DOCTORAL THESIS

Iodine(III) reagents and Gold(I) catalysts for developing new organic reactions

1) Direct C_{sp^2}-O bond formation mediated by diaryliodonium salts in the synthesis of 4-aryloxyquinolines

2) Chlorinations of arenes by the new PIFA/$AlCl_3$ system

3) Gold(I)-catalyzed direct C_{sp^3}-H bond activation in the synthesis of triarylindenes

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August 24, 2018

CERTIFICATE

This is to certify that Pradip Dhanraj Nahide has been working under my supervision since August 2014, 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 thesis entitled ***"Iodine(III) reagents and Gold(I) catalysts for developing new organic reactions****: 1) Direct C_{sp^2}-O bond formation mediated by diaryliodonium salts in the synthesis of 4-aryloxiquinolines 2) Chlorinations of arenes by the new PIFA/$AlCl_3$ system 3) Gold(I)-catalyzed direct C_{sp^3}-H bond activation in the synthesis of triarylindenes."* 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

Life is not easy for any of us. But what of that?

We must have perseverance and above all confidence in ourselves.

We must believe that we are gifted for something

and that this thing must be attained.

-***Marie Curie***

Learning gives creativity,

Creativity leads to thinking,

Thinking provides knowledge

Knowledge makes you great

-***A. P. J. Abdul Kalam***

Acknowledgement

The work described in this thesis would not have been possible without the help of many people and accompanied with encouragement, hardship, trust, and frustration. I realized though only my name appears on the cover of this thesis but many people including my family members, well-wishers, my friends, colleagues and various institutions have contributed to accomplish this huge task.

This doctoral dissertation has been carried out at the University of Guanajuato, Mexico under the supervision of **Dr. César Rogelio Solorio Alvarado** to whom I would like to express all my gratitude and respect for giving me the opportunity to be part of his research group. This work would not have been possible without his guidance and involvement, his support and encouragement on daily basis from the start of the project till date. Under his guidance I successfully overcame many difficulties and learnt a lot. His own zeal for perfection, passion, unflinching courage and conviction has always inspired me to do more. Not only as Ph.D. guide but also as a friend he has been motivating and helping me in my all the tough times of research work. His passion for science has always inspired me to grow as a chemist. For all these, I sincerely thank him from bottom of my heart and will be truly indebted to him throughout my life time.

Obviously, this dissertation was impossible without the scholarship. I would like to thank the "Dirección de Apoyo a la Investigación y al Posgrado" from the University of Guanajuato and **CONACyT**, which funded this Ph.D. program (Sept 2014–July 2018).

I would also like to thank professor **Dr. Marisa Kozlowski** (University of Pennsylvania, USA) who welcomed me in her group for a short stay (Jan–Oct 2018) and allowed me to work on discovering new reactions using transition metals. Also, I am thankful for her time and guidance throughout my stay. Thanks to Mikhail Madison for the visa and administrative process. The stay was great with my lab mates from UPenn. Thank you, Gang Hong, Cris Ochoa, Adriana Jemison, Prasanna Sreevatsan, Peter Amadeo, Houng Kang**,** Sergei Tcyrulnikov, Kyle Niederer, Dr. Yexenia Nieves-Quinones, Dr. Charles Hendrick, Dr. Rauful alam, Phil Gilmartin, Tom Paniak. Also, thanks to Dr. Patrick Walsh and Dr. Gary Molander for the use of their labs and equipment**.**

I am also very grateful to the professors at the University of Guanajuato for their help. In personal coordinator's Dr. Marco A. G. Revilla, Dr. Esthela Ramos Ramírez. My tutorial committee members Dr. Eulalia Ramirez Oliva and Dr. Eduardo J. Baez. Also, Dr. Ramón A. Núñez (National laboratory, UG-CONACyT. LACAPFEM), Dr. Kazimierz Wrobel and Dr. Katarzyna Wrobel, have been a tremendous help with characterization of compounds through the use Mass and NMR spectrometry. For the biological assays thanks to Dr. Rafael Ortiz Alvarado. For consistent help in chemistry, the use of chemicals and lab, thanks to Dr. Oracio Serrano. Thanks to my Ph.D. defense juris, Dr. Marisa Kozlowski, Dr. Rocío Gámez, Dr. J. Oscar C. Jimenez-Halla, Dr. Alonso-Castro AJ, Dr. Marco Ramirez for being in the exam and thesis revision.

Of course, I would like to thank all the group members of CRSA. Thanks to Jessica Gutiérrez, Adriana G. Cabrera, Claudia Barrón L, Kevin Juarez, Beto, Luisa, Perla Ramirez, Velayudham R. for their help in the lab. Thank you Shrikant Pharande and Murali V. for the help and guidance throughout my stay. My house-mates Harold Viveros and Sebastian Morales and Diego Castro thank you guys for the great moments that we had together in Guanajuato. Thank you, Merit Maldonado, Nandu, Arturo Aranda, Armando Alcazar, Juan Diego, Nancy Montoya, Adrián Villagz and Josimar, Exiquio Foraste Quito, Alonso León Jaime for lots of love in the stay of Mexico. Thanks to all my Indian and Mexicans friends whose names are not mentioned but they are closed to my heart.

Dedicated

Finally, I would like to dedicate this thesis especially to my family, my father Dhanraj Nahide, my soul my life my mother Latabai Nahide, my lovely sister Suvarsha Suryavanshi, my brother-in-law Mahesh Suryavanshi, my brother Omraj Nahide and his wife Namrata Nahide. 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 in the world to have such a lovely and caring family, standing beside me with their love and unconditional support.

My special thanks to the people who are very close to my hearts, Fernando Amezquita, Virginia Odemarys, Diana Mendoza, Carolina Arriola Pérez, and Karina I. Del Real Avila. Thank you to the lovely person Enrique Vazquez Lopez, whose love, care and food always make me happy. Without your food, I couldn't survive in Mexico. Also, thanks to Ana Rodriguez, Erika Rodriguez, Esperanza Ramirez and Luisa Ramirez for lots of love and care in the Buen Comer. Thank you so much Yuvraj Satkar for being there in my tough times and happy moments as a friend.

I owe thanks to a very special person of my life my friend **Julieta Guerra** for her continued and unfailing love, support, and understanding during my pursuit of the Ph.D. degree in Mexico that made the completion of thesis possible. You were always around at times I thought that it is impossible to continue, you helped me to keep things in perspective. I greatly value her contribution and deeply appreciate her belief in me. The words would never say how grateful to you and your family. I consider myself the luckiest in the world to have such a person like you. My life in Mexico without you and your family was impossible. Thank you for care, unconditional love and help.

I thank the almighty for giving me the strength and patience to work through all these years so that today I can stand proudly with my head held high.

…….. a ustedes dedico esta tesis y desde luego

mil gracias por su apoyo……

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CONACYT

Consejo Nacional de Ciencia y Tecnología

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FOMIX

Fondos Mixtos

prodep

TIPO SUPERIOR

At the moment of the writing of this thesis, the results presented herein have yielded the publications presented below.

Gold(I)-catalyzed high-yielding synthesis of indenes by direct C_{sp}^3-H bond activation.

Pradip D. Nahide, J. Oscar C. Jiménez-Halla, Ortiz-Alvarado, R.; César R. Solorio-Alvarado
Manuscript submitted.

Practical, mild and efficient electrophilic bromination of phenols by a new I^{III}-based reagent: the PIDA–$AlBr_3$ system

Yuvraj Satkar, Velayudham Ramadoss, *Pradip D. Nahide*, Ernesto García-Medina, Kevin A. Juárez-Ornelas, Angel J. Alonso-Castro, Ruben Chávez-Rivera, J. Oscar C. Jiménez-Halla; César R. Solorio-Alvarado.

RSC Adv. **2018**, *8*, 17806-17812.

Procedimiento sin metales de transición para la síntesis de 2-aril-4-ariloxiquinolinas a través de la formación del enlace C_{sp}^2-O utilizandosales bisarilo de yodo (III).
Solicitud de Patente en Trámite: MX/a/2017/014873
Inventores: César Rogelio Solorio Alvarado, Pradip D. Nahide y Marco Antonio Ramírez Morales.

In situ formed I^{III}-based reagent for the electrophilic *ortho*-chlorination of phenols and phenol ethers: The use of PIFA-$AlCl_3$ system

Nahide, P. D.; Ramadoss, V.; Juárez-Ornelas, Kevin A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J. M. J.; Alonso-Castro, Á. 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**, *31*, 485-493.

Mild, rapid, and efficient metal-free synthesis of 2-aryl-4-aryloxyquinolines via direct C_{sp}^2-O bond formation by using diaryliodonium salts.

Nahide, P. D.; Solorio-Alvarado, C. R. *Tetrahedron Lett*. **2017**, *58*, 279-284.

Synthesis and biological evaluation of new 3,4-diarylmaleimides as enhancers (modulators) of Doxorubicin cytotoxic activity on cultured tumor cells from a real case of breast cancer

Gutierrez-Cano, J. R.; Nahide, P. D; Ramadoss, V.; Satkar, Y.; Ortiz-Alvarado, R.; Alba-Betancourt, Cl.; Claudia L. Mendoza-Macías, and Solorio-Alvarado C. R.
J. Mex. Chem. Soc. **2017**, *61* (1), 41-49.

Four-step scalable formal synthesis of ningalin C
Ramadoss, V.; *Nahide P. D*.; Juárez-Ornelas, K. A.; Rentería-Gómez M.; Ortiz-Alvarado, R.; Solorio- Alvarado, C. R.
ARKIVOC. **2016***, iv*, 385-394.

Index

Prologue

This dissertation is divided into 7 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, general objectives of this thesis are described.

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

4. In the fourth section, the chapter I describes an efficient ligand- and transition metal-free procedure for the direct C_{sp^2}–O bond formation for the arylation of 2-aryl-4-quinolones. Also, biological screening of the synthesized 2-aryl-4-aryloxyquinolines derivatives were carried out. An important natural product graveoline with its 2-aryl-4-methoxyquinolines derivatives were synthesized for future biological screening.

5. In the fifth section, the chapter II contains the direct and highly regioselective electrophilic *ortho*-chlorination of phenols and phenol ethers with the use of PIFA-$AlCl_3$ System. A new and *in situ* formed reagent generated by mixing PIFA {bis[(trifluoroacetoxy)iodobenzene]} and $AlCl_3$ was introduced to carry out the *ortho*-chlorination of phenols and phenol ethers.

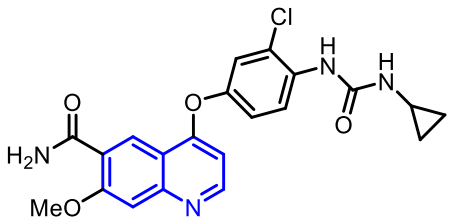
6. In the sixth section the chapter III describes a new gold(I)-catalyzed synthesis of indenes by direct C_{sp}^3-H bond activation. The scope of the developed methodology was explored for electron-neutral, electron-poor as well as electron-rich derivatives including the dibenzofurane and carbazole heterocycles. The reaction mechanism involves a C_{sp}^3-H bond activation as a key step, which proceeds via a pericyclic [1,5]-H migration-cyclization giving rise to a gold(I)-carbene, which finally evolve to a 1,2,3-triarylindene. The mechanism therein described was supported by DFT calculations at (SMD:dichloroethane)ONIOM(M08-HX/*mixed-basis*:PM6) level.

7. The annexes A describes the work carried out in the distance program at the University of Pennsylvania on chemoselective activation of C_{sp}^3–H bonds over C_{sp}^2–H bonds for the Pd(II) and Cu(I)-catalyzed oxidative coupling of alkylarenes with fluorenes. Also, in the annex B and C 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.

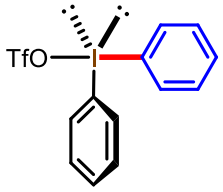
Resume

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

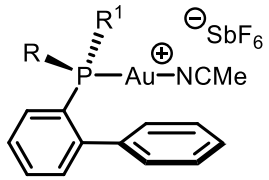
1. In the general introduction, there are three topics discussed based on the research carried out in the doctoral thesis. In the first part, transition metal catalyzed or metal-free synthesis of quinolones and their biological importance, In the second part, the background of hypervalent iodine compounds, their synthesis methods and applications in organic synthesis and in the third part, gold(I) catalysis with wide use in organic transformation have been described.



Lenatinib

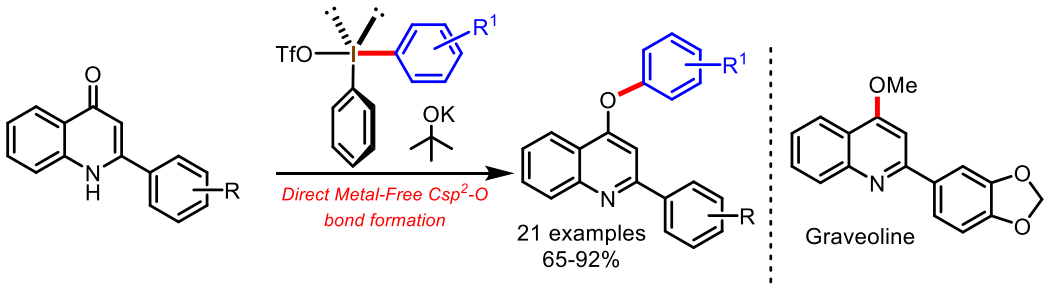


Diaryliodonium salt



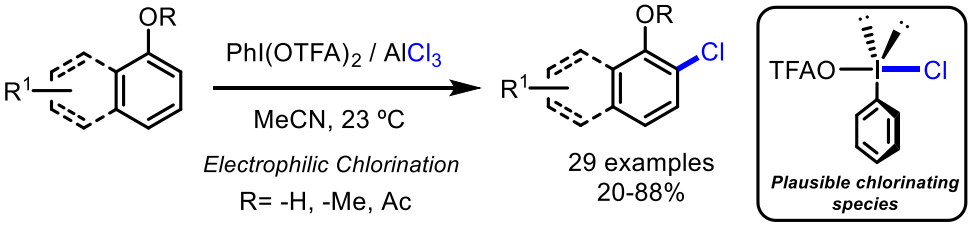
Cationic gold(i) complexes

2. In the chapter I, we developed a mild, rapid and efficient metal-free procedure for the synthesis of 2-aryl-4-aryloxyquinolines via direct C_{sp}^2-O bond formation by using diaryliodonium salts was developed. Also, in the biological screening of synthesized 2-aryl-4-aryoxyquinolines, antifungal activity was found. Additionally, a natural compound graveoline and its 2-aryl-4-methoxyquinolines derivatives were prepared.



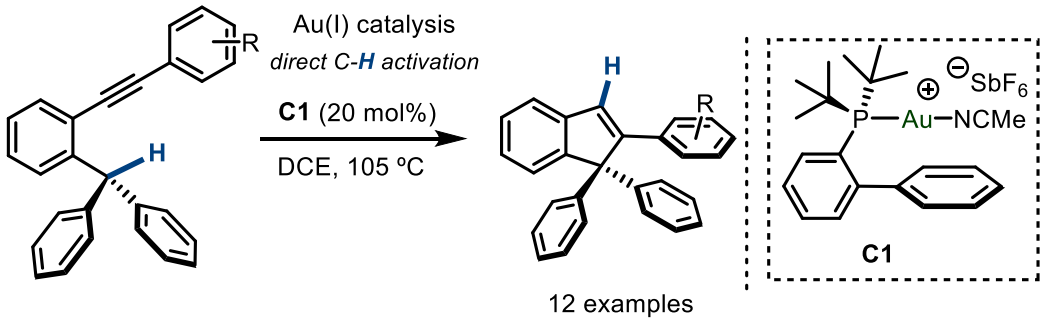
Tetrahedron Lett. **2017**, *58*, 279–284.

3. In the chapter II, A new and *in situ* formed reagent generated by mixing PIFA {bis[(trifluoroacetoxy)iodobenzene]} and $AlCl_3$ was introduced in the organic synthesis for the direct and highly regioselective *ortho*-chlorination of phenols and phenol ethers. An efficient electrophilic chlorination for these electron-rich arenes as well as the scope of the reaction are described. An easy, practical, and open-flask reaction allowed us to introduce a chlorine atom, which is a highly important functional group in organic synthesis.



Eur. J. Org. Chem. **2018**, 485–493.

4. In the chapter III, we developed a catalytic, practical and high-yielding procedure for the synthesis of indenes by direct C_{sp}^3-H activation under gold(I) catalysis. The scope of the protocol was determined by synthesizing some electron-neutral, electron-poor as well as electron-rich derivatives including the dibenzofurane and carbazole heterocycles. The mechanism of this reaction was elucidated by DFT calculations at (SMD:dichloroethane)ONIOM(M08-HX/*mixed-basis*:PM6) level. Thereby we found a pericyclic transformation involving a [1,5]-H shift generating a gold(I)-carbene that evolve to the indene derivative. This operating mechanism allowing us to elucidate the catalytic cycle. In comparison with several reports, our protocol presents a direct activation of the C_{sp}^3-H bond without previous formation of a gold(I)-carbene or gold (I)-vinylidene.



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.

Specifically, we aimed at addressing the following objectives in the thesis.

Chapter I

- We planned to develop a metal free procedure for the synthesis of 2-aryl-4-oxyarylquinolines by diaryliodonium salts and the application of 2-arylquinolones for the synthesis of the natural compounds graveoline, graveolinine and their derivatives.

Chapter II

- We planned to develop a new mild methodology for the chlorination of phenol and phenol-ethers using I(III) regent useful in the organic synthesis.

Chapter III

- We proposed the development of a new C_{sp}^3-H activation mode catalyzed by cationic gold(I) complexes as well as the elucidation of the reaction mechanism in this transformation by using DFT calculations.

General Introduction

Quinolines chemistry.

I.1. Quinolones precedents.

Nitrogen-containing heterocyclic core are frequently found in a variety of naturally occurring alkaloids and biologically active molecules[1] that can be used in therapeutic areas.[2] Compounds that contain 4-substituted quinoline motifs are of pharmaceutical importance. The quinolones are defined as a bicyclic heteroaromatic core, which require a R-substituted nitrogen at the 1-position and a carbonyl at the C4-position (Figure I.1).[3]

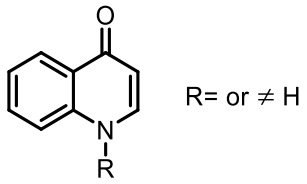


Figure I.1. General 4-quinolone core structure**.**

Several molecules containing the fluoroquinolones[4] core structure shows high activity against a broad range of bacteria as well as antimalarial effects,[5] anticancer,[6] antiviral[7] and are antidiabetic agents.[8] Also, some 4-quinolones are specifically identified as non-fluorinated or non-carboxylated quinolones used as anticancer drugs, HIV inhibitors and anti-anxiety agents.[9]

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Several variations to the naphthyridine scaffold were investigated leading to the different generation of quinolone antibiotics (Figure I.2).

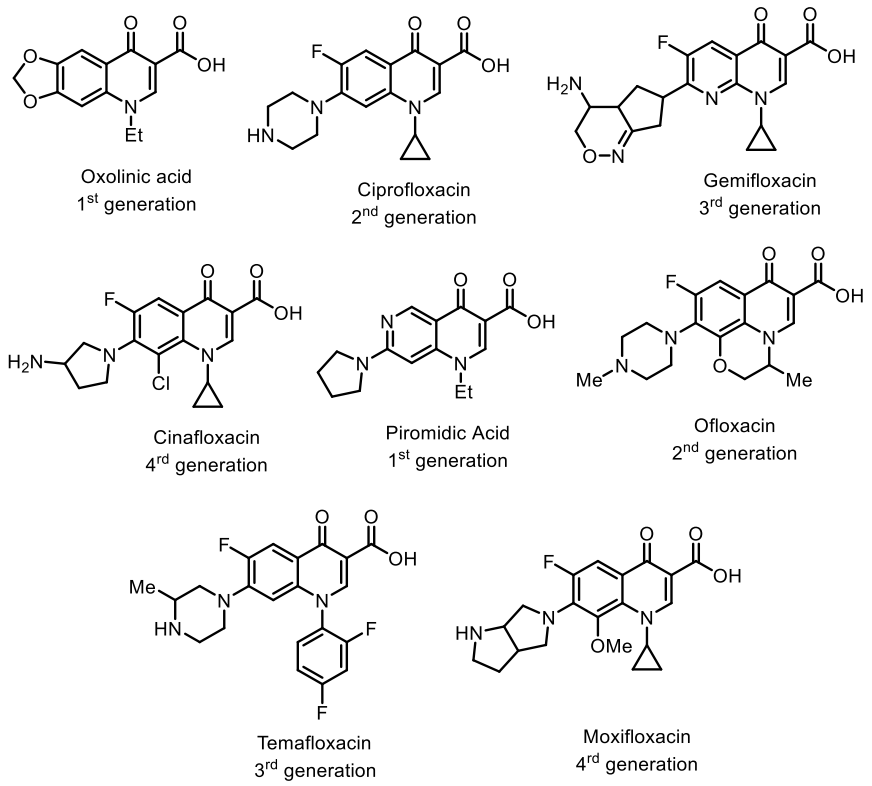

Figure I.2. Several antibacterial containing the quinolone core.

Modification in the quinolone moieties lead to different biological activities depending on the groups available in the structure.[10] Ciprofloxacin, patented by Bayer in 1983, is the most successful of this class and has been prescribed worldwide; Also, is often employed as a drug of last resort when other antibiotics fail.[10c-f]

13, 547-551. (c) Eissenstat, M. A.; Kuo, G. H.; Weaver, J. D.; Wentland, M. P.; Robinson, R. G.; Klingbeil, K. M.; Danz, D. W.; Corbett, T. H.; Coughlin, S. A. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 1021-1026.

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I.2. Synthesis of 4-arylquinolones.

The importance of 4-arylquinolones heterocycles in medical chemistry and the development of synthetic methodology to access them is continually imperative. There are various synthetic routes towards 4-quinolones that have been reported.[11] The classical approaches are based on cyclocondensation such as Camps cyclizations,[12] Conrad-Limpach,[13] Niementowski,[14] Gould–Jacobs,[15] Dieckmann cyclization,[16] Snieckus synthesis[17] and Biere-Seelen[18] synthesis widely employed (Figure I.3).

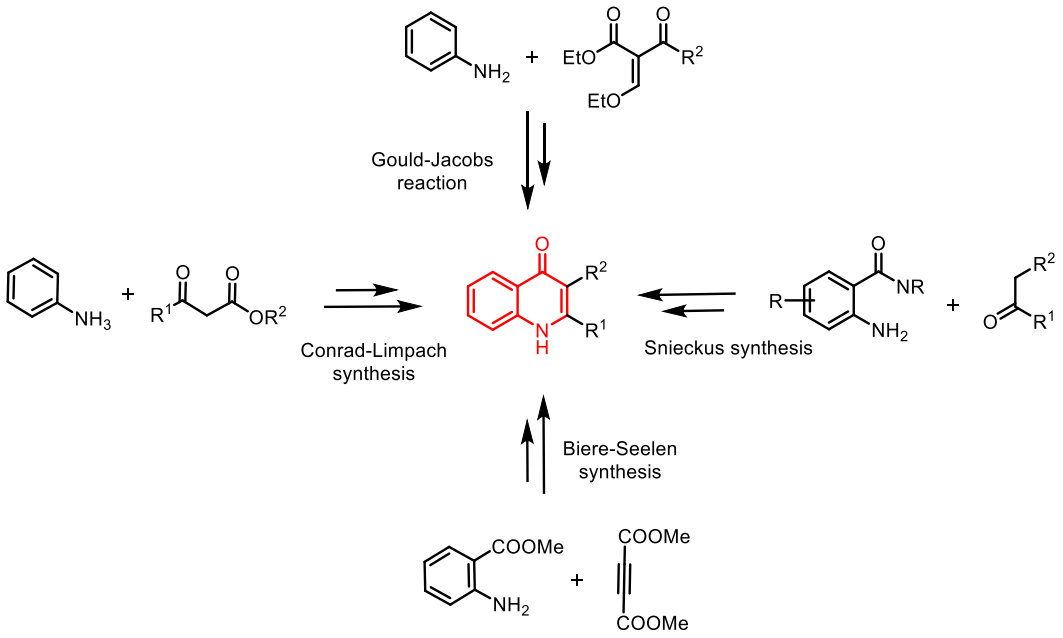

Figure I.3. Some classical methods of quinolones synthesis.

11. (a) Reitsema, R. H. *Chem. Rev*. **1948**, *43*, 43-68. (b) López, S. E.; Rebollo, O.; Salazar, J.; Charris, J. E.; Yánez, C. *J. Fluorine Chem*. **2003**, 120, 71-75. (c) Boteva, A. A.; Krasnykh, O. P. *Chem. Heterocycl. Compd*. **2009**, *45*, 757-785. (d) Romek, A.; Opatz, T. *Eur. J. Org. Chem*. **2010**, 5841-5849. (e) Liu, Q.-L.; Li, Q.-L.; Fei, X.-D.; Zhu, Y.-M. *ACS Comb. Sci*. **2011**, *13*, 19-23 (f) Zhao, J.; Zhao, Y.; Fu, H. *Org. Lett*. **2012**, *14*, 2710-2713. (g) Iaroshenko, V. O.; Knepper, I.; Zahid, M.; Dudkin, S.; Kuzora, R.; Villinger, A.; Langer, P. *Org. Biomol. Chem*. **2012**, *10*, 2955-2959. (h) Shao, J.; Huang, X.; Hong, X.; Liu, B.; Xu, B. *Synthesis*. **2012**, *44*, 1798-1805. (i) Victor, N. J.; Muraleedharan, K. M. *Adv. Synth. Catal*. **2014**, *356*, 3600-3614.
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15. (a) Gould, R. G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890-2895. (b) Lucia, P. *Antimicrobial Susceptibility Standards***. 2003**.
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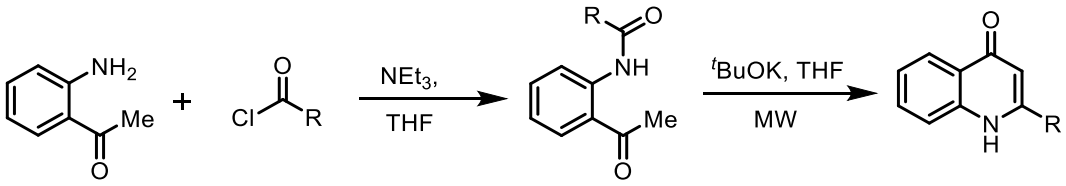
17. Chong, R. J.; Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett*. **1986**, 27, 5323-5326.
18. Biere, H.; Seelen, W. Justus Liebigs Annalen Der Chemie **1976**, 1972-1981.

Often these methods need extremely harsh conditions including temperatures of 250 °C or strong acids/bases such as polyphosphoric acid or Eaton's reagent that dramatically limit the substrate scope of these transformations. Hence synthetic methodologies based on milder reaction conditions are actively sought. Recent developments in transition-metal catalysis have opened a few viable routes catalyzed by Cu,[12] Pd[19, 20] and Au[21] metals. In 2012, E.F. Marques *et. al*. report the synthesis of a library of 4- quinolinones under microwave (MW) irradiation using base instead of conventional heating. The newly synthesized 4-quinolinones were shown to be potent inhibitors of cathepsins L and V (Scheme I.1).[22,23] Also, the synthesis of quinolones from *ortho*-amidoacetophenones by trimethylsilyl trifluoromethanesulfonate (TMSOTf) [24] and cyclization using NaOH is reported. [25]



Scheme I.1. Microwave assisted synthesis of 4-quinolinones.

In 2015, Long *et. al.* reported a novel metal-free oxidative intramolecular Mannich reaction. The developed reaction between secondary amines and unmodified ketones, affording a simple and direct access to a broad range of 2-arylquinolin-4(1*H*)-ones through C_{sp}^3−H activation/C_{sp}^3−C_{sp}^3

19. (a) Kalinin, V. N.; Sbostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett*. **1992**, *33*, 373-376. (b) Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773-6784. (c) Haddad, N.; Tan, J.; Farina, V. *J. Org. Chem*. **2006**, *71*, 5031-5034. (d) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett*. **2008**, *10*, 2609-2612. (e) Zhao, T.; Xu, B. *Org. Lett*. **2010**, *12*, 212-215. (f) Takahashi, I.; Morita, F.; Kusagaya, S.; Fukaya, H.; Kitagawa, O. *Tetrahedron: Asymmetry*. **2012**, *23*, 1657-1662. (g) Iaroshenko, V. O.; Knepper, I.; Zahid, M.; Kuzora, R.; Dudkin, S.; Villinger, A.; Langer, P. *Org. Biomol. Chem*. **2012**, *10*, 2955-2959. (h) Fei, X.-D.; Zhou, Z.; Li, W.;Zhu, Y.-M.; Shen, J.-K. *Eur. J. Org. Chem*. **2012**, 3001-3008. (i) Iaroshenko, V. O.; Zahid, M.; Mkrtchyan, S.; Gevorgyan, A.; Altenburger, K.; Knepper, I.; Villinger, A.; Sosnovskikh, V. Y.; Langer, P. *Tetrahedron*. **2013**, *69*, 2309-2318. (j) Wang, Y.; Liang, H.; Chen, C.; Wang, D.; Peng, J. *Synthesis*. **2015**, *47*, 1851-1860.
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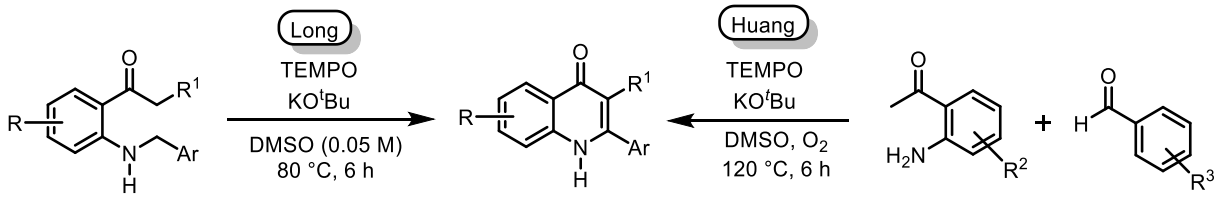
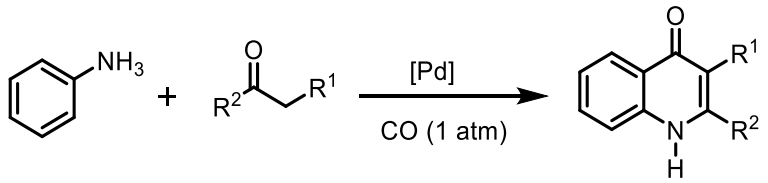
22. Marques, E. F.; Bueno, M. A.; Duarte, P. D.; Silva, L. R.S.P.; Martinelli, A. M.; dos Santos, C. Y.; Severino, R. P.; Brömme, D.; Vieira, P. C.; Corrêa, A. G. *Eur. J. Med. Chem.* **2012**, *54*, 10-21.
23. Rocha, D. H. A.; Pinto, D. C.G.A.; Silva, A. M.S.; *Tetrahedron*, **2015**, *71*, 7717-7721.
24. Chen, Y-R.; Cho, Y. C.; Shih, T-L. *Tetrahedron*. **2016**, *72*, 2006-2011.
25. Ding, D.; Li, X.; Wang, X.; Yongli, D.; Shen, J. *Tetrahedron Lett*. **2006**, *47*, 6997–6999.

bond formation from readily available *N*-arylmethyl-2-aminophenylketones, using TEMPO as the oxidant and KO^{t}Bu as the base (Scheme I.2).[26a] Also, Huang *et. al.* reported transition-metal-free efficient intermolecular cyclization of 2-aminoacetophenones with aldehydes for the synthesis of 2-aryl-4-quinolones through C–C and C–N bond formation (Scheme I.2).[26b]



Scheme I.2. Metal-free synthesis of 2-aryl-quinolones.

Recently, palladium catalyzed carbonylation[27] for constructing 4-quinolones by using CO as carbonyl source have been reported. In 2017, Lei *et. al.* developed a palladium-catalyzed oxidative carbonylation of ketones, amines with carbon monoxide for the synthesis of 4-quinolones (Scheme I.3).[28]

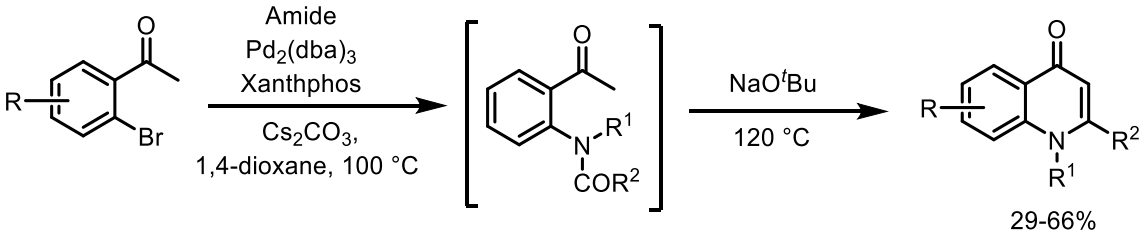


Scheme I.3. Cross-dehydrogenative-coupling for the synthesis of 2-aryl-quinolones.

In addition, the Pd(0)-catalyzed multicomponent[29] carbonylative coupling of terminal acetylenes with 2-iodoanilines under elevated pressures of carbon monoxide has previously been described.[30]

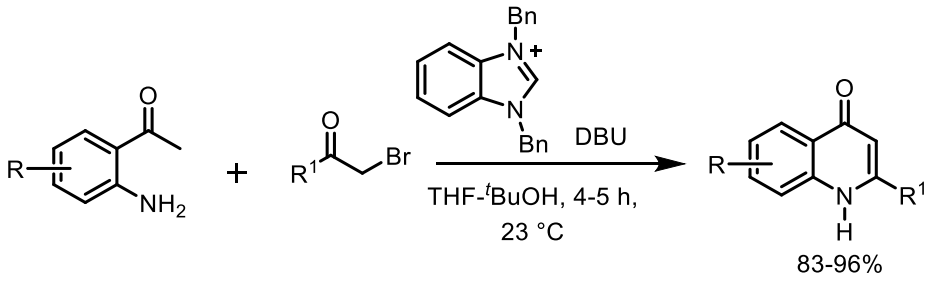
26. (a) Hu, W.; Lin, J-P.; Song, L-R.; Long, Y-Q. *Org. Lett.* **2015**, *17*, 1268−1271. (b) Ma, H.; Guo, C.; Zhan, Z.; Lu, G.; Zhang, Y.; Luo, X.; Cuia, X. F.; Huang, G. *New. J. Chem.* **2017**, *41*, 5280.
27. (a) Torii, S.; Okumoto, H.; Long, H. X. *Tetrahedron Lett.* **1990**, *31*, 7175. (b) Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1991**, *32*, 237. (c) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1992**, *33*, 373. (d) Haddad, N.; Tan, J.; Farina, V. *J. Org. Chem.* **2006**, *71*, 5031.
28. Wu, J.; Zhou, Y.; Wu, T.; Zhou, Y.; Chiang, C-W.; Lei, A. *Org. Lett.* **2017**, *19*, 6432−6435.
29. Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101−4111.
30. (a) Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7125−7128. (b) Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1991**, *32*, 237−240. (c) Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron.* **1993**, *49*, 6773−6784.

Another palladium-catalyzed synthesis of 2-substituted 4-quinolones via amidation of 2′-bromoacetophenones followed by base-promoted intramolecular cyclization were developed by Huang *et. al*. (Scheme I.4).[19d]



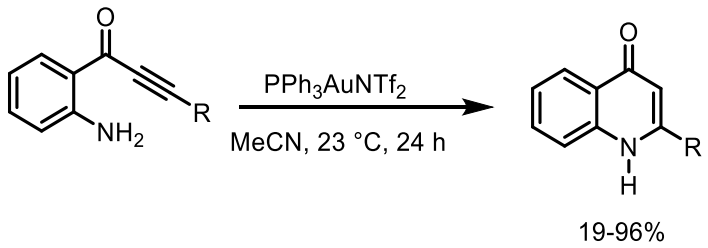
Scheme I.4. Palladium-catalyzed synthesis of 4-quinolones.

Recently Rai *et. al.* developed the domino synthesis of 2-aryl-4-quinolones through acetylation of 2-aminobenzaldehydes with α-haloketones followed by intramolecular azaheterocyclisation. This method represents a new extension of the Allan–Robinson and Friedländer reactions and uses *N*-heterocyclic carbene catalysis to construct 2-aryl-4-quinolones (Scheme I.5). [31]



Scheme I.5. *N*-heterocyclic carbene catalyzed synthesis of 2-aryl-4-quinolones.

Also, a mild and atom-economic alternative for the synthesis of 2-aryl-4-quinolones is known by using cationic gold(I) species (Scheme I.6).[21]



Scheme I.6. Gold(I)-catalyzed synthesis of 2-substituted 4-quinolones.

31. Rai, V. K.; Verma, F.; Sahu, G. P.; Singh, M.; Rai, A.; *Eur. J. Org. Chem.* **2018**, 537–544.

I.3. Synthesis of 4-arylquinolines

The 4-quinolones are also versatile synthetic intermediates due to their facile derivatization of the 4-hydroxyl group.[32] The 4-substituted quinolines are quite prevalent pharmacophores. They are also part of several clinically used drugs, [33] where their major occurrence is among antimalarial drugs and kinases inhibition[34a] involved in cancer progression. Camptothecin is a quinoline alkaloid discovered in 1966 by Wall and Wani through systematic screening of natural products for anticancer drugs.[33c] The 2-(2-fluorophenyl)-6,7-methylenedioxy quinolin-4-one monosodium phosphate (CHM-1-P-Na) is a preclinical anticancer agent, showing excellent antitumor activity in a SKOV-3 xenograft nude mice model (Figure I.4).[34b-c]

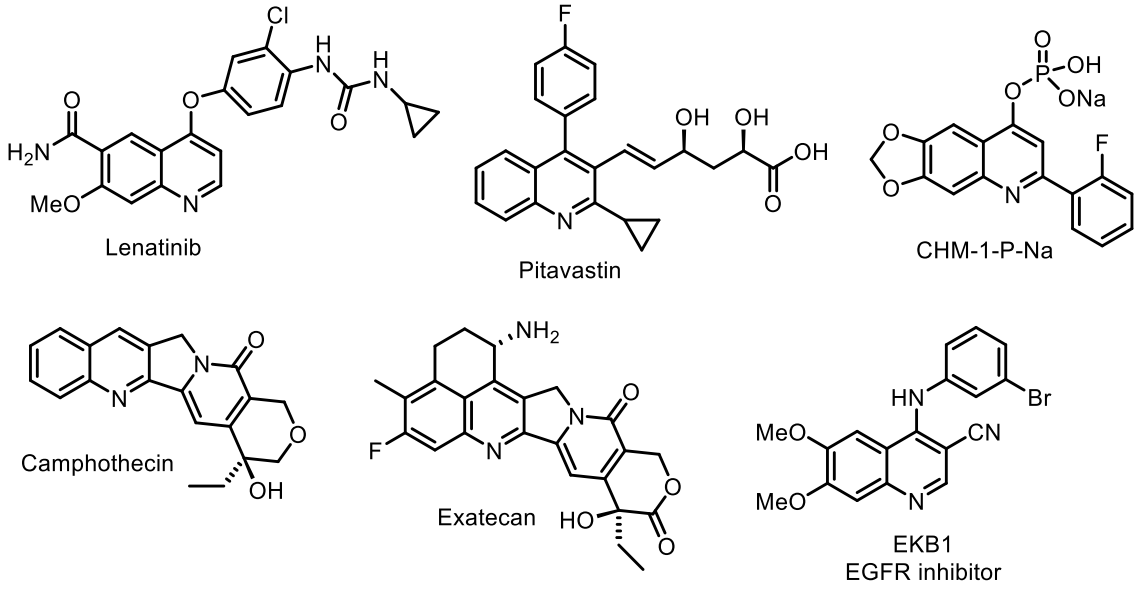


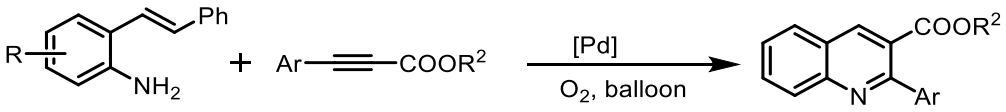
Figure I.4. Quinoline based natural products and kinase inhibitors.

32. 4-Quinolones have two tautomeric forms: either the hydroxy tautomer as 4-hydroxyquinoline or the carbonyl tautomer as 4-quinolones, although these compounds exist favorably in the keto form. For more information, see: (a) Pfister-Guillouzo, G.; Guimon, C.; Frank, J.; Ellison, J.; Katritzky, A. R.; Liebigs, J. *Ann. Chem*. **1981**, 366. (b) Mphahlele, M. J.; El-Nahas, A. M. *J. Mol. Struct.* **2004**, *688*, 129.

33. (a) Howard, B. F. *Chem. News*. **1931**, *142*, 129–133. (b) Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tibenderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; D'Alessandro, U. *Malar. J*. **2011**, *10*, 144. (c) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. I.; Sim, G. A. *J. Am. Chem. Soc*. **1966**, *88*, 3888–3890.

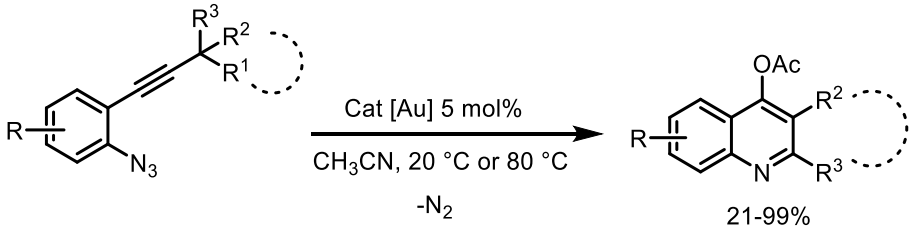
34. (a) Solomon, V. R.; Lee, H. *Curr. Med. Chem*. **2011**, *18*, 1488–1508. (b) Chou, L. C.; Chen, C. T.; Lee, J. C.; Way, T. D.; Huang, C. H.; Huang, S. M.; Teng, C. M.; Yamori, T.; Wu, T. S.; Sun, C. M.; Chien, D. S.; Qian, K.; Morris-Natschke, S. L.; Lee, K. H.; Huang, L. J.; Kuo, S. C. *J. Med. Chem*. **2010**, *53*, 1616–1626. (c) Chou, L. C.; Tsai, M. T.; Hsu, M. H.; Wang, S. H.; Way, T. D.; Huang, C. H.; Lin, H. Y.; Qian, K.; Dong, Y.; Lee, K. H.; Huang, L. J.; Kuo, S. C. *J. Med. Chem*. **2010**, *53*, 8047–8058.

In addition to the classical methods, the recent years have seen the emergence of not only transition-metal involving Pd,[35] Au,[36] Rh,[37] Ag,[38] Ir, Ru and Co-catalyzed[39] transformations. Also, metal-free approaches for the synthesis of different substituted quinolines. In 2016, Jiang *et.al* reported Pd-catalyzed oxidative cyclization of *o*-vinylanilines and alkynes with molecular oxygen to construct 2,3-disubstituted quinolines (Scheme I.7).[35a]



Scheme I.7. Synthesis of 2,3-disubstituted quinolines through Pd catalysis.

Gagosz *et. al.* reported synthesis of polyfunctionalized quinolines a gold-catalyzed 1,3-acetoxy shift/cyclization/1,2-group shift sequence. transformation proceeds under mild reaction conditions, is efficient, and tolerates a large variety of functional groups (Scheme I.8).[37c]



Scheme I.8. Gold(I)-catalyzed formation of functionalized quinolines.

35. For recent reviews on quinoline synthesis: (a) Bharate, J. B.; Vishwakarma, R. A.; Bharate, S. B. *RSC Adv*. **2015**, *5*, 42020. (b) Shraddha, M. P.; Patel, K D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv*. **2014**, *4*, 24463. (c) Contelles, J. M.; Mayoral, E. P.; Samadi, A.; Carreiras, M. D. C.; Soriano, E. *Chem. Rev*. **2009**, *109*, 2652-2671.
36. For palladium catalyzed reactions, see: (a) Zheng, J.; Li, Z.; Huang, L.; Wu, W.; Li, J.; Jiang, H. *Org. Lett*. **2016**, *18*, 3514-3517. (b) Li, C.; Li, J.; An, Y.; Peng, J.; Wu, W.; Jiang, H. *J. Org. Chem*. **2016**, *81*, 12189-2196. (c) Luo, J.; Huo, Z.; Fu, J.; Jina, F.; Yamamoto, Y. *Org. Biomol. Chem*. **2015**, *13*, 3227. (d) Ji, X.; Huang, H.; Li, Y.; Chen, H.; Jiang, H. *Angew. Chem., Int. Ed*. **2012**, *51*, 7292. (e) Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett*. **2008**, *10*, 173-175.
37. For gold catalyzed reactions, see: (a) Jin, H.; Tian, B.; Song, X.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed*. **2016**, *55*, 1268. (b) Zhu, S.; Wu, L.; Huang, X. *J. Org. Chem*. **2013**, *78*, 9120-9126. (c) Gronnier, C.; Boissonnat, G.; Gagosz, F. *Org. Lett*. **2013**, *15*, 4234-4237.
38. For rhodium catalyzed reactions, see: (a) Yu, S.; Li, Y.; Zhou, X.; Wang, H.; Kong, L.; Li, X. *Org. Lett*. **2016**, *18*, 2812-2815. (b) Neuhaus, J. D.; Morrow, S. M.; Brunavs, M.; Willis, M. C. *Org. Lett.* **2016**, *18*, 1562-1565.
39. For iridium, ruthenium and cobalt catalyzed reactions, see: (a) Wang, R.; Fan, H.; Zhao, W.; Li, F. *Org. Lett*. **2016**, *18*, 3558-3561. (b) Zhang, M.; Roisnel, T.; Dixneuf, P. H. *Adv. Synth. Catal*. **2010**, *352*, 1896-1903. (c) Kong, L.; Yu, S.; Zhou, X.; Li, X. *Org. Lett*. **2016**, *18*, 588-591.

Hypervalent iodine chemistry.

I.4. Hypervalent I(III) compounds.

In the past few decades the use of iodine has been developed continuously in the organic synthesis. This mainly due to the mild and highly selective oxidizing properties, benign environmental green character, and commercial availability of hypervalent iodine reagents. The most common organic iodine (III) and iodine (V) derivatives have been successfully used in organic synthesis as versatile reagents for various selective oxidative transformations of complex organic molecules. Several functionalization of carbonyl compounds, ligand transfer reactions, oxidative coupling processes among the most important have been reported in the literature.[40] While hypervalent iodine describes compounds containing an iodine atom with oxidation states 3+, 5+ or 7+.

The purpose of the present introduction is to summarize the chemistry of hypervalent iodine(III) compounds with emphasis on recent synthetic applications. This class of organic I(III) compounds are basically classified on the type of ligand attached to the iodine. The following classes of iodine(III) reagents have are known for broad application in organic synthesis (Figure I.5).[41]

40. For books on the chemistry of hypervalent iodine see a) A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, VCH, New York, NY, **1992**, pp. 414; b) A. Varvoglis in *Hypervalent Iodine in Organic Synthesis Academic Press*, London, **1997**, pp. 223; c) V. Zhdankin, P. J. Stang, *Chemistry of Hypervalent Compounds,* Wiley-VCH, New York, **1999**, pp. 414; d) T. Wirth, *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis Springer Berlin Heidelberg, Berlin*, **2003**; e) V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, **2013**, pp. 468.) T. Kaiho, *Iodine chemistry and applications*, Wiley, Hoboken, NJ, **2015**, pp. 636.

41. For reviews on the chemistry of hypervalent iodine see 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; d) Zhdankin, V. *ARKIVOC*. **2009**, 1–62; e) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev*. **2016**, *116*, 3328–3435 f) Zhdankin, V. V. *Science of Synthesis***. 2007**,31a, 161. (e) Ochiai, M. Coord. Chem. Rev. **2006**, *250*, 2771-2781.

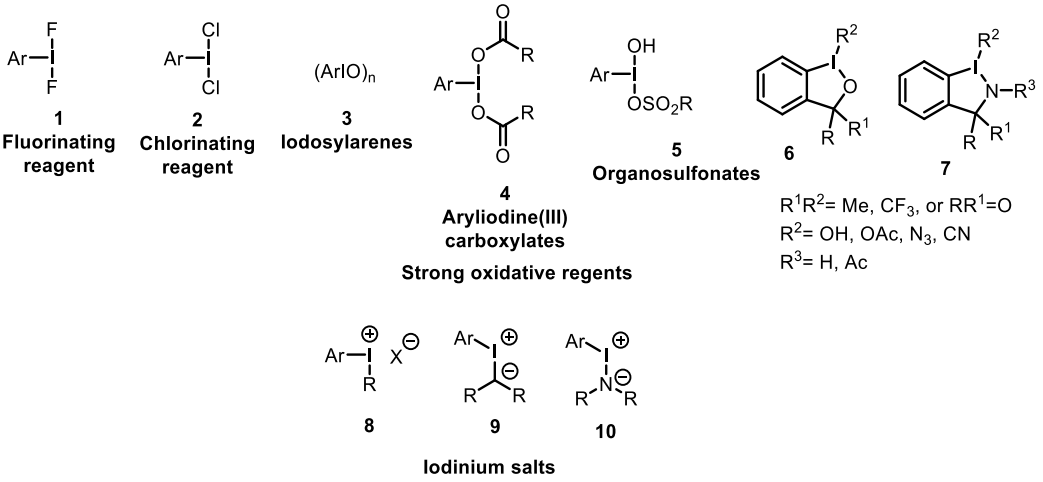
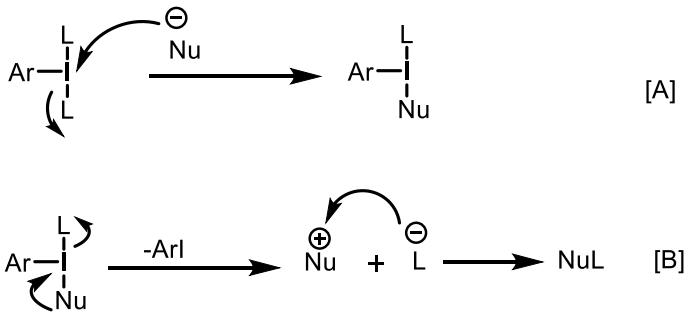


Figure I.5. Types of polyvalent iodine(III) compounds.

The compounds **1** and **2** are effective for fluorination and chlorination in organic synthesis. The strong oxidizing agents 4-7 have found widespread application as reagents for oxygenation and oxidative functionalization of organic substrates. Also, iodonium salts **8-10** have been used for several organic transformations. The most important and commercially available representatives of aryliodine(III) carboxylates are (diacetoxyiodo)benzene $PhI(OAc)_2$ abbreviated as PIDA and [bis(trifluoroacetoxy)iodo]benzene $PhI(OCOCF_3)_2$, abbreviated as PIFA. In the aryliodine(III) organosulfonates, the commercially available [hydroxy(tosyloxy)iodo]benzene PhI(OH)OTs, is abbreviated as HTIB and is also known as Koser's reagent. The heterocyclic iodanes **6** and **7** are non-oxidizing reagents and have higher stability than the acyclic analogs. Diaryliodonium salts **8** have diverse reactivity due to the exceptional leaving group ability of the -IAr fragment. They are defined as a positively charged 8-I-2 species with two carbon ligands and negatively charged counterion. Their application can be found in numerous organic transformations as cationic photoinitiators and synthetic reagents. Iodonium ylides **9** and **10** are knows as carbene and nitrene precursors. The bonding in hypervalent I(III) reagents is one typical carbon-iodine σ bond, as well as one hypervalent 3-centre-4- electron (3c–4e) bond[42] between the iodine atom and its two ligands. The highly polarized hypervalent bond serves to rationalize both the electrophilic character[43] of the central iodine atom, as well as the geometry. The iodine atom in λ^3-iodanes, RIX_2, has a total 10 electrons. They have an overall geometry of a distorted trigonal bipyramid

42. a) Pimentel, G. C. *J. Chem. Phys*. **1951**, *19*, 446–448. b) Hach, R. J.; Rundle, R. E. *J. Am. Chem. Soc*. **1951**, *73*, 4321–4324.
43. Pinto de Magalhaes, H.; A. Togni, H. P. Lethi, *J. Org. Chem*. **2017**, *82*, 11799–11805.

with two heteroatom ligands X occupying the axial positions, and the least electronegative carbon ligand R and both electron pairs residing in equatorial positions. In the hypervalent model, the bonding in RIX_2 uses the non-hybridized 5p orbital of iodine in the linear X–I–X bond. The general reactivity of I(III) compounds is shown below (Scheme I.9).



Scheme I.9. General reactivity of I(III) reagents.

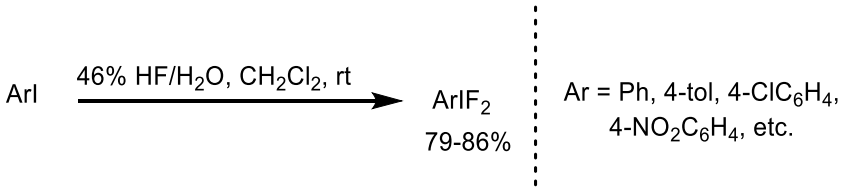
The predictable mechanisms often initiate with incorporation of a nucleophile via ligand exchange (Scheme I.9 [A]). The subsequent reductive elimination of iodoarene occurs with formation of a new bond between the nucleophile and one of the iodane initial ligands (Scheme I.9 [B]).

I.5. Preparation of Iodine(III) Compounds.

I.5.1 (Difluoroiodo)arenes.

There are several synthetic methodologies available for the preparation hypervalent I(III) reagents and the selected have been described here. The (Difluoroiodo)arenes can prepared by treatment of iodosylarenes with 40-46% aqueous hydrofluoric acid followed by crystallization of resulting (Difluoroiodo)arenes from hexane (Scheme I.10).[44]

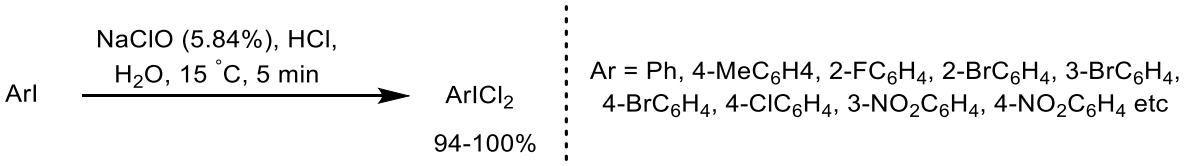
44. a) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis.* **2002**, 1802-1803. (b) Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, 395-403.



Scheme I.10. (Difluoroiodo)arenes synthesis using iodoarenes.

I.5.2 (Dichloroiodo)arenes.

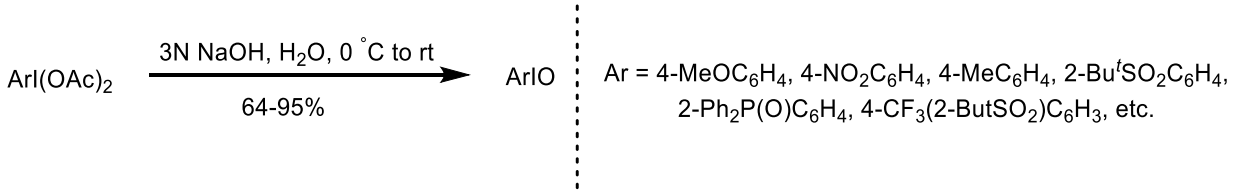
A recently reported convenient and mild approach to (dichloroiodo)arenes[45] consists of the chlorination of iodoarenes using concentrated hydrochloric acid and aqueous sodium hypochlorite (Scheme I.11).



Scheme I.11. (Dichloroiodo)arenes synthesis using iodoarenes.

I.5.3. Iodosylarenes.

The most important representative of iodosylarenes, the iodosylbenzene, is best prepared by alkaline hydrolysis of (diacetoxyiodo)benzene. The same procedure can be used for the preparation of a variety of *ortho*-, *meta*-, and *para*-substituted iodosylbenzenes from the respective (diacetoxyiodo)arenes (Scheme I.12).[46]

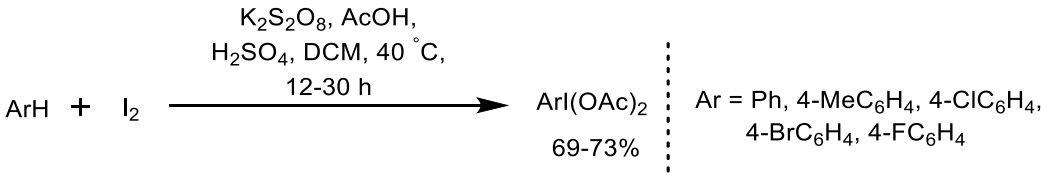


Scheme I.12. Synthesis of iodosylarenes.

45. Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, 551-557.
46. Hiller, A.; Patt, J. T.; Steinbach, J. *Magn. Reson. Chem.* **2006**, *44*, 955-958. (a) Saltzman, H.; Sharefkin, J. G. *Org. Synth. Coll. Vol. V* **1973**, 658. (b) Meprathu, B. V.; Protasiewicz, J. D. *ARKIVOC* **2003**, *(vi)*, 83-90. (c) Meprathu, B. V.; Justik, M. W.; Protasiewicz, J. D. *Tetrahedron Lett.* **2005**, *46*, 5187-5190.

I.5.4. [Bis(acyloxy)iodo]arenes.

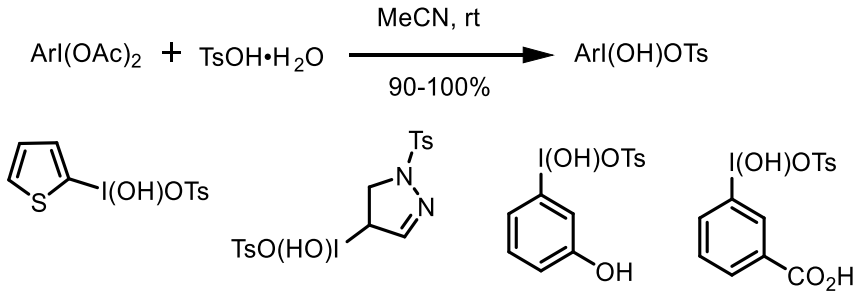
The [Bis(acyloxy)iodo]arenes[47] can be prepared by the reported methodology, which employs the interaction of arenes with iodine and potassium peroxodisulfate in acetic acid (Scheme I.13).



Scheme I.13. Synthesis of [Bis(acyloxy)iodo]arenes using arenes.

I.5.5. Aryliodine(III) organosulfonates

[Hydroxy(tosyloxy)iodo]arenes are usually prepared by a ligand exchange reaction of (diacetoxyiodo)arenes with *p*-toluenesulfonic acid monohydrate in acetonitrile (Scheme I.14). [48]



Scheme I.14. Synthesis aryliodine(III) organosulfonates.

A convenient modified procedure for the preparation of various [hydroxy(sulfonyloxy)iodo]arenes consists of the one-pot reaction of iodoarenes and *m*-CPBA in the presence of sulfonic acids in a small amount of chloroform at room temperature.[49]

47. Hossain, M. D.; Kitamura, T. *Tetrahedron Lett.* **2006**, *47*, 7889

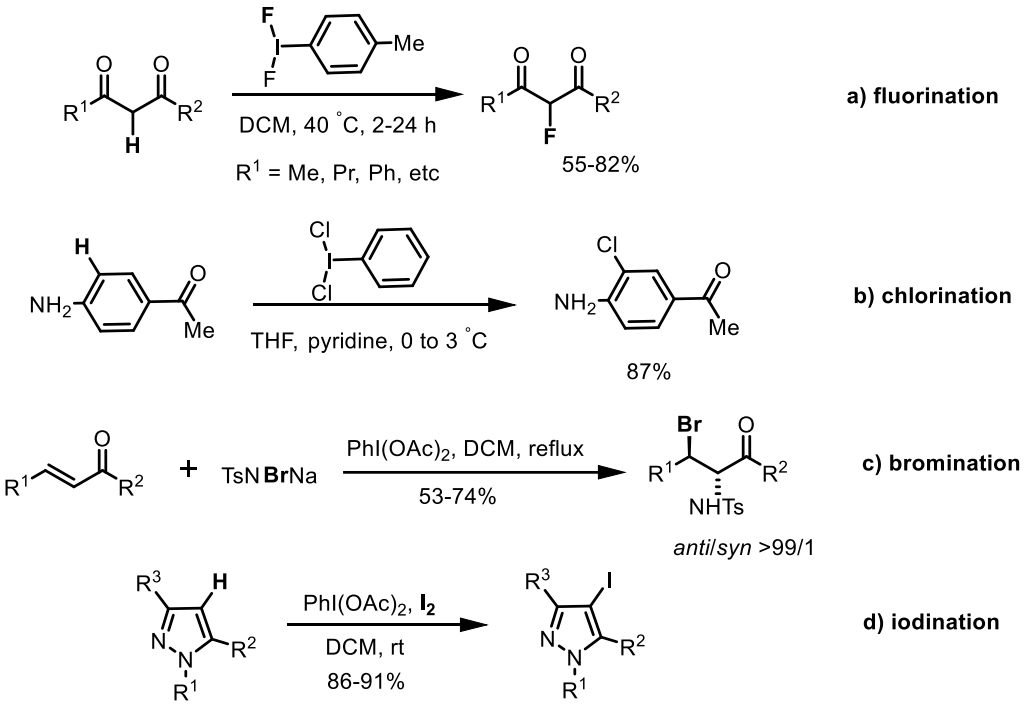
48. (a) Yusubov, M. S.; Funk, T. V.; Chi, K.-W.; Cha, E.-H.; Kim, G. H.; Kirschning, A.; Zhdankin, V. V. *J. Org. Chem.* **2008**, *73*, 295-297. (b) Moroda, A.; Togo, H. *Tetrahedron* **2006**, *62*, 12408-12414. (c) Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T. *Eur. J. Org. Chem.* **2001**, 1569-1579. (d) Lee, B. C.; Lee, K. C.; Lee, H.; Mach, R. H.; Katzenellenbogen, J. A. *Bioconjugate Chem.* **2007**, *18*, 514-523. (e) Nabana, T.; Togo, H. *J. Org. Chem.* **2002**, *67*, 4362-4365. (f) Yamamoto, Y.; Togo, H. *Synlett.* **2005**, 2486-2488. (e) Tohma, H.; Maruyama, A.; Maeda, A.; Maegawa, T.; Dohi, T.; Shiro, M.; Morita, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 3595-3598. (g) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Shiro, M.; Kita, Y. *Chem. Commun.* **2005**, 2205.

49. Yamamoto, Y.; Togo, H. *Synlett* **2005**, 2486-2488.

I.6. Applications of hypervalent I(III) reagents.

I.6.1 Halogenations

(Dihaloiodo)arenes have found practical application as reagents for halogenation of various organic substrates. Various β-dicarbonyl compounds can be selectively fluorinated at the α-position by 4(difluoroiodo)toluene (Scheme I.15a).[50] (Dichloroiodo)arenes used for electron rich aminoacetophenone is selectively chlorinated with (dichloroiodo)benzene to give product in good yield (Scheme I.15b).[51]



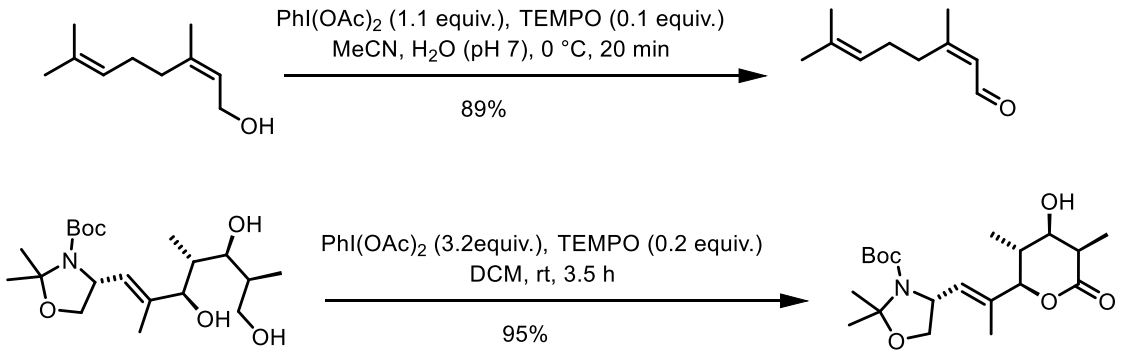
Scheme I.15. Halogenation using (dihaloiodo)arenes.

In 2008, Xia, Wu, and Wang developed a new, metal-free and convenient procedure for the aminobromination of electron-deficient olefins using Bromamine-T as nitrogen and bromine source promoted by (diacetoxyiodo)benzene (Scheme I.15c)[52]. Substituted pyrazoles can be iodinated to the corresponding 4-iodopyrazole derivatives by treatment with iodine and PIDA or polymer-supported PIDA at room temperature (Scheme I.15d).[53]

50. Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *ARKIVOC.* **2003**.
51. Zanka, A.; Takeuchi, H.; Kubota, A. *Org. Process Res. Dev*. **1998**, 2, 270-273.
52. Xia, J.-J.; Wu, X.-L.; Wang, G.-W. *ARKIVOC*. **2008**, (xvi) 22-28.
53. Cheng, D.-P.; Chen, Z.-C.; Zheng, Q.-G. *Synth. Commun*. **2003**, 33, 2671-2676.

I.6.2. Oxidation of alcohols.

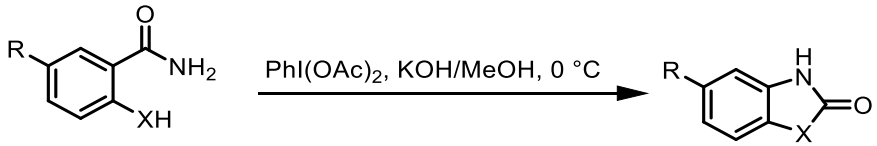
The use of PIDA in oxidation of nerol with catalytic amount of TEMPO have been reported by Ragan *et al*.[54] and a similar PIDA-TEMPO promoted γ-lactonization has recently been utilized in the asymmetric total synthesis of the antitumor (+)-eremantholide A (Scheme I.16).[55]



Scheme I.16. PIDA-mediated oxidation of alcohols.

I.6.3. Oxidative rearrangements and fragmentations.

[Bis(acyloxy)iodo]arenes and aryliodine(III) organosulfonates are commonly used as the reagents in various cationic rearrangements and fragmentations. The oxidative rearrangement of anthranilamides or salicylamides to the respective heterocycles have been reported (Scheme I.17).[56]



Scheme I.17. PIDA mediated synthesis of heterocycles.

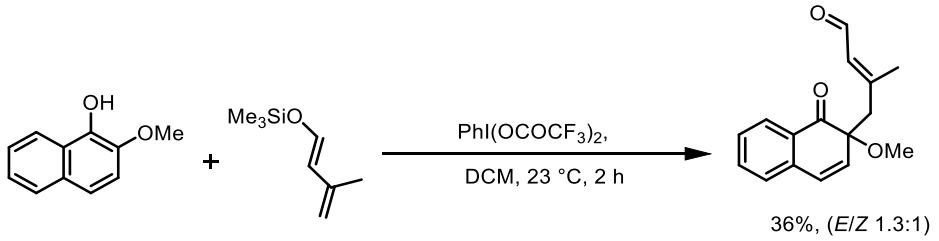
PIFA has also been used as a reagent for the Hofmann rearrangement, as illustrated by the conversion of amide to the respective amine.[57] A similar PIFA-induced Hofmann rearrangement

54. Piancatelli, G.; Leonelli, F.; Do, N.; Ragan, J. *Org. Synth.* **2006**, *83*, 18.
55. Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267-1270.
56. Prakash, O.; Batra, H.; Kaur, H.; Sharma, P. K.; Sharma, V.; Singh, S. P.; Moriarty, R. M. *Synthesis*. **2001**, 541.
57. Davis, M. C.; Stasko, D.; Chapman, R. D. *Synth. Commun.* **2003**, *33*, 2677-2684.

has been used for the preparation of both enantiomers of *trans*-2- aminocyclohexanecarboxylic acid from *trans*-cyclohexane-1,2-dicarboxylic acid.[58]

I.6.4. Oxidative dearomatization of phenolic substrates.

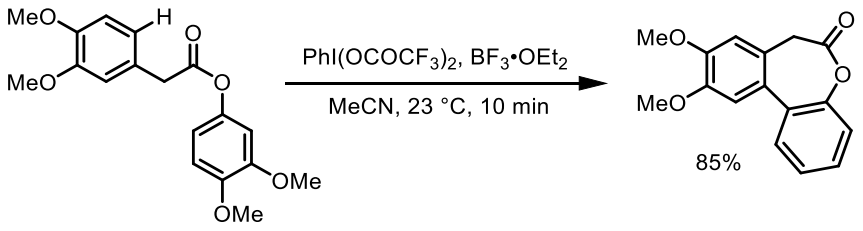
[Bis(acyloxy)iodo]arenes are commonly used as the reagents for various synthetically useful oxidative transformations of phenolic compounds. The PIFA-mediated oxidative nucleophilic substitution of the 2-alkoxynaphthol with the silyl enol ether leading to the highly functionalized naphthoid cyclohexa-2,4-dienone, which is an important intermediate product in the synthesis of aquayamycin-type angucyclinones (Scheme I.18).[59]



Scheme I.18. PIFA-mediated regioselective protocol for the oxidative dearomatization.

I.6.5. Oxidative coupling of aromatic substrates.

The oxidative cyclization of 3,4-dimethoxyphenyl-3,4-dimethoxyphenylacetate leading the seven membered lactone was carried out using PIFA by White *et. al.*[60] The direct nucleophilic substitution of electron-rich phenol ethers using PIFA and Lewis acid and involving aromatic cation radical intermediates was originally developed by Kita and coauthors in 1994 (Scheme I. 19).[61]

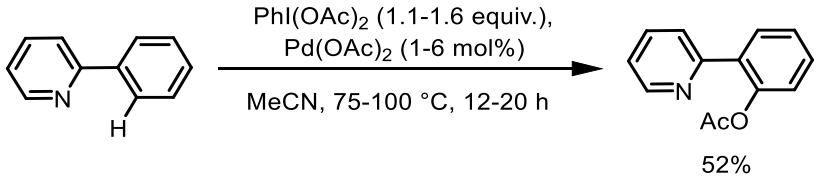


Scheme I.19. Oxidative coupling using PIFA.

58. Berkessel, A.; Glaubitz, K.; Lex, J. *Eur. J. Org. Chem.* **2002**, 2948.
59. Lebrasseur, N.; Fan, G.-J.; Quideau, S. *ARKIVOC* **2004**, *(xiii)*, 5. (b) Lebrasseur, N.; Fan, G.-J.; Oxoby, M.; Looney, M. A.; Quideau, S. *Tetrahedron*. **2005**, *61*, 1551-1562.
60. Taylor, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron.* **2007**, *63*, 11377.
61. Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

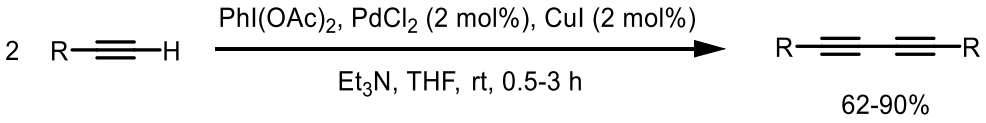
I.6.6. Transition metal catalyzed reactions.

In 2004, Sanford *et. el*. developed $Pd(OAc)_2$ mediated selective acetoxylation of C-H bonds adjacent to coordinating functional groups with PIDA (*e.g*., pyridine in substrate) (Scheme I.20).[62]



Scheme I.20. Acetoxylation using PIDA**.**

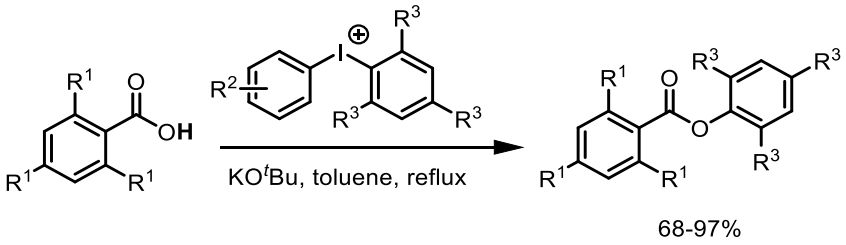
Yan and coauthors have developed an efficient procedure for synthesis of symmetrical conjugated diynes from terminal alkynes using PIDA as oxidant under palladium catalyzed conditions (Scheme I.21).[63]



Scheme I.21. Synthesis of conjugated diynes using PIDA.

I.6.7. Transformations using diaryliodonium salts.

In 2011, Olofsson *et. al*. developed an efficient arylation of carboxylic acids with diaryliodonium salts, which have excellent stability and solubility in different organic solvents. This transition metal-free conditions are compatible with a range of functional groups, and good chemoselectivity is observed with unsymmetrical diaryliodonium salts (Scheme I.22).[64]



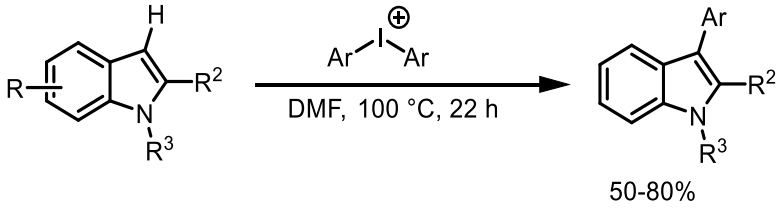
Scheme I.22. Synthesis of aryl esters using diaryliodonium salts.

62. Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 2300-2301.

63. a) Yan, J.; Wu, J.; Jin, H. J. *Organomet. Chem*. **2007**, 692, 3636-3639.

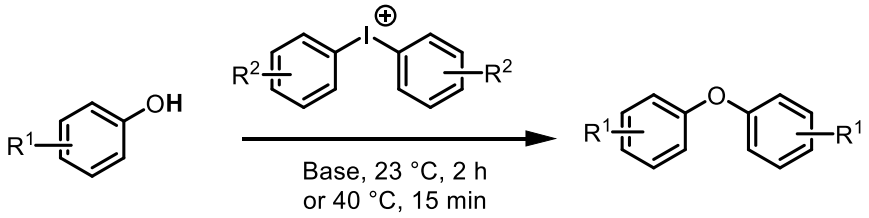
64. Petersen, T. B.; Khan, R.; Olofsson, B. *Org. Lett*. **2011**,*13*, 3462-3465.

Another method for the direct C-arylation of unreactive C-H bonds of indoles and pyrroles with differently substituted diaryliodonium salts were reported to efficiently proceed in the absence of metal catalyst (Scheme I. 23).[65]



Scheme I.23. Metal-free direct arylations of indoles.

This protocol proved broadly applicable, thereby enabling-H bond functionalizations of free (NH)- as well as *N*-substituted indoles and pyrroles. Another examples of transition metal free synthesis of diaryl ethers has been developed by Oloffson *et. al*. The scope includes *ortho*- and halo-substituted diaryl ethers, which are difficult to obtain by metal-catalyzed protocols (Scheme I.24).



Scheme I.24. Arylation of functionalized phenols.

Other than this, there are several metal-free arylation approaches using diaryliodoniumsalts have been reported for heterocycle nucleophiles[66]. Also, application in α-arylation strategies including asymmetric synthesis, metal catalyzed cross-coupling reactions, deromatization of phenols, macromolecular chemistry, as benzene precursors, photochemistry and polymerization have been reported in the literature.[67]

65. Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R.; Ackermann, L. *Org. Lett*. **2011**,*13*, 2358-2360.
66. Crowder, J. R.; Glover, E. E.; Grundon, M. F.; Kaempfen, H. X. *J. Chem. Soc*. **1963**, 4578.
67. For the uses of diaryliodonium salts see review: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed*. **2009**, *48*, 9052 –9070; (b) Yusubov M. S.; Yu, D. S.; Larkina, M.; Zhdankin, V. V. *ARKIVOC*, **2013** (i) 364-395; (c) Sun, C-L.; Shi, Z.-J. *Chem. Rev*. **2014**, *114*, 9219−9280; Yoshimura, A.; Zhdankin, V. V. *Chem. Rev*. **2016**, *116*, 3328–3435.

Gold chemistry.

I.7. Background of the gold(I) reactivity.

In the history, the metal “Gold” has been used by our ancestors in the different ways as in jewelry, currency, chinaware, beautiful arts and so forth but the metallic stable gold had not taken attention for the chemists until recent years. The reason for the neglect of gold as a potential catalyst in chemistry might be the cost, which could be unaffordable. Talking about gold in the periodic table, is the well-known transition metal, belonging to group 11, with the atomic number 79. There are total 36 radioisotopes have been synthesized[68] so far and ^{197}Au is the naturally occurring isotope of gold is well known. The properties of gold include dense, soft, malleable and ductile metal. It exists in the oxidation states 0, 1+, 2+, and 5+.[69] The physical properties of gold were exploited in industrial application,[70] optical and electronics for connections, soldering and coating (Figure I.6).

Figure I.6. Gold in the periodic table of the elements.

Although gold has been known for thousands of years, its application in organic chemistry and catalysis is continuously in progress.

68. G. Audi, O. Bersillon, J. Blachot, A. H. Wapstra, *Nucl. Phys. A* **2003**, *729*, 3-128
69. C. F. Shaw III, *Chem. Rev.* **1999**, *99*, 2589-2600
70. For a review on optical constants of noble metals (Cu, Ag, Au), see: P. B. Johnson, R. W. Christy, *Phys. Rev. B* **1972**, *6*, 4370-4379.

I.7.1. The first examples of use of gold salts and complexes.

Initially in 1972 and 1976, the reports on the use of gold(III) salts in the rearrangement of strained small ring hydrocarbons[71] and asymmetric aldol reaction of aldehydes with isocyanoacetates have been documented.[72] Due to the property of high affinity of gold salts or complexes towards alkynes in the catalysis, in 1976, the first reaction in which alkynes are activated by gold(III) salts was reported by the group of Thomas (Scheme I.25).[73]

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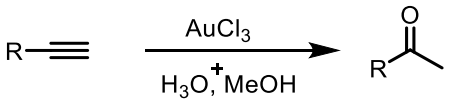
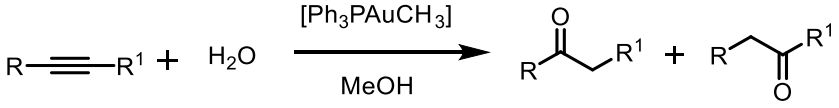


Scheme I.25. First example of the use of gold(III) salts in catalysis.

Later, Fukuda and Utimoto in 1991,[74] demonstrated the potential use of gold as catalyst effective hydration of unactivated alkynes into ketones and the similar reaction with alcohols to form acetals. The more attention towards gold catalysis in the scientific community raised when the work of Teles using gold(I) complexes as catalysts for the hydration of alkynes was published (Scheme I.26).[75] Later, Hyashi and Tanaka published an extended version of this investigation in 2002.[76]



Scheme I.26. First example of the use of a cationic gold(I)complex as catalyst.

71. (a) Gassman, P. G.; Meyer, G. R.; Williams, F. J. *J. Am. Chem. Soc*. **1972**, *94*, 7741-7748; (b) Meyer, L.-U.; de Meijere, A. *Tetrahedron Lett*. **1976**, *17*, 497-500.
72. Ito, Y.; Sawamura, Hayashi, M.T. *J. Am. Chem. Soc*. **1986**, *108*, 6405-6406
73. Nomran, R. O. C.; Parr, W. J. E.; Thomas, C. B.; *J. Chem. Soc*., Perkin Trans. **1976**, *1*, 1983-1987.
74. (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729-3733. (b) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *56*, 3729-3733.
75. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.
76. E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed*. **2002**, *41,* 4563- 4565.

After this, the interest in homogenous and heterogenous gold catalysis[77] has been seen and it was called as "catalysis gold rush"[78] for new synthetic opportunities in organic chemistry area.[79] According to the theory formulated in 1923 by Lewis as a part of the electron-pair theory of acid-base[80] and in 1963 by Pearson about the concept of hard and soft Lewis acid and bases (HSAB),[81] gold(I) and gold(III) can be defined as soft Lewis acids.

I.8. Reactivity and chemical nature of gold.

Experimental and theoretical calculation were explained to understand the general behavior of gold(I) complexes.[82] The strong Lewis acidity of gold(I) species and the stronger bond between gold are mainly due to the relativistic effects expressed in the contracted 6s and 6p orbitals of gold.[83] The gold has high nuclear charge and it shows the relativistic effects, which is defined as irregular periodic behavior from the high velocity of the internal shell electrons traveling at close to the speed of light.[84]

Another interesting property of gold is the unusual electronegativity of 2.5[85] as compared to carbon of 2.4, which implies that most bonding electrons density would be located in gold. The effects of expansion of 5d orbitals in gold causes a diffuse electronic bond, diminishing the electron-electron repulsions, gold carbenoid behavior [86]and very high ionization energy (9.22 eV).[87] Also, due to relativistic effects, oxidation of gold(I) to form gold(II) usually does not occur.

77. A. S. K. Hashmi, *Gold Bull*. **2004**, *37*, 51-65.
78. A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993.
79. A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387-391.
80. (a) Lewis, G. N. *J. Frank. Inst.* **1938**, *226*, 293-313. (b) Ebbing, D. D.; Gammon, S. D. *General Chemistry* 8th ed. Boston, MA: Houghton Mifflin. **2005**.
81. (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539. (b) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581-586. (c) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 643-648.
82. (a) D. J. Gorin, F. D. Toste, *Nature*. **2007**, *446*, 395-403; (b) M. Pernpointner, A. S. K. Hashmi, *J. Chem. Theory Comput.* **2009**, *5*, 2717-2725 (c) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456. (d) Pyykkö, P. *Inorg. Chim. Acta.* **2005**. *358*, 4113-4130 (e) Gorin D.; Toste, F. D. *Nature* **2007**, *446*, 395-403
83. For more information on the relativistic effects, see: (a) K. S. Pitzer, *Acc. Chem. Res.* **1979**, *12*, 272-276; (b) P. Pyykkö, *Chem. Rev.* **1988**, *88*, 563-594; (c) L. J. Norrby, *J. Chem. Educ.* **1991**, *68*, 110-113
84. (a) Pitzer, K. S. *Acc. Chem. Res.* **1979**, *12*, 272-276. (b) McKelvey, D. R. *J. Chem. Educ.* **1983**, *60*, 112-116
85. Electronegativity is given in Pauling scale.
86. Neale, R. S. *J. Phys. Chem.* **1964**, *68*, 143–146.
87. Shapiro, N. D.; Toste, F. D. *Synlett*. **2010**, *5*, 675-691.

I.9. Gold(I) catalysts.

The strong affinity towards alkynes of simple chloride salts such as $AuCl_3$ or $NaAuCl_4$, which is proved to be carbophilic enough to activate alkynes to proceed nucleophilic attacks has been reported. [88] $AuCl_3$, $AuBr_3$, and polynuclear gold complexes[89] are proved to be catalytically active, although they are hygroscopic, light sensitive and decompose above 160 ˚C, which results in the production of molecular halogen and metallic gold.[90] The reactivity of the complexes depends on the ligands attached to the gold and their electron donating properties, which tell us about near to the electrophilicity of the complexes (Figure I.7).[91]

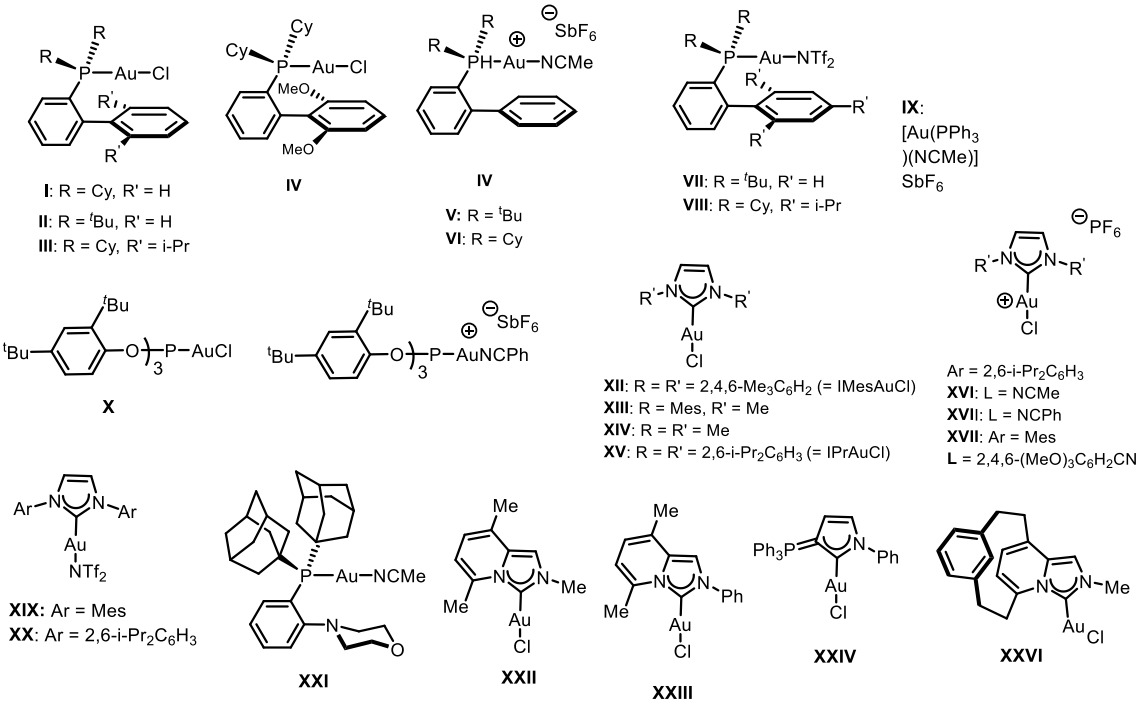


Figure I.7. Representative neutral and cationic gold(**I**) complexes.

The synthesis of the catalysts **I**-**VI** was reported by Echavaren *et. al*. group to carry out gold(I)-catalyzed reactions.[92] *N*-Heterocyclic carbenes (NHC) are highly donating ligands, rendering the

88. See the first examples of the gold catalyzed reaction.
89. E. S. Smirnova, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 9023-9026.
90. Wiber, E.; Wiber, N.; Holleman, A. F. *Inorganic Chemistry* 101 ed, Academic Press, **2001**, 1286-1287.
91. D. J. Gorin, B. D. Sherry, F. D. Toste, Chem. Rev. 2008, 108, 3351-3378; (b) Y. W. Wang, A. D. Lackner, F. D. Toste, Acc. Chem. Res. 2013,
92. C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

corresponding gold(I) complexes less reactive, thus very selective.[93] Cationic phosphine-complexes[94] are crystalline, non-hygroscopic, active and stable catalyst under ambient conditions for long time. The use of the bulky-biphenyl based phosphine ligands can be seen in the pd catalyzed cross couplings.[95] The most electrophilic gold(I) complexes are those who bear phosphine ligands. It is important to mention that gold(I) complexes adopt a linear coordination geometry.[96] Both Phosphine and phosphite with related donor ligands forms linear L-Au-X complexes. The catalyst of type **I**-**IV**, **X**, and **XII**-**XV** show poor catalytic activity as compared to cationic complexes **V**-I**X**, **XI** and **XVI-XX**. The cationic complexes, which are mentioned in the above figure arise from the corresponding neutral complexes, where the ligand is chloride anion, and is easily abstracted by a Ag(I) salts (with a non-coordinating anion) in the presence of labile ligand (often acetonitrile or benzonitrile) lead to the desired cationic complexes. The main advantages of this type of cationic complexes are leading solubilization in the reaction the media, stable in the solid state and no need to be activated. The gold complexes containing a labile bis(trifluoromethanesulfonyl)amide (NTf_2) as ligand and from **I-VI** are very active catalyst.[97] The synthesis and applications of the gold(I) complexes such as bulky bis-adamantyl phosphine ligand containing **XXI** (used in hydroaminations of alkynes with dialkylamines),[98] phosphite complexes **X**[99] bearing (tris(2,6-di-*tert*-butylphenyl)phosphite as the ligand) and cationic counterpart **XI**[100]

93. For the synthesis of NHC Au(I) complexes, see: (a) P. De Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411-2418; (b) P. De Frémont, E. D. Stevens, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, S. P. Nolan, *Chem. Commun.* **2006**, 2045-2047. For some applications of the NHC Au(I) complexes, see: (a) X.-Y. Lin, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9*, 2645-2648.
94. E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.
95. 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.
96. For discussion about the choice of coordination number in d10 complexes of group 11 metals, see: Carvajal, M. A.; Novoa, J. J.; Álvareze, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465–1477.
97. Structures **I**-**V** were confirmed by X-ray crystallography, see ref. 23a. (a) Partyka, D. V.; Robilotto, T. J.; Hunter, A. D.; Gray, T. G. *Organometallics* **2008**, *27*, 28-32. Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
98. Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026–18029.
99. (a) López, S.; Herrero-Gómez, H.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032. (b) **X** structure was confirmed by X-Ray crystallography: Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279.
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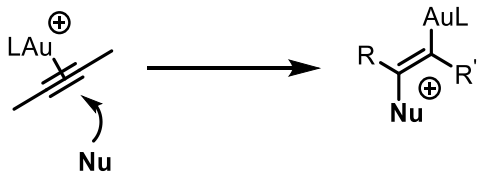
(highly electrophilic), *N*-heterocyclic carbenes (NHC) **XII**-**XV** (useful as precatalyst),[101,92a] NHC complexes **XXII-XV (**study their -acceptor properties),[102] Cationic NHC complexes[99,99] **XVI**-**XVIII** and those bearing labile ligands such as NTf_2 **XX-XXI**[103] have been described.

I.9.1. Gold(I) complexes-catalyzed reactions.

The high affinity towards alkynes shown by the gold(I) complexes allow them to activate alkynes and addition of various heteronucleonucleophiles such as oxygen,[104,105] nitrogen,[106,107,108] sulfur,[109,110] fluorine[111], as well as sulfoxides[112], imines[113], azides[114], amines[115] both by intra- and intermolecularly have been reported.[116] Even though this type of reaction can also be catalyzed by mercury(II), the high toxicity and low TON limited their opportunity in the synthesis[117] (Scheme I. 27).



Scheme I.27. Nucleophilic attack to an alkyne activated by gold(I) complexes.

101. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179. (a) Deetlefs, M.; Raubenheimer, H. G.; Esterhuysen, M. W. *Cat. Today.* **2002**, *72*, 29-41. (b) Schneider, S. K.; Herrmann, W. A.; Herdtrweck, E. Z. *Anorg. Allg. Chem.*, **2002**, *629*, 2363-2370. For NHC-Au(III) complexes see: (c) de Frémont, P.; Singh, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376-1385.

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110. Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081-4803

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112. (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160-4161. (b) Davies, P. W.; Albrecht, S. J.-C. *Angew. Chem. Int. Ed.* **2009**, *48*, 8372-8375.

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114. Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc*. **2005**, *127*, 11260-11261.

115. (a) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352. (b) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181-3184.

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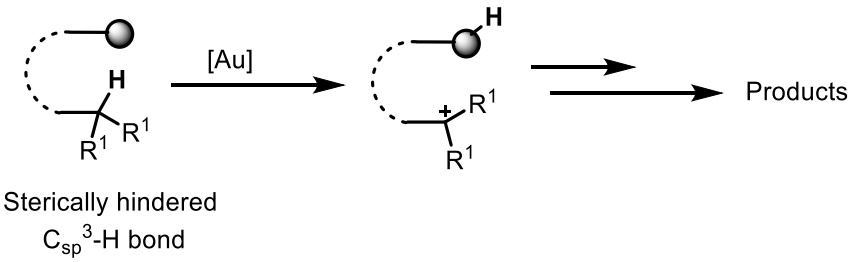
117. Reichert, J. S.; Bailey, J. H.; Niewland, J. A. *J. Am. Chem. Soc.* **1923**, *45*, 1553-1557.

I.10. Redox–neutral C_{sp}^3-H bond functionalization.

The several applications of gold(I) complexes have been described recently.[118] Although transition-metal-mediated C-H bond functionalization is a promising strategy in the organic syhthesis to construct C-C and C-X (X=heteroatom) bonds and several transformations, the use of external redox reagents usually decreases the atom economy of the chemical process. We will discuss about the recent achievements of homogenous gold catalyzed redox-neutral C_{sp}^3-H bond functionalization and cycloisomeration. A metal-catalyzed cycloisomerization reactions typically refer to transformations of polyunsaturated acyclic substrates, where the reorganization of simple and double bonds leads to new cyclized products. Generally, selective functionalization of C-H bonds is achieved by the assistance of directing groups. However, the directing-group strategy do not only require additional operations for first introduction and subsequent removal of directing groups, but it also functionalizes the less hindered C_{sp}^3-H bonds.[119] Thus, development of new methods to selectively break sterically hindered C_{sp}^3-H bond is still challenge. The proper use of electrophilic gold(I) complexes can lead to activate an unsaturated moiety followed by a hydride shift process, generating a carbocation for further functionalization (Scheme I.28).



Scheme I.28. Gold(I)-catalyzed hydride-shift strategy for C_{sp}^3-H bond functionalization.

Remarkably, gold(I)-catalyzed hydride-shift C-H bond functionalization process, depends on the substrates possesses a migrating hydrogen with a relatively high hydridic character, such as benzylic hydrogen, hydrogen adjacent to heteroatom.

118. Dorel, R.; Echavarren, A. M. *Chem. Rev*. **2015**, *115*, 9028−9072

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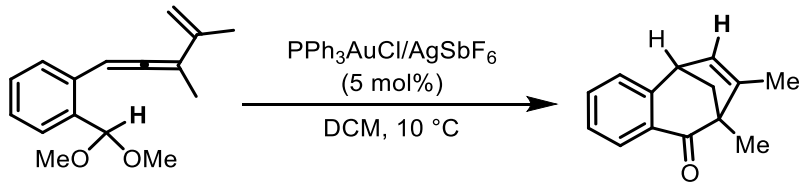
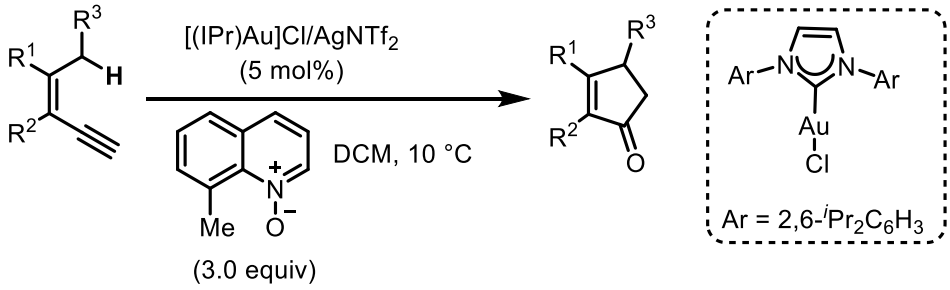
In 2008, Liu *et. al*. reported a cationic gold-catalyzed stereoselective cycloisomerization reaction of allenene-acetal providing a powerful protocol for the synthesis of bicyclo[3.2.1]oct-6-en-2-one that was the key intermediate for construction of bioactive (-)-cytisine (Scheme I.29).[120]



Scheme I.29. Gold(I)-catalyzed cycloisomerization/1,5-H shift of allenene-acetals.

Later Liu *et. al*. reported a gold(I)-catalyzed *O*-atom transfer/1,5-H shift of *cis*-substituted 3-en-1-ynes in the presence of *N*-oxides. The consumption of starting material was totally observed in the combination of IPrAuCl and $AgNTf_2$ (Scheme I.30).[121]



Scheme I.30. Gold(I)-catalyzed *O*-atom transfer/1,5-H shift of *cis*-substituted 3-en-1-ynes.

Similarly, Zhang and co-workers also reported a similar intramolecular cyclization reaction using amine *N*-oxides bearing an *N*-methylene group and a terminal alkyne moiety.[122] In 2010, the same group documented a gold(I)-catalyzed redox neutral $C_{sp}{}^3$-H bond functionalization for tandem construction of furan-fused azepines in good yields (Scheme I.31).[123] Additionally, they described the enantioselective synthesis of furan-fused azepines using chiral phosphine ligand in the presence of gold catalyst. Another same type of reaction was observed when oxophilic $Sc(OTf)_3$ was used.[124]

120. Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**. *130*, 16488-16489.

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122. Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394-8395.

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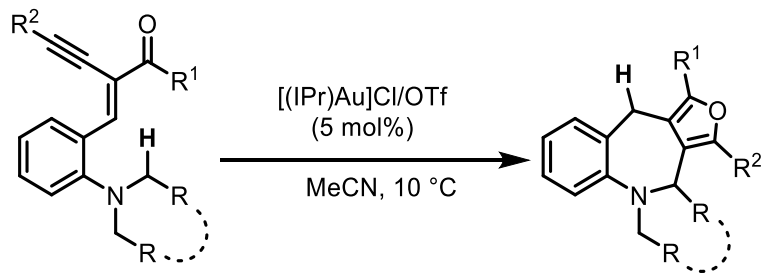
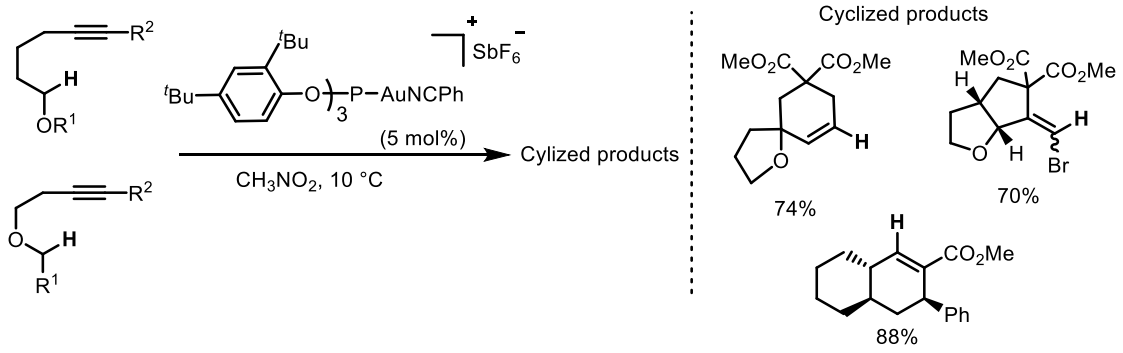
124. Zhou, G.; Liu, F.; Zhang, J. *Chem.–Eur. J.* **2011**, *17*, 3101-3104



Scheme I.31. Gold(I)-catalyzed cycloisomerization/1,5-H shift for furan-fused azepines.

In 2010, Gagosz *et. al*. reported a homogeneous gold(I)-catalyzed cycloisomerization reaction through hydroalkylation of alkynyl ethers to produce a range of structurally complex spiro or fused dihydrofurans and dihydropyrans via a 1,5-hydride shift/cyclization sequence (Scheme I.32). [125]



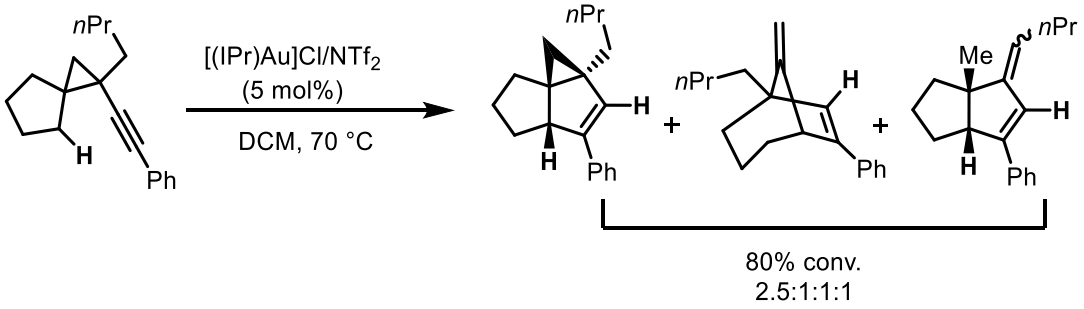
Scheme I.32. Gold(I)-catalyzed 1,5-H shift/cycloisomerization of alkynyl-ethers

The authors proposed that 6-*exo* activation of alkynyl-ethers by gold(I) catalyst, promoted a 1,5-hydride shift from the C_{sp}^3-H bond (adjacent to oxygen atom) to the alkyne. Based on deuterium-labeling study, the 1,6-hydride shift mechanism for the formation of six membered cyclic products was excluded. After that Gagosz and co-workers developed gold(I)-catalyzed hydride shift model to allenes and subsequent cyclization sequence.[126]

125. Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543-3552.

126. Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133*, 7696-7699.

In 2012, Ballesteros *et. al*. discovered an unprecedented gold(I)-catalyzed 1,5-hydride shift process from an unreactive methylene C-H bonds to the alkyne, leading to the subsequent selective cyclization (Scheme I.33).[127]



Scheme I.33. Gold(I)-catalyzed 1,5-H shift/cycloisomerization facilitated by alkylspirocyclopropanes.

The restricted geometry in the starting material may facilitate the 1,5-hydride shift for the gold(I) alkyne activation. The products were controlled under microwave irradiation by changing the gold-complex or reaction temperature. Also, the C_{sp}^3–H bond functionalization induced by gold(I)–carbene and gold-vinylidene have been reported in the recent years. Metal-carbenoid shows a green and powerful tool to construct new C-C bonds.[128] In 2005, Nolan and co-workers developed the first gold catalyzed carbene-transfer[129] reactions from ethyl diazoacetate (EDA).[130] Cyclopropanation of olefins and insertion of the carbene units into N-H, O-H and C_{sp}^2-H bonds were achieved. Then gold(I)-catalyzed carbene insertion into C_{sp}^3–H bonds and aromatic C_{sp}^2-H bonds[131] with other C_{sp}^3-H bonds, which remains unreacted were developed.

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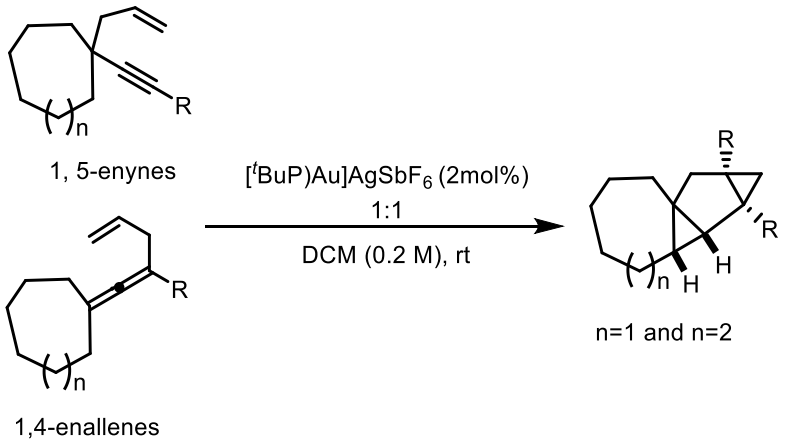
130. Fructos, M. R.; de Fremont, P.; Nolan, S. P.; Diaz-Requejo, M. M.; Perez, P. J. *Organometallics*, **2006**, *25*, 2237-2241.

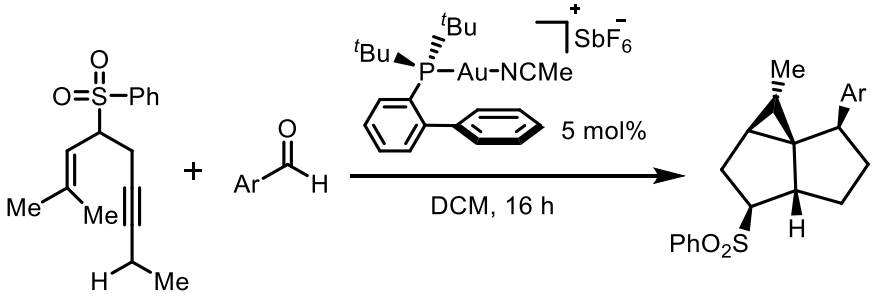
131. I. Rivilla, B. P. Gomez-Emeterio, M. R. Fructos, M. M. Diaz- Requejo and P. J. Perez, *Organometallics*, **2011**, *30*, 2855-2860

The cycloisomerization of 1,5-enynes terminated by C_{sp}^3- H bond insertion into the gold-carbene intermediate was developed by Toste *et. al*.[132] for the construction of tetracyclododecane and tetracyclotridecane derivatives (Scheme I.34).



Scheme I.34. Gold(I)-catalyzed cycloisomerization/C-H insertion reaction of 1,5-enynes and 1,4-enallenes.

In the same year Malacria *et. al*. also reported a gold(I)-catalyzed cycloisomerization of 1,5-enynes under room temperature.[133] Echavaren *et. al.* reported cycloisomerization/C_{sp}^3-H insertion reaction while studying gold-catalyzed cycloaddition reactions of 1,5- and 1,6-enynes with carbonyl compounds (Scheme I.35).[134]



Scheme I.35. Gold(I)-catalyzed cycloisomerization/C-H insertion reaction of 1,5- enynes with aldehyde.

132. Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809-2811.

133. Lemiere, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L; Malacria, M. *J. Am. Chem. Soc.*, **2009**, *131*, 2993-3006

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CHAPTER I

I(III)-mediated synthesis of 2-aryl-4-aryloxyquinolines via direct C_{sp^2}-O bond formation.

Chapter I

Introduction.

Heterocyclic molecules are ubiquitous in pharmaceutics and other biologically active molecules.[135] The quinoline nucleus is an important fragment for the human life.[136] Quinolines and their derivatives are present in a wide range of pharmaceuticals and natural products with unique biological activities and have received considerable attention from the organic and medicinal chemistry community.[137] Relevant biological activities like antimalarial,[138] antibacterial,[139] antiparasitary,[140] antifungal,[141] antiinflammatory,[142] analgesic,[143] cardiovascular[144] and hypoglycemic[145] among the most important have been described. It is ubiquitous in nature and usually sought after in medicinal chemistry[146] and organometallic chemistry[147] among other relevant areas. Specifically, 2-aryl-4-aryloxy functionalized quinolines represent a tremendously important core in clinical and medicinal research.[148]

135. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257.
136. Angali, P. D.; Singh, D. *IJPSR*. **2016**, 7, 1-13.
137. (a) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH; Weinhaim, 2012. (b) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A. E., Katrizky, A. R., Rees, C. W., Scrivem, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 5, p 245. (c) Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 166. (d) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488. (e) Gorka, A. P.; de Dios, A.; Roepe, P. D. *J. Med. Chem*. **2013**, *56*, 5231.
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139. Ma, X.; Zhou, W.; Brun, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 986-989.
140. Rossiter, S. Peron, S. J.; Whitfield, P. J.; Jones, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4806-4808.
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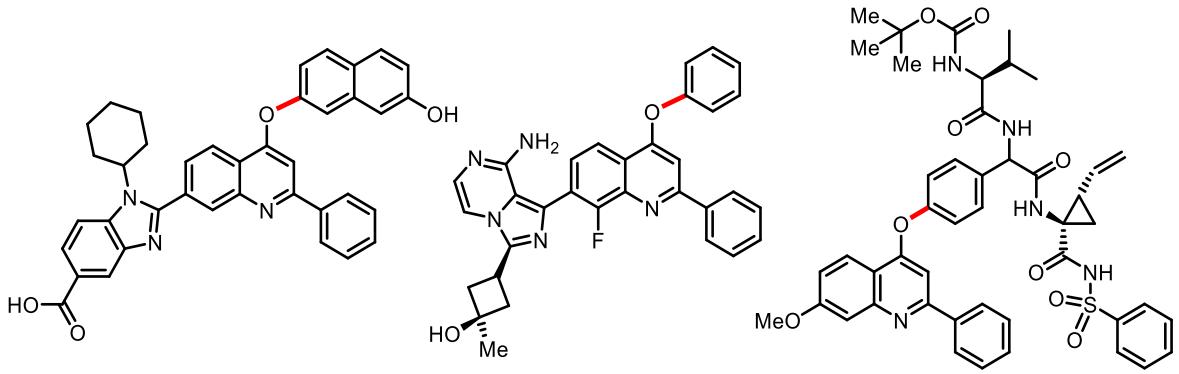
144. Hu, B.; Jetter, J.; Kaufman, D. et al. *Bioorg. Med. Chem*. **2007**, *15*, 3321-3333.
145. See ref. 8
146. Evans, J. F.; Leveille, C.; Mancini, J. A. et al. *Mol. Pharmaceutics*. **1991**, *40*, 22-27.
147. Youliang, W.; Zhitong, Z.; Liming, Z. *J. Am. Chem. Soc.* **2015**, *137*, 5316-5319.
148. Örtqvist, P.; Peterson, S. D.; Åkerblom, E. et al. *Bioorg. Med. Chem.* **2007**, *15*, 1448-1474.

Essentially, the recent trends about the anti-diabetic,[149] anti-cancer[150] and anti-viral[151] investigation points towards a combined synthetic and computational calculations strategy. In such a way is possible to find easier a properly drug for a plausible treatment in the short- or medium-term. In this sense, the 2-aryl-4-aryloxyquinoline moiety has been widely used (Figure. 1.1).



Antiviral against *Flaviviridae* family

Receptor inhibitor on Insulin-like growth factor-1

P2 scaffold in hepatitis C NS3 protease inhibitor

Figure 1.1. Representative anti-diabetic and anti-viral developed drugs containing the 2-aryl-4-aryloxyquinoline structure.

Representative methods to synthesize 2-aryl-4-aryloxyquinolines involve the starting synthesis of 2-aryl-4-quinolones followed by the change of carbonyl group for the corresponding chlorine or fluorine. Afterwards, a direct nucleophilic aromatic substitution with a naphthol derivative in basic media affords the incorporation of the of the desired C-O bond in the aryloxy group. This approach is a two-step procedure.[152] Described protocols for C-O bond formation in aryl derivatives, usually imply the use of Cu-[153] or Pd-[154] catalyzed cross-coupling reactions. These procedures commonly require costly ligands and are often low yielding or not tolerant in presence of heterocyclic groups. Additionally, they can contaminate the final compounds.

149. Jin, M.; Petronella, B. A.; Cooke, A. et al. *ACS. Med. Chem. Lett.* **2013**, *4*, 627-631.

150. Marganakop, S. B.; Kamble, R. R.; Taj, T.; Kariduraganvar, M. Y. *Med. Chem. Res.* **2012**, *21*, 185 191.

151. Massari, S.; Daelemans, D.; Manfroni, G. et al. *Bioorg. Med. Chem.* **2009**, *17*, 667-674.

152. (a) Andersen, K. E.; Lundt, B. F.; Jøegensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1996**, *31*, 417-425 (b) Cope, H.; Mutter, R.; Heal, W. et al. *Eur. J. Med. Chem.* **2006**, *41*, 1124-1143; (c) Hoekstra WJ, Paterl HS, Liang X, et al. *J. Med. Chem.* **2005**, *48*, 2243-2247.

153. D'Angelo, N. D.; Peterson, J. J.; Booker, S. J. et al. *Tetrahedron Lett.* **2006**, *47*, 5045-5048.

154. Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321-4326.

Recently hypervalent λ^3-iodane[155] derivatives have emerged as an excellent alternative in transition metal-free reactions. Specifically, the Olofsson method[156] for the C-O bond formation by using diaryliodonium salts is efficient, mild and shows broad toleration of functional groups, including heterocyclic systems. In this regard during our quest towards the total synthesis of the naturally occurring graveoline from *Rutta sp.,* we needed the methylation at 4-position in the 2-phenyl-4-quinolone.

We questioned ourselves about the use of some other groups like an aryl to be attached in the oxygen of the quinolone for synthesizing analogues of this natural compound. We found in the diaryliodonium chemistry an excellent, direct, and non-toxic tool for this transformation. It is important to mention that during the experimental course of our work, Karade[157] and Kumar[158] reported a closely related idea. Karade described the direct arylation of 4-aryl-6- methyl-pyrimidine-2(1*H*)-one derivatives. On the other hand, Kumar prepared in one-pot procedure 2- and 4-aryloxyquinolines based on a microwave assisted *O*-arylation of quinolones.

While various diaryliodonium salts were investigated in the preparation of 4-aryloxyquinolines, the synthesis of 2-aryl-4-aryloxyquinolines was limited to one example. Considering the importance of such framework in bioactive compounds, we described herein an easy, mild, and efficient procedure for synthesizing in one pot 2-aryl-4- aryloxyquinolines starting from the corresponding functionalized 4-quinolones by using conventional heating and non-symmetrical iodonium salts.

155. Zhdankin, V. *ARKIVOC*. **2009**, i, 1-62.

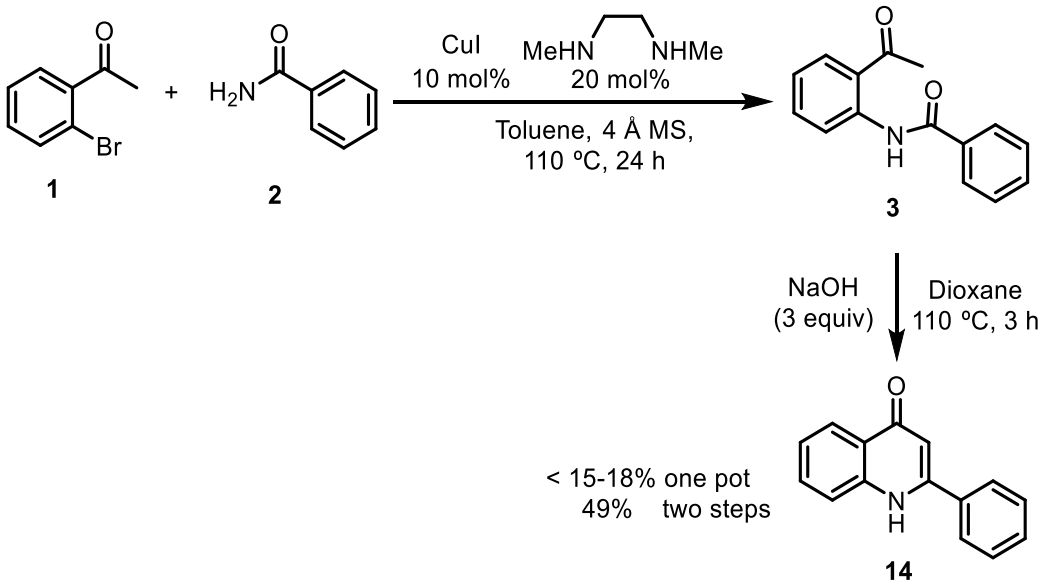
156. (a) Jalalian, N.; Ishikawa, E. E.; Sila, Jr. L. F.; Olofsson, B. *Org. Lett*. **2011**, *13*, 1552-1555; (b) Tolnai, G. L.; Nilsson, U. J.; Olofsson, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 11226-11230.

157. Thorat, P. B.; Waghmode, N. A.; Karade, N. N. *Tetrahedron Lett*. **2014**, *55*, 5718-5721.

158. Mehara, M. K.; Tantak, M. P.; Kumar, I.; Kumar, D. *Synlett*. **2016**, *27*, 604-610.

Results and discussion.

We started with the synthesis of 2-aryl-4-quinolones via a one-pot Buchwald procedure. Initially we used the same amount of CuI (10 mol%) and DMEDA (20 mol%) used in this procedure to give *N*-ketoarylamides followed by cyclization to afford 2-arylquinoline. But the poor 15-18% yield for one-pot reaction was obtained (Scheme 1.1).[159]



Scheme 1.1. Synthesis of 2-aryl-4-quinolones by using the Buchwald procedure.

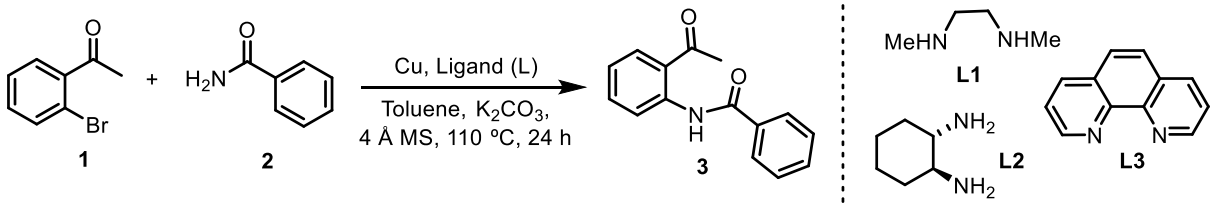
However, after several attempts we could not reproduce the methodology, obtaining only poor yields in the C-N coupling step.

159. See ref. 12.

Optimization of the C-N coupling.

Then we decided to optimize this sequence starting with the C-N coupling to develop a robust and general procedure (Table 1.1).

Table 1.1. Optimization of the C-N coupling to get acetylphenylbenzamide **3.**



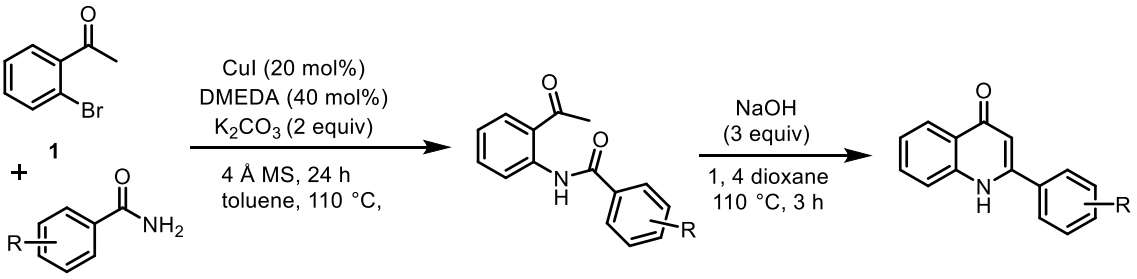
Entry	$PhCONH_2$ (equiv)	Cu (mol%)	L (mol%)	Yield of 3 (%)[a]
1	1.2	CuI (10)	L1 (20)	37
2	1.2	CuI (20)	L1 (40)	61
3	1.2	CuI (40)	L1 (80)	45
4	1.5	CuI (20)	L1 (40)	50
5	***2.0***	***CuI (20)***	***L1 (40)***	***67***
6	2.5	CuI (20)	L1 (40)	75
7	2.0	CuI (20)	L3 (40)	5[b]
8	2.0	CuI (20)	L2 (40)	< 5[b]
9	2.0	CuBr (20)	L1 (40)	37[b]
10	2.0	$Cu(OAc)_2$ (20)	L1 (40)	60[b]
11	2.0	$Cu(OAc)_2$ (20)	L3 (40)	13[b]

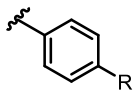
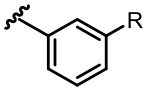
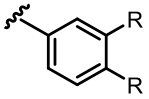
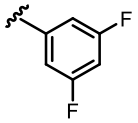
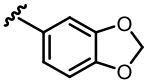
[a]All of the reactions were carried out using benzamide (1.0 equiv), K_2CO_3 (2 equiv) in toluene (0.3 M). [b]Isolated yields. [c]The yields were determined using anisole as internal standard.

The described conditions[12] gave low to moderate yields (37– 61%) even changing the amount of ligand and copper (entries **1–3**). Keeping 20 mol% of copper iodide and 40 mol% of DMEDA but increasing the equivalents of benzamide (1.5–2.5) gave rise to significantly better yields (50–75%) (entries **4–6**). Some other ligands like *o*-phenathroline, *trans*-1,2-dicyclohexylamine and different copper sources did not produce higher yields (entries **7–11**). The optimized conditions for this cross-coupling reaction are described in entry **5**. Even though entry **6** shows a slightly better yield, this required a big amount of benzamide. With the optimized conditions in hand, we were ready to prepare the series of 2-aryl-4-quinolones (Table 1.2).

Synthesis of 2-aryl-4-quinolones.

Table 1.2. Synthesis of 2-aryl-4-quinolones under optimized conditions for the C-N coupling reaction.



Structure	Entry	3-13[a] (R)	14-24[a] (R)
	**1**	**3**, 67% (-H)	**14**, 88%
	2	**4,** 69% (-Me)	**15**, 93%
	3	**5**, 70% (-OMe)	**16**, 96%
	4	**6**, 62% (-Cl)	**17**, 90%
	5	**7**, 65% (-F)	**18**, 93%
	**6**	**8**, 70% (-Cl)	**19**, 85%
	7	**9**, 68% (-CF_3)	**20**, 90%
	**8**	**10**, 34% (-OMe)	**21**, 91%
	9	**11**, 69% (-Cl)	**22**, 93%
	**10**	**12**, 72%	**23**, 87%
	**12**	**13**, 44%	**24**, 91%

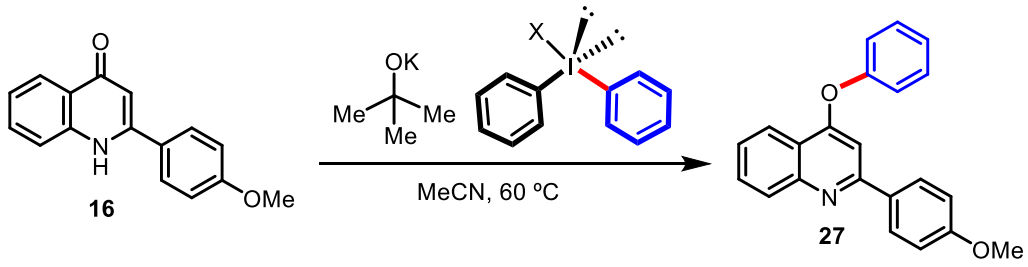
[a]Isolated yields.

Several 2-aryl-4-quinolones were synthesized in excellent yields (87–96%) with different electron donating and electron-withdrawing groups at the 2-aryl fragment. Thus, electron-donor (Entries **2**–**3**, **8** and **12**), electron attractor (Entries **4**–**7**, and **9**–**10**) as well as electron-neutral (Entry **1**) substituents were incorporated. We considered important the former optimization, which was carried out. This in the context to describe a complete, robust, and reproducible procedure for the synthesis of highly functionalized 2-aryl-4-aryloxyquinolines starting from simple and/or commercial starting materials. At this point we were ready to test our hypothesis. Then it was

decided to optimize the direct *O*-arylation in **16** as model. The use of acetonitrile and potassium tert-butoxide were the starting conditions based upon previous reports[160] (Table 1.3).

Optimization of the reaction conditions for the synthesis of 2-aryl-4-aryloxyquinolines.

Table 1.3. Optimization of the direct C_{sp}^2-O bond formation in the metal-free one-pot synthesis of 2-aryl-4-aryloxyquinolines.



Entry	^{t}BuOK (equiv)	X$^{\ominus}$ (equiv)	Yield %[a]
1	1.2	$^{\ominus}PF_6$ (1.2)	60
2	1.2	$^{\ominus}$OTf (1.2)	72
3	1.2	$^{\ominus}$Cl (1.2)	65
4	1.2	$^{\ominus}NO_3$ (1.2)	69
5	1.2	$^{\ominus}$OTf (1.5)	77
6	*1.2*	$^{\ominus}$*OTf (2.0)*	*80*
7	1.2	$^{\ominus}NO_3$ (1.5)	72
8	1.2	$^{\ominus}NO_3$ (1.8)	76
9	1.2	$^{\ominus}NO_3$ (2.0)	78
10	***1.5***	$^{\ominus}$***NO$_3$ (2.0)***	***85***[b]

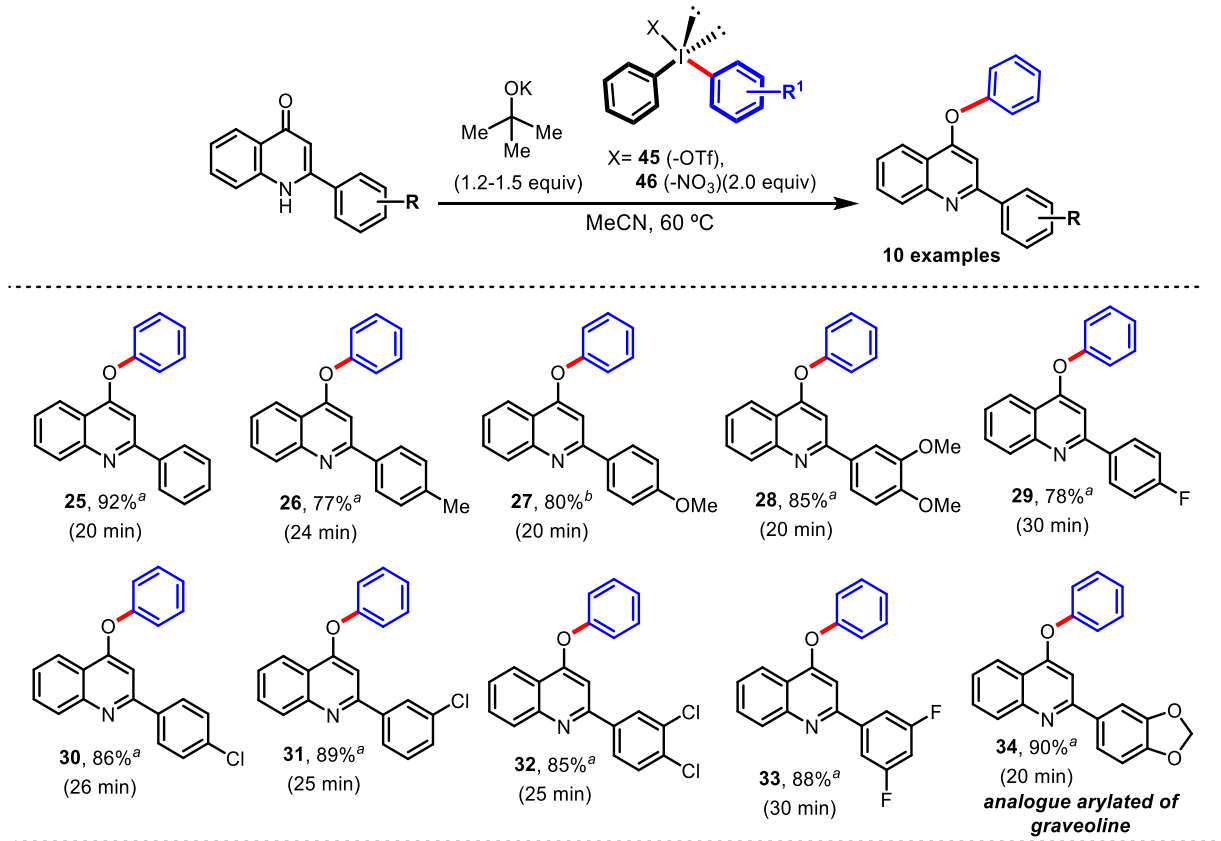
[a]Isolated yields. [b]Complicate chromatographic purification.

Also fixed the reaction temperature at 60 ˚C was crucial to get shorter reaction times. Usually overnight period was necessary to complete the starting material at 40 ˚C. In the initial screening it was considered the use of hexafluorophosphate, triflate, chlorine and nitrate iodonium salts maintaining 1.2 equiv of base (Entries **1**–**4**). All entries yielded good results, highlighting triflate 72% (entry **2**) and nitrate 69% (entry **4**) as the best anions. Then, we focused our attention to optimize the reaction using these two salts. On the treatment with 1.2–1.5 equiv of triflate salt the yield increases from 77% until 80% (Entries **5** and **6**). Regarding to the nitrate, a slightly bigger

160. Zhdankin, V.; Stang, P. J. *Chem Rev.* **2002**, *102*, 2523–2584.

amount of salt (1.5–2 equiv) was necessary. Thus with 1.5 equiv, 72% of yield was observed (Entry **7**), and with 1.8 and 2.0 equiv (Entries **8** and **9**) 76% and 78%, respectively, were obtained. Finally, in the increase to 1.5 equiv of base, we found an excellent 85% of yield. In this way, the entries **6** and **10** were the best conditions and they validated our hypothesis. With optimal conditions for the direct C_{sp}^2-O bond formation, the scope in the 1,4-quinolone was explored with **14-24** as starting materials (Scheme 1.2). The commercially available diaryliodonium salts were used to see the scope of the reaction.

Substrate scope of the developed methodology

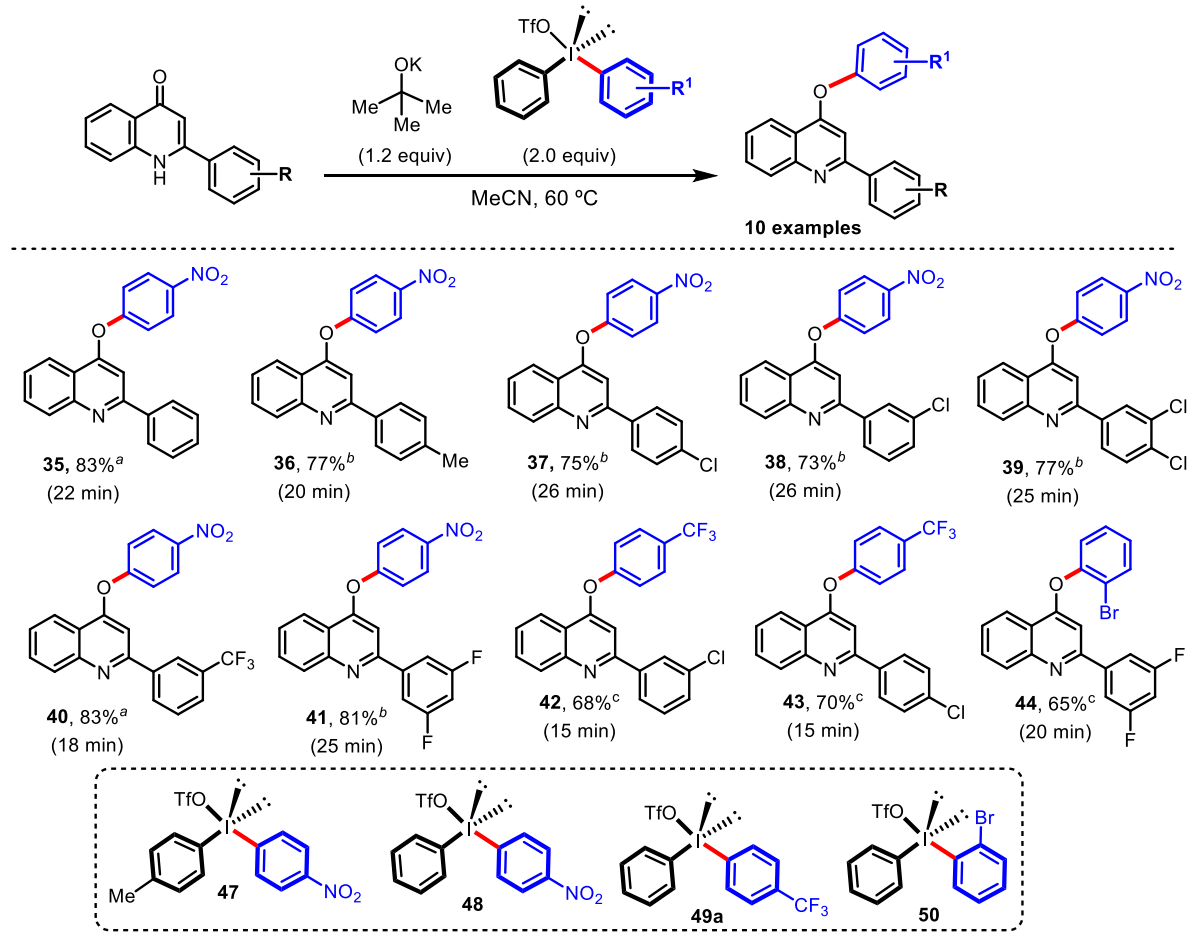


[a]Ph_2INO_3 (2 equiv), ^{t}BuOK (1.5 equiv). [b]Ph_2IOTf (2 equiv), ^{t}BuOK (1.2 equiv).

Scheme 1.2. Scope at the 2-arylquinolone for the direct C-O arylation by using iodonium salts.

All the reactions were carried out by using conventional heating under very mild temperature conditions. Also, very short reaction times (20–30 min) were observed to complete the starting material. Additionally, good to excellent yields (77–92%) were obtained after chromatography purification. This procedure tolerates electron-neutral (**25**), electron-rich (**26-28, 34**) and electron

poor (**29–33**) functional groups at the 2-aryl fragment of the quinolone. To complete the scope of the developed procedure, we decided to test different iodonium salts[161] with the 2-arylquinolones **14-24** (Scheme 1.3).



[a]Iodonium salt **47** was used. [b]Iodonium salt **48** was used. [c]Iodonium salts **49-50** was used.

Scheme 1.3. Scope at the iodonium salt for the direct C-O arylation in 2-arylquinolones

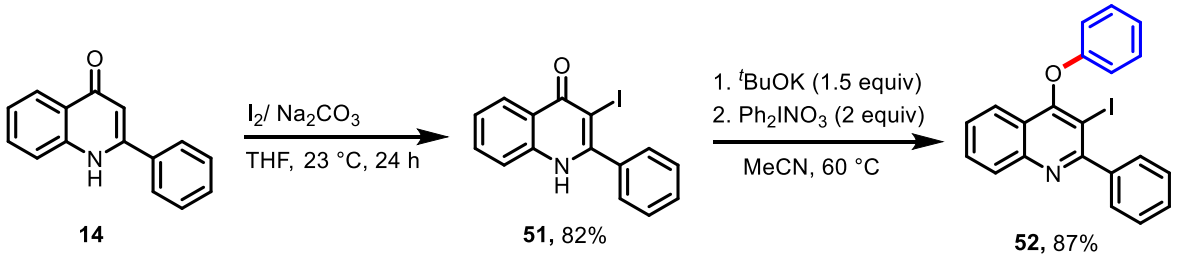
Iodonium salts **47-50** were synthesized and used. As shown for the phenyl group (Scheme 1.3), p-nitrophenyl, p-trifluorophenyl and 2-bromophenyl groups were transferred directly to electroneutral (**35**, 83%), electron-rich (**36**, 77%) and electron-poor (**37-44**, 65–83%) 2-aryl-4-quinolones (Scheme 1.4). The yields of the 4- aryloxyquinolines obtained were moderate to good. In this part, it is of crucial importance to mention three points: 1) The procedure in general is totally regioselective, since only O-arylation was observed at least by the NMR detection limit. 2) The

161. Bielawski, M. Zhu, M. Olofsson, B. *Adv Synth Catal*. **2007**, *349*, 2610-2618.

protocol is totally chemoselective the electron-poor aryl is exclusively transferred. This result was in the same for all the examples (Scheme 1.4) and agrees with the DiMagno[162,163], observation. Additionally, our procedure avoids the use of symmetrical iodonium the use of symmetrical iodonium salts, which is a strong limitation in previous reports.[24] This implies the use of pre-functionalized substrates to access into this class of symmetric salts and is wasted the half of such functionalized molecule in the reaction process. 3) The procedure tolerates important substituents like chlorine, fluorine or trifluoromethyl which are relevant in medicinal chemistry. In fact, we focused on the application of the developed procedure to the synthesis of these potentially biological active of derivatives.

Application: synthesis of iodinated quinoline.

To test the application of the synthesized compounds by our procedure, we decide to carry out the following short sequence of reactions to prepare the iodinated quinoline **52** as potential starting building block in different organic reactions (Scheme 1.4).



Scheme 1.4. Application of the developed procedure to the synthesis of quinoline.

The quinolone **14** was iodinated to yield **51**[164] in good 82% of yield. This compound was arylated under our optimized conditions giving rise to the quinoline **52** in excellent 87% of yield. The presence of a bulky iodine close to the arylation center did not affect the reaction

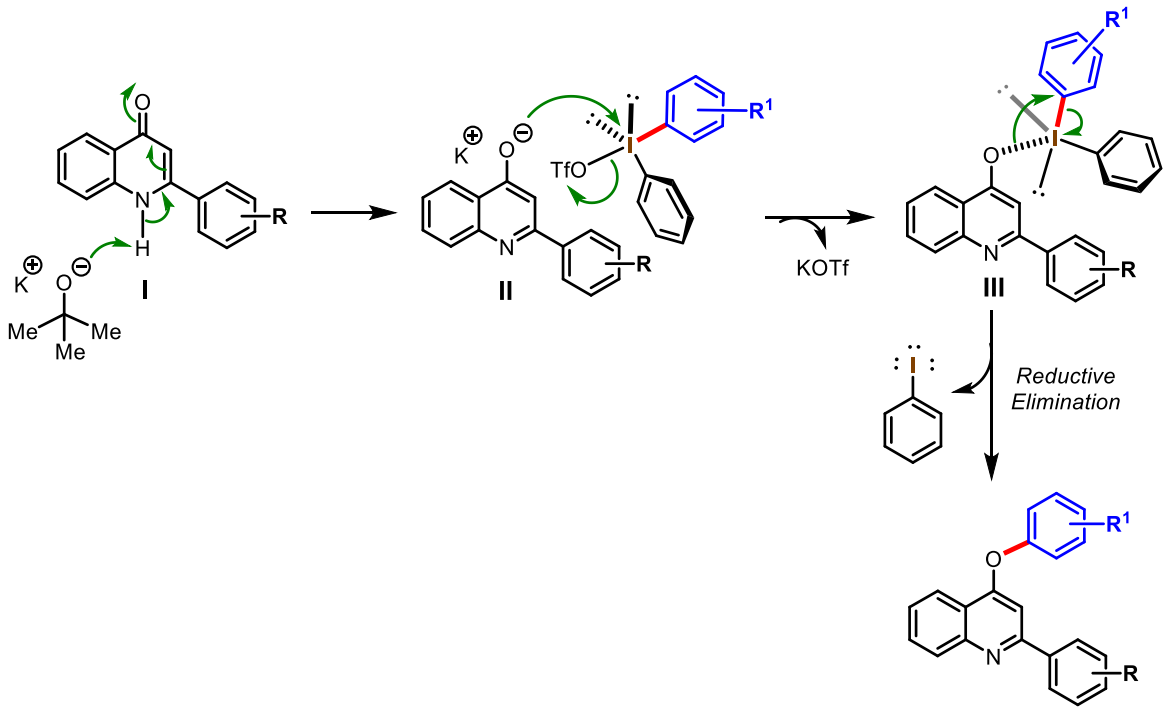
162. Wang, B. Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4079–4083.

163. Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Himo, F.; Olofsson, B. *Chem. Eur. J.* **2013**,*19*, 10334-10342.

164. Mphahlele, M. J. Nwamadi, M. S.; Mabeta, P. *J. Heterocycl. Chem.* **2006**, 46, 255-260.

Proposed reaction mechanism of C-O bond formation.

Finally, according to the precedents of the iodonium salts chemistry,[21, 165, 166] it is plausible to propose the following mechanism of reaction (Scheme 1.5).



Scheme 1.5. Proposed mechanism of reaction for the direct C-O arylation of 2-aryl-4-quinolones by using iodonium salts.

The mechanism starts with the deprotonation of quinolone **I** by potassium tert-butoxide to generate **II**. This bidentade anion regioselectively attacks at the electrophilic iodine center in the salt giving rise to **III**. The evolution of this intermediate via reductive elimination yields compounds **25-44** and **52** with a concomitant releasing of iodobenzene.

165. Yoshimura A, Zhdankin V. *Chem. Rev*. **2016**, *116*, 3328-3435.

166. Merrit, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052-9070.

Total synthesis of graveoline.

Polysubstituted quinoline is an important core in many natural products and agrochemicals.[167] They show several activities such as antimalarial, schistosomiasis and antifungal.[168] Among these, 4-alkoxy quinolines are prevalent pharmacophores (Figure 1.2).

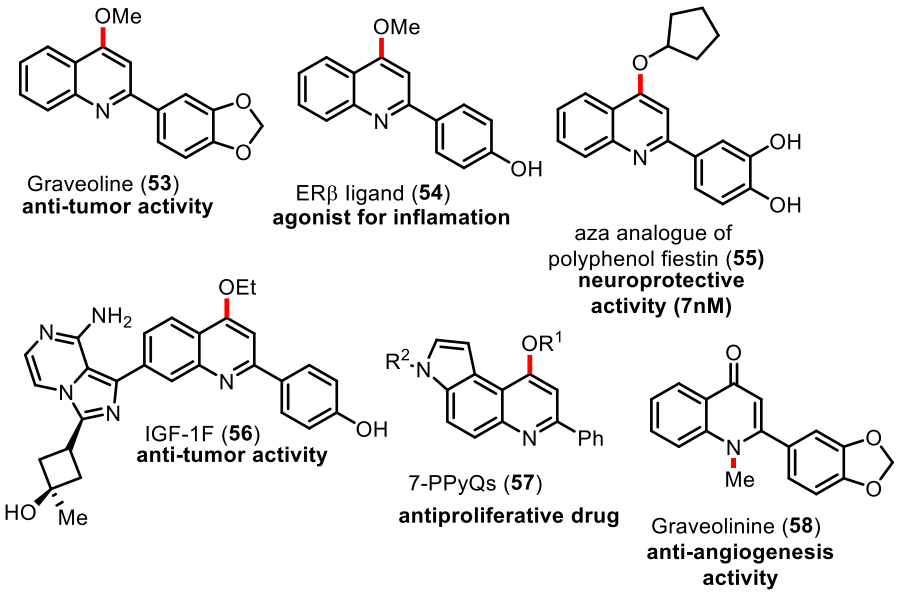


Figure 1.2. Biologically active 4-alkoxyquinoline pharmacophores.

For example, graveoline (**53**) shows antitumor activity, whereas ERβ ligand (**54**) possessing 4-alkoxy quinoline core acts as selective agonist in treating inflammation. On the other hand, quinoline derivative (**55**) is used as a neuroprotective drug, 4-ethoxy quinoline (**56**) shows IGF-1R inhibition activity, and 7-PPyQ (**57**) is an antiproliferative drug. Graveoline (**53**) and Graveolinine (**58**) are alkaloids isolated from biological sources such as *Haplophyllum dubium*, *H. foliosum, H. perforatum, Ruta graveolens*. Rue *(Ruta graveolens)* is a plant native of Balkan Peninsula (Southern Europe) and northern Africa to which many therapeutic properties have been described over the centuries. This is a common plant in southern China, which showed

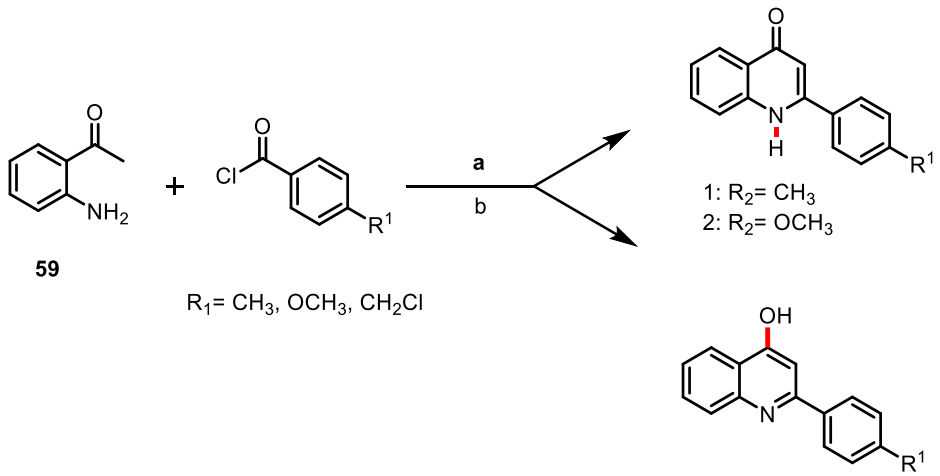
167. (a) Michael, J. P. *Nat. Prod. Rep*. **2007**, *24*, 223. (b) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem*. **2010**, *45*, 3245. (c) Ahmed, N.; Brahmbhatt, K. G.; Sabde, S.; Mitra, D.; Singh, I. P.; Bhutani, K. K. *Bioorg. Med. Chem*. **2010**, *18*, 2872. (d) Musiol, R.; Serda, M.; Bielowka, S. H.; Polanski, *J. Curr. Med. Chem*. **2010**, *17*, 1960. (e) Solomon, V. R.; Lee, H. *Curr. Med. Chem*. **2011**, *18*, 1488. (f) Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tienderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; Alessandro, D. U. *Malar. J*. **2011**, *10*,144.

168. (g) Michael, J. P. *Nat. Prod. Rep*. **2001**, *18*, 543. (h) Chen, Y. J.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem*. **2001**, *44*, 2374. (i) Kalluraya, B.; Sreenivasa, S. *Farmaco*. **1998**, *53*, 399.

comprehensive pharmacological activities such as antibacterial, spasmolytic, anti-tumor.[169] and anti-angiogenesis.[170]

Methodologies to prepare graveoline and graveolinine.

In the recent literature starting from 1-(2-aminophenyl)ethenone with substituted benzoyl chlorides in the presence of strong base ^{t}BuOK Huang *et.al* synthesized graveoline and graveolinine derivatives with evaluation of anti-angiogenesis activity (Scheme 1.6).[36]



Scheme 1.6. Reagents: a) THF, rt; b) ^{t}BuOH/^{t}BuOk.

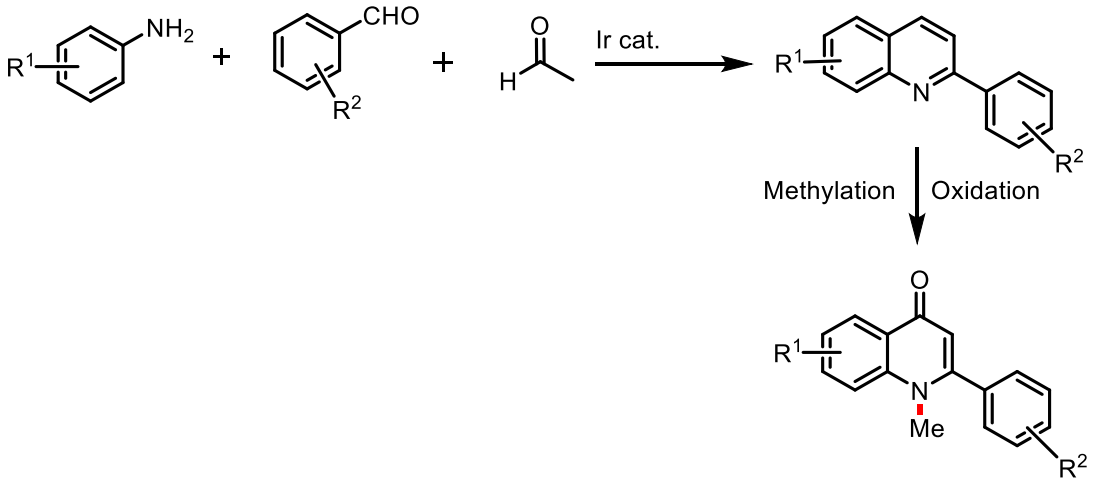
Also, three component iridium catalyzed coupling reaction of an aniline, an aromatic aldehyde and acetaldehyde gave corresponding substituted quinoline and then *N*-Methylation of the quinolines with methyl triflate followed by oxidation with potassium ferricianate gave the graveolinine[171] (Scheme 1.7). Also, an efficient synthesis of the 4*H*-quinolone alkaloid graveoline has been achieved by a route featuring an Pd(II)-catalysed reductive *N*-heterocyclization [CO(3 MPa), $Pd(TMB)_2$, TMPhen, 170 ˚C, 3 h] of 2'-nitrochalcone as a key step. [172]

169. a) Ivanovaa, A.; Mikhovaa, B.; Najdenskib, H.; Tsvetkovab, I.; Kostovaa, I. *Fitoterapia*. **2005**, *76*, 344-347. b) Wu, T.S.; Shi, L.S.; Wang, J.J.; Iou, S.C.; Chang, H.C.; Chen, Y.P.; Kuo, Y.H.; Chang, Y.L.; Teng, C.M. *J. Chin. Chem. Soc*. **2003**, *50*, 171-178. c) Stashenko, E.E.; Acosta, R.; Martinez, J.R. *J. Biochem. Biophys. Methods.* **2000**, *43*, 379-390. d) Olive, A.; Meepagala, K.M.; Wedge, D.E.; Harries, D.; Hale, A.L.; Aliotta, G.; Duke, S. O. *J. Agric. Food Chem.* **2000**, *51*, 890-896.

170. Zeng-Yun, A.; Yi-Yong Yan 1, Peng, D.; Tian-Miao Ou, Jia-Heng Tan, Shi-Liang Huang, Lin-Kun An, Lian-Quan Gu, Zhi-Shu Huang. *Eur. J. Org. Chem.* **2010**, *45*, 3895-3903.

171. Nakajima, T.; Inada, T.; Shimizu, I. *Heterocycles*, 2**006**, *69*, 497 -504.

172. Annunziata, R.; Cenini, S.; Palmisanoc, G.; Tollarib, S. *Synth. Commun*. **1996**. 26, 495-501.

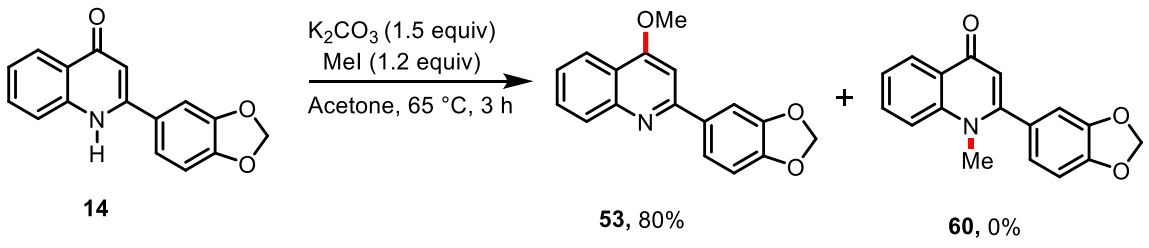


Scheme 1.7. Iridium catalyzed synthesis of graveoline.

While working on synthesis of the natural product graveoline, in 2017 Gharpure *et. al.* published paper on Lewis acid promoted oxonium Ion driven carboamination of alkynes for the synthesis of 4-alkoxy quinolines. This methodology allowed them to synthesize potent drug molecules like graveoline and ERβ ligand.[173] A single step, divergent synthesis of graveoline (**53**), which is shortest and most efficient synthesis reported until date in this paper.

Results and discussion.

Considering the biological importance of the natural products of 4-alkoxy quinoline moiety, the prepared quinolones allowed us to synthesize graveoline and its analogues to carry out biological assays. The synthetic route started with the methylation of compound **14** to afford **53** in 80% of yield. Unfortunately, after several attempts we did not succeed in the preparation of graveolinine **60** (Scheme 1.8).



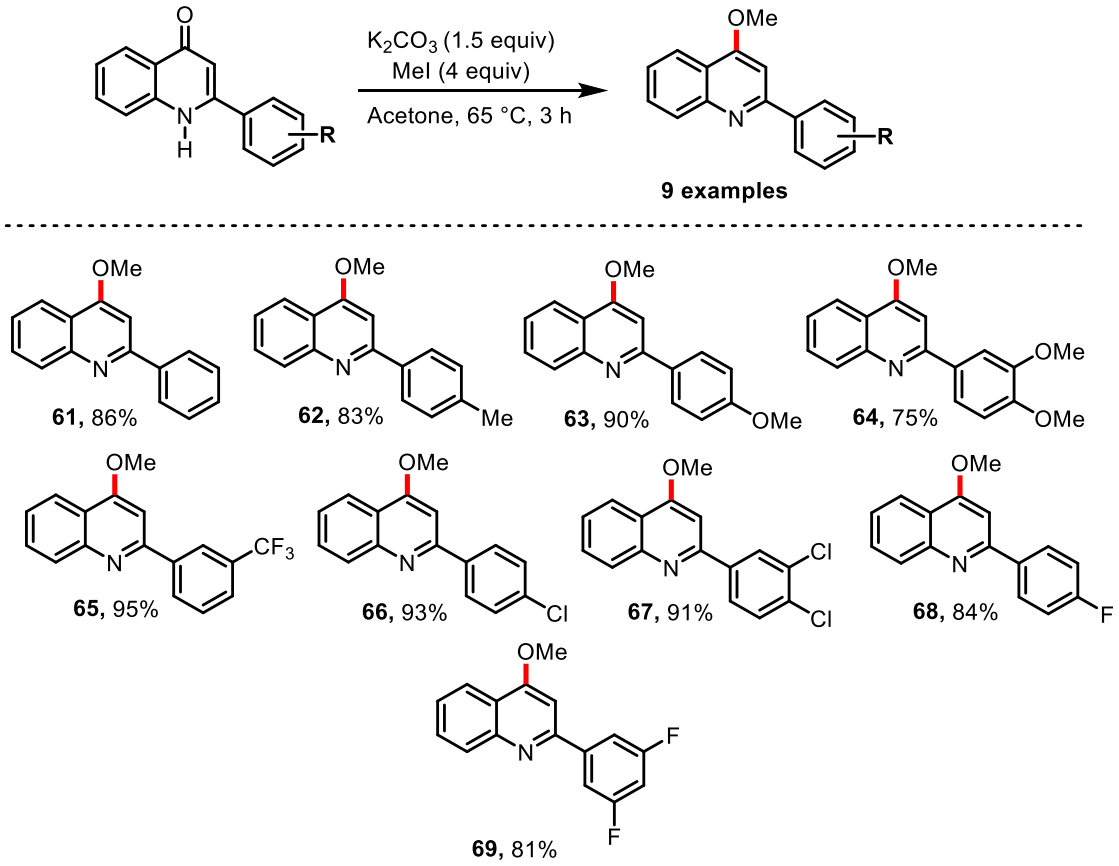
Scheme 1.8. Synthesis of graveoline.

173. Nanda, S. K.; Adate, P. A.; Shelke, Y. G.; Gharpure, S. J. *J. Org. Chem.* **2017**, *82*, 2067-2080.

Because the major product in the methylation reaction of quinolone **14** with different bases tried gave us *o*-arylation instead of *N*-methylation (Scheme 1.8). After that we started to synthesize the different substituted 4-alkoxyquinolines to carry out their biological assays.

Synthesis of 2-aryl-4-methoxyquinolines.

The substituted 2-arylquinolines were used to make 2-aryl-4-methoxyquinolines using the optimized procedure (Scheme 1.9).



Scheme 1.9. Synthesis of 4-methoxy quinoline.

The yields obtained for 2-aryl-4-methoxy quinolines were moderate to good. This procedure tolerates electron-neutral (**61**, 86%), electron rich (**62**-**64**) and electron poor (**65**-**69**) functional groups at the 2-aryl fragment of the quinolone. Also, we observed only *O*-methylated product instead of *N*-methylated 2-arylquinolone**.**

Biological activity of 2-aryl-4-aryloxyquinolines (25, 27-34, 35, 37-42).[174]

Mucormycosis.

The antifungal activity of 2-aryl-4aryloxiquinolines *(***25***,* **27**-**34**, **35**, **37**-**42***)* was evaluated against *M. circinelloides* This is a dimorphic fungus belonging to order mucorales.[175] Mucormycosis, is a serious but rare fungal infection caused by a group of molds called mucormycetes and we refer to a group of mycosis caused by fungi of the order mucorales.These fungi live throughout the environment, particularly in soil and in association with decaying organic matter, such as leaves, compost piles, or rotten wood.[176] The types of fungi that most commonly cause mucormycosis are: *Rhizopus* species, *Mucor* species,*Apophysomyces* species,and *Lichtheimia* (formerly *Absid ia*) species. Mucormycosis most commonly affects the sinuses or the lungs in people who have weakened immune systems. It frequently infects the sinuses, brain, or lungs. While infection of the oral cavity or brain are the most common forms of mucormycosis, the fungus also affects other areas of the body such as the gastrointestinal tract, skin, and other organ systems.

Organisms used.

The strain of *M. circinelloides* R7B (ATCC 90680, auxotrophic strain to leucine derived from strain ATCC 1216b) was used (Roncero et al., 1989), and the strain *M. circinelloides* M5, mutant in the adh1- gene (derived from the wild strain R7B of *Mucor circinelloides*, of spontaneous origin selected in the presence of 0.6% allyl alcohol) (was kindly donated by Dr. Víctor Meza Carmen) (Table 1.4).

Strains	Relevant phenotype
R7B	Aly^S, Leu^-
M5	Aly^R, Leu^-

Table 1.4. Phenotype of the *M. circinelloides* strains.

174. The biological assays or activity was carried out by our collaborator Dr. Rafael Ortiz Alvarado, U. M. S. N. H. Morelia, Michoacán, México.

175. Lubbenhusen, T.L.; Nielsen, J.; McIntyre, M. *J. Appl. Microbiol*. **2003**, 95 1152–1160.

176. Richardson M. *Clin Microbiol Infect.* **2009**, 15, 2-9.

Germination speed.

The process of germination is very important in the virulence of fungi, because this represents the speed to colonize a biological niche. In this case, the speed of germination in the different strains was analyzed, for which the spores were inoculated in liquid YPG medium and subjected to aerobic growth. To observe the germination speed of strains R7B and M5, 25 mL Erlenmeyer flasks were inoculated 500,000 spores per milliliter of YPG culture medium, using a total of 5 mL of medium, then incubated at 28 °C, with constant shaking at 200 rpm. We counted between 100-200 cells at random in the determined times, to determine the percentage of germination of the different strains of *M. circinelloides* (Figure 1.3). We carried out the biological assays of 2-aryl-4-aryloxyquinolines (**25**, **27**-**34**, **35**, **37**-**42**) and found that quinolines **30**, **38**, **34**, **41** and **33** showed the highest biological activity.

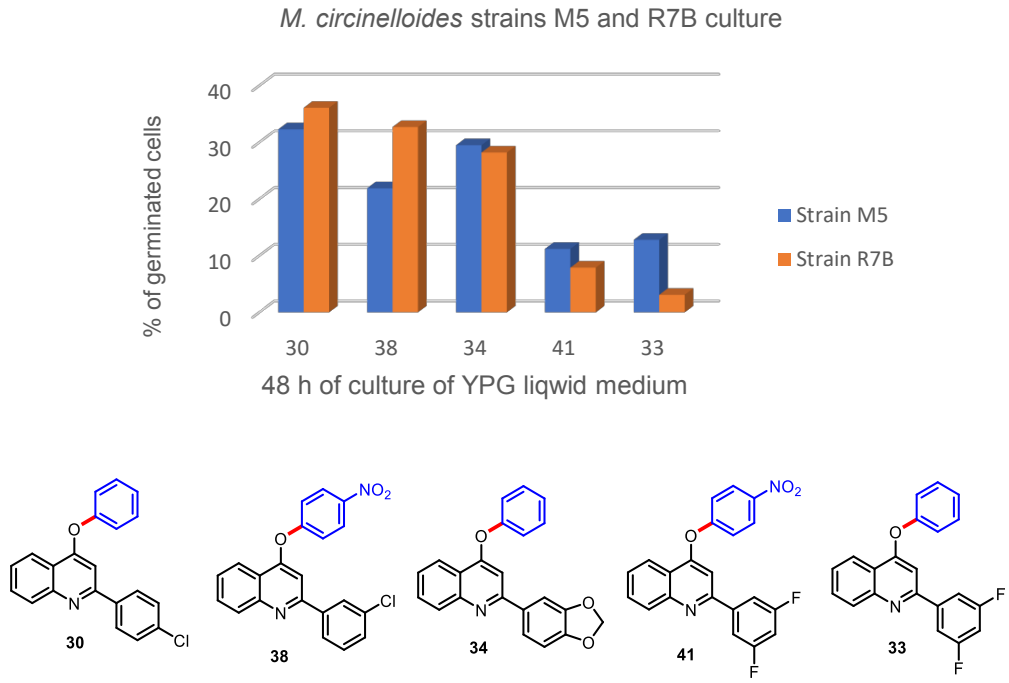


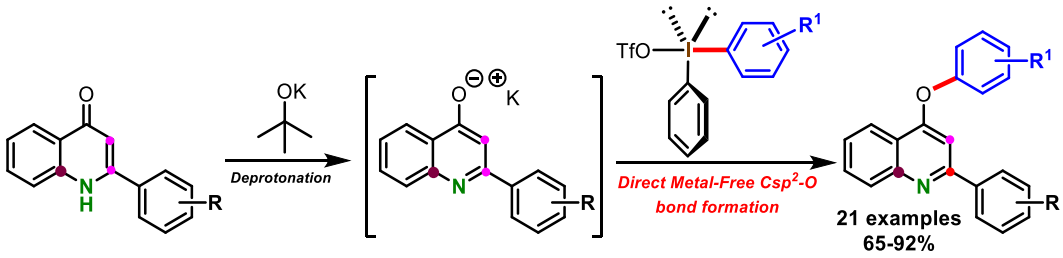
Figure 1.3. Effect of tested molecules on the germination of *M. circinelloides* strain M5 (mutant and deficient in alcohol dehydrogenase adh-) and wild R7B strain of *M. circinelloides* during aerobic germination with YPG culture medium. $5x10^5$ spores were inoculated per milliliter of YPG medium under conditions of constant agitation (125 rpm) at 28 °C.

The total percentage of germination in medium and percentage of differentiation towards yeast or hyphae in aerobic conditions, *Mucor circinelloides* with the wild strain R7B and M5 evaluated, and observation was done after 48 hours of incubation (concentrations of **25**, **27**-**34**, **35**, and **37**-**42** molecules, 100 µg/ml of culture medium). The molecules **30**, **38**, **34**, **41** and **33** gave the best results as compared to other tested 2-aryl-4-arylixyquinolines. The best activity was found for the electron poor molecules containing groups -NO_2 and -F. These results allow us to carry out the assays to determine the IC_{50} for each quinoline molecule. Additionally, it is necessary to determine if the quinolines with the highest activity are fungistatic or fungicides. These studies will be carried out in a future work.

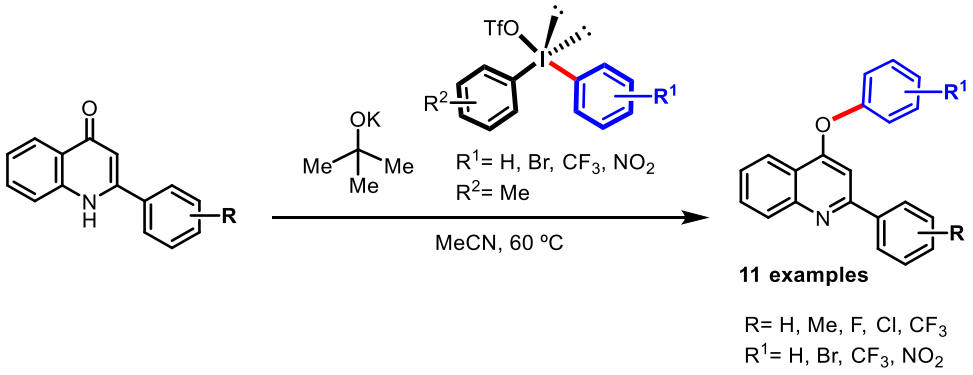
.

Conclusions.

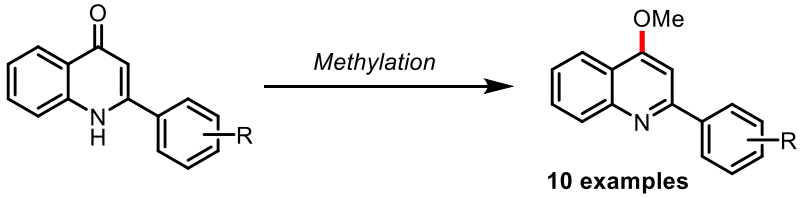
- We developed a mild, efficient, and operationally simple procedure for the direct arylation of 2-aryl-4-quinolones, to produce in one-pot a new C_{sp}^2-O bond under metal- and ligand-free conditions. To the best of our knowledge, this is the first work with a wide application totally directed to the synthesis of functionalized bioactive 2-aryl-4-aryloxyquinoline core, containing groups like -Cl, -F or $–CF_3$ relevant in medicinal chemistry. The procedure was carried out with the use of conventional heating.



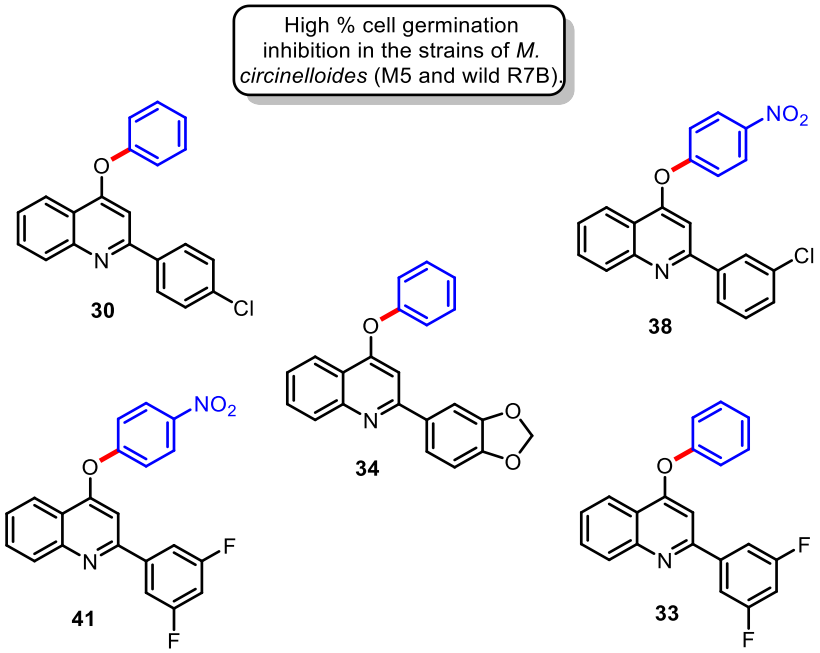
- Our protocol shows totally regio- and chemoselectivity allowing for synthesizing exclusively *O*-arylquinolines by using simple non-symmetrical iodonium salts. This represents a more atom-economical protocol regarding to those previously described, which use symmetrical salts. The procedure has a broad scope and tolerates different functional groups nature.



- The synthesized 2-arylquinolines by our optimized conditions allowed us to prepare biologically important natural compound graveoline and its derivatives.



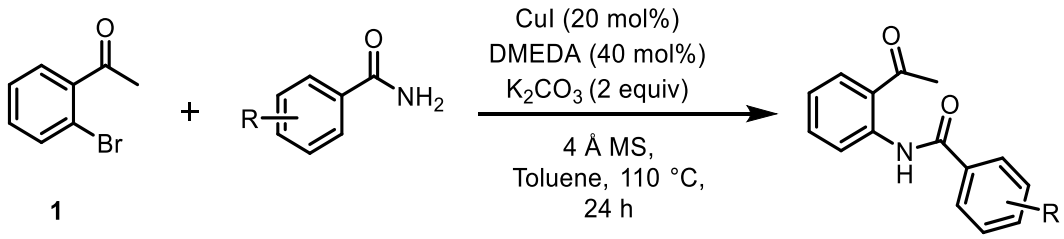
- The biological importance of synthesized 2-aryl-4-aryoxyquinolines were evaluated. The best antifungal activity for the molecules synthesized quinolines **30**, **38**, **34**, **41** and **33** was found for the strains of *M. circinelloides* M5 and wild R7B. Additional experiments are necessary to determine the IC_{50} of these biological active quinolines as well as identify if the observed cell germination inhibition is because of fungicide or fungistatic activity.



Experimental section

Synthesis of *N*-ketoarylamides **(3-13).**

General procedure A.



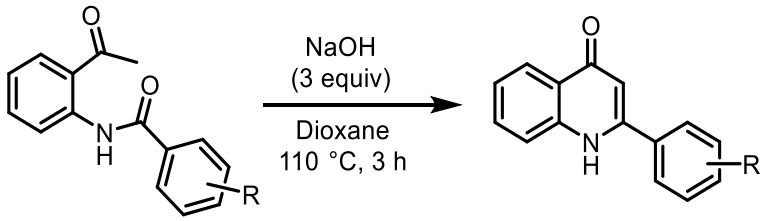
The following compounds were synthesized based upon reported literature procedure[12] under our optimized cross-coupling conditions.

An oven-dried round-bottom flask with a Teflon stir bar was charged with amide (2.0 equiv, 1.00 mmol), CuI (20 mol%, 0.10 mmol), base (2 equiv, 1.00 mmol), and 200 mg activated 4 Å molecular sieves. The roundbottom flask was sealed with a rubber septum, evacuated, and refilled with nitrogen (this sequence was performed three times). Under nitrogen, 2' bromoacetophenone (1.0 equiv, 0.50 mmol), *N*, *N*'- dimethylethylenediamine (40 mol%, 0.2 mmol), and toluene (3 mL) were each added via syringe. The round-bottom flask was then placed in a preheated oil bath at 110 °C. The reaction was heated with stirring for 24 h until TLC showed completion of the reaction. The crude of reaction obtained was cooled to room temperature. Toluene was removed under *vacuo* then water (5 mL) was added to the reaction mixture. The biphasic mixture was extracted with ethyl acetate (3x15 mL). The organic extracts were collected, dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo* to remove solvent. The product was purified by column chromatography on silica gel (100-200 mesh) with EtOAc/hexane system, to afford the corresponding *N*-ketoarylamides.

Synthesis 2-arylquinolin-4(1*H*)-ones **(14-24).**

The compounds were synthesized according to reported literature procedure.[12] ^{13}C NMR was not possible to get due to high insolubility of 2-arylquinolin-4(1*H*)-ones. However full evidence of ^{1}H, IR and HRMS support the authenticity of the molecules.

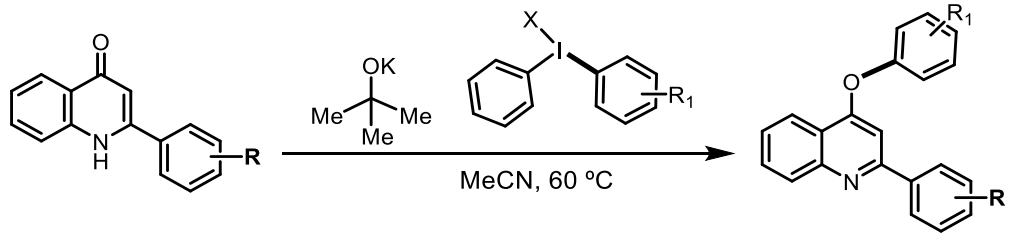
General procedure B.



An oven-dried round-bottom flask with a Teflon stir bar was charged with *N*- ketoarylamide (1.00 equiv) and NaOH (3.00 equiv). Anhydrous 1,4-dioxane (3-5 mL) was added via syringe. The round-bottom flask was then sealed with Teflon septa and the reaction was placed in a preheated oil bath at 110 °C. The reaction mixture was stirred for 2 h. Then it was removed from the oil bath and allowed to reach room temperature. The reaction mixture was then dissolved in ethanol (3 mL) and concentrated *in vacuo* to remove solvent. Next water (10 mL) and hexane (30 mL) were added to the flask and sonicated for two minutes. The biphasic mixture was neutralized to pH ~7 with 1 *M* HCl and saturated $NaHCO_3$ solution. A solid precipitated out of the water layer and the heterogeneous mixture was filtered through a Buchner funnel. The solid powder was rinsed with hexane (30 mL) and water (10 mL). The solid was collected and transferred to a round bottom flask with ethanol and concentrated in vacuo to remove residual solvent to afford 2-arylquinolin-4(1*H*)-ones.

Synthesis of 2-aryl-4-aryloxyquinolines **(25-44).**

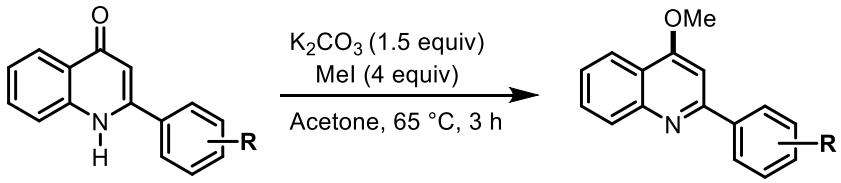
General procedure C.



Under an inert atmosphere in 10 mL round-bottom flask were added 2-Aryl-4-quinolone (1.00 equiv), potassium *tert*-butoxide (1.50 equiv) and acetonitrile (3 mL). The round bottom flask was then placed in a preheated oil bath at 60 °C. After 10 min diaryliodonium salt (2.00 equiv) was added to the reaction mixture. The reaction mixture was continued stirring for 20-30 min until TLC showed completion of the reaction, solvent was removed and then added water (20 mL) to the reaction mixture and it was extracted with ethyl acetate (2×10 mL). The organic phase was separated, washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product thus obtained was purified by silica gel (100–200) column chromatography to afford the pure aryloxyquinoline.

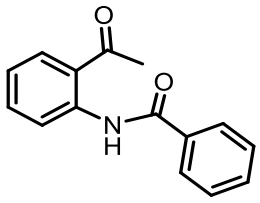
Synthesis of 2-aryl-4-alkoxyquinolines **(61-69).**

General procedure D.



Under an inert atmosphere in 10 mL round-bottom flask were added 2- Aryl-4-quinolone (1.00 equiv), potassium K_2CO_3 (1.5 equiv) and acetone (5 mL). The round-bottom flask was then placed in a preheated oil bath at 65 °C. After 10 min Iodomethane (4 equiv) was added to the reaction mixture. The reaction mixture was continued stirring for 3 h until TLC showed completion of the reaction, solvent was removed and then added water (20 mL) to the reaction mixture and it was extracted with ethyl acetate (2×10 mL). The organic phase was separated, washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product thus obtained was purified by silica gel (100–200) column chromatography to afford the pure 2-aryl-4-alkoxyquinolines.

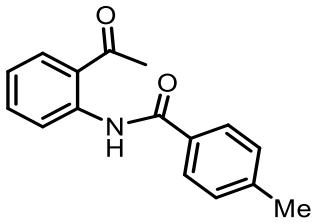
N-(2-acetylphenyl) benzamide **(3).**



This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and benzamide in 67% yield as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.70 (s, 1H), 8.99 (d, *J* = 8.5 Hz, 1H), 8.10-8.04 (m, 1H), 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.65-7.60 (m, 1H), 7.59-7.49 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 2.72 (s, 1H); HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1025; found: 240.1018. Spectral data match with those reported in the literature.[177]

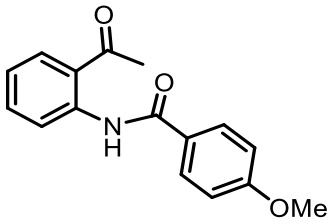
177. Verma, A.; Kumar, S. *Org. Lett*. **2016**, *17*, 4388-4391.

N-(2-acetylphenyl)-4-methylbenzamide **(4).**



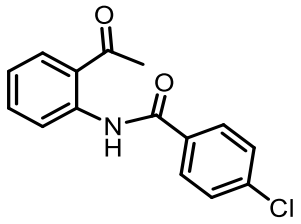
This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 4-methylbenzamide in 69% yield as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.66 (s, 1H), 8.99 (d, *J* = 8.5 Hz, 1H), 7.97 (t, *J* = 6.9 Hz, 3H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.1 Hz, 1H), 2.72 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 166.2, 142.6, 141.7, 135.5, 132.1, 131.9, 129.6, 127.6, 122.4, 122.0, 120.9, 28.7, 21.6; HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$: 254.1181; found: 254.1166. Spectral data match with those reported in the literature.[177]

N-(2-acetylphenyl)-4-methoxybenzamide **(5).**



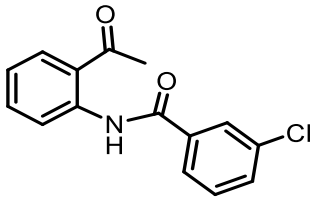
This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 4-metoxylbenzamide in 70% yield as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.64 (s, 1H), 8.98 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 6.8 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 2H), 2.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 165.7, 162.7, 141.8, 135.4, 131.9, 129.5, 127.2, 122.2, 121.9, 120.8, 114.1, 55.5, 28.7; HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_3$ $[M+H]^+$: 270.1130; found: 270.1115. Spectral data match with those reported in the literature.[177]

N-(2-acetylphenyl)-4-chlorobenzamide **(6).**



This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 4-Chlorolbenzamide in 62% yield as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.72 (s, 1H), 8.95 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 2.73 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 165.1, 141.4, 138.5, 135.6, 133.4, 132.0, 129.2, 129.0, 122.8, 122.1, 121.0, 28.7. HRMS (ESI) m/z calcd for $C_{15}H_{13}ClNO_2$ $[M+H]^+$: 274.0635; found: 274.0622. Spectral data match with those reported on the literature.[178]

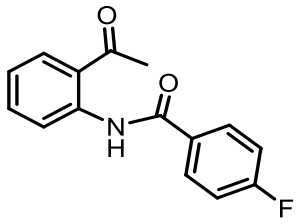
N-(2-acetylphenyl)-3-chlorobenzamide **(11).**



This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 3-Chlorolbenzamide in 62% yield as white solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 12.66 (s, 1H), 8.87 (d, *J* = 8.5 Hz, 1H), 8.00 (s, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 12.2, 5.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 164.8, 141.2, 136.7, 135.6, 135.2, 132.1, 132.0, 130.2, 128.2, 125.3, 122.9, 122.1, 121.0, 28.7. Spectral data match with those reported on the literature.[12]

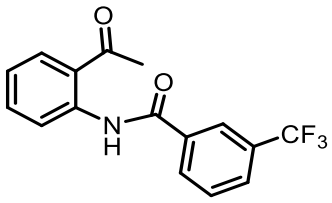
178. A. Ilangovan, G. Satish, Org. Lett. **2013**, *15*, 5726-5729.

N-(2-acetylphenyl)-4-fluorobenzamide **(7).**



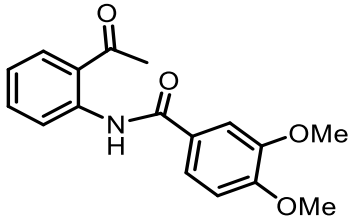
This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 4-flurobenzamide in 62% yield as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.69 (s, 1H), 8.94 (d, *J* = 8.5 Hz, 1H), 8.11-8.04 (m, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 11.5, 4.2 Hz, 1H), 7.22 -7.11 (m, 3H), 2.72 (s, 3H). Spectral data match with those reported on the literature.[177]

N-(2-acetylphenyl)-3-(trifluoromethyl)benzamide **(9).**



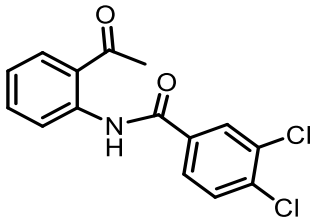
This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 3-trifluoromethylbenzamide in 68% yield as white solid. R_f = 0.32 (10% AcOEt/hexane). m.p=102-104 °C. IR (KBr, cm^{-1}): 1677, 1647, 1606, 1588, 1538, 1492, 1450, 1435, 1359, 1315, 1247, 1164, 1116, 1092, 1072, 963, 902, 816, 763, 742, 723, 692; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.85 (s, 1H), 8.96 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.37 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.23 -7.19 (m, 1H), 2.74 (s, 1H);^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 164.6, 141.2, 135.8, 135.6, 132.0, 131.7, 131.4, 131.2, 130.4, 129.5, 128.66 (q, *J* = 3.6 Hz), 127.1, 125.12 (dd, *J* = 7.8, 3.8 Hz), 125.12 (dd, *J* = 7.8, 3.8 Hz), 124.9, 123.1, 122.8, 122.1, 120.9, 120.6, 28.7; HRMS (ESI) m/z calcd for $C_{16}H_{13}F_3NO$ $[M+H]^+$: 308.0898; found: 308.0894.

N-(2-acetylphenyl)-3,4-dimethoxybenzamide **(10).**



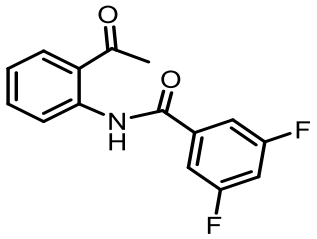
This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 3,4-dimethoxybenzamide in 34% yield as light-yellow solid. R_f = 0.38 (15 % AcOEt/hexane). mp=138-140 °C. IR (KBr, cm^{-1}): 1674, 1650, 1600, 1584, 1512, 1450, 1358, 1341, 1315, 1268, 1248, 1219, 1176, 1131, 1099, 1023, 960, 865, 811, 757, 718, 641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (s, 1H), 8.97 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.15 (s, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 4.00 (s, 1H), 3.96 (s, 1H), 2.72 (s, 1H);^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 165.8, 152.3, 149.2, 141.7, 131.9, 127.5, 122.3, 121.9, 120.7, 120.6, 110.8, 110.7, 56.1, 56.1, 28.7; HRMS (ESI) m/z calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1236; found: 300.1239.

N-(2-acetylphenyl)-3,4-dichlorobenzamide **(11).**



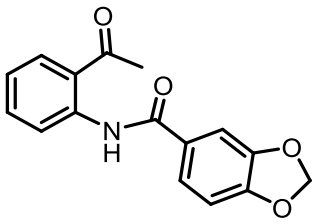
This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 3,4-dichlorobenzamide in 69% yield as white solid. R_f = 0.32 (8% AcOEt/hexane). mp=122-124 °C. IR (KBr, cm^{-1}): 1680, 1646, 1611, 1592, 1539, 1454, 1365, 1322, 1251, 1230, 1168, 757, 742; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.91 (d, *J* = 8.4 Hz, 1H), 8.17 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 203.6, 163.9, 141.1, 136.6, 135.6, 134.8, 133.6, 132.0, 130.9, 130.1, 126.4, 123.1, 122.1, 120.9, 28.7.; HRMS (ESI) m/z calcd for $C_{15}H_{12}Cl_2NO_2$ $[M+H]^+$: 308.0245; found: 308.0233.

N-(2-acetylphenyl)-3,5-difluorobenzamide **(12).**



This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and 3,5-difluorobenzamide in 72% yield as white solid. R_f = 0.35(15 % AcOEt/hexane). mp= 102-104 °C. IR (KBr, cm^{-1}): 1685, 1647, 1608, 1592, 1537, 1450, 1359, 1316, 1252, 1163, 1123, 1020, 986, 962, 856, 791, 755, 744, 721, 610; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.91 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.66 -7.63 (m, 1H), 7.60-7.58 (m, 2H), 7.23 -7.19 (m, 1H), 7.01 (tt, *J* = 8.5, 2.3 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 163.6 (t, *J* = 3.0 Hz), 163.30 (d, *J* = 250.7 Hz), 163.20 (d, *J* = 250.7 Hz), 162.26 (d, *J* = 12.4 Hz), 140.9, 138.4 (t, *J* = 8.2 Hz), 135.6, 132.0, 123.2, 122.1, 120.9, 110.9 (d, *J* = 6.8 Hz)110.7 (d, *J* = 6.5 Hz), 107.4 (t, *J* = 25.4 Hz), 28.6; HRMS (ESI) m/z calcd for $C_{15}H_{12}F_2NO_2$ $[M+H]^+$: 276.0836; found: 276.0823.

N-(2-acetylphenyl) benzo[*d*] [1,3] dioxole-5-carboxamide **(13).**

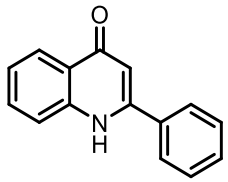


This compound was synthesized according to the general procedure **A** by using 2´-bromoacetophenone and benzo[*d*] [1,3] dioxole-5-carboxamide in 44% yield as yellow solid. R_f = 0.35 (20 % AcOEt/hexane); mp= 157-158 °C. IR (KBr, cm^{-1}): 1667, 1649, 1605, 1582, 1529, 1506, 1493, 1441, 1359, 1312, 1277, 1255, 1158, 1107, 1034, 959, 925, 856, 819, 747, 729, 708, 611, 520; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.59 (s, 1H), 8.94 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 6.8 Hz, 1H), 7.64 (d, *J* = 9.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.55 (s, 1H) 7.15 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.06 (s, 2H), 2.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 165.5, 151.0, 148.3, 141.7, 135.5, 131.9, 129.3, 122.6, 122.4, 122.0, 120.9, 108.3, 108.2, 101.9, 28.7; HRMS (ESI) m/z calcd for $C_{16}H_{14}NO_4$ $[M+H]^+$: 284.0923; found: 284.0935.

Synthesis 2-arylquinolin-4(1*H*)-ones **(14-24).**

The following synthesized compounds **14-19, 21** and **24** spectroscopically are in the agreement with the literature. New compounds are described here. ^{13}C NMR was not possible to get due to high insolubility of 2-arylquinolin-4(1*H*)-ones. However full evidence of ^{1}H, IR and HRMS support the authenticity of the molecules.

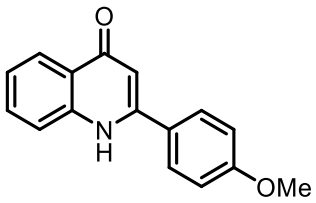
2-phenylquinolin-4(1*H*)-one **(14).**



The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **3**, in 88% yield as light-yellow solid. m.p > 250 ºC. (ethanol) (lit mp: 254 °C).[43] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 3.7 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.62 –7.57 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 3H), 6.33 (s, 1H), 3.33 (s, 1H). IR (neat) cm^{-1} 3069, 2971, 1634, 1591, 1547, 1503, 1473, 1442, 1411, 1355, 1320, 1255, 1141, 831, 796, 764, 570, 538, 495.HRMS (ESI) m/z calcd for $C_{15}H_{12}NO$ $[M+H]^+$: 222.0919; found: 222.0919. Spectral data match with those reported on the literature.[179]

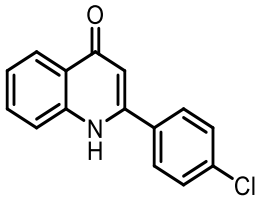
179. See ref. 177.

2-(4-methoxyphenyl)quinolin-4(1*H*)-one **(16).**



The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **5**, in 96% yield as light-yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 11.67 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.33 (s, 1H), 3.85 (s, 3H); IR (neat) cm^{-1} 3076, 2965, 1635, 1610, 1595, 1580, 1543, 1505, 1441, 1413, 1318, 1299, 1247, 1188, 1029, 833, 802, 755, 574, 539, 461; HRMS (ESI) m/z calcd for $C_{16}H_{14}NO_2$ [M+H] $^{+}$: 252.1024; found: 252.1019. Spectral data match with those reported on the literature.[179]

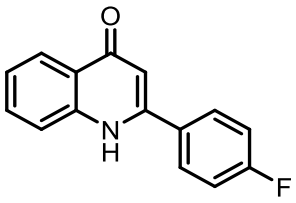
2-(4-chlorophenyl)quinolin-4(1*H*)-one **(17).**



The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **6**, in 90% yield as light-yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 11.72 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 9.5 Hz, 3H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.35 (s, 1H); IR (neat) cm^{-1} 3067, 2969, 1634, 1601, 1575, 1545, 1502, 1475, 1440, 1355, 1252, 1140, 1093, 827, 759, 542; HRMS (ESI) m/z calcd for $C_{15}H_{11}ClNO$ [M+H] $^{+}$: 256.0529; found: 256.0524. Spectral data match with those reported on the literature.[180]

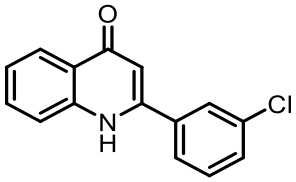
180. Sun, F.; Zhao, X.; Shi, D. Q.; **2011**, *52*, 5633-5635.

2-(4-fluorophenyl)quinolin-4(1*H*)-one **(18).**



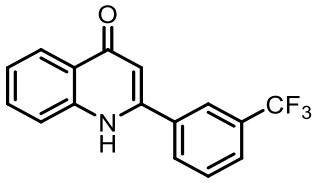
The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **7**, in 93% yield as light-yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 11.76 (s, 1H), 8.10 (d, *J* = 7.4 Hz, 1H), 7.93 (s, 1H), 7.81 (d, *J* = 7.1 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.67 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H); IR (neat) cm^{-1} 3069, 2971, 1606, 1634, 1591, 1547, 1501, 1473, 1442, 1411, 1355, 1255, 1164, 1141, 1020, 811, 796, 831, 764, 633, 570, 538, 515, 495; HRMS (ESI) m/z calcd $C_{15}H_{11}FNO$ for [M+H] $^+$: 240.08247; found:240.0832. Spectral data match with those reported on the literature.[178]

2-(3-chlorophenyl)quinolin-4(1*H*)-one **(19).**



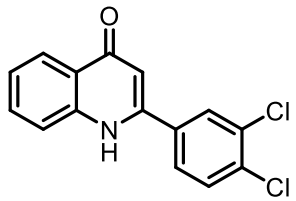
The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **8**, in 85% yield as light-yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 11.73 (s, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.69-7.64 (m, 3H), 7.47 (t, *J* = 9.2 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 3H), 6.50 (s, 3H); IR (neat) cm^{-1} 3092, 3067, 2969, 1634, 1601,1575, 1545, 1475, 1440, 1355, 1319, 1252, 1093, 1013, 827, 759, 522; HRMS (ESI) m/z calcd $C_{15}H_{11}ClNO$ for [M+H] $^+$: 256.0529; found: 256.0533. Spectral data match with those reported on the literature.[178]

2-(3-(trifluoromethyl)-phenyl)-quinolin-4(1*H*)-one **(20).**



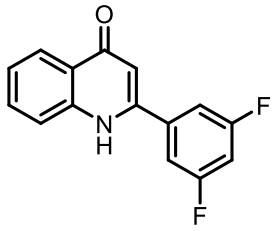
The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **9**, in 90% yield as light-yellow solid. R_f = 0.35 (85% AcOEt/hexane). m.p > 250 ºC. IR (KBr, cm^{-1}): 3266, 3101, 2993, 1636, 1606, 1589, 1549, 1500, 1421, 1405, 1355, 1332, 1314, 1252, 1229, 1175, 1124, 1102, 1072, 1022, 1000, 983, 961, 948, 875, 849, 834, 792, 763, 693, 670, 661, 652, 585, 524, 492; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.91 (s) 8.24 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.10 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.48 (s, 1H); HRMS (ESI) m/z calcd for $C_{16}H_{11}F_3NO$ $[M+H]^+$: 290.0793; found: 290.0794.

2-(3,4-dichlorophenyl) quinolin-4(1*H*)-one **(22).**



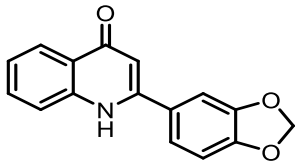
The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **11**, in 93% yield as light-yellow solid. R_f = 0.36 (80% AcOEt/hexane). m.p > 250 ºC. IR (KBr, cm^{-1}): 3429, 3238, 3091, 3068, 1635, 1602, 1590, 1567, 1540, 1506, 1477, 1442, 1411, 1381, 1354, 1318, 1250, 1161, 1133, 1108, 1077, 1021, 1032, 953, 885, 835, 826, 802, 756, 738, 712, 686, 679, 616, 557, 544; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.78 (s, 1H), 8.17 (s, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 6.46 (s, 1H). HRMS (ESI) m/z calcd for $C_{15}H_{10}Cl_2NO$ $[M+H]^+$: 290.0139; found: 290.0145.

2-(3,5-difluorophenyl) quinolin-4(1*H*)-one **(23).**



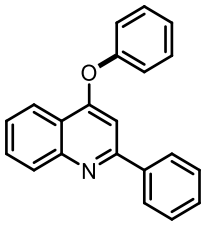
The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **12**, in 87% yield as light-yellow solid. R_f = 0.34 (85% AcOEt/hexane). m.p.> 250 ºC. IR (KBr, cm^{-1}): 3096, 2974, 1599, 1552, 1509, 1446, 1354, 1298, 1253, 1232, 1140, 1122, 1026, 992, 852, 838, 789, 733, 752, 661, 556, 485; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.80 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 9.2 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.51 (s, 1H); HRMS (ESI) m/z calcd for $C_{15}H_{10}F_2NO$ $[M+H]^+$: 258.0730; found: 258.0749.

2-(benzo[*d*][1,3]dioxol-5-yl)quinolin-4(1*H*)-one **(24).**



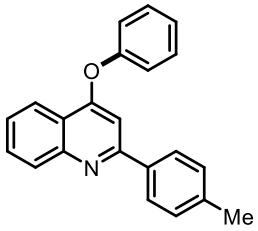
The following compound was obtained according to the general procedure **B**, by using *N*-ketoarylamide **13**, in 91% yield as light-yellow solid; ^{1}H NMR (500 MHz, DMSO) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 1.4 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.31 (s, 1H), 6.15 (s, 2H); Ir (neat) cm^{-1} 3088, 3060, 2974, 1634, 1598, 1555, 1507, 1434, 1262, 1046, 1040, 941, 810, 750, 576. Spectral data match with those reported on the literature.[178]

4-phenoxy-2-phenylquinoline (**25)**



The following compound was obtained according to the general procedure **C**, by using 2-phenylquinolin-4(1*H*)-one **14** and Ph_2INO_3 in 92% yield as white solid. R_f = 0.37 (10% AcOEt/hexane). mp= 54-56 °C (lit mp= 69-71°C). IR (KBr, cm^{-1}): 1593, 1579, 1486, 1419, 1356, 1213, 926, 748, 766, 700, 545, 469; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.2 Hz, 1H), 8.21 (bs, 1H), 7.96 (d, *J* = 7.1 Hz, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 7.1 Hz, 2H), 7.43-7.39 (m, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.03 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 158.7, 154.8, 149.9, 139.9, 130.5, 130.4, 129.5, 129.4, 128.8, 127.6, 126.0, 125.6, 121.8, 121.0, 120.7, 102.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}NO$ $[M+H]^+$: 298.1232; found: 298.1226. Spectral data match with those reported on the literature.[181]

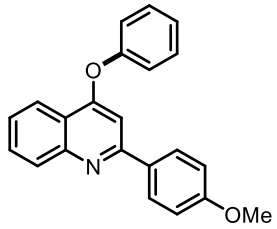
4-phenoxy-2-(*p*-tolyl)-quinolone **(26).**



The following compound was obtained according to the general procedure **C**, by using 2-(*p*-tolyl)-quinolin-4(1*H*)-one **15** and Ph_2INO_3 in 77% yield as white solid. R_f = 0.33 (15% AcOEt/hexane). mp= 86-88 °C. IR (KBr, cm^{-1}): 1598, 1576, 1501, 1488, 1424, 1353, 1214, 922, 789, 817, 761, 693, 543, 479. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.27 -7.25 (m, 1H), 7.24 (d, *J* = 7.3 Hz, 3H), 7.02 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 158.6, 154.8, 149.9, 139.5, 137.06, 130.4, 130.4, 129.5, 129.4, 127.5, 125.8, 125.5, 121.8, 121.0, 120.7, 102.6, 21.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}NO$ $[M+H]^+$: 312.1388, found: 312.1386.

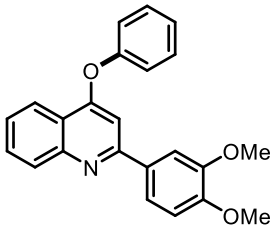
181. See ref. 158.

2-(4-methoxyphenyl)-4-phenoxyquinoline **(27).**



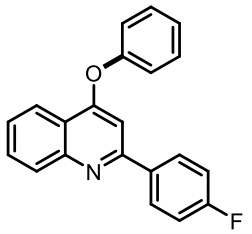
The following compound was obtained according to the general procedure **C**, by using 2-(4-methoxyphenyl)quinolin-4(1*H*)-one **16** and Ph_2IOTf in 80% yield as white solid. R_f = 0.33 (15% AcOEt/hexane). mp= 118-120°C. IR (KBr, cm^{-1}): 1582, 1600, 1501, 1487, 1426, 1360, 1253, 1257, 1173, 1036, 926, 829, 764, 752, 699. 544, 534; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.00 (s, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 161.0, 158.2, 154.8, 149.8, 132.3, 130.4, 130.4, 129.2, 128.9, 125.7, 125.5, 121.8, 121.0, 120.5, 114.2, 102.2, 55.5. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}NO_2$ $[M+H]^+$: 328.1338, found: 328.1318.

2-(3, 4-dimethoxyphenyl)-4-phenoxyquinoline **(28).**



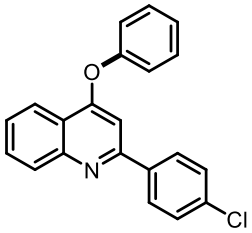
The following compound was obtained according to the general procedure **C**, by using 2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one **21** and Ph_2INO_3 in 85% yield as yellow solid. R_f = 0.38 (20% AcOEt/hexane). mp= 66-68 °C. IR (KBr, cm^{-1}): 1597, 1548, 1519, 1503, 1489, 1457, 1424, 1312, 1241, 1218, 1168, 1133, 1080, 1020, 889, 874, 813, 764, 746, 684, 492; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.1 Hz, 1H), 8.18 (s, 1H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.58-7.53 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.01 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.02 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 158.1, 154.9, 150.5, 149.8, 149.4, 132.7, 130.4, 130.4, 129.2, 125.7, 125.5, 121.8, 120.9, 120.6, 120.2, 111.0, 110.7, 102.4, 56.18; 56.10. HRMS (ESI) *m/z* calcd for $C_{23}H_{20}NO_3$ $[M+H]^+$: 358.1443, found: 358.1456.

2-(4-fluorophenyl)-4-phenoxyquinoline **(29).**



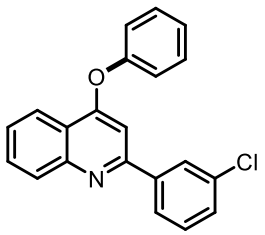
The following compound was obtained according to the general procedure **C**, by using 2-(4-fluorophenyl)quinolin-4(1*H*)-one **18** and Ph_2INO_3 in 78% yield as white solid; R_f = 0.28 (10% AcOEt/hexane). mp= 68-70 °C. IR (KBr, cm^{-1}): 1596, 1587, 1558, 1501, 1488, 1426, 1406, 1378, 1351, 1213, 1154, 1086, 1056, 923, 833, 827, 760, 747, 693, 545, 523, 496; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.2 Hz, 1H), 8.20 (bs, 1H), 7.96 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 6.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.92 (2C, d, *J* = 249.3 Hz), 162.6, 157.5, 154.7, 149.8, 136.0, 130.6, 130.5, 129.50 (d, *J* = 8.4 Hz), 129.4, 126.10, 125.7, 121.8, 121.0, 120.6, 115.77 (2C, d, *J* = 21.5 Hz), 102.2. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}FNO$: $[M+H]^+$: 316.1138, found: 316.1130.

2-(4-chlorophenyl)-4-phenoxyquinoline **(30).**



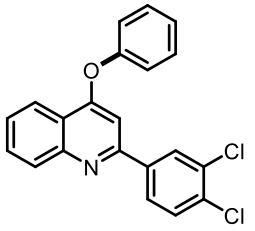
The following compound was obtained according to the general procedure **C**, by using 2-(4-chlorophenyl)quinolin-4(1*H*)-one **17** and Ph_2INO_3 in 86% yield as white solid. R_f = 0.36 (15% AcOEt/hexane). mp= 64-66 °C. IR (KBr, cm^{-1}): 1619, 1598, 1577, 1554, 1510, 1425, 1346, 1353, 1088, 1007, 921, 833, 819, 826, 765, 750, 716, 691; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.1 Hz, 1H), 8.17 (bs, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 157.3, 154.7, 149.8, 138.2, 135.7, 130.7, 130.5, 129.4, 129.0, 128.9, 126.2, 125.7, 121.9, 121.0, 120.7, 102.2. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClNO$ $[M+H]^+$: 332.0842, found: 332.0815.

2-(3-chlorophenyl)-4-phenoxyquinoline **(31).**



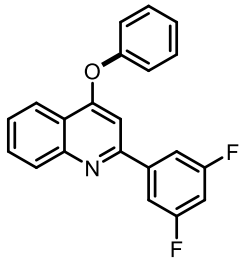
The following compound was obtained according to the general procedure **C**, by using 2-(3-chlorophenyl)quinolin-4(1*H*)-one **19** and Ph_2INO_3 in 89% yield as white solid. R_f = 0.36 (15% AcOEt/hexane). mp= 64-66 °C. IR (KBr, cm^{-1}): 1586, 1553, 1490, 1433, 1411, 1346, 1217, 1168, 1089, 838, 786, 755, 695; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.2 Hz, 1H), 8.22 (bs, 1H), 7.99 (s, 1H), 7.80 (t, *J* = 7.0 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 6.2 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 6.99 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 157.0, 154.6, 149.8, 141.6, 134.9, 130.7, 130.5, 130.0, 129.5, 129.4, 127.7, 126.3, 125.7, 125.6, 121.8, 121.0, 120.8, 102.3. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClNO$ $[M+H]^+$: 332.0842, found: 332.0815.

2-(3,4-dichlorophenyl)-4-phenoxyquinoline **(32).**



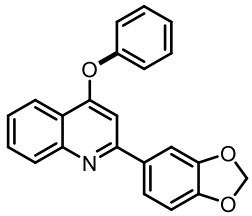
The following compound was obtained acording to the general procedure **C**, by using 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one **22** and Ph_2INO_3 in 85% yield as white solid. R_f = 0.31(12 % AcOEt/hexane). mp= 146-148 °C. IR (KBr, cm^{-1}): 1587, 1488, 1424, 1332, 1207, 1068, 934, 813, 772, 692, 501; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.17 (s, 1H), 8.12 (d, *J* = 2.1 Hz, 1H), 7.82 -7.76 (m, 2H), 7.61- 7.58 (m, 1H), 7.53 -7.49 (m, 3H), 7.37 -7.33 (m, 1H), 7.24 (dt, *J* = 9.0, 1.8 Hz, 2H), 6.96 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 155.8, 154.5, 149.7, 139.6, 133.6, 133.1, 130.8, 130.6, 130.5, 129.4, 129.4, 126.6, 126.5, 125.83, 121.9, 120.9, 120.8, 101.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{14}Cl_2NO$ $[M+H]^+$: 366.0452, found: 366.0478.

2-(3, 5-difluorophenyl)-4-phenoxyquinoline **(33).**



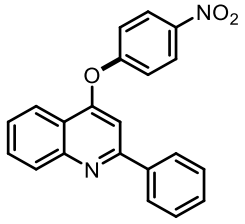
The following compound was obtained according to the general procedure **C**, by using 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one **23** and Ph_2INO_3 in 88% yield as white solid. R_f = 0.37 (15% AcOEt/hexane). mp= 100-102 °C. IR (KBr, cm^{-1}): 1627, 1600, 1585, 1561, 1510, 1491, 1441, 1423, 1359, 1292, 1235, 1207, 1113, 1170, 986, 894, 840, 777, 760, 694, 652, 557, 492; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 5.0 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 13.0, 4.9 Hz, 4H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.94 (s, 1H), 6.85 (t, *J* = 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.46 (d, *J* = 248.1 Hz), 163.36 (d, *J* = 248.0 Hz), 162.9, 155.8, 154.5, 149.7, 143.23 (t, *J* = 9.0 Hz), 130.8, 130.6, 129.6, 126.6, 125.9, 121.9, 121.0, 110.5 (d, *J* = 6.3 Hz), 110.3 (d, *J* = 6.5 Hz), 104.6 (t, *J* = 25.6 Hz), 101.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{14}F_2NO$ $[M+H]^+$: 334.1043, found: 334.1027.

2-(benzo[*d*] [1, 3] dioxol-5-yl)-4-phenoxyquinoline **(34)**



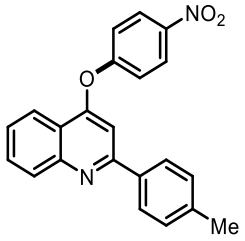
The following compound was obtained according to the general procedure **C**, by using 2-(benzo[*d*][1,3]dioxol-5-yl)quinolin-4(1*H*)-one **24** and Ph_2INO_3 in 90% yield as white solid. R_f= 0.42 (15% AcOEt/hexane). mp= 140-142 °C. IR (KBr, cm^{-1}): 1618, 1600, 1586, 1490, 1445, 1346, 1413, 1245, 1206, 1038, 934, 842,763, 752, 695, 527; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 -7.47 (m, 4H), 7.42 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.31 (dd, *J* = 14.6, 7.1 Hz, 1H), 7.23 (d, 1H), 6.95 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.00 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 158.0, 154.7, 149.8, 148.9, 148.3, 134.3, 130.5, 130.4, 129.3, 125.8, 125.6, 121.8, 121.0, 120.6, 108.5, 108.0, 102.2, 101.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{16}NO_3$ $[M+H]^+$: 342.1130, found: 342.1146.

4-(4-nitrophenoxy)-2-phenylquinoline **(35).**



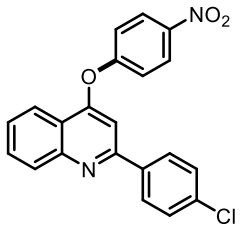
The following compound was obtained according to the general procedure **C**, by using 2-phenylquinolin-4(1*H*)-one **14** and diphenyliodonium salt **47** in 83% yield as white solid. R_f = 0.33 (10% AcOEt/hexane). mp= 128-130°C. IR (KBr, cm^{-1}): 1601, 1590, 1580, 1523, 1484, 1413, 1344, 1226, 1156; 1084; 1020; 916; 858; 769, 695, 670.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.2 Hz, 2H), 8.24 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.51-7.46 (m, 3H), 7.31 (s, 1H), 7.29 (d, *J* = 2.1 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 160.1, 158.5, 150.2, 144.3, 139.1, 130.8, 129.8, 129.8, 128.9, 127.5, 126.6, 126.3, 121.4, 120.7, 119.6, 105.5. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}N_2O_3$ $[M+H]^+$: 343.1083, found: 343.1112.

4-(4-nitrophenoxy)-2-(p-tolyl)quinoline **(36).**



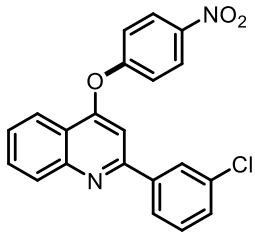
The following compound was obtained according to the general procedure **C**, by using 2-(*p*-tolyl)-quinolin-4(1*H*)-one **15** and diphenyliodonium salt **48** in 77% yield as white solid. R_f = 0.37 (12% AcOEt/hexane). mp= 142-144 °C. IR (KBr, cm^{-1}): 1589, 1517, 1486, 1341, 1227, 920, 857, 825, 768.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.1 Hz, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.30 (s, 1H), 7.28 (d, *J* = 1.4 Hz, 4H), 2.41 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 160.0, 158.6, 150.3, 144.3, 140.1, 136.3, 131.0, 130.9, 129.7, 127.4, 126.5, 126.4, 121.4, 120.7, 119.5, 105.6, 21.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_2O_3$ $[M+H]^+$: 357.1239, found: 357.1227.

2-(4-chlorophenyl)-4-(4-nitrophenoxy)quinoline **(37).**



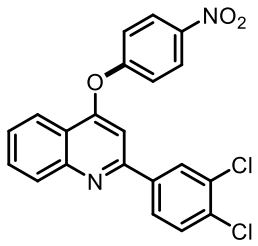
The following compound was obtained according to the general procedure **C**, by using 2-(4-chlorophenyl)quinolin-4(1*H*)-one **17** and diphenyliodonium salt **48** in 75% yield as white solid. R_f = 0.37 (12% AcOEt/hexane). mp= 142-144 °C. IR (KBr, cm^{-1}): 1588, 1574, 1515, 1488, 1416, 1345, 1248, 1111, 1089, 1012, 921, 849, 827, 759, 748, 722, 689, 666, 541, 479; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.1 Hz, 2H), 8.22 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 9.1 Hz, 2H), 7.24 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 160.4, 157.3, 150.2, 144.5, 137.5, 136.2, 131.1, 129.8, 129.2, 128.8, 127.0, 126.4, 121.5, 120.8, 119.7, 105.2. HRMS (ESI) *m/z* calcd for $C_{21}H_{14}ClN_2O_3$ $[M+H]^+$: 377.0693, found: 377.0615.

2-(3-chlorophenyl)-4-(4-nitrophenoxy)quinoline **(38).**



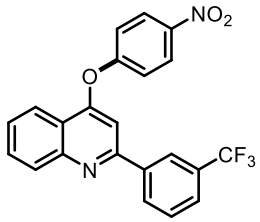
The following compound was obtained according to the general procedure **C**, by using 2-(3-chlorophenyl)quinolin-4(1*H*)-one **19** and diphenyliodonium salt **48** in 73% yield as white solid. R_f = 0.36 (15% AcOEt/hexane). mp= 154-156 °C. IR (KBr, cm^{-1}) 1589, 1555, 1516, 1483, 1435, 1407, 1344, 1240, 1222, 851, 876, 761, 676; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2H), 8.31 (s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 5.8 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 7.23 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 160.4, 157.0, 150.2, 144.5, 140.9, 135.2, 131.1, 130.2, 129.9, 129.8, 127.7, 127.1, 126.4, 125.6, 121.5, 120.9, 119.7, 105.3. HRMS (ESI) *m/z* calcd for $C_{21}H_{14}ClN_2O_3$ $[M+H]^+$:377.0693, found: 377.0684.

2-(3,4-dichlorophenyl)-4-(4-nitrophenoxy)quinoline **(39).**



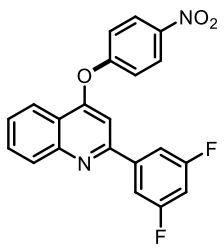
The following compound was obtained according to the general procedure **C**, by using 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one **22** and diphenyliodonium salt **48** in 77% yield as white solid. R_f = 0.29 (15% AcOEt/hexane). mp= 152-154 °C. IR (KBr, cm^{-1}): 1589, 1515, 1488, 1424, 1344, 1325, 1229, 1210, 1158, 1027, 935, 876, 861, 844, 764, 740; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.30 (s, 1H), 8.19 (d, *J* = 9.1 Hz, 2H), 7.87 (dd, *J* = 17.1, 8.5 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 2H), 7.20 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 160.6, 155.9, 150.2, 144.6, 138.9, 134.2, 133.4, 131.3, 130.9, 129.9, 129.4, 127.2, 126.5, 126.5, 121.5, 120.9, 119.7, 104.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{13}Cl_2N_2O_3$ $[M+H]^+$: 411.0303, found: 411.0283.

4-(4-nitrophenoxy)-2-(3-(trifluoromethyl) phenyl) quinolone **(40).**



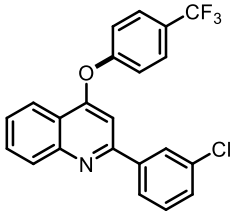
The following compound was obtained according to the general procedure **C**, by using 2-(3-(trifluoromethyl)phenyl)quinolin-4(1*H*)-one **20** and diphenyliodonium salt **48** in 83% yield as white solid; R_f = 0.32 (15% AcOEt/hexane). mp= 116-118 °C. IR (KBr, cm^{-1}): 1600, 1608, 1584, 1515, 1419, 1489, 1414, 1342, 1245, 1231, 1163, 1123, 1110, 885, 852, 767, 750, 695; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (t, *J* = 2.7 Hz, 2H), 8.34 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.18 (t, *J* = 7.3 Hz, 2H), 7.84 (dd, *J* = 11.3, 4.2 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.61 (td, *J* = 7.5, 3.0 Hz, 2H), 7.30 (s, 2H), 7.29 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 160.8, 160.5, 156.9, 150.3, 144.5, 139.9, 131.6, 131.4, 131.3, 131.1, 130.7,130.0, 129.5, 127.2, 126.5, 126.4, 125.2, 124.5 (dd, *J* = 7.1, 3.3 Hz), 123.1, 121.5, 121.0, 119.6, 105.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{13}F_3N_2O_3$: $[M+H]^+$: 411.0957, found: 410.0988.

2-(3, 5-difluorophenyl)-4-(4-nitrophenoxy) quinolone **(41).**



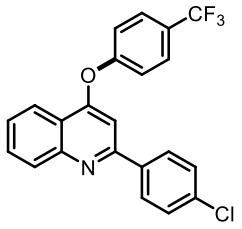
The following compound was obtained according to the general procedure **C**, by using 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one **23** and diphenyliodonium salt **48** in 81% yield as white solid. R_f = 0.31(12 % AcOEt/hexane). mp= 164-166 °C. IR (KBr, cm^{-1}): 1589, 1517, 1486, 1425, 1341, 1227, 920, 857, 825, 768; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.2 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.84 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.65 -7.54 (m, 3H), 7.30 (d, *J* = 9.2 Hz, 2H), 7.20 (s, 1H), 6.89 (tt, *J* = 8.6, 2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5 (d, *J* = 248.5 Hz), 162.47 (d, *J* = 248.6 Hz), 160.6, 155.83 (t, *J* = 3.0 Hz), 150.0, 144.6, 142.45 (t, *J* = 8.4 Hz), 131.3, 129.9, 127.4, 126.5, 121.5, 121.1, 119.8, 110.55 (d, *J* = 6.6 Hz), 110.39 (d, *J* = 6.5 Hz). 105.09 (t, *J* = 25.4 Hz). 104.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{13}F_2N_2O_3$: $[M+H]^+$: 379.0894, found: 379.0927.

2-(3-chlorophenyl)-4-(4-(trifluoromethyl)phenoxy)quinoline **(42).**



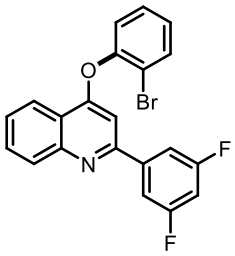
The following compound was obtained according to the general procedure **C**, by using 2-(3-chlorophenyl)quinolin-4(1H)-one **19** and diphenyliodonium salt **49** in 68% yield as white solid. R_f = 0.36 (10% AcOEt/hexane). mp= 98-100 °C. IR (KBr, cm^{-1}): 1613, 1593, 1557, 1503, 1482, 1434, 1412, 1321, 1220, 1160, 1065, 1065, 861, 842, 766, 719, 590; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 8.06 (s, 1H), 7.82 (dd, *J* = 14.5, 6.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.41 (dd, *J* = 7.6, 4.6 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.11 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4, 157.9, 157.0, 149.9, 141.1, 135.0, 131.1, 130.1, 129.7, 129.7, 127.9 (q, *J* = 3.7 Hz), 127.7, 127.7, 127.44, 126.81, 125.6, 125.1, 122.9, 121.7, 120.9, 120.5, 103.8. HRMS (ESI) *m/z* calcd for $C_{22}H_{14}ClF_3NO$: $[M+H]^+$: 400.0716, found: 400.0748.

2-(4-chlorophenyl)-4-(4-(trifluoromethyl) phenoxy) quinolone **(43).**



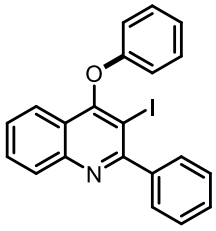
The following compound was obtained according to the general procedure **C**, by using 2-(4-chlorophenyl)quinolin-4 (1*H*)-one **17** and diphenyliodonium salt **49** in 70% yield as white solid. R_f = 0.37 (12% AcOEt/hexane). mp= 104-106 °C. IR (KBr, cm^{-1}): 1595, 1576, 1504, 1490, 1422, 1354, 1320, 1223, 1167, 1131, 1093, 1063, 1014, 920, 863, 830, 768, 605, 545; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.1 Hz, 1H), 8.22 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.10 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4, 157.9, 157.3, 150.0, 137.8, 136.0, 131.0, 129.6, 129.1, 128.9, 127.93 (q, *J* = 3.5 Hz), 127.7, 127.4, 126.6, 125.1, 123.0, 121.7, 120.8, 120.5, 103.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{14}ClF_3NO$: $[M+H]^+$: 400.0716, found: 400.0748.

4-(2-bromophenoxy)-2-(3,5-difluorophenyl) quinoline **(44).**



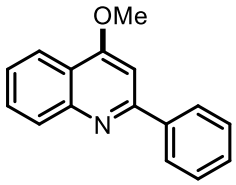
The following compound was obtained according to the general procedure **C**, by using 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one **23** and diphenyliodonium salt **50** in 65% yield as white solid. R_f = 0.35 (10 % AcOEt/hexane). mp= 158-160 °C; IR (KBr, cm^{-1}): 1606, 1588, 1555, 1515, 1491, 1414, 1342, 1208, 1230, 1159, 1071, 875, 803, 766, 694; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (t, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 14.2, 6.9 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.52 -7.49 (m, 3H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 6.85 (dd, *J* = 11.9, 5.3 Hz, 1H), 6.77 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4 (d, *J* = 248.2 Hz), 163.35 (d, *J* = 248.2 Hz), 161.8, 155.81 (t, *J* = 3.0 Hz), 151.1, 149.6, 134.6, 131.0, 130.6, 129.5, 127.8, 126.8, 126.0, 123.2, 121.9, 121.4, 121.0, 120.8, 120.5, 116.3, 110.65 (d, *J* = 6.4 Hz), 110.49 (d, *J* = 6.3 Hz), 104.75 (t, *J* = 25.4 Hz), 101.3. HRMS (ESI) *m/z* calcd for $C_{21}H_{13}BrF_2NO$: $[M+H]^+$: 412.0149, found: 412.0156.

3-Iodo-4-phenoxy-2-phenylquinoline **(52).**



The following compound was obtained according to the general procedure **C**, by using 3-iodo-2-phenylquinolin-4(1*H*)-one **51** and Ph_2INO_3 in 83% yield as white solid; R_f = 0.37 (10 % AcOEt/hexane). mp= 144-146 °C. IR (KBr, cm^{-1}): 1569, 1478, 1371, 1217, 1074, 1025, 759, 698, 614, 584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 1H), 7.89 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.69 -7.67 (m, 2H), 7.52 -7.46 (m, 4H), 7.34-7.30 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.91-6.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 159.5, 157.3, 149.2, 142.5, 130.9, 130.0, 129.7, 129.5, 129.0, 128.1, 127.5, 122.9, 122.6, 115.7, 89.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}INO$: $[M+H]^+$: 424.0198, found: 424.0232.

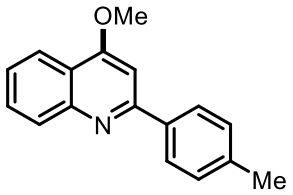
4-methoxy-2-phenylquinoline **(61).**



This compound was synthesized according to the general procedure **D** by using 2-phenylquinolin-4(1*H*)-one **14** and Iodomethane in yield 86% (25 mg) as an amorphous white solid: mp: 66-68 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 3H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 6.4 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.19 (s, 1H), 4.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 159.0, 149.3, 140.5, 130.1, 129.39, 129.35, 128.9, 127.7, 125.5, 121.7, 120.5, 98.1, 55.8; IR (Diamond ATR) cm^{-1} 3059, 2947, 2849, 1618, 1590, 1582, 1556, 1492, 1444, 1418, 1354, 1266, 1221, 1160, 1111, 1066, 1028, 1018, 987, 897, 836, 772, 755, 698, 690, 666. Spectral data match with those reported on the literature.[182]

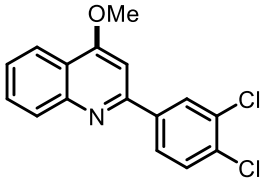
182. Mphahlele, M. J.; Mogamisi, F. K.; Tsanwani, M.; Hlatshwayo, S. M.; Mampa, R. M. *J. Chem. Res.* **1999**, (S), 706-707.

4-methoxy-2-(*p*-tolyl)quinoline **(62).**



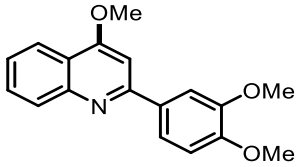
This compound was synthesized according to the general procedure **D** by using 2-(p-tolyl)quinolin-4(1*H*)-one **15** and Iodomethane in yield 83% (30 mg) as an amorphous white solid: mp: 94-96 ^{o}C ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.17 (s, 1H), 4.12 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 158.9, 149.3, 139.4, 137.7, 130.0, 129.6, 129.2, 127.5, 125.3, 121.7, 120.4, 97.9, 55.7, 21.4; IR (Diamond ATR) cm^{-1} 3012, 2975, 2937, 1590, 1552, 1501, 1445, 1416, 1357, 1374, 1265, 1224, 1192, 1183, 1158, 1111, 1071, 1021, 984, 889, 814, 766, 727, 687; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO$ $[M+H]^+$: 249.1154; found: 250.1226. Spectral data match with those previously reported.[182]

2-(3,4-dichlorophenyl)-4-methoxyquinoline **(67).**



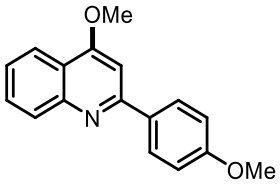
This compound was synthesized according to the general procedure **D** by using 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one **22** and Iodomethane in yield 91% (40mg) as an amorphous white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.98 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 4.14 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 156.1, 149.2, 140.3, 133.6, 131.1, 130.8, 130.4, 129.5, 129.3, 126.7, 126.0, 121.8, 120.6, 97.4, 55.9; IR (Diamond ATR) cm^{-1} 3070, 2922, 1594, 1548, 1507, 1442, 1417, 1356, 1221, 1132, 1112, 1074, 1027, 1019, 986, 917, 821, 754, 714, 674; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}Cl_2NO$ $[M+H]^+$: 303.0218; found: 304.0288.

2-(3,4-dimethoxyphenyl)-4-methoxyquinoline **(64).**



This compound was synthesized according to the general procedure **D** by using 2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one **21** and Iodomethane in yield 75% (38 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent, as an amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 7.83 (s, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.15 (s, 1H), 6.99 (d, *J* = 7.1 Hz, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 158.4, 150.4, 149.4, 149.2, 133.4, 130.0, 129.1, 125.2, 121.7, 120.4, 120.2, 111.0, 110.7, 97.6, 56.1. 56.1, 55.7; IR (Diamond ATR) cm^{-1} 3014, 2967, 2918, 1595, 1586, 1447, 1405, 1504, 1425, 1345, 1136, 1254, 1234, 1170, 1147, 1111, 1036, 1017, 985, 883, 871, 835, 816, 806, 769, 749, 733, 704; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_3$ $[M+H]^+$: 295.1208; found: 296.1280. Spectral data match with those previously reported.[183]

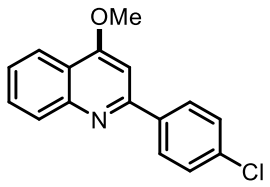
4-methoxy-2-(4-methoxyphenyl)quinoline **(63).**



This compound was synthesized according to the general procedure **D** by using 2-(4-methoxyphenyl)quinolin-4(1*H*)-one **16** and Iodomethane in yield 90% (41 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent as an amorphous white solid;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 1H), 8.08 (t, J = 8.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.14 (s, 1H), 7.04 (d, J = 8.7 Hz, 1H), 4.12 (s, 1H), 3.89 (s, H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 160.9, 158.4, 149.2, 133.0, 130.0, 129.1, 129.0, 125.2, 121.7, 120.3, 114.2, 97.5, 55.7, 55.5; IR (Diamond ATR) cm^{-1} 3058, 2930, 2852, 1590, 1582, 1554, 1504, 1452, 1438, 1423, 1407, 1362, 1290, 1253, 1222, 1169, 1152, 1109, 1026, 1018, 984, 901, 843, 825, 763, 790, 784, 686; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO_2$ $[M+H]^+$: 265.1103; found: 266. 1190. Spectral data match with those previously reported.[182]

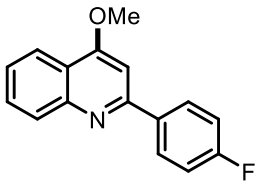
183. Kumar, K. H.; Perumal, P. T. *Tetrahedron*. **2007**, 63, 9531-9535.

2-(4-chlorophenyl)-4-methoxyquinoline **(66).**



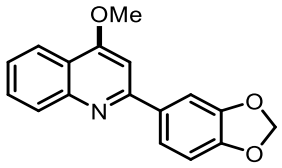
This compound was synthesized according to the general procedure **D** by using 2-(4-chlorophenyl)quinolin-4(1*H*)-one **17** and Iodomethane in yield 93% (43 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent as an amorphous white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 3H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.0 Hz, 3H), 7.14 (s, 2H), 4.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.16, 157.6, 149.2, 138.9, 135.5, 130.2, 129.3, 129.0, 128.9, 125.7, 121.8, 120.5, 121.8, 97.7, 55.8; IR (Diamond ATR) cm^{-1} 3067, 2934, 1588, 1576, 1556, 1507, 1491, 1441, 1420, 1380, 1357, 1216, 1163, 1112, 1086, 1009, 989, 898, 868, 827, 810, 762, 686; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}ClNO$ $[M+H]^+$: 269.0607; found: 270. 0676. Spectral data match with those previously reported.[182]

2-(4-fluorophenyl)-4-methoxyquinolin **(68).**



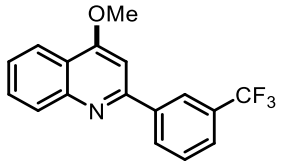
This compound was synthesized according to the general procedure **D** by using 2-(4-fluorophenyl)quinolin-4(1*H*)-one **18** and Iodomethane in yield 84% (30 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent as an amorphous white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.3 Hz, 1H), 8.11 ((t, *J* = 7.6 Hz, 2H), 8.08 (d, J = 8.5 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 8.1 Hz, 2H), 7.13 (s, 1H), 4.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8 (d, *J* = 248.7 Hz), 163.0, 157.7, 149.2, 136.6 (d, *J* = 3.0 Hz), 130.2, 129.5 (d, *J* = 8.4 Hz), 129.2, 125.5, 121.7, 120.4, 115.77 (d, *J* = 21.6 Hz), 97.7, 55.7; IR (Diamond ATR) cm^{-1} 3061, 2999, 1590, 1556, 1501, 1441, 1424, 1403, 1375, 1354, 1218, 1158, 1111, 1096, 1070, 1017, 984, 901, 846, 822, 806, 765, 757, 732. Spectral data match with those previously reported.[182]

2-(benzo[*d*][1,3]dioxol-5-yl)-4-methoxyquinoline **(53).**



This compound was synthesized according to the general procedure **D** by using 2-(benzo[d][1,3]dioxol-5-yl)quinolin-4(1*H*)-one **24** and Iodomethane in yield 80% (40 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent as an amorphous white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H), 4.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 158.1, 148.9, 148.8., 148.4, 134.5, 130.2, 128.8, 125.4, 121.9, 121.7, 120.3, 108.5, 108.1 101.5, 97.7, 55.8; IR (Diamond ATR) cm^{-1} 3000, 2916, 1589, 1457, 1501, 1491, 1441, 1413, 1346, 1245, 1063, 1110, 1033, 1018, 985, 928, 880, 831, 807, 764, 727, 698, 669. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}NO_3$ $[M+H]^+$: 279.0973; found: 280.0977.Spectral data match with those previously reported.[184]

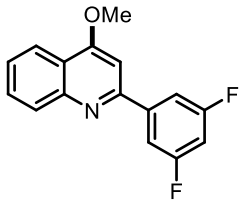
4-methoxy-2-(3-(trifluoromethyl)phenyl)quinoline **(65).**



This compound was synthesized according to the general procedure **D** by using 2-(3-(trifluoromethyl)phenyl)quinolin-4(1*H*)-one **20** and Iodomethane in yield 95% (42 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent as an amorphous white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.32 (d, *J* = 7.7 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 11.9, 7.3 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.18 (s, 1H), 4.16 (s, 3H); IR (Diamond ATR) cm^{-1} 3035, 2949, 2925, 1587, 1560, 1509, 1485. 1449, 1461, 1420, 1322, 1281, 1237, 1223, 1150, 1105, 1095, 1017, 1074, 1064, 992, 914, 894, 874, 805, 764, 693, 686.

184. Rodrigues, T.; Reker, D. Kunze, Jens.; Schneider P.; Schneider, G. *Angew. Chem. Int. Ed*. **2015**, *54*, 10516-10520.

2-(3,5-difluorophenyl)-4-methoxyquinoline **(69).**



This compound was synthesized according to the general procedure **D** by using 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one **23** and Iodomethane in yield 81% (25 mg) purified by silica gel column chromatography using PE:EA = 10:1 as eluent as an amorphous white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.11 (s, 1H), 6.90 (t, *J* = 8.5 Hz, 1H), 4.14 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5 (d, J = 248.0 Hz), 163.3, 163.4 (d, J = 248.0 Hz), 156.06 (q, *J* = 2.6 Hz), 149.0, 143.77 (t, *J* = 9.1 Hz), 130.4, 129.4, 126.1, 121.8, 120.8, 110.5 (d, *J* = 6.4 Hz), 110.4 (d, *J* = 6.4 Hz), 104.5 (t, *J* = 25.5 Hz), 97.5, 55.8; IR (Diamond ATR) cm^{-1} 3067, 2921, 1625, 1600, 1591, 1559, 1512, 1477, 1438, 1417, 1359, 1293, 1240, 1190, 1159, 1133, 1109, 985, 963, 884, 878, 832, 824, 799, 762, 734, 174, 663.

Procedure and results of the biological assay of 2-aryl-4-aryloxyquinolines.

Culture media.

YPG Medium (Glucose, Gelatine Peptone, yeast extract): Each liter of medium contained 3 g of yeast extract (BD Bioxon), 10 g of gelatin peptone (BD Bioxon), 20 g of dextrose (BD Bioxon) and 20 g of bacteriological agar (BD Bioxon) in case of solid medium. The pH was adjusted to 4.5 (Bartnicky-García., 1968). For the sterilization process, the autoclave was used at 121 °C, with a pressure of 25 atm for 15 minutes.

Minimum medium.

a) YNB

Each liter of medium contained 5 g of ammonium phosphate, 6.7 g of nitrogenous base of dehydrated yeast, 20 g of Dextrose (BD Bioxon) and 20 g of bacteriological agar (BD Bioxon). The pH was adjusted to 4.5 (Bartnicky-García., 1968).

b) Medium B

This medium contained 20 g of dextrose for each liter, 7.5 g of ammonium sulfate and 20 g of bacteriological agar (Valle-Maldonado., 2011).

For both cases sterilization was performed at 121 °C at a pressure of 25 atm for 15 minutes. Given that the strains used have auxotrophy to leucine, the medium was added with 10 mL of leucine for each liter of medium using leucine with a concentration of 2%.

Corroboration of the phenotype of the strains used.

To corroborate the phenotype, 500 spores/mL of the strains R7B and M5 were inoculated in YPG medium with allyl alcohol at 0.3% and 0.6%. The allylic alcohol was added to the solid medium using a spatula. It was allowed to dry and subsequently incubated at 28 °C in the presence of light for 4 to 5 days.

Growth conditions.

Obtaining spores (solid medium)

50 spores /mL of *M. circinelloides* medium were inoculated in Petri dishes with solid YPG medium and kept at 28 ° C in the presence of light for 4 to 5 days. The spores were collected by adding 5 mL of sterile distilled H_2O on the plates, a scraping was carried out with a plastic handle on the surface of the plate, thus dragging the spores. Subsequently, the spores were aspirated and deposited in a 50 mL corning tube. The spores were concentrated by centrifuging at 5000 g for 10 minutes at room temperature, washed with sterile distilled H_2O and centrifuged as the previous condition. The spores were resuspended in 10 mL of sterile distilled H2O. The spores were counted in a hematocytometer (PGC Scientific) using the 40X objective of an ATC 2000 optical microscope (Leika), depositing 15 µL in the upper part (upper chamber) and 15 µL in the lower part (lower chamber), respectively. The end grids and the center grids were counted for both cells of the camera. This quantity was multiplied by the factor of 25,000 which corresponds to the depth of the Neubauer chamber (5x104 mL) and the result obtained corresponds to the cell concentration expressed in spores per milliliter of each stock of the samples. The spores were stored at 4 ° C and used in a maximum of 15 days after obtaining them.

Obtaining mycelium (liquid medium)

To carry out aerobic growth 500,000 spores were inoculated per milliliter of culture medium. In the filamentous growth the flasks were incubated at 28 ° C, with constant agitation of 200 rpm, using 5 mL of medium in 25 mL flasks. This procedure was performed on both the wild type strain R7B and the mutant M5 (adh-).

Quantification of growth

Cell growth was determined by measuring the total biomass generated in liquid medium, which was represented as dry weight per mL of medium used. The biological samples of *M. Circinelloides* (mycelium) were collected on previously dry and heavy filter paper. The cells were washed twice with sterile distilled water. The filter paper with the biomass was dried for 96 hours at 80 ° C. After drying and cooling, the filters were weighed again to determine the dry weight of the cells, until it remained constant. The significant results are those that are verified for molecules: (a) **33** (b) **34** (c) **30** (d) **38** (e) **41**, which are described below

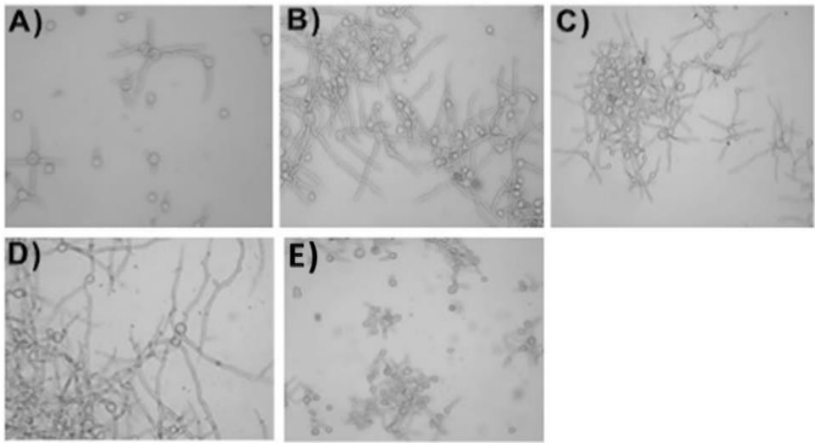


Figure 1.4. Morphological aspect of M. circinelloides during aerobic germination with different development times. A) YPG medium, 3 h; B) half YPG, 6 h; C) half YPG 12 h; D) YPG medium, 24 h, E) YPG 48 h in culture medium.

Effect on the germination of *M. Circinelloides.*

The speed of germination in the different strains was analyzed, for which the spores were inoculated in liquid YPG medium and subjected to aerobic growth.

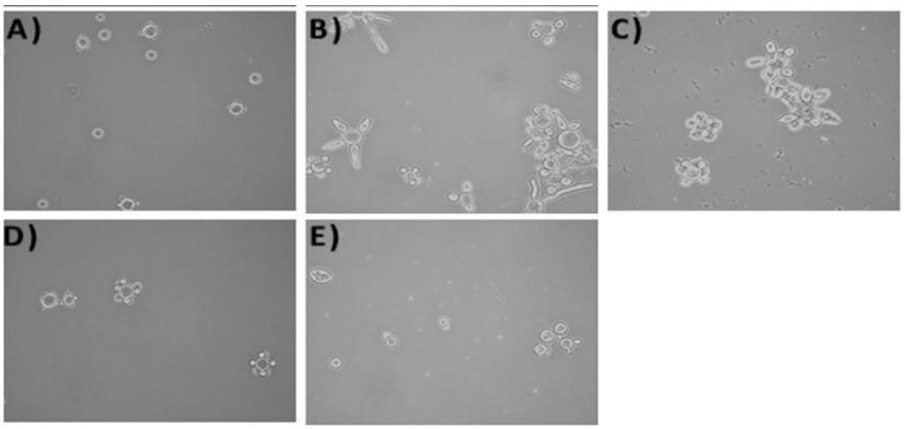


Figure 1.5. Morphological appearance of *M. circinelloides* wild strain, M5 (deficient in dehydrogenated alcohol, adh-gene) during aerobic germination with YPG culture medium. Observation after 48 hours of incubation: (a) **33** (b) **34** (c) **30** (d) **38** (e) **41** (concentrations of each molecule, 100 µg / ml of culture medium). The difference in the germination is observed, observation made at 400X.

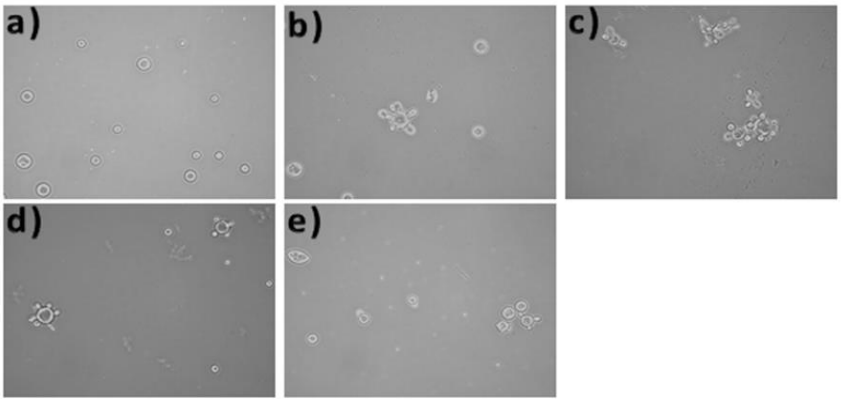


Figure 1.6. Morphological appearance of *M. Circinelloides* wild strain (R7B) during aerobic germination with YPG culture medium. Observation at 48 h of incubation: (a) **33** (b) **34** (c) **30** (d) **38** (e) **41**. (Concentrations of each molecule, 100 µg/ml of culture medium). The difference in the germination is observed, observation made at 400X Carls Zeiss.

Chapter II

Electrophilic *ortho*-chlorination of phenol and phenol-ethers: The use of PIFA/$AlCl_3$ system

ACUERDO DE DIVULGACIÓN

Los que suscriben Pradip D. Nahide, Velayudham Ramadoss, Kevin A. Juárez-Ornelas, Yuvraj Satkar, Rafael Ortíz-Alvarado, Juan M. J. Cervera-Villanueva, Ángel J. Alonso-Castro, Juan R. Zapata-Morales, Marco A. Ramírez-Morales, Alan J. Ruiz-Padilla, Martha A. Deveze-Álvarez y César R. Solorio Alvarado manifestamos:

1. Que somos coautores del artículo titulado: *"In Situ Formed I(III)-Based Reagent for the Electrophilic ortho-Chlorination of Phenols and Phenol-Ethers: The Use of PIFA-$AlCl_3$ System",* publicado en la revista de divulgación científica *European Jouranl of Organic Chemistry.*
2. Nuestra conformidad en la divulgación total del contenido del artículo antes mencionado, en el Capítulo II de la tesis elaborada por el M.C. Pradip D. Nahide.
3. Que dicha divulgación en la disertación antes mencionada, no genera conflicto de intereses a ninguno de los coautores del artículo.

Lo anterior con fundamento en los artículos 4, 18-20, 21 fracc I y 80 de la Ley Federal del Derecho de Autor.

Leído y firmado este acuerdo por todos los manifestantes a los 24 días del mes de agosto de 2018.

Dr. César Rogelio Solorio Alvarado
M.C. Pradip D. Nahide
M.C. Velayudham Ramadoss
M.C. Kevin A. Juárez Ornelas
M.C. Yuvraj Satkar
Dr. Rafael Ortiz Alvarado
Dr. Juan M. J. Cervera Villanueva
Dr. Ángel J. Alonso Castro
Dr. Juan R. Zapata Morales
Dr. Marco A. Ramírez Morales
Dr. Alan J. Ruiz Padilla
Dra. Martha Alicia Deveze Álvarez

Chapter II

Introduction.

Chlorinated compounds are ubiquitous in nature. They are found in naturally occurring compounds[185] agrochemicals,[186] synthetic intermediates,[187] and materials science[188] among others. Specifically, chlorophenols are a relevant class of substrates as they are very important in the industrial and pharmacological area[189] (Figure 2.1).

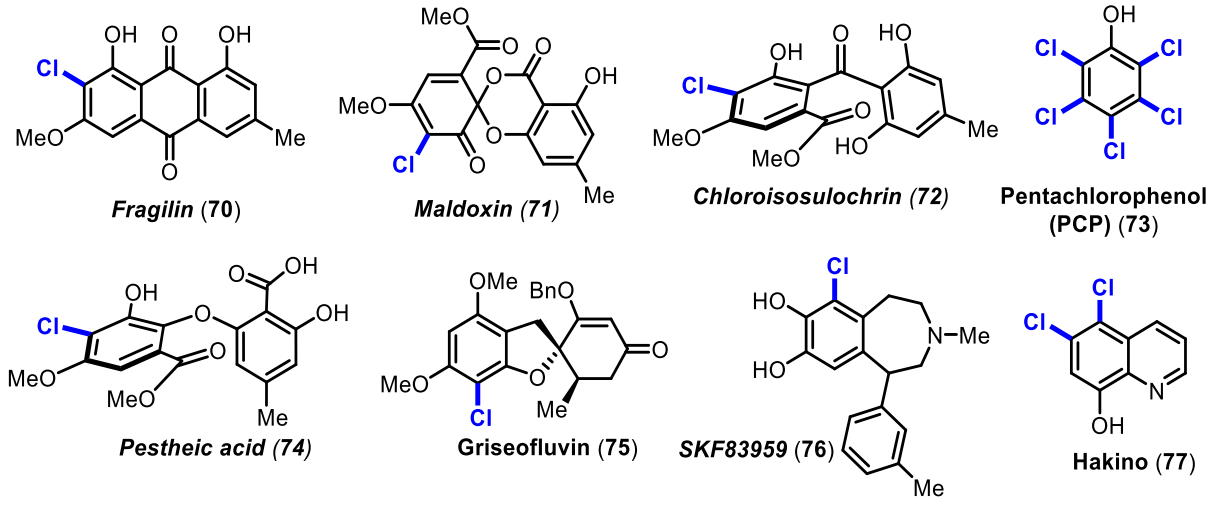


Figure 2.1. Relevance of chlorophenol core.

185. a) Rønnest, M. H.; Raab, M. S.; Anderhub, S.; Boesen, S.; Krämer, A.; Larsen, T. O.; Clausen, M. H. *J. Med. Chem.* **2012**, *55*, 652–660; b) Boger, D. L., *Med. Res. Rev.* **2001**, *21*, 356–381; c) Liu, L.; Liu, S.; Jiang, L.; Chen, X.; Guo, L.; Che, Y. *Org. Lett.* **2008**, *10*, 1397–1400; d) Liu, L.; Li, Y.; Liu, S.; Zheng, Z.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. *Org. Lett.* **2009**, *11*, 2836–2839; e) Liu, L.; Bruhn, T.; Guo, L.; Götz, D. C. G.; Brun, R.; Stich, A.; Che, Y.; Bringmann, G.; *Chem. Eur. J.* **2011**, *17*, 2604–2613; f) Liu, L. *Mycology.* **2011**, *2*, 37–45.

186. a) Krieger, R. *Hayes' Handbook of Pesticide Toxicology*, Vol. 1; Elsevier: London, **1991**; b) Latch, D. E.; Packer, J. L.; Stender, B. L.; VanOverbeke, J.; Arnold, W. A.; McNeill, K. *Environ. Toxicol. Chem.* **2005**, *24*, 517–525.

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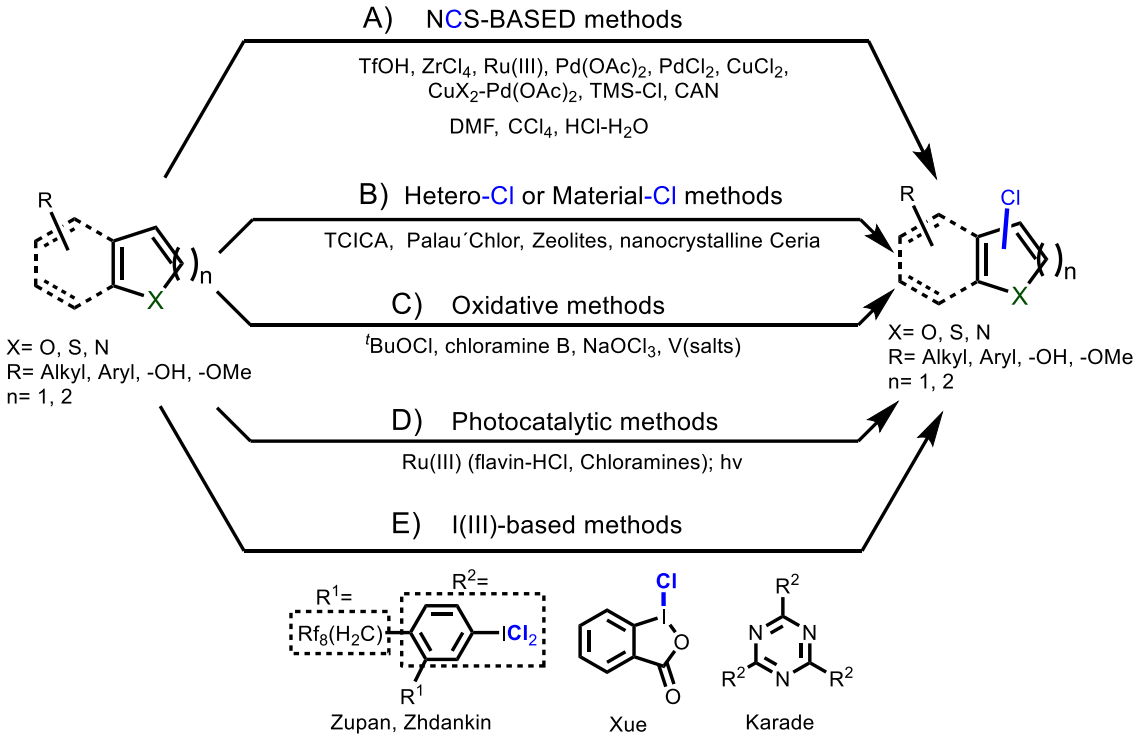
The synthesis of aryl chlorides has been widely described. In big scale, the industrial chlorination uses chlorine gas, however, it is hazardous and special attention is required.[190] In the academic laboratory, some chlorination procedures for aryls including phenol and its derivatives are available. A broadly described protocol implies the use of *N*-chlorosuccinimide in DMF,[191] CCl_4,[192] or HCl/H_2O[193] (Scheme 2.1A).



Scheme 2.1. Different chlorinating methods for arenes.

190. a) Jaeger, D. A., Clennan, M. W., Leyden, D. E., Murthy, R. S. S. *Tetrahedron Lett.* **1987**, *28*, 4805–4808; b) Watson, W. D. *J. Org. Chem.* **1985**, *50*, 2145– 2148; c) De Kimpe, N., De Bucyk, L.; Verhé, R.; Wychuyse, F.; Schamp, N. *Synth. Commun.* **1979**, *9*, 575–582.

191. Radhakrishnmurti, P. S.; Sahu, S. N. *Indian J. Chem. Sect. B* **1978**, *16B*, 81–82.

192. Gruter, G. J. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473–4481.

193. Sharma, S. K. *Res. J. Chem. Sci.* **2015**, *5*, 54–73.

However, due to the relative low electrophilicity at the chlorine atom, a reagent activation with Lewis bases (Ph_3PS),[194] strong Brønsted acids (TfOH)[195] metallic Lewis acids [$ZrCl_4$[196] Ru^{III},[197] $Pd(OAc)_2$,[198] $PdCl_2$ or $CuCl_2$,[199] $CuX_2/Pd(OAc)_2$[200]], nonmetallic Lewis acids (TMS Cl[201]) or oxidants (CAN,[202] CAN-HCl[203]) is commonly necessary in order to make the chlorine atom enough electrophilic to be attacked by the arene. On the other hand, significant efforts have been made to develop more mild and reactive chlorination reagents such as trichloroisocyanuric acid(TCICA), 1,3-dichloro- 5,5-dimethylhydantoin (DCDMH), 2,2,6,6-tetramethylpiperidine (TMPH)/SO_2Cl_2,[204] zeolites,[205] and nanocrystallineCeria[206] (Scheme 2.1B).

Recently, Baran et al. described an elegant and broad method for the chlorination of heteroarenes. This approach uses the guanidine-based reagent (Palau′Chlor®).[207] Worth to mention are also the strong oxidative chlorinating methods, which use *t*BuOCl,[208] chloramine B,[209] $NaOCl_3$/HCl/AcOH,[210] or divanadium salts (with H_2O_2[211] or Selectfluor®[212]) (Scheme 2.1C).

194. Maddox, S. M.; Nalbandian, C. J.; Smith, D. E. Gustafson, J. L.; *Org. Lett.* **2015**, *17*, 1042–1045.
195. Sun, X., Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4440– 4444; *Angew. Chem.* **2013**, *125*, 4536.
196. Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett.* **2005**, *18*, 2837–2842
197. Q. Yu, L. Hu, Y. Wang, S. Zheng, J. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 15284–15288; *Angew. Chem.* **2015**, *127*, 15499.
198. a) Zhang, P.; Hong, L.; Li, G.; Wang, R. *Adv. Synth. Catal.* **2015**, *357*, 345– 349; b) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 10800–10804; *Angew. Chem.* **2013**, *125*, 11000; c) Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal.* **2011**, *353*, 1285–1305.
199. Jafarpour, F.; Hazrati, H.; Zarei, S.; Izadidana, S. *Synthesis.* **2014**, *46*, 1224–1228.
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202. Bose, A.; Mal, P. *Tetrahedron Lett.* **2014**, *55*, 2154–2156.
203. Tale, N. P.; Shelke, A. V.; Karade, N. N. *Synth. Commun.* **2012**, *42*, 2959– 2965.
204. Chlorinating procedures involving reagents which contain N–Cl bond: a) for TCICA: Mendonca, G. F; de Mattos, M. C. S.; *Curr. Org. Synth.* **2013**, *10*, 820–836; b) for DCDMH, this protocol describes a highly *ortho*-chlorination of anilines: Xion, X.; Yeung, Y.-Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 16101–16105; *Angew. Chem.* **2016**, *128*, 16335; c) for TMP-Cl formed by using TMPH/SO_2Cl_2, this protocol describes a regioselective *ortho*chlorination of phenols: Saper, N. I.; Snider, B. B. *J. Org. Chem.* **2014**, *79*, 809–813.
205. a) Boltz, M.; Losch, P.; Louis, B.; Rioland, G.; Tzanis, G.; Daou, T. J. *RSC Adv.* **2014**, *4*, 27242–27249; b) Mendonca, G. F.; Bastos, A. R.; Boltz, M.; Louisb, B.; Paleb, P.; Estevesa, P. M.; Mattos, M. C. S. *Appl. Catal. A* **2013**, *460–461*, 46–51.
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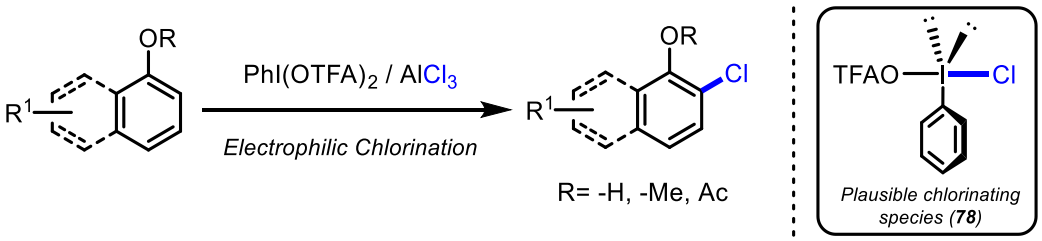
209. Lu, Z.; Li, Q. Tang, M.; Jiang, P.; Zheng, H.; Yang, X. *Chem. Commun.* **2015**, *51*, 14852–14855.
210. Moon, B. S.; Choi, H. Y.; Koh, H. Y.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 472–476.
211. Mizuno, N.; Kamata, K.; Yamaguchi, K. *Catal. Today*. **2012**, *185*, 157–161.
212. Shi, L. Zhang, D.; Lin, R.; Zhang, C.; Li, X.; Jiao, N. *Tetrahedron Lett.* **2014**, *55*, 2243–2245

The arene chlorination by photocatalysis with flavin hydrochloride[213] or chloramines in presence of Ru^{III} complexes[214] are also valuable alternatives (Scheme 2.1D). Finally, the chlorination of arenes including phenols and phenol ethers by using hypervalent iodine(III)-based reagents were initially described by Zupan and Zhdankin[215] Karade[216] and Xue[217] also described achlorination of some arenes by using iodine(III)-based reagents (Scheme 2.1E).

Even though a vast amount of chlorinating procedures for arenes is available, all of them show relevant disadvantages, for example, the reagent activation or preparation, costly acquisition, or polymerization. Regarding the iodine(III)-based chlorinating methods, the low solubility is an important drawback. Herein we described the first iodine(III)-based chlorinating reagent generated in situ by the easy mix of bis[(trifluoroacetoxy) iodobenzene] (PIFA) and $AlCl_3$. The reagent **78** is fully soluble in the organic solvent and is used in the same reaction flask. The use of inexpensive reagents and the fast in situ reagent formation are the main advantages of our procedure over those previously described We apply this protocol to the direct chlorination of some phenols and phenol ethers (Scheme 2.2).



Scheme 2.2. Electrophilic ortho- Chlorination of phenols and phenol ethers.

Results and discussion.

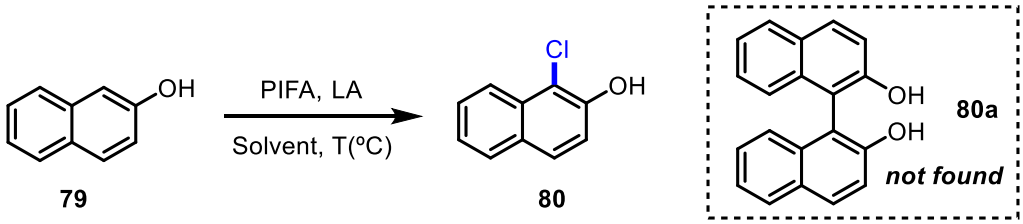
The total synthesis of dimeric naturally occurring compounds is one of the research interests in our group. We are currently carrying out the synthesis of a variety alkaloids. While searching for a new route to dimeric natural products through the dimerization of naphthol by using PIFA and a Lewis acid.

213. Hering, T.; Mühldorf, B.; Wolf, R.; König, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 5342–5345; *Angew. Chem.* **2016**, *128*, 5428.
214. Hering, T. König, B. *Tetrahedron.* **2016**, *72*, 7821–7825.
215. a) Šket, B.; Zupan, M.; Zupet, P. *Tetrahedron.* **1984**, *40*, 1603–1606; b) Chen, J. M.; Zeng, X. M.; Middleton, K.; Zhdankin, V. V. *Tetrahedron Lett.* **2011**, *52*, 1952–1955.
216. P. B. Thorat, B. Y. Bhong, N. N. Karade, *Synlett.* **2013**, *24*, 2061–2066.
217. a) Wang, M.; Zhang, Y.; Wang, T.; Wang, C. Xue, D.; Xiao, J. *Org. Lett.* **2016**, *18*, 1976–1979; b) A relevant I^{III}-based reagent for ethoxychlorination was recently identified by ESI: Nocquet-Thibault, S.; Minard, C.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Tetrahedron.* **2014**, *70*, 6769–6775.

we surprisingly observed selective halogenation at the alpha position rather than dimerization with $AlCl_3$, in such a way that the development of the present chlorinating method was a serendipitous discovery. We carried out a Lewis acid screening, looking for a new ligand-activation procedure[218] in the PIFA-mediated oxidative dimerization of phenols (Table 2.1).[219]

Optimization of the reaction conditions for chlorination of 2-napthol 79.

Table 2.1. Ligand screening and optimization in the PIFA-$AlCl_3$ mediated chlorination of 2-naphthol (**79**).[220]



79 **80**

Entry	**LA** (Equiv.)	**Solvent**	**T** (ºC)	**Time** (h)	**Yield** %
1	BF_3 (1.0)	DCM	-78	2	n. r.
2	BF_3 (1.0)	DCM	23	1	c. m.
3	$GaCl_3$ (1.0)	DCM	23	0.5	dec.
4	$AlCl_3$ (1.0)	DCM	23	3	60[a]
5	$AlCl_3$ (2.0)	DCM	23	2	63[a]
6	$AlCl_3$ (1.0)	CH_3Cl	23	3	30[b]
7	$AlCl_3$ (1.5)	$CHCl_3$	23	2.5	40[b]
8	$AlCl_3$ (2.0)	$CHCl_3$	23	2.5	41[b]
9	$AlCl_3$ (1.0)	MeCN	23	2	n.c.r
10	$AlCl_3$ (1.5)	MeCN	23	2	n.c.r
11	$AlCl_3$ (2.4)	MeCN	23	2	63[b,c]

All the reactions were carried out by using 1 equiv of PIFA. [a] very complicated chromatography purification; [b] Isolated yield; [c] 1.2 equiv of PIFA were used. LA = Lews acid; n.r.= no reaction was observed; c.m.= complex reaction mixture; dec.= decomposition of starting material; n.c.r.= not completed reaction.

218. Dohi, T.; Morimoto, K.; Murayama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007–2010.

219. a) Dohi, T.; Minamitsuji, Y.; Murayama, A.; Hirose, S.; Kita, T. *Org. Lett.* **2008**, *10*, 3559–3562. b) Dohi, T. Ito, M.; Itani I.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, I. *Org. Lett.* **2011**, *13*, 6208–6211. c) Morimoto, K.; Yam-aoka, N.; Ogawa, C.; Nakae, T.; Fujioka, H.; Dohi, T.; Kita, Y. *Org. Lett.* **2010**, *12*, 3804–3807.

220. The optimization of the reaction conditions was carried out with the help of M.C. Adriana Cabrera.

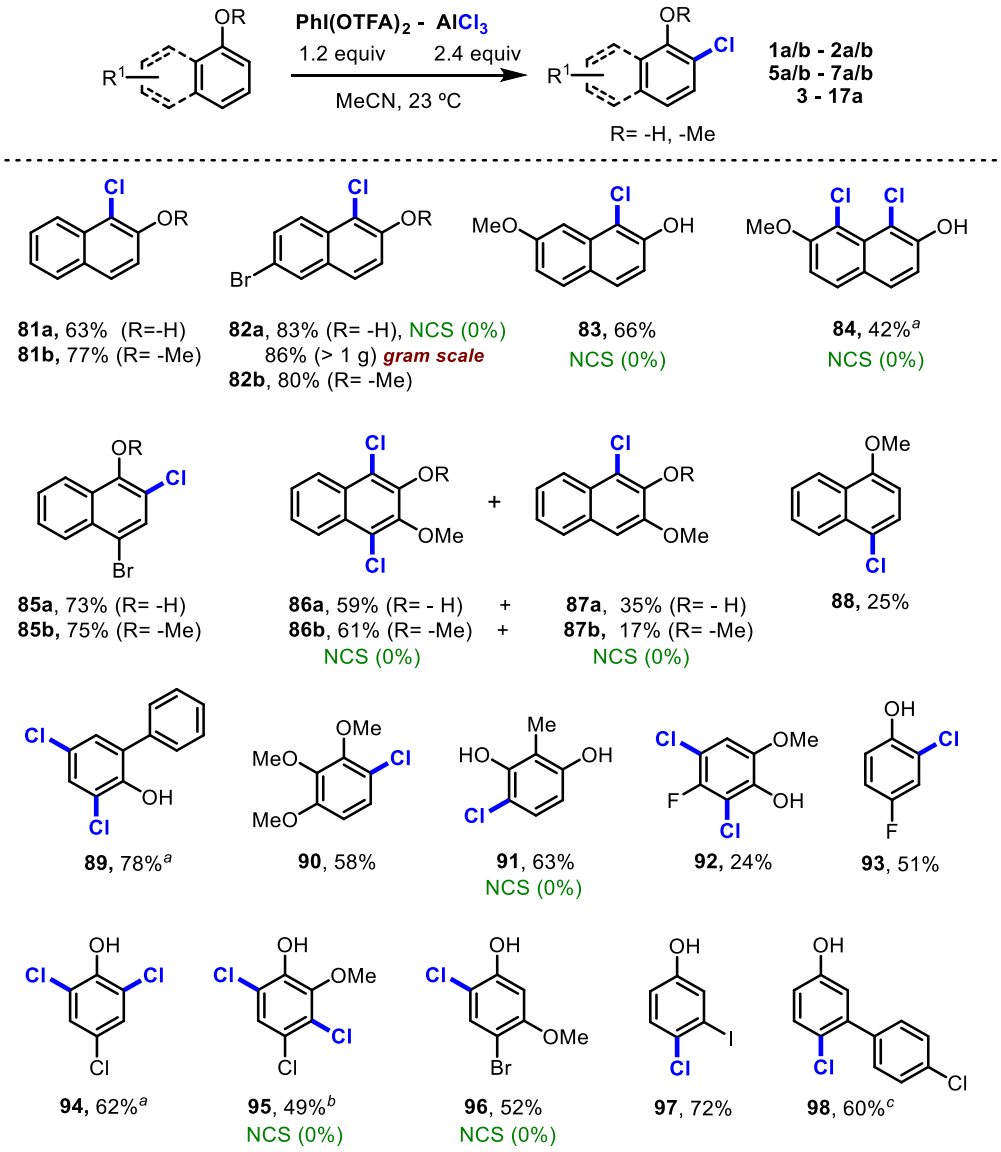
After carrying out some reactions and testing different Lewis acids, we could not find the desired 2-naphthol dimer **80a**. Instead, we found **80** as the product of the chlorination reaction at the α position (Table 2.1). When using $BF_3{\cdot}Et_2O$, the reaction did not proceed or gave a complex mixture (Entries **1** and **2**). The use of $GaCl_3$ only led to decomposition of the starting material (Entry **3**). Surprisingly, by using $AlCl_3$ at 23 °C, we observed the formation of 1-chloro-2-naphthol **80** in a good yield of 60 % as the main product (Entry **4**).

The formation of the corresponding dimer was not observed. At this point, we rationalized that the only source of chlorine atoms comes from the Lewis acid ($AlCl_3$). Thus, this necessarily implicates the oxidation of Cl^- by the iodine(III) reagent to give an electrophilic "Cl^+" equivalent. Subsequently, the 2-naphthol reacted to give **80**. To the best of our knowledge, this is the first report that describes and supports the oxidation of chlorine atoms in $AlCl_3$ by an iodine(III) reagent. With this hypothesis, we focused our attention to develop a new procedure for direct chlorination of phenols by using this novel PIFA–$AlCl_3$ system.

Next, we tested two equivalents of $AlCl_3$ to increase the amount of chlorine atoms. We found a shorter reaction time along with a slightly increased yield (Entry **5**). Nevertheless, using dichloromethane always provided a complex reaction mixture. The use of chloroform for screening different $AlCl_3$ equivalents produced moderate yields (30–41 %) at 23 °C in 2.5–3 h (Entries **6–8**). Finally, the screening of 1, 1.5, and 2.4 equivalents of $AlCl_3$ in acetonitrile (Entries **9–11**), gave the best yields and cleaner reactions. Thus, the optimized conditions were 2.4 equiv. of $AlCl_3$ at 23 °C with a reaction time of only 2 h (Entry **11**). Additionally, the reaction does not require a protection gas atmosphere.

With this new reagent for the chlorination of 2-naphthol and with its optimized conditions, we proceeded to test the scope of the protocol with different phenols. We also decided to test the procedure on some phenol ethers Some naphthols and phenols containing either electron-donating or electron-withdrawing groups were tested (Scheme 2.3).

Scope of the developed methodology.



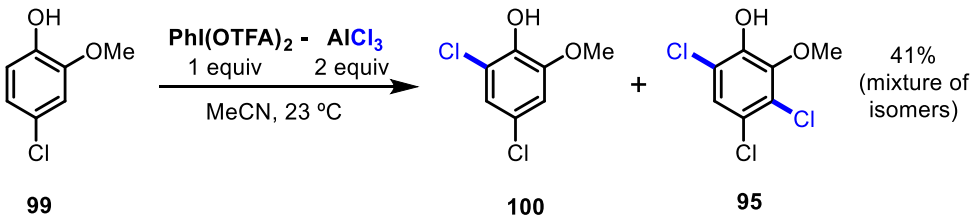
The reactions were carried out by using 1.2 equiv. of PIFA and 2.4 equiv. of $AlCl_3$. [a] 1.8 equiv. of PIFA and 3.6 equiv. of $AlCl_3$ were used to get a single compound since an *o*/*p* mixture was observed under the optimized conditions. [b] 2.4 equiv. of PIFA and 4.8 equiv. of $AlCl_3$ were used to get a single compound since an *o*/*p* mixture was observed under the optimized conditions. [c] The *ortho*-regioisomer was obtained in 25 %.

Scheme 2.3. Scope for the chlorination of phenols, naphthols, and phenol ethers by using the PIFA-$AlCl_3$ system.[221]

221. The compounds **81a-b**, **85a-b**, **86a-b**, **87-a-b**, **90**, **91**, **92**, **95** and **96** were synthesized by Msc.Velayudham Ramadoss.

The 2-napthol, as well as its methyl ether, were regioselectively chlorinated in *ortho* position in excellent yields of 63 % and 77 %, respectively (**81a**, **b**). The electronegativity of the bromine substituent did not affect the reaction. We found yields of 83 %and 73 % (**82a** and **85a**, respectively) for the chlorination of 6-bromo-2-naphthol and 4-bromo-1 naphthol. In fact, the gram scale reaction proceeded in good 86 % for **82a**. Its corresponding methyl ethers also proceed in 80 % and 75 % of yield (**82b**, **85b**). On the other hand, the electron-rich 7-methoxy-2-naphthol gave a good yield of 66 % for the monochlorinated (**83**) and 42 % for dichlorinated (**84**) product.[222] An additional example with 3-methoxy-2-naphthol as starting material gave a separable mixture of the mono- and dichlorinated naphthols **86a** (59 %) and **87a** (35 %), respectively. The methyl ether analogues **86b** (61 %) and **87b** (17 %) were also obtained and separated without any problem by column chromatography. Some attempts to control the mono- or dichlorination processes led to complex reaction mixtures.

For completing the series of naphthols, 1-methoxynaphthalene was chlorinated in a modest yield of 25 % at the *para* position in respect to the methoxy group. Regarding to the phenol derivatives, those containing electron- donating groups like phenyl (**89**), methoxy (**90**), or methyl (**91**) were *ortho*-chlorinated from good to excellent yields (58– 78 %). The presence of any halogen in the phenol core was well tolerated by our procedure. Thus, 5-fluoro-2-methoxyphenoland 4-fluorophenol were chlorinated in 24 % and 51 % yield (**92** and **93**, respectively). To get the bichlorinated product the reaction was optimized because standard conditions gave a regioisomeric mixture (Scheme 2.4).



Scheme 2.4. Regioisomers with standard conditions obtained.

The chlorophenols **94** and **95** were also obtained in 62% and 49 % yield starting from 4-chlorophenol and 4-chloro-2-methoxyphenol **99** respectively. The 4- bromo-3-methoxyphenol gave rise to bromophenol **96** in moderate 52 % yield.

222. Several attempts to optimize reaction to get better yields for mono- or bichlorination gave only complex reaction mixtures.

Finally, the 3-iodophenol and 3-(4-chlorphenyl) phenol were chlorinated in excellent yields of 72 % and 60 %, yielding **97**[223] and **98** chlorinated at the *para* position in respect to the hydroxyl group. The examples **88**, **97**, and **98** were exceptions to the general *ortho*-chlorination reaction observed for this series. All of the reactions were completed under very mild temperatures (23 °C), in short periods of time and in open flask. Thereby, the *ortho*-chlorination is a remarkable aspect in our method that we discuss as follows. The naphthols **81a/b**, **82a/b**, **85a/b**, **86a/b**, and **87a/b** were obtained as regioselective *ortho*chlorinated compounds, which match with those previously described.[224] Compound **89** shows a coupling of J = 2.5 Hz at δ = 7.22 and 7.24 ppm, consistent with coupling at the *meta* position of the benzene ring, which contains the chlorine atoms. Therefore, this suggests an *ortho*-chlorinated structure as shown in Scheme 2. The ^{1}H NMR spectra of compounds **90** and **91** show signals at δ = 7.06 and 6.62 ppm with a coupling constant of J = 8.5 Hz, which implies an *ortho* coupling as well as the chlorination for both arenes. Aromatic compounds **92** to **96** showed mono- or dichlorination from 24 % to 62 % of yield. In a general way, all these examples were chlorinated in *ortho* and *ortho, para* positions in respect to the hydroxyl group.

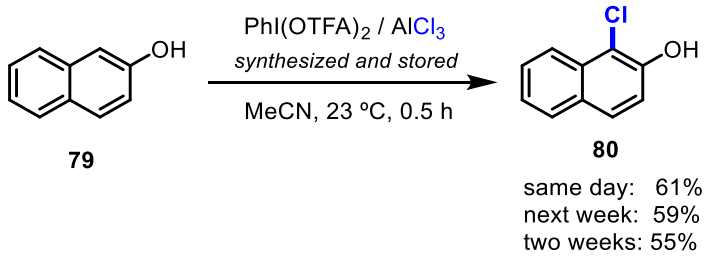
To support the *ortho* selectivity in our protocol, it is important to mention that: 1) compound **89** was formed as a mixture of *ortho* and *para* regioisomers in a ratio of 3:1[225] The *para* product was observed as the minor regioisomer. Then, an additional optimization was carried out to get a single dechlorinated product (Scheme 2) the *ortho*-disubstituted naphthols with the hydroxyl group in the middle of both substituents ***did not react*** even when heating the reaction mixture at 80 °C for 12 h (see Scheme 2.5). The former observation alludes to an initial ***orthochlorination*** instead to the known *para* reactivity, which fully supports the *ortho* regioselectivity observed in our protocol. However, compounds **97** and **98** were exceptions to the aforementioned regioselectivity. A broad set of experiments in synergy with theoretical calculations is necessary to genera ize our protocol and find out a detailed mechanism of reaction, which fully explain the *ortho*/*para* ratios. At this point, the series of examples herein described demonstrated a reaction with initial *ortho* selectivity. One notable aspect in our work is the remarkable reactivity of our in situ formed reagent. It was effective in the chlorination of a variety of naphthols and phenols to give **82a**, **83**, **84**, **86b**, **87b**, **91**, **95** and **96** those could not be obtained by using NCS instead.

223. Maddox, S. M; Dinh, A. D.; Armenta, F.; Um, J.; Gustafson, J. L. *Org. Lett.* **2016**, *18*, 5476–5479.

224. References that described the spectroscopic data of synthesized chlorinated naphthols. For **8a** and **81b**: Ohkubo, K. *Chem. Asian. J.* **2016**, *11*, 996–999. For **85a**: Stevens, C. L.; Beereboom, J. J.; Rutherford Jr, K. G.; *J. Am. Chem. Soc.* **1955**, *77*, 4590–4593. For **85b**: Lorz, E.; Baltzly, R. *J. Am. Chem. Soc.* **1951**, *73*, 93–95. For **86b**: Bell, F.; Buck, K. R. *J. Chem. Soc.* **1963**, 4626–4633.

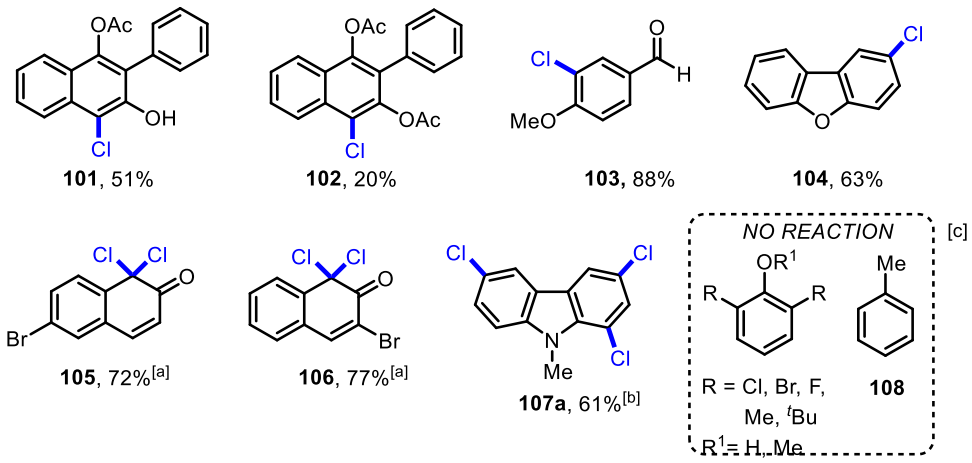
225. The *ortho*/*para* regioselectivity found is much lower compared with those described by professor Gustafson in reference 56.

This observation broadly supports the advantage of our procedure over those NCS-based methodologies. Also, we found that after storing our chlorinating reagent for two weeks at 4 °C,[226] it essentially maintained its reactivity [Equation (2.1)]. [227]



(**2.1**)

On the other hand, for testing additional functional-group tolerance and limitations in our protocol, we set up some more elaborated phenols and a heterocycle. 3-Hydroxy-2-phenylnaphthalen-1-yl acetate was regioselectively *ortho*-chlorinated with respect to the hydroxy group to give **101** in moderated 51 % yield (Scheme 2.5).



The reactions were carried out by using 1.2 equiv. of PIFA and 2.4 equiv. of $AlCl_3$. [a] 2.4 equiv. of PIFA and 4.8 equiv. of $AlCl_3$ were used. [b] 4 equiv. of PIFA and 6 equiv. of $AlCl_3$ were used; the tetrachlorinated derivative was obtained in 13 % (see the Supporting Information for full details). [c] The chlorination reaction did not proceed at 23 ºC or 80 ºC during 12 h. The new carbon-chlorine bond formed is highlighted in red color.

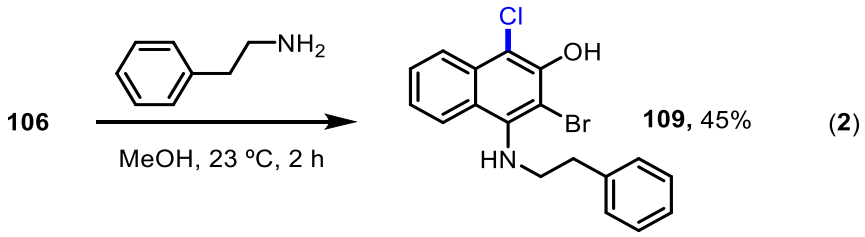
Scheme 2.5. Scope and limitations in the arene chlorination by using the PIFA–$AlCl_3$ system.

The analogue biacetylated 1,3-naphthodiol was also *ortho*-chlorinated with respect to the 3-acetoxy group yielding **102** in 20 %. These examples expand the scope of our procedure at the

226. The synthesis of our regent consists on the easy mix of PIFA-$AlCl_3$ in 1.2:2.4 ratio in MeCN followed by solvent evaporation after 30 minutes. Based upon Scheme 4, we considered for stoichiometry calculations, that the weight of the obtained solid is a mixture of **IV** and **X**. The purification of reagent **IV** has not been successfully carried out.

227. This set of experiments for determining the reactivity and stability of our proposed PhI(OTFA)Cl was carried out by MSc. Yuvraj Satkar.

hydroxyl group of naphthol by including the acetyl functionality. An *p*-anisaldehyde was also chlorinated to give an excellent 88 % of yield to get **103**. Dibenzofuran was chlorinated at *para* position to the oxygen to give **104** in 63 %.[228] Even though this example does not show the previously observed regioselectivity for our developed procedure, it can be applied in principle to *O*-heterocyclic systems. On the other hand, looking for conditions toward dichlorination of 6-bromo-2-naphthol and 3-bromo-2-napthol, we found a very attractive chlorinative dearomatization, which yields *gem*-chlorohydronaphthalenes. This reaction proceeds in excellent yields of 72 % for **105** and 77 % for **106**. Finally, the applicability of *N*-heterocycles was demonstrated by the trichlorination of the *N*-methylcarbazole giving rise to **107** in 61 % of yield. According to the literature,[229] compounds such as **105** and **106** are starting materials in the synthesis of highly substituted anilines. Thus, to test the applicability of our synthesized compounds, we decide to use **106** in the synthesis of a highly functionalized aniline. Thereby aniline **109** was successfully synthesized in 45 % yield and in only two hours of reaction. [Equation (2.2)].



Regioselectivity of compound 82b.

Also, the absolute regioselectivity of compound **82b** was determined by X-ray crystallographic analysis (Figure 2.2).

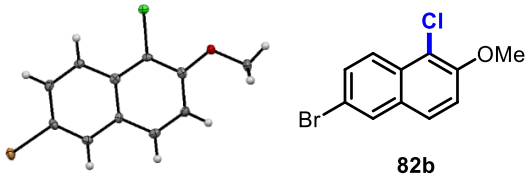


Figure 2.2 ORTEP diagram of Compound **82b** at 50% probability level.

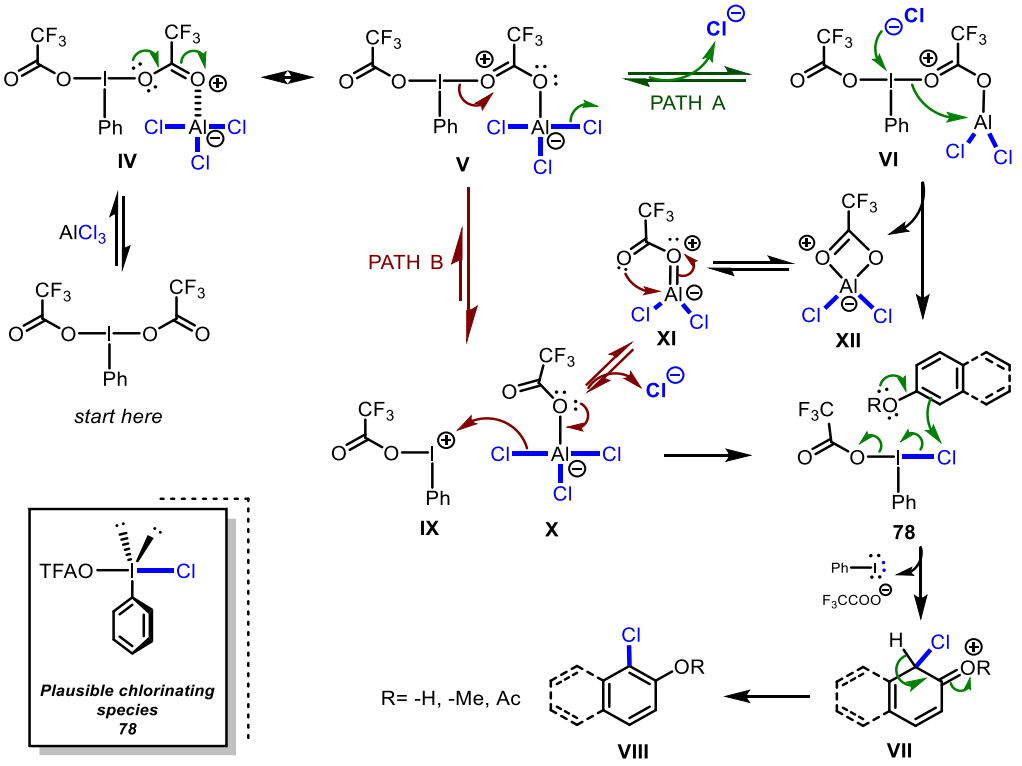
This crystal structure has been deposited with the Cambridge Crystallographic Database (CCDC) the deposition number is CCDC **1544797.**

228. The compound **104** was synthesized by Adriana Cabrera.

229. Brittain, J. M.; Calvert, D. J.; de la Mare, P. B. D.; Jones, T. C.; Newman, P. A.; Waters, J. M. *J. Chem. Soc. Perkin. Trans.* **1983**, *2,* 247–253.

Proposed reaction mechanism for *ortho*-chlorination reaction.

Finally, according to the experimental observations, we rationalized a plausible chlorinating species like **78** to explain the **C**–**Cl** bond formation in the chlorination reaction. Thus, we propose the following mechanism of reaction (Scheme 2.6).

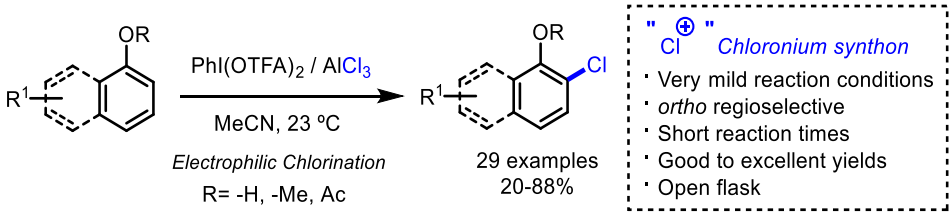


Scheme 2.6. Mechanistic proposal for the *ortho*-chlorination reaction observed in our developed method.

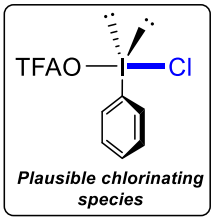
PIFA coordinates to $AlCl_3$ to give **IV**, which is in resonance with **V**. Two possible pathways are envisioned. The pathway A implies the release of a chloride anion giving rise to **VI**. Thus, the released chloride attacks to the electrophilic iodine center to produce aluminate **XII** and the intermediate **78**. This intermediate is a plausible reagent, proposed to be the chlorinating species formed in situ. Afterwards, the naphthol regioselectively attacks the chlorine atom to produce the intermediate **VII**. Finally, the loss of a proton aromatizes gives the arene and yields the *ortho*chlorinated phenol. On the other hand, pathway B starts with dissociation of **V** giving rise to **IX** and **X**. This is in equilibrium with **XI**, whereby a chloride anion is lost, which then attacks **IX** to produce the proposed chlorinating species **78**. The rest of the mechanism proceeds as described previously by generation of intermediate **VII** and final phenol **VIII**.

Conclusions.

- We have developed a new procedure for the *ortho*-selective chlorination of phenols and phenol ethers. Our protocol takes place under very mild conditions, short reaction times, in good to excellent yields, and in an open flask. The method scope includes the methyl and acetyl groups at the oxygen atom of the phenol and was applied to the chlorination of the dibenzofuran and *N*-methylcarbazole.



- This novel protocol has an I(III)-based reagent, which is formed in situ and contains a chlorine atom attached to the hypervalent iodine center. Our theoretical calculations support the formation of structure **78** (Scheme 2.6) as the plausible chlorinating species.



Finally, to the best of our knowledge, this is the first method that oxidizes the chlorine atoms originating from $AlCl_3$, and they are used as an electrophilic source of chlorine in the chlorination of phenols. All the previous features described in our protocol represent an Important advantage over other chlorination procedures that have been described previously.

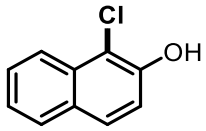
Experimental Section

Chlorination of phenol and phenol ethers **(80-98, 101-107).**

General procedure for chlorination A.

A 25 mL dry round-bottomed flask was charged with PIFA (1.2 equiv.) and dry acetonitrile [0.33 M] at 25 °C. Afterwards, $AlCl_3$ (2.4 equiv.) was suspended and the mixture was stirred for 10 min. A yellowish precipitate appears and then the corresponding phenol derivative (1 equiv.) was added to the mixture. The reaction proceeded for 2–12 h until the starting material was fully consumed as judged by TLC. The reaction mixture was extracted with EtOAc (3 × 10 mL) and water (10 mL). The organic extracts were collected, dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to remove the solvent. The product was purified by column chromatography on silica gel (100– 200 mesh) with EtOAc/hexane system

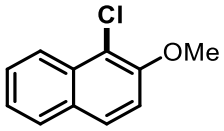
1-Chloronaphthalen-2-ol **(81a).**



The following compound was obtained according to the general procedure **A** for chlorination by using 2-napthtol in 63 % yield as a colorless liquid.^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.6 Hz, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 7.73 (d, J = 8.9 Hz, 1 H), 7.59 (t, J = 8.8 Hz,1 H), 7.42 (t, J = 7.9 Hz, 1 H), 7.27 (s, 1 H), 5.90 (s, 1 H) ppm; ^{13}C 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 ppm; IR cm^{-1} 3496, 3393, 3061, 2962, 1625, 1600, 1468, 1195, 1150, 809, 746; HRMS (ESI^+) calcd. for $C_{10}H_7ClO$ [M+H]: 179.0185, found 179.0111. The spectroscopic data match with those previously described.[230]

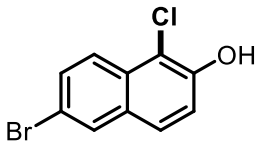
230. Ginsburg, D. *J. Am. Chem. Soc*. **1951**, *73*, 2723–2725.

1-Chloro-2-methoxynaphthalene **(81b).**



The following compound was obtained according to the general procedure **A** for chlorination by using 2-methoxynaphthalene in 77 % yield as white solid. m.p.47- 49 °C.^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.23 (d, *J* = 8.5 Hz, 1 H), 7.80 (t, *J* = 7.0 Hz, 2 H), 7.58 (t, *J* = 8.2 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 9.0 Hz, 1 H) 4.05 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): *δ* 152.5, 131.8, 129.5, 128.0, 127.9, 127.4, 124.3, 123.4, 116.9, 113.7, 57.0 ppm; IR cm^{-1} 3051, 2975, 1625, 1504, 1269, 1067, 801; HRMS (ESI+) calcd. for $C_{11}H_9ClO_2$ [M+H]: 193.0342, found 193.0424. The spectroscopic data match with those previously described.[231]

6-Bromo-1-chloronaphthalen-2-ol **(82a).**



The following compound was obtained according to the general procedure **A** for chlorination by using 6-Bromo-2-napthol in 83 % yield as a white solid. m.p. 84–86 °C. ^{1}H NMR (400 MHz, CDCl3): *δ* = 7.81 (d, *J* = 9.9 Hz, 2 H), 7.51 (d, *J* = 8.7 Hz, 2 H), 7.17 (d, *J* = 7.4 Hz, 1 H), 5.84 (s, 1 H) ppm; ^{13}C 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 ppm; IR (KBr) cm^{-1} 3423, 1621, 1567, 1589, 1498, 1464, 1404, 1381,1353, 1338, 1198, 1183, 1148, 1132, 1066, 1000, 938, 897, 805, 556, 514; HRMS (ESI–): calcd. for $C_{10}H_5BrCl_2O$ [M–H]: 255.9291, found 254.1203.

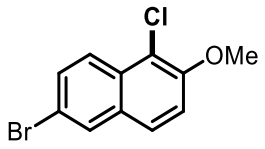
Gram scale reaction

This scalable reaction was carried out by using PIFA (2.45 g, 1.2 euqiv), $AlCl_3$ (1.52 g, 2.4 equiv.) and 6-Bromo-2-napthol (1.06 g, 1 equiv.). The reaction was completed in 3 h and purified by column chromatography to yield 1.05 g of **82a** (86 %). The spectroscopic data match with those previously described.[232]

231. Franzen, H. Stauble, G. *J. Prakt. Chem*. **1922**, *103*, 352–390.

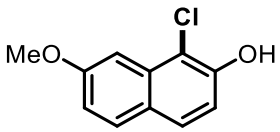
232. Matsunaga, N. Ojida, A.; Tanaka, T.; Hara, T. Yamaoka, M.; Kusaka, M.; Tasaka, A.; Kaku, T. *Bioorg. Med. Chem.* **2011**, *19*, 1751–1770.

6-Bromo-1-chloro-2-methoxynaphthalene **(82b).**



The following compound was obtained according to the general procedure **A** for chlorination by using 2-bromo-6-methoxynaphthalene in 80 % yield as white solid. m.p. 76–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 9.1 Hz, 1 H), 7.88 (d, J = 1.8 Hz, 1 H), 7.62 (d, J = 9.0 Hz, 1 H), 7.55 (dd, J = 9.1, 1.9 Hz, 1 H), 7.25 (d, J = 9.1 Hz, 1 H), 3.97 (s, 3 H) ppm; ^{13}C NMR (126 MHz, CDCl3): δ = 153.0, 130.9, 130.6, 130.6, 130.0, 127.1, 125.5, 118.3, 117.3, 114.8, 57.1 ppm. The spectroscopic data match with those previously described.[233]

1-Chloro-7-methoxynaphthalen-2-ol **(83).**

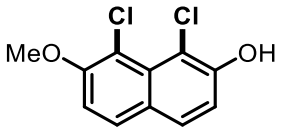


The following compound was obtained according to the general procedure **A** for chlorination by using 7-methoxy-2-napthol in 66 % yield as a with solid. m.p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.8 Hz, 1 H), 7.62 (d, J = 8.7 Hz, 1 H), 7.33 (s, 1 H), 7.11 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 8.9 Hz, 1 H), 5.90 (s, 1 H), 3.97 (s, 1 H) ppm; ^{13}C 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 ppm; IR (KBr) 3391, 2934, 1517, 1623, 1427, 1443, 1400, 1280, 1249, 1123, 1188, 1023, 1007, 837, 803, 603, 548, 523 cm^{-1}. The spectroscopic data match with those previously described.[234]

233. Rana, S.; Bag S.; Patra, T.; Maiti, D. *Adv. Synth. Catal.* **2014**, *356*, 2453–2458.

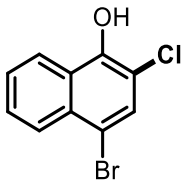
234. Mariano, A. E.; Mendieta, P. B. Hu, Q.; Engel, M. Hartmann, W. R. *J. Med. Chem*. **2013**, *56*, 6101–6107.

1, 8-Dichloro-7-methoxynaphthalen-2-ol **(84).**



The following compound was obtained according to the general procedure **A** for chlorination by using 7-methoxy-2-napthol in 42 % yield as a dark red solid. m.p. 84–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, J = 9.0 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.15 (d, J = 9.0 Hz, 2 H), 6.44 (s, 1 H), 4.01 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.3, 152.2, 129.6, 129.2, 128.9, 126.6, 115.5, 111.5, 111.4, 57.1 ppm; IR (KBr) cm^{-1} 3474, 1618, 1514, 1462, 1438,1358, 1325, 1285, 1246, 1222, 1138, 1093, 963, 894, 830, 794, 761, 729, 553, 529, 453. The spectroscopic data match with those previously described.[235]

4-Bromo-2-chloronaphthalen-1-ol **(85a).**

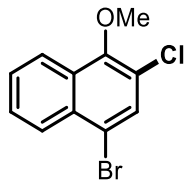


The following compound was obtained according to the general procedure **A** for chlorination by using 4-bromo-1-naphtol in 73 % yield as withe solid. m.p. 90-92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (dd, J = 8.2, 7.8 Hz, 1 H), 8.17 (dd, J =8.5, 8.2 Hz, 1 H), 7.71–7.51 (m, 3 H), 6.0 (s, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 128.9, 128.0, 127.7, 127.0, 126.9, 126.8, 125.5, 124.4, 122.5, 122.5 ppm; IR (KBr) cm^{-1} 3360, 2923, 1716, 1518, 851,753; HRMS (ESI+) calcd. for $C_{10}H_6BrClO$ [M+H]: 256.9108, found 256.5110. The spectroscopic data match with those previously described.[236]

235. Guy, A.; Lemaire, M.; Guetté, J. P. *Tetrahedron*. **1982**, *38*, 2347–2354

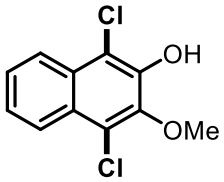
236. Stevens, C. L., Beereboom Jr., J. J.; Rutherford, K. G., *J. Am. Chem. Soc*. 1955, 77, 4590–4593.

4-Bromo-2-chloro-1-methoxynaphthalene **(85b).**



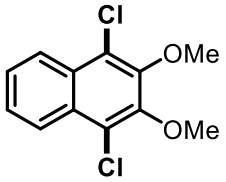
The following compound was obtained according to the general procedure for chlorination by using 4-bromo-1-methoxynaphthalene in 75 % yield as a colourless solid. m.p. 53- 56 °C. ^{1}H NMR (500 MHz, CDCl3): *δ* = 8.17 (m, 2 H), 7.78 (s, 1 H), 7.62 (m, 2 H), 4.03 (s, 3 H) ppm; ^{13}C NMR (126 MHz, CDCl3) *δ* 151.7, 131.8, 130.7, 129.7, 127.5, 127.7,127.5, 122.9, 122.4, 117.7, 61.5 ppm; IR (KBr) cm^{-1} 2917, 2849, 1578, 1449, 1365, 1247, 1211, 979, 691; HRMS (ESI+) calcd. for $C_{11}H_8BrClO$ [M+K]: 310.5380, found 310.1464.

1,4-Dichloro-3-methoxynaphthalen-2-ol **(86a).**



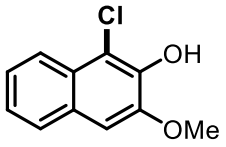
The following compound was obtained according to the general procedure for chlorination by using 3-methoxy-2-napthol in 59 % yield as with solid. m.p. 128–130 °C. ^{1}H NMR (500 MHz, CDCl3): *δ* = 8.19 (d, *J* = 8.4 Hz, 1 H), 8.12 (d, *J* = 8.4 Hz, 2 H), 7.58 (dd, *J* = 10.7, 0.9 Hz, 1 H), 7.51 (dd, *J* = 10.7, 0.9 Hz, 1 H), 6.29 (s, 1 H), 4.07 (s, 3 H) ppm.;^{13}C NMR (126 MHz, CDCl3): *δ* = 144.8, 144.2, 128.6, 127.3, 126.3, 125.6, 124.2, 123.2, 122.3, 113.1, 61.4 ppm; HRMS (ESI–) calcd. for $C_{11}H_8Cl_2O_2$ [M–H]: 240.9901, found 240.9703.

1,4-Dichloro-2,3-dimethoxynaphthalene **(86b).**



The following compound was obtained according to the general procedure for chlorination by using 2,3-dimethoxynaphthalene in 61 % yield as a colourless solid. m.p. 48–50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 4.4 Hz, 2 H), 7.59 (d, J = 4.4 Hz, 2 H), 4.03 (s, 6 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.2, 128.7, 126.9, 124.4, 123.2, 61.3 ppm; IR (KBr):cm^{-1} 3051, 2975, 1625, 1504, 1269, 1067, 801; HRMS (ESI+) calcd. for $C_{12}H_{10}Cl_2O_2$ [M +H]: 257.0058, found 257.0151. The spectroscopic data match with those previously described.[237]

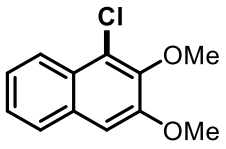
1-Chloro-3-methoxynaphthalen-2-ol **(87a).**



The following compound was obtained according to the general procedure for chlorination by using 3-methoxy-2-naphtol in 35 % yield as a colorless solid. m.p. 62–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.6 Hz, 1 H), 7.71 (d, J = 7.2 Hz, 1 H), 7.47 (dd, J = 13.7,1.2 Hz, 1 H), 7.40 (dd, J = 12.2, 1.1 Hz, 1 H), 7.09 (s, 1 H), 6.24 (s, 1 H), 4.05 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.1, 142.1, 128.6, 126.9, 126.8, 125.2, 124.7, 122.9, 113.5, 104.8, 56.1 ppm; IR (KBr) cm^{-1}= 3415, 2920, 1633, 1462, 1017, 820; HRMS (ESI+) calcd. for $C_{11}H_9ClO_2$ [M + H]: 209.0291, found 209.0383.

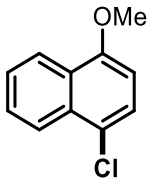
237. See ref.[90]

1-Chloro-2,3-dimethoxynaphthalene **(87b).**



The following compound was obtained according to the general procedure for chlorination by using 2,3-dimethoxynaphthalene in 17 % yield as a yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 4.0 Hz, 1 H), 7.72 (d, *J* = 6.7 Hz, 1 H), 7.47 (d, *J* = 4.6 Hz, 2 H), 7.13 (s, 1 H), 4.0 (s, 3 H), 3.98 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.4, 145.8, 131.1, 126.7, 126.6, 126.1, 124.8, 124.3, 124.0, 106.0, 60.9, 55.9ppm; IR (KBr) cm^{-1} 3068, 2941, 1588, 1456, 1396, 1244, 994, 746. HRMS (ESI+) calcd. for $C_{12}H_{11}ClO_2$ [M+H]: 223.0448, found 223.0544.

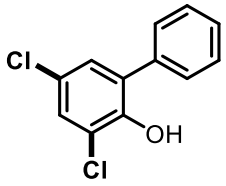
1-Chloro-4-methoxynaphthalene **(88).**



The following compound was obtained according to the general procedure for chlorination by using 1-methoxynaphthalene in 25 % yield as slightly yellow oil. ^{1}H NMR (500 MHz, CDCl3): δ = 8.29 (d, *J* = 8.4 Hz, 2 H), 8.20 (d, *J* = 8.5 Hz, 2 H), 7.62 (t, *J* = 7.1 Hz, 2 H), 7.54 (t, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 6.73 (d, *J* = 8.2 Hz, 2 H), 4.00 (s, 6 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.8, 131.4, 127.6, 126.8, 126.1, 125.9, 124.4, 123.4, 122.6, 104.0, 55.8 ppm. The spectroscopic data match with those previously described.[238]

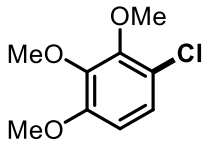
238. Orazi, V. O. O.; Salellas, J. F.; Fondovila, M. E.; Corral, R. A., Mercere, N. M. I.; Alvarez, E. C. *Anales de la Asociacion Quimica Argentina* **1952**, *40*, 61–73.

3,5-Dichloro-[1,1′-biphenyl]-2-ol **(89).**



The following compound was obtained according to the general procedure for chlorination by using [1,1′-biphenyl]-2-ol, 1.8 equiv. of PIFA and 3.6 equiv. of AlCl3 in 78 % yield as white solid. m.p. 38–40 °C. ^{1}H NMR (500 MHz, CDCl3): δ = 7.51 (d, *J* = 7.0 Hz, 2 H), 7.46 (dd, *J* = 10.1, 4.7 Hz, 2 H), 7.40 (t, *J* = 6.7 Hz, 1 H), 7.34 (d, *J* = 2.5 Hz, 1 H), 7.22 (d, *J* = 2.5 Hz, 1 H), 5.66 (s, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.4, 136.0, 130.8, 129.3, 129.1, 128.8, 128.2, 127.8, 125.5, 121.3 ppm. HRMS (ESI–) calcd. for $C_{12}H_7Cl_2O$ [M–H]: 236.9879, found 236.9629.

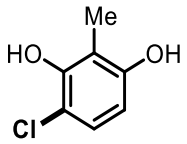
1-Chloro-2,3,4-trimethoxybenzene **(90).**



The following compound was obtained according to the general procedure for chlorination by using 1,2,3-trimethoxybenzene in 58 % yield as colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.8 Hz, 1 H), 6.62 (d, *J* = 8.8 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.85 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.7, 150.0, 143.6, 123.9, 119.9, 107.8, 61.12, 61.11, 56.2 ppm. IR (KBr) cm^{-1}= 2942, 2836, 1594, 1476, 1253, 1000, 777; HRMS (ESI+) calcd. for $C_9H_{11}ClO_3$ [M +H]: 203.0397, found 203.0488. The spectroscopic data match with those previously described.[239]

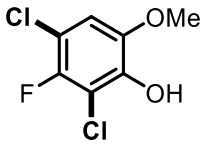
239. Friedman, D.; Ginsburg, D. *J. Org. Chem.* **1958**, *23*, 16–17.

4-Chloro-2-methylbenzene-1,3-diol **(91).**



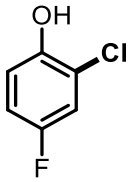
The following compound was obtained according to the general procedure for chlorination by using 2-methylbenzene-1,3-diol in 63 % yield as withe solid. m.p. 34–36 °C. ^{1}H NMR (500 MHz, CDCl3): δ = 7.01 (d, J = 8.5 Hz, 1 H), 6.39 (d, J = 8.7 Hz, 1 H), 5.66 (s, 1 H), 5.31 (s, 1 H), 2.19 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.6, 150.0, 125.5, 112.0, 111.6, 108.0, 8.8 ppm.

2,5-Dichloro-3-fluoro-6-methoxyphenol **(92).**



The following compound was obtained according to the general procedure for chlorination by using 3-fluoro-6-methoxyphenol in 24 % yield as colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (s, 1H), 5.93 (s, 1 H), 3.92 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 142.1, 123.7, 123.6, 119.8, 110.7, 56.6 ppm; IR (KBr) cm^{-1} 3510, 3031, 2943, 1597, 1482, 1397, 1269, 1050, 833, 853; HRMS (ESI+) calcd. for $C_7H_5Cl_2FO_2$ [M+]: 209.9651, found 209.9085.

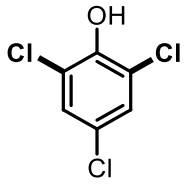
2-Chloro-4-fluoro-phenol **(93).**



The following compound was obtained according to the general procedure for chlorination by using 4-fluoro-phenol in 51 % yield as a with solid. m.p. 51–53 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (dd, J = 7.9, 2.9 Hz, 1 H), 6.97 (dd, J = 9.0, 5.1 Hz, 1 H), 6.91 (ddd, J = 9.0, 7.9, 2.9 Hz, 1 H) ppm;^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.4 (d, J = 241.7 Hz), 148.0 (d, J = 2.8 Hz), 119.9 (d, J = 10.9 Hz), 116.7 (d, J = 8.4 Hz), 116.0 (d, J = 26.4 Hz), 115.4 (d, J = 22.9 Hz) ppm; IR (KBr) 3515, 3062, 1600, 1495, 1410, 1321, 1259, 1203, 1070, 906, 861, 829, 783, 588 cm^{-1}. The spectroscopic data match with those previously described.[240]

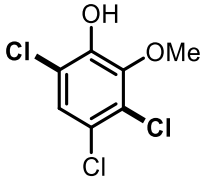
240. Finger, G. C.; Reed, F. H.; Tehon, L. R. *Illinois. State. Geol. Survey. Circ.* **1955**, *199*, 1–15.

2,4,6-Trichlorophenol **(94).**



This compound was synthesized according to the general procedure for chlorination by using 4-chlorophenol, 1.8 equiv. of PIFA and 3.6 equiv. of $AlCl_3$ in 62 % yield as a withe solid. m.p. 69–71 ° C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 2H), 5.80 (s, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.7, 125.5, 128.2, 147.0 ppm. The spectroscopic data match with those previously described.[241]

2,3,4-Trichloro-6-methoxyphenol **(95).**

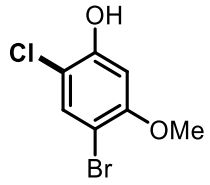


The following compound was obtained according to the general procedure for chlorination by using 4-chloro-6-methoxyphenol 2.4 equiv. of PIFA and 4.6 equiv. of $AlCl_3$ in 49 % yield as a brownish solid. m.p. 30–32 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 5.92 (s, 1 H), 3.92 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.7, 142.1, 123.7, 123.6, 119.7, 110.7, 56.6 ppm. The spectroscopic data match with those previously described.[242]

241. Castroviejo, M. P.; Fernandez, Y.; Fananas, F. J.; Sanz, R. *J. Org. Chem.* **2005**, *70*, 6548–6551.

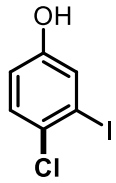
242. Wallis, A. F. A.; Smith, T. J.; Wearne, R. H. *International Symposium on Wood and Pulping Chemistry, 8th, Helsinki. June 6–9*, **1995**, *3*, 377–382.

4-Bromo-2-chloro-5-methoxyphenol **(96).**



The following compound was obtained according to the general procedure for chlorination by using 4-bromo-5-methoxyphenol in 52 % yield as a brownish solid. m.p. 41–43 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 6.62 (s, 1 H), 3.86 (s, 3 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.9, 151.6, 131.9, 111.4, 102.0, 100.4, 56.5 ppm.

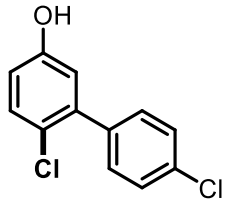
2-Chloro 3-iodophenol **(97).**



This compound was synthesized according to the general procedure for chlorination by using 3-iodophenol in 72 % yield as white solid. m.p. 78–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 2.8 Hz, 1 H), 7.24 (d, J = 2.0 Hz, 1 H), 6.79 (dd, J = 8.7, 2.8 Hz, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 130.1, 129.6, 127.0, 117.0, 98.0 ppm. The spectroscopic data match with those previously described.[243]

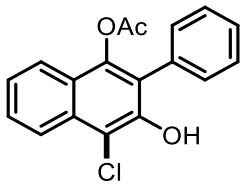
243. Andrew, D.; Felipe, A.; Joann, U.; Gustafson, J. L.; Madox, S. *Org. Lett.* **2016**, *18*, 5476–5479.

4-Chloro-3-(4-chlorophenyl)phenol **(98).**



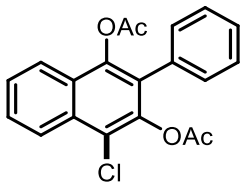
This compound was synthesized according to the general procedure for chlorination by using 3-(4-chlorophenyl)phenol in 60 % yield as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, J = 9.0 Hz, 2 H), 7.36 (d, J = 9.0 Hz, 2 H), 7.32 (d, J = 9.0 Hz, 2 H), 6.79 (s, 1 H), 6.78 (d, J = 9.0 Hz, 2 H), 4.96 (br. s, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.5, 140.6, 137.7, 134.0, 131.2, 130.9, 128.5, 124.1, 118.2, 116.1 ppm.

4-Chloro-3-hydroxy-2-phenylnaphthalen-1-yl acetate **(101).**



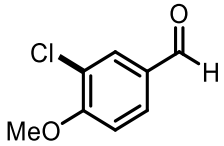
The following compound was obtained according to the general procedure for chlorination by using 3-hydroxy-2-phenylnaphthalen-1-yl acetate in 51 % yield as slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.5 Hz, 1 H), 7.79 (d, J = 8.4 Hz, 1 H), 7.63 (t, J = 7.7 Hz, 1 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1, 147.5, 143.9, 132.3, 130.8, 130.1, 128.6, 128.5, 128.3, 125.1, 123.6, 123.3, 123.2, 122.1, 112.1, 20.47 ppm. HRMS (ESI+) calcd. for $C_{18}H_{14}ClO_3$ [M + H]: 311.0480, found 311.0553.

4-Chloro-2-phenylnaphthalene-1,3-diyl acetate **(102).**



The following compound was obtained according to the general procedurefor chlorination by using 2-phenylnaphthalene-1,3-diyl acetate in 20 % yield as pale-yellow oil.^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, J = 8.5 Hz, 2 H), 7.84 (d, J = 8.4 Hz, 2 H), 7.67 (t, J = 7.1 Hz, 2 H), 7.59 (t, J = 7.1 Hz, 2 H), 7.45–7.37 (m, 6 H), 7.32 (d, J = 8.2 Hz, 4 H), 2.07 (s, 6 H), 2.03 (s, 6 H) ppm.^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.7, 168.2, 143.81, 143.3, 132.6, 130.9, 130.0, 129.9, 128.3, 128.2, 127.4, 126.5, 124.9, 122.3, 122.2, 115.5, 29.9, 20.4 ppm. HRMS (ESI+) calcd for $C_{20}H_{16}ClO_4$ [M + H]: 355.0737, found 355.0726.

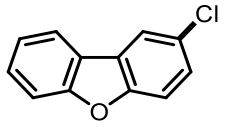
3-Chloro-4-methoxybenzaldehyde **(103).**



The following compound was obtained according to the general procedure for chlorination by using 4-methoxybenzaldehyde in 88 % yield as faint yellow solid. m.p. 42–44 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.85 (s, 1 H), 7.91 (d, J = 2.0 Hz, 1 H), 7.78 (dd, J = 8.5, 2.0 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 4.00 (s, 1 H) ppm; ^{13}C NMR (126 MHz, CDCl3): δ = 189.8, 160.0, 131.4, 130.6 130.5, 123.9, 111.8, 56.6 ppm; IR (KBr) cm^{-1} 1697, 1597, 1568, 1504, 1315, 1276, 1256, 1199, 1059, 1013, 894, 818, 714, 687, 638, 616, 556.The spectroscopic data match with those previously described.[244]

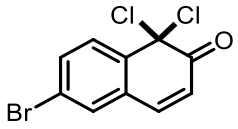
244. Julien, P.; Duwald, R.; Hilali, E. M. E.; Duchene, A.; Thibonneta, J.; Ngi, I. S. *Adv. Synth. Catal.* **2013**, *355*, 2936–294.

2-Chlorodibenzo[*b*,*d*]furan **(104).**



The following compound was obtained according to the general procedure for chlorination by using dibenzofuran in 63 % yield as withe solid. m.p. 99–101 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94–7.89 (m, 4 H), 7.57 (d, *J* = 8.3 Hz, 2 H), 7.51–7.47 (m, 4 H), 7.41 (dd, *J* = 8.3, 1.7 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 2 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.9, 154.6, 128.4, 128.1, 128.0, 127.30, 123.2, 120.1, 120.6, 113.1, 112.8, 112.0 ppm. The spectroscopic data match with those previously described.[245]

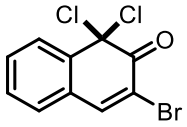
6-Bromo-1,1-dichloronaphthalen-2(1*H*)-one **(105).**



The following compound was obtained according to the general procedure for chlorination by using 6-Bromo-2-napthol in 72 % yield as orange solid. m.p. 40–42 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 1 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 7.48 (s, 1 H), 7.36 (d, *J* = 9.8 Hz, 1 H), 6.39 (d, *J* = 9.9 Hz, 1 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.3, 143.3, 139.5, 134.1, 132.1, 131.2, 128.7, 124.9, 124.0, 79.9 ppm; IR (KBr) cm^{-1} 1688, 1582, 1553, 1481, 1308, 1281, 1236, 1198, 1080, 926, 890, 792, 790, 693, 646, 563; HRMS (ESI): calcd. for $C_{10}H_5BrCl_2O$ [M–H]: 288.8823, found 288.2923.

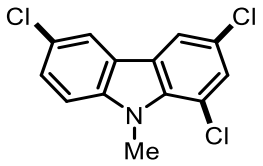
245. Oita, K.; Johnson, R. G.; Gilman, H. *J. Org. Chem.* **1955**, *20*, 657–67.

3-Bromo-1,1-dichloronaphthalen-2(1*H*)-one **(106).**



The following compound was obtained according to the general procedure for chlorination by using 6-Bromo-2-napthol in 72 % yield as orange solid. m.p. 46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.6 Hz, 1 H), 7.85 (s, 1 H), 7.56 (d, J = 14.3 Hz, 1 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.29 (d, J = 7.2 Hz, 1 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.5, 146.1, 140.1, 131.6, 131.1, 129.7, 129.2, 127.1, 118.4, 80.6 ppm; IR (KBr) cm^{-1} 1705, 1604, 1562, 1343, 1227, 1147, 955, 923, 826, 813, 759, 746, 681, 656, 621, 580. 530; HRMS (ESI–): calcd. for $C_{10}H_6BrClO$ [M–H]: 288.8823, found 288.2921.

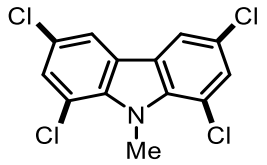
1,3,6-Trichloro-9-methyl-9*H*-carbazole **(107a).**



The following compound was obtained according to the general procedure for chlorination by using *N*-methylcarbazole, 4 equiv. of PIFA and 6 equiv. of $AlCl_3$ in 61 % yield as white solid. m.p. 136–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.87 (s, 1 H), 7.47 (d, J = 8.7 Hz, 1 H), 7.41 (s, 1 H), 7.33 (d, J = 8.7 Hz, 1 H), 4.19 (s, 1 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.7, 135.3, 127.8, 127.4, 125.64, 125.60, 124.7, 122.7, 120.2, 118.9, 116.8, 110.3, 32.3 ppm; IR (KBr) cm^{-1} 2921, 1315, 1448, 1279, 1077, 844, 791, 697. The spectroscopic data match with those previously described.[246]

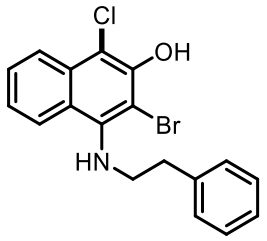
246. Mishra, A. K.; Nagarajaiah, H.; Moorthy, J. N. *Eur. J. Org. Chem.* **2015**, *2015*, 2733–2738.

1,3,6,8-Tetrachloro-9-methyl-9*H*-carbazole **(107b).**



IR (KBr) 2922, 1556, 1453, 1264, 1043, 835, 715 cm^{-1}.; ^1H NMR (500 MHz, $CDCl^3$): δ = 7.81 (s, 1 H), 7.42 (s, 1 H), 4.49 (s, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.8, 129.0, 125.7, 125.6, 118.7, 117.6, 35.1. ppm. The spectroscopic data match with those previously described.[247]

3-Bromo-1-chloro-4-(phenethylamino)naphthalen-2-ol **(109).**



A 25 mL dry round-bottomed flask was charged with compound **106** (1.0 equiv.), phenylethylamine (1.2 equiv.) and dissolved in methanol [0.3 M]. The reaction was stirred by 2 h. Then reaction mixture was evaporated and purified by chromatography column by using ethyl acetate/hexane to yield **109** in 45 % yield as grey solid. m.p. 66–68 °C. IR (KBr): $\tilde{\nu}$ = 3496, 2926, 1578, 1496, 1453, 1387, 1344, 1217, 1145, 1105, 1029, 942, 813, 755, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.2 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.54 (t, J = 7.1 Hz, 1 H), 7.35 (d, J = 8.9 Hz, 1 H), 7.31 (d, J = 7.1 Hz, 2 H), 7.28–7.22 (m, 3 H), 6.16 (s, 1 H), 3.51 (t, J = 6.9 Hz, 2 H), 2.98 (t, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.0, 144.3, 139.0, 130.7, 128.9, 128.7, 128.0, 126.6, 124.6, 124.2, 124.0, 123.5, 108.3, 105.3, 51.9, 37.4 ppm.

247. Bonesi, S. M.; Erra-Balsells, R. *J. Heterocycl. Chem.* **1997**, *34*, 891–900.

CHAPTER III

Gold(I)-catalyzed direct C_{sp^3}-H Bond activation in the synthesis of triarylindenes

CHAPTER III

Introduction.

The indenes are compounds of great importance in organic synthesis.[248] They appear or are frequently found in naturally occurring compounds,[249] pharmaceutical drugs,[250] organic dyes,[251] and pigments [252] among the most representatives (Figure 3.1).

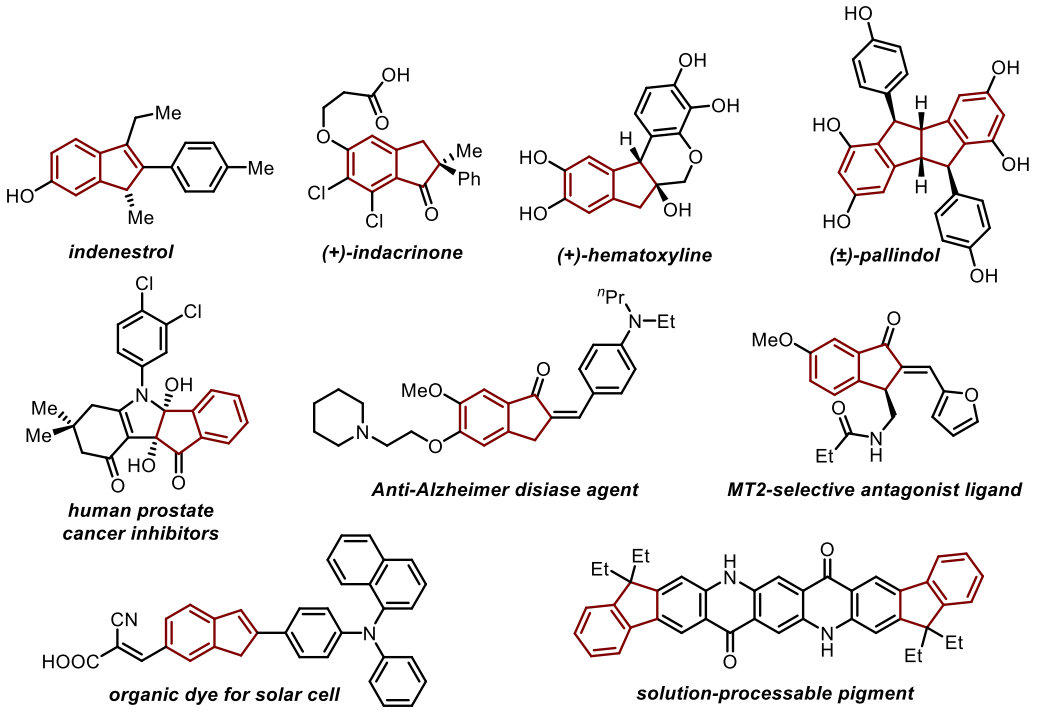


Figure 3.1. Examples highlighting the relevance of the indene core.

248. Chanda, T.; Shankar Singh, M. S. *Org. Biomol. Chem.* 2016, **14**, 8895-8910.

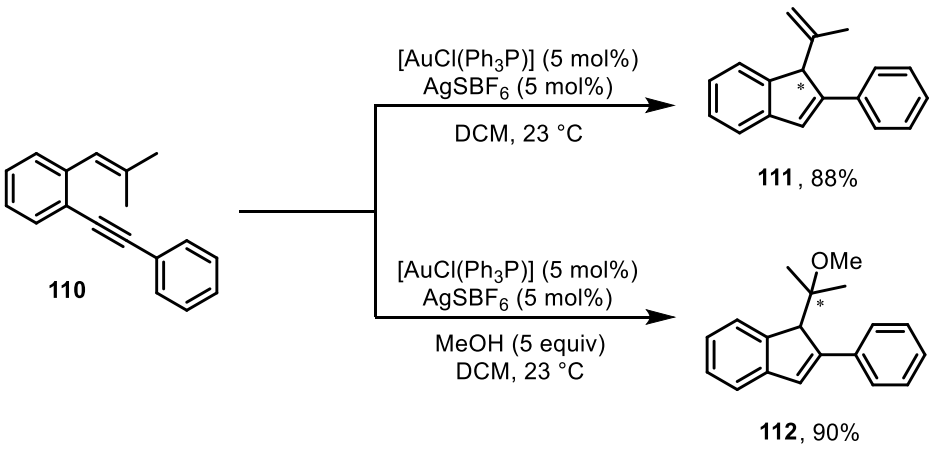
249. (a) Studies in Natural Products Chemistry, Vol, *51*, Copyright © Elsevier B. V. All right reserved. Chapter 8, Naseem Ahmed. 383-434. (b) (+)-indacrinone: Genet, J. P.; Ayad, T.; Ratovelomanana, V. *Chem. Rev.* **2014**, *114*, 2824-2880. (c) (+)-hematoxcyline: Yadav, J. S.; Mishara, A. K.; Das, S. *Tetrahedron.* **2014**, *70*, 7560-7566. (d) (±)-pallindol: Keylor, M. H.; Matsuura, B. S.; Stephenson, C. R. J. *Chem. Rev.* **2015**, *115*, 8976-9027.

250. a) Anti-Alzheimer: Huang, L.; Lu, C.; Sun, Y.; Mao, F.; Luo, Z.; Su, T.; Jiang, H.; Shan, W.; Li, X. *J. Med. Chem.* **2012**, *55*, 8483-8492. b) MT2-selective antagonist ligands: Zhang, X.; Wang, Z.; Huang, Q.; Luo, Y.; Xie, X. Lu, W. *RSC Adv.* **2014**, *4*, 25871-25874.

251. Organic dye for solar cell: Lin, Y. D.; Chow, T. J. *J. Mater. Chem.* **2011**, *21*, 14907-14916

252. Solution-Processable pigment: Zou, Y.; Yuan T.; Yao, H.; Frazier, D. J.; Stanton, D. J.; Sue, H. J.; Fang, L. *Org. Lett.* **2015**, *17*, 3146-3149

To date, several procedures for the synthesis of indenes have been reported. Among the most representative, those involving metal-free,[253] transition metal-free[254] or metal-catalyzed[255] conditions have been extensively described. Particularly, the gold(I)-catalyzed cycloisomerization of enynes[256] has been a broadly exploited tool for building up different organic architectures such as indenes. For examples, in the recent literature, Sanz and *et. al*. reported gold(I)-catalyzed 5-endo-dig cyclization of o-(alkynyl)styrenes in the synthesis of enantiomerically enriched indenes. Compound **111** was formed in 88% of yield using 2',2'-dimethyl *o*-(phenylethynyl)styrene **110** in the presence of the cationic gold(I) complex generated in situ from 5 mol% of [AuCl(Ph_3P)] and 5 mol% of $AgSbF_6$. Also, the presence five equivalents of methanol observed the formation of compound **112** in excellent yield 90% (Scheme 3.1).[257]



Scheme 3.1. Gold(I)-catalyzed asymmetric synthesis of indene.

253. a) Gabriele, B.; Mancuso, R.; Velti, L. *Chem. Eur.J.* **2016**, *22*, 5056-5094. b) Hong, B. C.; Sarshar, S. *Org. Prep. Proced. Int.* **1993**, 31, 1-86. c) López-García, M.; Alfonso, I.; Gotor, V. *Chem. Eur.J.* **2004**, *10*, 3006-3014. d) Begouin, J. M.; Capitta, F.; Wu X.; Nigerman, M. *Org. Lett.* **2013**, 15, 1370-1373.

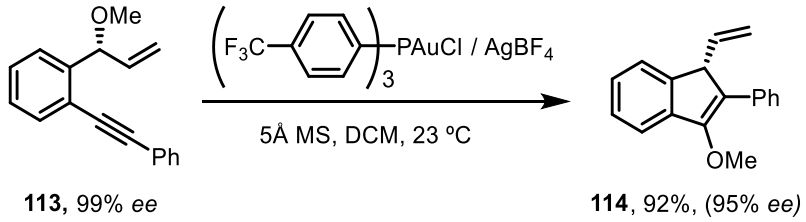
254. a) Zhu, X.; Mitsui, C.; Tsuji, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 13596-13597. b) Chen, Y. Y.; Chen, Z. Y.; Zhang, N. N.; Chen, J. H.; Zhang, X. J.; Yan, M. *Eur. J. Org. Chem.* **2016**, 599-606.

255. Using Cu: a) Zhu, Z. B.; Shi, M. *Chem. Eur. J.* **2008**, 14, 10219-10222. b) Shao, L. X.; Zhang, Y. P.; Qi, M. H.; Shi, M. *Org. Lett.* **2007**, 9, 117-120. Using Fe: a) Liu, C. R.; Yang, F. L.; Jin, Y. Z.; Ma, X. T.; Cheng, D. J.; Li, N.; Tian, S. K. *Org. Lett.* **2010**, *12*, 3832-3835. Using Zr: a) Xi, Z.; Guo, R.; Mito, S.; Yan, H.; Kanno, K. I.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2003**, *68*, 1252-1257. Using Pd: Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251-262. Using Pt: a) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471-5475. b) S. Yang, Z. Li, Jian, X.; He, C., *Angew. Chem. Int. Ed.* 2009, **48**, 3999-4001.

256. Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev*. **2008**, *108*, 3326-3350.

257. Martínez, A.; García-García, A.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew, Chem. Int. Ed.* **2010**, *49*, 4633-4637.

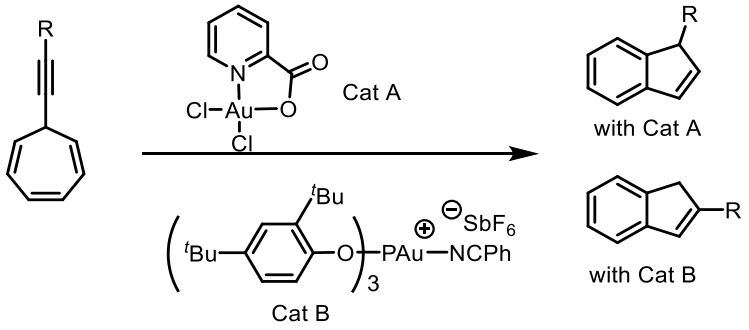
In 2006 Toste *et. el*. reported gold(I)-catalyzed carboalkoxylation of alkynes proceeds with chirality transfer, providing a rapid entry into functionalized enantioenriched indenyl ethers from readily available benzylic ethers (Scheme 3.2).[258]



113, 99% *ee* **114**, 92%, (95% *ee)*

Scheme 3.2. Gold(I)-catalyzed carboalkoxylation of alkynes.

Another reported gold(I)-catalyzed synthesis of indenes by Echavaren *et. al.* is based on the generation of fluxional barbaralyl intermediates from 7-alkynyl cycloheptatrienes under very mild conditions (Scheme 3.3).[259]



Scheme 3.3. Synthesis of indenes through generation of fluxional barbaralyl intermediates.

The gold-stabilized barbaralyl intermediates evolve to furnish 1- or 2-substituted indenes, depending on the catalyst. The formation of 1-substituted indenes involves a remarkable transformation in which the alkyne carbon atoms end up at the bridge of the indene. Use of highly electrophilic phosphite–gold(I) complex forms substituted indenes.

258. (a) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062-12063. b) Zi, W.; Toste, F. D. *J. Am. Chem. Soc.* 2013, **135**, 12600-12603.

259. (a) McGonigal, P. R.; de León C.; Wang, Y.; Homs, A.; Solorio-Alvarado, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2012**, *51*, 13093-13096. b) Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc*. **2011**, *133*, 11952-119955. c) Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc*. **2010**, *132*, 11881-1883.

All these protocols proceed via two-step cycloisomerization of the starting material, 1) formation of a cyclopropyl gold(I)-carbene or an oxonium gold(I)-vinylidene and 2) evolution of this intermediate into the corresponding indene. On the other hand, of relevant synthetic attractive the gold(I)-catalyzed C_{sp}^3-H bond activation[260] approach has been very recently explored.

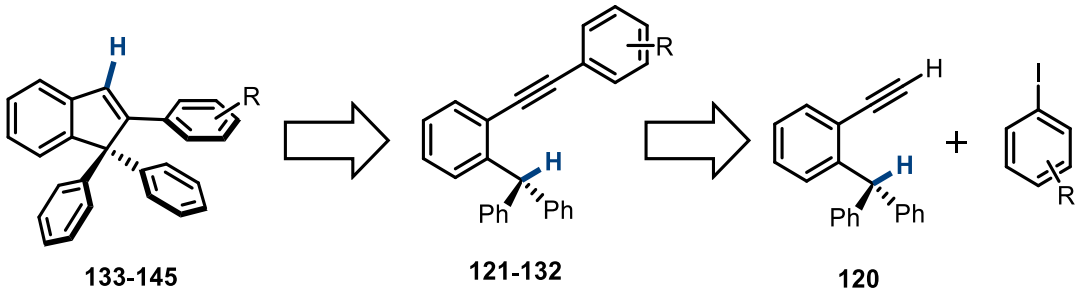
Considering the importance indenes moiety in the different areas of chemistry, herein we described the gold(I)-catalyzed C_{sp}^3-H bond activation strategy to the synthesis of the indene nucleus. Thus, our development proceeds by the direct C_{sp}^3-H bond activation and take place via a concerted reaction. This process also affords a gold(I)-carbene after the cyclization without a cyclopropane or oxonium intermediate. In regards to the gold(I)-catalyzed redox-neutral C_{sp}^3-H bond activation,[260] is worth to mention that a gold(I)-carbene[261] is initially formed as the necessary key step to promote such activation that usually occurs by [1,*n*]-H migration.[261d-f] This transformation leads to the formation a carbocation that evolves by cyclization and protodeauration. In contrast, our procedure represents a new and direct activation mode, which did not form in principle the gold(I)-carbene to activate the C_{sp}^3-H bond. Instead a pericyclic [1,5]-H migration takes place giving rise to the direct C_{sp}^3-H bond activation-cyclization intermediate, which contains the gold(I)-carbene. This carbene progress to the final indene via [1,2]-H shift concomitant gold(I) catalyst regeneration. This catalytic cycle was supported by our DFT theoretical calculations.

260. Au(I)-catalyzed C_{sp}^3-H: (a) Xie, J.; Pan, C.; Abdukaer, A.; Zhu, C. *Chem. Soc. Rev.* 2014, **43**, 5245-5256. (b) Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2011**, 47, 2354-2356. (c) Xie, J.; Li, H.; Xue, Q.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.,* **2012**, *354*, 1646-1650. Sequence cycloisomerization/ C_{sp}^3-H activation via [1,5]-*H* migration: (d) Bhunia, S.; Liu, R. S. *J. Am. Chem. Soc.* **2008**, *130*, 16488-16489. (e) Zhou, G.; Zhang, J. *Chem. Commun.,* **2010**, *46*, 6593-6595. (f) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem Soc.* **2009**, 131, 2809-2811.

261. Gold(I)-carbenes proposed as intermediates: (a) Echavarren, A. M. *Nat. Chem.* **2009**, 1, 431-433. (b) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, *21*, 7332-7339. (c) Gorina, D. J.; Toste, F. D. *Nature,* **2007**, *446*, 395-403

Result and discussion.

Inspired by the recent gold(I)-catalyzed redox-neutral C_{sp}^3-H bond activation reports, we hypothesize that starting materials such as **151**-**162** could give rise to indenes of the type 19-31. Thus, we decided to describe our gold(I)-catalyzed C_{sp}^3-H bond activation approach and, we could anticipate based upon the alkyne design, that the transformation could carry out via [1,5]-H shift. The convergent retrosynthetic analysis of this hypothesis is outlined (Scheme 3.4).



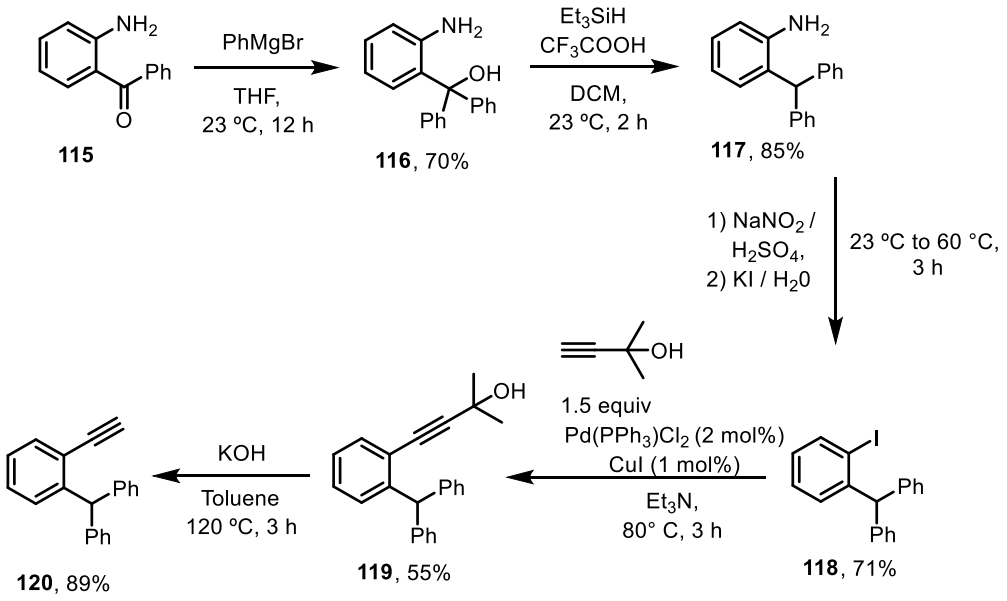
Scheme 3.4. Retrosynthetic analysis for the synthesis of indene derivatives.

In the retrosynthesis, the final indenes **133**-**145** are the products of the gold(I)-catalyzed C_{sp}^3-H bond activation of the alkynes **121**-**132**, which were obtained from the Sonogashira alkynylation[262] between alkyne **120** and different commercially available aryl iodides. Thus, the synthesis of the starting alkyne **120** was envisioned as a linear five-step synthesis and the procedure followed as described in the literature shown below (Scheme 3.5).[263]

262. Chinchilla, R.; Nájera, C. *Chem. Rev*. **2007**, *107*, 874–922.

263. Chen, Y-Y.; Chen, Z-Y.; Zhang, N-N.; Chen, J-H.; Zhang, X-J.; Yan, M. Eur. J. *Org. Chem.* **2016**, 599–606.

Synthesis of starting alkyne.



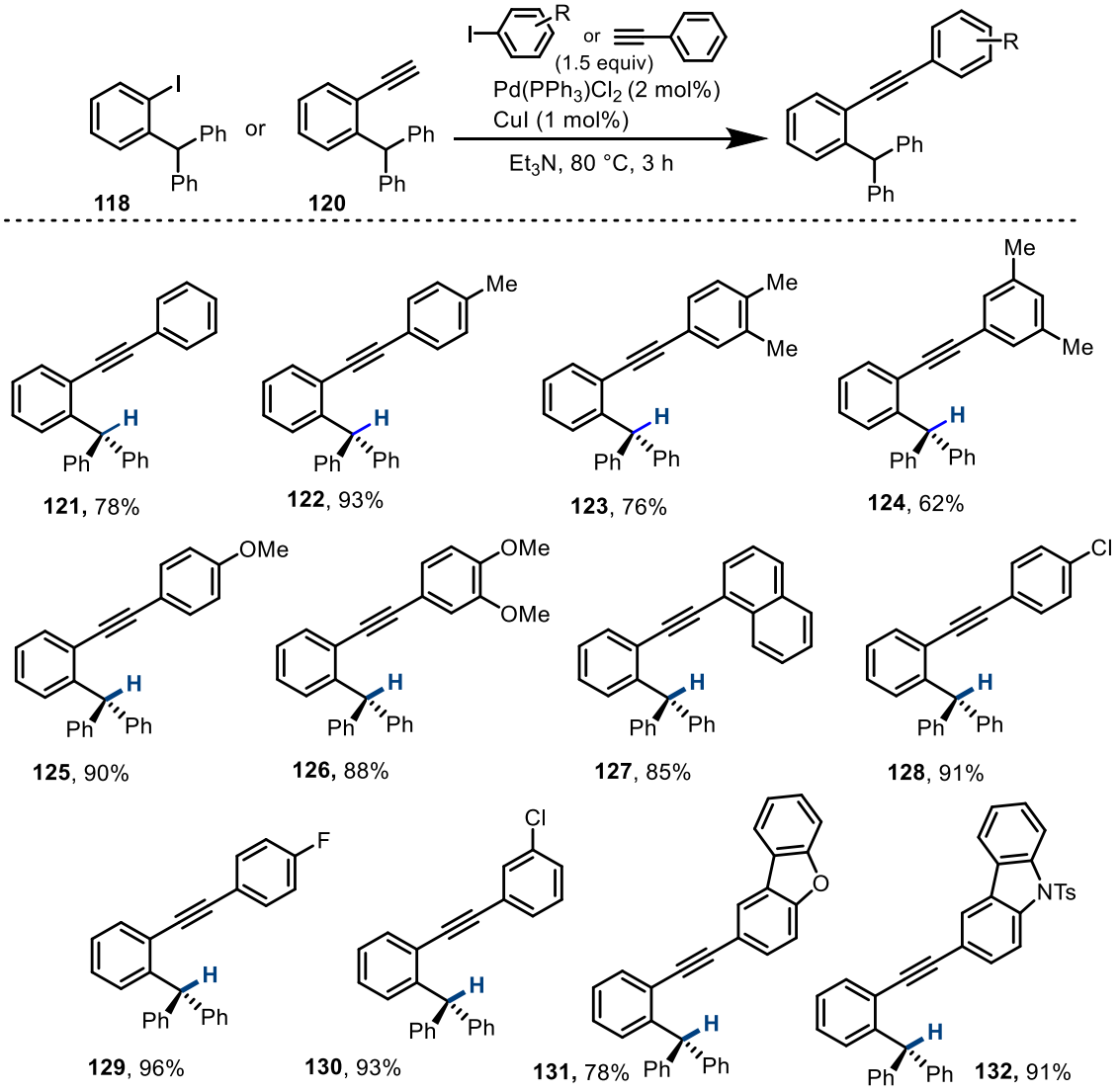
Scheme 3.5. Synthetic route for accessing to the alkyne **120**.

We started with the addition of prepared phenylmagnesium bromide to the commercially purchased 2-aminobenzophenone **115** to get **116**, in good 70% yield. Then followed by reduction in the acidic conditions using Et_3SiH and trifluoracetic acid produced the desired C_{sp}^3-H bond containing product **117** in excellent 85% yield. The Sandmeyer-type iodination[264] furnished iodinated compound **118** in 71% yield. Then, a consecutive Sonogashira alkynylation with 2-methylbut-3-yn-2-ol produced **119** in 55% yield, which upon deprotection in the basic treatment, finally gave starting alkyne **120** in 89%.

Once the alkyne **120** was obtained, we proceeded to synthesize the starting materials **121**-**132** by a second Sonogashira alkynylation using different substituted commercially available iodoarenes (Scheme 3.6).

264. Filimonov, V. D.; Trusova, M.; Postnikov, P.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Chi, K.-W. *Org. Lett*. **2008**, *10*, 3961-3964.

Synthesis of substituted alkynes using Sonogashira reaction.



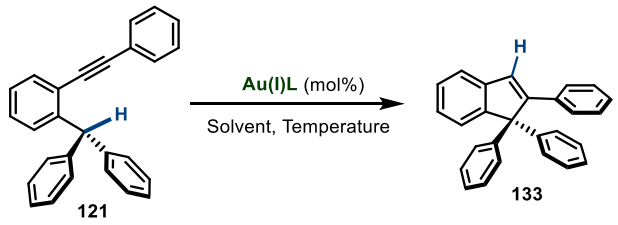
[a]This compound was synthesized using the iodide **118** and phenylacetylene. [b] This compound was synthesized by the Sonogashira alkynylation of **120** using commercially available iodinated compounds. [c]Iodinated heterocycles were prepared.

Scheme 3.6. Synthesis of the alkynyl triphenylmethanes **121**-**132**.

In this way, different alkynyl triphenylmethanes containing single Csp^3-H bond as well as distinct electronic-nature aryl groups were synthesized. Thus, electron-neutral **121**), electron-rich (**122**–**127**) and electron-poor (**128**–**130**) derivatives were obtained in moderate to excellent overall yields (62-96%). Finally, two more derivatives containing heterocycles (**131** and **132**) were obtained in 78 and 91% of yield respectively for testing the further scope of this reaction. With the starting alkynes **121**–**132** synthesized, we carried out the optimization reaction to demonstrate

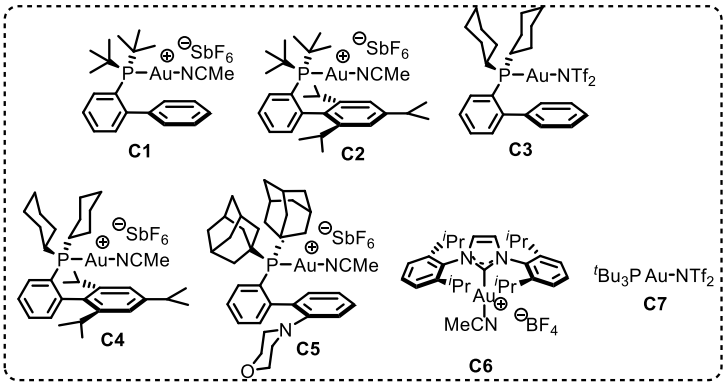
the hypothesis of our new activation mode of the C_{sp}^3-H bond. The alkyne **120** was used as model system and different cationic gold(I)-complexes[265] were tested as catalyst sources (Table 3.1).

Table 3.1 Optimization of the new gold(I)-catalyzed C_{sp}^3-H bond activation mode in the synthesis of 1,1,2-triarylindenes.



Entry	Au(I)L (mol%)	Solvent	Temp (˚C)	Yield (%)[a]
1	C1 (5)	MeCN	23	n.r.
2	C1 (5)	DCE	23	n.r.
3	C1 (10)	DCE	23	n.r.
4	C1 (5)	DCE	60	n.r.
5	C1 (5)	DCE	80	n.r.
6	C1 (10)	DCE	90	50
7	C1 (15 + 5)	DCE	105	81
8	*C1 (20)*	*DCE*	*105*	***>99***
9	C2 (20)	DCE	105	9
10	C3 (20)	DCE	105	81
11	C4 (20)	DCE	105	25
12	C5 (20)	DCE	105	30
13	C6 (20)	DCE	105	45
14	C7 (20)	DCE	105	11
15	-	DCE	105	n.r.

[a]The chemical yields were determined by GC. n.r. = no reaction observed.



265. (a) Brown, T. J.; Widenhoefer, R. A. *Chem. Rev.* 2011, 30, 6003-6009. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Bañuel, E.; Nevado C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

The great reactivity of the cationic gold(I)-complex **C1** (Echavarren catalyst)[266] is well known.[125b-c] Thereby we decided to start the optimization by using 5 mol% of **C1** in acetonitrile and 1, 2-dichloroethane at room temperature (Table **1**, entries **1** and **2**), after 12 hours we found no reaction. We decide to use 1, 2-dichloroethane in the rest of the optimization process due to slightly starting material decomposition was observed. By increasing the catalyst amount to 10 mol% or heating to 60°C or 80°C no reaction was observed (Entries **3**-**5**).

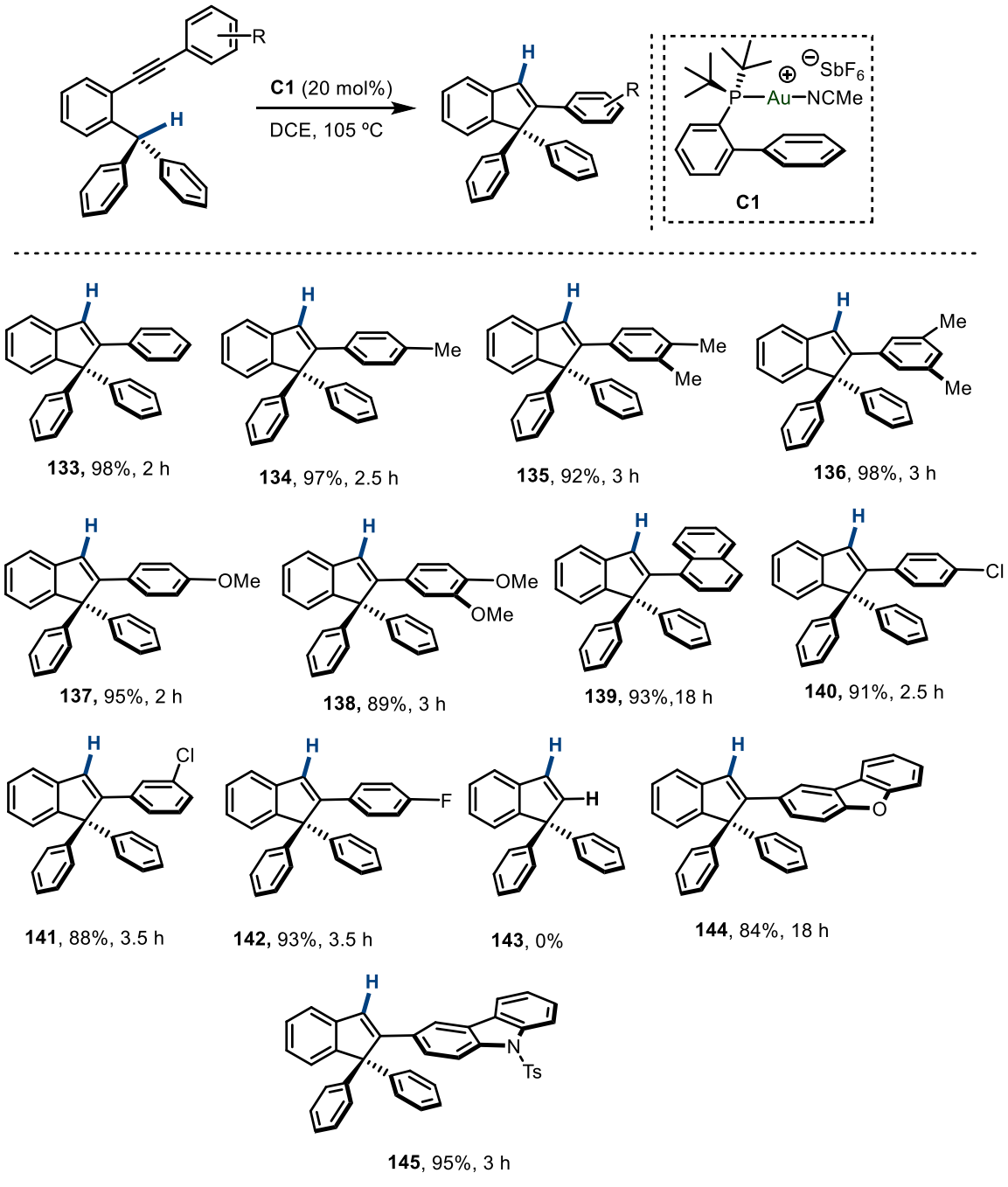
To our delight with 10 mol% of **C1** at 90°C we found the desired indene **133**, nevertheless just the 50% of the reaction advance was detected by GC (Entry **6**). This experiment in principle validated our hypothesis showing the desired C_{sp}^3-H bond activation. In the following reaction we tested 15 mol% of **C1** at 105 °C, after 12 hours we still found remaining starting material. Then additional 5 mol% of catalyst was added to complete the starting material consumption. In such a way the reaction was completed in additional 12 hours furnishing the desired indene 19 in 81% of yield (Entry **7**). From this experiment we identify the catalytic charge of **C1** in 20 mol% and the temperature in 105 °C, since less amount of catalyst or lower temperature did not fully consume the starting material. In order to test these observed conditions, in the next reaction was initially used 20 mol% of **C1** at 105 °C, gratifyingly after only 2 h of reaction, more than 99% of yield was determined by GC analysis and the structure was confirmed by ^{1}H and ^{13}C NMR (Entry **8**). Some other gold(I) catalysts such as **C2** to **C7** were assayed by using the optimized conditions in entry 8, however yields from 9% to 81% were observed (Entries **9** to **14**). Finally, a control experiment was carried out in absence of catalyst to determine if a thermic [1,5]-H migration[267] more than a metal-catalyzed C_{sp}^3-H bond activation is taking place. Under these conditions we could not find **133** at least by the NMR detection limits after 24 hours.

At this point it was determined as the optimal conditions those in entry **8**. Thereby we proceed to explore the scope of our new developed C_{sp}^3-H bond activation procedure (Scheme 3.7).

266. The cationic gold(I)-complex C1 is known as Echavarren catalyst: Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Bañuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *117*, 6302-6304.

267. a) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, 109, 3136-3138. b) W. H. N. Nijhuis, Verboom, W.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Org. Chem.* 1989, **54**, 199-209.

Scope for the new gold(I)-catalyzed synthesis of indenes.



Scheme 3.7. Scope for the new gold(I)-catalyzed C_{sp^3}-H bond activation mode in this work.

This developed procedure yields 1,1,2-triarylindenes. The explored scope was determined mainly for the electronic nature at the 2-aryl of the indene. Thereby, our protocol tolerated the electron-

neutral phenyl group giving rise to **133** in 98% yield in only 2 hours. Also, different electron-rich aryls containing one or two methyl groups proceed with excellent in 92 to 98% of yield (**134-136**) in no more than 3 hours of reaction. The presence of methoxy groups at the 2-aryl moiety furnished **137** and **138** in 95% and 89% of yield in only 3.5 hours. Even the bulky 1-naphtyl substituent produced **139** in a very good 93% of yield after 18 hours, this result showed that the reaction is kinetically sensitive to steric hindrance but chemically useful. The scope was expanded to electron-poor aryls containing 3-chloro (**140**), 4-chloro (**141**) and 4-fluor (**142**) obtaining high yields ranging from 88-33%. The reaction was also tested with the 2-aryl-free starting alkyne **120** but the expected product **143** was not found. Finally, the dibenzofuran and carbazole heterocycles were perfectly allowed by the reaction giving rise to **144** and **145** in 84%, 18 hrs. and 95%, 3 h respectively. The former results confirmed that bulky substituents slow down the reaction time, nevertheless have no a negative impact in yield.

After this reaction scope exploration is important to highlight some relevant aspects of our procedure, 1) the hypothesis about the new gold(I)-catalyzed $C_{sp}{}^3$-H bond activation mode to synthesize 1,1,2-triarylindenes from the alkynyl triphenylmethanes **132**-**145** was probed, 2) the procedure is high-yielding, 3) short reaction times ranging from 2 to 3.5 hours were observed for mono-annular aryls (4) the bis- or tris-annular aryls with a relevant steric bulkiness just delay the kinetics of reaction but did not showed a negative impact in it, since a high yield is also observed, 5) this developed protocol tolerates electron-poor, electron-rich, electron-neutral aryls as well as heterocycles and even aryl-free derivatives. Accordingly, we carried out DFT calculations with the help of Dr. J. Oscar C. Jiménez-Halla to support the reaction mechanism.

At this point, we considered of main relevance to describe the reaction pathway, which gives rise to the synthesized indenes in the developed procedure. Accordingly, we carried out theoretical calculations at the (SMD:dichloroethane)ONIOM(M08-HX/*mixed-basis*:PM6) level to support the reaction mechanism (see experimental section for further details), (Figure 3.2).

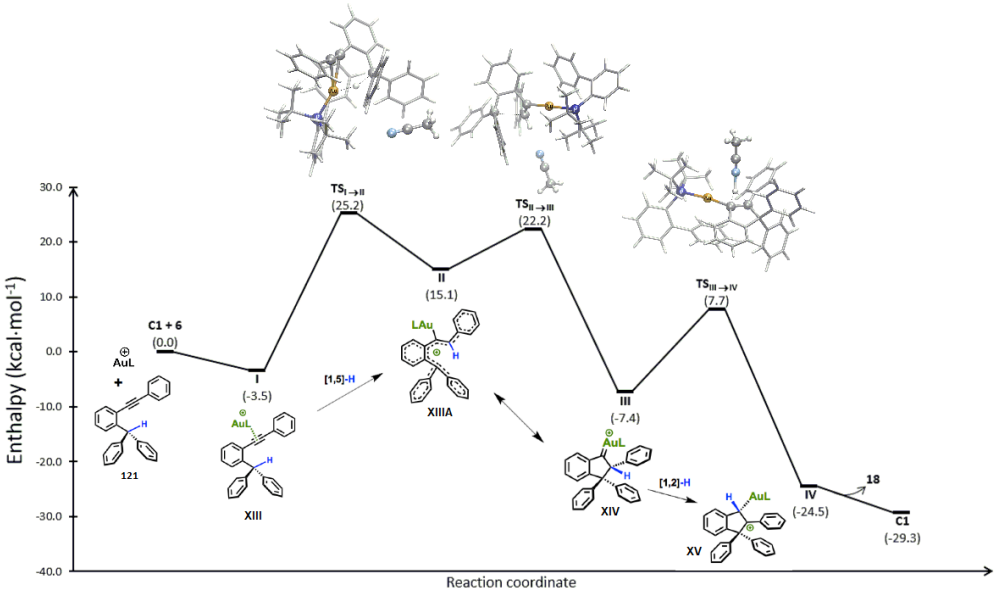
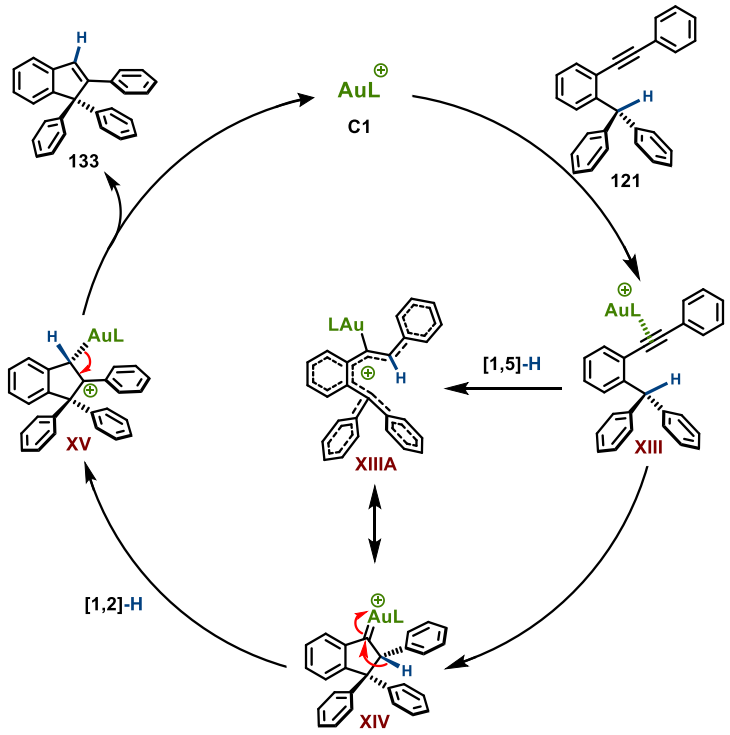


Figure 3.2. Energy profile of the calculated reaction mechanism between **C1** and **121** to obtain **133**. Relative energies are expressed as enthalpy values.

Figure 3.2 shows the calculated energy profile (for free energy values, see Figure 3.11. in the experimental section). The reaction starts with the coordination of the cationic gold(I)-complex **C1** to **6** to provide **XIII**. The C_{sp}^3-H bond activation takes place at this point through a [1,5]-H shift defined by the transition state $TS_{I\rightarrow II}$, which affords the stabilized carbocation **XIIIA**. The energy barrier of this step is high enough (28.7 kcal·mol^{-1}) to explain the need of heating up (105 °C) the reaction to proceed. In this six-membered ring TS, the metal centre abstracts and, downhill, delivers the hydrogen to the vicinal carbon of the double bond. The positive charge remains delocalized through the carbon backbone in **XIII**, which defined an endothermic reaction by 18.6 kcal·mol^{-1}. In the next step, the new ring is formed through the C-C bond formation in $TS_{II\rightarrow III}$ leading to carbene **XIV** (exothermic step: –22.5 kcal·mol^{-1}). This step is in fact the representation of a resonant form between **XIIIA** and **XIV**. This energy barrier takes only 7.1 kcal·mol^{-1} and is faster than the reverse energy barrier (10.1 kcal·mol^{-1}) for turning back to **XIII**. Next, **XIV** evolves via [1,2]-H shift[21] giving rise to **XIV** which is more exothermic by –17.1 kcal·mol^{-1}. The energy barrier of this step is calculated through $TS_{III\rightarrow IV}$ ($\Delta H^{\ddagger}$ = 15.1 kcal·mol^{-1}) and it is important to make notice about the role of the acetonitrile acting as a base for assisting this reaction step in the transition state. We also located an analogous of $TS_{III\rightarrow IV}$ without the acetonitrile influence and this was almost 6.0 kcal·mol^{-1} higher in energy than the former one. Finally, gold(I)-complex C1

delivers back the electron-pair to the indene ring and releases product **133** which is –4.8 kcal·mol^{-1} more favoured. Overall, this process has a total reaction energy of ΔH_R = –29.3 kcal·mol^{-1}. Based upon the mechanic studies as well as the experimental results obtained and the know chemistry of gold(I) catalysis,[268] we have compiled the following reaction mechanism. (Scheme 3.8).

Reaction reaction mechanism.



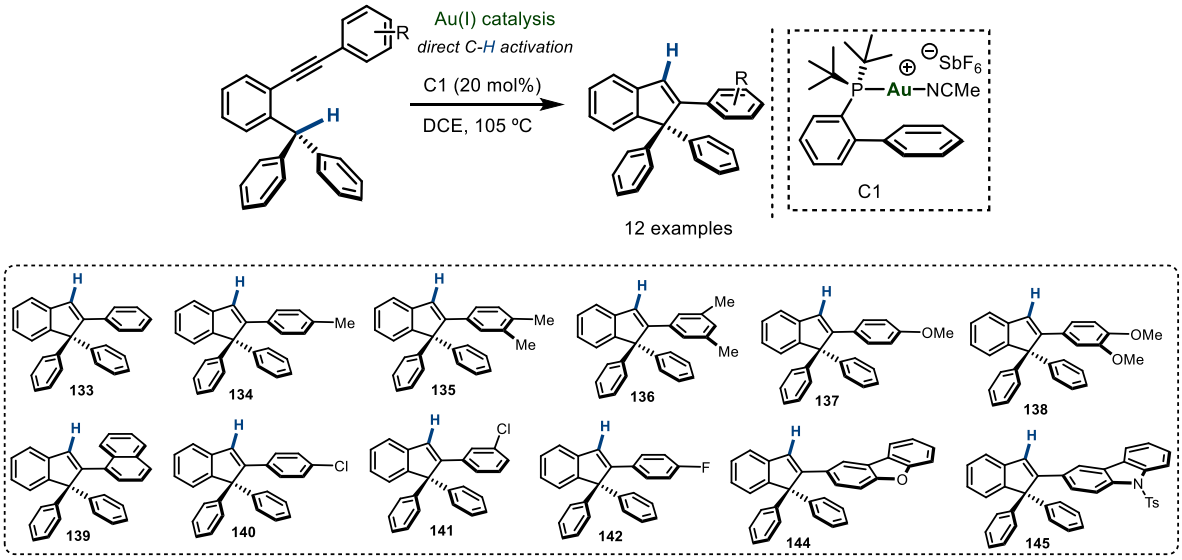
Scheme 3.8. Reaction mechanism for the new gold(I)-catalyzed C_{sp}^3-H bond activation mode in the 1,1,2-triarylindenes synthesis.

The catalytic cycle starts with coordination of **C1** to alkyne affording **XIII**. Then the C_{sp}^3-H bond activation takes place via [1,5]-H shift yielding **XIIIA** which is in resonance with the gold(I) carbene **XIV**. This carbene evolves via [1,2]-H shift giving rise to **XV**. Finally, the loss of the godl(I) complex lead to the formation of indene derivative **133** concomitant catalyst regeneration. The catalytic, practical and high-yielding procedure for the synthesis of indenes by direct C_{sp}^3-H activation under gold(I) catalysis was developed.

268. (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015,** *115*, 9028-9072. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657-1712. (c) Krause, N., Winter, C. *Chem. Rev.* **2011**, *111*, 1994-2009. (d) Li, Z.; Brower.; C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. e) Hasmi, A. S. K. *Chem. Rev.* 2007, **107**, 3180-3211.

Conclusions.

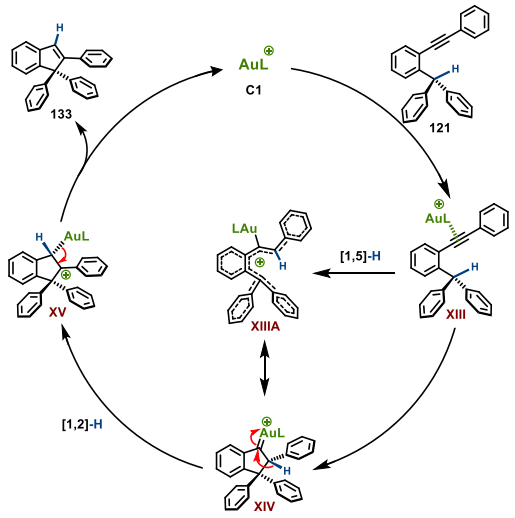
- We have developed a catalytic,[269] high-yielding, and new activation mode for the direct gold(I)-catalyzed C_{sp}^3-H bond activation of alkynyl triphenylmethanes for the synthesis of 1,1,2-triarylindenes.



- The procedure tolerates all the electronic-nature groups at the 2-indenyl position including electron-rich, -poor and -neutral aryls as well as 2-aryl-free and 2-heteroaryls. The short reaction times generally found in mono-annular aryls and the nearly quantitative yields are particularly important features in this development.

- The reaction mechanism was elucidated by theoretical calculations at the (SMD:dichloroethane)ONIOM(M08-HX/*mixed-basis*:PM6) level. It was determined that the operating mechanism involves a C_{sp}^3-H bond activation as a key step, which proceeds via a pericyclic [1,5]-H migration-cyclization giving rise to a gold(I)-carbene.

269. Even though 20 mol% of **C1** could be not considered as catalytic reaction, the concept is clear and our development is inside it: "*A catalyst is a substance that increases the rate of a reaction without modifying the overall standard Gibbs energy in the reaction; the process is called catalysis. The catalyst is both a reactant and a product of the reaction*". Laidler, K. J. *Pure & Appl. Chem.* **1996**, *68*, 149-142.

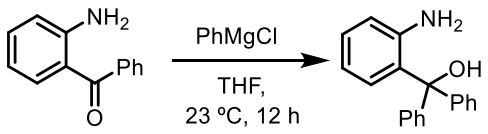


This evolves by [1,2]-H shift with concomitant loss of the gold(I)-complex to furnish the desired triarylindenes. To the best of our knowledge, in contrast with previous procedures where the formation of the gold(I)-carbene as first step is necessary to activate the C_{sp^3}-H bond, in the present development this key step proceeds directly without any intermediate.

Experimental section

Synthesis of starting materials 116-120.

Spectroscopic data for **116**-**122**, **130**, **133-134**, **137**, **and 141** matches with those in literature.[270] Spectroscopic data for unknown compounds **123-124**, **126-129**, **131**-**132***,* **135-136**, **138-140**, **142** and **144-145** are described here.

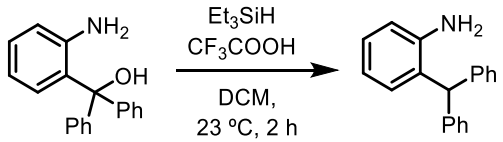


116

Synthesis of (2-aminophenyl)diphenylmethanol **(116).** Phenylmagnesium Chloride (2 *M* in 2-methyltetrahydrofuran; 15 mL, 30 mmol) or prepared PhMgBr was added to a flame dried 250 mL round bottom flask containing a solution of (2-aminophenyl)(phenyl)methanone (7.0 g, 15.0 mmol) in THF (40 mL) at room temp. The mixture was stirred at room temp. for 12 h. Then the reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/EtOAc, 5:1) to give (2-aminophenyl)diphenylmethanol **116** (6.8 g, 70 %) as a pale-yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 –7.31 (m, 10H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 5.21 (s, 1H), 3.67 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.8, 144.1, 133.4, 129.9, 128.8, 128.2, 127.9, 127.5, 119.3, 119.2, 82.4. Spectral data match with those reported on the literature.[270a]

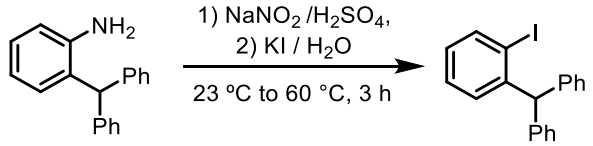
270. (a) Chen, Y-Y; Chen, Z. -Y; Zhang, N. -N; Chen, J. -H; Zhang, X. -J; Yan, M. *Eur. J. Org. Chem*. **2016**, 599–606. (b) Heinz, L. G.; Yushchenko, O.; Neuburger, M.; Vauthey, E. Wenge, Oliver S. *J Phys. Chem. A*, **2015**, *11*, 5676–5684.



116 **117**

Synthesis of 2-benzhydrylaniline **(117).** Et_3SiH (2.78 mL, 36 mmol) and CF_3COOH (5.5 mL, 72 mmol) were added to a flame dried 250 mL round bottom flask containing a solution of (2-aminophenyl)diphenylmethanol **116** (5 g, 18 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temp. for 2 h. Solid Na_2CO_3 (7.6 g, 72 mmol) and water (60 mL) were then successively added. The mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/EtOAc, 10:1) to give 2-benzhydrylaniline **117** (4 g, 85 %) as a pale-yellow solid.

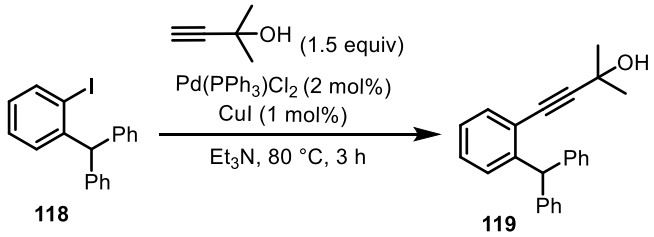
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 6H), 7.17 (d, *J* = 7.3 Hz, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.75 – 6.68 (m, 3H), 5.51 (s, 1H), 3.49 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 142.5, 130.0, 129.6, 129.2, 128.6, 127.5, 126.7, 118.7, 116.3, 52.3. Spectral data match with those reported on the literature.[270a]



117 **118**

[(2-iodophenyl)methylene]dibenzene **(118).** A flame dried 250 mL round bottom flask containing a solution of 2-benzhydrylaniline **117** (4 g, 15 mmol), CH_3COOH (12 mL), concentrated H_2SO4 (12 mL), and water (12 mL) was stirred at 0 °C for 15 min. After this time, a solution of $NaNO_2$ (2.2 g, 32 mmol) in water (7 mL) was slowly added to the mixture. After the mixture became a brown liquid, a solution of KI (10.7 g, 65 mmol) in water (4 mL) was added in one portion. The mixture was warmed to room temp. and stirred for 1 h at 60 °C. Sodium sulfite (7.5 g, 56 mmol) was then added, and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexanes) to give [(2-iodophenyl)methylene]dibenzene **118** (4.1 g, 71 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.80 (m, 2H), 7.30 –7.28 (m, 5H), 7.07 (d, *J* = 7.4 Hz, 5H), 6.93 (d, *J* = 6.2 Hz, 2H), 5.84 (s, 1H). Spectral data match with those reported on the literature.[270a]

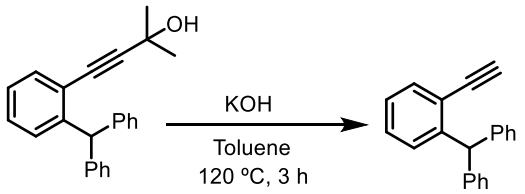


118 119

4-(2-benzhydrylphenyl)-2-methylbut-3-yn-2-ol **(119)**[270b] A flame dried 100 mL round bottom flask charged with nitrogen containing $Pd(PPh_3)_2Cl_2$ (67 mg, 2 mol%) and CuI (10 mg, 1 mol%) were dissolved in Et_3N (10 mL), and [(2-iodophenyl)methylene]dibenzene **118** (1.8 g, 4.8 mmol) and 2-methylbut-3-yn-2-ol (613 mg, 7.29 mmol) were added to the solution. The resulting mixture was stirred under a nitrogen atmosphere at room temp. for 2 h. The reaction was then quenched with saturated aqueous NH_4Cl (15 mL), and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (9:1 Hexanes/EtOAc) to give compound **119** (862 mg, 55 %) as a yellow solid. m.p= 113-115 ˚C; IR (ATR Diamond) cm^{-1} 3141, 3021, 1595, 1492, 1476, 1447, 1373, 1361, 1286, 1265, 1162, 1076, 1028, 968, 917, 818, 757, 747, 726, 700.

^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 2H), 7.23 (d, *J* = 6.2 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 4H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.99 (s, 1H), 1.49 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 143.4, 132.5, 129.7, 129.5, 128.4, 128.3, 126.43, 126.41, 123.1, 99.0, 81.1, 65.6, 54.8, 31.3; HRMS (EI) *m*/*z* calcd for $C_{29}H_{24}$ $[M+H]^+$: 327.1749; found: 327.1744.



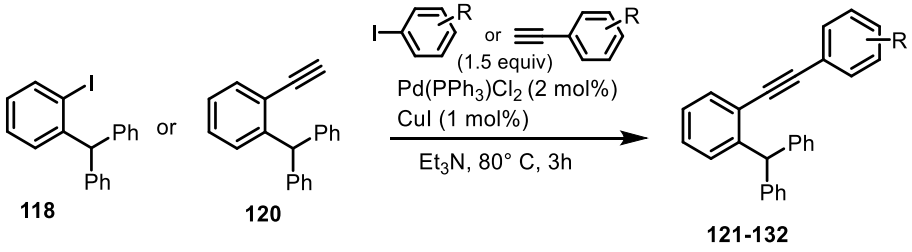
119 **120**

4 ((2-ethynylphenyl)methylene)dibenzene **(120).** A flame dried 100 mL round bottom flask containing 4-(2-benzhydrylphenyl)-2-methylbut-3-yn-2-ol **119** (862 mg, 2.64 mmol) was dissolved in toluene (20 ml), and freshly powdered KOH (593 mg, 10.57 mmol) was added. After heating to reflux for3 hours, the solvent was removed on a rotary evaporator. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether) to give compound **120** (637 mg, 89 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.26 (s, 6H), 7.31–7.18(m, 8H), 7.11 (d, *J* = 7.4 Hz, 4H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.12 (s, 1H), 3.21 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5 143.3, 133.2, 129.7, 129.6, 128.8, 128.3, 126.4, 126.3, 122.5, 82.3, 81.9, 54.3. Spectral data match with those reported on the literature.[270a]

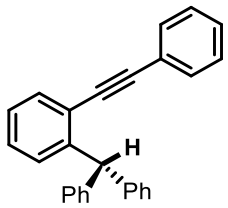
General procedure A for the synthesis starting alkynes **121-132.**



118 **120** **121-132**

In a flame dried pressure tube charged with nitrogen containing $Pd(PPh_3)_2Cl_2$ (2 mol%) and CuI (1 mol%) were dissolved in Et_3N (5 mL), and [(2-iodophenyl)methylene]dibenzene (1 equiv) or aryiodides (1.5equiv) and phenyl acetylene (1.5 equiv) or ((2-ethynylphenyl)methylene)dibenzene (1 equiv) were added to the solution. The resulting mixture was stirred under a nitrogen atmosphere at 80 ˚C for 3 h. The reaction was then quenched with saturated aqueous NH_4Cl (15 mL), and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexanes) to give compound corresponding alkynes **121-132.**

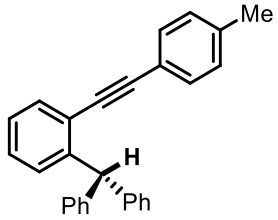
{[2(Phenylethynyl)phenyl]methylene}dibenzene **(121).**



This compound was synthesized according to the general procedure **A** by using ((2-iodophenyl)methylene)dibenzene **118** and phenyl acetylene in 78% yield as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 3.6 Hz, 2H), 7.31–7.21 (m, 11H), 7.15 (d, *J* = 7.5 Hz, 4H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.15 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 143.4, 132.5, 131.6, 129.7, 129.5, 128.4, 128.39, 128.35, 126.4, 123.7, 123.4, 94.3, 88.3, 54.8. Spectral data match with those reported on the literature.[270a]

((2-(*p*-tolylethynyl)phenyl)methylene)dibenzene **(122).**

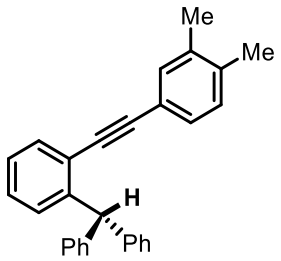


This compound was synthesized according to the general procedure **A** by ((2-ethynylphenyl)methylene)dibenzene **120** and 1-iodo-4-methylbenzene in 93% yield as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.33–7.22 (m, 11H), 7.15 (t, *J* = 8.3 Hz, 6H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.17 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 143.4, 138.4, 132.4, 131.5, 129.7, 129.5, 129.1, 128.4, 128.2, 126.4, 123.8, 120.3, 94.4, 87.6, 54.8, 21.6. Spectral data match with those reported on the literature.[270a]

((2-((3,5-dimethylphenyl)ethynyl)phenyl)methylene)dibenzene **(123).**

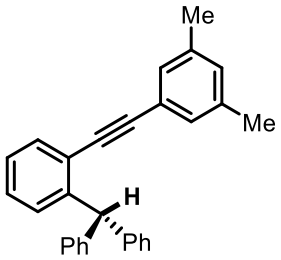


This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-iodo-3,4-dimethylbenzene in 76% yield as white solid. m.p=124-126 ˚C; IR (ATR Diamond) cm^{-1} 2920, 1597, 1492, 1479, 1443, 1076, 1030, 847, 818, 760, 741, 723, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.30–7.06 (m, 15H), 6.98 (d, *J* = 6.8 Hz, 1H), 6.14 (s, 1H), 2.26 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 143.5, 137.3, 136.7, 132.7, 132.4, 129.7, 129.7, 129.5, 129.0, 128.3, 128.1, 126.3, 123.8, 120.6, 94.6, 87.4, 54.8, 19.9, 19.7; HRMS (EI) *m*/*z* calcd for $C_{29}H_{24}$ $[M]^+$: 372.1878; found: 372.1873.

((2-((3,5-dimethylphenyl)ethynyl)phenyl)methylene)dibenzene **(124).**

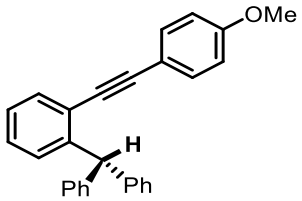


This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-iodo-3,5-dimethylbenzene in 62% yield as white solid. m.p= 122-124 ˚C'; IR (ATR Diamond) cm^{-1} 2918, 2850, 1595, 1494, 1473, 1448, 1078, 1022, 890, 812, 756, 727, 700.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.8 Hz, 1H), 7.32 –7.22 (m, 8H), 7.15 (d, *J* = 7.3 Hz, 4H), 6.99-6.95 (s,4 H), 6.15 (s, 1H), 2.30 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 143.5, 137.9, 132.4, 130.2, 129.8, 129.5, 129.3, 128.4, 128.2, 126.4, 123.8, 123.0, 94.7, 87.6, 123.0, 54.8, 21.2; HRMS (EI) *m*/*z* calcd for $C_{29}H_{24}$ $[M]^+$: 372.1878; found: 372.1876.

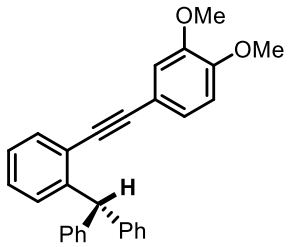
((2-((4-methoxyphenyl)ethynyl)phenyl)methylene)dibenzene **(125).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-iodo-4-methoxybenzene in 90% yield as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 6H), 7.23 (t, *J* = 6.8 Hz, 4H), 7.15 (d, *J* = 7.6 Hz, 4H), 6.98 (d, *J* = 6.9 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.15 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 145.9, 143.5, 133.0, 132.3, 129.7, 129.5, 128.3, 128.0, 126.3, 124.0, 115.5, 114.0, 94.3, 87.0, 55.4., 54.8. Spectral data match with those reported on the literature.[270a]

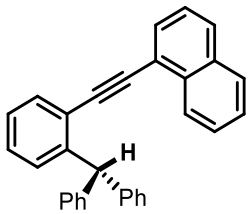
((2-((3,4-dimethoxyphenyl)ethynyl)phenyl)methylene)dibenzene **(126).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-iodo-3,4-dimethoxybenzene in 88% yield as white solid. m.p. 125-127 °C; IR (ATR Diamond) cm^{-1} 2920, 1597, 1514, 1443, 1327, 1251, 1228, 1130, 1024, 845, 800, 761, 726, 700.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.7 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 4H), 7.23 –7.20 (m, 4H), 7.15 (t, *J* = 8.8 Hz, 4H), 6.97 (t, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 7.6 Hz, 2H), 6.13 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 148.6, 145.9, 143.5, 132.3, 129.7, 129.5, 128.3, 128.1, 126.43, 126.40, 124.8, 123.9, 115.6, 114.3, 111.0, 94.4, 86.8, 56.8, 56.0, 54.8; HRMS (EI) *m*/*z* calcd for $C_{29}H_{24}O_2$ $[M]^+$: 404.1776; found: 404.1771.

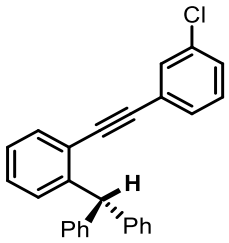
1-((2-benzhydrylphenyl)ethynyl)naphthalene **(127).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-iodonapthalene in 85% yield as white solid. m.p. 93-95°C; IR (ATR Diamond) cm^{-1} 2920, 2851, 1594, 1492, 1477, 1396, 1157, 1078, 1030, 910, 859, 793, 768, 756, 726, 699.

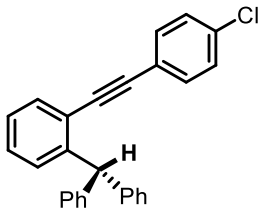
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 6.2 Hz, 1H), 7.45-7.54 (m, 3 H), 7.36–7.27 (m, 8H), 7.20 (d, *J* = 7.4 Hz, 4H), 7.07 (d, *J* = 6.6 Hz, 1H), 6.33 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 143.6, 133.2, 132.8, 130.5, 129.8, 128.8, 128.5, 128.4, 128.3, 126.8, 126.5, 126.5, 126.4, 125.3, 123.8, 121.1, 93.0, 92.2, 54.8; HRMS (EI) *m*/*z* calcd for $C_{31}H_{22}$ $[M]^+$: 394.1722 found: 394.1704.

((2-((3-chlorophenyl)eynyl)phenyl)methylene)dibenzene **(128).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 3-chloro-4-iodobenzene in 93% yield as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.36–7.26 (m, 12H), 7.17 (d, *J* = 7.2 Hz, 4H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.14 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 143.2, 134.2, 132.6, 131.5, 129.7, 129.65, 129.61, 128.7, 128.5, 128.4, 126.52, 126.51, 125.1, 123.1, 92.8, 89.5, 54.9. Spectral data match with those reported on the literature.[270a]

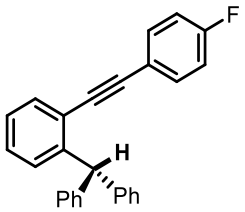
((2-((4-chlorophenyl)ethynyl)phenyl)methylene)dibenzene **(129).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-chloro-4-iodobenzene in 91% yield as white solid. m.p. 107-109°C; IR (ATR Diamond) cm^{-1} 2922, 1597, 1489, 1446, 1089, 1032, 1012, 823, 809, 756, 745, 736, 719, 697.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.8 Hz, 1H), 7.20-7.13 (m, 12H), 7.03 (d, *J* = 6.9 Hz, 4H), 6.89 (d, *J* = 7.1 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 143.3, 134.3, 132.8, 132.5, 129.7, 129.6, 128.7, 128.6, 128.4, 126.4, 123.3, 121.9, 93.1, 89.3, 54.8. HRMS (EI) *m/z* calcd for $C_{27}H_{19}Cl$ [M]+: 378.1175; found: 378.1167.

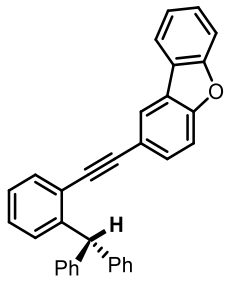
((2-((4-fluorophenyl)ethynyl)phenyl)methylene)dibenzene **(130).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 1-fluoro-4-iodobenzene in 96% yield as white solid. m.p=112-114 ˚C; IR (ATR Diamond) cm^{-1} 2922, 1599, 1449, 1224, 1155, 1079, 841, 799, 756, 726, 702.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.6 Hz, 1H), 7.34-7.15 (m, 14H), 7.02 (d, *J* = 7.7 Hz, 3H), 6.14 (s, 1H); ^{13}C NMR (126 MHz) δ 162.62 (d, *J* = 249.5 Hz), 146.1, 143.3, 133.48 (d, *J* = 8.5 Hz), 132.5, 129.7, 129.6, 128.4, 126.4, 123.5, 119.52 (d, *J* = 3.3 Hz), 115.71 (d, *J* = 22.0 Hz), 93.2, 88.0, 54.8; HRMS (EI) *m*/*z* calcd for $C_{27}H_{19}F$ $[M]^{+}$: 362.1471; found: 362.1465.

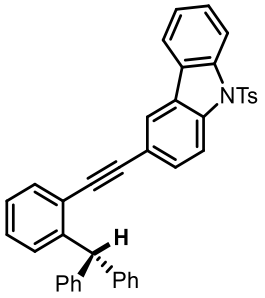
2-((2-benzhydrylphenyl)ethynyl)dibenzo[*b*,*d*]furan **(131).**



This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 2-iododibenzo[*b*,*d*]furan in 85% yield as white solid. m.p. 92-94°C; IR (ATR Diamond) cm^{-1} 3024, 1597, 1485, 1448, 1242, 1192, 1118, 1021, 838, 808, 744, 725, 699.

^{1}H NMR (500 MHz,) δ 8.17-7.71 (m, 7H), 7.64 –7.44 (m, 14H), 6.45 (s, 1H); ^{13}C NMR (126 MHz,) δ 156.7, 155.9, 146.0, 143.5, 132.4, 130.7, 129.8, 129.6, 128.4, 128.3, 127.7, 126.4, 126.4, 124.5, 124.2, 123.8, 123.7, 123.1, 120.9, 117.9, 111.9, 111.8, 94.5, 87.5, 54.9; HRMS (EI) *m*/*z* calcd for $C_{33}H_{22}O$ $[M]^+$: 434.1671; found: 434.1652.

3-((2-benzhydrylphenyl)ethynyl)-9-tosyl-9*H*-carbazole **(132).**

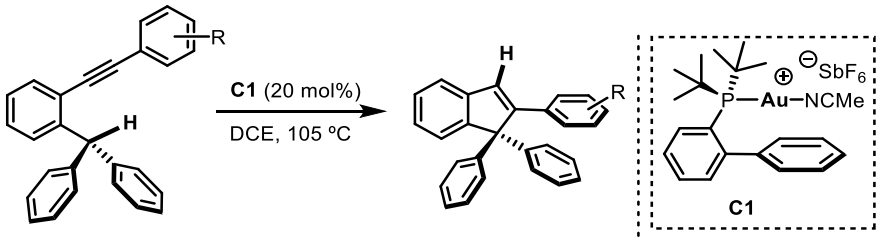


This compound was synthesized according to the general procedure **A** by using ((2-ethynylphenyl)methylene)dibenzene **120** and 3-iodo-9-tosyl-9*H*-carbazole in 91% yield as white solid. m.p=190-192 ˚C; IR (ATR Diamond) cm^{-1} 2924, 1595, 1445, 1368, 1172, 1089, 980, 809, 823, 755, 715, 670, 570, 699, 650, 610, 590, 539, 485.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 4H), 7.25-7.23 (m, 4H), 7.16 (d, *J* = 7.6 Hz, 4H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.16 (s, 1H), 2.27 (s, 3H).

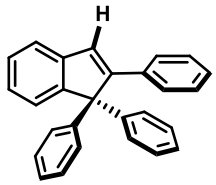
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 145.2, 143.4, 138.8. 138.0, 134.9, 132.5, 130.7, 129.89, 129.81, 129.6, 128.4, 128.4, 127.9, 126.6, 126.5, 126.4, 125.9, 124.2, 123.6, 123.4, 120.2, 119.0, 115.3, 115.2, 94.2, 88.2, 54.9, 21.6; HRMS (EI) *m*/*z* calcd for $C_{40}H_{29}NO_2S$ $[M]^+$: 587.1919; found: 587.1916.

General procedure B for the synthesis of final compounds **133-145**.



In a flame dried pressure tube charged with nitrogen containing starting alkynes **121-132** (1 equiv) and catalyst **C1** (20 mol%) were dissolved in DCE (3 mL). The resulting mixture was stirred at 80 ˚C for 2-18 h. The reaction was monitored by TLC and the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexanes) to give compound corresponding indenes **133-145.**

1,1,2-triphenyl-1*H*-indene **(133).**

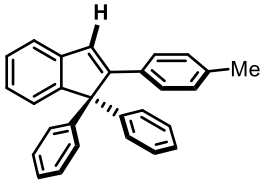


This compound was synthesized according to the general procedure **B** using compound **121** in 2 h (98% yield) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.32 (dd, *J* = 7.5, 2.1 Hz, 4H), 7.24 (s, 1H), 7.24 –7.16 (m, 11H), 7.11 (t, *J* = 7.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 155.0, 142.1, 135.5, 129.0, 128.8, 128.2, 128.0, 127.9, 127.5, 127.1, 126.8, 126.2, 124.6, 121.6, 68.9. Spectral data match with those reported on the literature.[270a]

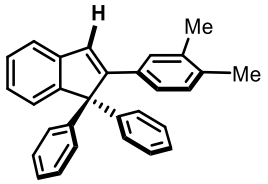
1,1-diphenyl-2-(*p*-tolyl)-1*H*-indene **(134).**



This compound was synthesized according to the general procedure **B** using compound **122** in 2.5 h (97% yield) as white solid.

^{1}H NMR (400 MHz) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.43 –7.28 (m, 14H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 154.9, 142.3, 142.2, 137.3, 132.5, 128.85, 128.81, 128.2, 127.8, 127.0, 126.7, 126.0, 124.6, 121.4, 68.7, 21.2. Spectral data match with those reported on the literature.[270a]

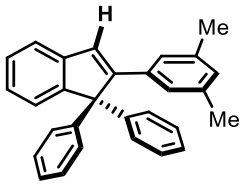
2-(3,4-dimethylphenyl)-1,1-diphenyl-1*H*-indene **(135).**



This compound was synthesized according to the general procedure **B** using compound **123** in 3 h 91% yield as white solid. m.p=103-105 ˚C; IR (ATR Diamond) cm^1 2919, 1596, 1489, 1449, 1187, 1080, 1020, 989, 920, 876, 819, 750, 739, 698, 668.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.34–7.33 (m, 4H), 7.24-7.17 (m, 10H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 2.18 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 155.0, 142.4, 142.3, 136.16, 136.13, 132.9, 129.2, 129.1, 128.8, 128.17, 128.10, 127.0, 126.7, 125.9, 125.4, 124.6, 121.3, 68.7, 29.8, 19.9, 19.6; HRMS (EI) *m*/*z* calcd for $C_{29}H_{24}$ $[M]^+$: 372.1878; found: 327.1862.

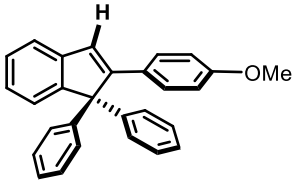
2-(3,5-dimethylphenyl)-1,1-diphenyl-1*H*-indene **(136).**



This compound was synthesized according to the general procedure **B** using compound **124** in 2.5 h (91% yield) as white solid. m.p=128-130 ˚C; IR (ATR Diamond) cm^1 2916, 1488, 1183, 1080, 1032, 918, 841, 745, 731, 667, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.33 (dd, *J* = 7.5, 1.9 Hz, 4H), 7.25 –7.18 (m, 9H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 2H), 6.82 (s, 1H), 2.18 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 155.2, 142.34, 142.3,1 137.2, 135.4 129.3, 128.8, 128.1, 127.0, 126.7, 126.0, 125.9, 124.6, 121.4, 68.8, 21.4; HRMS (EI) *m*/*z* calcd for $C_{29}H_{24}$ $[M]^+$: 372.1878; found: 372.1865.

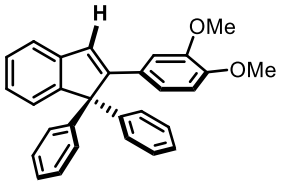
2-(4-methoxyphenyl)-1,1-diphenyl-1*H*-indene **(137).**



This compound was synthesized according to the general procedure **B** using compound **125** in 2 h (96%) yield as white solid.

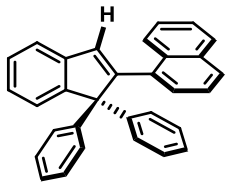
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.32 –7.30 (m, 6H), 7.24 –7.14 (m, 9H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 155.3, 154.73, 142.5, 142.3, 129.2, 128.8, 128.2, 128.1, 127.3, 127.0, 126.7, 125.8, 124.6, 121.2 113.5, 68.7, 55.2. Spectral data match with those reported on the literature.[270a]

2-(3,4-dimethoxyphenyl)-1,1-diphenyl-1*H*-indene **(138).**



This compound was synthesized according to the general procedure **B** using compound **126** in 3.5 h (89%) yield as white solid. m.p=95-97 ˚C; IR (ATR Diamond) cm^{-1} 2922, 1594, 1506, 1446, 1369, 1242, 1167, 1140, 1023, 980, 743, 699, 670, 614, 572; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 4H), 7.25-7.17 (m, 8H) 7.15 (s, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.85 (s, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 3.81 (3, 1H), 3.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 154.8, 148.6, 148.2, 142.4, 142.2, 128.9, 128.6, 128.2, 127.7, 127.1, 126.8, 125.9, 124.6, 121.3, 120.7, 111.2, 110.7, 68.6, 55.8, 55.7; HRMS (EI) *m/z* calcd for $C_{29}H_{24}O_2$ [M]+: 404.1776; found: 404.1773.

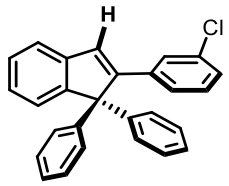
1-(1,1-diphenyl-1*H*-inden-2-yl)naphthalene **(139).**



This compound was synthesized according to the general procedure **B** using compound **127** in 18 h (93% yield) as white solid. m.p=176-178 ˚C; IR (ATR Diamond) cm^{-1} 2917, 2849, 1595, 1487, 1391, 1242, 1212, 1460, 1019, 772, 739, 698, 671, 654, 575.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.21 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.18 (dd, *J* = 8.2, 1.4 Hz, 4H), 7.13 –7.03 (m, 6H), 6.94 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 151.6, 142.5, 141.1, 135.0, 133.5, 133.4, 133.3, 128.6, 128.0, 127.8, 127.7, 127.1, 126.7, 126.0, 125.7, 125.6, 125.5, 125.4, 125.3, 124.6, 121.9, 71.8; HRMS (EI) *m*/*z* calcd for $C_{31}H_{22}$ $[M]^+$: 394.17221; found: 394.1717.

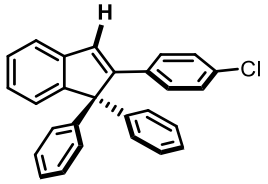
2-(3-chlorophenyl)-1,1-diphenyl-1*H*-indene **(140).**



This compound was synthesized according to the general procedure **B** using compound **128** in 3.5 h (88% yield) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 1.8 Hz, 1H), 7.29 (dd, *J* = 7.4, 2.4 Hz, 4H), 7.2 (s, 1H), 7.23 –7.18 (m, 8H), 7.17 (s, 1H), 7.14 (t, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 153.5, 141.8, 141.7, 137.3, 133.9, 130.1, 129.2, 128.7, 128.3, 127.8, 127.5, 127.2, 127.0, 126.6, 126.0, 124.7, 121.9, 68.8. Spectral data match with those reported on the literature.[270a]

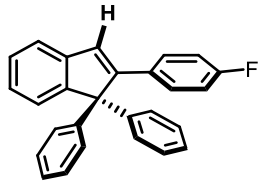
2-(4-chlorophenyl)-1,1-diphenyl-1*H*-indene **(141).**



This compound was synthesized according to the general procedure **B** using compound **128** in 2.5 h (91% yield) as white solid. m.p= 205-207 ˚C; IR (ATR Diamond) cm^{-1} 2920, 1594, 1487, 1444, 1179, 1089, 1034, 1014, 924, 824, 745, 697, 665, 459, 531.

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.34–7.28 (m, 7H), 7.26 (s, 1H), 7.25-7.22 (m, 6H), 7.20 –7.14 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 153.7, 141.9, 141.8, 133.9, 133.3, 129.4, 129.1, 128.7, 128.3, 128.2, 127.2, 126.9, 126.4, 124.6, 121.7, 68.8.

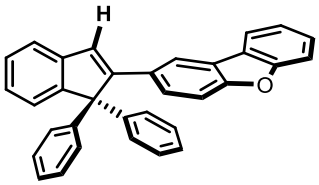
2-(4-fluorophenyl)-1,1-diphenyl-1*H*-indene **(142).**



This compound was synthesized according to the general procedure **B** using compound **129** in 3.5 h (93% yield) as white solid. m.p= 161-163 ˚C; IR (ATR Diamond) cm^{-1} 2923, 2853, 1596, 1504, 1465, 1448, 1224, 1161, 1098, 1080, 923, 875, 751, 829, 796, 743, 695, 666.

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 1H), 7.34-7.28 (m, 6H), 7.24 –7.15 (m, 9H), 7.12 (dd, *J* = 7.0 Hz, 1H), 6.86 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.28 (d, *J* = 247.7 Hz), 155.3, 154.0, 142.1, 141.9, 131.73 (d, *J* = 3.4 Hz), 129.62 (d, *J* = 7.9 Hz), 128.8, 128.7, 128.3, 127.1, 126.9, 126.2, 124.7, 121.6, 115.02 (d, *J* = 21.3 Hz), 68.9; HRMS (EI) *m*/*z* calcd for $C_{27}H_{19}F$ $[M]^+$: 362.1471; found: 362.1468.

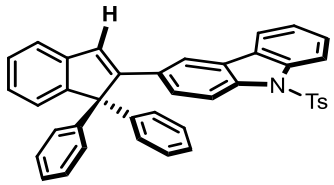
2-(1,1-diphenyl-1*H*-inden-2-yl)dibenzo[*b*,*d*]furan **(144).**



This compound was synthesized according to the general procedure **B** using compound **131** in 18 h (91% yield) as white solid. m.p=183-185 ˚C; IR (ATR Diamond) cm^{-1} 2924, 1728, 1595, 1448, 1246, 1194, 1141, 1021, 917, 815, 744, 68, 672, 643, 619, 545, 575, 509; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.90 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.55-7.36 (m, 10H), 7.29 (dd, *J* = 10.7, 5.2 Hz, 3H), 7.22 (dd, *J* = 10.7, 5.2 Hz, 8H), 7.14 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 155.2, 142.3, 142.1, 130.8, 128.9, 128.8, 128.31, 127.4, 127.3, 127.1, 126.9, 126.1, 124.7, 124.2, 124.0, 122.8, 121.5, 120.6, 120.0, 111.7, 111.1, 69.1; HRMS (EI) *m*/*z* calcd for $C_{33}H_{22}O$ $[M]^+$: 434.1671; found: 434.1655.

3-(1,1-diphenyl-1*H*-inden-2-yl)-9-tosyl-9*H*-carbazole **(145).**



This compound was synthesized according to the general procedure **B** using compound **132** in 3 h (95% yield) as white solid. m.p= 246-248 ˚C; IR (ATR Diamond) cm^{-1} 3030, 1594, 1509, 1446, 1369, 1242, 1167, 1140, 1023, 980, 808, 743, 699, 670, 614, 572.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.69 (dd, *J* = 8.4 Hz, 3H), 7.55 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.46 (dd, *J* = 7.1, 5.3 Hz, 2H), 7.37 –7.35 (m, 3H), 7.33 –7.27(m, 5H), 7.22 –7.21 (m, 6H), 7.16 (dd, *J*= 8.3Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 154.7, 145.0, 142.2, 142.0, 138.6, 137.6, 135.0, 131.8, 129.8, 129.2, 128.8, 128.3, 127.5, 127.2, 126.9, 126.6, 126.4, 126.2, 126.1, 124.7, 123.9, 121.6, 120.0, 119.2, 115.1, 114.6, 69.0, 21.6; HRMS (EI) *m*/*z* calcd for $C_{40}H_{29}NO_2S$ $[M]^+$: 587.1919; found: 587.1902.

Computational methodology.

We have performed gas-phase geometry optimizations using the Gaussian16 rev. A.03 program.[271] The potential energy surface (PES) of the reactions reported in this work was explored using a combined semi-empirical-DFT approach (two-layered ONIOM scheme)[272] (see Figure 3.3). We treated the diphenyl phosphine part of Au(I) complex, the isonitrile core and the [2(phenylethynyl)phenyl]methylene (Figure 3.3) with the global-hybrid, meta-GGA density-functional M08-HX developed by Zhao and Truhlar,[273] in combination with the split-valence double-ζ quality basis set with one function 6-31G(d) for C and H and two polarization functions, 6-31G(2d) for N and P and the modified LANL2DZ pseudopotential for Au.[274] For the outer part, we defined the t-Butyl groups of the Au(I) complex, phenyl groups of the substrate and the methyl group of isonitrile as the steric hindrance contributors, described at the semi-empirical PM6 level[275] as this can give good weak interactions such as hydrogen bonds, and has been shown to be significantly better for reproducing ab initio TS structures and barrier heights.[276] We also utilized electronic embedding in our calculations to incorporate the partial charges of the PM6 region into the DFT Hamiltonian.[277] This computational level of theory is called ONIOM(M08-HX/*mixed–basis*:PM6) where *mixed–basis* stands for the combination described above (6-31G(d)–6-31G(2d)–mod-LANL2DZ). Finally, we have computed the S-value test which is low (0.63 kcal·mol^{-1}) and therefore, our ONIOM2 partition scheme is very suitable for this study.

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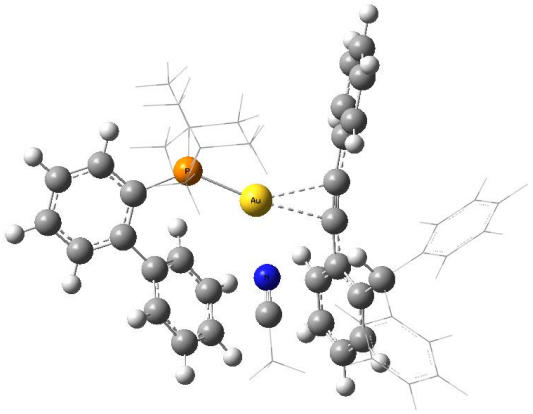

Figure 3.3. Partition scheme used for ONIOM calculations. The high layer is represented in ball and stick mode whereas the low layer is shown as wireframe draw.

Also, the solvent effect was considered by performing single-point calculations over each optimized geometry using the polarizable continuum model (PCM) and setting up Truhlar and coworkers' SMD solvation radii[278] using dichloroethane as the solvent of reaction.

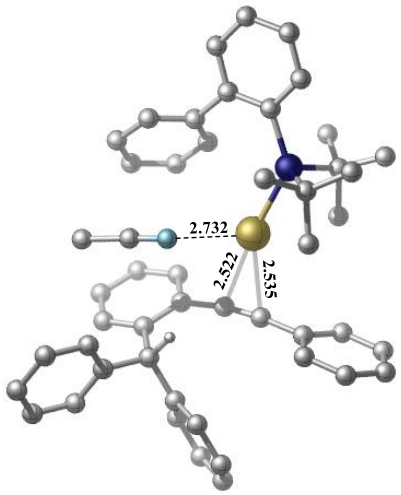

Figure 3.4. Optimized geometry of the reaction adduct **XIII**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.[279]

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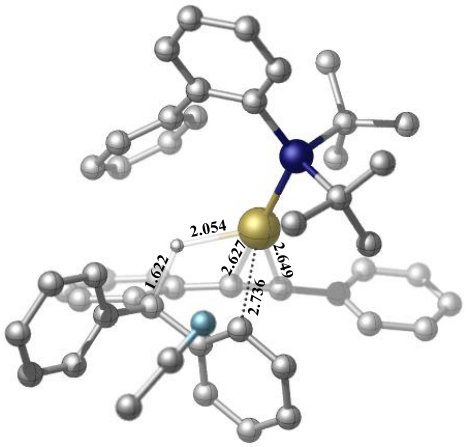

Figure 3.5. Optimized geometry of the transition state **I→II**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.

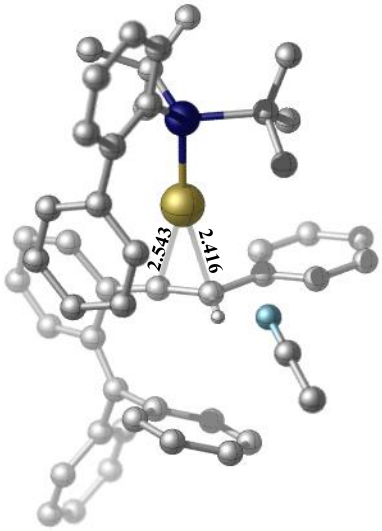

Figure 3.6. Optimized geometry of the intermediate **XIIIA**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.

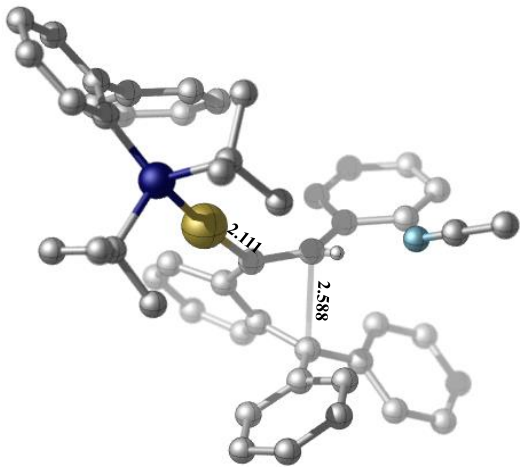

Figure 3.7. Optimized geometry of the transition state **II→III**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.

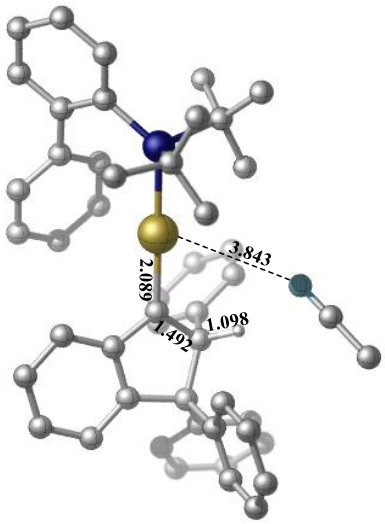

Figure 3.8. Optimized geometry of the intermediate **XIV**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.

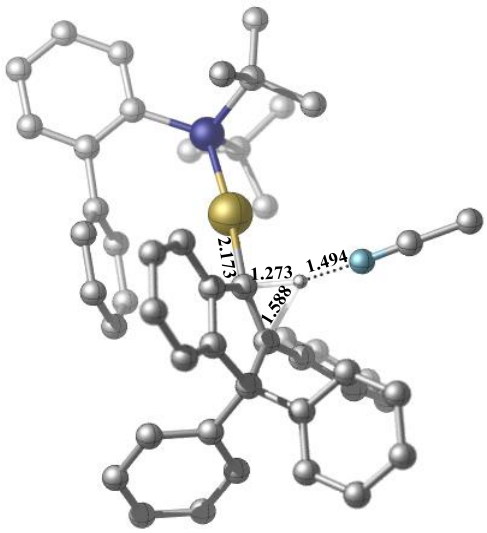

Figure 3.9. Optimized geometry of the transition state **III→IV**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.

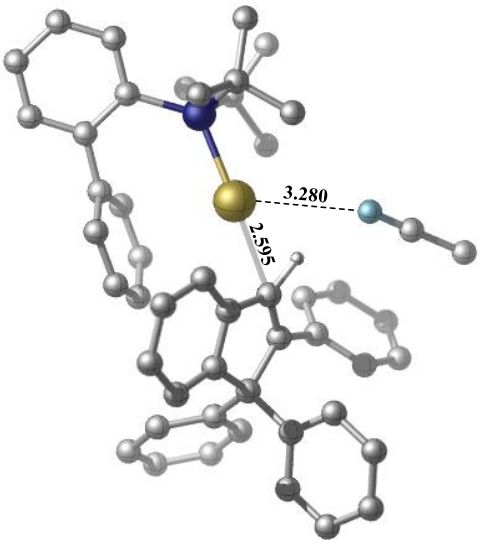

Figure 3.10. Optimized geometry of the intermediate **XV**. Bond distances are given in Angstroms. Hydrogens were omitted for clarity.

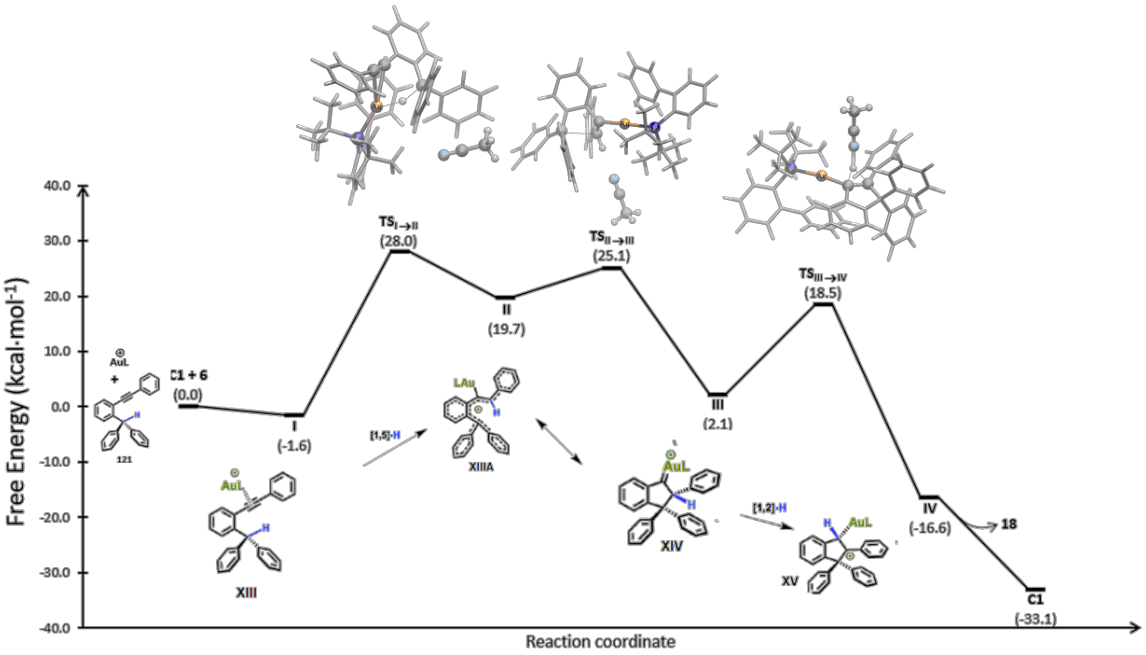

Figure 3.11. Free energy profile for the calculated reaction mechanism between C1 and 121 to get product **133**.

(Calculations were done at the (SMD:dichloroethane)ONIOM(M08-HX/mixed□basis:PM6) level).

Table 3.2. Cartesian coordinates (xyz) of the optimized geometries for all the compounds involved in the reaction mechanism.

C1

E(scf) = −578.519481534200 a.u.

C	2.495086	1.983280	0.484145
C	1.273426	1.391684	0.160731
C	0.103017	2.172992	0.286062
C	0.183134	3.505677	0.717595
C	1.413220	4.072652	1.029945
C	2.572153	3.307945	0.913649
H	3.413773	1.396682	0.390548
H	−0.735800	4.085456	0.804273
H	1.466825	5.109504	1.362826
H	3.542914	3.742417	1.154260
C	−1.177207	1.602605	−0.018537
C	−2.251291	1.098315	−0.265998
C	−3.511570	0.476092	−0.547216
C	−4.622063	1.245104	−0.929794
C	−3.644136	−0.917985	−0.439667
C	−5.839087	0.628099	−1.200603
H	−4.516346	2.326648	−1.011915
C	−4.864345	−1.527172	−0.712200
H	−2.778740	−1.508956	−0.133323
C	−5.963787	−0.757300	−1.093673
H	−6.696638	1.232253	−1.497595
H	−4.959244	−2.609755	−0.624689
H	−6.919194	−1.237455	−1.306720
C	1.157882	−0.057915	−0.338123
H	0.447203	−0.035136	−1.203568
C	2.495928	−0.579850	−0.834779
C	3.363009	−1.298700	0.000257
C	2.869174	−0.327187	−2.164796

I

E(scf) = −1612.310359278357 a.u.

C	3.634379	−2.362721	−1.416669
C	3.130700	−1.165275	−0.903816
C	2.021590	−0.594648	−1.570160
C	1.459259	−1.202266	−2.699032
C	1.984539	−2.393843	−3.188094
C	3.070195	−2.975872	−2.538548
H	4.494302	−2.831871	−0.932487
H	0.614169	−0.718780	−3.191448
H	1.552604	−2.859874	−4.074295
H	3.497694	−3.905282	−2.914129
C	1.467442	0.650216	−1.099202
C	1.188712	1.784323	−0.725820
C	1.009002	3.157600	−0.333689
C	0.454439	4.082506	−1.232340
C	1.420643	3.571786	0.942635
C	0.309845	5.411117	−0.848794
H	0.157676	3.752843	−2.228256
C	1.272854	4.903959	1.314050
H	1.867046	2.845850	1.623254
C	0.715624	5.821526	0.422403
H	−0.112590	6.132591	−1.547006
H	1.599807	5.229602	2.300693
H	0.604380	6.864741	0.716523
C	3.718949	−0.458913	0.332037
H	2.836785	−0.140553	0.947541
C	4.573773	−1.391969	1.171866
C	5.901580	−1.674696	0.817456
C	4.032177	−1.959741	2.334836

C	4.586162	−1.763335	−0.491452
H	3.083100	−1.502103	1.034115
C	4.093429	−0.792055	−2.651024
H	2.207265	0.236538	−2.820126
C	4.954566	−1.511905	−1.816365
H	5.252724	−2.324517	0.161519
H	4.376907	−0.593093	−3.683236
H	5.906478	−1.875185	−2.197187
C	0.559031	−0.985479	0.707851
C	−0.104304	−2.145893	0.276265
C	0.658574	−0.715822	2.079584
C	−0.665781	−3.020489	1.209247
H	−0.174567	−2.370180	−0.786776
C	0.092156	−1.593227	3.009008
H	1.170715	0.181913	2.425430
C	−0.570854	−2.745766	2.577623
H	−1.176410	−3.920023	0.869922
H	0.167394	−1.374977	4.073117
H	−1.011498	−3.426227	3.302709

121

E(scf) = −1033.777359752151 a.u.

Au	1.134564	−0.464531	−0.135759
P	−1.123295	−0.678022	0.097077
C	−1.262106	−1.341781	1.893082
C	−1.355873	−2.052010	−1.210969
C	−0.270545	−3.097805	−0.914778
H	−0.399663	−3.596281	0.062115
H	−0.334418	−3.917643	−1.654874
H	0.769704	−2.737046	−1.003693
C	−1.039388	−1.347983	−2.537403
H	−1.058106	−2.072773	−3.369938
C	6.670805	−2.532343	1.607634
H	6.341109	−1.210061	−0.066733
C	4.806301	−2.817313	3.122542
H	3.018115	−1.717349	2.645487
C	6.123865	−3.109559	2.758584
H	7.704054	−2.744926	1.330468
H	4.385122	−3.249742	4.029759
H	6.727559	−3.774896	3.375306
C	4.503936	0.790190	−0.033559
C	4.678385	1.778773	0.948737
C	5.067959	0.966757	−1.303524
C	5.402758	2.936193	0.655167
H	4.268862	1.637118	1.946826
C	5.789757	2.129523	−1.592350
H	4.950202	0.204726	−2.072615
C	5.957289	3.115971	−0.616778
H	5.542155	3.698840	1.420696
H	6.225834	2.263594	−2.582232
H	6.522244	4.019166	−0.843520
Au	−0.908445	0.431203	−0.279871
P	−3.148756	0.478991	0.287952
C	−3.775708	1.657547	−1.095535
C	−2.876115	1.390853	1.959435
C	−1.563611	2.174101	1.775205
H	−1.519352	2.809190	0.873081
H	−1.446029	2.895885	2.607491
H	−0.650055	1.551199	1.871286
C	−2.669429	0.278984	2.992757
H	−2.381499	0.707022	3.966518
H	−3.579442	−0.306194	3.190991
H	−1.865685	−0.428768	2.735656
C	−4.003527	2.318777	2.391903

H	−1.782960	−0.584649	−2.815112
H	−0.039365	−0.885532	−2.576995
C	−2.733966	−2.695943	−1.247619
H	−2.811830	−3.389281	−2.102275
H	−2.963397	−3.298606	−0.358937
H	−3.555436	−1.973636	−1.381378
C	−1.953638	−2.698157	1.973772
H	−1.432630	−3.493475	1.416549
H	−1.993735	−3.046340	3.019872
H	−2.999392	−2.672449	1.637274
C	0.205120	−1.456293	2.348094
H	0.736038	−0.489385	2.417022
H	0.236169	−1.840356	3.387371
H	0.802578	−2.191708	1.781979
C	−2.012732	−0.318387	2.742577
H	−1.554874	0.686519	2.747709
H	−3.064557	−0.195512	2.445046
H	−2.041476	−0.636771	3.797387
C	−2.278121	0.681687	−0.203108
C	−3.620588	0.397618	−0.484187
C	−1.815272	2.014155	−0.230154
C	−4.505348	1.420029	−0.811202
H	−3.972563	−0.638260	−0.469872
C	−2.716299	3.026085	−0.579288
C	−4.047055	2.735076	−0.866547
H	−5.545769	1.188013	−1.029223
H	−2.360791	4.055901	−0.603811
H	−4.731673	3.540396	−1.128194
C	−0.409658	2.377979	0.109253
C	0.451762	2.870779	−0.878442
C	0.070808	2.204507	1.413522
C	1.781869	3.159291	−0.569222
H	−3.837022	2.674206	3.421834
H	−4.080926	3.224517	1.768996
H	−4.991765	1.831790	2.403610
C	−4.744461	2.732506	−0.619533
H	−4.312455	3.418961	0.126108
H	−5.061425	3.366745	−1.463812
H	−5.673302	2.320710	−0.201618
C	−2.490192	2.289518	−1.659800
H	−1.865974	1.596829	−2.254151
H	−2.760885	3.074193	−2.393955
H	−1.886719	2.833457	−0.908580
C	−4.452987	0.790192	−2.158834
H	−3.838412	−0.051164	−2.522365
H	−5.412159	0.368728	−1.819190
H	−4.697568	1.390526	−3.049660
C	−4.413196	−0.792140	0.560920
C	−5.603566	−0.362719	1.166025
C	−4.230053	−2.155618	0.254908
C	−6.613913	−1.263460	1.481331
H	−5.727514	0.696732	1.415450
C	−5.259994	−3.048323	0.590130
C	−6.434844	−2.614950	1.193547
H	−7.530383	−0.912096	1.950952
H	−5.134462	−4.101664	0.339810
H	−7.217174	−3.334057	1.431693
C	−3.029110	−2.719425	−0.419457
C	−2.418160	−3.864311	0.108560
C	−2.555042	−2.200131	−1.631389
C	−1.358639	−4.474727	−0.558511
H	−2.783320	−4.276962	1.050196
C	−1.483392	−2.799952	−2.289339
H	−3.063792	−1.339350	−2.088684

H	0.078048	3.011221	−1.893724
C	1.398725	2.498850	1.724471
H	−0.610084	1.828102	2.188628
C	2.257258	2.970952	0.729940
H	2.445338	3.540852	−1.344866
H	1.759305	2.369159	2.744224
H	3.292355	3.210062	0.972601
N	3.284928	−0.385107	−0.374731
C	4.421011	−0.329636	−0.512090
C	5.858178	−0.263797	−0.686592
H	6.379662	0.016269	0.251884
H	6.282213	−1.237213	−1.010317
H	6.150808	0.483197	−1.453194
C	−0.881017	−3.938283	−1.754561
H	−0.911264	−5.378791	−0.144747
H	−1.143644	−2.400195	−3.244595
H	−0.055657	−4.415691	−2.282629
N	0.335836	−1.567147	1.108490
C	0.874763	−2.566217	0.908999
C	1.593319	−3.812940	0.710968
H	1.611363	−4.108930	−0.355356
H	2.652659	−3.721883	1.036387
H	1.147061	−4.643947	1.286731

$TS_{I \rightarrow II}$

E(scf) = −1612.251094142660 a.u.

ν_{min} = −637.2 cm^{-1}

C	3.815804	1.033067	−2.392836
C	2.711144	1.267842	−1.567626
C	1.706575	2.140488	−2.042955
C	1.824651	2.750780	−3.299302
C	2.942692	2.513359	−4.093099
C	3.939001	1.651764	−3.636364
H	4.598148	0.346875	−2.059801
H	1.033717	3.417772	−3.640587
H	3.032227	2.997174	−5.064627
H	4.816248	1.454170	−4.251416
C	0.534460	2.438931	−1.262661
C	−0.433155	2.911209	−0.678206
C	−1.548611	3.596973	−0.082743
C	−2.498703	4.211144	−0.916432
C	−1.683655	3.676214	1.311765

II

E(scf) = −1612.272396054096 a.u.

C	4.009186	−2.920719	−0.843183
C	3.500054	−1.635665	−0.356550
C	2.013837	−1.464493	−0.420585
C	1.195924	−2.676234	−0.579767
C	1.762869	−3.851495	−0.910451
C	3.200228	−3.967563	−1.094583
H	5.091900	−3.028952	−0.938060
H	0.113179	−2.582967	−0.464394
H	1.138464	−4.732080	−1.058670
H	3.617996	−4.921214	−1.411921
C	1.467211	−0.255085	−0.406120
C	1.112307	1.033248	−0.436391
C	0.993485	1.860692	−1.667549
C	1.322672	1.347030	−2.929237
C	0.524454	3.173952	−1.550571
C	1.190741	2.146357	−4.058466

C	−3.569517	4.895811	−0.353821
H	−2.382403	4.149683	−1.998158
C	−2.761498	4.360264	1.863910
H	−0.929181	3.211462	1.950268
C	−3.703694	4.968622	1.033918
H	−4.302042	5.377724	−0.999981
H	−2.862587	4.426441	2.946128
H	−4.544059	5.507513	1.470057
C	2.543362	0.568488	−0.251374
H	1.242134	−0.363430	−0.513173
C	3.615664	−0.401900	0.151934
C	4.903541	0.069091	0.460689
C	3.336030	−1.770169	0.257298
C	5.904978	−0.828269	0.836491
H	5.121343	1.136033	0.405918
C	4.341717	−2.665251	0.636455
H	2.331524	−2.139253	0.050402
C	5.627929	−2.197773	0.919485
H	6.907355	−0.460890	1.060051
H	4.120448	−3.730294	0.710474
H	6.415146	−2.898023	1.199480
C	2.084552	1.398356	0.917241
C	1.164611	0.858041	1.833881
C	2.620962	2.675645	1.135744
C	0.820541	1.586544	2.979021
H	0.846569	−0.199322	1.766905
C	2.248059	3.406810	2.268230
H	3.330049	3.100544	0.423229
C	1.350671	2.863204	3.192888
H	0.155876	1.141500	3.722545
H	2.667545	4.401428	2.434133
H	1.080716	3.426236	4.086832
H	1.691027	0.322234	−3.012193
C	0.393667	3.971091	−2.686426
H	0.261837	3.560240	−0.563172
C	0.725370	3.459057	−3.939287
H	1.455556	1.748479	−5.037481
H	0.033885	4.995047	−2.591639
H	0.626128	4.082815	−4.826897
C	4.362732	−0.711241	0.153794
H	0.971261	1.561561	0.520715
C	5.835558	−0.935074	0.092028
C	6.523407	−0.723350	−1.112499
C	6.531564	−1.328920	1.243657
C	7.906492	−0.915353	−1.161824
H	5.983004	−0.409162	−2.003740
C	7.914491	−1.523284	1.183755
H	5.998365	−1.480288	2.180823
C	8.602295	−1.317126	−0.016441
H	8.444899	−0.749944	−2.095162
H	8.458205	−1.832596	2.076676
H	9.681292	−1.466496	−0.058857
C	3.957480	0.542271	0.846048
C	3.405566	0.479674	2.134389
C	4.201535	1.786054	0.243813
C	3.095632	1.660628	2.814476
H	3.228086	−0.487114	2.605939
C	3.879766	2.961671	0.926964
H	4.644885	1.833247	−0.750850
C	3.329868	2.900915	2.212064
H	2.689034	1.613029	3.823431
H	4.071307	3.927945	0.460154
H	3.102125	3.819551	2.748595
Au	−1.064428	−0.015100	−0.430443

Au	−0.649913	0.347308	−0.149238	P	−3.311588	−0.408956	−0.553852
P	−2.237309	−1.303801	0.262002	C	−3.407508	−1.775765	−1.894776
C	−3.791428	−0.535319	−0.597034	C	−3.753864	1.319428	−1.244588
C	−2.398087	−1.204063	2.170577	C	−2.871945	1.536933	−2.480489
C	−2.450164	0.298761	2.484517	H	−3.111976	0.852486	−3.312543
H	−3.390367	0.775616	2.152760	H	−3.045503	2.548955	−2.889367
H	−2.425395	0.449663	3.578069	H	−1.783432	1.508939	−2.293263
H	−1.604704	0.890414	2.098886	C	−3.311930	2.276665	−0.128566
C	−1.098878	−1.818589	2.692842	H	−3.498595	3.321967	−0.428297
H	−1.027809	−1.727261	3.790458	H	−3.872121	2.148021	0.809197
H	−1.007963	−2.897695	2.500689	H	−2.232090	2.243268	0.108122
H	−0.175331	−1.337487	2.322261	C	−5.226190	1.519087	−1.575775
C	−3.599990	−1.910354	2.788503	H	−5.392539	2.529504	−1.985841
H	−3.583158	−1.797258	3.884910	H	−5.609230	0.827095	−2.335563
H	−4.571189	−1.516444	2.459397	H	−5.879249	1.455785	−0.693813
H	−3.604997	−2.998146	2.606927	C	−4.353742	−1.429026	−3.038675
C	−4.938983	−0.248273	0.367305	H	−4.063641	−0.516775	−3.585985
H	−4.682880	0.490976	1.144767	H	−4.361975	−2.236623	−3.789360
H	−5.800100	0.173305	−0.175688	H	−5.398156	−1.317748	−2.718817
H	−5.318261	−1.149440	0.872411	C	−1.955197	−1.885039	−2.396400
C	−3.261678	0.787756	−1.177441	H	−1.247179	−2.288009	−1.645747
H	−2.472923	0.677150	−1.940621	H	−1.906110	−2.625137	−3.218995
H	−4.077372	1.300549	−1.723892	H	−1.554543	−0.964250	−2.852085
H	−2.969338	1.523291	−0.406791	C	−3.836174	−3.083947	−1.230086
C	−4.276882	−1.466581	−1.705782	H	−3.199000	−3.393611	−0.392060
H	−3.514552	−1.680246	−2.475672	H	−4.872672	−3.062638	−0.862302
H	−4.639069	−2.434486	−1.330332	H	−3.800314	−3.913114	−1.955270
H	−5.127183	−1.020167	−2.244854	C	−4.386064	−0.818296	0.841935
C	−2.061716	−3.040967	−0.251390	C	−5.772077	−0.869781	0.639505
C	−2.826114	−4.010411	0.412809	C	−3.841912	−1.105824	2.110451
C	−1.149039	−3.441383	−1.253123	C	−6.627168	−1.181622	1.691199
C	−2.683388	−5.363219	0.124951	H	−6.184883	−0.669646	−0.350781

H	−3.536091	−3.705013	1.188278
C	−1.011775	−4.811158	−1.518285
C	−1.763650	−5.764151	−0.840679
H	−3.285507	−6.096973	0.656852
H	−0.314511	−5.118689	−2.297720
H	−1.639736	−6.820078	−1.075955
C	−0.333291	−2.498650	−2.063976
C	1.052385	−2.681048	−2.167533
C	−0.930049	−1.449092	−2.772411
C	1.823317	−1.811284	−2.935824
H	1.524279	−3.503445	−1.627185
C	−0.158277	−0.570378	−3.533303
H	−2.024514	−1.341987	−2.748986
C	1.221346	−0.750767	−3.614583
H	2.903272	−1.953775	−2.997394
H	−0.637282	0.243107	−4.078242
H	1.827631	−0.066781	−4.209309
N	1.988938	−1.762635	3.699862
C	3.098051	−1.650187	3.988539
C	4.500986	−1.507022	4.346979
H	5.129363	−1.356177	3.448217
H	4.663027	−0.642128	5.015098
H	4.879278	−2.403083	4.871600

$TS_{II \rightarrow III}$

E(scf) = −1612.261221791709 a.u.

ν_{min} = −91.5 cm^{-1}

C	−3.689220	−2.310348	−2.119461
C	−2.977524	−1.236653	−1.549201
C	−1.577507	−1.382496	−1.314510
C	−0.874515	−2.473692	−1.868664
C	−1.592653	−3.491936	−2.465241
C	−4.719411	−1.417709	3.154705
C	−6.096565	−1.450220	2.951845
H	−7.702036	−1.217791	1.525229
H	−4.302821	−1.642648	4.135976
H	−6.758932	−1.695073	3.780967
C	−2.367947	−1.142093	2.361638
C	−1.656496	0.016989	2.693622
C	−1.681358	−2.354651	2.224734
C	−0.271635	−0.037528	2.867459
H	−2.181601	0.969584	2.787625
C	−0.298132	−2.406564	2.399116
H	−2.238994	−3.258863	1.975665
C	0.409273	−1.245939	2.713460
H	0.276238	0.874762	3.108097
H	0.230611	−3.352123	2.278940
H	1.493858	−1.281980	2.832179
N	−0.534907	3.101288	1.844723
C	−0.356502	3.906457	2.648988
C	−0.137116	4.925120	3.663090
H	0.601664	5.679303	3.332205
H	−1.070389	5.469056	3.903742
H	0.238742	4.489958	4.607844

III

E(scf) = −1612.310387577454 a.u.

C	−3.618268	−1.241919	−2.864584
C	−2.949084	−0.773835	−1.738520
C	−1.532799	−0.784536	−1.717889
C	−0.781395	−1.271347	−2.805537
C	−1.459584	−1.762603	−3.909285
C	−2.864046	−1.738962	−3.931206

C	−2.996624	−3.418081	−2.575622	H	−4.706027	−1.204749	−2.931114
H	−4.764975	−2.231082	−2.275265	H	0.309054	−1.251705	−2.759503
H	0.206034	−2.537179	−1.736803	H	−0.914204	−2.148197	-4.769049
H	−1.073543	−4.372319	−2.841693	H	−3.383014	−2.107615	−4.816608
H	−3.538605	−4.227301	−3.060855	C	−1.020933	−0.168189	−0.529973
C	−1.018004	−0.422166	−0.412382	C	−2.177680	0.056103	0.385964
C	−1.787646	−0.013259	0.664637	C	−1.915034	−1.044424	1.431447
C	−2.598738	−0.874422	1.553943	C	−2.182330	−2.391830	1.169181
C	−2.572035	−2.278010	1.491404	C	−1.342990	−0.681509	2.656569
C	−3.349312	−0.252599	2.564344	C	−1.952399	−3.356545	2.150009
C	−3.304476	−3.033785	2.402136	H	−2.596698	−2.691181	0.202175
H	−1.957689	−2.775861	0.739229	C	−1.094398	−1.648867	3.627448
C	−4.085405	−1.017792	3.467540	H	−1.121399	0.371420	2.849325
H	−3.337314	0.836077	2.636899	C	−1.409562	−2.987036	3.380681
C	−4.066722	−2.410271	3.387753	H	−2.195671	−4.400097	1.950154
H	−3.268433	−4.121684	2.347557	H	−0.671546	−1.355651	4.587661
H	−4.666706	−0.522625	4.243914	H	−1.230748	−3.740824	4.146656
H	−4.629769	−3.006229	4.104058	C	−3.494857	−0.083796	−0.471929
C	−3.591508	0.029966	−1.191373	H	−2.100322	1.017516	0.910746
H	−1.582888	0.969785	1.100438	C	−4.581969	−0.821731	0.285809
C	−4.962912	0.050579	−0.669221	C	−5.152612	−2.017107	−0.167049
C	−5.832694	1.131243	−0.951792	C	−5.028793	−0.266197	1.500105
C	−5.451969	−1.025609	0.103114	C	−6.160755	−2.643144	0.576244
C	−7.136560	1.135428	−0.465197	H	−4.824331	−2.486038	−1.092067
H	−5.492062	1.962099	−1.575295	C	−6.030915	−0.894782	2.239296
C	−6.757643	−1.010557	0.595659	H	−4.588800	0.660253	1.866715
H	−4.802461	−1.877136	0.331165	C	−6.602977	−2.085931	1.777290
C	−7.601528	0.067729	0.315421	H	−6.600669	−3.572198	0.212779
H	−7.802154	1.969600	−0.694109	H	−6.368972	−0.458626	3.179505
H	−7.118464	−1.843584	1.201598	H	−7.387542	−2.575456	2.354011
H	−8.623985	0.078468	0.699960	C	−3.985364	1.287013	−0.935633
C	−3.015877	1.298811	−1.691794	C	−5.359478	1.531257	−1.088924

C	−3.031796	2.465992	−0.903003
C	−2.526063	1.356215	−3.009664
C	−2.597042	3.677200	−1.440734
H	−3.372854	2.417140	0.134074
C	−2.102425	2.575991	−3.542891
H	−2.491102	0.453274	−3.622427
C	−2.143631	3.736782	−2.764440
H	−2.615377	4.580540	−0.830601
H	−1.744576	2.621961	−4.572468
H	−1.824711	4.689972	−3.188948
Au	1.027714	0.096969	−0.347333
P	3.277986	0.703834	−0.103422
C	3.113709	1.960624	1.347469
C	3.540109	1.578513	−1.790951
C	2.142594	2.121097	−2.141986
H	1.671416	2.717675	−1.342466
H	2.213217	2.808169	−3.003487
H	1.433881	1.341712	−2.481594
C	3.933269	0.473226	−2.778145
H	3.966161	0.870586	−3.805006
H	4.937283	0.065023	−2.589101
H	3.232127	−0.371331	−2.809522
C	4.585766	2.686054	−1.805905
H	4.776886	3.023561	−2.836704
H	4.270804	3.582575	−1.248471
H	5.561250	2.366087	−1.408048
C	3.982757	3.205700	1.211471
H	3.749091	3.808528	0.319928
H	3.837120	3.872253	2.075729
H	5.056863	2.977932	1.192870
C	1.620224	2.329903	1.356893
H	0.953279	1.519784	1.710422
C	−3.076488	2.304026	−1.270805
C	−5.814434	2.773011	−1.541183
H	−6.090942	0.753538	−0.856111
C	−3.533346	3.543951	−1.726102
H	−2.003106	2.138105	−1.194299
C	−4.903799	3.784643	−1.858641
H	−6.885607	2.948715	−1.652183
H	−2.817392	4.320096	−1.994344
H	−5.260462	4.748997	−2.219969
Au	0.986650	0.231572	−0.110832
P	3.250326	0.799405	0.230420
C	3.279831	1.169370	2.121183
C	3.275468	2.394308	−0.834871
C	1.861093	2.977448	−0.667260
H	1.526311	3.084395	0.377641
H	1.831381	4.004812	−1.072787
H	1.084191	2.443625	−1.244724
C	3.468923	1.917035	−2.280053
H	3.356134	2.760940	−2.979753
H	4.475951	1.515599	−2.469677
H	2.741476	1.161706	−2.605253
C	4.346993	3.414334	−0.472569
H	4.439777	4.175985	−1.263346
H	4.117266	3.970339	0.448252
H	5.350698	2.974446	−0.360792
C	3.870270	2.526453	2.485729
H	3.365839	3.375673	2.003640
H	3.780539	2.702244	3.570274
H	4.943875	2.597087	2.264930
C	1.794682	1.094954	2.512304
H	1.355254	0.085133	2.426446
H	1.677679	1.342962	3.583439

H	1.439778	3.140244	2.089585
H	1.245407	2.733854	0.404600
C	3.484259	1.219526	2.635554
H	2.930739	0.276381	2.789037
H	4.556596	0.981883	2.698991
H	3.263787	1.842039	3.515715
C	4.708602	−0.360038	0.215800
C	5.989239	0.194428	0.084022
C	4.557693	−1.728834	0.521594
C	7.125666	−0.589462	0.247794
H	6.089763	1.253550	−0.173431
C	5.716878	−2.503844	0.669840
C	6.984111	−1.945500	0.539171
H	8.113982	−0.146316	0.142398
H	5.607193	−3.561543	0.910583
H	7.865956	−2.571381	0.668779
C	3.238575	−2.407749	0.674595
C	2.939747	−3.511117	-0.136210
C	2.298809	−1.995318	1.628236
C	1.725988	−4.181942	0.000393
H	3.667743	−3.837676	-0.880454
C	1.075396	−2.656525	1.756756
H	2.533440	−1.145671	2.284884
C	0.791320	−3.753887	0.944145
H	1.509520	−5.042971	-0.632497
H	0.345300	−2.318653	2.494673
H	−0.154991	−4.284909	1.054333
N	−1.508409	2.827206	2.642394
C	−1.481245	3.721030	3.368292
C	−1.442802	4.854998	4.276541
H	−0.750434	5.662126	3.893196
H	−2.471445	5.308160	4.399462
H	1.151484	1.838957	2.005444
C	4.074960	0.064822	2.820259
H	3.699417	−0.954202	2.621232
H	5.144293	0.074017	2.564630
H	4.028636	0.191132	3.913228
C	4.691861	−0.205327	−0.214528
C	5.947463	0.410767	−0.298544
C	4.547801	−1.566929	−0.557183
C	7.061331	−0.302771	−0.728028
H	6.042761	1.471712	−0.044044
C	5.678202	−2.263647	−1.002952
C	6.920934	−1.643055	−1.086059
H	8.031608	0.186585	−0.789270
H	5.572008	−3.316563	−1.265572
H	7.786225	−2.210314	−1.426540
C	3.244586	−2.282691	−0.470483
C	2.694318	−2.884990	−1.608472
C	2.540432	−2.349763	0.738991
C	1.451979	−3.516937	−1.540215
H	3.241571	−2.843838	−2.551998
C	1.290264	−2.964551	0.805560
H	2.983809	−1.907057	1.642940
C	0.742540	−3.544599	−0.339469
H	1.031904	−3.982670	−2.432643
H	0.742663	−2.987842	1.749241
H	−0.233555	−4.028461	−0.289034
N	−1.028449	3.020086	1.602620
C	−1.842911	3.835151	1.593681
C	−2.882174	4.851353	1.572332
H	−3.436291	4.889752	2.529210
H	−2.467605	5.860921	1.396459
H	−3.623358	4.652070	0.772209

H	−1.082231	4.545048	5.302275

$TS_{III \rightarrow IV}$

E(scf) = −1612.280089910452 a.u.

ν_{min} = −687.9 cm^{-1}

C	−3.255454	−2.090986	−2.641372
C	−2.704004	−1.263672	−1.664289
C	−1.373779	−0.845015	−1.753791
C	−0.556158	−1.270394	−2.799933
C	−1.103253	−2.110175	−3.769893
C	−2.441359	−2.512577	−3.696467
H	−4.303485	−2.400242	−2.588559
H	0.481053	−0.947351	−2.859924
H	−0.486782	−2.455781	−4.602174
H	−2.850010	−3.160686	−4.466226
C	−1.022868	0.021468	−0.603396
C	−2.162738	0.177601	0.156588
C	−2.248556	0.998985	1.387761
C	−1.233560	0.909658	2.350950
C	−3.299919	1.908444	1.583810
C	−1.263924	1.713202	3.486257
H	−0.450638	0.156389	2.215198
C	−3.324274	2.726537	2.709930
H	−4.098659	1.993631	0.833031
C	−2.306440	2.626807	3.662042
H	−0.487598	1.623925	4.237511
H	−4.138914	3.433023	2.847961
H	−2.328944	3.258863	4.543798
C	−3.362332	−0.650929	−0.419420
H	−1.311648	1.260513	−0.634509
C	−3.722338	−1.673244	0.647874
C	−3.467807	−3.042107	0.458049

IV

E(scf) = −1612.337416783371 a.u.

C	−2.846808	−2.943652	−1.925378
C	−2.542736	−1.717327	−1.346352
C	−1.400848	−1.011602	−1.763366
C	−0.533424	−1.536133	−2.717854
C	−0.820490	−2.790195	−3.260648
C	−1.968525	−3.483614	−2.872537
H	−3.756561	−3.481903	−1.651329
H	0.349727	−0.978822	−3.038230
H	−0.154355	−3.223887	−4.006118
H	−2.191680	−4.451003	−3.321332
C	−1.343097	0.251931	−1.015608
C	−2.368455	0.335967	−0.128666
C	−2.568526	1.480079	0.784111
C	−1.596098	1.768448	1.751547
C	−3.694867	2.310986	0.681707
C	−1.725203	2.882970	2.578765
H	−0.754660	1.080322	1.878742
C	−3.819018	3.426681	1.504559
H	−4.466155	2.087501	-0.060278
C	−2.832340	3.718611	2.451027
H	−0.965238	3.091159	3.331153
H	−4.696648	4.066407	1.416150
H	−2.941978	4.583832	3.103698
C	−3.322482	−0.888157	−0.303585
H	−0.765662	1.146626	−1.303417
C	−3.589501	−1.585611	1.021778
C	−3.359039	−2.957080	1.200755
C	−4.126494	−0.850021	2.094245

C	−4.319903	−1.259288	1.854015	C	−3.642061	−3.574912	2.424526
C	−3.790184	−3.969024	1.456001	H	−2.956386	−3.570994	0.396708
H	−3.011001	−3.403712	−0.466046	C	−4.401522	−1.465523	3.316394
C	−4.636756	−2.184910	2.843053	H	−4.355705	0.209066	1.975558
H	−4.550323	−0.210733	2.021825	C	−4.159042	−2.832468	3.487580
C	−4.373199	−3.548565	2.651379	H	−3.461060	−4.643724	2.543372
H	−3.586560	−5.030637	1.286487	H	−4.815988	−0.879535	4.137194
H	−5.097687	−1.848548	3.774499	H	−4.379980	−3.314373	4.439660
H	−4.625909	−4.269529	3.421906	C	−4.619324	−0.427340	−0.965738
C	−4.535593	0.201070	−0.869930	C	−5.867324	−0.891032	−0.528714
C	−5.864153	−0.133933	−0.547550	C	−4.562542	0.437382	−2.073850
C	−4.293011	1.325680	−1.686109	C	−7.039888	−0.472961	−1.167809
C	−6.925308	0.663931	−0.997654	H	−5.945043	−1.587810	0.308019
H	−6.091699	−1.022679	0.045862	C	−5.734029	0.851808	−2.709185
C	−5.353071	2.111081	−2.141752	H	−3.599935	0.774893	−2.457351
H	−3.281751	1.557377	−2.006580	C	−6.978481	0.401821	−2.254501
C	−6.673884	1.784877	−1.793851	H	−8.005117	−0.839206	−0.816199
H	−7.950780	0.391982	−0.741907	H	−5.678983	1.519008	−3.568980
H	−5.160660	2.971871	−2.785336	H	−7.892778	0.724326	−2.751893
H	−7.502289	2.403047	−2.145814	Au	1.116420	0.485942	−0.222517
Au	1.074005	0.394477	−0.170502	P	3.407510	0.461131	−0.114872
P	3.367789	0.583782	0.040522	C	3.705835	1.754154	1.276471
C	3.642694	1.425310	1.748204	C	3.707763	1.149595	−1.876313
C	3.704261	1.787797	−1.410523	C	2.523554	2.097062	−2.125990
C	2.678060	2.930036	−1.241010	H	2.333306	2.834894	−1.330108
H	2.866334	3.531637	−0.331167	H	2.723402	2.718679	−3.019919
H	2.768178	3.630398	−2.084589	H	1.575980	1.587932	−2.388692
H	1.631190	2.597545	−1.241097	C	3.596482	−0.066890	−2.804193
C	3.351034	0.970062	−2.659864	H	3.609698	0.255280	−3.858918
H	3.410698	1.598613	−3.566655	H	4.442251	−0.764958	−2.707235
H	4.045022	0.137959	−2.841334	H	2.670496	−0.645744	−2.682932
H	2.325810	0.565712	−2.653723	C	5.042468	1.852636	−2.084822

C	5.112868	2.348348	−1.510498	H	5.236294	2.000274	−3.160460
H	5.224746	2.969752	−2.410467	H	5.077460	2.857517	−1.642030
H	5.393452	2.992082	−0.662875	H	5.905330	1.283022	−1.703481
H	5.888688	1.563790	−1.593485	C	4.572509	2.931534	0.845372
C	4.362737	2.768198	1.659236	H	4.182003	3.481729	−0.021239
H	3.817257	3.513892	1.063109	H	4.645610	3.671282	1.660007
H	4.482564	3.203782	2.663164	H	5.609330	2.640288	0.626070
H	5.379721	2.684918	1.248646	C	2.285837	2.229768	1.635545
C	2.203623	1.620966	2.255740	H	1.648750	1.446840	2.085190
H	1.664207	0.671154	2.436200	H	2.347998	2.998109	2.430501
H	2.225212	2.115167	3.246851	H	1.758150	2.754880	0.816366
H	1.590215	2.285159	1.633581	C	4.353474	1.048315	2.467906
C	4.417725	0.475392	2.658149	H	3.776893	0.190749	2.855389
H	3.935224	−0.511769	2.794910	H	5.369828	0.685446	2.254620
H	5.444973	0.294682	2.317571	H	4.460590	1.742757	3.316324
H	4.514070	0.903613	3.669263	C	4.479363	−0.980004	0.117613
C	4.433643	−0.875312	−0.142692	C	5.825309	−0.896840	−0.260912
C	5.774444	−0.726293	−0.520599	C	3.948757	−2.190609	0.604019
C	3.888159	−2.168513	0.007173	C	6.647788	−2.015206	−0.168616
C	6.572398	−1.843751	−0.774552	H	6.224539	0.046641	−0.648369
H	6.199542	0.277071	−0.637758	C	4.785295	−3.308451	0.673012
C	4.701332	−3.280061	−0.270746	C	6.122274	−3.221848	0.292494
C	6.028455	−3.120156	−0.658510	H	7.693037	−1.946310	−0.463199
H	7.611772	−1.710903	−1.068989	H	4.376680	−4.247771	1.044249
H	4.273310	−4.277801	−0.152504	H	6.760381	−4.101710	0.360013
H	6.637239	−3.996097	−0.857509	C	2.524237	−2.267549	1.034414
C	2.491938	−2.410603	0.480136	C	1.568926	−2.887127	0.220739
C	1.539907	−2.971952	−0.379750	C	2.118120	−1.615057	2.203843
C	2.120768	−2.070888	1.784423	C	0.215631	−2.820246	0.553158
C	0.230628	−3.171078	0.063437	H	1.884517	−3.389837	−0.694509
H	1.823761	−3.233120	−1.402629	C	0.766382	−1.550844	2.540652
C	0.815160	−2.279708	2.230544	H	2.871826	−1.129163	2.835866

H	2.873723	−1.640718	2.462774	C	−0.184867	−2.140758	1.706664
C	−0.134286	−2.825109	1.359744	H	−0.524952	−3.285397	−0.099424
H	−0.514749	−3.584727	−0.624314	H	0.453777	−1.042691	3.452975
H	0.546244	−2.029669	3.257287	H	−1.243375	−2.079347	1.972068
H	−1.158881	−2.980726	1.709583	N	−0.267824	3.409808	−0.766223
N	−1.270635	2.753603	−0.643734	C	−1.026264	4.265422	−0.628842
C	−1.313361	3.866478	-0.960265	C	−1.974283	5.355631	-0.469534
C	−1.389591	5.261718	−1.343449	H	−2.026873	5.699924	0.580714
H	−2.434917	5.634559	−1.328360	H	−1.701290	6.229199	−1.091495
H	−0.809939	5.913650	−0.658575	H	−2.997035	5.050084	−0.763242
H	−1.001796	5.431640	−2.369767				

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E(scf) = −578.566420934768 a.u.

C	−3.123165	−0.304684	0.126729
C	−1.872550	−0.476882	−0.447229
C	−1.739636	−1.126384	−1.686164
C	−2.858418	−1.614095	−2.358476
C	−4.114972	−1.445086	−1.774116
C	−4.248298	−0.797547	−0.544642
H	−3.231718	0.208382	1.085328
H	−2.756711	−2.115901	−3.321817
H	−5.002951	−1.819823	−2.284847
H	−5.237940	−0.671321	−0.104485
C	−0.321336	−1.151150	−2.044936
C	0.429932	−0.539604	−1.103408
C	1.899908	−0.426306	−1.135277
C	2.580664	0.605456	−0.472215
C	2.662032	−1.366459	−1.849851
C	3.968045	0.707537	−0.537912
H	2.015331	1.348251	0.098063
C	4.046697	−1.263112	−1.919307

H	2.158555	−2.204695	−2.333294
C	4.707677	−0.222713	−1.265118
H	4.473272	1.521763	−0.017422
H	4.616007	−2.008048	−2.476234
H	5.793925	−0.144605	−1.314144
C	−0.484474	−0.022244	0.042814
H	0.063724	−1.593019	−2.964316
C	−0.538444	1.494578	0.155468
C	−1.006940	2.097561	1.334277
C	−0.196914	2.305700	−0.937712
C	−1.103155	3.488124	1.425699
H	−1.297919	1.481202	2.185308
C	−0.294658	3.696560	−0.842535
H	0.142658	1.854279	−1.870789
C	−0.744003	4.292182	0.339534
H	−1.462739	3.945730	2.345857
H	−0.023068	4.316382	−1.695644
H	−0.818961	5.374926	0.412305
C	−0.066460	−0.706460	1.336194
C	0.904073	−0.133507	2.173201
C	−0.618100	−1.949047	1.685903
C	1.301211	−0.782110	3.344932
H	1.358496	0.822765	1.909894
C	−0.219932	−2.595412	2.859271
H	−1.359438	−2.421817	1.040467
C	0.738555	−2.013605	3.693752
H	2.054643	−0.327085	3.985531
H	−0.657367	−3.557541	3.120460
H	1.048153	−2.517563	4.606527