DOCTORAL THESIS

1) IODINE(III)-MEDIATED THE ELECTROPHILIC IODINATION OF FREE-ANILINES USING THE PIDA/NH4I SYSTEM.

AND

2) GOLD(I)-CATALYZED INTERMOLECULAR ALKYNE DIMERIZATION FOR THE SYNTHESIS OF PENTACYCLIC BISINDOLIC TRANS-FUSED SYSTEM VIA DOMINO PROCESS.

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CERTIFICATE

This is to certify that Narendra Sukalal Mali 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 this of thesis entitled 1) *IODINE(III)-MEDIATED THE ELECTROPHILIC IODINATION OF FREE-ANILINES USING THE PIDA/NH4I SYSTEM. AND 2) GOLD(I)-CATALYZED INTERMOLECULAR ALKYNE DIMERIZATION FOR THE SYNTHESIS OF PENTACYCLIC BISINDOLIC TRANS-FUSED SYSTEM VIA DOMINO PROCESS.* The thesis fully covers 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 Supervisor Department of Chemistry University of Guanajuato.

Prof. Dr. César Rogelio Solorio Alvarado

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

Title: *1) IODINE(III)-MEDIATED THE ELECTROPHILIC IODINATION OF FREE-ANILINES USING THE PIDA/NH4I SYSTEM.*

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Date Defended/Approved: November 2022

" Take a risk in your life,

If you win, you can lead!

If you lose, you can guide!

-Swami Vivekananda…….

"Confidence and hard work are the best medicine,

To kill the disease called failure.

It will make you a Successful person.

-A. P. J. Abdul Kalam…….

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Thanks to God the great for blessing me and giving me the power and persistence to complete my studies.

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Last but not least, Thanks to my all prayers and friends from India for your unexpecting help, love, and support…..

Dedicated

Finally, I would like to dedicate this thesis, especially to my family, my father Sukalal. M. Mali, my soul my life my mother Sunita S. Mali, My sisters Kirti A. Mali, Neha N. Mali, My brother-in-law Aasaram G. Mali, Nikhil S. Mali, My lovely niece Yutika, cute nephew Parth and my grandfather Gangaram S. Mali, and my grandmother Indubai G. Mali, and my uncles, Dipak. G. Mali and Bhaskar. G. Mali Without their support and love, it was impossible to achieve my goals in the life. My family is my strength and my guidance. I consider myself the luckiest person in the world to have such a lovely and caring family, standing beside me with their love and unconditional support.

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a la Investigación y al Posgrado

GUANAJUATO
Secretaría de Innovación,
Ciencia y Educación Superior

List of Publications

This thesis is based on the following publications. The contribution by the author to each publication is clarified in Annex.

1) **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.
2) **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.
3) **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.
4) **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. and Gutiérrez-Hernández, R., *ACS omega*, 2022 *7*, 6944-6955.

5) **Iodine(III)-Mediated Iodination of Free-Anilines through Acetyl Hypoiodite Formation: Study of the Reaction Pathway.**
   Mali, N., Ibarra-Gutiérrez, J. G., Lugo ,L. I., Ortíz-Alvarado, R., Chacón-García, L., Navarro-Santos, P., Jiménez-Halla, J. O. C., Solorio-Alvarado, C.R. *Eur. J. Org. Chem, 2022 (Manuscript Accepted).*

Index

Prologue

This dissertation is divided into 6 sections: First section is the resume of the thesis. The second section is a short general introduction referring to the topics that were addressed in the work of investigation. The next four sections are chapters I, II, III 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 I-III and annex A and B.

2. In the second section, the general objectives of this thesis are described.

3. In the third section, the general introduction of chapter I the thesis contains a short overview about hypervalent iodine (III) chemistry and gold chemistry about each of the projects that were investigated, and which will be discussed in chapters II-III.

4. In the fourth section, the chapter II we developed a new gold(I)-catalyzed intermolecular alkyne dimerization for the Synthesis of pentacyclic bisindolic *trans*-fused system via domino process.

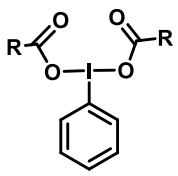
5. In the fifth section, the chapter III contains the Iodine(III)-Mediated Iodination of Free-Anilines via Acetyl Hypoiodite Formation. Mechanistic Study of the Reaction Pathway.

6. In the sixth section, annex A and B section, are included the copies of ^{1}H and ^{13}C NMR spectra for all the synthesized compounds in the thesis and the published articles.

Resume

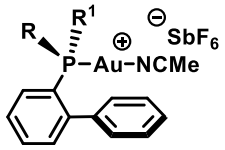
This dissertation contains one general introduction and two experimental chapters, which are outlined below.

1. In chapter I dissuasion about the general introduction, there are two topics discussed based on the research carried out in the doctoral thesis. In the first part, the background of hypervalent iodine compounds, their synthesis methods, and applications in organic synthesis, and in the second part, gold(I) catalysis with wide use in organic transformation have been described.



R = CH_3, CF_3

Hypervalent iodine(III) reagents

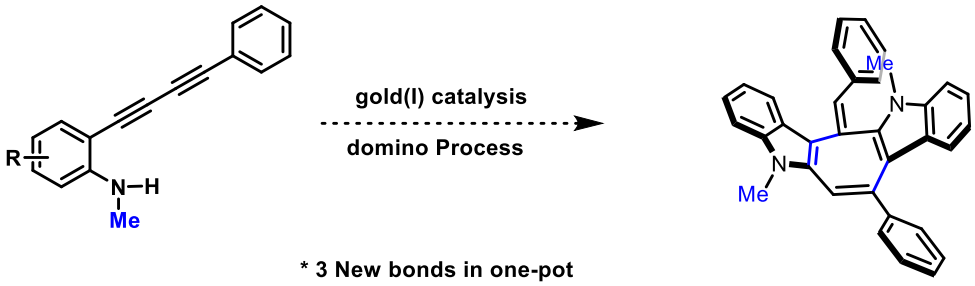


R = ^{t}Bu

R1 = Cy

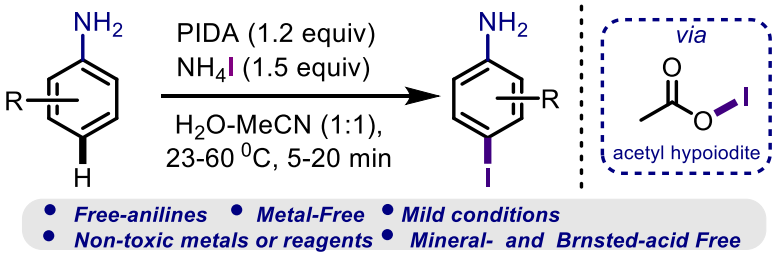
Cataonic gold(I) complexes

2. In chapter II, we developed a gold(I)-catalyzed intermolecular alkyne dimerization for the Synthesis of pentacyclic bisindolic trans-fused system via domino process The scope of the protocol was determined by synthesizing some electron-neutral, electron-poor as well as electron-rich derivatives. Also, we studied X-Ray Crystallography, The mechanism of this reaction is following an intermolecular pathway by *5-endo-dig* cyclization to pentacyclic bisindolic trans-fused dimer.



*** 3 New bonds in one-pot**
*** Pentacyclic Non-Aromatic system**
*** *Trans*-fused bis-indolic system**
*** 7 atom ring**

3. In chapter III, The first iodine(III)-mediated *para*-selective iodination protocol for free-anilines as well as the mechanistic elucidation of the reaction pathway is described. The developed method proceeded under clean, non-toxic, efficient and in general mild reaction conditions. To the best of our knowledge this report describes for the first time a procedure focused specifically on the introduction of an iodine atom in free anilines using PIDA [(diacetoxyiodo)benzene] and ammonium iodide which formed *in situ* acetyl hypoiodite (AcO-I) as the halogenating species. Our DFT calculations suggest a reaction mechanism that highlights the role of the ammonium cation in the AcO-I formation and halogenation. Considering there are few procedures for the iodine atom introduction in anilines using non-acidic conditions, herein we described an initial report on a mild and operationally simple alternative using iodine(III) reagents.



General objectives of the thesis

This doctoral dissertation is focused on the development of new procedures mediated by hypervalent iodine(III) reagents as well as catalyzed by cationic gold(I) complexes directed towards their applications in the synthesis of new organic molecules.

Chapter I

➢ We will discuss about the hypervalent iodine(III) and gold(I) cationic complexes, those are playing a very important role and their application in organic transformation.

Chapter II

➢ We will plan the development of a new gold(I)-catalyzed intermolecular alkyne dimerization for the Synthesis of pentacyclic bisindolic trans-fused system via domino process.

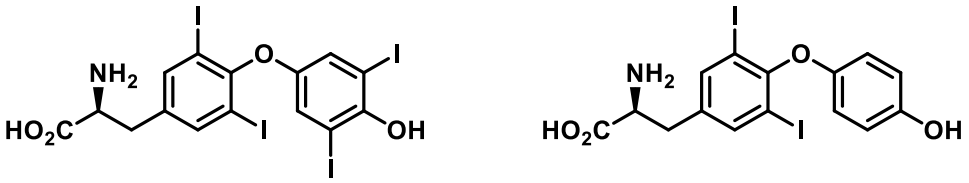
Chapter III

➢ We proposed the development the first iodine(III)-mediated *para*-selective iodination protocol for free-anilines as well as the mechanistic elucidation of the reaction pathway.

Iodine Chemistry

1.1. Iodine Precedents.

Iodine is a 53rd number element in the periodic table and is represented by the symbol "I" and shows the non-metallic character of the halogen group. Iodine was found by French chemist Bernard Courtois,[1] in the year 1811 It was near the seaweed´s ash. And further J. L. Gay Lussac,[2] gave its name "Iodine" in 1813. The iodine is a purple-gray blackish color. The iodine gives purple color when heated it's also not completely soluble in water but soluble in some solvents like carbon tetrachloride. Iodine is very important for humans for the proper functioning nervous system, and brain. The iodine-containing core is frequently found in especially I some radioactive isotopes that are very useful in the application of nuclear medicine in the imaging thyroid gland, which can help to regulate metabolism and generate iodine-containing hormones drugs,[3] like (S)-thyroxine (T4) and (S)-triiodothyronine (T3)[4,5] (Figure 1.1).



(*S*)-Thyroxine T_4 (*S*)-Triiodothyronine T_3

Figure 1.1. The iodine-containing core of thyroid gland hormone.

1. Swain, P.A.; Bernard C. *Bull. Hist. Chem*, **2005,** *30,* 1777-1838.
2. Rosenfeld, L, *J. Chem Edu.* **2000,** *77***,** 984.
3. Roy, G.; Nethaji, M.; Mugesh, G. *Org. Biomol. Chem*. **2006**, *4*, 2883− 2887.
4. Larsen, P.R. *J. Clin. Endocrinol.* Metab. **1975**, *41*, 1098−1104.
5. Robertson, I.; Boddy, K.; Hooper, M.J.; Stevenson, R.D.; McGhie, T.; Alexander, W.D.; Wilson, G.M. *Clin. Endocrinol*.**1976**, *5*, 151-157.

Among the most modified iodophenol and heterocyclic structures which are ubiquitous from the marine natural products like terpenes or proteinoids origin from sponges *Topsetina sp.*[6] *or coral genus Clavularia Viridis.*[7] Iodoarenes are also important such as electrophiles in cross-coupling reactions like Stille, Suzuki as well as Sonogashira alkynylation and Mizoroki-Heck olefination (Figure 1.2).

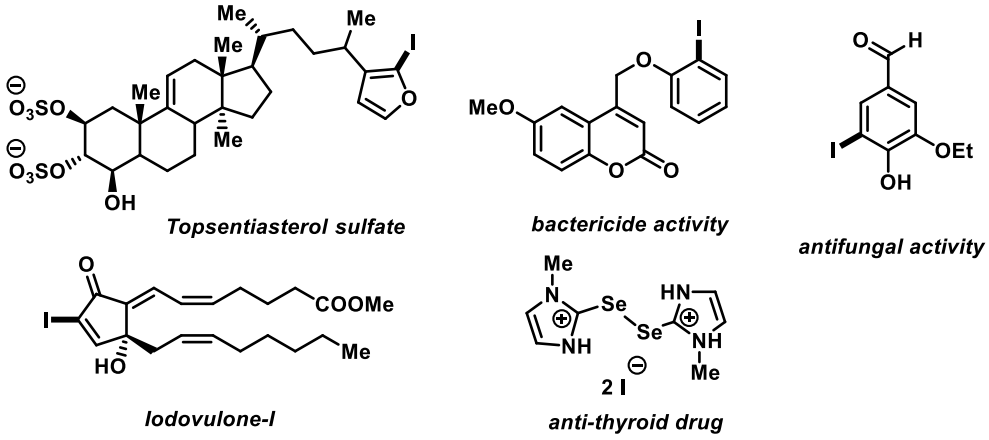


Figure 1.2. Several antibacterial iodine-containing cores of iodoarenes heterocyclic cores.

Modification of iodine substituted moieties leads to showing different biological activities such as Iodo-4-aryloxy-methyl coumarins bactericide activities,[8] also the method of protecting substance showing antifungal activities[9] and imidazole moieties useful treatment for the anti-thyroid drugs.[10]

6. a) Ihssen, J.; Schubert, M.; Thöny-Meyer, L.; Richter, M. *PLoS One,* **2014**, *9,* 89924. b) 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. *J. Org. Chem.* **2019**, *84*, 4149-4164.
7. Satish, G., Sharma, A., Gadidasu, K.K., Vedula, R.R. and Penta, S., *Chem. Heterocycl. Compd.* **2016**, *52*, 409-414.
8. Jeyachandran, M.; Ramesh, P.; Sriram, D.; Senthilkumar, P.; Yogeeswari, P. *Bioorg. Med. Chem. Lett.* **2012**.*22,* 4807-4809.
9. Dascalu, A.E.; Ghinet, A.; Lipka, E.; Furman, C.; Rigo, B.; Fayeulle, A.; Billamboz, M. *Fitoterapia*, **2020**, *143*, 104581.
10. Divi, R.L.; Chang, H.C.; Doerge, D.R. *Biochem. Pharmacol*, **1997**, *54,* 1087-1096.

1.2 hypervalent iodine compounds.

In the modern synthesis of organic compounds iodine has been a cornerstone role due to its heaviest element in the periodic table and shows nonmetallic character which has the ability to form a three-center-four-electron (3c-4e) bond (L−I−L) known as "hypervalent bond". Nowadays hypervalent iodine gained popularity due to its mild and highly selective oxidizing properties. The history of hypervalent iodine reagent was first synthesized by German chemist Conrad Willgerodt,[11] in 1886. It was the first example of a hypervalent iodine reagent, (dichloroiodo)benzene [$PhICl_2$]. Among the unprecedented development due to being diverse and showing a great deal of heavy metal and readily available also suitable for environmentally benign (Figure 1.3).

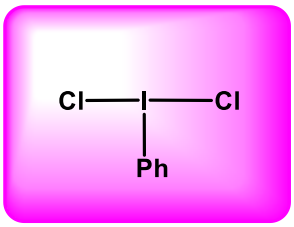


Figure 1.3. The structure of hypervalent iodine(III) species PIDA.

The most commonly hypervalent iodine reagents are iodine(III) and iodine(V) derivatives and are useful for the oxidative transformation in organic synthesis it has useful application like oxidative coupling reaction, the ligand exchange reaction, carbon-carbon, and carbon-nitrogen bond formation are reported in the literature.[12] Furthermost important hypervalent iodine classes are used as an oxidant or electrophilic reagents (Figure 1.4).[13]

11. Willgerodt, C. *J. Prakt. Chem*. **1886**, *33*, 154–160.
12. (a) Varvoglis, A. *Org. Chem. of Poly. Iodine*, VCH, *New York,* **1992**, 414. (b) Matveeva, E.D.; Proskurnina, M.V.; Zefirov, N.S. *Heteroat. Chem***. 2006**, *17*, 595-617.
13. (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. b) Zhdankin, V. V.; Stang, P. *J. Chem. Rev*. **2002**, *102*, 2523–2584. (c) Zhdankin, V. V.; Stang, P. *J. Chem. Rev*. **2008**, *108*, 5299– 5358.

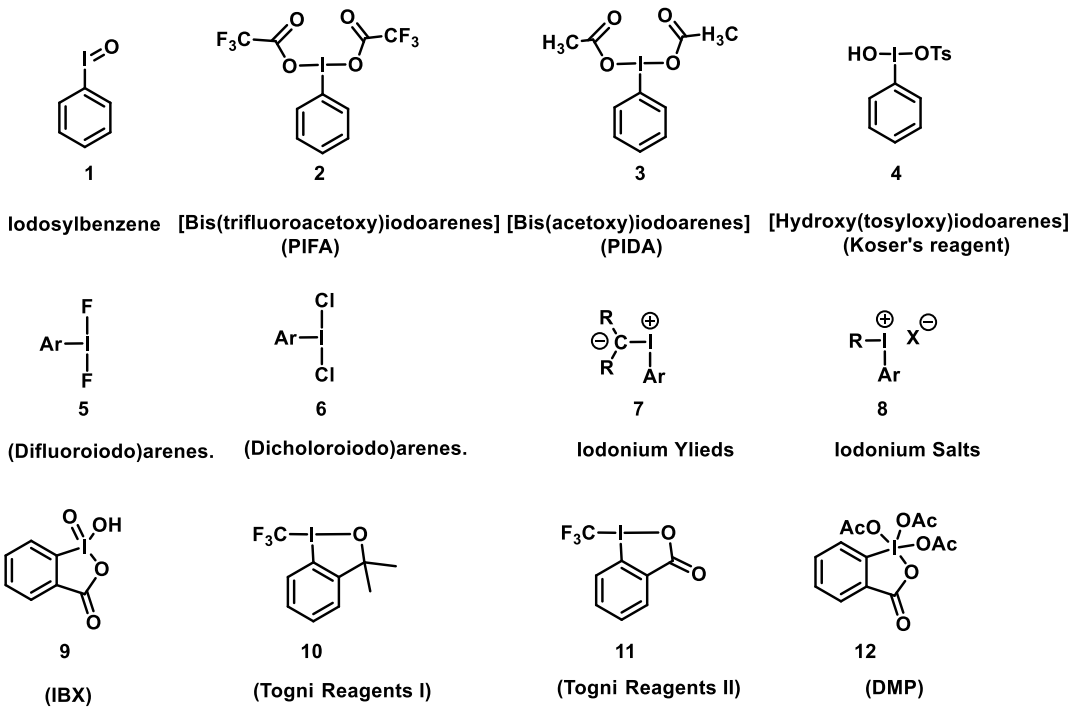


Figure 1.4. Types of Iodinated hypervalent iodine reagents.

The hypervalent reagents,[14] have different oxidation states like iodine(III) and iodine (V) that are commercially available and very useful for organic transformation, and stable at normal room temperature. Compounds **1**, **2**, **3,** and **4** belong to the Iodine(III) oxidation state and found widespread application as reagents for halogenation. Also, **5** and **6** are effective in chlorination and fluorination in organic transformation. Compounds **7**, and **8** are iodonium which is used for several organic transformations. The reagent iodine(V) like **9**, **10**, **11,** and **12** their application found in numerous organic transformations.

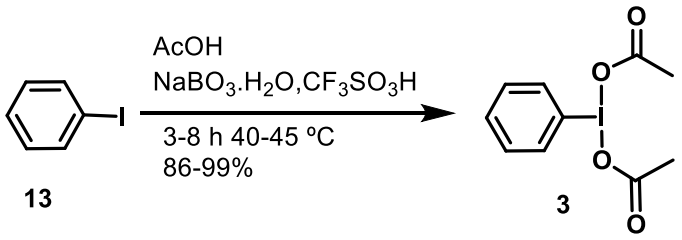
14. (a) Boye, A.C.; Meyer, D.; Ingison, C.K.; French, A.N; Wirth, T. *Org. Lett*, **2003**, *12*, 2157-2159. (b) Shah, A.U.H.A.; Khan, Z.A.; Choudhary, N.; Lohölter, C.; Schäfer, S.; Marie, G.P.; Farooq, U.; Witulski, B. and Wirth, T. *Org. Lett.* **2009**, *11*, 3578-3581.

1.3. Preparation method of hypervalent iodine-(III) reagents.

In the hypervalent iodine(III) reagents can be prepared by applying various methods which are described as follows.

1.3.1 Triflic acid applying preparation of (PIDA'S).

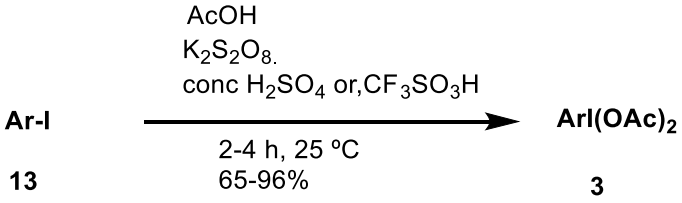
The most effective method applied for the preparation of [bis(acetoxy)iodo]arenes PIDA **3** by the addition of trifluoromethanesulfonic acid (triflic acid) in the reaction of iodoarenes **13** with sodium perborate in presence of acetic condition by applying acetic acid at 40-45 °C For the less time and obtaining excellent yield (**Eq. 1**).[15]



[1]

1.3.2 Pottasium peroxodisualfate using a preparation of (PIDA'S).

One more convenient method for the synthesis of [bis(acetoxy)iodo]arenes PIDA **3** can carried out at room temperature in the presence of potassium peroxodisulfate and a mixture of the acetic acid and concerted sulfuric acid or trifluoromethane sulfonic acid. The advantage of this method reaction is finished within 2-4 hours and obtained a high yield (**Eq. 2**).[16]



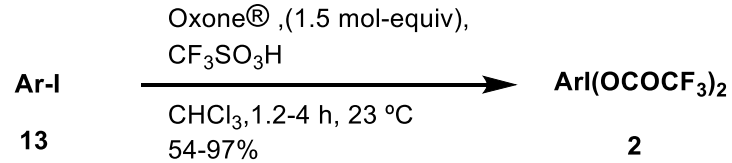
[2]

Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 3-$CF_3C_6H_4$
3-$NO_2C_6H_4$, 1-$C_{10}H_7$, 4-FC_6H_4.

15. Hossain, M.D.; Kitamura, T. *J. Org. Chem*. **2005**, *70*, 6984-6986.
16. Hossain, M.D.; Kitamura, T. *Synth*. **2005**, 1932-1934.

I.3.3 Oxone® applying preparation of (PIFA).

The general convenient synthesis of [bis(trifluoroacetoxy)iodo]arenes **2** is carried out by corresponding aryl iodide **13** with Oxone® and trifluoroacetic acid in chloroform at room temperature within 2-4 hours and the advantage of this synthesis if required less time and gives a high yield,[17] also the product is more stable in room temperature (**Eq. 3**).

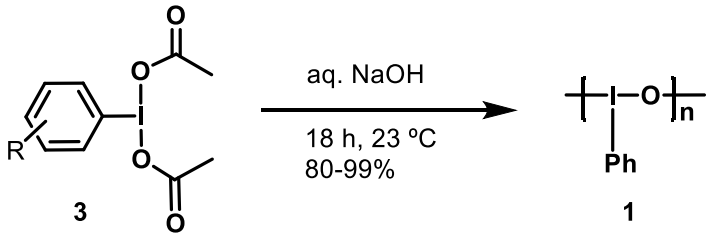


[3]

Ar = C_6H_5, 4-FC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-$CF_3C_6H_4$
3,5-$(CF_3)_2C_6H_3$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$HOOCC_6H_4$,3-$HOOCC_6H_4$, C_6F_5.

1.3.4 Synthesis of Iodosylarenes.

There are several procedures described for the synthesis of iodosylarenes **1**. But this is one of the most effective and convenient ways from the PIDA **3** with aq. NaOH was stirred to room temperature within 18 hours and obtained a good amount of yield.[18] This procedure can be applied to the substituted iodosylbenzene (**Eq. 4**).



[4]

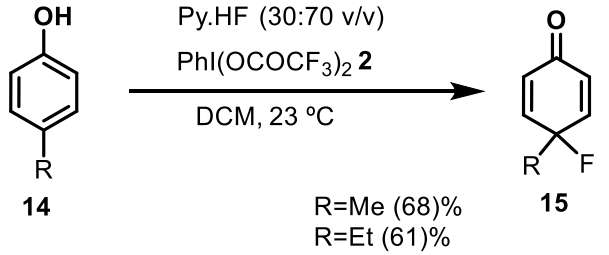
17. Zagulyaeva, A. A.; Yusubov, M.S.; V.V. Zhdankin. *J. Org. Chem*. **2010**, *75*, 2119-2122.
18. (a) Ghosh, S. K.; Hu, M.; Comito, R. J. *Eur. J. Chem.* **2021**, *27*, 17601-17608. (b) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563-1565.

1.4 Recent study and application of hypervalent iodine-(III) reagents.

Hypervalent iodine reagents have useful applications in reactions such as halogenation, carbon-carbon bond formation, carbon-hetero bond formation, and sigmatropic reactions.

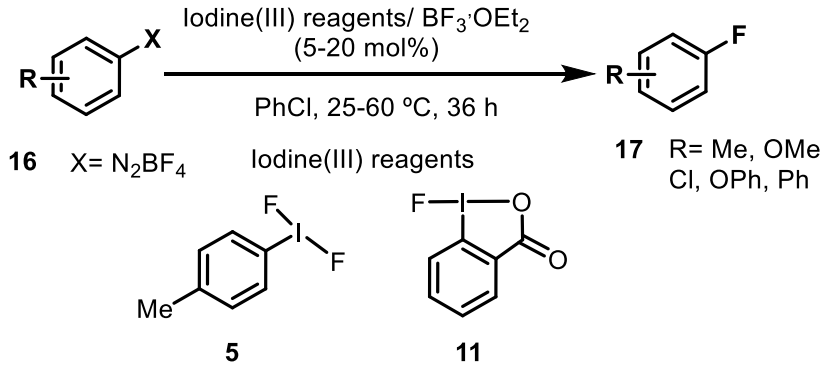
1.4.1 Fluorination.

Fluorination is particularly important in aromatic compounds, Jacques *et al*.[19] described methods on 4-substituted phenol **14** by using PIFA [bis(trifluoroacetoxy)iodobenzene] **2** and PPHF (pyridinium polyhydrogen fluoride). In this oxidation, reaction PIFA and Olas reagent as the fluoride source. The result was to obtain mono- and polycyclic 4-fluorocyclohexa-2,5-dienes **15** with high yields (**Eq. 5**).



[5]

Hu and co-workers[20] have reported the efficient and catalytic procedure of Balz-Schiemann by using iodine(III) reagents **5** and **11** to get fluorinated arenes **17** from substituted aryls **16**. This reaction took place in mild conditions that are safe to carry out and obtained various substituted examples with moderate and good yields (**Eq. 6**).

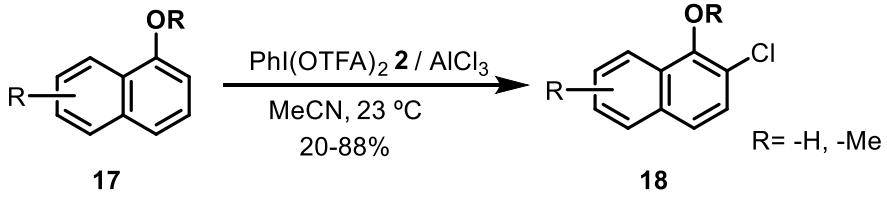


[6]

19. Karam, O.; Jacquesy, J.C.; Jouannetaud, M.P. *Tetrahedron Lett.* **1994**, *35*, 2541- 2544.
20. Xing, B.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed*. **2018**, *57*, 9896-9900.

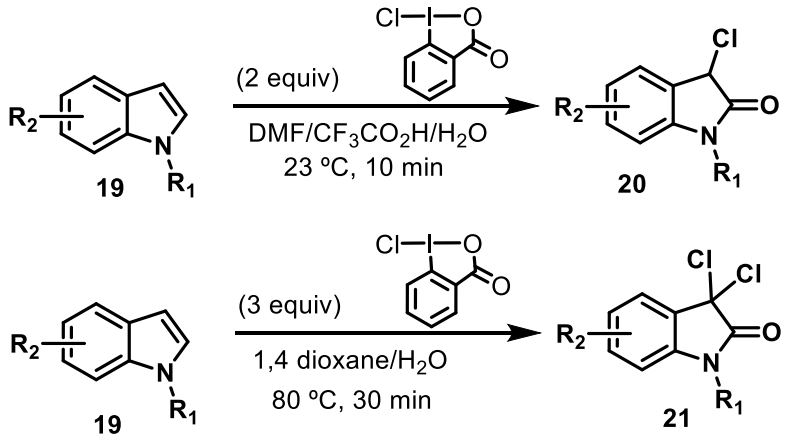
I.4.2 Chlorination.

In 2017, Solorio-Alvarado and co-workers[21] developed an elegant and broad efficient method of chlorination for various substituted phenols and naphthols from various substituted compounds **17** by applying the PIFA **2** /$AlCl_3$ system. The regioselective *ortho*-chlorination phenol yielded and phenol-ethers **18** at room temperature with excellent yield (**Eq. 7**)



[7]

Recently Yu co-workers[22] developed iodine(III)-catalyzed C-2 selective oxidation to get mono chlorination of oxindoles **20** from **19** or C-3 selective bis-chlorination of indoles **21** from the substituted indoles **19**. This reaction proceeds in a one-pot transformation. This method prefers to form on chlorooxidation of indoles C-2 and C-3 sites and which take place with high yield (**Scheme 1**).

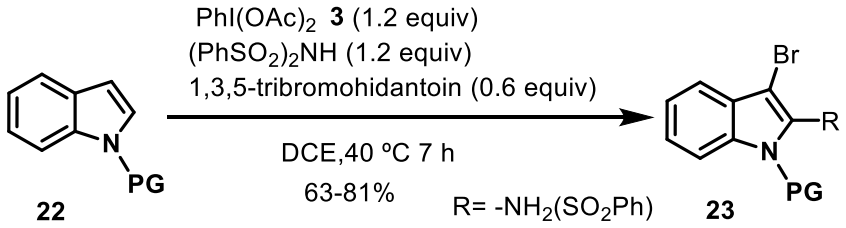


Scheme 1. 1-chloro 1,2-benziodoxol-3-one mediated synthesis of 3-chlorooxindoles.

21. 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. *Eur. J. Org. Chem*, **2018**, 485-493.
22. Jiang, X.; Yang, L.; Yang, W.; Zhu, Y.; Fang, L.; Yu, C. *Org. Biomol. Chem*. **2019**, *17*, 6920-6924

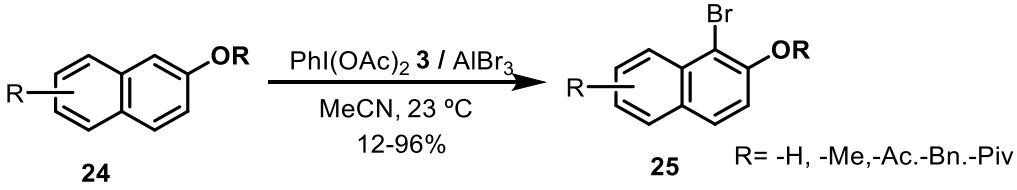
1.4.3 Bromination.

In 2012 Togo,[23] reported efficient and novel Csp^2-H functionalization of indoles via 1,3-migration of imide groups from the protected indoles **22**. In this synthesis, they have applied metal-free conditions which are useful for environmentally sustainable and easy to handle. They have used imide-combined with PIDA **3** which is converted into 2-bis(sulfonyl)amino-3-bromo-indoles **23** in a one-pot process and high yield (**Eq. 8**).



[8]

In 2018 Solorio-Alvarado and co-workers,[24] developed a new efficient electrophilic bromination procedure to get phenols and heterocycles **25** from substituted aryls **24** by applying the PIDA **3** /$AlBr_3$ system. This showed broad scope and is also applicable for mild reaction conditions and applicable for the gram-scale reaction which can be obtained at a high yield (**Eq. 9**).

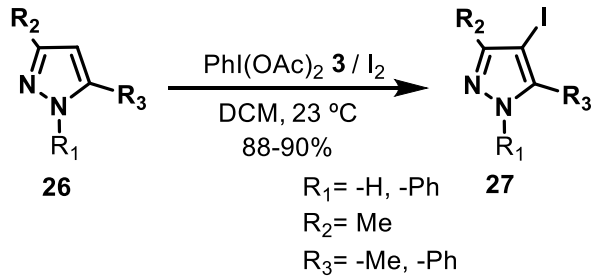


[9]

23. Moriyama, K.; Ishida, K.; Togo, H. *Chem. Commun,* **2015**, *51*, 2273-2276.
24. 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.

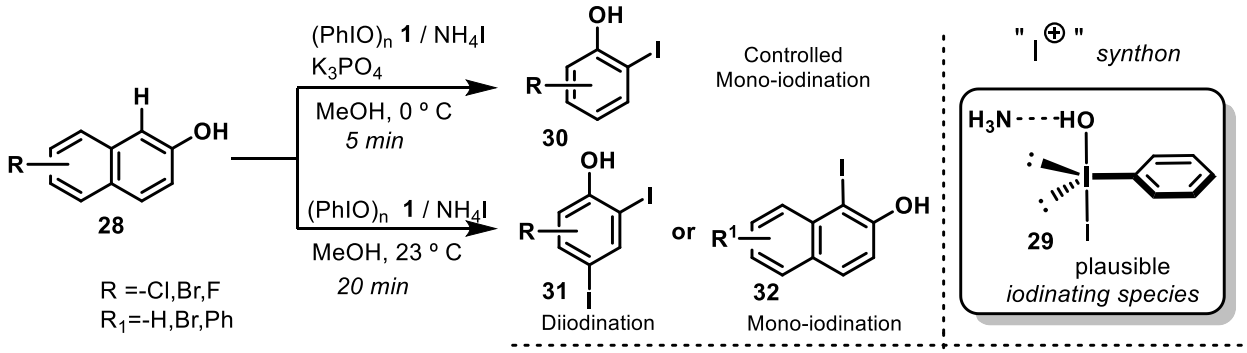
1.4.4 Iodination.

Iodine substituted aryl or heteroaryls are very important, especially in organic synthesis. In 2003 Chen and co-workers,[25] synthesized iodinated pyrazoles **27** from substituted pyrazoles **26** by using PIDA **3** /I_2 system in dichloromethane at room temperature. This system is broadly used and quite easy for carrying out high yields of iodinating derivatives (**Eq. 10**)



[10]

In 2018 Solorio-Alvarado co-workers,[26] developed a new iodinating species **29** the electrophilic iodination procedure for phenols from substituted aryls **28** by using iodine(III) **1** /NH_4I with K_3PO_4 to get selectively mono-iodination **30** for several examples of substituted phenols the advantage of K_3PO_4 acts as a buffering agent also within short reaction time. While the absence of K_3PO_4 phenols produced di-iodinating derivatives **31** one of the best benefits of this system on naphthol which can be also produced mono-iodination of naphthol **32** and other heterocyclic derivatives with high yields (**Scheme 2**).



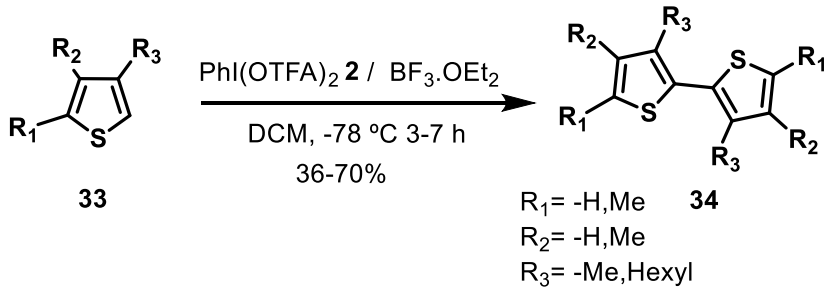
Scheme 2. The (PhIO)n/NH_4I system-mediated controlled mono or di-iodination of phenols.

25. Cheng, D. P.; Chen, Z. C.; Zheng, Q. G. *Syn. Commun*, **2003**, *33*, 2671-2676.
26. 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. *J. Org. Chem.* **2019**, *84*, 4149-4164.

1.4.5. Carbon-Carbon bond formation.

Carbon-carbon (C-C) bond-forming reactions are very important in organic transformations because C-C bonds form the backbone of every organic molecule, whether it is naturally occurring or synthetic. This is an important class of reactions for developing basic organic reactions. Due to its importance in organic chemistry, various C–C bond-forming reactions using transition metal or metal-free conditions are known in the literature. Therefore, iodine has made a great contribution in the field of C-C bond formation reactions.

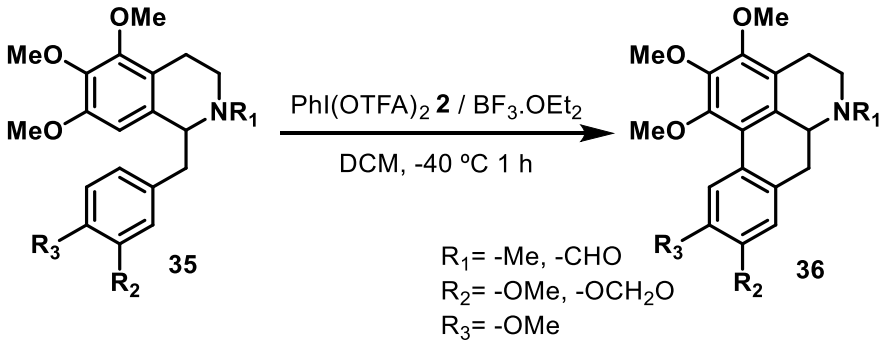
In 2000 Kita and co-workers[27] reported oxidative biaryl coupling reaction of phenol and ether derivatives by using oxidative hypervalent iodine(III) reagent, phenyliodide(III), bis trifluoroacetate (PIFA) **2** in presence of BF_3•OEt_2 to produce a variety of substituted biphenyl and binaphthyl compounds. Among the same group developed oxidative coupling of alkylthiophene **34** derivatives from the 2,2'-bithiophene **33** by using PIFA **2** and BF_3•OEt_2 system which can give to high yield (**Eq. 11**).



[11]

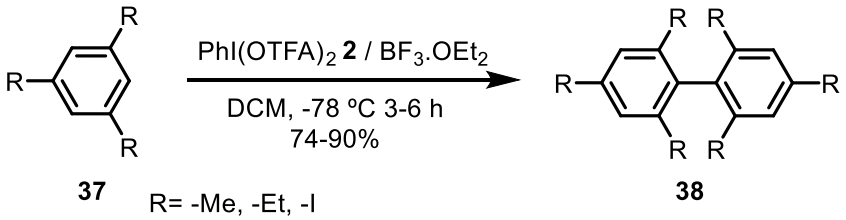
27. Tohma, H.; Iwata, M.; Maegawa T.; Kiyono, Y.; Maruyama, A.; Kita, Y. *Org. Biomol. Chem*, **2003**, *1*, 1647-1649.

In 2007 another oxidative the C-C bond formation reaction by using PIFA **2** and BF_3•OEt_2 system towards broad scope in the synthesis of biologically active molecules. Ruchirawat and co-workers[28] showed the application of oxidative C-C bond formation in the synthesis of pentasubstituted aporphine alkaloids **36** from substituted aryl moiety **35** to forming biaryl systems (**Eq. 12**).



[12]

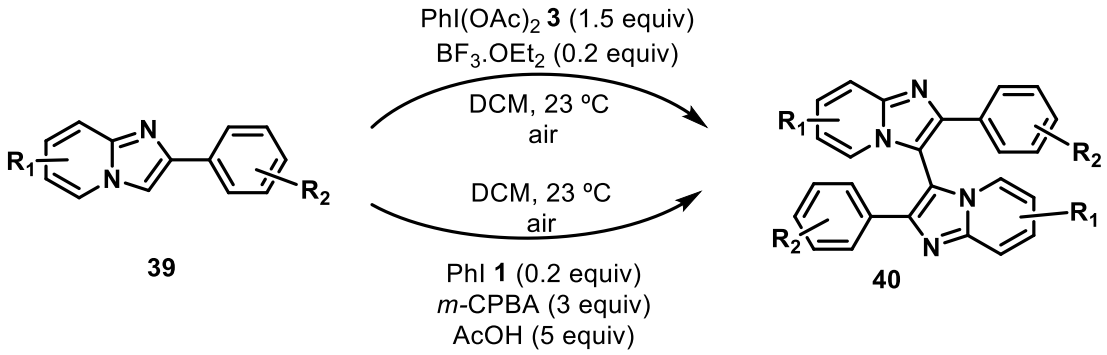
Since the process proceeds through the generation of cationic radical intermediates, this was originally proposed by Kita[29] via the interaction of phenolic ethers or other electron-rich aromatic substrates with PIDA or PIFA. In addition to phenolic electron-rich substrates, electron-rich aromatic substrates are also coupled using [bis(acyloxy)iodo]arenes under oxidative conditions. Kita and co-workers reported a facile and efficient oxidative coupling reaction that can be applied to various alkyl arenes prepared by applying PIFA **2** and BF3•OEt2 systems to alkyl biaryls **38** from substituted aryls **37** as well as BTI-promoted direct oxidation of iodinated arenes the coupling reaction (**Eq. 13**).[30]



[13]

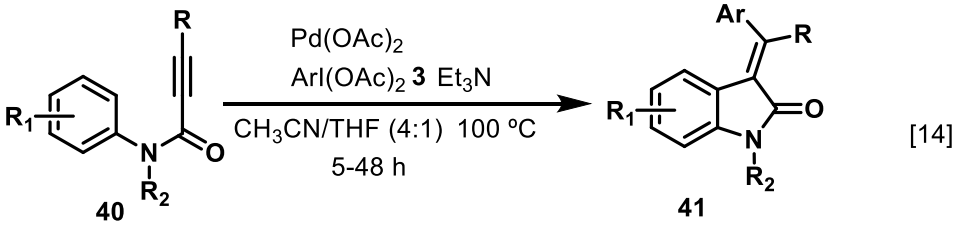
28. Pingaew, R.; Ruchirawat, S. *Synlett,* **2007**,*15*, 2363–2366.
29. Hamamoto, H.; Hata, K.; Nambu, H.; Shiozaki, Y.; Tohma, H.; Kita, Y. *Tetrahedron Lett*. **2004**, *45*, 2293-2295.
30. (a) Tohma, H.; Iwata, M.; Maegawa, T.; Kita, Y. *Tetrahedron Lett*. **2002**, *43*, 9241-9244. (b) Mirk, D.; Willner, A.; Froehlich, R.; Waldvogel, S. R. *Adv. Synth. Catal*. **2004**, *346*, 675-681.

Subsequently, in 2017 Sakhuja and co-workers achieved the homocoupling of 2-arylimidazo heterocycles from substituted imidazole **39**. The transformation of this by using a PIDA **3** /BF_3•OEt_2-accelerated the protocol at room temperature. And the other hand desirable biimidazo **40** heterocycles are also achieved by a catalytic amount of iodobenzene **1** and *m-CPBA*/AcOH which can also give a good amount of yield (**Scheme 3**).[31]



Scheme 3. The homocoupling of dimer 2-arylimidazo.

Another protocol was developed by Tang an interesting C-H functionalization by using PIDA **3** with Et_3N and oxidative addition iodine(III) which can be transformed to construct carbon-carbon bond formation. This system is applicable for the electron-rich and electron-deficient aryl or alkyne substituted anilides **41** to form 3-(1-arylmethylene)oxindoles **42** moieties and obtaining moderate and good yield without using bases (**Eq. 14**).[32]



[14]

R= -H, -Me, -Ar.
R_1= -Me, -OMe, -Cl, -NO_2.
R_2=-H, -Me, -Ac, -Bn

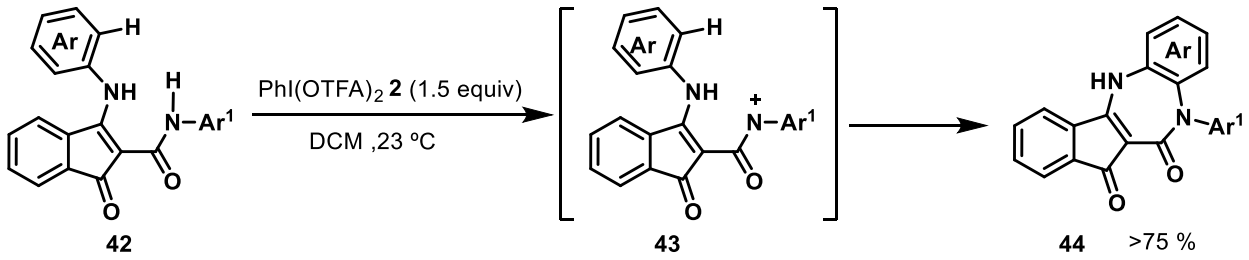
31. Shakoor, S. A.; Mandal, S.K.; Sakhuja,R. *Eur. J. Org. Chem.* **2017**, *18,* 2596–2602.
32. Tang, S.; Peng, P.; Zhong, P.; Li, J.H. *J. Org. Chem*. **2008** *73*, 5476–5480.

I.4.6. Carbon-Hetero bond formation reaction.

Another important class of organic reaction is the C-Hetero bond formation reaction. The heterocycles are found in a variety of biologically active natural as well as synthetic compounds. These hetero-carbon compounds were used for a very long time as traditional medicines.

Hetero-annulation reaction constitutes a broad range of organic reactions which can be achieved under metal-free conditions using hypervalent iodine(III) as a reagent.

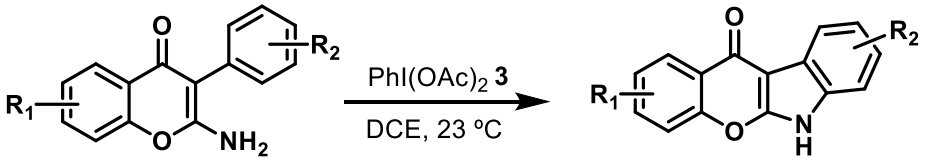
In 2009 Malamidou and co-workers reported efficient and novel oxidative Csp^2-N bond formation by applying [bis(trifluoroacetoxy)iodobenzene] PIFA **2** in DCM at room temperature for the synthesis of indenodiazepinones **44** via intramolecular cyclization to nitrenium ion intermediate generation **43** from substituted moiety **42**. This metal-free system is broadly used for the intramolecular oxidative Csp^2-N bond formation the yield is the example depending upon substituents on the ring. (**Scheme 4**).[33]



Scheme 4. PIFA-mediated intramolecular cyclization of indenodiazepinones.

33. Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Hadjipavlou-Litina, D. *J. Org. Chem.* **2009**, *74*, 7315-7321.

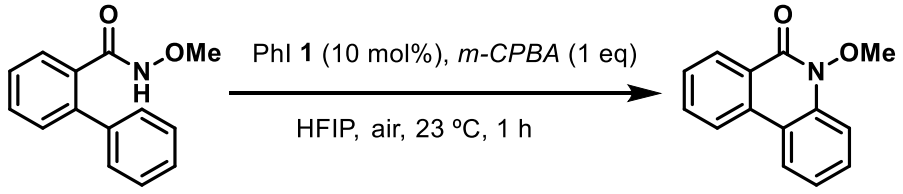
In 2015, Zhao and co-workers synthesized four rings fused heterocycle chromeno[2,3-*b*]indol-11(6*H*)-ones **46** from the substituted chroman **45**. This method is very useful due to the use as metal-free reagent [bis(acetoxy)iodo]arenes] PIDA **3** for the oxidative intramolecular cyclization and the best way for carbon-nitrogen bond formation. This method is also useful for substituted aryl moieties at room temperature with high yield (**Eq. 15**).[34]



45 **46** [15]

R_1= -H, -F, -Cl, -Br, -OBn, -OMe, -Me
R_2= -H, -F, -Cl, -Br, -OMe, -Me

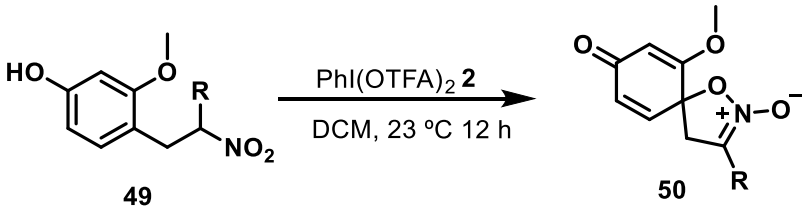
Recently Liang and co-workers developed a novel and efficient synthesis of phenanthridinones **48** via oxidative C−H amidation of *N*-methoxybenzamides **47** under *in situ* generations of hypervalent iodine(III) using Iodosylbenzene **1** with *m*-CPBA as co-oxidant, and HFIP. This method is very easy to handle at room temperature in the open flask with excellent yield (**Eq. 16**).[35]



47 **48** [16]

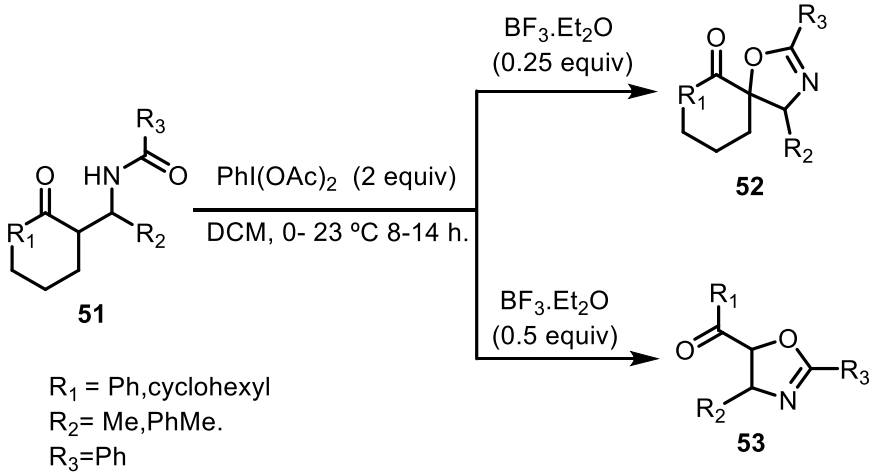
34. Sun, J.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem*. **2015**, *80*, 1200-1206
35. Liang, D.; Yu, W.; Nguyen, N.; Deschamps, J. R.; Imler, G. H.; Li, Y.; MacKerell Jr, A. D.; Jiang, C.; Xue, F. *J. Org. Chem*. **2017,** *82*, 3589−3596

In 2007 Marsini and co-workers reported of novel and efficient by using PIFA **2** to the stereoselective transformation of spironitronates **50**. This mechanistic route involved *ipso* oxidative addition cyclization of nitro-components **49**. This methodology is very applicable and easy to handle at room temperature with high yield (**Eq. 17**).[36]



49 50 [17]

In 2017 one of the efficient C-O bond formation processes was developed by Suryavanshi and co-workers, This method is applicable under hypervalent iodine conditions for the synthesis of spirooxazolines **52** and **53** oxazolines in quantitative yields from β-amidoketones **51** via oxidative functionalization using PIDA in combination with Lewis acid BF_3•OEt_2. Also, this reaction undergoes *via* formation of α-iodo substituted ketone followed by elimination to give oxazolines **(Scheme 5).**[37]



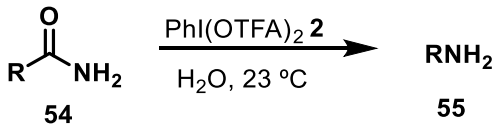
Scheme 5. Synthesis of oxazoles and spiro-oxazole.

36. Marsini, M. A.; Huang, Y.; Van De Water, R.W.; Pettus, T. R. *Org. Lett*. **2007**, *9*, 3229-3232.
37. Chavan, S. S.; Rupanwar, B.D.; Kamble, R.B.; Shelke, A.M.; Suryavanshi, G. *Org. Chem. Front.* **2018**, *5*, 544-548.

I.4.7. Rearrangements.

As discussed above the hypervalent iodine reagents have been used for various C-C, C-hetero bond formation and oxidation reactions which acts as the best replacement for toxic transition metals. The scope of hypervalent iodine is not limited for these reactions but it is also used in the various rearrangements which will discuss in this part as follows.

In 1984, Loudon,[38] developed the conversion of aliphatic amides **54**, into amines **55**, using hypervalent iodine(III) reagents like PIFA **2**. Whereas aromatic amines were oxidized further due to the iodine(III) reagent. The reaction works *via* isocyanate intermediate which hydrolyses immediately to the amine. The retention of configuration was observed in the case of chiral amides (**Eq. 18**).



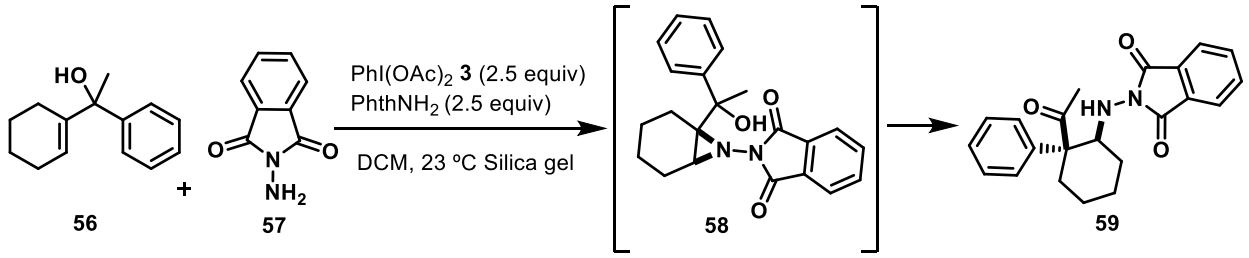
[18]

Oxidative rearrangements with aryl group migrations using hypervalent iodine reagents have been discovered some time ago.

Aryl group migration or rearrangement under oxidative conditions using hypervalent iodine reagents has gained great importance in this class of reactions. Recently, in the last decade, these reactions were discovered. Alkenes were common synthons used in combination with hypervalent iodine in organic synthesis.

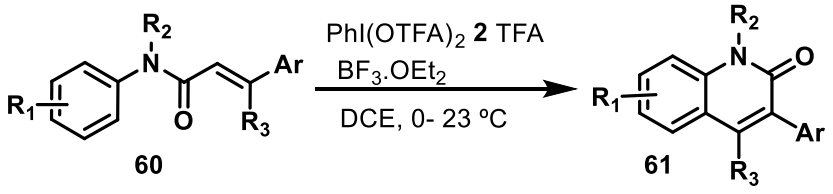
38. a) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem*. **1984**, *49*, 4277-4284. b) Boutin, R.H.; Loudon, G. M. *J. Org. Chem*. **1984**, *49*, 4277-4284.

Besides, In 2007 Tu and co-workers subjected tertiary substituted allylic alcohols **56** and aminoisoindoline **57** under oxidative aryl rearrangement using PIDA **3** to give β-amidoketones **59.** The reaction mechanistically works via formation of aziridine ring **58** followed by silica gel accelerated aryl migration which can give β-amidoketones with good yield (**Scheme 6**).[39]



Scheme 6. PIDA-mediated Synthesis of β-amidoketones.

Another rearrangement example come from Zhao and co-workers synthesizing 3-arylquinolin-2-one **61** from readily available *N*-methyl-*N*-phenylcinnamamides **62** with phenyliodine bis(trifluoroacetate) PIFA **2** in the presence of Lewis acid. This novel procedure not only give oxidative (Sp^2 or Sp^3) bond formation but also 1,2-aryl migration. (**Eq. 19**).[40]



[19]

R_1 = -H, -Me, -OMe, -F, -Cl, -Br, $-CF_3$, $-CO_2Me$
R_2= -Me, -Bn
R_3= -H, -Ar

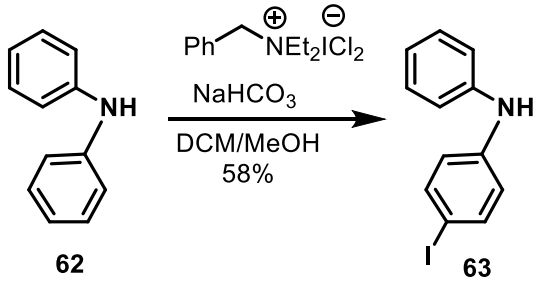
39. Zhang, E.; Tu, Y.Q.; Fan, C.A.; Zhao, X.; Jiang, Y.J.; Zhang, S.Y. *Org. Lett.* **2008**, *10,* 4943-4946.
40. Liu, L.; Lu, H.; Wang, H.; Yang, C.; Zhang, X.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2013**, *15*, 2906-2909.

1.5. Recent literature Iodination of anilines.

The Iodinated anilines having a great significance in organic transformation mostly are useful of synthetic organic chemistry, due to the important intermediate in biologically active compounds and useful in cross-coupling reactions like Sonagashira alkynylation, Suzuki, and stille.

The several methods researchers reported in the literature but in, a few important iodination methods are described in the following.

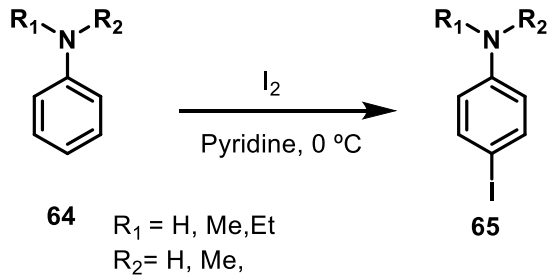
In 2001 Tour has reported the synthesis of 4-iodo-*N*-phenylaniline **63** reagents from diphenylamine **62** by using benzyltriethylammonium dichloroiodate in the presence of sodium bicarbonate in methanol. The benefit of this method is environmentally friendly and easy for handling to give a moderate good yield (**Eq. 20**).[41]



62 **63** [20]

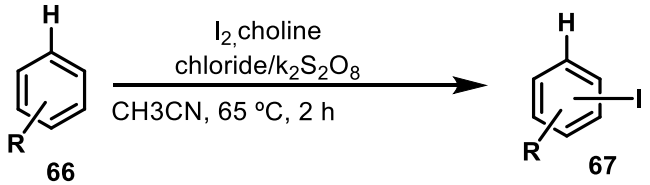
41. Monnereau, C.; Blart, E.; Odobel, F. *Tetrahedron Lett*. **2005**, *46*, 5421-5423.

In 2005 Odobel and co-workers reported selectively *para*-iodination to get several anilines **65** from substituted anilines **64** by using very cheap and mild reaction conditions which are easy for handling. They have used source as molecular iodine in a mixture of pyridine/dioxane (1/1 vol) and obtained a high yield (**Eq. 21**).[42]



[21]

Recently Karunakaran reported simple and efficient method of iodination to get aromatic compounds **67** from substituted aryls **66.** The protocol uses molecular iodine, choline chloride and potassium peroxodisulfate at heating condition in acetonitrile to give moderate to good product yield (**Eq. 22**).[43]



[22]

R = -OH, -NH_2, -CH_3, -Br, -Cl

42. Kosynkin, D.V.; Tour, J.M. *Org. Lett.,* **2001**, *3,* 991-992.
43. Parthiban, D.; Karunakaran, R. *Asian J. Chem*. **2018**, *30*, 1659-1663.

Gold Chemistry

1.6. Introduction.

Gold has been the most precious metal for thousands of years due to naturally occurring element form can be mined directly from the earth. In the past years ancient civilization used by artifacts as representation of wealth and god. Also, the Mayan art or Egyptian burial masks look as beautiful as when they were first cast, emphasizing the resilience and inertness of metallic gold. The nowadays biggest use of gold metal for making jewelry and coin, currency due to the unreactive and durable nature of metallic. Gold has been used in dentistry and more recently in electronics as it is also highly conductive to electricity. The justification about the gold in the periodic table has the symbol Au and 79 atomic number[44] In (figure 1.5)and a series of transition metals belonging to the group, 11, as well as possesses the electronic configuration [Xe] $4f^{14}$ $5d^{10}$ $6s^{1}$. Its oxidation state varies from 1^{-} to 5^{+} but is commonly useful from 1^{+} to 3^{+}. Early alchemists avoided in compared to other transition metals when chemists really began to explore homogeneous catalysis.

Nowadays has improved modern chemistry, and gold has been using the catalyst. The use of gold complexes in homogeneous catalysis remains a recent advance in the field of organic synthesis, mostly due to the assumed chemical inertia of metallic gold.

Figure 1.5 The general use of gold with atomic number.

44. Bardají, M.; Laguna, A. *J. Chem. Educ.* **1999**, *76*, 201.

1.6.1. Relativistic effect and Chemical nature of gold.

The special properties of gold are due to unique nature; gold arise nuclear charge on itself called relativistic effect. Many transition metal has good regular periodic behavior in the sixth period, but gold has disturbed the periodic behavior due to high nuclear charge also the high velocity of the internal shell electrons passing at close to the speed of light. According to the Schrödinger equation.[45,46] The strong contraction of the 6s and 6p orbitals and expansion of the 5d orbital can indicate a relativistic effect in most exemplified as describing well realistically shape expressed theoretically and properly (Figure 1.6)[47,48,49]

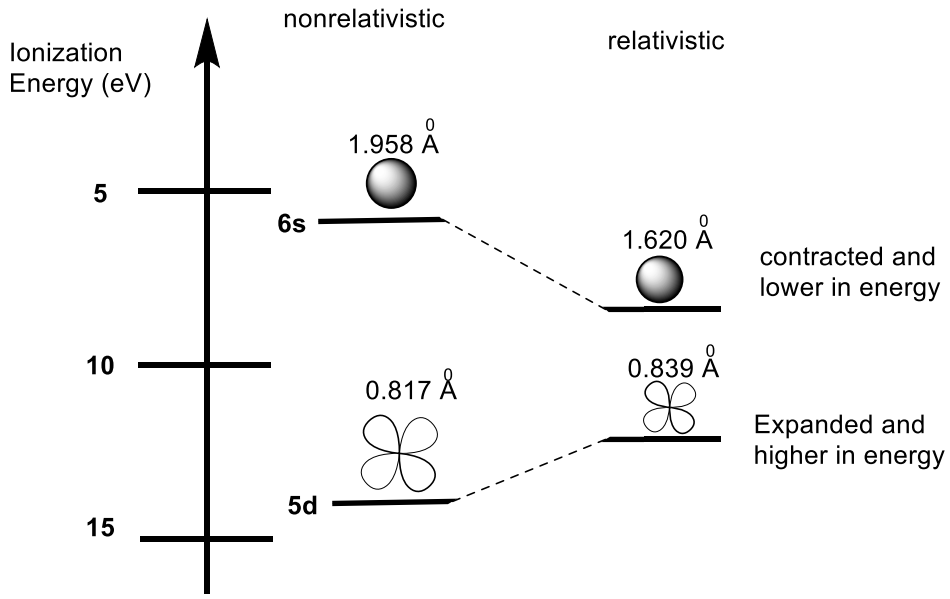


Figure 1.6. The calculated sizes and energies contraction of 6s and 5d orbitals of gold.

The most important experimental observed point discussed follows.

45. Schrödinger, E. *Phys. Rev*. **1926**, *26*, 1049-1070.
46. Dirac, P. A. M. *Proc. R. Soc.* **1928**, *117*, 610-624.
47. Pyykkö, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 4412-4456.
48. Pyykkö, P. *Inorg. Chim. Acta.* **2005**, *358*, 4113-4130.
49. Pyykkö, P. *Inorg. Chim. Acta.* **2005**, *358*, 4113-4130.

1.6.2. The effect of 6s and 6p orbitals contraction.

The gold has tendency to make stronger bond due to contraction on 6s and 6p orbitals, most important point is cationic form of gold(I) has ability to outstanding Lewis acidity instead of other cationic metals of the group 11 in the periodic table. Besides of this gold has one more interesting property originated which can be avoided the relativistic effect due to the high electronegativity 2.5[50] compare with carbon 2.4 this indicates that the bond between C-Au, observed gold has more electron density corresponding to electronegativity trend which can be disobeyed relativistic effect.

1.6.2.1 The expansion of 5d orbitals.

The expansion of 5d orbital effect on increasing high ionization energy (9.22 eV).[51] Due to disturbing the electronic crowd and diminishing electron-electron repulsion, this effect is relevant in catalysis because as a corollary of this relativistic effect. Also, the important result 5d orbital shows gold carbenoid behavior.

1.6.2.2 Gold(I) Act as a Soft Lewis Acid.

Another more important fact about gold(I) complexes, gold complexes are excellent Lewis acids. Lewis generalizes the concept in 1923. This can be important for the easy-to-understand electron-pair theory of acid bases.[52,53]

In case of talking more about gold, complexes could diffuse orbitals, they have preferred orbitals instead of charge interactions. However, they can be soft Lewis acid and react with the soft species like (π- systems) and exist more oxophilic.

50. Electronegativity is given in Pauling scale.
51. Neale, R. S. J. Phys. Chem. **1964**, *68*, 143–146.
52. W.B Jensen *R. Chem. Techno*. **1982***, 55, 881–901.*
53. Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 561.

An among in 1963 Pearson modified the hard and soft Lewis acid bases (HSAB).[54] About the statement clarified that in case metal atom high positive charge and smaller ionic sizes tend to be hard Lewis acid and which affect goes to low polarizable. In the other hand in case of soft acid has bigger ionic size low charge which affect goes to low highly polarizable (figure 1.7).[55,56]

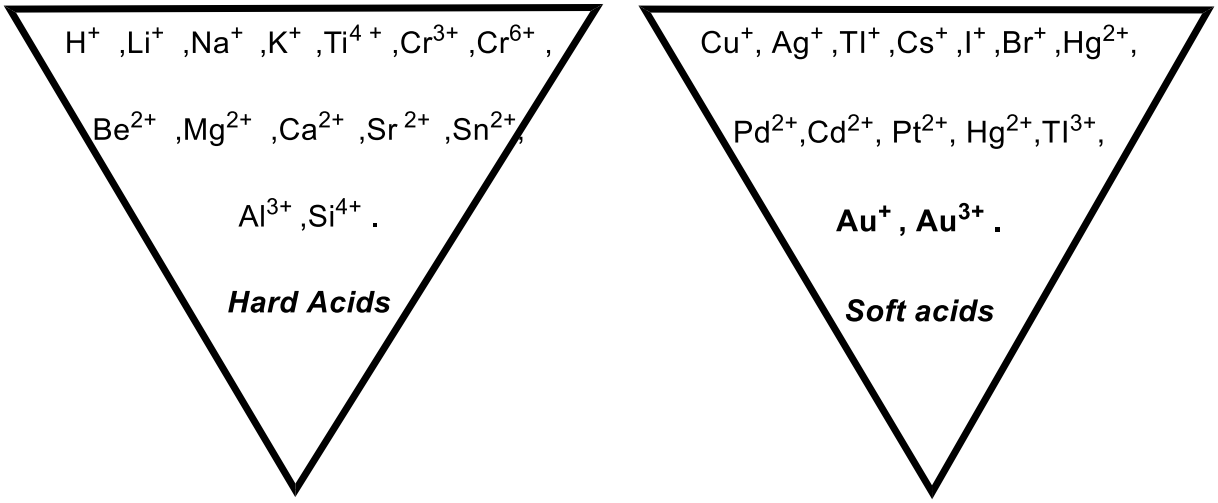


Figure 1.7. Gold act as soft Lewis acid.

In the (figure 1.7). has separately mentioned some of the periodic elements those are indicating hard acid and soft acid depending on the present charge and gold(I)and gold(III) acting as soft Lewis acid.

54. Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539.
55. Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581-586.
56. Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 643-648.

1.6.3. Types of the homogeneous gold catalysts.

Generally, two type of classified gold catalyst mainly exist 1^+ and 3^+ oxidation states. Both the types are extensively used for organic transformation. We shall see more information gold(I) catalyst.

1.6.3.1.Gold(I)-Catalysts.

Gold(I)-catalyst are d^{10} complexes and showed both form LAuX and L_2Au^+ composition. They are indicating a linear, coordinated geometry.[57] The reactivity of the complexes depends on ligand attached to the gold and their electron-donating properties. In the case of this class of complexes need strong σ-donor-like ligands for the stabilizing metal center (figure 1.8).

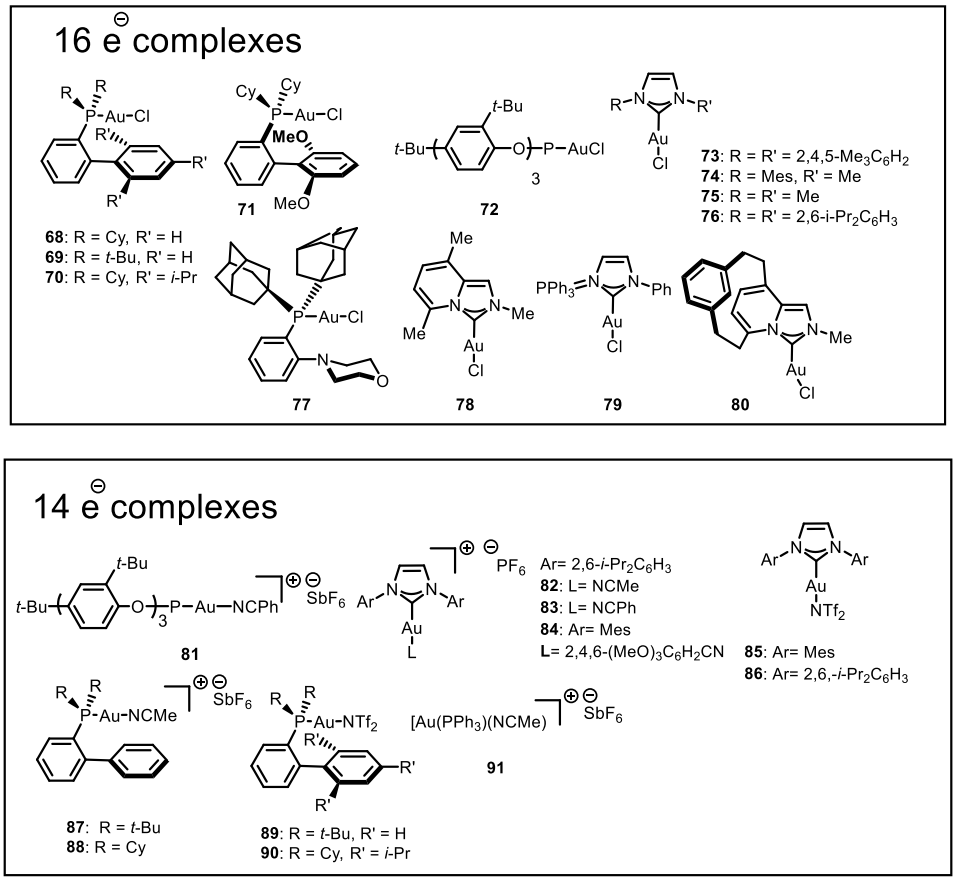


Figure 1.8. Some of the most useful 16 e^- and 14 e^- gold(I) complexes.

57. For discussion about the choice of coordination number in d^{10} complexes of group 11 metals, see Carvajal, M. A.; Novoa, J. J.; Álvareze, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465–1477.

Notably, there are classified two types of electron donating complexes, 16 electron complexes and 14 electron complexes.

The 16 electron complexes such as **68,69,70,71,72,73,74,75,76,78,79** and **80** have showing higher catalytic activity compared to the 14 electron complexes like **81,82,83,84,85,86,87,89,90** and **91**. The extraction of cationic from generally from the halogen sources, commonly using 1 equivalent of Ag(I) salt and non-coordinating species[58]. The benefit of these class complexes, they are soluble in the reaction medium and stable in solid-state.

The more explanation about gold(I) cationic complexes are we can find with bulky-biphenyl based phosphines as ligands which can come out by Pd-cross coupling reactions[59] Related complexes containing a labile bis(trifluoromethanesulfonyl)amide (NTf_2) as ligand have been reported showing similar properties[60]

While synthesis talks about **68**-**71** and **87** to **88** complexes which have been reported by the Echavaren co-worker's to developing gold(I)-catalyzed reactions[61].

As well as some of the bulky catalysts like bis-adamantyl phosphine ligand **77** to **80** such used in hydroamination of alkynes with di-alkylamines, also **72**[62] relevance of bearing tris-(2,6-di-tert-butylphenyl)phosphite as the ligand and cationic counterpart **81**[63] highly electrophilic, some *N*-heterocyclic carbene (NHC) used as a precatalyst,[64]

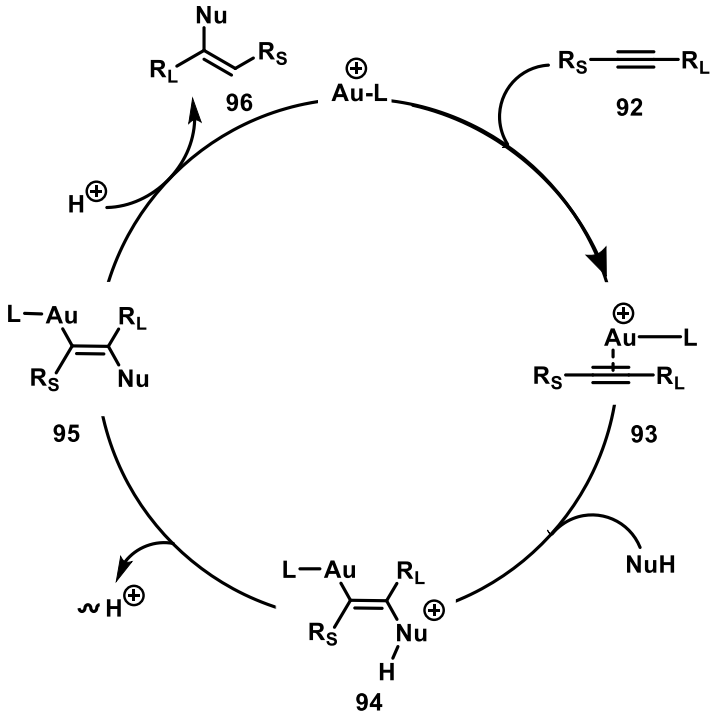
58. (a) Nieto-Oberhuber, C; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693. (c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron Lett.* **2007**, *63*, 6306-6316.
59. (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.
60. (a) de Frémont, P.; Scott, N. M.; Stevens, E. D; Nolan, S. P. *Organometallics*. **2005**, *24*, 2411-2418 (b) de Frémont, Stevens, E.D.; Fructos, M.R.; Díaz-Requejo, M.M.; Pérez, P.J.; Nolan, S.P. *Chem Commun*. **2006**, 2045-2047. (c) Liu, X. Y.; Ding, P.; Huang, J. S.; Che, C, M.; *Org. Lett*. **2007**, *9*, 2645-2648.
61. (a) Partyka, D. V.; Robilotto, T. J.; Hunter, A. D.; Gray, T. G. *Organometallics* **2008**, *27*, 28-32. (b) Mézailles, N.; Ricard, L..; Gagosz, F. *Org. Lett*. **2005**, *7*, 4133-4136.
62. López, S.; Herrero-Gómez, H.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032. (b) 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.
63. Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem*. **2008**, *73*, 7721-7730.
64. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179

A similar NHC included complexes like **77** to **78** and **84**, **85** and **86** to study their-acceptor properties.[65] such more cationic **82**-**84**[66] and those bearing labile properties such as NTf_2 **77** and **86**[67] have been reported.

65. Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542- 2546.
66. López, S.; Herrero-Gómez, H.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2006**, *118*, 6175-6178.
67. Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007,** *46*, 5156-5159.

1.6.4. General mechanism of gold(I) catalyst.

The beneficial role of gold catalyst which can be reacting out under air to gold-catalyzed reaction, the cationic gold(I) complexes have a good affinity to coordinate with the alkynes,[68] allenes, and additionally also with an alkene, readily create an electrophilic center which can be towards nucleophilic attack. In a mechanistic way, gold is very rarely preferred via β-hydride elimination in most cases of proton replaced by the protodeauration process. In additionally representing carbene species,[69] and producing carbenium ions. This concept is very useful for functionalization and cyclization reactions. In a discussion about the general mechanism of briefing based on the catalytic cycle (**Scheme 6**).



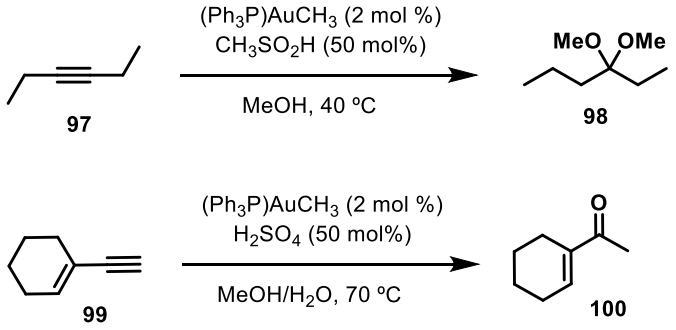
Scheme 6. General mechanism of gold-catalyzed alkyne functionalization.

68. Brooner, R. E. M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed*. **2013**, *52*, 11714−11724.
69. Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Eur. J. Chem.* **2015**, *21*, 7332−7339.

The catalytic cycle starts with alkyne **92** coordination and affording **93**. Then stereoselective nucleophilic trans attack and form **94.** Further loss of H^+ and give rise to **95** which can be followed by protodeuration and finally give expected product **96** with the catalyst generation (**Scheme 6**).[70]

1.6.5. Gold(I)-catalyzes first application.

Several application homogenous gold complexes were reported recently, but the first example **97** alkyne was reported by Hayashi[71] in 1986 for developing asymmetric aldol reaction **98** by using ferrocenylphosphine-gold(I) complex then further Teles and Tanaka[72,73] in 1998 and 2002 modified towards first application of gold catalysis. The main purpose of this class of catalysts avoiding toxic metals like mercury used gold catalysis electrophilic activation of alkyne **99** and obtained the expected product **100** (**Scheme 7**).



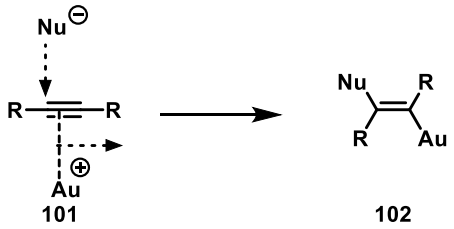
Scheme 7. First application example of gold(I) catalyst.

70. Collado, A.; Nelson, D. J.; Nalon, S.P. *Chem. Rev*. **2021**, 121, 8559-8682.
71. Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.
72. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed*. **1998,** *37* , 1415–1418.
73. Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M, *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.

1.6.6. Homogenous Gold complexes activate of alkynes or allenes .

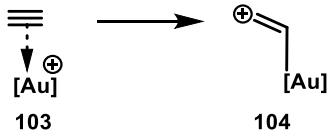
The homogenous gold catalyst has good ability to coordinate with carbon-carbon multiple bonds like sp^2-or sp-hybridized. (*e.g*. allenes, alkynes), and additionally applicable for sp^3 dicarbonyl compounds.

A simple example of in presence of nucleophile gold activate the alkyne **101** and exhibit 'slippage'. In this type of slippage producing relaxation of symmetry of bonding orbitals **102** which can be correlated with orthogonal orbitals moving towards between nucleophile to π-ligands and going to the metal center (**Eq. 23**).[74]



[23]

subsequently well discussed is the π-acid concept with metal which is reported by Furstner in 2007 with gold catalyst. In this method gold coordinate between an alkyne **103** and introducing electron density inducing positive charge **104** (**Eq. 24**).

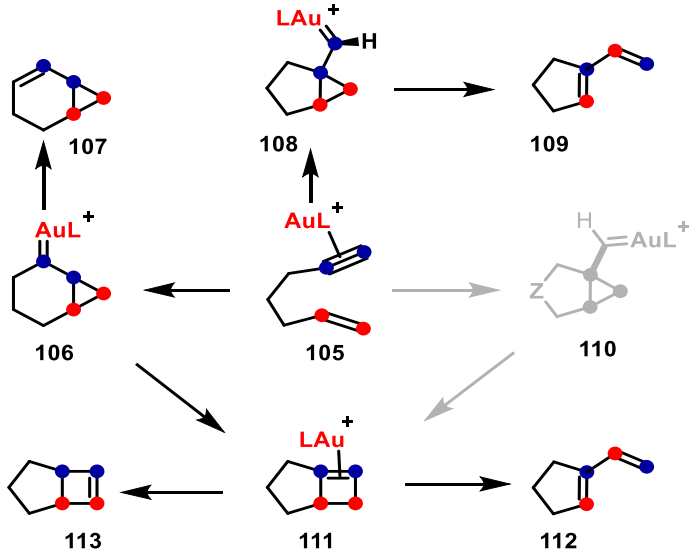


[24]

74. Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed*. **2007**, *46*, 3410-3449

1.6.6.1 Enyne Cycloisomerization.

The cycloisomerization of enynes is one of the most fascinating topics in homogenous gold catalysis. Because gold complexes give selectively transformation and are synthetically useful. Comparatively other metals like Pt or Pd, also have a good ability to transform but gold is more effective than other transition metals. Furthermore, gold(I) activates alkynes it depends upon which functional group having of alkynes. Also, reaction matter of which kind of substrate is used as the length between alkyne moieties.



Scheme 8. Gold catalyzed enynes cycloisomaerization reactions.

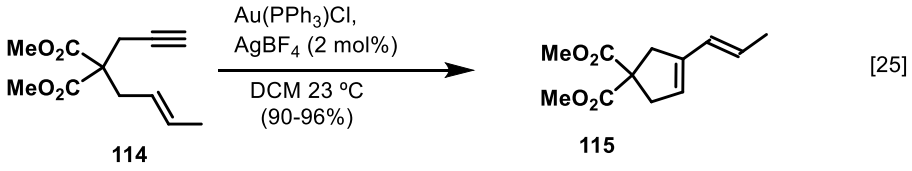
The most common type of gold catalyzes the reactions of enyne cycloisomerization having a similar mechanism, depending on very selective activation of alkyne moiety with a nucleophilic attack of multiple bonds which can be preferred in both ways like Exo or endo can take place. in case of cycloaddition reactions gold(I) mechanism 1,n-enyens **105** procced trough ring closing system to give **106** further give **107** beside of this gold coordinate with alkyne **105** to cyclic five-membered ring **108** to proceed five-membered alkene ring **109** and another side **105** possibly ring closing and gives **110** also **106** and **110** which showing their possibilities to form **111** and further has cationic cyclobutene form one side **112** and other side **113** cyclobutene compound be showed in (**Scheme 8**)[75].

75. Obradors, C.; Echavarren, A. M. *Acc. Chem. Res*, **2014**, *47*, 902-912.

1.6.6.2. Transformation of Cycloisomerization reactions.

The cyclization of 1,6-enynes has been reported in various reactions as atom-economical and productive transformations using cationic gold(I) complexes. Such useful involvement like rearrangements reaction, [4+2] cyclization, as well as 1,5 H-migration.

In 2004 Nieto Obradors and Echavarren reported[76] selectively transformation of enynes, in this class of terminal alkyne and disubstituted alkene react by using [$Au(PPh_3)Cl$] and $AgBF_4$ to give selectively single cleavage rearrangement of a diene **114** to form the five-membered cyclic product **115** with high yield in (**Eq. 25**)

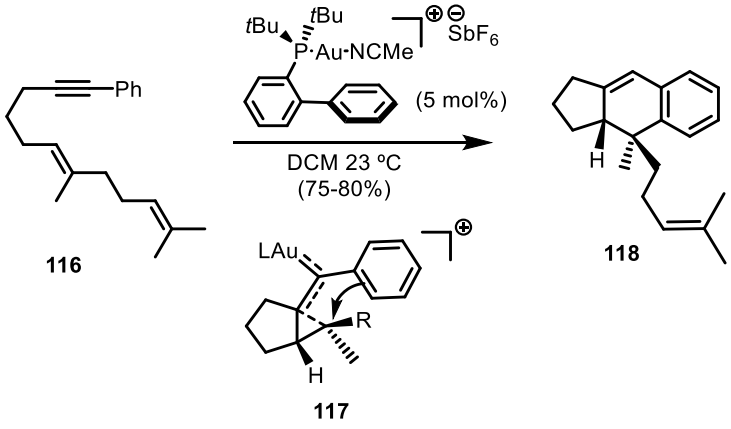


114 115 [25]

In transition metal complexes acting as catalyst to produce variety of cycloisomerization. In case 1,6 enynes and alkyne metal carbene generally producing intermediates but in cycloaddition reaction mechanistically quite different. In 2007 Echavarren and coworkers introduced [4+2] cyclization by using gold(I) complex for synthesizing tricyclic derivatives.

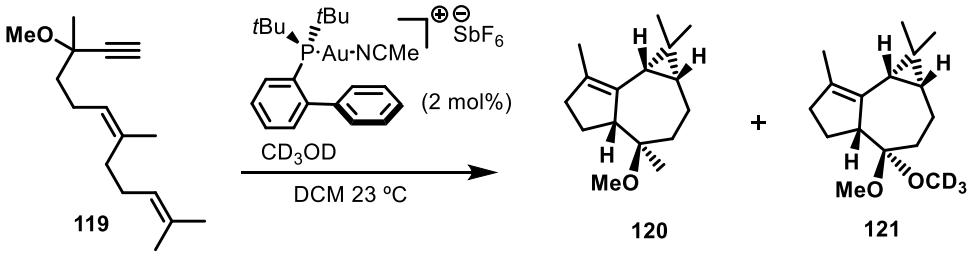
76. Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2004**, *43*, 2402–2406.

This reaction starting from the 1,6 enyne alkyne **116** with alkene and stereospecific forming intermediate **117** which can evolve Friedel Crafts-type reaction and gives the cyclic product **118** (**Eq. 26**).[77]



[26]

Subsequently in 2009, Echavarren and co-workers reported 1,5-OR group migration via gold(I)-catalyze intramolecular cylclopronation form the tricyclic compound **119** which can be related to golbulol **120** and epiglobulol **121** (**Eq. 27**).[78]



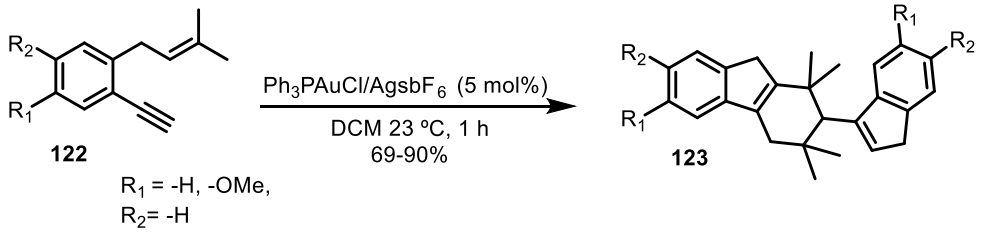
[27]

77. Nieto-Oberhuber, C.; Perez-Galan, P.; Herrero-Gomez, E.; Lauterbach, T.; Rodríguez, C.; Lopez, S.; Bour, C.; Rosellon, A.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279.
78. Jimenez-Nunez, E.; Reducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M *Angew. Chem. Int. Ed.* **2009**, *48*, 6152–6155.

1.6.7. Recent literature gold(I)-catalyzed dimerization aromatic compounds.

The area of organic synthesis, gold catalysis highly applicable for the organic transformation, the reaction of dimerization with diyne system are applied for constructing new building moieties. Which is most interesting part of dimer because of the alkyne can possess nucleophilic to electrophilic nature between two terminal alkynes and forming further transformation.

In 2017, Hemmert and co-workers have reported benzene-tethered 1,6-enynes **122** by using gold(I)-catalyst via cycloisomerization-dimerization to give substituted aromatic moiety **123** at room temperature with high yield (**Eq. 28**).[79]

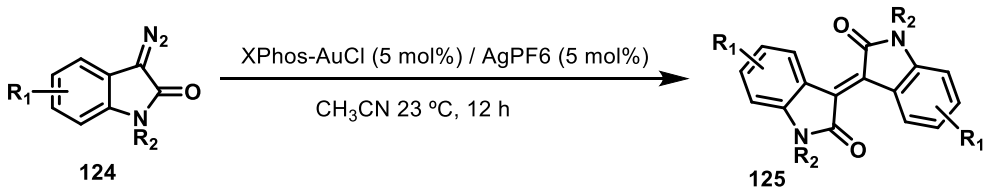


[28]

In 2018, Zhang and co-workers developed a new and efficient method for the dimerization of 3-diazooxindoles dimer **125** from substituted **124** derivatives by using gold(I)-catalyst. This reaction is useful for the substituted isoindigos derivatives as well as obtaining excellent selectivity with *N*-protected group also which can be helpful for the construct both indole moieties.

79. Álvarez-Pérez, M.; Frutos, M.; Viso, A.; Fernandez de la Pradilla, R.; de la Torre, M. C.; Sierra, M. A.; Gornitzka, H.; Hemmert, C. *J. Org. Chem,* **2017**. *82*, 7546-7554.

Additionally, isoindigos has many application in both pharmaceutical as well as material science, also exhibited high efficiency on a gram scale and easy to handle at room temperature (**Eq. 29**).[80]



124 **125**

R_1 = -OMe, -Me, -F, -Cl, -Br, -I, -NO_2

R_2= -Me, -Ts, -Boc, -Bn

[29]

80. Yao, X.; Wang, T.; Zhang, Z. *Eur. J. Org. Chem.* **2018**, 4475-4478.

CHAPTER-2

Gold(I)-catalyzed intermolecular alkyne dimerization for the Synthesis of pentacyclic bisindolic trans-fused system via domino process.

CHAPTER-2

2.1. Introduction.

Pentacyclic polyaromatic heterocyclic indoles are widely used in medicinal chemistry, natural products, and functional materials due to their diverse biological,[81] physical and chemical properties such as eburnamonine and RS-2135 exhibit high Antiarrhythmic activity[82] in the fight against myocardial infarction. Due to these properties, many efforts have been made to construct these heterocycles (Figure 1.9).

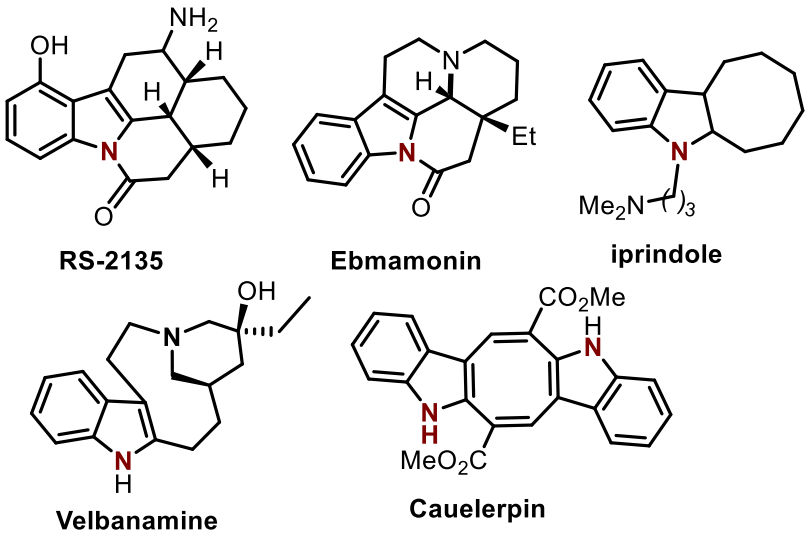


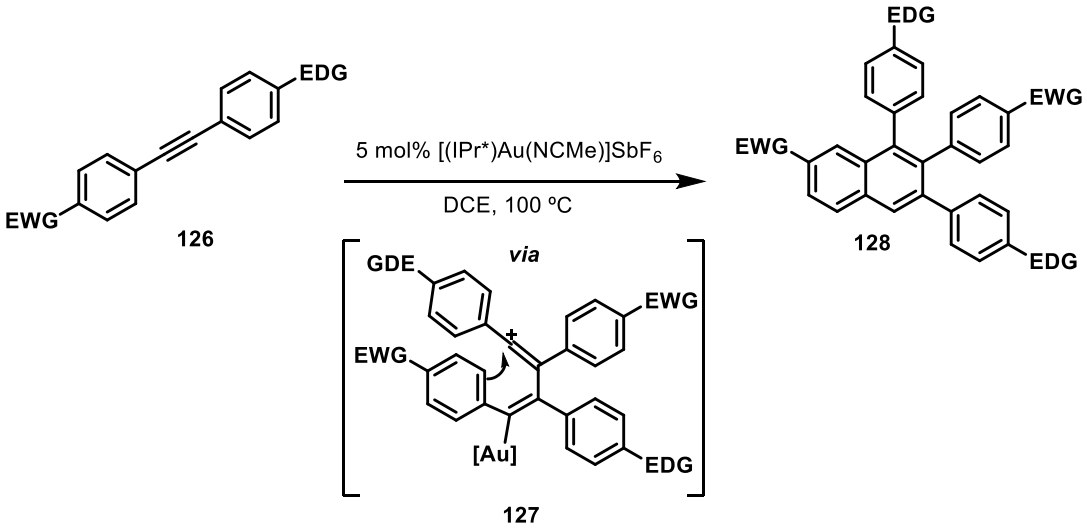
Figure 2.1. Example highlighting the relevance of the indene core

81. Welsch, M.E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.
82. Lazareno, S.; Birdsall, B.; Fukazawa, T.; Gharagozloo, P.; Hashimoto, T.; Kuwano, H.; Popham, A.; Sugimoto, M.; Birdsall, N. J. M. *Life Sci*. **1999**, *64*, 519-526.

Among one of the most abundant heterocycles in natural products and marketed drugs and is therefore classified as a privileged structure in drug discovery, Polycyclic indoles fused to medium-sized rings are key for pharmaceutically relevant compounds Structural motifs such as the pharmaceutically relevant ipridiidine,[83] alkaloid velbanamine[84] and the dual alkaloid caulerpine.[85]

2.2. Previous work on gold(I)-catalyzed dimerization of alkynes.

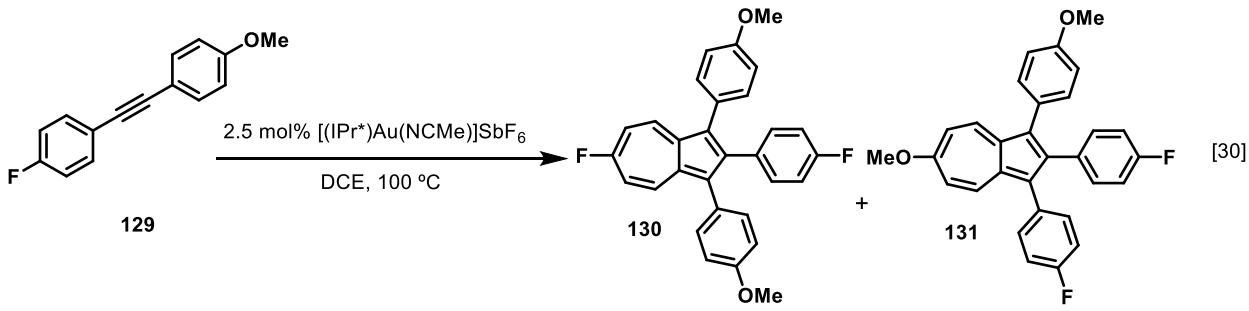
In 2018, Hashmi introduced an intermolecular dimerization process in the presence of cationic gold catalysts that can generate highly reactive vinyl cationic intermediates **127** on selective alkynes **126** In the case of both alkynes, a push-pull reaction was shown to capture vinyl cations via nucleophilic attack on electron-deficient aryl groups to form highly substituted naphthalenes **128** (**Scheme 9**).[86]



Scheme 9. Gold-catalyze intermolecular dissymmetric reaction of dimer.

83. Okabe, A.; Harada, S.; Takeda, T.; Nishida, A. *Eur. J. Org. Chem.* **2019**, 3916–3920.
84. Greiner, L.C.; Inuki, S.; Arichi, N.; Oishi, S.; Suzuki, R.; Iwai, T.; Sawamura, M.; Hashmi, A.S.K.; Ohno, H. *Eur. J. Chem.* **2021**. *27*, 12992-12997.
85. Liu, Y.; Morgan J. B.; Coothankandaswamy, V.; Liu, R.; Jekabsons, M. B.; Mahdi, F.; Nagle, D. G.; Zhou, Y. D. *J. Nat. Prod.* **2009**, *72*,2104-2109.
86. Weingand, V.; Wurm, T.; Vethacke, V.; Dietl, M.C.; Ehjeij, D.; Rudolph, F.; Rominger, F.; Xie, J.; Hashmi, A. S. K. *Eur. J. Chem.* **2018**, *24*, 3725 –3728**.**

Subsequently, in 2018 Hashmi[87] revised the concept of intermolecular dimerization of azulenes. The process shows dimerization of diarylalkynes with *ortho*- or *para*-fluorine atoms or push-pull non-symmetric electron-rich alkynes **129**. In the presence of gold(I) catalyst, two alkynes can generate vinyl cations in one step and transfer to substituted azulenes, which is economical affordable for the synthesis of substituted azulenes **130** and **131** (**Eq. 30**).

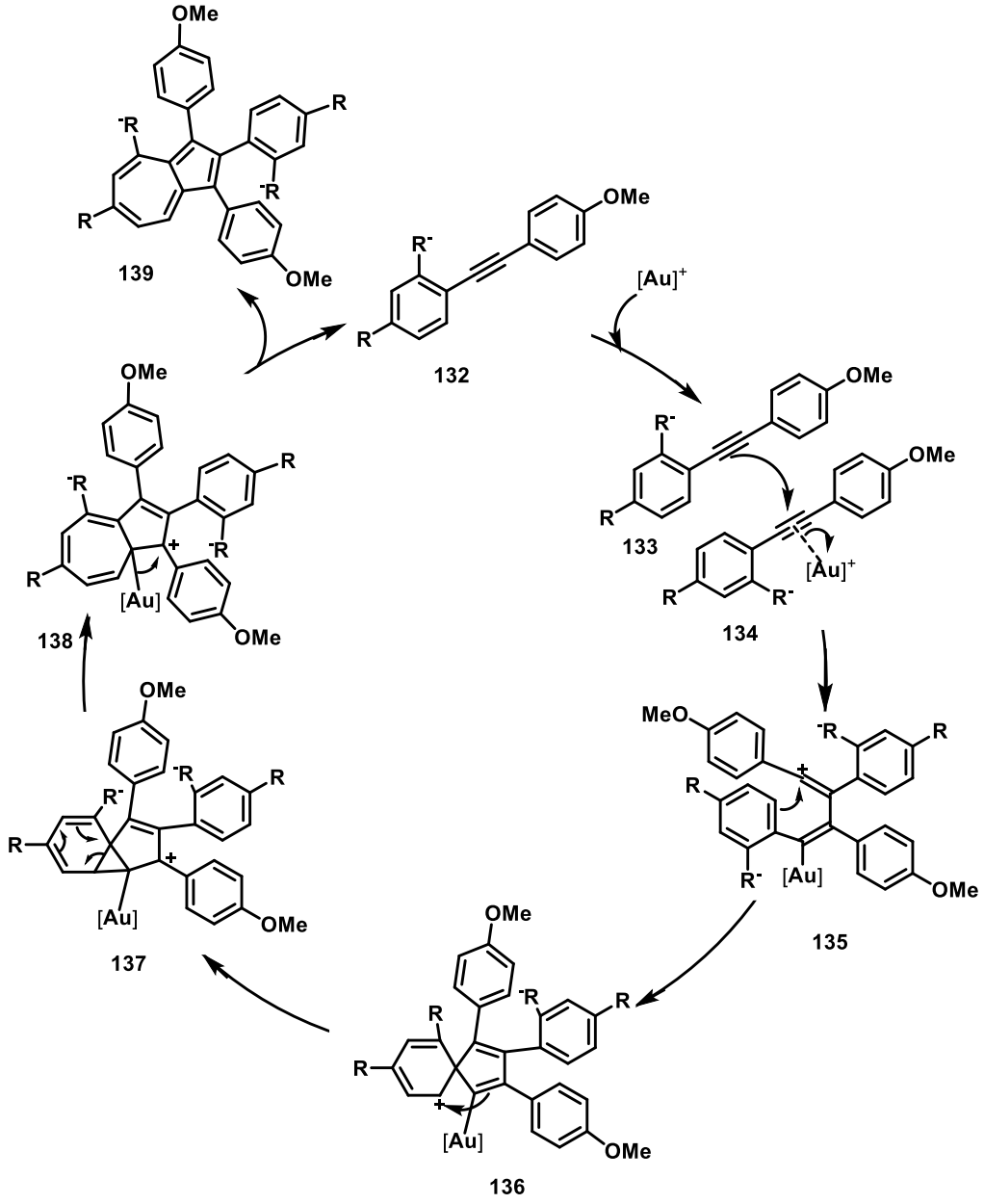


[30]

An explanation of the proposed mechanism describes that, based on a substituted substrate **132** the firstly gold catalyst coordinates with a diarylalkyne and forms a π-complex **133** with one of the diarylalkynes **134** followed by an activated alkyne bond may be more inclined to attack the other triple bond, resulting in the energetic intermediate vinyl cation **135**. The vinyl cation can be controlled by the selective nucleophilic attack, and more nucleophilic carbon atoms can be attacked by more selective electrophilic centers, where gold catalysts can be attached. The vinyl cations then attack the less electron-rich aromatics of the substituted *ortho*- or *para-fluo*rine, which can show a strong +M effect. Due to the fluorine-dependent substituent position, a direct attack on **136** in the *ortho* or *para* position occurs. The additional cationic tricyclic species results in isomerization ring expansion **137** to gold-linked azulene **138** Eventually, gold can regenerate, and form substituted azulene species **139** (**Scheme 10**).

87. Claus, V.; Schukin, M.; Harrer, S.; Rudolph, M.; Rominger, F.; Asiri, A.M.; Xie, J.; Hashmi, A.S.K. *Angew. Chem. Int. Ed.* **2018** *, 57,* 12966-12970.

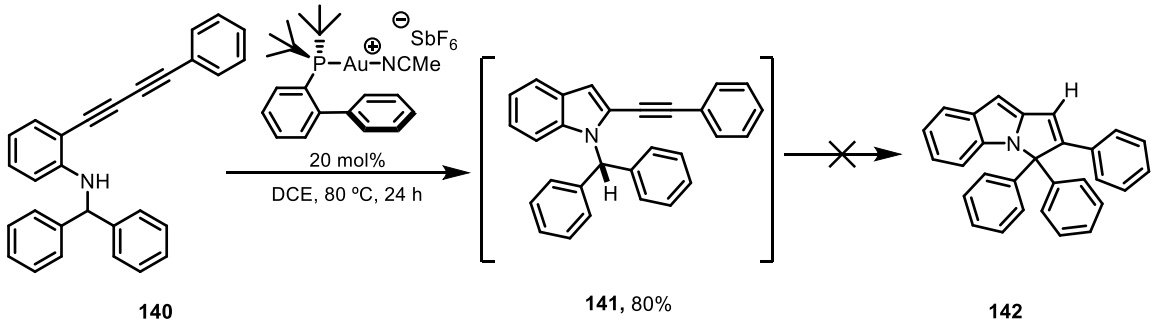
2.2.1. Mechanism.



Scheme 10. mechanism of gold(I)-catalyzed intermolecular dimerization of azulenes.

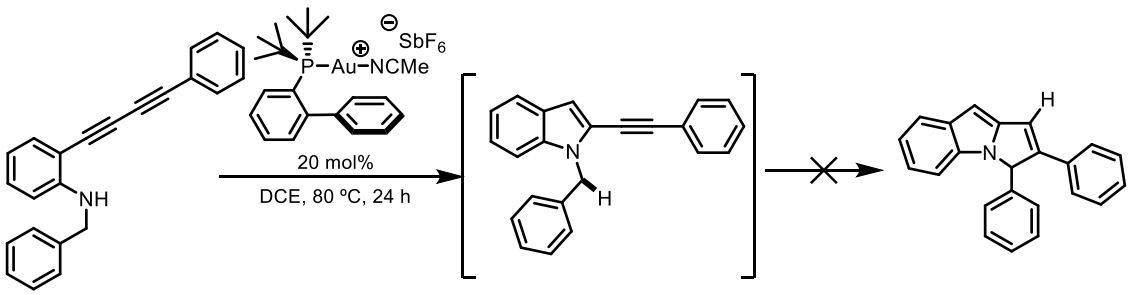
2.3. Present work.

In the present work we have before trying to synthesis of polyaromatic heterocycles pyrrolo[1,2-*a*] indoles **143** by Au(I)-catalyzed tandem cyclization/ C-H activation/cyclization method but we get first cyclization of indole moiety **141** from (2-phenyl *N*-substituted) moiety **140**. (**Eq. 31**).



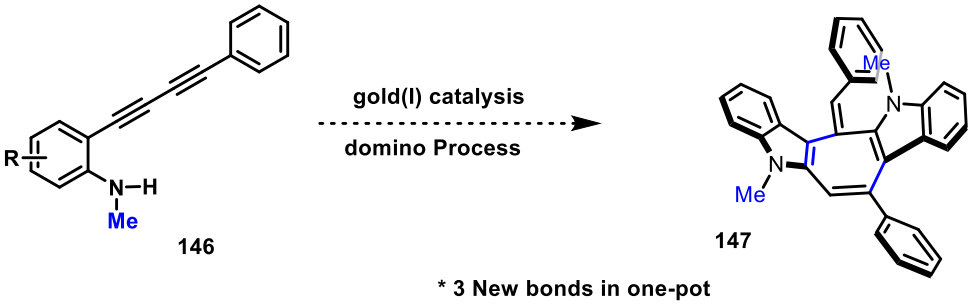
140 **141,** 80% **142** [31]

Based on that we have changing our strategy to avoid bulkiness to get C-H activation and cyclization of indole moiety **145** from the (1-phenyl *N*-substituted) moiety **140** but we get first cyclization of indole moiety **144** (**Eq. 32**).



143 **144,** 70 % **145** [32]

Among we changed our strategy, and we are trying with (methyl *N*-substituted) aniline **146** towards the Gold(I)-catalyzed intermolecular dimerization of internal alkynes synthesis of pentacyclic indole system containing a central seven-membered ring through a domino process **147** (**Eq. 33**).



[33]

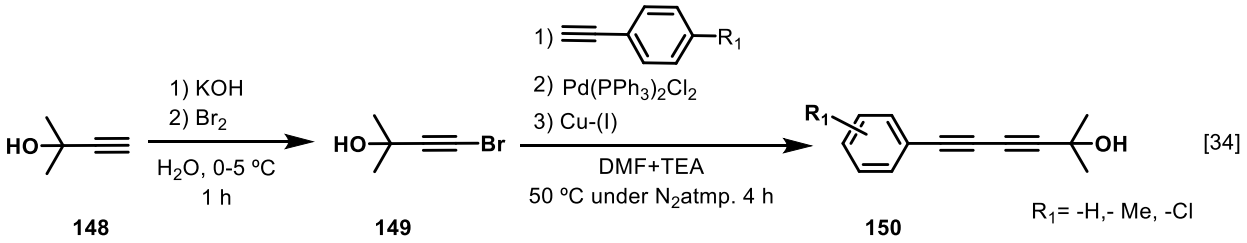
*** 3 New bonds in one-pot**
*** Pentacyclic Non-Aromatic system**
*** *Trans*-fused bis-indolic system**
*** 7 atom ring**

In this work we get inspired from the previous works like intermolecular cyclization of alkynes and we decide to describe our gold(I)-catalyze one-pot dimerization approach. Thus, the synthesis of polyaromatic indole obtained by domino process in one pot method and special character like form three new bond, pentacyclic non-aromatic trans-fused bis indole system and inside having a seven-membered ring.

2.4. Result and discussion.

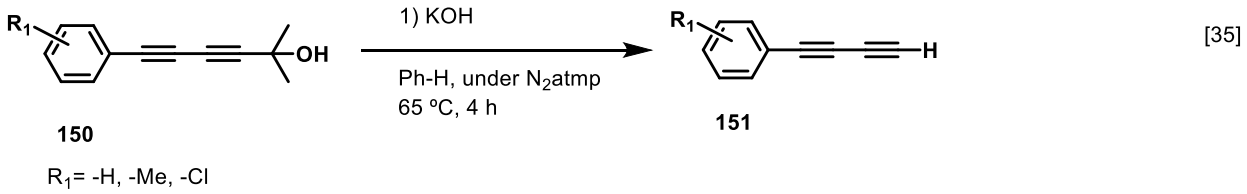
2.4.1 Synthesis of starting material.

Thus, synthesis of the starting material having several step based on the describe literature[88,89,90.] We started to synthesize terminal bromoalkyne **149** from the commercially available 2-methylbut-3-yn-2-ol **148**. Then **149** going towards the Pd-catalyzed cross-coupling reaction with substituted phenylacetylene in DMF and TEA at 50 °C under the nitrogen atmosphere in 4 hours to give **150** diynes (**Eq. 34**).



[34]

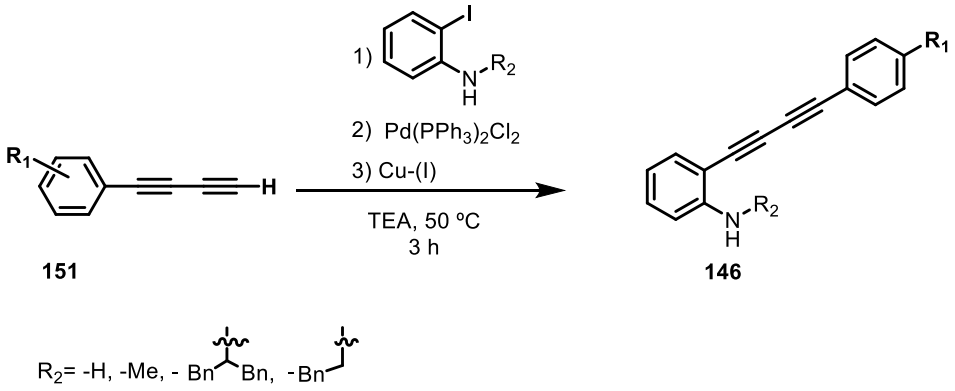
Further, deprotection of diynes **150** by applying basic treatment of KOH in benzene at 65°C under nitrogen atmosphere in 4 hours to give deprotected **151** diynes (**Eq. 35**).



[35]

88. Marino, J. P.; Nguyen, H. N. *J. Org. Chem*, **2002**, *67*, 6841-6844.
89. Weng, Y.; Cheng, B.; He, C.; Lei, A.; *Angew. Chem. Int. Ed.* **2012,** *124,* 9685-9689
90. Govdi, A. I.; Danilkina, N. A.; Ponomarev, A.V.; Balova, I. A.; *J. Org. Chem*. **2019**, *84,* 1925-1940.

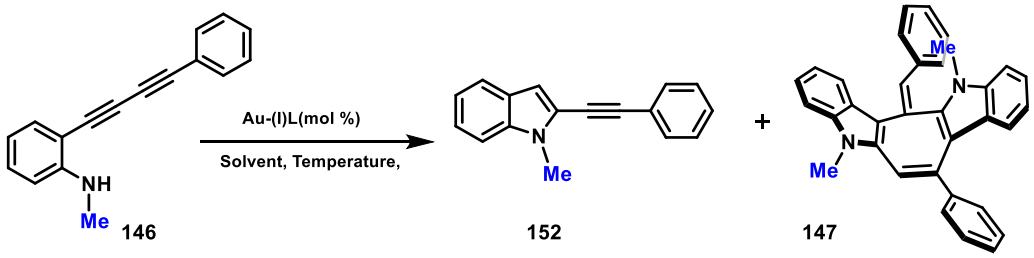
Then consecutive Sonogashira alkylation reaction[91] with diynes **151** and substituted 2-iodoaniline compounds to give desired compound **146** (**Eq. 36**).



[36]

91. Wang, Y.; Zhou, Y.; Ma, X.; Song, Q. *Org. Lett*, **2021**, *23,* 5599-5604.

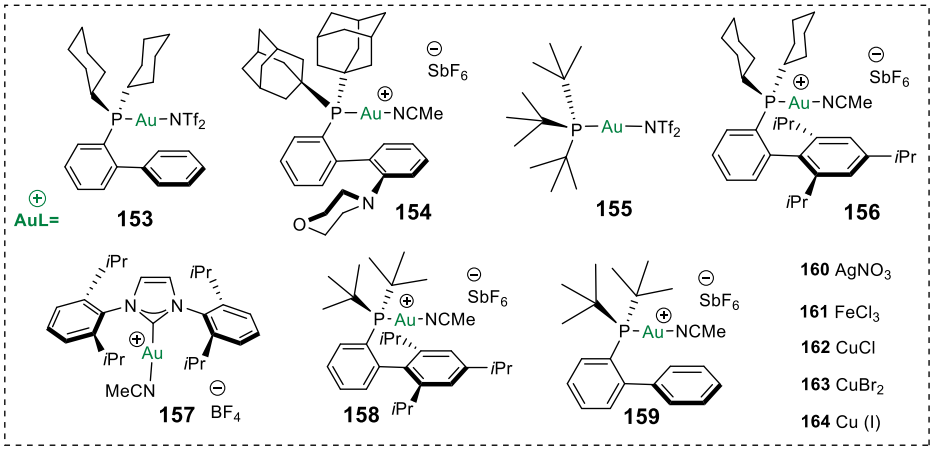
Table 1. Optimization table of new Gold(I)-catalysed intermolecular dimerization of internal alkynes, synthesis of pentacyclic indole system.



146 152 147

ENTRY	Catalyst Au(I)L	mol%	Solvent	T (°C)	Time (h)	Yield % [a, b, c] 146/152/147
1	**159**	5	DCM	23	24	---/40/---[a]
2	**159**	10	DCM	23	24	---/70/---[a]
3	**159**	10	DCE	60	24	---/91/---[a]
4	**159**	10+10	DCE	80	24	---/8/58[a]
5	**159**	11	DCE	110	16	---/7/60[b]
6	**153**	11	DCE	110	16	---/27/73[a]
7	**154**	11	DCE	110	16	---/17/83[a]
8	**155**	11	DCE	110	16	---/16/84[a]
9	**153**	11	DCE	110	16	---/60/---[C]
10	**154**	11	DCE	110	16	---/---/27[C]
11	**155**	11	DCE	110	16	---/89/---[C]
12	**156**	11	DCE	110	16	---/---/15[C]
13	**157**	11	DCE	110	16	---/---/19[C]
14	**158**	11	DCE	110	16	---/---/17[C]
15	**159**	11	DCE	110	20	---/---/30[C]
16	**160**	11	DCE	110	20	---/20/---[C]
17	**161**	11	DCE	110	20	5/21/---[C]
18	**162**	11	DCE	110	20	45/10/---[C]
19	**163**	11	DCE	110	20	2/5/---[C]
20	**164**	11	DCE	110	20	6/7/---[C]
21	**157**	5	Solvent free	110	20	---/45/---[C]
22	**157**	7.5	Solvent free	110	20	---/5/15[C]
23	**157**	10	Solvent free	110	20	---/---/16[C]
24	**159**	5	Solvent free	110	20	---/20/5[C]
25	**159**	7.5	Solvent free	110	20	---/1/8[C]
26	**159**	10	Solvent free	110	20	---/3/15[C]

All the reactions were carried out without the use of inert atmosphere yet in sealed tubes. [a] The reaction yields were determined by HPLC. [b] The reaction yields were isolated from the column chromatography. [C] The reaction yields were calculated by ^{1}H NMR spectras.



The optimization reaction we carried out by hypothesis of our new internal alkyne dimerization. This alkyne **146** is used as with several different cationic gold(I)-complexes.

The tremendous reactivity of the cationic gold(I)-complexes is great observed, In optimization we determined three different types of yields method firstly with HPLC, second with purified with column chromatography and finally with the ^{1}H NMR detection. Therefore we agreed to start the optimization reaction condition firstly using 5 mol% of **159** in Dichloromethane at room temperature after 24 hours we obtained compound **152** with 40 % yield only, then we decided to increase amount of same catalyst as 10 mol% in dichloromethane and at room temperature until 24 hours we obtained same compound **152** with 70 %, (Table 1, entries 1,2), Then we decided to use 1,2-dichloroethane for the remaining optimization entries, then we moved to apply towards heating conditions gradually 60 ^{0}C by the same catalyst with 10 mol %, in dichloroethane after 24 hours later we found compound **152** with 91%, (entry 3).

Further, we have changed the heating condition to up to 80 $^{\circ}C$ with 10 mol% with **159** catalyst in dichloroethane and we found the desired product additionally we were added 10 mol% more for completion of starting material and we obtained **152** first indole cyclize compound 8% and desired dimer compound **147** with 58% (entry 4). In the following reaction, we tested 11 mol% of **159** catalyst with 110 $^{\circ}C$, and we found 7 % compounds **152** and 60% compounds **147** (entry 5) in this entry of the yield we have isolated from the column and further (entry 6 to 8). compound product yield determined by HPLC analysis. However, we apply other gold(I) catalysis such as **153, 154,** and **155** were tested assuming by optimization condition (entry 5),

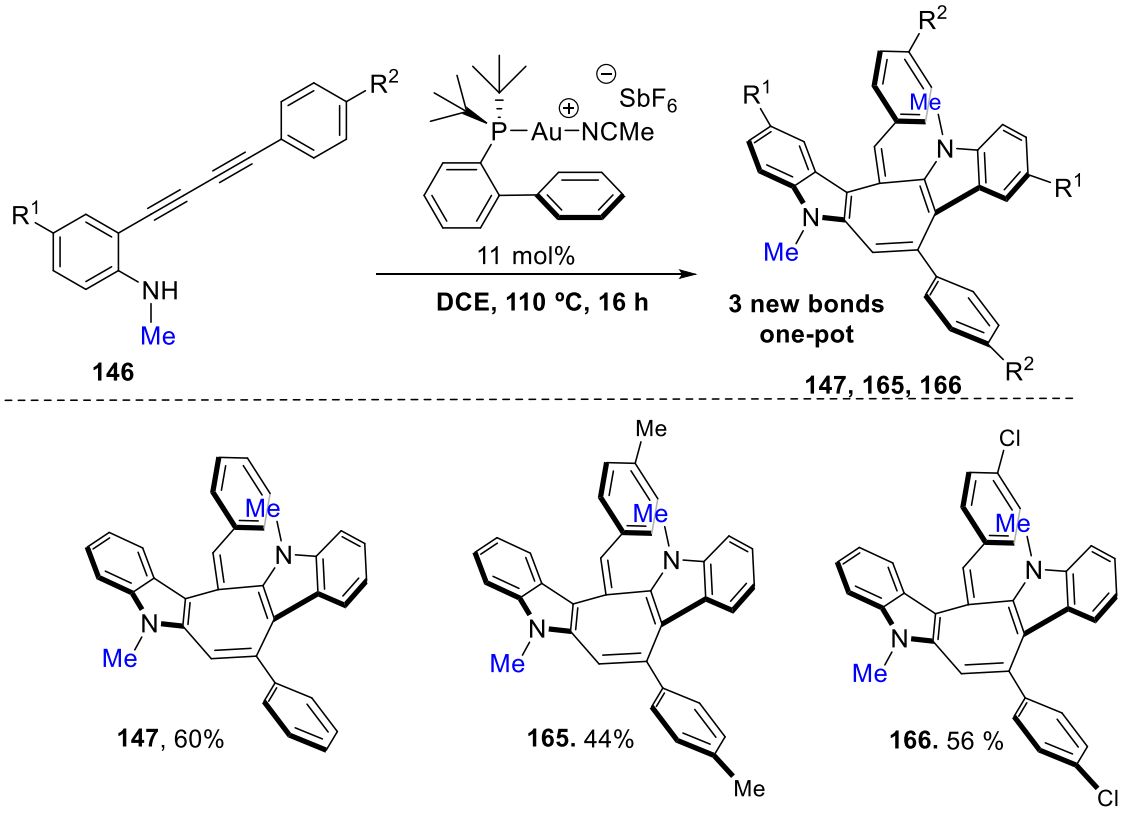
At this condition determined condition those entry **5** we proceed to explore the scope of dimerization because of this entry yield we determined experimentally from the column. however, the yield of catalyst **153** give to **152** 27% and **147** 73% (entry 6). Then catalyst **154** give to **152** 17% and **147** 83% (entry 7). and **154** give to **152** 16% and **147** 84% yield (entry 8).

Among we determined yield by using ^{1}H NMR method, in this optimization we carried out from (entry 9-27). However, we apply gold(I) catalyst and other than gold(I) catalyst such as **153,** to **164** were tested assuming by optimization condition (entry 5).

In this catalyst **153,** give to **152,** 60 % (entry 9). Then catalyst **154,** give to **147,** 27 % (entry 10), catalyst **155**, gives to **152,** 89% (entry 11), catalyst **156**, gives **147,** 15 % (entry 12), catalyst **157**, gives **147,** 19 % (entry 13), catalyst **158**, gives **147,** 17 % (entry 14), catalyst **159**, gives **147,** 30 % (entry 15), catalyst **160**, gives **147,** 20 % (entry 16), catalyst **161**, gives **146,** 5 % and **147,** 15 % (entry 17), catalyst **162**, gives **146,** 45 % and **147,** 10 % (entry 18), catalyst **163**, gives **146,** 2 % and **147,** 5 % (entry 19), catalyst **164**, gives **146,** 6 % and **147,** 7 % (entry 20),

Further we apply some different mol % with catalyst and without solvent in case of catalyst **157,** 5 mol % **,** gives **147,** 15 % (entry 21), same catalyst **157,** with 7.5 mol % gives **152,** 5 % and gives **147,** 15 % (entry 22), same catalyst **157,** with 10 mol % gives **147,** 16 % (entry 23), with catalyst **159,** 5 mol %**,** gives **152**, 20% and **147,** 5 % (entry 24), same catalyst **159,** with 7.5 mol % gives **152,** 1 % and gives **147,** 8 % (entry 25), same catalyst **159,** with 10 mol % gives **152,** 3 % **147,** 15 % (entry 26).

2.4.2 Scope for the new gold(I)-catalyzed one pot dimerization.

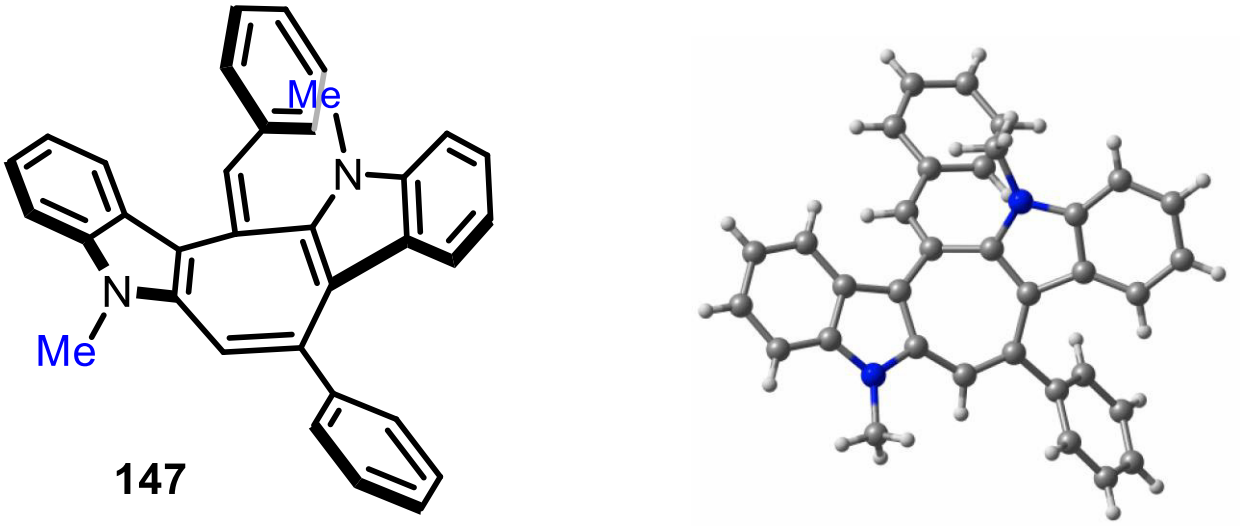


Scheme 11. Scope for the new gold(I)-catalyze one pot dimerization.

Based on developed procedure yield of cyclohepta-dimerize indole. The scope determined by mainly neutral dimerize indoles. Therefore, our method developed electron neutral phenyl group obtaining rise to **147** 60% within 16 hours, then we also developed electron-rich aryls containing one-methyl group to gives 44% of yield **165** and with 4-Cl substituted derivative to gives 56% yield **166.** Which can be exhibiting good result in (**scheme 11**) .

2.4.3 X-Ray crystallography structure.

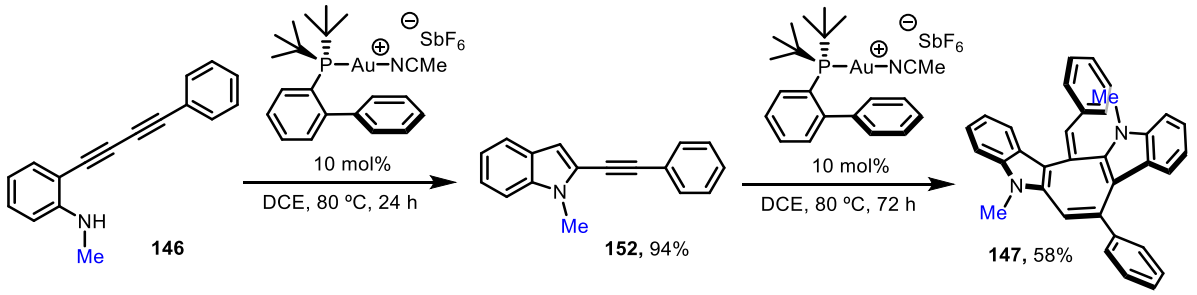
The characterization of gold(I)-catalyzed pentacyclic dimerize indole, accordingly, we carried out x-ray crystallography with the help of Dr. Gerardo González García and his support to the confirmation for x-ray structure **147** (**scheme 12**).



Scheme 12. Crystallographic structure of one pot dimerization trans-fused indoles.

2.4.4 The reaction of 1st Cyclize indole to pentacyclic polyaromatic dimer.

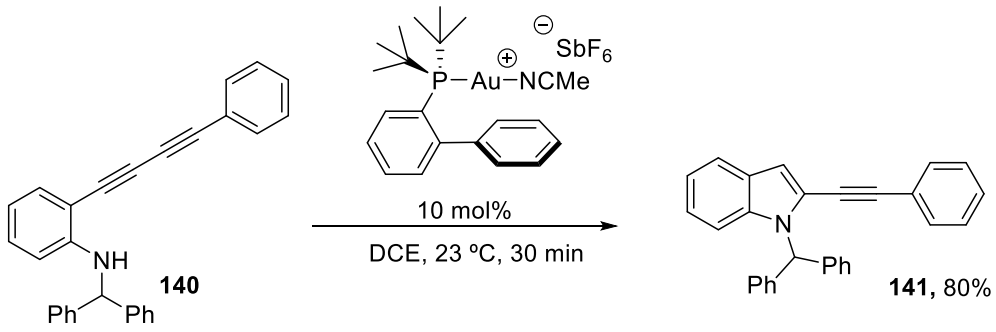
Some of the different we trying to synthesize pentacyclic polyaromatic dimer. We used compound **146** as starting material and applying **159** gold(I) cationic complex 10 mol% in Dichloroethane 80 °C until 24 hours and we obtained compound **152** with 94% yield. Then we again apply 10 mol% **159** catalyst in same temperature 72 hours, and we get full conversion of product **147** with 58% yield (**Eq. 35**).



[37]

2.4.5 The scope of nitrogen 1st cyclize indole.

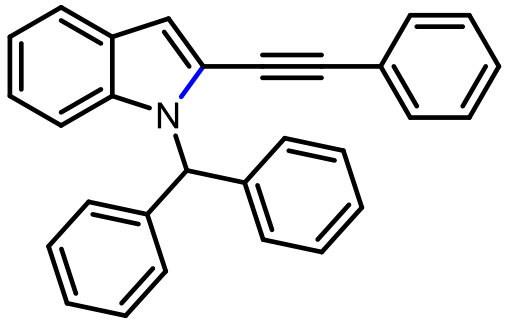
Among we find out some scope on nitrogen-based reactions, firstly we tried with biphenyl substituted **140** as a starting material and applying with the 10 mol % of **159** catalyst in Dichloroethane room temperature within 30 min we get cyclize indole further we trying to dimerization but due to the steric hindrance of bulky phenyl groups obtained **141** with 80 % yield (**Eq. 38**).



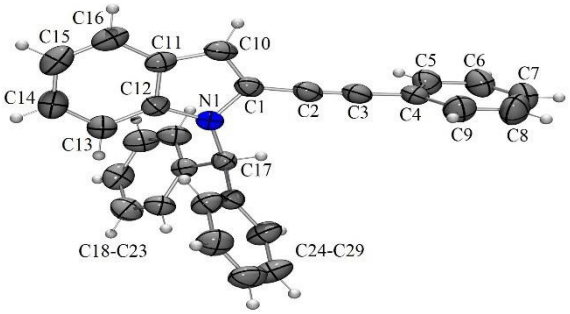
[38]

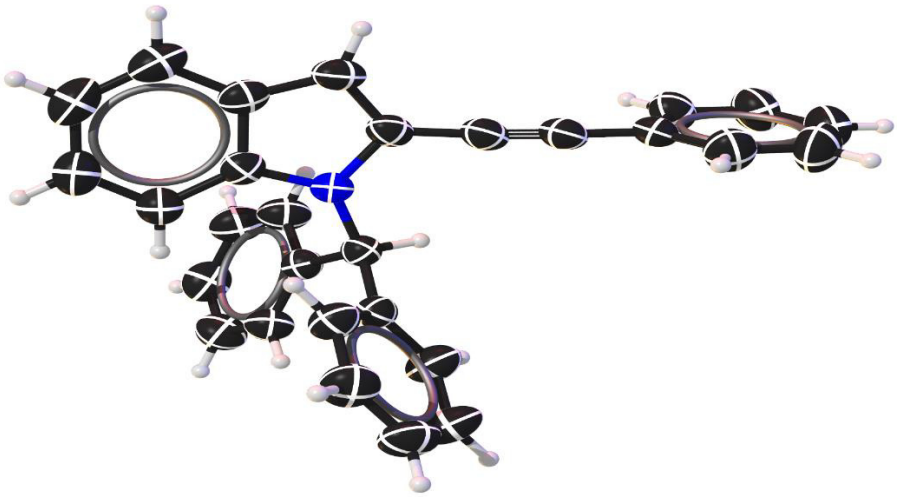
2.4.6 X-Ray crystallography structure.

The characterization of Gold(I)-catalyzed cyclize indole, accordingly, we carried out x-ray crystallography with the help of Dr. Gerardo González García and his support to the confirmation for x-ray structure **141** (**scheme 13**).



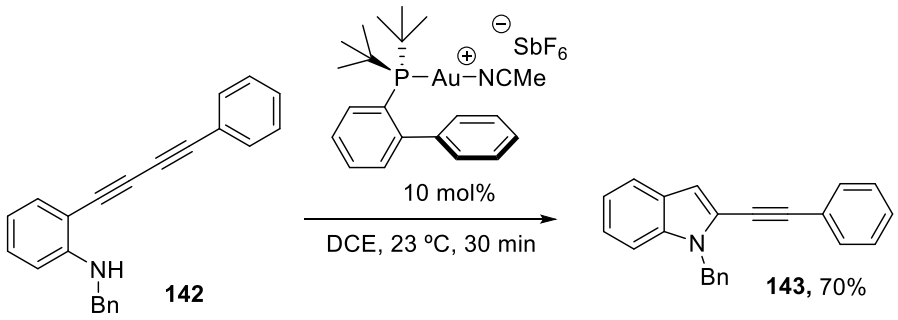
141





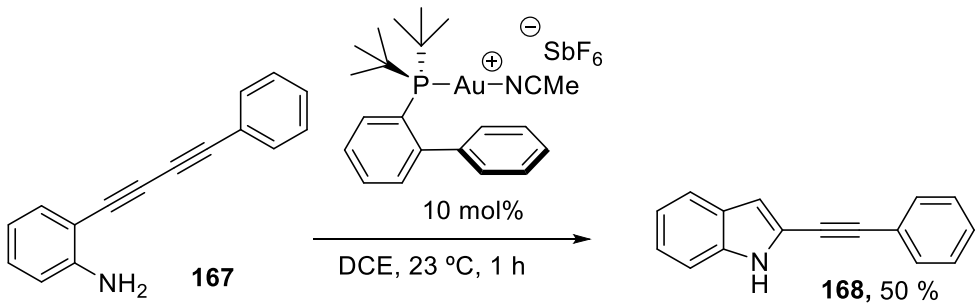
Scheme 13. Crystallographic structure of cyclize indoles.

Further we changed our strategy due to avoid bulkiness and apply single phenyl substituted **142** as a starting material and applying with the 10 mol % of **159** catalyst in Dichloroethane room temperature until 30 min and that time also we obtained 1st cyclization of indole **143** with 70 % yield (**Eq. 39**).



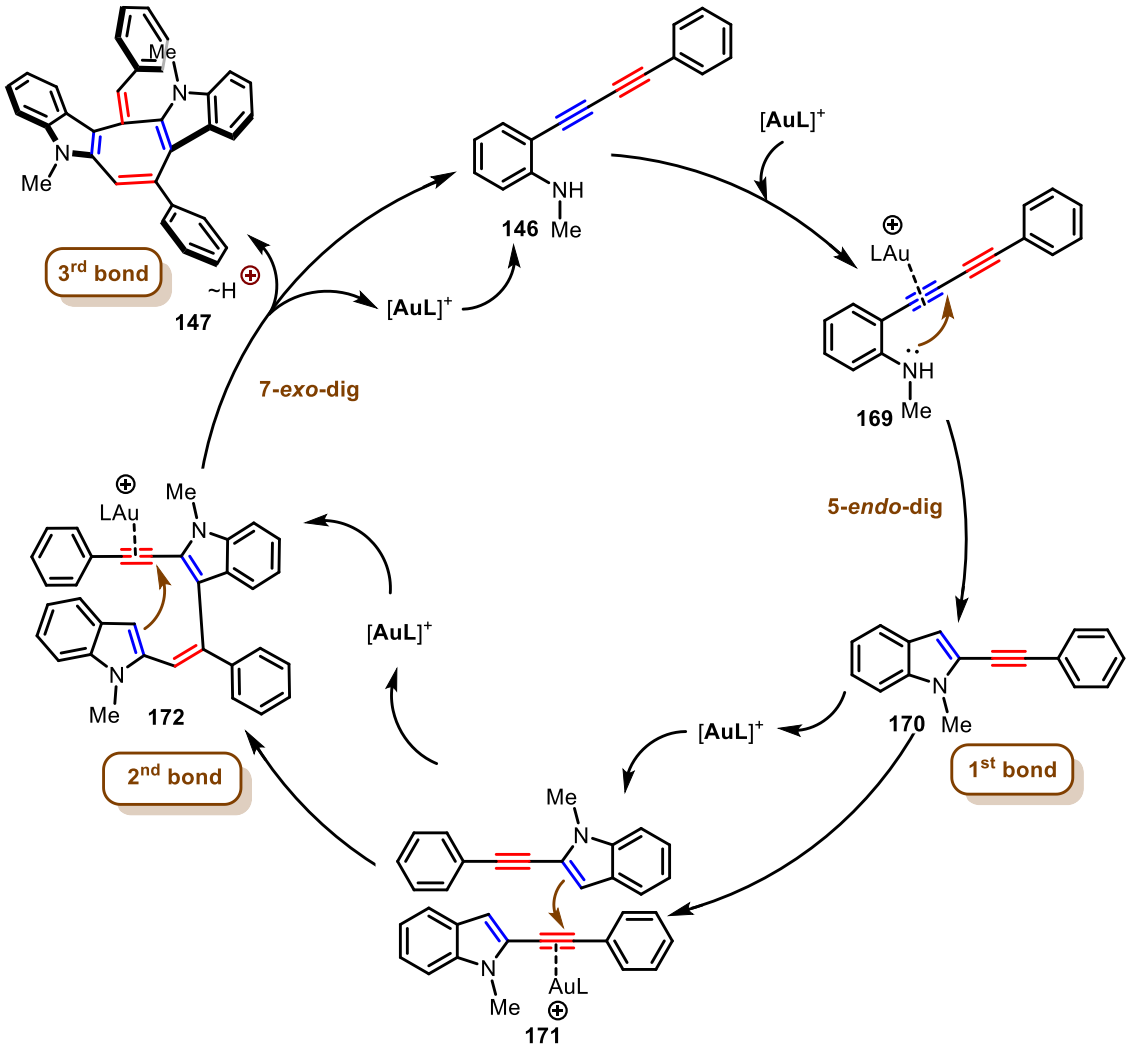
[39]

Then we think to try without substituted on free anilines **167** as a starting material and applying with the 10 mol % of **159** catalyst in Dichloroethane 23 °C until 1 hours and that time also we obtained 1st cyclization of indole **168** with 50 % yield (**Eq. 40**).



[40]

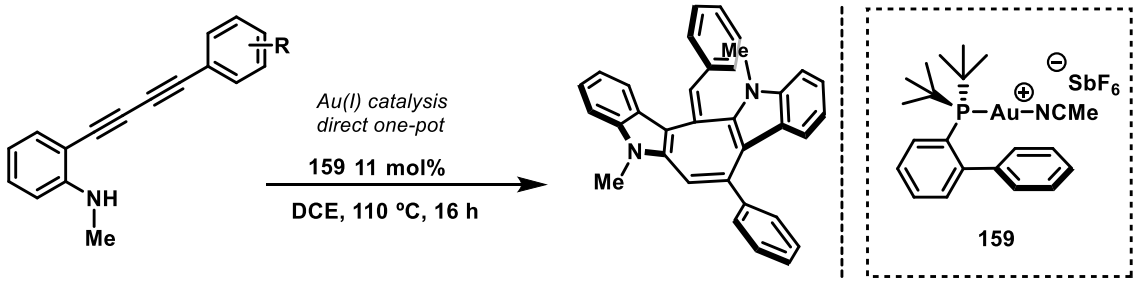
2.5. Mechanism.



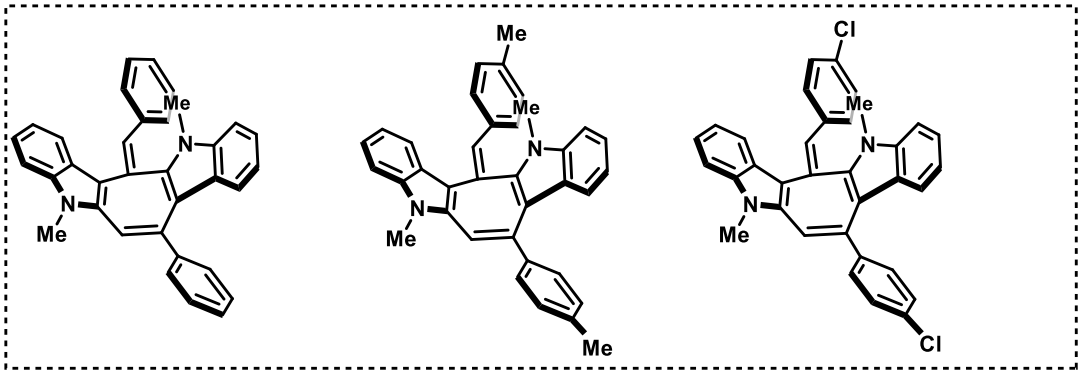
Scheme 13. Mechanistic pathway for the gold(I)-catalysed one-pot synthesis of pentacyclic polyaromatic heterocyclic indoles via cyclization-dimerization.

The mechanism starts from compound **146** where the gold(I) catalyst is coordinated to an alkyne to give intermediate **169.** The lone nitrogen pair is then preferentially attacked by *5-endo-dig* cyclization to form the first bond as well as the five-membered indole **170** complex. This **170** complex undergoes a nucleophilic attack on the electrophilic alkyne via the **171** complex, forming a second bond **172** Finally, *7-exo-dig* cyclizes to form a third bond, leading to pentacyclic dimer **147** cyclization and concomitant catalyst regeneration (**Scheme 13).**

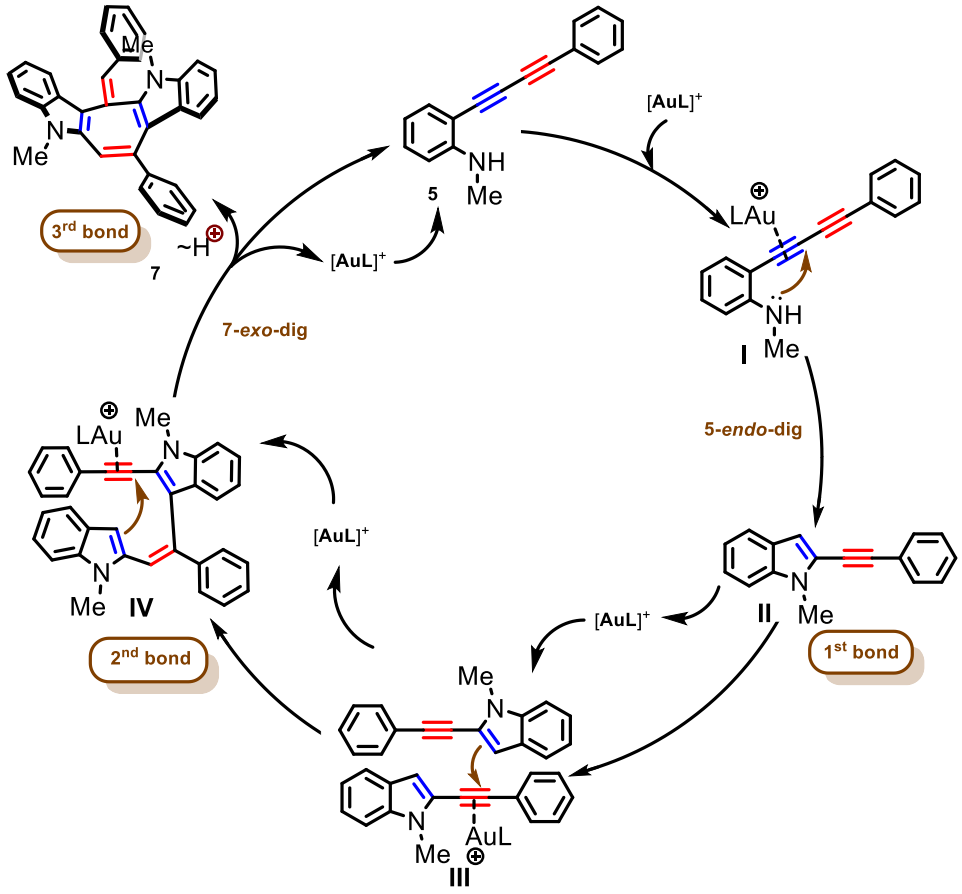
- **2.6 Conclusion.**
- We have developed a catalytic, good yielding and new intermolecular gold(I)-catalyzed one-pot synthesis of pentacyclic polyaromatic heterocyclic indoles via cyclization-dimerization.



- In this procedure including methyl and 4-cl substituted and trans fused having seven-member non-aromatic ring particularly important feature in development of intermolecular dimerization.



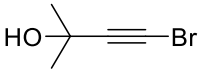
- The reaction plausible mechanism indicated by was followed by intermolecular cycloaddition pathway via followed by *5-endo* dig system.



This evolves by the nucleophilic addition on another electrophilic gold which can be activated, and first alkyne possess electrophilic center itself and form seven-member ring, and finally seven-*exo-dig* form 3rd bond towards pentacyclic dimer.

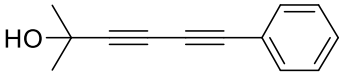
Experimental Section

4-bromo-2-methylbut-3-yn-2-ol



The following compound was obtained by using Potassium hydroxide pellets (59.11 g, 1063.2 mmol, 5.2 equiv) were added to a round-bottom flask with a stir bar and then dissolved in water (200 mL). The resulting solution was cooled in an ice bath. Bromine (7.9 mL,153.35 mmol, 0.75 equiv) was then added dropwise to the vigorously stirred solution. After 15 min, 2-methyl-3-butyn-2-ol (17.16 mL, 153.35 mmol, 1.3 equiv) was added slowly with an addition funnel. The reaction solution was stirred in the ice bath for 30 min, then warmed to room temperature. The aqueous solution was extracted with Et_2O (5 x 50 mL). The combined etheral phase was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography (90 : 10 hexane: EtOAc) to afford the product as a yellow oil (25 g,75 % yield). ^{1}H NMR spectrum agrees with literature.[92] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.92 (s, 1), 1.52 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 84.6, 66.4, 42.9, 31.34. HRMS (ESI+): m/z calcd. for C_5H_8BrO $[M+H]^+$ = 162.9759 found 162.9759.

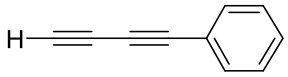
2-methyl-6-phenylhexa-3,5-diyn-2-ol



The following compound was obtained according to the type of Sonogashira reaction, by using 4-bromo-2-methylbut-3-yn-2-ol (2.0 g 12.2691 mmol,1 equiv) as starting material and phenylacetylene (2.67 ml,2 equiv) In triethylamine and DMF as solvent under the nitrogen atmosphere 50 °C 6 hours after completing the crude was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product (1.4 g 61.94%) yellow solid m.p = 63-65 °C. IR (neat) v/cm^{-1} the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[93] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.46 (m, 2H), 7.38 – 7.29 (m, 3H), 2.16 (s, 1H), 1.58 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.6, 129.7, 128.5, 121.6, 86.8, 78.9, 73.6, 67.9, 65.9, 31.4. . HRMS (ESI+): m/z calcd. for $C_{13}H_{13}O$ $[M+H]^+$ = 185.0966 found 185.1159.

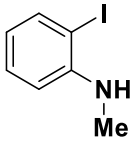
92. Ji, X.; Nie, J.; Peng, X.; Hu, J.; Xu, X.; Huang, Y.; Li, Y.; Jiang, H, *Org. Lett.* **2022**. *18,* 3384-3388.
93. Tzouras, Ma. X.; Peng, N. V.; Van Hecke, K. M.; Nolan, S. P, *J. Org. Chem.* **2022**. *87*, 4883-4893.

buta-1,3-diyn-1-ylbenzene



The following compound was obtained by using 2-methyl-6-phenylhexa-3,5-diyn-2-ol (800 mg, 4.3421 mmol, 1 equiv) was treated with powdered KOH (536 mg, 3.68 mmol, 2.2 equiv) in benzene (8 mL) After 3 h at reflux, crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (300 mg 54.76%) pale yellow oil the spectroscopy data below ^{1}H NMR spectrum agrees with literature.[94] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.49 (m, 2H), 7.41 – 7.29 (m, 3H), 2.48 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.9, 129.8, 128.9, 121.5, 75.8, 73.6, 71.4, 68.6. HRMS (ESI+): m/z calcd. for $C_{10}H_7$ $[M+H]^+$ = 127.0548 found 127.0239.

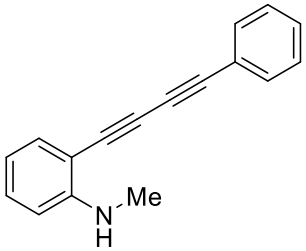
2-iodo-*N*-methylaniline



The following compound was obtained by using 2-iodoaniline as starting material (3 g 13.6967 m.mol.1 equiv)) and NaH (60% in mineral oil, 328.7 mg 13.6967 mmol 1 equiv) dissolved in THF (30 mL). The resulting mixture was stirred at 0 °C for 30 min. Then iodomethane (1.27 mL 20.5451 mmol 1.5 equiv) was added dropwise for 10 min. 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. with the system (only Hexane) to afford product (2.70 g 84.58 %) yellow Liquid the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[95] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 – 7.65 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 6.48 (t, *J* = 7.5 Hz, 1H), 4.22 (s, 1H), 2.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 138.9, 129.7, 118.7, 110.1, 85.4, 31.7. HRMS (ESI+): m/z calcd. for C_7H_9IN $[M+H]^+$ = 233.9780 found 233.9777.

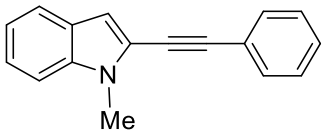
94. Govdi, A. I.; Danilkina, N. A.; Ponomarev, A. V.; Balova, I. A, *J. Org. Chem.* **2019.** *84,* 1925-1940.
95. Le, C. M.; Hou, X.; Sperger, T.; Schoenebeck, F.; Lautens, M, *Angew. Chem. Int. Ed.* **2015**. *54,* 15897-15900.

_N_- methyl-2-(phenylbuta-1,3-diyn-1-yl) aniline



The following compound was obtained according to of Sonogashira reaction, by using 2-iodo-*N*-methylaniline (0.05mL 0.4290 mmol ,1 equiv) as starting material and buta-1,3-diyn-1-ylbenzene (0.09 mL 0.8581 m mol ,2 equiv) the crude was purified by flash column chromatography over silica gel with the system (only Hexane) to afford product (60 mg 60%) yellow solid m.p = 133-2135 °C. IR (neat) v/cm^{-1} 3421.4, 2818.3, 1597.3, 1510.3 731.7. the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[4] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.39 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 4H), 7.23 – 7.13 (m, 1H), 6.63 – 6.47 (m, 2H), 4.67 (s, 2H), 2.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6, 133.6, 132.7, 131.4, 129.5, 128.8, 122.1, 116.4, 109.3, 105.9, 82.9, 79.9, 79.5, 74.3, 30.6. HRMS (ESI+): m/z calcd. for $C_{17}H_{14}N$ $[M+H]^+$ = 232.1126 found 232.1132.

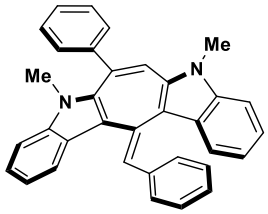
_1_- methyl-2-(phenylethynyl)-1,_H_-indole



The following compound was obtained by using *N*- methyl-2-(phenylbuta-1,3-diyn-1-yl) as starting material (50 mg 0.21626 mmol ,1 equiv) as starting material and gold-(I) (16 mg 0.02162 mmol in DCE 24 h, after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (47 mg %) white solid .m.p = 133-135 °C. IR (neat) v/cm^{-1} 3055.3, 1499.7, 1377.7, 811.7,798.2, the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[96] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 – 7.54 (m, 3H), 7.39 (dd, *J* = 5.2, 2.1 Hz, 3H), 7.33 – 7.26 (m, 2H), 7.15 (ddt, *J* = 7.8, 6.5, 1.4 Hz, 1H), 6.86 (s, 1H), 3.89 (s, 3H). HRMS (ESI+): m/z calcd. for $C_{17}H_{14}N$ $[M+H]^+$ = 232.1126 found 232.1128.

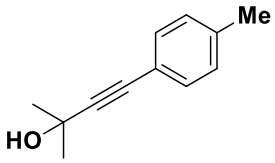
96. Garcia Ruano, J. L.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S; Fraile, A, *Angew. Chem. Int. Ed.* **2012**. *51*, 2712-2716.

(E)-13-benzylidene-5,8-dimethyl-6-phenyl-8,13-dihydro-5H-cyclohepta[1,2-b:5,4-b']diindole.



The following compound was obtained by using *N*- methyl-2-(phenylbuta-1,3-diyn-1-yl) as starting material (60 mg 0.25951 mmol ,1 equiv) as starting material and gold-(I) (22 mg 0.02854 mmol in DCE 16 h, after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (36 mg %) yellow solid . m.p = 244-246 °C. IR (neat) ν/cm^{-1} 3050.9, 2919.8, 1725.0 1464.9, 1663.8 the spectroscopy data below. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.47 – 7.30 (m, 3H), 7.29 – 7.20 (m, 2H), 7.20 – 7.13 (m, 3H), 7.12 (d, *J* = 7.7 Hz, 3H), 7.07 (d, *J* = 6.9 Hz, 3H), 6.86 (s, 1H), 6.79 (t, *J* = 7.0 Hz, 1H), 6.50 (d, *J* = 8.1 Hz, 1H), 3.78 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 139.5, 139.7, 138.5, 137.8, 137.2, 135.5, 129.1, 128.9, 128.9, 128.6, 128.5, 127.9, 127.1, 126.8, 124.8, 124.5, 122.9, 122.7, 121.4, 120.3, 119.8, 118.8, 118.1, 113.7, 112.7, 110.5, 109.4, 30.4, 30.8. HRMS (ESI+): m/z calcd. for $C_{34}H_{27}N_2$ $[M+H]^+$ = 463.2174 found 463.2170.

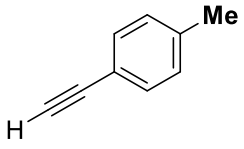
2-methyl-4(*p*-tolyl)but-3-yn-2-ol



The following compound was obtained according to Sonogashira reaction, by using 1-Iodo-4-methylbenzene (6.0 g 27.5178 mmol,1 equiv) as starting material and 2-methyl-3-butyn-2-ol (4.9 ml 55.0357,2 equiv) and keep stir reaction under the nitrogen atmosphere 6 hours room temperature the crude was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford the product (4.5 g 93.85%) brown liquid the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[97] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 2.34 (s, 3H), 2.27 (s, 1H), 1.62 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 131.6, 129.9, 119.7, 93.3, 82.3, 65.7, 31.6, 21.5.

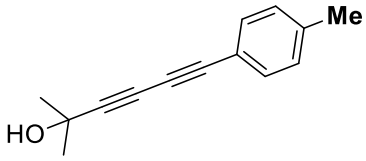
97. Chen, X.; Li, M.; Liu, Z.; Yang, C.; Xie, H.; Hu, X.; Su, S. J.; Jiang, H.; Zeng, W, *Org. Lett.* **2021.** *23*, 6724-6728.

1-methyl-4-methylbenzene.



The following compound was obtained by using 2-methyl-4(*p*-tolyl)but-3-yn-2-ol (4.0 g, 22.9568 mmol, 1 equiv) was treated with powdered KOH (3.8 g, 68.8705 mmol, 3 equiv) in tolune (40 mL) The resulting mixture was heated at 105 °C and stirred for 24 hours. Toluene was recovered by reduced pressure and the reaction crude was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL), dried over $MgSO_4$ and the solvent removed. Purification by flash column chromatography afforded the terminal acetylenes reflux, crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (2.1g 78.75%) brown oil the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[98] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 3.03 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 132.5, 129.9, 119.6, 83.9, 76.7, 21.6.

2-methyl-6(p-tolyl)hexa3,5-diyn-2-ol

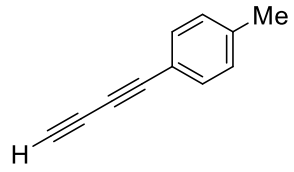


The following compound was obtained according to the type of Sonogashira reaction, by using 4-bromo-2-methylbut-3-yn-2-ol (2.0 g 12.4828 mmol, 1 equiv) as starting material and 1-methyl-4-methylbenzene (2.3 mL 18.7242 m. mol ,1.5 equiv)) In triethyl amine and DMF as solvent under the nitrogen atmosphere 50 °C 6 hours. The reaction mixture was quenched with water and the organic layer was extracted with ethyl acetate (3 x 40 mL). The combined extracts were washed with brine, dried over $Na2SO_4$, concentrated under reduced pressure, and purified by flash column chromatography over silica gel with system (5% EtOAc/Hexane) to afford product (1.25g 50.51.%) brown solid the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[99] ^{1}H NMR (500 MHz,

98. Zha, G. F.; Fang, W. Y.; Li, Y. G.; Leng, J.; Chen, X.; Qin, H. L, *J. Am. Chem. Soc.* 2018, *140*, 17666-17673.
99. Weng, Y.; Cheng, B.; He, C.; Lei, A, *Angew. Chem. Int. Ed.* **2012.** *124*, 9685-9689.
100. Govdi, A. I.; Danilkina, N. A.; Ponomarev, A. V.; Balova, I. A, *J. Org. Chem.* **2019.** *84*, 1925-1940.

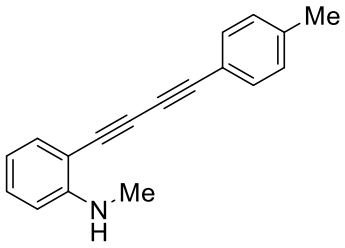
Chloroform-*d*) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.35 (s, 3H), 2.12 (s, 1H), 1.57 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 132.7, 129.4, 118.5, 86.8, 79.3, 72.6, 67.3, 65.9, 31.7, 21.7.

1-(buta-1,3-diyn-1-yl)-4/methylbenzene



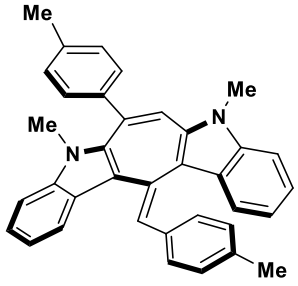
The following compound was obtained by using 2-methyl-6(p-tolyl)hexa3,5-diyn-2-ol (900.mg, 4.5394 mmol, 1 equiv) was treated with powdered KOH (509.4 mg. 9.0789 mmol, 2 equiv) in Tolune (10 mL) The resulting mixture was heated at 80 ° C and stirred for 40 min. after crude was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL), dried over $MgSO_4$ and the solvent removed. Purification by flash column chromatography afforded the terminal acetylenes reflux, crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (400 mg 62.86 %) brown Liquid the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[100] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 132.8, 129.7, 118.0, 75.8, 73.5, 71.8, 68.4, 21.7. HRMS (ESI+): m/z calcd. for $C_{11}H_9$ $[M+H]^+$ = 141.0704 found 141.0909.

_N_-methyl-2-(_p_-tolylbuta-1,3-diyn-1-yl)aniline



The following compound was obtained according to of Sonogashira reaction, by using 2-iodo-*N*-methylaniline (0.05mL 0.4290 mmol ,1 equiv) as starting material and phenylacetylene (120.30 mg, 0.8581 m. mol 2 equiv) was heated at 50 °C the crude was extracted with ethyl acetate (15 x 2 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (20 mL), dried over $MgSO_4$ and the solvent removed. crude was purified by flash column chromatography over silica gel with the system (only Hexane) to afford the product (65 mg 62.34 %) yellow solid m.p = 106-108 °C. IR (neat) ν/cm^{-1} 3471.9, 2815,9. 1597.8 1506.1, 1170.9, the spectroscopy data below. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.19 – 7.10 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.59 – 6.45 (m, 2H), 4.74 (s, 1H), 2.82 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 139.7, 133.4, 132.4, 131.3, 129.8, 118.8, 116.4, 109.3, 105.8, 83.8, 79.6, 78.6, 73.5, 30.3, 21.7. HRMS (ESI+): m/z calcd. for $C_{18}H_{16}N$ $[M+H]^+$ = 246.1283 found 246.1289.

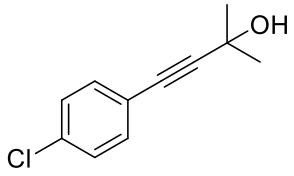
***(E)*-5,8-dimethyl-13(4-methylbenzylidene)-6-(p-tolyl),8,13-dihydro-5*H*-cyclohepta[1,2-*b*:5,4-b']diindole.**



The following compound was obtained by using *N*-methyl-2-(*p*-tolylbuta-1,3-diyn-1-yl) aniline as starting material (45 mg 0.18343 mmol ,1 equiv) as starting material and gold-(I) (15 mg 0.020177 m mol in DCE was heated at 110 °C 16 h , after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (20 mg %) yellow solid m.p = 252-254°C. the spectroscopy data below. IR (neat) ν/cm^{-1} 2924.3, 1725.6, 1462.3, 1120.1, 735.9, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H),

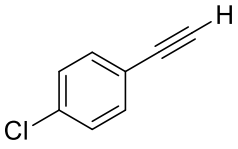
7.41 – 7.27 (m, 7H), 7.24 – 7.19 (m, 2H), 7.11 (s, 3H), 6.98 – 6.91 (m, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 3.90 (s, 3H), 3.45 (s, 3H), 2.54 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 139.5, 138.9, 138.0, 137.7, 137.2, 136.9, 135.6, 134.8, 129.4, 129.9, 128.8, 128.7, 127.8, 126.5, 124.4, 123.8, 122.6, 121.9, 121.3, 119.8, 119.6, 118.6, 117.9, 113.3, 111.9, 109.9, 109.3, 30.3, 29.9, 21.4, 21.3. HRMS (ESI+): m/z calcd. for $C_{36}H_{31}N_2$ $[M+H]^+$ = 491.2487 found 491.2485.

4-(4-Chorophenyl)-2-methylbut-3-yn-2-ol



The following compound was obtained according to Sonogashira reaction, by using 1-chloro-4-Iodo benzene (6.0 g 25.1625 mmol,1 equiv) as starting material and 2-methyl-3-butyn-2-ol (4.5 ml 50.3250,2 equiv) and keep stir reaction under the nitrogen atmosphere 6 hours room temperature the crude was purified by flash column chromatography over silica gel with system (5% EtOAc/Hexane) to afford product (4.5 g 91.87%) brown solid m.p = 62-64 °C. the spectroscopy data below IR (neat) v/cm^{-1} 3248.8, 2985.0 1486.7, 1088.8, 823.0. ^{1}H NMR spectrum agrees with literature.[97] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 2.08 (s, 1H), 1.59 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4, 132.9, 128.7, 121.6, 94.8, 81.9, 65.7, 31.5. HRMS (ESI+): m/z calcd. for $C_{11}H_{12}ClO$ $[M+H]^+$ = 195.0577 found 195.0668.

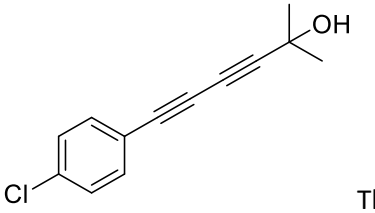
1-chloro-4-ethylbenzene



The following compound was obtained by using 4-(4-Chorophenyl)-2-methylbut-3-yn-2-ol (4.5 g, 23.1172 mmol, 1 equiv) was treated with powdered KOH (3.8 g, 69.3516 mmol, 3 equiv) in Tolune (40 mL) The resulting mixture was heated at 65 ^{o}C and stirred for 24 hours. Toluene was recovered by reduced pressure and the reaction crude was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL), dried over $MgSO_4$ and the solvent removed. crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (1.7g 53.83%) white solid m.p = 30-32 °C. IR (neat) v/cm^{-1} 3261.4, 1486.8 1087.3, 1013.9, 822.8, the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[98] ^{1}H NMR

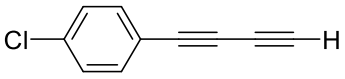
(500 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 3.11 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 133.5, 128.8, 120.7, 82.6, 78.3. HRMS (ESI+): m/z calcd. for C_8H_6Cl $[M+H]^+$ = 137.0158 found 137.0020.

6-(4-chlorophenyl)-2-methylhexa-3,5-diyn-2-ol



The following compound was obtained according to type of Sonogashira reaction, by using 4-bromo-2-methylbut-3-yn-2-ol (1.4 g 7.7348 mmol, 1 equiv) as starting material and 1-chloro-4-ethylbenzene (1.5 g 11.6022 m.mol ,1.5 equiv)) In triethyl amine and DMF as solvent under the nitrogen atmosphere 50 °C 6 hours. The reaction mixture was quenched with water and the organic layer was extracted with ethyl acetate (3 x 40 mL). The combined extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography over silica gel with system (4% EtOAc/Hexane) to afford product (1.25 g 50.51.%) white solid m.p = 106-108 °C. the spectroscopy data below. IR (neat) v/cm^{-1} 3250.1, 2985.0, 1486.5, 1163.4, 905.0 ^{1}H NMR spectrum agrees with literature.[99] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 2.26 (s, 1H), 1.58 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 133.8, 128.9, 120.5, 87.4, 77.6, 74.6, 66.9, 65.8, 31.9. HRMS (ESI+): m/z calcd. for $C_{13}H_{12}ClO$ $[M+H]^+$ = 219.0577 found 219.0263.

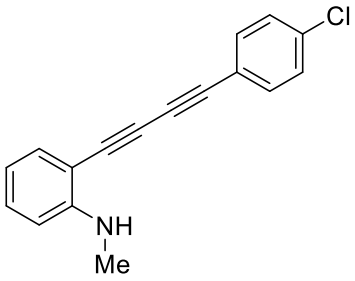
1-(buta-1,3-diyn-1-yl)-4-chlorobenzene



The following compound was obtained by using 6-(4-chlorophenyl)-2-methylhexa-3,5-diyn-2-ol (500.mg, 2.2864 mmol, 1 equiv) was treated with powdered KOH (256.5 mg. 4.5728 mmol, 2 equiv) in benzene (5mL) The resulting mixture was heated at 75 °C and stirred for 2 h. after crude was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL), dried over $MgSO_4$ and the solvent removed, crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (270 mg 73.53 %) brown liquid the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[100] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 2.50 (s, 1H). ^{13}C NMR (126

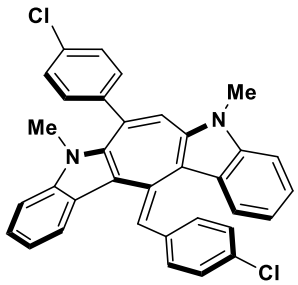
MHz, $CDCl_3$) δ 135.9, 134.1, 129.3, 119.6, 74.7, 74.7, 71.9, 68.3. HRMS (ESI+): m/z calcd. for $C_{10}H_6ClO$ $[M+H]^+$ = 161.0158 found 161.0126.

2-((4-chlorophenyl)buta-1,3-diyn-1-yl)-*N*-methylaniline



The following compound was obtained according to of Sonogashira reaction, by using 2-iodo-*N*-methylaniline (0.05mL 0.3861 mmol ,1 equiv) as starting material and 1-chloro-4-ethynylbenzene (120.30 mg, 0.8581 m. mol 2 equiv) the crude was extracted with ethyl acetate (15 x 2 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (20 mL), dried over $MgSO_4$ and the solvent removed. crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (65 mg 63.34 %) brown solid m.p = 64-66 °C. IR (neat) v/cm^{-1} 3411.6, 2916.1, 1597.9, 1088.1, 818.7, the spectroscopy data below. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.22 (m, 3H), 7.21 – 7.15 (m, 1H), 6.60 – 6.49 (m, 2H), 4.74 (s, 1H), 2.85 (s, 3H ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 135.4, 133.6, 133.3, 131.3, 129.1, 120.7, 116.4, 109.9, 105.4, 81.7, 79.8, 79.8, 75.1, 30.3. HRMS (ESI+): m/z calcd. for $C_{17}H_{13}ClN$ $[M+H]^+$ = 266.0737 found.

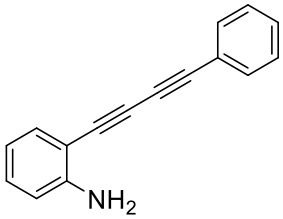
***(E)*-13-(4-Chlorobenzylidene)-6-(4-Chlorophenyl)-5,8-dimehtl-8.13-dihydro-5H-Cyclohepta[1,2-b':5,4-b']diindole.**



The following compound was obtained by using 2-((4-chlorophenyl)buta-1,3-diyn-1-yl)-*N*-methylaniline as starting material (50 mg 0.18815 mmol ,1 equiv) as starting material and gold-(I) (15 mg 0.020696 m. mol in DCE was heated at 110 °C 16 h , after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to

afford product (28 mg 56 %) yellow solid m.p = 314-316°C. the spectroscopy data below. IR (neat) v/cm^{-1} 2925.2, 1719.0 1463.8, 1088.1, 740.4. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.03 – 7.94 (m, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.23 (q, *J* = 7.9 Hz, 2H), 7.18 – 7.07 (m, 5H), 7.01 (d, *J* = 20.7 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.81 (d, *J* = 7.1 Hz, 2H), 6.53 (d, *J* = 8.1 Hz, 1H), 3.74 (s, 3H), 3.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9, 139.1, 138.9, 138.3, 136.8, 136.8, 135.9, 133.8, 132.9, 130.3, 129.6, 128.8, 128.3, 127.4, 126.0, 125.3, 124.3, 123.6, 122.6, 121.3, 120.2, 118.8, 118.5, 114.6, 113.6, 111.8, 110.3, 109.5, 30.49, 30.1. HRMS (ESI+): m/z calcd. for $C_{34}H_{25}Cl_2N_2$ $[M+H]^+$ = 531.1395 found

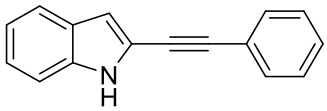
2-(phenylbuta-1,3-diyn-1-yl)aniline



The following compound was obtained according to the Sonogashira reaction, by using 2-iodo-aniline (80 mg 0.3649 mmol,1 equiv) as starting material and buta-1,3-diyn-1-ylbenzene (92.08 mg, 0.7299 m.mol 2 equiv) the crude was extracted with ethyl acetate (15 x 2 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (20 mL), dried over $MgSO_4$ and the solvent removed. crude was purified by flash column chromatography over silica gel with the system (5% EtOH/ Hexane) to afford the product (56 mg 70.57 %) brown solid m.p = 60-62 °C. the spectroscopy data below. IR (neat) v/cm^{-1} 3462.5, 3371.9, 1611.9, 1485.5, 745.5, ^{1}H NMR spectrum agrees with literature.[101] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 6.6 Hz, 2H), 7.32 – 7.24 (m, 4H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.62 (t, *J* = 7.3 Hz, 2H), 4.18 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 133.2, 132.5, 130.8, 129.8, 128.8, 121.9, 118.9, 114.5, 106.3, 82.8, 79.6, 78.7, 74.7. HRMS (ESI+): m/z calcd. for $C_{16}H_{12}N$ $[M+H]^+$ = 218.0970 found 218.0974.

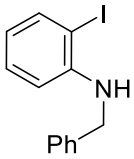
101. Kawada, Y.; Ohmura, S.; Kobayashi, M.; Nojo, W.; Kondo, M.; Matsuda, Y.; Matsuoka, J.; Inuki, S.; Oishi, S.; Wang, C.; Saito, T, *Chem. Sci.* **2018**. *9*, 8416-8425.

2-(phenylethynyl)-1H-indole



The following compound was obtained by using 2-(phenylbuta-1,3-diyn-1-yl)aniline as starting material (30 mg 0.1380 mmol ,1 equiv) as starting material and gold-(I) (10.66 mg 0.0138 m mol in DCE 1 h, after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (15 mg %) white solid m.p = 162-164 °C. IR (neat) ν/cm^{-1} 3369.1, 1594.8, 1441.6, 794.7, 744.3, the spectroscopy data below. ^{1}H NMR spectrum agrees with literature.[102] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.20 (m, 4H), 7.22 – 7.13 (m, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.77 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 131.9, 128.7, 128.6, 127.9, 123.8, 122.7, 121.0, 120.6, 118.9, 110.8, 108.9, 92.9, 81.9. HRMS (ESI+): m/z calcd. for $C_{17}H_{14}N$ $[M+H]^+$ = 218.0970 found 218.0972.

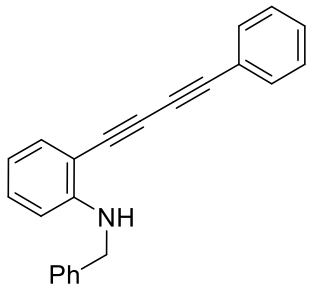
***N*-benzyl-2-iodoaniline.**



The following compound was obtained by using 2-idodainilne (332 mg 1.52020 m mol 1.3 equiv) with benzyl bromide (0.14 ml 1.169385m mol 1 equiv) and $NaHCO_3$ (147mg 1.754078 m mol 1.5 equiv) in DMF was heated at 50 °C until complete consumption of was indicated by TLC (about 2 h) then mixture Cooled to room temperature the mixture was quenched with water and organic layer extracted 3 times with EtOAc. The combined organic layer washed with brine, dried with anhydrous $MgSO_4$, and concentrated in *vacuo* the crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (310 mg 85%) colorless liquid the spectroscopy data matches[103] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.16 (m, 5H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 6.37 (t, *J* = 7.1 Hz, 1H), 4.55 (s, 1H), 4.32 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 139.3, 129.5, 128.8, 128.7, 127.5, 127.3, 118.9, 111.9, 85.4, 48.5. HRMS (ESI+): m/z calcd. for $C_{13}H_{13I}N$ $[M+H]^+$ = 310.0093 found

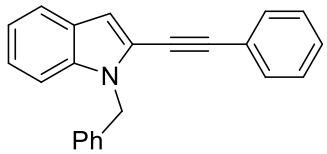
102. Iioka, R.; Yorozu, K.; Sakai, Y.; Kawai, R.; Hatae, N.; Takashima, K.; Tanabe, G.; Wasada, H.; Yoshimatsu, M*, Eur. J. Org. Chem.* 2021, .**10**, 1553-1558.
103. Lizos, D. E.; Murphy, J. A, *Org. Biomol. Chem,* **2003.** 1,117-122.

***N*-benzyl-2-(Phenylbuta-1,3-diyn-1-yl)aniline.**



The following compound was obtained according to Sonogashira reaction, *N*-benzhyl-2-iodoaniline (290 mg, 0.93805 mmol, 1 equiv) starting material and buta-1,3-diyn-1-ylbenzene (0.36 mL 2.81416 m. mol,3 equiv) and keep stir reaction under the nitrogen atmosphere 6 hours at 50 °C temperature the crude was purified by flash column chromatography over silica gel with the system only Hexane) to afford the product (156 mg 54.10 %) brown solid. m.p = 98-100 °C. IR (neat) ν/cm^{-1} 3418.0, 1596.7, 1505.7 1294.3, 753.1. The spectroscopy data below. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 (s, 2H), 7.30 (td, *J* = 11.9, 10.7, 7.7 Hz, 8H), 7.21 (dd, *J* = 13.5, 7.0 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.57 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 1H), 4.40 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 138.9, 133.5, 132.5, 131.7, 129.3, 128.8, 128.9, 127.4, 127.2, 121.9, 116.9, 110.3, 105.9, 83.1, 79.7, 78.8, 74.2, 47.9. HRMS (ESI+): m/z calcd. for $C_{23}H_{18}N$ $[M+H]^+$ = 308.1439 found

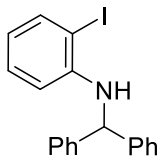
***1*- benzyl-2-(phenylethynyl)-1,*H*-indole**



The following compound was obtained by using *N*-benzhydryl-2-(Phenylbuta-1,3-diyn-1-yl)aniline as starting material (50 mg 0.16297 mmol ,1 equiv) as starting material and gold-(I) (12 mg 0.01627 m. mol in DCE 30 min at room temperature, after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (35 mg 70 %) light yellow solid m.p = 152-154 °C. IR (neat) ν/cm^{-1} 3031.3, 2199.7, 1493.9, 1342.1, 789.7. The spectroscopy data below. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.17 (qd, *J* = 12.2, 10.5, 5.2 Hz, 5H), 7.07 (t, *J* = 7.4

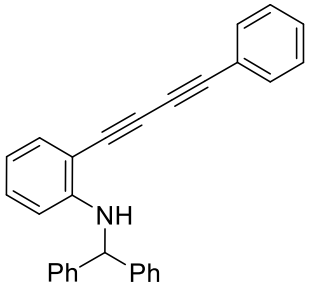
Hz, 1H), 6.87 (s, 1H), 5.46 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 137.1, 131.6, 128.8, 128.7, 128.6, 127.7, 127.6, 126.9, 123.7, 122.7, 122.7, 121.2, 120.5, 110.8, 108.9, 95.9, 81.3, 48.8. . HRMS (ESI+): m/z calcd. for $C_{23}H_{18}N$ $[M+H]^+$ = 308.1439 found

_N_-benzhydryl-2-iodoaniline.



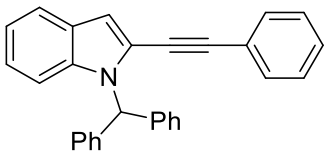
The following compound was synthesized by using a solution of 2-iodoaniline (300 mg 1.36967 mmol 1 equiv) in DMF (10 mL) at rt was added bromodiphenylmethane (676 mg, 2.73950 mmol) and EtN(pr-*i*)$_2$ 3 ml and the reaction mixture was heated at 45°C overnight After the volatiles were removed under reduced pressure, the residue was dissolved in EtOAc, washed with water (3x) and brine and dried over $MgSO_4$. was purified by flash column chromatography over silica gel (hexanes to 5% EtOAc/hexanes) gave the *N*-benzhydryl-2-iodoaniline. (380 mg, 72 % yield) as a white solid. m.p = 68-70 °C. IR (neat) v/cm^{-1} 3389.7, 3026.2, 1580.5, 1314.3, 1280.5, 746.3. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 6.8 Hz, 8H), 7.25 – 7.16 (m, 2H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.36 (dd, *J* = 17.9, 7.9 Hz, 2H), 5.49 (s, 1H), 4.78 (s, 1H). HRMS (ESI+): m/z calcd. for $C_{19}H_{16}IN$ $[M+H]^+$ = 385.0327 found

_N_-benzhydryl-2-(Phenylbuta-1,3-diyn-1-yl)aniline.



The following compound was obtained according to Sonogashira reaction, *N*-benzhydryl-2-iodoaniline (120 mg, 311.49 mmol, 1 equiv) starting material and buta-1,3-diyn-1-ylbenzene (0.16 mL 1.2459 m. mol,4 equiv) and keep stir reaction under the nitrogen atmosphere 6 hours at 50 °C temperature the crude was purified by flash column chromatography over silica gel with the system only Hexane) to afford the product (80 mg 66.97%) brown solid. m.p = 98-100 °C. IR (neat) v/cm^{-1} 3060.8, 2208.6, 1597.3, 1491.0, 742.7. The spectroscopy data below. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 6.5 Hz, 1H), 7.33 – 7.17 (m, 15H), 7.01 (ddd, *J* = 8.6, 7.4, 1.6 Hz, 1H), 6.55 (td, *J* = 7.5, 1.0 Hz, 1H), 6.36 (d, *J* = 8.3 Hz, 1H), 5.53 (d, *J* = 4.9 Hz, 1H), 5.19 (d, *J* = 5.0 Hz, 1H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 142.7, 133.5, 132.4, 130.9, 129.7, 128.9, 128.5, 127.6, 127.4, 121.8, 116.9, 111.8, 106.2, 82.9, 79.8, 78.6, 73.9, 62.5.. HRMS (ESI+): m/z calcd. for $C_{29}H_{22}N$ $[M+H]^+$ = 384.1752 found.

1-benzhydryl-2-(phenylethynyl-1-H-indole.



The following compound was obtained by using *N*-benzhydryl-2-(Phenylbuta-1,3-diyn-1-yl)aniline as starting material (80 mg 0.20861 mmol ,1 equiv) as starting material and gold-(I) (16 mg 0.02086 m mol in DCE 30 min, at room temperature, after completion reaction isolated from crude was purified by flash column chromatography over silica gel with system (only Hexane) to afford product (64 mg 80 %) light brown solid m.p = 156-158 °C. IR (neat) v/cm^{-1} 2924.7, 1719.1, 1448.9 1348.0, 722.6. the spectroscopy data below.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 6.4, 2.9 Hz, 1H), 7.26 (m, *J* = 24.9, 7.6 Hz, 15H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.91 (s, 1H), 6.80 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9, 136.8, 131.5, 128.8, 128.7, 128.5, 128.3, 127.8,

123.2, 122.8, 122.7, 121.2, 120.7, 112.6, 109.5, 96.5, 81.7, 63.8. HRMS (ESI+): m/z calcd. for $C_{29}H_{22}N$ $[M+H]^+$ = 384.1752 found 384.1749.

CHAPTER-3

Iodine(III)-Mediated The electrophilic Iodination of Free-Anilines Using the PIDA/NH4I System.

CHAPTER-3

3.1. Introduction

Iodinated aryls are an important class of organic compounds. They are the best electrophilic counterparts in the Stille[104] or Suzuki[105] cross-coupling reactions as well as in the Mizoroki-Heck[106] olefination and Sonogashira[107] alkynylation. Particularly, iodinated anilines, are broadly used as radiocontrast medium[108] in cholecystography. Representative examples such as GSK1120212 (JTP-74057-DMSO) effective against cancer cell lines diatrizoate, ioxaglate, iohexol, ioversol or iopodate sodium have been used.[109] Also, iopanoic acid has been used in the long-term treatment of Grave´s disease.[110] The presence of iodo anilines is significatively described in non-linear optics,[111] as quiral auxiliar[112] and in the syntnesis of antimicrobials,[113] anti-inflamatories,[114] quinolones,[115] Abl kinase-inhibitors[116] and in fullerene functionalization[117] (Figure 3.1).

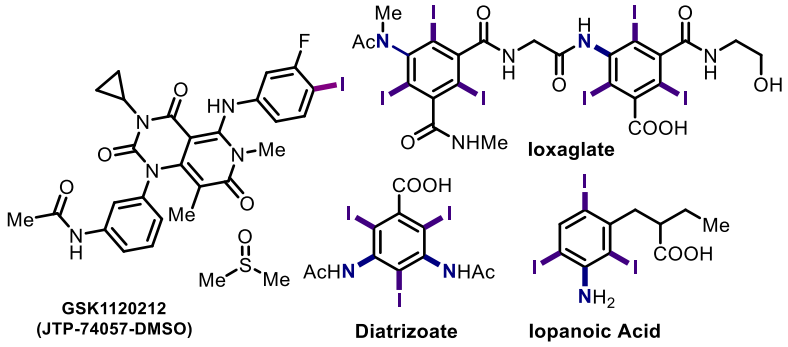


Figure 3.1. Relevance of iodinated anilines.

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105. Martin, R; Buchwald S. L. *Acc.Chem.Res*, **2008**, *41*, 1461-1473.
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In regard of the iodoaniline core synthesis, the first described protocols inovled the direct use of aniline in harsh acidic conditions. These uses molecular iodine in different mineral-acids media for activating the halogen as a good electrophile.[118] Other general protocols for the aromatic iodination **166** are non-specific for anilines, require of strong metallic oxidants and have narrow application scope just for few *N*-substituted anilines **165**.[119] On the other hand, specific iodination for the aniline nuclei is restricted to few methods. Examples of transtion-metal-free protocols require I_2 in polar solvents[120] or in mix with oxidants.[121] The use of ICl,[122] NIS[123] or the oxidation of the idodie anion from KI with $KClO_3$[124] or H_2O_2[125] has been described as I^+ equivalent regents. Another important strategy for aniline iodination, needs of the dichloroiodate anion. The $ICl_2^{\ominus}$ as reagent, has been used with different cations such as Na^+,[126] K^+,[127] Py^+R,[128] $Bn_2Et_3N^+$[129] and Bn_2DABCO^{2+}.[130]

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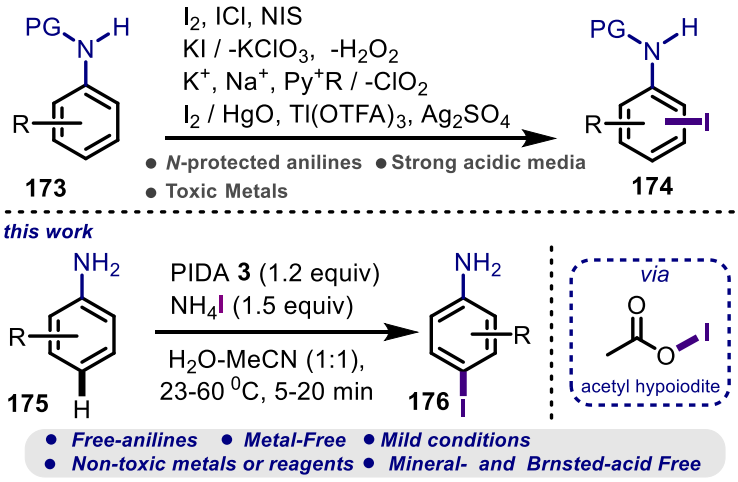
Finally, the specific metal-mediated methods for the aniline iodination are resticted to the use of HgO,[131] $Tl(OTFA)_3$[132] and Ag_2SO_4 in mix with molecular iodine[133] (Scheme 14).



Scheme 14. Described procedures for iodination of anilines.

As part of our research interest on the iodine(III) chemistry,[134] we started a program for the developing of new oxidative procedures[135] focused mainly to the aromatic introduction of aryls,[136] and inorganic groups (-Cl,[137]-Br,[138]-I,[139]and $-NO_2$[140]). The obtained compounds by our procedures, have been used in the

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total synthesis of natural compounds[141] whose main aim is the evaluation as plausible drug-candidates for mycose[142] or in cancer therapy.[143]

Considering the few procedures available for synthesizing iodoanilines starting from non-*N*-substituted materials **175**, the aggressive acidic media required, the highly toxic metals used and the relevance of the iodo; herein we describe the first iodine(III)-mediated procedure for the iodination of free anilines **176** under non-BrØnsted or mineral acids, metal-free, mild, non-toxic and in general operationally simple reaction conditions using PIDA **3** as oxidant and ammonium iodide as iodine atom source.

141. (*a*) Ramadoss, V.; Alonso-Castro, Á. J.; Campos-Xolalpa, N.; Solorio-Alvarado, C. R. *J. Org. Chem.* **2018**, *83,* 10627-10635; (*b*) V. Ramadoss, A. J. Alonso-Castro, N. Campos-Xolalpa, Ortiz-Alvarado, R.; Yahuaca-Juárez, B.; Solorio-Alvarado, C. R. *RSC Adv*. **2018**, *8,* 30761-30776.
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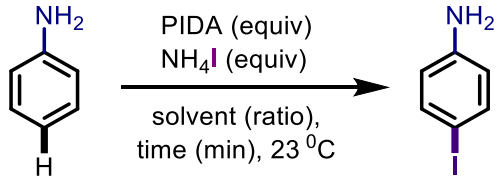
3.2 Results

Inspired in our previous results on iodination of phenols[144] using iodine(III) reagents and ammonium iodide, we decided to apply it to the iodination of anilines. The different conditions tested are following described (Table 1).

Table 1. Optimization of the iodine(III)-mediated iodination of free anilines. [a]



175 **176**

Entry	PIDA (equiv)	NH_4I (equiv)	Solvent (ratio)	Time (min)	Yield (%)[b]
1	1.2	2.4	MeOH	10	c. r. m.
2	1.2	2.4	MeOH-H_2O (1:1)	10	c. r. m.
3	2.2	3.4	H_2O	12 h	32
4	2.2	3.4	MeCN	24 h	45
5	2.2	3.4	MeCN-H_2O (5:2)	3 h	38
6	2.2	3.4	MeCN-H_2O (1:1)	2 h	42
7	1.0	1.0	MeCN-H_2O (1:1)	10	40
8	1.2	1.1	MeCN-H_2O (1:1)	5	44
9	1.2	1.3	MeCN-H_2O (1:1)	5	57
10	1.2	1.4	MeCN-H_2O (1:1)	5	65
11	*1.2*	*1.5*	*MeCN-H_2O (1:1)*	*5*	*76*
12	- -	1.5	MeCN-H_2O (1:1)	5	n. r.
13	1.2	- -	MeCN-H_2O (1:1)	5	c. r. m.

[a] Reaction conditions: aniline (0.5 mmol), solvent (0.3 *M*), open flask. [b] Isolated yields.
PIDA= [(diacetoxyiodo)benzene]. c.r.m.= complex reaction mixture. n.r.= no reaction.

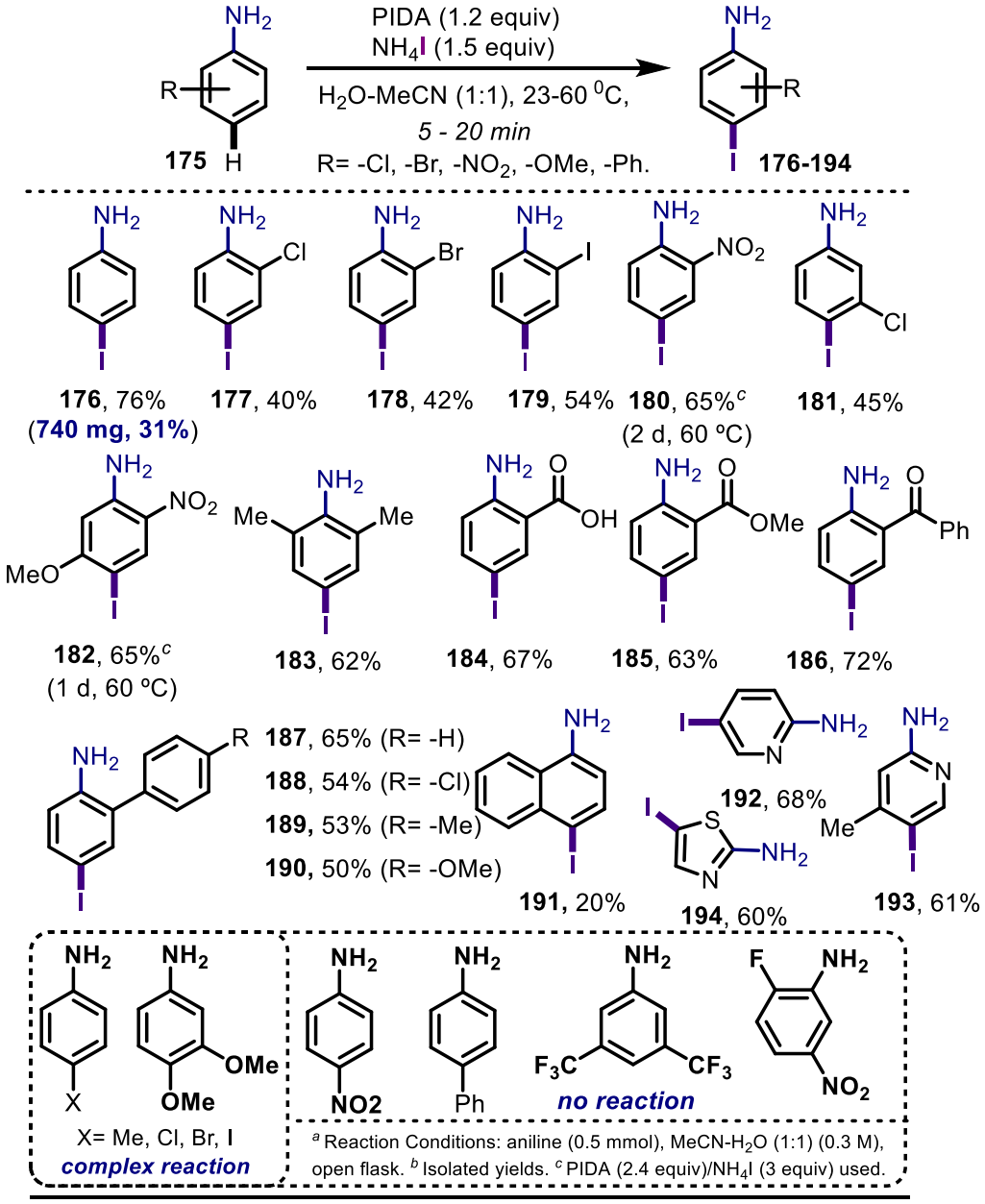
144. Nahide, P. D.; Jiménez-Halla, J. O. C.; Wrobel, K.; Solorio-Alvarado, C. R.; Ortiz-Alvarado, R.; Yahuaca-Juárez, B. *Org. Biomol. Chem,* **2018,** *16*, 7330-7335.

Initial examination to validate our hypothesis started with 1.2 equiv of PIDA and 2.4 equiv of ammonium iodide with aniline in methanol or in methanol-water (1:1). After 10 minutes of reaction the starting material was fully consumed but a very complex reaction mixture was observed (entries 1 and 2). We considered using only water as solvent. Due to the low solubility of PIDA, an excess in both reagents up to 2.2 and 3.4 equivalents of PIDA and ammonium iodide respectively were used. Gratifyingly a 32% yield of 4-iodoaniline 2 was obtained after 12 h of reaction (entry 3). The *ortho*- regioisomer was not observed at least by the detection limit of NMR. Under the same stoichiometry, the reaction showed a 45% yield in acetonitrile, however 24 hours were necessary (entry 4).

These results driving us to consider both solvents for test in reaction, since water accelerates the process and acetonitrile dissolve effectively the organic reagents. Thus, keeping the previous amount of reagents, a mixture of acetonitrile and water (5:2) yields 38% of 2 in 3 hours of reaction (entry 5). The change to (1:1) solvent ratio increased the yield to 42% and diminish the time to 2 hours (entry 6). At this point we found the best solvent ratio regarding time and yield. Then, we decided to optimize the reagents using 1 equivalent of oxidant and ammonium iodide, to our delight compound 2 was obtained in 40% yield after only 10 minutes of reaction (entry 7).

A slight increase to 1.2 equiv of PIDA and 1.1 of ammonium iodide give rise to 2 in 44% yield in 5 minutes of reaction (entry 8). Consecutive and systematic increases in reagents (entries 9-11), showed a stoichiometry yield-sensitive reaction form 57-76%. The best result was using 1.2 equiv of PIDA and 1.5 equiv of ammonium iodide (entry 11). Control experiments using only oxidant or ammonium iodide did not show any reaction (entries 12 and 13).

Identified the optimal conditions, we proceeded to explore the scope of the new developed protocol (Scheme 15).



Scheme 15. Scope of the PIDA/NH_4I-mediated iodination of free anilines.

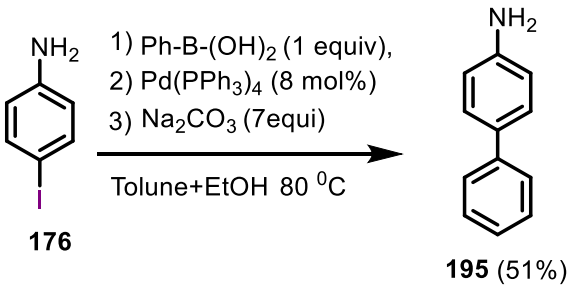
The iodination of the simple aniline take place also in gram scale to get **176** in 31% yield. On the other hand, the iodination of the free 2-chloro-, 2-bromo-, 2-iodine-, 2-nitro and 3-chloroanilines give rise to the corresponding iodinated products **177-181** in yields ranging from 40-65%. Duplicating amount of reagents and heating at 60 °C for 2 days led to the iodinated aniline **180** which has the strong electron-attracting nitro group. The same was observed for iodinated aniline **182** that needs of 1 day heating at 60 ºC. The iodination process took place regioselectively on the *para* position regarding the amino group of aniline. Also, very short reaction times to complete the reactions were required, usually from 5 to 20 minutes.

Iodination of alkyl aniline led to the formation of **183** in 62% yield. Anilines containing carboxylic acids, esters o ketones were also successfully iodinated to get **184-186** in 63-72% yield. A small group of free anilines containing different substituted aryls at C-2, yielded the corresponding iodinated products **187**-**190** in modest 50-65% yields with the *para* regioselectivity previously observed. The 1-amino naphthalene gave the corresponding iodinated derivative **191** in 20% yield. Finally, some heterocycles including pyridines and 2-aminothiazole were iodinated under our developed conditions to get the corresponding iodoanilines **192**-**194** in 60-58% yield. Other free *para*-substituted anilines with small groups such as methyl, chlorine, bromine, iodine or methoxy gave a complex reaction mixture of products becoming not suitable starting materials for our procedure.

Based on these results, we could hypothesize an initial *para* iodination which formed a non-aromatic 4,4-disubstituted product that evolved by decomposition. Therefore, trying to induce the iodination at C-2 of the aniline, we synthesized the 4-phenylaniline. This compound with a bulky group at C-4 did not react under our optimized conditions. We attribute the lack of reactivity to the steric hindrance by the phenyl at C-4 as well as the iodine atom. To complete the scope exploration, other free anilines containing strong electron-withdrawing groups such as -F, -NO_2, or -CF_3 did not react even with higher amounts of reagents or heating

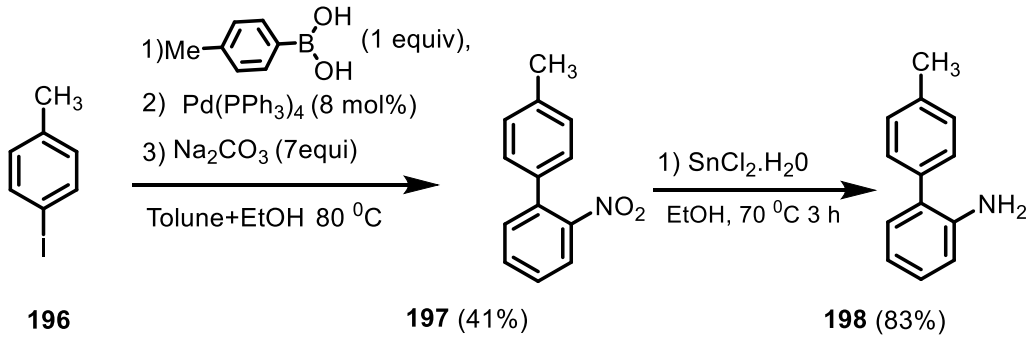
Therefore, trying to induce the iodination at C-2 of the aniline, we synthesized the 4-phenylaniline. This compound with bulky group at C-4 did not react under our optimized conditions. We attribute the absence of reactivity to the steric hindrance by the phenyl at C-4 as well as the iodine atom. To complete the scope exploration, other free anilines containing strong electron-attracting groups such as -F, -NO_2, or -CF_3 did not react even with higher amount of reagents or heating.

3.4 Scheme of synthesis starting material via Suzuki–Miyaura cross-coupling reactions pathway.



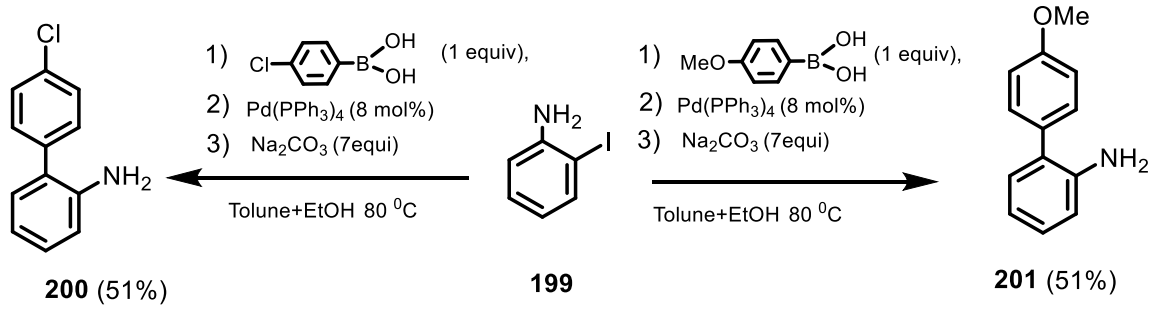
Scheme 15. Synthesis of 1,1 biphenyl-4-amine.

Starting from the 4-iodoaniline **176** synthesized biphenyl 4-amine **195** followed by Suzuki–Miyaura cross-coupling reaction pathway. The using phenyl boronic acid (1 equiv) and $Pd(PPh_3)_4$ 8 mol % and Na_2CO_3 2M (1 mL, 7 equiv) were successively added and heated at 80 ºC for 8 h. to give 51% yield **195** desired product.



Scheme 15. Synthesis of 4-methyl-2-nirto-1,1,-biphenyl to 4-methyl-nirto-1,1,-biphenyl-2 amine

Starting from the 4-iodotolune **196** via followed by Suzuki–Miyaura cross-coupling reaction pathway. The using 4-methylphenyl boronic acid (1 equiv) and $Pd(PPh_3)_4$ 8 mol % and Na_2CO_3 2M (1 mL, 7 equiv) were successively added and heated at 80 ºC for 8 h. to give 41% yield **197** desired product. Then next step synthesis of 4'-methyl-[1,1'-biphenyl]-2-amine from 4-methyl-2-nirto-1,1,-biphenyl by using $Sncl_2.2H_2O$ and heat up to 70 ºC for 3 hours to give 83% yield **198** desired product.

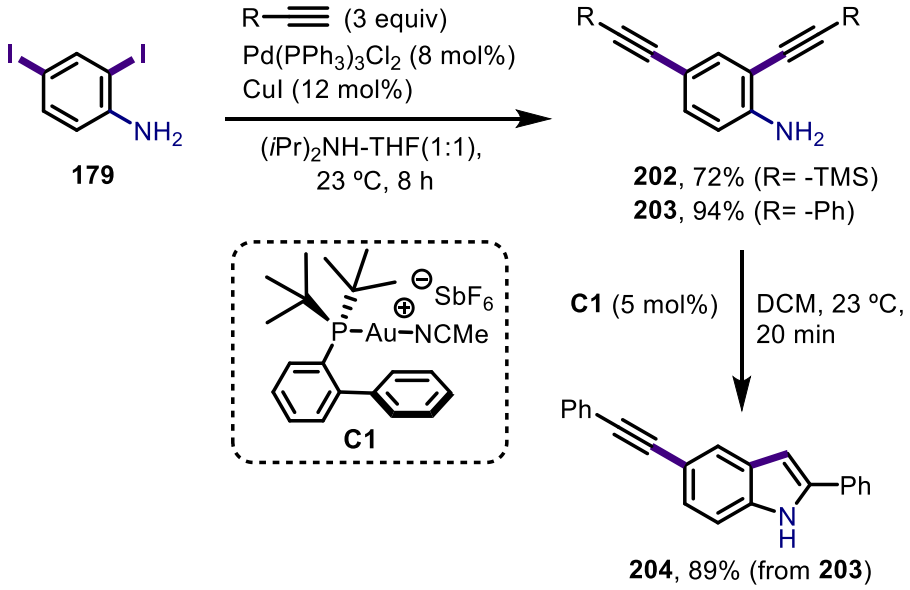


200 (51%) **199** **201** (51%)

Scheme 15. Synthesis of 4-chloro-1,1biphenyl-2-amine and 4-methoxy-1,1-biphenyl-2-amine

Starting from the 2-iodo aniline **199** followed by Suzuki−Miyaura cross-coupling reaction pathway. The using 4-chlorophenyl boronic acid 4-methoxyphenyl boronic acid (1 equiv) and $Pd(PPh_3)_4$ 8 mol % and Na_2CO_3 2M (1 mL, 7 equiv) were successively added and heated at 80 ºC for 8 h. to give 51% yield **200** and **201** desired product.

To demonstrate the utility of our developed protocol, we carried out the following short synthetic route (Scheme 16).



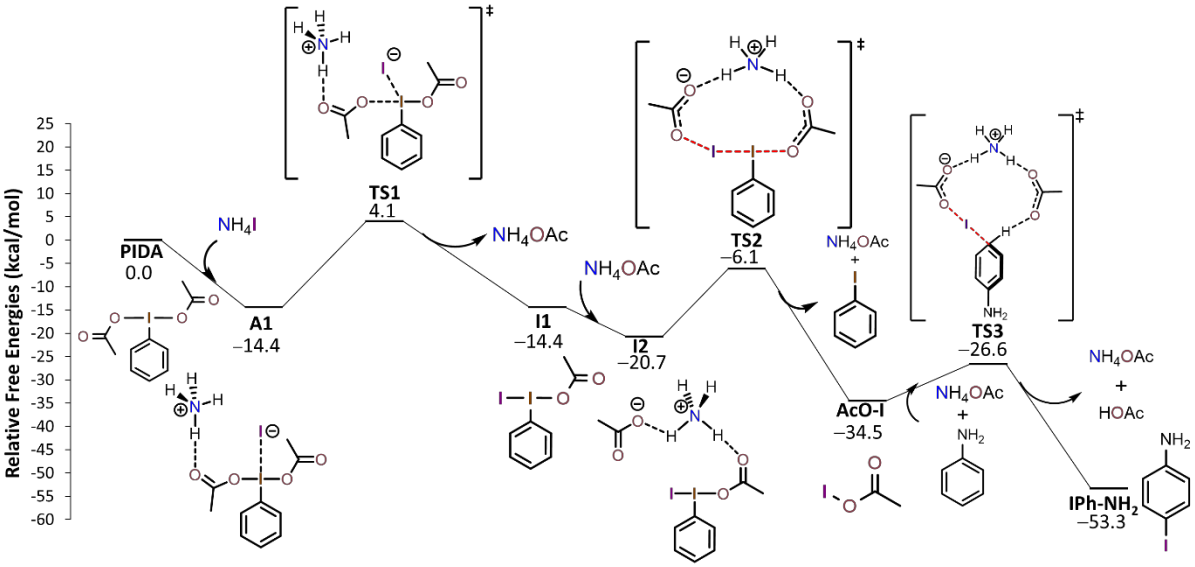
Scheme 16. Synthetic utility of the obtained iodinated anilines.

Starting from the synthesized diiodo aniline **179**, the Sonogashira alkynylation with TMS-acetylene as well as with phenylacetylene gave rise to double alkynylated products **202** and **203** in 72 and 94% yield, respectively. The following gold(I)-catalyzed cycloisomerization reaction[145] using 5 mol% of Echavarren´s catalyst **C1**,[146] led to the formation of the functionalized indole **204** in 89% yield starting from **203**.

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

146. C. R. Solorio-Alvarado, A. M. Echavarren, *J. Am. Chem. Soc.,* 2010, **132**, 11881-11883.

Scheme 17. Energy profile for the calculated iodination mechanism of free anilines using the PIDA/NH_4I system (SMD: water ω B97X-D/def2-SVPP level.



To obtain more insights into the mechanistic details on the iodination of aniline via PIDA and ammonium iodide, we performed theoretical calculations at the (SMD:water):ωB97X-D/def2-SVPP level (see the SI for computational details). According to the calculated reaction mechanism (Scheme 2), first **PIDA** interacts with ammonium iodide to give intermediate **A1** (DG_{R1} = -14.4 kcal/mol). Then the acetate of **PIDA**, which interacts with ammonium ion, dissociates (via transition state **TS1**, $DG_1^{\neq}$ = +18.5 kcal/mol) forming **I1** (DG_{R2} = 0.0 kcal/mol). Next, the ammonium acetate and **I1** forms adduct **I2** (DG_{R3} = -6.3 kcal/mol). The geometry of this adduct allows the acetate of ammonium acetate to displace the iodine atom of **I1**, while last acetate of **I1** dissociates (**TS2**, $DG_2^{\neq}$ = +14.6 kcal/mol) leading to **AcO-I** (DG_{R4} = -13.8 kcal/mol). Finally, the last reaction step is the *para* iodination of aniline (DG_{R5} = -18.8 kcal/mol).

For this, we found three transition states that involves **AcO-I** interacting with: 1) ammonium acetate (through **TS3**, $DG_3^{\neq}$ = +7.9 kcal/mol), 2) acetate anion (**TS4**, $DG_4^{\neq}$ = +25.2 kcal/mol) and 3) two water molecules (**TS5-2**, $DG_5^{\neq}$ = +26.7 kcal/mol). Among these, **TS3** has the lowest energy barrier (see SI for further information). Therefore, ammonium cation has an important effect in **TS3**; it bridges both acetates via hydrogen bonds making iodine of **AcO-I** more electrophilic and catalyses the **AcO-I** formation and the halogenation process. *Ortho* Iodination resulted thermodynamically ($DG_{R5\text{-}p}$ = -6.2 kcal/mol) and kinetically (**TS3-*o***, $DG_{3\text{-}p}^{\neq}$ = +12.6 kcal/mol) less favorable than *para-Iodination*, which is consistent with experimental observation (see SI). Overall, the reaction is exergonic (DG_R° = -53.3 kcal/mol) and thecalculated total energy barrier of +18.5 kcal/mol is in line with the reported conditions. According to the performed theoretical calculations, our developed iodination process was carried out through the *in situ* generation of acetyl hypoiodite (AcO-I) which is the iodinating species

Regarding AcO-I formation, this highly reactive halogenating reagent has been previously synthesized by reacting I_2 with AcOAg,[147] $Pb(OAc)_4$,[148] $Hg(OAc)_2$,[149] AcOOH,[150] oxone/Ac_2O/AcOH[151] or with the AcOAg/ICl[152] system. In regard the use of iodine(III) reagent the AcO-I formation it has been described by reaction of PIDA with I_2,[153] NaI,[154] NIS and NH_4I for this work. To date AcO-I it has not been isolated, however Lusztyk[141] described the ^{1}H NMR characterization in $CDCl_3$.

147. Heusler, K.; Kalvoda, J. *Angew. Chem, Int. Ed. Engl.* **1964**, *3*, 525-538.
148. Chen, E. M.; Keefer, R. M.; Andrews, L. *J, Am. Chem. Soc.* **1967**, *89*, 428-430.
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150. Hokamp, T.; Strom, A.; Yusuboy, T.M.; Wirth,T. *Synlett.* **2018**, *29,* 415-418.
151. Giri, R.; Yu, J.-Q. *John Wiley, and Sons: Hoboken,* NJ, **2008**.
152. Courtneidge, J. L.; Lusztyk, J. D. Pagé, *Tetrahedron Lett.* **1994,** *35*, 1003-1006.
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154. Beltran, R.; Nocquet-Thibault, S.; Blanchard, F.; Dodd, R. H.; Cariou, K.; *Org. Biomol. Chem.* **2016**, *14,* 8448-8451.

Thus, to test the plausibility of our mechanistic proposal, we carried out a NMR study to identify the formation of AcO-I by mixing PIDA and NH_4I in the solvent system [CD_3CN-D_2O (1:1)] that we used in our procedure (Figure 3.2)

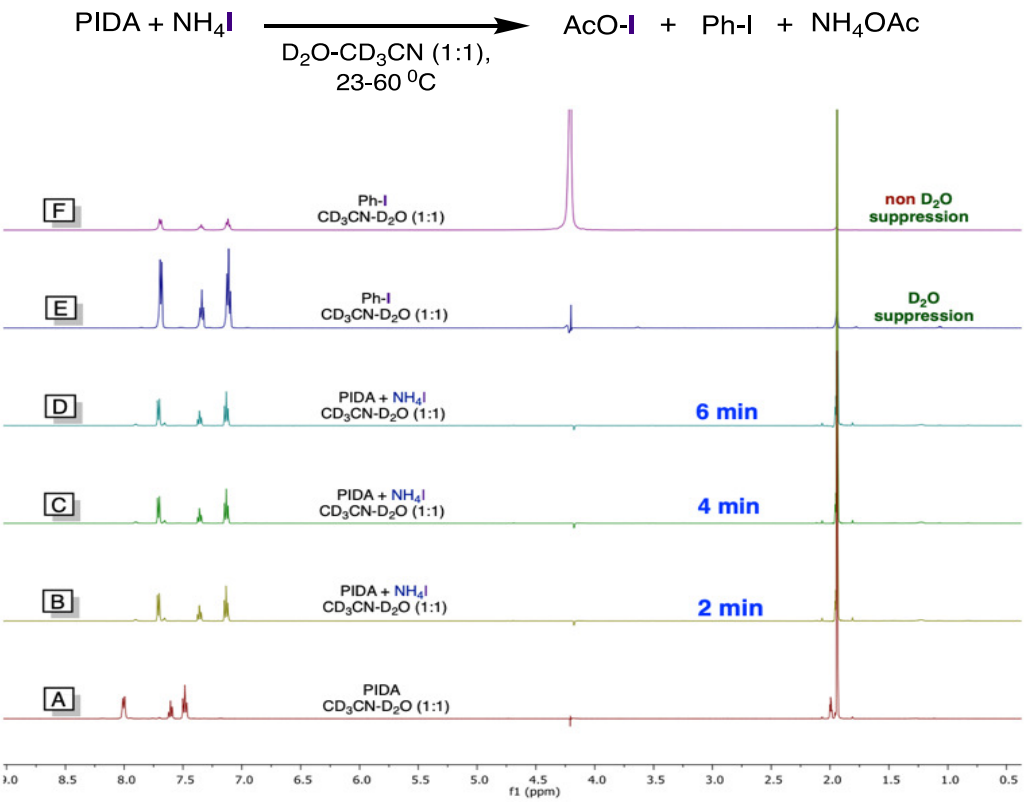
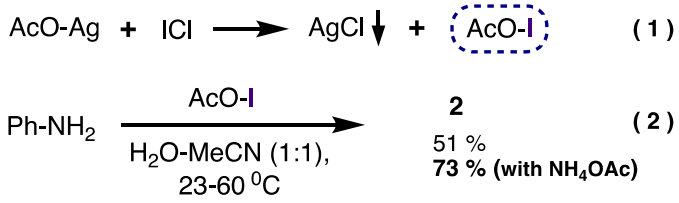


Figure 3.2. Indirect identification of AcO-I by the reaction of PIDA and NH_4I in CD_3CN-D_2O (1:1). Water signal suppression for experiments A-E.

All the spectra in the study were obtained in **CD_3CN-D_2O (1:1).** We started by the acquisition of the ^1H spectrum of the commercially available PIDA **(Figure 3.2).** Next, according with our iodination conditions we mixed 1 equivalent of PIDA with 1.5 equivalents of ammonium iodide. After 2 minutes, the spectrum showed the fully consumption of PIDA in a very fast reaction. Also, all the phenyl ring signals shifted to high field by around 0.5 ppm. Additionally, one singlet overlapped with the residual signal of the **CD_3CN** at d 1.94 ppm, which was assigned to a methyl group was putatively attributed to the AcO-I formation **(Figure 3.2B)**.

The following two spectra corresponding to 4 and 6 minutes showed the same profile (**Figures 3.2C** and **3.2D**). Starting from PIDA and NH_4I, the AcO-I synthesis implies necessarily the iodobenzene (Ph-I) formation. Therefore, the ^1H NMR of the commercial Ph-I was obtained (**3.2 Figures E and F**). This spectrum (**Figure 3.2E**) matches perfectly with those obtained at 2, 4 and 6 minutes (**Figures 3.2B-D**), confirming the Ph-I formation as result of the reaction between PIDA and ammonium iodide, and in consequence the AcO-I formation. Even though these spectroscopic results match with those reported by Lusztyk, we considered an indirect identification of the AcO-I, based on the overlapping with deuterated solvent and since the HRMS analysis did not show the corresponding molecular peak. However, the Ph-I formation as the sole product involves the AcO-I production.

Finally, to confirm the AcO-I as the iodinating species in our protocol, we synthesized it using the AcOAg/ICl system and carried out an iodination reaction with aniline in our solvent system MeCN-H_2O (1:1) (Eq.1 and 2).



This way, an equimolar amount of silver acetate and iodine monochloride were mixed at 0 ^0C either.

Precaution of AgCl indicate the acetyl hypoiodite formation. Then a 1:1 MeCN-H_2O mixture was added followed by aniline. In one experiment the reaction was carried out directly after the ACO-I formation and in a second experiment, one equivalent of aniline and one equivalent of NH4OH were added according to stoichiometry of procedure (see fig.3.2) delight we observed the iodination of aniline to get 2 in both experiments . it was obtained a 51% yield in the experiment only with the prepared ACO-I and 73% yield using ammonium acetate. The former result is very close to the obtained (76%, see scheme 2.3 A) by mixing PIDA/NH4I. This indicate that ammonium acetate plays important role as additive, assisting and favoring the iodination step, such as it is described (TS3) in our theoretical calculations.

This set of theoretical and experimental results of the mechanistic study confirm that the acetyl hypoiodite is the halogenating species in our developed iodination procedure and the ammonium cation is key for increasing the yield.

In fact, it is acting as a catalyst due to its regeneration once the iodination process has been completed. This set of theoretical and experimental results of the mechanistic study confirms that the acetyl hypoiodite is the halogenating species in our developed iodination procedure and that the ammonium cation is key for increasing the yield, catalyzing the AcO-I formation and the iodination step.

Finally, considering all the mechanistic and experimental evidence we postulated the reaction mechanism for this process (Figure 3).

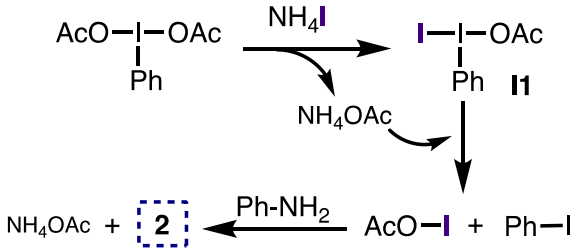
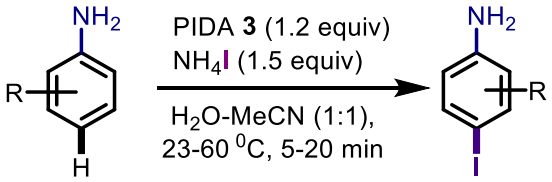


Figure 3.3 Reaction mechanism for the iodination of free-anilines using the PIDA/NH4I system (illustration with aniline to get 4-iodoaniline)

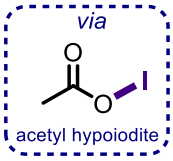
Figure 3.3 Reaction mechanism for the iodination of free-anilines using the PIDA/NH4I system (illustration with aniline to get 4-iodoaniline). The reaction started by the ligand exchange between PIDA and NH4I to get intermediate I1 with concomitant release of ammonium acetate. Then, I1 evolves in less than two minutes to form acetyl hypoiodite (AcO-I) and iodobenzene via reductive elimination catalyzed by ammonium acetate. Final iodination of aniline with AcO-I, as the halogenating species, gives rise to the observed iodinated products with the regeneration of ammonium acetate.

3.5 Conclusions.

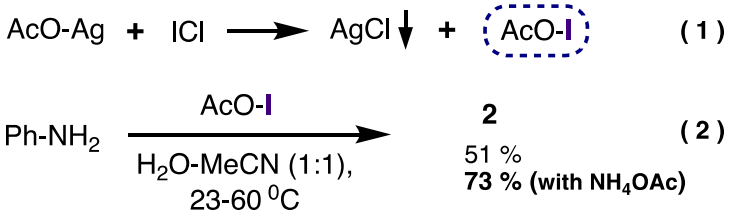
In summary, we have developed a metal-free, mild, non-toxic and in general an operationally simple protocol for the *para*-selective iodination of free anilines under mineral- and Brønsted-acid-free conditions.



The theoretical and experimental results on the reaction mechanism confirmed that the halogenating species of our process is acetyl hypoiodite (AcO-I) which is formed *in situ* in less than 2 minutes by reacting PIDA and ammonium iodide.



This species is stable in water and reacted as a soft electrophile exclusively at the C-4 of the aniline core. Ammonium cation assisted the AcO-I formation but also it was important to favor the aromatic iodination step and therefore, the chemical yield of reaction.

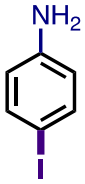


The use of this new methodology allowed us the development of the first iodination protocol of free anilines under very mild conditions.

General Procedure for Iodination.

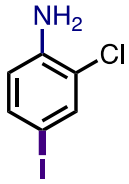
A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with the corresponding anilines (0.5 mmol, 1 equiv) and MeCN-H_2O (1:1) at 23 °C. After dissolving and obtaining a homogeneous mixture, NH_4I (0.8 mmol, 1.5 equiv) was added and stirred for 2 min. Then PIDA (0.6 mmol, 1.2 equiv) was added and stirred at 25 °C until full consumption of the starting material (usually 5 min to 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.

4-Iodo-aniline



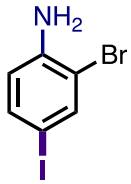
The following compound was obtained according to the general procedure for iodination using aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **4-Iodo-aniline** (89 mg, 75%) gram scale (740 mg, 31%), as a light-yellow solid. The reaction time for this example was 10 min. R_f = 0.65 (1% EtOAc/Hexane). m.p. = 59−61 °C. Rf = 0.65 (10 % EtOAc/Hexane). IR (neat) ν/cm^{-1}= 3398, 3192, 1610, 1475, 1275. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 3.67 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 138.6, 117.4, 79.5. HRMS (ESI+): m/z calcd. for C_6H_7IN $[M+H]^+$ = 219.9623, found 219.9614.

2-chloro-4-iodoaniline



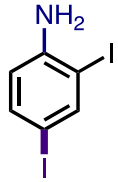
The following compound was obtained according to the general procedure for iodination using 2-chloro aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **2-chloro-4-iodoaniline** (43 mg, 43%) as a white solid. The reaction time for this example was 20 min. R_f = 0.5 (1% EtOAc/Hexane). m.p. = 69−70 °C. IR (neat) ν/cm^{-1}= 3427, 3337, 1600, 1469, 810. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.7 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 4.07 (bs, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 142.8, 137.3, 136.7, 120.7, 117.5, 78.8. HRMS (ESI+): m/z calcd. for C_6H_6INCl $[M+H]^+$ = 253.9233, found 253.9224.

2-bromo-4-iodoaniline



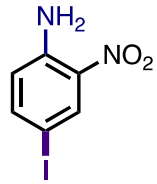
The following compound was obtained according to the general procedure for iodination using 2-bromo aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **2-bromo-4-iodoaniline** (68 mg, 42%) as a brown solid. The reaction time for this example was 20 min. R_f = 0.5 (1 % EtOAc/Hexane). m.p. = 82−85 °C. IR (neat) ν/cm^{-1} 3392, 3298, 1604, 1469, 1390, 1305. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 1.8 Hz, 1H), 7.35 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 4.12 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) 144.1, 140.3, 137.1, 117.5, 110.6, 78.5. HRMS (ESI+): m/z calculated for C_6H_6INBr [M + H]+ = 297.8728, found 297.8685.

2,4-diiodoaniline



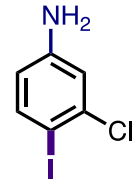
The following compound was obtained according to the general procedure for iodination using 2-iodo aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (1% EtOAc/Hexane) to afford **2,4-diiodoaniline** (43 mg, 54%) as a light pink solid. The reaction time for this example was 20 min. R_f = 0.4 (2 % EtOAc/Hexane). m.p. = 93−95 °C. IR (neat) ν/cm^{-1}= 3373, 3282, 1619, 1455, 1369, 1284. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 4.12 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 145.9, 138.4, 116.8, 84.9, 79.8. HRMS (ESI+): m/z calcd. for $C_6H_6NI_2$ $[M+H]^+$ = 345.8590, found 345.8566.

4-iodo-2 nitroaniline



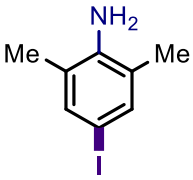
The following compound was obtained according to the general procedure for iodination using 2-nitro aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford **4-iodo-2 nitroaniline** (63 mg, 65%) as orange solid. The reaction time for this example was 48 hours and double amount of each reagent were used. R_f = 0.5 (10 % EtOAc/Hexane). m.p. = 125−126 °C. IR (neat) ν/cm^{-1}= 3481, 3373, 1614, 1484, 1325 ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.56 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.10 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 143.8, 134.4, 133.4, 120.7, 76.4. HRMS (ESI+): m/z calcd. for $C_6H_6O_2N_2I$ $[M+H]^+$ = 264.9474, found 264.9445.

3-chloro-4-iodoaniline



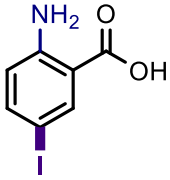
The following compound was obtained according to the general procedure for iodination using 3-chloro aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **3-chloro-4-iodoaniline** (45 mg, 45%) as a white solid. The reaction time for this example is 15 min. R_f = 0.5 (1% EtOAc/Hexane). m.p. = 61−63 °C. IR (neat) ν/cm^{-1}= 3332, 1610, 1455, 995, 850, 806. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.32 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.76 (bs, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 147.8, 140.6, 138.9, 115.8, 115.8, 82.7. HRMS (ESI+): m/z calcd. for C_6H_6INCl $[M+H]^+$ = 253.9233, found 253.9224.

4-Iodo-2,6-dimethylaniline



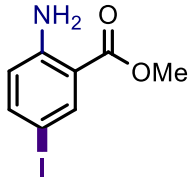
The following compound was obtained according to the general procedure for iodination using aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **4-Iodo-2,6-dimethylaniline** (64 mg, 62 %) as a brown solid. The reaction time for this example was 10 min. R_f = 0.65 (4% EtOAc/Hexane). m.p. = 36−38 °C. Rf = 0.55 (2 % EtOAc/Hexane). IR (neat) ν/cm^{-1}= 3412, 2901, 1625, 1456, 730.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.24 (s, 2H), 3.43 (s, 2H), 2.13 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 136.6, 124.5, 79.4, 17.8. HRMS (ESI+): m/z calcd. for $C_8H_{11}IN$ $[M+H]^+$ = 247.9936, found.247.9937

2-amino-5-iodobenzoic acid.



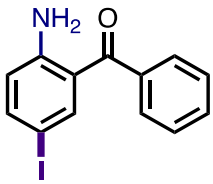
The following compound was obtained according to the general procedure for iodination using aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford **2-amino-5-iodobenzoic acid.** (65 mg, 67 %) as a light-yellow solid. The reaction time for this example was 10 min. R_f = 0.65 (10% EtOAc/Hexane). m.p. = 188−190 °C. IR (neat) ν/cm^{-1}= 3500, 3385, 1658, 1219, 809. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 2H), 7.92 (s, 1H), 7.47 – 7.41 (m, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 2.50 (d, *J* = 2.4 Hz, 1H).^{13}C NMR (126 MHz, DMSO) δ 168.9, 150.8, 141.9, 138.8, 119.2, 112.0, 74.1. HRMS (ESI+): m/z calcd. for $C_7H_7INO_2$ $[M+H]^+$ = 263.9521, found. 263.9510

Methyl 2-amino-5-iodobenzoate.



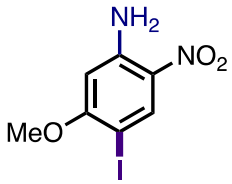
The following compound was obtained according to the general procedure for iodination using aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford **Methyl 2-amino-5-iodobenzoate.** (58 mg, 63 %) as a white solid. The reaction time for this example was 10 min. R_f = 0.65 (15% EtOAc/Hexane). m.p. = 84−86 °C. IR (neat) v/cm^{-1}= 3470, 3385, 1658, 1219, 809. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 2H), 7.92 (s, 1H), 7.47 – 7.41 (m, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 2.50 (d, *J* = 2.4 Hz, 1H).^{13}C NMR (126 MHz, DMSO) δ 168.9, 150.8, 141.9, 138.8, 119.2, 112.0, 74.1. HRMS (ESI+): m/z calcd. for $C_8H_9INO_2$ $[M+H]^+$ = 277.9678, found.277.9676

(2-amino-5-iodophenyl)(phenyl)methanone.



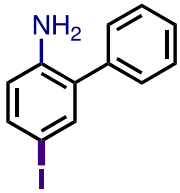
The following compound was obtained according to the general procedure for iodination using (2-aminophenyl)(phenyl)methanone as starting material. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford **(2-amino-5-iodophenyl)(phenyl)methanone** (62 mg, 75%) as a yellow solid. The reaction time for this example was 20 min. R_f = 0.5 (5 % EtOAc/Hexane). m.p. 102-104°C. IR (neat) v/cm^{-1} = 3423, 3314, 2922, 1610, 1237, 1143. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.58 –7.41 (m, 5H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.04 (bs, 2H). ^{13}C NMR δ 197.9, 150.6, 142.3, 139.4, 131.7, 129.3, 128.7, 128.7, 120.6, 119.5, 75.9. HRMS (ESI+): m/z calcd. for $C_{13}H_{11}INO$ $[M+H]^+$= 323.9885, found 323.9884.

4-iodo-5-methoxy-2-nitroaniline



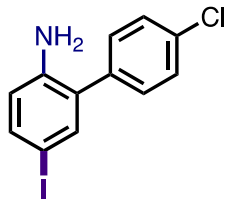
The following compound was obtained according to the general procedure for iodination using 5-methoxy-2-nitroaniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/Hexane) to afford **4-iodo-5-methoxy-2-nitroaniline** (57 mg, 65%) as a yellow solid. The reaction time for this example was 24 h and double amount of each reagent were used. R_f = 0.4 (8% EtOAc/Hexane). m.p. = 165−170 °C. IR (neat) ν/cm^{-1} = 3447, 3373,1305, 835, 650. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 6.25 (s, 2H), 6.11 (s, 1H), 3.90 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 146.9, 137.2, 127.9, 97.8, 71.4, 56.9. HRMS (ESI+): m/z calcd. for $C_7H_8O_3N_2I$ $[M+H]^+$= 294.9580, found 294.9607.

5-iodo-[1,1'-biphenyl]-2-amine



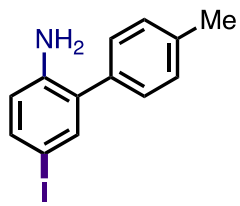
The following compound was obtained according to the general procedure for iodination using [1,1'-biphenyl]-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **5-iodo-[1,1'-biphenyl]-2-amine** (57 mg, 65%) as a red color liquid. The reaction time for this example was 20 min. R_f = 0.65 (5% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3380, 2921, 1607, 1477, 810,) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 3.8 Hz, 2H), 7.42–7.40 (m, 2H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.36 (t, *J* = 7.1 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 3.81 (bs, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 138.7, 138.5, 137.9, 130.3, 129.9, 129.1, 127.8, 117.8, 79.9. HRMS (ESI+): m/z calcd. for $C_{12}H_{11}IN$ $[M+H]^+$ = 295.9636, found 295.9940.

4'-chloro-5-iodo-[1,1'-biphenyl]-2-amine



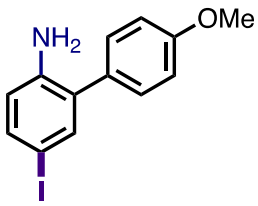
The following compound was obtained according to the general procedure for iodination using 4'-chloro[1,1'biphenyl]-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford **4'-chloro-5-iodo-[1,1'-biphenyl]-2-amine** (57 mg, 54%) as a yellow solid. The reaction time for this example was 20 min. R_f = 0.5 (5% EtOAc/Hexane). m.p. = 96−98 °C. IR (neat) ν/cm^{-1}= 3472, 3378, 1606, 1475, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.5, 2.1 Hz, 3H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 1H), 3.67 (bs, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 138.5, 137.4, 136.8, 133.9, 130.9, 129.8, 128.8, 117.8, 79.7. HRMS (ESI+): m/z calcd. for $C_{12}H_{10}ClIN$ $[M+H]^+$= 329.9546, found 329.9559.

5-iodo-4'-methyl-[1,1'-biphenyl]-2-amine



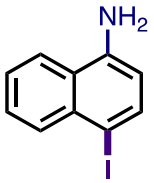
The following compound was obtained according to the general procedure for iodination using 4'-mehtyl[1,1'biphenyl]-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (4% EtOAc/Hexane) to afford **5-iodo-4'-methyl-[1,1'-biphenyl]-2-amine** (45 mg, 53%) as a red color liquid. The reaction time for this example was 20 min. R_f = 0.4 (2% EtOAc/Hexane). IR (neat) ν/cm^{-1}= 3377, 1610, 1481, 1290, 1265. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 8.2 Hz, 1H), 3.36 (bs, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 138.7, 137.5, 136.8, 135.3, 130.7, 129.7, 128.8, 117.6, 79.6, 21.4 HRMS (ESI+): m/z calcd. for $C_{12}H_{10}ClIN$ $[M+H]^+$ = 310.0093, found 310.0106.

5-iodo-4'-methoxy-[1,1'-biphenyl]-2-amine



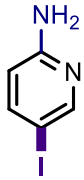
The following compound was obtained according to the general procedure for iodination using 4'-mehtoxy[1,1'-biphenyl]-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (10% EtOAc/Hexane) to afford **5-iodo-4'-methoxy-[1,1'-biphenyl]-2-amine** (41 mg, 50%) as yellow color solid. The reaction time for this example was 20 min. R_f = 0.6 (15% EtOAc/Hexane). IR (neat) ν/cm^{-1}= 3472, 3377, 1610, 1513, 1245. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.41–7.36 (m, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.54 (d, *J* = 7.9 Hz, 1H), 3.86 (s, 3H), 3.63 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 143.4, 138.7, 136.7, 130.3, 130.4, 129.9, 117.7, 114.7, 79.7, 55.7. HRMS (ESI+): m/z calcd. for $C_{12}H_{10}ClIN$ $[M+H]^+$= 326.0042, found 326.0061.

4-iodonaphthalen-1-amine



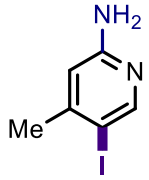
The following compound was obtained according to the general procedure for iodination using naphthalen-1-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (2% EtOAc/Hexane) to afford **4-iodonaphthalen-1-amine** (19 mg, 20%) as red color solid. The reaction time for this example was 20 min. R_f = 0.5 (4% EtOAc/Hexane). IR (neat) ν/cm^{-1}= 2919, 2850, 1593, 1384,755. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.78 (m, 1H), 7.78–7.74 (m, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.52–7.42 (m, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 4.70 (bs, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9, 135.8, 134.7, 128.7, 126.8, 125.8, 123.5, 121.6, 120.5, 79.3 HRMS (ESI+): m/z calcd. for $C_{10}H_9IN$ $[M+H]^+$ = 269.9780, found 269.9770.

5-iodopyridine-2-amine.



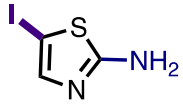
The following compound was obtained according to the general procedure for iodination using pyridine-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford **5-iodopyridine-2-amine.** (80 mg, 68 %) as a Brown solid. The reaction time for this example was 10 min. R_f = 0.55 (20% EtOAc/Hexane). m.p. = 126−128 °C. IR (neat) ν/cm^{-1}= 3385, 3124, 1632, 1580, 819. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.62 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 4.44 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 153.7, 145.5, 111.6, 77.9. . HRMS (ESI+): m/z calcd. for $C_5H_6IN_2$ $[M+H]^+$ = 220.9576, found. 220.9574

5-iodo-4-methylpyridin-2-amine.



The following compound was obtained according to the general procedure for iodination using 4-methylpyridine-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford **5-iodo-4-methylpyridin-2-amine.** (67 mg, 61 %) as a Brown solid. The reaction time for this example was 10 min. R_f = 0.55 (20% EtOAc/Hexane). m.p. = 106−108 °C. IR (neat) ν/cm^{-1}= 3420, 3148, 1639, 1269, 851. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 6.48 (s, 1H), 5.21 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 153.6, 152.4, 110.6, 85.8, 27.3. HRMS (ESI+): m/z calcd. for $C_6H_8IN_2$ $[M+H]^+$ = 234.9732, found.234.9723

5-iodothiazol-2-amine



The following compound was obtained according to the general procedure for iodination using , thiazol-2-amine as starting material. The crude material was purified by flash column chromatography over silica gel with the system (5 % EtOAc/Hexane) to afford **5-iodothiazol-2-amine** (68 mg, 60%), as brown color solid. The reaction time for this example was 20 min. R_f = 0.5 (10% EtOAc/Hexane). IR (neat) ν/cm^{-1}= 2919, 2850, 1593, 1384, 755. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (s, 1H), 5.22 (bs, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 146.9, 55.8. HRMS (ESI+): m/z calcd. for $C_{10}H_9IN$ $[M+Na]^+$= 248.8959, found 248.8949.

[1,1'-biphenyl]-2-amine is commercially available. 4-aminobiphenyl,[1] 4'-chloro-[1,1'biphenyl]-2-amine,[8] 4'-mehtyl [1,1'biphenyl]-2-amine[8] and 4'-mehtoxy [1,1'-biphenyl]-2-amine[8] were synthesized according to the procedures previously described.

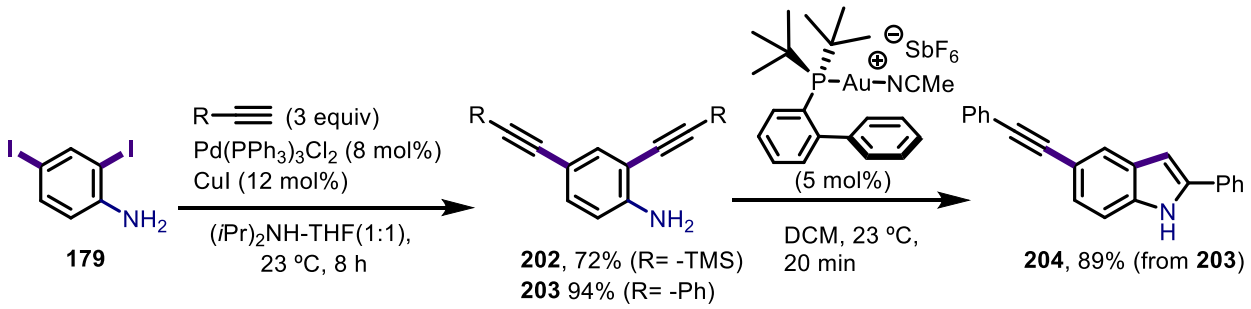
4-aminobiphenyl. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 8.2 Hz, 4H), 7.18 – 7.10 (m, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 3.60 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 141.9, 131.7, 128.9, 128.4, 126.5, 126.8, 115.5.

4'-chloro-[1,1'biphenyl]-2-amine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, *J* = 2.0 Hz, 4H), 7.18 (td, *J* = 8.0, 1.5 Hz, 1H), 7.11 (d, *J* = 1.2 Hz, 1H), 6.84 (t, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.73 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 138.2, 133.5, 130.6, 130.7, 129.2, 128.9, 126.5, 119.1, 115.9.

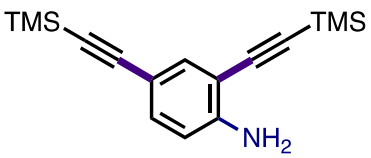
4'-mehtyl [1,1'biphenyl]-2-amine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.11 – 7.03 (m, 2H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 3.50 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 136.9, 136.6, 130.8, 129.6, 129.7, 128.4, 127.8, 118.8, 115.7, 21.3.

Synthetic Utility of the Synthesized Iodoanilines

General route of synthesis

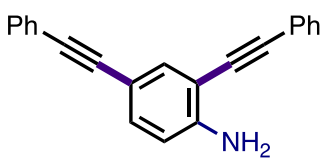


2,4-bis((trimethylsilyl)ethynyl)aniline



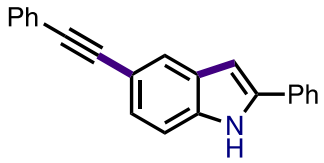
A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2,4-diiodoaniline (130 mg, 0.376 mmol, 1 equiv) and ethynyltrimethylsilane (0.156 mL, 1.13 mmol, 3 equiv) in 2 mL of (*i*-Pr)$_2$NH and 2 mL of THF. Then Cu(I) (8.4 mg, 12 mol%) and $(Ph_3P)_2PdCl_2$ (20.8 mg, 8 mol%) were added under the nitrogen atmosphere. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/hexane) to afford **2,4-bis((trimethylsilyl)ethynyl)aniline** (78 mg, 72%) as a white solid m.p. = 80−82 °C IR (neat) ν/cm^{-1}= 2953, 2144, 1735, 1249, 955. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 4.38 (bs, 2H), 0.25 (s, 9H), 0.21 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 136.9, 133.6, 113.9, 112.2, 107.8, 105.3, 100.9, 100.4, 91.7, 0.3, 0.2. HRMS (ESI+): m/z calcd. for $C_{16}H_{24}NSi_2$ $[M+H]^+$ = 286.1447, found 286.1442.

2,4-bis(phenylethynyl)aniline



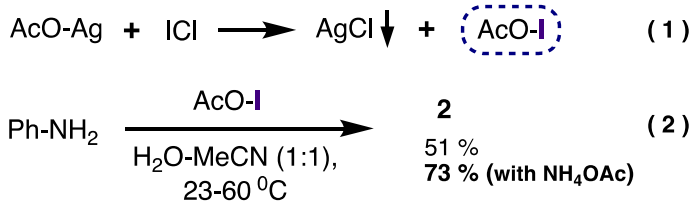
A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2,4-diiodoaniline (130 mg, 0.376 mmol, 1 equiv) and phenylacetylene (0.124 mL, 1.13 mmol, 3 equiv) in 2 mL of $(i\text{-Pr})_2NH$ and 2 mL of THF. Then CuI (8.4 mg, 12 mol%) and $(Ph_3P)_2PdCl_2$ (20.8 mg, 8 mol%) were added. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/hexane) to afford **2,4-bis(phenylethynyl)aniline** (105 mg, 94%) as a white solid. m.p. = 142−144 °C. IR (neat) ν/cm^{-1}= 3472, 3375, 2204, 1612, 1500. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.56–7.48 (m, 4H), 7.38–7.29 (m, 7H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.45 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 135.6, 133.4, 131.6, 131.5, 128.7, 128.5(x2), 127.9, 123.8, 123.5, 114.3, 112.5, 108.3, 95.2, 89.9, 87.6, 85.6. HRMS (ESI+): m/z calcd. for $C_{22}H_{16}N_1[M+H]^+$= 294.1283, found 294.1284

2-phenyl-5-(phenylethynyl)-1*H*-indole



A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2,4-bis(phenylethynyl)aniline **2-phenyl-5-(phenylethynyl)-1*H*-indole** (60 mg, 0.204 mmol, 1 equiv) and dissolved in 2 mL of dry DCM. Then gold(I) catalyst **C1** (7.8 mg, 0.0102 mmol, 5 mol%) was added to the solution. The reaction was completed after 20 minutes. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/hexane) to afford the corresponding indole derivative **184** (53.5 mg, 89%) as a light brown solid. m.p = 220-222 °C. IR (neat) ν/cm^{-1}= 3425, 2208, 1486, 1300, 891. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.85 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.56 (d, *J* = 7.1 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.40–7.28 (m, 6H), 6.82 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 136.6, 132.1, 131.6, 129.3, 129.2, 128.4, 128.2, 127.9, 126.2, 125.4, 124.6, 124.1, 115.0, 111.1, 100.2, 91.1, 87.3. HRMS (ESI+): m/z calcd. for $C_{22}H_{16}N_1[M+H]^+$= 294.1283, found 294.1278.

1. Experiment of AcO-I formation using AcOAg/ICl and reaction with aniline



Procedure From AcOAg/ICl.

A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with silver acetate (202 mg, 1.2 mmol) in 2 mL of ether and added iodine monochloride (196 mg, 0.06 mL, 1.2 mmol). After the precipitation of silver acetate, 2 mL of MeCN-H_20 (1:1) was added followed by aniline (100 mg, 0.1 mL, 1.1 mmol). The reaction was stirred at room temperature for 10 minutes. After the fully consumption of the starting material the reaction was stopped. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/hexane) to afford (120 mg, 51%) of a brown solid which correspond to 4-iodoaniline **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 2H).

Procedure From AcOAg/ICl with NH_4OAc.

A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with silver acetate (202 mg, 1.2 mmol) in 2 mL of ether and added iodine monochloride (196 mg, 0.06 mL, 1.2 mmol). After the precipitation of silver acetate, 2 mL of MeCN-H_20 (1:1) containing ammonium acetate (77 mg, 1.0 mmol) was added followed by aniline (100 mg, 0.1 mL, 1.1 mmol). The reaction was stirred at room temperature for 10 minutes. After the fully consumption of the starting material the reaction was stopped. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/hexane) to afford (173 mg, 73%) of a brown solid which correspond to 4-iodoaniline **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 2H).

Computational Methodology

All the gas-phase theoretical calculations were performed using the Gaussian 09 rev. C.01 program.[1] First, we carried out geometry optimizations, with no restrictions, using the range-divided ωB97X-D[2] density functional in combination with the Ahlrichs' basis set def2-SVPP. [3] 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.

Also, we performed calculations for including the solvent effect through the PCM model[4] using the SMD parameters[5] according to the Truhlar's model using water (ε = 80.4) as solvent. These calculations were performed as single points of the optimized geometry at the level of theory mentioned above. 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.

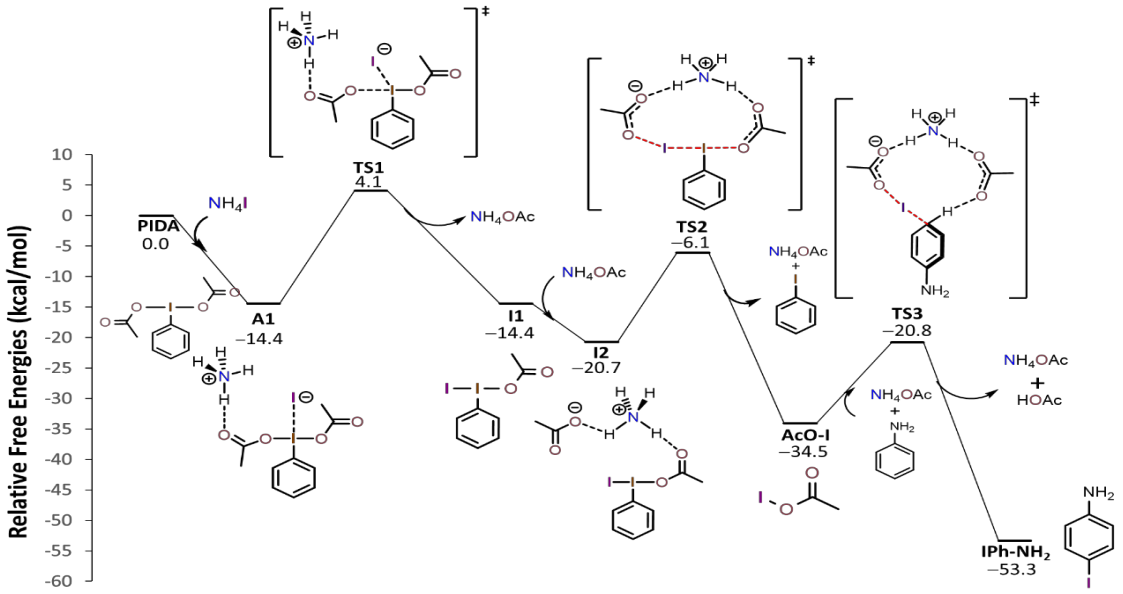


Figure S1. Proposed favorable reaction mechanism for the Iodination of aniline via hypoiodite intermediate calculated at the (SMD:water)ωB97X–D/def2-SVPP.

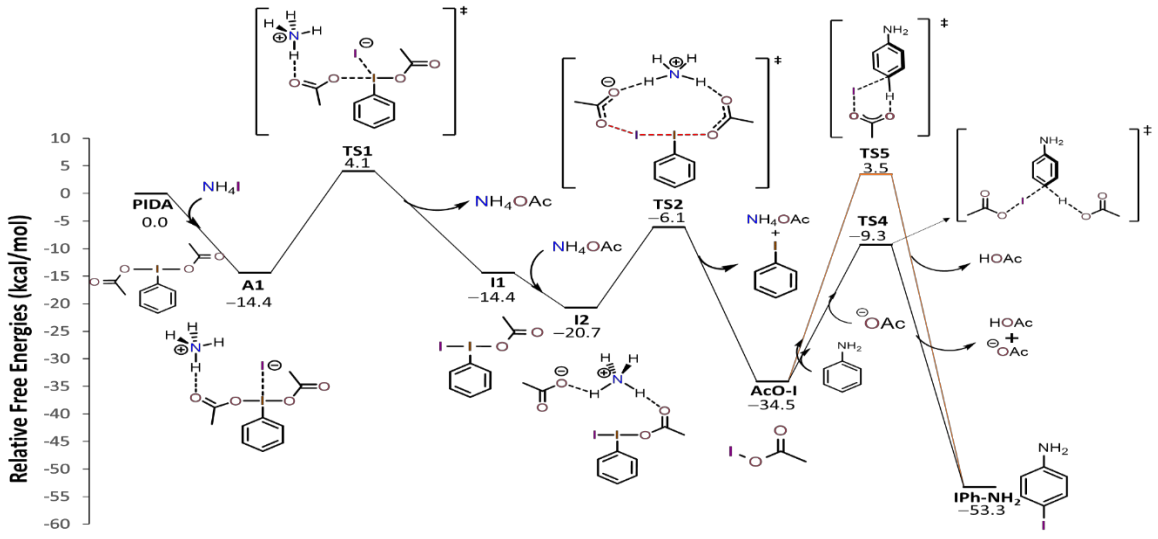


Figure S2. Energy profile of the Iodination of aniline via hypoiodite without ammonia cation calculated at (SMD:water)ωB97X–D/def2-SVPP.

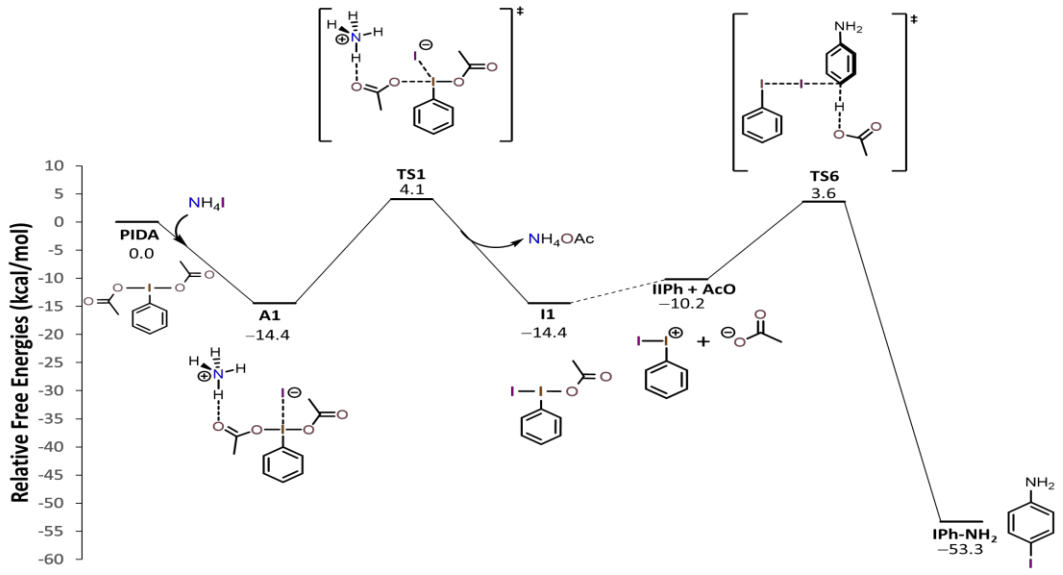


Figure S3. Energy profile of the Iodination of aniline via dissociation of **I1** calculated at (SMD:water)ωB97X–D/def2-SVPP.

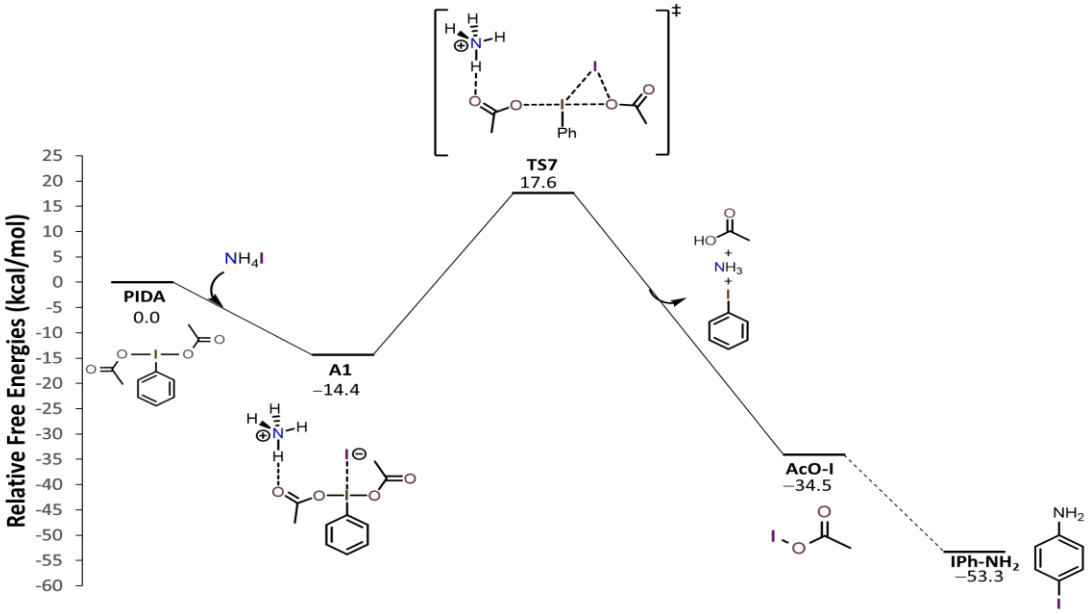


Figure S4. Energy profile of the generation of hypoiodite via de concerted pathway calculated at the (SMD:water)ωB97X–D/def2- SVPP.

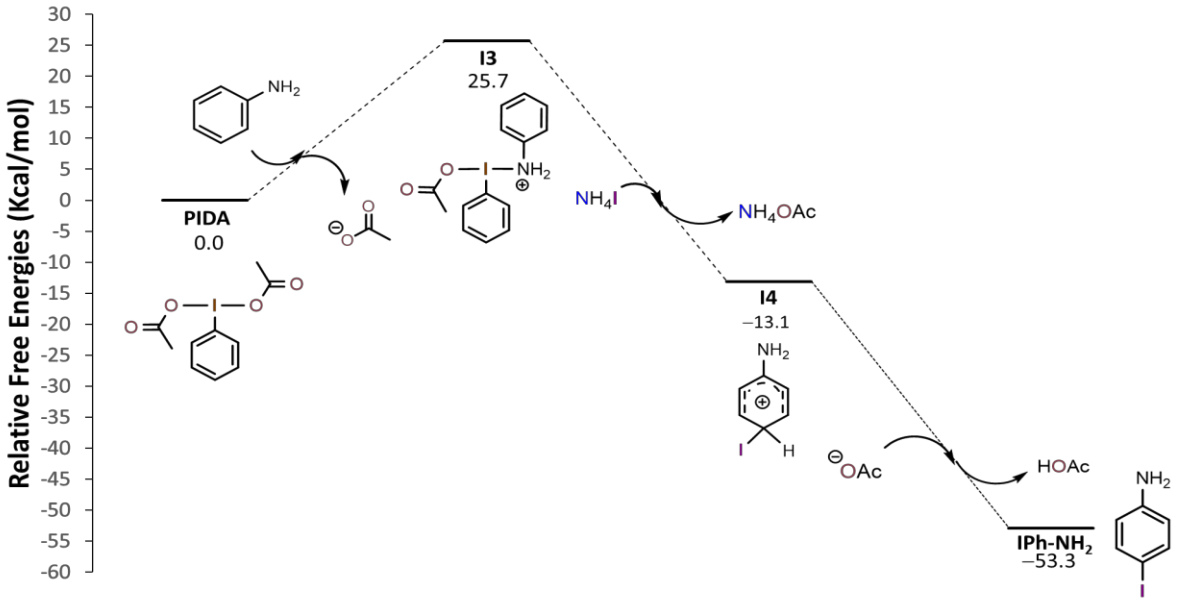
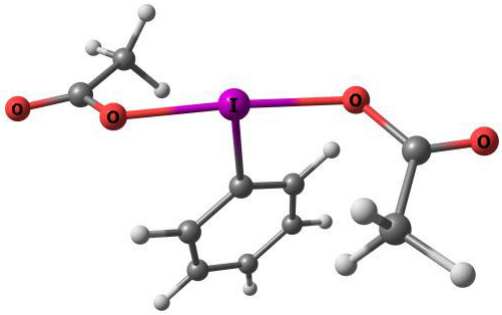


Figure S5. Energy profile of the Iodination of aniline via intermediate of **I3** calculated at (SMD:water)ωB97X–D/def2-SVPP.

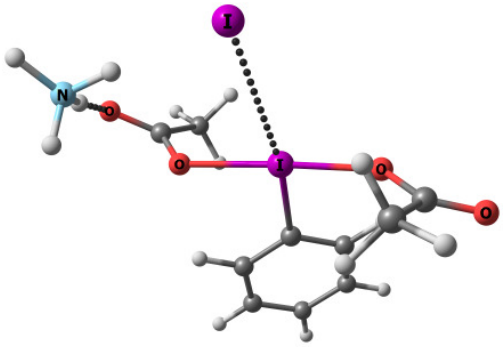
Table S1. Cartesian coordinates (in x–y–z format) of all the optimized structures involved in the reaction mechanisms calculated at the ωB97X-D/def2-SVPP level



PIDA

E(scf) = –985.5315598 a.u

C	0.849057	3.103191	0.860031
C	0.860088	1.707601	0.869223
C	–0.000153	1.044780	0.000013
C	–0.860621	1.707363	–0.869158
C	–0.850082	3.102954	–0.859861
C	–0.000632	3.798796	0.000107
H	1.513834	3.645710	1.537454
H	1.528485	1.155665	1.533859
H	–1.528831	1.155239	–1.533825
H	–1.515060	3.645279	–1.537242
H	–0.000831	4.892049	0.000162
I	0.000156	–1.087721	–0.000014
O	1.980721	–1.003004	0.691876
O	–1.980390	–1.003515	–0.691906
C	3.090223	–0.720270	–0.005418
O	4.146301	–0.638149	0.559760
C	–3.089951	–0.720872	0.005353
O	–4.145931	–0.638392	–0.559946
C	2.940745	–0.503755	–1.500999
H	2.468350	–1.372479	–1.990871
H	2.315450	0.383198	–1.708266
H	3.936890	–0.343322	–1.936123
C	–2.940625	–0.504956	1.501028
H	–2.468179	–1.373828	1.990586
H	–2.315434	0.381976	1.708691
H	–3.936822	–0.344780	1.936127

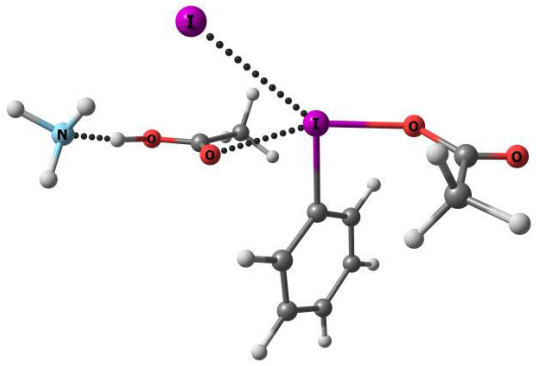


A1

E(scf) = –1340.4468889 a.u

C	4.137137	–1.713499	1.004541
C	2.783568	–1.411414	0.849459
C	2.431836	–0.298603	0.088700
C	3.385703	0.519090	–0.511203
C	4.734621	0.200847	–0.341456
C	5.111254	–0.910634	0.411180
H	4.427571	–2.583123	1.600955
H	2.018157	–2.037763	1.312242
H	3.087363	1.398380	–1.087602
H	5.494156	0.835916	–0.805632
H	6.170261	–1.150029	0.540456
I	0.347843	0.204461	–0.146039
O	–0.150870	–1.896725	0.413602
O	0.963488	2.088631	–0.692123
C	–0.323617	–2.888232	–0.405336
O	–1.191895	–3.734235	–0.183764
C	0.955129	3.199853	0.079997
O	1.614009	4.138632	–0.265828
C	0.544607	–2.983350	–1.636259
H	0.207963	–2.232646	–2.373858
H	1.600739	–2.774661	–1.399227
H	0.443767	–3.980243	–2.087552
C	0.091246	3.182742	1.320967
H	–0.945186	2.883813	1.082781
H	0.487224	2.467724	2.063774
H	0.095579	4.187807	1.764894
N	–2.890572	–2.447441	1.392664
H	–2.223563	–3.066896	0.800879
H	–2.970678	–1.494475	0.911948
H	–3.823055	–2.863073	1.480244

H	–2.480478	–2.299549	2.319837
I	–3.071287	0.619873	–0.140969

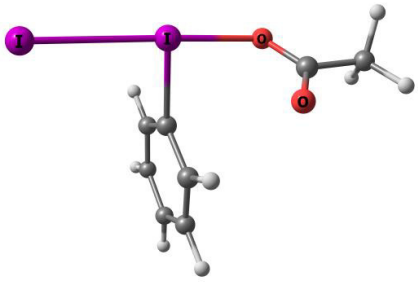


TS1

E(scf) = –1340.4247127 a.u

ν_{min} = –87.30 cm^{-1}

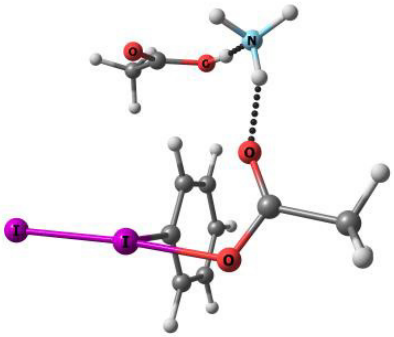
C	–2.317252	2.626016	1.843510
C	–1.457161	1.592538	1.475234
C	–1.667686	0.962712	0.252671
C	–2.703307	1.318749	–0.604475
C	–3.552903	2.357843	–0.217943
C	–3.360672	3.009411	0.999252
H	–2.169329	3.132209	2.801340
H	–0.630847	1.300248	2.126629
H	–2.867719	0.788701	–1.545912
H	–4.372866	2.651584	–0.878843
H	–4.032573	3.819283	1.295781
I	–0.423693	–0.686765	–0.304235
O	1.054959	1.524632	–0.044222
O	–2.221329	–1.613357	–0.945025
C	1.417905	2.275610	–0.951290
O	2.491027	2.992530	–0.865418
C	–3.144913	–2.186057	–0.151931
O	–4.159380	–2.585401	–0.652211
C	0.668764	2.397028	–2.251685
H	0.932943	3.329231	–2.770974
H	0.953248	1.546050	–2.896166
H	–0.417205	2.350138	–2.074916
C	–2.852152	–2.286723	1.331118
H	–1.908125	–2.825229	1.520652
H	–2.766172	–1.282278	1.782081
H	–3.680057	–2.823555	1.814573
N	3.801470	2.079698	1.165816
H	3.563550	1.081177	1.069570
H	3.456840	2.389756	2.076296
H	4.819563	2.166611	1.162143
H	3.049218	2.706502	–0.002663
I	2.611491	–1.385656	0.230045



I1

E(scf) = –1055.1235960 a.u

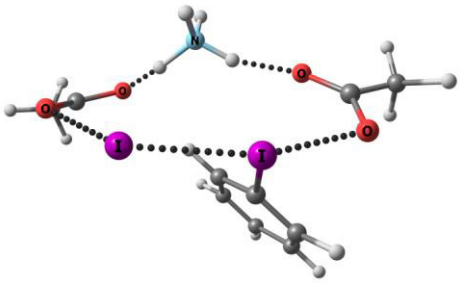
C	-1.513719	2.949847	1.132172
C	-1.250424	3.806871	0.064227
C	-0.659932	3.318935	-1.102223
C	-0.324552	1.970116	-1.207425
C	-0.596811	1.139211	-0.123860
C	-1.186636	1.595621	1.050673
H	-1.978610	3.332591	2.044599
H	-1.506728	4.867008	0.141350
H	-0.454019	3.990802	-1.939767
H	0.147956	1.585839	-2.114362
H	-1.413229	0.909441	1.868477
I	-0.080220	-0.903264	-0.268903
I	2.653394	-0.260123	0.205316
O	-2.178485	-1.282009	-0.771532
C	-3.012731	-1.302435	0.243031
O	-2.701858	-1.062926	1.392367
C	-4.425643	-1.653362	-0.176567
H	-4.793437	-0.904779	-0.897588
H	-4.433821	-2.631176	-0.685042
H	-5.080881	-1.679564	0.705628



I2

E(scf) = –1340.4745018 a.u.

C	–0.408458	–0.457039	3.555943
C	–1.660433	0.101594	3.294565
C	–2.053447	0.379866	1.985346
C	–1.195488	0.103984	0.919284
C	0.044604	–0.452036	1.212166
C	0.464052	–0.743924	2.506929
H	–0.103221	–0.673317	4.583343
H	–2.339920	0.322149	4.122472
H	–3.035321	0.808927	1.767366
H	–1.492995	0.319850	–0.109330
H	1.444614	–1.183593	2.702629
I	1.331331	–0.926447	–0.388485
I	2.477595	1.652887	–0.318323
O	0.473103	–2.973246	–0.236195
C	–0.754141	–3.119046	–0.640734
O	–1.433120	–2.217840	–1.108506
C	–1.286029	–4.524339	–0.446758
H	–0.551152	–5.266014	–0.796535
H	–1.445156	–4.698017	0.631163
H	–2.240043	–4.646689	–0.979393
N	–3.812224	–0.627114	–1.793380
H	–4.627340	–1.146798	–2.122199
H	–3.405030	–0.128768	–2.588883
H	–4.048849	0.593231	–0.810267
H	–3.099505	–1.299580	–1.477861
O	–4.115744	1.476700	–0.253963
C	–3.242473	2.350428	–0.720257
O	–2.483127	2.116563	–1.637565
C	–3.249192	3.654628	0.041386
H	–4.280276	3.979752	0.251137
H	–2.740847	3.502652	1.010005
H	–2.705349	4.422604	–0.526524

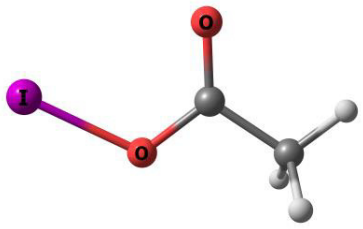


TS2

E(scf) = –1340.4450389 a.u.

ν_{min} = –148.57 cm^{-1}

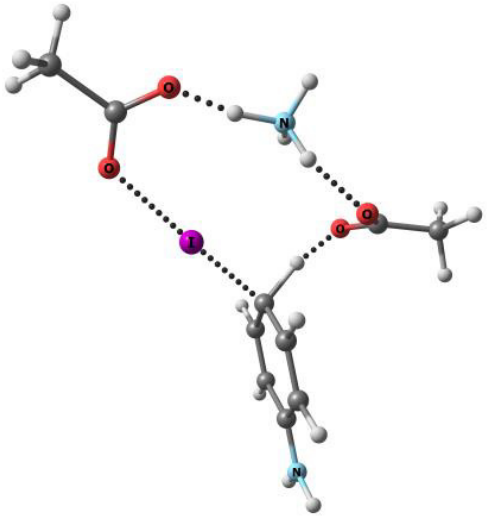
C	2.685354	2.373166	–1.998370
C	1.793074	3.372978	–1.610674
C	0.654119	3.044835	–0.878265
C	0.393034	1.719549	–0.525151
C	1.296525	0.745276	–0.928366
C	2.444367	1.042948	–1.657034
H	3.581455	2.623677	–2.572816
H	1.988150	4.414498	–1.880321
H	–0.050097	3.820538	–0.566293
H	–0.516041	1.488929	0.035669
H	3.154767	0.264123	–1.940095
I	1.034999	–1.299890	–0.384899
I	–1.738304	–1.113014	–0.614195
O	3.210278	–0.780544	0.602831
C	3.056510	–0.087427	1.660316
O	1.970493	0.265565	2.152477
C	4.345487	0.372391	2.325514
H	5.139437	–0.380165	2.203689
H	4.678726	1.300765	1.828761
H	4.174040	0.590254	3.390480
N	–0.762811	0.231090	2.574844
H	–0.780672	0.656819	3.506770
H	–0.987600	–0.763087	2.676170
H	–1.597712	0.733914	1.926721
H	0.231681	0.297442	2.228095
O	–2.611965	1.467185	1.380375
C	–3.681881	1.138504	0.769316
O	–3.910701	0.064775	0.184941
C	–4.759287	2.212336	0.736797
H	–4.872573	2.672102	1.731663
H	–4.441143	3.007465	0.039787
H	–5.716254	1.795844	0.390328



AcO–I

E(scf) = –525.9711258 a.u.

C	1.339405	–1.189108	0.000000
O	2.099629	–0.264308	0.000000
O	0.000000	–1.076041	0.000000
C	1.721501	–2.651942	0.000000
H	1.303407	–3.149933	0.889481
H	1.303407	–3.149933	–0.889481
H	2.817020	–2.734528	0.000000
I	–0.765779	0.807613	0.000000

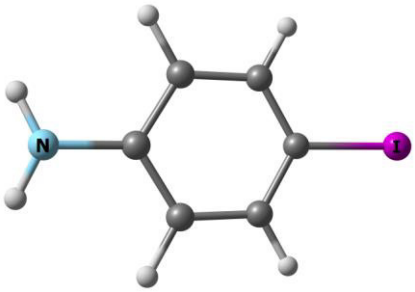


TS3

E(scf) = –1098.5859789 a.u.

ν_{min} = –528.66 cm^{-1}

I	–0.819485	–0.905526	–0.186078
O	–3.177547	–1.404948	–0.058430
C	–4.041891	–0.533786	0.213067
O	–3.849922	0.697008	0.362573
C	–5.463738	–1.037252	0.415277
H	–5.611249	–2.006138	–0.084251
H	–5.636544	–1.172569	1.497572
H	–6.189098	–0.294046	0.049139
C	1.967640	–0.231643	1.039670
C	1.370241	–0.355871	–0.254646
C	2.129295	–1.069588	–1.232206
H	1.090193	0.802069	–0.677539
C	3.214931	–0.732819	1.322699
H	1.420185	0.322420	1.808733
C	3.945194	–1.428144	0.323915
H	3.654725	–0.602233	2.315979
C	3.375400	–1.582827	–0.966957
N	5.169542	–1.930632	0.595804
H	3.937352	–2.111583	–1.742671
H	1.706060	–1.192814	–2.234649
H	5.691913	–2.438643	–0.105553
H	5.577951	–1.836176	1.516262
H	2.060948	4.517127	–1.215710
H	3.176868	3.644503	–0.145351
C	2.153819	4.053552	–0.220379
C	1.165967	2.908915	–0.076910
O	1.056476	2.135336	–1.086473
O	0.540745	2.765002	0.987928
H	2.007448	4.802406	0.572123
N	–1.921593	2.328631	–0.076234
H	–2.359499	3.253575	–0.035216
H	–1.064410	2.325126	0.545937
H	–1.547241	2.173840	–1.019613
H	–2.677732	1.537591	0.153978

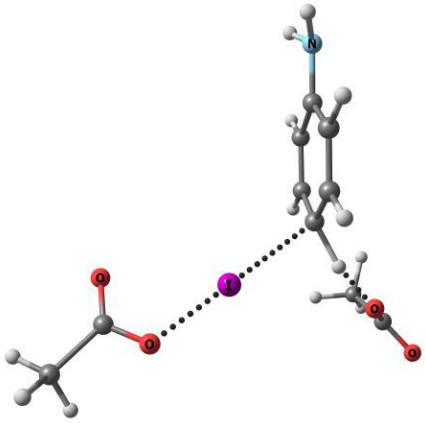


IPh–NH_2

E(scf) = –584.456116410 a.u.

C	–0.165217	0.000015	–0.003383
C	–0.867566	–1.205550	–0.004426
C	–2.258816	–1.204795	–0.006052
C	–2.982564	0.000027	–0.007017
C	–2.258838	1.204815	–0.006035
C	–0.867551	1.205550	–0.004428
H	–0.334014	–2.159550	–0.003021

H	–2.795292	–2.158773	–0.010733
H	–2.795259	2.158825	–0.010650
H	–0.334023	2.159563	–0.003040
N	–4.364308	–0.000039	–0.052119
H	–4.836966	–0.850041	0.230253
H	–4.837037	0.850025	0.229955
I	1.941246	–0.000003	0.002266
H	2.407711	2.244438	1.756963
H	0.635726	2.415628	1.70034
C	1.588036	2.950397	1.52979
C	1.687436	3.415758	0.062254
O	1.555361	2.489978	–0.81383
O	1.888626	4.600207	–0.174562
H	1.653175	3.812797	2.211838

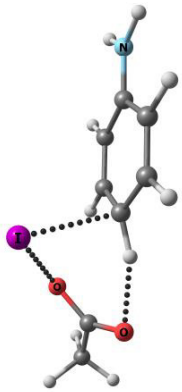


TS4

E(scf) = –1041.5350416 a.u.

ν_{min} = –598.70 cm^{-1}

I	–1.000887	0.010086	–0.28874
O	–3.181813	0.056967	–0.426668
C	–3.894445	–0.74047	0.315457
O	–3.484519	–1.556188	1.114836
C	–5.388174	–0.534626	0.063529
H	–5.659999	0.514531	0.268402
H	–5.618119	–0.730493	–0.997504
H	–5.975514	–1.208161	0.70586
C	1.848884	–0.584328	1.075477
C	1.521566	–0.060696	–0.19298
C	2.00956	–0.780114	–1.30501
H	1.407922	1.191482	–0.398634
C	2.590608	–1.747291	1.232226
H	1.493372	–0.065806	1.972816
C	3.047025	–2.453159	0.104883
H	2.816011	–2.129241	2.234141
C	2.753439	–1.94396	–1.173504
N	3.805935	–3.606209	0.25092
H	3.116502	–2.474776	–2.060782
H	1.794602	–0.396479	–2.308685
H	3.818639	–4.232569	–0.545995
H	3.710563	–4.089242	1.1371

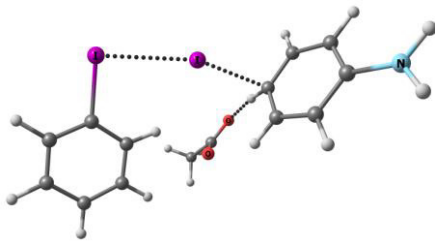


TS5

E(scf) = = –813.1928806 a.u.

ν_{min} = –293.35 cm^{-1}

I	–0.496332	1.436067	–0.109206
O	–2.004493	–0.560541	–0.794067
C	–2.699058	–1.158811	0.102117
O	–2.39472	–1.28703	1.288532
C	–4.018765	–1.728743	–0.417301
H	–4.731718	–0.898593	–0.562762
H	–3.876188	–2.217144	–1.39486
H	–4.434924	–2.440262	0.312232
C	0.857511	–1.204606	–0.639723
C	0.493224	–0.761915	0.671974
C	1.55382	–0.40014	1.565182
H	–0.491953	–1.03094	1.091456
C	2.167385	–1.188448	–1.064568
H	0.050177	–1.518777	–1.306044
C	3.188086	–0.749114	–0.190741
H	2.4236	–1.496141	–2.082162
C	2.853147	–0.372464	1.149684
N	4.471649	–0.691619	–0.598188
H	3.652786	–0.071028	1.832849
H	1.301817	–0.117172	2.590954
H	5.202869	–0.366577	0.021027
H	4.729188	–0.947561	–1.542896

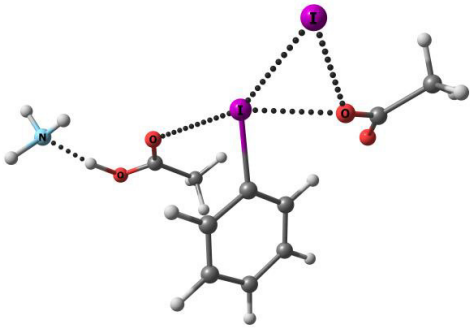


TS6

E(scf) = =–1343.2526882 a.u.

ν_{min} = –81.45 cm^{-1}

C	2.593048	2.323391	1.172409
C	3.854450	2.396974	1.754936
C	4.691002	1.282652	1.741927
C	4.271742	0.089837	1.144830
C	3.005107	0.043376	0.564498
C	2.156899	1.146009	0.564410
H	1.894934	3.170411	1.166499
H	4.193280	3.323981	2.228168
H	5.683483	1.332044	2.195304
H	4.934013	–0.779993	1.138420
H	1.150600	1.156906	0.133613
I	2.403631	–1.781261	–0.351103
I	–0.749923	–0.908575	–0.546579
O	–0.521443	2.589076	0.044023
C	–0.695358	2.974940	–1.145297
O	–1.586260	2.571977	–1.928747
C	0.306803	4.001802	–1.693475
H	0.522729	4.767937	–0.915515
H	1.259655	3.484896	–1.938433
H	–0.074096	4.491367	–2.616071
C	–4.015681	–0.360923	–0.918568
C	–4.906237	–0.858990	–0.002883
C	–4.832379	–0.448808	1.362073
C	–3.826037	0.465051	1.773670
C	–2.930480	0.954694	0.859119
C	–3.019997	0.596074	–0.531228
H	–4.077700	–0.667379	–1.965050
H	–5.682468	–1.569838	–0.306605
H	–3.768031	0.760598	2.823944
H	–2.127409	1.664140	1.099738
H	–2.516939	1.320528	–1.248015
N	–5.712526	–0.938369	2.253692
H	–6.432298	–1.590191	1.974504
H	–5.674267	–0.660398	3.230019



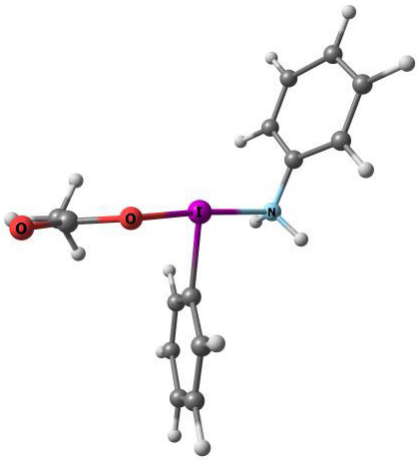
TS7

E(scf) = = –1341.3298457 a.u.

ν_{min} = –110.00 cm^{-1}

C	2.750635	1.908649	2.068000
C	1.938675	0.856866	1.644285
C	0.982025	1.106658	0.660542
C	0.791980	2.367539	0.107849
C	1.610633	3.407856	0.551353
C	2.588356	3.182456	1.520919
H	3.509255	1.728964	2.835009
H	2.067235	–0.142655	2.066292
H	0.009362	2.550211	–0.642292
H	1.474917	4.406178	0.126046
H	3.224252	4.005451	1.859367
I	–0.092032	–0.581731	–0.042830
O	2.844312	–1.227432	–0.616602
O	–2.094042	1.076120	–0.104206
C	3.745666	–0.523534	–1.044622
O	5.008184	–0.883993	–1.016462
C	–2.511254	2.001033	–0.913121
O	–1.771754	2.737131	–1.549563
C	3.526331	0.849648	–1.621459
H	2.523500	0.921611	–2.066640
H	3.590417	1.589395	–0.803564
H	4.300150	1.090669	–2.365390
C	–4.024881	2.085729	–1.031286
H	–4.407914	1.170161	–1.514215
H	–4.487118	2.150643	–0.032858
H	–4.295475	2.964066	–1.635982
N	4.899444	–3.319638	0.066767

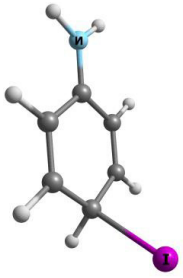
H	5.088984	–1.815273	–0.598126
H	5.138334	–4.114348	–0.528272
H	5.288167	–3.486816	0.995929
H	3.879716	–3.263412	0.142245
I	–2.954808	–1.372786	0.351037



I3

E(scf) = = –1044.3638691 a.u.

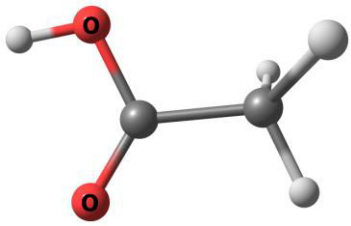
C	–5.312445	0.294218	0.007750
C	–4.666985	0.138500	1.234394
C	–3.404499	–0.449187	1.294653
C	–2.797054	–0.888089	0.117180
C	–3.432332	–0.731167	–1.115826
C	–4.694369	–0.141689	–1.164239
H	–6.302265	0.754944	–0.035047
H	–5.149466	0.473237	2.156128
H	–2.903793	–0.574594	2.260241
H	–2.952922	–1.076737	–2.037453
H	–5.197405	–0.025959	–2.127519
N	–1.461512	–1.429912	0.163338
H	–1.305260	–2.126028	–0.571874
I	0.066355	0.469195	–0.223637
C	1.604358	–0.964721	–0.081673
C	1.836652	–1.590437	1.143125
C	2.378341	–1.203817	–1.215554
C	2.876299	–2.516842	1.218904
H	1.241108	–1.361871	2.031766
C	3.419069	–2.127259	–1.111174
H	2.195330	–0.682168	–2.158404
C	3.662130	–2.782969	0.096246
H	3.079254	–3.020998	2.167192
H	4.042241	–2.331785	–1.985502
H	4.478604	–3.506205	0.165495
O	1.364704	1.931544	–0.716366
C	2.236778	2.600617	0.118016
O	2.940535	3.411370	–0.388836
C	2.228107	2.243662	1.584276
H	1.230159	2.387806	2.032699
H	2.535649	1.194158	1.736118
H	2.944280	2.896593	2.101759
H	–1.267965	–1.886614	1.058924



I4

E(scf) = = –584.8000926 a.u.

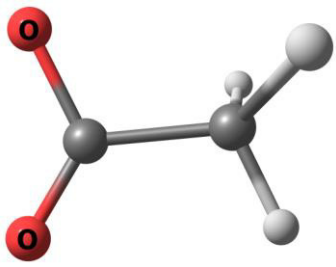
C	0.969729	–0.391986	0.000000
C	1.027221	0.396439	1.247465
C	1.027221	1.747337	1.248969
C	1.004820	2.469798	0.000000
C	1.027221	1.747337	–1.248969
C	1.027221	0.396439	–1.247465
H	1.692203	–1.224225	0.000000
H	1.059975	–0.150006	2.195175
H	1.049988	2.305131	2.188765
H	1.049988	2.305131	–2.188765
H	1.059975	–0.150006	–2.195175
N	0.977300	3.786535	0.000000
H	0.966057	4.318186	–0.867905
H	0.966057	4.318186	0.867905
I	–0.965772	–1.441893	0.000000



AcOH

E(scf) = = –228.8294266 a.u.

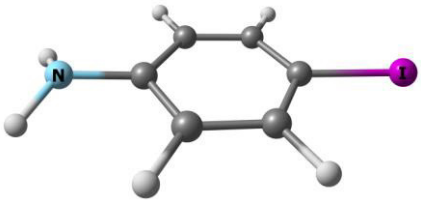
C	0.000000	0.155491	0.000000
O	0.205496	1.338535	0.000000
O	–1.243438	–0.358691	0.000000
H	–1.863467	0.391560	0.000000
C	1.046112	–0.926468	0.000000
H	0.922473	–1.566903	0.888954
H	0.922473	–1.566903	–0.888954
H	2.045382	–0.470646	0.000000



AcO^-

E(scf) = = –228.2521335 a.u.

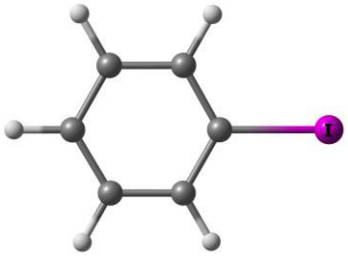
C	0.000000	0.221670	0.000000
C	0.045939	–1.352059	0.000000
H	–0.490036	–1.741094	0.887528
H	–0.490036	–1.741094	–0.887528
H	1.082168	–1.736460	0.000000
O	1.103385	0.798677	0.000000
O	–1.150601	0.701447	0.000000



$Ph–NH_2$

E(scf) = = –287.2816970 a.u.

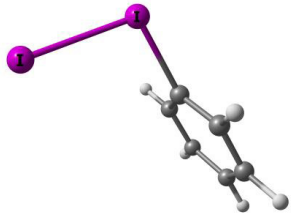
C	0.003395	–1.881320	0.000000
C	0.003736	–1.170704	1.200758
C	0.003736	0.221478	1.206548
C	0.004345	0.942446	0.000000
C	0.003736	0.221478	–1.206548
C	0.003736	–1.170704	–1.200758
H	0.002503	–2.974421	0.000000
H	0.002816	–1.707279	2.154535
H	0.007858	0.763612	2.157801
H	0.007858	0.763612	–2.157801
H	0.002816	–1.707279	–2.154535
N	0.050215	2.328803	0.000000
H	–0.255723	2.792044	–0.847498
H	–0.255723	2.792044	0.847498



Ph–I

E(scf) = = –529.1613990 a.u.

C	0.000000	0.000000	–3.341249
C	0.000000	1.206059	–2.641274
C	0.000000	1.213055	–1.246044
C	0.000000	0.000000	–0.555551
C	0.000000	–1.213055	–1.246044
C	0.000000	–1.206059	–2.641274
H	0.000000	0.000000	–4.434677
H	0.000000	2.156475	–3.182342
H	0.000000	2.161492	–0.703306
H	0.000000	–2.161492	–0.703306
H	0.000000	–2.156475	–3.182342
I	0.000000	0.000000	1.551596

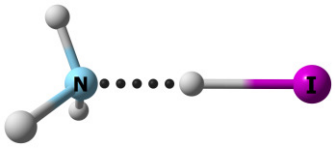


I–Ph

E(scf) = = –826.6373117 a.u.

C	3.427240	–0.762352	1.214321
C	4.038575	–1.081178	–0.000316
C	3.427808	–0.760349	–1.214712
C	2.193003	–0.115374	–1.231754
C	1.610549	0.190397	0.000192
C	2.192496	–0.117276	1.231864
H	3.912135	–1.015769	2.160404
H	5.006996	–1.588040	–0.000512

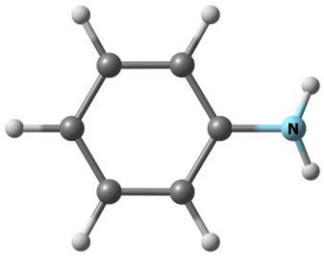
H	3.913166	–1.012168	–2.160985
H	1.712736	0.135335	–2.180725
H	1.711865	0.131996	2.181031
I	–0.230880	1.206812	0.000377
I	–1.987892	–0.844068	–0.000317



NH_4I

E(scf) = = –354.8633621 a.u.

N	0.000000	0.000000	-2.775338
H	0.000000	0.959304	-3.127014
H	-0.830782	-0.479652	-3.127014
H	0.830782	-0.479652	-3.127014
H	0.000000	0.000000	-1.179043
I	0.000000	0.000000	0.565801



Ph-NH_2

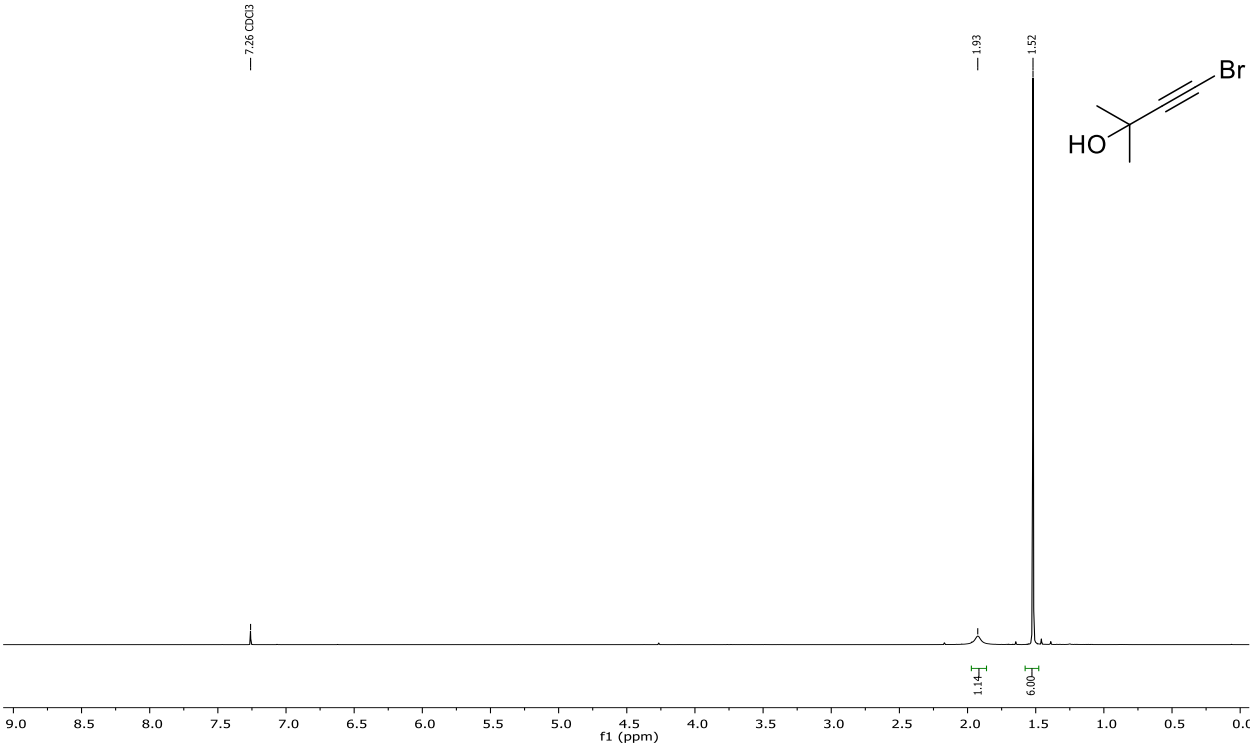
E(scf) = = –287.2816970 a.u.

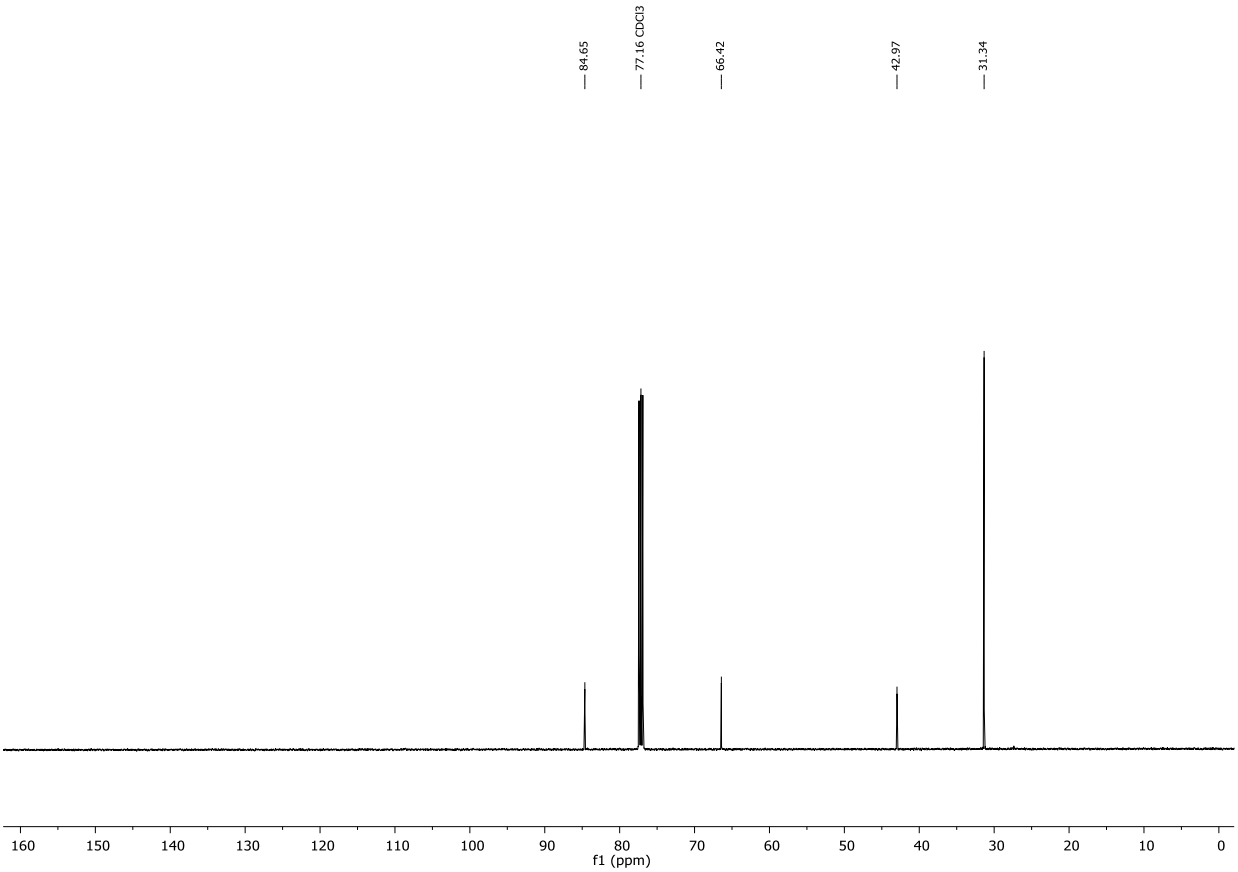
C	0.003395	-1.881320	0.000000
C	0.003736	-1.170704	1.200758
C	0.003736	0.221478	1.206548
C	0.004345	0.942446	0.000000
C	0.003736	0.221478	-1.206548
C	0.003736	-1.170704	-1.200758
H	0.002503	-2.974421	0.000000
H	0.002816	-1.707279	2.154535
H	0.007858	0.763612	2.157801
H	0.007858	0.763612	-2.157801
H	0.002816	-1.707279	-2.154535
N	0.050215	2.328803	0.000000
H	-0.255723	2.792044	-0.847498
H	-0.255723	2.792044	0.847498

^{1}H and ^{13}C NMR Spectra of

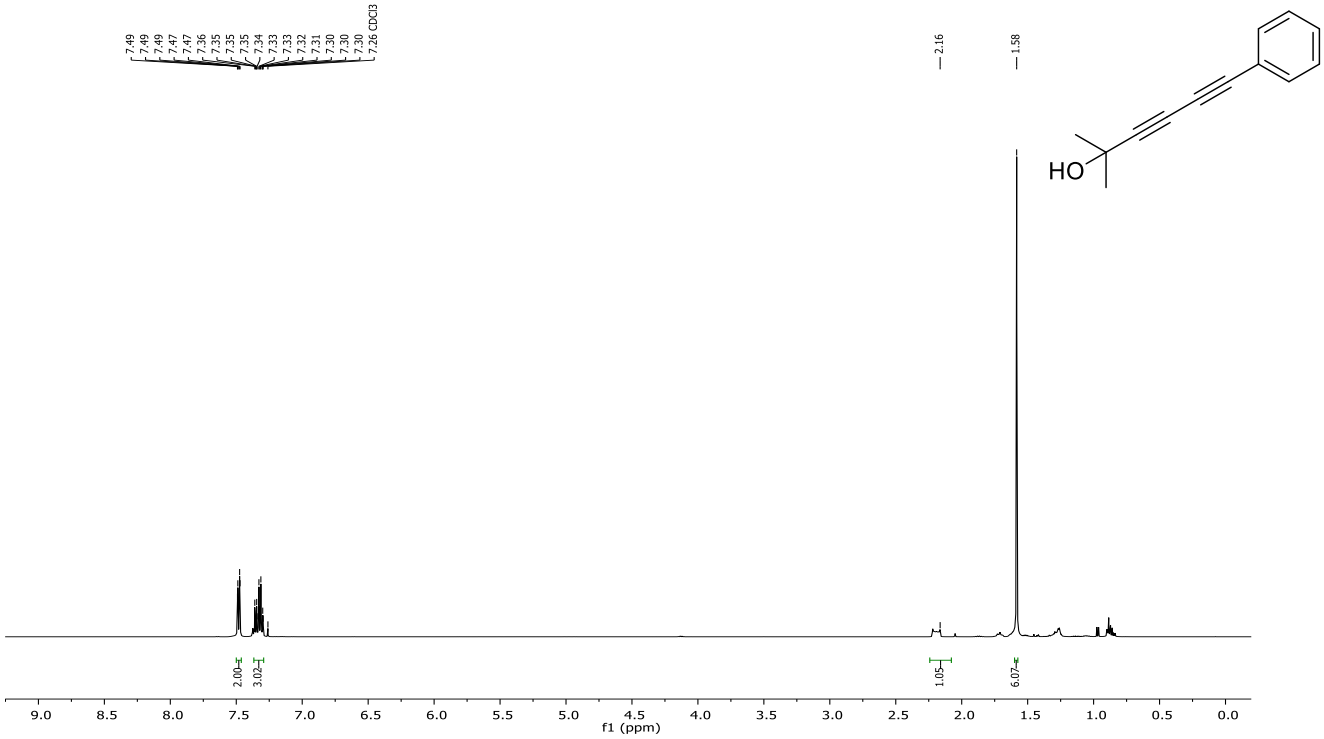
Chapters II.

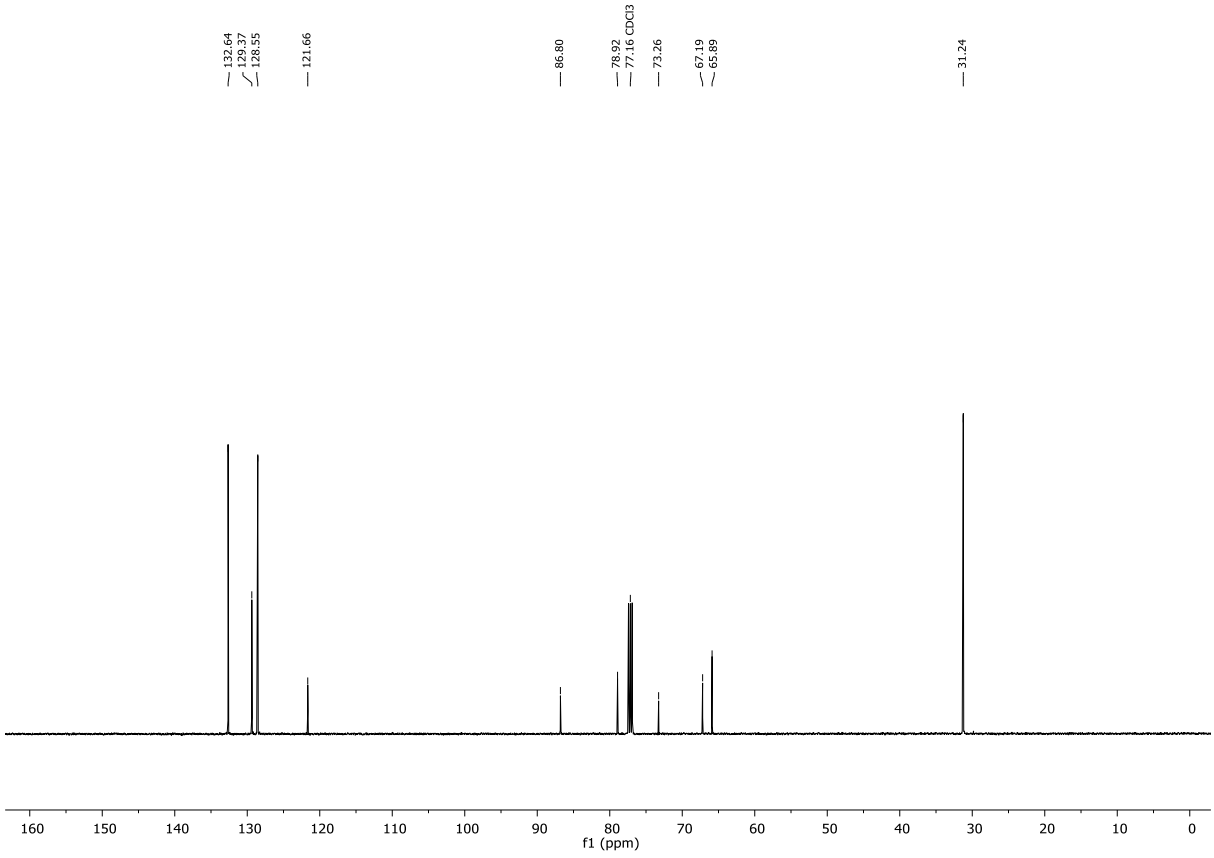
4-bromo-2-methylbut-3-yn-2-ol



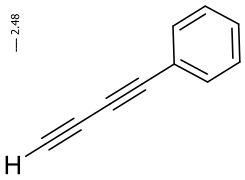


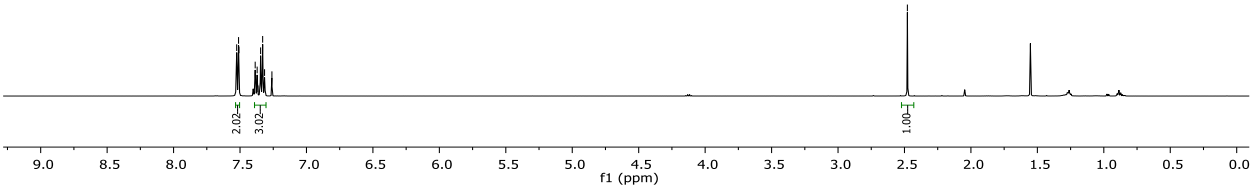
2-methyl-6-phenylhexa-3,5-diyn-2-ol

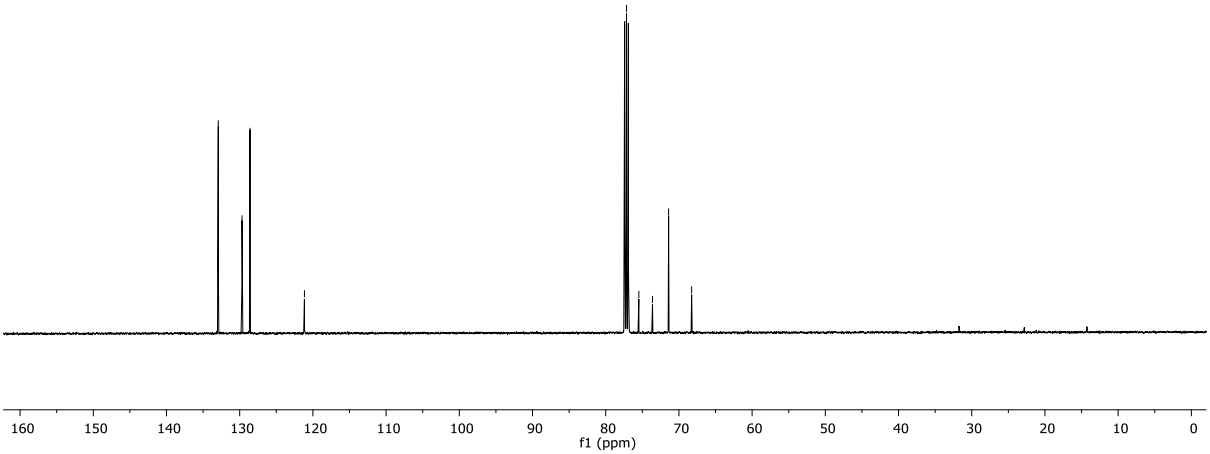




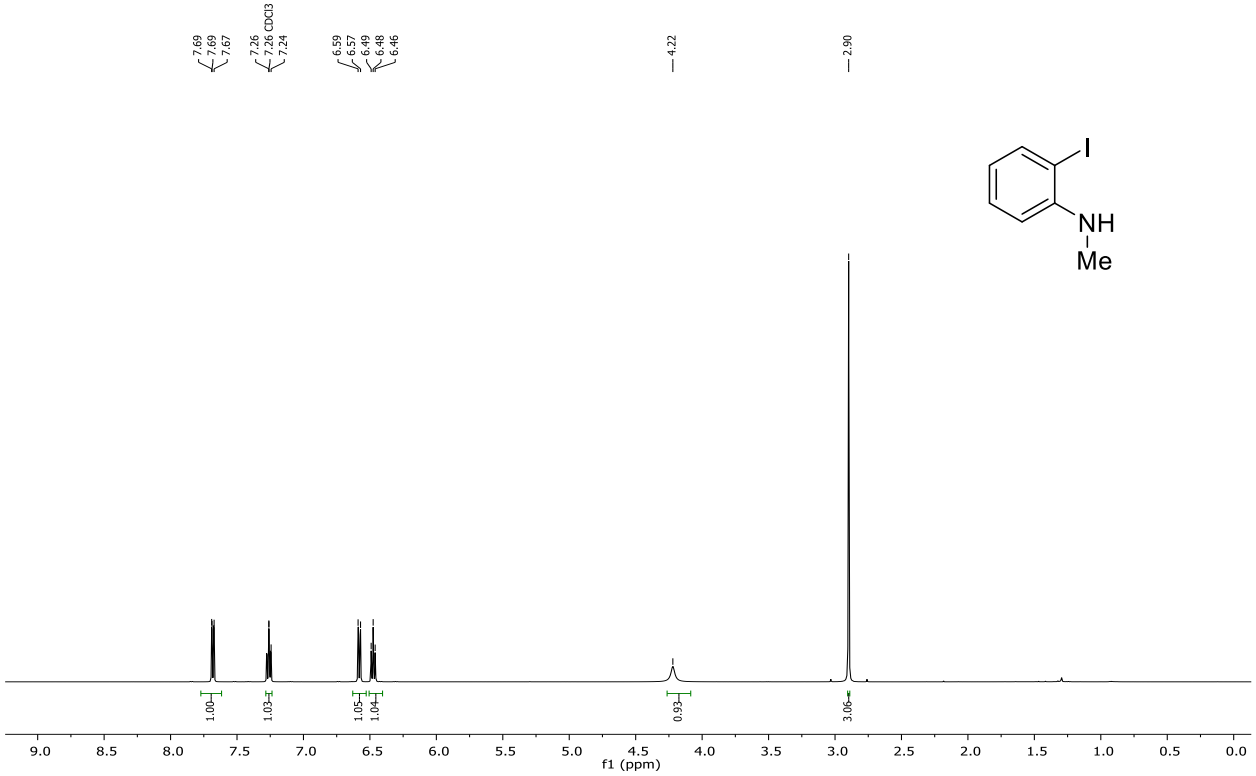
buta-1,3-diyn-1-ylbenzene

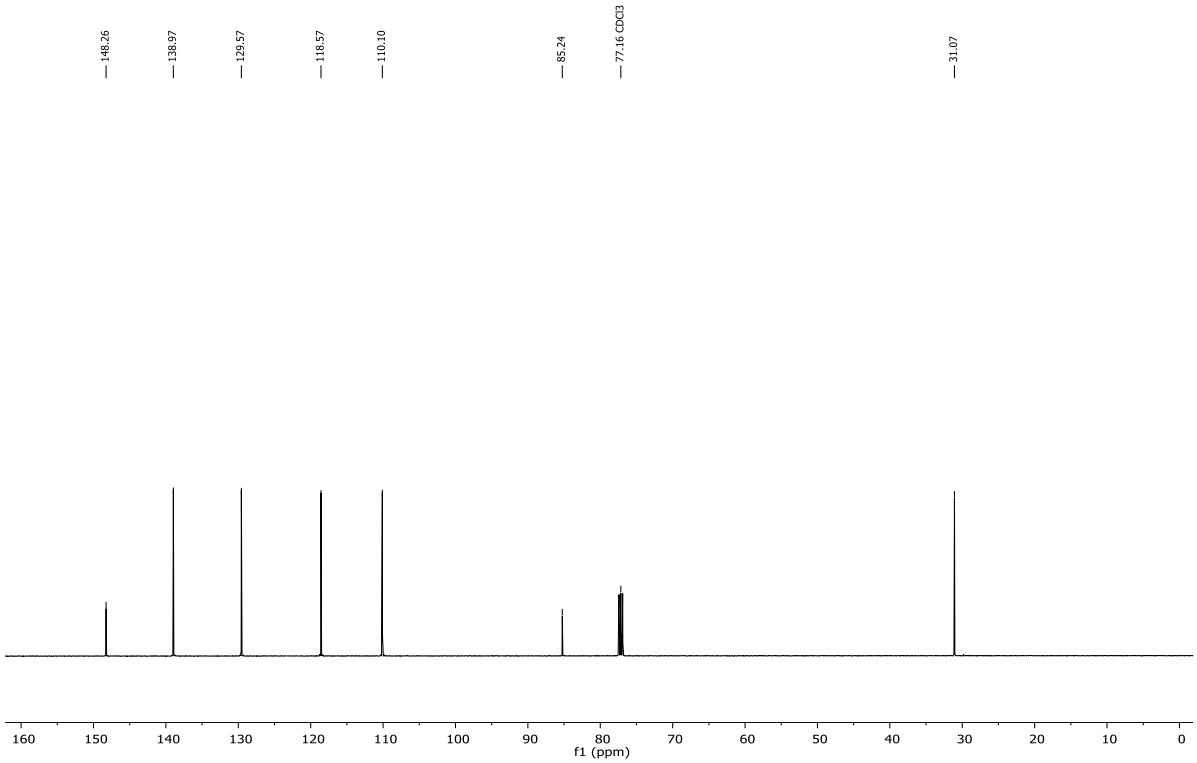




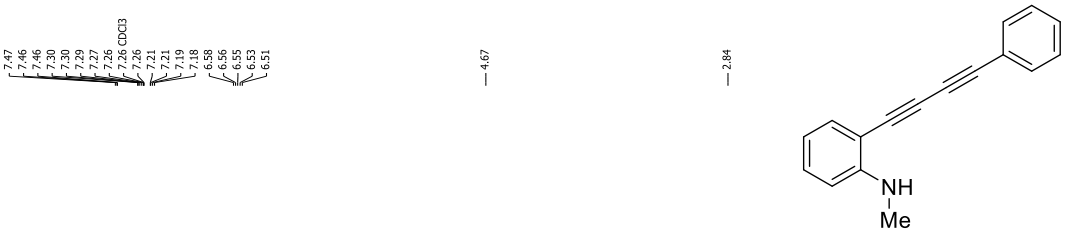


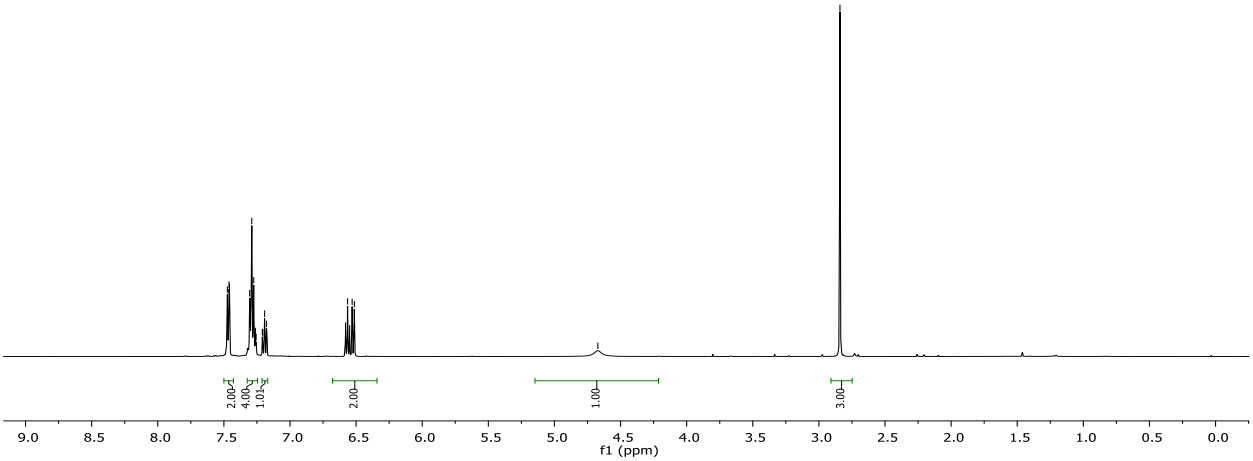
2-iodo-*N*-methylaniline

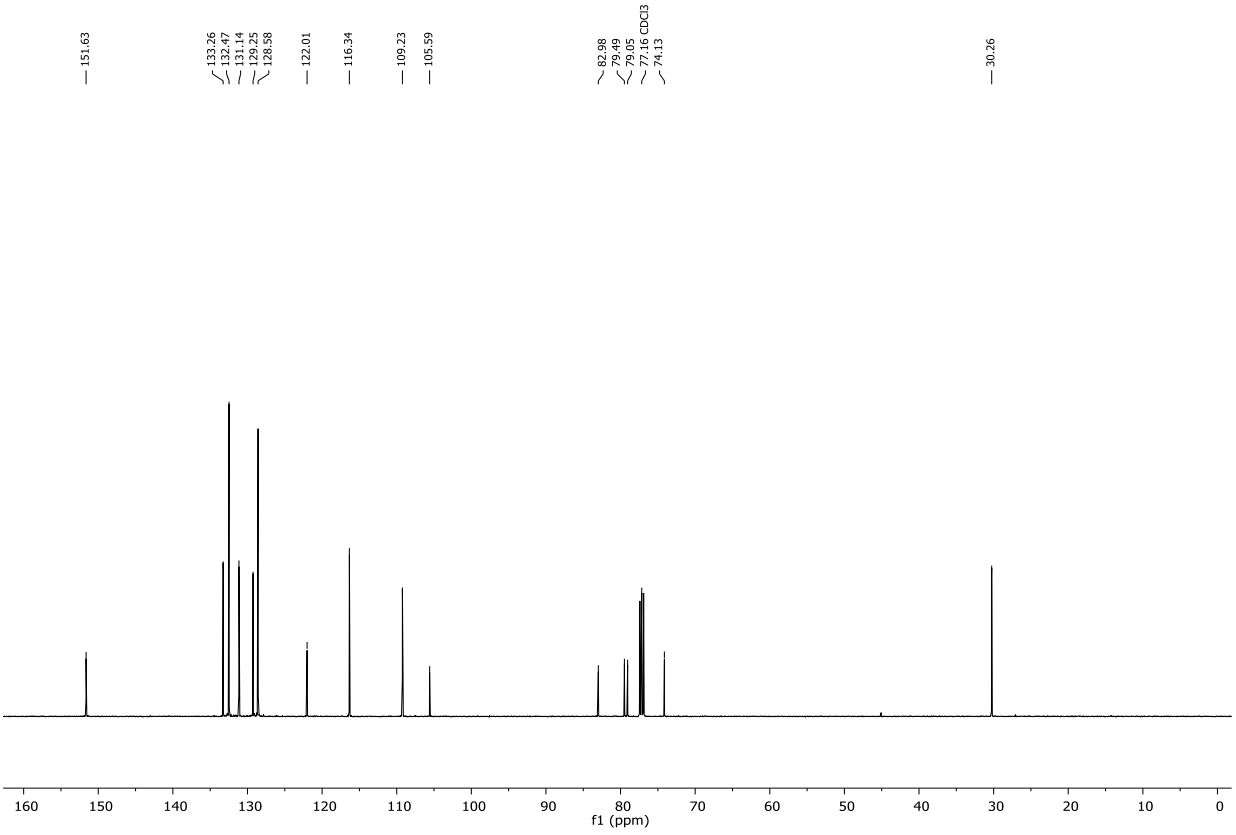




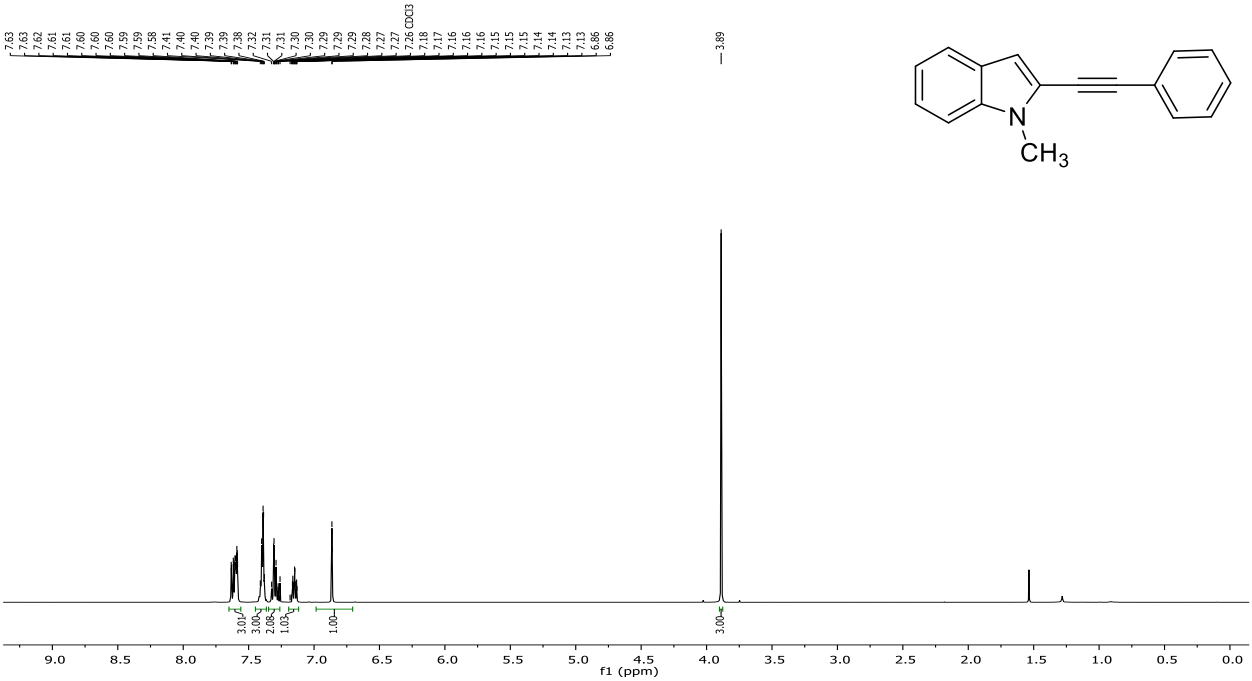
_N_-methyl-2-(phenylbuta-1,3-diyn-1-yl)aniline

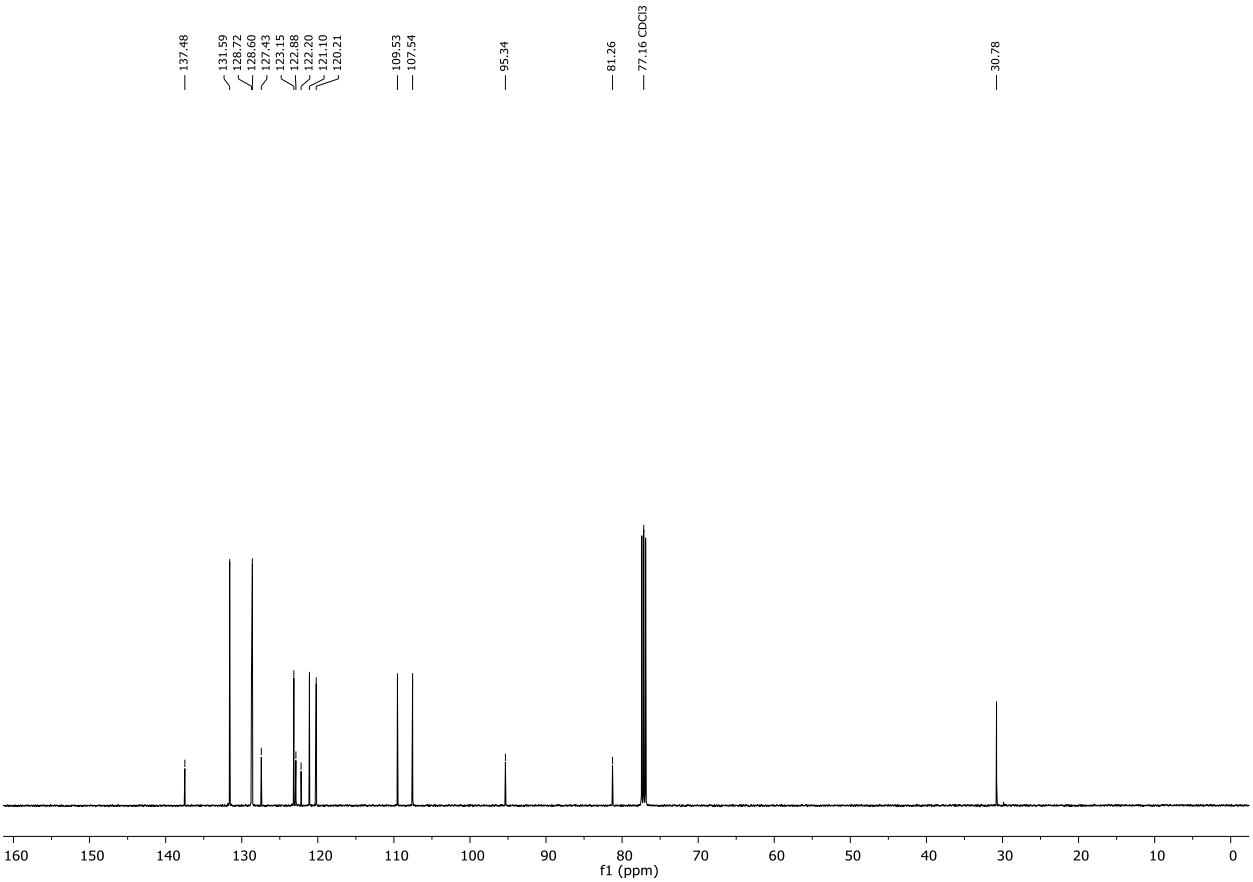




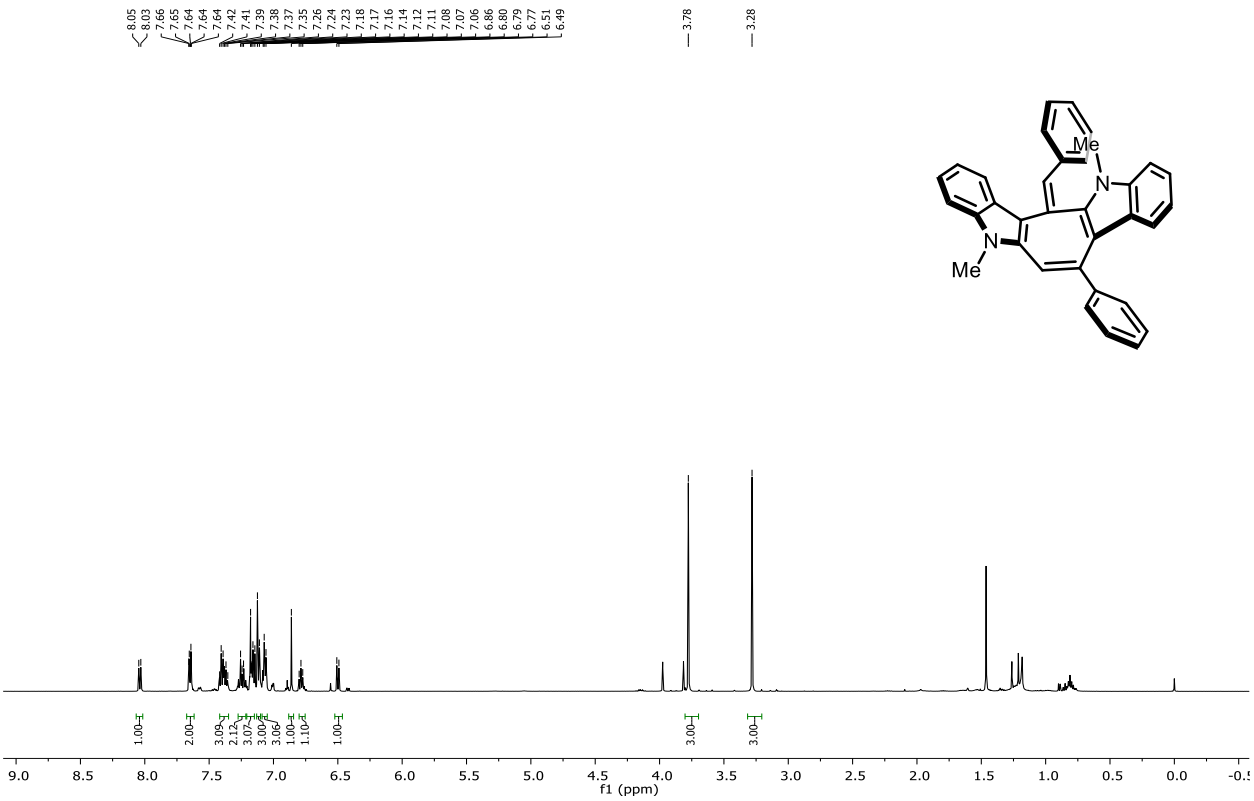


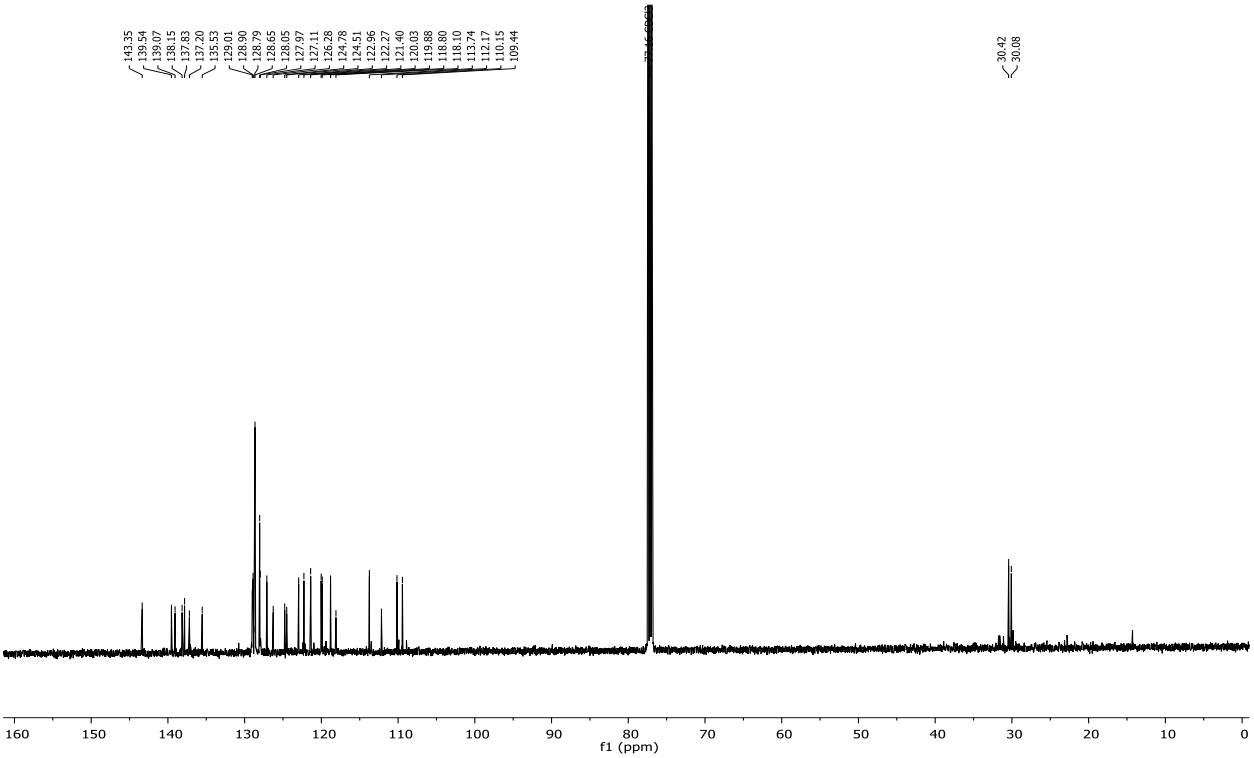
***1*- methyl-2-(phenylethynyl)-1,*H*-indole**



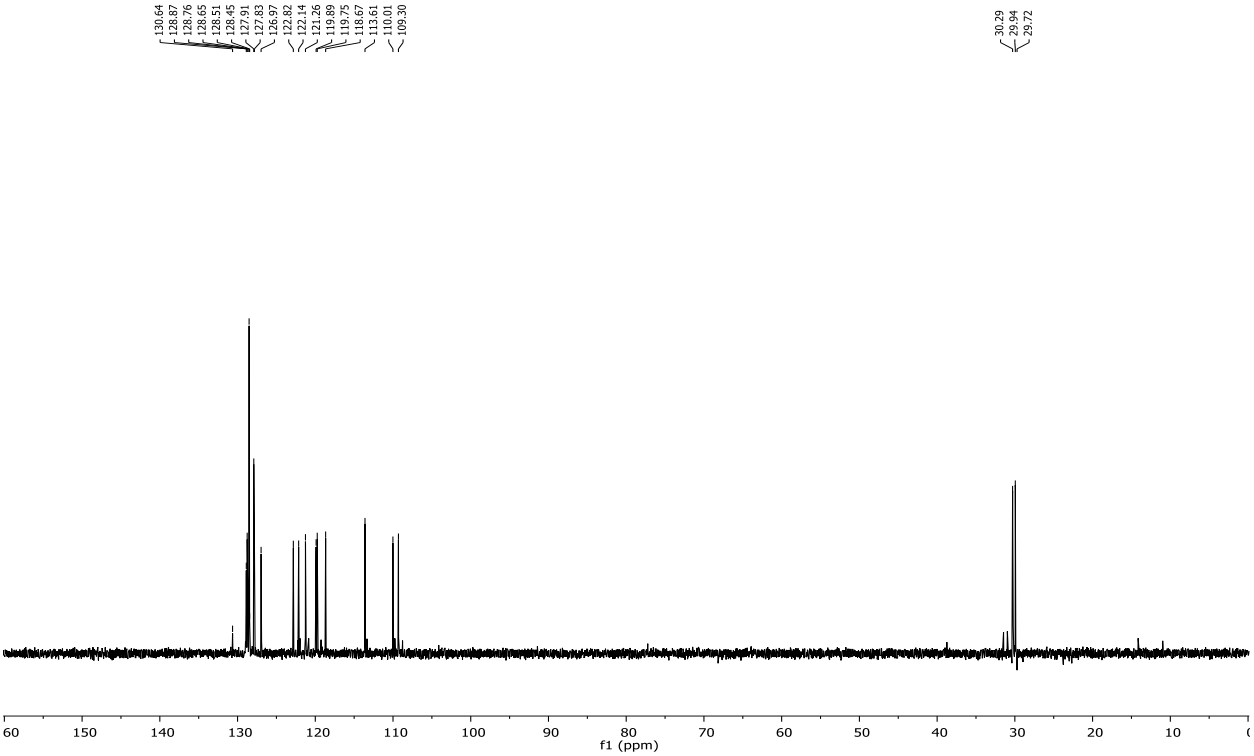


(E)-13-benzylidene-5,8-dimethyl-6-phenyl-8,13-dihydro-5H-cyclohepta[1,2-b:5,4-b']diindole.





DEPT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128.87
128.76
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128.45
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127.83
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122.82
122.14
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119.89
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118.67
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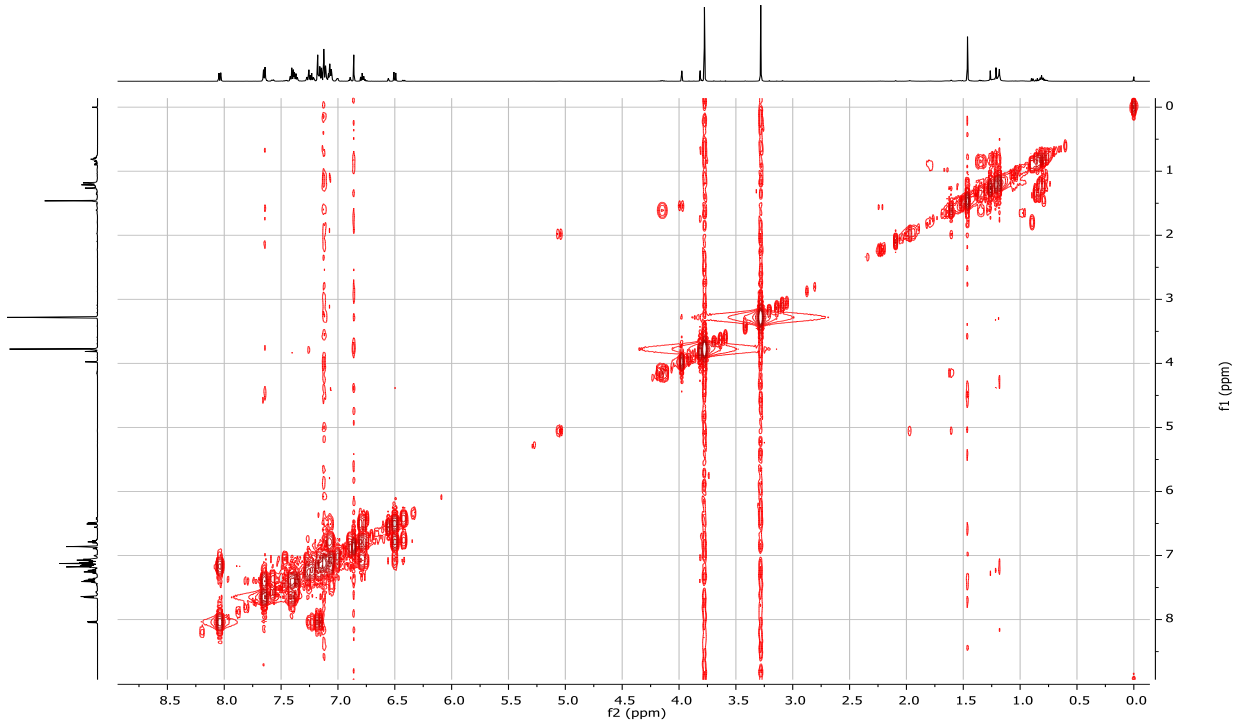
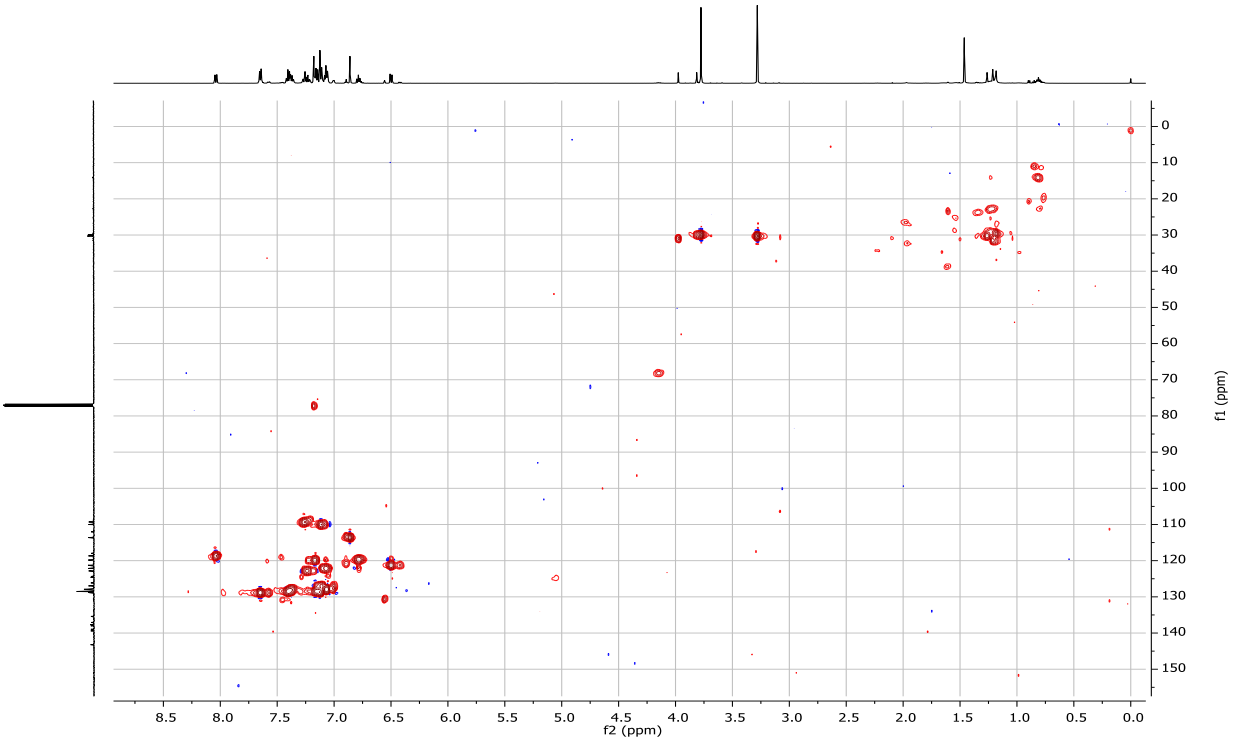
110.01
109.30
30.29
29.94
29.72
f1 (ppm)

COSY


f2 (ppm)
f1 (ppm)

HSQC



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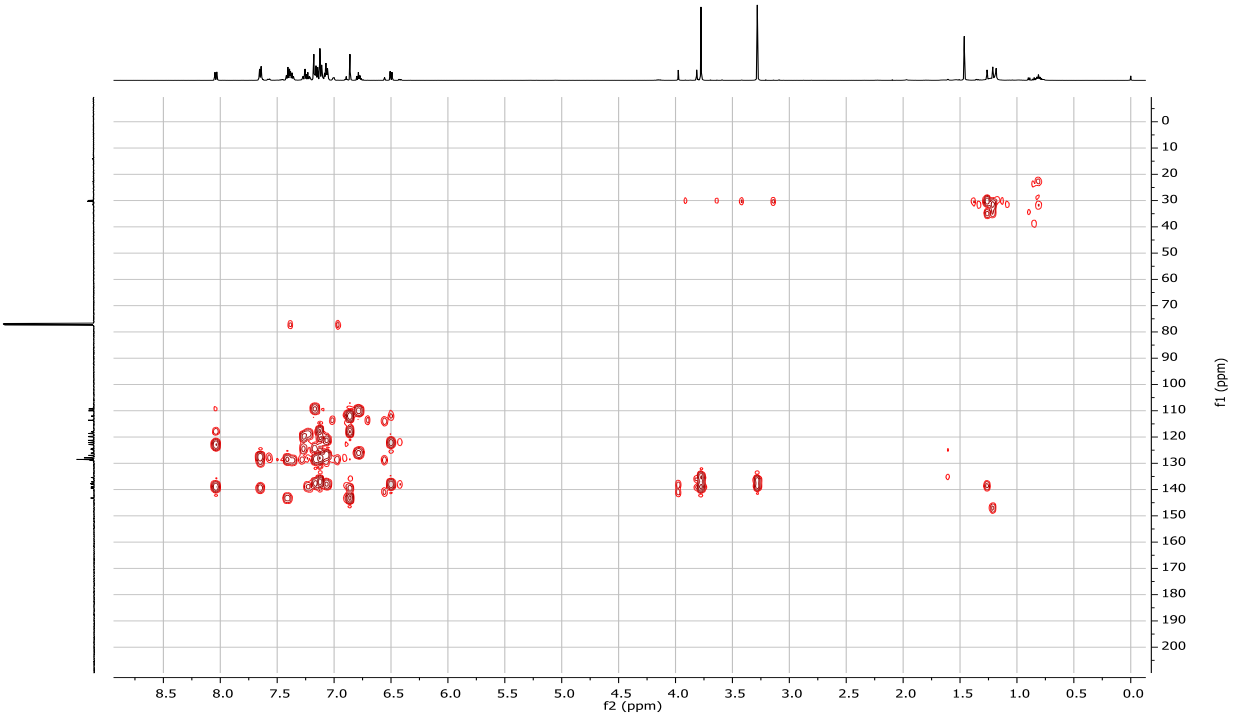

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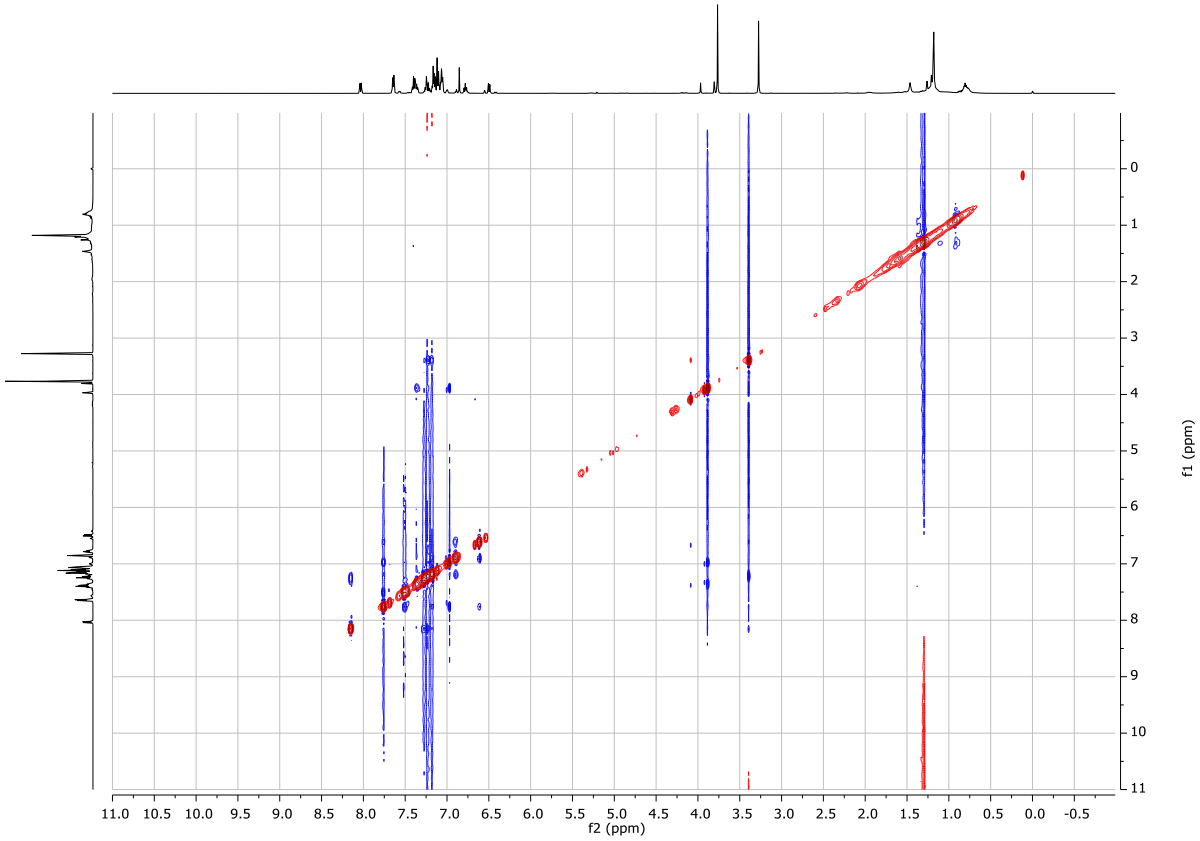
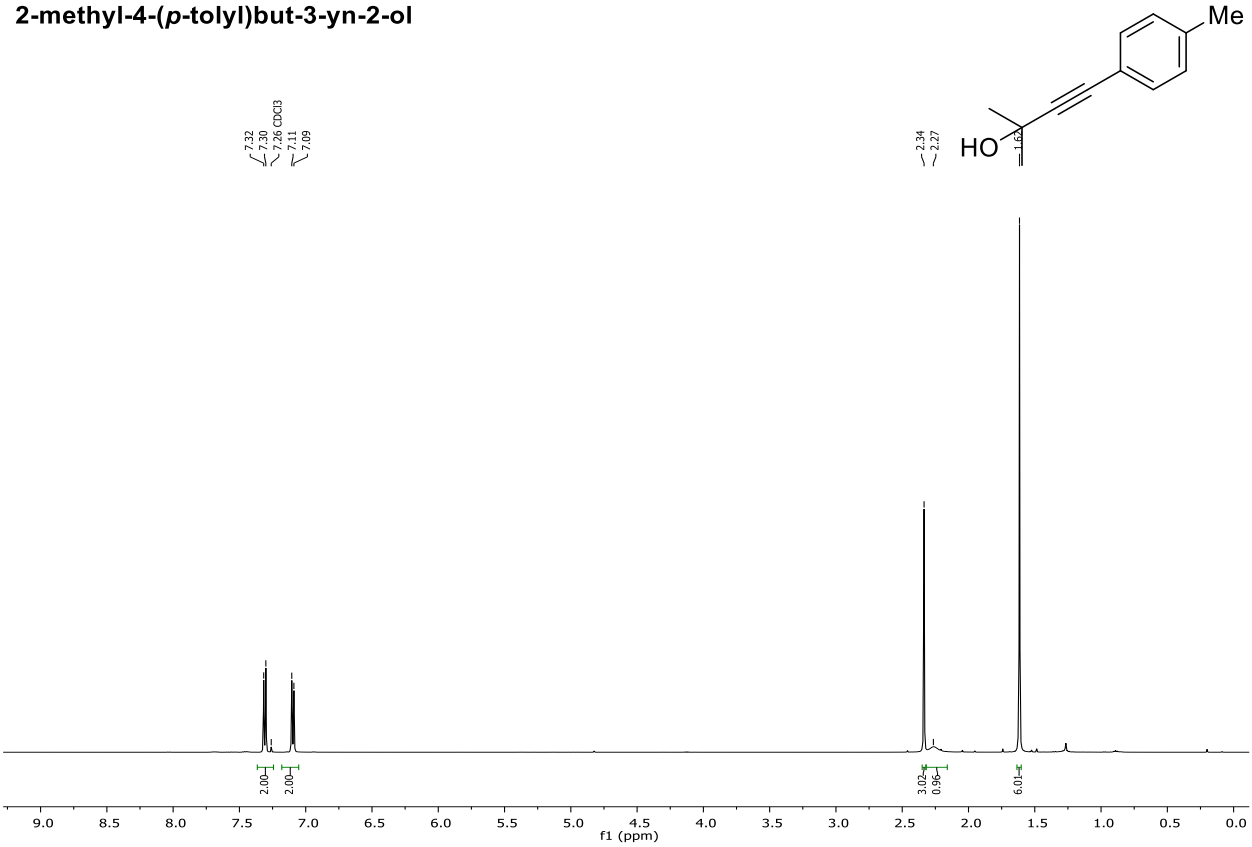
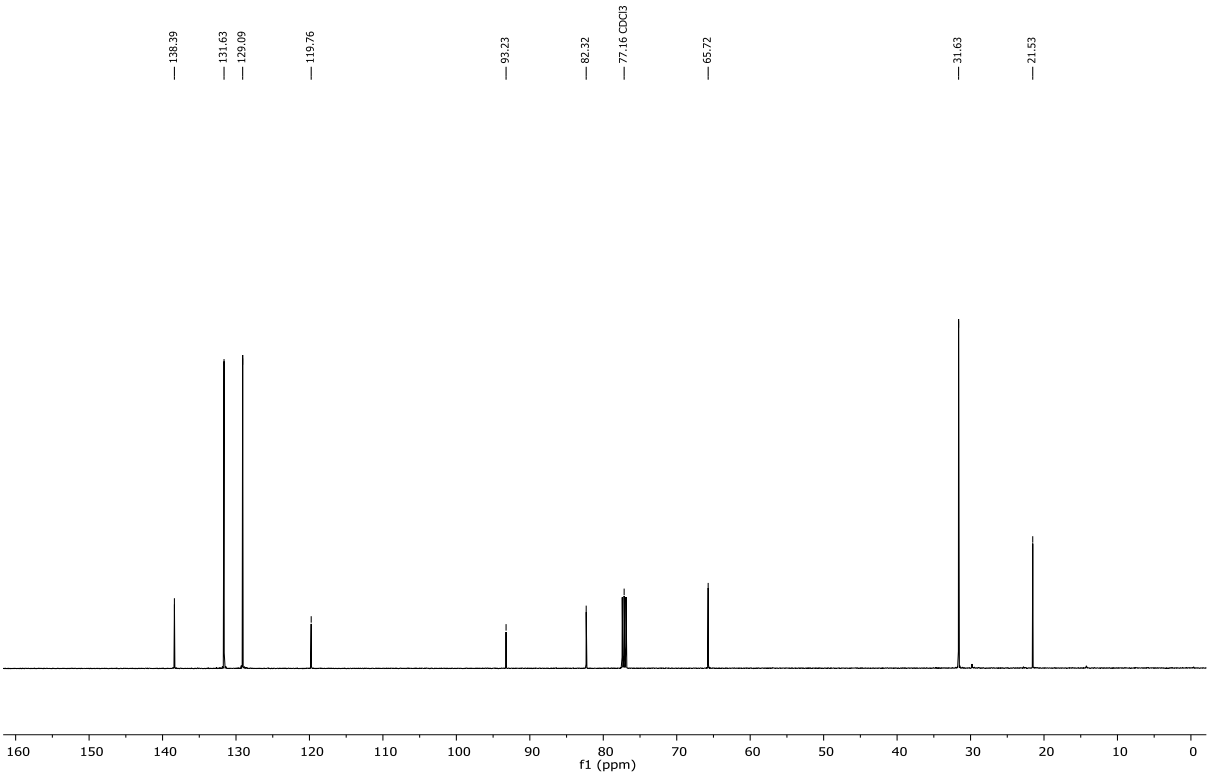
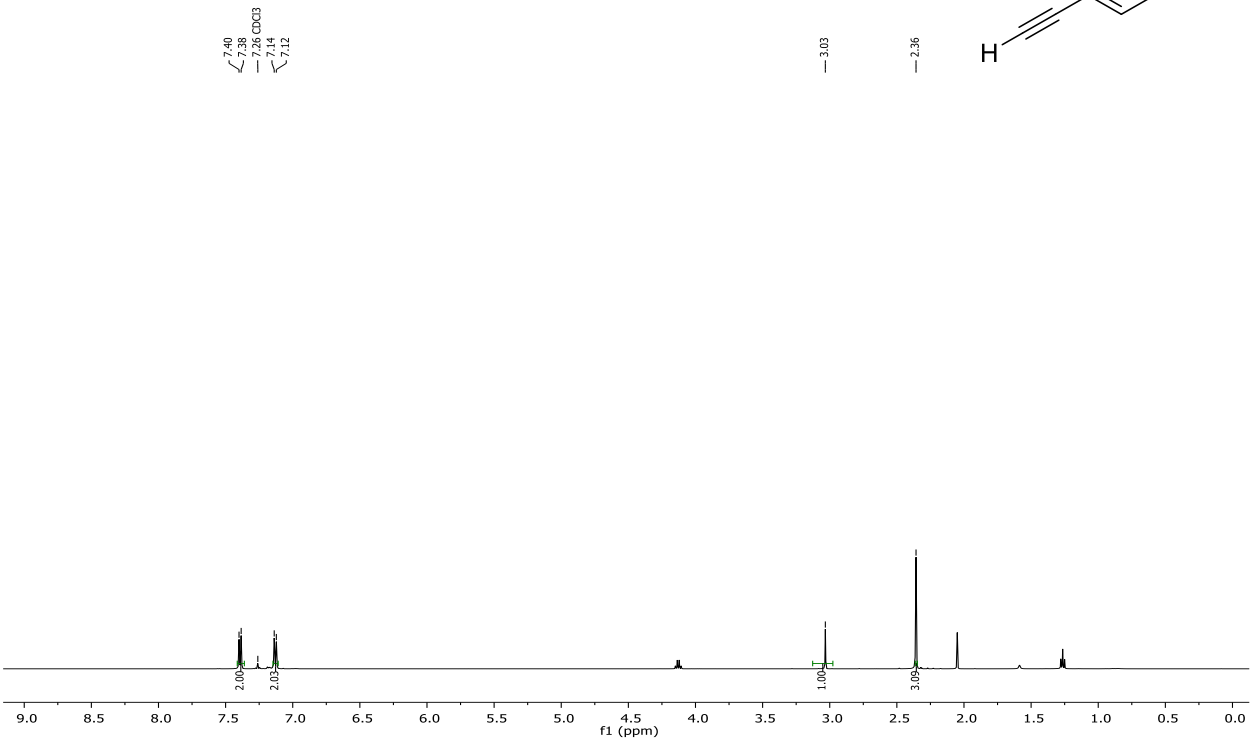


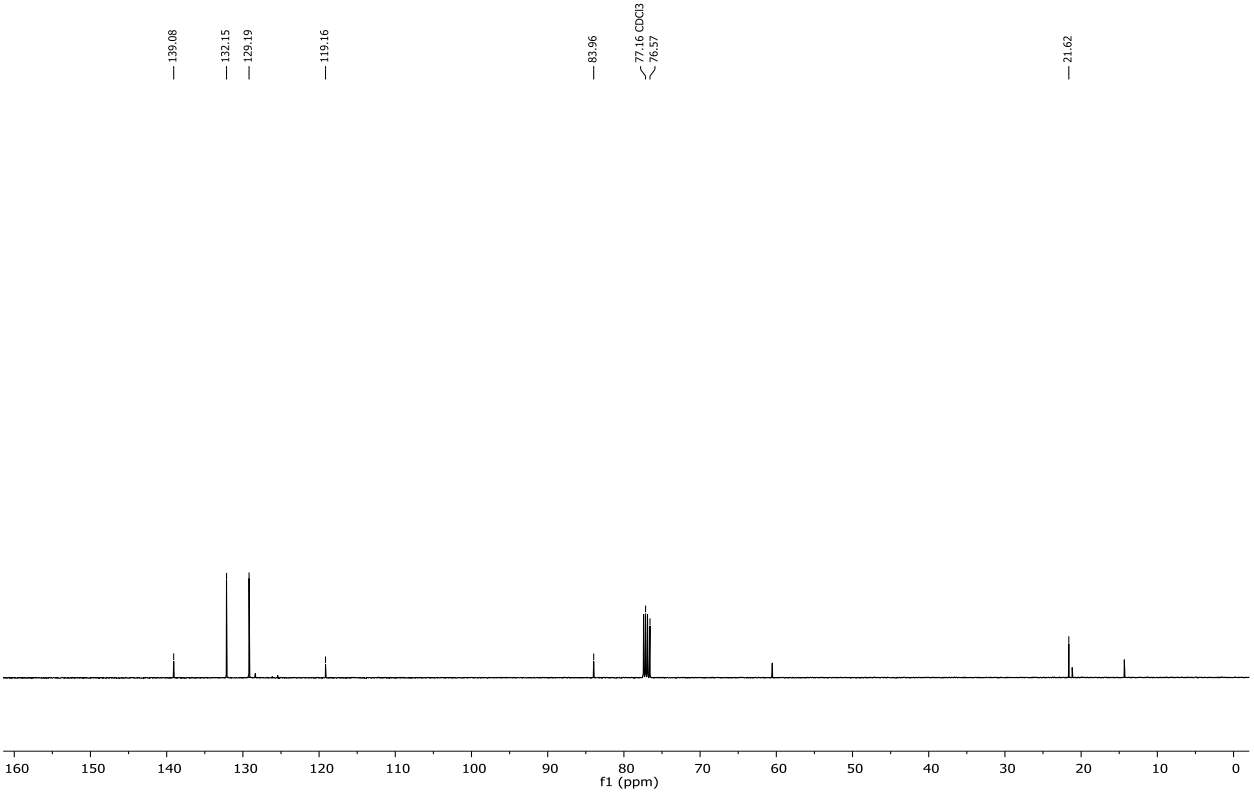
2-methyl-4-(*p*-tolyl)but-3-yn-2-ol



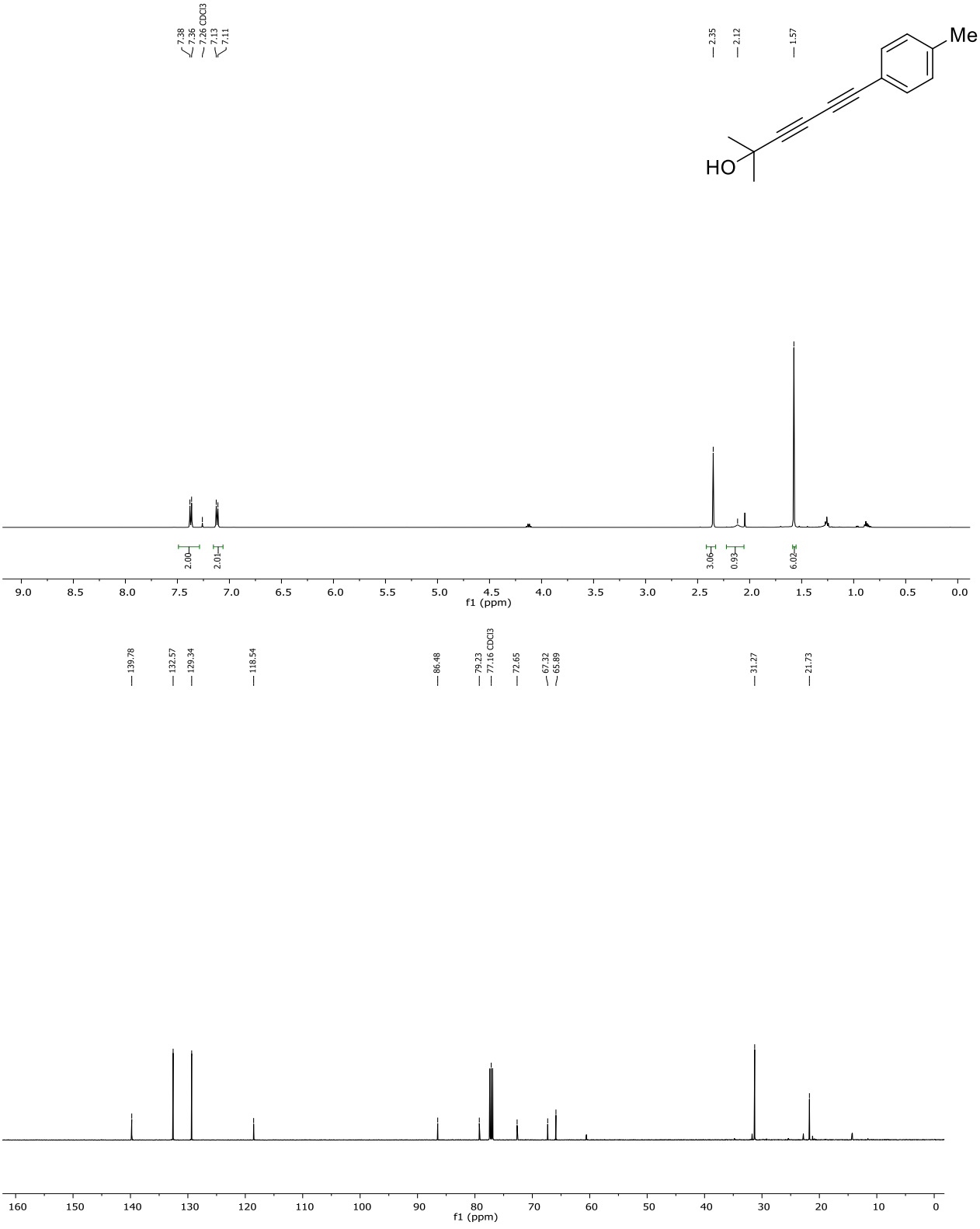


1-ethynyl-4-methylbenzene

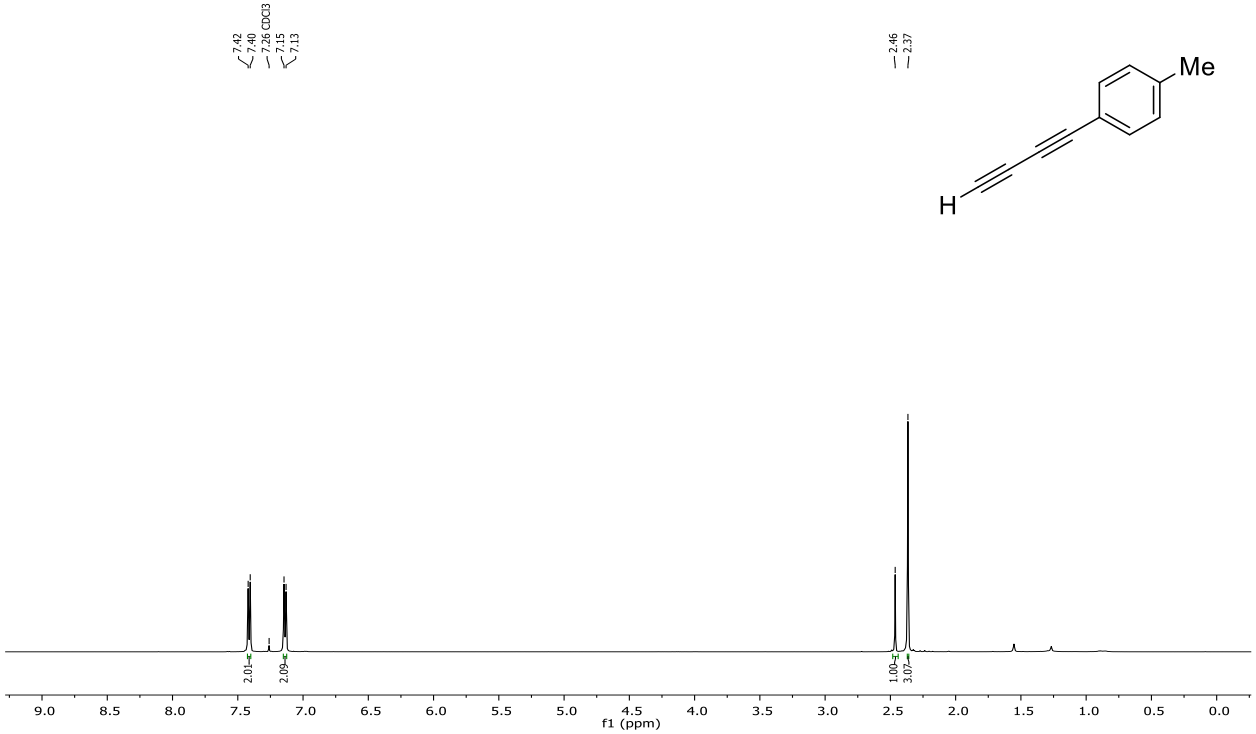


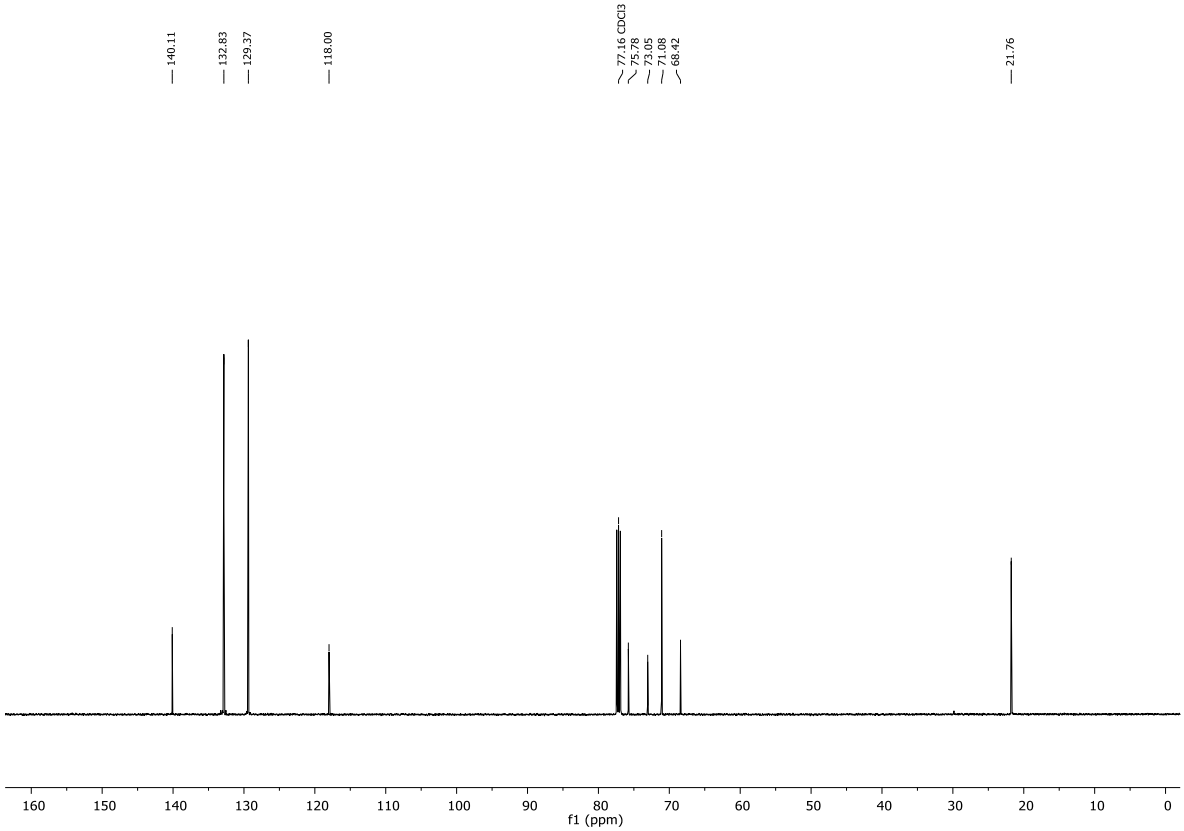


2-methyl-6-(*p*-tolyl)hexa-3,5-diyn-2-ol

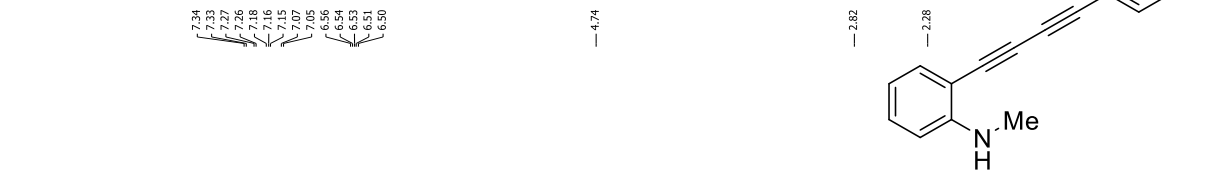


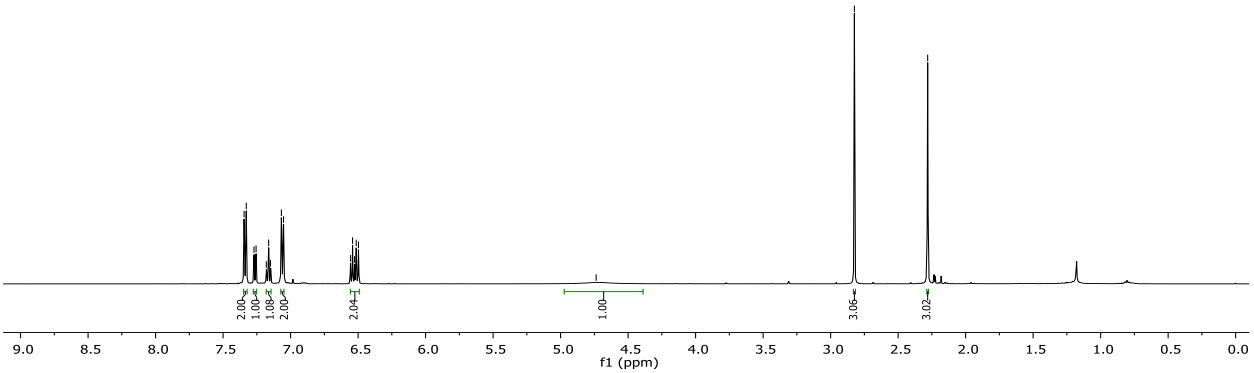
1-(buta-1,3-diyn-1-yl)-4-methylbenzene

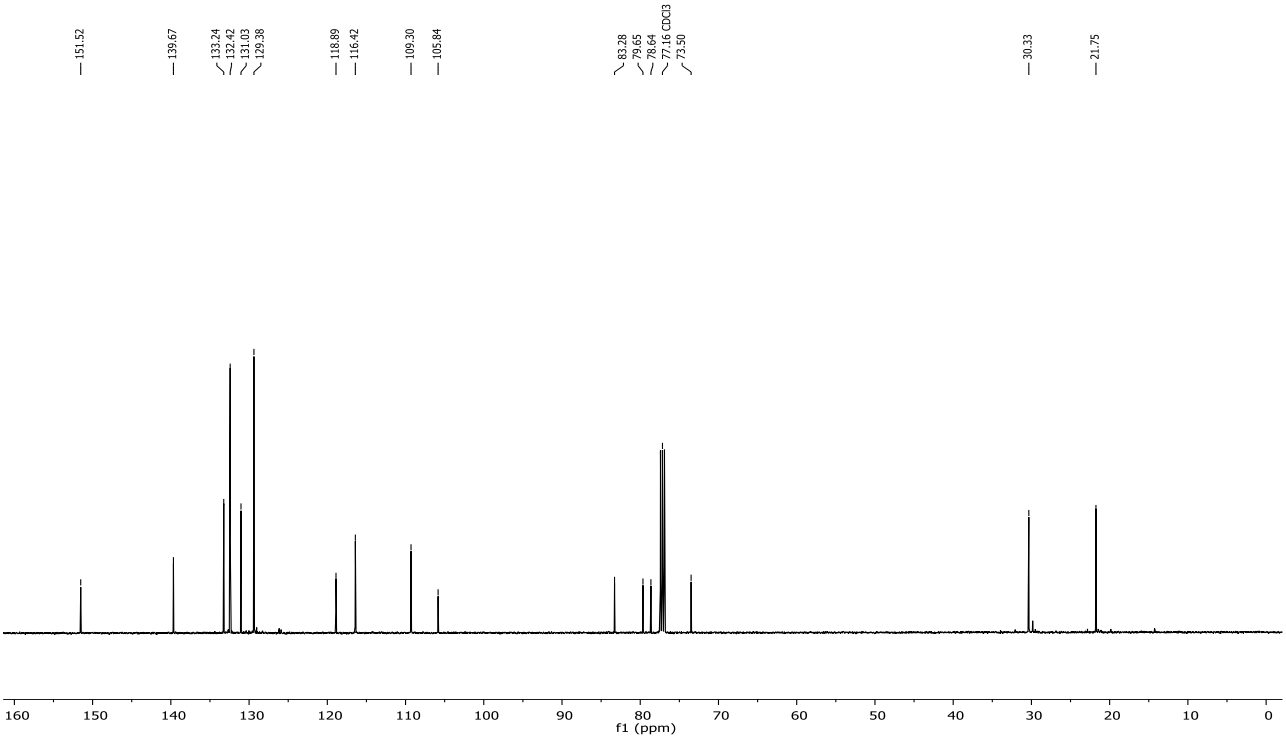




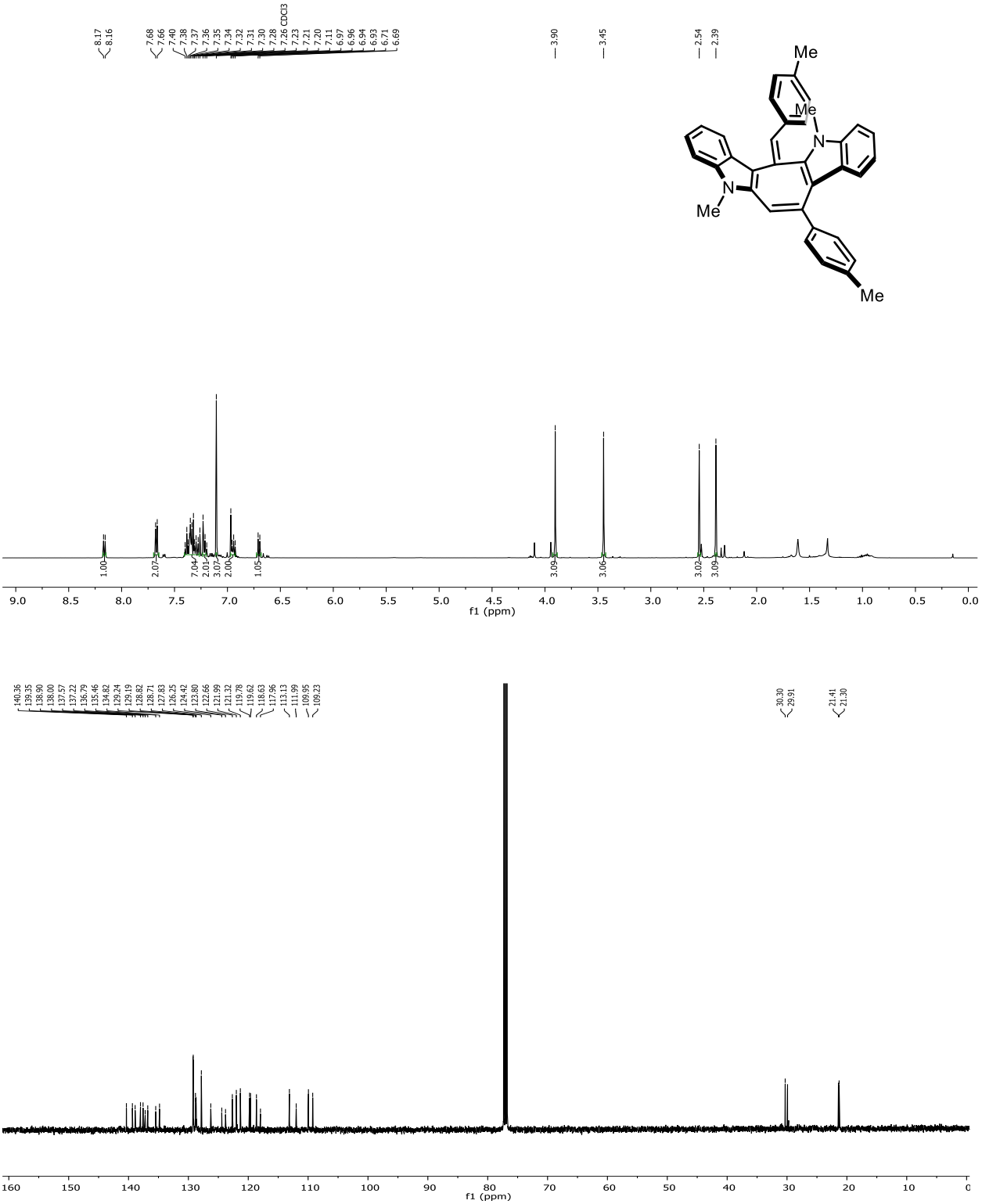
_N_-methyl-2-(_p_-tolylbuta-1,3-diyn-1-yl)aniline



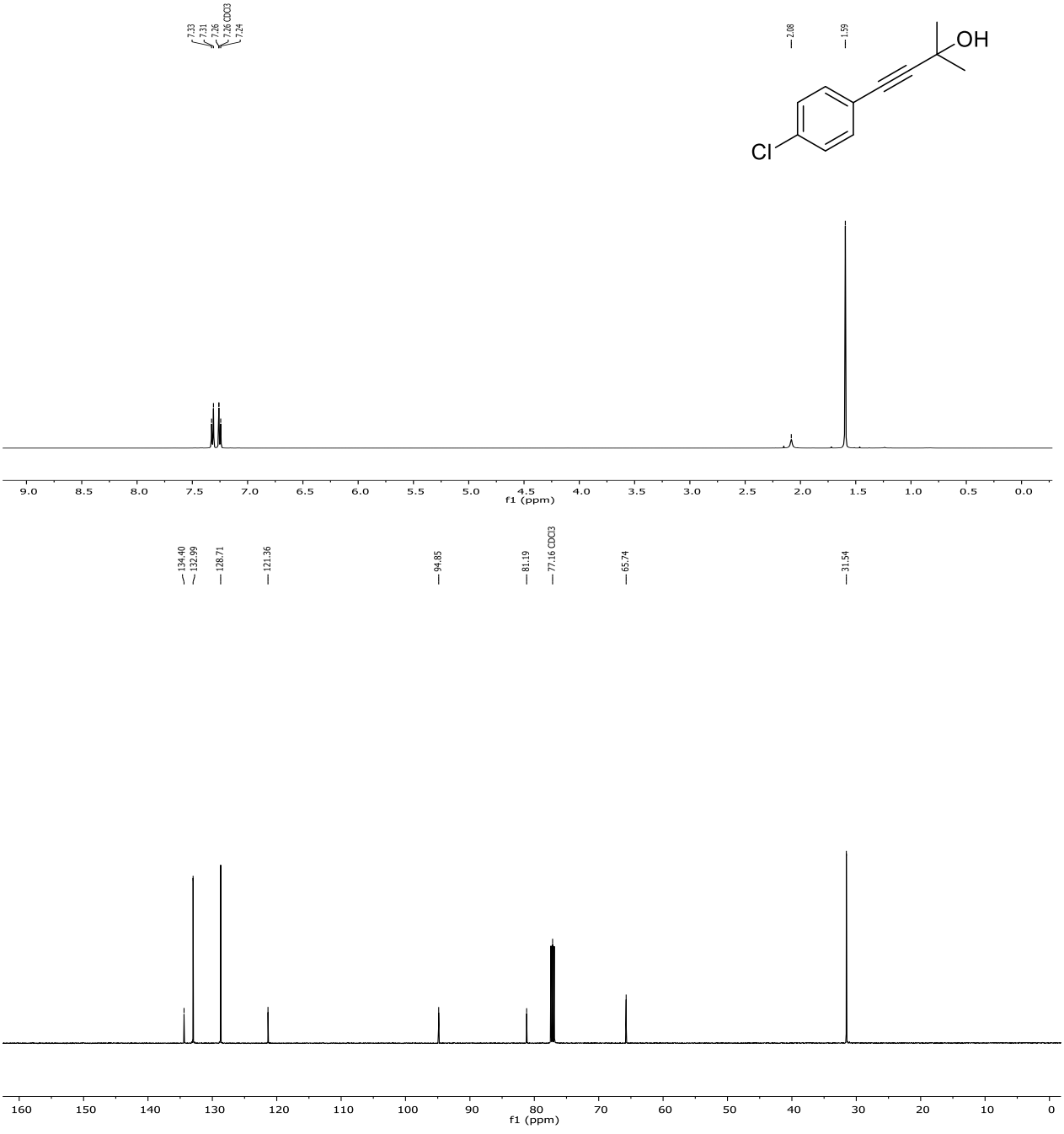




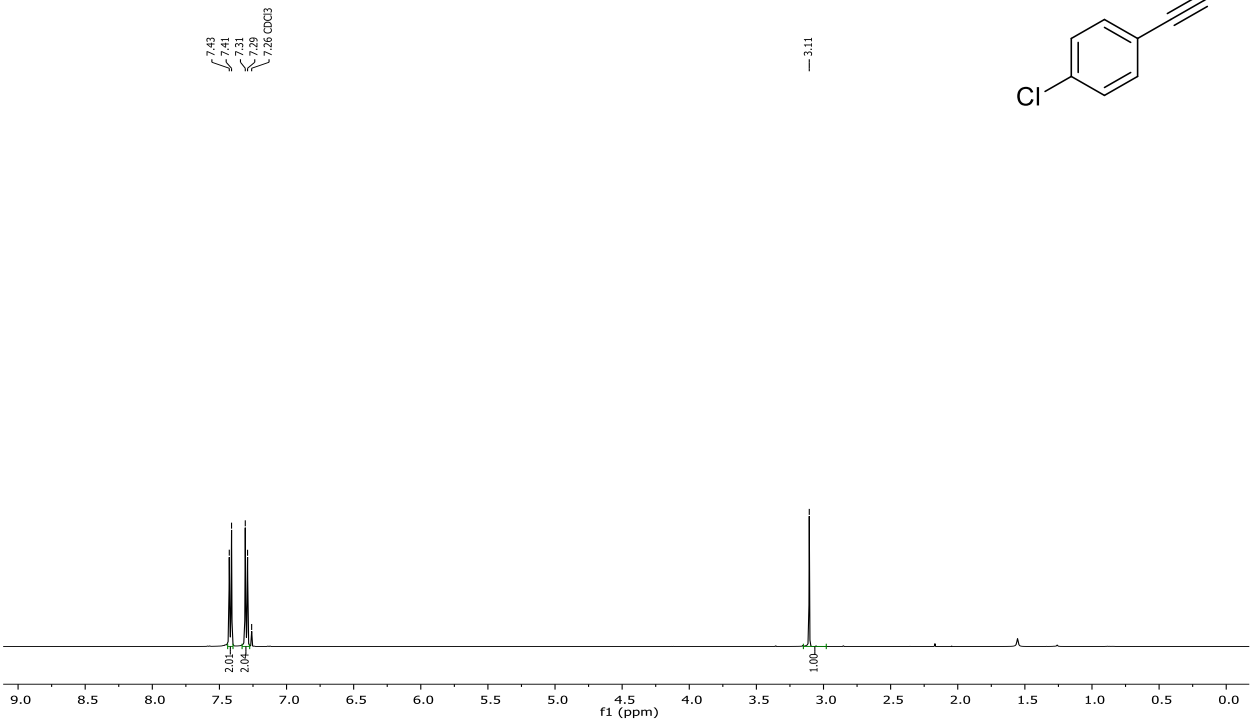
(*Z*)-5,11-dimethyl-6-(4-methylbenzylidene)-13-(*p*-tolyl)-6,11-dihydro-5*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindole

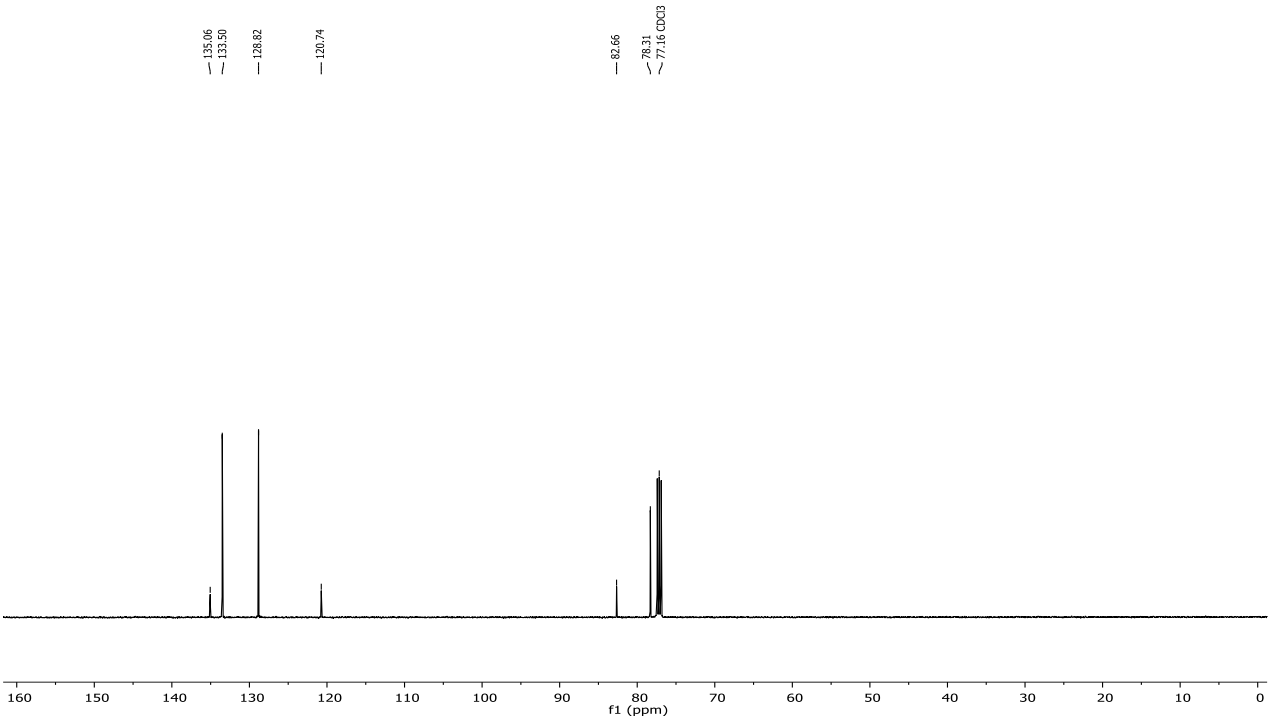


4-(4-chlorophenyl)-2-methylbut-3-yn-2-ol

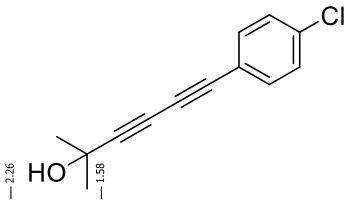


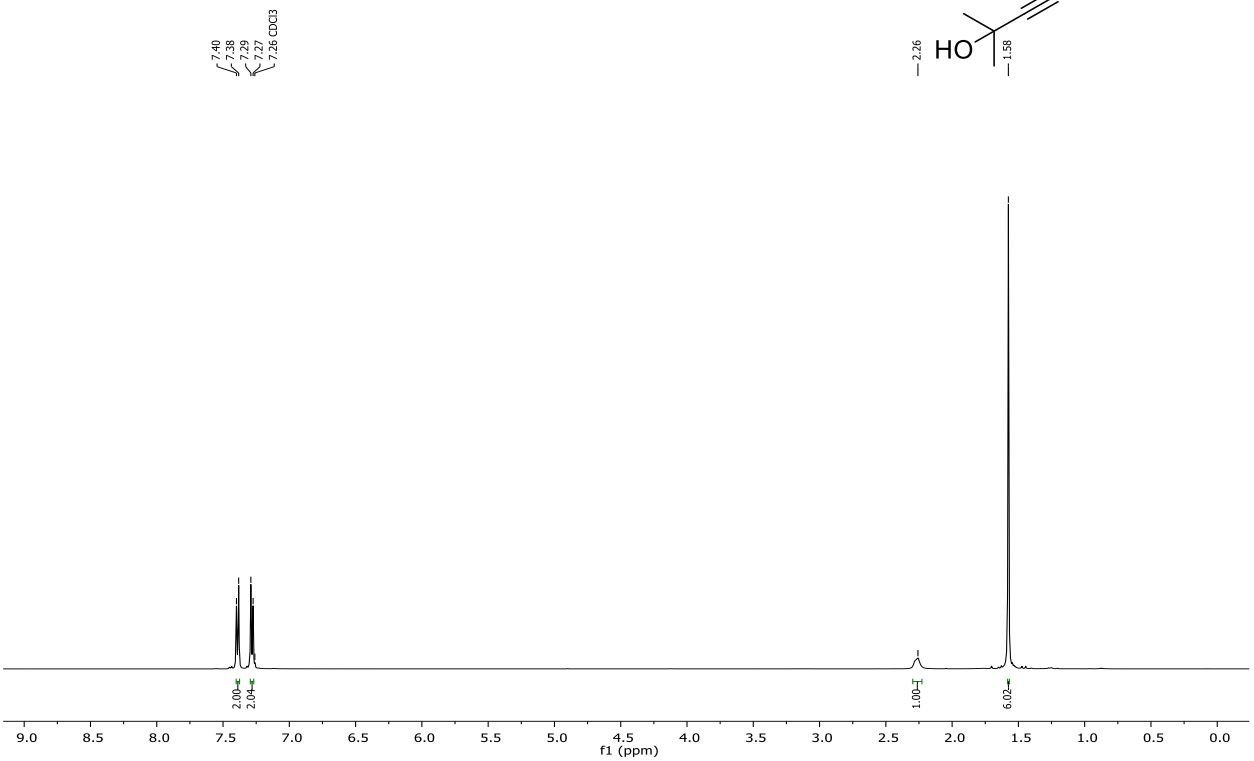
1-chloro-4-ethynylbenzene

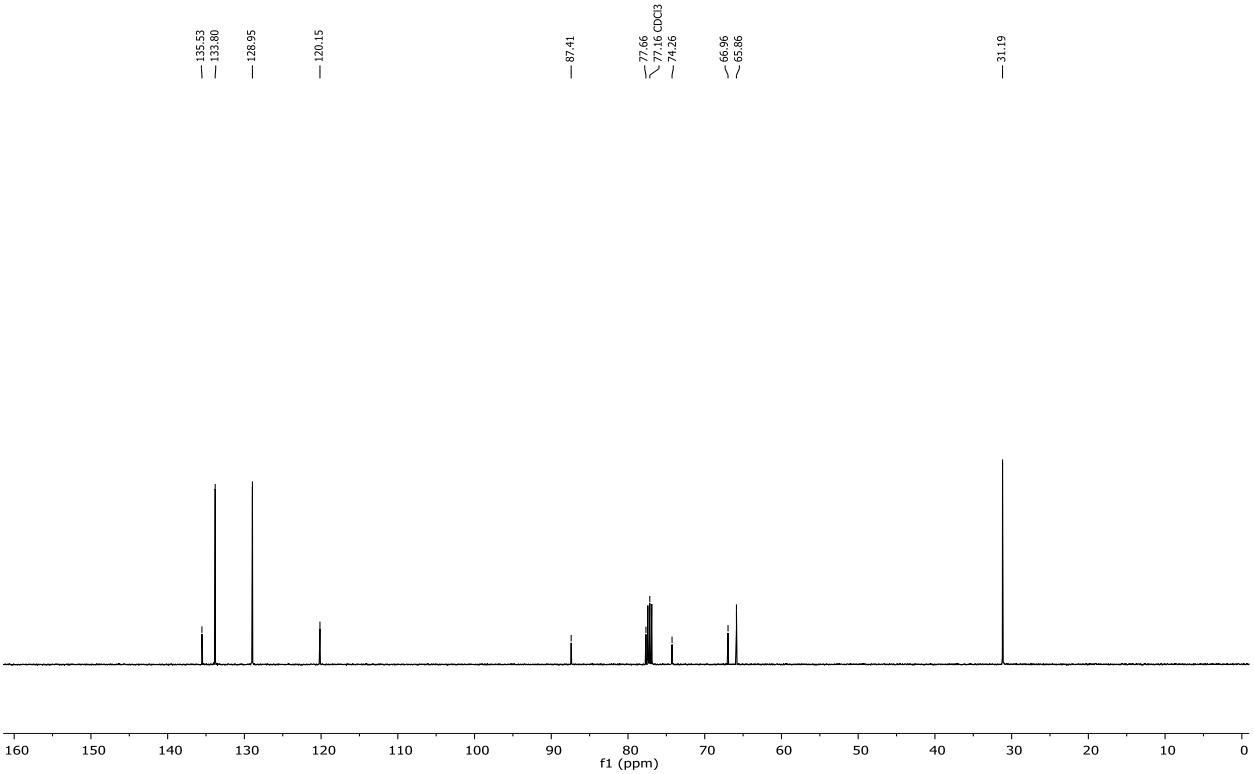




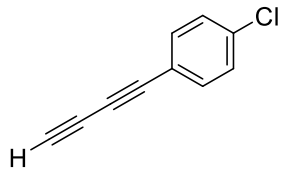
6-(4-chlorophenyl)-2-methylhexa-3,5-diyn-2-ol

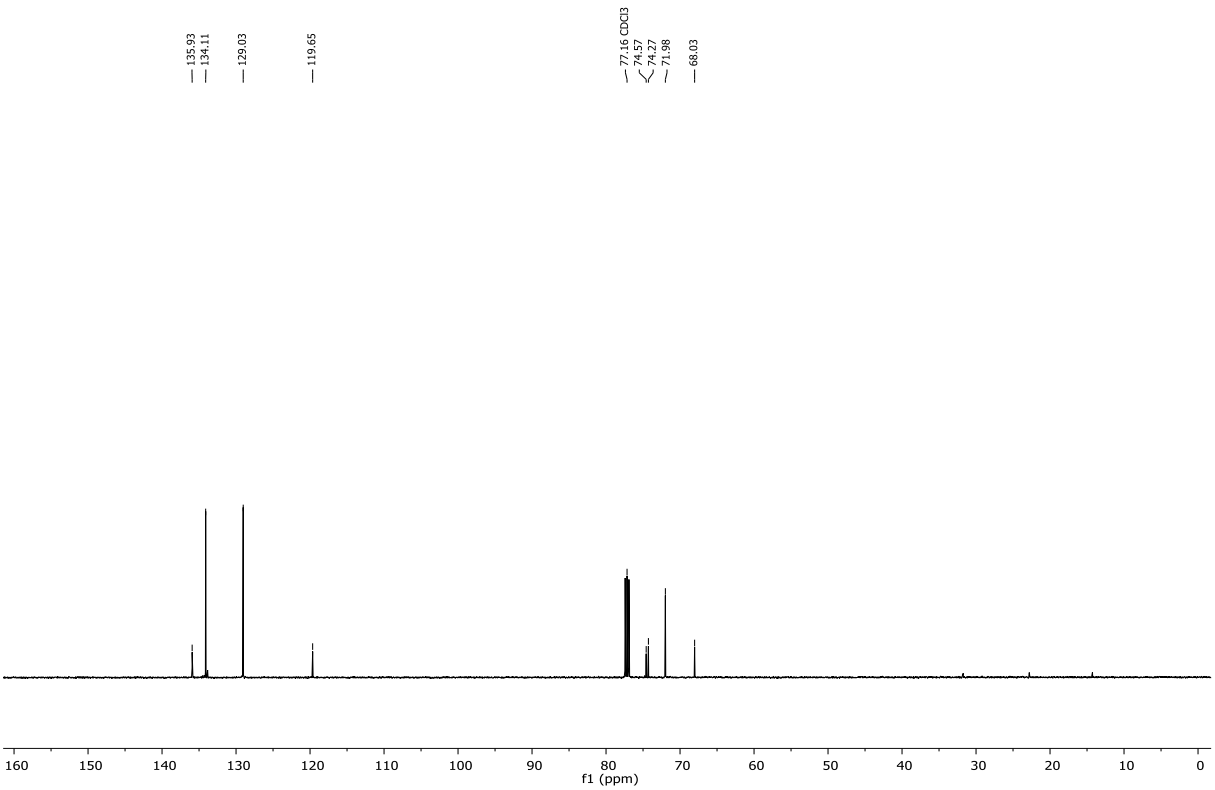




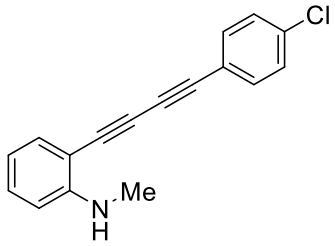


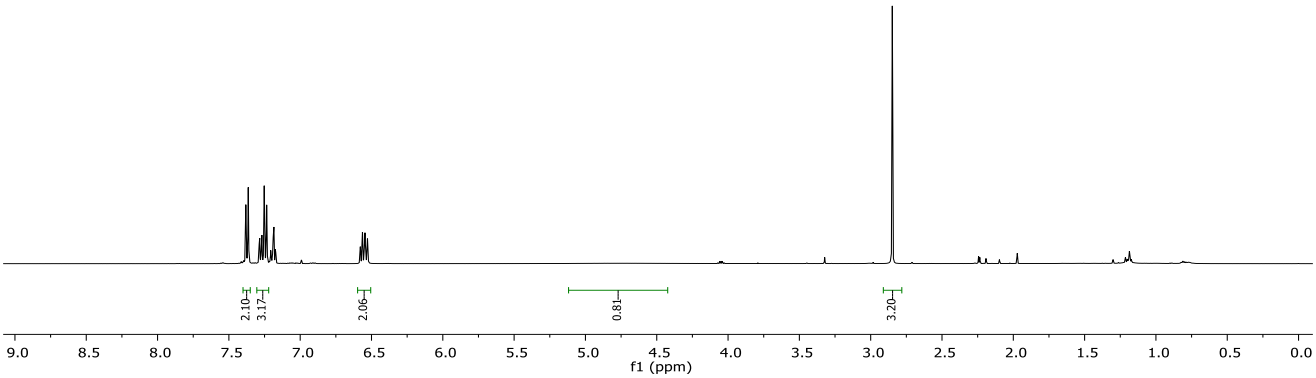
1-(buta-1,3-diyn-1-yl)-4-chlorobenzene

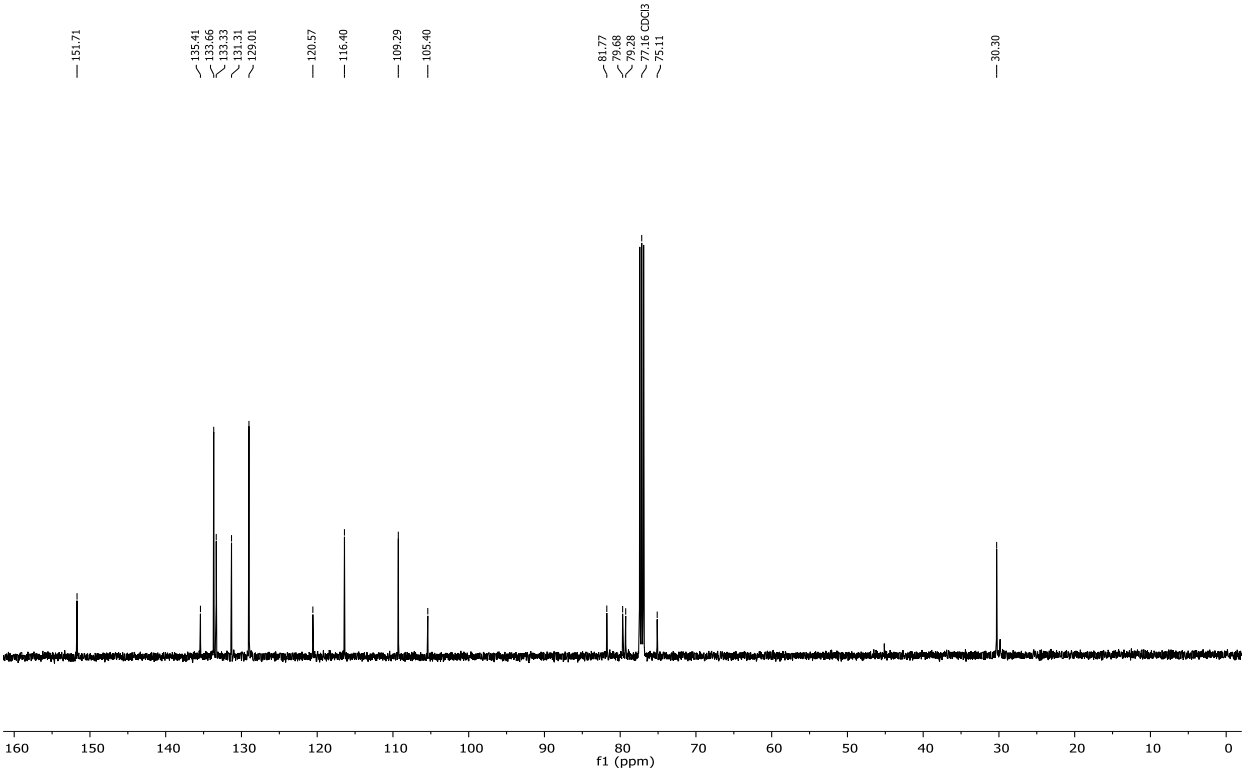




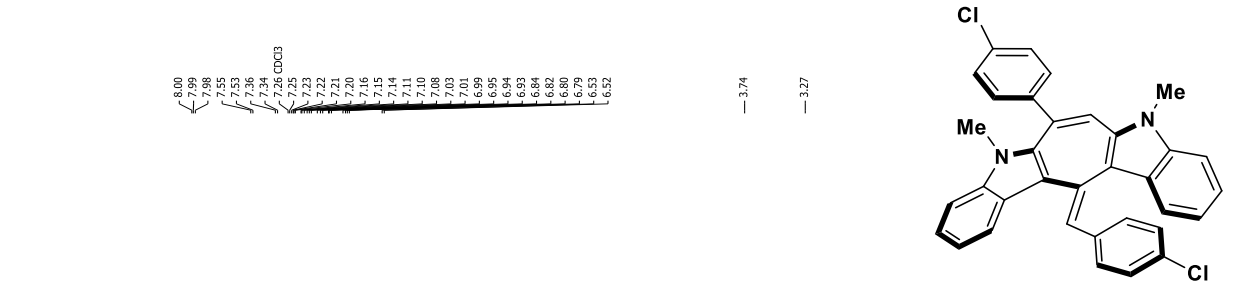
2-((4-chlorophenyl)buta-1,3-diyn-1-yl)-*N*-methylaniline

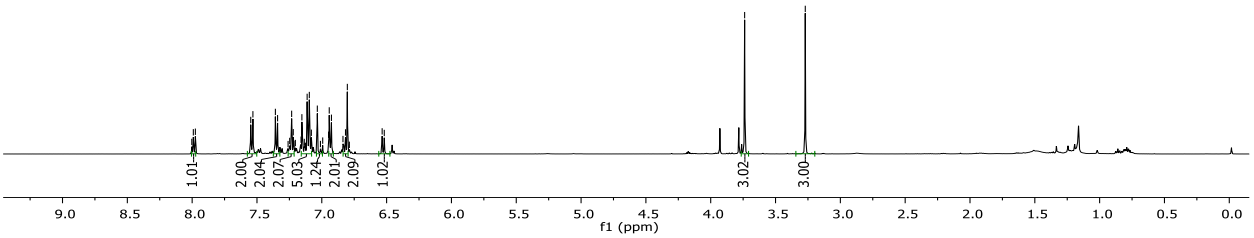


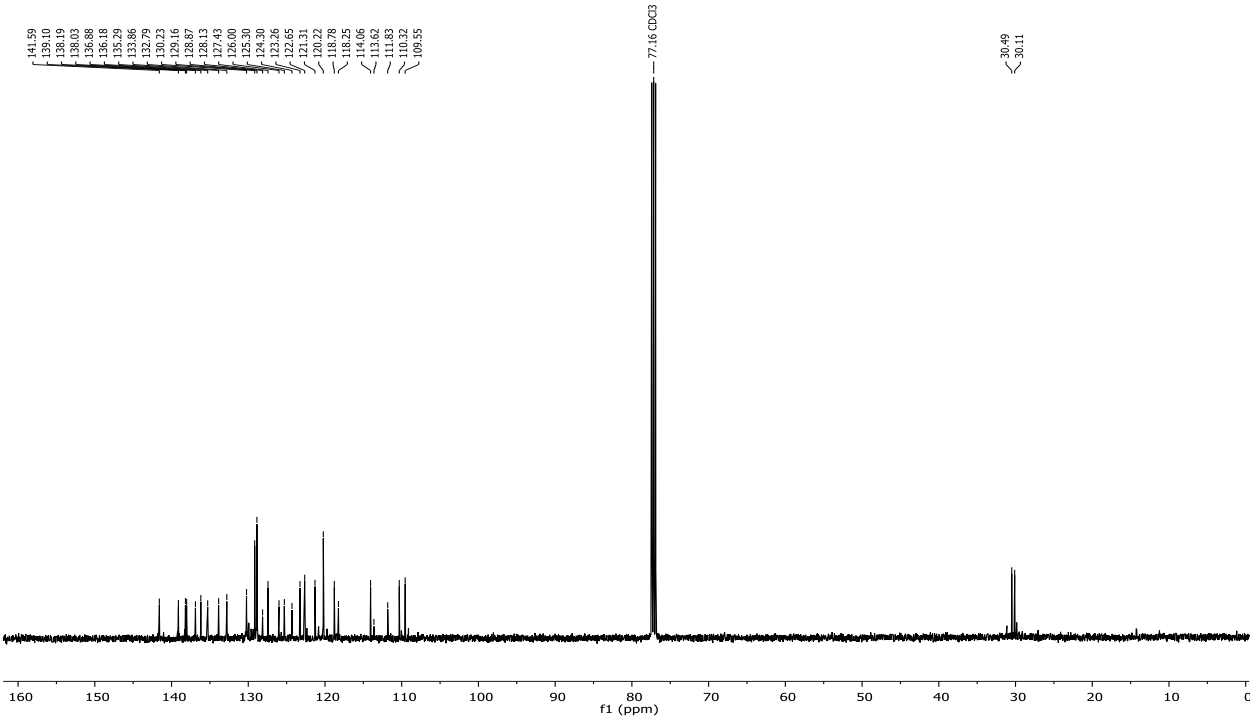




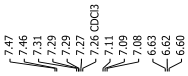
***(E)*-13-(4-Chlorobenzylidene)-6-(4-Chlorophenyl)-5,8-dimehtl-8.13-dihydro-5H-Cyclohepta[1,2-b':5,4-b']diindole.**

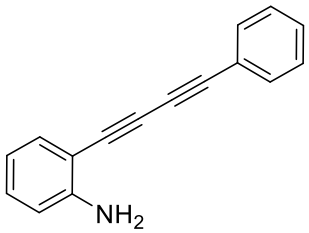


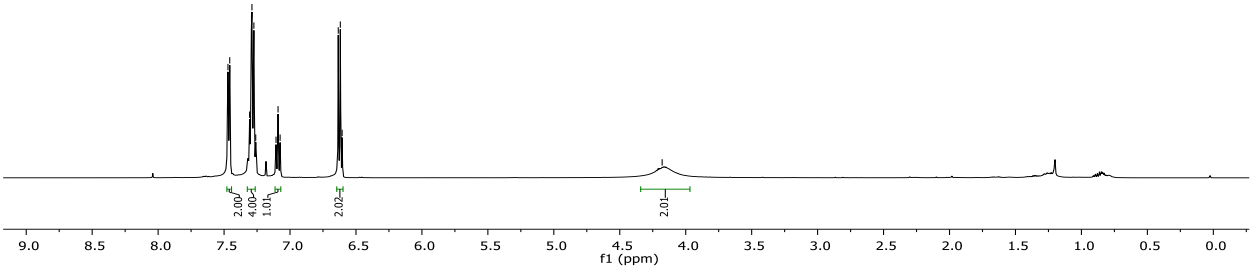


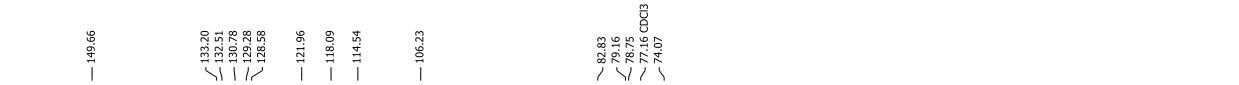


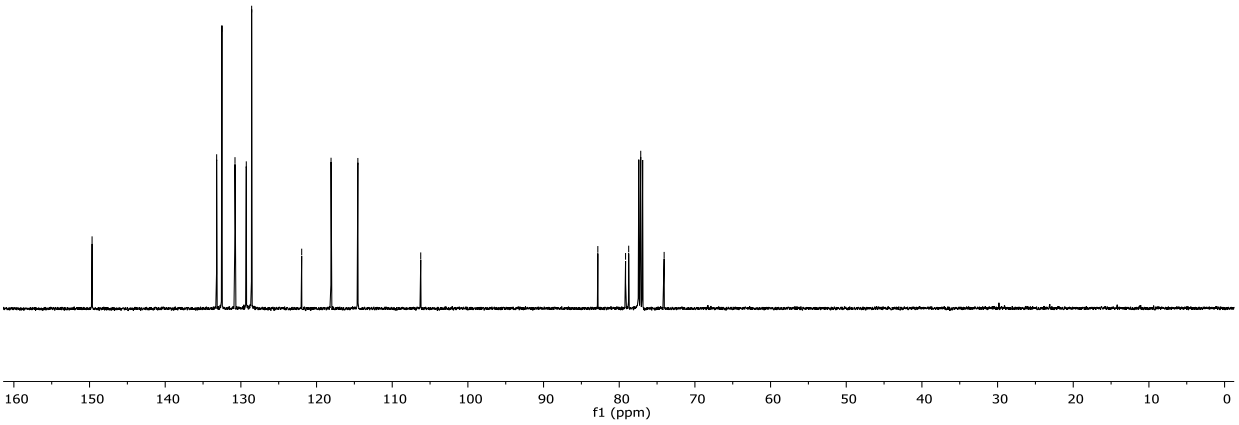
2-(phenylbuta-1,3-diyn-1-yl)aniline



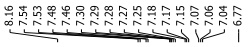


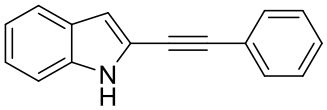


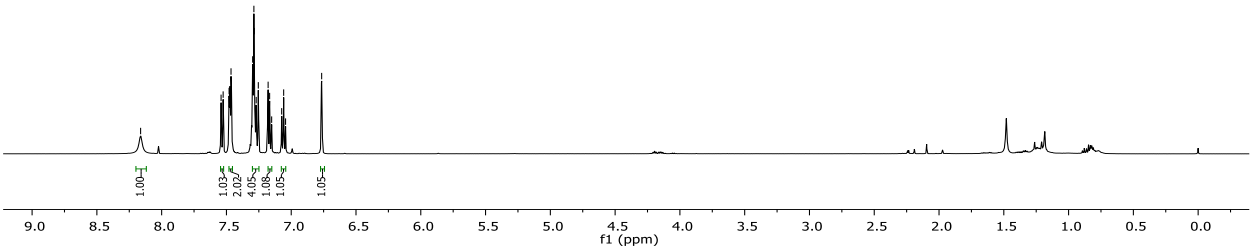


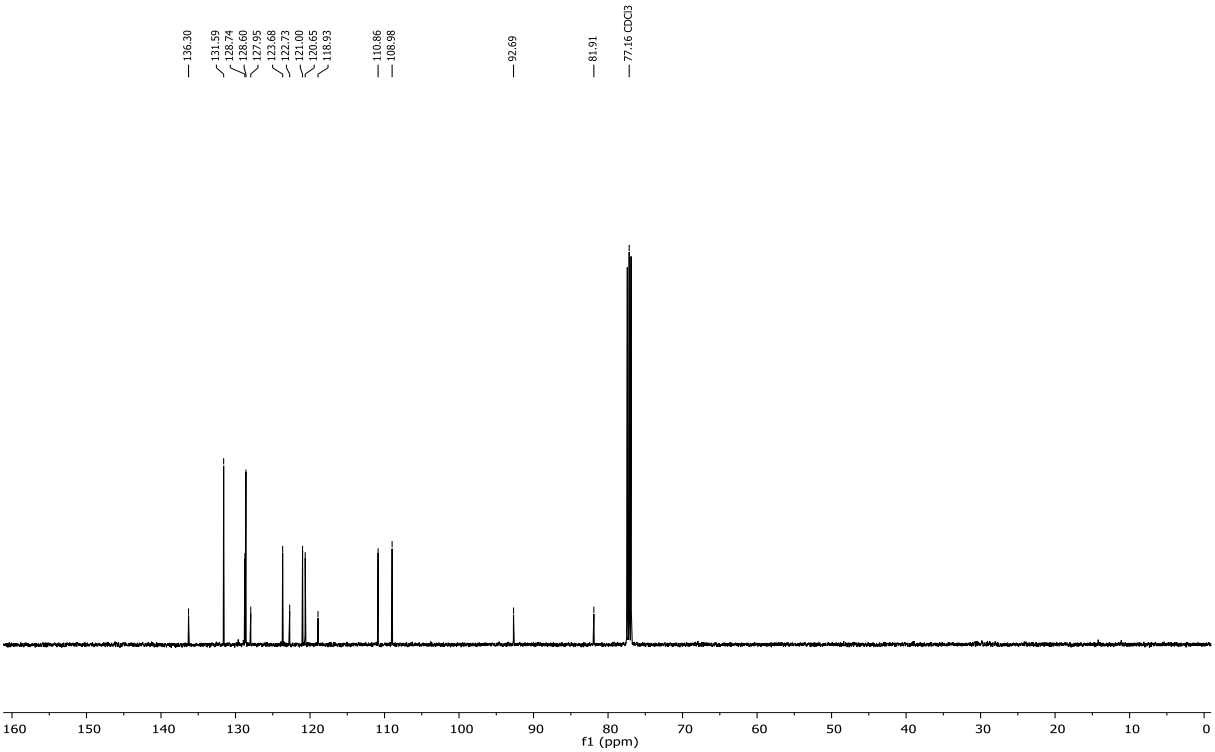


2-(phenylethynyl)-1*H*-indole

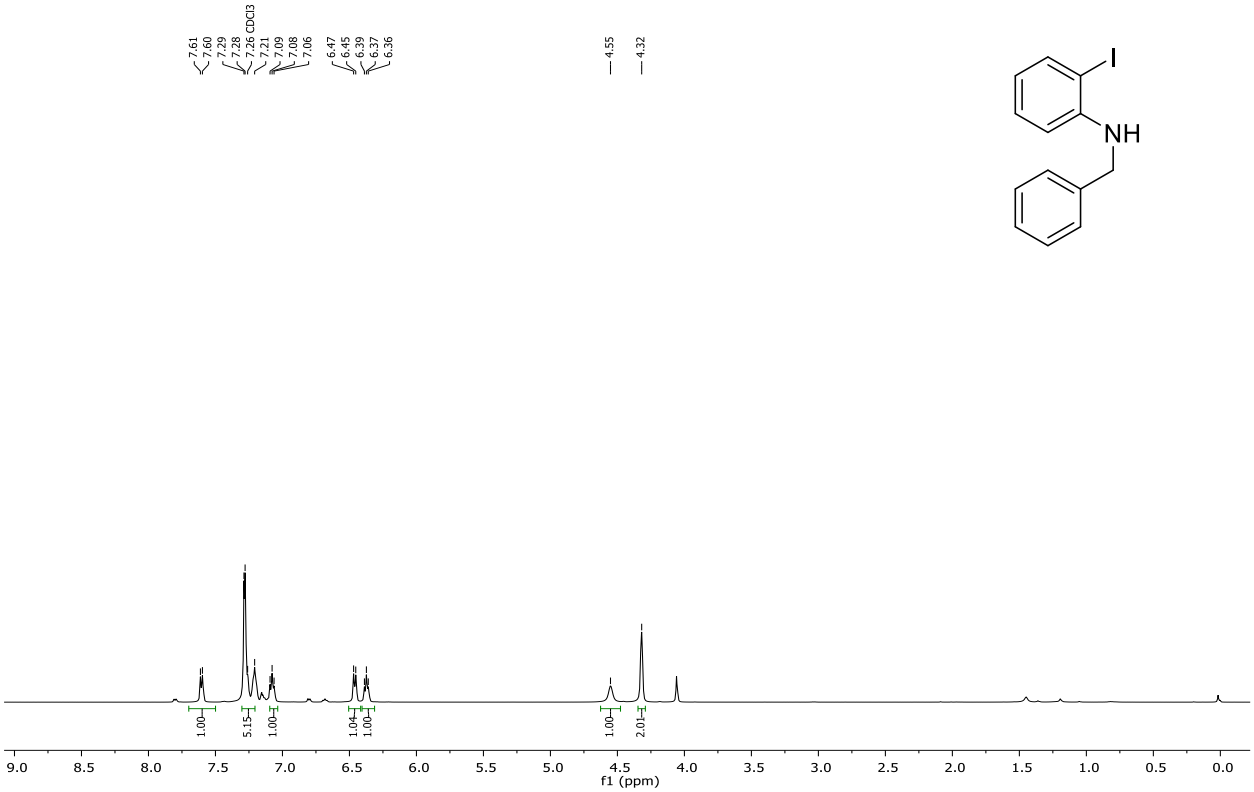


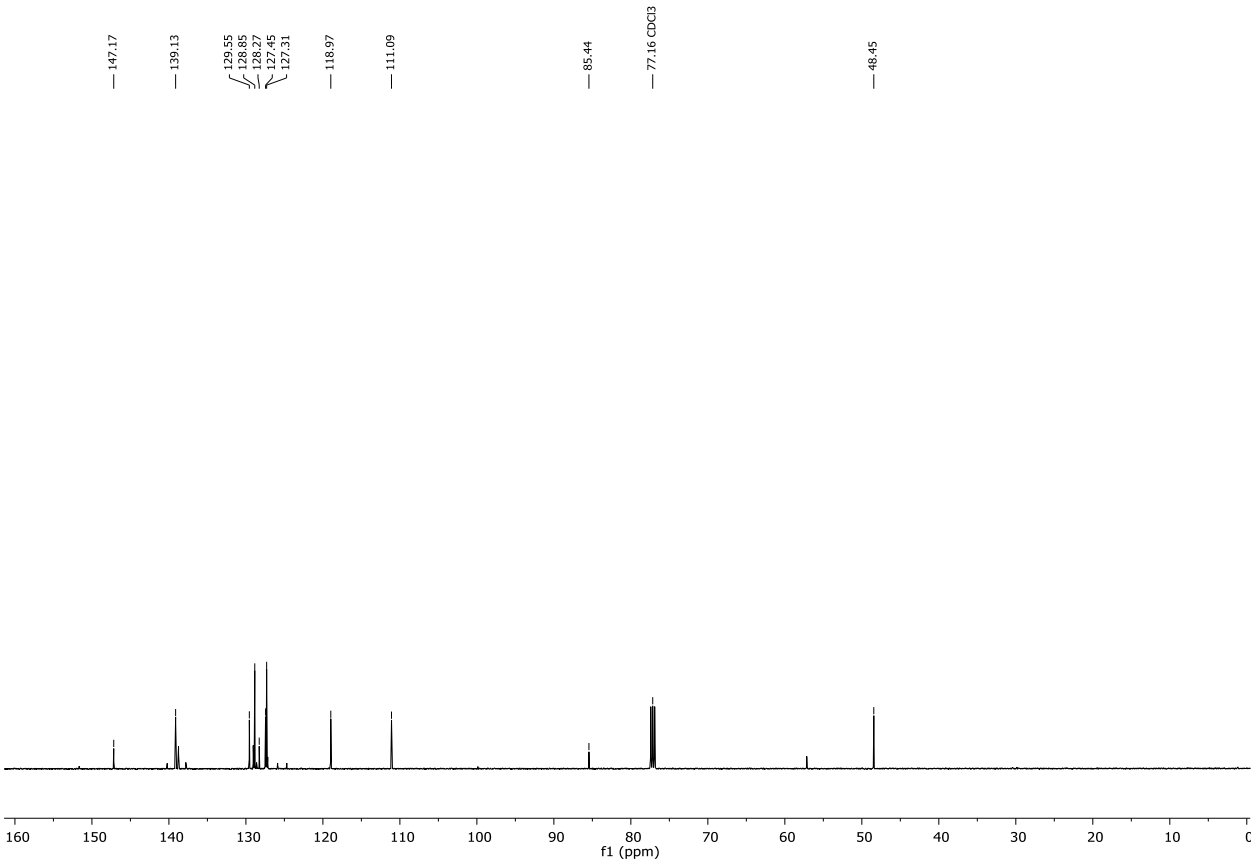




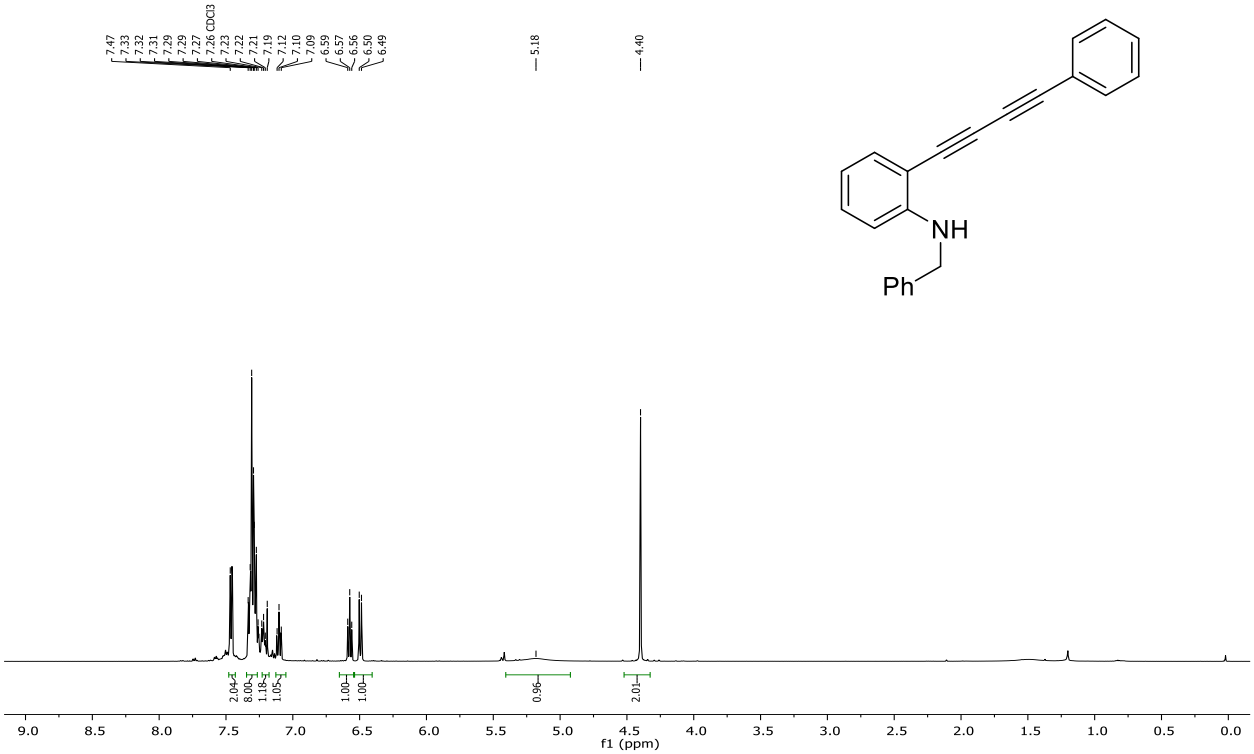


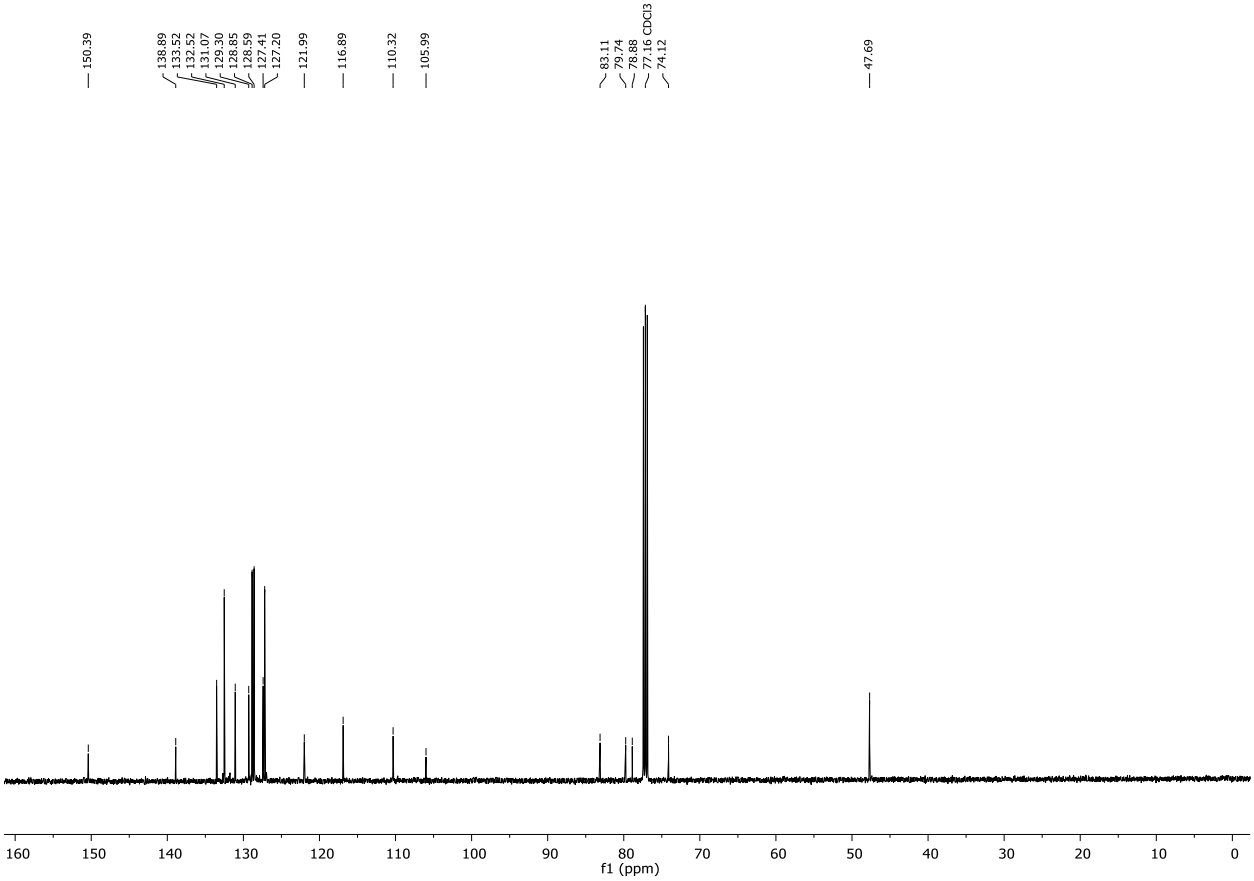
_N_-benzyl-2-iodoaniline.



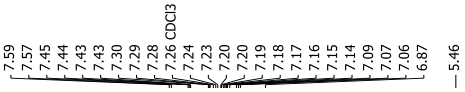


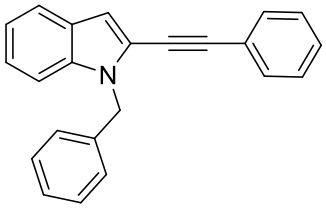
***N*-benzyl-2-(Phenylbuta-1,3-diyn-1-yl)aniline.**

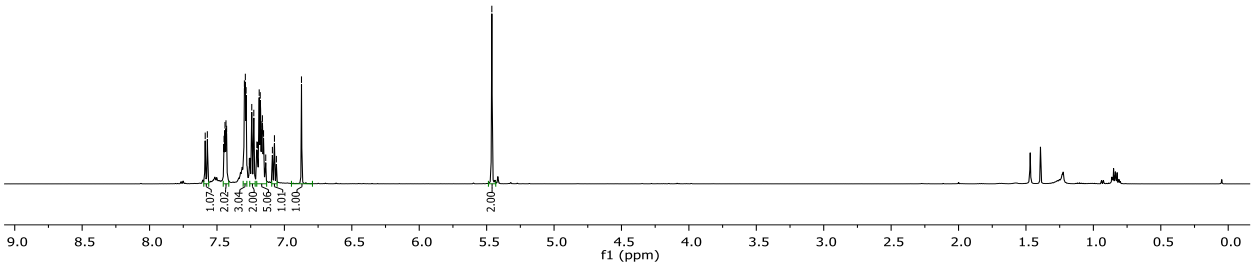


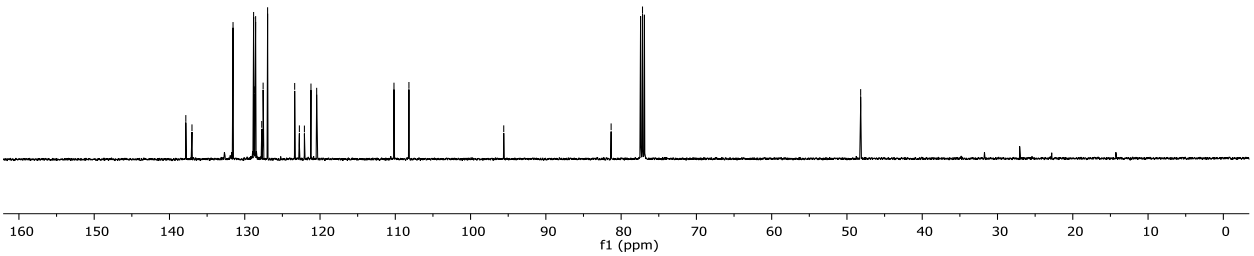


1- benzyl-2-(phenylethynyl)-1,*H*-indole

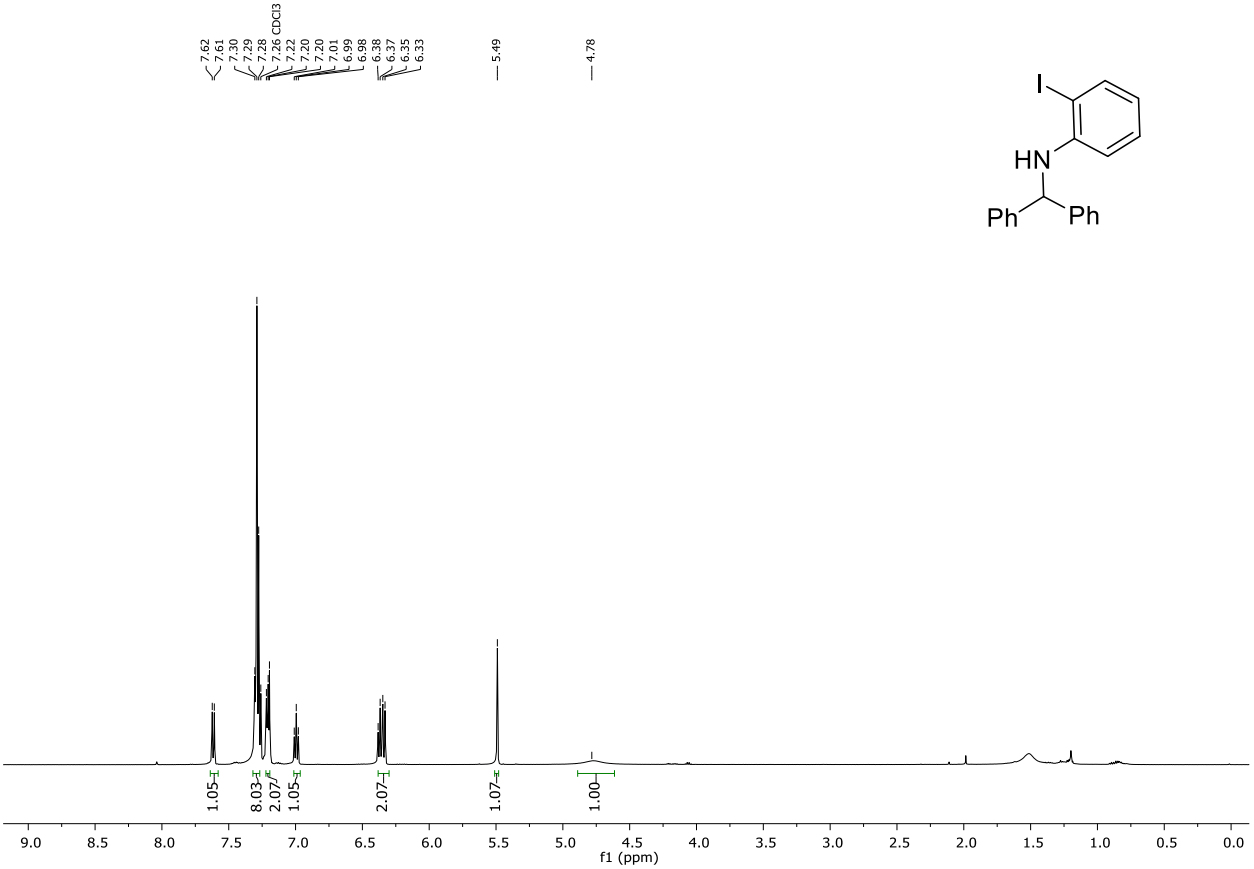


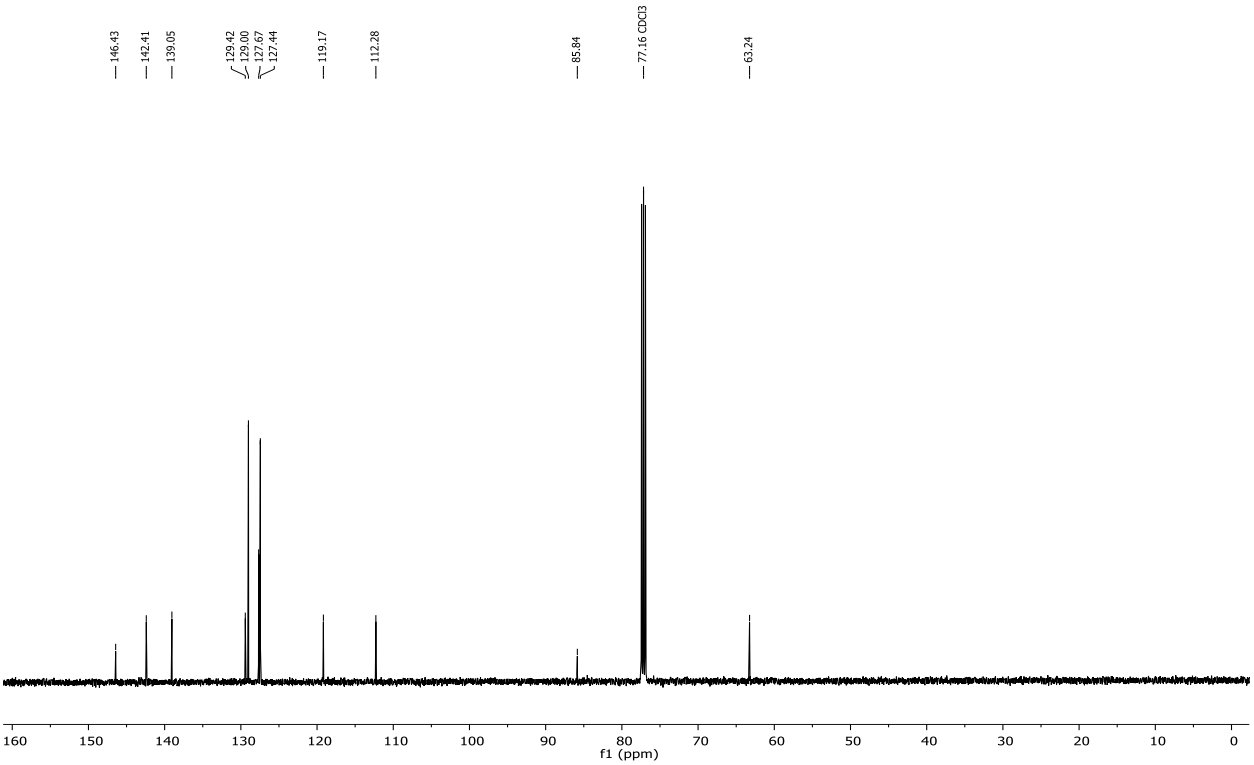




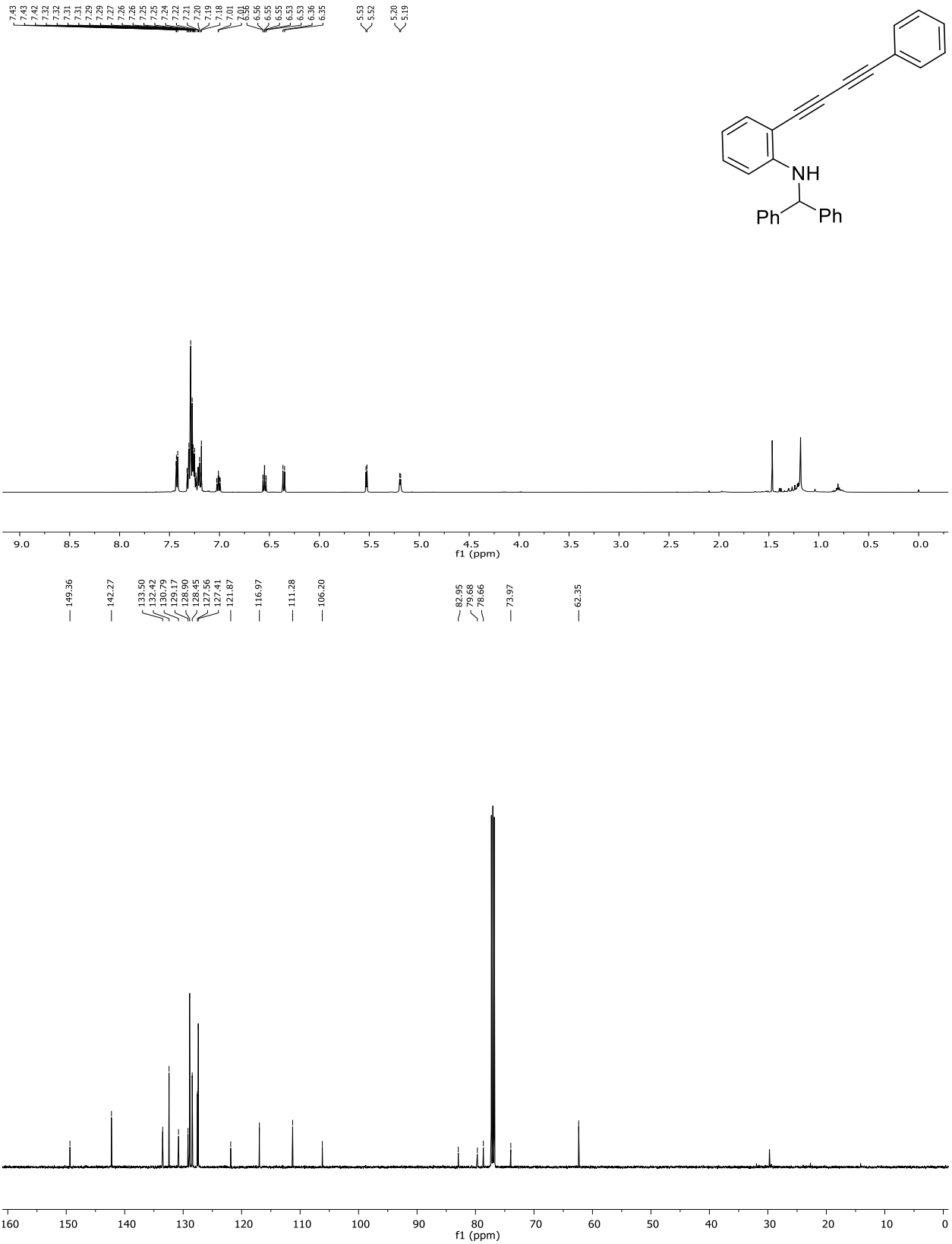


***N*-benzhydryl-2-iodoaniline.**

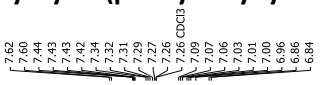


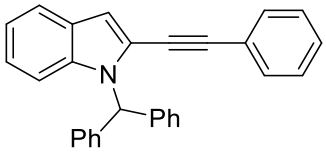


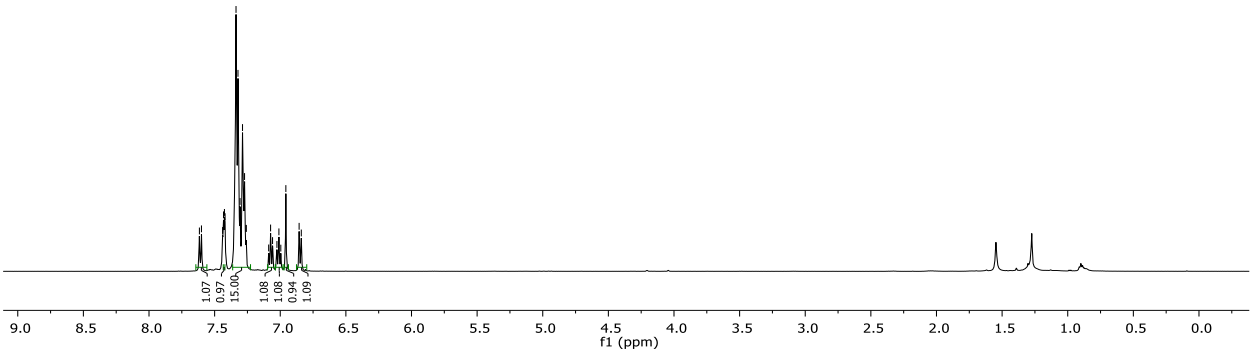
***N*-benzhydryl-2-(Phenylbuta-1,3-diyn-1-yl)aniline.**

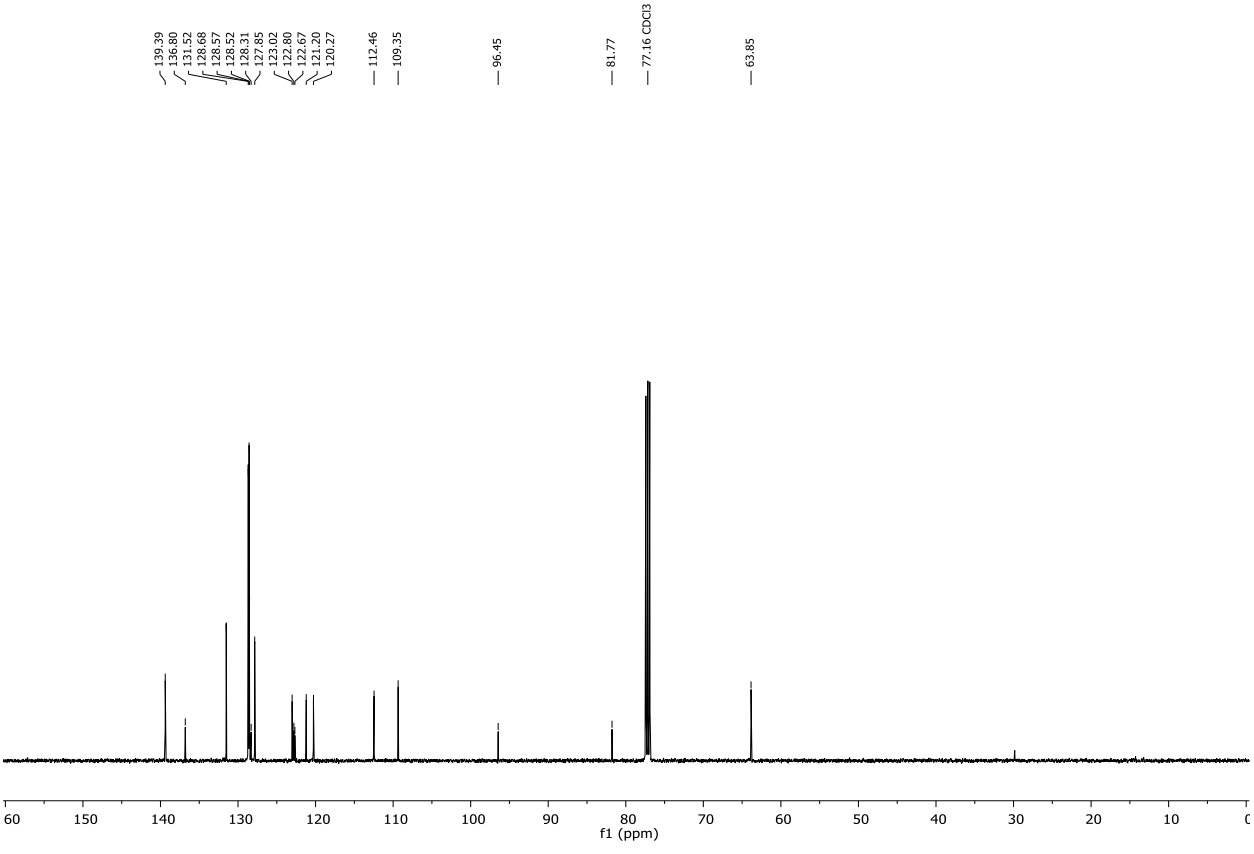


1-benzhydryl-2-(phenylethynyl-1-H-indole.



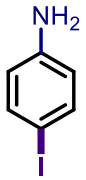


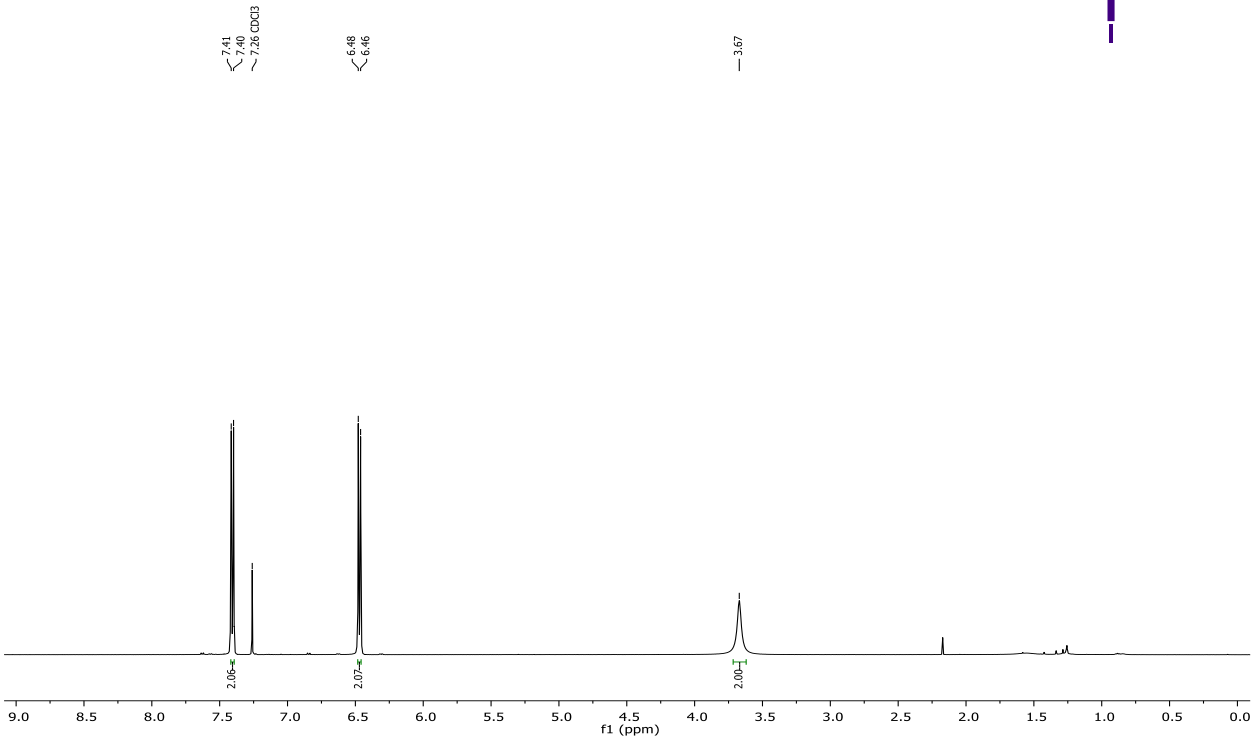


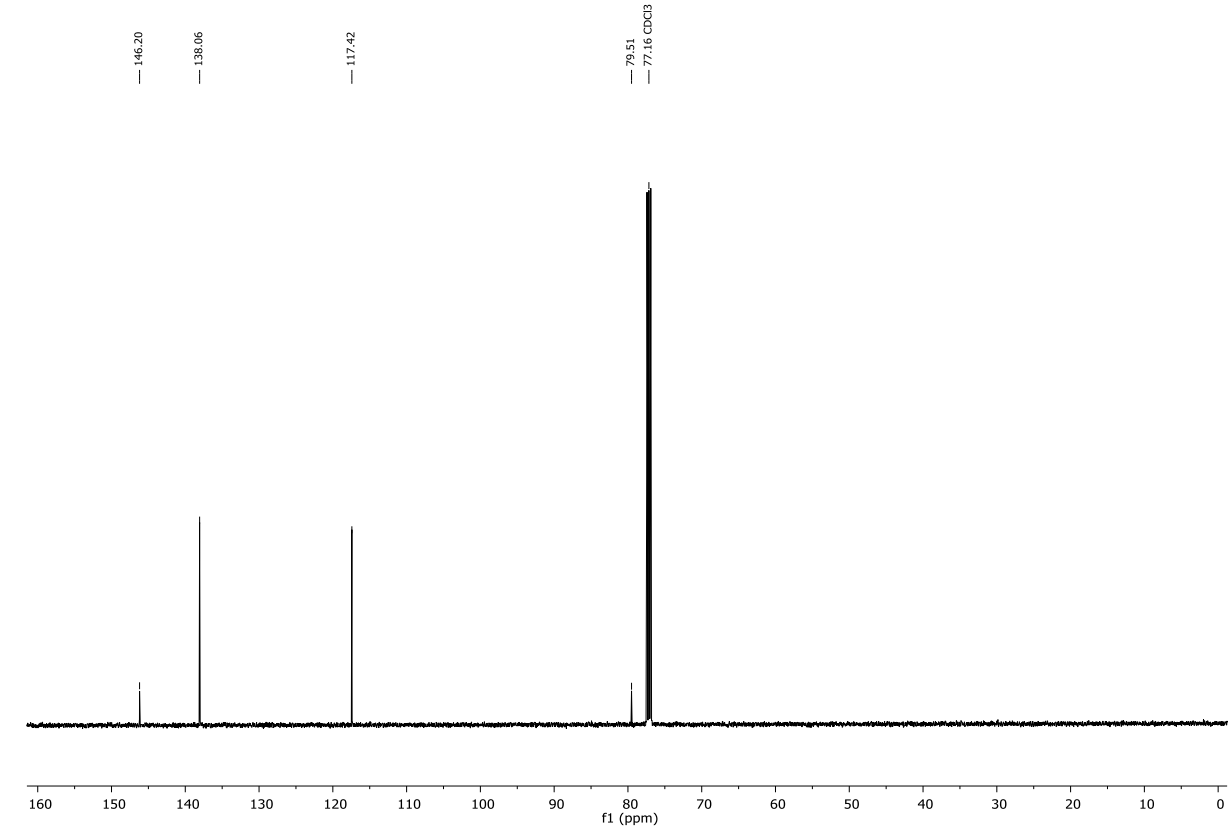


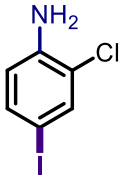
^{1}H and ^{13}C NMR Spectra of

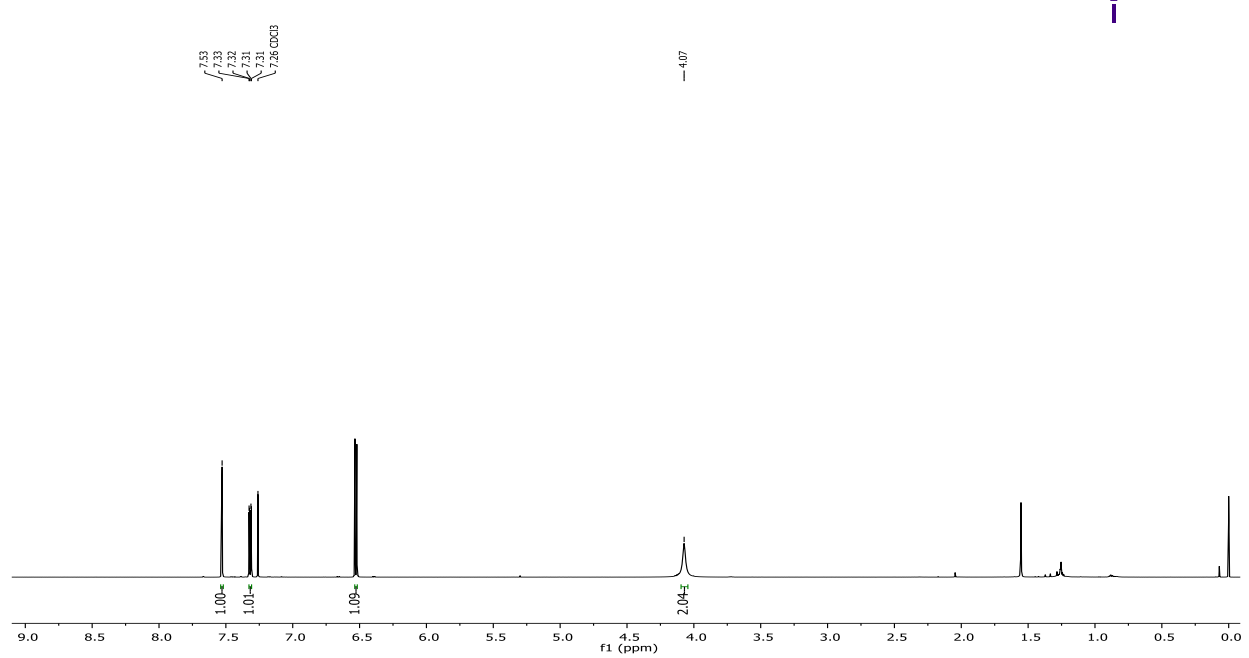
Chapters III.

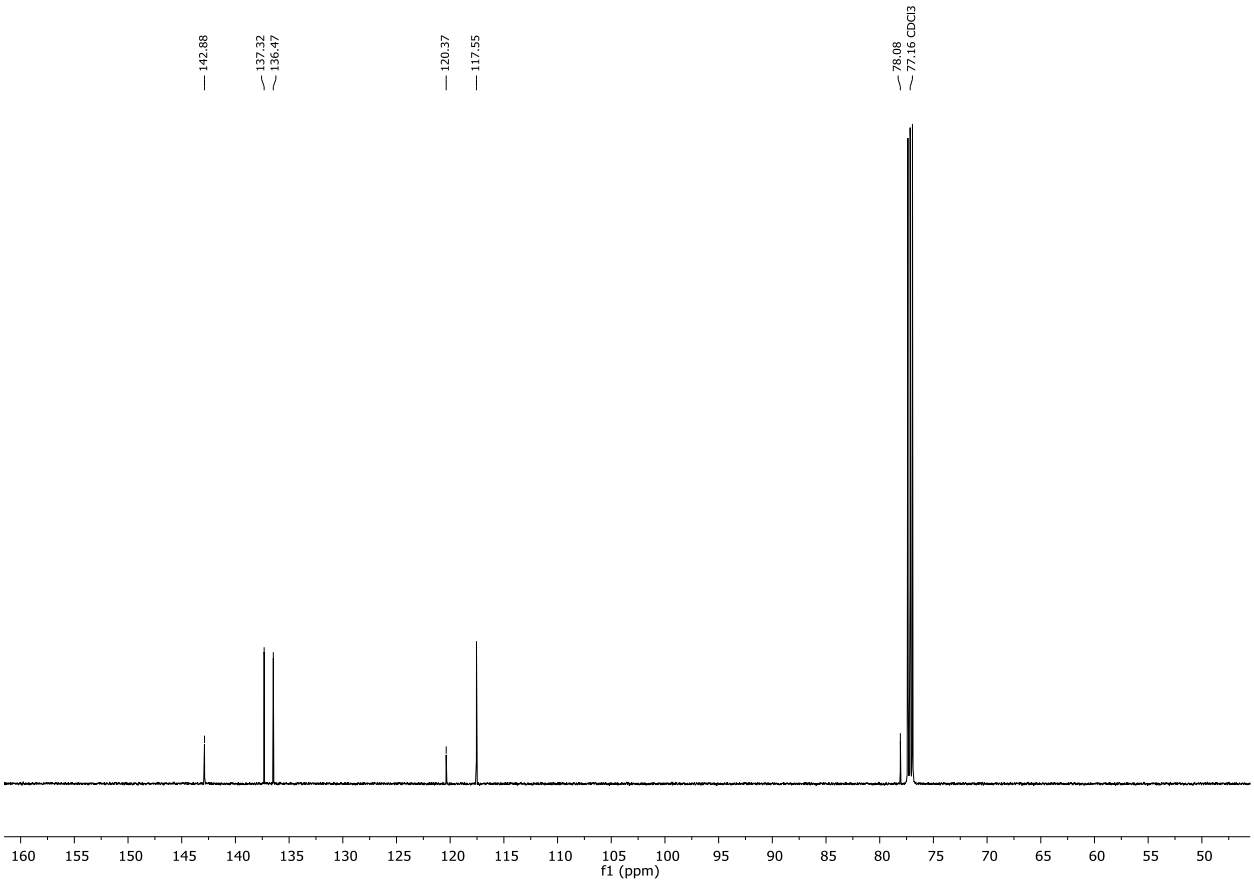

NH2
I

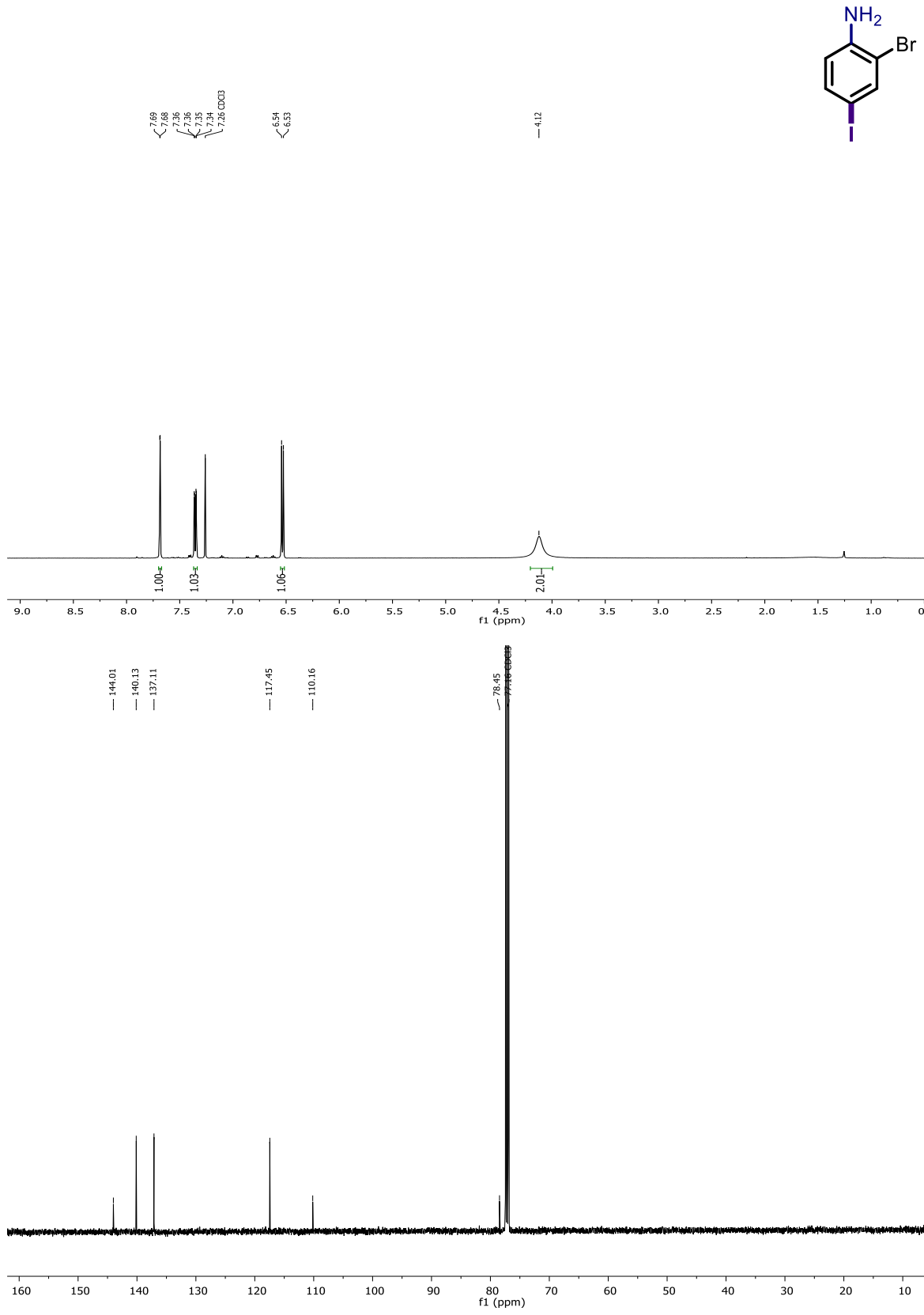

7.41
7.40
7.26 CDCl3
6.48
6.46
3.67
2.06
2.07
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

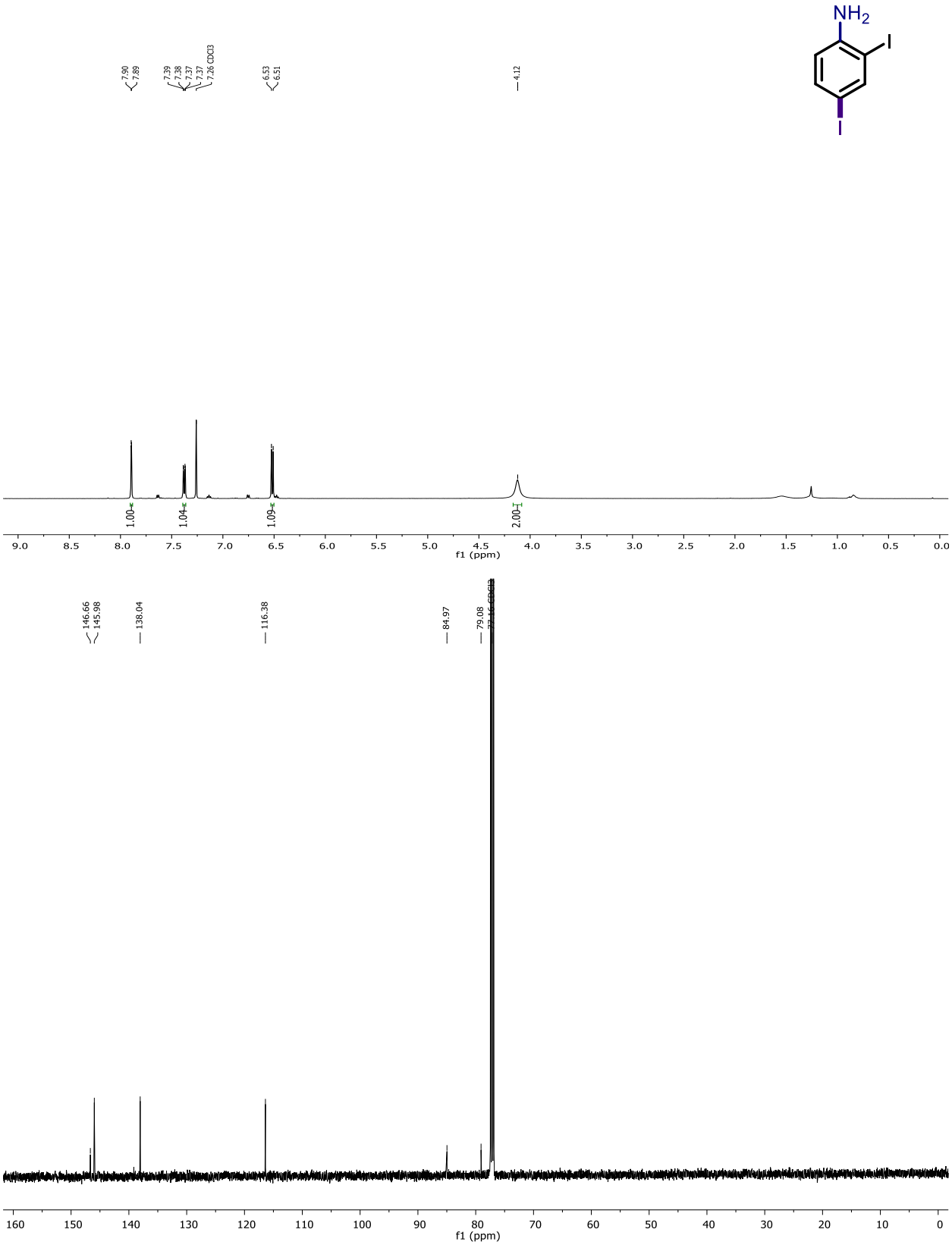

146.20
138.06
117.42
79.51
77.16 CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

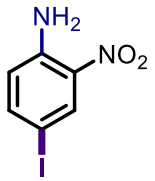

NH2
Cl
I

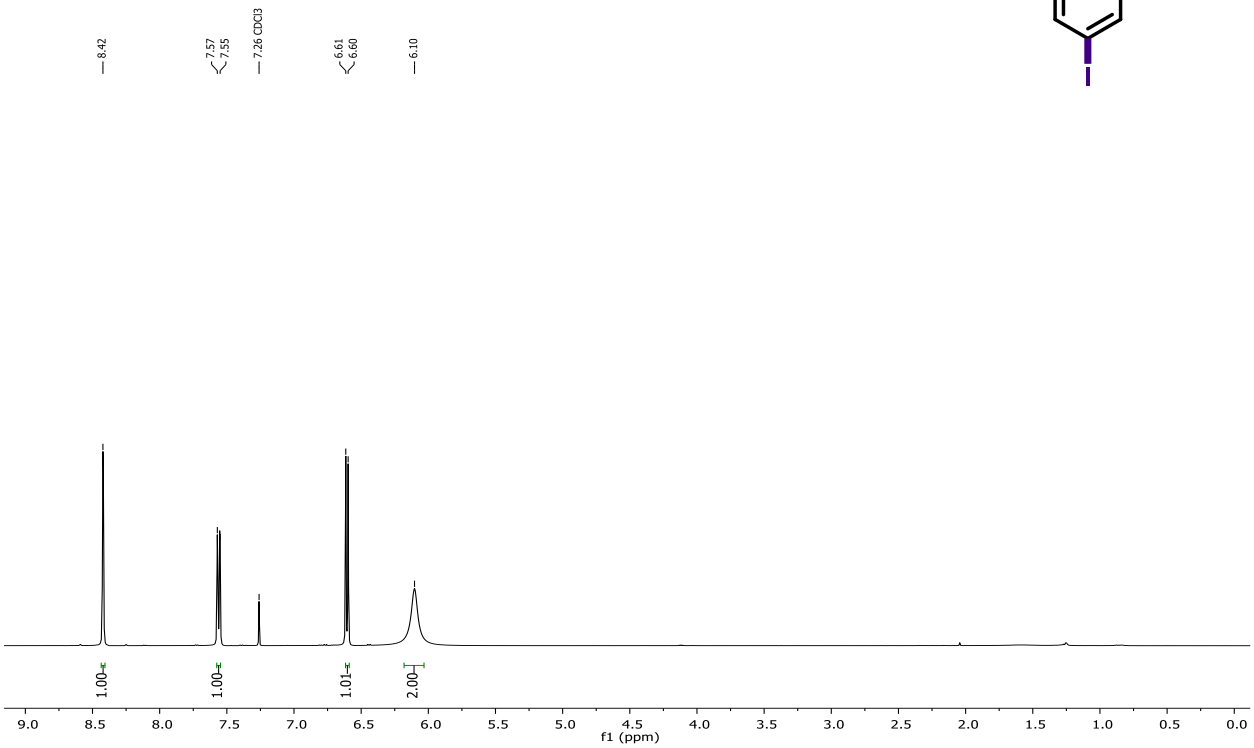

7.53
7.33
7.32
7.31
7.31
7.26 CDCl3
4.07
1.00
1.01
1.09
2.04
f1 (ppm)

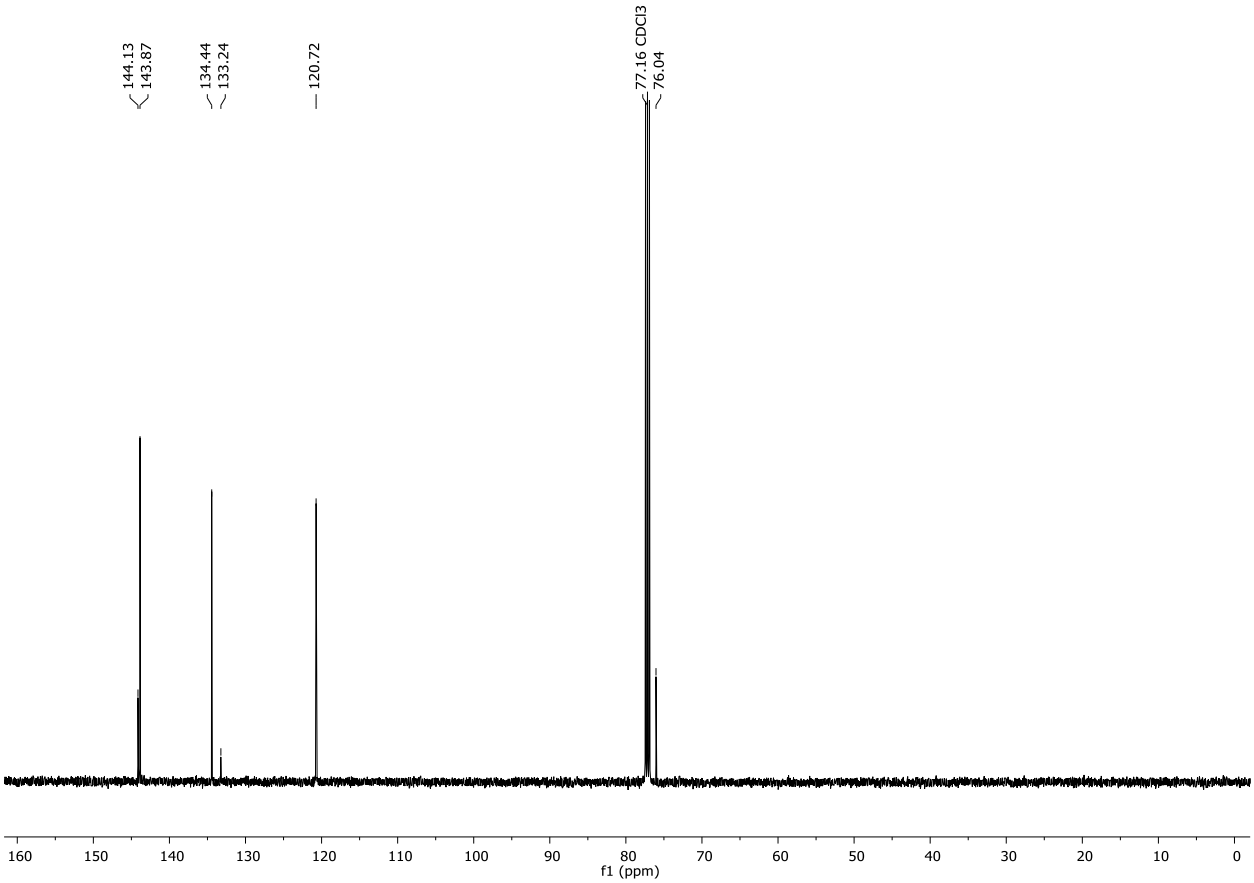

142.88
137.32
136.47
120.37
117.55
78.08
77.16 CDCl3
f1 (ppm)

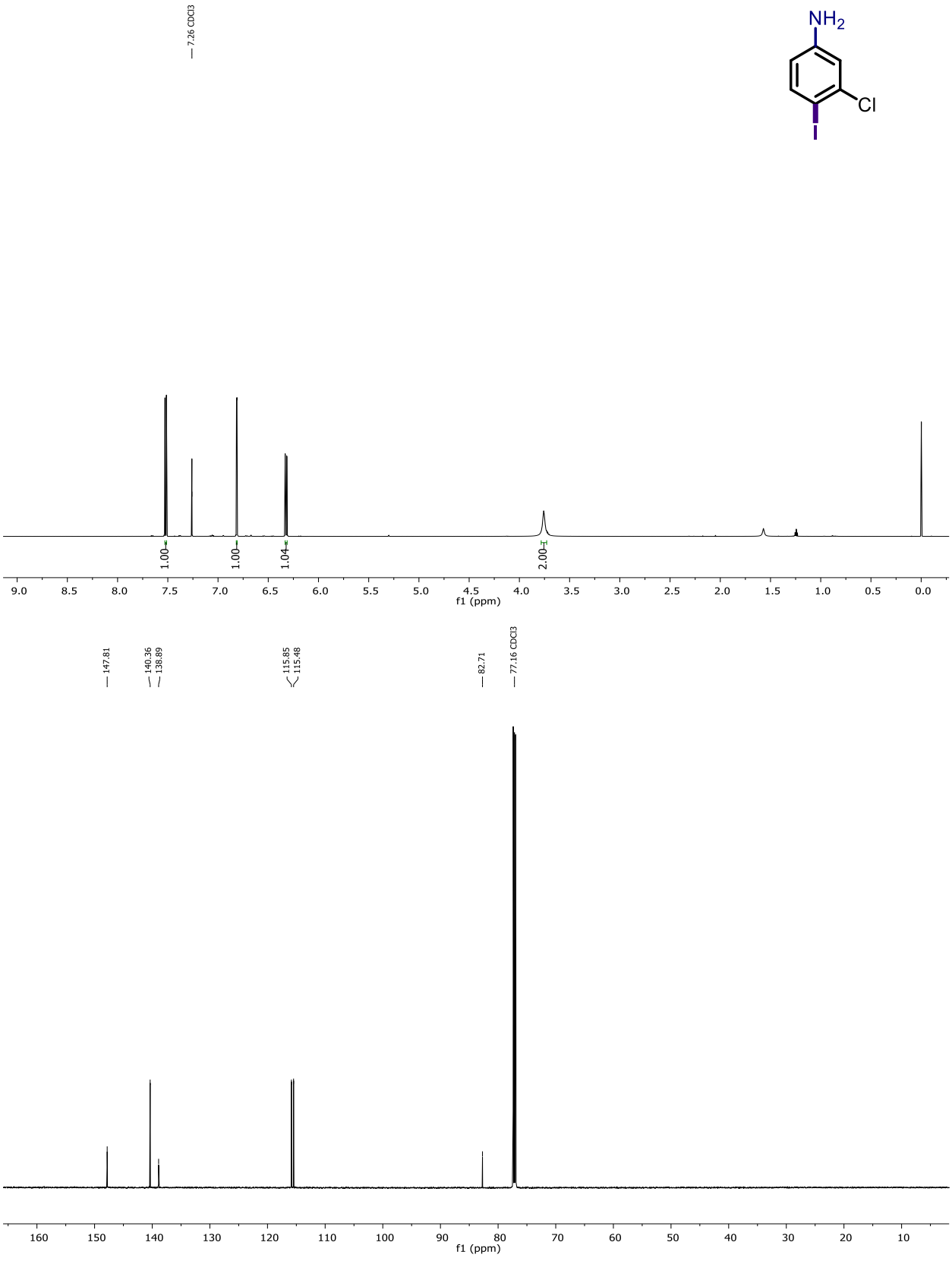

NH2
Br
7.69
7.68
7.36
7.36
7.35
7.34
7.26 CDCl3
6.54
6.53
4.12
1.00
1.03
1.06
2.01
f1 (ppm)
144.01
140.13
137.11
117.45
110.16
78.45
f1 (ppm)

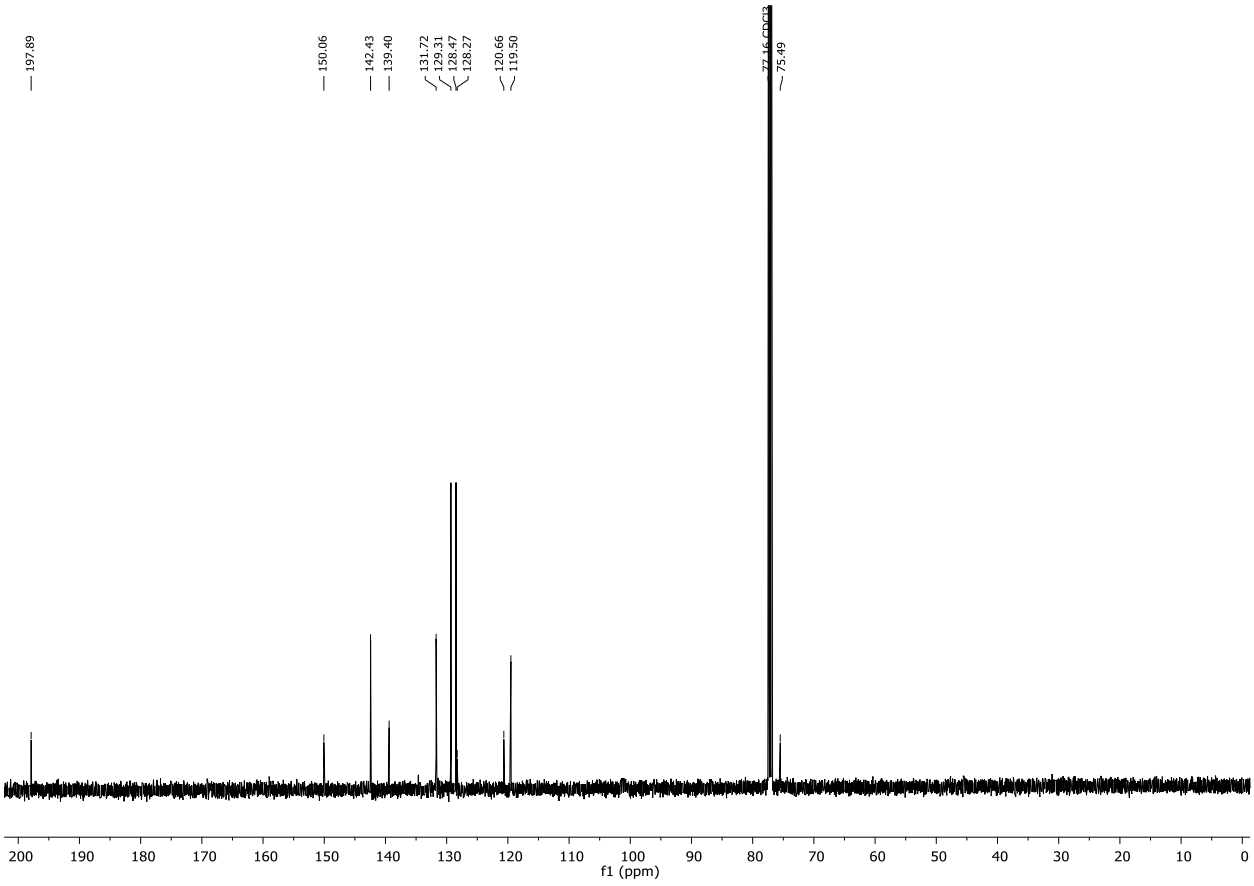

NH2
I
I
7.90
7.89
7.39
7.38
7.37
7.37
7.26 CDCl3
6.53
6.51
4.12
1.00
1.04
1.09
2.00
f1 (ppm)
146.66
145.98
138.04
116.38
84.97
79.08
f1 (ppm)

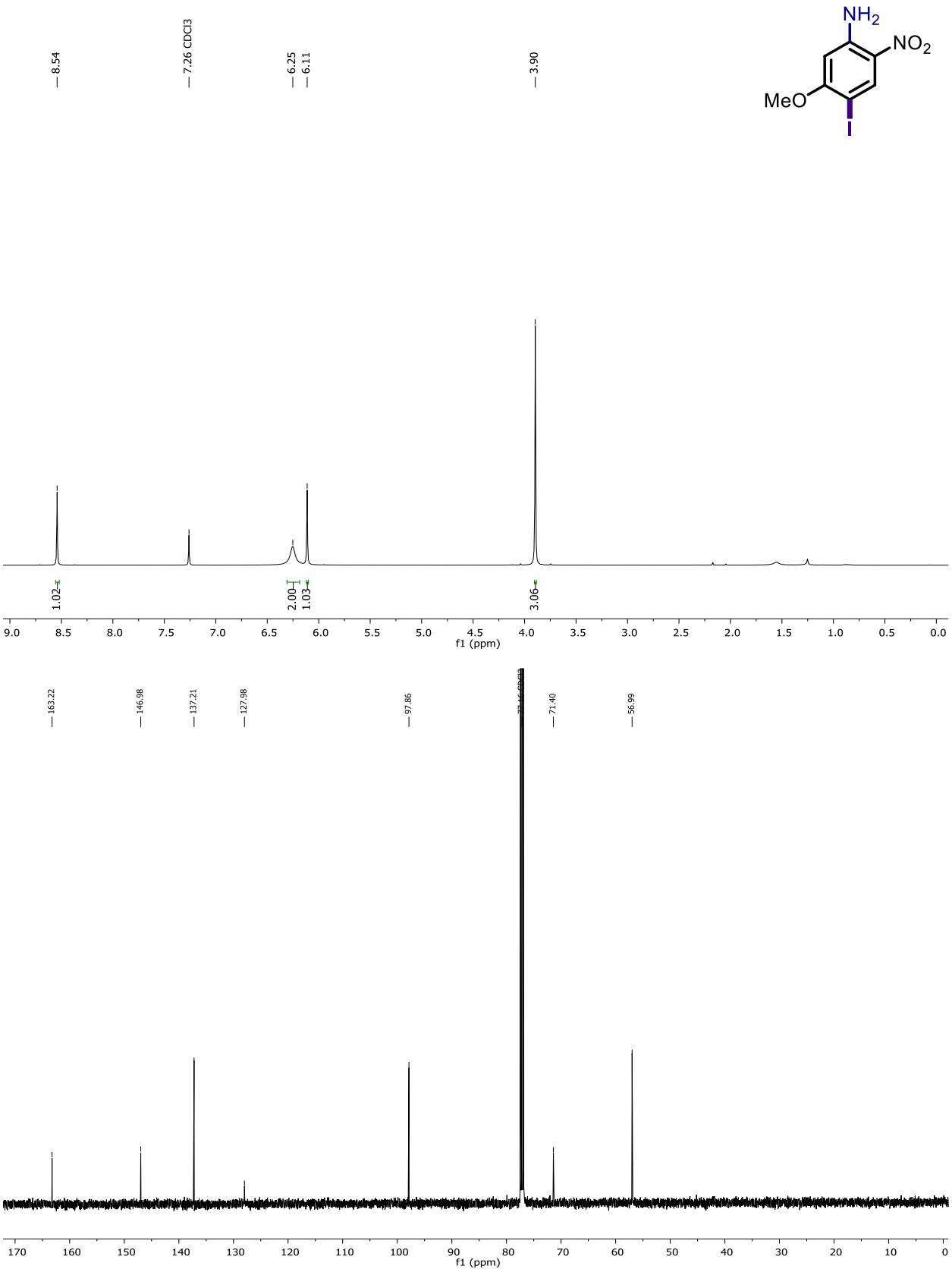

NH2
NO2
I

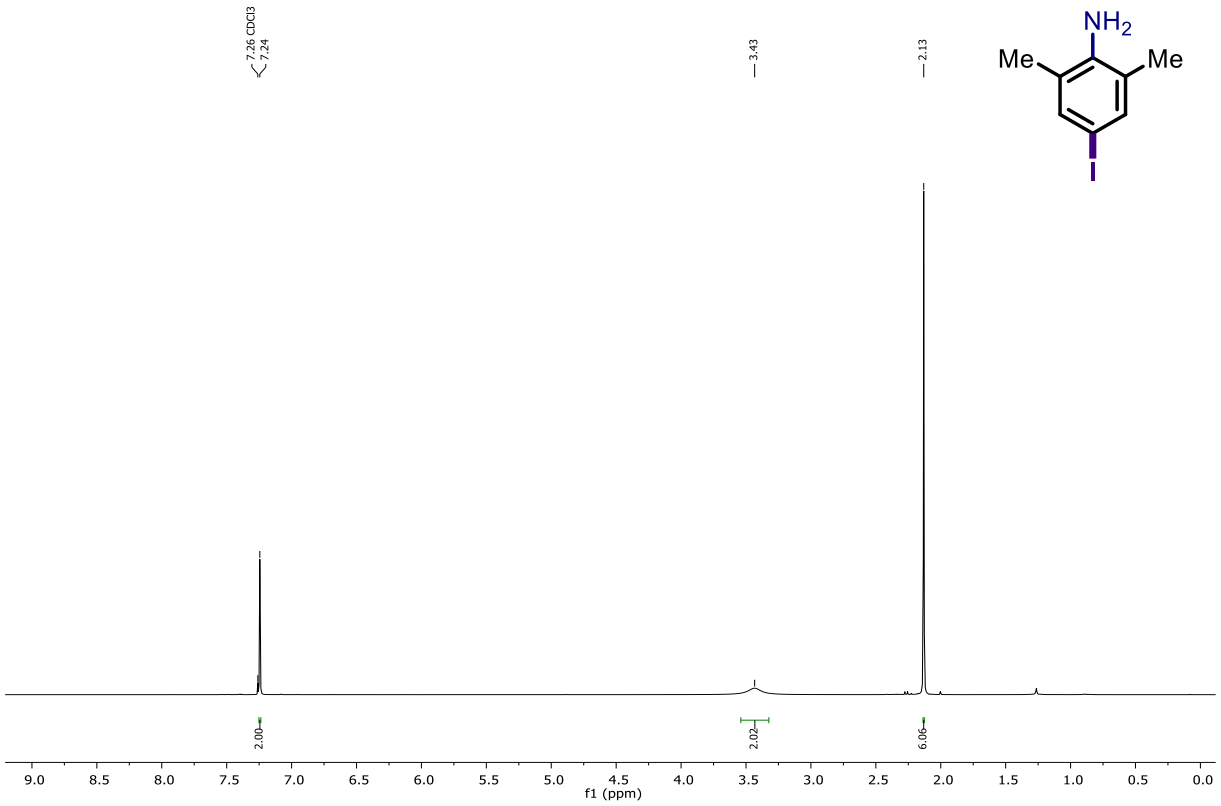

8.42
7.57
7.55
7.26 CDCl3
6.61
6.60
6.10
1.00
1.00
1.01
2.00
f1 (ppm)

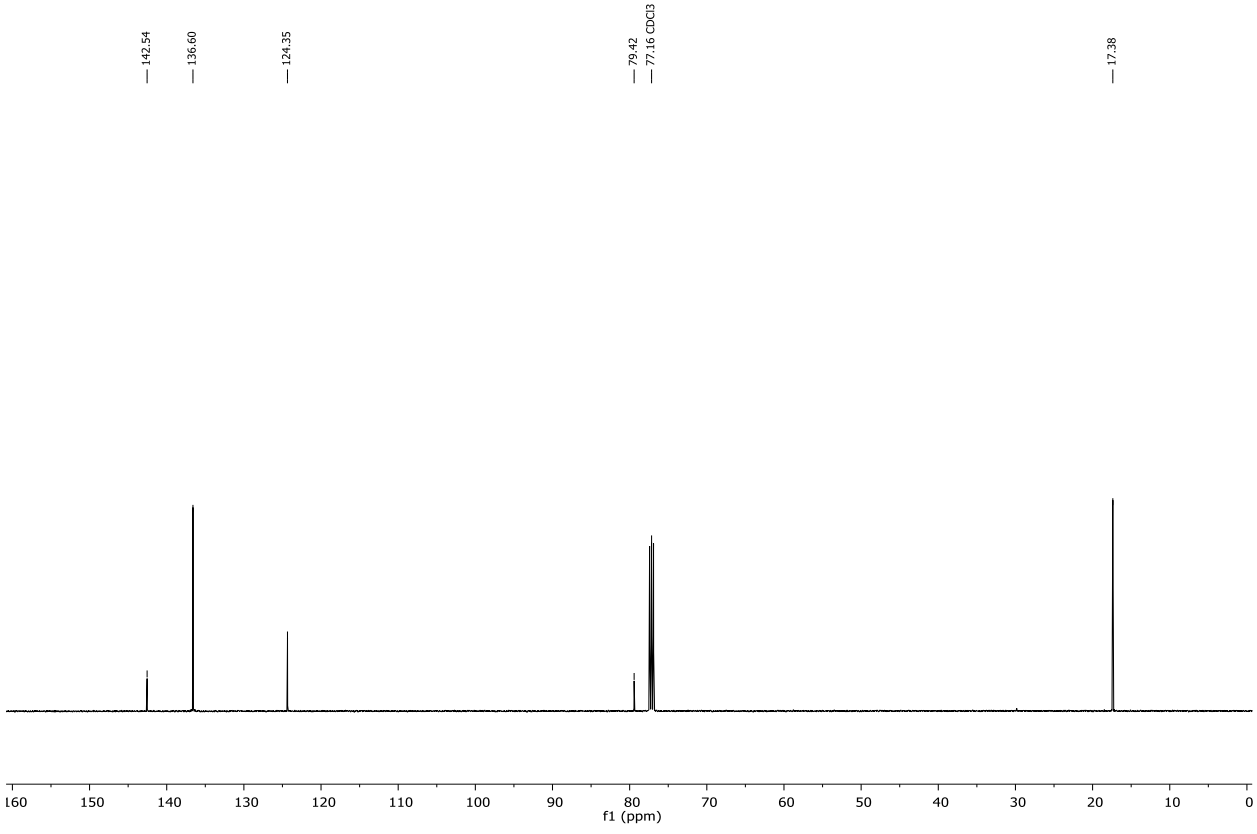

144.13
143.87
134.44
133.24
120.72
77.16 CDCl3
76.04
f1 (ppm)

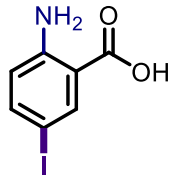

7.26 CDCl3
NH2
Cl
I
1.00
1.00
1.04
2.00
f1 (ppm)
147.81
140.36
138.89
115.85
115.48
82.71
77.16 CDCl3
f1 (ppm)

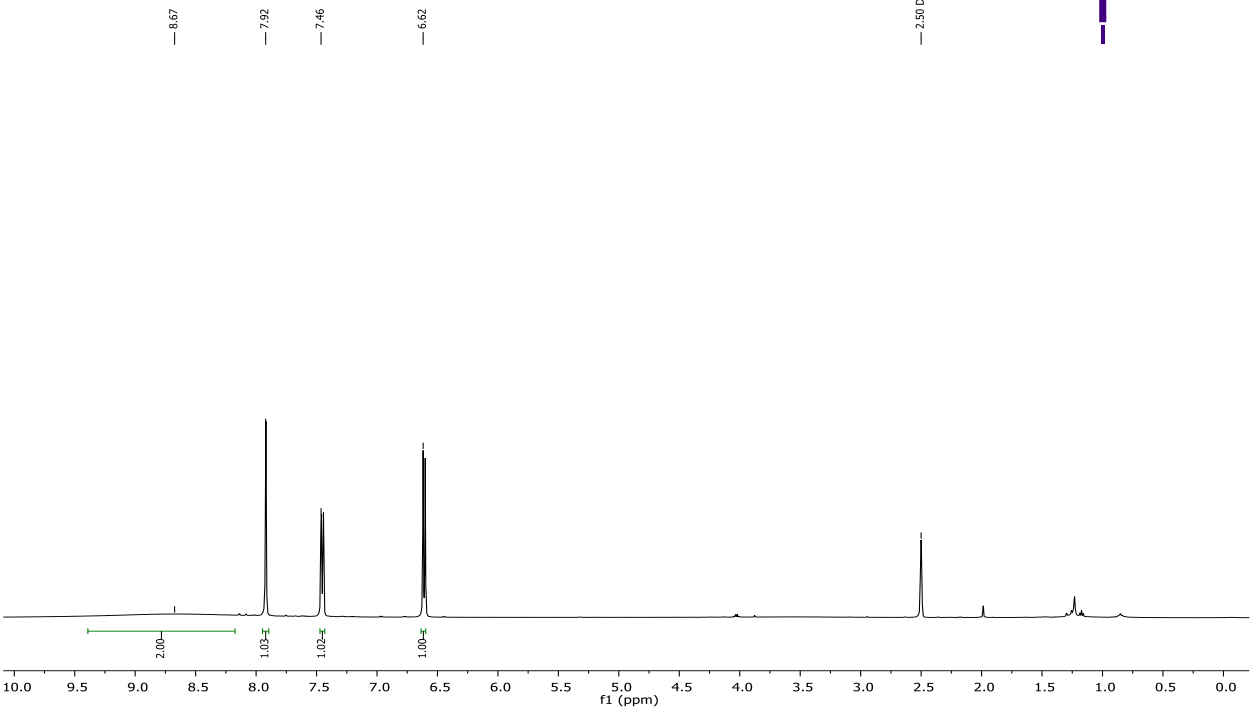

197.89
150.06
142.43
139.40
131.72
129.31
128.47
128.27
120.66
119.50
77.16
75.49
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

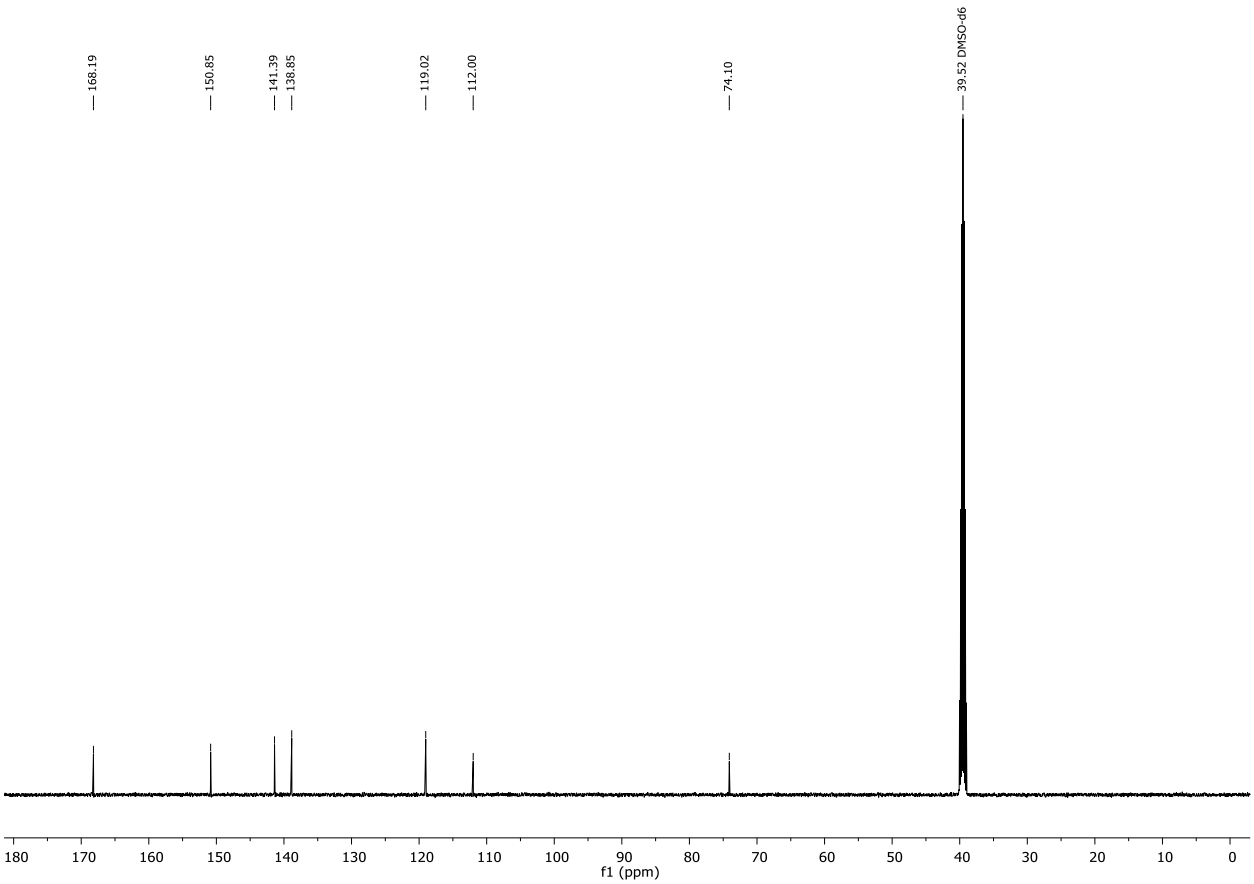

8.54
7.26 CDCl3
6.25
6.11
3.90
NH2
NO2
MeO
I
1.02
2.00
1.03
3.06
f1 (ppm)
163.22
146.98
137.21
127.98
97.86
77.16 CDCl3
71.40
56.99
f1 (ppm)

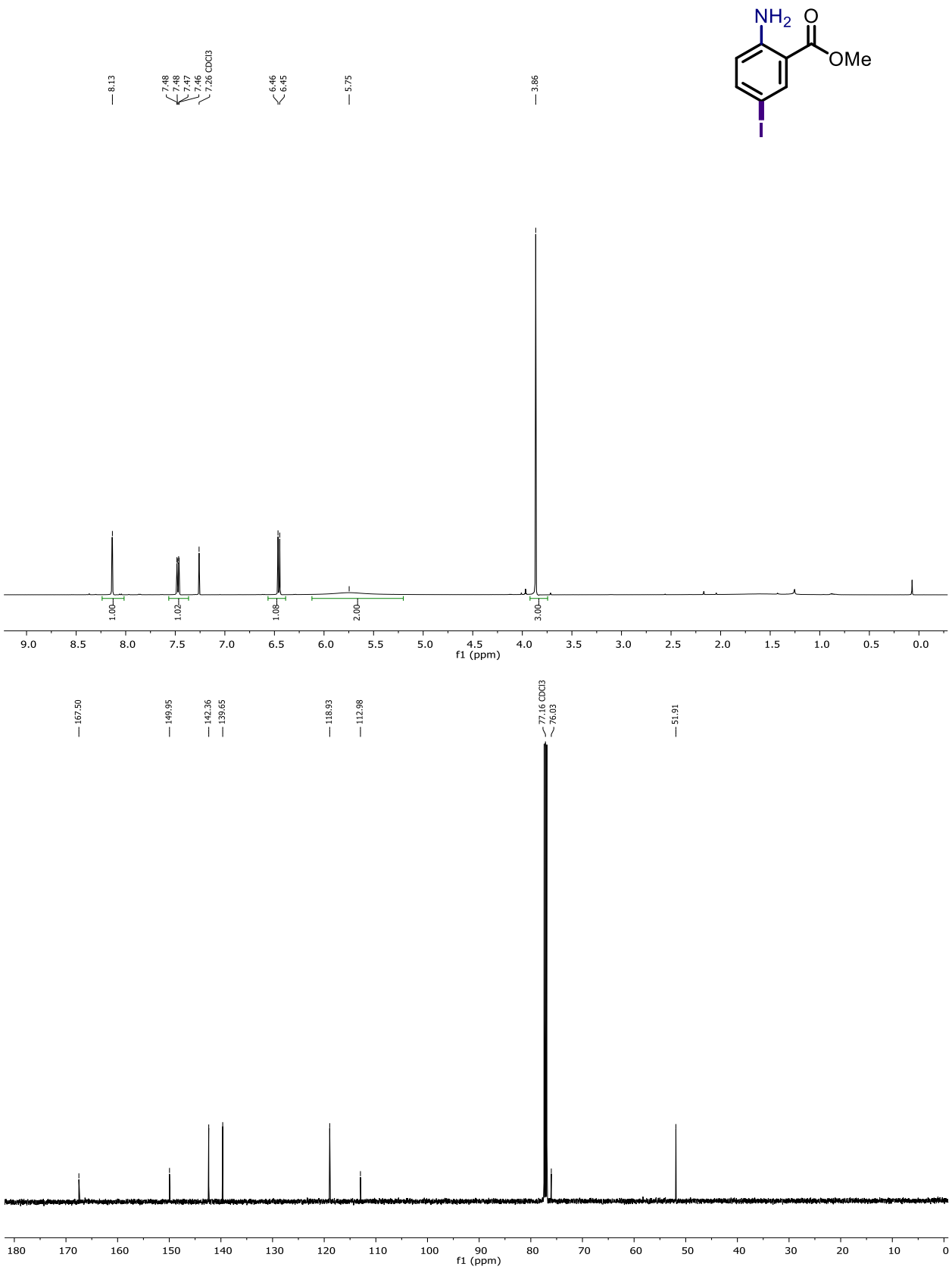

7.26 CDCl3
7.24
3.43
2.13
NH2
Me
Me
I
2.00
2.02
6.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

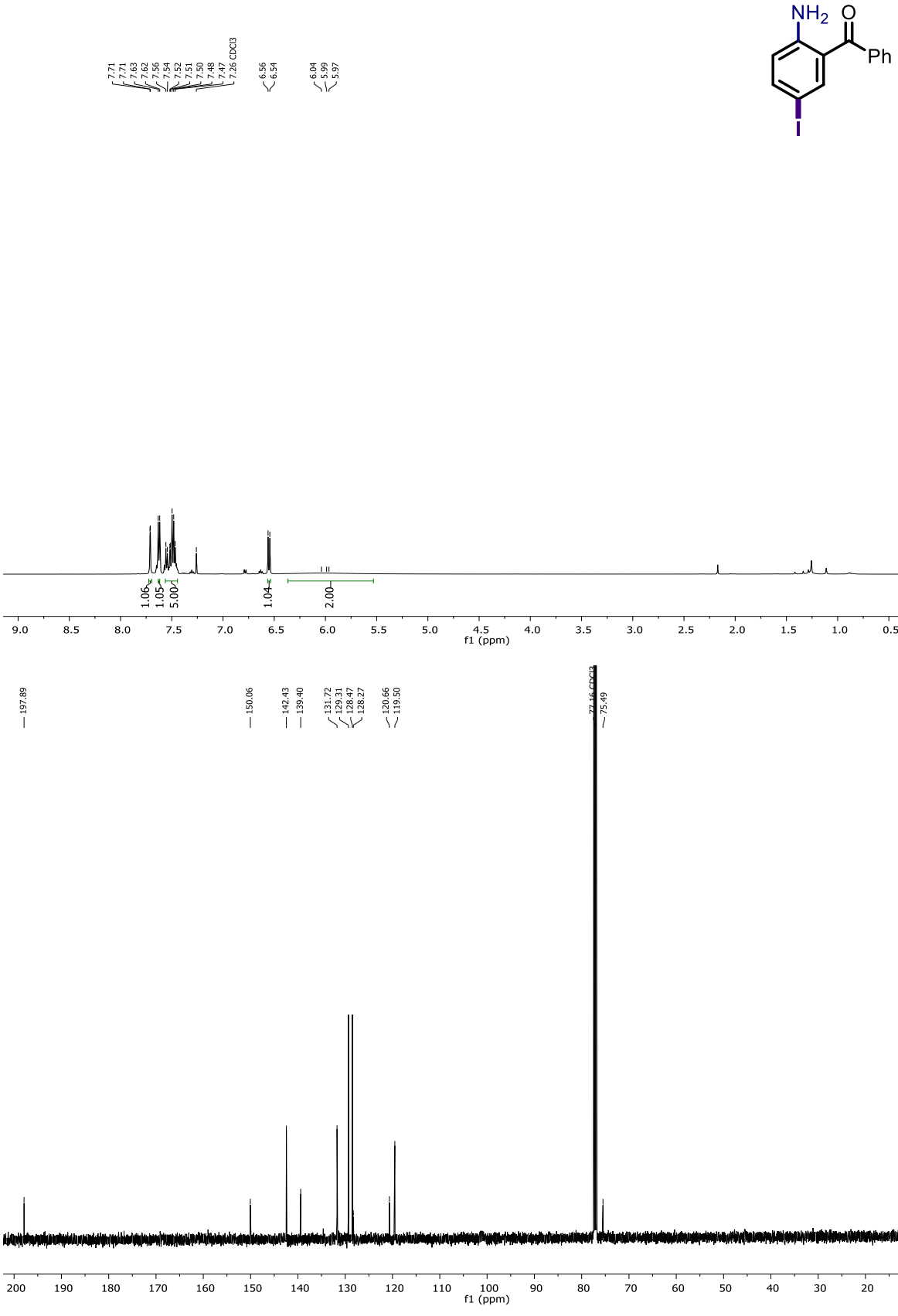

142.54
136.60
124.35
79.42
77.16 CDCl3
17.38
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

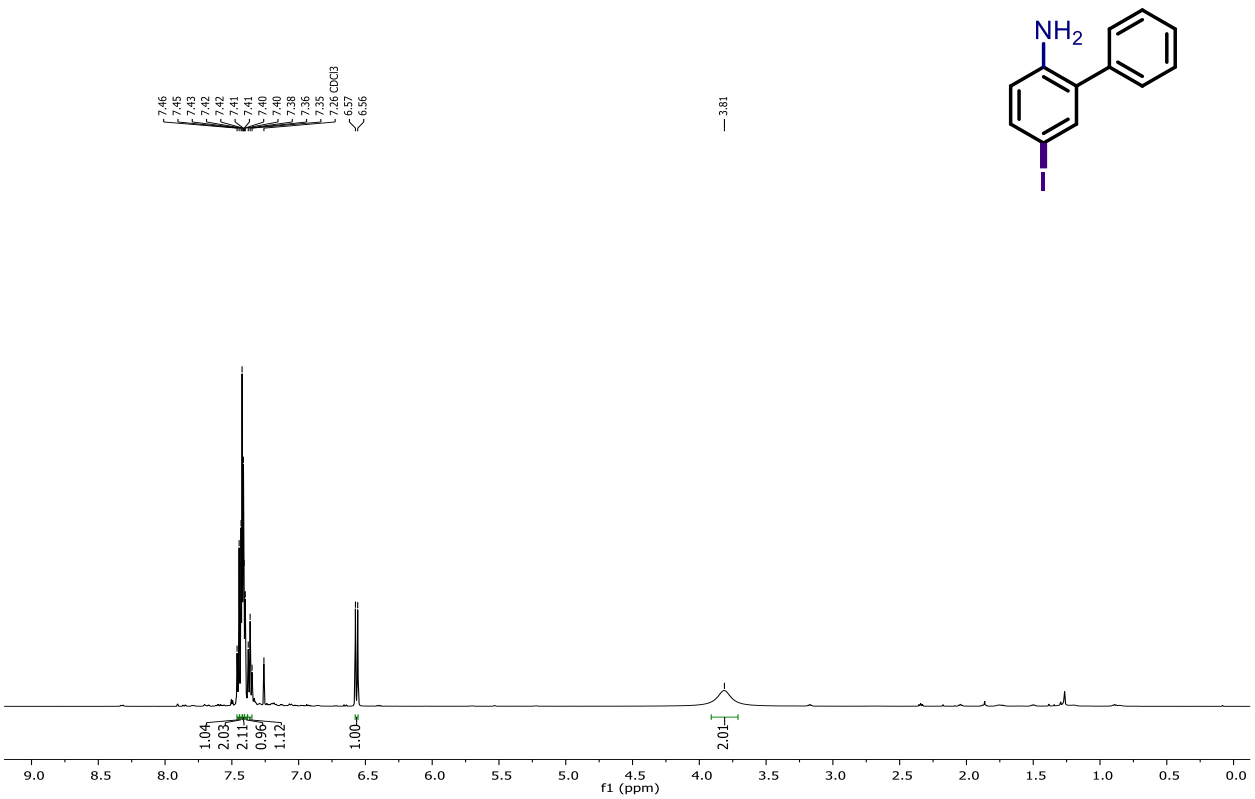

NH2
O
OH
I

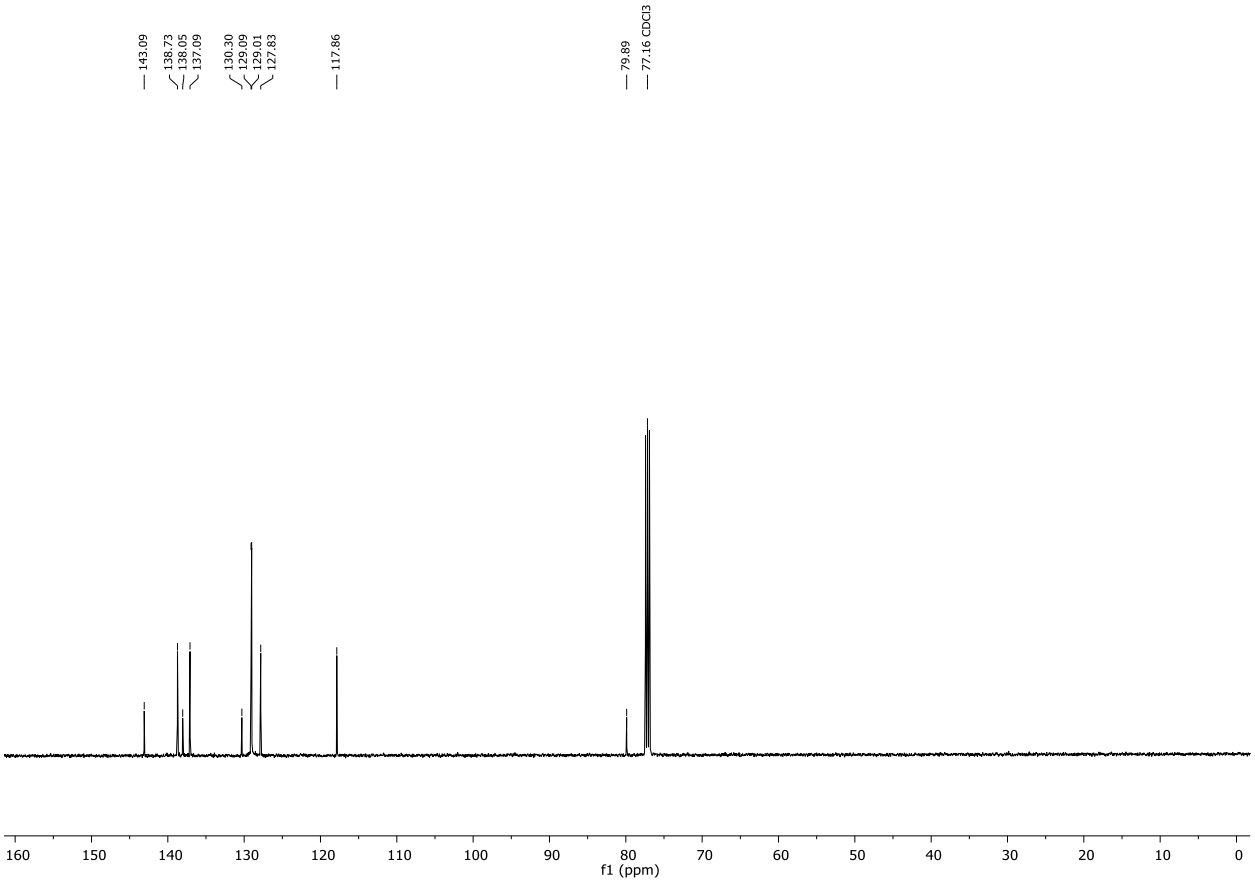

8.67
7.92
7.46
6.62
2.50 DMSO-d6
2.00
1.03
1.02
1.00
f1 (ppm)

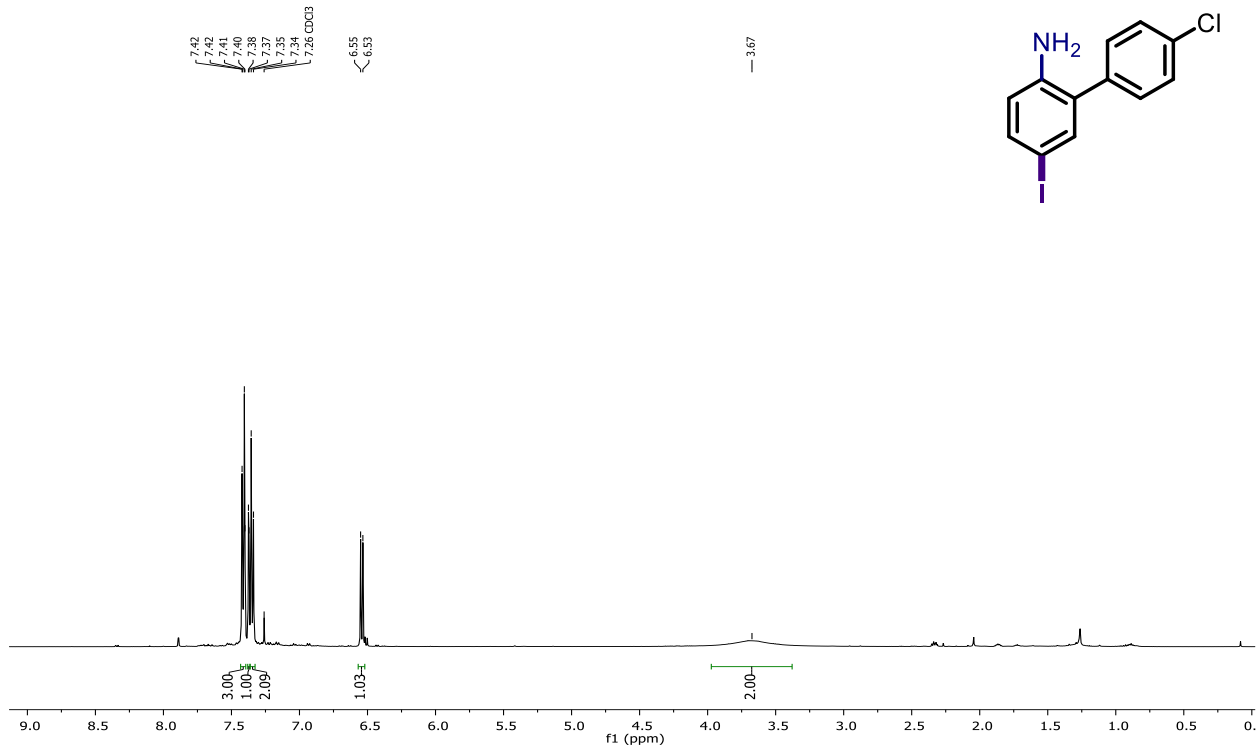

168.19
150.85
141.39
138.85
119.02
112.00
74.10
39.52 DMSO-d6
f1 (ppm)

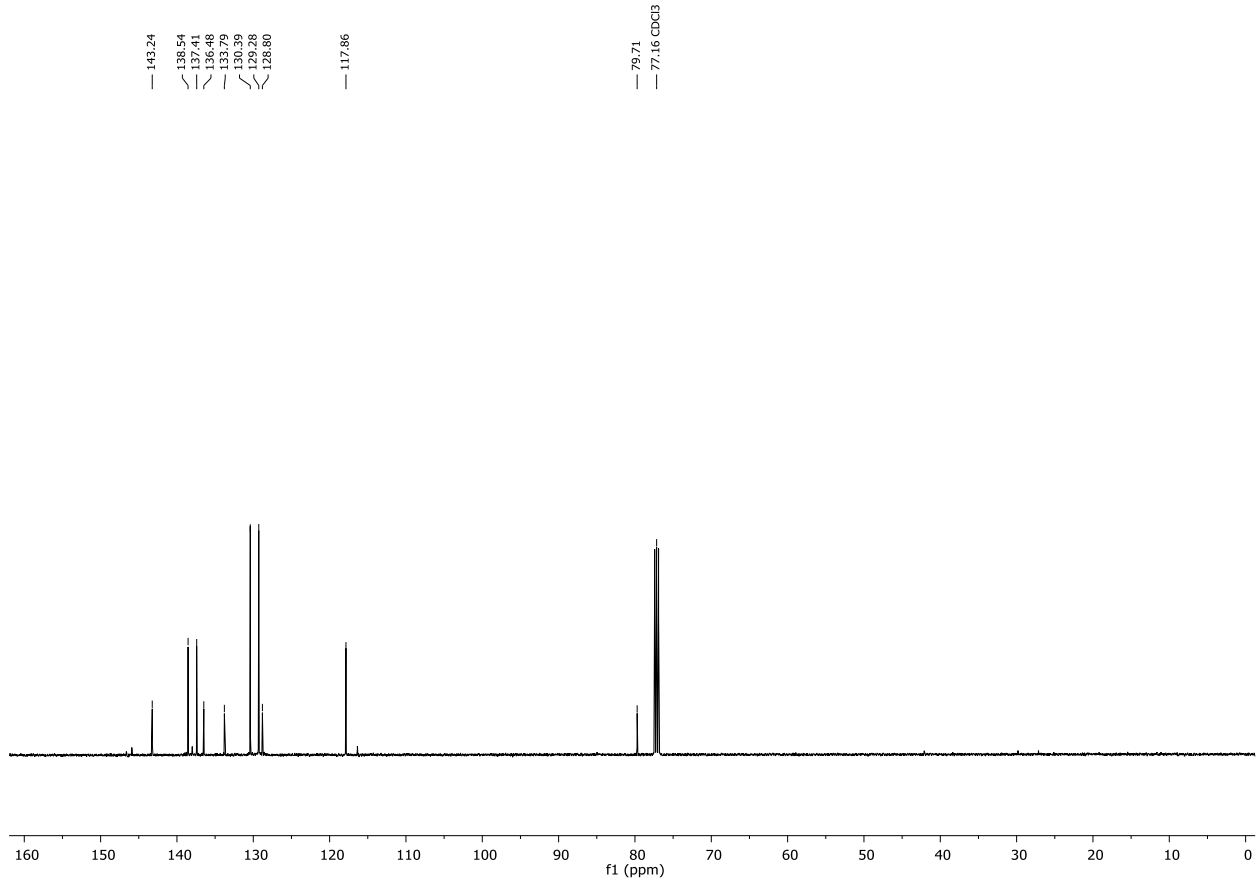

NH2
O
OMe
I
8.13
7.48
7.48
7.47
7.46
7.26 CDCl3
6.46
6.45
5.75
3.86
1.00
1.02
1.08
2.00
3.00
f1 (ppm)
167.50
149.95
142.36
139.65
118.93
112.98
77.16 CDCl3
76.03
51.91
f1 (ppm)


7.71
7.71
7.63
7.62
7.56
7.54
7.52
7.51
7.50
7.48
7.47
7.26 CDCl3
6.56
6.54
6.04
5.99
5.97
NH2
O
Ph
I
1.06
1.05
5.00
1.04
2.00
f1 (ppm)
197.89
150.06
142.43
139.40
131.72
129.31
128.47
128.27
120.66
119.50
77.16 CDCl3
75.49
f1 (ppm)

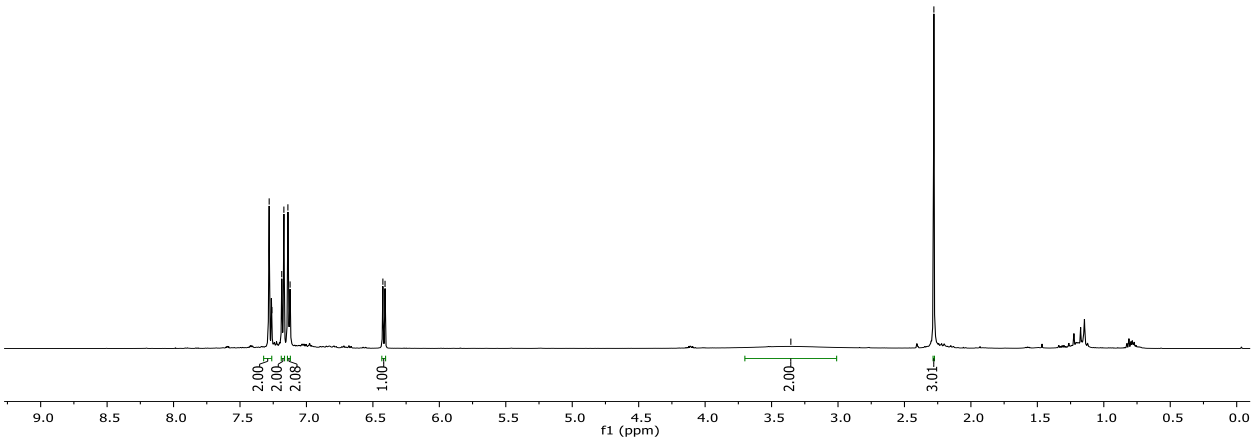

NH2
I
7.46
7.45
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.38
7.36
7.35
7.26 CDCl3
6.57
6.56
3.81
1.04
2.03
2.11
0.96
1.12
1.00
2.01
f1 (ppm)

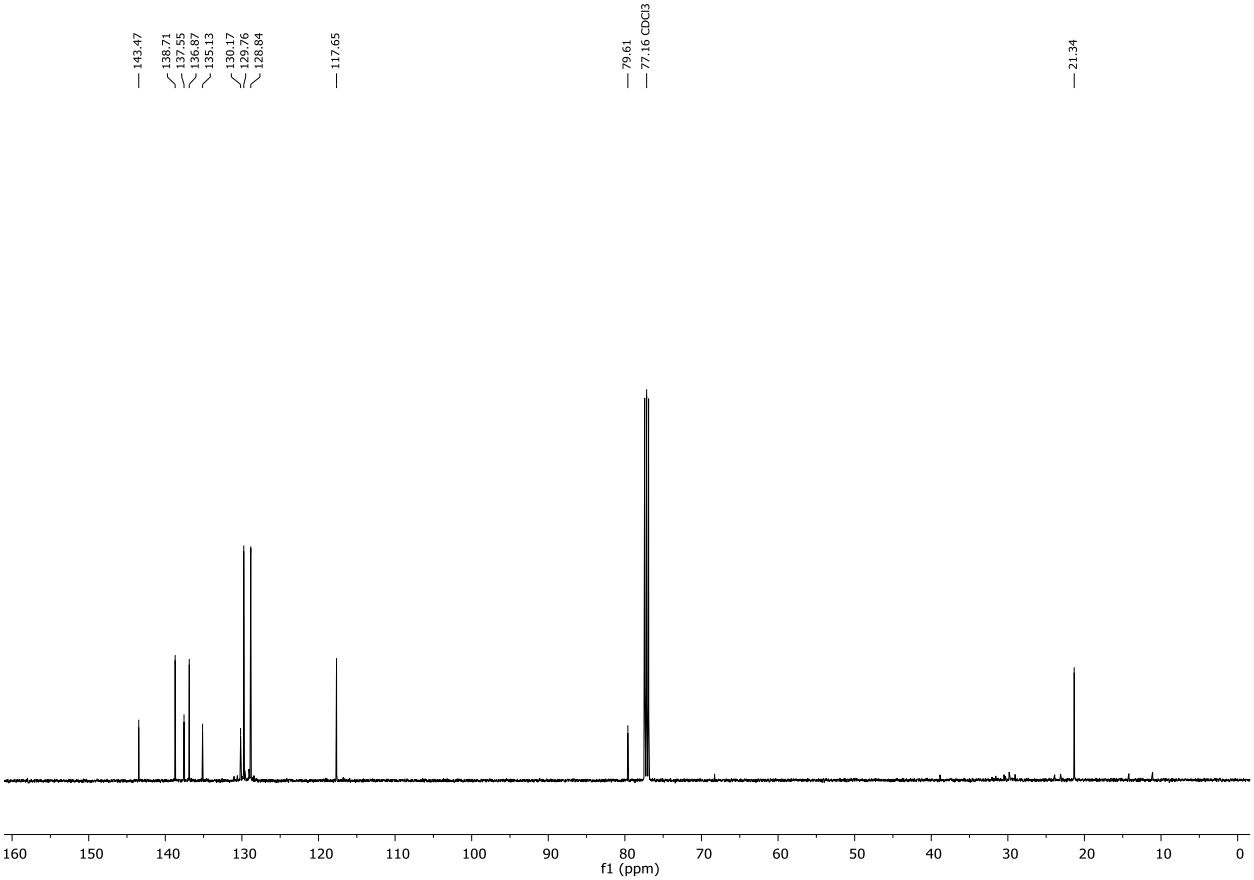

143.09
138.73
138.05
137.09
130.30
129.09
129.01
127.83
117.86
79.89
77.16 CDCl3
f1 (ppm)

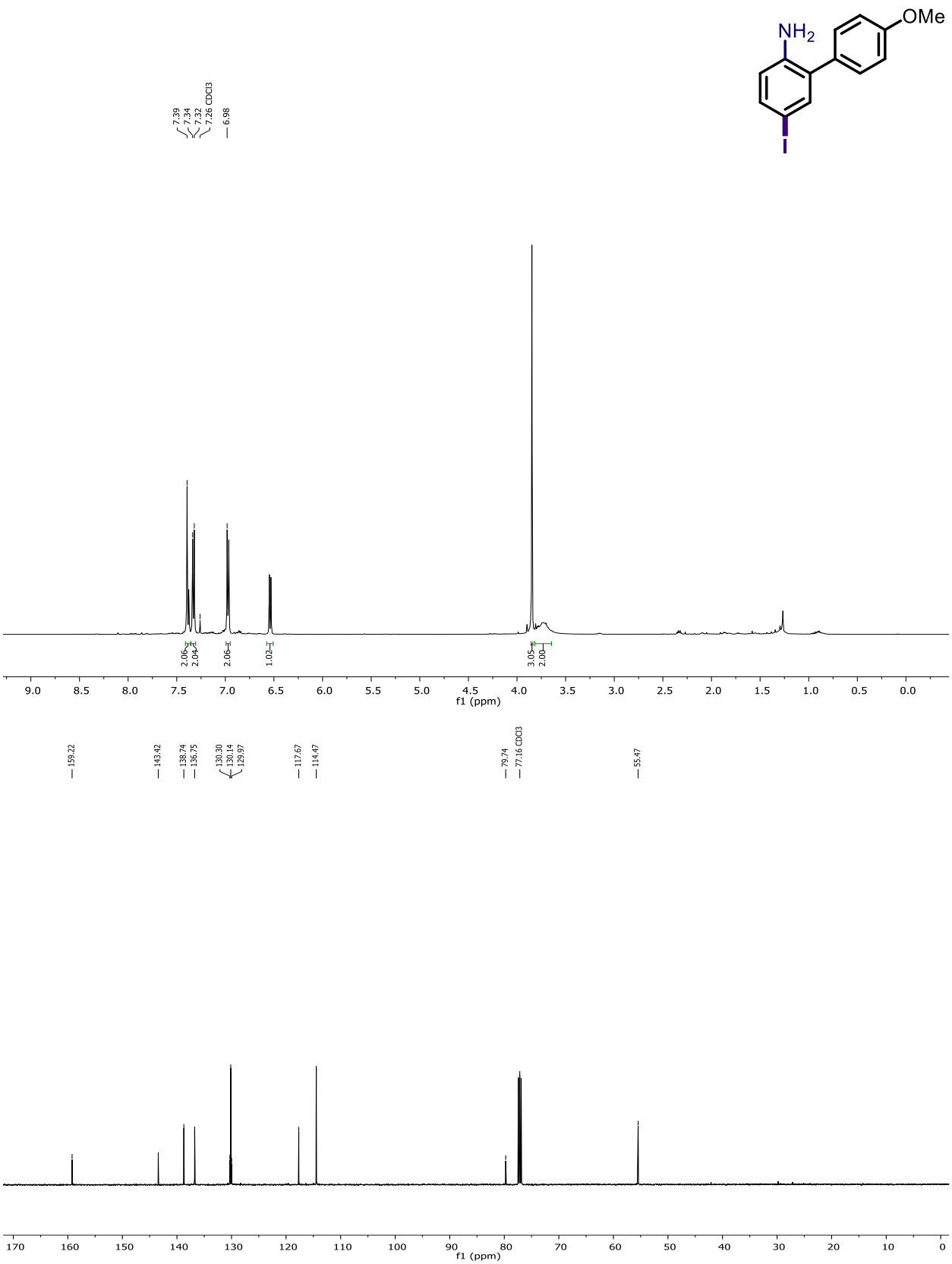

7.42
7.42
7.41
7.40
7.38
7.37
7.35
7.34
7.26 CDCl3
6.55
6.53
3.67
NH2
Cl
I
3.00
1.00
2.09
1.03
2.00
f1 (ppm)


143.24
138.54
137.41
136.48
133.79
130.39
129.28
128.80
117.86
79.71
77.16 CDCl3
f1 (ppm)


NH2
Me
I

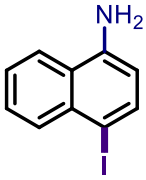

7.28
7.26 CDCl3
7.19
7.17
7.14
7.12
6.42
6.41
3.36
2.28
2.00
2.00
2.08
1.00
2.00
3.01
f1 (ppm)

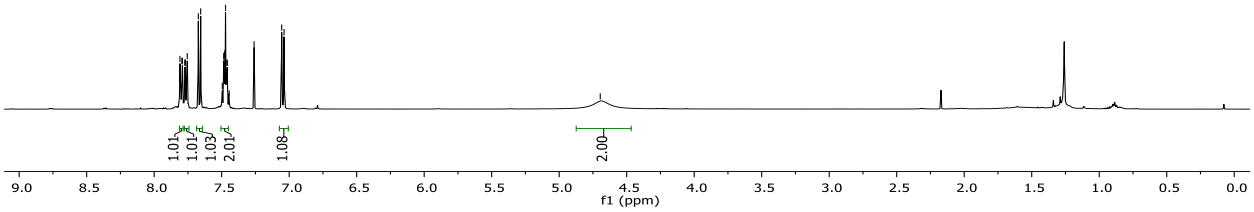

143.47
138.71
137.55
136.87
135.13
130.17
129.76
128.84
117.65
79.61
77.16 CDCl3
21.34
f1 (ppm)

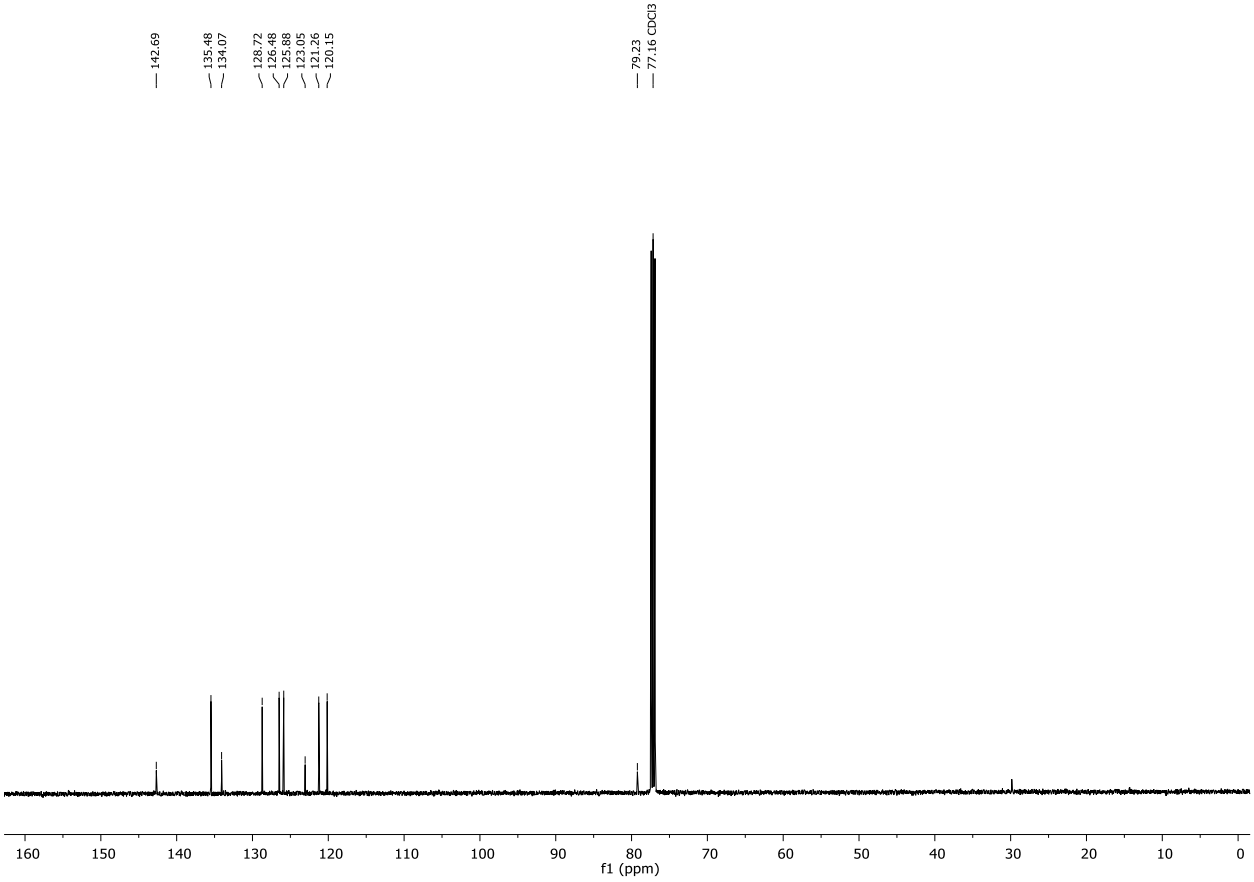

NH2
OMe
I
7.39
7.34
7.32
7.26 CDCl3
6.98
2.06
2.04
2.06
1.02
3.05
2.00
f1 (ppm)
159.22
143.42
138.74
136.75
130.30
130.14
129.97
117.67
114.47
79.74
77.16 CDCl3
55.47
f1 (ppm)

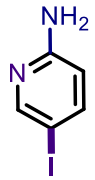

7.81
7.79
7.79
7.77
7.77
7.75
7.67
7.66
7.50
7.48
7.48
7.48
7.47
7.46
7.46
7.44
7.26 CDCl3
7.06
7.04

4.70

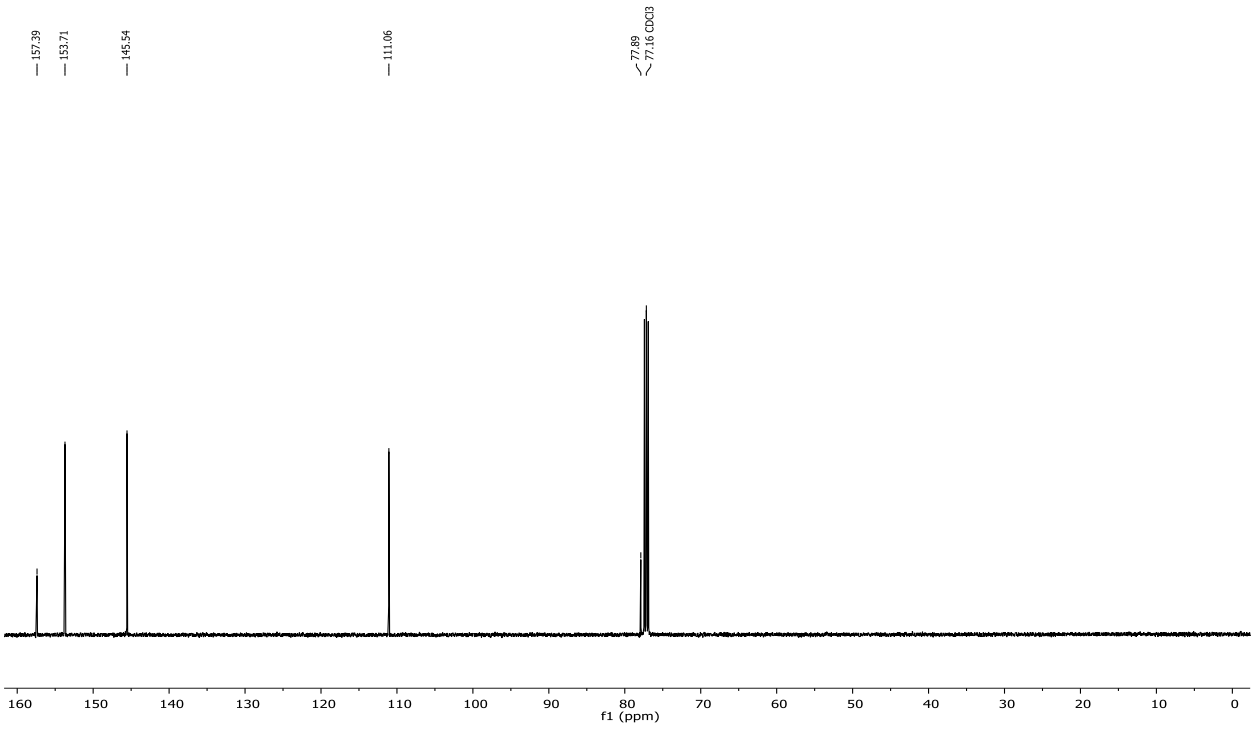

NH2
I


1.01
1.01
1.03
2.01
1.08
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

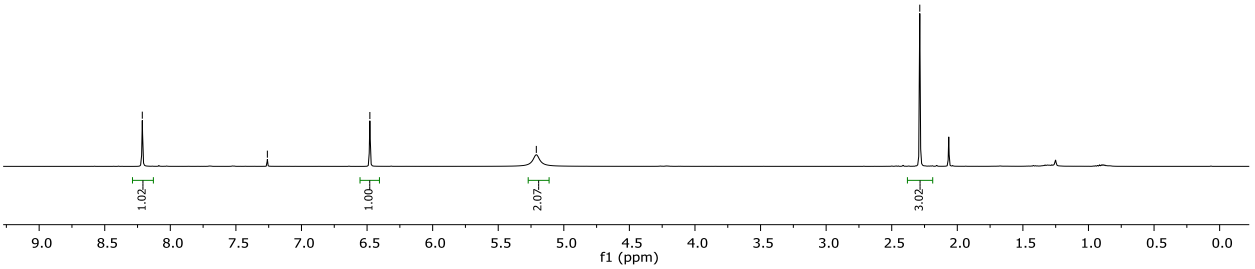

142.69
135.48
134.07
128.72
126.48
125.88
123.05
121.26
120.15
79.23
77.16 CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

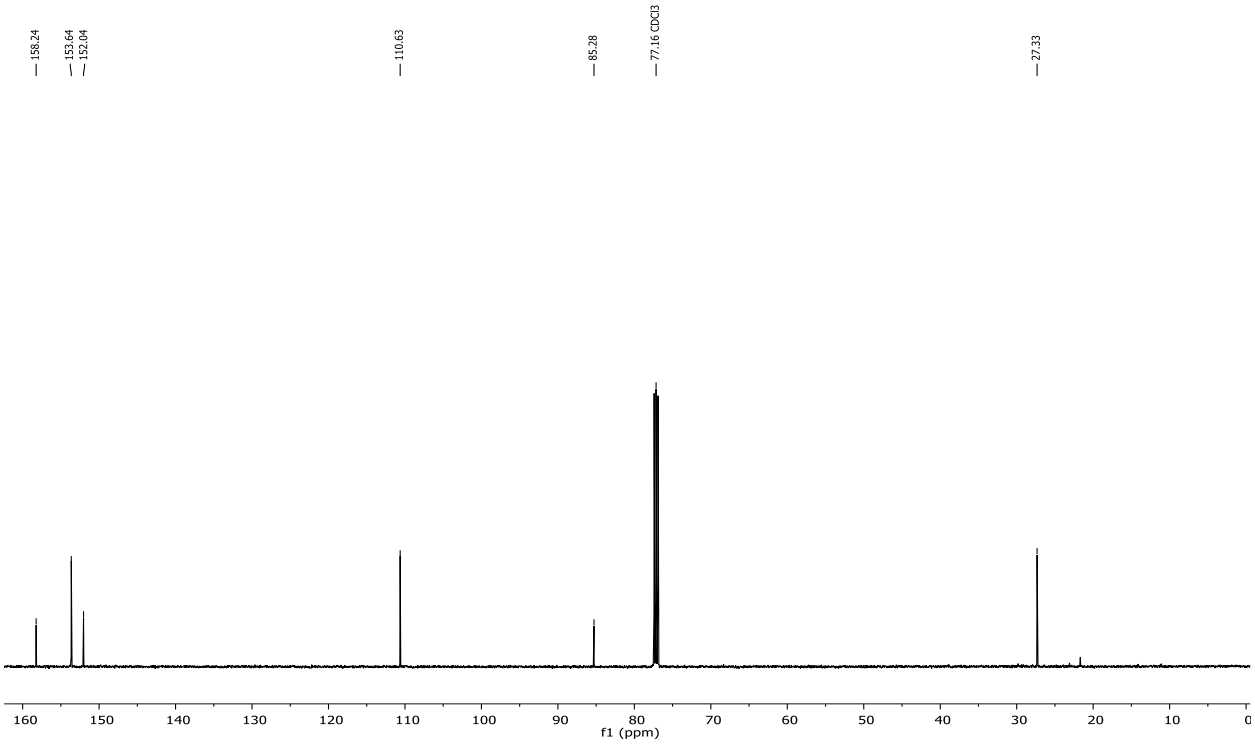

NH2
N
I

8.21
7.63
7.62
7.61
7.61
7.26 CDCl3
6.36
6.34
4.44
1.06
1.00
1.03
2.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


157.39
153.71
145.54
111.06
77.89
77.16 CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.21
7.26 CDCl3
6.48
5.21
2.29
NH2
N
Me
I


1.02
1.00
2.07
3.02
f1 (ppm)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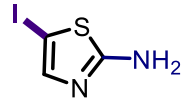
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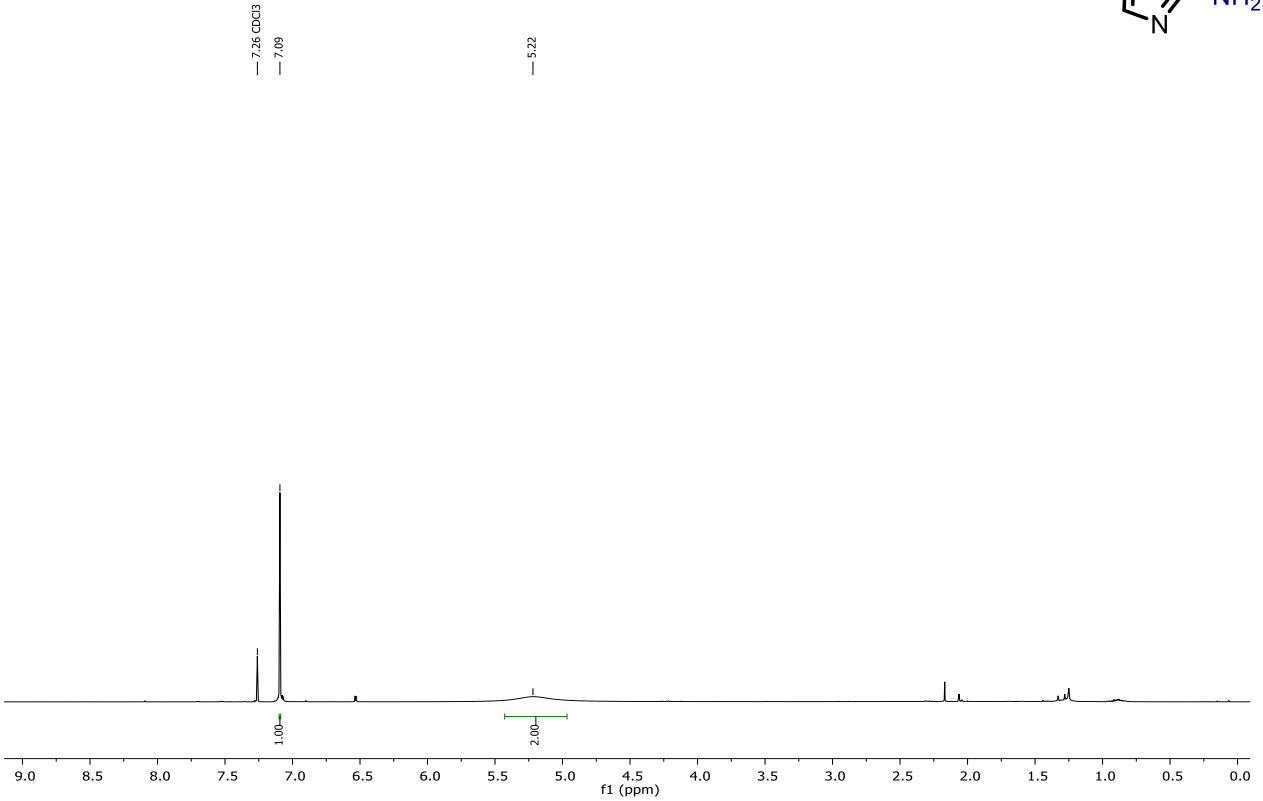
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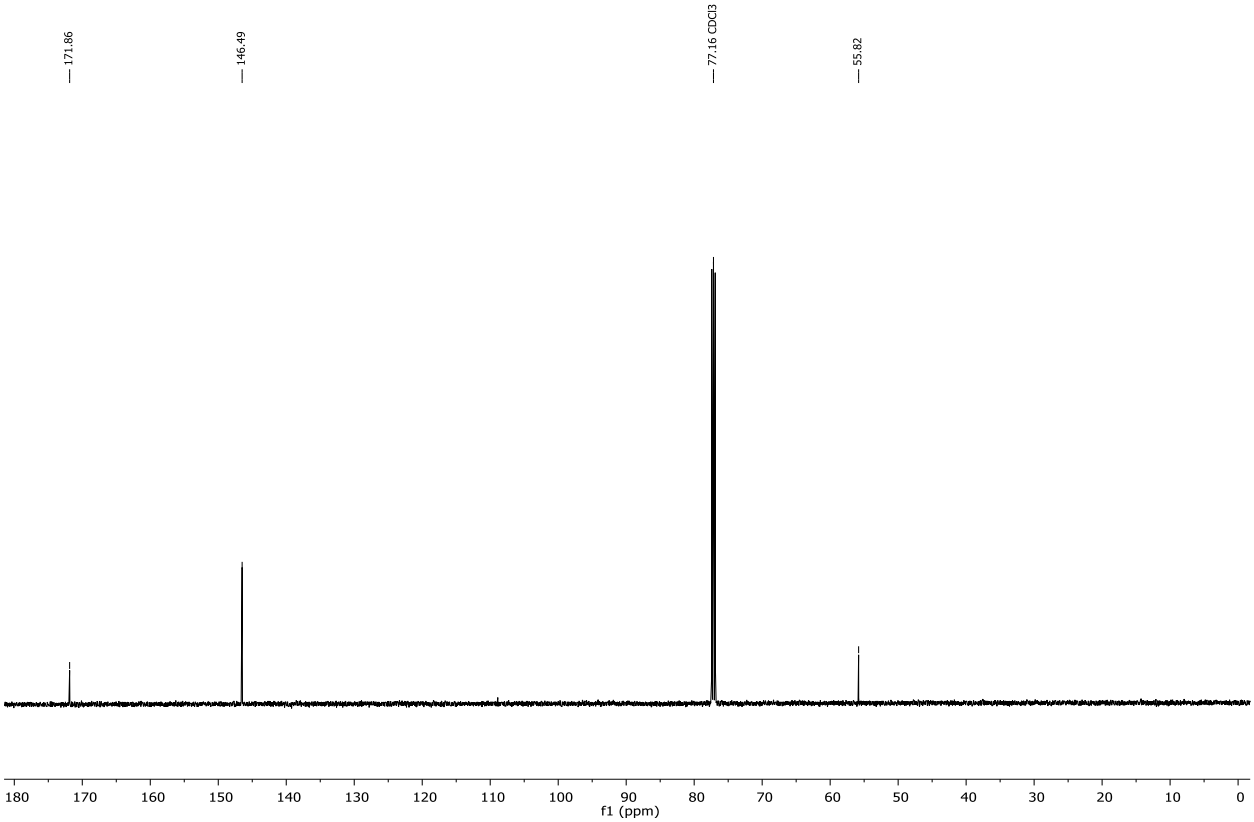
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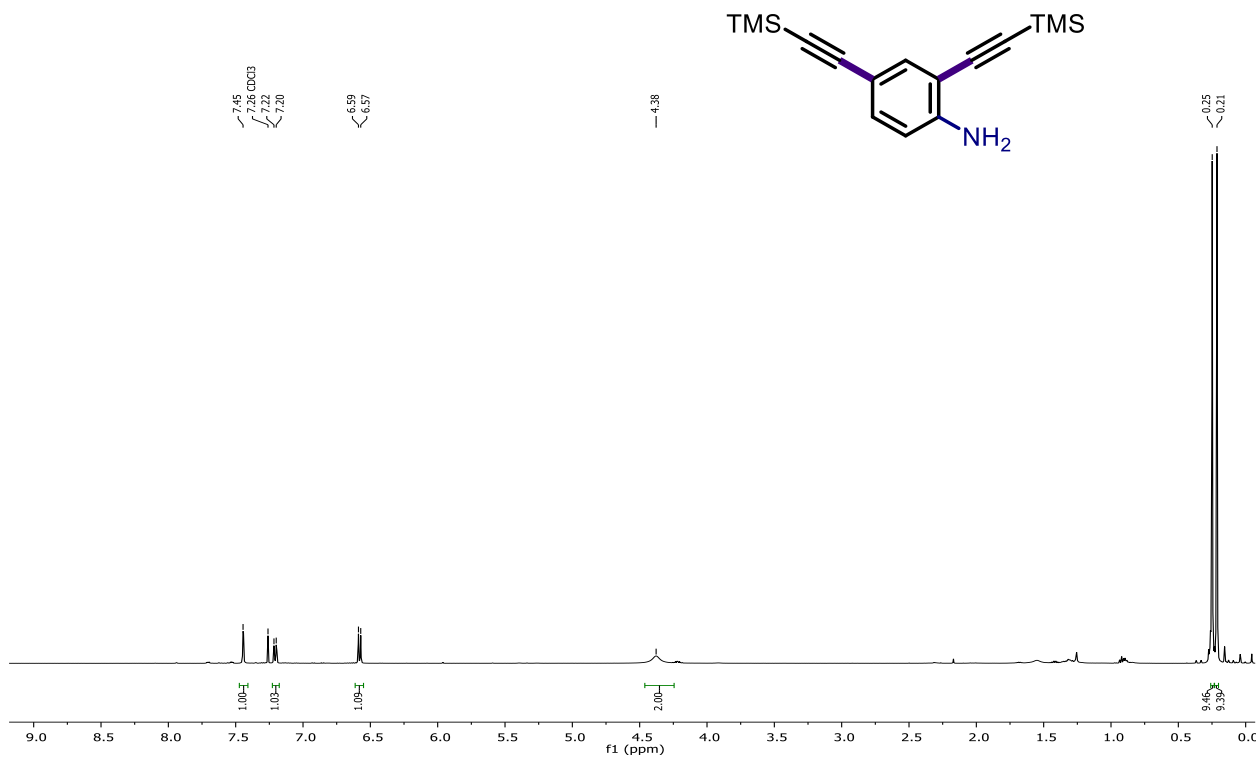
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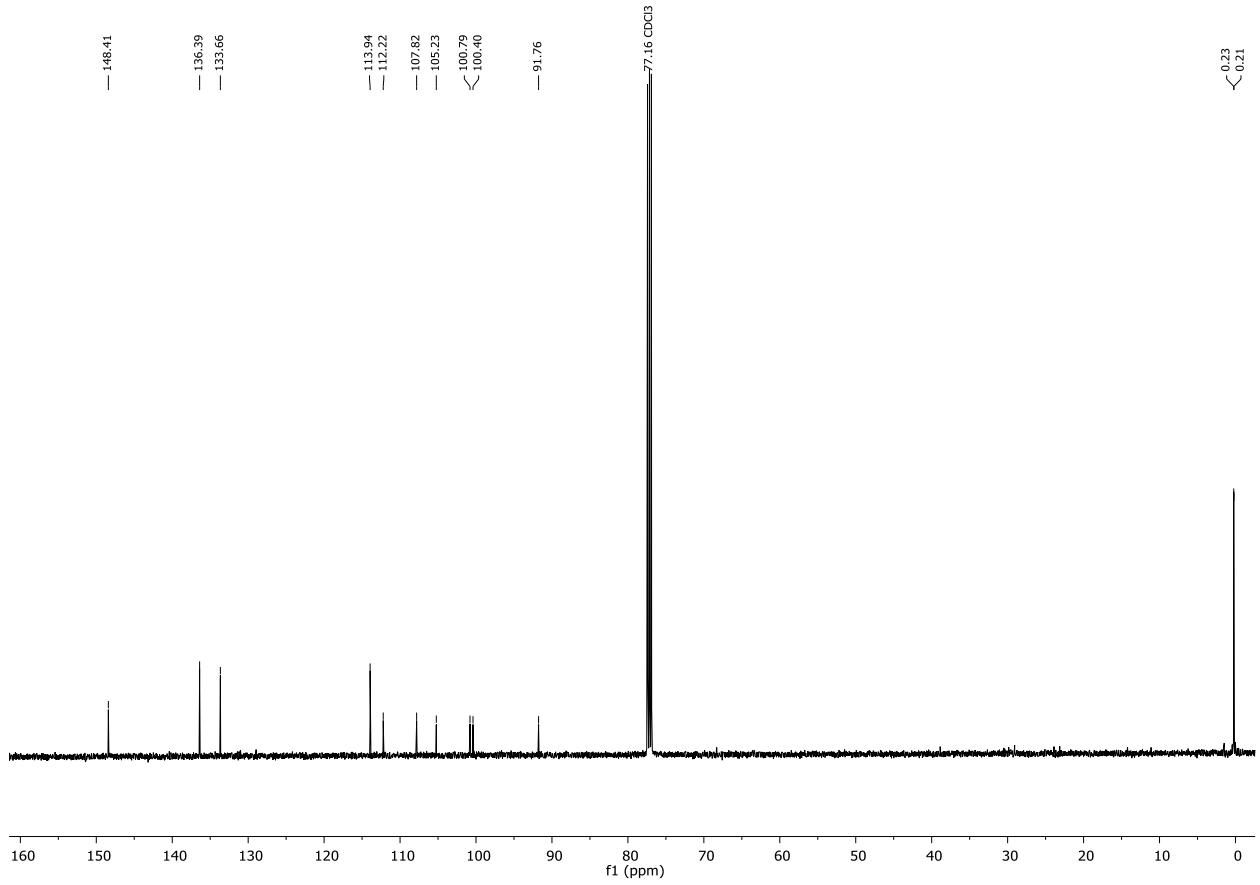
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f1 (ppm)


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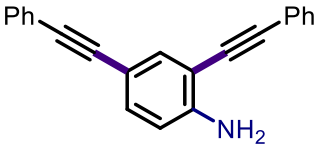
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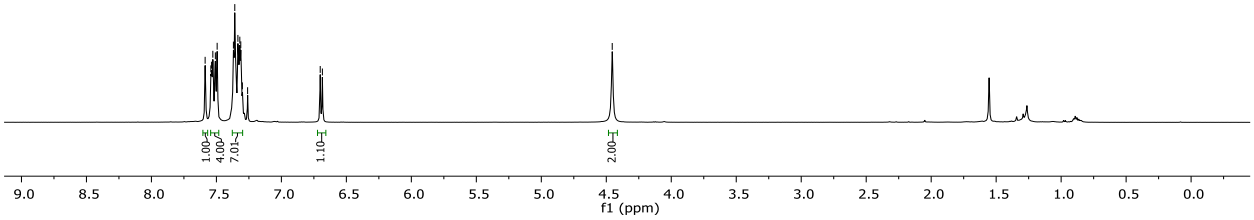
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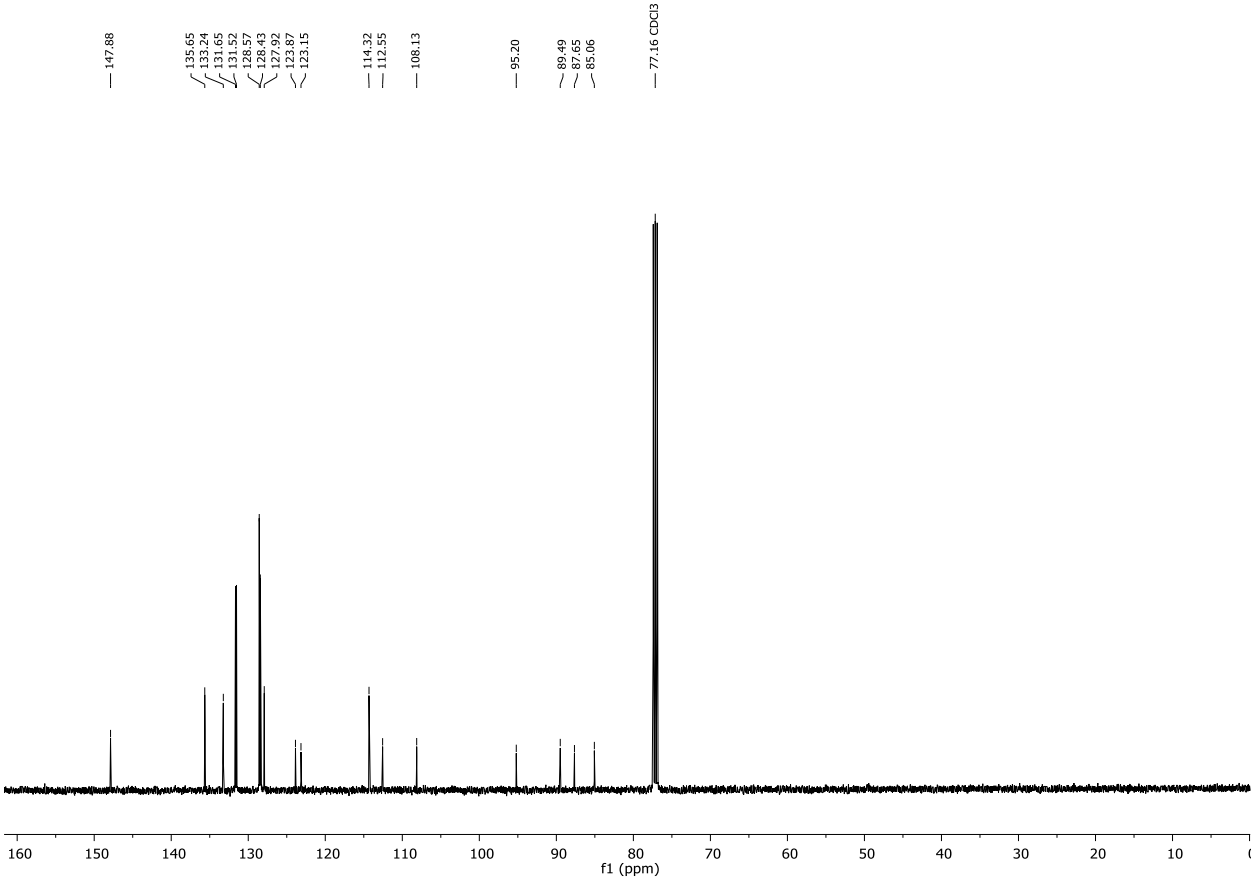
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85.06
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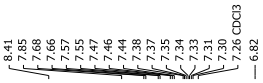
f1 (ppm)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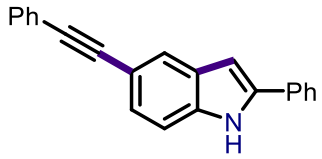
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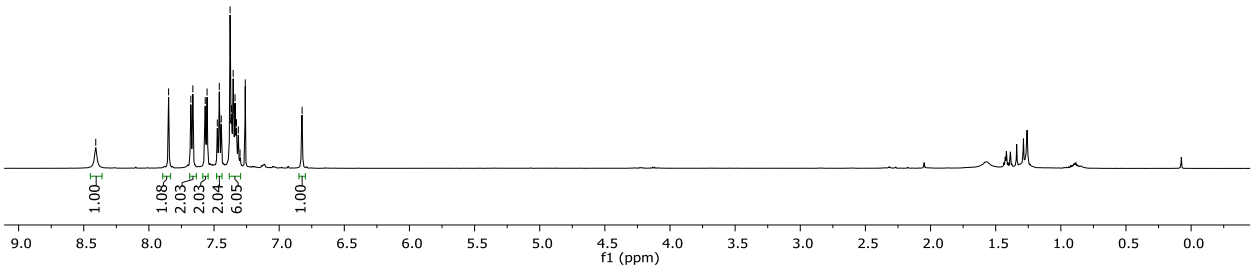
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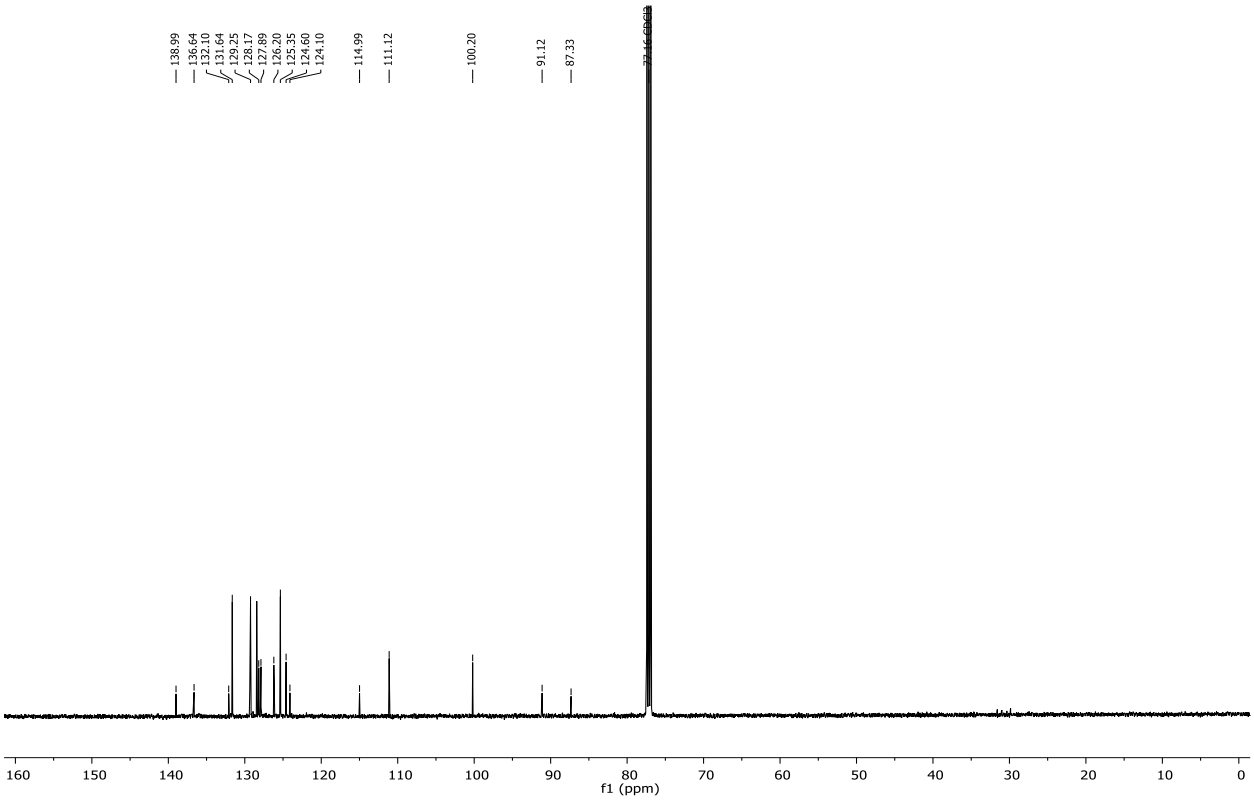
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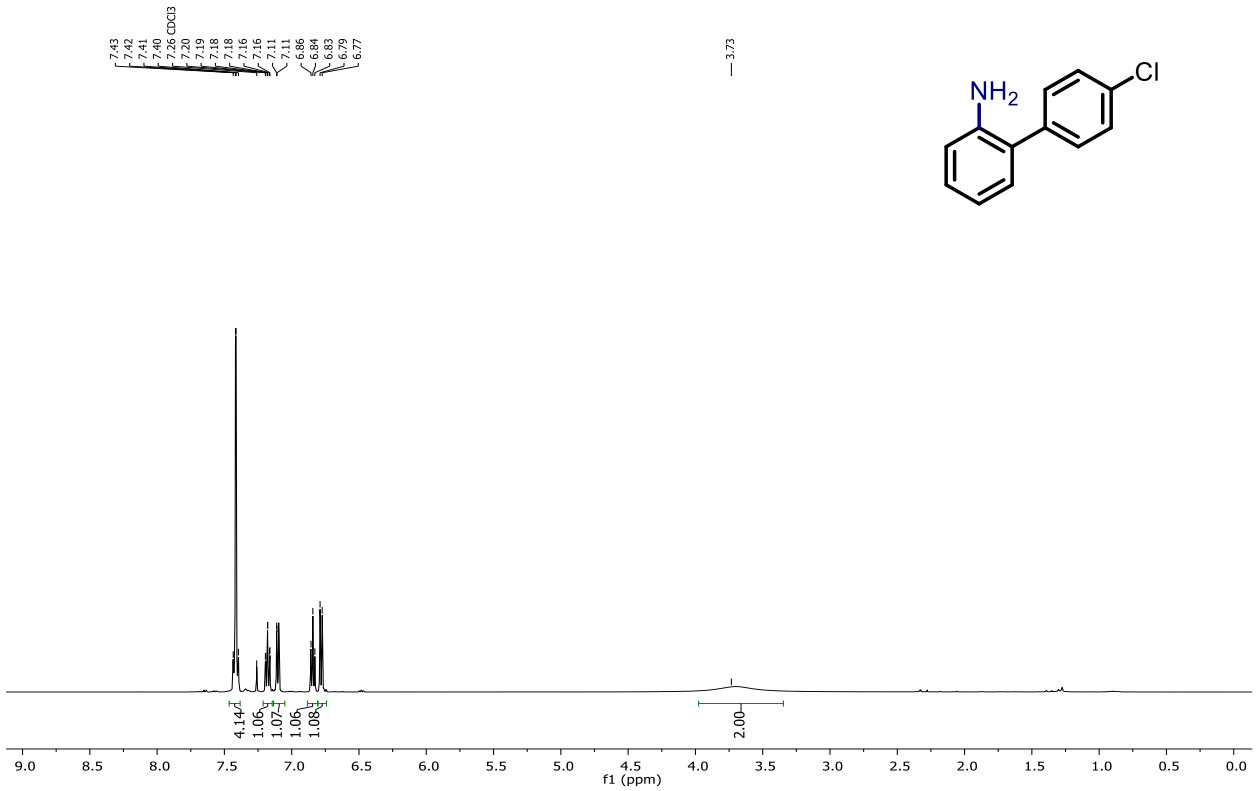
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6.84
6.83
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Cl
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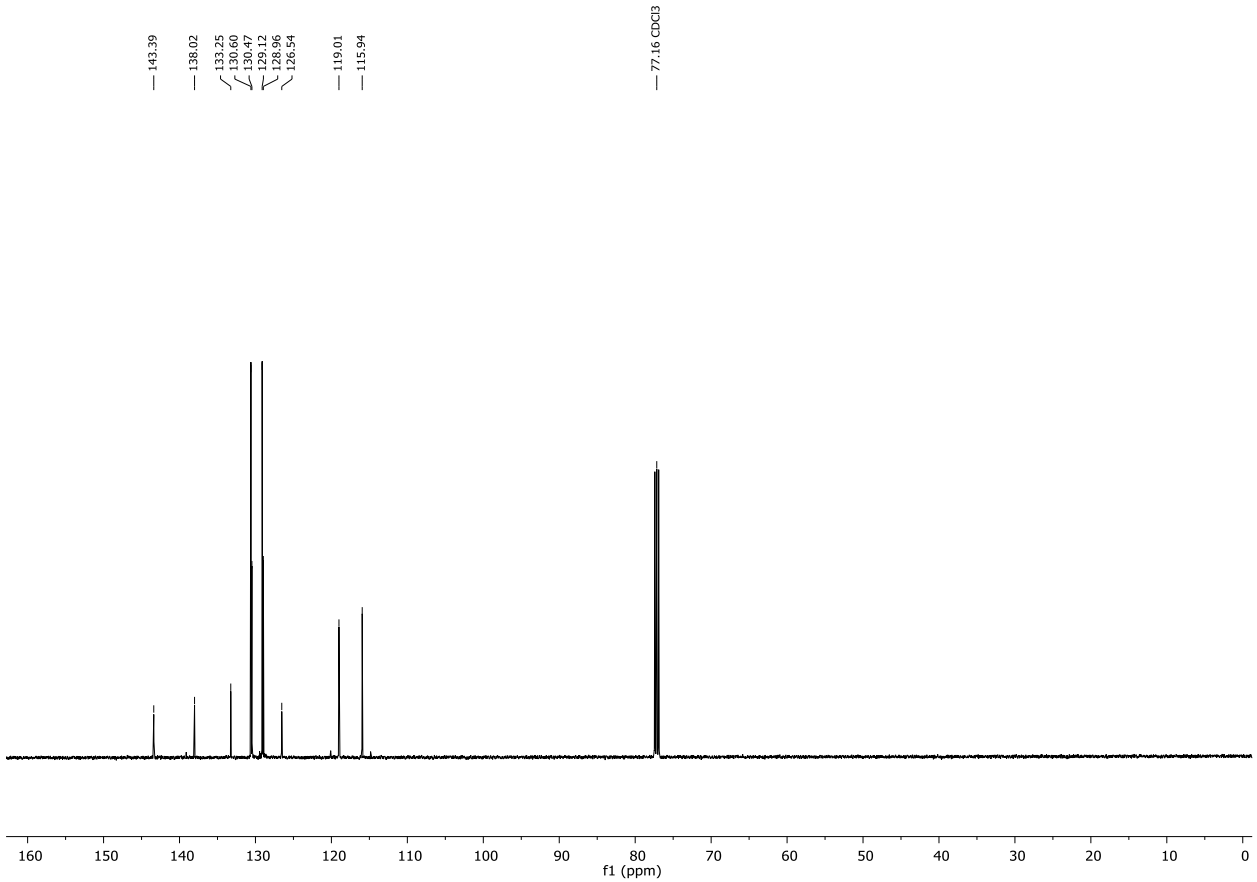
1.06
1.08
2.00
f1 (ppm)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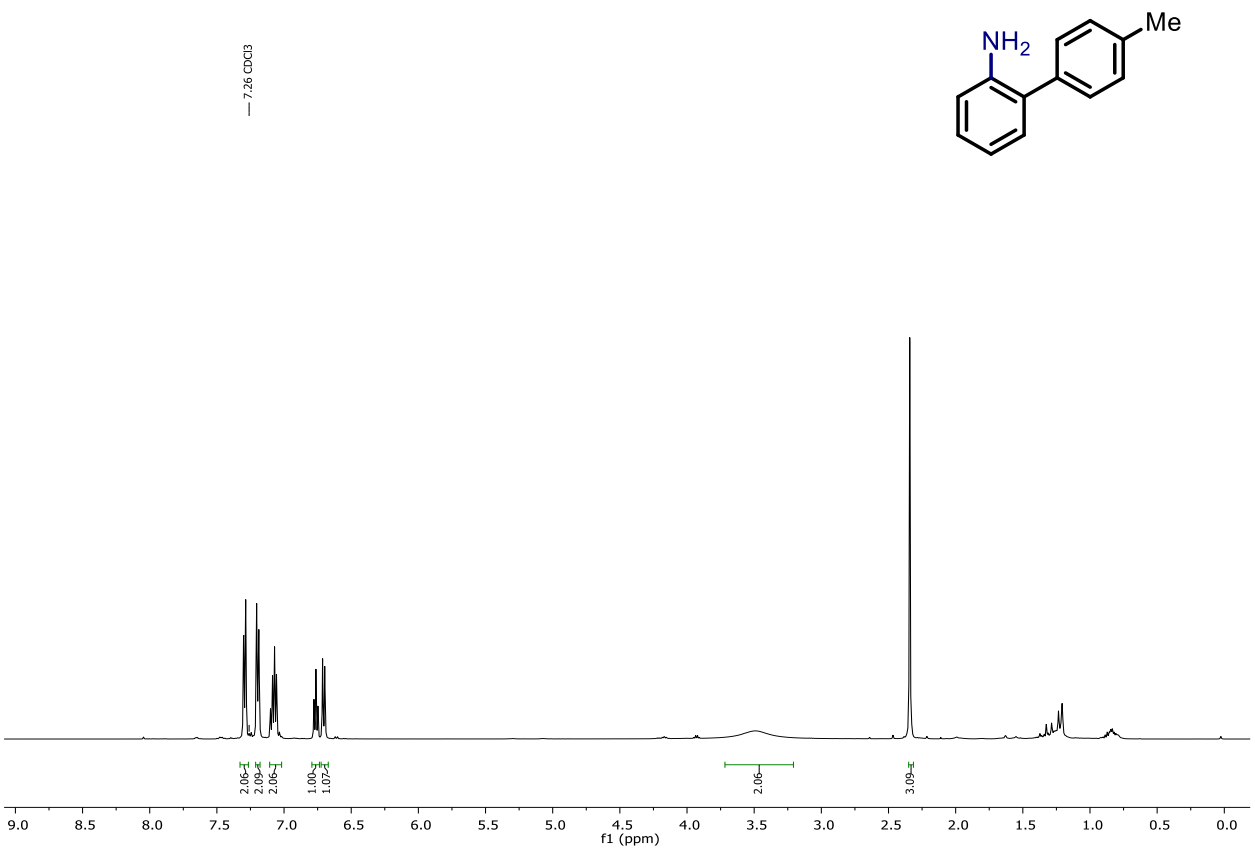
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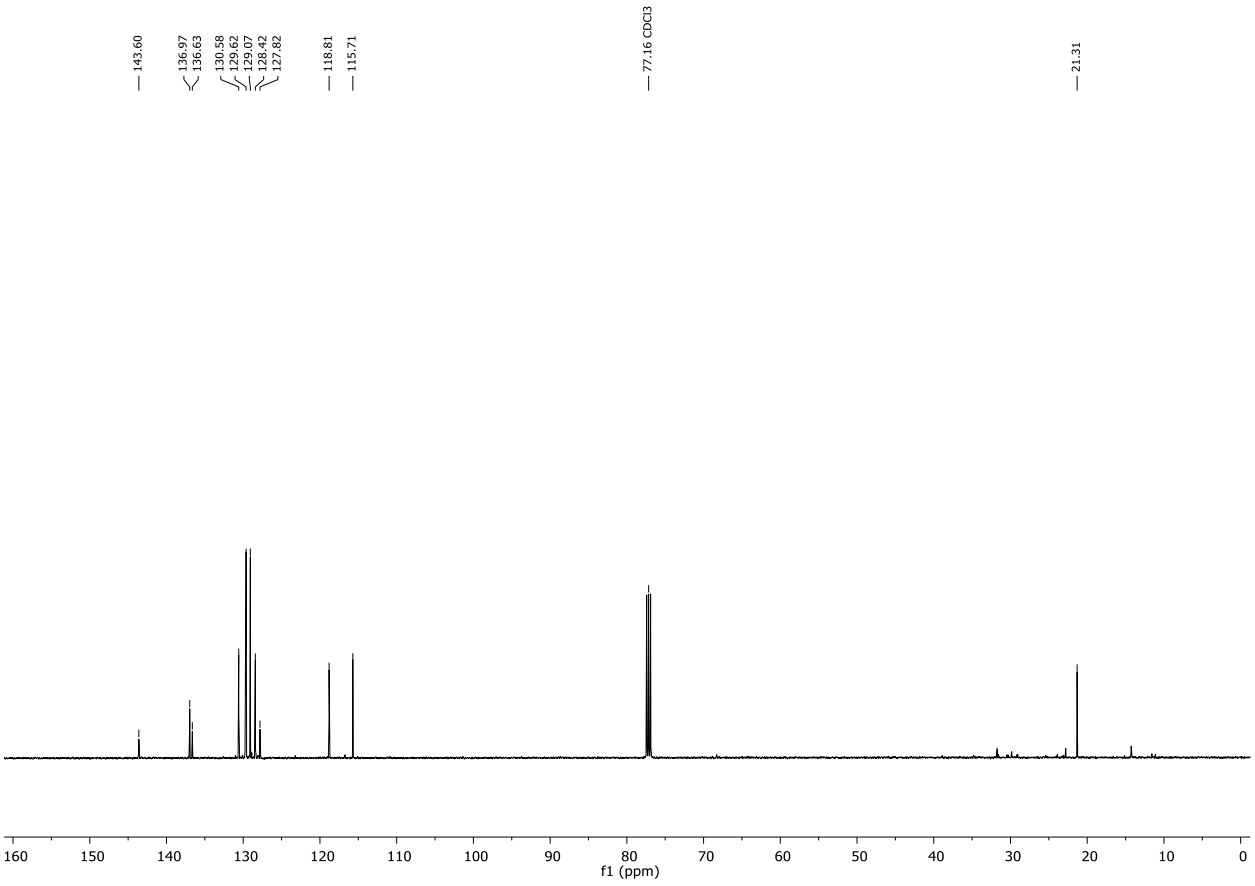
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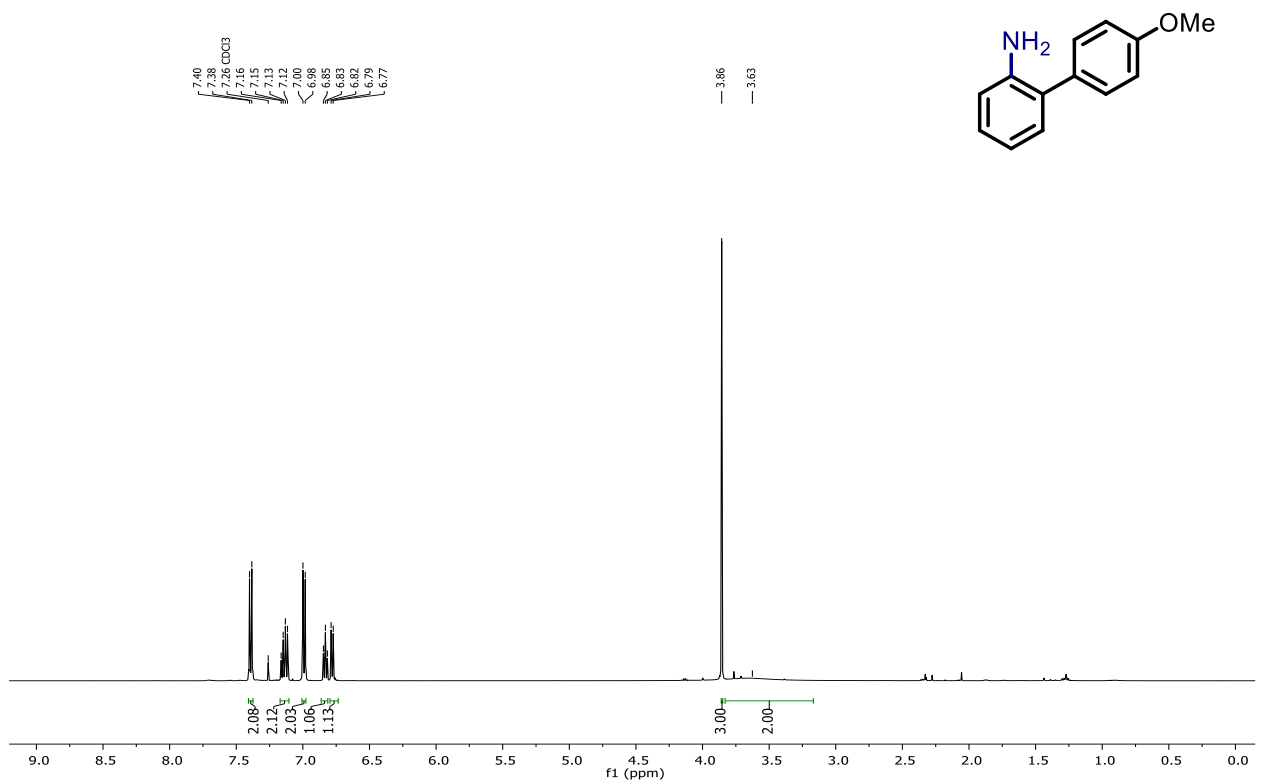
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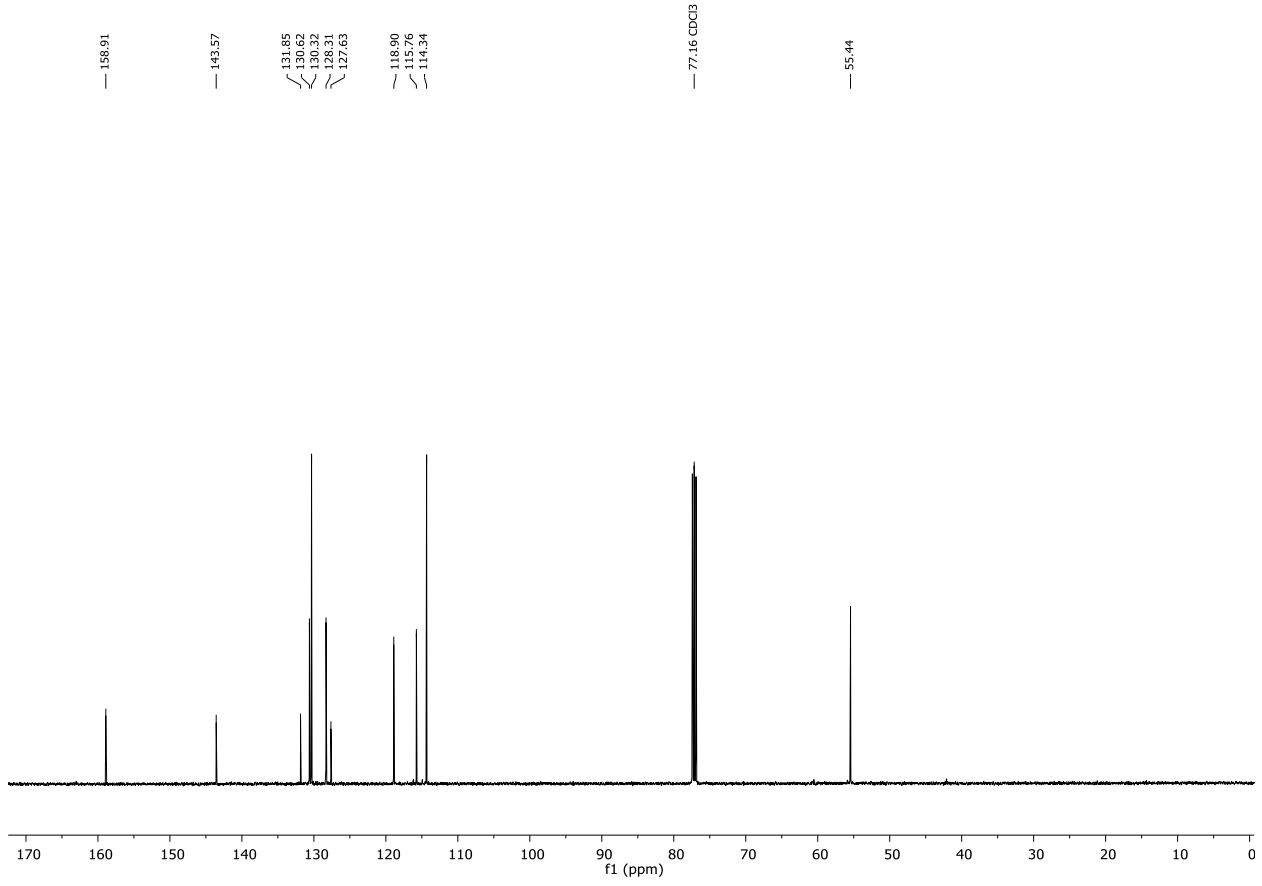
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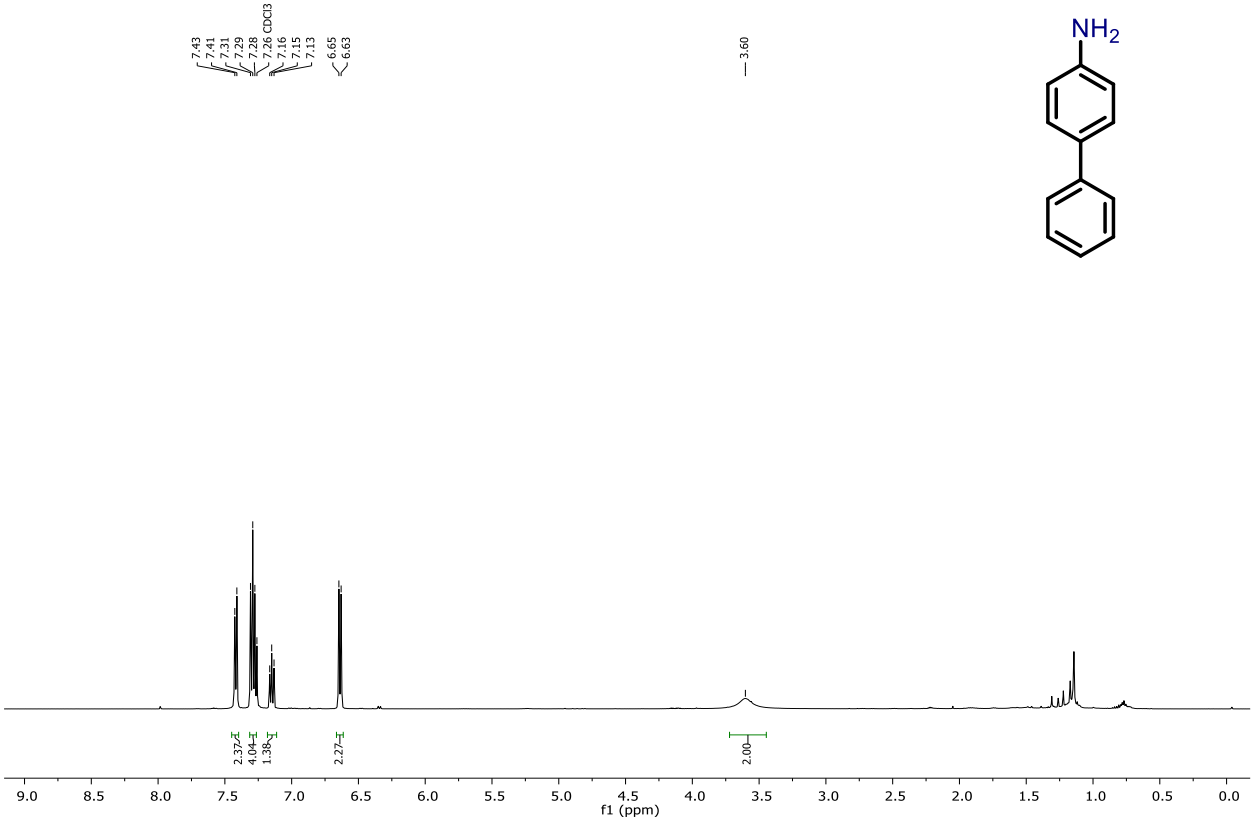
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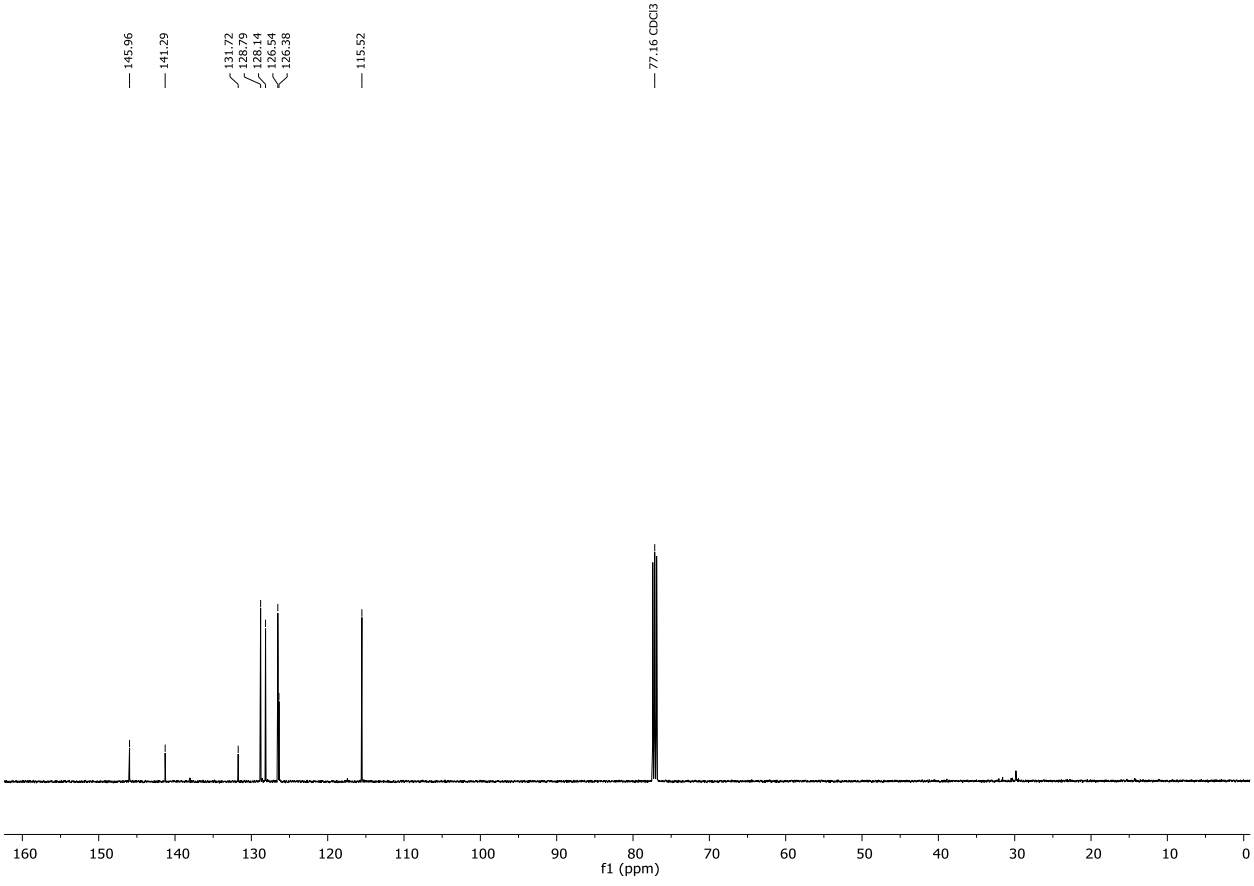
2.00
f1 (ppm)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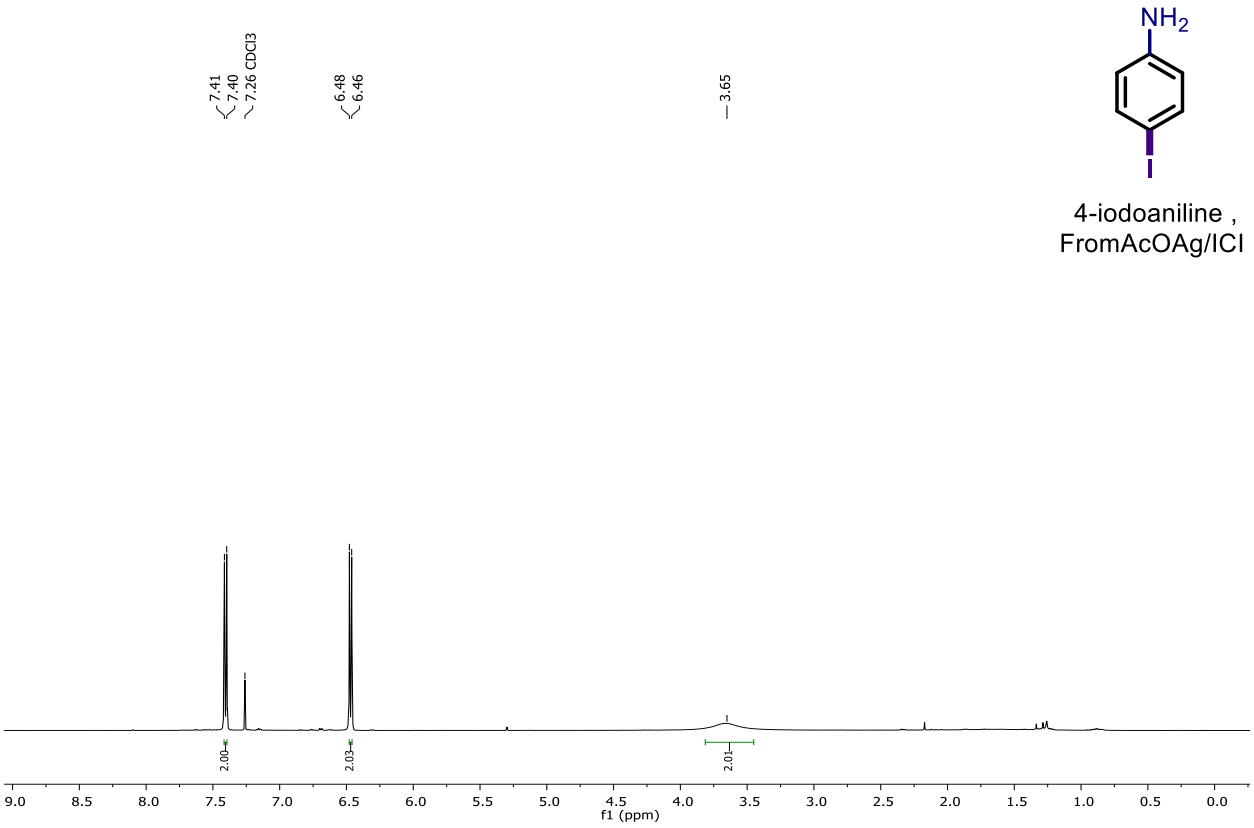
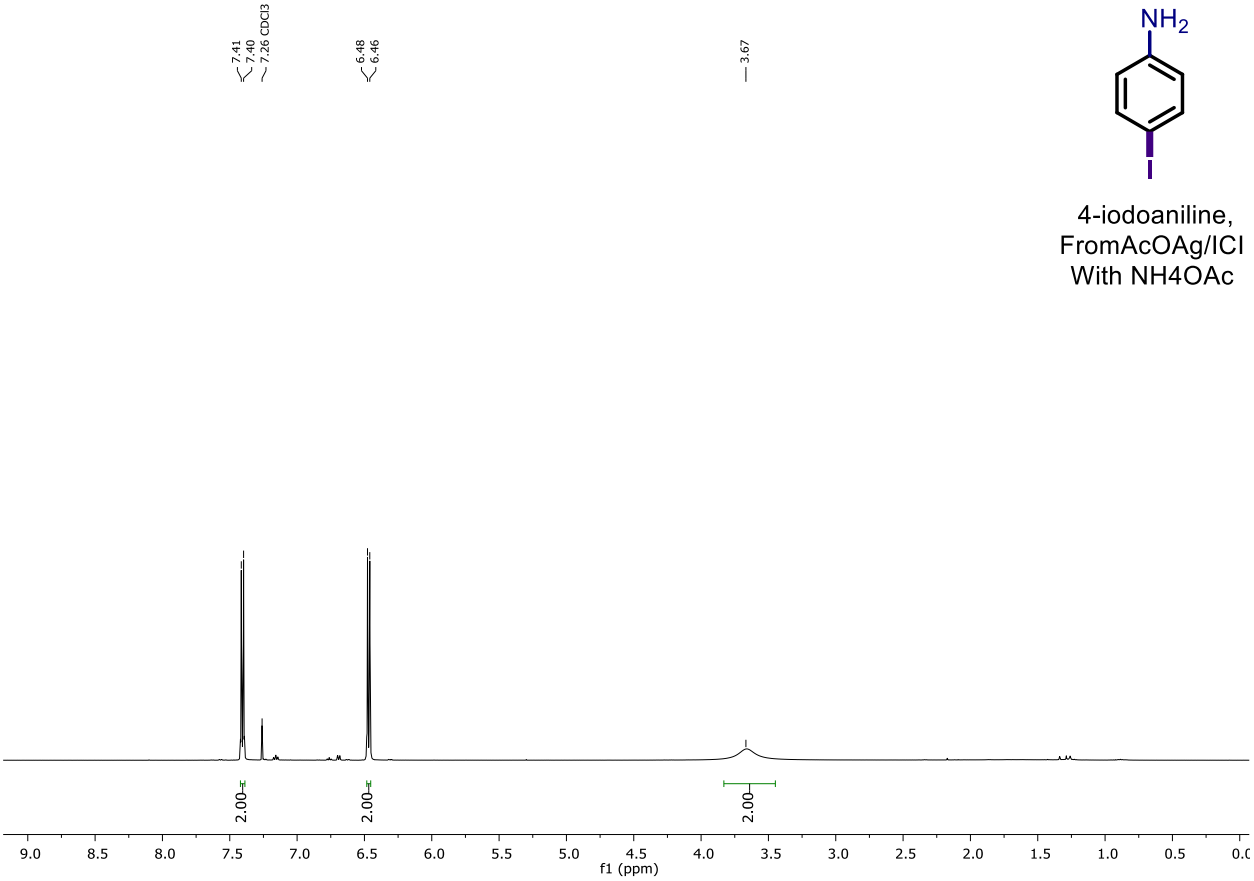


4-iodoaniline ,
FromAcOAg/ICl



4-iodoaniline,
FromAcOAg/ICl
With NH4OAc

ANNEX B.

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

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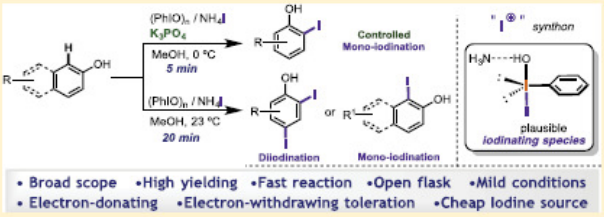
Supporting Information

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 PhII(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-

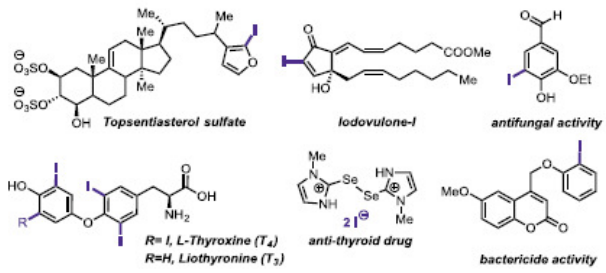


Figure 1. Relevance of the iodoarene moiety.

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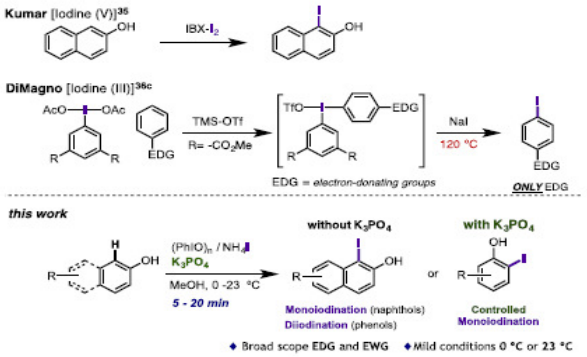
Scheme 1. Hypervalent Iodine Strategies for the Iodination of Arenes and Phenols



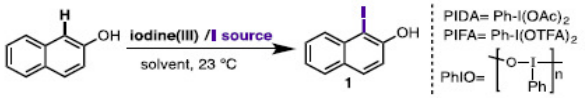
valent-based iodination procedures of phenols, the very few of them that are available are synthetically restricted in several ways, the most significant being low selectivity,[35] polyhalogenation, expensive starting materials,[36] more than one preparation step, limitation to electron-rich arenes, 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

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.

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

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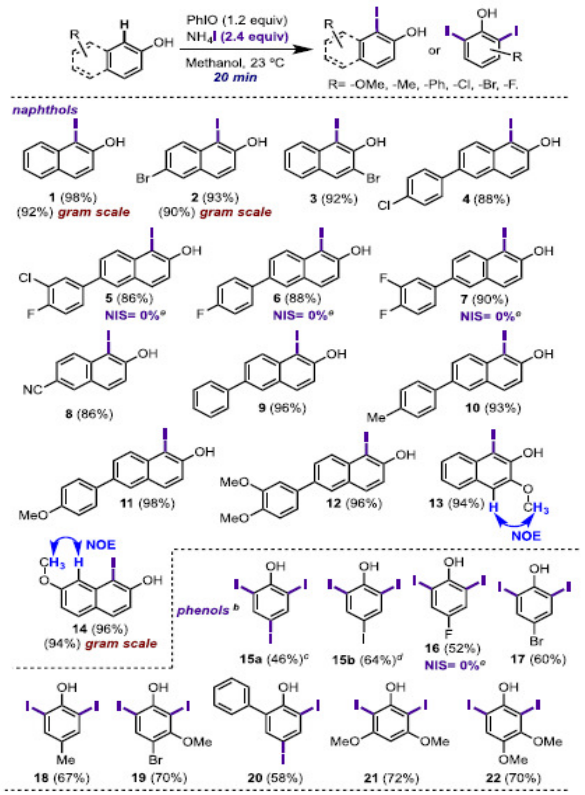
the scope of the new procedure with respect to changes in the aryl unit (Scheme 2).

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

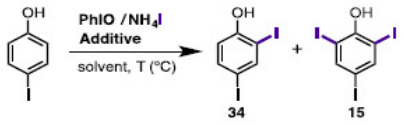


[a]Reaction conditions: 2-naphthol (0.5 mmol), methanol (0.15 M), open flask. [b]PhIO (2.4 equiv)/NH_4I (4.8 equiv) were used. [c]Synthesized from phenol. [d]Synthesized from 4-iodophenol. [e]Reaction conditions: phenol (0.5 mmol), NIS (1.2 equiv), TFA (10 mol %), MeCN (0.15 M) at 23 °C by 12 h.

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

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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.

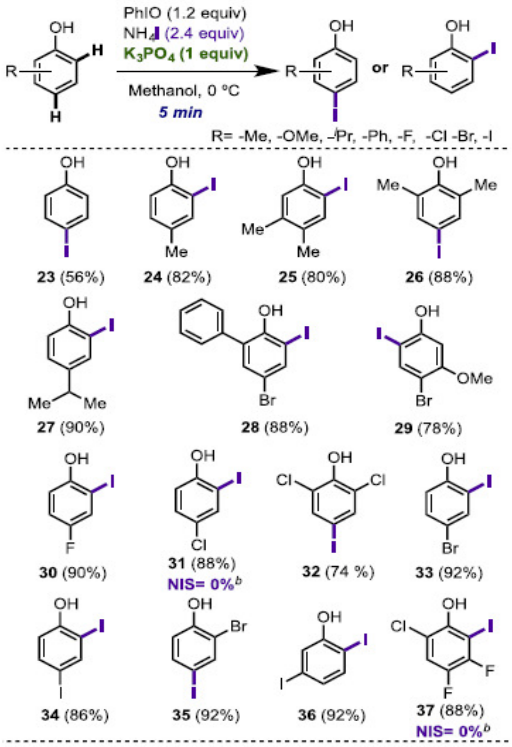
After this analysis and determination of the optimal conditions, we explored the scope of the controlled monoiodination of phenols (Scheme 3).

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.

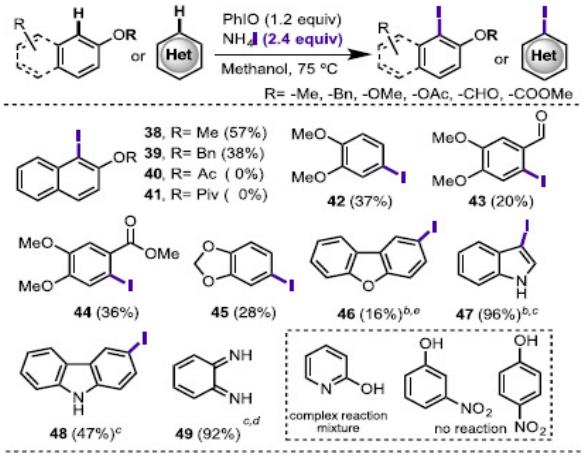
The following set of trials was devised to determine the tolerance of our procedure in the presence of (1) different functional groups at the phenolic oxygen, (2) functionalized phenols with more than one functional group, (3) functionalities other than phenol present in the aryl moiety, and (4) heterocycles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

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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).

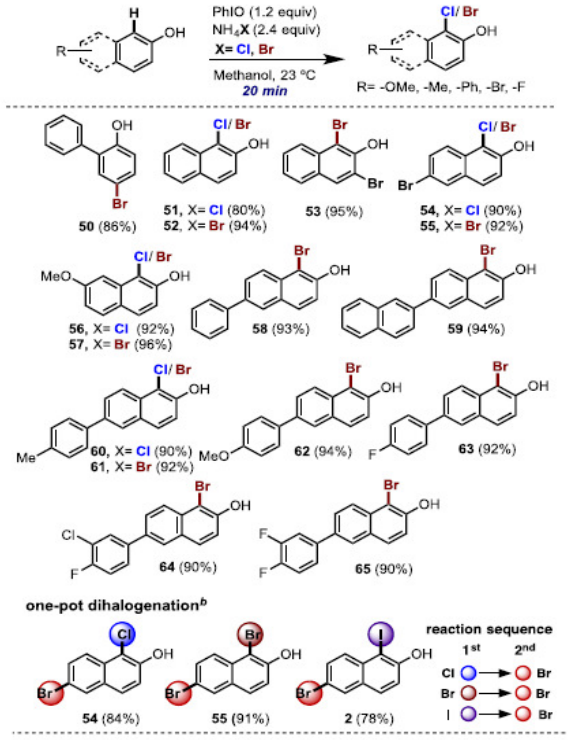
The ammonium chloride and bromide were mainly employed under the optimized standard conditions (Scheme 5) in order to introduce these halides into a range of phenols. In this way, 2-phenylphenol was brominated in 86% yield, giving rise to **50**. The chlorination and bromination of 2-naphthol, 6-bromo-2-naphthol, 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).

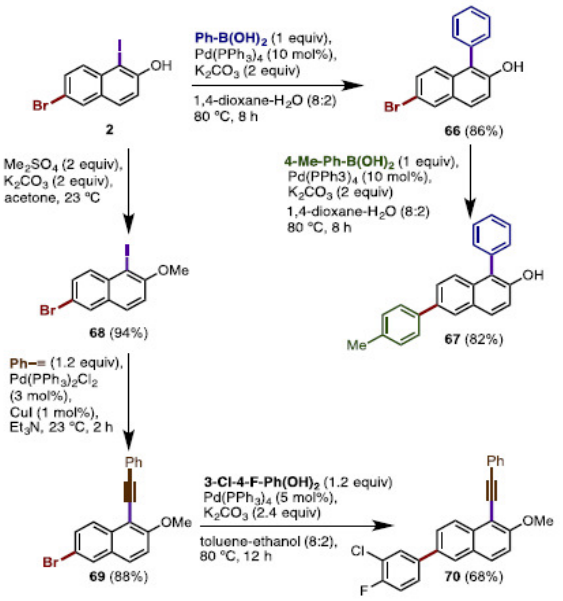
The synthetic applicability of the derivatives obtained through our procedure was illustrated with the compound 6-bromo-1-iodo-2-naphthol (**2**) which possesses two halide

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



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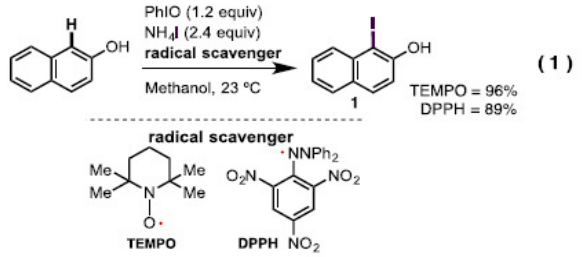
groups with different reactivities. We considered the synthesis of **2** as an excellent opportunity to carry out two distinct orthogonal reaction sequences: sequential double Suzuki cross-coupling, and Sonogashira alkynylation/Suzuki cross-coupling. In the first sequence, regioselective Suzuki cross-coupling 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.

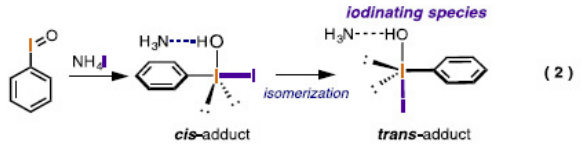
Finally, in order to gain more insight into the reaction mechanism, we decided to carry out the iodination of 2-naphthol in the presence of the radical scavengers TEMPO[42] (tetramethylpiperidine *N*-oxide) and DPPH (2,2-diphenyl-1-picrylhydrazyl) in order to determine if a radical or cationic pathway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

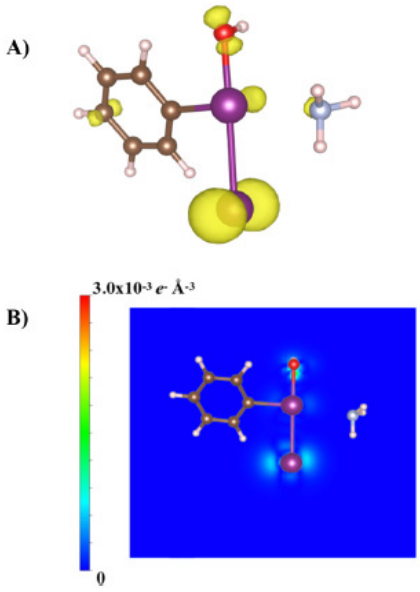


Figure 2. (a) The Fukui function for electrophilic attack of the plausible iodinating active species and (b) its 2D projection. Color code for atoms in brackets: C (brown), O (red), I (purple), (N) light blue, and H (pink).

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.

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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,

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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),

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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

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(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,

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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.

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*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

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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-

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(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)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

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

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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

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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.

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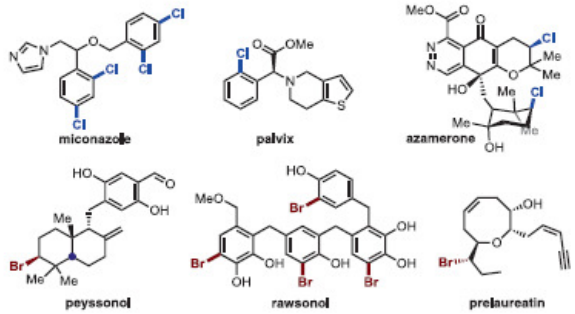
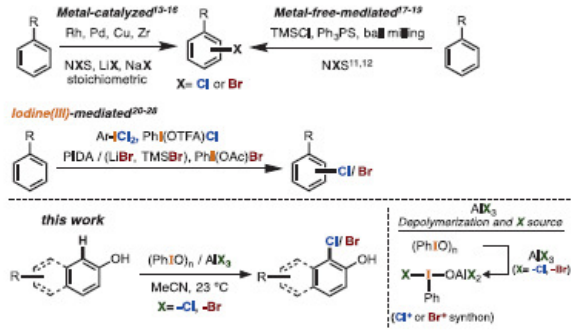


Fig. 1. Relevance of the aromatic chloride and bromide core.

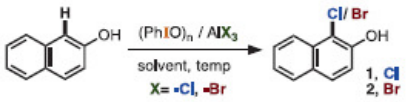


Scheme 1. Representative methods for the chlorination and bromination of arenes.

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]



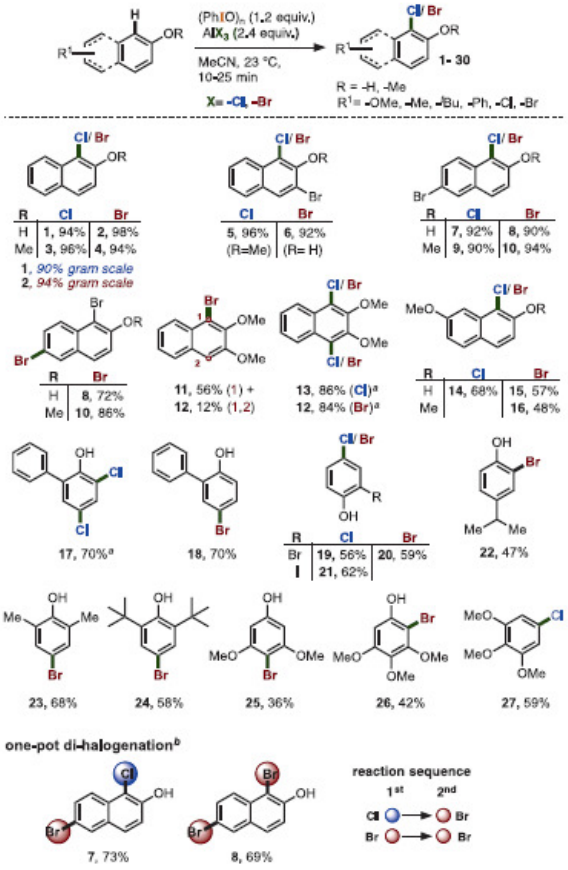
Entry	$(PhIO)_n$ (equiv.)	AlX_3 (equiv.)	Solvent, Temp (°C)	Yield (%)[b]
1	1.1	$AlCl_3$ (1.2)	MeCN, 23	58
2	1.2	$AlCl_3$ (1.5)	MeCN, 23	71
3	1.2	$AlCl_3$ (2.4)	MeCN, 40	69
4	***1.2***	***$AlCl_3$ (2.4)***	***MeCN, 23***	***94***
5	1.2	$AlCl_3$ (2.4)	MeOH, 23	n. r.
6	1.2	$AlCl_3$ (2.4)	THF, 23	48
7	1.2	$AlCl_3$ (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.

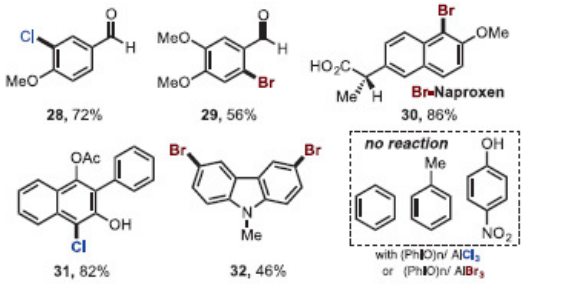
With the optimal chlorination and bromination conditions in hand, we proceeded to explore the scope of this protocol (Scheme 2).

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).

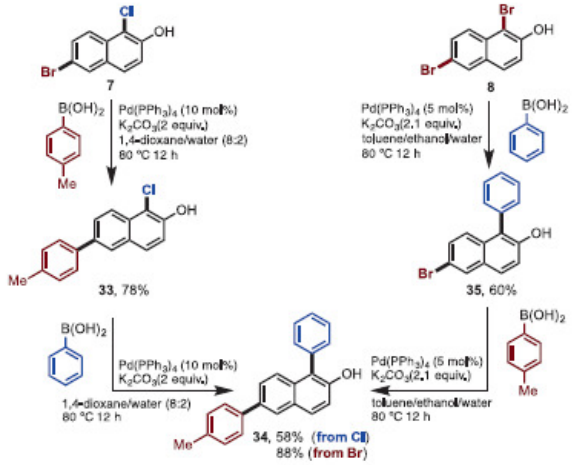
Next, various functional groups were explored to determine the tolerance of the reaction (Scheme 3).

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.

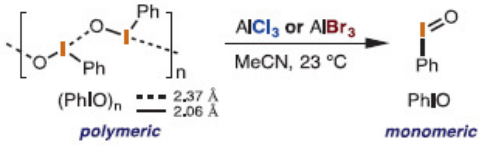


Fig. 2. Proposed depolymerization of (PhIO)n using AlX_3 (X = Cl, Br).

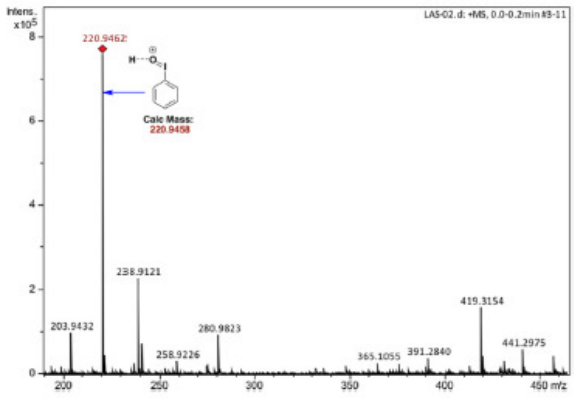
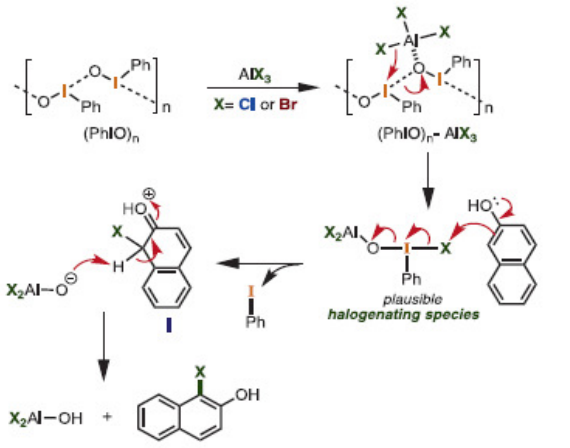


Fig. 3. Identification of monomeric PhIO after the AlX_3 promoted depolymerization of (PhIO)n.



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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.05.019.

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REVIEW ARTICLE

Oxidative Halogenation of Arenes, Olefins and Alkynes Mediated by Iodine(III) Reagents

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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*).

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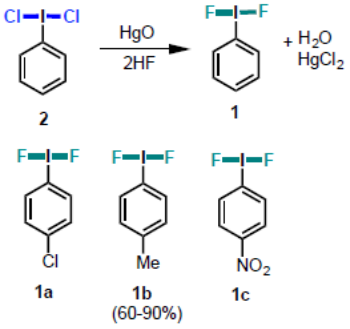
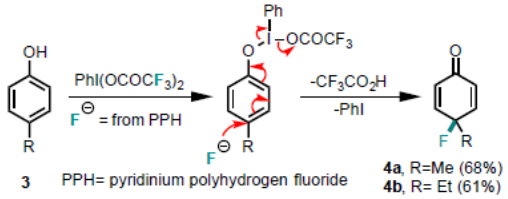
One of the initial methods for the one-step preparation of difluoroiodobenzene derivatives using HIR (**2**) was described by Carpenter in 1966 [10]. In this protocol, fluorine sources such as F_2, SF_4 or XeF_4 were avoided. The synthesis of 4-iodotoluene difluoride and derivatives **1a-c** was achieved 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**).

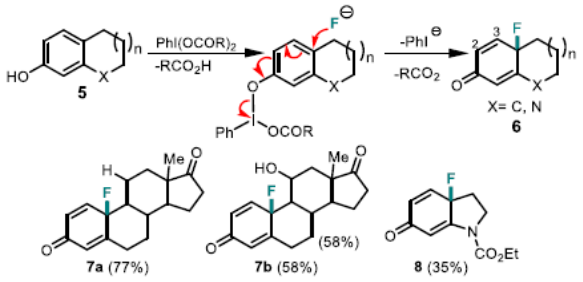


Scheme 2. Putative fluorination of aromatic phenols **4a-b** using PIFA and PPHF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

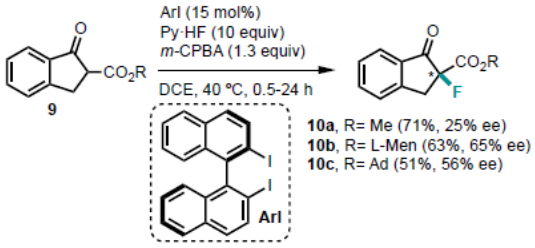
In 2004, Karam *et al.* [13] reported a fluorination procedure using phenols of type **5**. The combination of PPHF with PIDA diacetoxyiodo(benzene) gave rise to the fluorination of angular fluorocyclohexenones in low to moderate yields. The procedure was also applied to the *ipso*-fluorination of estrogen 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**).

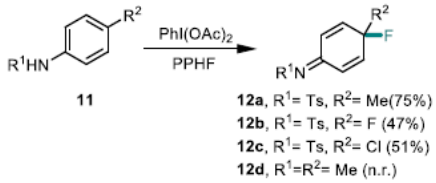
Afterward, Jouannetaud *et al.* [15] carried out the reaction of *para*-substituted anilines (**11**) in the presence of PIDA and PPHF, giving easy access to new 4-fluorinated cyclohexa-2,5-dienimines (**12**). These fluorinated derivatives **12** were obtained in low to moderate yields (18-75%). The 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*).



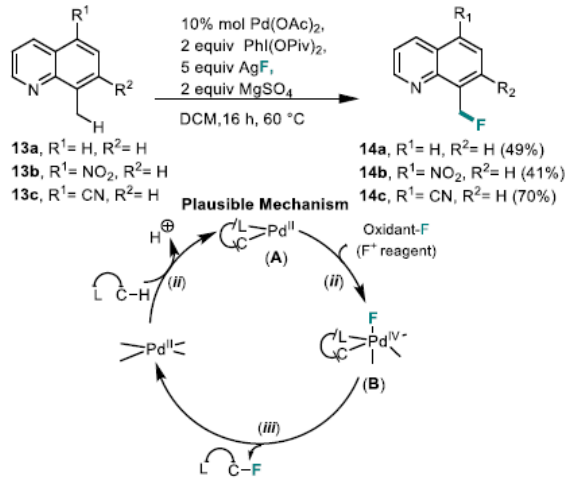
Scheme 5. Synthesis of 4-halo-4-alkylcyclohexa-2,5-dienimines (**12**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**.

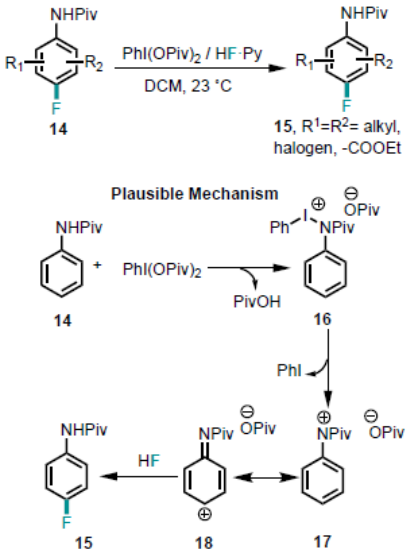
Interestingly, in the proposed catalytic cycle, the fluoride atom is the oxidizing agent (Pd^{II} to Pd^{IV}) and the source of the fluorine atom (Scheme **6**).

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).

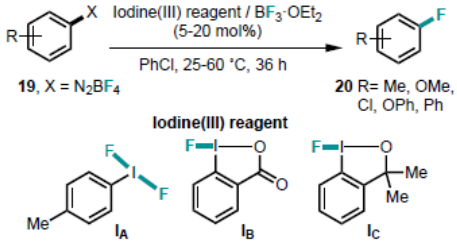


Scheme 6. Palladium-catalyzed C-H fluorination of 8-methylquinoline derivatives **13a-c** using $PhI(OPiv)_2$ as oxidant. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



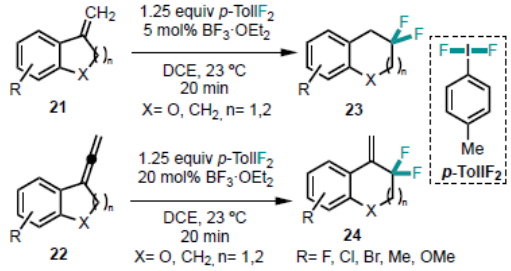
Scheme 7. Regioselective *para*-fluorination of anilides **14** mediated by $PhI(OPiv)_2$ / Py·HF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).

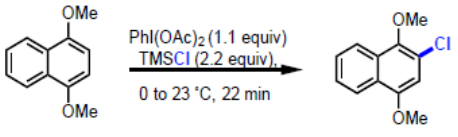


Scheme 9. Difluorinative ring expansions of 3-alkenyl- and 3-allenyl-benzofuranes using p-(difluoroiodo)toluene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3. OXIDATIVE CHLORINATION OF ARENES MEDIATED BY λ^3-IODANES

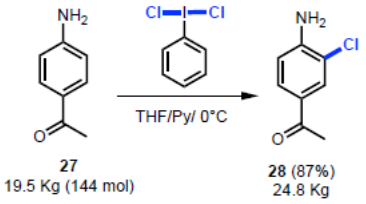
Another class of relevant compounds is the chloroarenes. Herein we describe some representative procedures for the chlorination of these compounds using novel hypervalent iodine(III) reagents as oxidants.

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**).



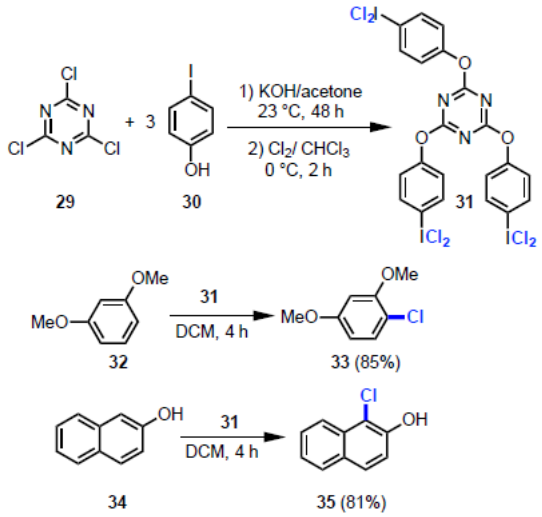
Scheme 10. Chlorination of 1,4-dimethoxynaphthalene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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*).

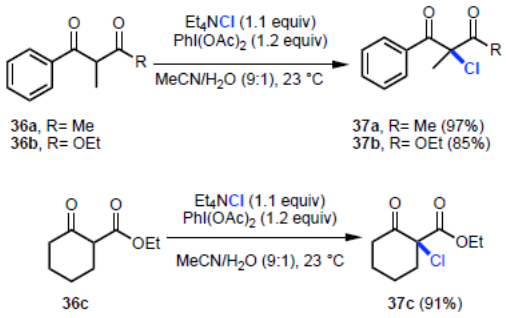
Interestingly, Karade *et al.* [22] described a method for the preparation of the recyclable hypervalent iodine(III) **31**. The iodine reagent was synthesized from 4-iodophenol **30** and 2,4,6-trichloro-1,3,5-triazine **29** to form 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine **31** as a recyclable 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**).



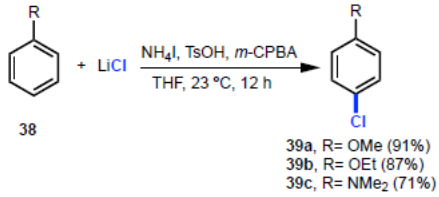
Scheme 12. Preparation of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine (**31**) and use in the chlorination of some arenes (**33**, **35**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).

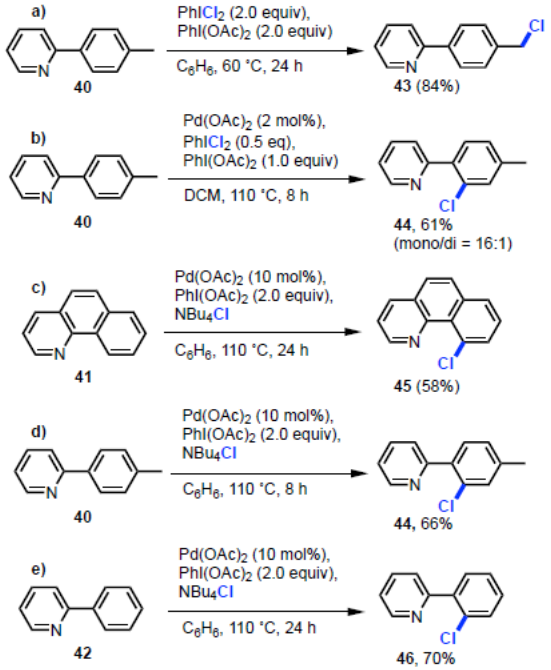
Regarding the catalytic reactions using hypervalent iodine reagents, Min *et al.* [24] developed regioselective chlorination of electron-rich aromatic compounds **38**. The protocol uses NH_4I, *m*-CPBA and LiCl to form *in situ*, the hypervalent iodane intermediate. In this way, the monochlorinated 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*).

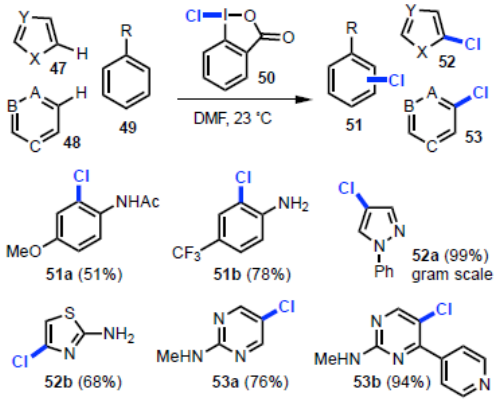


Scheme 15. Some examples of Pd-catalyzed C-H chlorination by *in situ*-generation of PhI(OAc)Cl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).

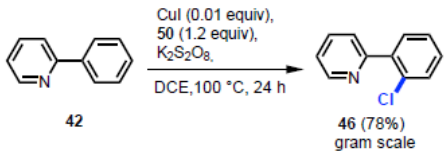
On the other hand, the palladium-catalyzed chlorination of benzo[*h*]quinoline and the *p*-tolylpyridine derivatives **40**-**42** by using $Pd(OAc)_2$, $PhI(OAc)_2$ and ammonium chloride as a chlorine source, produced the corresponding halogenated derivatives **44**-**46** in moderate to good yields (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*).

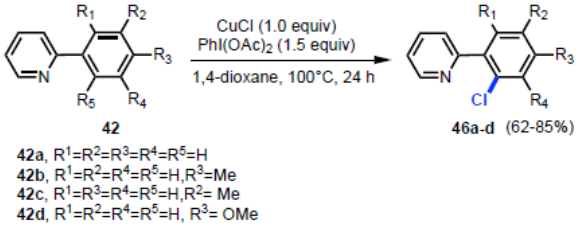
A regioselective copper-catalyzed method to successfully obtain chlorinated aryl heterocycles (**46**) was described by Parvathaneni [27]. This protocol combines **50** with copper iodide and $K_2S_2O_8$ as additive. Also, the procedure takes place in a gram scale within good yields (78%) (Scheme **17**).



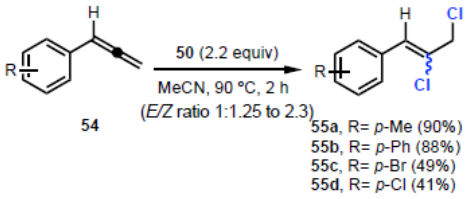
Scheme 17. Copper-catalyzed *orto*-chlorination of aryl pyridines. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).

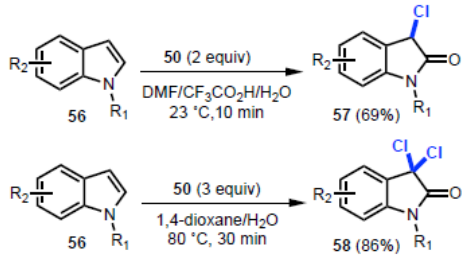


Scheme 18. *ortho*-chlorination of an aromatic compound using PIDA and CuCl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



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*).

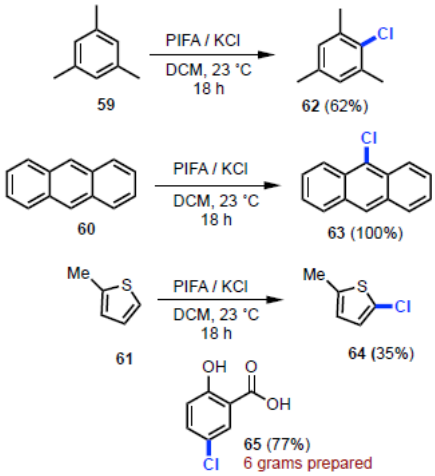
Later, in 2019, Yu *et al.* [30] described the transformation of a wide range of indoles **56** into 3-chloro-2-oxindoles (**57**-**58**). The reaction proceeds *via* the selective oxidation of C-2 with concomitant mono- or bis-chlorination at C-3. This iodine(III)-promoted chloro-oxidation is a one-pot transformation which takes place in moderate to high yields (65-99%) with excellent functional group compatibility (Scheme **20**).



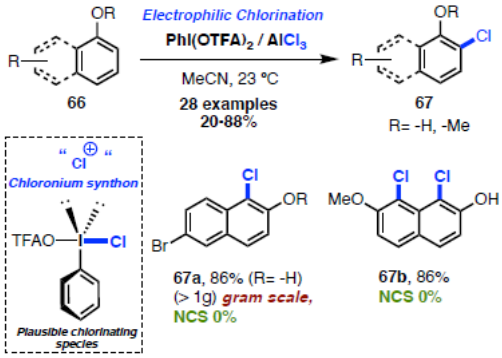
Scheme 20. Synthesis of 3-chlorooxindoles mediated by 1-chloro-1,2-benziodoxol-3-one **50**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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*).



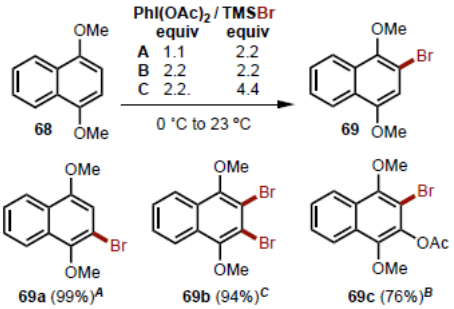
Scheme 22. Chlorination of arenes mediated by the PIFA/$AlCl_3$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. OXIDATIVE BROMINATION OF ARENES MEDIATED BY λ^3-IODANES

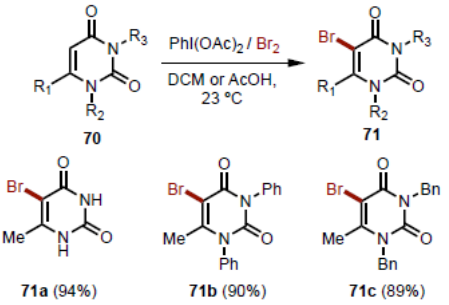
Concerning the brominated derivatives, due to their high relevance in organic synthesis, there is an increasing interest in accessing such important core. Herein we review some relevant protocols of bromination mediated by iodine(III) reagents.

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*).

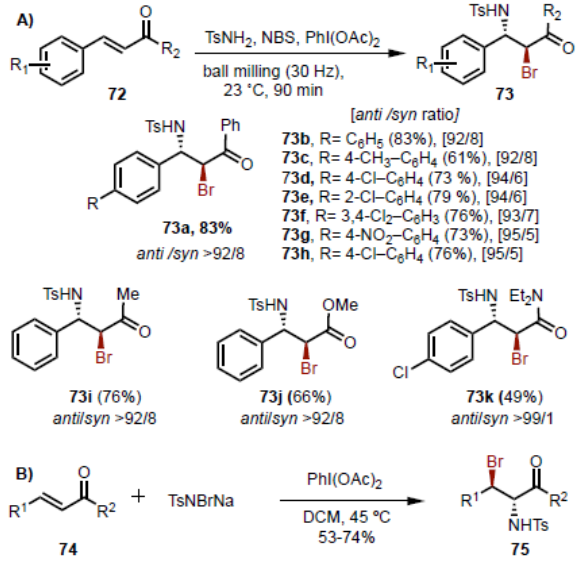
Later, Wang *et al.* [34] reported an oxidative iodine(III)-based procedure for the aminobromination of α, β-unsaturated ketones, esters, and amides **72**. The protocol displayed excellent diastereoselectivities under mechanical ball milling conditions, using $TsNH_2$ and NBS as the nitrogen and bromine 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].

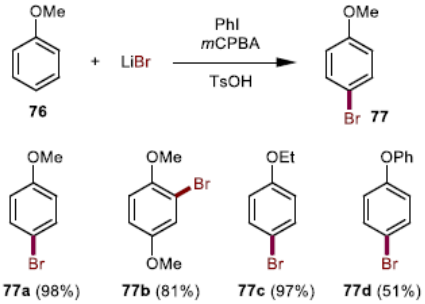
Another iodine(III)-catalyzed protocol for the regioselective monobromination of electron-rich arenes **76** was reported by Zhou *et al.* [36]. The procedure allowed the bromination of different phenols-ethers and heterocycles in excellent yields. The mechanism proposes the formation *in situ* of the 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

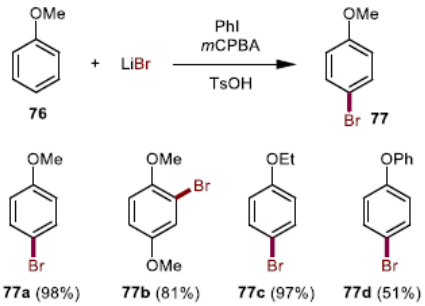
source. The mechanism of this reaction involves an S_N2 ring-opening reaction which explains the high *anti*-stereoselectivity of the brominated products **79**. Additionally, this methodology is characterized by high yields, short reaction times and easy workup procedure (Scheme **27**).



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*).

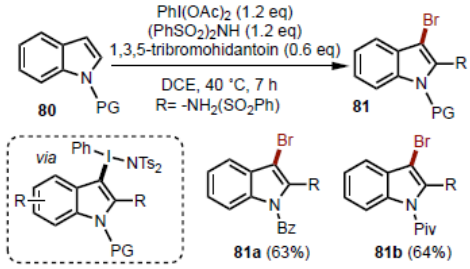


Scheme 26. Iodine(III)-catalyzed bromination of electron-rich arenes using PhI(OTs)Br. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



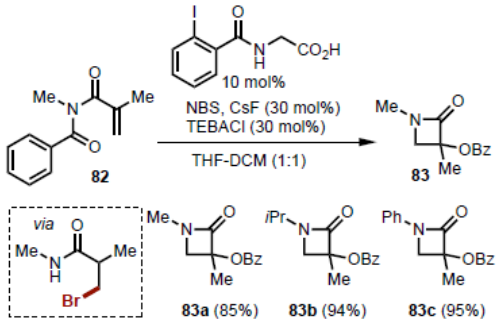
Scheme 27. Synthesis of vicinal methoxy-bromides from olefins using PIDA and PTAB. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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*).

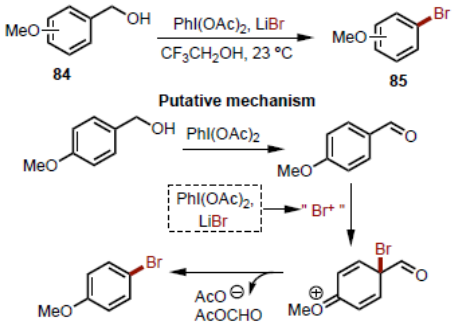
Also, the Gulder group [39] reported a one-pot synthesis of β-lactams under iodine(III)-catalyzed conditions. This cascade of reaction involves the bromination/rearrangement/cyclization sequence with excellent yields. In general, this three-step one-pot reaction gave direct access to isoserine derivatives from simple imines (Scheme **29**).



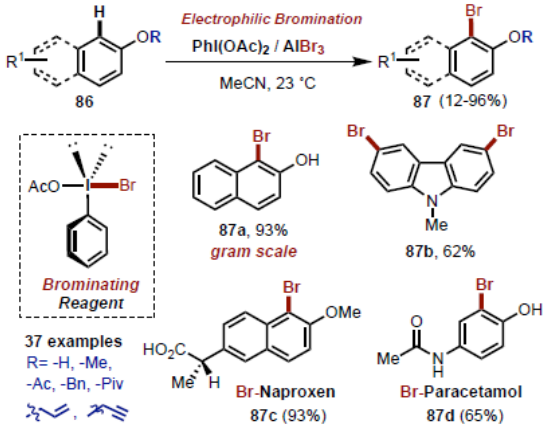
Scheme 29. Iodine(III)-catalyzed triple cascade reaction to obtain β-lactams. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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*).

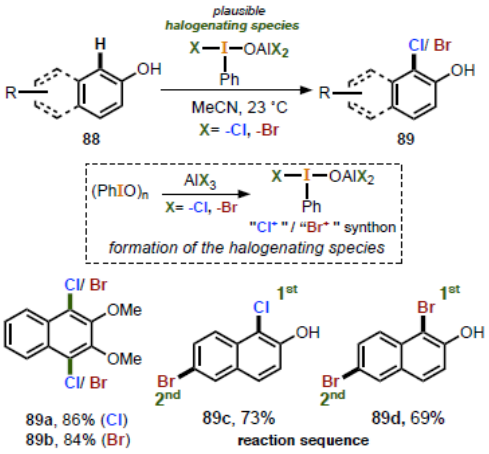


Scheme 31. Bromination of arenes mediated by the PIDA/$AlBr_3$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).

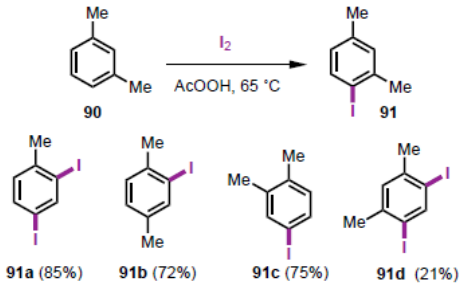
5. OXIDATIVE IODINATION OF ARENES MEDIATED BY λ^3-IODANES

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**).

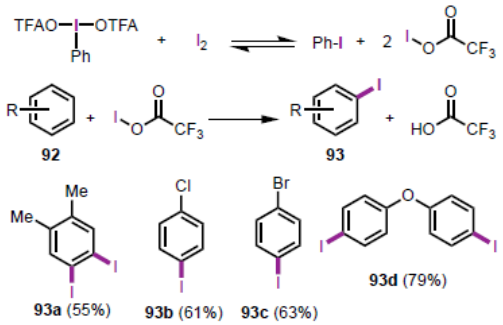


Scheme 33. Kinetic study and development of the iodination procedure of arenes using I_2/AcO_3H. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

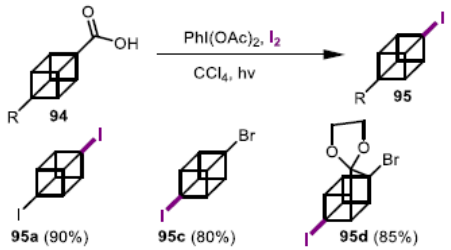
Initial examples of iodination with hypervalent iodines were reported in 1979 by Merkushev *et al.* [44]. They described the iodination of xylenes **92** in the presence of PIFA or iodosobenzene and molecular iodine using chloroform as solvent. The iodination procedure was fast and proceeded smoothly, 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**).

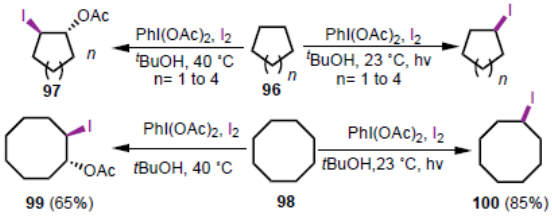


Scheme 34. Iodination of different arenes using PIFA/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



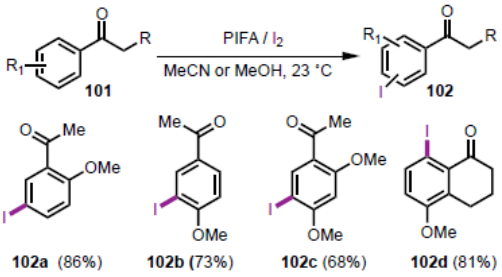
Scheme 35. Hypervalent iodine(III) mediated decarboxylative-iodination of homocubyl and cubyl carboxylic acids. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).



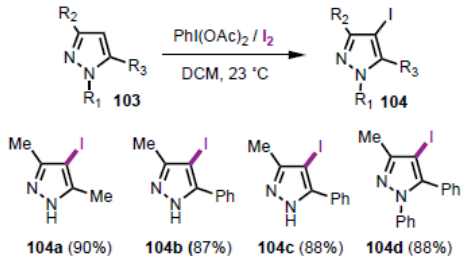
Scheme 36. Photochemical and thermal iodination of hydrocarbons with PhI(OAc)$_2$/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).



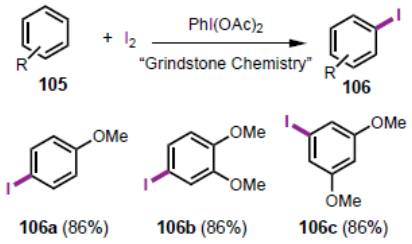
Scheme 37. Electrophilic aromatic-iodination of alkyl- and aryl ketones mediated by the PIFA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).



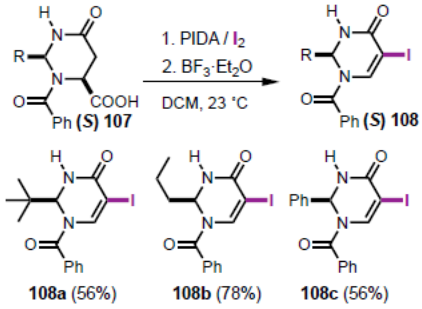
Scheme 38. Iodination of pyrazole derivatives mediated by PIDA/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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*).

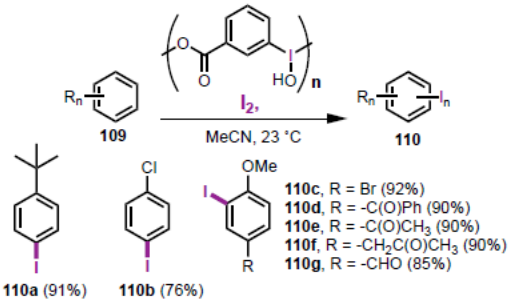
In 2007, Juaristi *et al.* [50] developed an iodination procedure for the synthesis of α-substituted β-aminoacids, using the PIDA/I_2 system. The reaction proceeded with perhydropyrimidinone-6-carboxylic acids **107** in DCM at room temperature to afford the expected mixture of the reduced enones and 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**.

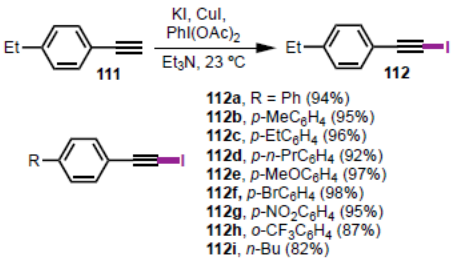
The *m*-iodobenzoic acid can easily be removed by simple acidification or by resin extraction (Scheme **41**).



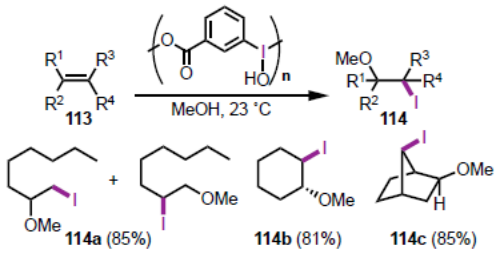
Scheme 41. Mono-iodination of arenes with *m*-iodosylbenzoic acid and molecular iodine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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**).

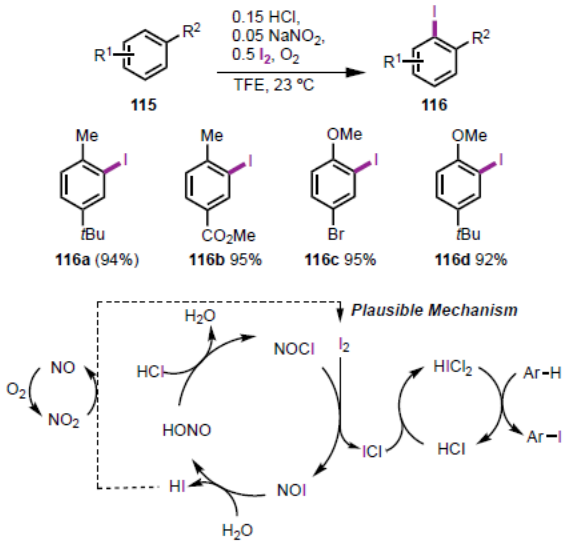
Yusubov *et al.* [53] developed another approach using *m*-iodosylbenzoic acid and molecular iodine for the iodination of alkenes and alkynes **113**. This efficient and facile method afforded the iodinated products **114** in good yields under mild conditions. The final purification of *m*-iodosylbenzoic 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*).

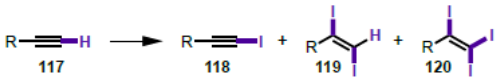


Scheme 43. Iodomethoxylations of alkenes using hypervalent *m*-iodosylbenzoic and molecular iodine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



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

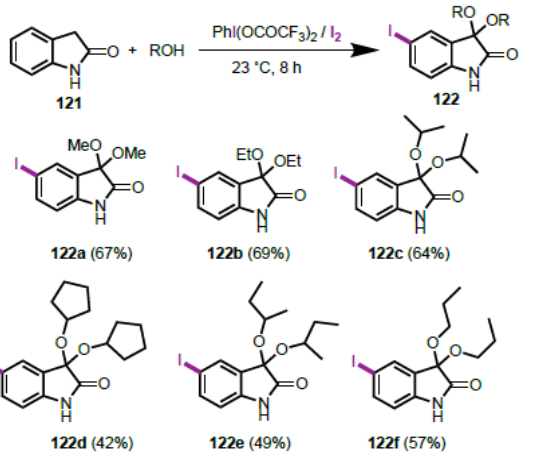


alkyne	method	mayor product	%yield (2:3:4)
R= *p*-tolyl	A	**2a**	99 (100:0:0)
	B	**3a**	99 (0.8:98.8:0.4)
	C	**4a**	93(3.7:3.2:93.1)
R= Ph	A	**2b**	93(100:0:0)
	B	**3b**	97(0.2:97.6:2.2)
	C	**4b**	91(0.8:0.7:98.5)
R= *m*-tolyl	A	**2c**	98(100:0:0)
	B	**3c**	98(0.9:98.1:1.0)

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*).



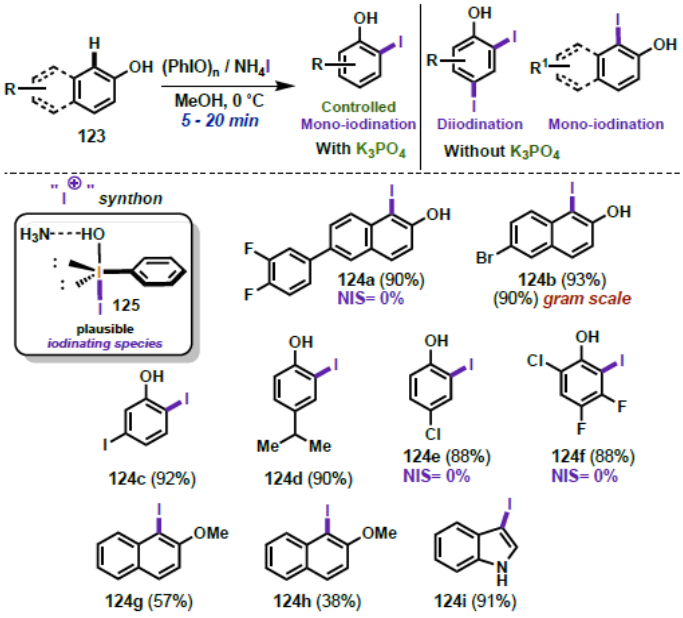
Scheme 46. Iodoalkoxylation of arenes mediated by the PIFA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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.

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Article

Gold(I)-Catalyzed Synthesis of 4*H*-Benzo[*d*][1,3]oxazines and Biological Evaluation of Activity in Breast Cancer Cells

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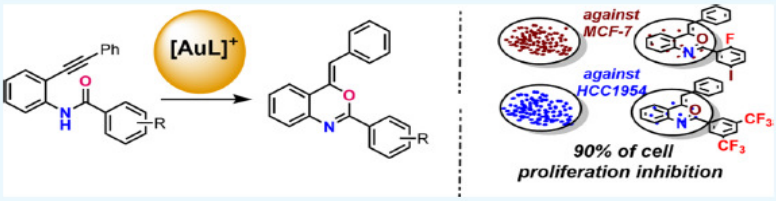

ABSTRACT: The first gold(I)-catalyzed cycloisomerization procedure applied to the synthesis of substituted 4*H*-benzo[*d*][1,3]-oxazines has been developed starting from *N*-(2-alkynyl)aryl benzamides. The chemoselective oxygen cyclization via the 6-*exo*-dig pathway yielded the observed heterocycles 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-

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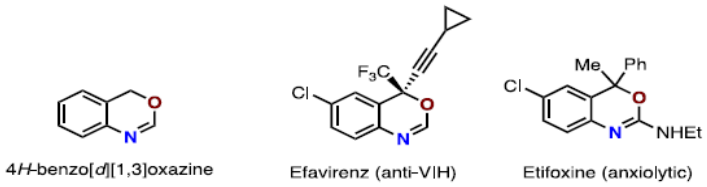

Figure 1. 4*H*-Benzo[*d*][1,3]oxazine core and examples of relevance.

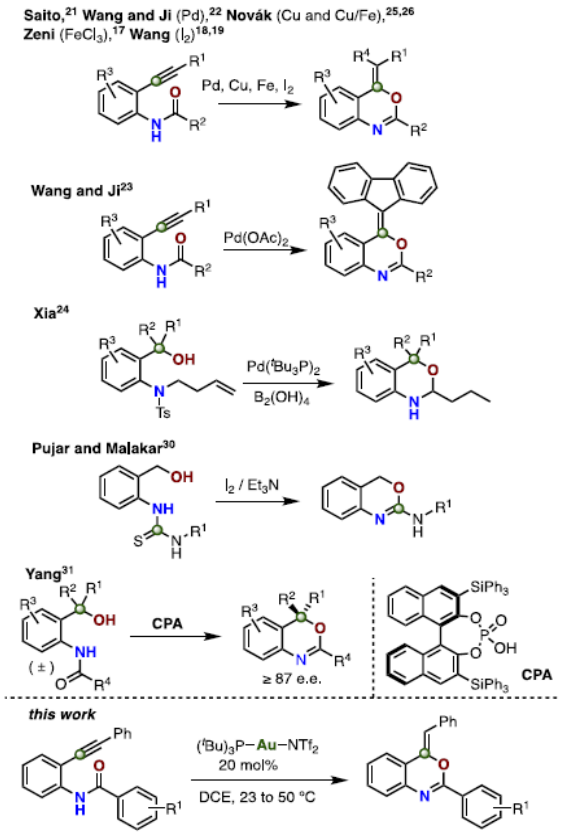

Figure 2. Described procedures for the synthesis of 4*H*-benzo[*d*]-[1,3]oxazines and our developed protocol.

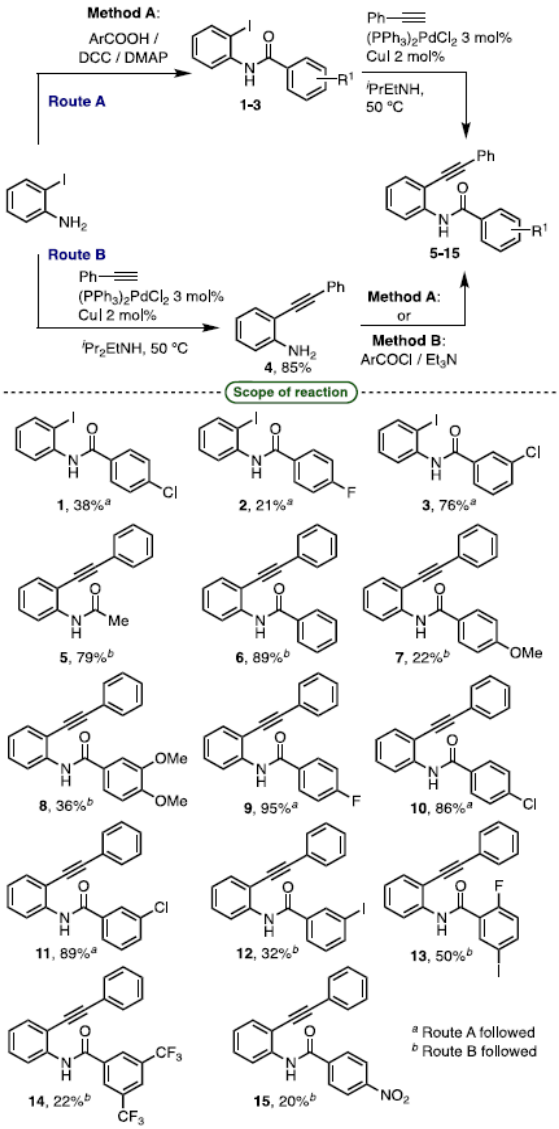

Figure 3. Routes for the synthesis of *N*-(2-alkynyl)aryl benzamides 5−15.

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).

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)

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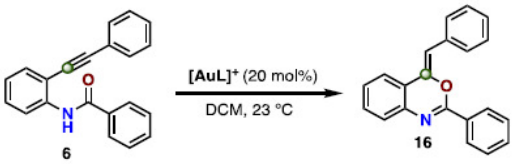
(method A) produced 2-iodobenzamides **1**−**3** in low to good yields (21−76%). The following Sonogashira alkynylation using phenyl acetylene under catalytic conditions of $(Ph_3P)_2PdCl_2$ and CuI led to the formation of *N*-(2-alkynyl)aryl benzamides **5**−**15**. On the other hand, route B started 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.

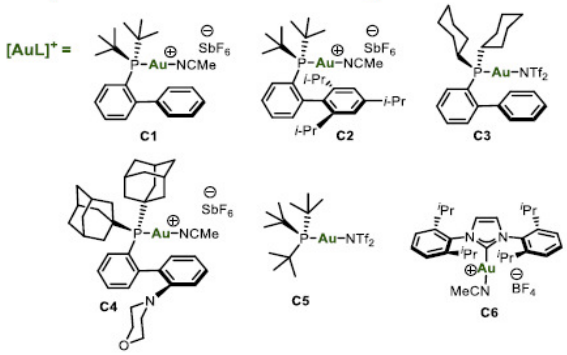
After having the *N*-(2-alkynyl)aryl benzamides produced, we proceeded to test and optimize our hypothesis on the gold(I)-catalyzed synthesis of 4*H*-benzo[*d*][1,3]oxazines. Accordingly, several cationic gold(I) complexes were assayed to determine the best yield (Table 1).

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.

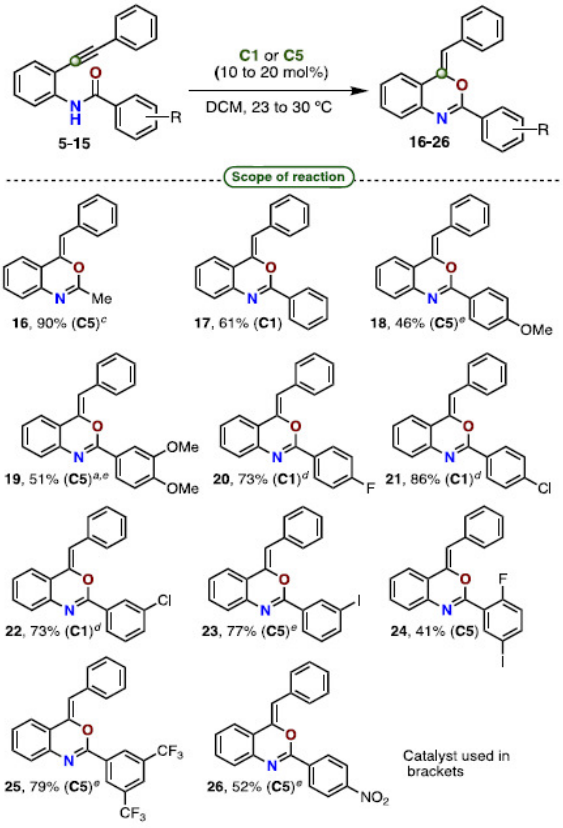


The optimization was carried out using *N*-(2-alkynyl)aryl benzamide **6** as a model. In such a way, we started by testing the cationic catalyst **C1** (Echavarren's catalyst)[31] using increasing amounts of the catalyst starting from 5 to 15 mol %; however, the full consumption of the starting material 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.

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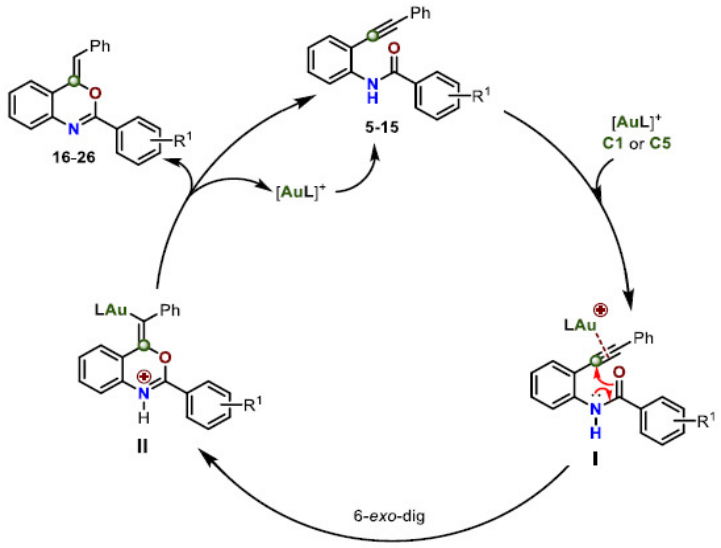

Figure 4. Plausible reaction mechanism of the gold(I)-catalyzed synthesis of 4*H*-benzo[*d*][1,3]oxazines.

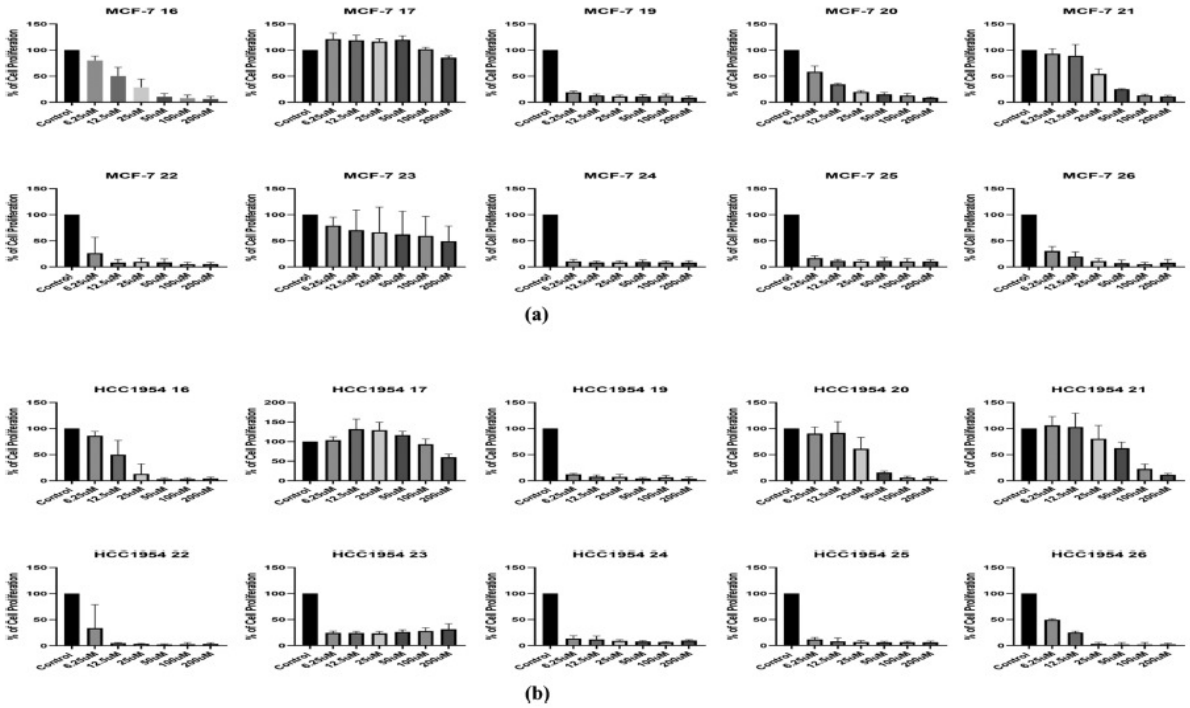

Figure 5. Differential effect of the 4*H*-benzo[*d*][1,3]oxazine compounds **16**−**26** in the proliferation of MCF-7 and HCC1954 cell lines. (a) MCF-7 cells were treated with increasing doses of compounds **16**−**26**. (b) HCC1954 cells were treated with increasing doses of compounds **16**−**26**. 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

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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 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.

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

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.

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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

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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,

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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

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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

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Copies of ^{1}H and ^{13}C for compounds **1**−**26** and curves of dose−response of the compounds **16**−**26** (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

In memory of our colleague and friend Kevin.

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RESEARCH ARTICLE

Iodine(III)-Mediates Free-Aniline Iodination Through Acetyl Hypoiodite Formation: Study of the Reaction Pathway

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In memory of Kevin

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Abstract: The first iodine(III)-mediated *para*-selective iodination protocol for free-anilines as well as the mechanistic elucidation of the reaction pathway is described. The developed method proceeded under clean, non-toxic, efficient and in general mild reaction conditions. To the best of our knowledge this report describes for the first time a procedure focused specifically on the introduction of an iodine atom in free anilines using PIDA [(diacetoxyiodo)benzene] and ammonium iodide which formed *in situ* acetyl hypoiodite (AcO-I) as the halogenating species. Our DFT calculations suggest a reaction mechanism that highlights the catalytic role of the ammonium cation in the AcO-I formation and halogenation. Considering there are few procedures for the iodine atom introduction in anilines using non-acidic conditions, herein we described an initial report on a mild and operationally simple alternative using iodine(III) reagents.

Introduction

Iodinated aryls are an important class of organic compounds. They are the best electrophilic counterparts in the Stille[1] or Suzuki[2] cross-coupling reactions as well as in the Mizoroki-Heck[3] olefination and Sonogashira[4] alkynylation. Particularly, iodinated anilines, are broadly used as radiocontrast medium[5] in cholecystography. Representative examples such as GSK1120212 (JTP-74057·DMSO) effective againts cancer cell lines, ioxaglate, diatrizoate, iohexol, ioversol or iopodate sodium have been used.[6] Also, iopanoic acid has been used in the long-term treatment of Grave´s disease.[7] The presence of iodo anilines is significatively described in non-linear optics,[8] as quiral auxiliar[9] and in the syntnesis of antimicrobials,[10] anti-inflamatories,[11] quinolones,[12] Abl kinase-inhibitors[13] and in fullerene functionalization[14] (Figure 1).

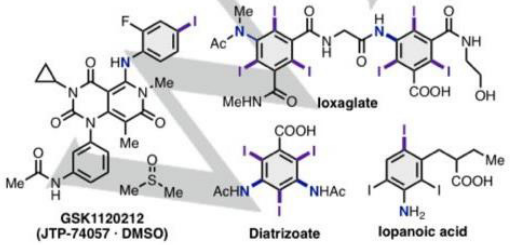
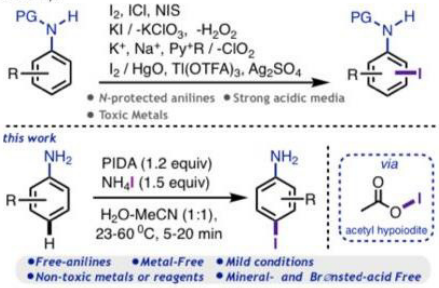


Figure 1. Representative examples of relevant iodinated anilines.

In regard of the iodoaniline core synthesis, the first described protocols involved the direct use of aniline in harsh acidic conditions. These use molecular iodine in different mineral-acids media to activate the halogen as a good electrophile.[15] Other general protocols for the aromatic iodination are non-specific for anilines, require of strong metallic oxidants and have a narrow application scope just for a few *N*-substituted anilines.[16] On the other hand, specific iodination for the aniline nuclei is restricted to few methods. Examples of transtion-metal-free protocols require I_2 in polar solvents[17] or mixed with oxidants.[18] The use of ICl,[19] NIS[20] or the oxidation of the iodie anion from KI with $KClO_3$[21] or H_2O_2[22] has been described as I^+ equivalent regents. Another important strategy for aniline iodination, makes use of the dichloroiodate anion. The $^{\ominus}ICl_2$ species as reagent has been used with different cations such as Na^+,[23] K^+,[24] Py^+R,[25] $Bn_2Et_3N^+$[26] and Bn_2DABCO^{2+}.[27] Finally, the specific metal-mediated methods for aniline iodination are resticted to the use of HgO,[28] $Tl(OTFA)_3$[29] and Ag_2SO_4 mixing with molecular iodine[30] (Scheme 1).



Scheme 1. Described procedures for iodination of anilines.

As part of our research interest on the iodine(III) chemistry,[31] we started a program for the development of new oxidative procedures[32] focused mainly on the aromatic introduction of aryls,[33] and inorganic groups (-Cl,[34] -Br,[35] -I,[36] and -NO_2[37]). Under our methodology, the obtained compounds have been used in the total synthesis of natural products[38] aiming to evaluate them as plausible drug-candidates for mycoses[39] or in cancer therapy.[40]

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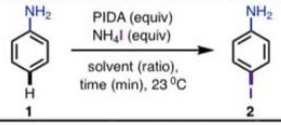
Considering the few procedures available to synthesize iodoanilines starting from non-*N*-substituted materials, the aggressive acidic media required, the highly toxic metals used and the relevance of these structures; herein we describe the first iodine(III)-mediated procedure for the iodination of free anilines under non-BrØnsted or mineral acids, metal-free, mild, non-toxic and in general, operationally simple reaction conditions using PIDA as oxidant and ammonium iodide as the iodine atom source.

Results and Discussion

Inspired by our previous results on the iodination of phenols[36] using iodosylbenzene and ammonium iodide, we decided to apply a similar methodology for the iodination of anilines. The different conditions tested are described as follows (Table 1).

Table 1. Optimization of the iodine(III)-mediated iodination of free anilines.[a]



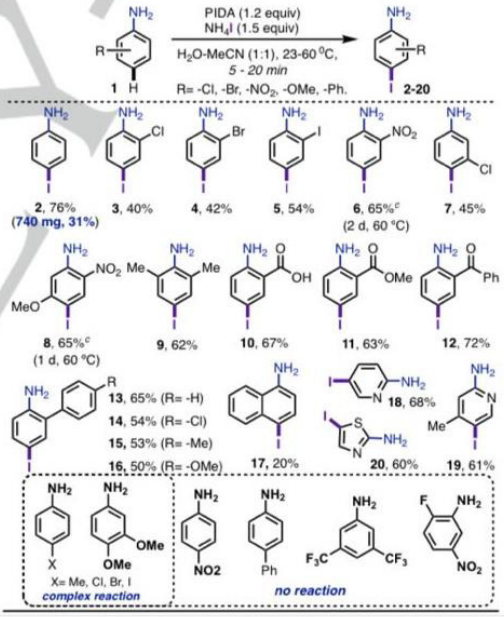
Entry	PIDA (equiv)	NH_4I (equiv)	Solvent ratio	Time (min)	Yield (%)[b]
1	1.2	2.4	MeOH	10	c. r. m.
2	1.2	2.4	MeOH-H_2O (1:1)	10	c. r. m.
3	2.2	3.4	H_2O	12 h	32
4	2.2	3.4	MeCN	24 h	45
5	2.2	3.4	MeCN-H_2O (5:2)	3 h	38
6	2.2	3.4	MeCN-H_2O (1:1)	2 h	42
7	1.0	1.0	MeCN-H_2O (1:1)	10	40
8	1.2	1.1	MeCN-H_2O (1:1)	5	44
9	1.2	1.3	MeCN-H_2O (1:1)	5	57
10	1.2	1.4	MeCN-H_2O (1:1)	5	65
11	*1.2*	*1.5*	*MeCN-H_2O (1:1)*	*5*	*76*
12	- -	1.5	MeCN-H_2O (1:1)	5	n. r.
13	1.2	- -	MeCN-H_2O (1:1)	5	c. r. m.

[a] Reaction conditions: aniline (0.5 mmol), solvent (0.3 *M*), open flask. [b] Isolated yields. PIDA= [(diacetoxyiodo)benzene]. c.r.m.= complex reaction mixture. n.r.= no reaction.

Initial examination to validate our hypothesis started with 1.2 equiv of PIDA and 2.4 equiv of ammonium iodide with aniline in methanol or in methanol-water (1:1). After 10 minutes, the starting material was fully consumed but a very complex reaction mixture was observed (entries 1 and 2). Thus, we considered using only water as solvent. Due to the low solubility of PIDA, an excess of both reagents up to 2.2 and 3.4 equivalents of PIDA and ammonium iodide, respectively, were used. Gratifyingly, a 32% yield of 4-iodoaniline **2** was obtained after 12 hours of reaction (entry 3). The *ortho*- regioisomer was not observed at least by the detection limit of NMR. Under the same stoichiometry, the reaction showed a 45% yield in acetonitrile, however 24 hours were necessary (entry 4). These results drove us to consider testing both solvents in reaction, since water accelerates the process and acetonitrile dissolve effectively the organic reagents. Thus, keeping the previous ratio of reagents, a mixture of acetonitrile and water (5:2) yields 38% of **2** after 3 hours (entry 5). A 1:1 solvent ratio increased the yield to 42% and diminished the time to 2 hours (entry 6). At this point we found the best solvent ratio regarding time and yield. Then, we decided to optimize the reagents using 1 equivalent of oxidant and ammonium iodide. To our delight, compound **2** was obtained in 40% yield after only 10 minutes of reaction (entry 7). A slight increase to 1.2 equiv of PIDA and 1.1 of ammonium iodide gave rise to **2** in 44% yield after 5 minutes of reaction (entry 8). Consecutive and systematic increases in reagents (entries 9-11), showed a stoichiometric yield-sensitive reaction yielding 57-76% of product. The best result was achieved using 1.2 equiv of PIDA and 1.5 equiv of ammonium iodide (entry 11). Control experiments using only oxidant or ammonium iodide did not show any reaction (entries 12 and 13).

Once the optimal conditions were stablished, we proceeded to explore the scope of the new developed protocol (Table 2).

Table 2. Scope of the PIDA/NH_4I-mediated iodination of free anilines.[a, b]



[a] Reaction Conditions: aniline (0.5 mmol), MeCN-H_2O (1:1) (0.3 *M*), open flask. [b] Isolated yields. [c] PIDA (2.4 equiv)/NH_4I (3 equiv) used.

Iodination of the simple aniline takes place also in gram scale to get **2** in 31% yield. On the other hand, the iodination of the free 2-chloro-, 2-bromo-, 2-iodo-, 2-nitro and 3-chloroanilines gave rise to the corresponding iodinated products **3-7** in yields ranging from 40-65%. Duplicating the amount of reagents and heating at

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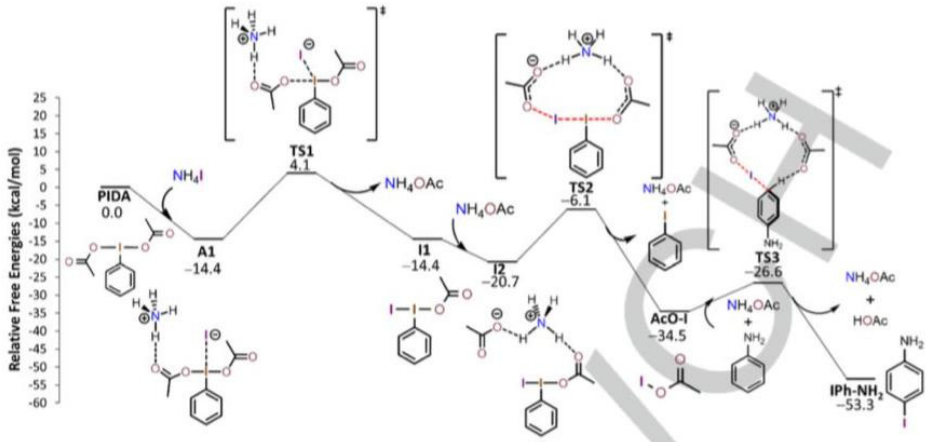
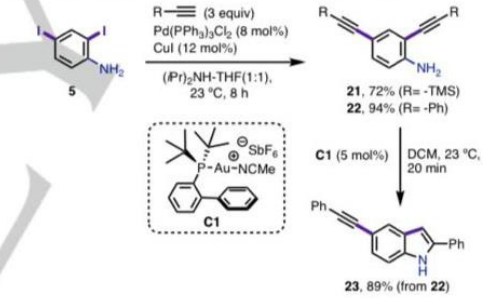


Scheme 2. Energy profile for the calculated iodination mechanism of free anilines using the PIDA/NH_4I system at the (SMD:water):ωB97X-D/def2-SVPP level.

60 °C for 2 days led to the iodinated aniline **6** which has the strong electron-attracting nitro group. The same was observed for iodinated aniline **8** that needs of 1 day heating at 60 °C. The iodination process took place regioselectively on the *para* position regarding the amino group of aniline. Also, very short reaction times to complete the reactions were required, usually from 5 to 20 minutes.

Iodination of alkyl aniline led to the formation of **9** in 62% yield. Anilines containing carboxylic acids, esters o ketones were also successfully iodinated to get **10-12** in 63-72% yield. A small group of free anilines containing different substituted aryls at C-2, yielded the corresponding iodinated products **13-16** in modest 50-65% yields with the *para* regioselectivity previously observed. The 1-amino naphthalene gave the corresponding iodinated derivative **17** in 20% yield. Finally, some heterocycles including pyridines and 2-aminothiazole were iodinated under our developed conditions to get the corresponding iodoanilines **18-20** in 60-58% yield. Other free *para*-substituted anilines with small groups such as methyl, chlorine, bromine, iodine or methoxy gave a complex reaction mixture of products becoming not suitable starting materials for our procedure. Based on these results, we could hypothesize an initial *para* iodination which formed a non-aromatic 4,4-disubstituted product that evolved by decomposition. Therefore, trying to induce the iodination at C-2 of the aniline, we synthesized the 4-phenylaniline. This compound with a bulky group at C-4 did not react under our optimized conditions. We attribute the lack of reactivity to the steric hindrance by the phenyl at C-4 as well as the iodine atom. To complete the scope exploration, other free anilines containing strong electron-withdrawing groups such as -F, $-NO_2$, or $-CF_3$ did not react even with higher amounts of reagents or heating.

To demonstrate the utility of our developed protocol, we carried out the following short synthetic route (Scheme 3).



Scheme 3. Synthetic utility of the obtained iodinated anilines.

Starting from the synthesized diiodo aniline **5**, the Sonogashira alkynylation with TMS-acetylene as well as with phenylacetylene gave rise to double alkynylated products **21** and **22** in 72 and 94% yield, respectively. The following gold(I)-catalyzed cycloisomerization reaction[41] using 5 mol% of Echavarren´s catalyst **C1**,[42] led to the formation of the functionalized indole **23** in 89% yield starting from **22**.

To obtain more insights into the mechanistic details on the iodination of aniline via PIDA and ammonium iodide, we performed theoretical calculations at the (SMD:water):ωB97X-D/def2-SVPP level (see the SI for computational details). According to the calculated reaction mechanism (Scheme 2), first **PIDA** interacts with ammonium iodide to give intermediate **A1** (ΔG_{R1} = −14.4 kcal/mol). Then the acetate of **PIDA**, which interacts with ammonium ion, dissociates (via transition state **TS1**, $\Delta G_1^{\ddagger}$ = +18.5 kcal/mol) forming **I1** (ΔG_{R2} = 0.0 kcal/mol). Next, the ammonium acetate and **I1** forms adduct **I2** (ΔG_{R3} = −6.3 kcal/mol). The geometry of this adduct allows the acetate of ammonium acetate to displace the iodine atom of **I1**, while last

acetate of **I1** dissociates (**TS2**, $\Delta G_2^{\neq}$ = +14.6 kcal/mol) leading to **AcO-I** (ΔG_{R4} = −13.8 kcal/mol). Finally, the last reaction step is the *para* iodination of aniline (ΔG_{R5} = −18.8 kcal/mol).

For this, we found three transition states that involves **AcO-I** interacting with: 1) ammonium acetate (through **TS3**, $\Delta G_3^{\neq}$ = +7.9 kcal/mol), 2) acetate anion (**TS4**, $\Delta G_4^{\neq}$ = +25.2 kcal/mol) and 3) two water molecules (**TS5-2**, $\Delta G_5^{\neq}$ = +26.7 kcal/mol). Among these, **TS3** has the lowest energy barrier (see SI for further information). Therefore, ammonium cation has an important effect in **TS3**; it bridges both acetates via hydrogen bonds making iodine of **AcO-I** more electrophilic and catalyses the **AcO-I** formation and the halogenation process. *Ortho* Iodination resulted thermodynamically ($\Delta G_{R5\text{-}p}$ = −6.2 kcal/mol) and kinetically (**TS3-o**, $\Delta G_{3\text{-}p}^{\neq}$ = +12.6 kcal/mol) less favorable than *para* Iodination, which is consistent with experimental observation (see SI). Overall, the reaction is exergonic (ΔG_R' = −53.3 kcal/mol) and the calculated total energy barrier of +18.5 kcal/mol is in line with the reported conditions. According to the performed theoretical calculations, our developed iodination process was carried out through the *in situ* generation of acetyl hypoiodite (AcO-I) which is the iodinating species.

Regarding AcO-I formation this highly reactive halogenating reagent has been previously synthesized by reacting I_2 with Pb(OAC),[43] Hg(OAc),[44] AcO_3H,[45] oxone/Ac_2O/AcOH,[46], AcOAg,[47] or with the AcOAg/ICl[48] system. In regard the use of iodine(III) reagent the AcO-I formation it has been described by reaction of PIDA with I_2,[47] NaI,[49] NIS[50] and NH_4I for this work. To date it AcO-I has not been isolated, however Lusztyk[47] described the ^{1}H NMR characterization in $CDCl_3$. Thus, to test the plausibility of our mechanistic proposal, we carried out a NMR study to identify the formation of AcO-I by mixing PIDA and NH_4I in the solvent system [CD_3CN-D_2O (1:1)] that we used in our procedure (Figure 2).

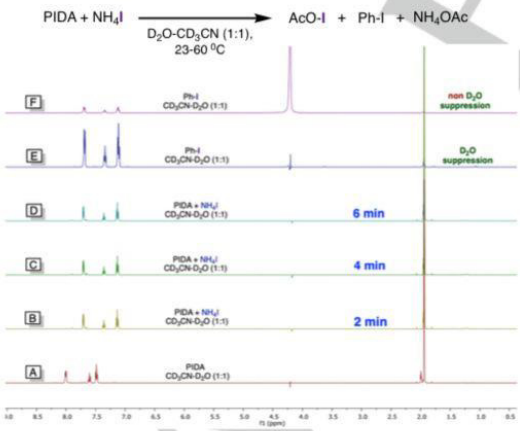
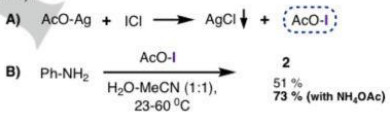


Figure 2. Indirect identification of AcO-I by the reaction of PIDA and NH_4I in CD_3CN-D_2O (1:1). Water signal suppression for experiments A-E.

All the spectra in the study were obtained in CD_3CN-D_2O (1:1). We started by the acquisition of the ^{1}H spectrum of the commercially available PIDA (Figure 2A). Next, according with our iodination conditions we mixed 1 equivalent of PIDA with 1.5 equivalents of ammonium iodide. After 2 minutes, the spectrum showed the fully consumption of PIDA in a very fast reaction. Also, all the phenyl ring signals shifted to high field by around 0.5 ppm. Additionally, one singlet overlapped with the residual signal of the CD_3CN at δ 1.94 ppm, which was assigned to a methyl group, was putatively attributed to the AcO-I formation (Figure 2B). The following two spectra corresponding to 4 and 6 minutes showed the same profile (Figures 2C and 2D). Starting from PIDA and NH_4I, the AcO-I synthesis implies necessarily the iodobenzene (Ph-I) formation. Therefore, the ^{1}H NMR of the commercial Ph-I was obtained (Figures E and F). This spectrum (Figure 2E) matches perfectly with those obtained at 2, 4 and 6 minutes (Figures 2B-D), confirming the Ph-I formation as result of the reaction between PIDA and ammonium iodide, and in consequence the AcO-I formation. Even though these spectroscopic results match with those reported by Lusztyk,[47] we considered an indirect identification of the AcO-I, based on the overlapping with deuterated solvent and since the HRMS analysis did not show the corresponding molecular peak. However, the Ph-I formation as the sole product involves the AcO-I production. It is important to highlight that previous reports using iodine(III) reagents[43-50] just assume or demonstrate by theoretical calculation the formation of AcO-I, nevertheless this is the first report with an indirect experimental demonstration of AcO-I is forming by mixing PIDA/NH_4I (1:1.5).

To confirm the AcO-I as the iodinating species in our protocol, we synthesized it using the AcOAg/ICl[48] system and carried out an iodination reaction with aniline in our solvent system MeCN-H_2O (1:1) (Scheme 4).



Scheme 4. Confirmation of the AcO-I formation as the iodinating species in our developed protocol.

This way, an equimolar amount of silver acetate and iodine monochloride were mixed at 0 °C in ether. Precipitation of AgCl indicated the acetyl hypoiodite formation (Scheme 4A). Then a 1:1 MeCN-H_2O mixture was added followed by aniline. In one experiment the reaction was carried out directly after the AcO-I formation and in a second experiment, one equivalent of aniline and one equivalent of NH_4OAc were added (Scheme 4B) according to the stoichiometry of the procedure (see Fig 2). To our delight we observed the iodination of aniline to get **2** in both experiments. It was obtained a 51% yield in the experiment only with the prepared AcO-I and 73% yield using ammonium acetate. The former result is very close to the obtained (76%, see Table 2) by mixing PIDA/NH_4I. This indicates that ammonium acetate plays an important role as additive, assisting and favoring the iodination step, such as it is described (**TS3**) in our theoretical calculations. In fact, it is acting as a catalyst due to its regeneration once the iodination process has been completed. This set of theoretical and experimental results of the mechanistic study confirms that the acetyl hypoiodite is the halogenating species in our developed iodination procedure and that the ammonium cation is key for increasing the yield, catalyzing the AcO-I formation and the iodination step.

Finally, considering all the mechanistic and experimental evidence we postulated the reaction mechanism for this process (Figure 3).

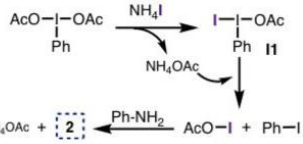


Figure 3. Reaction mechanism for the iodination of free-anilines using the PIDA/NH_4I system (illustration with aniline to get 4-iodoaniline).

The reaction started by the ligand exchange between PIDA and NH_4I to get intermediate **I1** with concomitant release of ammonium acetate. Then, **I1** evolves in less than two minutes to form acetyl hypoiodite (AcO-I) and iodobenzene via reductive elimination catalyzed by ammonium acetate. Final iodination of aniline with AcO-I, as the halogenating species, gives rise to the observed iodinated products with the regeneration of ammonium acetate.

Conclusions

In summary, we have developed a metal-free, mild non-toxic and in general an operationally simple protocol for the *para*-selective iodination of free anilines under mineral and- Brønsted-acid-free conditions. The theoretical and experimental results on the reaction mechanism confirmed that the halogenating species of our process is acetyl hypoiodite **(AcO-I)** which is formed *in situ* in less than 2 minutes by reacting PIDA and ammonium iodide. This species is stable in water and reacted as a soft electrophile exclusively at the C-4 of the aniline core. Ammonium cation assisted and catalyzed the AcO-I formation but also it was important to favor the aromatic iodination step and therefore, the chemical yield of reaction. The use of this new methodology allowed us the development of the first iodination protocol of free anilines under very mild conditions.

Experimental Section

General Methods. Compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, Melting Point, IR and High-Resolution Mass Spectroscopy. Copies of ^{1}H-NMR and ^{13}C-NMR spectra are provided for all new compounds. 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 to tetramethylsilane (TMS, 0.0 ppm) and 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 13C NMR spectra were measured relative to $CDCl_3$ (δ = 77.16 ppm) Melting points were measured using a Fisher-Johns apparatus. IR spectra were measured using a Perkin-Elmer System 2000 FT-IR. Compounds were applied in a thin film on a KBr pellet or ATR diamond. High-resolution mass (HRMS) analysis was obtained using GC-MS Thermo Scientific™ DFS™.

General Procedure for Iodination. A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with the corresponding anilines (0.5 mmol, 1 equiv) and MeCN-H_2O (1:1) at 23 °C. After dissolving and obtaining a homogeneous mixture, NH_4I (0.8 mmol, 1.5 equiv) was added and stirred for 2 min. Then PIDA (0.6 mmol, 1.2 equiv) was added and stirred at 25 °C until full consumption of the starting material (usually 5 min to 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. **Compound 5 (Table 2)**. The following compound was obtained according to the general procedure for iodination using 2-iodo aniline as starting material. The crude material was purified by flash column chromatography over silica gel with the system (1% EtOAc/Hexane) to afford **5** (43 mg, 54%) as a light pink solid. The reaction time for this example was 20 min. R_f = 0.4 (2 % EtOAc/Hexane). m.p. = 93−95 °C. IR (neat) ν/cm^{-1}= 3373, 3282, 1619, 1455, 1369, 1284. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 4.12 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 145.9, 138.4, 116.8, 84.9, 79.8. HRMS (ESI+): m/z calcd. for $C_6H_6NI_2$ $[M+H]^+$ = 345.8590, found 345.8566.

Procedure for the Synthesis of AcO-I From AcOAg/ICl with NH_4OAc. A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with silver acetate (202 mg, 1.2 mmol) in 2 mL of ether and added iodine monochloride (196 mg, 0.06 mL, 1.2 mmol). After the precipitation of silver acetate, 2 mL of MeCN-H_20 (1:1) containing ammonium acetate (77 mg, 1.0 mmol) was added followed by aniline (100 mg, 0.1 mL, 1.1 mmol). The reaction was stirred at room temperature for 10 minutes. After the fully consumption of the starting material the reaction was stopped. The crude material was purified by flash column chromatography over silica gel with the system (5% EtOAc/hexane) to afford (173 mg, 73%) of a brown solid which correspond to 4-iodoaniline **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 2H).

† These two authors contributed equally to this work.

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Keywords: acetyl hypoiodite • hypervalent iodine reagents • iodination of free-anilines • iodine(III) chemistry • PIDA/NH_4I

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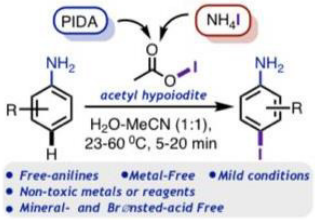

The first iodine(III)-mediated *para*-selective iodination of free-anilines via the *in situ* formed acetyl hypoiodite as halogenating species is described. This procedure allows a cheap, efficient and easy way to get acetyl hypoiodite in less than 2 minutes by combining PIDA and NH_4I. Experimental ant theoretical calculations supported the mechanism that proceed under mild conditions.

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