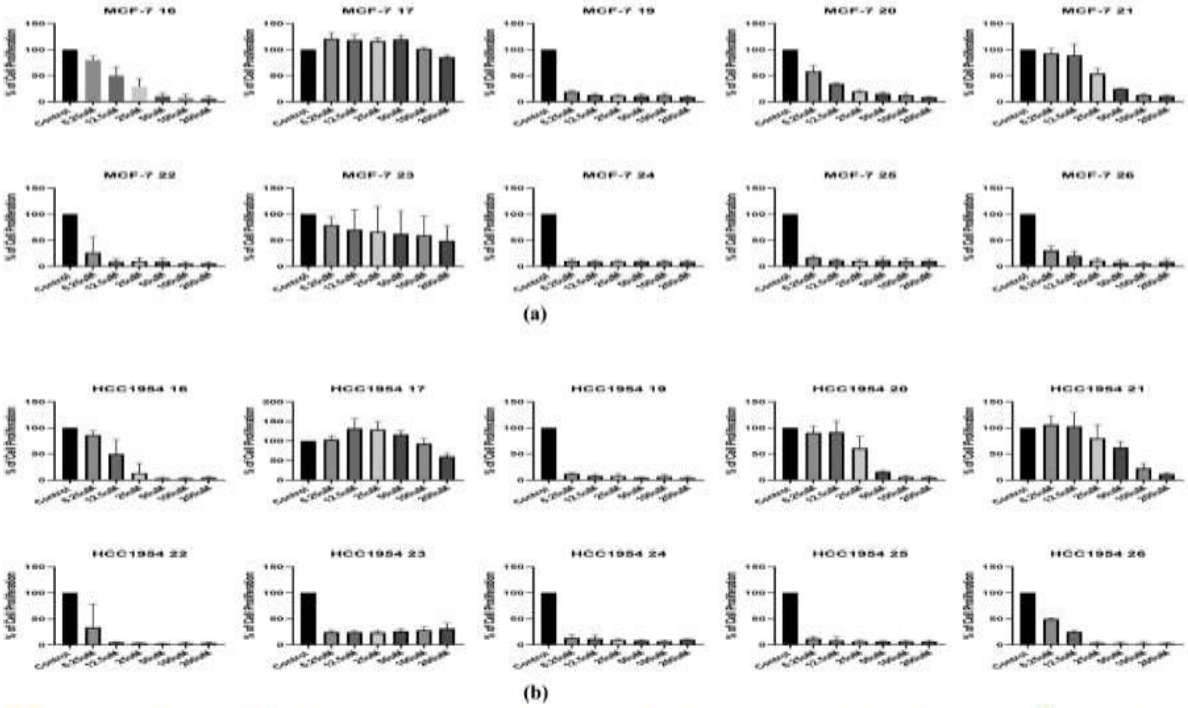


Figure 5. Differential effect of the 4*H*-benzo[*d*][1,3]oxazine compounds 16−26 in the proliferation of MCF-7 and HCC1954 cell lines. (a) MCF-7 cells were treated with increasing doses of compounds 16−26. (b) HCC1954 cells were treated with increasing doses of compounds 16−26. Control cells were cells treated with DMSO.

oxazines were designed to consistently have a benzylidene group at C-4; then, the most relevant variations were present in the aryl group at C-2. In such a way, the gold(I)-catalyzed cycloisomerization of the starting *N*-(2-alkynyl)aryl benzamides 5−15 allowed the formation of highly substituted 4-benzyliden-2-aryl-4*H*-benzo[*d*][1,3]oxazines 16−26. This procedure tolerated the methyl group (16) with an excellent yield of 90% and the phenyl ring (17) at 61%. Also, electron-rich aryls containing one or two methoxy groups (18 and 19) yielded the corresponding oxazines in 46 and 51%, respectively. Interestingly, these reactions needed soft heating at 30 °C to complete the starting material consumption. Other examples containing

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

electron-attracting groups in the aryl at C-2 such as fluorine (**20**), chlorine (**21** and **22**), iodine (**23**), fluorine and iodine (**24**), trifluoromethyl (**25**), or the nitro group (**26**) could be successfully obtained, generally with good yields (73−86%); only two of these examples gave rise to modest 41 and 52% yields. In this set of electron-attracting derivatives, the aryls with iodine, trifluoromethyl, and nitro groups were heated at 30 °C to complete the reaction.

It is important to highlight that the reactions to obtain the family of the synthesized oxazines were carried out under very mild conditions such as room temperature or 30 °C, without the use of an inert atmosphere and under operationally easy to handle conditions since they just needed the mixture of the starting material and the gold(I) catalyst in dry DCM. These characteristics represent a significant improvement regarding the previously described metal-catalyzed procedures, by considering that they required heating at 70 °C or more and a nitrogen atmosphere and that the palladium catalyst or the phosphines used had to be sometimes manipulated in a glovebox.

Finally, according to several reports on the gold(I) chemistry,[37,38] it is possible to propose the following reaction mechanism (Figure 4).

The mechanism starts with the coordination of the cationic gold(I) complexes **C1** or **C5** to the *N*-(2-alkynyl)aryl benzamides **5**−**15** to get the intermediate **I**. The following chemoselective attack of the oxygen of amide to the internal carbon of the triple bond led to the formation of the vinylidene gold(I) benzoxazonium **II** via stereoselective 6-*exo*-dig cyclization; certainly, this explains the exclusive formation of the *Z*-isomer in the obtained products. The final protodeauration gives rise to the observed 4-benzyliden-2-aryl-4*H*-benzo[*d*][1,3]-oxazines **16**−**26** with the concomitant regeneration of the catalyst, which continues with another cycle.

Biological Evaluation in BC. The new 4*H*-benzo[*d*][1,3]-oxazines presented a remarkable effect on cell proliferation inhibition with important difference between MCF-7 and HCC1954 response to the compounds (Figure 5a,b) that could be attributable to the molecular background of cells, while the former is Erb-B2 receptor tyrosine kinase 2 (HER)+/−, estrogen receptor (ER)+, and progesterone receptor (PR)+ and the latter is HER+, ER−, PR−.[39−41] The proliferation inhibition in MCF-7 was as follows: 24, 25, 19, 18, 22, 21, 16 and 20. It should be noted that compounds **23** and **17** did not have effects on cell proliferation inhibition. In contrast, while compounds 24, 25, 19, 18, 22, and 20 showed a statistically significant effect from the concentration of 6.25 μM, compounds **16** and **21** presented effects at 12.5 and 25 μM, respectively, in MCF-7 cells (Figure 5a). In contrast, it must be noted that in HCC1954 cells, the 4*H*-benzo[*d*][1,3]oxazines presented different effects, specifically with compound **23** which showed 70% proliferation inhibition from 6.25 μM in HCC1954, while in MCF-7, a null effect was recorded (Figure 5a,b). The most potent effect of 4*H*-benzo[*d*][1,3]oxazines in HCC1954 cells was as follows: 25, 19, 24, 20, 23, 22, 16, 18, 21, and 17. Another difference was that in HCC1954 cells, all the compounds showed a stronger effect compared to that of MCF-7; therefore, it seems that HCC1954 is more susceptible to 4*H*-benzo[*d*][1,3]oxazines than MCF-7, Table 3 and Figure S2. The substituents in the aryl at C-2 of 4*H*-benzo[*d*][1,3]oxazines seem to be important in achieving cell proliferation inhibition since it can be noticed that compounds **17** and **23** are the simplest in regard to this structural feature (Table 2). The benzoxazines have been reported as promising

Table 3. IC_{50} of 4*H*-Benzo[*d*][1,3]oxazines in BC Cells

compound	MCF7 (μM)	HCC1954 (μM)
16	12.20	12.09
17	95.82	87.37
19	3.485	3.375
20	7.172	27.65
21	24.92	47.28
22	4.189	5.190
23		3.114
24	3.408	3.275
25	3.529	3.373
26	4.148	6.280

inhibitors of cell proliferation with IC_{50} ranking from 1 to 200 μM. Mbaba reported an IC_{50} of 11 μM in HCC70 cells,[42] while Bollu reported 1.1−41.5 μM in MDA-MB-231 cells.[43] It should be noted that different compounds were tested in different cell lines. In contrast, de Brito et al. tested benzoxazines in MCF-7 cells, showing an IC_{50} of 21.8 and 28.8 μM for two different oxazines.[44] In our present work, the IC_{50} ranked from 3.1 to 95 μM with astounding difference with compound **23** showing effects in HCC1954 but not in MCF-7 cells, Figure S1 (see the Supporting Information). The observed different effect could be explained based on the cells' molecular context that finally results in cellular responses.[45] Expression difference of ER, PR, and HER2 could account for this singular specific effect. ER and PR can regulate gene transcription either by directly binding to DNA response elements directly or indirectly via other transcription factors such as induction and coregulator recruiting[46] and noncoding RNA regulation.[47] In addition, ER and PR could interact with several proteins and regulate cell signaling pathways through nongenomic mechanisms.[48,49] The molecular and cellular mechanism underlying the effect of 4*H*-benzo[*d*][1,3]oxazines is under study in our research group.

■ CONCLUSIONS

In summary, we developed the first gold(I)-catalyzed cycloisomerization protocol of *N*-(2-alkynyl)aryl benzamides, which was applied to the synthesis of substituted 4-benzyliden-2-aryl-4*H*-benzo[*d*][1,3]oxazines **16**−**26** in modest to excellent yields. The developed procedure took place under very mild reaction conditions such as room temperature or heating at 30 °C and without the use of an inert atmosphere. These characteristics represent important advantages over the previously described metal-catalyzed procedures that are usually carried out under stronger heating and argon atmosphere conditions. MCF-7 and HCC1954 BC cells presented different effects to 4*H*-benzo[*d*]-[1,3]oxazines, remarkably with compound **23**, which elicited 70% proliferation inhibition in HCC1954 versus a null effect on MCF-7 cells. Stronger to weaker compound effects on MCF-7 cells were as follows: 24, 25, 19, 18, 22, 21, 16, and 20. Compounds **23** and **17** recorded a null effect. In HCC1954 cells, the effect of the compounds was as follows: 25, 19, 24, 20, 23, 22, 16, 18, 21, and 17. This suggests that the HCC1954 cell line is more susceptible to 4*H*-benzo[*d*][1,3]oxazines than MCF-7 cells. Additionally, it could be speculated that the substituents in the aryl at C-2 of 4*H*-benzo[*d*][1,3]oxazines is important in achieving cell proliferation inhibition; nevertheless, further experiments are needed to validate our hypothesis.

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an inert atmosphere using dry solvents and anhydrous conditions and were capped with a rubber septum unless otherwise mentioned. Reactions were followed by thin-layer chromatography (0.25 mm Merck silica gel plates 60F-254) using UV light as the visualizing agent. Flash column chromatography employed silica gel (40−60 μm, 230−400 mesh) purchased from Sigma-Aldrich. The new compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, and high-resolution mass spectra (HR-MS). The corresponding copies for ^{1}H and ^{13}C NMR spectra are provided. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance III (500 MHz) spectrometer. All ^{1}H NMR data were reported in δ units, parts per million (ppm) and were calibrated relative to the signals for residual chloroform (7.26 ppm) in deuterochloroform ($CDCl_3$). The ^{13}C NMR data reported were obtained with ^{1}H decoupling unless otherwise stated. The following abbreviations explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet. Infrared (IR) spectra were recorded using a PerkinElmer system 2000 FT-IR spectrometer. HR-MS was performed on a Bruker Daltonics ESI-QTOF-MS maXis impact using ESI-TOF (electrospray ionization−time of flight).

Synthesis. *Method A. Acylation of 2-(Phenylethynyl)-aniline.*[51] A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-(phenylethynyl)-aniline (0.1 g, 0.517 mmol, 1 equiv) in DCE (4 mL). Then, DIPEA (0.15 mL, 4 equiv) at 0 °C was added. After dissolving and obtaining a homogeneous mixture, the corresponding acyl chloride (0.12 mL, 2 equiv) was added and stirred at 23 °C for 5 h. The completion of the reaction was determined by TLC analysis. To quench the reaction, H_2O (30 mL) was added. The aqueous phase was extracted with DCM (3 × 25 mL), dried over Na_2SO_4, filtrated, and finally concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel with an EtOAc/hexanes system to obtain the desired products.

Method B. Amidation of 2-Iodoanilines. A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-iodoaniline (0.5 g, 2.283 mmol, 1 equiv) or 2-(phenylethynyl)aniline (0.1 g, 0.518 mmol, 1 equiv) in DCM (4 mL). Next, the corresponding benzoic acids (1.553 mmol, 3 equiv) were added and stirred at 23 °C until a homogeneous mixture was obtained. Afterward, DCC (1.554 mmol, 3 equiv) and DMAP (0.517 mmol, 1 equiv) were added at 23 °C for 24 h. The completion of the reaction was determined by TLC analysis. The aqueous phase was extracted with DCM (3 × 25 mL); the organic phase was dried over Na_2SO_4, filtrated, and concentrated at reduced pressure. The crude products were purified by flash chromatography on silica gel with an EtOAc/hexanes system to obtain the desired products.

Sonogashira Alkynylation Procedure.[52] A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2-iodoaniline (0.500 g, 2.283 mmol, 1 equiv) or 2-iodobenzamides (0.100 g, 0.0280 mmol, 1 equiv) in 15 mL of ^{i}PrEtNH and stirred for 10 min at 50 °C. Then, CuI (0.0056 g, 3 mol %) and $(Ph_3P)_2PdCl_2$ (0.0084 g, 3 mol %) were added for 10 min while maintaining the temperature. Subsequently, phenylacetylene (0.336 mL, 1.2 equiv) was added dropwise. The mixture was stirred at 50 °C for 3 h. The completion of the reaction was determined by TLC analysis. Afterward, the reaction was cooled until room temperature and quenched with H_2O (30 mL). The aqueous phase was extracted with DCM (3 × 25 mL), collected, dried over Na_2SO_4, filtrated, and concentrated at reduced pressure. The crude products were purified by flash chromatography on silica gel with an EtOAc/hexanes system to obtain the desired products.

Procedure for Gold(I) Catalysis. Although our optimization showed that generally, the cycloisomerization proceeded with 20 mol % catalyst, some indicated examples needed 3 or 10 mol % only.

General Procedure for Gold(I)-Catalyzed Synthesis of 4*H*-Benzo[*d*][1,3]oxazine. A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with the corresponding *N*-(2-alkynyl)aryl benzamides (1 equiv) in anhydrous DCM (2 mL) and stirred at 23 or 30 °C. Then, gold(I) catalyst **C1** or **C5** (3 or 10 or 20 mol %) was added, without a nitrogen atmosphere. The completion of the reaction was determined by TLC analysis. The reaction was allowed to reach room temperature and quenched by adding three drops of Et_3N and H_2O (30 mL). The aqueous phase was extracted with DCM (3 × 25 mL), then dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The crude products were purified by flash chromatography on silica gel with an EtOAc/hexanes system to obtain the desired product.

Examples in Figure 3. *4-Chloro-N-(2-iodophenyl)-benzamide* ***1***. The following compound was obtained according to Method B, using 2-iodoaniline (0.5 g, 2.2835 mmol, 1 equiv) as a starting material and 4-chlorobenzoic acid (1.0687 g, 6.8507 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 1% EtOAc/hexane to afford the product **1** (310 mg, 38%) as a white solid. mp = 143−145 °C. IR (neat) ν/cm^{-1}: 3262 (s), 2927 (w), 1647 (s), 1522 (s), 1307 (m), 1019 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (dt, J = 8.4, 1.7 Hz, 1H), 8.22 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.82 (dd, J = 8.1, 1.6 Hz, 1H), 7.50 (dd, J = 8.4, 1.9 Hz, 2H), 7.41 (t, J = 7.8 Hz, 1H), 6.90 (t, J = 7.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.9, 138.9, 138.7, 138.5, 133.4, 129.6, 129.9, 128.7, 126.4, 121.9, 90.6. HRMS (ESI+) m/z: calcd for $C_{13}H_{10}ClINO$ $[M + H]^+$, 357.9496; found, 357.9524.

4-Fluoro-N-(2-iodophenyl)benzamide ***2***. The following compound was obtained according to Method B, using 2-iodoaniline (0.5 g, 2.2835 mmol, 1 equiv) as a starting material and 4-fluorobenzoic acid (0.9592 g, 6.8507 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 1% EtOAc/hexane to afford the product **2** (160 mg, 21%) as a white solid. mp = 127−130 °C. IR (neat) ν/cm^{-1}: 3221 (m), 3163 (m), 1645 (s), 1496 (s), 1232 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.98 (dd, J = 8.6, 5.3 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.20 (t, J = 8.4 Hz, 2H), 6.92−6.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0 (d, J = 254 Hz), 164.1, 138.7, 138.0, 130.5 (d, J = 3 Hz), 129.4 (d, J = 9 Hz), 129.3, 126.0, 121.6, 115.9 (d, J = 19 Hz), 90.2. HRMS (ESI+) m/z: calcd for $C_{13}H_{10}FINO$ $[M + H]^+$, 341.9791; found, 341.9811.

3-Chloro-N-(2-iodophenyl)benzamide ***3***. The following compound was obtained according to Method B, using 2-iodoaniline (0.5 g, 2.2835 mmol, 1 equiv) as a starting material and 3-chlorobenzoic acid (1.0687 g, 6.8507 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 2% EtOAc/hexane to afford the product **3** (624 mg, 76%) as a white solid. mp = 123−125 °C. IR (neat) ν/cm^{-1}: 3281 (m), 2929 (m), 1651 (s), 1530 (s), 1272 (s), 1128 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

Hz, 1H), 7.79 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.1 Hz, 1H), 7.29 (d, J = 8.0 Hz, 3H), 7.08 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 141.7, 140.5, 135.8, 134.6, 132.4, 130.2, 129.9, 129.6, 129.5, 129.2, 127.2, 98.7. HRMS (ESI+) m/z: calcd for $C_{13}H_{10}ClINO$ $[M + H]^+$, 357.9496; found, 357.9512.

2-(Phenylethynyl)aniline **4**. The following compound was obtained according to the Sonogashira Alkynylation Procedure, using 2-iodoaniline (0.500 g, 2.283 mmol, 1 equiv) as a starting material and phenylacetylene (0.336 mL, 1.2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 5% EtOAc/hexane to afford the product 4 (380 mg, 85%) as an orange solid. The spectroscopic data were consistent with those previously described in the literature.[21] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58−7.51 (m, 2H), 7.41−7.30 (m, 4H), 7.15 (td, J = 7.8, 1.5 Hz, 1H), 6.79−6.72 (m, 2H), 4.40 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.3, 132.2, 131.5, 129.7, 128.4, 128.2, 123.3, 118.3, 114.6, 108.2, 94.8, 85.8.

N-(2-(Phenylethynyl)phenyl)acetamide **5**. Compound 5 was obtained according to Method A, using 2-(phenylethynyl)-aniline (0.1 g, 0.517 mmol, 1 equiv) as a starting material and acetyl chloride (0.07 mL, 2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 10% EtOAc/hexane to afford the product 5 (111.6 mg, 79%) as a yellow solid. The spectroscopic data correlated with those described previously.[21] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.57−7.52 (m, 2H), 7.50 (dd, J = 7.8, 1.6 Hz, 1H), 7.40 (p, J = 4.0 Hz, 3H), 7.35 (td, J = 7.8, 1.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.1, 138.9, 131.6, 131.5, 129.7, 128.9, 128.6, 123.4, 122.3, 119.3, 111.8, 96.4, 84.2, 25.0.

N-(2-(Phenylethynyl)phenyl)benzamide **6**. Compound 6 was obtained according to Method A, using 2-(phenylethynyl)-aniline (0.1 g, 0.517 mmol, 1 equiv) as a starting material and benzoyl chloride (0.12 mL, 2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 10% EtOAc/hexane to afford the product 6 (141.0 mg, 89%) as a yellow solid. The spectroscopic data corresponded to those described in the literature.[21] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.64 (d, J = 8.3 Hz, 1H), 7.97 (dd, J = 7.6, 1.7 Hz, 2H), 7.60−7.52 (m, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.45−7.37 (m, 4H), 7.15−7.10 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0, 139.1, 134.9, 132.0, 131.5, 131.4, 129.9, 129.0, 128.9, 128.6, 127.0, 123.5, 122.2, 119.1, 112.2, 97.0, 84.5.

4-Methoxy-N-(2-(phenylethynyl)phenyl)benzamide **7**. The reaction was carried out according to Method B, using 2-(phenylethynyl)aniline (0.1 g, 0.518 mmol, 1 equiv) as a starting material and 4-methoxybenzoic acid (0.2362 g, 1.5536 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 4% EtOAc/hexane to afford the product 7 (374 mg, 22%) as a white solid. The spectroscopic data were consistent with those previously described.[50] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 7.95−7.91 (m, 2H), 7.55 (tt, J = 7.6, 4.7, 2.0 Hz, 3H), 7.44−7.38 (m, 4H), 7.10 (t, J = 7.6 Hz, 1H), 6.99−6.95 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.6, 162.6, 139.3, 131.5, 131.4, 129.9, 128.9, 128.9, 128.6, 127.1, 123.3, 122.3, 119.0, 114.1, 112.0, 96.8, 84.6, 55.5.

3,4-Dimethoxy-N-(2-(phenylethynyl)phenyl)benzamide **8**. It was obtained according to Method B, using 2-(phenylethynyl)aniline (0.1 g, 0.518 mmol, 1 equiv) as a starting material and 3,4-methoxybenzoic acid (0.2828 g, 1.5536 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 5% EtOAc/hexane to afford the product 8 (672 mg, 36%) as a yellow solid. mp = 128−131 °C. IR (neat) ν/cm^{-1}: 3410 (m), 3323 (m), 2929 (s), 2850 (s), 1675 (m), 1626 (m), 1573 (m), 1507 (s), 1266 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (s, 1H), 8.62 (d, J = 8.4 Hz, 1H), 7.57−7.51 (m, 5H), 7.40 (dd, J = 5.0, 1.9 Hz, 4H), 7.11 (dd, J = 8.4, 7.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.7, 152.2, 149.2, 139.3, 131.5, 131.4, 129.9, 129.0, 128.6, 127.5, 123.3, 122.2, 119.7, 119.0, 112.0, 110.2, 110.3, 96.7, 84.5, 56.1, 55.7. HRMS (ESI+) m/z: calcd for $C_{23}H_{20}NO_3$ $[M + H]^+$, 358.1443; found, 358.1467.

4-Fluoro-N-(2-(phenylethynyl)phenyl)benzamide **9**. The following compound was obtained according to the Sonogashira Alkynylation Procedure, using 4-fluoro-*N*-(2-iodophenyl)-benzamide (0.08 g, 0.2346 mmol, 1 equiv) as a starting material and phenylacetylene (0.309 mL, 1.2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 1% EtOAc/hexane to afford the product 9 (70 mg, 95%) as a light-brown solid. mp = 142−144 °C. IR (neat) ν/cm^{-1}: 3300 (s), 3061 (m), 2925 (m), 2440 (w), 2212 (w), 1652 (s), 1607 (s), 1505 (s), 1447 (s), 1226 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.59 (d, J = 8.3 Hz, 1H), 7.99−7.95 (m, 2H), 7.54 (ddd, J = 9.8, 7.5, 2.7 Hz, 3H), 7.41 (tq, J = 8.3, 2.6 Hz, 4H), 7.15 (dt, J = 8.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.5, 139.8, 131.7, 131.5, 130.1, 129.6, 129.8, 129.5, 128.8, 123.8, 122.3, 119.9, 116.4, 116.7, 112.4, 97.9, 84.7. ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.1 (d, J = 258 Hz), 164.1, 139.0, 131.6, 131.5, 131.2 (d, J = 3 Hz), 130.1, 129.5 (d, J = 9 Hz), 129.2, 128.8, 123.8, 122.3, 119.2, 116.1 (d, J = 22 Hz), 112.4, 97.1, 84.5. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}FNO$ $[M + H]^+$, 316.1138; found, 316.1161.

4-Chloro-N-(2-(phenylethynyl)phenyl)benzamide **10**. The reaction was carried out according to the Sonogashira Alkynylation Procedure, using 4-chloro-*N*-(2-iodophenyl)-benzamide (0.1 g, 0.2801 mmol, 1 equiv) as a starting material and phenylacetylene (0.369 mL, 1.2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 1% EtOAc/hexane to afford the product **10** (80 mg, 86%) as a light-brown solid. mp = 144−147 °C. IR (neat) ν/cm^{-1}: 3292 (m), 2925 (m), 2859 (m), 2214 (w), 1730 (m), 1649 (s), 1528 (s), 1447 (s), 1317 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.58 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.55−7.51 (m, 3H), 7.46−7.39 (m, 6H), 7.39 (dt, J = 12.9, 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.4, 138.9, 138.9, 133.8, 131.7, 131.8, 130.4, 129.6, 129.3, 128.8, 128.5, 123.9, 122.5, 119.3, 112.7, 97.2, 84.5. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}ClNO$ $[M + H]^+$, 332.0842; found, 332.0863.

3-Chloro-N-(2-(phenylethynyl)phenyl)benzamide **11**. The following compound was obtained according to the Sonogashira Alkynylation Procedure, using 3-chloro-*N*-(2-(phenylethynyl)-phenyl)benzamide (0.1 g, 0.3020 mmol, 1 equiv) as a starting material and phenylacetylene (0.398 mL, 1.2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 2% EtOAc/hexane to afford the product **11** (82 mg, 89%) as a white solid. mp = 145−147 °C. IR (neat) ν/cm^{-1}: 3292 (s), 2929 (s), 1726 (m), 1651 (s), 1524 (s), 1311 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.61 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 7.6, 1.6 Hz, 1H), 7.60−7.52 (m, 4H), 7.46−7.38 (m, 5H), 7.14 (t, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.6, 138.7, 136.7, 135.14, 132.1, 131.5, 131.4, 130.3, 129.9, 129.1,

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

128.7, 127.1, 125.3, 123.8, 122.0, 119.1, 112.4, 97.3, 84.3. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}ClNO$ $[M + H]^+$, 332.0842; found, 332.0865.

3-Iodo-N-(2-(phenylethynyl)phenyl)benzamide **12**. The following compound was obtained according to Method B, using 2-(phenylethynyl)aniline (0.1 g, 0.518 mmol, 1 equiv) as a starting material and 3-iodobenzoic acid (0.3852 g, 1.5536 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 2% EtOAc/hexane to afford the product **12** (71 mg, 32%) as a yellow solid. mp = 143−145 °C. IR (neat) ν/cm^{-1}: 3285 (m), 2957 (s), 2855 (s), 1728 (m), 1260 (m). ^1H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.60 (d, J = 8.3 Hz, 1H), 8.29 (d, J = 2.3 Hz, 1H), 7.96−7.93 (m, 1H), 7.90 (dd, J = 7.9, 1.5 Hz, 1H), 7.62−7.54 (m, 3H), 7.45−7.39 (m, 4H), 7.23 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 163.3, 142.5, 140.9, 138.9, 135.6, 131.4, 130.5, 130.0, 129.2, 129.0, 128.7, 126.4, 123.8, 119.0, 112.3, 93.8, 84.1. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}INO$ $[M + H]^+$, 424.0198; found, 424.0224.

2-Fluoro-5-iodo-N-(2-(phenylethynyl)phenyl)benzamide **13**. Compound **13** was obtained according to Method B, using 2-(phenylethynyl)aniline (0.1 g, 0.518 mmol, 1 equiv) as a starting material and 2-fluoro-5-iodobenzoic acid (0.4131 g, 1.5536 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 10% EtOAc/hexane to afford the product **13** (115 mg, 50%) as a yellow solid. mp = 130−132 °C. IR (neat) ν/cm^{-1}: 3391 (s), 2927 (s), 1724 (m), 1683 (s), 1451 (m), 1266 (s), 753 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 9.42 (d, J = 15.0 Hz, 1H), 8.62 (d, J = 8.4 Hz, 1H), 8.53 (dd, J = 7.5, 2.4 Hz, 1H), 7.81 (ddd, J = 8.4, 4.8, 2.4 Hz, 1H), 7.57 (td, J = 7.8, 2.6 Hz, 3H), 7.45−7.36 (m, 4H), 7.14 (t, J = 7.5 Hz, 1H), 6.96 (dd, J = 11.7, 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.1 (d, J = 253 Hz), 159.4, 142.4 (d, J = 9 Hz), 140.9, 138.8, 131.9, 131.4, 129.6, 128.7, 128.3, 123.9, 123.0 (d, J = 12 Hz), 122.3, 119.9, 118.3 (d, J = 26 Hz), 112.7, 96.6, 88.0, 83.9. HRMS (ESI+) m/z: calcd for $C_{21}H_{14}FINO$ $[M + H]^+$, 442.0104; found, 442.0141.

N-(2-(Phenylethynyl)phenyl)-3,5-bis(trifluoromethyl)-benzamide **14**. The following compound was obtained according to Method B, using 2-(phenylethynyl)aniline (0.1 g, 0.518 mmol, 1 equiv) as a starting material and 3,5-bis(trifluoromethyl)benzoic acid (0.4008 g, 1.5536 mmol, 3 equiv). The crude material was purified by flash column chromatography over silica gel with the system 5% EtOAc/hexane to afford the product **14** (49 mg, 22%) as a yellow solid. mp = 140−144 °C. IR (neat) ν/cm^{-1}: 3281 (m), 2929 (m), 1651 (s), 1530 (s), 1272 (s), 1128 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 8.41 (s, 2H), 8.07 (s, 1H), 7.59 (dd, J = 7.8, 1.5 Hz, 1H), 7.56−7.50 (m, 2H), 7.48−7.36 (m, 4H), 7.19 (t, J = 7.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.3, 138.5, 137.4, 133.0 (d, J = 34 Hz), 132.1, 131.8, 130.4, 129.7, 129.1, 127.6 (d, J = 4 Hz), 124.9, 123.2 (d, J = 273 Hz), 122.0, 119.7, 113.1, 98.1, 84.1. HRMS (ESI+) m/z: calcd for $C_{23}H_{14}F_6NO$ $[M + H]^+$, 434.0980; found, 434.1005.

4-Nitro-N-(2-(phenylethynyl)phenyl)benzamide **15**. The following compound was obtained according to Method A, using 2-(phenylethynyl)aniline (0.1 g, 0.517 mmol, 1 equiv) as a starting material and 4-nitrobenzoyl chloride (0.1920, 1.0357 mmol, 2 equiv). The crude material was purified by flash column chromatography over silica gel with the system 10% EtOAc/hexane to afford the product **15** (35 mg, 20%) as an orange solid. The spectroscopic data correspond to those already described in the literature.[21] ^1H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.58 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H), 7.57 (dd, J = 7.7, 1.4 Hz, 1H), 7.55−7.50 (m, 2H), 7.48−7.39 (m, 4H), 7.18 (t, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.8, 149.9, 140.3, 138.3, 131.3, 130.0, 129.4, 129.3, 128.8, 128.1, 124.3, 124.1, 121.9, 119.3, 112.6, 97.3, 84.1.

Examples in Table 2. *(Z)-4-Benzylidene-2-methyl-4H-benzo[d][1,3]oxazine* **16**. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using *N*-(2-(phenylethynyl)phenyl)acetamide (0.030 g, 0.1276 mmol, 1 equiv) as a starting material and gold(I) catalyst **C1** (0.0030 g, 0.0038 mmol, 3 mol %). The crude material was purified by flash column chromatography over silica gel with the system 5% EtOAc/hexane to afford the product **16** (28 mg, 90%) as a white solid. The spectroscopic data matched with those previously described in the literature.[21] ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.51−7.41 (m, 5H), 7.37 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 6.64 (s, 1H), 2.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.3, 139.6, 137.6, 134.0, 128.9, 128.6, 128.5, 125.0, 123.5, 120.2, 115.9, 111.4, 27.8.

(Z)-4-Benzylidene-2-phenyl-4H-benzo[d][1,3]oxazine **17**. This compound was obtained according to the Procedure for Gold(I) Catalysis, using *N*-(2-(phenylethynyl)phenyl)-benzamide (0.030 g, 0.1009 mmol, 1 equiv) as a starting material and gold(I) catalyst **C5** (0.013 g, 0.0201 mmol, 20 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **17** (19 mg, 61%) as a yellow solid. The spectroscopic data matched with those previously described in the literature.[21] ^1H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, J = 7.7 Hz, 2H), 7.74 (d, J = 7.7 Hz, 2H), 7.54 (dq, J = 20.5, 7.4 Hz, 5H), 7.43 (tt, J = 15.9, 7.7 Hz, 5H), 6.27 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.3, 131.8, 131.4, 129.3, 128.7, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.4, 126.6, 122.4, 121.9, 121.1.

(Z)-4-Benzylidene-2-(4-methoxyphenyl)-4H-benzo[d]-[1,3]-oxazine **18**. This compound was obtained according to the Procedure for Gold(I) Catalysis, using 4-methoxy-*N*-(2-(phenylethynyl)phenyl)benzamide (0.026 g, 0.0794 mmol, 1 equiv) as a starting material and gold(I) catalyst **C5** (0.010 g, 0.0158 mmol, 20 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **18** (12 mg, 46%) as a white solid. mp = 95−98 °C. IR (neat) ν/cm^{-1}: 3072 (m), 2931 (s), 1675 (s), 1321 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 7.68−7.63 (m, 3H), 7.58−7.55 (m, 1H), 7.34 (d, J = 7.3 Hz, 2H), 7.25−7.20 (m, 4H), 7.19−7.15 (m, 1H), 6.79 (s, 2H), 6.77 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 163.4, 141.8, 138.7, 133.4, 133.2, 129.6, 128.6, 128.5, 127.9, 127.6, 124.3, 123.1, 121.1, 114.1, 109.1, 55.9. HRMS (ESI+) m/z: calcd for $C_{22}H_{18}NO_2$ $[M + H]^+$, 328.1338; found, 328.1366.

(Z)-4-Benzylidene-2-(4-fluorophenyl)-4H-benzo[d][1,3]-oxazine **20**. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using 4-fluoro-*N*-(2-(phenylethynyl)phenyl)benzamide (0.049 g, 0.1372 mmol, 1 equiv) as a starting material and gold(I) catalyst **C1** (0.0735 g, 0.0137 mmol, 10 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **20** (36 mg, 73%) as a yellow solid. mp = 130−132 °C. IR (neat) ν/cm^{-1}: 2929 (s), 2853 (m), 1588 (m), 1507 (m), 1221 (s), 766 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.45−7.37 (m, 4H), 7.35−7.28 (m, 2H), 7.25−7.21 (m, 2H), 6.22 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

165.4 (d, J = 253 Hz), 154.5,145.6, 139.2, 135.0, 131.9, 130.9, 130.5 (d, J = 9 Hz), 129.8, 128.8 (d, J = 5 Hz), 128.3, 127.1, 122.3, 121.9, 116.9 (d, J = 23 Hz), 102.2. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}FNO$ $[M + H]^+$, 316.1138; found, 316.1165.

(Z)-4-Benzylidene-2-(4-chlorophenyl)-4H-benzo[d][1,3]-oxazine ***21***. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using (Z)-4-chloro-*N*-(2-(phenylethynyl)phenyl)benzamide (0.035 g, 0.1057 mmol, 1 equiv) as a starting material and gold(I) catalyst **C1** (0.0816 g, 0.0095 mmol, 10 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **21** (30 mg, 86%) as a yellow solid. mp = 143−145 °C. IR (neat) ν/cm^{-1}: 2929 (s), 2855 (m), 1679 (s), 1600 (s), 1256 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26−8.13 (m, 2H), 7.69 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.35−7.27 (m, 2H), 7.24 (d, J = 7.1 Hz, 2H), 7.14 (t, J = 8.6 Hz, 2H), 6.22 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.3, 145.3, 138.8, 138.1, 135.6, 134.8, 131.5, 130.6, 130.0, 129.6, 129.4, 129.2, 129.1, 127.0, 122.0, 102.0. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}ClNO$ $[M + H]^+$, 332.0842; found, 332.0869.

(Z)-4-Benzylidene-2-(3-chlorophenyl)-4H-benzo[d][1,3]-oxazine ***22***. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using 3-chloro-*N*-(2-(phenylethynyl)phenyl)benzamideoxazine (0.030 g, 0.0906 mmol, 1 equiv) as a starting material and gold(I) catalyst **C1** (0.0699 g, 0.0090 mmol, 10 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **22** (22 mg, 73%) as an orange solid. mp = 94−97 °C. IR (neat) ν/cm^{-1}: 2923 (s), 1722 (m), 1317 (s), 749 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88−7.85 (m, 1H), 7.66−7.64 (m, 1H), 7.49−7.45 (m, 2H), 7.33−7.27 (m, 5H), 7.21−7.15 (m, 3H), 7.15−7.11 (m, 2H), 6.78 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.0, 141.2, 138.5, 137.2, 134.6, 132.8, 130.6, 129.9, 129.6, 128.8, 128.6, 128.5, 128.1, 125.0, 123.9, 121.2, 114.6, 110.4. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}ClNO$ $[M + H]^+$, 332.0842; found, 332.0865.

(Z)-4-Benzylidene-2-(3-iodophenyl)-4H-benzo[d][1,3]-oxazine ***23***. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using 3-iodo-*N*-(2-(phenylethynyl)phenyl)benzamide (0.022 g, 0.0520 mmol, 1 equiv) as a starting material and gold(I) catalyst **C5** (0.0070 g, 0.0104 mmol, 20 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **23** (16 mg, 73%) as a white solid. mp = 90−93 °C. IR (neat) ν/cm^{-1}: 2922 (s), 1684 (s), 1452 (s), 1318 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.3 Hz, 1H), 7.78 (s, 1H), 7.64 (s, 2H), 7.56 (s, 1H), 7.35−7.29 (m, 3H), 7.25 (s, 1H), 7.19 (s, 2H), 7.11 (d, J = 7.3 Hz, 1H), 6.95 (s, 1H), 6.77 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.7, 141.5, 141.2, 139.4, 138.5, 137.3, 133.3, 130.1, 129.5, 128.9, 128.6, 128.1, 125.1, 124.0, 121.2, 114.8, 110.4, 93.9. HRMS (ESI+) m/z: calcd for $C_{21}H_{15}INO$ $[M + H]^+$, 424.0198; found, 424.0235.

(Z)-4-Benzylidene-2-(2-fluoro-5-iodophenyl)-4H-benzo-[d]-[1,3]oxazine ***24***. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using 2-fluoro-5-iodo-*N*-(2-(phenylethynyl)phenyl)benzamide (0.096 g, 0.2176 mmol, 1 equiv) as a starting material and gold(I) catalyst **C5** (0.0295 g, 0.0435 mmol, 20 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **24** (39 mg, 41%) as a white solid. mp = 93−95 °C. IR (neat) ν/cm^{-1}: 3072 (m), 2931 (s), 1675 (s), 1321 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.55−7.52 (m, 1H), 7.44 (ddd, J = 7.8, 4.8, 2.2 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 14.8 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 6.69 (s, 1H), 6.48 (t, J = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.6, 163.8, 159.2 (d, J = 256 Hz), 141.8, 140.1, 139.1 (d, J = 2 Hz), 137.7, 132.3 (d, J = 9 Hz), 130.8, 128.8, 127.8, 125.1, 124.1, 120.6, 117.8 (d, J = 22 Hz), 115.1, 111.2, 86.3. HRMS (ESI+) m/z: calcd for $C_{21}H_{14}FINO$ $[M + H]^+$, 442.0104; found, 442.0139.

(Z)-4-Benzylidene-2-(3,5-bis(trifluoromethyl)phenyl)-4H-benzo[d][1,3]oxazine ***25***. The following compound was obtained according to the Procedure for Gold(I) Catalysis, using *N*-(2-(phenylethynyl)phenyl)-3,5-bis(trifluoromethyl)-benzamide (0.043 g, 0.0992 mmol, 1 equiv) and gold(I) catalyst **C5** (0.0135 g, 0.0198 mmol, 20 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **25** (33 mg, 79%) as a white solid. mp = 105−108 °C. IR (neat) ν/cm^{-1}: 2925 (m), 1732 (w), 1454 (w), 1140 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 8.2 Hz, 1H), 7.87 (s, 2H), 7.72−7.66 (m, 2H), 7.46−7.41 (m, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 7.12−7.04 (m, 3H), 6.80 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.4, 140.4, 138.5, 137.9, 132.9, 130.2 (d, J = 3 Hz), 129.6, 129.2, 128.9, 128.52, 125.8, 124.7, 122.1 (d, J = 273 Hz), 121.3, 115.1, 111.4. HRMS (ESI+) m/z: calcd for $C_{23}H_{14}F_6NO$ $[M + H]^+$, 434.0980; found, 434.1009.

(Z)-4-Benzylidene-2-(4-nitrophenyl)-4H-benzo[d][1,3]-oxazine ***26***. Compound **26** was obtained according to the Procedure for Gold(I) Catalysis, using 4-nitro-*N*-(2-(phenylethynyl)phenyl)benzamide (0.020 g, 0.0854 mmol, 1 equiv) as a starting material and gold(I) catalyst **C5** (0.0080 g, 0.0116 mmol, 20 mol %). The crude material was purified by flash column chromatography over silica gel with the system hexane to afford the product **26** (11 mg, 52%) as a red solid. The spectroscopic data matched with those previously described in the literature.[21] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04−7.99 (m, 3H), 7.66 (t, J = 8.2 Hz, 3H), 7.37 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.5 Hz, 2H), 7.13 (d, J = 7.5 Hz, 2H), 7.09 (t, J = 7.5 Hz, 1H), 6.79 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 149.8, 141.2, 140.7, 138.5, 133.0, 131.2, 129.0, 128.8, 128.5, 125.5, 124.5, 123.5, 121.3, 114.9, 111.0.

Biological Assays on BC. *Cell Lines*. The tumor cell lines MCF-7 and HCC1954 were grown in Dulbecco's modified Eagle medium (Invitrogen Corporation, Carlsbad, CA, United States) enriched with 5% fetal bovine serum. Medium change and passage were achieved every 3 and 4 days, respectively. The MCF-7 and HCC1954 cell lines were generously provided by Professor V. Treviño from ITSM.

Cell Proliferation Analysis. The method for quantifying cell proliferation was carried out with the use of crystal violet dye in 1× phosphate-buffered saline (2.7 mM KCl, 1.8 mM KH_2PO_4, 136 mM NaCl, 10 mM Na_2HPO_4 pH 7.4). The treated cells were incubated in methanol for 15 min and washed two times with water. Cells were dyed with 0.1% crystal violet and washed three times with water. Crystal violet was recovered with 10% acid acetic to be analyzed in a microplate reader Multiskan GO spectrophotometer (Thermo Scientific, Ratastic, Finland).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06637.

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

Copies of ^{1}H and ^{13}C for compounds **1**−**26** and curves of dose−response of the compounds **16**−**26** (PDF)

AUTHOR INFORMATION

Corresponding Authors

Jesús Adrián López − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*; Email: jalopez@uaz.edu.mx

Luis Chacón-García − *Laboratorio de Diseño Molecular, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, 58033 Morelia, Michoacán, Mexico*; orcid.org/0000-0001-8877-4817; Email: lchacon@umich.mx

César R. Solorio-Alvarado − *División de Ciencias Naturales y Exactas, Departamento de Química, Universidad de Guanajuato, 36050 Guanajuato, Guanajuato, Mexico*; orcid.org/0000-0001-6082-988X; Email: csolorio@ugto.mx

Authors

Luis A. Segura-Quezada − *División de Ciencias Naturales y Exactas, Departamento de Química, Universidad de Guanajuato, 36050 Guanajuato, Guanajuato, Mexico*

Karina R. Torres-Carbajal − *División de Ciencias Naturales y Exactas, Departamento de Química, Universidad de Guanajuato, 36050 Guanajuato, Guanajuato, Mexico*

Narendra Mali − *División de Ciencias Naturales y Exactas, Departamento de Química, Universidad de Guanajuato, 36050 Guanajuato, Guanajuato, Mexico*

Dipak B. Patil − *División de Ciencias Naturales y Exactas, Departamento de Química, Universidad de Guanajuato, 36050 Guanajuato, Guanajuato, Mexico*

Mauricio Luna-Chagolla − *División de Ciencias Naturales y Exactas, Departamento de Química, Universidad de Guanajuato, 36050 Guanajuato, Guanajuato, Mexico*

Rafael Ortiz-Alvarado − *Instituto de Ciencias Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, 58000 Morelia, Michoacán, Mexico*

Melissa Tapia-Juárez − *Laboratorio de Diseño Molecular, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, 58033 Morelia, Michoacán, Mexico*

Ixamail Fraire-Soto − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*

Jorge Gustavo Araujo-Huitrado − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*

Angelica Judith Granados-López − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*

Rosalinda Gutiérrez-Hernández − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*

Claudia Araceli Reyes-Estrada − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*

Yamilé López-Hernández − *MicroRNAs and Cancer Laboratory, Universidad Autónoma de Zacatecas, 98066 Zacatecas, Zacatecas, Mexico*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c06637

Author Contributions

L.A.S.-Q., K.R.T.-C., N.M., D.B.P., M.L.-C., and R.O.-A.: organic synthesis, M.T.-J.: spectroscopic analysis, I.F.-S., J.G.A.-H., A.J.G.-L., R.G.-H., C.A.R.-H., and Y.L.-H.: biological evaluation, and J.A.L., L.C.-G., and C.R.S.-A.: analysis, discussion, and writing paper.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to CONACyT (FORDECYT-PRONACES/610286/2020) for financial support. We acknowledge the DCNyE, the Chemistry Department, and the National Laboratory UG-CONACyT (LACAPFEM) of the University of Guanajuato. We thank CONACyT for fellowships to L.A.S.-Q., K.R.T.-C., N.M., D.B.P., M.L.-C., and I.F.-S. We thank M. C. Daniel Ruiz Plaza for his kind help in the NMR laboratory.

DEDICATION

In memory of our colleague and friend Kevin.

REFERENCES

(1) Zhang, Y.-R.; Xie, J.-W.; Huang, X.-J.; Zhu, W.-D. Construction of functionalized 2,3-dihydro-1,4-benzoxazines via [5 + 1] annulations of 2-halo-1,3-dicarbonyl compounds with imines. *Org. Biomol. Chem.* **2012**, *10*, 6554−6561.

(2) (a) Liu, Y.-L.; Hsu, C. W.; Chou, C.-I. Silicon-Containing Benzoxazines and their Polymers: Copolymerization and Copolymer Properties. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1007−1015. (b) Gilbert, E.; Taverna, M. E.; Dieser, M. F.; Morales, G.; Spontón, M.; Estenoz, D. Synthesis and Characterization of New Thermosetting Polybenzoxazines with Other Functional Groups in the Network. *J. Polym. Res.* **2018**, *25*, 1−12.

(3) Sugimoto, Y.; Otani, T.; Oie, S.; Wierzba, K.; Yamada, Y. Mechanism of Action of a New Macromolecular Antitumor Antibiotic, C-1027. *J. Antibiot.* **1990**, *43*, 417−421.

(4) (a) Zinad, D. S.; Mahal, A.; Mohapatra, R. K.; Sarangi, A. K.; Paramata, M. R. F. Medicinal Chemistry of Oxazines as promising agents in drug discovery. *Chem. Biol. Drug Des.* **2020**, *95*, 16−47. (b) Hannath, K. M.; Chandra, M.; Krishnakumar, K. Biological Potentials of Oxazines as Promising Agents for Drug Discovery - A Short Review. *Int. J. Pharm. Sci. Rev. Res.* **2020**, *63* (2), 102−106.

(5) Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Lundeen, S.; Marschke, K. B.; Zhang, Z. 6-Aryl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-ones: a novel class of potent, selective, and orally active nonsteroidal progesterone receptor antagonists. *J. Med. Chem.* **2002**, *45*, 4379−4382.

(6) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; et al. 2-amino-4*H*-3,1-benzoxazin-4-ones as inhibitors of C1r serine protease. *J. Med. Chem.* **1998**, *41*, 1060−1067.

(7) Girard, C.; Liu, S.; Cadepond, F.; Adams, D.; Lacroix, C.; Verleye, M.; Gillardin, J.-M.; Baulieu, E.-E.; Schumacher, M.; Schweizer-Groyer, G. Etifoxine improves peripheral nerve regeneration and functional recovery. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 20505−20510.

(8) Bastos, M. M.; Costa, C. C. P.; Bezerra, T. C.; da Silva, F. d. C.; Boechat, N. Efavirenz a nonnucleoside reverse transcriptase inhibitor of first-generation: Approaches based on its medicinal chemistry. *Eur. J. Med. Chem.* **2016**, *108*, 455−465.

(9) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. Design and synthesis of 4*H*-3,1-benzoxazin-4-ones as potent alternate substrate inhibitors of human leukocyte elastase. *J. Med. Chem.* **1990**, *33*, 464−479.

(10) Zhang, P.; Terefenko, E. A.; Fensome, A.; Zhang, Z.; Zhu, Y.; Cohen, J.; Winneker, R.; Wrobel, J.; Yardley, J. Potent nonsteroidal

progesterone receptor agonists: synthesis and SAR study of 6-aryl benzoxazines. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787−790.
(11) Ataollahi, M. R.; Sharifi, J.; Paknahad, M. R.; Paknahad, A. Breast cancer and associated factors: a review. *J. Med. Life* **2015**, *8*, 6−11.
(12) Sun, Y.-S.; Zhao, Z.; Yang, Z.-N.; Xu, F.; Lu, H.-J.; Zhu, Z.-Y.; Shi, W.; Jiang, J.; Yao, P.-P.; Zhu, H.-P. Risk Factors and Preventions of Breast Cancer. *Int. J. Biol. Sci.* **2017**, *13*, 1387−1397.
(13) Sharma, G. N.; Dave, R.; Sanadya, J.; Sharma, P.; Sharma, K. K. Various types and management of breast cancer: an overview. *J. Adv. Pharm. Technol. Res.* **2010**, *1*, 109−126.
(14) Ferlay, J.; Colombet, M.; Soerjomataram, I.; Mathers, C.; Parkin, D. M.; Piñeros, M.; Znaor, A.; Bray, F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer* **2019**, *144*, 1941−1953.
(15) Akram, M.; Iqbal, M.; Daniyal, M.; Khan, A. U. Awareness and current knowledge of breast cancer. *Biol. Res.* **2017**, *50*, 33.
(16) Comşa, Ş.; Cimpean, A. M.; Raica, M. The Story of MCF-7 Breast Cancer Cell Line: 40 years of Experience in Research. *Anticancer Res.* **2015**, *35*, 3147−3154.
(17) Booms, A.; Coetzee, G. A.; Pierce, S. E. MCF-7 as a Model for Functional Analysis of Breast Cancer Risk Variants. *Cancer Epidemiol., Biomarkers Prev.* **2019**, *28*, 1735−1745.
(18) Soule, H. D.; Vazquez, J.; Long, A.; Albert, S.; Brennan, M. A human cell line from a pleural effusion derived from a breast carcinoma 2. *J. Natl. Cancer Inst.* **1973**, *51*, 1409−1416.
(19) Lal, K.; Yadav, P. Recent Advancements in 1,4-Disubstituted 1*H*-1,2,3-Triazoles as Potential Anticancer Agents. *Anticancer Agents Med. Chem.* **2018**, *18*, 21−37.
(20) Rivera-Avalos, E.; de Loera, D.; Araujo-Huitrado, J. G.; Escalante-García, I. L.; Muñoz-Sánchez, M. A.; Hernández, H.; López, J. A.; López, L. Synthesis of Amino Acid-Naphthoquinones and In Vitro Studies on Cervical and Breast Cell Lines. *Molecules* **2019**, *24*, 4285−4298.
(21) Saito, T.; Ogawa, S.; Takei, N.; Kutsumura, N.; Otani, T. Palladium-catalyzed highly regio- and stereoselective synthesis of 4-alkylidene-4*H*-3,1-benzoxazines from N-acyl-o-alkynylanilines. *Org. Lett.* **2011**, *13*, 1098−1101.
(22) Cai, Z.-J.; Li, F.-H.; Wang, S.-Y.; Ji, S.-J. Palladium-Catalyzed Cascade Arene/Alkyne Annulation: Synthesis of Fluorene-Benzoxazine Derivatives. *Org. Lett.* **2016**, *18*, 4810−4813.
(23) Ding, L.; Niu, Y.-N.; Xia, X.-F. Pd-Catalyzed Tandem Isomerization/Cyclization for the Synthesis of Aromatic Oxazaheterocycles and Pyrido[3,4-*b*]indoles. *J. Org. Chem.* **2021**, *86*, 10032−10042.
(24) Sinai, Á.; Mészáros, Á.; Gáti, T.; Kudar, V.; Palló, A.; Novák, Z. Copper-catalyzed oxidative ring closure and carboarylation of 2-ethynylanilides. *Org. Lett.* **2013**, *15*, 5654−5657.
(25) Pinheiro, R. d. C.; Back, D. F.; Zeni, G. Iron(III) Chloride/Dialkyl Diselenides-Promoted Cascade Cyclization of ortho-Diynyl Benzyl Chalcogenides. *Adv. Synth. Catal.* **2019**, *361*, 1866−1873.
(26) Vandavasi, J. K.; Kuo, K.-K.; Hu, W.-P.; Shen, H.-C.; Lo, W.-S.; Wang, J.-J. A convenient method to construct (*Z*)-oxazines via 6-*exo*-dig iodocyclization and synthesis of indolin-3-one. *Org. Biomol. Chem.* **2013**, *11*, 6520−6525.
(27) Putta, V. P. R. K.; Vodnala, N.; Gujjarappa, R.; Tyagi, U.; Garg, A.; Gupta, S.; Pujar, P. P.; Malakar, C. C. Reagent-Controlled Divergent Synthesis of 2-Amino-1,3-Benzoxazines and 2-Amino-1,3-Benzothiazines. *J. Org. Chem.* **2020**, *85*, 380−396.
(28) Rajkumar, S.; Tang, M.; Yang, X. Chiral Phosphoric Acid Catalyzed Kinetic Resolution of 2-Amido Benzyl Alcohols: Asymmetric Synthesis of 4*H*-3,1-Benzoxazines. *Angew. Chem., Int. Ed. Engl.* **2020**, *59*, 2333−2337.
(29) Nahide, P. D.; Jiménez-Halla, J. O. C.; Wrobel, K.; Solorio-Alvarado, C. R.; Ortiz Alvarado, R.; Yahuaca-Juárez, B. Gold(I)-catalysed high-yielding synthesis of indenes by direct Csp(3)-H bond activation. *Org. Biomol. Chem.* **2018**, *16*, 7330−7335.
(30) Jadhav, P. D.; Liu, J.; Li, R.-S. Gold(I)-Catalyzed Highly Enantioselective [4 + 2]-Annulations of Cyclopentadienes with Nitrosoarenes via Nitroso-Povarov versus Oxidative Nitroso-Povarov Reactions. *ACS Catal.* **2020**, *10*, 5840−5845.
(31) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. Gold(I)-catalyzed cyclizations of 1,6-enynes: alkoxycyclizations and *exo/endo* skeletal rearrangements. *Chem.—Eur. J.* **2006**, *12*, 1677−1693.
(32) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-catalyzed C-N bond-forming processes: the first amidation of aryl sulfonates, aqueous amination, and complementarity with Cu-catalyzed reactions. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655.
(33) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. Novel Electron-Rich Bulky Phosphine Ligands Facilitate the Palladium-Catalyzed Preparation of Diaryl Ethers. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378.
(34) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. A P,N-ligand for palladium-catalyzed ammonia arylation: coupling of deactivated aryl chlorides, chemoselective arylations, and room temperature reactions. *Angew. Chem., Int. Ed. Engl.* **2010**, *49*, 4071−4074.
(35) Tang, H.; Menzel, K.; Fu, G. C. Ligands for palladium-catalyzed cross-couplings of alkyl halides: use of an alkyldiaminophosphane expands the scope of the Stille reaction. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5079−5082.
(36) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. High turnover number and rapid, room-temperature amination of chloroarenes using saturated carbene ligands. *Org. Lett.* **2000**, *2*, 1423−1426.
(37) Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028−9072.
(38) (a) Mato, M.; Franchino, A.; García-Morales, C.; Echavarren, A. M. Gold-Catalyzed Synthesis of Small Rings. *Chem. Rev.* **2021**, *121*, 8613−8684. (b) Fustero, S.; Miró, J.; Sánchez-Roselló, M.; Del Pozo, C. Tandem Gold Self Relay Catalysis for the Synthesis of 2,3-Dihydropyridin-4(1*H*)-ones: Combination of s and p Lewis Acid Properties of Gold Salts. *Chem.—Eur. J.* **2014**, *20*, 14126−14131.
(39) Gazdar, A. F.; Kurvari, V.; Virmani, A.; Gollahon, L.; Sakaguchi, M.; Westerfield, M.; Kodagoda, D.; Stasny, V.; Cunningham, H. T.; Wistuba, I. I.; et al. Characterization of paired tumor and non-tumor cell lines established from patients with breast cancer. *Int. J. Cancer* **1998**, *78*, 766−774.
(40) Brandes, L. J.; Hermonat, M. W. Receptor status and subsequent sensitivity of subclones of MCF-7 human breast cancer cells surviving exposure to diethylstilbestrol. *Cancer Res.* **1983**, *43*, 2831−2835.
(41) Souto, E. B.; Doktorovova, S.; Campos, J. R.; Martins-Lopes, P.; Silva, A. M. Surface-tailored anti-HER2/neu-solid lipid nanoparticles for site-specific targeting MCF-7 and BT-474 breast cancer cells. *Eur. J. Pharm. Sci.* **2019**, *128*, 27−35.
(42) Mbaba, M.; Dingle, L. M. K.; Cash, D.; Mare, J.-A. d. l.; Laming, D.; Taylor, D.; Hoppe, H. C.; Edkins, A. L.; Khanye, S. D. Repurposing a polymer precursor: Synthesis and in vitro medicinal potential of ferrocenyl 1,3-benzoxazine derivatives. *Eur. J. Med. Chem.* **2020**, *187*, 111924.
(43) Bollu, R.; Palem, J. D.; Bantu, R.; Guguloth, V.; Nagarapu, L.; Polepalli, S.; Jain, N. Rational design, synthesis and anti-proliferative evaluation of novel 1,4-benzoxazine-[1,2,3]triazole hybrids. *Eur. J. Med. Chem.* **2015**, *89*, 138−146.
(44) de Brito, M. R. M.; Peláez, W. J.; Faillace, M. S.; Militão, G. C. G.; Almeida, J. R. G. S.; Argüello, G. A.; Szakonyi, Z.; Fülöp, F.; Salvadori, M. C.; Teixeira, F. S.; Freitas, R. M.; Pinto, P. L. S.; Mengarda, A. C.; Silva, M. P. N.; Da Silva Filho, A. A.; de Moraes, J. Cyclohexene-fused 1,3-oxazines with selective antibacterial and antiparasitic action and low cytotoxic effects. *Toxicol. In Vitro* **2017**, *44*, 273−279.
(45) Hanahan, D.; Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **2011**, *144*, 646−674.
(46) Tanos, T.; Rojo, L. J.; Echeverria, P.; Brisken, C. ER and PR signaling nodes during mammary gland development. *Breast Cancer Res.* **2012**, *14*, 210−221.

https://doi.org/10.1021/acsomega.1c06637
ACS Omega 2022, 7, 6944−6955

(47) Du, Z.; Gao, W.; Sun, J.; Li, Y.; Sun, Y.; Chen, T.; Ge, S.; Guo, W. Identification of long noncoding RNAmediated transcriptional dysregulation triplets reveals global patterns and prognostic biomarkers for ER+/PR+, HER2 and triple negative breast cancer. *Int. J. Mol. Med.* **2019**, *44*, 1015−1025.

(48) Zhao, Y. G.; Chen, Y.; Miao, G.; Zhao, H.; Qu, W.; Li, D.; Wang, Z.; Liu, N.; Li, L.; Chen, S.; et al. The ER-Localized Transmembrane Protein EPG-3/VMP1 Regulates SERCA Activity to Control ER-Isolation Membrane Contacts for Autophagosome Formation. *Mol. Cell* **2017**, *67*, 974−989.e6.

(49) Kolesnikov, N. N.; Veryaskina, Y. A.; Titov, S. E.; Rodionov, V. V.; Gening, T. P.; Abakumova, T. V.; Kometova, V. V.; Torosyan, M. K.; Zhimulev, I. F. Expression of micrornas in molecular genetic breast cancer subtypes. *Cancer Treat. Res. Commun.* **2019**, *20*, 100026.

(50) Okuma, K.; Ozaki, S.; Nagahora, N.; Shioji, K. Synthesis of 3.1-benzothiazines from 2-alkenyl- and 2-alkynylanilides and Lawesson reagent. *Heterocycles* **2011**, *83*, 1303−1313.

(51) Chaisan, N.; Kaewsri, W.; Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. $PtCl_4$-catalyzed Cyclization of *N*-acetyl-2-alkynylanilines: A Mild and Efficient Synthesis of *N*-Acetyl-2-substituted indoles. *Tetrahedron Lett.* **2018**, *59*, 675−680.

(52) (a) Wang, Y.; Zhou, Y.; Ma, X.; Song, Q. Solvent-Dependent Cyclization of 2-Alkynylanilines and $ClCF_2COONa$ for Divergent Assembly of *N*-(Quinolin-2-yl)amides and Quinolin-2(1*H*)-ones. *Org. Lett.* **2021**, *23*, 5599−5604. (b) Nahide, P. D.; Jiménez-Halla, J. O. C.; Wrobel, K.; Solorio-Alvarado, C. R.; Ortiz Alvarado, R.; Yahuaca-Juárez, B. Gold(I)-Catalyzed High-Yielding Synthesis of Indenes by Direct C_{sp}^3-H Bond Activation. *Org. Biomol. Chem.* **2018**, *16*, 7330−7335.