UNIVERSIDAD DE GUANAJUATO

CAMPUS GUANAJUATO

DIVISIÓN DE CIENCIAS NATURALES Y EXACTAS

SÍNTESIS TOTAL DE LA NINGALINA C: DESARROLLO DE LA METODOLOGÍA PARA LA OBTENCIÓN DE SU NÚCLEO NAFTALENO

TESIS

PARA OBTENER EL TITULO DE MAESTRO EN CIENCIAS QUÍMICAS

PRESENTA

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UNIVERSIDAD DE GUANAJUATO
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CERTIFICADO

Por medio de la presente hacemos constar que este trabajo de investigación titulado: ***"SÍNTESIS TOTAL DE LA NINGALINA C: DESARROLLO DE LA METODOLOGÍA PARA LA OBTENCIÓN DE SU NÚCLEO NAFTALENO"*** que presenta el Q.F.B. Luis Alberto Segura Quezada, alumno de esta Universidad, para obtener el título de Maestro en Ciencias Químicas, es una idea original y ha sido realizado bajo nuestra dirección en la División de Ciencias Naturales y Exactas de la Universidad de Guanajuato, Campus Guanajuato. La tesis cubre en su totalidad los requisitos de calidad para la obtención del título de Maestro en Ciencias Químicas bajo la normativa vigente del Posgrado en Química de la División de Ciencias Naturales y Exactas del Departamento de Química en la Universidad de Guanajuato.

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El misterio es la cosa más bonita que podemos experimentar. Es la fuente de todo arte y ciencia verdaderos.

Albert Einstein

Soy de donde haya alguien que sonría, que me de la mano, que me bese. Soy de donde son los que resisten, sobreviven, los que se quitan un pedazo de pan de la boca para dárselo al otro. De allí soy. Allí me encuentro.

Benito Taibo

Mira las estrellas y no a tus pies. Intenta entender qué es lo que ves y pregúntate qué es lo que hace que el universo exista. Ten curiosidad

Stephen Hawking

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DEDICATORIA

En la memoria de mi mami Rosy (†) y a mi tía Carmelita (†)

A mis padres: Mamá gracias por ser mi fiel compañera, mi mejor amiga y mi protectora. Papá muchas gracias por tus consejos, tu valentía y amor a la vida. Sacaron la mejor versión de mí, sin ustedes no hubiera sido posible este logro. Son el mejor regalo que la vida me pudo dar y lo que más admiro en esta vida.

Y con mucho amor y cariño para ti…

Flory

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Al momento de escribir esta tesis, los resultados presentados en este documento han derivado en las publicaciones y distinciones que se presentan a continuación:

Distinciones:

- **Premio Municipal de la Juventud 2019.**
  Categoría Ciencia y Tecnología. San Francisco del Rincón, Guanajuato, México.

- **Premio primer lugar categoría Modalidad Oral-Nivel Maestría del concurso de carteles y ponencias orales.**
  En el 6º Encuentro de Estudiantes, Octubre **2019**: Investigación e Innovación en la DCNE.

- Distinción en el número virtual de la ***ACS***: **Celebrating Chemistry in Latin America 2020** del artículo *J. Org. Chem.* **2019**, *84*, 4149-4164

Publicaciones:

- **HALÓGENOS, UNA HISTORIA PERIÓDICA**
  Jocelyne Jacqueline Olvera Montalvo, ***Alberto Segura Quezada*** y César R. Solorio Alvarado. Naturaleza y tecnología, **2019**, 6(2), 1-11.

- **Iodine(III)-Mediated, Controlled Di- or Monoiodination of Phenols**
  Yuvraj Satkar, Luisa F. Yera-Ledesma, Narendra Mali, Dipak Patil, Pedro Navarro-Santos, ***Luis A. Segura-Quezada***, Perla I. Ramírez-Morales, and César R. Solorio-Alvarado. *J. Org. Chem.* **2019**, *84*, 4149-4164. https://doi.org/10.1021/acs.joc.9b00161

- **Oxidative Halogenation of Arenes, Olefins and Alkynes Mediated by Iodine(III) Reagents**
  Luis A. Segura-Quezada, Karina R. Torres-Carbajal, Yuvraj Satkar, Kevin A. Juárez Ornelas, Narendra Mali, Dipak B. Patil, Rocío Gámez-Montaño, Juan R. Zapata-Morales, Selene Lagunas-Rivera, Rafael Ortíz-Alvarado,César R. Solorio-Alvarado. *Mini Rev. Org. Chem.,* **2021**, 18 (2), 159-172. DOI: 10.2174/1570193X17999200504095803

- **Discovery of novel fungistatic 4-aryloxyquinolines on Mucor circinelloides, biological evaluation of activity and QSAR study**
  Pradip D. Nahide, Clara Alba-Betancourt, Rubén Chávez-Rivera, Pamela Romo-Rodríguez, Manuel Solis- Hernández, ***Luis A. Segura-Quezada***, Karina R. Torres-Carbajal, Rocío Gámez-Montaño, Martha A. Deveze-Álvarez, Marco A. Ramírez-Morales, Angel J. Alonso-Castro, Juan R. Zapata-Morales, Alan J. Ruiz-Padilla, Claudia L. Mendoza-Macías, Victor Meza-Carmen, Rafael Ortíz-Alvarado, Luis Chacón-García and César R. Solorio-Alvarado. *Manuscrito enviado Archiv der Pharmazie, ~~Febrero **2021** ID ardp.202100054.~~*

ÍNDICE GENERAL

Anexos

ACRÓNIMOS Y ABRAVIATURAS

sp.	Especie	**g**	Gramo
spp.	Especies	**MeOH**	Metanol
SNC	Sistema Nervioso Central	**TLC**	Cromatografía en capa fina
D.	*Didemnum*	**AcOEt**	Acetato de Etilo
E.	*Escherichia*	**ºC**	Grado Celsius
P.	*Pseudomonas*	**equiv.**	Equivalentes
C.	*Candida*	**min**	Minutos
HIV-1	Virus de la inmunodeficiencia humana	**ml**	Mililitro
$MeNO_2$	Nitrometano	**mmol**	Milimol
$NaBH_4$	Borohidruro de Sodio	**mg**	Miligramos
$KMNO_4$	Permanganato de Potasio	**ppm**	Partes por millón
$MeSO_3H$	Ácido metanosulfónico	**Hz**	Hertz
BBr_3	Tribromuro de boro	**RMN**	Resonancia magnética nuclear
NH_4Cl	Cloruro de Amonio	**$CDCl_3$**	Cloroformo deuterado
NH_4OAc	Acetato de amonio	**^{13}C**	Carbono-13
Et_3N	Trietilamina	**^{1}H**	Hidrógeno-1
CuI	Yoduro de cobre	***J***	Constante de acoplamiento
DCM	Diclrorometano	**δ**	Desplazamiento químico
DCE	Diclroroetano	**s**	Fuerte o singulete
THF	Tetrahidrofurano	**d**	Doblete
$Pd(PPh_3)_3Cl_3$	Cloruro de bis (trifenilfosfina)paladio(II)	**m**	Multiplete
Na_2SO_4	Sulfato de Sodio	**IR**	Infrarrojo

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PROLOGO

El contenido de este trabajo plasma el desarrollo experimental hacia una nueva y novedosa ruta sintética para acceder el alcaloide Ningalina C. En el primer capitulo nos adentramos en la literatura donde encontramos una basta biblioteca de alcaloides de interés sintético dada la actividad biológica que se ha encontrado de estos en diferentes organismos vivos. Por ello la importancia en la síntesis orgánica de proponer rutas novedosas y eficientes para acceder a ellas. La síntesis total revolucionó la perspectiva para obtener compuestos presentes en la naturaleza, en nosotros recae la responsabilidad de utilizar esta estrategia y explotar todas las herramientas sintéticas para así obtener compuestos de interés con rutas atractivas dada su economía atómica y sencillez.

En el capitulo dos nos adentramos a la síntesis de ningalinas, donde damos un vistazo a las síntesis descritas en orden cronológico y destacando la actividad biológica de estas.

El capitulo tres presenta los resultados iniciales obtenidos de nuestra síntesis propuesta para acceder al núcleo de naftaleno de la Ningalina C.
Por ultimo los anexos que incluyen la copia de los espectros de ^{1}H y ^{13}C de RMN del capítulo IV así como aquellos artículos tanto de divulgación como indexados en el JCR y las constancias de las distinciones obtenidas hasta el día de hoy.

- **Capitulo I.** Aquí se plasma con detalle la procedencia taxonómica del tunicado del genero *Didemnum sp.* así como aquellos metabolitos secundarios que han sido sintetizados de este invertebrado marino, también se resalta la relevancia de su actividad biológica activa.

- **Capitulo II.** Abordamos las síntesis descritas para Ningalina C mediante una reseña bibliográfica, así como la procedencia de estos metabolitos secundarios. En orden cronológico se abordan las síntesis descritas, así como el investigador que las describió. Cabe resaltar que pese a su importancia aún no se describe sintéticamente toda la familia de ningalinas.

- **Capitulo III.** En nuestra ruta sintética se prevé obtener una biblioteca importante de derivados de Ningalina C mediante la fabricación de una plataforma en común vía síntesis total. Es aquí donde describimos nuestra estrategia retrosintética que será el parteaguas para nuestra propuesta.

- **Capitulo IV.** En este capitulo describimos todo lo que hemos implementado para acceder a la plataforma molecular en común, con principal énfasis en la obtención del naftaleno.

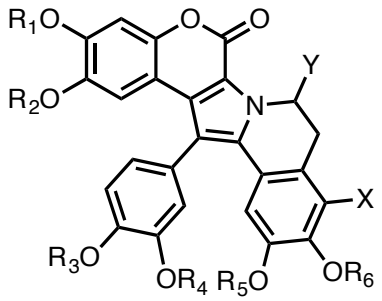
- **Anexo A.** Este capitulo contiene la información espectroscópica con la que se ha elucidado todo aquel producto de nuestra síntesis.

- **Anexo B.** Aquí encontraremos aquellos documentos que soportan el trabajo realizado durante mi paso en la maestría donde resalta el primer autor en la revisión de hipervalentes de yodo(III) y el premio municipal de la juventud 2019.

RESUMEN GENERAL

Capítulo I

En esta capitulo nos adentraremos al mundo de *Didemnum sp.* destacando sus bondades químicas ya que los metabolitos secundarios que han sido aislados de este invertebrado marino, han sido fuente de inspiración para realizar ensayos *in vitro* esto con base a la estructura y propiedades químicas que poseen. Resultado de ello se ha encontrado que algunos metabolitos secundario poseen actividad biológica antitumoral/anticancerígena, antimicrobiana, antiviral, antifúngica, antidiabética, antimalárica y efecto en el SNC. Con lo anterior se sustenta la importancia de ahondar en la síntesis de estos productos naturales, por ello daremos un viaje en el tiempo destacando las síntesis que han sido descritas. Esta revisión comienza con la primer síntesis descrita en 1993 hasta la más reciente en 2021. Ejemplo de ellos son las Lamerianas los cuales son metabolitos secundarios con actividad biológica activa (Figura R-1).



	R_1	R_2	R_3	R_4	R_5	R_6	X	Y
Lamelarina A1	H	Me	H	H	Me	Me	OMe	OH
Lamelarina φ	Ac	Me	Ac	Me	Ac	Me	OMe	H
Lamelarina I	H	Me	Me	Me	Me	Me	OMe	OH

Figura R-1. Análogos de Lameriana *Didemnum* sp. con actividad biológica.

Capítulo II

Las familia de ningalinas son metabolitos secundarios aislados de la ascidia de genero *Didemnum* sp. en el arrecife de Ningaloo al noroeste de Australia. Hasta el día de hoy se han aislado las Ningalinas A-G y se han sintetizado todas a, excepción de las E y F. Este capítulo es el encargado de mostrar el panorama de la importancia de esta familia de metabolitos secundarios, así como las síntesis que han sido descritas y los ensayos de actividad biológica que han realizado en ellos. Existen grupos de investigación que han explotado un sinfín de herramientas sintéticas para obtener estos metabolitos y con ello resaltar la importancia biológica de ellos como en el caso de la Ningalina C, la cual presenta actividad biológica y ah sido objeto de estudio para investigar las causantes de esta actividad (Figura R-2). En nuestro grupo de investigación hasta el día de hoy se ha logrado la síntesis formal de la Ningalina C.

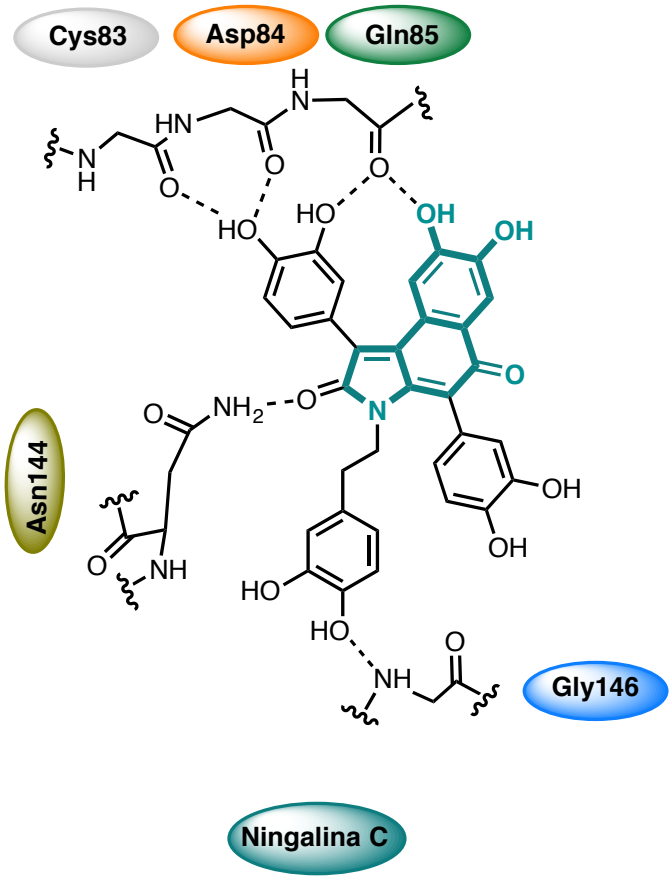


Figura R-2. Docking de Ningalina C con la quinasa $CDK5^{D144N}/p^{25}$.

Capítulo III

Como en toda síntesis total, un paso determinante es la elaboración de una retrosíntesis que sirva como herramienta para escoger herramientas sintéticas que ayuden a la obtención de los metabolitos secundarios de interés. Por ello dedicamos este capítulo que contiene nuestra propuesta de retrosintética donde empleamos reacciones de alto interés sintético y que son fácilmente reproducibles. Lo que nos garantiza obtener la síntesis total de la Ningalina C y con ello la plataforma molecular en común (Figura R-3) que nos permitirá obtener análogos de Ningalina C.

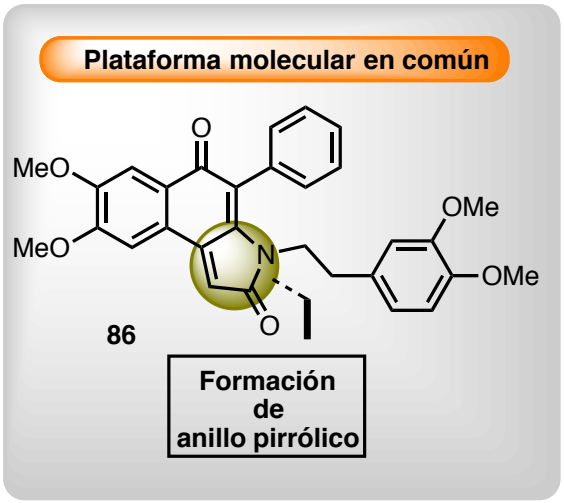
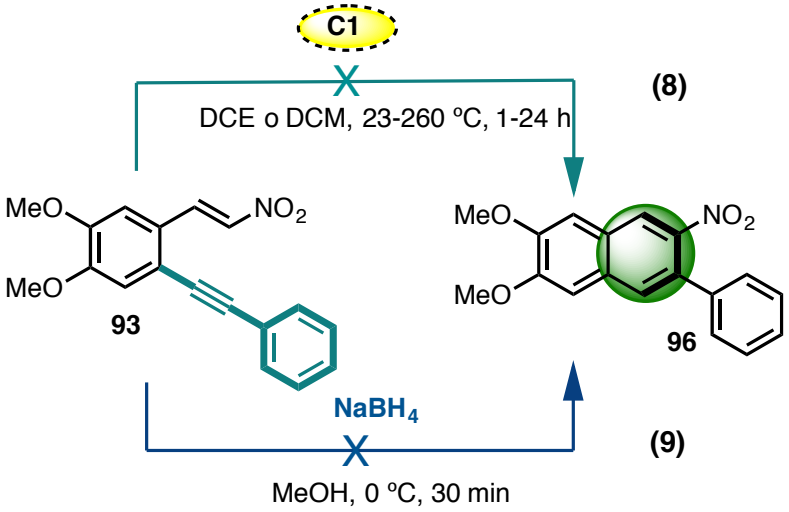


Figura R-3. Plataforma molecular en común.

Capítulo IV

Hasta el momento hemos logrado obtener avances importantes los cuales nos han servido para tener una visión de los alcances de nuestra propuesta sintética. Hemos logrado tener una síntesis divergente por lo que podemos analizar todas las posibles vías para la obtención de la Ningalina C. Las reacciones que se han empleado han mostrado buenos rendimientos y se han podido obtener buenos resultados pese al poco tiempo dedicado a la experimentación de este proyecto. Cabe resaltar que se han intentado novedosas rutas como la cicloisomerización con catalizadores de oro(I), pese a ello no se logro con éxito la obtención del naftaleno **96** (Ec. 8). Al igual que metodologías de reducción con las que se promueve la formación de un carbanión que podría realizar un ataque nucleofílico al alquino y con ello obtener el naftaleno **96** (Ec. 9). Aún falta un camino por recorrer y con ello obtener

la síntesis de la Ningalina C, por ahora se presentan los resultados obtenidos hasta el momento.



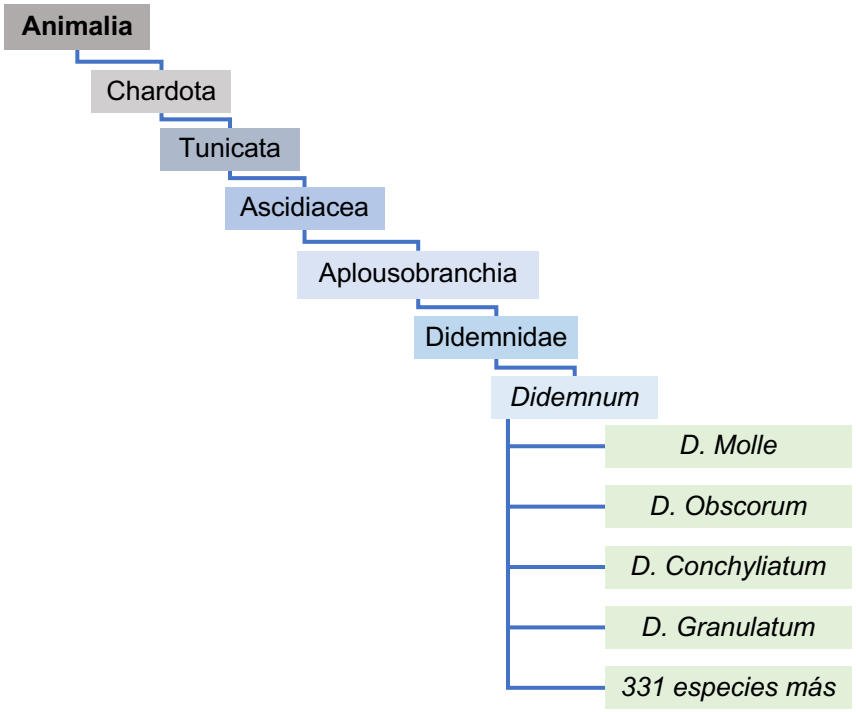
Capítulo I

Síntesis de alcaloides marinos provenientes de organismos del género *Didemnum* spp.

1.1 *Didemnum spp.* el tunicado marino fuente de inspiración para la síntesis de productos naturales

1.1.1 Taxonomía de *Didemnum spp.*

Diferentes especies marinas nos proveen un gran número de moléculas que resultan atractivas dada su actividad biológica, por ello es de gran importancia su aislamiento, caracterización y síntesis. Tal es el caso del invertebrado marino del género *Didemnum spp.* dicho taxón fue nombrado y descrito en 1816 por el francés Julio-César Savigny.[1] (Esquema 1).



Esquema 1. Clasificación taxonómica de *Didemnum spp*.

Al mes de marzo del 2021, *Didemnum spp.* (Figura 1) cuenta con 335 especies descritas en la *Worl Registred of Marine Species*[2] y a diciembre del 2019 se han reportado al menos 212 metabolitos secundarios (en su mayoría alcaloides) provenientes de 69 especies de *Didemnum* spp.[3] *Didemnum spp.* se ha encontrado en un número importante de costas alrededor del mundo, al grado que se ha

[1] Savigny, J. C. Memoires sur les animaux sans vertebres. *Paris*. **1816**, *2*, 1-239

[2] Shenkar, N .; Gittenberger, A .; Lambert, G .; Rius, M .; Moreira da Rocha, R .; Swalla, BJ; Turon, X. Base de datos mundial de ascidiacea. Didemnum Savigny, 1816. **2021** Consultado a través de: *World Register of Marine Species* en: http://www.marinespecies.org/aphia.php?p=taxdetails&id=103456 el **2021-03-31**

[3] Youssef, D. T. A. Almagthali, H. Shaala, L. A. Schmidt, E. W. Secondary Metabolites of the Genus Didemnum: A Comprehensive Review of Chemical Diversity and Pharmacological Properties. *Mar. Drugs* **2020**, *18*, 307 https://doi.org/10.3390/md18060307.

catalogado como una especie invasora.[4] Debido al gran tránsito de embarcaciones, estas ascidias pueden ser transportadas y diseminadas en los cascos de dichas embarcaciones y ser un vector importante para su distribución en el hábitat. En nuestro país se tiene registro de *Didemnum* sp. en la costa de Baja California desde 1975[5] por Lewin y en 2008[6] por Rodríguez y colaboradores.

Figura 1. Ilustración del tunicado *Didemnum* sp. ejemplificado con *Didemnum molle*.[7]

1.1.2 Aislamiento e importancia de metabolitos secundarios de *Didemnum spp.*

Con el descubrimiento de nuevas especies de *Didemnum sp.* surgió el interés por caracterizar los componentes que los constituyen. En 1981 Ireland[8] aísla y caracteriza por primera vez el metabolito 1,3-difenetilurea **1** proveniente del invertebrado *Didemnum molle* (Figura 1). Con el paso del tiempo se observó que estos metabolitos poseen centros miméticos con centros farmacóforos que se encuentran descritos en la literatura, por ello la importancia de investigar su actividad biológica. En los metabolitos de *Didemnum sp.* se ha detectado actividad antitumoral/anticancerígena **(2-6)**, antimicrobiana **(7-9)**, antiviral **(10)**, antifúngica **(11)**, antidiabética **(1)**, contra efectos neurodegenerativos en el SNC **(44)** y antimalárica **(12)** (Tabla 1 y Esquema 2). En la siguiente tabla se describen los metabolitos más representativos de cada tipo de actividad, la mayoría de ellos son potenciales drogas activas en comparación con las drogas que se encuentran actualmente aprobadas por la Administración de Medicamentos y Alimentos (FDA, por sus siglas en inglés).

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[4] Herborg, L.-M. O'Hara, P. Therriault, T. W. Forecasting the Potential Distribution of the Invasive Tunicate *Didemnum* Vexillum. *J. Appl. Ecol.* **2009**, *46*, 64–72. https://doi.org/10.1111/j.1365-2664.2008.01568.x.

[5] Lewin, R. A. Prochlorophyta as a proposed new division of algae. *Nature* **1975**, *261*, 697–698. https://doi.org/10.1038/261697b0

[6] Rodriguez, L. F.; Ibarra-Obando, S. E. Cover and Colonization of Commercial Oyster (Crassostrea Gigas) Shells by Fouling Organisms in San Quintin Bay, Mexico. *J. Shellfish Res.* **2008**, 27, 337–343. https://doi.org/10.2983/0730-8000(2008)27[337:cacoco]2.0.co;2.

[7] Naturalista, CONABIO https://colombia.inaturalist.org/photos/188188. Descarga 03 de abril de 2021, Observación de Jan (Arny) Messersmith en Papúa Nueva Guinea.

[8] Ireland, C. M. Durso, A. R. Scheuer, P. J. N,N' Diphenethylurea, A Metabolite From the Marine Ascidian Didemnum Ternatanum. *J. Nat. Prod.* **1981**, *44*, 360–361. https://doi.org/10.1021/np50015a022.

Tabla 1. Metabolitos secundarios obtenidos de *Didemnum* spp. con actividad biológica descrita en la literatura.

Actividad Biológica	Metabolitos Secundario	Actividad	Especie
Antitumoral/ Anticancerígena	**2** Lamelarina A1[9]	Cáncer de Colon	*D. obscurum*
	3 Lamelarina φ[10]		
	4 Lamelarina I[11]	Línea célular A549	*Didemnum sp.*
	5 Mollamida C[12]	Cáncer Pulmón	*D. molle*
	6 Fascaplysin[1314]		*Didemnum sp.*
Antimicrobiana	**7** Didemnaketal F[15]	*E. Coli*	*Didemnum sp.*
	Rodriguesines A **8** y B **9***mezcla[16]	*P. aeruginosa* P1	*Didemnum sp*
Antiviral	**10** Didemniserinolípido A[17]	HIV-1	*D. guttatum*
Antifúngica	**11** (*R*)-(*E*)-1-Aminotridec-5-en-2-ol[18]	*C. albicans*	*Didemnum sp.*
Antidiabética	**1** 1,3-difenetilurea[19]	Células 3T3-L1	*D. molle*
Efecto en el *SNC*	**44** Ningalina G [20]	Inhibidor de quinasas	*Didemnum sp.*
Antimaláricos	**12** Lepadina F [21]	*P. falciparum* clon K1	*Didemnum sp.*

[9] Plisson, F. Huang, X. Zhang, H. Khalil, Z. Capon, R. J. Lamellarins as Inhibitors of P-Glycoprotein-Mediated Multidrug Resistance in a Human Colon Cancer Cell Line. *Chem. Asian J.* **2012**, *7*, 1616–1623. https://doi.org/10.1002/asia.201101049.

[10] Malla Reddy, S. Srinivasulu, M. Satyanarayana, N. Kondapi, A. K. Venkateswarlu, Y. New Potent Cytotoxic Lamellarin Alkaloids from Indian Ascidian Didemnum Obscurum. *Tetrahedron.* **2005**, *61*, 9242–9247. https://doi.org/10.1016/j.tet.2005.07.067.

[11] Carroll, A. Bowden, B. Coll, J. Studies of Australian Ascidians. I. Six New Lamellarin-Class Alkaloids From a Colonial Ascidian, Didemnum Sp. *Aust. J. Chem.* **1993**, *46*, 489. https://doi.org/10.1071/ch9930489.

[12] Donia, M. S. Wang, B. Dunbar, D. C. Desai, P. V. Patny, A. Avery, M. Hamann, M. T. Mollamides B and C, Cyclic Hexapeptides from the Indonesian TunicateDidemnum Molle. *J. Nat. Prod.* **2008**, *71*, 941–945. https://doi.org/10.1021/np700718p.

[13] Rath, B. Hochmair, M. Plangger, A. Hamilton, G. Anticancer Activity of Fascaplysin against Lung Cancer Cell and Small Cell Lung Cancer Circulating Tumor Cell Lines. *Marine Drugs*. **2018**, *16*, 383. https://doi.org/10.3390/md16100383.

[14] Segraves, N. L. Lopez, S. Johnson, T. A. Said, S. A. Fu, X. Schmitz, F. J. Pietraszkiewicz, H. Valeriote, F. A. Crews, P. Structures and Cytotoxicities of Fascaplysin and Related Alkaloids from Two Marine Phyla—*Fascaplysinopsis* Sponges and *Didemnum Tunicates*. *Tetrahedron Lett.* **2003**, *44*, 3471–3475. https://doi.org/10.1016/s0040-4039(03)00671-3. f

[15] Shaala, L. Youssef, D. Ibrahim, S. Mohamed, G. Badr, J. Risinger, A. Mooberry, S. Didemnaketals F and G, New Bioactive Spiroketals from a Red Sea Ascidian Didemnum Species. *Marine Drugs*. **2014**, *12*, 5021–5034. https://doi.org/10.3390/md12095021.

[16] Kossuga, M. H. Lira, S. P. McHugh, S. Torres, Y. R. Lima, B. A. Gonçalves, R. Veloso, K. Ferreira, A. G. Rocha, R. M.; Berlinck, R. G. S. Antibacterial Modified Diketopiperazines from Two Ascidians of the Genus Didemnum. *J. Braz. Chem. Soc. 2009*, *20*, 704–711. https://doi.org/10.1590/s0103-50532009000400014.

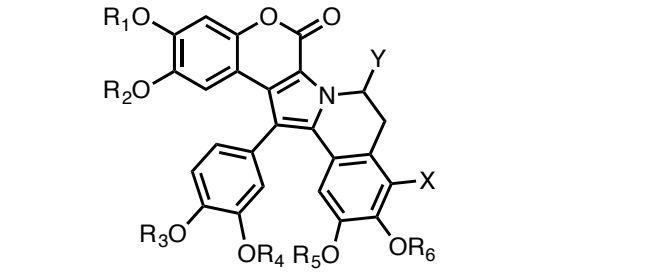
[17] Mitchell, S. S. Rhodes, D. Bushman, F. D. Faulkner, D. J. Cyclodidemniserinol Trisulfate, a Sulfated Serinolipid from the Palauan AscidianDidemnumguttatumThat Inhibits HIV-1 Integrase. *Org. Lett.* **2000**, *2*, 1605–1607. https://doi.org/10.1021/ol005866o.

[18] Searle, P. A. Molinski, T. F. Structure and Absolute Configuration of (*R*)-(*E*)-1-Aminotridec-5-En-2-Ol, an Antifungal Amino Alcohol from the Ascidian Didemnum Sp. *J. Org. Chem*. **1993**, *58*, 7578–7580. https://doi.org/10.1021/jo00078a045.

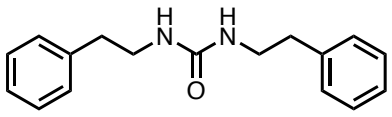
[19] Choi, S.-S. Cha, B.-Y. Kagami, I. Lee, Y.-S. Sasaki, H. Suenaga, K. Teruya, T. Yonezawa, T. Nagai, K. Woo, J.-T. N,N′-Diphenethylurea Isolated from Okinawan Ascidian Didemnum Molle Enhances Adipocyte Differentiation in 3T3-L1 Cells. *J. Antibiot.* **2011**, *64*, 277–280. https://doi.org/10.1038/ja.2010.168.

[20] Plisson, F. Conte, M. Khalil, Z. Huang, X.-C. Piggott, A. M. Capon, R. J. Kinase Inhibitor Scaffolds against Neurodegenerative Diseases from a Southern Australian Ascidian,Didemnumsp. *Chem. Med. Chem.* **2012**, *7*, 983–990. https://doi.org/10.1002/cmdc.201200169.

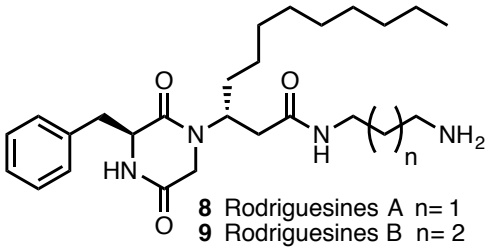
[21] Wright, A. D. Goclik, E. König, G. M. Kaminsky, R. Lepadins D−F: Antiplasmodial and Antitrypanosomal Decahydroquinoline Derivatives from the Tropical Marine TunicateDidemnumsp. *J. Med. Chem.* **2002**, *45*, 3067–3072. https://doi.org/10.1021/jm0110892.



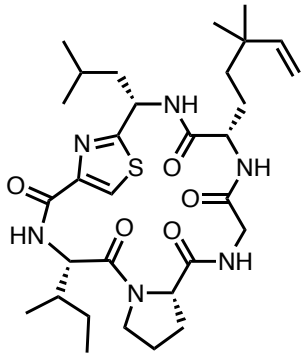
		R_1	R_2	R_3	R_4	R_5	R_6	X	Y
2	Lamelarina A1	- H	- Me	-H	-H	-Me	-Me	-OMe	-OH
3	Lamelarina φ	-Ac	- Me	-Ac	-Me	-Ac	-Me	-OMe	-H
4	Lamelarina I	-H	- Me	-Me	-Me	-Me	-Me	-OMe	-OH



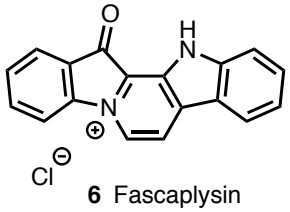
1 1,3-difenetilurea



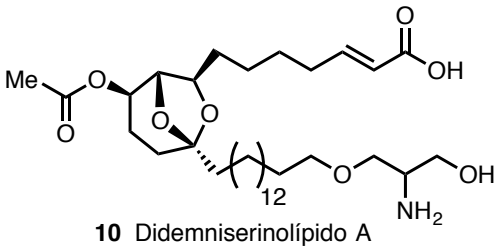
8 Rodriguesines A n= 1
9 Rodriguesines B n= 2



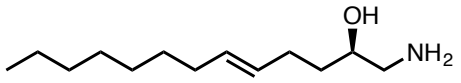
5 Mollamida C



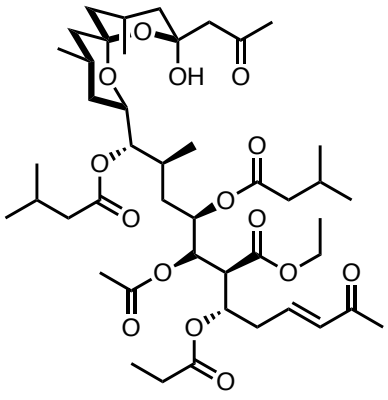
6 Fascaplysin



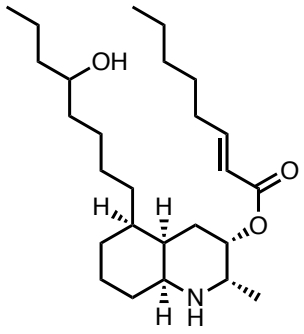
10 Didemniserinolípido A



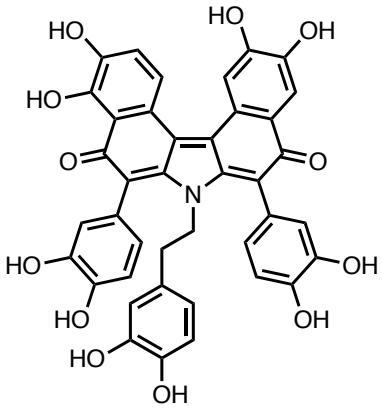
11 (*R*)-(*E*)-1-Aminotridec-5-en-2-ol



7 Didemnaketal F



12 Lepadina F



44 Ningalina G

Esquema 2. Metabolitos secundarios con actividad biológica proveniente de *Didemnum* sp.

1.1.3 Síntesis de metabolitos secundarios de *Didemnum spp.*

Está clara la importancia de los metabolitos secundarios aislados de *Didemnum spp.* por ello se dedica esta sección donde se describirán aquellos que se han sintetizado hasta el día de hoy así como la estructura del metabolito secundario obtenido. En orden cronológico (Tabla 2):

Pattenden[22] en 1993 desarrolla la primera síntesis total de un metabolito secundario aislado de *Didemnum sp.* en su trabajo describe la síntesis total de la Ciclodidemnamida **13**, el cual es un metabolito secundario asilado de *D. molle*.

Cinco años más adelante en 1998, se describen las siguientes síntesis:
Andersen[23] describe la síntesis total de la Granulatimida **14** y la Isogranulatimida **15**, metabolitos secundarios aislados de *D. granulatum* la cual fue colectada de la costa de Brasil. Cava[24] describe la síntesis total de Didemnimida A **16** y B **17**, metabolitos aislados de *D. conchyliatum.* Pattenden[25] de nuevo realiza la síntesis total de la Ciclodidemnamida, ahora con otro enfoque sintético donde obtiene mejores rendimientos.

Para 1999 Davidson[26] describe la síntesis total de la familia de Didemnolinas A **18**, B **19**, C **20** y D **21**, partiendo del imidazol logran obtener una plataforma molecular en común la cual le permitió sintetizar los cuatro metabolitos secundarios obtenidos de *Didemnum sp.* En el 2000 Pattenden[27] logra la síntesis total de Ciclodidemnamida **13**, esta vez logrando asignar la configuración del ciclopéptido de Ciclodidemnamida.

En el 2001 se describieron dos síntesis totales, la primera por Tu[28] donde logra obtener Espirocetal A **22** y B **23**, las cuales se aislaron de *Didemnum sp.*

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[22] Boden, C. D. J. Norley, M. C. Pattenden, G. Total Synthesis of the Thiazoline-Based Cyclopeptide Cyclodidemnamide. *Tetrahedron Lett.* **1996**, *37*, 9111–9114. https://doi.org/10.1016/s0040-4039(96)02099-0.

[23] Berlinck, R. G. S. Britton, R. Piers, E. Lim, L. Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. Granulatimide and Isogranulatimide, Aromatic Alkaloids with G2 Checkpoint Inhibition Activity Isolated from the Brazilian Ascidian *Didemnum granulatum*: Structure Elucidation and Synthesis. *J. Org. Chem.* **1998**, *63*, 9850–9856. https://doi.org/10.1021/jo981607p.

[24] Hughes, T. V. Cava, M. P. Total Synthesis of Didemnimide A and B. *Tetrahedron Lett.* **1998**, *39*, 9629–9630. https://doi.org/10.1016/s0040-4039(98)02211-4.

[25] Norley, M. C. Pattenden, G. Total Synthesis and Revision of Stereochemistry of Cyclodidemnamide, a Novel Cyclopeptide from the Marine Ascidian *Didemnum Molle*. *Tetrahedron Lett.* **1998**, *39*, 3087–3090. https://doi.org/10.1016/s0040-4039(98)00365-7.

[26] Schumacher, R. W. Davidson, B. S. Synthesis of Didemnolines A-D, N9-Substituted β-Carboline Alkaloids from the Marine Ascidian *Didemnum Sp. Tetrahedron*. **1999**, *55*, 935–942. https://doi.org/10.1016/s0040-4020(98)01100-4.

[27] Boden, C. D. J. Norley, M. Pattenden, G. Total Synthesis and Assignment of Configuration of the Thiazoline-Based Cyclopeptide Cyclodidemnamide Isolated from the Sea Squirt *Didemnum Molle. J. Chem. Soc., Perkin Trans.* **2000**, *1*, 883–888. https://doi.org/10.1039/a909363j.

[28] Jia, Y. X. Wu, B. Li, X.; Ren, S. K. Tu, Y. Q. Chan, A. S. C. Kitching, W. Synthetic Studies of the HIV-1 Protease Inhibitive Didemnaketals: Stereocontrolled Synthetic Approach to the Key Mother Spiroketals. *Org. Lett*. **2001**, *3*, 847–849. https://doi.org/10.1021/ol007016e.

La segunda por Muñoz[29] donde describe la síntesis total de Minalemina A **24** y B **25**, que fueron aisladas de *D. rodriguesi*.

Un año después en el 2002 Ley[30] describe la síntesis total y configuración absoluta de (+)-Didemniserinolípido B **26**, esto gracias a la implementación de un método asistido por microondas.

Kelly[31] en 2005 describe la síntesis total de las Dimnolamida A **27** y B **28** las cuales las obtiene a partir de la resina de Wang, estos metabolitos secundarios son aislados de *D. molle*. Dubovitskii[32] en el 2007 describe la síntesis total de 3-bromofascaplysin **29**, 10-bromofascaplysin **30** y 3,10-bromofascaplysin **31**. Estos obtenidos a partir de una plataforma molecular en común, estos metabolitos secundarios fueron aislados de *Didemnum sp.* En 2008 Hsung[33] en una síntesis total de 19 pasos para obtener la (+)-Lepadina F **32**, un metabolito secundario aislado de D*idemnum sp.*

En 2011 Pingaew[34] describe la síntesis total de análogos de bengacarbolina 2,2'-bis-indolilmetanos **33**, dichos metabolitos resultaron tener actividad biológica frente a líneas celulares de cáncer de higado HepG2.

En 2013 Amat[35] describe la síntesis total estereoselectiva de las (-)-Lepadina A **34**, C **35**, el paso clave de esta síntesis es ciclocondensación estereoselectiva que lo llevó a la obtención de una plataforma molecular en común donde obtuvo estos metabolitos secundarios.

Sasaki[36] en 2014 describe la síntesis total y revisión de la estructura de Didemnaketal B **36**. Sasaki postula la configuración absoluta de este metabolito secundario, la cual fue erróneamente asignada.

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[29] Expósito, A. Fernández-Suárez, M. Iglesias, T. Muñoz, L. Riguera, R. Total Synthesis and Absolute Configuration of Minalemine A, a Guanidine Peptide from the Marine Tunicate *Didemnum Rodriguesi*. *J. Org. Chem.* **2001**, *66*, 4206–4213. https://doi.org/10.1021/jo010076t.

[30] Kiyota, H. Dixon, D. J. Luscombe, C. K. Hettstedt, S. Ley, S. V. Synthesis, Structure Revision, and Absolute Configuration of (+)-Didemniserinolipid B, a Serinol Marine Natural Product from a Tunicate *Didemnum sp*. *Org. Lett.* **2002**, *4*, 3223–3226. https://doi.org/10.1021/ol026421y.

[31] You, S.-L. Kelly, J. W. Total Synthesis of Didmolamides A and B. *Tetrahedron Lett.* **2005**, *46*, 2567–2570. https://doi.org/10.1016/j.tetlet.2005.02.097.

[32] Zhidkov, M. E. Baranova, O. V. Balaneva, N. N. Fedorov, S. N. Radchenko, O. S. Dubovitskii, S. V. The First Syntheses of 3-Bromofascaplysin, 10-Bromofascaplysin and 3,10-Dibromofascaplysin—Marine Alkaloids from *Fascaplysinopsis Reticulata* and *Didemnum Sp.* by Application of a Simple and Effective Approach to the Pyrido[1,2-a:3,4-*b*']Diindole System. *Tetrahedron Lett*. **2007**, *48*, 7998–8000. https://doi.org/10.1016/j.tetlet.2007.09.057.

[33] Li, G. Hsung, R. P. Slafer, B. W. Sagamanova, I. K. Total Synthesis of (+)-Lepadin F. *Org. Lett.* **2008**, *10*, 4991–4994. https://doi.org/10.1021/ol802068q.

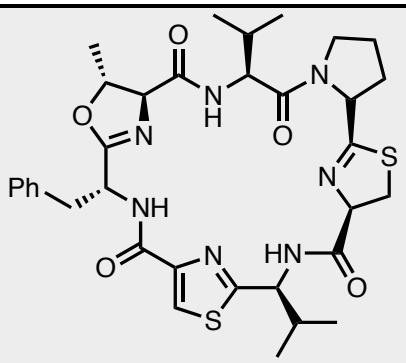
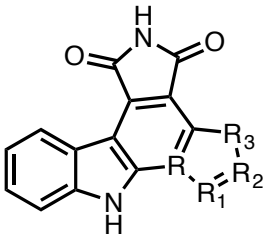
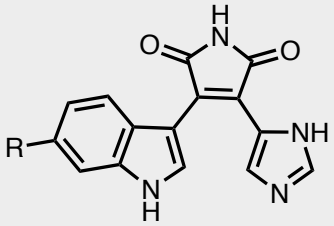
[34] Pingaew, R. Prachayasittikul, S. Ruchirawat, S. Prachayasittikul, V. Synthesis and Cytotoxicity of Novel 2,2′-Bis- and 2,2′,2″-Tris-Indolylmethanes-Based Bengacarboline Analogs. *Arch. Pharm. Res.* **2012**, *35*, 949–954. https://doi.org/10.1007/s12272-012-0601-1.

[35] Amat, M. Pinto, A. Griera, R. Bosch, J. Stereoselective Synthesis of (−)-Lepadins A–C. *Chem. Commun.* **2013**, *49*, 11032. https://doi.org/10.1039/c3cc46801a.

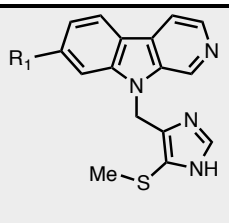
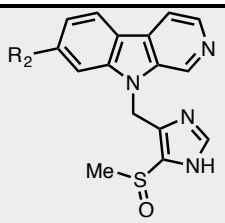
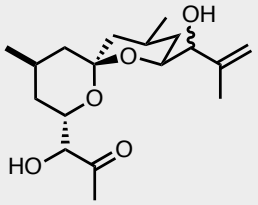
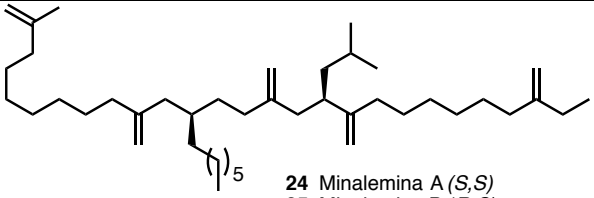
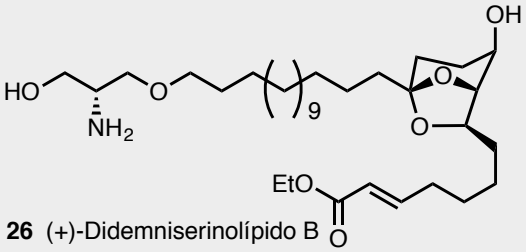
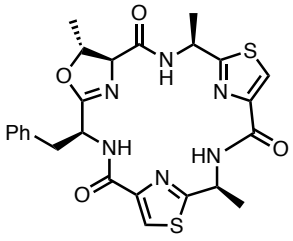
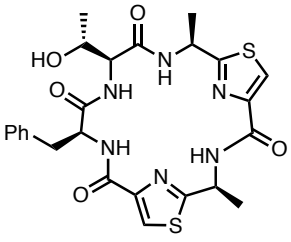
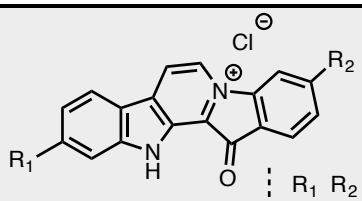
[36] Fuwa, H. Muto, T. Sekine, K. Sasaki, M. Total Synthesis and Structure Revision of Didemnaketal B. *Chem. Eur. J.* **2014**, *20*, 1848–1860. https://doi.org/10.1002/chem.201303713.

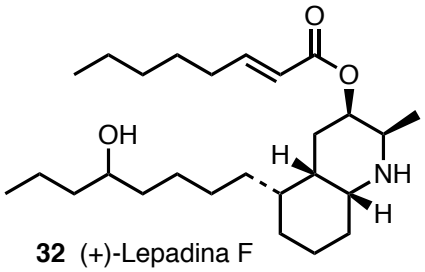
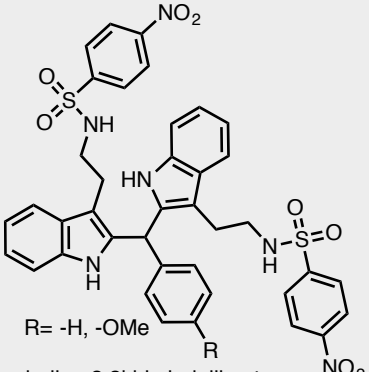
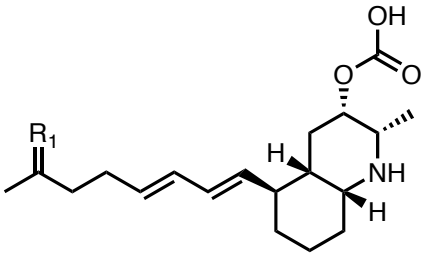
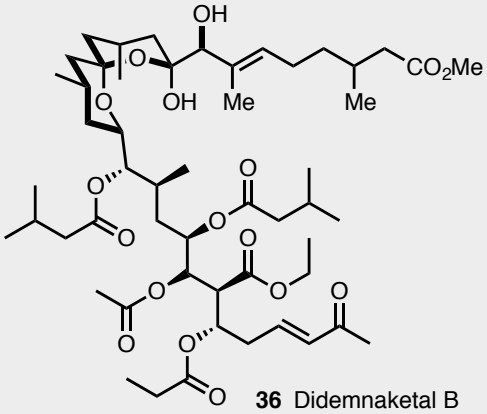
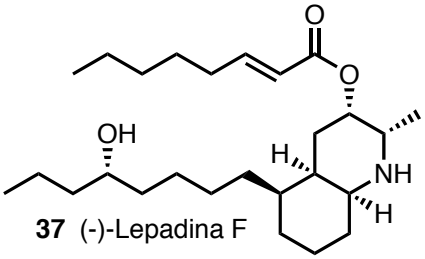
Por último, este año Chen[37] describe la síntesis total de la (-)-Lepadina F **37**, el paso clave de esta síntesis es la reacción estereoselectiva de Diels-Alder. Este metabolito secundario fue aislado de *Didemnum sp.*

Tabla 2. Síntesis descritas de metabolitos secundarios de *Didemnum spp*.

Año	Investigador	Compuesto	Especie
1993	Pattenden	 **13** Cicloodidemnamida	*D. molle*
1998	Andersen	 R R_1 R_2 R_3 **14** Granulatimida -C -N -C -NH **15** Isogranulatimida -N -C -N -C	*D. granulatum*
1998	Cava	 **16** Didemnimida A R= -H **17** Didemnimida B R= -Br	*D. conchyliatum*
	Pattenden	**13** Cicloodidemnamida	*D. molle*

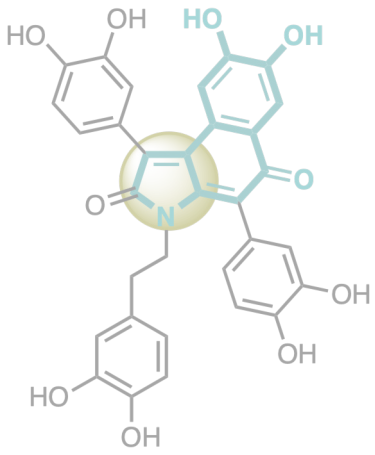
[37] Gu, H. Hu, Y. Jia, Y. Zhou, Q. Luo, G. Chen, X. Total Synthesis of (−)-Lepadin F Based on a Stereoselective Diels–Alder Reaction Controlled by a Ketolactone-type Dienophile. *Chem. Eur. J.* 2021, 27 (12), 4141–4149. https://doi.org/10.1002/chem.202004778.

1999	Davidson	  **18** Didemnolinas A R_1= -Br **20** Didemnolinas C R_2= -Br **19** Didemnolinas B R_1= -H **21** Didemnolinas D R_2= -H	*Didemnum sp.*
2000	Pattenden	**13** Cicloodidemnamida	*D. molle*
2001	Tu	 **22** Espirocetal A α-OH **23** Espirocetal B β-OH	*Didemnum sp.*
	Muñoz	 **24** Minalemina A *(S,S)* **25** Minalemina B (*R,S)*	*D. rodriguesi*
2002	Ley	 **26** (+)-Didemniserinolípido B	*Didemnum sp.*
2005	Kelly	 **27** Didmolamida A  **28** Didmolamida B	*D. molle*
2007	Dubovitskii		*Didemnum sp.*

2008	Hsung	 **32** (+)-Lepadina F	*Didemnum sp.*
2011	Pingaew	 R= -H, -OMe **33** bengacarbolina 2,2'-bis-indolilmetanos	*Didemnum sp.*
2013	Amat	 **34** (-)-Lepadina A R_1= $-H_2$ **35** (-)-Lepadina C R_1= -O	*Didemnum sp.*
2014	Sasaki	 **36** Didemnaketal B	*Didemnum sp.*
2021	Chen	 **37** (-)-Lepadina F	*Didemnum sp.*

Capítulo II

Síntesis total descritas para la familia de Ningalinas



2.1 Historia de la familia de ningalinas

2.1.1 Aislamiento de Ningalinas y síntesis descritas

Los metabolitos secundarios extraídos de *Didemnum* spp. resultan moléculas muy atractivas por su complejidad estructural y con ello su actividad biológica. Por ello al descubrir una nueva especie de este invertebrado se volvió de suma importancia describir los metabolitos que lo constituyen. En 1997 Fenical[38] aísla y describe por primera vez una nueva familia de metabolitos: Las Ningalinas. Fenical describe las ningalinas A **38**, B **39**, C **40** y D **41**. Posteriormente en 2012 Capon[39] describe las ningalinas E **43**, F **44** y G **45**. Estos metabolitos contienen en su estructura base un anillo pirrólico que a su vez forma dos núcleos moleculares base: el 2,3-dihidro-5*H*-benzo[*e*]indol-5-ona **46** y 1-aril-cromeno[3,4-*b*]pirrol-4(3*H*)-ona **47** (Esquema 3). Esta descrito en la literatura que estos núcleos moleculares base son los responsables de la actividad biológica de las ningalinas. Está familia de ningalinas A-G fue aislada y caracterizada de la especie *Didemnum* sp. la cual fue encontrabá en el arrecife de Ningaloo al noroeste de Australia. Dicho arrecife por su gran diversidad de flora y fauna en 2011 fue nombrado por la UNESCO Patrimonio de la Humanidad en 2011[40] (Figura 2).

Figura 2. Ubicación del arrecife de Ningaloo, Patrimonio de la Humanidad desde 2011.

La importancia de esta nueva familia de ningalinas va de la mano con su actividad biológica, así algunos de estos metabolitos secundarios han mostrado ser potenciales agentes que revierten la resistencia a múltiples fármacos (MDR por sus siglas en ingles),[41] así como anti-HIV-1 IIIB,[42] también se han descrito propiedades inhibidoras de quinasas en enfermedades neurodegenerativas.[40]

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[38] Kang, H. Fenical, W. Ningalins A−D: Novel Aromatic Alkaloids from a Western Australian Ascidian of the Genus *Didemnum*. *J. Org. Chem.* **1997**, *62*, 3254–3262 https://doi.org/10.1021/jo962132+

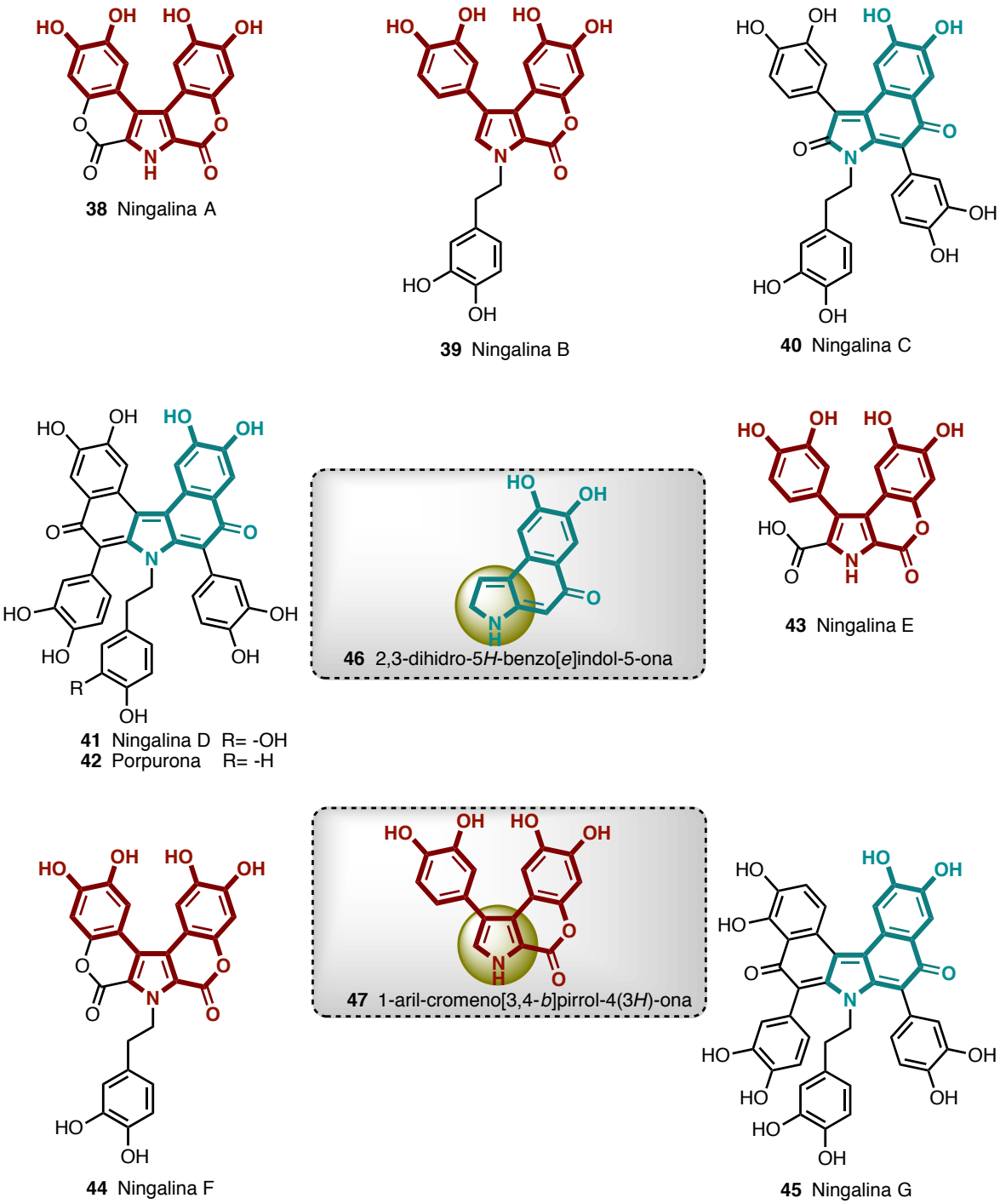
[39] Plisson, F. Conte, M. Khalil, Z. Huang, X.-C. Piggott, A. M. Capon, R. J. Kinase Inhibitor Scaffolds against Neurodegenerative Diseases from a Southern Australian Ascidian, *Didemnum* sp. *Chem. Med. Chem.* **2012**, *7*, 983-990. https://doi.org/10.1002/cmdc.201200169.

[40] UNESCO World Heritage Centre. (2011). Centro del Patrimonio Mundial -. World Heritage Convention, UNESCO. Visitado el 5 de abril 2021, de https://whc.unesco.org/es/list/1369

[41] Chou, T.-C. Guan, Y. Soenen, D. R. Danishefsky, S. J. Boger, D. L. Potent Reversal of Multidrug Resistance by Ningalins and Its Use in Drug Combinations against Human Colon Carcinoma Xenograft in Nude Mice. *Cancer Chemother Pharmacol*. **2005**, *56*, 379-390. https://doi.org/10.1007/s00280-005-1019-y.

[42] Fan, G. Li, Z. Shen, S. Zeng, Y. Yang, Y. Xu, M. Bruhn, T.; Bruhn, H.; Morschhäuser, J.; Bringmann, G.; Lin, W. Baculiferins A–O, O-Sulfated Pyrrole Alkaloids with Anti-HIV-1 Activity, from the Chinese Marine Sponge Iotrochota Baculifera. *Bioorg. Med. Chem.* **2010**, *18*, 5466-5474. https://doi.org/10.1016/j.bmc.2010.06.052.

Por ello la necesidad de obtener rutas sintéticas eficientes para obtener estos metabolitos secundarios y emplearlos para realizar ensayos biológicos que sustenten su importancia e identificar las potenciales aplicaciones en el desarrollo de nuevos fármacos.



Esquema 3. Familia de Ningalinas provenientes de *Didemnum* sp. y su núcleo molecular base.

2.1.2 Síntesis descritas de Ningalinas y estudios de actividad biológica

En 1998 Boger[43] describe la primer síntesis total de Ningalina A y con ello el primer ensayo de actividad biológica en cáncer de colon humano (HCT116/VM46), derivado de este estudios se concluye que este alcaloide resultó ser débilmente activo. Nuevamente Boger en el 2000[44] describe la primera síntesis total de Ningalina B y análogos, de igual manera realiza ensayos en cáncer de colon humano (HCT116/VM46), donde los análogos resultaron tener más actividad que la propia Ningalina B.

Por otro lado, Steglich en el 2000[45] describe la primer síntesis total de Ningalina C, todas las síntesis de Ningalina C se discutirán a detalle en el siguiente capítulo. Un poco más delante, Bullington en 2002[46] describe una síntesis total de Ningalina B, en su trabajo sólo describe la síntesis del alcaloide. Después Ruchirawat[47] describe la segunda síntesis total de Ningalina C en 2002. Boger en 2003[48] realiza la síntesis de derivados de Ningalina B, en sus ensayos de actividad biológica en cáncer de colon humano (HCT116/VM46), encontraron que algunos análogos sintetizados mostraron una actividad superior a los fármacos convencionales aprobados por la FDA. Gupton en 2002[49] describe una nueva síntesis total de Ningalina B a partir de derivados de sales de iminiovinílogas, en su trabajo sólo describe la síntesis total y no realiza ensayos biológicos. En 2004[50] Boger realiza una nueva síntesis de Ningalina B y análogos, donde al introducir sustituyentes metoxilos en el anillo pirrólico mejora la actividad biológica en cáncer de colon humano (HCT116/VM46). Boger para 2005 describe la primer síntesis total de Ningalina D y análogos, donde se hizo estudio de su actividad biológica frente a la cepa de cáncer de colon humano (HCT116/VM46) y una línea celular de leucemia murina (L1210). Los análogos resultaron revertir la MDR con mayor efectividad que los análogos de está y otras ningalinas descritas en su grupo de investigación. Gupton en 2009[51] describe una nueva

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[43] Boger, D. L. Boyce, C. W. Labroli, M. A. Sehon, C. A. Jin, Q. Total Syntheses of Ningalin A, Lamellarin O, Lukianol A, and Permethyl Storniamide A Utilizing Heterocyclic Azadiene Diels-Alder Reactions. *J. Am. Chem. Soc.* **1999**, *121*, 54-62 https://doi.org/10.1021/ja982078+

[44] Boger, D. L. Soenen, D. R. Boyce, C. W. Hedrick, M. P. Jin, Q. Total Synthesis of Ningalin B Utilizing a Heterocyclic Azadiene Diels−Alder Reaction and Discovery of a New Class of Potent Multidrug Resistant (MDR) Reversal Agents. *J. Org. Chem.* **2000**, *65*, 2479-2483. https://doi.org/10.1021/jo9916535.

[45] Peschko, C. Steglich, W. First Total Synthesis of the Marine Alkaloids Purpurone and Ningalin C. *Tetrahedron Lett.* **2000**, *41*, 9477-9481. https://doi.org/10.1016/s0040-4039(00)01614-2.

[46] Bullington, J. L. Wolff, R. R. Jackson, P. F. Regioselective Preparation of 2-Substituted 3,4-Diaryl Pyrroles: A Concise Total Synthesis of Ningalin B. *J. Org. Chem.* **2002**, *67*, 9439-9442. https://doi.org/10.1021/jo026445i.

[47] Namsa-aid, A. Ruchirawat, S. Efficient Synthesis of Ningalin C. *Org. Lett.* **2002**, *4*, 2633-2635. https://doi.org/10.1021/ol026074s.

[48] Soenen, D. R. Hwang, I. Hedrick, M. P. Boger, D. L. Multidrug Resistance Reversal Activity of Key Ningalin Analogues. *Bioorg Med Chem Lett*. **2003**, *13*, 1777-1781. https://doi.org/10.1016/s0960-894x(03)00294-4.

[49] Gupton, J. T. Clough, S. C. Miller, R. B. Lukens, J. R. Henry, C. A. Kanters, R. P. F. Sikorski, J. A. The Application of Vinylogous Iminium Salt Derivatives to the Synthesis of Ningalin B Hexamethyl Ether. *Tetrahedron.* **2003**, *59*, 207-215. https://doi.org/10.1016/s0040-4020(02)01475-8.

[50] Tao, H. Hwang, I. Boger, D. L. Multidrug Resistance Reversal Activity of Permethyl Ningalin B Amide Derivatives. *Bioorg Med Chem Lett* **2004**, *14*, 5979-5981. https://doi.org/10.1016/j.bmcl.2004.10.002.

[51] Gupton, J. T. Giglio, B. C. Eaton, J. E. Rieck, E. A. Smith, K. L. Keough, M. J. Barelli, P. J. Firich, L. T. Hempel, J. E.; Smith, T. M. Kanters, R. P. F. The Application of Vinylogous Iminium Salt Derivatives to Efficient Formal Syntheses of the Marine

síntesis total para la obtención de Ningalina B, junto con ella a partir de una plataforma en común logra la síntesis de diferentes metabolitos. En 2010 Wan[52] describe la síntesis total de Ningalina B y análogos estructurales, en los que se encontró que los análogos revertían la resistencia al paclitaxel (taxol) del cáncer de mama MDA435/LCC6MDR. Jia en 2011[53] describe una nueva síntesis total de Ningalina B, en su aportación a partir de un de una plataforma estructural logra la síntesis de otros metabolitos. En 2012 cuando Capon[40] describió las nuevas Ningalinas E-G en su estudio sobre el mecanismo de inhibición de quinasas en enfermedades neurodegenerativas realizó un ensayo Docking donde logró identificar que los sitios de acoplamiento de las Ningalinas con la quinasa CDK5^{D144N}/p^{25} (Figura 3).

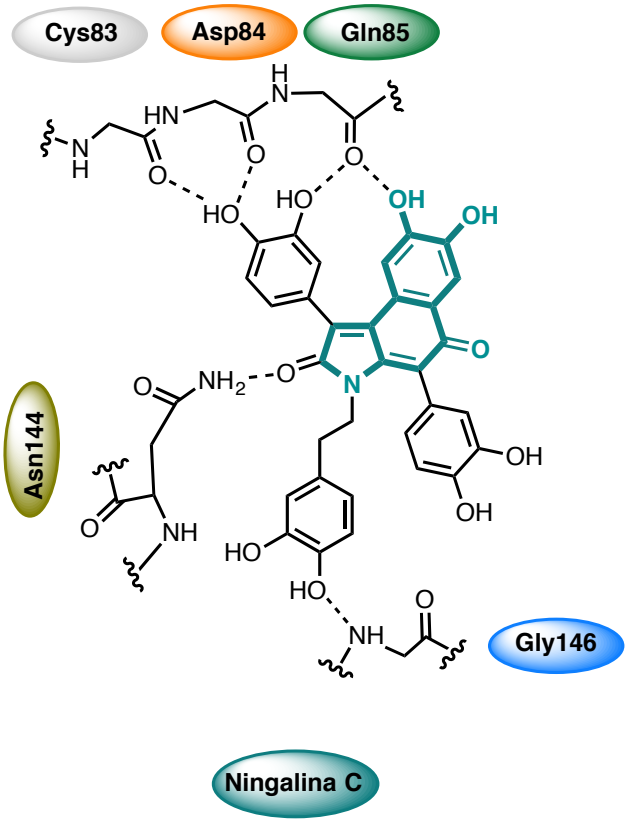

Figura 3. Docking de Ningalina C con la quinasa CDK5^{D144N}/p^{25}.

Alkaloids Lamellarin G Trimethyl Ether and Ningalin B. *Tetrahedron.* **2009**, *65*, 4283-4292. https://doi.org/10.1016/j.tet.2009.03.085.

[52] Zhang, P. Y. Wong, I. L. K. Yan, C. S. W. Zhang, X. Y. Jiang, T. Chow, L. M. C. Wan, S. B. Design and Syntheses of Permethyl Ningalin B Analogues: Potent Multidrug Resistance (MDR) Reversal Agents of Cancer Cells. *J. Med. Chem.* **2010**, *53*, 5108-5120. https://doi.org/10.1021/jm100035c.

[53] Li, Q. Jiang, J. Fan, A. Cui, Y.; Jia, Y. Total Synthesis of Lamellarins D, H, and R and Ningalin B. *Org. Lett.* **2011**, *13*, 312-315. https://doi.org/10.1021/ol1027877.

En 2014 Wan[54] sintetiza la Ningalina B y análogos de ella, con los cuales realizó estudios en líneas celulares de cáncer de mama (MDA435/LCC6) y leucemia humana K562/P-gp. Uno de los análogos funcionó como gran modulador de la resistencia a fármacos mediada por P-gp.

El siguiente año de nuevo Wan[55] realizo de la síntesis de Ningalina B y nuevos análogos, de nuevo realizó ensayos de actividad biológica en cáncer de mama con sobreexpresión de P-gp (LCC6MDR) siendo muy efectivo uno de los análogos sintetizados por Wan.

Para 2016 en nuestro grupo de investigación Solorio-Alvarado[56] publicó la síntesis formal de Ningalina C. Cho en 2017[57] realiza por primera vez la síntesis total de la Ningalina G y la segunda de Ningalina D, a partir de una plataforma en común pudo obtener ambos metabolitos.

De nuevo Cho en 2018[58] describe la cuarta y ultima síntesis total de Ningalina C. Khan en 2019[59] describe la síntesis total de Ningalina B, en esta propuesta emplea la síntesis de pirroles 1,2,4-trisustituidos vía *one-pot*, libre de metales de transición y ácidos o bases.

Yan en 2019[60] describe la síntesis total de Ningalina B, una síntesis que consta de cinco pasos y al final obtienen el alcaloide con buenos rendimientos. Saito en 2020[61] describe una síntesis de Ningalina B, una síntesis catalizada con Rutenio para lograr la cicloisomerización que dará lugar a una plataforma, mediante esta plataforma es obtenida la Ningalina C.

Por último la más reciente de todas las síntesis ningalinas descrita por Okano en el 2020[62] obtiene una síntesis total de Ningalina B, una síntesis a partir de una plataforma molecular donde obtienen otros metabolitos de *Didemnum sp*. el paso clave de está propuesta es la danza halógena de α,β-dibromopirrol.

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[54] Yang, C. Wong, I. Jin, W. Jiang, T. Chow, L. Wan, S. B. Modification of Marine Natural Product Ningalin B and SAR Study Lead to Potent P-Glycoprotein Inhibitors. *Mar. Drugs.* **2014**, *12*, 5209-5221. https://doi.org/10.3390/md12105209.

[55] Wang, Z.; Wong, I. L. K.; Li, F. X.; Yang, C.; Liu, Z.; Jiang, T.; Jiang, T. F.; Chow, L. M. C.; Wan, S. B. Optimization of Permethyl Ningalin B Analogs as P-Glycoprotein Inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 5566-5573. https://doi.org/10.1016/j.bmc.2015.07.027.

[56] Ramadoss, V. Nahide, P. D. Juárez-Ornelas, K. A. Rentería-Gómez, M. Ortiz-Alvarado, R. Solorio-Alvarado, C. R. A Four-Step Scalable Formal Synthesis of Ningalin C. *Arkivoc.* **2016**, *4*, 385-394. https://doi.org/10.3998/ark.5550190.p009.631.

[57] Kim, J.-Y. Kim, D.-H. Jeon, T.-H. Kim, W.-H. Cho, C.-G. Total Syntheses of Ningalins D and G. *Org. Lett.* **2017**, *19*, 4688-4691. https://doi.org/10.1021/acs.orglett.7b02372.

[58] Kim, W. Kim, J. Cho, C. Total Synthesis of Ningalin C. *Bull. Korean Chem. Soc.* **2018**, *39*, 1463-1466. https://doi.org/10.1002/bkcs.11609.

[59] Kumar, V. Awasthi, A. Metya, A. Khan, T. A Metal-Free Domino Process for Regioselective Synthesis of 1,2,4-Trisubstituted Pyrroles: Application toward the Formal Synthesis of Ningalin B. *J. Org. Chem.* **2019**, *84*, 11581-11595. https://doi.org/10.1021/acs.joc.9b01520.

[60] Wu, C.-K. Weng, Z. Yang, D.-Y. One-Pot Construction of 1-Phenylchromeno[3,4-*b*]Pyrrol-4(3*H*)-One: Application to Total Synthesis of Ningalin B and a Pyrrolocoumarin-Based Electrochromic Switch. *Org. Lett.* **2019**, *21*, 5225-5228. https://doi.org/10.1021/acs.orglett.9b01830.

[61] Watanabe, T. Mutoh, Y. Saito, S. Synthesis of Lactone-Fused Pyrroles by Ruthenium-Catalyzed 1,2-Carbon Migration-Cycloisomerization. *Org. Biomol. Chem*. **2020**, *18*, 81-85. https://doi.org/10.1039/c9ob02363a.

[62] Morikawa, D. Morii, K. Yasuda, Y. Mori, A.; Okano, K. Convergent Total Synthesis of Lamellarins and Their Congeners. *J. Org. Chem.* **2020**, *85*, 8603-8617. https://doi.org/10.1021/acs.joc.0c00998.

Tabla 3. Síntesis descritas de Ningalinas.

Síntesis de Ningalinas		
Tipo	Investigador	Año
Ningalina A	Boger	2000
Ningalina B	Boger	2000, 2003, 2004
	Bullington	2002
	Gupton	2003, 20019
	Wan	2010, 2014, 2015
	Jia	2011
	Khan	2019
	Yan	2019
	Saito	2020
	Okano	2020
Ningalina C	***Steglich***	***2000***
	Ruchirawat	***2002***
	Cho	***2018***
Ningalina D	Boger	2005
	Cho	2017
Ningalina E*	--	--
Ningalina F*	--	--
Ningalina G	Cho	2017

**No hay síntesis descritas para Ningalina E y F.*

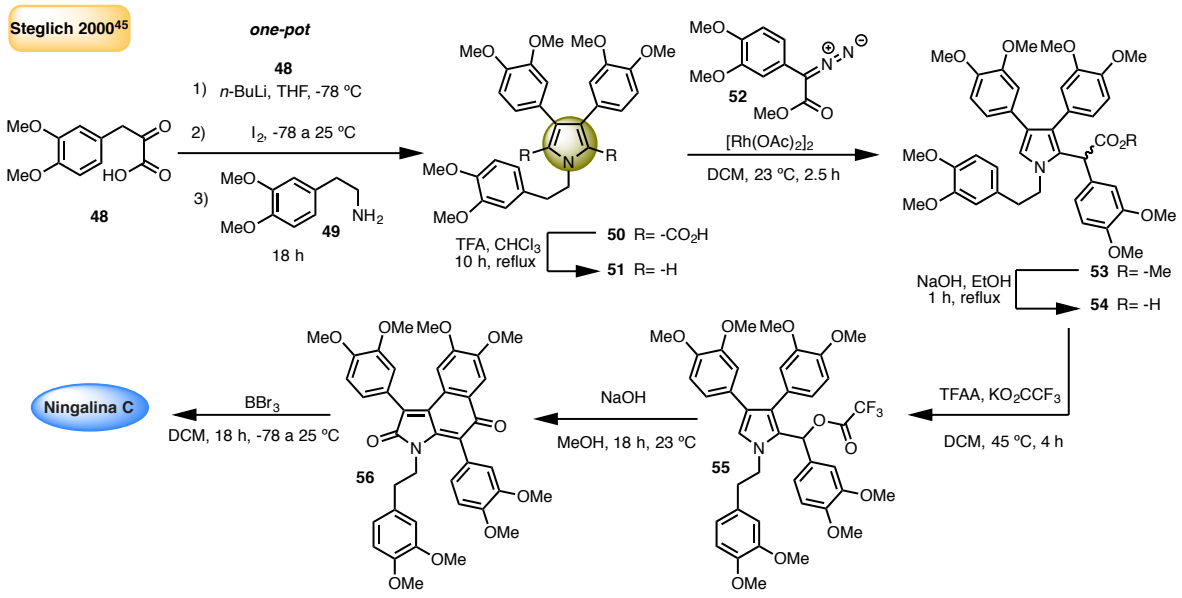
2.1.3 Síntesis total descritas de Ningalina C

En la actualidad sólo se han descrito cuatro síntesis totales para la síntesis de Ningalina C y una síntesis formal descrita por nuestro grupo de investigación. En este capítulo se describirán los aspectos o etapas de reacción determinantes para la obtención de este metabolito. En las síntesis descritas sólo se realizo la síntesis sin determinar si existía o no actividad biológica.

Steglich en el 2000[45] describe una síntesis convergente en la cual obtiene la Porpurona **42** (Esquema 3) y la Ningalina C.

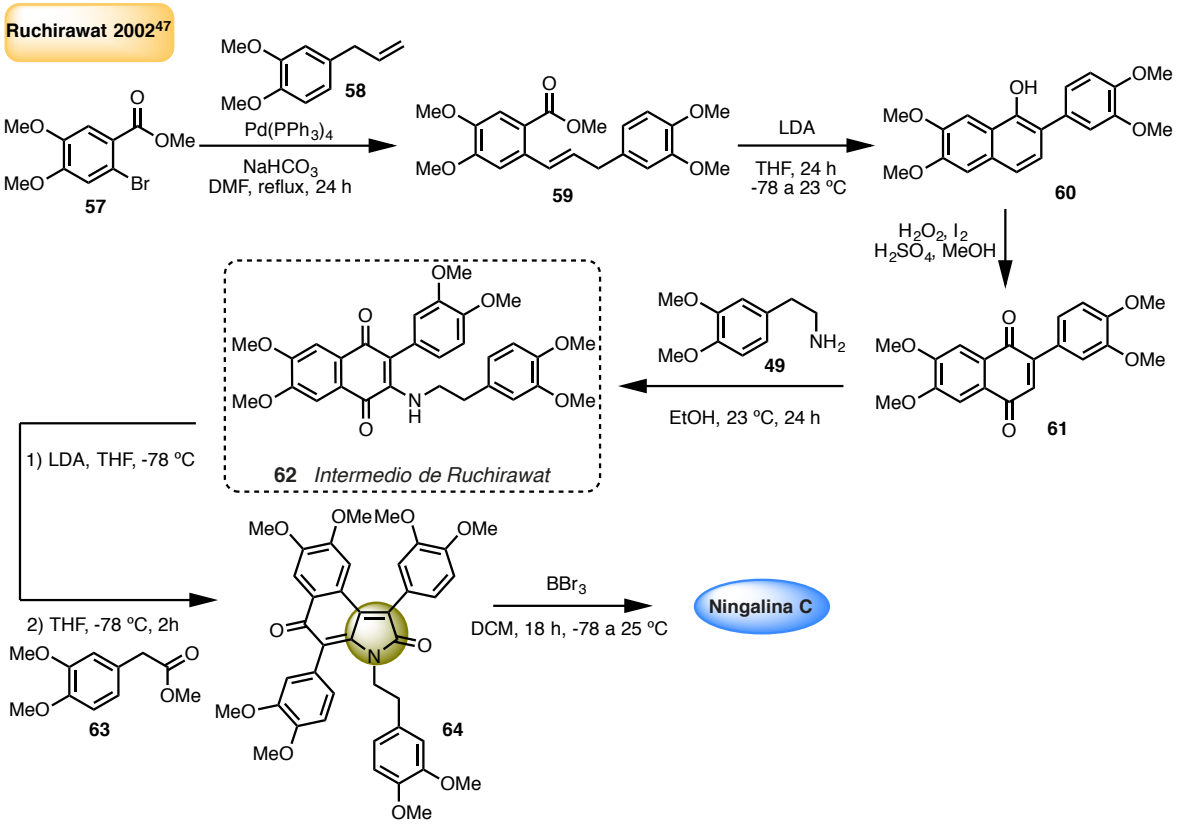
Está reacción comienza con la formación del anillo pirrólico vía *one-pot*, iniciando con la dimerización de dos moléculas de 3-(3,4-dimetoxifenil)ácido pirúvico **48**, posterior a ello una condensación con

3,4-dimetoxifenetilamina **49**. Obteniendo así **50** con el cual se obtendrá la Porpurona y posterior a una descarboxilación se obtendrá **51** con el que se obtendrá Ningalina C. Con **51** y 2-diazo-2-(3,4-dimetoxifenil)acetato de metilo **52** se obtiene la monoalquilación catalizada por Rh(II) para obtener **53**. Posterior a la saponificación de éster de **53** obtenemos a **54** con el que logró mediante una reacción Friedel-Crafts intramolecular obtener a **55**. Posterior a ello, obtuvo a **56** donde logró la formación de la amida en el anillo pirrólico y la formación del carbonilo en la porción del naftol. Por último, mediante la desprotección de los hidroxilos obtiene la Ningalina C con un 90% de rendimiento (Esquema 4).



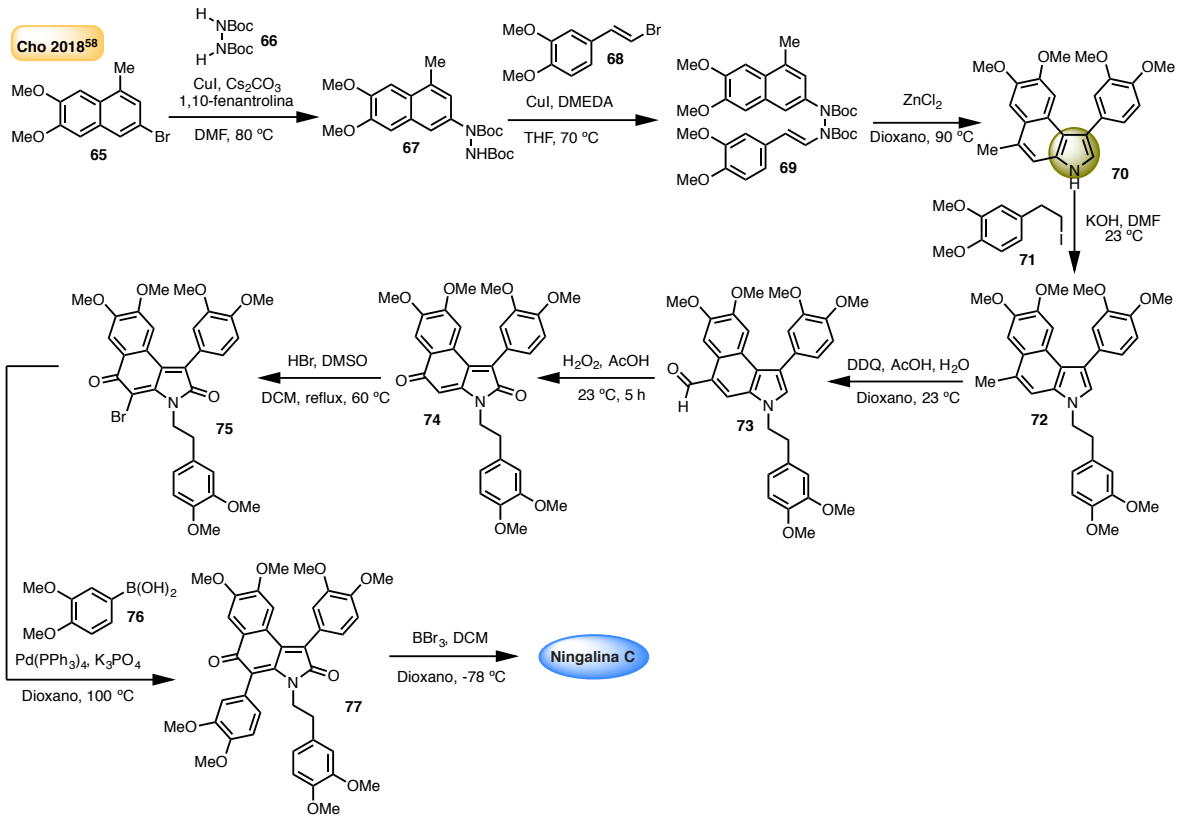
Esquema 4. Síntesis Total de Ningalina C propuesta por Steglich en el 2000.

Ruchirawat en 2002[47] describe la segunda síntesis de Ningalina C, comienza con una reacción de Mizoroki-Heck empleando el metil 2-bromo-4,5-dimetoxibenzoato **57** y eugenol **58** donde obtiene a **59**, posterior a ello se lleva al cabo una ciclación para la obtención de **60**. Empleando **60** mediante la oxidación del naftol con diisopropilamida de litio se obtiene a **61**. Mediante una adición nucleófila empleando 3,4-dimetoxifenetilamina **49** en **61** obtiene el *intermedio de Ruchirawat* **62**. La formación del anillo pirrólico sucede con la síntesis de la pirrolidona empleando el *intermedio de Ruchirawat* y 2-(3,4-dimetoxifenil)acetato de metilo **63** y con ello se obtiene a **64**. En **64** empleando tribromuro de boro sucede la desmetilación en los hidroxilos y con ello obtiene a la Ningalina C con un rendimiento del 73% (Esquema 5).



Esquema 5. Síntesis Total de Ningalina C propuesta por Ruchirawat en 2002.

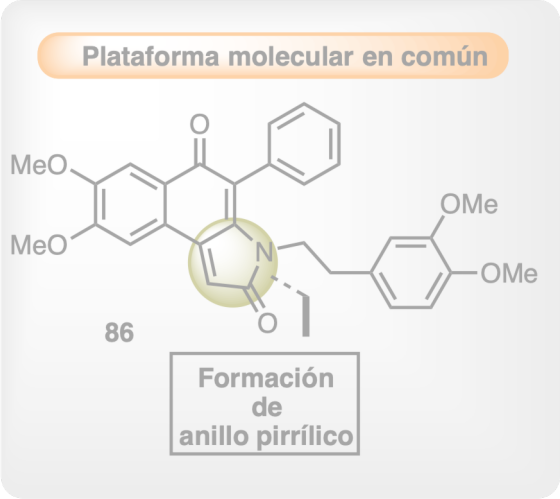
Cho en 2018[58] realizó una síntesis que emplea 9 pasos de reacción la cual comienza con la formación del enlace carbono-nitrógeno con el bromuro de arilo **65** y la bis-Boc-Hidrazina **66** con lo que se obtiene a **67**. Posterior a esta, se hace reaccionar una molécula más de bromuro de arilo **68** para obtener **69**, posteriormente en otra etapa de reacción acurre un reordenamiento [3,3]-sigmatrópico catalizado con ácido con lo que se obtiene el anillo pirrólico **70**. Al emplear el yoduro de arilo **71** logro la formación del enlace carbono-nitrógeno y obtiene a **72**. Empleando 2,3-dicloro-5,6-diciano-1,4-benzoquinona logra la oxidación de **72** y obtiene a **73**. Con **73** y mediante una oxidación, hidrólisis y una oxidación de Baeyer-Villiger para obtener **74** con el que se realiza una bromación y obtiene a **75**. Posterior a ello realiza reacción de Suzuki-Miyaura empleando el respectivo ácido borónico **76** y obtiene a **77**. Para finalizar la desmetilación empleando tribromuro de boro para la obtención de Ningalina C (Esquema 6).



Esquema 6. Síntesis Total de Ningalina C propuesta por Cho en 2018.

Capítulo III

Nuestra estrategia para la obtención de la Ningalina C

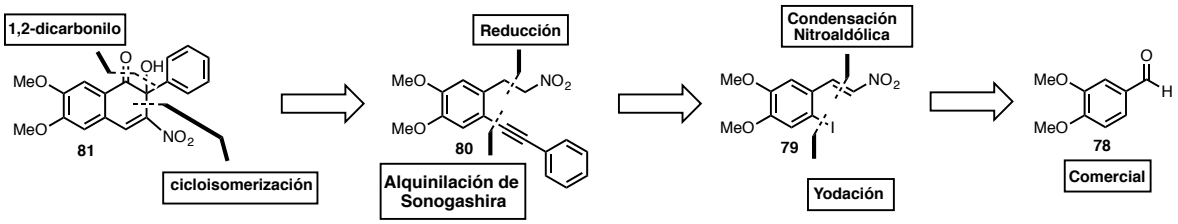


3.1 Estrategia retrosintética

El objetivo de nuestra síntesis total y la parte innovadora es la síntesis de una plataforma molecular en común para la obtención de Ningalina C y análogos estructurales. Con ello podemos tener acceso a una nueva biblioteca de Ningalinas que en un futuro se someterán a ensayos biológicos. Como en toda síntesis total echamos mano de la estrategia retrosintética con el fin de simplificar ideas e ir trazando una ruta químicamente más eficiente. Nuestra propuesta sintética es la siguiente:

3.1.1 Formación del naftaleno

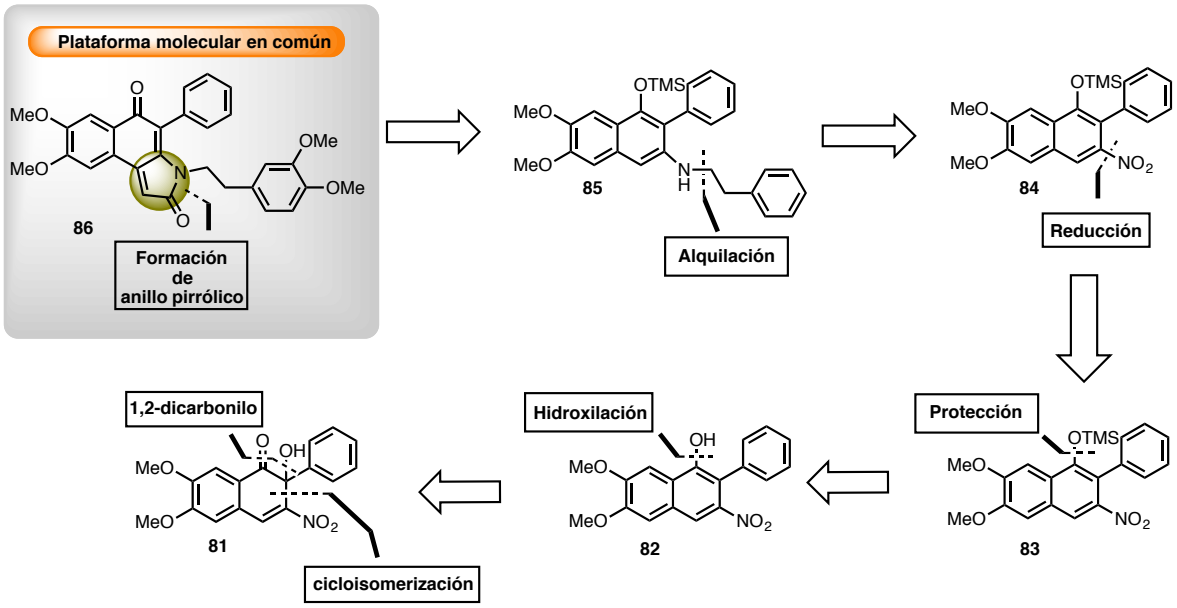
A partir del producto comercial 3,4-dimetoxibenzaldehído **78** comienza la síntesis total con su yodación empleando yodo molecular y posteriormente una nitración aldólica con $MeNO_2$ para obtener a **79**, con ello se realiza un reacción de Sonogashira empleando fenilacetileno y posterior a ello una reducción olefínica empleando $NaBH_4$ para obtener **80**, posterior a ello se lleva al cabo una oxidación en el alquino obteniendo la adición dicarbonilo 1,2 empleando $KMnO_4$, con ello e *in situ* se obtiene la cicloisomerización para obtener a **81** (Esquema 7).



Esquema 7. Obtención del núcleo naftaleno de Ningalina C.

3.1.2 Obtención de la plataforma molecular en común

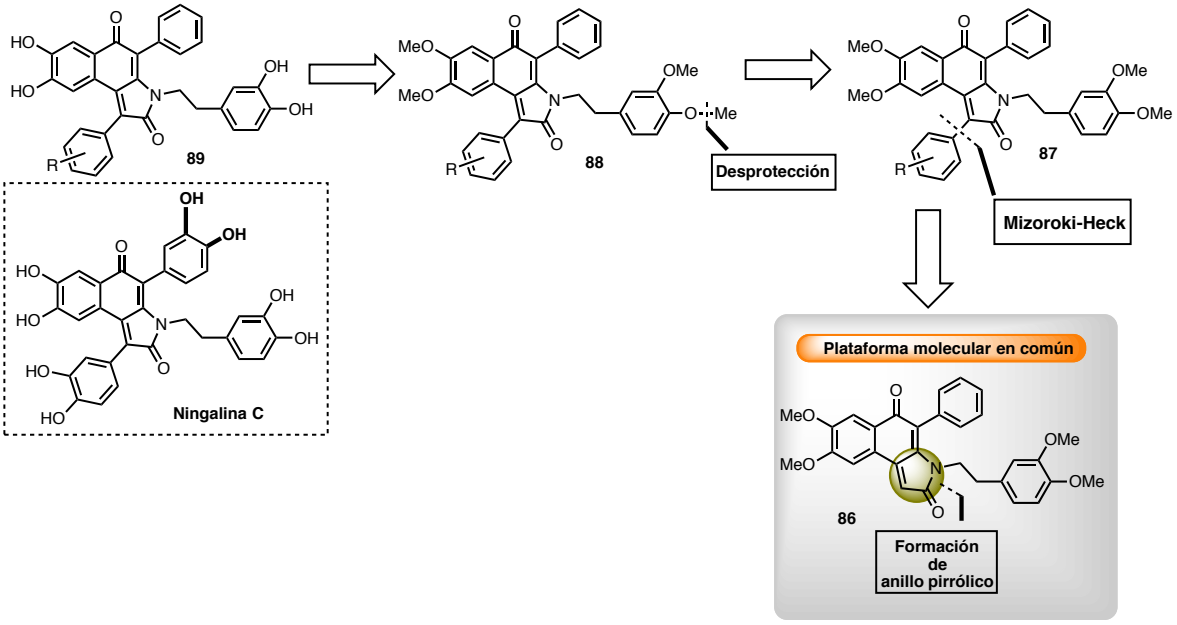
Posteriormente con empleando **81** en $MeSO_3H$ se obtiene el naftol **82** y a partir de este se realizará una sililación regioselectiva y se obtiene **83**. Después de esta protección se realiza una reducción empleando $NaBH_4$, con ello obtenemos nuestra amina **84**, a partir de ello se lleva al cabo la alquilación en la amina empleando 3,4-dimetoxifenetilamina y con ello se llevará al cabo la desililación para obtener a **85**. Empleando cloruro de 2-oxoacetilo se logrará la formación de la quinona con la que se obtendrá nuestro anillo pirrólico **86**, con ello se obtiene nuestra plataforma molecular la cual es la fuente de inspiración de está nueva metodología (Esquema 8).



Esquema 8. Obtención de la plataforma molecular de Ningalina C.

3.1.3 Obtención de Ningalina C y análogos

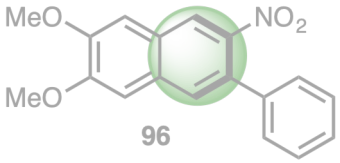
Con nuestra plataforma sintetizada **86** mediante una olefinación de Mizoroki-Heck empleando diferentes yoduros de arilo **87**. Por último, sucederá la desprotección del grupo hidroxilo empleando BBr_3 **88** y finalmente obtenemos la Ningalina C y sus análogos **89** (Esquema 9).



Esquema 9. Obtención de Ningalina C y análogos.

Capítulo IV

Resultados y discusiones

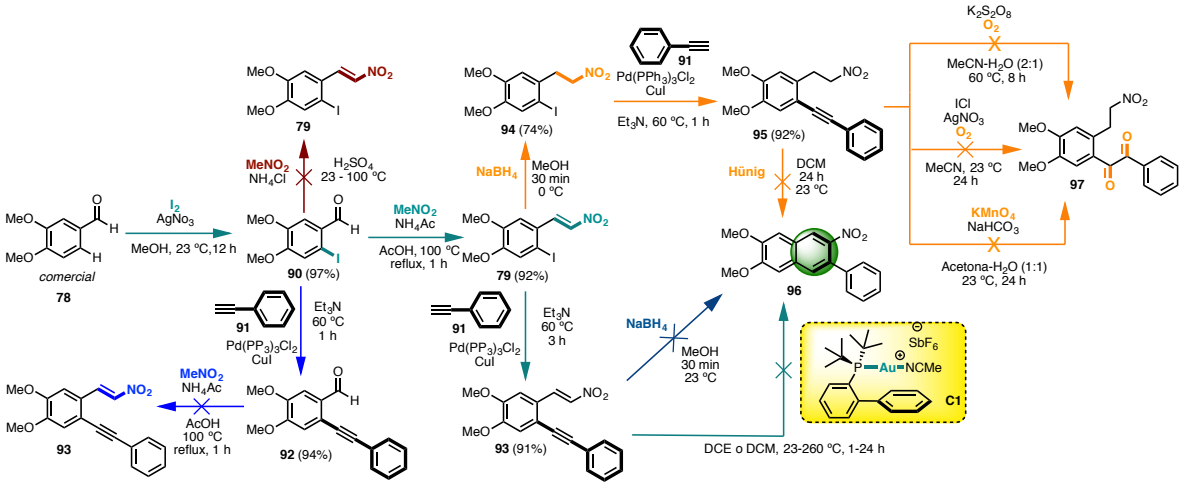


96

4.1 *Obtención del naftaleno*

En este capitulo se presentarán los resultados obtenidos en el periodo febrero-abril del 2021, tiempo en el que se ha permitido el regreso a las actividades las cuales se suspendieron por la contingencia a causa de la COVID-19. Pese al poco tiempo, se tiene el material suficiente para presentar lo siguiente.

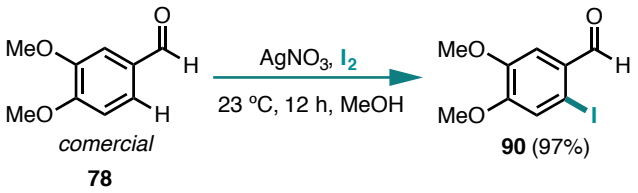
En nuestra propuesta sintética de Ningalina C el paso determinante es la obtención del naftaleno. Por ello hemos realizado los siguientes ensayos para obtenerlo (Esquema 10):



Esquema 10. Estrategia sintética para la obtención del núcleo naftaleno de la Ningalina C.

a. Yodación del 3,4-dimetoxibenzaldehído 78

Comenzamos con la yodación del 3,4-dimetoxibenzaldehído **78** empleando una reacción ya conocida empleando nitrato de plata y yodo molecular, a 23 ºC por 12 horas en metanol. Resultado de ello obtuvimos al 2-yodo-4,5-dimetoxibenzaldehído **90** con un rendimiento del 97% (Ec. 1).



(1)

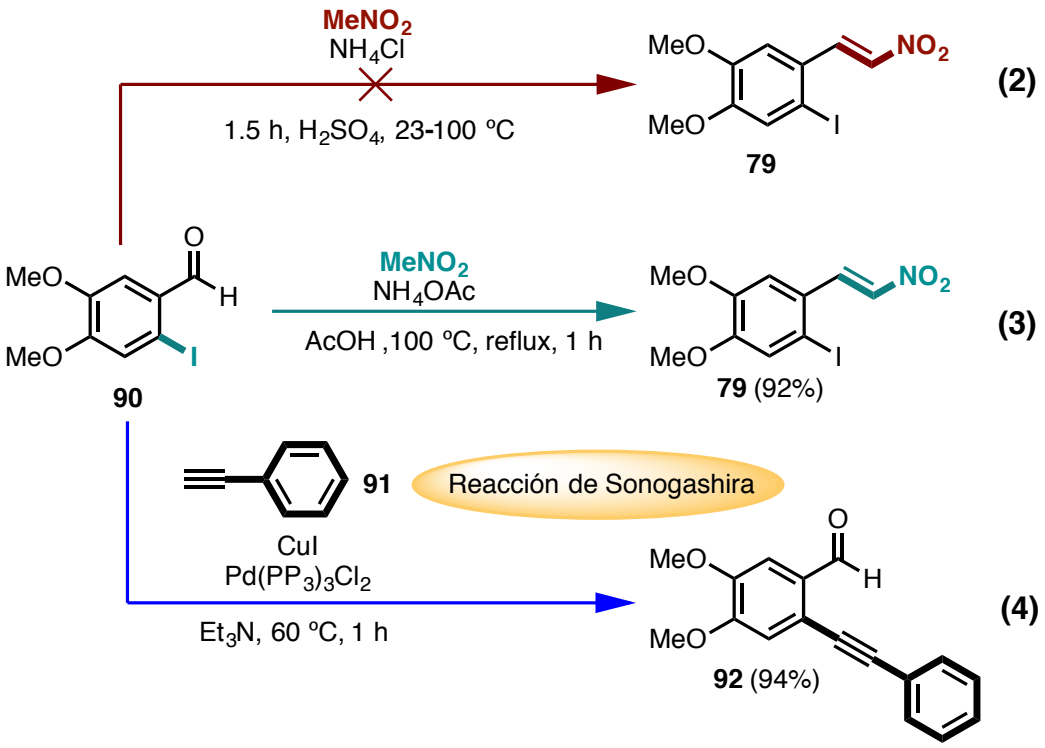
A partir de la obtención de **90** comenzamos a experimentar más con las posibles vías para obtener nuestro naftaleno. Con ello nos encargamos de obtener la ruta más eficiente.

b. **Reacciones empleando 2-yodo-4,5-dimetoxibenzaldehído 90**

La condensación nitroaldólica del 2-yodo-4,5-dimetoxibenzaldehído **90** comenzó con el sistema de $MeNO_2/NH_4Cl$ y H_2SO_4 como disolvente. Se desarrollaron dos entradas en 1.5 h de reacción entrada a 100 ºC y otra a 23 ºC (Ec. 2). En ambos casos no se observó reacción para la obtención de **79**.

Con ello se procedió a emplear otro sistema, el sistema $MeNO_2/NH_4OAc$ en ácido acético esto a reflujo por una hora. Con este sistema se logró con éxito la condensación, obteniendo 92% del (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno **79** (Ec. 3).

Por otro la se realizo una reacción de Sonogashira empleando fenilacetileno **91** con **90** y con ello se obtuvo la alquinilación con un rendimiento de 94% del 4,5-dimetoxi-2-(feniletinil)benzaldehído **92** (Ec. 4).



c. **Reacciones empleando (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno 79**

Con el objetivo de obtener el naftaleno de la Ningalina C nos dimos a la tarea de formar el correspondiente enino, por ello se realizó una reacción de Sonogashira empleando fenilacetileno **91** (Ec. 5). Para obtener la alquinilación, se realizaron las siguientes reacciones para optimizar la obtención del enino: Para todas las entradas se empleo Et_3N como disolvente a 60 ºC, para la entrada **1** se emplearon 3 mol% del catalizador de paladio y 1 mol% de CuI en una hora de reacción y no se

observo reacción. Para la entrada **2** se empleó el mismo % molar de paladio y CuI en dos horas de reacción y no se observo reacción. Para al entrada **3** se utilizo 4 mol% y 3 mol% de paladio y CuI respectivamente en tres horas de reacción y con ello se obtuvo con éxito un rendimiento del 91% de (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno **93** (Tabla 4).

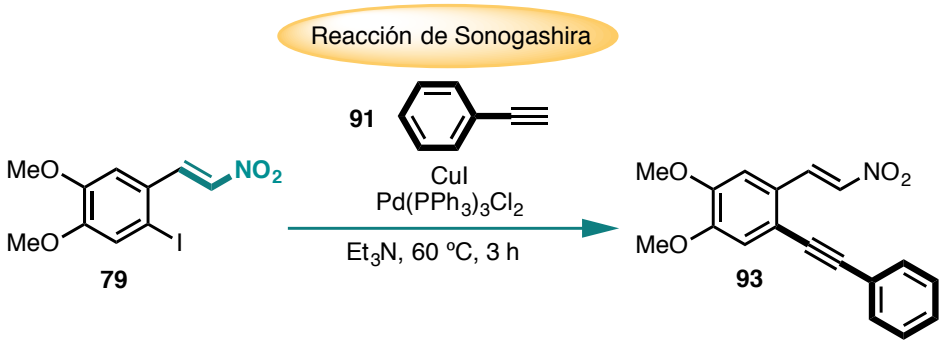
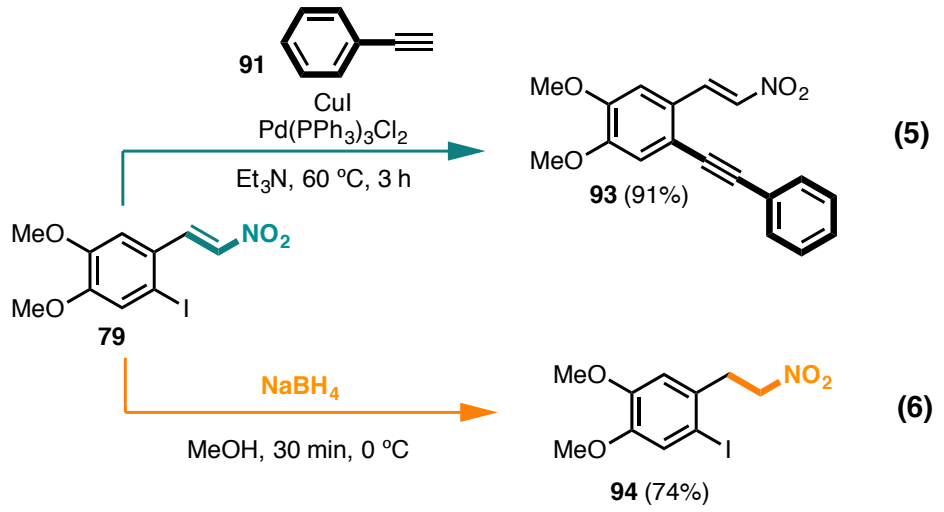


Tabla 4. Optimización de reacción de Sonogashira para la obtención del enino **93**.

Entrada	**$Pd(PPh_3)_3Cl_2$ mol%**	**CuI mol%**	**Tiempo h**	**Rendimiento %**
1	3	1	1	n. r.
2	3	2	2	n. r.
3	4	2	3	91%

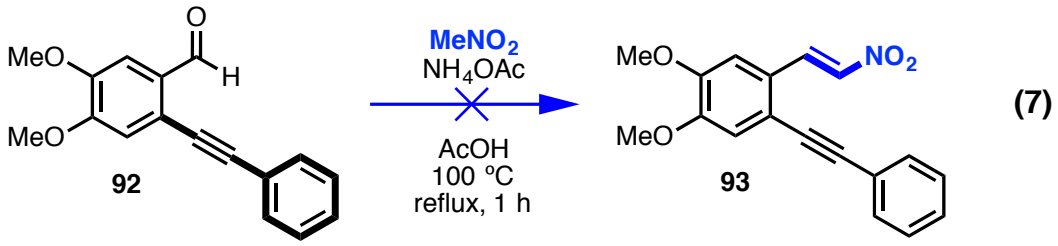
n. r. = no hay reacción observada

Con el fin de obtener una nueva alternativa y diversificar las rutas dentro de nuestra síntesis total se procedió a la reducción de la porción olefínica resultado de la condensación nitroaldólica. Para ello se empleó una reducción ya conocida y muy bien descrita en la literatura. Con **79** disuelto en metanol y empleando como agente reductor al $NaBH_4$ por 30 minutos a temperatura de 0 ºC. Con lo que se obtuvo con éxito a 1-yodo-4,5-dimetoxi-2-(2-nitroetil)benceno **94** con un rendimiento del 74% (Ec. 6).



d. **Reacción empleando 4,5-dimetoxi-2-(feniletinil)benzaldehído 25**

Empleando **91** para obtener el enino por otra vía y con ello comparar cual es la más eficiente se procede con la reacción de condensación empleando el sistema $MeNO_2/NH_4OAc$ en acido acético a reflujo por una hora y no se observó la nitración aldólica para obtener (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno **93** (Ec. 7).



(7)

e. **Reacción empleando (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno 93**

Con base a la línea de investigación desarrollada en nuestro grupo de investigación la química de oro sería de gran ayuda para obtener el naftaleno a partir de la formación de nuestro enino (Ec. 8). Aquí se presentará la optimización que realizamos para su obtención lo cual no fue posible. La naturaleza química de nuestro enino deficiente de electrones no permitió la cicloisomerización. Empleando como catalizador al (Acetonitrilo)[(2-bifenil)di-terc-butilfosfina]hexafluoroantimoniato de oro(I) **(C1)** se realizaron los siguientes ensayos con nuestro enino (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno **93** (Tabla 5).

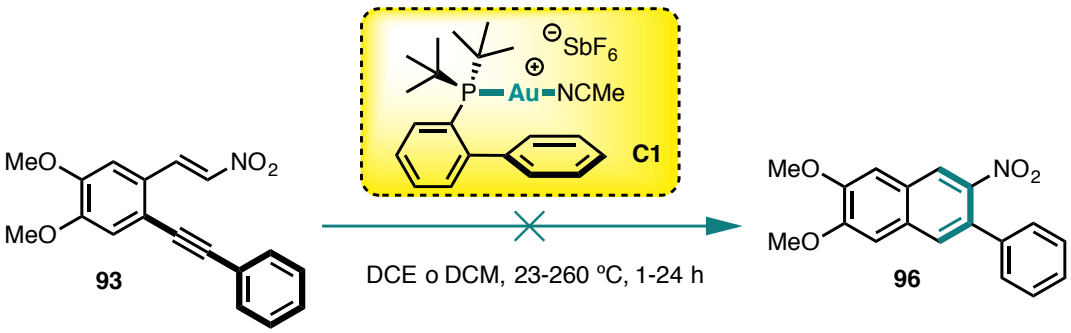


Tabla 5. Optimización de reacción catalizada por oro **C1** para la obtención de 2,3-dimetoxi-6-nitro-7-fenilnaftaleno **96**

Entrada	**Disolvente**	**Temperatura ºC**	**C1 mol%**	**Tiempo h**	**Rendimiento %**
1	DCM	23	5	1	n. r.
2	DCM	23	10	1	n. r.

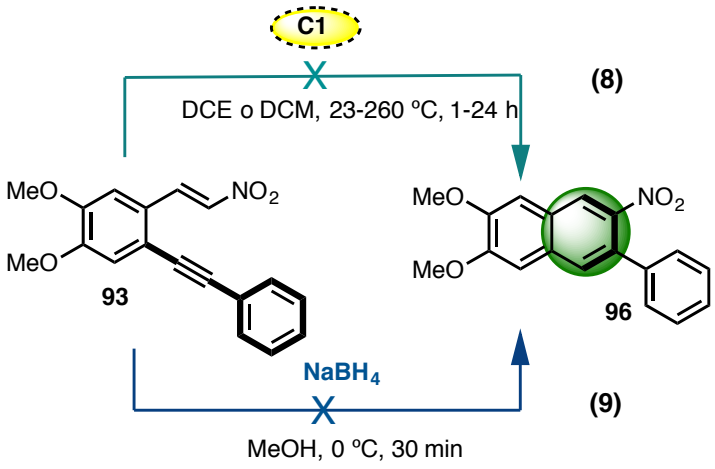
3	DCM	60	20	3	n. r.
4	DCM	110	30	24	n. r.
5	DCE	130	20	3	n. r.
6	DCE	180	40	3	n. r.
7	DCE	180	70	24	n. r.
8	DCE	260	50	24	Descomposición

n. r. = no hay reacción observada

Para la entrada **1** se utilizó a **93** con 5 mol% de **C1** en DCM a temperatura ambiente por una hora de reacción donde se obtuviera **96**. Para **2** se aumentó al doble la carga catalítica hasta 10 mol% a temperatura ambiente por una hora en DCM y no se observó reacción. En la entrada **3** se utilizó 20 mol% de **C1** y se elevó la temperatura de 60 ºC por tres horas en DCM y no se observó reacción. En la entrada **4** se utilizó 30 mol% del catalizador **C1** y se elevó la temperatura a 110 ºC en DCM, la reacción se dejó 24 h y no se observó reacción. Con base en los resultados obtenidos y la experiencia en el grupo con los catalizadores de oro se decidió cambiar de disolvente para aumentar la temperatura empleando DCE se realizaron las siguientes entradas:

Para la entrada **5** se utilizo 20 mol% del catalizador de oro **C1** a 130 ºC por 3 horas y no se observó reacción. En la entrada **6** se duplicó la carga catalítica hasta 40 mol% de **C1** a 180 ºC por 24 horas y no se observó reacción. Para él penúltimo ensayo en la entrada **7** se llevó a 180 ºC y se empleó 70 mol% de **C1** por 24 horas y no se observó reacción. En un último ensayo en la entrada **8** se empleó 50 mol% de **C1** y se llevó hasta 260 ºC por 24 horas, donde se observó descomposición de las materias primas de la reacción. Por lo que no fue posible obtener el naftaleno empleando la cicloisomerización catalizada por complejos catiónicos de oro(I).

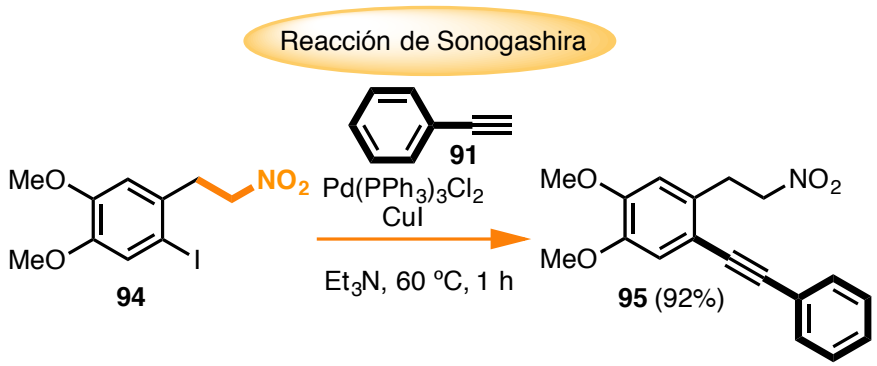
Otra opción sintética que empleamos para obtener la cicloisomerización de **96** fue la reducción del enino (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno **93**. Esto empleando $NaBH_4$ en metanol a 0 ºC por 30 min. Se aisló el producto obtenido de está reacción dando como resultado la descomposición del material de partida (Ec. 9).



f. Reacción empleando 1-yodo-4,5-dimetoxi-2-(2-nitroetil)benceno 94

Con **94** nos fue posible obtener mediante una reacción de Sonogashira la alquinilación empleando fenilacetileno **91**. Utilizando las mismas condiciones que se utilizaron para la obtención del 4,5-dimetoxi-2-(feniletinil)benzaldehído **92** con un rendimiento del 92% (Ec. 10).

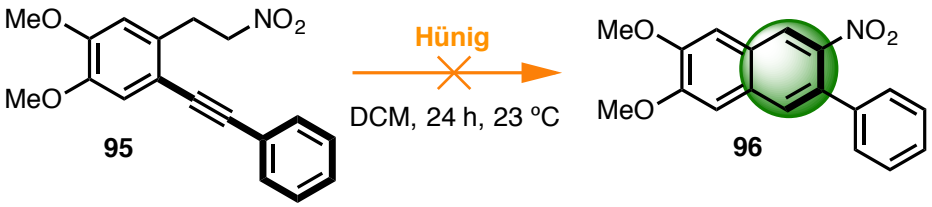
Con ello logramos obtener a 1,2-dimetoxi-4-(2-nitroetil)-5-(feniletinil)benceno **95**, con un rendimiento del 92%



(10)

g. Reacción empleando 1,2-dimetoxi-4-(2-nitroetil)-5-(feniletinil)benceno 95

Con la intención de obtener la cicloisomerización y obtener el naftaleno **96** y empleando a **95** nos dimos a la tarea de emplear una base que abstrajera el hidrogeno del carbono alfa al grupo nitro, con el fin de que este carbanión realizara un ataque nucleofílico al alquino. Para ello utilizamos como base a la *N,N*-Diisopropiletilamina mejor conocida como base de Hünig con lo que no se observó reacción.



(11)

Posterior a ellos nos dimos a la tarea de la obtención de 1,2-dicarbonilos en nuestro alquino mediante la oxidación de **95**. Para ello empleamos las siguientes estrategias encontradas en la bibliografía con las que no se obtuvo reacción alguna:

I) Metodología de Chao 2021[63]

Con el fin de agregar a nuestra síntesis total estrategias atractivas decidimos emplear está propuesta de Chao en la cual vía radicalaria logra la obtención de 1,2-dicarbonilos a partir de la oxidación de alquinos. Empleando nuestro alquino **95** en presencia de persulfato de potasio (2 equiv.) en una mezcla de acetonitrilo-agua (2:1) y con un globo con aire, esto a 60 ºC por 8 horas (Ec. 12, Tabla 6).

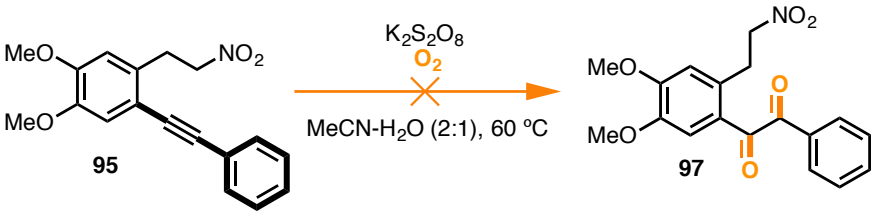


Tabla 6. Optimización para la oxidación del alquino de **95** para la obtención del 1,2-dicarbonilo **97**

Entrada	$K_2S_2O_8$ (Equiv.)	Tiempo h	Rendimiento %
1	2	8	n. r.
2	2	72	d.c.
3	4	8	n. r.
4	8	24	d.c.
5	12	24	d.c.

n. r. = no hay reacción observada, d.c. = descomposición de material de partida

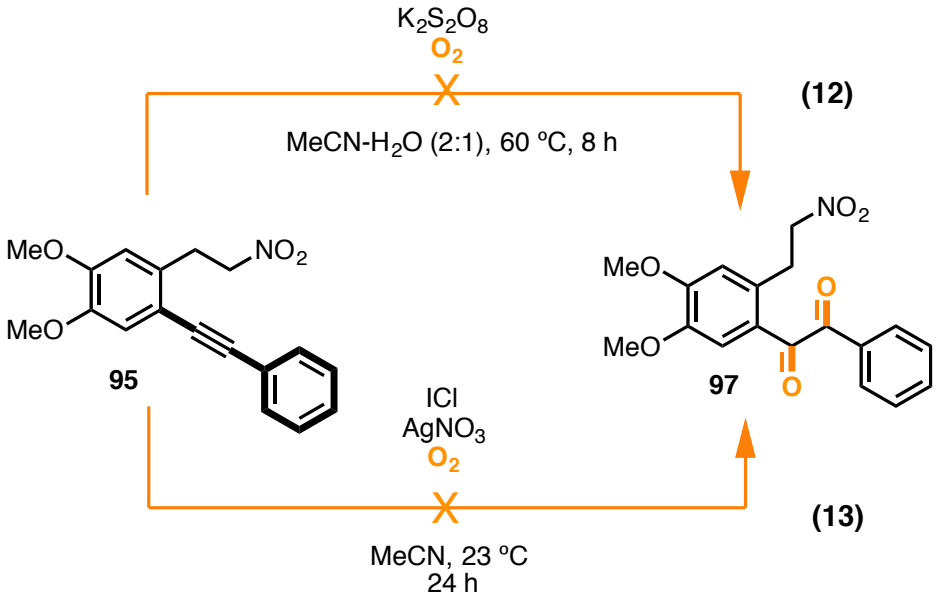
Nosotros comenzamos con nuestra entrada **1** con las condiciones que propone Chao sin observar reacción alguna a las 8 horas, por lo que en nuestra entrada **2** se monitoreó hasta las 78 horas y con ello se obtuvo la descomposición de la materia prima, esto comprobado por los espectros de RMN de ^{1}H y ^{13}C. Por lo que decidimos aumentar el número de equivalentes del persulfato y se llevaron al cabo las siguientes tres entradas:

La entrada **3** se montó con 4 equivalentes no se observó reacción alguna a las 4 horas, para la entrada **4** con 8 equivalentes a las 8 y no se observó reacción. Y por último la entrada **5** con 12 equivalentes a las 3 horas y se observó la descomposición del material de partida. Por lo que se decidió buscar otra metodología ya que no se logró la obtención del 1,2-dicarbonilo **97**.

[63] Shen, D. Wang, H. Zheng, Y. Zhu, X. Gong, P. Wang, B. You, J. Zhao, Y. Chao, M. Catalyst-Free and Transition-Metal-Free Approach to 1,2-Diketones via Aerobic Alkyne Oxidation. *J. Org. Chem.* **2021**, *86*, 5354–5361. https://doi.org/10.1021/acs.joc.0c03010.

II) Metodología de Yan en 2019[64]

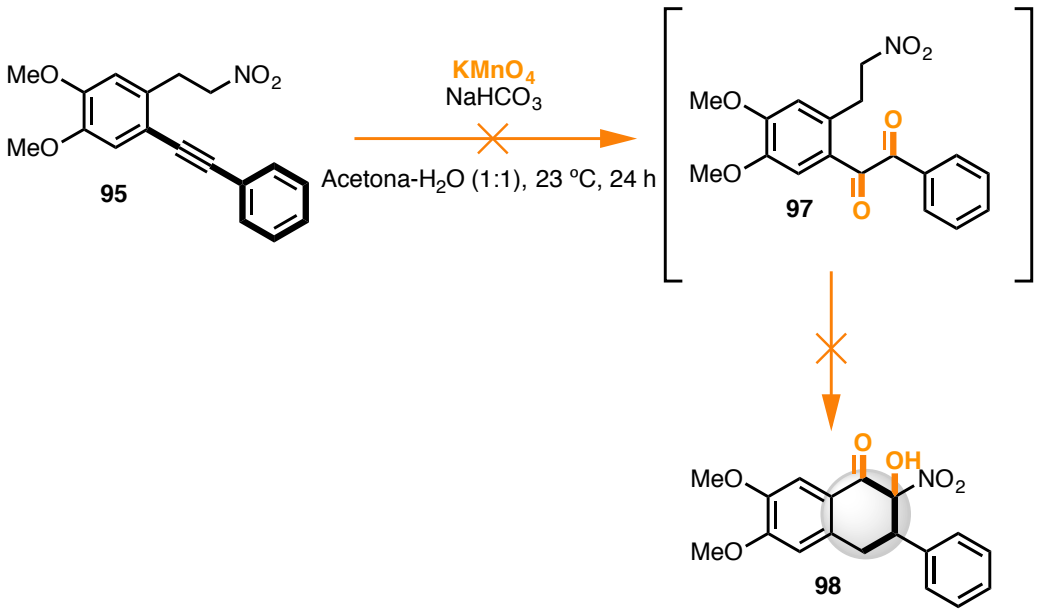
Yan propone la oxidación de alquinos en una reacción vía radical catalizada con el sistema cloruro de yodo y nitrato de plata. Donde empleamos al alquino **95** en presencia de ICl (0,5 equiv.) y $AgNO_3$ (3,0 equiv.), en acetonitrilo a 23 ºC y con un globo de aire en 4 horas de reacción (Ec. 13). Utilizando los mismos equivalentes que la metodología de Yan, se monitoreó cada hora hasta completar las 4 horas propuestas en su metodología sin observar el consumo de material de partida y monitoreó por 24 horas donde se observó la descomposición del material de partida, esto sustentado por los espectros de RMN de ^{1}H y ^{13}C. Por ello se decidió aumentar al doble los equivalentes de ICl y $AgNO_3$ y de nuevo se observó la descomposición del material de partida. Con base a los resultados se decidió implementar una nueva metodología.



III) Metodología de Yuvraj Satkar en 2020

Con base a los resultados obtenidos para la obtención de la Ningalina D durante sus estudios de doctorado del Dr. Yuvraj. Nos dimos a la tarea de reproducirlos con el fin de obtener el núcleo naftaleno de forma *in-situ* empleando permanganato de potasio y bicarbonato de sodio como base. Montamos la reacción con el 1,2-dimetoxi-4-(2-nitroetil)-5-(feniletinil)benceno **95**. Con 3 equivalentes del $KMnO_4$ y uno de bicarbonato de sodio, estos en acetona-agua (1:1) por 24 horas a 23 ºC y se obtuvo la descomposición de la materia prima, por lo que no fue posible la obtención del intermedio **97** y el naftaleno **98** (Ec. 14).

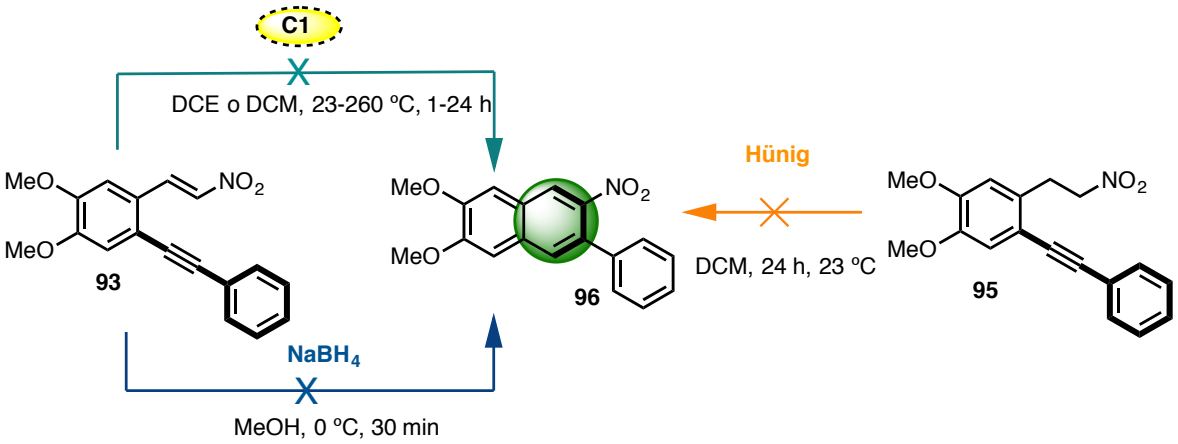
[64] Yang, W. Chen, Y. Yao, Y. Yang, X. Lin, Q. Yang, D. ICl/$AgNO_3$ Co-Catalyzed Radical Oxidation of Diaryl- and Alkylarylalkynes into 1,2-Diketones. *J. Org. Chem.* **2019**, *84*, 11080–11090. https://doi.org/10.1021/acs.joc.9b01667.


MeO
MeO
NO2
95
KMnO4
NaHCO3
Acetona-H2O (1:1), 23 °C, 24 h
NO2
MeO
MeO
O
O
97
O
OH
NO2
MeO
MeO
98

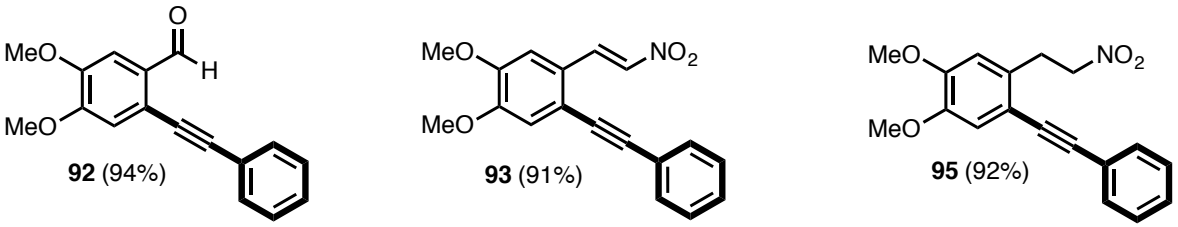
(14)

4.2 Conclusiones

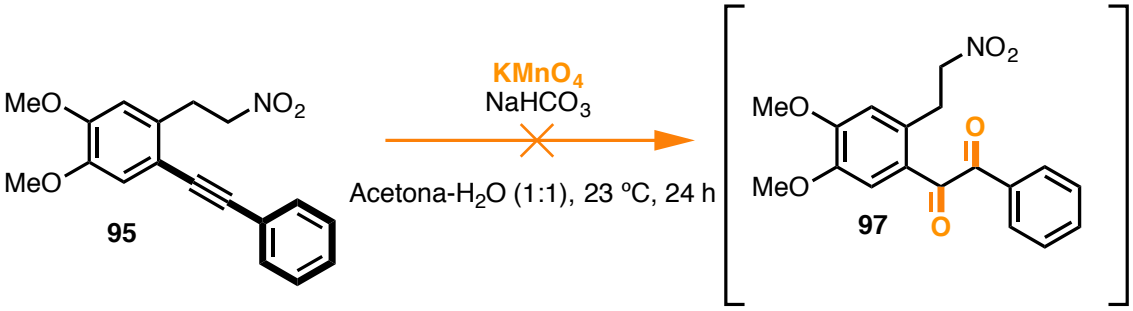
I. El poco tiempo que se dedico a la experimentación debido a la contingencia a causa de la COVID-19, fue el principal motivo por el cual se muestra sólo el avance para la obtención de del naftaleno de la Ningalina C, Pese a ello han obtenido resultados clave y contundentes sobre está nueva síntesis total de Ningalina C.



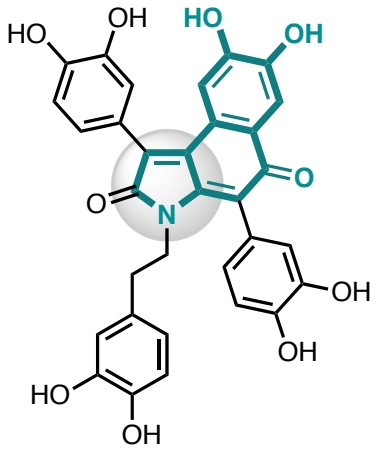
II. En nuestra propuesta hemos logrado la diversificación de posibles rutas a partir del veratraldehído **78** para la obtención de nuestro naftaleno. Con ello nos encargamos de encontrar la ruta sintética más eficiente y desde luego que emplee reacciones de alto interés sintético que sean reproducibles. Cabe resaltar que los rendimientos obtenidos hasta el momento han sido bastante buenos y moderados.



III. Pese al intento de reproducir los resultados del Dr. Yuvraj no fue posible la obtención de la oxidación del alquino **97** y la ciclación oxidativa obtenida *in situ* a través del intermedio 1,2-dicarbonilo **98**.



IV. Si bien Cho, Ruchirawat y Steglich ya describieron una síntesis total de Ningalina C nuestra propuesta cumple con la calidad e innovación necesaria que sustentan nuestra propuesta sintética. Pese a estos resultados no dudamos obtener la Ningalina C y sus análogos en un futuro cercano.

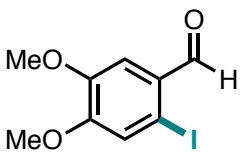


40 Ningalina C

4.3 Sección Experimental

Todas las reacciones sensibles a la humedad y al oxígeno se llevaron al cabo en matraces de fondo redondo secados al horno y purgados bajo atmósfera inerte. A menos que se especifique lo contrario, todos los materiales comerciales se usaron tal como se recibieron sin purificación adicional. Los disolventes anhidros se adquirieron de Sigma-Aldrich en botellas SureSeal. La cromatografía en columna se realizó usando gel de sílice de tamaños 100-200 y malla 230-400 (Sigma-Aldrich). La cromatografía en capa fina se realizó con placas de TLC gel de sílice 60 F256 y la visualización se efectuó con luz UV de longitud de onda corta (254 nm). Los compuestos se caracterizaron usando ^{1}H RMN y ^{13}C RMN. Los datos de compuestos conocidos se compararon con los datos de caracterización de la literatura existente, y se proporcionan las referencias. Los espectros de RMN de ^{1}H y ^{13}C se registraron con instrumentos de 500 MHz y Bruker advance de 125 MHz usando disolventes deuterados adquiridos de Sigma-Aldrich como $CDCl_3$. Los espectros de ^{1}H se referenciaron con tetrametilsilano (TMS, 0.0 ppm) o cloroformo ($CDCl_3$, 7.26 ppm) y se informan de la siguiente manera: desplazamiento químico, multiplicidad (s = singulete, d = doblete, t = triplete, q = cuarteto, m = multiplete), constante de acoplamiento (Hz) e integración. Se midieron los desplazamientos químicos de los espectros de RMN de ^{13}C con respecto a $CDCl_3$ (δ = 77,16 ppm). Todos los materiales de partida se sintetizaron de acuerdo con los procedimientos descritos en la bibliografía. Los análisis de masas de alta resolución (HRMS) se obtuvieron mediante el siguiente procedimiento: Las muestras se introdujeron mediante infusión directa a 3 µL min^{-1} en la fuente de ionización por electropulverización (ESI) de un espectrómetro de masas de tiempo de vuelo cuadrupolo (Bruker Daltonics ESI- QTOF-MS maXis impact), equipado con Data Analysis 4.1. El ESI se hizo funcionar en modo positivo con un voltaje de pulverización de iones de 4 500 V, gas seco de nitrógeno 4 L min^{-1}, temperatura de secado 180 °C y presión de gas 0,4 bar. La calibración de masa se realizó basándose en grupos de formiato de sodio. La nomenclatura química se generó usando Chemdraw. Los espectros infrarrojos (IR) se registraron usando un espectrómetro FT-IR 2000 del sistema PerkinElmer. Los puntos de fusión de los sólidos se midieron usando un aparato de punto de fusión Fisher-Johns.

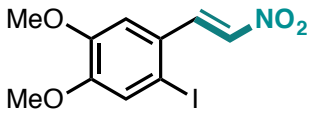
(90) 2-yodo-4,5-dimetoxibenzaldehido



En un matraz de 150 ml de fondo redondo secado al horno, purgado con Argón y equipado con un agitador magnético se cargo con 3,4-dimetoxibenzaldehído **78** (5,0 g, 0.03 mmol, 1,0 equiv.), $AgNO_3$

(9,45 g, 1,86 equiv.) y yodo (10,38 g, 1,0 equiv.) en metanol (100 ml). Se agito por toda la noche a temperatura ambiente, hasta que se consumió completamente el material de partida a juzgar por TLC. Al finalizar el exceso de yodo se eliminó con una solución saturada de tiosulfato de sodio y se extrajo la fase acuosa con DCM (3 x 25 ml), la fase orgánica se secó sobre Na_2SO_4 la cual se concentró a presión reducida y se colocó al vacío. Al final se aislaron 8,54 g (0.0292 mmol) de 2-yodo-4,5-dimetoxibenzaldehido **90,** con un rendimiento del 97% como un sólido amarillo paja. Los datos espectroscópicos de este compuesto coinciden con los descritos anteriormente.[65] R_f= 0,47 (20% AcOEt/Hexano) ^{1}H RMN (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.40 (s, 1H), 7.30 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H). ^{13}C RMN (125 MHz, $CDCl_3$) δ 194.74, 154.34, 149.63, 128.25, 121.66, 110.97, 92.61, 77.16, 76.91, 76.65, 56.36, 55.95.

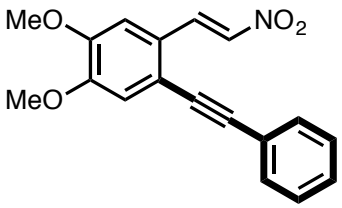
(70) (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno



En un matraz de 25 ml de fondo redondo secado al horno, purgado con Argón y equipado con un agitador magnético se cargó 5 ml de AcOH. Posterior a eso se agrego 2-yodo-4,5-dimetoxibenzaldehído **90** (2,0 g, 0.0017 mmol, 1,0 equiv.) y NH_4Oac (0,528 g, 1,0 equiv.). Después de disolver y obtener una mezcla homogénea, se agregó gota a gota el $MeNO_2$ (5,180 ml, 14,0 equiv.). Para después colocar el matraz a reflujo a temperatura de 90-100 ºC en agitación durante una hora. Una vez completada la reacción determinada por análisis de TLC, se detuvo la reacción y se agregaron 15 ml de agua fría y se observó un precipitado amarillo. Se realizó un filtrado al vacío empleando agua, se concentró el sólido amarillo el cual se dejó secar y se colocó al vacío. Al final se aislaron 2,12 g (0.0063 mmol) de (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno **79,** con un rendimiento del 92% como un sólido amarillo brillante. R_f= 0,18 (10% AcOEt/Hexano). IR (neat) v/cm^{-1}= 3092,1659, 1486, 1334, 1204, 952, 838. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 13.4 Hz, 1H), 7.44 (d, *J* = 13.4 Hz, 1H), 7.33 (s, 1H), 6.98 (s, 1H), 3.91 (d, *J* = 8.0 Hz, 6H). ^{13}C RMN (125 MHz, $CDCl_3$) δ 152.63, 149.75, 142.46, 137.14, 125.69, 122.33, 109.40, 93.62, 56.39, 56.13. HRMS (ESI): m/z calculado para $C_{10}H_{11}INO_4$ $[M+H]^+$= 335,9733, encontrado 335,9812.

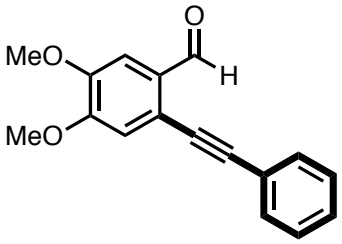
(93) (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno

[65] Moorthy, J. N. Senapati, K. Kumar, S. IBX−I_2 Redox Couple for Facile Generation of IOH and I^+: Expedient Protocol for Iodohydroxylation of Olefins and Iodination of Aromatics. *J. Org. Chem.* **2009**, *74*, 6287–6290. https://doi.org/10.1021/jo9007892.



En un matraz de 50 ml de fondo redondo secado al horno, purgado con Argón y equipado con un agitador magnético se cargó con (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno **79** (0,5 g, 0.0068 mmol, 1,0 equiv.) en 15 ml de Et_3N y se agitó por 10 min a 60 ºC. Después se agregó CuI (0,0065 g, 2 mol%) y $Pd(PPh_3)_3Cl_3$ (0,048 g, 4 mol%) por 10 min manteniendo la temperatura y posteriormente se agregó fenilacetileno **91** (0,131 ml, 1,2 equiv.) gota a gota. La mezcla se agitó a 60 ºC durante 3 horas. Una vez completada la reacción, determinada por análisis de TLC, se detuvo la reacción, se dejó enfriar a temperatura ambiente y se agregaron 15 ml de agua. Se extrajo la fase acuosa con DCM (3 x 25 ml), la fase orgánica se secó sobre Na_2SO_4 la cual se concentró a presión reducida. Se purificó mediante cromatografía en columna sobre sílice gel con el sistema 15% AcOEt/Hexano. Al final se aislaron 0,481 g (0.0015 mmol) de (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(feniletinil)benceno **93**, con un rendimiento del 91% como un sólido naranja. Los datos espectroscópicos de este compuesto coinciden con los descritos anteriormente.[66] R_f= 0,18 (10% AcOEt/Hexano). ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 13.6 Hz, 1H), 7.73 (d, *J* = 13.6 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.40 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.08 (s, 1H), 6.99 (s, 1H), 3.96 (d, *J* = 8.8 Hz, 6H). ^{13}C RMN (125 MHz, $CDCl_3$) δ 152.12, 149.69, 137.30, 136.37, 131.56, 128.96, 128.58, 124.51, 122.40, 119.70, 114.77, 109.07, 95.95, 86.37, 56.24, 56.13.

(94) 4,5-dimetoxi-2-(feniletinil)benzaldehído



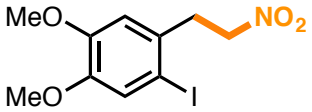
En un matraz de 50 ml de fondo redondo secado al horno, purgado con Argón y equipado con un agitador magnético se cargó con 4,5-dimetoxi-2-(feniletinil)benzaldehído **90** (0,5 g, 0.0017 mmol, 1,0 equiv.) en 15 ml de Et_3N y se agitó por 10 min a 60 ºC. Después se agregó CuI (0,0065 g, 1 mol%) y $Pd(PPh_3)_3Cl_3$ (0,048 g, 3 mol%) por 10 min manteniendo la temperatura y posteriormente se agregó fenilacetileno **91** (0,131 ml, 1,2 equiv.) gota a gota. La mezcla se agitó a 60 ºC durante 3 horas. Una vez completada la reacción, determinada por análisis de TLC, se detuvo la reacción, se dejó enfriar

[66] Arigela, R. K. Samala, S. Mahar, R. Shukla, S. K. Kundu, B. Synthesis of Triazolo Isoquinolines and Isochromenes from 2-Alkynylbenzaldehyde via Domino Reactions under Transition-Metal-Free Conditions. *J. Org. Chem.* **2013**, *78*, 10476–10484. https://doi.org/10.1021/jo401929q.

a temperatura ambiente y se agregaron 15 ml de agua. Se extrajo la fase acuosa con DCM (3 x 25 ml), la fase orgánica se secó sobre Na_2SO_4 la cual se concentró a presión reducida. Se purificó mediante cromatografía en columna sobre sílice gel con el sistema Hexano. Al final se aislaron 0,43 g (0.0016 mmol) de 4,5-dimetoxi-2-(feniletinil)benzaldehído **92**, con un rendimiento del 91% como un sólido amarillo. Los datos espectroscópicos de este compuesto coinciden con los descritos anteriormente.[67] R_f= 0,48 (10% AcOEt/Hexano).

^{1}H RMN (500 MHz, $CDCl_3$) 10.50 (s, 1H), 7.58 – 7.52 (m, 2H), 7.43 (s, 1H), 7.41 – 7.32 (m, 3H), 7.06 (s, 1H), 3.97 (d, *J* = 16.4 Hz, 6H). ^{13}C RMN (125 MHz, $CDCl_3$) δ 190.34, 153.54, 149.64, 131.44, 130.06, 128.78, 128.41, 122.35, 121.47, 114.18, 108.11, 94.86, 84.71, 56.21, 56.03.

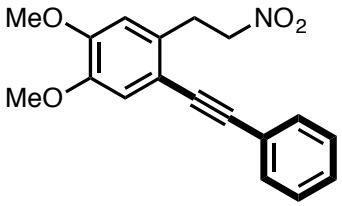
(94) 1-yodo-4,5-dimetoxi-2-(2-nitroetil)benceno



En un matraz de 50 ml de fondo redondo secado al horno, purgado con Argón y equipado con un agitador magnético se cargó 25 ml de MeOH. Posterior a eso se agregó (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno **79** (2,0 g, 0,0059 mmol, 1 equiv.) y se dejo 15 min a 0 ºC. Después de disolver y obtener una mezcla homogénea, se agregó gota a gota una solución de 10 ml de metanol con $NaBH_4$ (2,70 g, 0,0716 mmol, 12 equiv.). Posterior a ellos se mantuvo a 0 ºC en agitación durante una hora. Una vez completada la reacción, determinada por análisis de TLC, se agregó una solución saturada de NH_4Cl para inactivarla y se extrajo la fase acuosa con DCM (3 x 25 ml), la fase orgánica se secó sobre Na_2SO_4 la cual se concentró a presión reducida. Se purificó mediante cromatografía en columna sobre sílice gel con el sistema 5% AcOEt/Hexano. Al final se aislaron 1,493 g (0,0044 mmol) de 1-yodo-4,5-dimetoxi-2-(2-nitroetil)benceno **94,** con un rendimiento del 74% como un sólido naranja. R_f= 0,58 (10% AcOEt/Hexano). IR (neat) v/cm^{-1}= 3022, 2960, 2848, 1600, 1492, 756, 690. ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.74 (s, 1H), 4.59 (t, *J* = 7.4 Hz, 2H), 3.85 (d, *J* = 2.4 Hz, 6H), 3.37 (t, *J* = 7.4 Hz, 2H). ^{13}C RMN (125 MHz, $CDCl_3$) δ 149.17, 148.50, 130.10, 121.46, 112.43, 87.31, 74.42, 55.75, 55.56, 37.41. HRMS (ESI): m/z calculado para $C_{18}H_{18}NO_4$ $[M+H]^+$= 312.1236, encontrado 312.1248.

(95) 1,2-dimetoxi-4-(2-nitroetil)-5-(feniletinil)benceno

[67] Yu, S. Wu, J. He, X. Shang, Y. Ferrocenyl Bisoxazoline as an Efficient Non-phosphorus Ligand for Palladium-catalyzed Copper-free Sonogashira Reaction in Aqueous Solution. *Appl. Organometal. Chem.* **2017**, *32*, 4156. https://doi.org/10.1002/aoc.4156.



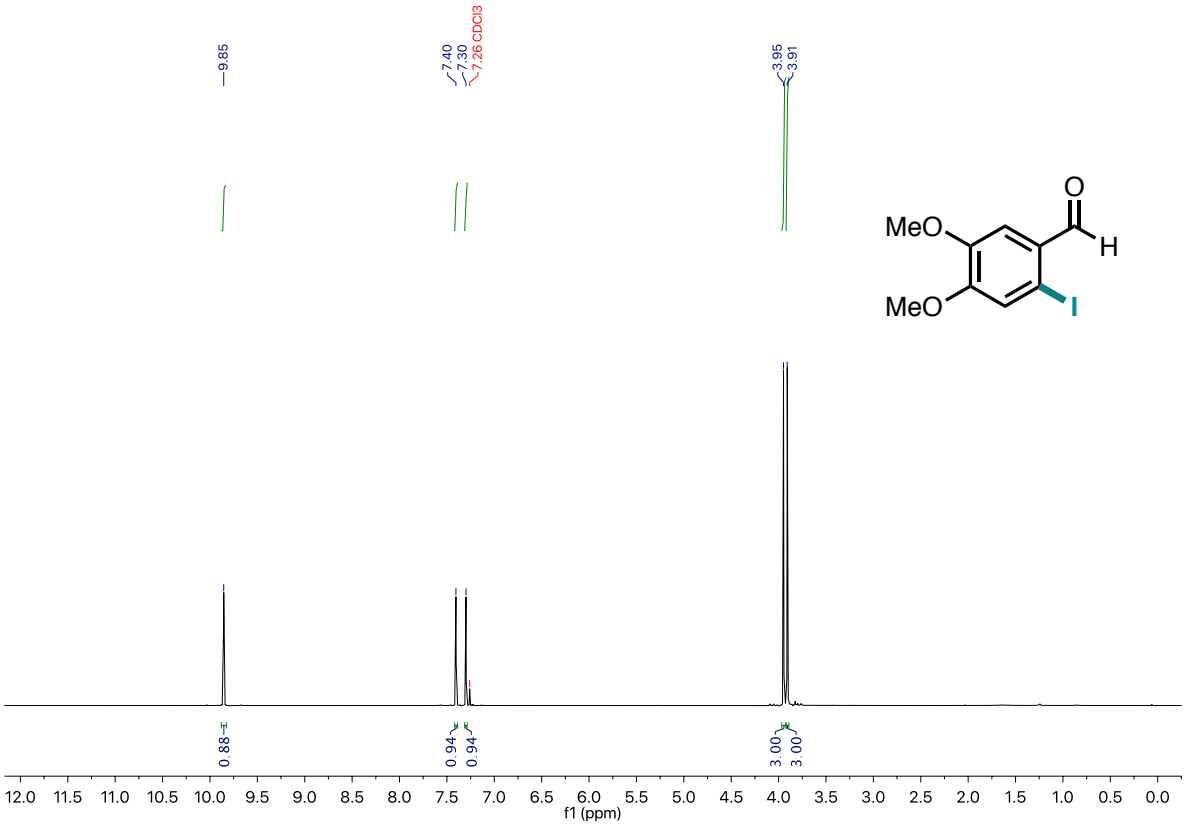
En un matraz de 50 ml de fondo redondo secado al horno, purgado con Argón y equipado con un agitador magnético se cargó con 1-yodo-4,5-dimetoxi-2-(2-nitroetil)benceno **94** (1,0 g, 0,0029 mmol, 1,0 equiv.) en 15 ml de Et_3N y se agitó por 10 min a 60 ºC. Después se agregó CuI (0,0056 g, 1 mol%) y $Pd(PPh_3)_3Cl_3$ (0,0624 g, 3 mol%) por 10 min manteniendo la temperatura y posteriormente se agregó fenilacetileno (0,3909 ml, 1,2 equiv.) gota a gota. La mezcla se agitó a 60 ºC durante 3 horas. Una vez completada la reacción, determinada por análisis de TLC, se detuvo la reacción, se dejó enfriar a temperatura ambiente y se agregaron 15 ml de agua. Se extrajo la fase acuosa con DCM (3 x 25 ml), la fase orgánica se secó sobre Na_2SO_4 la cual se concentró a presión reducida. Se purificó mediante cromatografía en columna sobre sílice gel con el sistema 5% AcOEt/Hexano. Al final se aislaron 0,8510 g (0,0027 mmol) de 1,2-dimetoxi-4-(2-nitroetil)-5-(feniletinil)benceno **95**, con un rendimiento del 92% como un sólido amarillo café. R_f= 0,32 (20% AcOEt/Hexano). IR (neat) v/cm^{-1}= 3022, 2960, 2848, 1600, 1492, 756, 690. ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.6, 2.1 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.03 (s, 1H), 6.74 (s, 1H), 4.72 (t, *J* = 7.5 Hz, 2H), 3.90 (s, 6H), 3.50 (t, *J* = 7.5 Hz, 2H). ^{13}C RMN (125 MHz, $CDCl_3$) δ 150.01, 148.50, 131.78, 131.02, 128.89, 128.84, 123.34, 115.23, 115.17, 112.89, 93.39, 87.26, 75.75, 56.45, 56.42, 33.07. HRMS (ESI): m/z calculado para $C_{18}H_{18}NO_4$ $[M+H]^+$= 312.1236, encontrado 312.1248.

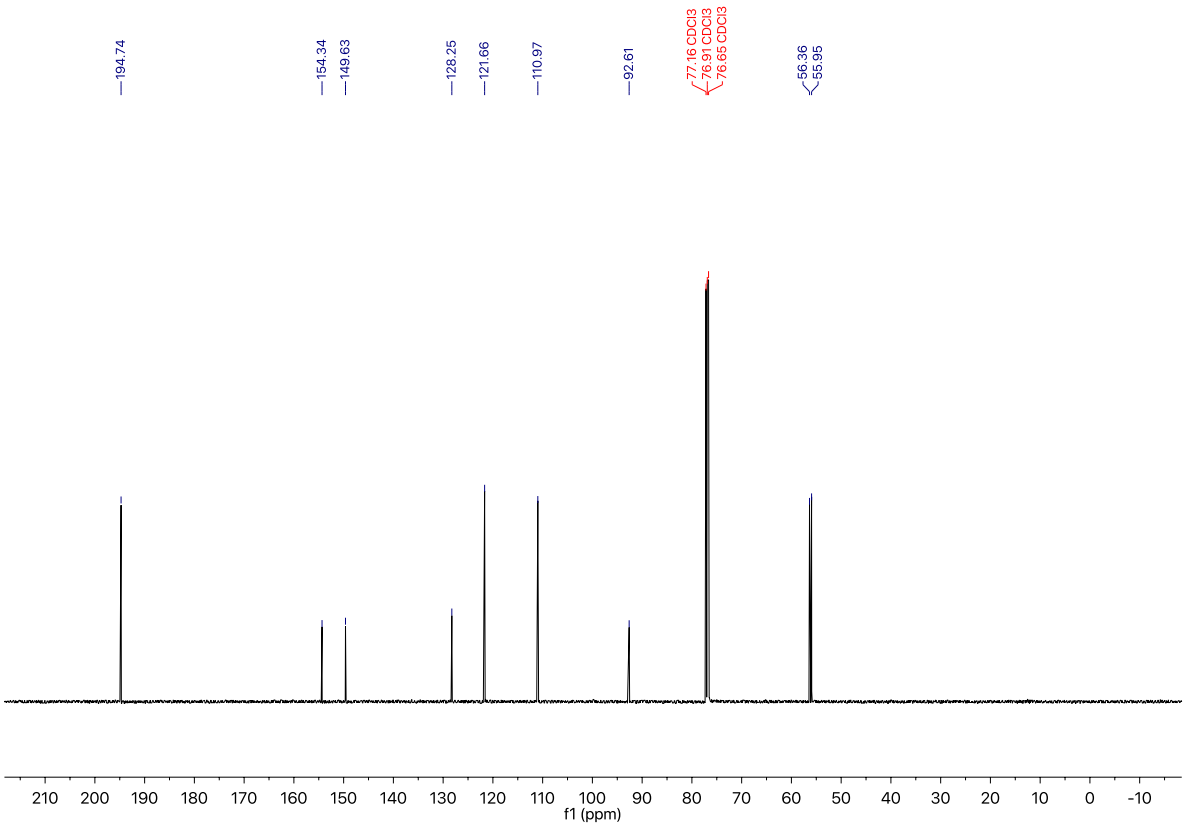
Anexos

Anexo A

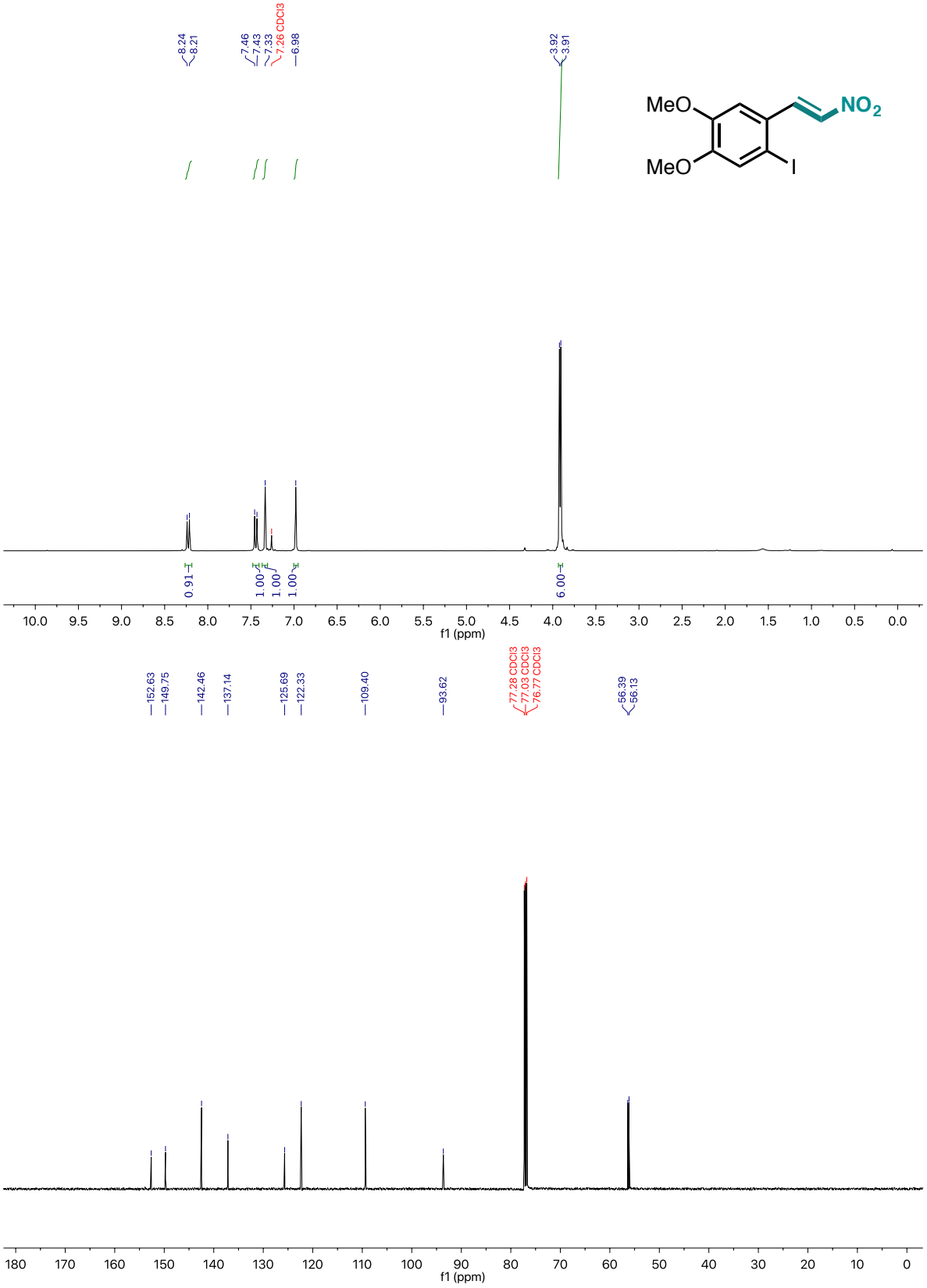
Copias de los espectros de ^{1}H y ^{13}C de RMN del capítulo IV

(90) 2-yodo-4,5-dimetoxibenzaldehido

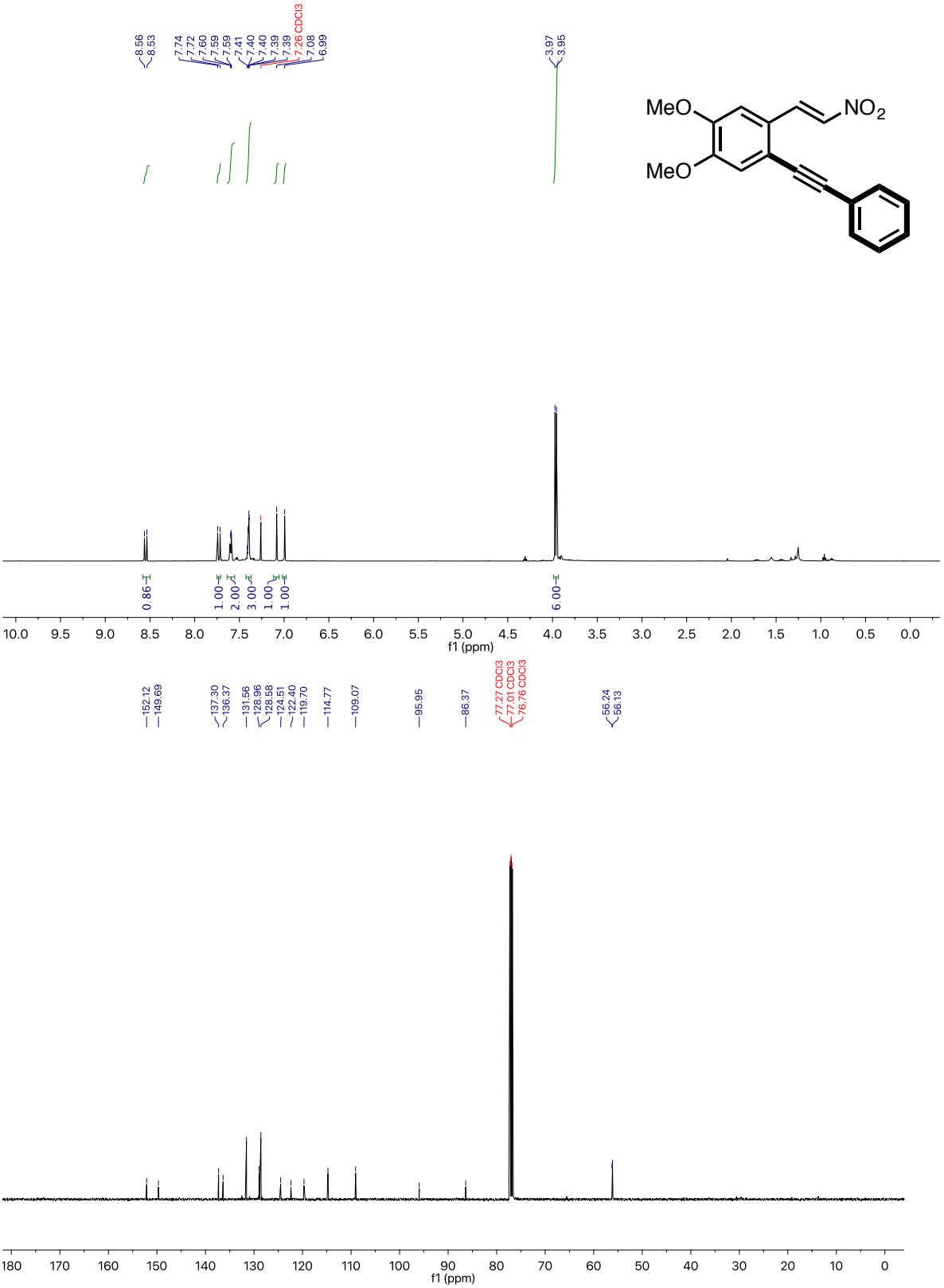




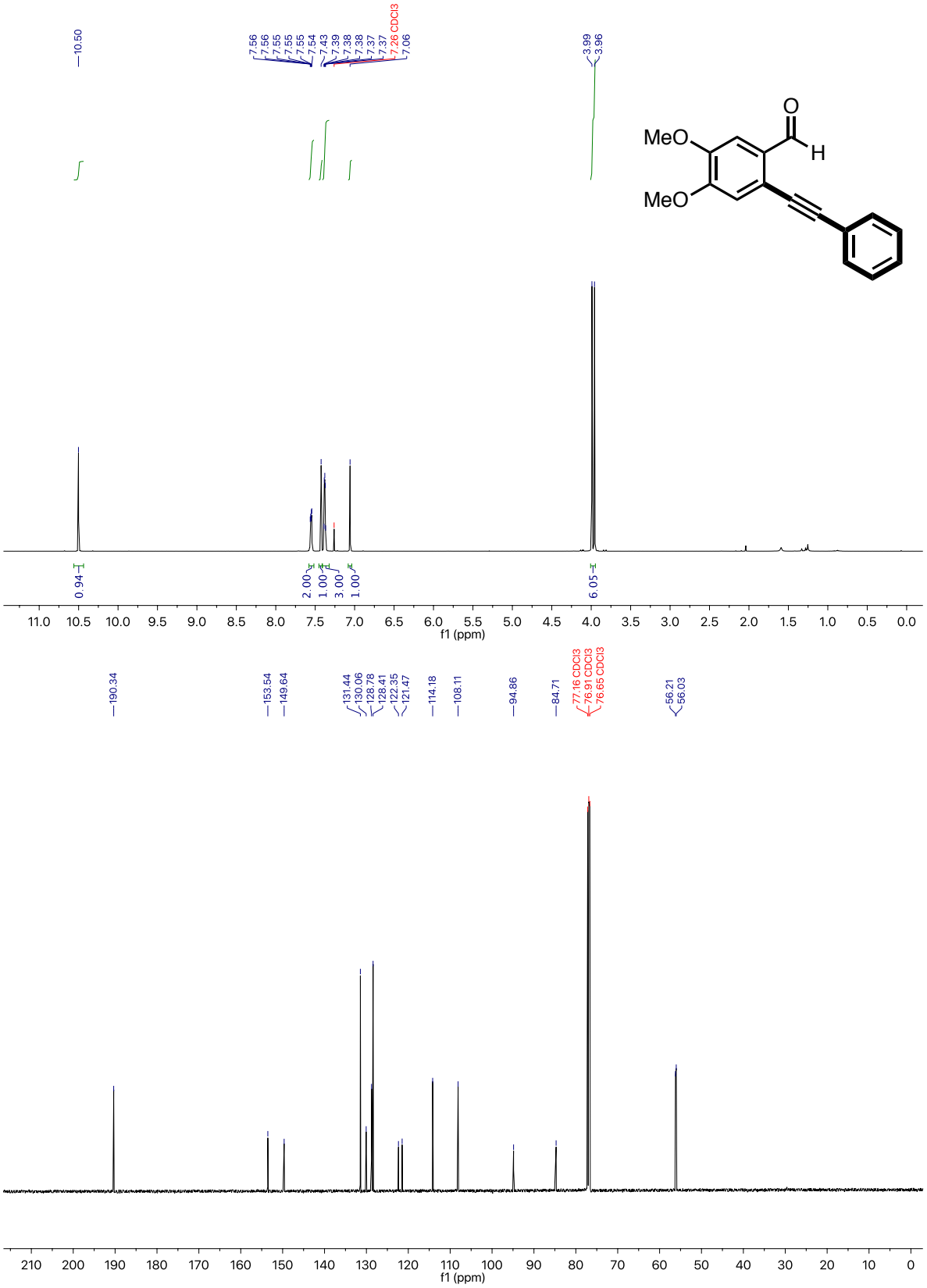
(79) (*E*)-1-yodo-4,5-dimetoxi-2-(2-nitrovinil)benceno



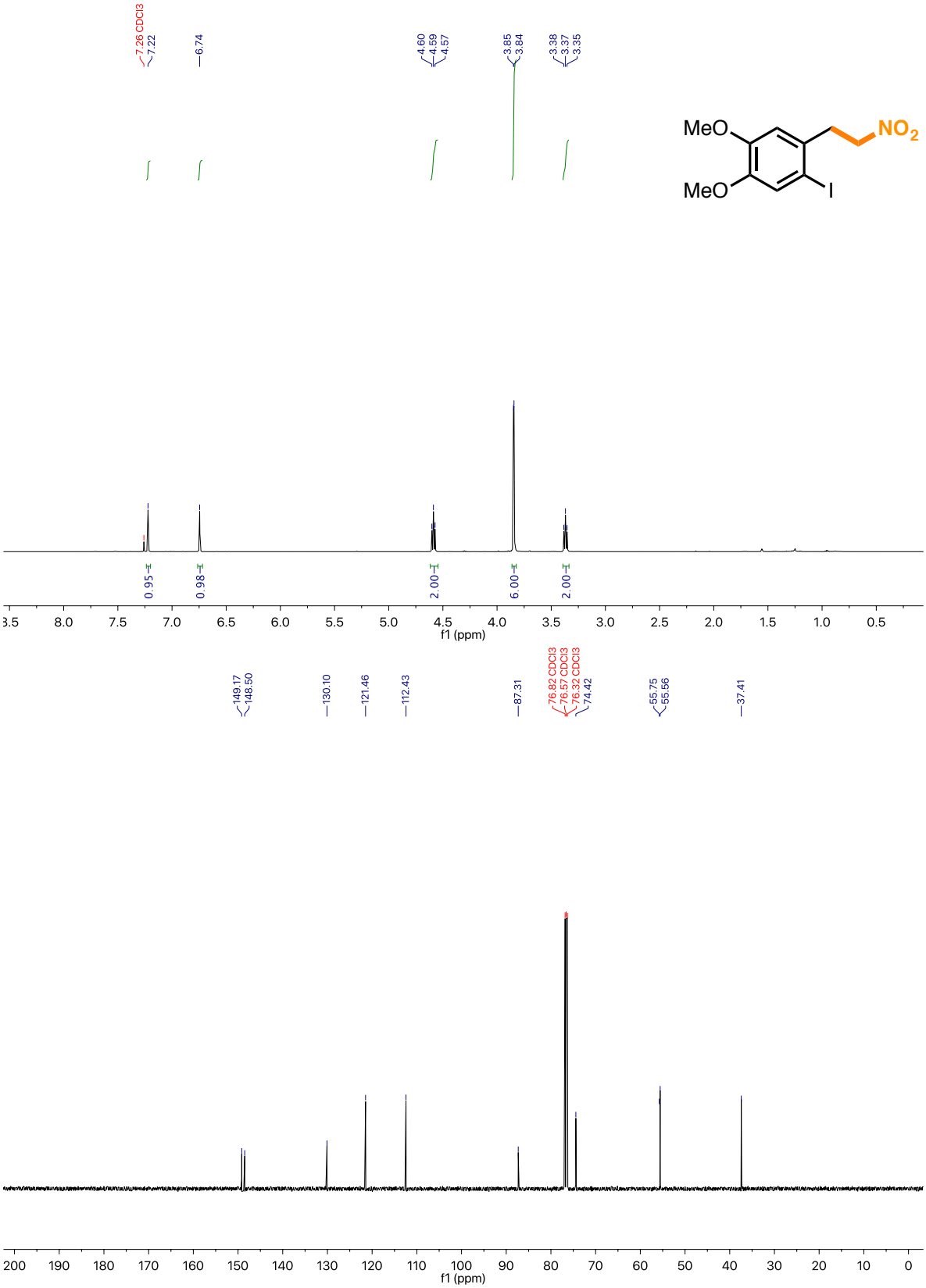
(93) (*E*)-1,2-dimetoxi-4-(2-nitrovinil)-5-(phenylethynyl)benzene



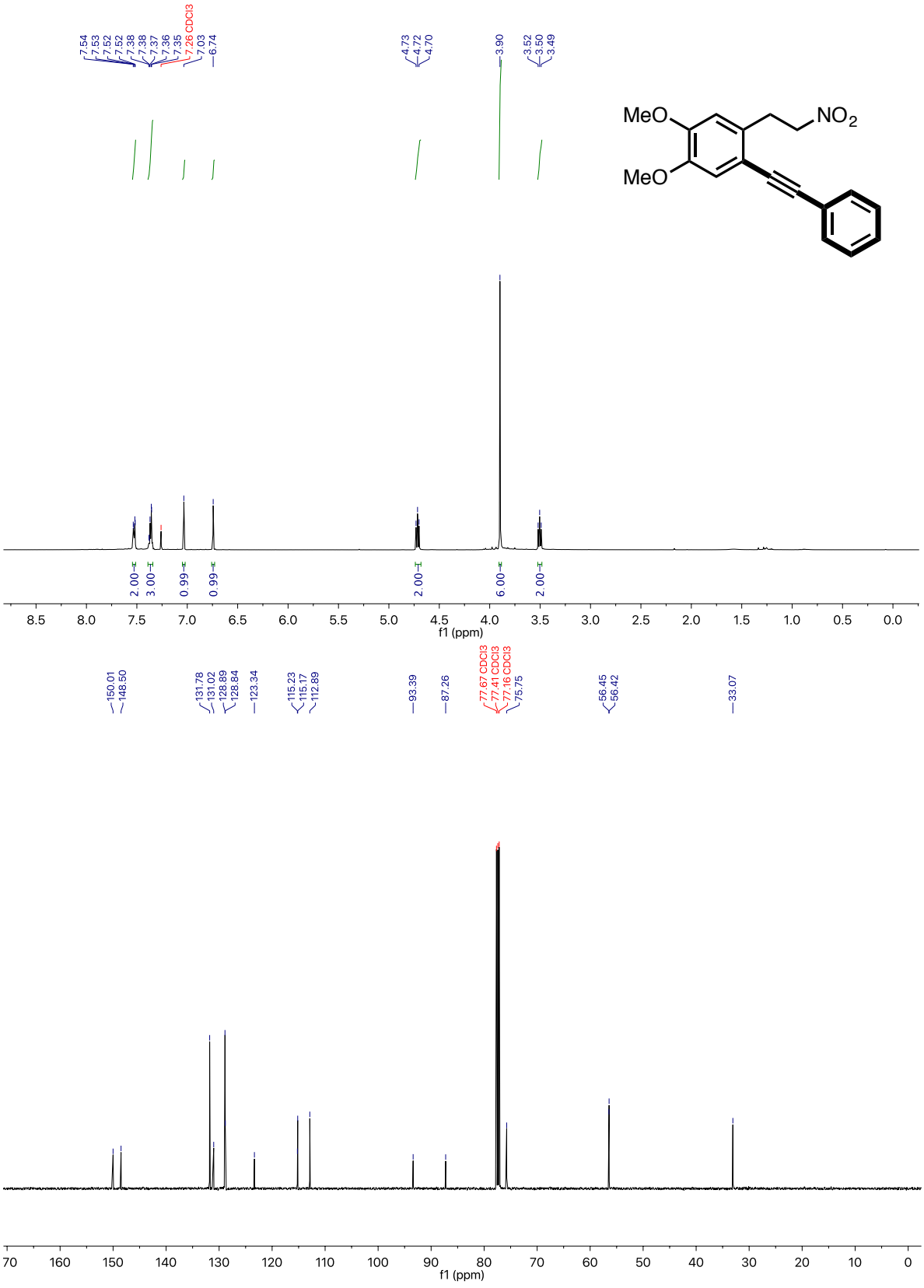
(92) 4,5-dimetoxi-2-(feniletinil)bezaldehído



(94) 4,5-dimetoxi-2-(feniletinil)bezaldehído



(95) 1,2-dimetoxi-4-(2-nitroetil)-5-(feniletinil)benceno



Anexo B

Copias de distinciones y manuscritos publicados

MES DE LA Juventud 2019

SAN FRANCISCO DEL RINCÓN 2018-2021 Ciudad de Confianza y Emprendimiento

El Honorable Ayuntamiento a través de la Coordinación de Atención a la Juventud, otorgan este Reconocimiento a:

Luis Alberto Segura Quezada

Por su desempeño y valiosa participación en el

PREMIO MUNICIPAL DE LA JUVENTUD 2019

CIENCIA Y TECNOLOGÍA

C.P. Javier Casillas Saldaña
Presidente Municipal

C. Laura Francisca Sánchez Chavez
Coordinadora de Atención a la Juventud

UNIVERSIDAD DE GUANAJUATO

La Universidad de Guanajuato
otorga la presente

CONSTANCIA

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en el 6to Encuentro Anual de Estudiantes: Investigación e Innovación en la DCNE,
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HALÓGENOS, UNA HISTORIA PERIÓDICA

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RESUMEN: Uno de los medios para organizar la disciplina de muchos científicos a lo largo de la historia y que continuará siendo la base de muchos argumentos, es la tabla periódica. Clasificando los elementos como metaloides, tierras raras, metales y no metales, entre los que destacan los "halógenos" uno de los grupos de elementos de dicha tabla más importantes en la química orgánica. Muchas de las propiedades químicas de los elementos se basan en su configuración electrónica, dando con ello similitud entre elementos adyacentes pertenecientes al mismo grupo. El esfuerzo de los científicos del siglo XIX para sistematizar la química de los elementos, era refutable pero acertado.

ABSTRACT: One of the main strategies to organize the chemistry areas by the scientist during the history and which it will be continuing the base of many arguments, es the periodic table. Classifying the elements as metalloids, rare earth, metals and non-metals, among the more representatives are the "halogens", which is one of the more important group in organic chemistry. A lot of the chemical properties of the elements are based on their electronic configuration, which gives similarities among the contiguous elements in the same group. The effort of the scientists of the XIX century to organize the chemistry of the elements were refutable nevertheless successful.

Palabras Clave: Halógenos, Tabla Periódica, Descubrimiento de elementos

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1. INTRODUCCIÓN

Los halógenos correspondientes al grupo 17 o 7A son uno de los elementos de mayor importancia en la química orgánica, siendo estos los partícipes de reacciones y síntesis orgánica en los laboratorios [Petrucci y Bissonnette, 2011]. Organizándose acorde a su masa molar y electronegatividad, nos ayudan a entender el porqué de las reacciones, por ende, la manera en la que estos participan para que la reacciones se lleven a cabo.

2. PROPIEDADES PERIÓDICAS DE LOS HALÓGENOS

Flúor

- Punto de ebullición (pe): 85°K.
- Punto de fusión (pf): 53°K
- Configuración electrónica: $[He]2s^2 2p^5$
- Radio atómico (Å): -
- Radio iónico (Å):1,36
- Radio covalente (Å): 0,72
- 1.ª Energía de ionización: 1681,0 $Kj \cdot mol^{-1}$
- Electronegatividad: 4.0
- Afinidad Electrónica: 328 $Kj \cdot mol^{-1}$

Cloro

- Configuración electrónica: $[Ne]3s^2 3p^5$
- Radio atómico (Å): -
- Radio iónico (Å): 1,81
- Radio covalente (Å): 0,99
- Energía de ionización: 1251,2 Kj·mol-1
- Electronegatividad: 3.0
- Afinidad electrónica: 349 Kj·mol-1

Bromo

- Configuración electrónica: [Ar] $3d^{10}\ 4s^2\ 4p^5$
- Radio atómico (Å): -
- Radio iónico (Å): 1,95 (-1), 0,39 (+7)
- Radio covalente (Å): 1,14
- Energía de ionización: 1140 $Kj \cdot mol^{-1}$
- Electronegatividad: 2.96
- Afinidad electrónica: 325 $Kj \cdot mol^{-1}$

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Yodo

- Configuración electrónica: $[Kr]4d^{10}5s^{2}5p^{5}$
- Radio atómico (Å): -
- Radio iónico (Å): 2,16
- Radio covalente (Å): 1,33
- Energía de ionización: 1008,4 $Kj{\cdot}mol^{-1}$
- Electronegatividad: 2.5
- Afinidad electrónica: 295,2 $Kj{\cdot}mol^{-1}$

Astato

- Configuración electrónica: $[Xe]4f^{14}5d^{10}6s^{2}6p^{5}$
- Radio atómico (Å): -
- Radio iónico (Å): -
- Radio covalente (Å): -
- Energía de ionización: 920 Kj·mol-1
- Electronegatividad: 2.0
- Afinidad electrónica: 270,2 $Kj{\cdot}mol^{-1}$

3. DESCUBRIMIENTO DE LOS HALÓGENOS

Flúor

Muchos fueron los intentos de obtener el flúor en su forma más pura, pero no se tuvo éxito alguno, debido a su alta reactividad que cobró la vida de varios químicos, a los cuales se les conoce como "mártires del flúor" [Quiñones y Estrada, 2014]. Esto no fue motivo suficiente como para que científicos predecesores analizaran las técnicas empleadas para su obtención, tal es el caso de Edmond Frémy quien en 1884 intentó aislarlo mediante electrólisis y fue el primero en obtener ácido fluorhídrico puro, pero no cumpliendo el objetivo principal.

Dos años más tarde, el aprendiz de Edmon Frémy, Henri Moissan continuó con el intento mediante técnicas de electrólisis del fluoruro de hidrógeno combinado con KF, mediante el uso de una celda electrolítica, para ello colocó un cátodo de cobre y ánodo de níquel, logrando aislar el elemento flúor (Fig. 1.) en su forma pura [Quiñones y Estrada, 2014].

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Figura 1. Fluorita fuente natural del flúor.

Cloro

Carl Wilhelm Scheele siendo el descubridor del oxígeno y con el fin de seguir trabajando en su obtención mediante otros métodos químicos, hizo reaccionar pirolusita MnO_2 con ácido clorhídrico;

$$MnO_2 + 4HCl \longrightarrow Cl_2 + MnCl_2 + 2H_2O$$

Sin embargo, al realizar dicha reacción en 1774 obtuvo al elemento cloro (Fig. 2.) sin darse cuenta [Quiñones y Estrada, 2014]. Como muchos de los científicos investigadores, Scheele trabajaba bajo condiciones muy peligrosas y tenía el hábito de probar las sustancias que descubría, por lo que al estar trabajando con mercurio sufrió intoxicación, lo que causó su muerte.

Figura 2. Salmuera fuente natural del cloro.

Yodo

Para el año 1811, Bernardo Courtois era hijo de un fabricante de salitre (sal obtenida del $NaNO_3$/KCl usado en la fabricación de pólvora negra), el cual ayudaba a su padre recolectando residuos de algas con el fin de obtener KNO_3 [Quiñones y Estrada, 2014]. Al quemar estas mismas, extraía sus cenizas con agua y posteriormente las purificaba por cristalización fraccionada, al terminar quedaban impurezas de azufre las cuales eliminaba calentándolas con H_2SO_4, pero al ser un joven innovador y curioso añadió un exceso de ácido y observó que

se desprendían vapores que condensaban como cristales en forma de agujas violetas y con un brillo un tanto metálico [Quiñones y Estrada, 2014].

Quizá se pregunten… ¿Por qué usaba algas?

Estas tenían la particularidad de extraer iones del yodo (Fig. 3.) que se encontraba presente en el mar.

Como se trataba de un joven que ayudaba en las labores de su padre, no pudo continuar con su investigación por lo que cedió a sus amigos Desormes y Clément su descubrimiento, los cuales en 1813 anunciaron el descubrimiento de dicha sustancia sin desacreditar a su verdadero descubridor y amigo. Dicha noticia llega a oídos de Davy y Gay Lussac los cuales demostraron que se trataba de un nuevo elemento químico [Quiñones y Estrada, 2014]. Lussac al observar los vapores violetas que habían llamado la atención del joven Courtois nombra a dicho elemento como "Iodine" del griego (violeta).

Figura 3. Yodo puro.

Bromo

Simplemente una historia peculiar…

Como se darán cuenta, al prestar atención al descubrimiento del Yodo, comprenderán mejor la siguiente anécdota.

En 1825 Antonio Balard quiso perfeccionar el trabajo hecho por Courtois, obteniendo el yodo de manera diferente. A partir de los residuos de ceniza salina, empleaba extracción fraccionada, pero en ciertas fracciones se encontraba con un liquido rojizo con un aroma fuerte similar al cloro y desagradable, por lo que a su mente llego que se trataba de una mezcla de yodo y cloro [Anónimo, 2016].

Años antes el científico Liebig había estudiado este líquido, pero jamás le dio

la mínima importancia y lo dejó en un armario.

Balard prosiguió con su investigación ya que, al actuar agua y almidón sobre la disolución procedente de las cenizas de algas marinas, se formaban dos capas: la inferior de color azul (haciendo la suposición de que se trataba del yodo) y la superior (líquida y de tono rojizo). El informe acerca del nuevo descubrimiento llega a la Academia de Ciencias y nombraron al nuevo elemento como Bromo (Fig. 4) el cual se deriva del griego "Bromos (mal olor)" [Anónimo, 2016].

Liebig al saber del nuevo elemento de Balard corrió a su armario donde había quedado en el olvido aquel líquido, del cual hubiera sido el descubridor si no se hubiera anticipado a conclusiones, por lo que a dicho armario lo llamo "armario de las equivocaciones". Tiempo después Liebig redactó la siguiente frase "No fue Balard quien descubrió el bromo, sino el bromo lo descubrió a él".

Figura 4. Bromo

Astato

Este elemento es el más joven de los halógenos, ya que su descubrimiento fue en 1940 por los científicos Dale R. Corson, Ross Mackenzie y Gino Segré, los cuales mediante un ciclotrón bombardearon fragmentos de Bi con partículas alfa aislando dicho elemento [Fernando Pino, 2015]. Sus descubridores le otorgaron el nombre hoy conocido "Astato (inestable)" (Fig. 5.) en base a que se trata del halógeno más pesado y de los más inestables, por ende, es altamente radioactivo y poco se sabe de el.

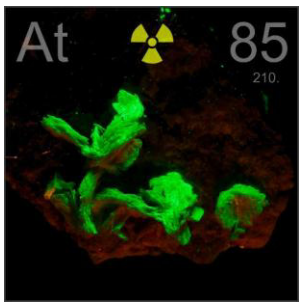

Figura 5. Astato

4. FUENTES NATURALES DE LOS HALÓGENOS Y SUS APLICACIONES

Previo a ello, es necesario recordar que debido a la ata reactividad de los halógenos, estos se encuentran en la naturaleza únicamente formando compuestos [Shriver y Atkins, 2008].

Flúor

El flúor se encuentra presente en la corteza terrestre en minerales como la fluorita (CaF_2), criolita (Na_3AlF_6) y las fluoroapatitas ($Ca_5(PO_4)_3$). Como sabemos, el flúor es el elemento oxidante de mayor fuerza, por lo que su obtención a partir de sus compuestos no podría realizarse con una oxidación con otro elemento [Shriver y Atkins, 2008].

Usos industriales

- Fabricación del sólido UF_6 empleado para procesar combustible nuclear.
- SF_6 usado como gas aislante en dispositivos eléctricos de alto voltaje.
- HF empleado para el grabado de vidrios y la producción de teflón.
- CF_3CH_2F como refrigerante en el aire acondicionado (no contaminante).
- Presente en pastas dentales.

Cloro

Se encuentran principalmente como NaCl en mares y lagos salinos, para obtenerlo de manera pura se requiere de métodos como la electrólisis, en el cual se implementa sal de roca fundida o mejor conocida como “salmuera” [Albert y Geoffrey, 2000].

Usos industriales

- Empleado en productos blanqueadores (papel, textiles) y desinfectantes.
- El $KClO_3$ se usa en la cabeza de los cerillos junto con otros compuestos que generan fricción.
- Producción de plásticos como el PVC y PVDC.
- En la química orgánica empleado como catalizador para la obtención de polietileno y polipropileno.
- En la metalurgia se emplea para la fabricación de Ti (cohetes), Al, Mg, Ni y Si en forma pura.

Bromo

Naturalmente se encuentra formando bromuros alcalinos y alcalinotérreos [Albert y Geoffrey, 2000].

- Empleado en la síntesis orgánica.
- Los bromuros orgánicos son usados como pesticidas y los inorgánicos son empleados en la revelación de fotografías.
- En la industria farmacéutica, tal como en el tratamiento contra la epilepsia y como sedante.
- Usado como aditivo en la gasolina que tenían como antidetonante $(CH_3CH_2)_4Pb$.

Yodo

Se encuentra formando los yodatos de sodio ($NaIO_3$) y de potasio (KIO_3) en lugares con nitratos de metales alcalinos [Shriver y Atkins, 2008]. Recordando también su presencia en las algas marinas como se había mencionado en su descubrimiento. Sin embargo, la manera actual de obtenerlo es mediante salmueras[1] de pozos petrolíferos [Atkins y Jones, 2012].

1. Salmueras: Agua saturada de sal.

Usos industriales

- El yodo como tal cuenta con pocos usos, sin embargo, disuelto en EtOH es empleado como antiséptico.
- Yoduros agregados a la sal de mesa "sales yodadas" esto debido a que el yodo es un elemento esencial para los seres vivos.

Astato

Se obtiene mediante la desintegración de U y Th. Este elemento posee alrededor de 20 isótopos, por lo que su tiempo de vida es de aproximadamente 7.5 horas, desintegrándose debido a la captura electrónica y por emisiones alfa [Shriver y Atkins, 2008]. Debido a su corto tiempo de vida, resulta imposible obtener grandes cantidades de este elemento.

Usos industriales

Como se ha mencionado previamente el At tiene un tiempo de vida media corto, por lo que aún no se han denotado usos implementados con certeza, caso de ello es su empleo para atacar células cancerosas.

5. LOS HALÓGENOS COMO HOY LOS CONOCEMOS

Si bien se recuerda en el año de 1869 Dmitri Mendeleev y Lothar Meyer propusieron la ley periódica, los trabajos realizados por Mendeleev fueron de mayor impacto que los de Meyer, el motivo era muy claro, este primero, dejó espacios en blanco al realizar la tabla periódica los cuales correspondían a elementos aún no descubiertos, además de que realizó la corrección de las masas atómicas del In y U [Petrucci y Bissonnette, 2011]. Lo sorprendente era el hecho de que Mendeleev sabía que aún había elementos por descubrir, lo que ocurrió al poco tiempo, por lo que científicos de la época no tardaron en reconocer y aceptar dicha tabla [Petrucci y Bissonnette, 2011].

A pesar de sus acertadas incertidumbres, Mendeleev, no llegó a considerar un espacio para los gases nobles ni halógenos [Petrucci y Bissonnette, 2011]. Estos últimos fueron clasificados por el químico Döbereiner, el cual, al observar similitudes en la masa atómica de algunos de los halógenos como Cl, Br y I, los denomina "triadas" argumentando que la masa de la triada es intermedia entre la de los otros dos [Chang y Goldsby, 2013].

¿algún comentario final?

REFERENCIAS

Libros:

Ralph H. Petrucci, F. Geoffrey Herring, Jeffry D. Madura y Carey Bissonnette. Química General. Décima edición PEARSON EDUCACIÓN, S. A., Madrid, 2011
Páginas consultadas: 360 a 386

Raymond Chang y Kenneth A. Goldsby Química. Undécima edición, 2013. McGRAW-HILL/INTERAMERICANA EDITORES, S.A. DE C.V.
Páginas consultadas: 328 a 349, 356 a 358.

Catherine E. Housecroft y Alan G. Sharpe Química Inorgánica. Segunda edición PEARSON EDUCACIÓN, S. A., Madrid, 2006
Páginas consultadas: 468 a 477

Peter Atkins y Loretta Jones Principios de Química *Los caminos del descubrimiento*. Quinta edición Médica Panamericana, 2012
Páginas consultadas: 654 a 659

Shriver y Peter Atkins
Química Inorgánica. Cuarta edición
McGraw – Hill Interamericana, 2008
Páginas consultadas: 400 a 425

F. Albert Cotton y Geoffrey Wilkinson, F.R.S.
Advanced Inorganic Chemistry 2000
LIMUSA, S. A.
Páginas consultadas: 587 a 593

Brown, Lemay y Bursten
Química: La ciencia central, 7ª Ed.
PRENTICE HALL
Páginas consultadas: 832 a 833

Artículos, pdf.:

Saúl Holgufn Quiñones J. M. Daniel Estrada Guerrero. (2014). El hidrógeno, los gases nobles y los halógenos. En Halógenos UAM (1 - 53). México, D.F.: Universidad Autónoma Metropolitana (División de Ciencias Básicas e Ingeniería Departamento de Ciencias Básicas).

José Antonio Bustelo Lutzardo, Javier García Martínez, Pascual Román Polo. (Recibido: 08/04/2011. Aceptado: 07/06/2011.). Los elementos perdidos de la tabla periódica: sus nombres y otras curiosidades. En Historia de la Química (1 - 8). Real Sociedad Española de Química 2012: Real Sociedad Española de Química.

Sitios Web:

Anónimo. (2016). EL ORIGEN DE LOS NOMBRES DEL YODO Y DEL BROMO. 10 de mayo de 2019, de Heurema Sitio web: http://www.heurema.com/Origenes/Origenes23-IBr/I-Br.pdf

Fernando Pino. (noviembre de 2015). Características del astato. 10 de mayo de 2019, de VIX Sitio web: https://www.vix.com/es/btg/curiosidades/5283/caracteristicas-del-astato

Anónimo. (2018). Propiedades Químicas. 2019, de Lenntech Sitio web: https://www.lenntech.es/services/services.htm

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

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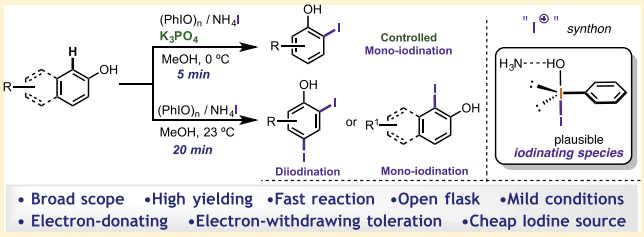
Supporting Information

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



INTRODUCTION

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

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

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

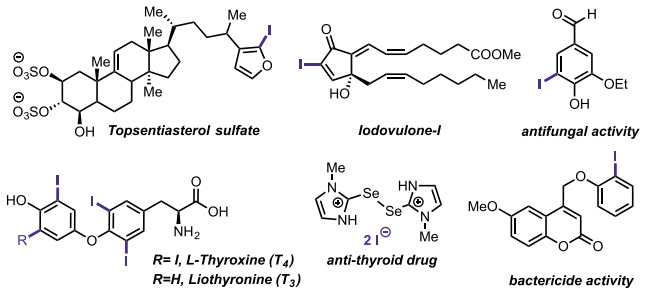


Figure 1. Relevance of the iodoarene moiety.

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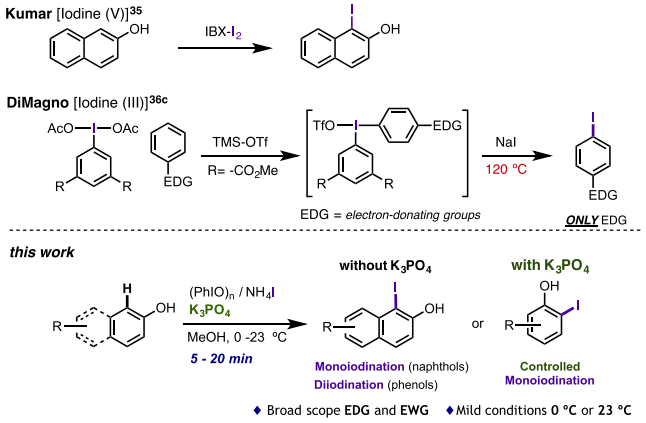
Scheme 1. Hypervalent Iodine Strategies for the Iodination of Arenes and Phenols



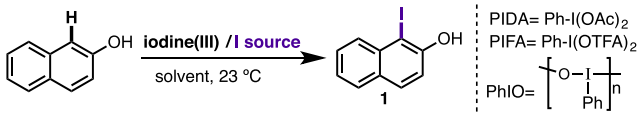
valent-based iodination procedures of phenols, the very few of them that are available are synthetically restricted in several ways, the most significant being low selectivity,[35] polyhalogenation, expensive starting materials,[36] more than one preparation step, limitation to electron-rich arenes,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

RESULTS

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

The starting conditions were based on our previous chlorination[38] and bromination[39] procedures. Thus, 1.2 equiv of PIDA or PIFA was used, along with 2.4 equiv of AlI_3 in acetonitrile at room temperature (Table 1, entries 1 and 2). Unfortunately, only molecular iodine was obtained as product in this trial. Different conditions were explored by changing the iodine(III) reagent from PIDA/PIFA to iodosylbenzene (PhIO). Iodide salts were also considered as the iodine atom source. In line with the results of Kita and co-workers, both PIFA and PIDA are prone to generate radicals when mixed with halogen salts having cations different to ammonium.[40] The topic about radical generation is outside of this work scope; hence PhIO was chosen as the iodine(III) reagent. Initial trials used potassium iodide in methanol to solubilize both PhIO and KI. In this way, **1** was isolated in a 17% yield (entry 3). The reaction in water as solvent showed poor conversion (<5%) and large quantities of unreacted starting material (entry 4). The use of 5 mol % of sulfuric acid as additive significantly increased the yield to 86% in methanol (entry 5) and 25% in water (entry 6). The (1:1) solvent combination of methanol and water did not improve the yield (entry 7); however, it demonstrated that the reaction is water tolerant. As acidic media gave considerably better yields, another protic iodide salt was explored. Surprisingly, use of 1.2

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



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

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

equiv of PhIO and 2.4 equiv of ammonium iodide in methanol at 23 °C provided 1-iodo-2-naphthol in nearly quantitative yield (98%) within 20 min (entry 8). This result highlighted several aspects of the process, such as the fast and high-yield reactions as well as its economical iodine atom source. Additionally, we avoid the possibility of the radical generation in the process since the ammonium cation is used. Changing the solvent to acetonitrile lowered the yield to 70% (entry 9). Decreasing the amount of PhIO (to 1.0 and 0.5 equiv) provided yields of only 80% and 40%, respectively (entries 10 and 11). On the other hand, the yield was not improved by decreasing the ammonium iodide loading to 1.5 equiv (entry 12). At this point, the possibility of the iodide anion oxidation generating molecular iodine was considered, which could be the iodinating active species in the process. To test this mechanistic hypothesis, experiments using molecular iodine in the absence of an iodine(III) reagent were carried out, using the conditions found to be best in the initial optimizations (entry 8). Thus, the reaction was tested with 1.0, 1.5, and 2.0 equiv of molecular iodine at 23 °C in methanol (entries 13–15) or trifluoroethanol (entry 16). Interestingly, the desired iodination was achieved with yields of 58%, 52%, 46%, and 57%, respectively. However, the yields remain far below that obtained in entry 8; thus molecular iodine was ruled out as the iodinating species. Control experiments were then carried out in order to complete the optimization. The use of PhIO in the absence of ammonium salt led to no reaction (entry 17). Similarly, the use of ammonium iodide without the iodine(III) reagent failed to produce **1**.

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

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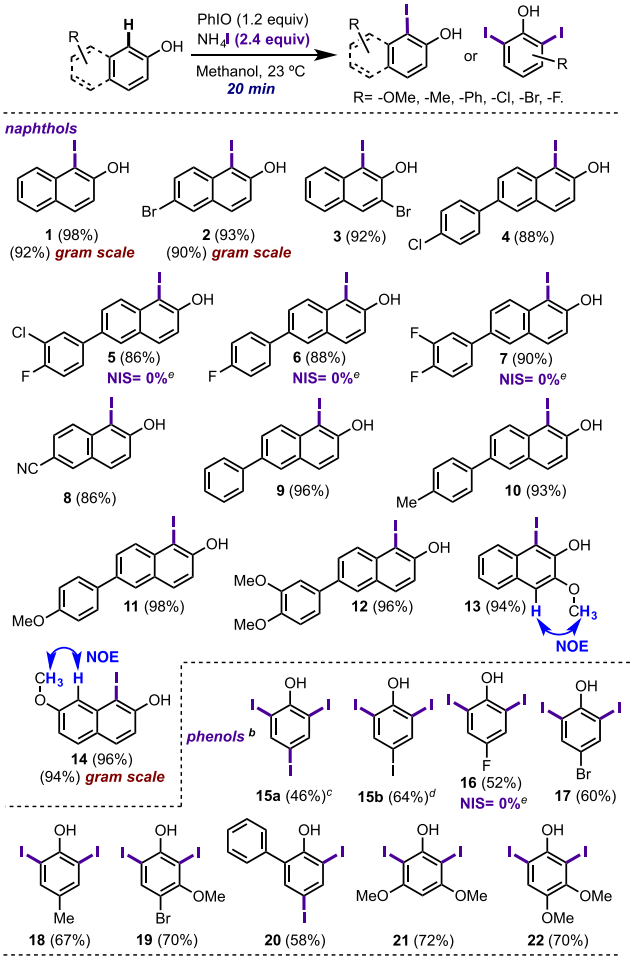
the scope of the new procedure with respect to changes in the aryl unit (Scheme 2).

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

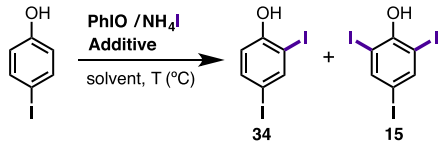


[a]Reaction conditions: 2-naphthol (0.5 mmol), methanol (0.15 M), open flask. [b]PhIO (2.4 equiv)/NH_4I (4.8 equiv) were used. [c]Synthesized from phenol. [d]Synthesized from 4-iodophenol. [e]Reaction conditions: phenol (0.5 mmol), NIS (1.2 equiv), TFA (10 mol %), MeCN (0.15 M) at 23 °C by 12 h.

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

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

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



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

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

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

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

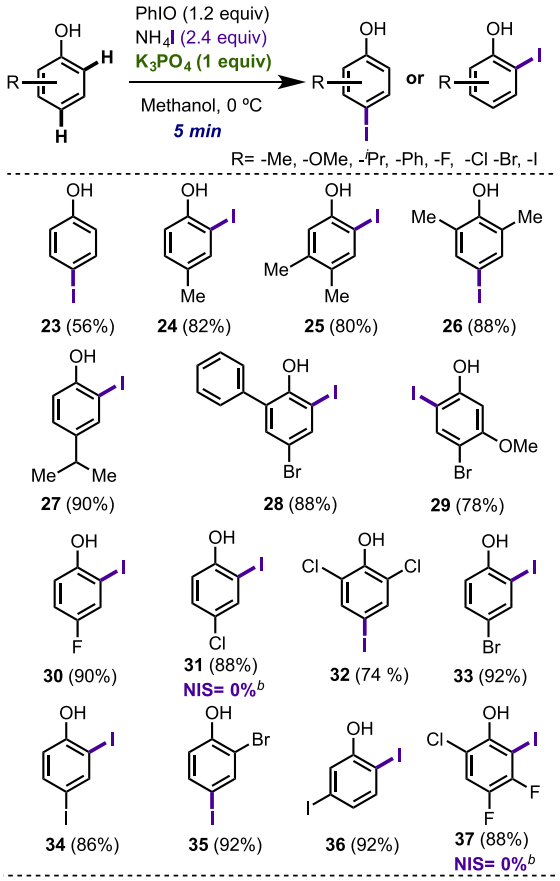
After this analysis and determination of the optimal conditions, we explored the scope of the controlled monoiodination of phenols (Scheme 3).

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

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

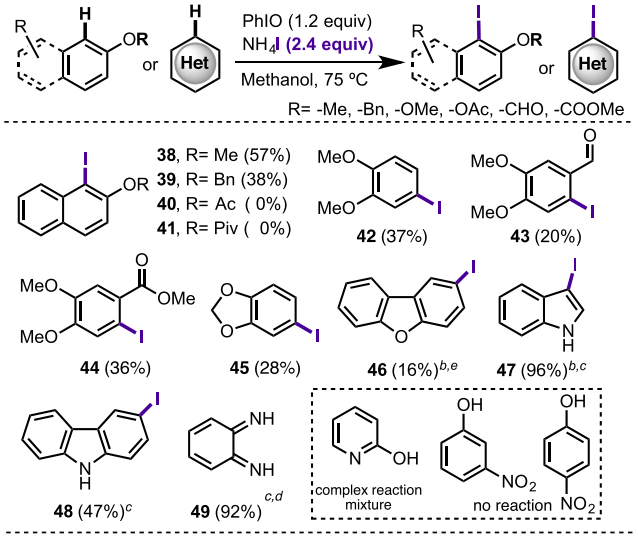
The following set of trials was devised to determine the tolerance of our procedure in the presence of (1) different functional groups at the phenolic oxygen, (2) functionalized phenols with more than one functional group, (3) functionalities other than phenol present in the aryl moiety, and (4) heterocycles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

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



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

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



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

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

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

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

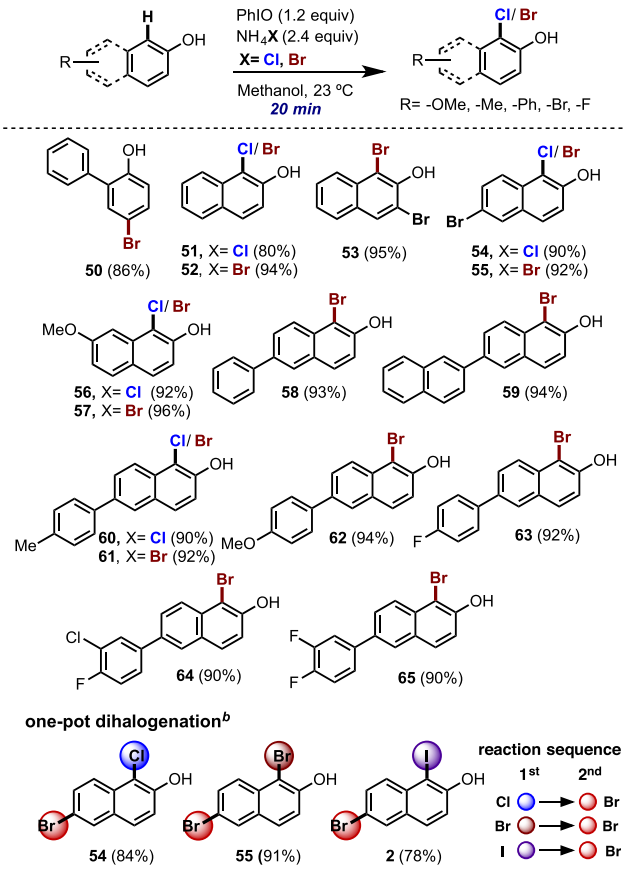
The ammonium chloride and bromide were mainly employed under the optimized standard conditions (Scheme 5) in order to introduce these halides into a range of phenols. In this way, 2-phenylphenol was brominated in 86% yield, giving rise to **50**. The chlorination and bromination of 2-naphthol, 6-bromo-2-naphthol,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

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

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

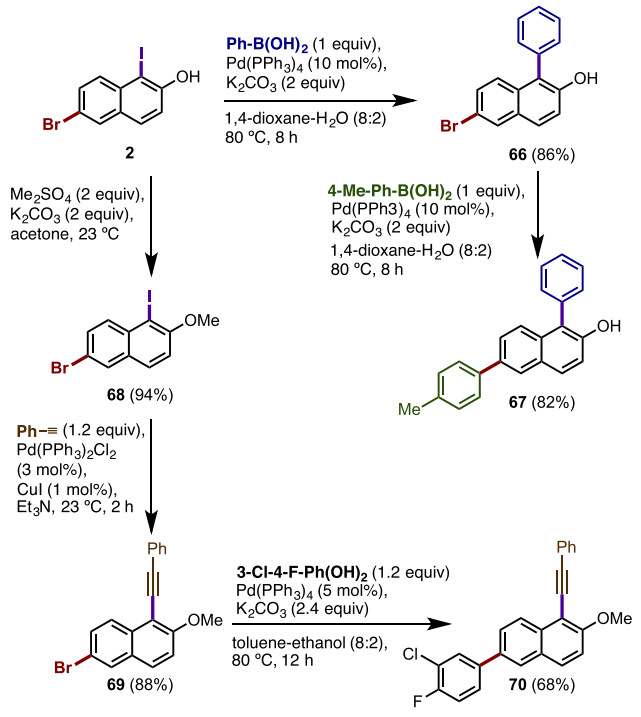
The synthetic applicability of the derivatives obtained through our procedure was illustrated with the compound 6-bromo-1-iodo-2-naphthol (**2**) which possesses two halide

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



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

Scheme 6. Synthetic Utility of the Synthesized Halogenated Derivatives



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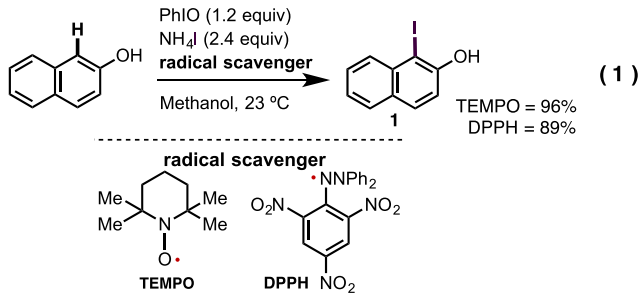
groups with different reactivities. We considered the synthesis of **2** as an excellent opportunity to carry out two distinct orthogonal reaction sequences: sequential double Suzuki cross-coupling, and Sonogashira alkynylation/Suzuki cross-coupling. In the first sequence, regioselective Suzuki cross-coupling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

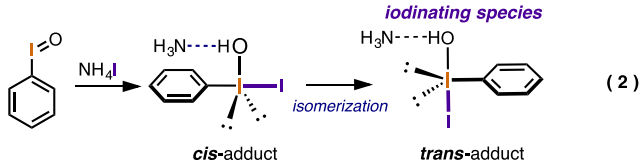
Finally, in order to gain more insight into the reaction mechanism, we decided to carry out the iodination of 2-naphthol in the presence of the radical scavengers TEMPO[42] (tetramethylpiperidine *N*-oxide) and DPPH (2,2-diphenyl-1-picrylhydrazyl) in order to determine if a radical or cationic pathway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



(1)

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

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



(2)

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

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

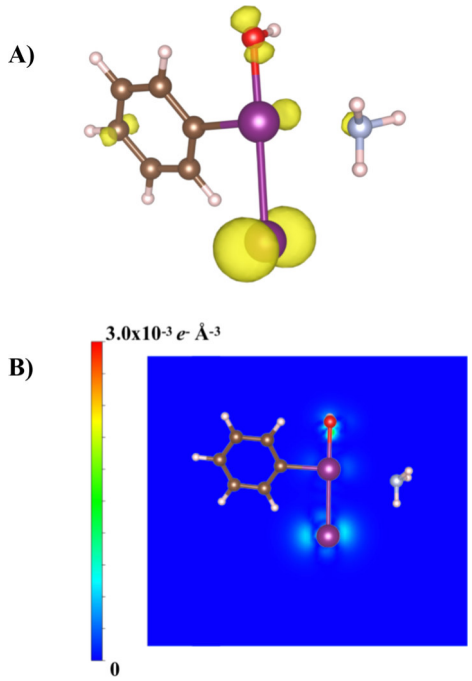


Figure 2. (a) The Fukui function for electrophilic attack of the plausible iodinating active species and (b) its 2D projection. Color code for atoms in brackets: C (brown), O (red), I (purple), (N) light blue, and H (pink).

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

■ CONCLUSIONS

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

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EXPERIMENTAL SECTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Fukui Function Calculations for PhII(OH)·NH$_3$. The reactivity of the iodinating species was analyzed by exploring a very useful covalent reactivity descriptor: the Fukui or frontier function, which is usually a reliable predictor of the regioselectivity of soft molecules.[44−46] Fukui functions are defined as the response of the electron density when the number of electrons (N) suffers an infinitesimal change, providing us information about the reactive sites of a molecular system.[47] Particularly to indicate how the electron density is redistributed when molecules react, thus, molecular regions suffering more charge rearrangements are the most reactive sites. The Fukui functions are obtained calculating the electron density of the $PhII(OH)\cdot NH_3$ with N, $N-1$, and $N+1$ electrons, respectively, at the ground state. The positive ($f^+(r)$) and negative ($f^-(r)$) forms of the Fukui functions are useful descriptors to evaluate nucleophilic or electrophilic attacks, respectively.[48]

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

■ ASSOCIATED CONTENT

Supporting Information

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

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

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

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

■ REFERENCES

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

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

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

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

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

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

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

(8) (a) Silva, L. F., Jr.; Olofsson, B. Hypervalent Iodine Reagents in The Total Synthesis of Natural Products. *Nat. Prod. Rep.* **2011**, *28*, 1722−1754. (b) Skulski, L. Organic Iodine (I, III and V) Chemistry: 10 Years of Development at the Medical University of Warsaw. *Molecules* **2000**, *5*, 1331−1371.

(9) Merritt, E. A.; Olofsson, B. Diaryliodoniumsalts-A Journey from Obscurity to Fame. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070.

(10) Sampson, P. Metal Catalyzed Cross-Coupling Reactions *J. J. Am. Chem. Soc.* **1998**, *120*, 11836−11837.

(11) Wang, L.; Ackermann, L. Ruthenium-catalyzed ortho-C−H halogenations of benzamides. *Chem. Commun.* **2014**, *50*, 1083−1085.

(12) Zhou, C.; Li, J.; Peddibhotla, S.; Romo, D. Mild Arming and Derivatization of Natural Products via an $In(OTf)_3$-Catalyzed Arene Iodination. *Org. Lett.* **2010**, *12*, 2104−2107.

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

(13) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. A Simple Catalytic Method for the Regioselective Halogenation of Arenes. *Org. Lett.* **2006**, *8*, 2523−2526.
(14) Branytska, O. V.; Neumann, R. An Efficient, Catalytic, Aerobic, Oxidative Iodination of Arenes Using the $H_5PV_2Mo_{10}O_{40}$ Polyoxometalate as Catalyst. *J. Org. Chem.* **2003**, *68*, 9510−9512.
(15) Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. Iodination of Alkyl Aryl Ethers by Mercury(II) Oxide-Iodine Reagent in Dichloromethane. *Synthesis* **1995**, 1273−1277.
(16) Racys, D. T.; Warrilow, C. E.; Pimlott, S. L.; Sutherland, A. Highly Regioselective Iodination of Arenes via Iron(III)-Catalyzed Activation of N-Iodosuccinimide. *Org. Lett.* **2015**, *17*, 4782−4785.
(17) Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V. S. A mild and simple regioselective iodination of activated aromatics with iodine and catalytic ceric ammonium nitrate. *Tetrahedron Lett.* **2007**, *48*, 81−83.
(18) Janjetovic, M.; Ekebergh, A.; Träff, A. M.; Hilmersson, G. Catalytic Iodination of the Aliphatic C-F Bond by $YbI_3(THF)_3$: Mechanistic Insight and Synthetic Utility. *Org. Lett.* **2016**, *18*, 2804−2807.
(19) Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. Silver(I)-Catalyzed Iodination of Arenes: Tuning the Lewis Acidity of N-Iodosuccinimide Activation. *J. Org. Chem.* **2016**, *81*, 772−780.
(20) Badri, R.; Gorjizadeh, M. A mild, efficient and selective iodination of aromatic compounds using iodine and 1,4-bis-(triphenylphosphonium)-2-butene peroxodisulfate. *Chin. Chem. Lett.* **2009**, *20*, 1439−1443.
(21) Patil, A. M.; Kamble, D. A.; Lokhande, P. D. A Metal-Free Iodination of Aryl Ethers and Phenols Using I_2. *ChemistrySelect* **2017**, *2*, 8418−8422.
(22) Vibhute, A.; Mokle, S.; Karamunge, K.; Gurav, V.; Vibhute, Y. A simple and efficient method for solvent-free iodination of hydroxylated aromatic aldehydes and ketones using iodine and iodic acid by grinding method. *Chin. Chem. Lett.* **2010**, *21*, 914−918.
(23) Pavlinac, J.; Zupan, M.; Stavber, S. Solvent-free iodination of organic molecules using the I_2/urea-H_2O_2 reagent system. *Org. Biomol. Chem.* **2007**, *5*, 699−707.
(24) Noda, Y.; Kashima, M. An Efficient and Regioselective Direct Aromatic Iodination Using Iodine and Nitrogen Dioxide. *Tetrahedron Lett.* **1997**, *38*, 6225−6228.
(25) Narender, N.; Reddy, K. S. K.; Mohan, K. V. V. K.; Kulkarni, S. J. Eco-friendly oxyiodination of aromatic compounds using ammonium iodide and hydrogen peroxide. *Tetrahedron Lett.* **2007**, *48*, 6124−6128.
(26) Edgar, K. J.; Falling, S. N. An Efficient and Selective Method for the Preparation of Iodophenols. *J. Org. Chem.* **1990**, *55*, 5287−5291.
(27) Lista, L.; Pezzella, A.; Napolitano, A.; d'Ischia, M. Mild and efficient iodination of aromatic and heterocyclic compounds with the $NaClO_2$/NaI/HCl system. *Tetrahedron* **2008**, *64*, 234−239.
(28) Hubig, S. M.; Jung, W.; Kochi, J. K. Cation Radicals as Intermediates in Aromatic Halogenation with Iodine Monochloride: Solvent and Salt Effects on the Competition between Chlorination and Iodination. *J. Org. Chem.* **1994**, *59*, 6233−6244.
(29) Bailey, L.; Handy, S. T. Aromatic iodination using N-iodosaccharin in room temperature ionic liquids. *Tetrahedron Lett.* **2011**, *52*, 2413−2414.
(30) Barluenga, J.; Gonzalez, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asensio, G. Acid-mediated reaction of bis(pyridine)iodonium(I) tetrafluoroborate with aromatic compounds. A selective and general iodination method. *J. Org. Chem.* **1993**, *58*, 2058−2060.
(31) Castanet, A. S.; Colobert, F.; Broutin, P. E. Mild and regioselective iodination of electron-rich aromatics with *N*-iodosuccinimide and catalytic trifluoroacetic acid. *Tetrahedron Lett.* **2002**, *43*, 5047−5048.
(32) Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. Synthetic methods and reactions. 181. Iodination of deactivated aromatics with N-iodosuccinimide in trifluoromethanesulfonic acid (NIS-CF_3SO_3H) via in situ generated superelectrophilic iodine(I) trifluoromethanesulfonate. *J. Org. Chem.* **1993**, *58*, 3194−3195.
(33) Tang, R.-J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83*, 930−938.
(34) Sun, K.; Lv, Y.; Wang, J.; Sun, J.; Liu, L.; Jia, M.; Liu, X.; Li, Z.; Wang, X. Regioselective, Molecular Iodine-Mediated C3 Iodination of Quinolines. *Org. Lett.* **2015**, *17*, 4408−4411.
(35) Moorthy, J. N.; Senapati, K.; Kumar, S. IBX-I_2 Redox Couple for Facile Generation of IOH and I^+: Expedient Protocol for Iodohydroxylation of Olefins and Iodination of Aromatics. *J. Org. Chem.* **2009**, *74*, 6287−6290.
(36) (a) Spyroudis, S.; Tarantili, P. Phenyliodoniophenolates from 1,3-Dihydroxybenzene Derivatives. *Tetrahedron* **1994**, *50*, 11541−11552. (b) Prakash, O.; Sharma, V.; Tanwar, M. P. Hypervalent iodine oxidation of α -substituted 2,4-dihydroxyacetophenones: synthesis of novel o-iodophenoxy ethers via rearrangement of iodonium ylides. *Can. J. Chem.* **1999**, *77*, 1191−1195. (c) Hu, B.; Miller, W. H.; Neumann, K. D.; Linstad, E. J.; DiMagno, S. G. An Alternative to the Sandmeyer Approach to Aryl Iodides. *Chem. - Eur. J.* **2015**, *21*, 6394−6398. (d) Daub, K. S.; Habermann, B.; Hahn, T.; Teich, L.; Eger, K. Synthesis of 3-Aryloxy-2-iodoemodines by Oxidation of Emodin with (Diacetoxyiodo)arenes. *Eur. J. Org. Chem.* **2004**, *2004*, 894−898. For activation modes of iodine(III) reagents: (e) Shu, S.; Li, Y.; Jiang, J.; Ke, Z.; Liu, Y. Mechanism of Hypervalent Iodine Promoted Fluorocyclization of Unsaturated Alcohols: Metathesis via Double Acids Activation. *J. Org. Chem.* **2019**, *84*, 458−462.
(37) Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. Regiospecific Reductive Elimination from Diaryliodonium Salts. *Angew. Chem., Int. Ed.* **2010**, *49*, 4079−4083.
(38) Nahide, P. D.; Ramadoss, V.; Juárez-Ornelas, K. A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J. M. J.; Alonso-Castro, A. J.; Zapata-Morales, J. R.; Ramírez-Morales, M. A.; Ruiz-Padilla, A. J.; Deveze-Álvarez, M. A.; Solorio-Alvarado, C. R. In Situ Formed iodine(III)-Based Reagent for the Electrophilic *ortho*-Chlorination of Phenols and Phenol-Ethers: The Use of PIFA-$AlCl_3$ System. *Eur. J. Org. Chem.* **2018**, *2018*, 485−493.
(39) Satkar, Y.; Ramadoss, V.; Nahide, P. D.; García-Medina, E.; Juárez-Ornelas, K. A.; Alonso-Castro, A. J.; Chávez-Rivera, R.; Jiménez-Halla, J. O. C.; Solorio-Alvarado, C. R. Practical, Mild and Efficient Electrophilic Bromination of Phenols by a New I(III)-based Reagent: The PIDA-$AlBr_3$ System. *RSC Adv.* **2018**, *8*, 17806−17812.
(40) (a) Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. Direct Lactone Formation by Using Hypervalent Iodine(III) Reagents with KBr via Selective Abstraction Protocol. *Org. Lett.* **2007**, *9*, 3129−3132. (b) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007−2010.
(41) Beitia, J. L. L. Tripotassium Phosphate: From Buffers to Organic Synthesis. *Synlett* **2011**, *2011*, 139−140.
(42) Carroll, M. A.; Nairne, J.; Smith, G.; Widdowson, D. A. Radical Scavengers: A Practical solution to the reproducibility issue in the fluoridation of diaryliodonium salts. *J. Fluorine Chem.* **2007**, *128*, 127−132.
(43) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. *Gaussian 16*, Revision A.03; Gaussian Inc.: Wallingford, CT, 2016.
(44) For an excellent discussion about *cis* and *trans* geometries in hypervalent iodine(III) derivatives, see: Sajith, P. K.; Suresh, C. H. Trans and Cis Influences in Hypervalent Iodine(III) Complexes: A DFT Study. *Inorg. Chem.* **2013**, *52*, 6046−6065.
(45) (a) Ayers, P. W.; Parr, R. G.; Pearson, R. G. Elucidating the hard/soft acid/base principle: A perspective based on half-reactions. *J. Chem. Phys.* **2006**, *124*, 194107. (b) Gazquez, J. L.; Mendez, F. The hard and soft acids and bases principle: an atoms in molecules viewpoint. *J. Phys. Chem.* **1994**, *98*, 4591−4593.
(46) Mendez, F.; Gazquez, J. L. Chemical-Reactivity of Enolate Ions - The Local Hard and Soft Acids and Bases Principle Viewpoint. *J. Am. Chem. Soc.* **1994**, *116*, 9298−9301.

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

(47) Ayers, P. W.; Parr, R. G. Variational Principles for Describing Chemical Reactions: The Fukui Function and Chemical Hardness Revisited. *J. Am. Chem. Soc.* **2000**, *122*, 2010−2018.
(48) Johnson, P. A.; Bartolotti, L. J.; Ayers, P. W.; Fievez, T.; Geerlings, P. Charge Density and Chemical Reactions: A Unified View from Conceptual DFT. In *Modern Charge-Density Analysis*; Gatti, C., Macchi, P., Eds.; Springer Netherlands: Dordrecht, 2012; pp 715−764.
(49) Crittall, M. R.; Fairhurst, N. W. G.; Carbery, D. R. Point-to-helical chirality transfer for a scalable and resolution-free synthesis of a helicenoidal DMAP organocatalyst. *Chem. Commun.* **2012**, *48*, 11181−11183.
(50) Zhao, C.; Guo, D.; Munkerup, K.; Huang, K.-W.; Li, F.; Wang, J. Enantioselective [3 + 3] atroposelective annulation catalyzed by *N*-heterocyclic carbenes. *Nat. Commun.* **2018**, *9*, 611.
(51) Mbatia, H. W.; Ulloa, O. A.; Kennedy, D. P.; Incarvito, C. D.; Burdette, S. C. Iodination of anilines and phenols with 18-crown-6 supported ICl_2^-. *Org. Biomol. Chem.* **2011**, *9*, 2987−2991.
(52) Kauch, M.; Hoppe, D. Synthesis of Halogenated Phenols by Directed *ortho*-Lithiation and *ipso*-Iododesilylation Reactions of *O*-Aryl *N*-Isopropylcarbamates. *Synthesis* **2006**, *2006*, 1578−1589.
(53) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. Iodination of Phenols by Use of Benzyltrimethylammonium Dichloroiodate (I-). *Chem. Lett.* **1987**, *16*, 2109−2112.
(54) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. S. R.; Basak, A. K.; Narsaiah, A. V. Efficient Halogenation of Aromatic Systems Using *N*-Halosuccinimides in Ionic Liquids. *Adv. Synth. Catal.* **2004**, *346*, 77−82.
(55) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. Synthesis of many different types of organic small molecules using one automated process. *Science* **2015**, *347*, 1221−1226.
(56) Yoshida, S.; Nagai, A.; Uchida, K.; Hosoya, T. Enhancing the Synthetic Utility of 3-Haloaryne Intermediates by Their Efficient Generation from Readily Synthesizable *ortho*-Iodoaryl Triflate-type Precursors. *Chem. Lett.* **2017**, *46*, 733−736.
(57) Kiran, Y. B.; Konakahara, T.; Sakai, N. A Green Reagent for the Iodination of Phenols. *Synthesis* **2008**, *2008*, 2327−2332.
(58) Yang, Y.; Zhang, L.; Deng, G.-J.; Gong, H. Simple, Efficient and Controllable Synthesis of Iodo/Di-iodoarenes via Ipsoiododecarboxylation/ Consecutive Iodination Strategy. *Sci. Rep.* **2017**, *7*, 40430−40439.
(59) Miles, K. C.; Le, C. C.; Stambuli, J. P. Direct Carbocyclizations of Benzoic Acids: Catalyst-Controlled Synthesis of Cyclic Ketones and the Development of Tandem aHH (acyl Heck−Heck) Reactions. *Chem. - Eur. J.* **2014**, *20*, 11336−11339.
(60) Sun, L.; Zhang, X.; Li, Z.; Ma, J.; Zeng, Z.; Jiang, H. A Versatile C−H Halogenation Strategy for Indole Derivatives under Electrochemical Catalyst- and Oxidant-Free Conditions. *Eur. J. Org. Chem.* **2018**, *2018*, 4949−4952.
(61) Naykode, M. S.; Humne, V. T.; Lokhande, P. D. A One-Pot Direct Iodination of the Fischer−Borsche Ring Using Molecular Iodine and Its Utility in the Synthesis of 6 Oxygenated Carbazole Alkaloids. *J. Org. Chem.* **2015**, *80*, 2392−2396.
(62) Wang, X.; Qin, W. Tetra(*p*-tolyl)borate-Functionalized Solvent Polymeric Membrane: A Facile and Sensitive Sensing Platform for Peroxidase and Peroxidase Mimetics. *Chem. - Eur. J.* **2013**, *19*, 9979−9986.
(63) Pan, C.; Zhu, Z.; Zhang, M.; Gu, Z. Palladium-Catalyzed Enantioselective Synthesis of 2-Aryl Cyclohex-2-enone Atropisomers: Platform Molecules for the Divergent Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2017**, *56*, 4777−4781.
(64) Naykode, M. S.; Humne, V. T.; Lokhande, P. D. A One-Pot Direct Iodination of the Fischer−Borsche Ring Using Molecular Iodine and Its Utility in the Synthesis of 6 Oxygenated Carbazole Alkaloids. *J. Org. Chem.* **2015**, *80*, 2392−2396.
(65) Ishikawa, S.; Manabe, K. DHTP Ligands for the Highly Ortho-Selective, Palladium-Catalyzed Cross-Coupling of Dihaloarenes with Grignard Reagents: A Conformational Approach for Catalyst Improvement. *Angew. Chem., Int. Ed.* **2010**, *49*, 772−775.
(66) Qian, X.; Han, J.; Wang, L. Copper-catalyzed selective ortho-arylations of 2-naphthol and phenol derivatives with diaryliodonium salts. *Tetrahedron Lett.* **2016**, *57*, 607−610.
(67) Guardado-Cruz, S. T.; Ortiz-Alvarado, R.; de León, C.; Solorio-Alvarado, C. R. Unprecedent and Scalable Copper (I)-Catalyzed Oxidation of the Csp^2-H bond on 2-phenylnaphthalene-1,3-diol with Atmospheric Oxygen: Synthesis of 2-hydroxy-3-phenyl-1,4-naphthoquinone via direct Csp^2-O bond formation. *Acta Univ.* **2017**, *27*, 62−68.
(68) Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. Atroposelective Synthesis of Axially Chiral Biaryldiols via Organocatalytic Arylation of 2-Naphthols. *J. Am. Chem. Soc.* **2015**, *137* (48), 15062−15065.
(69) Park, Y. H.; Ahn, H. R.; Canturk, B.; Jeon, S. I.; Lee, S.; Kang, H.; Molander, G. A.; Ham, J. A Facile One-Pot Preparation of Potassium Hydroxyaryl- and (Hydroxyalkyl)aryltrifluoroborates. *Org. Lett.* **2008**, *10* (6), 1215−1218.
(70) Kamal, A.; Reddy, M. K.; Ramaiah, M. J.; Srikanth, Y. V. V.; Rajender; Reddy, V. S.; Kumar, G. B.; Pushpavalli, S. N. C. V. L.; Bag, I.; Juvekar, A.; Sen, S.; Zingde, S. M.; Pal-Bhadra, M. Synthesis of Aryl-Substituted Naphthalene-Linked Pyrrolobenzodiazepine Conjugates as Potential Anticancer Agents with Apoptosis-Inducing Ability. *ChemMedChem* **2011**, *6* (9), 1665−1679.
(71) Georgiades, S. N.; Clardy, J. Preparation of a Psammaplysene-Based Library. *Org. Lett.* **2006**, *8*, 4251−4254.
(72) Wang, Y.; Gevorgyan, V. Synthesis of Active Hexafluoroisopropyl Benzoates through a Hydrogen-Bond-Enabled Palladium(II)-Catalyzed C-H Alkoxycarbonylation Reaction. *Angew. Chem., Int. Ed.* **2017**, *56*, 3191−3195.
(73) Kästner, J.; Carr, J. M.; Keal, T. W.; Thiel, W.; Wander, A.; Sherwood, P. DL-FIND: An Open- Source Geometry Optimizer for Atomistic Simulations. *J. Phys. Chem. A* **2009**, *113*, 11856.
(74) Ufimtsev, I. S.; Martínez, T. J. Quantum Chemistry on Graphical Processing Units. 3. Analytical Energy Gradients and First Principles Molecular Dynamics. *J. Chem. Theory Comput.* **2009**, *5*, 2619.
(75) Titov, A. V.; Ufimtsev, I. S.; Luehr, N.; Martínez, T. J. Generating Efficient Quantum Chemistry Codes for Novel Architectures. *J. Chem. Theory Comput.* **2013**, *9*, 213.

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REVIEW ARTICLE

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

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Abstract: Iodine(III)-based reagents have been broadly used in oxidative reactions for structural functionalization with several functional groups. Among the more relevant and useful synthetic transformations using these hypervalent λ^3-reagents, the fluorination, chlorination, bromination, as well as the iodination protocols, can be found. Herein, we present some of the most representative oxidative halogenation procedures of arenes, olefins and alkynes dating from the oldest to the more recent advances in the area, highlighting the discovery and application of new iodine(III)-based halogenating species.

Keywords: Bromination, chlorination, fluorination, iodination, iodine(III)-based reagent, oxidative halogenation.

1. INTRODUCTION

Halogenated aryls, olefins and alkynes are highly relevant and synthetically useful building blocks in several areas of the chemistry. Many specialized reviews on synthetic applications of specific classes of hypervalent iodine compounds have been published [1-5]. In this regard, the hypervalent iodine(III)-based reagents focused on the oxidative introduction of the full family of the halogens, have been extensively used for the fluorination, chlorination bromination and iodination of different arenes, heteroarenes, alkenes and alkynes. This review addresses the most relevant oxidative halogenations described in a summarized fashion during the period between 1966 to 2018.

2. OXIDATIVE FLUORINATION OF ARENES MEDIATED BY λ^3-IODANES

The fluorination of organic molecules is a field of synthesis that poses great challenges despite the progress made in recent decades. It is not surprising that fluorinated compounds play a role as templates of bioactive molecules. For example, 20% of compounds in the pharmaceutical industry include a molecule with a fluorine atom. In some cases, the replacement of hydrogen by its isostere fluorine increases the hydrophobicity leading to a delay in metabolism [6]. From the chemical and especially pharmaceutical point of view, adding fluorine at specific sites in substituted aromatic rings is an important task. The method of Balz [7], which has been used since the 1960s, many times requires diazotization with explosive diazofluoroborates. Therefore, alternatives have been designed for the synthesis of fluorinated aromatic compounds [8]. Fluorinated hypervalent iodine(III) reagents (HIR) represented initially by the difluoroiodobenzene, are promising replacements to the highly toxic heavy metal oxidants, since they possess characteristics such as broad availability, low toxicity, high stability against oxygen and moisture and their reactions usually proceed under mild conditions releasing iodobenzene in a safe manner. Thus, their versatility as synthetic tools in organic chemistry is currently increasing for chemical fluorination [9] (Fig. **1**).

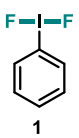

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Fig. (1). Structure of the hypervalent iodine(III) reagent difluoroidobenzene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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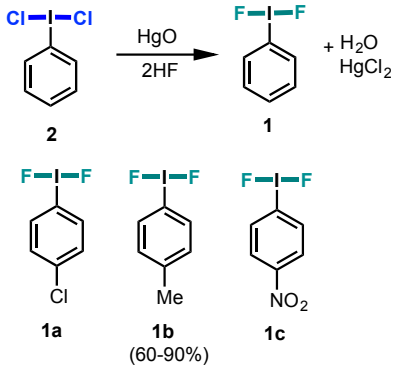
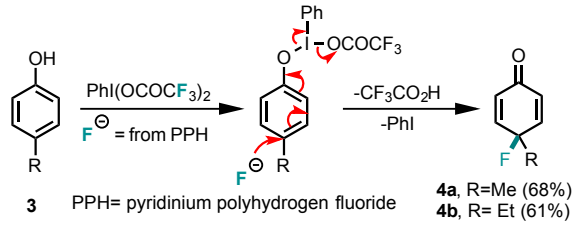
One of the initial methods for the one-step preparation of difluoroiodobenzene derivatives using HIR (**2**) was described by Carpenter in 1966 [10]. In this protocol, fluorine sources such as F_2, SF_4 or XeF_4 were avoided. The synthesis of 4-iodotoluene difluoride and derivatives **1a-c** was achieved in good yields (60-90%) (Scheme **1**).



Scheme 1. Synthesis of difluoroaryl-λ^3-iodanes **1a-c**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

With this background, Jacquesy *et al.* [11] described a new method for incorporating fluorine in aromatic compounds such as 4-substituted phenols (**3**), using the combination of PIFA [bis(trifluoroacetoxy)iodobenzene] and PPHF [12] (pyridinium polyhydrogen fluoride) to obtain mono- and polycyclic 4-fluorocyclohexa-2,5-dienes (**4**) in fairly good yields (61-77%) (Scheme **2**).

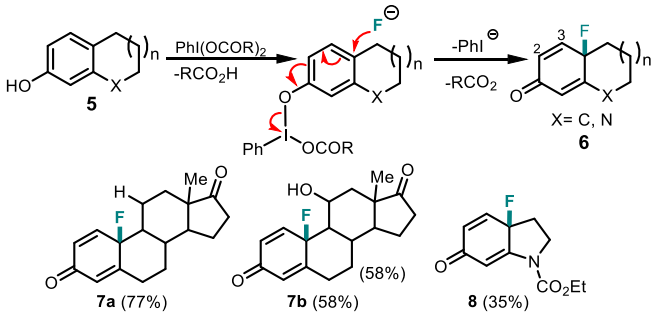


Scheme 2. Putative fluorination of aromatic phenols **4a-b** using PIFA and PPHF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

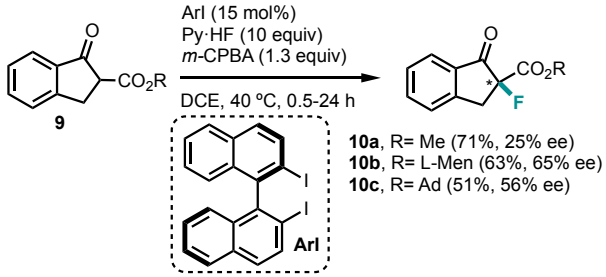
In 2004, Karam *et al.* [13] reported a fluorination procedure using phenols of type **5.** The combination of PPHF with PIDA diacetoxyiodo(benzene) gave rise to the fluorination of angular fluorocyclohexenones in low to moderate yields. The procedure was also applied to the *ipso*-fluorination of estrogen steroids (**7a-b**) within moderates yields (58-77%) as well as to the hydroindole **8** in moderate yield (35%) (Scheme **3**).

Later, Kita and Shibata [14] described enantioselective fluorination of indenones (**9**) catalyzed by the (*R*)-binaphthyldiiodide (**ArI**) which is oxidized *in situ* to the corresponding λ^3-iodane. This protocol proceeded in mild and effective reaction conditions (Scheme **4**).

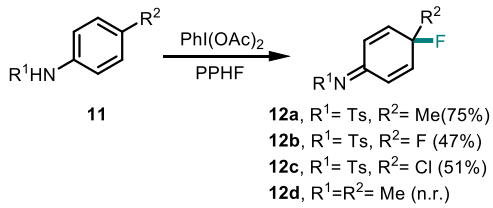
Afterward, Jouannetaud *et al.* [15] carried out the reaction of *para*-substituted anilines (**11**) in the presence of PIDA and PPHF, giving easy access to new 4-fluorinated cyclohexa-2,5-dienimines (**12**). These fluorinated derivatives **12** were obtained in low to moderate yields (18-75%). The protecting group on the aniline nitrogen atom and the substitution of the aromatic moiety have a crucial role in the success of the reaction (Scheme **5**).



Scheme 3. Preparation of substituted fluorocyclohexenones using PIFA. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 4. Enantioselective a-fluorination of 1,3-dicarbonyl-indenones, catalyzed by hypervalent iodine(III) reagents and Py·HF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



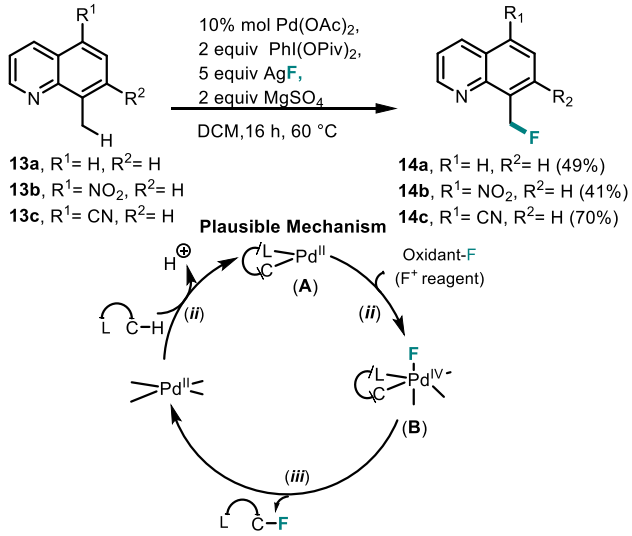
Scheme 5. Synthesis of 4-halo-4-alkylcyclohexa-2,5-dienimines (**12**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Following the timeline, the group of Sanford [16] described an example of palladium-catalyzed C-H fluorination for a variety of 8-mehtylquinoline derivatives **13**, using AgF as fluoride source in mixture with $PhI(OPiv)_2$ bis(*tert*-butylcarbonyloxy)-iodobenzene. The reaction proceeded in modest yields (41-59%) giving rise to the corresponding benzylic fluorination products **14**.

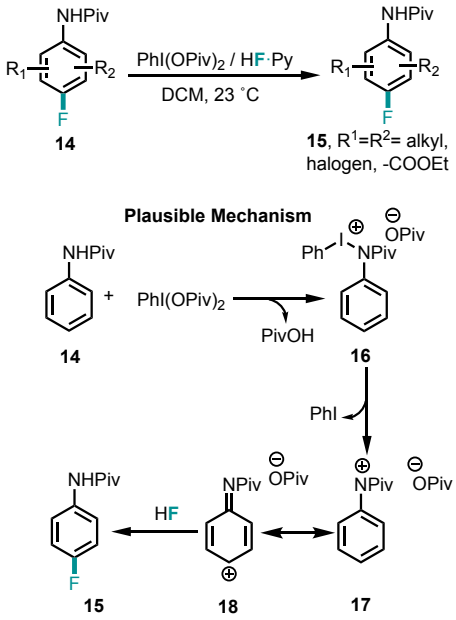
Interestingly, in the proposed catalytic cycle, the fluoride atom is the oxidizing agent (Pd^{II} to Pd^{IV}) and the source of the fluorine atom (Scheme **6**).

In 2013, Meng and Li [17] used several aromatic anilides **14** and developed regioselective *para*-fluorination obtaining the anilides **15**. The reaction took place in the presence of $PhI(OPiv)_2$ and pyridine-hydrogen fluoride (Py·HF). They obtained moderate to good yields (40-80%). Scheme **7** outlines a plausible mechanism. Herein the intermediate **16** was

obtained through the nucleophilic attack from the anilide **14** to $PhI(OPiv)_2$ following reductive elimination at the iodine atom with the concomitant generation of nitrenium ion **17**. Finally, the intermediate **18** was trapped by HF to give the corresponding fluorinated derivatives **15** (Scheme **7**).

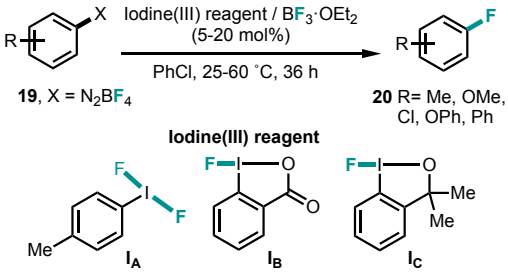


Scheme 6. Palladium-catalyzed C-H fluorination of 8-methylquinoline derivatives **13a-c** using $PhI(OPiv)_2$ as oxidant. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



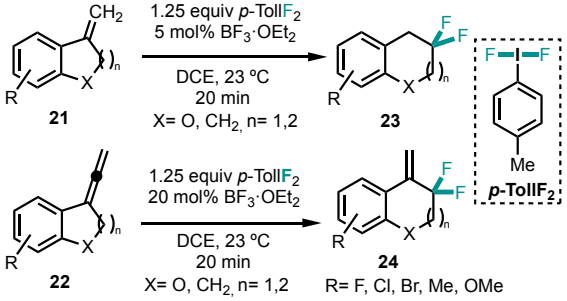
Scheme 7. Regioselective *para*-fluorination of anilides **14** mediated by $PhI(OPiv)_2$ / Py·HF. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Subsequently, Hu *et al.* [18] established an efficient iodine(III)-mediated method as a safe alternative to the potentially explosive Balz-Schiemann procedure. Compounds **20** were obtained in moderate to good yields (48-83%). The reaction took place under mild conditions allowing a wide range of functional groups (Scheme **8**).



Scheme 8. Iodine(III)-catalyzed Balz–Schiemann fluorination of arenes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Recently, Murphy *et al.* [19] described a novel chemoselective fluorinative ring expansion of the alkenylbenzofuranes **21** and **22** using (p-$TolIF_2$). The procedure supports a great variety of functional groups, including carbo- and heterocycles **23-24** with moderate to good yields (49-78%) (Scheme **9**).

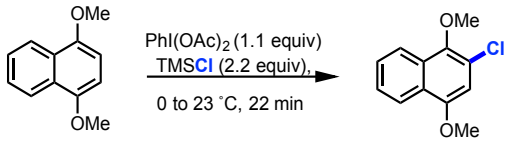


Scheme 9. Difluorinative ring expansions of 3-alkenyl- and 3-allenyl-benzofuranes using p-(difluoroiodo)toluene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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

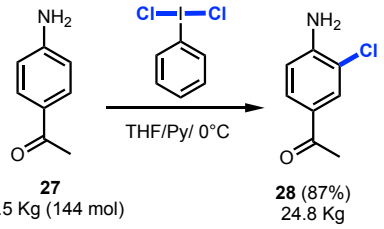
Another class of relevant compounds is the chloroarenes. Herein we describe some representative procedures for the chlorination of these compounds using novel hypervalent iodine(III) reagents as oxidants.

Evans *et al.* [20] described a method for the chlorination of 1,4-dimethoxynaphthalene by combining PIDA and trimethylsilyl chloride (TMS-Cl). 2-chloro-1,4-dimethoxynaphthalene (**26**) was obtained in 83% yield (Scheme **10**).



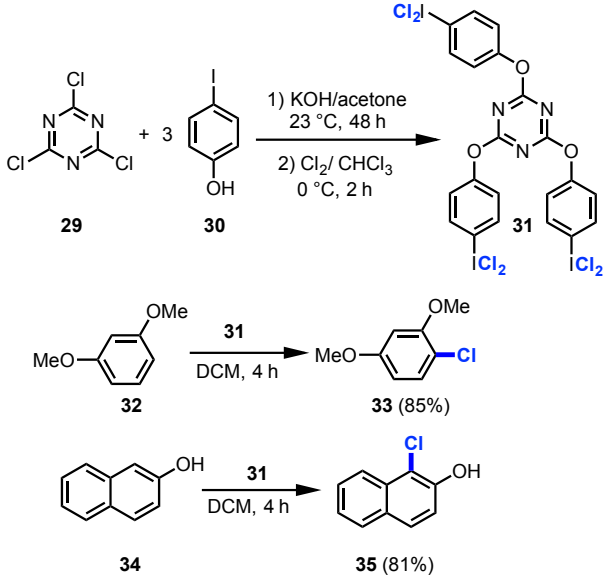
Scheme 10. Chlorination of 1,4-dimethoxynaphthalene. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

On the other side, in 1998, Zanka *et al.* [21] carried out large-scale monochlorination of 4-aminoacetophenone (**27**) (144 mol) using iodobenzene dichloride. The final process was scaled up to afford 24.8 kg (87% yield) with 94% purity (Scheme **11**).



Scheme 11. Monochlorination of 4-aminoacetophenone mediated by $PhICl_2$. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

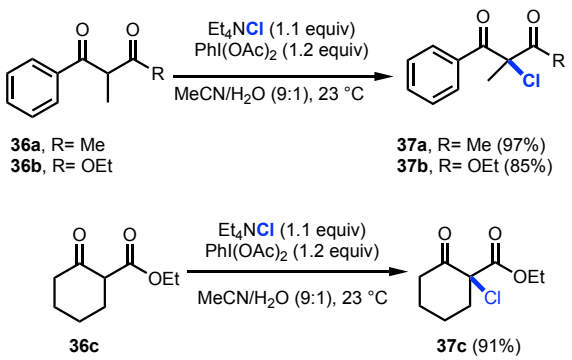
Interestingly, Karade *et al.* [22] described a method for the preparation of the recyclable hypervalent iodine(III) **31**. The iodine reagent was synthesized from 4-iodophenol **30** and 2,4,6-trichloro-1,3,5-triazine **29** to form 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine **31** as a recyclable analog non-polymeric of (dichloroiodo)benzene. This compound was used with various arenes (**32**, **34**) obtaining good to excellent yields (81-100%) of the corresponding chlorinated derivatives (**33**, **35**). The products were separated by simple filtration and recycling the iodide reagent (Scheme **12**).



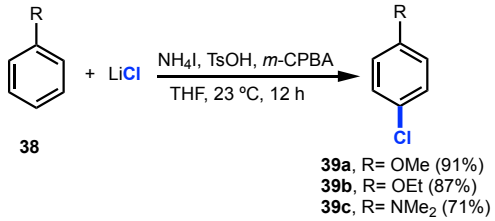
Scheme 12. Preparation of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine (**31**) and use in the chlorination of some arenes (**33**, **35**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

On the other hand, in 2014, Ibrahim *et al.* [23] set precedent for the use of ammonium salts, a source of halogens in the hypervalent iodine chemistry applied to the α-chlorination of 1,3-dicarbonyl compounds **36**. This protocol gave excellent yields (80% to 97%) under mild reaction conditions (Scheme **13**).

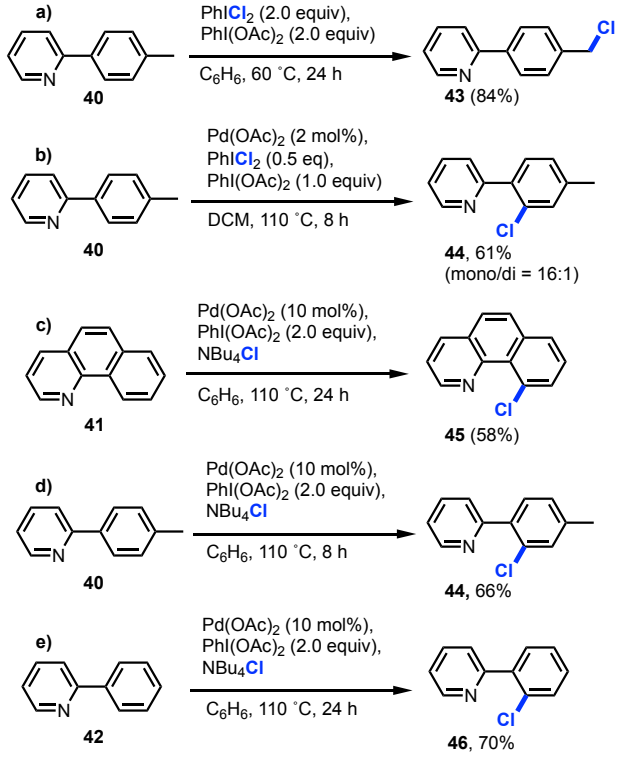
Regarding the catalytic reactions using hypervalent iodine reagents, Min *et al.* [24] developed regioselective chlorination of electron-rich aromatic compounds **38**. The protocol uses NH_4I, *m*-CPBA and LiCl to form *in situ*, the hypervalent iodane intermediate. In this way, the monochlorinated compounds **39** are obtained in moderate to good yields (71-91%) (Scheme **14**).



Scheme 13. α-Halogenation of 1,3-Dicarbonyl compounds using the Et_4NCl /PIDA system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 14. Catalytic *p*-chlorination of electron-rich arenes using the NH_4I/TsOH/*m*-CPBA/LiCl system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

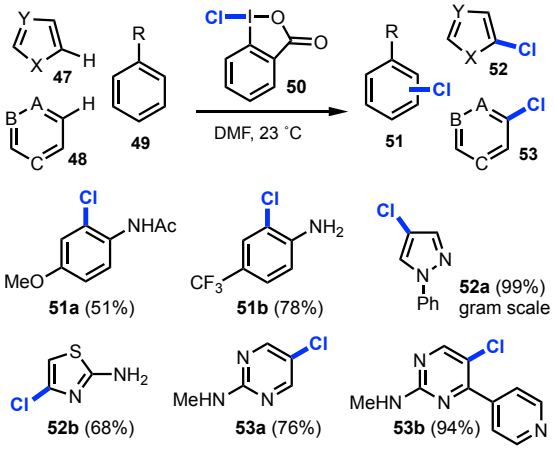


Scheme 15. Some examples of Pd-catalyzed C-H chlorination by *in situ*-generation of PhI(OAc)Cl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another chlorination protocol was developed by Kim *et al.* [25]. This procedure provides chemo- and regioselective C-H chlorination reaction at the benzylic or the aromatic position of *p*-tolylpyridine **40** if a stoichiometric or sub-stoichiometric amount of $PhICl_2$ is used (Scheme **15a-b**).

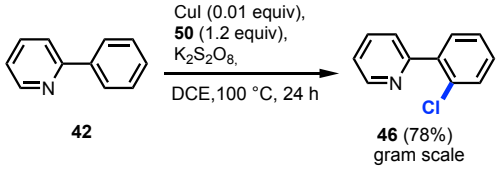
On the other hand, the palladium-catalyzed chlorination of benzo[*h*]quinoline and the *p*-tolylpyridine derivatives **40-42** by using $Pd(OAc)_2$, $PhI(OAc)_2$ and ammonium chloride as a chlorine source, produced the corresponding halogenated derivatives **44-46** in moderate to good yields (58-70%) (Scheme **15c-d**).

Subsequently, another chlorination method for arenes and heteroarenes (**47-49**) was developed by Xue [26]. Here, the use of the known iodine(III)-based chlorinating reagent 1-chloro-1,2-benziodoxol-3-one (**50**) allowed the access to several chlorinated carbo- and heterocycles (**51-53**) in moderate to good yields (62-82%) (Scheme **16**).



Scheme 16. Scope of chlorination by 1-chloro-1,2-benziodoxol-3-one (old-age reagent) in arenes and heteroarenes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

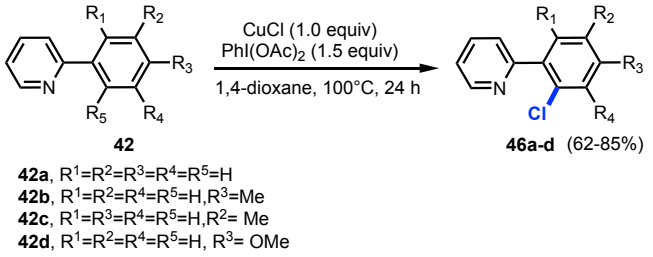
A regioselective copper-catalyzed method to successfully obtain chlorinated aryl heterocycles (**46**) was described by Parvathaneni [27]. This protocol combines **50** with copper iodide and $K_2S_2O_8$ as additive. Also, the procedure takes place in a gram scale within good yields (78%) (Scheme **17**).



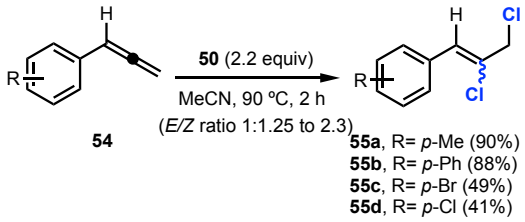
Scheme 17. Copper-catalyzed *orto*-chlorination of aryl pyridines. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The same group of Parvathaneni [28] explored the reaction with CuCl and $PhI(OAc)_2$ in several 2-arylpyridines **42.** Different chlorinated derivatives **46** were obtained in *ortho*-selective fashion with moderate to excellent yields (62-85%) (Scheme **18**).

In 2018, Murphy and Zhao [29] reported bis-chlorination of phenylallene derivatives **54** using the chlorinating hypervalent iodine(III)-based reagent **50**. This reaction allowed access to vicinal bis-chlorides **55** showing broad group tolerance and scope, in moderate to excellent yields (30- 93%) (Scheme **19**).

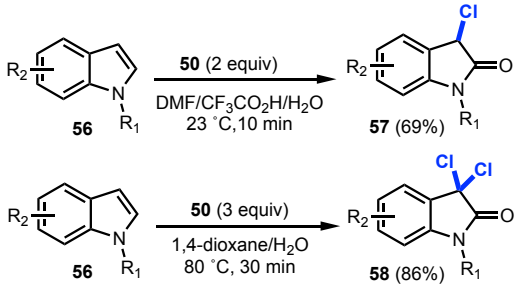


Scheme 18. *ortho*-chlorination of an aromatic compound using PIDA and CuCl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 19. Iodine(III)-mediated chlorination of phenylallene derivatives **54**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

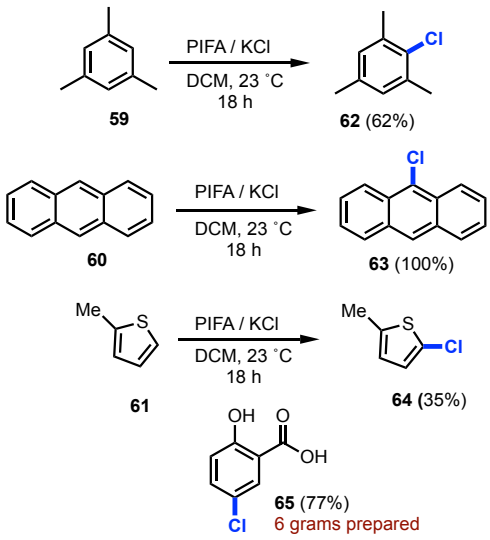
Later, in 2019, Yu *et al.* [30] described the transformation of a wide range of indoles **56** into 3-chloro-2-oxindoles (**57-58**). The reaction proceeds *via* the selective oxidation of C-2 with concomitant mono- or bis-chlorination at C-3. This iodine(III)-promoted chloro-oxidation is a one-pot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



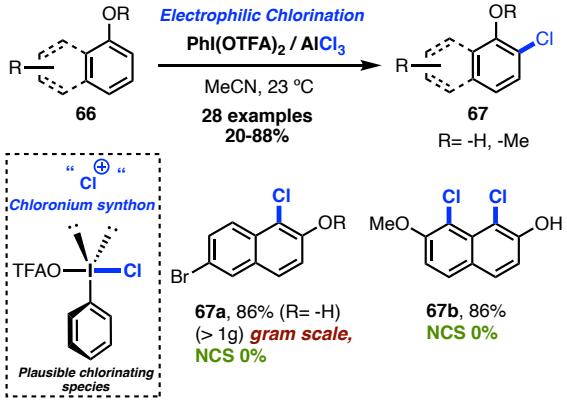
Scheme 20. Synthesis of 3-chlorooxindoles mediated by 1-chloro-1,2-benziodoxol-3-one **50**. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another chlorination protocol was described by Vallribera *et al.* [31]. Herein several arenes (**59-61**) were chlorinated using the mixture of PIFA and KCl, yielding the halogenated derivatives (**62-65**). Remarkably, this new methodology was successfully tested on a multigram scale to obtain 4-chloro salicylic acid **65** (6g, 77%) (Scheme **21**).

Recently, the group of Solorio-Alvarado [32] described electrophilic chlorination of different phenols and phenol-ethers (**66**) using the PIFA/$AlCl_3$ system. The procedure that allowed access to a wide range of chlorinated naphthols (**67**), is gram-scalable and the proposed chlorinating species resulted as even more reactive than common commercially available reagents such as NCS (Scheme **22**).



Scheme 21. Chlorination of arenes by using the PIFA-KCl system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



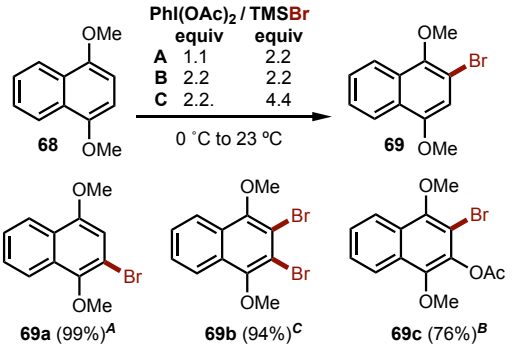
Scheme 22. Chlorination of arenes mediated by the PIFA/$AlCl_3$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. OXIDATIVE BROMINATION OF ARENES MEDIATED BY λ³-IODANES

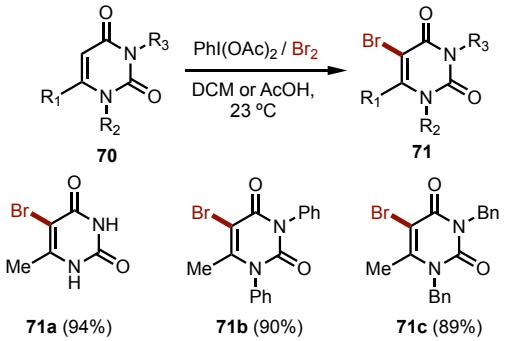
Concerning the brominated derivatives, due to their high relevance in organic synthesis, there is an increasing interest in accessing such important core. Herein we review some relevant protocols of bromination mediated by iodine(III) reagents.

In 1996, Evans *et al.* [20] reported novel haloacetoxylation of the 1,4-dimethoxynapthalene **68** using PIDA as an oxidant in the presence of TMS-Br as halogen source. The varied molar ratio of PIDA and TMS-Br gives rise to the mono- or bis-brominated or the bromoacetoxylated product **69**. The mechanism of this arene oxidation plausibly involves the formal addition of the acetoxyl anion to benzyne formed in 1,4-dimethoxynaphthalene (Scheme **23**).

In 2002, Chen *et al.* [33] described the bromination of methyluracil derivatives **70** using diacetoxyiodo(benzene) and molecular bromine. The method leads to the formation of the desired brominated methyluracils **71**, in yields usually higher than 90% (Scheme **24**).



Scheme 23. Bromination and acetoxylation of 1,4-dimethoxynaphthalene using PIDA and TMS-Br. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 24. Bromination of methyluracil mediated by the PIDA/Br_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

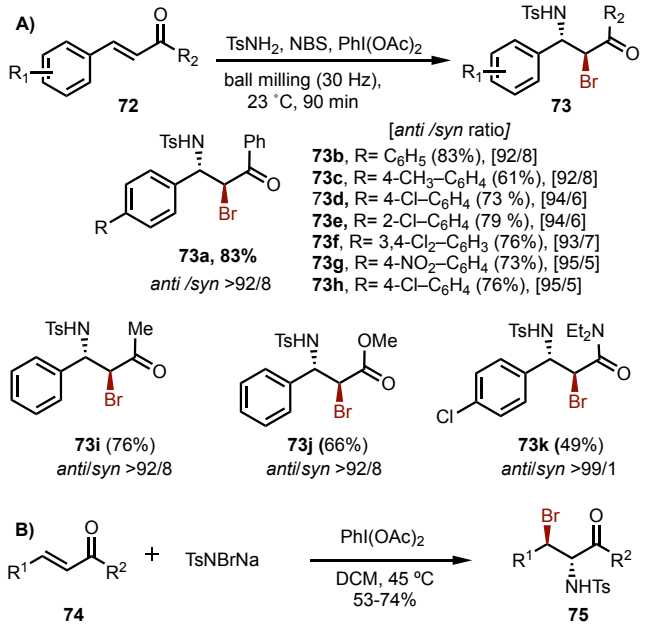
Later, Wang *et al.* [34] reported an oxidative iodine(III)-based procedure for the aminobromination of α, β-unsaturated ketones, esters, and amides **72**. The protocol displayed excellent diastereoselectivities under mechanical ball milling conditions, using $TsNH_2$ and NBS as the nitrogen and bromine sources respectively and (diacetoxyiodo)benzene as oxidant. The electron-donating olefins showed reversed regioselectivity and the corresponding bromoamine **73** was isolated with 77% of yield exclusively with *anti*-configuration (Scheme **25A**).

The same group in 2008 reported a procedure using bromamine-T as the nitrogen and bromine source for the aminobromination of electron-deficient olefins **74**. Excellent stereoselectivities were found for the corresponding reaction products **75** (Scheme **25B**) [35].

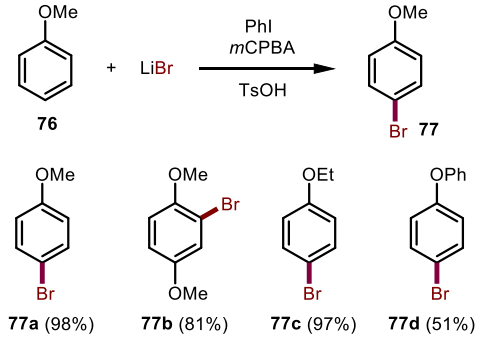
Another iodine(III)-catalyzed protocol for the regioselective monobromination of electron-rich arenes **76** was reported by Zhou *et al.* [36]. The procedure allowed the bromination of different phenols-ethers and heterocycles in excellent yields. The mechanism proposes the formation *in situ* of the Koser's type reagent [PhI(OTs)Br] following the electrophilic aromatic substitution. In this way, different brominated arenes **77** were obtained (Scheme **26**).

On the other hand, Hangirgekar *et al.* [37] developed a procedure for the facile regio- and stereoselective methoxybromination of olefins **78** using PIDA as oxidant and trimethyphenylammonium tribromide (PTAB) as a halogenating

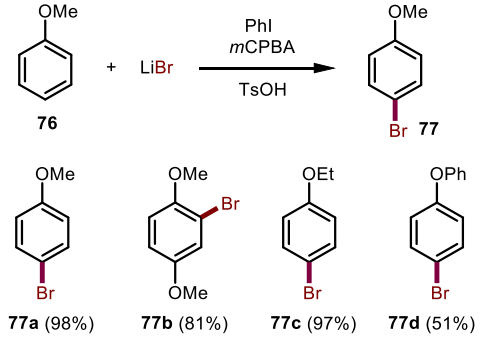
source. The mechanism of this reaction involves an S_N2 ring-opening reaction which explains the high *anti*-stereoselectivity of the brominated products **79**. Additionally, this methodology is characterized by high yields, short reaction times and easy workup procedure (Scheme **27**).



Scheme 25. Aminobromination of olefins promoted by $PhI(OAc)_2$. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

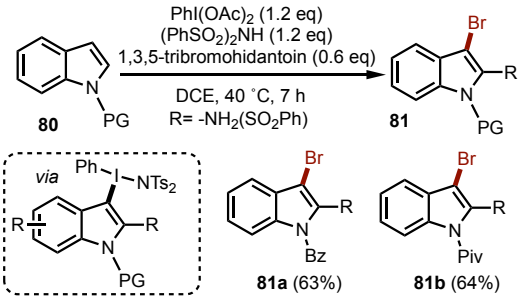


Scheme 26. Iodine(III)-catalyzed bromination of electron-rich arenes using PhI(OTs)Br. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



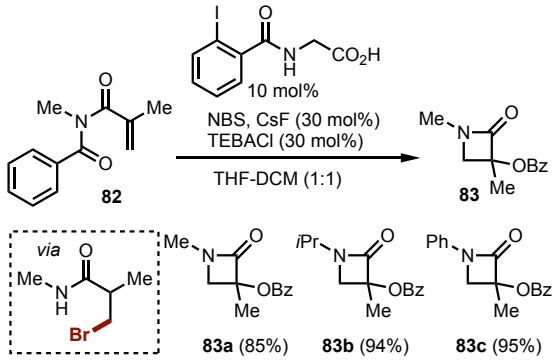
Scheme 27. Synthesis of vicinal methoxy-bromides from olefins using PIDA and PTAB. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another bromination procedure was described by Moriyama and Togo [38]. They developed a metal-free synthesis of 2-bis(sulfonyl)amino-3-bromo-indoles *via* the 1,3-migration of imide groups on indolyl(phenyl)iodonium imide. This protocol allowed the regioselective C_{sp^2}–H bromination of indoles in a two-step one-pot process (Scheme **28**).



Scheme 28. Regioselective C_{sp^2}–H bromo-amination of indoles mediated by PIDA and $(PhSO_2)NH$. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

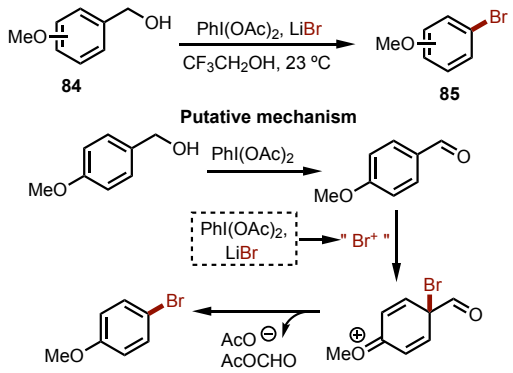
Also, the Gulder group [39] reported a one-pot synthesis of β-lactams under iodine(III)-catalyzed conditions. This cascade of reaction involves the bromination/rearrangement/cyclization sequence with excellent yields. In general, this three-step one-pot reaction gave direct access to isoserine derivatives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



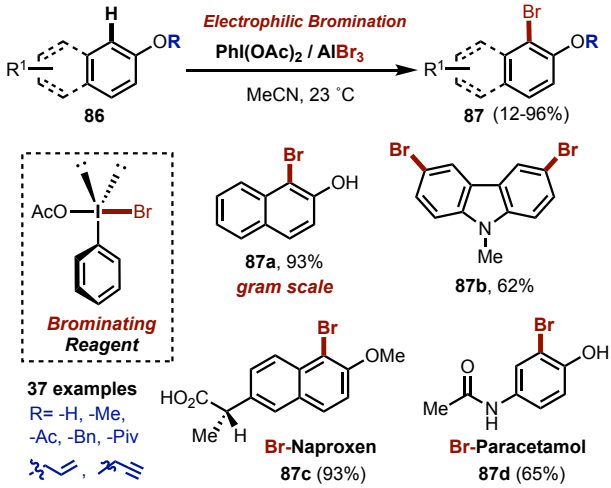
Scheme 29. Iodine(III)-catalyzed triple cascade reaction to obtain β-lactams. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Besides, Maegawa *et al.* [40] reported the first study about the dehydroxymethylbromination of methoxy-substituted benzyl alcohol derivatives **84** using (PIDA) and lithium bromide. This protocol involves the initial alcohol oxidation followed by the *ipso* attack of bromide to the arene with concomitant acetyl formate loss. The mono- or bis-brominated arenes **85** can be obtained by controlling the molar ratio of the hypervalent iodine(III) reagent and the lithium bromide (Scheme **30**).

Another relevant procedure to obtain brominated arenes was reported by Solorio-Alvarado [41]. The protocol described an efficient electrophilic bromination of several phenols and heterocycles **86**, with a broad scope of functional groups using the $PIDA/AlBr_3$ system. The gram-scale reaction proceeded with excellent yields and was applied to a wide range of different compounds including analgesics such as naproxen or paracetamol **87** (Scheme **31**).



Scheme 30. Conversion of benzylic alcohols into arene bromides. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

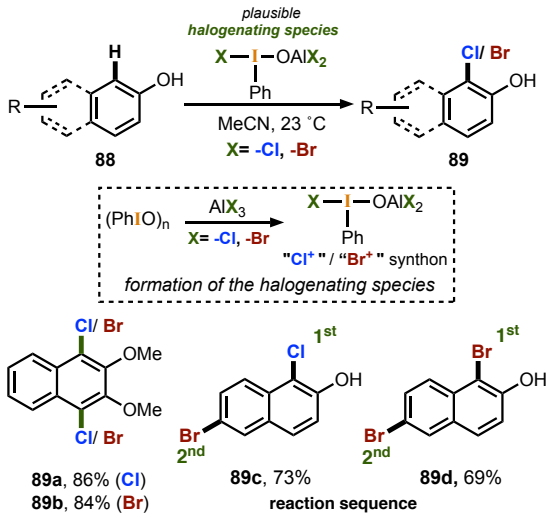


Scheme 31. Bromination of arenes mediated by the PIDA/$AlBr_3$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Moreover, a variant of the previous protocols of chlorination (PIFA/$AlCl_3$) [30] and bromination (PIDA/$AlBr_3$) [41] was described by the same group, using polymeric iodosylbenzene $(PhIO)_n$ [42] and the corresponding aluminum salt which carry a dual role in the depolymerization of iodosylbenzene and as halogen source (AlX_3; X= Cl, Br). The protocol was applied to a wide range of phenols and phenol-ethers **88** and some heterocycles obtaining different chlorinated and brominated arenes **89**. Additionally, the sequential bis-halogenation to obtain the chlorine-bromine and bromine-bromine phenols was achieved (Scheme **32**).

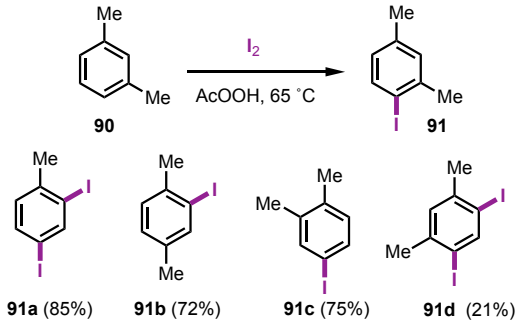
5. OXIDATIVE IODINATION OF ARENES MEDIATED BY λ³-IODANES

The iodine derivatives including aryl-, alkyl, alkenyl- or alkynyl iodides are a very important class of organic halides, especially in organic synthesis. They are the best electrophilic partners in the cross-coupling reactions and they are used as organic building blocks for several transformations. Along with the most relevant strategies for accessing these derivatives, hypervalent iodine chemistry has been used due to the low toxicity and generally easy handling. Herein we present a brief overview of some of the most representative iodination procedures which used hypervalent iodine reagents.



Scheme 32. Chlorination and bromination of arenes mediated by the $(PhIO)_n/AlX_3$ (X= Cl, Br) system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The very initial examples of iodination with hypervalent iodine reagents were reported in 1968 by Aoki *et al.* [43]. Herein, the relative rate of the iodination reaction was measured of some aromatic compounds **90** using molecular iodine in peracetic acid as solvent. A rate law was found which can be expressed as $I = k[I_2][CH_3CO_3H]$ where the electron-withdrawing substituents accelerated the rate of reaction. Representative aryliodides **91** obtained are outlined (Scheme **33**).

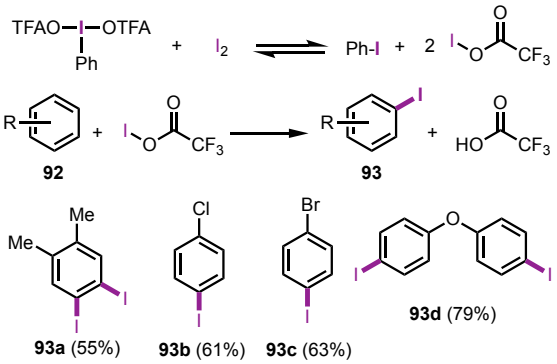


Scheme 33. Kinetic study and development of the iodination procedure of arenes using I_2/AcO_3H. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

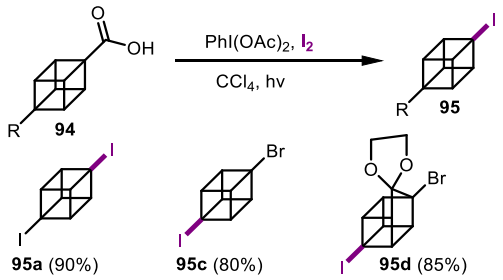
Initial examples of iodination with hypervalent iodines were reported in 1979 by Merkushev *et al.* [44]. They described the iodination of xylenes **92** in the presence of PIFA or iodosobenzene and molecular iodine using chloroform as solvent. The iodination procedure was fast and proceeded smoothly, with high yields at room temperature (Scheme **34**).

Subsequently, in 1988, Moriarty *et al.* [45] reported the decarboxylative-iodination of some cubane derivatives **94**. These homocubyl and cubyl carboxylic acids were treated with the PIDA/I_2 system in CCl_4 under irradiation condition giving rise to the corresponding iodinated products in excellent yields (80-90%). Also, the mechanism probably involves the hypervalent iodine(III) reagent prone to ligand exchange in one or two of the carboxylic acid groups to generate the

cubyl-acyloxy-hypervalent type system which upon irradiation generates the radical that is iodinated with molecular iodine (Scheme **35**).

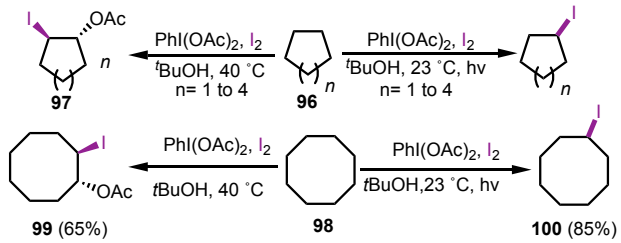


Scheme 34. Iodination of different arenes using PIFA/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



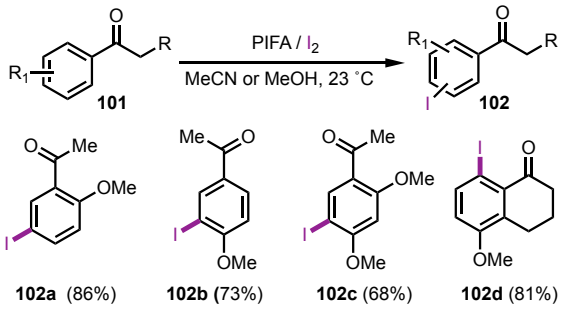
Scheme 35. Hypervalent iodine(III) mediated decarboxylative-iodination of homocubyl and cubyl carboxylic acids. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

On the other hand, C-H activation is an important and challenging concept in organic synthesis. In this regard, Barluenga *et al.* [46] developed a new protocol for the C-H iodination using hypervalent iodine(III) reagents. In this approach, the single as well as the double formal C-H bond activation occurs either in iodoalkanes or 1-acetoxy-2-iodocycloalkanes respectively **96-98**. The reaction proceeds by treating the alkanes with PIDA and I_2 in *tert*-butylalcohol under photochemical or thermal conditions, giving rise to the iodinated products **99-100**. The authors suggested that the reaction proceeded through a radical pathway to initially generate species of hypoiodite nature such as ^{t}BuO**I**. This approach shows different diastereoselectivities under thermal and photochemical conditions (Scheme **36**).



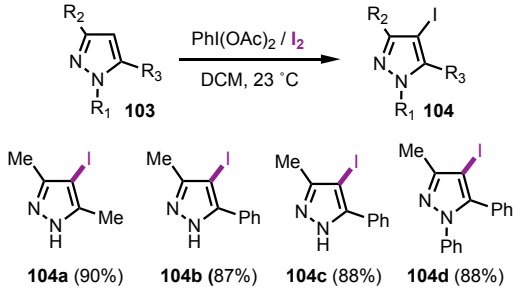
Scheme 36. Photochemical and thermal iodination of hydrocarbons with PhI(OAc)$_2$/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

A slight variant was reported in 2003 by Tingoli *et al.* [47]. Herein the iodination of aryl ketones **101** using PIFA and molecular iodine took place in acetonitrile or methanol to produce de-iodinated aromatic derivatives **102** (Scheme **37**).



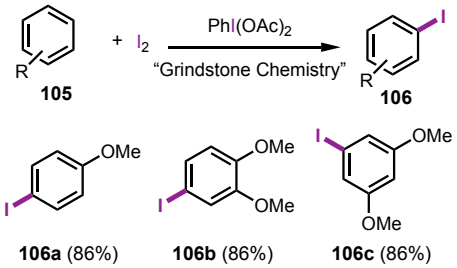
Scheme 37. Electrophilic aromatic-iodination of alkyl- and aryl ketones mediated by the PIFA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Also, Chen *et al.* [48] reported the iodination of pyrazoles **103** mediated by the broadly used PIDA/I_2 system. The reaction proceeded in dichloromethane at room temperature to yield the corresponding 4-iodopyrazole derivatives **104** generally in high yields (Scheme **38**).



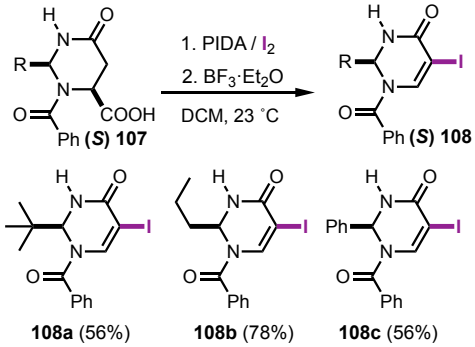
Scheme 38. Iodination of pyrazole derivatives mediated by PIDA/I_2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

An additional use of the PIDA/I_2 system was developed by Karade *et al.* [49] using the "Grindstone Chemistry" approach. This new approach allowed the mild, regioselective, and easy to handle iodination of different arenes **105** with a broad substrate scope, for accessing some iodoarene derivatives **106**. Improved yields and higher purities of the products were observed compared with those from established methods (Scheme **39**).



Scheme 39. Iodination of arenes with the PIDA/I_2 system under the grindstone chemistry approach. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

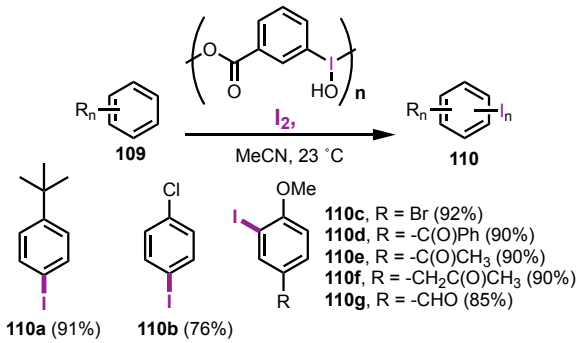
In 2007, Juaristi *et al.* [50] developed an iodination procedure for the synthesis of α-substituted β-aminoacids, using the PIDA/I_2 system. The reaction proceeded with perhydropyrimidinone-6-carboxylic acids **107** in DCM at room temperature to afford the expected mixture of the reduced enones and iodoenones. The addition of $BF_3{\cdot}Et_2O$ drives the reaction to the complete conversion into iodoenone **108** (Scheme **40**).



Scheme 40. Preparation of enantiopure iodoenones using the PIDA/I_2 system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Subsequently, Kirschning *et al.* [51] reported in 2007, a new approach for the iodination of arenes and heterocyclic compounds using a polymeric hypervalent iodine(III) reagent. In this approach, *m*-iodosylbenzoic acid performed the iodination of arenes **109** in the presence of molecular iodine, at room temperature, in acetonitrile, obtaining good yields of the corresponding iodinated arenes **110**.

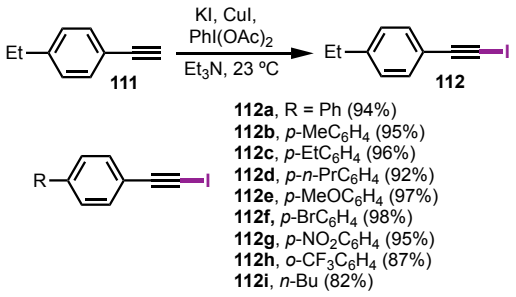
The *m*-iodobenzoic acid can easily be removed by simple acidification or by resin extraction (Scheme **41**).



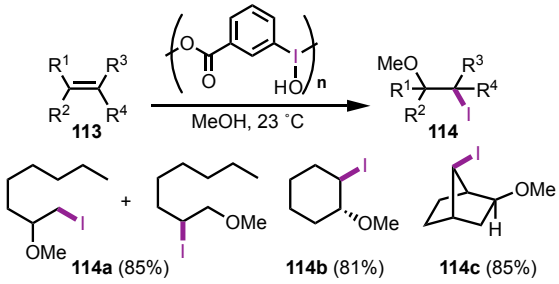
Scheme 41. Mono-iodination of arenes with *m*-iodosylbenzoic acid and molecular iodine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The iodination mediated by hypervalent iodine(III) reagents has also been applied to alkynes. In 2007, Yan *et al.* [52] reported the iodination of terminal alkynes **111** using PIDA, potassium iodide and copper(I). The protocol afforded 1-iodoalkynes **112** in good to excellent yields under mild conditions (Scheme **42**).

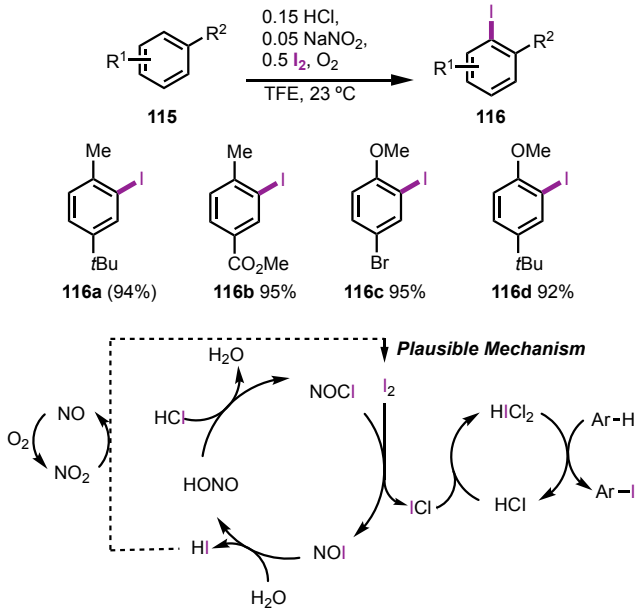
Yusubov *et al.* [53] developed another approach using *m*-iodosylbenzoic acid and molecular iodine for the iodination of alkenes and alkynes **113**. This efficient and facile method afforded the iodinated products **114** in good yields under mild conditions. The final purification of *m*-iodosylbenzoic acid by acidification or extraction by resins allowed easy isolation of the obtained products (Scheme **43**).



Scheme 42. Iodination of arenes mediated by PIDA/KI/CuI. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

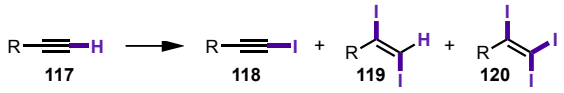


Scheme 43. Iodomethoxylations of alkenes using hypervalent *m*-iodosylbenzoic and molecular iodine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Scheme 44. Nitrite-mediated aerobic iodination of arenes by *in situ* generation of ICl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Later, Iskra *et al.* [54] reported an electrophilic aromatic iodination catalyzed by nitrous acid generated *in situ*. Different arenes are converted to the corresponding iodinated products *via* oxidative treatment at room temperature with catalytic quantities of iodine and nitrous acid in trifluoroethanol as the solvent. Dichloroiodic acid is proposed as the hypervalent iodinating reagent. A plausible mechanism for

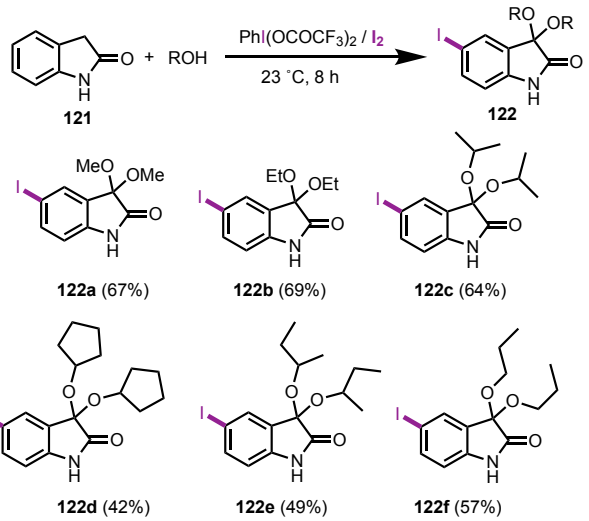


alkyne	method	mayor product	%yield (2:3:4)
R= *p*-tolyl	**A**	**2a**	99 (100:0:0)
	B	**3a**	99 (0.8:98.8:0.4)
	C	**4a**	93(3.7:3.2:93.1)
R= Ph	**A**	**2b**	93(100:0:0)
	B	**3b**	97(0.2:97.6:2.2)
	C	**4b**	91(0.8:0.7:98.5)
R= *m*-tolyl	**A**	**2c**	98(100:0:0)
	B	**3c**	98(0.9:98.1:1.0)

Method A: TBAI / $PhI(OAc)_2$ **Method B**: KI / $PhI(OAc)_2$

Method C: 1. TBAI / $PhI(OAc)_2$, 2. KI / $PhI(OAc)_2$, 3. KI / $PhI(OAc)_2$

Scheme 45. Iodination of alkynes mediated by PIDA/TBAI or PIDA/KI. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



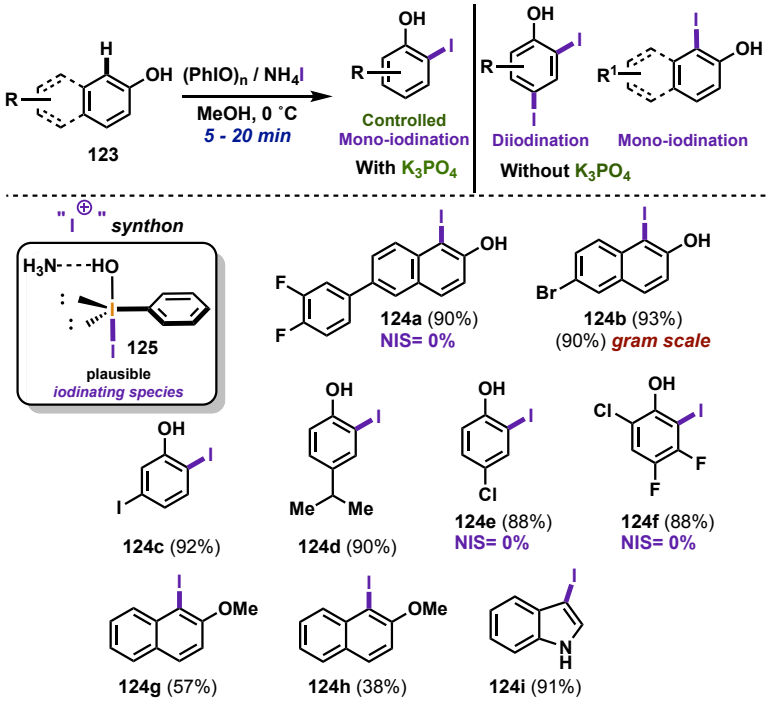
Scheme 46. Iodoalkoxylation of arenes mediated by the $PIFA/I_2$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

this reaction involves the interaction of sodium nitrate and hydrochloric acid to produce nitrosyl chloride. This reacts with molecular iodine to generate iodine chloride through a process that likely liberates nitrosyl iodide as a by-product. Iodine chloride reacts with arenes to produce iodinated product (Scheme **44**).

In 2017, Maruoka and Liu [55] developed a new practical approach for the chemoselective mono-, di-, and tri-iodination of alkynes using hypervalent iodine(III) reagents. The PIDA/TBAI (tetrabutylammonium iodide) system is selectively applied for mono-iodination, while the PIDA/KI system results in di-iodination. Combining the TBAI/PIDA and PIDA/KI systems in a one-pot protocol provided the corresponding tri-iodination products efficiently (Scheme **45**).

Kotagiri *et al.* [56] reported metal-free iodoalkoxylation of oxindoles **121** using the $PIFA/I_2$ system. In the first instance, the ketal formation at the benzylic carbon takes place, followed by the oxidative iodination leading to the formation of the observed functionalized compounds **122** (Scheme **46**).

Recently, another procedure for the electrophilic iodination of phenols **123** and phenol-ethers has been described in 2018 by Solorio-Alvarado [57]. The protocol is gram-scalable and in many cases more efficient than com-



Scheme 47. Controlled di- or monoiodination of arenes mediated by the $(PhIO)_n/NH_4I$ system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

mon procedures using iodinating reagents such as NIS. Additionally, the di-iodination of mono-annular phenols is a typical issue difficult to control. In this report, the mono-iodination of several phenols was exclusively obtained by buffering the reaction with K_3PO_4, while the reaction in the absence of this salt, usually produced di-iodinated derivatives. Additional computational studies revealed **125** as the most plausible iodinating species (Scheme **47**).

CONCLUSION

In summary, some of the most representative protocols for the halogenation of arenes, olefins and alkynes mediated by different types of iodine(III)-based reagents were described. Remarkably, every year there is a notable increased interest and demand for the use of iodine(III) chemistry positioned as one of the main tools in organic synthesis. There are several competitive advantages for using hypervalent iodine(III)-based reagents for the functional groups introduction, specifically concerning the full family of halogens in different aryls, heteroaryls, alkenes and alkynes, compared with the transition-metal transformation strategy. This oxidative approach for the functionalization of aromatic derivatives resulted generally in the fast, efficient, non-toxic and easy to handle reactions with the final introduction of the fluorine, chlorine, bromine and iodine atoms.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Lee, J.H.; Choi, S.; Hong, K.B. Alkene Difunctionalization Using Hypervalent Iodine Reagents: Progress and Developments in the Past Ten Years. *Molecules,* **2019**, *24*(14), 2634. http://dx.doi.org/10.3390/molecules24142634 PMID: 31331092

[2] Li, X.; Chen, P.; Liu, G. Recent advances in hypervalent iodine(III)-catalyzed functionalization of alkenes. *Beilstein J. Org. Chem.,* **2018**, *14*, 1813-1825. http://dx.doi.org/10.3762/bjoc.14.154 PMID: 30112085

[3] Zhdankin, V.V. Hypervalent iodine(III) reagents in organic synthesis. *ARKIVOC,* **2009**, *i*, 1-62.

[4] Yoshimura, A.; Zhdankin, V.V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.,* **2016**, *116*(5), 3328-3435. http://dx.doi.org/10.1021/acs.chemrev.5b00547 PMID: 26861673

[5] Peilleron, L.; Grayfer, T.D.; Dubois, J.; Dodd, R.H.; Cariou, K. Iodine(III)-mediated halogenations of acyclic monoterpenoids. *Beilstein J. Org. Chem.,* **2018**, *14*, 1103-1111. http://dx.doi.org/10.3762/bjoc.14.96 PMID: 29977382

[6] Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D.M.; Santi, C.; Ruzziconi, R.; Soloshonok, V.A. Fluorine-containing drugs approved by the FDA in 2018. *Chemistry,* **2019**, *25*(51), 11797-11819. http://dx.doi.org/10.1002/chem.201901840 PMID: 31099931

[7] Balz, G.; Schiemann, G. *Eur. J. Inorg. Chem.,* **1927**, *60*, 1186-1190.

[8] Tellitu, I. Explorando nuevas aplicaciones del reactive de yodo hipervalentes PIFA [bis(trifluoroacetoxi)yodobenceno] en la construcción de heterocíclos pirrolidínicos. *An. Quim.,* **2013**, *109*, 5-10.

[9] Kohlhepp, S.V.; Gulder, T. Hypervalent iodine(III) fluorinations of alkenes and diazo compounds: new opportunities in fluorination chemistry. *Chem. Soc. Rev.,* **2016**, *45*(22), 6270-6288. http://dx.doi.org/10.1039/C6CS00361C PMID: 27417189

[10] Carpenter, W. *J. Org. Chem.,* **1966**, *31*, 2688-2689. http://dx.doi.org/10.1021/jo01346a512

[11] Karam, O.; Jacquesy, J.C.; Jouannetaud, M.P. Nucleophilic *para*-fluorination of 4-alkylphenols by hypervalent iodine reagent and pyridinium polyhydrogen fluoride (PPHF), a novel route to 4-fluorocyclohexa-2,5-Dienones. *Tetrahedron Lett.,* **1994**, *35*, 2541-2544. http://dx.doi.org/10.1016/S0040-4039(00)77165-6

[12] Olah, G.A.; Shih, J.G.; Prakash, G.K.S. Fluorine-containing reagents in organic synthesis. *J. Fluor. Chem.,* **1986**, *33*, 377-396. http://dx.doi.org/10.1016/S0022-1139(00)85282-3

[13] Karam, O.; Martin-Mingot, A.; Jouannetaud, M.P.; Jacquesy, J.C.; Cousson, A. Efficient oxidative *ipso*-fluorination of *para*-substituted phenols using pyridinium polyhydrogen fluoride in combination with hypervalent iodine(III) reagents. *Tetrahedron,* **2004**, *60*, 6629-6638. http://dx.doi.org/10.1016/j.tet.2004.05.083

[14] Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, K.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. Iodoarene-catalyzed fluorination and aminofluorination by an Ar-I/HF·Pyridine/*m*CPBA system. *Chem. Sci. (Camb.),* **2014**, 2754-2760. http://dx.doi.org/10.1039/C3SC53107D

[15] Basset, L.; Martin-Mingot, A.; Jouannetaud, M.P.; Jacquesy, J.C. Access to new 4-fluorocyclohexa-2,5-dienimines using hypervalent iodine and pyridinium polyhydrogen fluoride. *Tetrahedron Lett.,* **2008**, *49*, 1551-1554. http://dx.doi.org/10.1016/j.tetlet.2007.12.082

[16] McMurtrey, K.B.; Racowski, J.M.; Sanford, M.S. Pd-catalyzed C-H fluorination with nucleophilic fluoride. *Org. Lett.,* **2012**, *14*(16), 4094-4097. http://dx.doi.org/10.1021/ol301739f PMID: 22844875

[17] Tian, T.; Zhong, W.H.; Meng, S.; Meng, X.B.; Li, Z.J. Hypervalent iodine mediated para-selective fluorination of anilides. *J. Org. Chem.,* **2013**, *78*(2), 728-732. http://dx.doi.org/10.1021/jo302099d PMID: 23228030

[18] Xing, B.; Ni, C.; Hu, J. Hypervalent iodine(III)-catalyzed Balz-Schiemann fluorination under mild conditions. *Angew. Chem. Int. Ed. Engl.,* **2018**, *57*(31), 9896-9900. http://dx.doi.org/10.1002/anie.201802466 PMID: 29932480

[19] Zhao, Z.; To, A.J.; Murphy, G.K. Difluorinative ring expansions of benzo-fused carbocycles and heterocycles are achieved with p-(difluoroiodo)toluene. *Chem. Commun. (Camb.),* **2019**, *55*(98), 14821-14824. http://dx.doi.org/10.1039/C9CC08310C PMID: 31763650

[20] Evans, P.A.; Brandt, T.A. Novel Haloacetoxylation of 1,4-dimethoxynaphthalenes using hypervalent iodine chemistry. *Tetrahedron Lett.,* **1996**, *37*, 6443-6446. http://dx.doi.org/10.1016/0040-4039(96)01427-X

[21] Zanka, A.; Takeuchi, H.; Kubota, A. Large-Scale Preparation of iodobenzene dichloride and efficient monochlorination of 4-Aminoacetophenone. *Org. Process Res. Dev.,* **1998**, *2*, 270-273. http://dx.doi.org/10.1021/op980024e

[22] Thorat, P.B.; Bhong, B.Y.; Karade, N.Y. 2,4,6-Tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine as a new recyclable hyperva-

lent iodine(III) reagent for chlorination and oxidation Reactions. *Synlett,* **2013**, *24*, 2061-2066.
http://dx.doi.org/10.1055/s-0033-1339495

[23] Galligan, M.J.; Akula, R.; Ibrahim, H. Unified strategy for iodine(III)-mediated halogenation and azidation of 1,3-dicarbonyl compounds. *Org. Lett.,* **2014**, *16*(2), 600-603.
http://dx.doi.org/10.1021/ol403504z PMID: 24372311

[24] Min, Z.; Ying-Guo, F. An efficient monochlorination of electron-rich aromatic compounds catalyzed by ammonium iodide. *J. Chem. Res.,* **2014**, *38*, 197-199.
http://dx.doi.org/10.3184/174751914X13929076043809

[25] Kang, K.; Lee, S.; Kim, H. Radical chlorination with hypervalent iodine(III) generated by ligand exchange: revisiting palladium(II)-catalyzed directed C-H chlorination. *Asian J. Org. Chem.,* **2015**, *4*, 137-140.
http://dx.doi.org/10.1002/ajoc.201402284

[26] Wang, M.; Zhang, Y.; Wang, T.; Wang, C.; Xue, D.; Xiao, J. Story of an age-old reagent: an electrophilic chlorination of arenes and heterocycles by 1-Chloro-1,2-Benziodoxol-3-One. *Org. Lett.,* **2016**, *18*(9), 1976-1979.
http://dx.doi.org/10.1021/acs.orglett.6b00547 PMID: 27074528

[27] Parvathaneni, S.P.; Perumgani, P.C. Regioselective chlorination of aryl C−H bonds with the hypervalent iodine(III) reagent 1-Chloro-1,2-Benziodoxol-3-One. *Asian J. Org. Chem.,* **2018**, *7*, 324-327.
http://dx.doi.org/10.1002/ajoc.201700620

[28] Perumgani, P.C.; Parvathaneni, S.P.; Surendra Babu, G.V.; Srinivas, K.; Mandapati, M.R. Copper(I) halide for regioselective *ortho*-halogenation of directed arenes. *Catal. Lett.,* **2018**, *148*, 1067-1072.
http://dx.doi.org/10.1007/s10562-018-2324-5

[29] Zhao, Z.; Murphy, G.K. Chlorination of phenylallene derivatives with 1-chloro-1,2-benziodoxol-3-one: synthesis of *vicinal*-dichlorides and chlorodienes. *Beilstein J. Org. Chem.,* **2018**, *14*, 796-802.
http://dx.doi.org/10.3762/bjoc.14.67 PMID: 29719576

[30] Jiang, X.; Yang, L.; Yang, W.; Zhu, Y.; Fang, L.; Yu, C. Controllable synthesis of 3-chloro- and 3,3-dichloro-2-oxindoles *via* hypervalent iodine-mediated chlorooxidation. *Org. Biomol. Chem.,* **2019**, *17*(28), 6920-6924.
http://dx.doi.org/10.1039/C9OB01173K PMID: 31282524

[31] Granados, A.; Jia, Z.; del Olmo, M.; Vallribera, A. *In-situ* generation of hypervalent iodine reagents for the electrophilic chlorination of arenes. *Eur. J. Org. Chem.,* **2019**, 2812-2818.
http://dx.doi.org/10.1002/ejoc.201900237

[32] Nahide, P.D.; Ramadoss, V.; Juárez-Ornelas, K.A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J.M.J.; Alonso-Castro, A.J.; Zapata-Morales, J.R.; Ramírez-Morales, M.A.; Ruiz-Padilla, A.J.; Deveze-Álvarez, M.A.; Solorio-Alvarado, C.R. *In Situ* formed I^{III}-based reagent for electrophilic *ortho*-chlorination of phenols and phenol-ethers: the use of PIFA/$AlCl_3$ system. *Eur. J. Org. Chem.,* **2018**, 485-493.
http://dx.doi.org/10.1002/ejoc.201701399

[33] Cheng, D.; Chen, Z.; Zheng, Q. Hypervalent iodine in synthesis 91: a mild and efficient method for the halogenation of 6-methyluracil derivatives. *J. Chem. Res.,* **2002**, 624-625.
http://dx.doi.org/10.3184/030823402103171032

[34] Wu, X-L.; Xia, J-J.; Wang, G-W. Aminobromination of olefins with $TsNH_{(2)}$ and NBS as the nitrogen and bromine sources mediated by hypervalent iodine in a ball mill. *Org. Biomol. Chem.,* **2008**, *6*(3), 548-553.
http://dx.doi.org/10.1039/B717333D PMID: 18219426

[35] Xia, J-J.; Wu, X-L.; Wang, G-W. Hypervalent iodine-promoted aminobromination of electron-deficient olefins with bromamine-T. *ARKIVOC,* **2008**, *16*, 22-28.

[36] Zhou, Z.; He, X. An Efficient and Regioselective Monobromination of electron-rich aromatic compounds using catalytic hypervalent iodine(III) reagent. *Synthesis,* **2011**, *2*, 207-209.
http://dx.doi.org/10.1055/s-0030-1258350

[37] Shirodkar, S.G.; Hangirgekar, S.P. A Regioselective and stereoselective methoxy bromination of olefins using diacetoxyiodobenzene and phenyltrimethyl ammoniumtribromide. *Orient. J. Chem.,* **2011**, *27*, 179-184.

[38] Moriyama, K.; Ishida, K.; Togo, H. Regioselective $C(_{sp^2})$-H dual functionalization of indoles using hypervalent iodine(III): bromoamination *via* 1,3-migration of imides on indolyl(phenyl)iodonium imides. *Chem. Commun. (Camb.),* **2015**, *51*(12), 2273-2276.
http://dx.doi.org/10.1039/C4CC09077B PMID: 25556519

[39] Patzelt, C.; Pöthig, A.; Gulder, T. Iodine(III)-catalyzed cascade reactions enabling a direct access to β-lactams and α-hydroxy-β-amino acids. *Org. Lett.,* **2016**, *18*(14), 3466-3469.
http://dx.doi.org/10.1021/acs.orglett.6b01658 PMID: 27380445

[40] Shibata, A.; Kitamoto, S.; Fujimura, K.; Hirose, Y.; Hamamoto, H.; Nakamura, A.; Miki, Y.; Maegawa, T. Dehydroxymethyl bromination of alkoxybenzyl alcohols by using a hypervalent iodine reagent and lithium bromide. *Synlett,* **2018**, *29*, 2275-2278.
http://dx.doi.org/10.1055/s-0037-1610980

[41] Satkar, Y.; Ramadoss, V.; Nahide, P.D.; García-Medina, E.; Juárez-Ornelas, K.A.; Alonso-Castro, A.J.; Chávez-Rivera, R.; Jiménez-Halla, J.O.C.; Solorio-Alvarado, C.R. Practical, mild and efficient electrophilic bromination of phenols by a new I(III)-based reagent: the PIDA–$AlBr_3$ system. *RSC Advances,* **2018**, *8*, 17806-17812.
http://dx.doi.org/10.1039/C8RA02982B

[42] Segura-Quezada, A.; Satkar, Y.; Patil, D.; Mali, N.; Wrobel, K.; González, G.; Zárraga, R.; Ortiz-Alvarado, R.; Solorio-Alvarado, C.R. Iodine (III)/AlX_3-mediate electrophilic chlorination and brominating of arenes. The Dual Role of AlX_3 (X=Cl, Br) in the $(PhIO)_n$ depolymerization and halogen Source. *Tetrahedron Lett.,***2019**, *60*, 1551-1555. Other relevant functional groups introduced using iodine(III) and aluminums salts. (a) For nitration of arenes using $(PhIO)_n$/$Al(NO_3)_3$ see: Juárez-Ornelas, K. A.; Jiménez-Halla, J. O. C.; Kato, T.; Solorio-Alvarado, C. R.; Maruoka, K. Iodine(III)-catalyzed electrophilic nitration of phenols *via* non-brönsted acidic NO_2^+ generation. *Org. Lett.***2019**, *21*, 315-1319. (b) For benzylic oxidation $(PhIO)_n$/$Al(NO_3)_3$ see: Yahuaca-Juárez, B.; González, G.; Ramírez-Morales, M. A.; Alba-Betancourt, C.; Deveze-Álvarez, M. A.; Mendoza-Macías, C. L.; Ortiz-Alvarado, R.; Juárez-Ornelas, K. A.; Solorio-Alvarado, C. R.; Maruoka, K. Iodine(III)-catalyzed benzylic oxidation by using the $(PhIO)_n$/$Al(NO_3)$ system. *Synth. Commun.,* **2020**, *50*, 539-548.

[43] Ogata, Y.; Aoki, K. Iodination of aromatic compounds with a mixture of iodine and peracetic acid. 111. Autocatalysis and relative rates. . *J. Am. Chem. Soc.,* **1968**, *90*, 6187-6191.
http://dx.doi.org/10.1021/ja01024a043

[44] Merkushev, E.B.; Simakhina, N.D.; Koveshnikova, G.M. A new convenient iodination method of aromatic compunds. *Syntheis,* **1980**, *80*, 486-487.
http://dx.doi.org/10.1055/s-1980-29066

[45] Moriarty, R.M.; Khosrowshahi, J.S.; Dalecki, T.M. Hypervalent iodine iodinative decarboxylation of cubyl and homocubyl carboxylic acids. *J. Chem. Soc. Chem. Commun.,* **1987**, *9*, 675-676.
http://dx.doi.org/10.1039/c39870000675

[46] Barluenga, J.; González-Bobes, F.; González, J.M. Activation of alkanes upon reaction with $PhI(OAc)_2$-I_2. *Angew. Chem. Int. Ed. Engl.,* **2002**, *41*(14), 2556-2558.
http://dx.doi.org/10.1002/1521-3773(20020715)41:14<2556::AID-ANIE2556>3.0.CO;2-C PMID: 12203532

[47] Panunzi, B.; Rotiroti, L.; Tingoli, M. Solvent directed electrophilic iodination and phenylselenenylation of activated alkyl aryl ketones. *Tetrahedron Lett.,* **2003**, *44*, 8753-8756.
http://dx.doi.org/10.1016/j.tetlet.2003.10.037

[48] Cheng, D-P.; Chen, Z-C.; Zheng, Q-G. Hypervalent iodine in synthesis. 90. A mild and efficient method for the iodination of pyrazoles. *Synth. Commun.,* **2003**, *33*, 2671-2676.
http://dx.doi.org/10.1081/SCC-120021987

[49] Karade, N.N.; Tiwari, G.B.; Huple, D.B.; Siddiqui, T.A.J. Grindstone chemistry: (diacetoxyiodo)benzene-mediated oxidative nuclear halogenation of arenes using NaCl, NaBr or I_2. *J. Chem. Res.,* **2006**, 366-368.
http://dx.doi.org/10.3184/030823406777946761

[50] Díaz-Sánchez, B.R.; Iglesias-Arteaga, M.A.; Melgar-Fernández, R.; Juaristi, E. Synthesis of 2-substituted-5-halo-2,3-dihydro-4(*H*)-pyrimidin-4-ones and their derivatization utilizing the Sonogashira coupling reaction in the enantioselective synthesis of α-substituted β-amino acids. *J. Org. Chem.,* **2007**, *72*(13), 4822-4825.
http://dx.doi.org/10.1021/jo0705115 PMID: 17523668

[51] Kirschning, A.; Yusubov, M.S.; Yusubova, R.Y.; Chi, K-W.; Park, J.Y. *m*-Iodosylbenzoic acid - a convenient recyclable reagent for

highly efficient aromatic iodinations. *Beilstein J. Org. Chem.,* **2007**, *3*(19), 19.
http://dx.doi.org/10.1186/1860-5397-3-19 PMID: 17543133

[52] Li, J.; Cheng, D.; Yan, J. Novel and efficient synthesis of 1-iodoalkynes. *Synlett,* **2007**, *15*, 2442-2444.

[53] Yusubov, M.S.; Yusubova, R.Y.; Kirschning, A.; Park, J.Y.; Chi, K-W. *m*-Iodosylbenzoic acid, a tagged hypervalent iodine reagent for the iodo-functionalization of alkenes and alkynes. *Tetrahedron Lett.,* **2008**, *49*, 1506-1509.
http://dx.doi.org/10.1016/j.tetlet.2007.12.120

[54] Iskra, J.; Murphree, S.S. Rapid aerobic iodination of arenes mediated by hypervalent iodine in fluorinated solvents. *Tetrahedron Lett.,* **2017**, *58*, 645-648.
http://dx.doi.org/10.1016/j.tetlet.2017.01.003

[55] Liu, Y.; Huang, D.; Huang, J.; Maruoka, K. Hypervalent iodine mediated chemoselective iodination of alkynes. *J. Org. Chem.,* **2017**, *82*(22), 11865-11871.
http://dx.doi.org/10.1021/acs.joc.7b01555 PMID: 28803465

[56] Kotagiri, R.; Adepu, R. Alkoxylation followed by iodination of oxindole with alcohols mediated by hypervalent iodine reagent in the presence of iodine. *Eur. J. Org. Chem.,* **2018**, *33*, 4556-4564.
http://dx.doi.org/10.1002/ejoc.201800723

[57] Satkar, Y.; Yera-Ledesma, L.F.; Mali, N.; Patil, D.; Navarro-Santos, P.; Segura-Quezada, L.A.; Ramírez-Morales, P.I.; Solorio-Alvarado, C.R. Iodine (III)-mediated, controlled di- or monoiodination of Phenols. *J. Org. Chem.,* **2019**, *84*(7), 4149-4164.
http://dx.doi.org/10.1021/acs.joc.9b00161 PMID: 30888169

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Discovery of novel fungistatic 4-aryloxyquinolines on Mucor circinelloides, biological evaluation of activity and QSAR study

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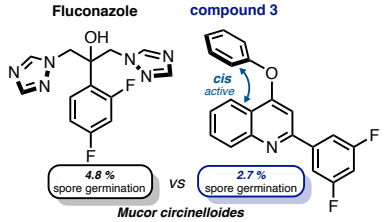

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Discovery of novel fungistatic 4-aryloxyquinolines on *Mucor circinelloides,* biological evaluation of activity and QSAR study

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KEYWORDS Fungistatic activity, *Mucor circinelloides*, Mucormycosis, 2-aryl-4-aryloxyquinolines, QSAR study

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Abstract

Zygomycetes are ubiquitous saprophytes in natural environments which transform organic matter. Some zygomycetes of gender *Mucor* have attracted interest in health sector. Due to its ability as opportunistic microorganisms infecting immuno-compromised people and to the few available pharmacological treatments, the mucormycosis is receiving worldwide attention. Related to the pathogenicity, the yeast-hyphae dimorphism of some *Mucor* species is the main and most studied aspect of the fungus biological cycle. Concerning to the pharmacological treatments, some triazole-based compounds such as fluconazole® are extensively used. Nevertheless, we focused in the quinolines since they are extensively used models for the design and development of new synthetic antifungal agents. In this study, the fungistatic activity on *M. circinelloides* of various 2-aryl-4-aryloxyquinoline-based compounds was discovered, in some cases, resulted better than reference compound fluconazole®. These quinoline derivatives were synthesized via the C_{sp}^2-O bond formation using diaryliodonium(III) salts chemistry. A QSAR study was carried out to correlated quantitatively the chemical structure of the tested compounds with their biological activity. The results highlighted an increased activity with the fluorine- and nitro-containing derivatives. In light of the few mucormycosis pharmacological treatments, herein we present some non-described molecules with excellent *in vitro* activities with potential use in the mucormycosis treatment.

1 | INTRODUCTION

Zygomycetes are ubiquitous saprophytes in natural environments that contribute to the transformation of organic matter.[1] In recent years, zygomycetes have attracted interest in different fields such as health sector.[2, 3] Some members of the zygomycetes have been described worldwide as emergent opportunistic pathogens in humans,[4] especially those with diabetes mellitus,[5] leucemia[6] or severe traumatic injuries.[7] This type of fungi can cause the deadly infection known as mucormycosis. Some of the reported mucormycosis etiologic agents species include *Apsidia trapeziformis*, *Cunninghamella spp*, *Mucor spp*, *Rhizomucor spp* and *Rhizopus spp*.[8, 9, 10]

In aspects related to zygomycetes pathogenicity, the yeast-hyphae dimorphism of some *Mucor* species is considered the main and most relevant studied aspect regarding the biological cycle of the fungi. Depending on the environmental conditions in which dimorphic species of *Mucor* are cultivated, the germination of spores produces vegetative cells of hyphae (mycelium) or spherical budding cells (yeasts).[11, 12] The production of mycelium or yeast cells can occur under aerobic or anaerobic conditions, according to the carbon source and/or the addition to the medium of morphogenetic compounds. Mycelial cells are able to grow adopting an oxidative or fermentative metabolism, depending on the cultivation conditions, whereas the production of yeast cells obligatorily requires the presence of hexoses. In this case the cells adopt a fermentative metabolism producing high levels of ethanol after growth under different conditions, such as anaerobiosis or growth in aerobiosis in the presence of morphogenetic compounds, such as dibutyryl cyclic AMP, certain amino acids and phenethyl alcohol (PEA).[13]

Growth conditions are key for *M. circinelloides*, as differing conditions determine the fate of asexual spores, which develop either as mycelia or yeast cells; this process, depends mostly on the availability of oxygen and carbon sources.[14, 15] Morphological changes are also related to fungal pathogenesis and disease development, in such away *M. circinelloides* can become a human opportunistic pathogen associated to its mycelia morphology.[16, 17] The lethal phenotype in humans is associated in part with the limited availability of antifungal therapies targeted against mucorales, for example, some clinical strains of *M. circinelloides* have been described as resistant to amphotericin, fluconazole and posaconazole, which are the primary antifungal compounds utilized in mucormycosis therapy.[18]

In this context there is an urgent need for developing new antifungal and fungistatic drugs, for generating novel therapeutic options. Accordingly, quinine a quinoline alkaloid isolated from the bark of the Cinchona tree in 1820, used in the treatment of malaria, played a historical role in the development of quinoline alkaloids as therapeutics.[19] These quinoline based-compounds have been isolated and identified from natural sources (plants, animals, and microorganisms),[20] and many studies have documented their antitumor,[21] antimalarial,[22] antibacterial,[23] antifungal,[24] antiviral,[25] antiparasitic and insecticidal,[26] anti-inflammatory,[27] antiplatelet and other activities.[28] The most successful drug-based on quinoline scaffold is chloroquine, which was specifically developed as antimalarial agent.[29] On the other hand consequent with the importance of the antifungal activity of the quinoline and 4-quinolone moieties these nucleus have been used as a scaffold for drug development for more than two centuries.[30] At the present, numerous quinoline-based compounds and drugs were developed, designed to target all stages of fungal life-cycle. In fact, quinolines still serve as inexhaustible models for design and development of new semisynthetic or synthetic quinoline/quinolone antimicrobial agents.[31]

In the present study, the biological activity of different 2-aryl-4-aryloxy- and 2-aryl-4-methoxyquinolines were assayed, the results conducted us to the discovery of the fungistatic activity on two different strains of *M. circinelloides* for several of the tested compounds. Finally, the QSAR study for assayed compounds, provided an explanation of the structure-activity relationship, evidencing the potential use of this type of compounds in the plausible treatment of mucormycosis.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

2.1.1. | Method A: Synthesis of *O*-aryloxyquinolines

A group of seventeen 2-aryl-4-aryloxyquinolones were synthesized by using a modified procedure of our previous report.[32] The starting materials correspond to their respective 2-aryl-4-quinolones which were prepared according to our optimized reaction conditions. Then, synthesis of compounds **1**-**17** started by reacting the 2-aryl-4-quinolone derivatives with sodium methoxide in acetonitrile at 60 ºC. This reaction generates a bidentate quinoline anion which *in situ* reacts with different diaryliodonium(III) salts giving rise to the formation of the O-C_{sp^2} bond by transferring the more electron-poor aryl. In such away highly functionalized 4-aryloxyquinolines were obtained in a mild and operationally simple protocol, involving conventional heating (Scheme 1).

2.1.2. | Method B: Synthesis of *O*-methoxyquinolines

A series of eight compounds containing a methoxy group in the fourth position were easily synthesized. Starting from the previously described 2-aryl-4-quinolones, the regioselective methylation of the oxygen proceeded smoothly by treatment with potassium carbonate and iodomethane in acetone at 65 ºC. In this way 2-aryl-4-methoxyquinolines **18**-**25** were obtained in good yields (scheme 1).

2.1.2. | Method C: Synthesis of 2-arylquinolines

A small group of 2-aryquinolines were synthesized via a Suzuki cross-coupling reaction. Thereby, starting from 2-bromoquinoline, the palladium-catalyzed cross coupling reaction with phenylboronic acid, 3,5-dimethylboronic acid and 3,5-diflurophenylboronic acid respectively in a (1:1) mixture of toluene-water at 80 ºC, leaded to the formation of the compounds **26**-**28** in modest yields after eight hours of reaction (Scheme 1).

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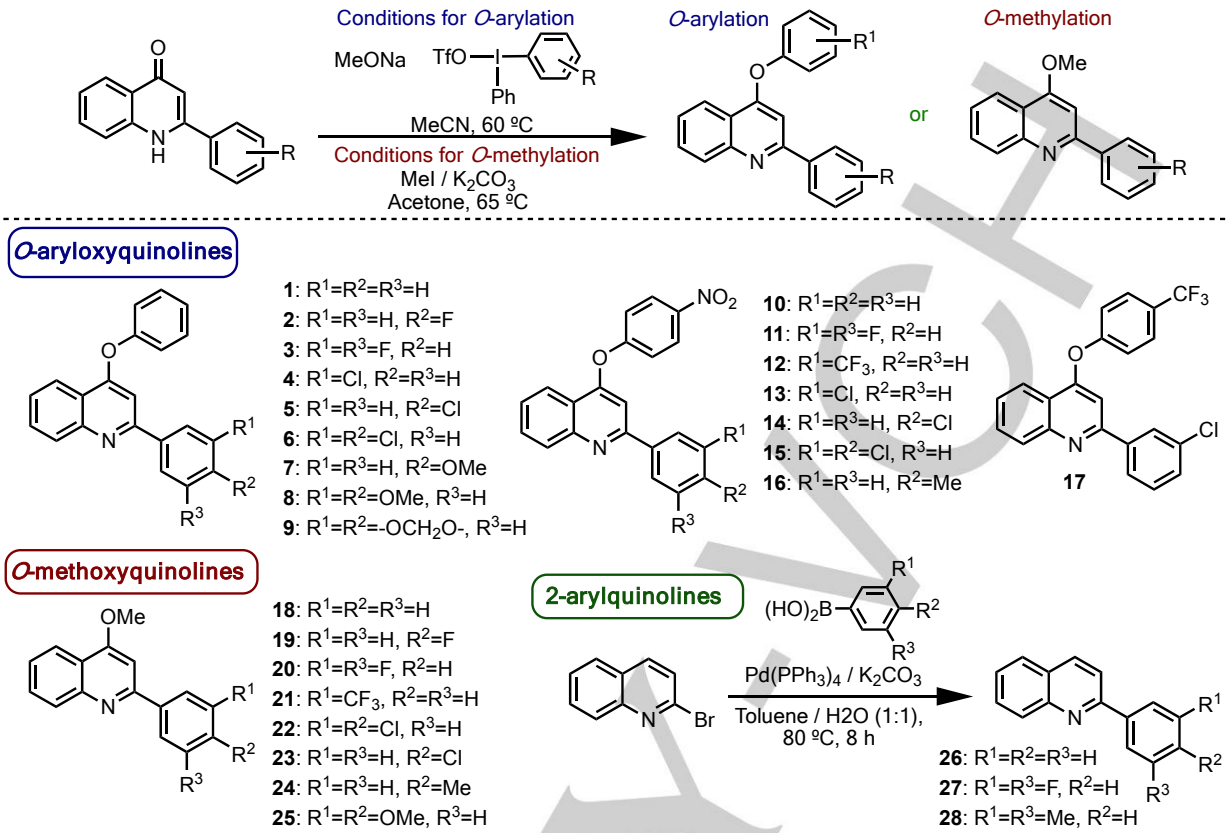

SCHEME 1. Synthesized quinoline compounds. Two types of quinolines were synthesized, o-arylated quinolines (1-17) and o-methylated quinolines (**18**-**25**).

2.2 | Biology

2.2.1 | Spore germination of *Mucor circinelloides*

The *Mucor circinelloides* spores as the infective form of the fungus were initially screened to identify the percentage of germination, thereby, the growth inhibition degree on two different strains was determined when incubated with the synthesized quinolines. Due that germination represents the beginning of the invasive stage of *M. circinelloides*, the inhibition of this process by the synthesized compounds is interesting to observe. The first studied strain is the wild-type R7B and the second one is the M5 strain which is a mutant in the adh1 gene and exhibit higher virulence compared with R7B.[33] In this first set of assays, all of the compounds **1**-**28** were tested at 100 mg/mL concentration in order to identify the more active compounds (Table 1).

Thus, the first group of essayed quinolines (**1**-**9**) containing a 4-phenoxy substituent displayed poor activity (c.a. 94% to 98% germination) for both strains when electron-neutral or electron-rich aryls (**1**, **7** and **8**) were present in the second position of the quinoline. Nevertheless, the quinoline with the heterocycle 1,3-benzodioxole (**9**) showed modestly good activity (c.a. 28% germination). For the chlorine-contain quinoline derivatives, low (**4**) to modest (**5** and **6**) activity was observed (36% to 89% germination). However, the fluorine-contain quinolines, displayed a remarkable substitution-dependent activity. If the fluorine is present at the 4´position (**2**) we have only modest activity (39% germination), but if the fluorine is present at the 3´and 5´positions (**3**) a very high activity was obtained and just 3.1% of germination for R7B strain was observed and a 12.8% of germination for the M5 strain. This difference in the activity for both strains may be due to the higher virulence of the M5 strain.

The following set of essayed quinolines (**10**-**16**) containing a 4-nitrophenoxy group behaved similarly. The quinolines with an electron-neutral (**10**) or electron-rich (**16**) aryl in the position 2 of the core, exhibited low biological activity and almost all of the spores germinated (>98%). The chlorine-containing quinolines with the chlorine atom at 4´ or 3´, 4´ (**14** and **15**) gave a poor activity (c.a. 81 to 83% germination), however if the chlorine is at the 3´position (**13**) a modestly good activity is observed (32% germination). Also, the substitution-dependent activity is present. Interestingly, this previous result was also obtained for the trifluoromethyl group at the 3´position (**12**). As expected, the 3´, 5´-difluoro-containing quinoline (**11**) displayed the best activity and only the 7.9% and 11.2% of germination was allowed for the R7B and M5 strains respectively.

Another group of 2-arylquinolines with a 4-methoxy group (**18**-**25**) were assayed. In this case, a dramatic decreasing in the biological activity was in general observed (**18**, **21**-**25**) with exception of those fluorine-containing which displayed modest (**20**) (32% germination) to good activity (**19**) (c.a. 17% germination). In this case the 3´,5´-difluoro pattern did not provide the best activity, instead, the fluorine in 4´position resulted in the best activity for this set of compounds.

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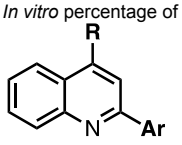
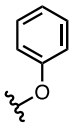
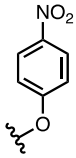
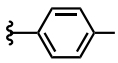
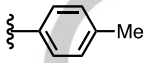
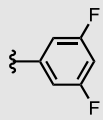
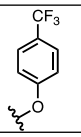
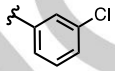
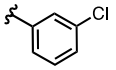
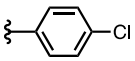
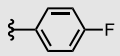
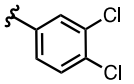
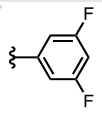
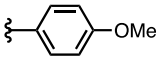
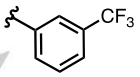
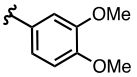
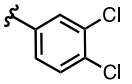
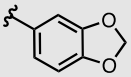
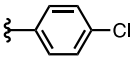
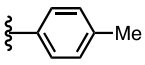
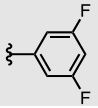
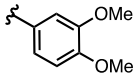
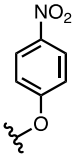
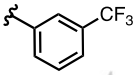
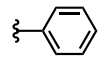
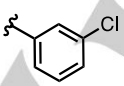
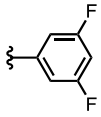
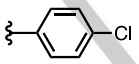
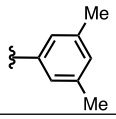
Table 1. *In vitro* percentage of spore germination for the wild-type R7B and mutant M5 strains of *Mucor circinelloides* at 100 mg/mL of the compounds **1** to **28**



Comp	R	Ar	% of germination R7B	% of germination M5	Comp	R	Ar	% of germination R7B	% of germination M5
1			97.4 ± 0.6	97.9 ± 2.5	**15**			83.9 ± 1.5	85.9 ± 2.8
2			39.8 ± 1.4	38.6 ± 1.3	**16**			98.1 ± 1.4	98.1 ± 0.7
3			3.1 ± 0.2	12.8 ± 0.6	**17**			42.2 ± 2.7	38.3 ± 1.2
4			89.1 ± 1.4	85.6 ± 2.6	**18**			97.8 ± 0.6	95.8 ± 1.5
5			36.1 ± 1.8	32.3 ± 1.6	**19**			17.1 ± 0.2	20.6 ± 0.5
6			60.8 ± 2.7	57.8 ± 3.4	**20**			32.8 ± 2.4	29.7 ± 1.2
7			94.3 ± 3.6	92.1 ± 0.7	**21**	**OMe**		88.9 ± 1.8	89.7 ± 1.2
8			98.1 ± 1.4	98.2 ± 0.8	**22**			96.1 ± 1.2	93.7 ± 0.8
9			28.2 ± 1.3	29.5 ± 1.2	**23**			98.1 ± 1.2	97.3 ± 0.6
10			98.1 ± 1.4	98.2 ± 1.6	**24**			81.9 ± 0.5	84.9 ± 2.6
11			7.9 ± 0.5	11.2 ± 0.4	**25**			97.1 ± 1.4	96.2 ± 1.8
12			32.8 ± 2.4	29.7 ± 1.2	**26**			98.1 ± 1.4	98.2 ± 0.8
13			32.7 ± 1.9	21.9 ± 1.1	**27**	**H**		57.5 ± 1.3	59.5 ± 1.2
14			81.7 ± 1.4	82.9 ± 1.6	**28**			84.9 ± 1.3	87.6 ± 2.6

At this point of our essays, the analysis of the obtained results preliminarily indicated three important structure-activity characteristics: 1) the 3´,5´-difluoro substitution in the aryl of the second position of the quinoline core, is absolutely necessary for an excellent biological activity (germination < 8%) for 4-aryloxy derivatives, 2) the presence of a 4-aryloxy group may increase the biological activity, based upon the fact almost all of the 4-methoxy derivatives with exception of those fluorine-containing, resulted inactive; and 3) the electron-neutral or electron-rich substituted aryls in the second position of the quinoline diminish drastically the biological activity of the compound.

Considering the previous preliminary conclusions, we decided to carry out additional essays using 2-arylquinolines without any substituent in the fourth position of the core but containing a phenyl (**26**), or a 3´,5´-difluorophenyl (**27**) or a 3´,5´-dmiethylphenyl

substituent in the second position of the quinoline. As previously observed, the electron-neutral (**26**) and electron-rich (**28**) derivatives resulted almost inactive (c.a. 84 to 98% germination). For the case of the 3´,5´-difluoro derivative (**27**) a modest biological activity was observed (57.5% germination). These obtained results confirmed our preliminary second and third conclusions (table 1).

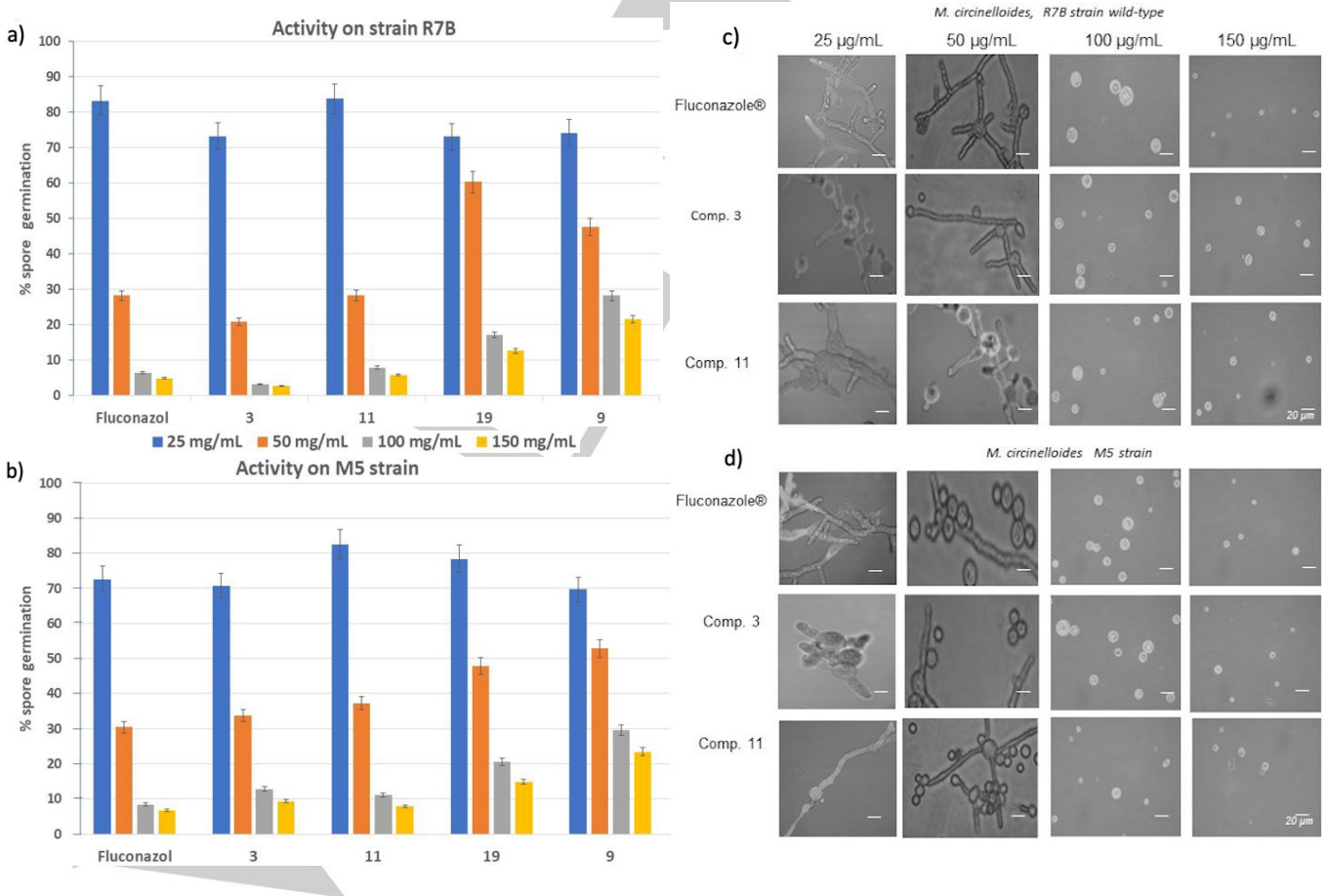
To complete these initial biological assays of activity, an inoculum of the tested cultures from compounds **3**, **9**, **11** and **19** as well as form the fluconazole® culture, were randomly taken and seeded in a fresh YPG media in absence of any compound. After its cultivation for 12 hours under standard conditions, we observed the spore germination and growth of the fungus in all of the five cultures. This experiment indicated that fluconazole® as well as our quinoline derivatives displayed ***fungistatic activity*** on both strains.

2.2.1 | Fungistatic activity on *Mucor circinelloides*

With previous results at hand, we choose the aforementioned compounds **3**, **9**, **11** and **19** as the more representative active and we proceeded to teste them at different concertations to determine if at lower or higher concertation a better or same the fungistatic activity could be observed (Scheme 2). Accordingly, additional concentrations of 150, 50 and 25 μg/mL were explored for these quinolines (Table 1).

Table 2. *In vitro* percentage of spore germination for the wild-type R7B and mutant M5 strains of *Mucor circinelloides* at 150, 50 and 25 mg/mL of the more active compounds **3**, **9**, **11** and **19**.

	25 μg/mL		50 μg/mL		100 μg/mL		150 μg/mL	
compound	**R7B**	**M5**	**R7B**	**M5**	**R7B**	**M5**	**R7B**	**M5**
3	73.3 ± 3.2	70.8 ± 2.9	20.8 ± 1.2	33.8 ± 2.1	3.1 ± 0.1	12.8 ± 0.6	2.7 ± 0.09	9.3 ± 0.5
11	83.9 ± 3.9	82.5 ± 3.2	28.3 ± 1.5	37.3 ± 1.9	7.9 ± 0.5	11.2 ± 0.4	5.8 ± 0.5	7.9 ± 0.5
19	73.1 ± 2.8	78.4 ± 2.8	60.3 ± 1.6	47.9 ± 2.7	17.1 ± 1.1	20.6 ± 0.5	12.6 ± 0.8	14.9 ± 0.8
9	74.2 ± 3.6	69.7 ± 3.8	47.6 ± 2.6	52.8 ±2.8	28.2 ± 1.4	29.5 ± 1.2	21.6 ± 1.1	23.4 ± 1.2
Fluconazole®	83.3 ± 4.4	72.6 ± 3.2	28.2 ± 1.6	30.4 ± 1.4	6.4 ± 0.5	8.4 ± 0.1	4.8 ± 0.4	6.7 ± 0.09



Scheme 2. Determination of the spore germination percentage on a) R7B and b) M5 strains for compounds **3**, **11**, **19**, and **9** at concentrations of 25, 50,100 and 150 μg/mL. c) Microscopic observations of the R7B and d) M5 strains in the presence of fluconazole and the more active fungistatic compounds **3** and **11**.

According to the table 2, for these additional assays the compounds **3** and **11** resulted the more actives at concentrations higher than 25 μg/mL. Also, commercially available fluconazole® was used as a known reference antimycotic compound. Screening of the compounds **3**, **11**, **19** and **9** at 25 μg/mL concentration, resulted all with poor activity (c.a. 70% to 83% germination) for both strains even for fluconazole®. The test at 50 μg/mL considerably increased the activity. In these cases, a modest effect (c.a. 47% to 60% germination) for compounds **9** and **19**; to modestly good effect (c.a. 20% to 37% germination) was observed for quinolines **3** and **11**. Finally, the activity for this set of four compounds (**3**, **11**, **19** and **9**) showed good (c.a. 12% to 23% germination) to very good activity (c.a. 2.7% to 9.3% germination) when incubated at 150 μg/mL concentration both strains.
In regard to the comparison against the fluconazole® activity, two different behaves can be identified. Concerning the activity on the R7B strain (Scheme 2a), the compound **3** remarkably displayed a consistent better activity for every assayed concentration (25, 50, 100 and 150 μg/mL) and resulted a better fungistatic than fluconazole®. The activity for M5 strain (Scheme 2b) was comparable, nevertheless, slightly lower for all the compounds tested compared with fluconazole®.
The obtained microscopic images for the different assayed concentrations of the compounds **3**, **11** and fluconazole® on the R7B strain (Scheme 2c) and the M5 strain (Scheme 2d) showed essentially a full spore germination when incubated at 25 μg/mL. Herein a morphogenetic differentiation into hyphae was observed. On the other hand, a significant decreased spore germination in general was observed when the concentration was increased at 50 μg/mL. In this case few mycelia in mix with several spores which did not get the germination and differentiation into hyphae were observed, this indicates the fungistatic effect of the compounds (Scheme 2c and 2d). Finally, when the tests were carried out at 100 μg/mL and 150 μg/mL the complete absence of mycelia can be clearly appreciated, and only non-germinated spores were observed, this indicated a stronger fungistatic effect in these concentrations. Herein is important to highlight the increased number of observed spores for the more active compounds which indicate a higher percentage of non-germination compared against those photos with few spores that indicate more germination, in consequence less-active compounds (Scheme 2c and 2d).
Fluconazole® is fungistatic rather than fungicidal, in consequence its treatment provides the opportunity for developing acquired resistance in the presence of this antifungal,[34] for this reason, the search for other compounds with a quinoline scaffold for new antifungal activities is important and has been revised.[35] Herein, we present the compounds **3** and **11** as potential candidates as an alternative or iterative treatment to Fluconazole®. This strategy could prevent totally or partially the plausible acquired resistance. Additionally, it is important to point that preparation of compounds **3** and **11** involves a less-expensive-reagent synthetic route.[36]

2.3 | Quantitative structure-activity relationship (QSAR) analysis

According to the obtained results, we anticipated a promising couple of new fungistatic quinoline-based scaffolds (**3** and **11**) which displayed comparable (compound **11**) or better (compound **3**) biological activity than fluconazole®. In consequence we considered that a structure-activity analysis is crucial to explain the behave of the biological activity as result of the explored substitution-pattern in the quinoline core.
Although the biological activity for the tested compounds is evident, the active site where the described compounds act is unknown to us. From a SAR (Structure Activity Relationship) analysis, it is possible to conclude that the groups in the substituted phenyl group at second position of the quinoline influence the activity. In general, electro-attractor groups favors while electro-donors affect negatively. However, some compounds do not match this prediction. Therefore, in order to explain the relationship between the structure in the series of compounds and their activity in the percentage of germination, a study of structure-quantitative activity relationship (QSAR) was carried out. For this analysis, the method of genetic algorithms by artificial intelligence was used. Additionally, it was exclusively considered the analogous series of quinolines substituted with the phenoxyl and 4-nitrophenoxyl groups at fourth position of the quinoline. Thus, 1664 physicochemical descriptors were determined for compounds **1**-**17** and were subjected to evolution using Dragon and MobyDigs (TALETE srl.) software. Afterwards 50 models were obtained as "best", multiple linear regression products with the highest statistical validation considering the lowest number of descriptors. From these, two mathematical models were selected that showed low correlation between the descriptors thus avoiding redundancy between them.

The models are described in equations 1 and 2 and the statistical parameters are summarized in Table 3.

%GERMINATION = 42**SPAN** + 304**Mor13v** - 1410**G2m** + 318 (**1**)

%GERMINATION = 32**SPAN** + 103**Mor13e** - 245**Mor23p** - 937**G2m** - 220 (**2**)

Table 3. Statistical parameters of the equations **1** y **2** (*n* = 17)

Equation	R	s	F_{calc} / F_{table}	Q2	SPRESS
42**SPAN** + 304**Mor13v** - 1410**G2m** + 318	0.876	0.127	9.571	0.790	1.649
32**SPAN** + 103**Mor13e** - 245**Mor23p** - 937**G2m** - 220	0.921	0.105	11.818	0.867	1.367

The values of the molecular descriptors are shown in Table 4. SPAN, is a geometric descriptor related to the radius of the molecular sphere while the Mor13e, Mor13v and Mor23p descriptors are related to Sanderson's electronegativities, van der Waals atomic volumes and atomic polarizability. The G2m descriptor is related to molecular size, shape, symmetry, and distribution of atoms.

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According to the QSAR results, it is evident that geometry plays an important role in the activity so we consider then that the conformation could affect the value of the descriptors and therefore of the activity. If true, information on possible interaction with the recipient would be obtained. Therefore, a conformational analysis using computational methods was performed using the Monte Carlo search method based on molecular mechanics and identifying the lowest energy conformer by means of single point energy calculation with a theory level of B3LYP/6-31G(d). Two main conformers were found: *syn* and *anti* with respect to the benzene ring of quinoline (Figure 1). A very low energy difference was found between the two conformers, which is not significant enough to observe both at room temperature, but it may be important from the point of view of molecular recognition with its receptor because of the well-known topology of interaction of ligands with their molecular targets. A molecular superposition analysis of all analyzed compounds shows the conformational similarity between the *syn*- and *anti*-groups of compounds and it is worth mentioning that, with the exception of compound **9**, all of them have preference over the *anti*-geometry with energy difference ranging from 0.25 to 3.25 kcal/mol. This result is interesting because compound **9** is the only one with electron-donating substitutes in the 2-phenyl and is also active despite having electron-donating substituents.

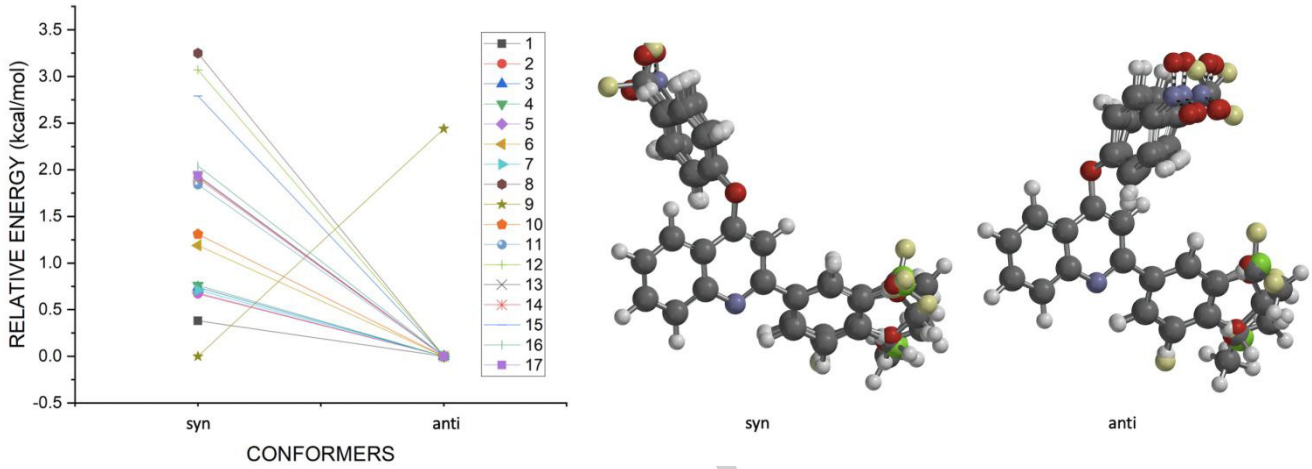

Figure 1. a) Relative energy-difference of compounds **1- 17** between their syn and *anti*-conformations, arbitrarily assigning a value of zero to the *anti*-structures. b) Superposition of structures **1 - 17** in their respective syn and *anti*-conformations as used in the QSAR study.

Although no correlation was found between the difference in energy of the two conformers and the biological activity; the descriptors obtained from both conformers were, as expected, different in magnitude. Their values were incorporated into equations 1 and 2. A high correlation was found between calculated and experimental activity when treating the *syn*-conformer, contrary to the *anti*-conformer (Figure 1).

Table 4. Summary of the calculated descriptors used in the QSAR models as well as the values obtained experimentally in percentage of germination and prediction values of each model for structures **1 - 17** in their *syn*- and *anti*-conformations.

Molecular descriptor						%Germination				
Compound	SPAN	Mor13e	Mor13v	Mor23p	G2m	Experimental	Calculated Equation 1		Calculated Equation 2	
							syn	*anti*	*syn*	*anti*
1	7.00	-0.39	-0.96	-1.19	0.16	98	95	48	105	47
2	6.80	-0.82	-1.12	-1.13	0.16	39	38	39	40	36
3	6.90	-0.86	-1.23	-1.00	0.16	13	8	35	7	34
4	6.90	-0.53	-1.00	-1.18	0.16	86	78	38	85	41
5	7.00	-0.47	-1.00	-1.07	0.20	32	26	42	30	46
6	7.40	-0.48	-1.00	-1.04	0.18	58	71	50	54	59
7	8.30	-0.81	-1.13	-1.20	0.17	92	83	89	97	90
8	7.90	-0.65	-1.03	-1.20	0.17	98	97	82	101	78
9	7.30	-1.02	-1.20	-1.15	0.17	30	20	40	31	32
10	7.70	-0.41	-1.08	-0.97	0.16	70	87	66	72	59
11	7.20	-0.70	-1.26	-0.94	0.16	11	12	54	19	53
12	7.50	-0.54	-1.17	-0.98	0.17	30	38	56	45	54
13	7.20	-0.42	-1.10	-0.97	0.18	22	32	72	36	69
14	7.50	-0.34	-1.09	-1.00	0.16	83	76	64	80	61
15	7.70	-0.40	-1.09	-0.99	0.17	86	70	71	68	74
16	8.30	-0.15	-1.09	-0.94	0.17	98	96	90	101	96
17	7.40	-0.71	-1.17	-1.00	0.16	38	48	47	39	57

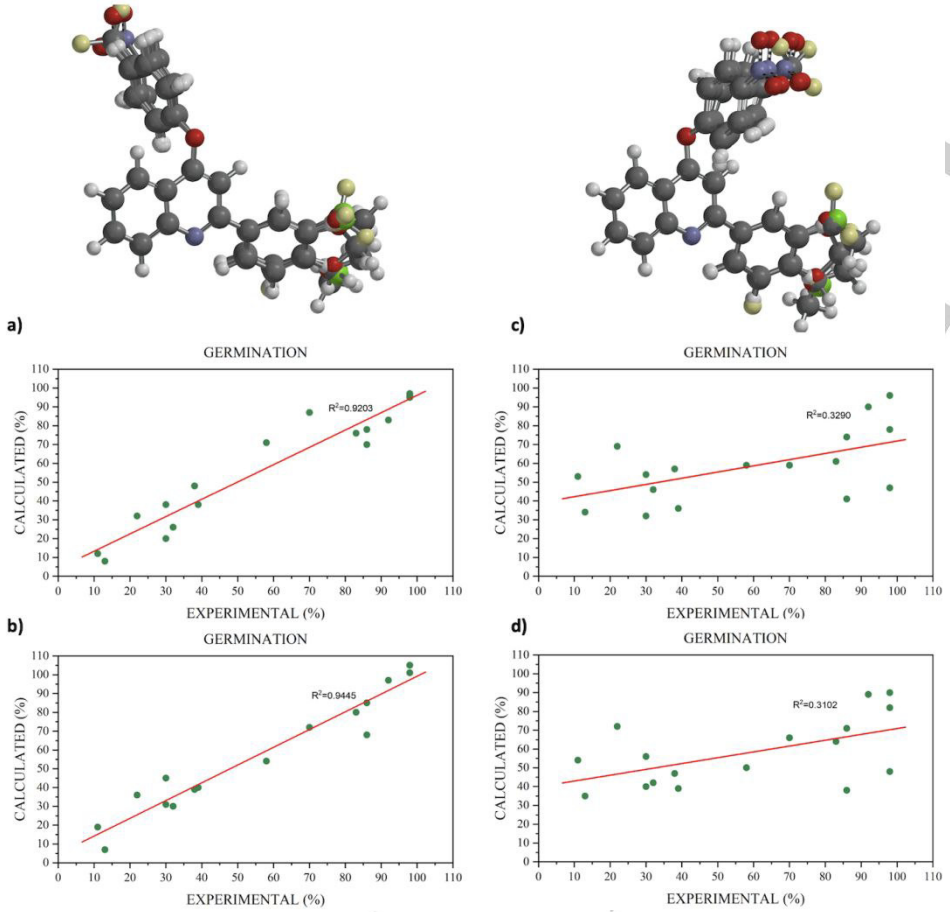

Figure 2. Experimental vs predicted (% germination from QSAR models) activity according to eq. 1 for: a) *syn*-conformer, b) *anti*-conformer and according to eq. 2 for: c) *syn*-conformer d) *anti*-conformer

From the results summarized in Table 4 as well as from the high correlation found between the experimental data and those calculated from equations 1 and 2 (Figure 2a and 2b), it can be seen that both QSAR models explain the biological activity as a function of their geometric and physicochemical properties (Sanderson's electronegativities, van der Waals atomic volumes and atomic polarizability) for the *syn*-former exclusively while for the *anti*-conformer no correlation could be found. Although we do not know the mechanism of molecular action and therefore the receptor on which these compounds act, this information is useful to design analogous structures either that favor the conformation *syn* or structures with anchored geometry similar to these.

3 | CONCLUSION

We discovered two new fungistatic 2-aryl-4-aryloxyquinolines-based compounds with biological activity which in one case is comparable (compound **11**) and in another case resulted better (compound **3**) than commercially available fluconazole®. The introduction of a phenoxy or 4-nitrophenoxy group in the fourth position of the quinoline core as well as the presence of two fluorine atoms at 3´and 5´positions of the phenyl group at second position of the quinoline nucleus were crucial for the best fungistatic activity against *Mucor circinelloides*. These new derivatives are excellent candidates as plausible alternatives to known fungistatic treatment with fluconazole®. In this regard some advantages such as an easier, shorter and less-expensive-reagent synthetic route can be highlighted. Additionally, the compounds **3** and **11** could be potentially used as iterative treatment for preventing the fungus resistance. In light of the few pharmacological treatments for attending mucormycosis, the compounds **3** and **11** can eventually be postulated as potentially strong candidates for a treatment.
Our QSAR analysis indicated that the best biological activity is conformationally *syn*-dependent. Although this computational analysis results are not definitive about the receptor interaction, it provided useful information for the design of new 2-aryl-4-aryloxyquinolines-based derivatives with higher probabilities of increase the fungistatic activity which would be favored with the *syn*-conformer.

4 | EXPERIMENTAL

4.1 | Chemistry

A total of twenty-eight compounds were synthesized and used in the experiments for testing their biological activity on R7B and M5 strains of *M. circinelloides*. Starting from a common 2-aryl-4-quinolone precursor, the *O*-aryloxyquinolines as well as the *O*-methoxyquinolines were synthesized (Figure 1). The synthesis of the 2-aryl-4-quinolones was carried via Cu-catalyzed C-N bond formation conditions between 2´-bromoacetophenone and

benzamide derivatives followed by cyclization.[37] Also, to identify if the 4-aryloxy or 4-methoxy groups have effect in the biological activity, three derivatives of 2-arylquinolines were synthesized removing these groups from its fourth position.

4.1.1 | General

All moisture and oxygen sensitive reactions were carried out in flame-dried round bottom flasks or using Schlenk techniques under an inert atmosphere of nitrogen, unless otherwise specified. NMR spectra were measured on ^{1}H and ^{13}C NMR and were acquired on Bruker Advance III (500 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin= quintuplet, sep=septet, dd = doublet-doublet, m = multiplet, b = broad), coupling constants (Hz), and assignment. Infrared (IR) spectra were recorded using a PerkinElmer system 2000 FT-IR spectrometer. High-resolution mass (HRMS) analyses were obtained under the following procedure: Samples were introduced by direct infusion at 3 μL min^{-1} to the electrospray ionization (ESI) source of a quadrupole time-of-flight mass spectrometer (Bruker Daltonics ESI-QTOF-MS maXis impact), equipped with Data Analysis 4.1. ESI was operated in positive mode with ion spray voltage 4 500 V, nitrogen dry gas 4 L min^{-1}, drying temperature 180 °C, and gas pressure 0.4 bar. Mass calibration was accomplished based on sodium formate clusters. The products were purified by flash column chromatography (silica gel 60, Merck and Sigma-Aldrich, 230-400 mesh) or preparative thin layer chromatography silica gel (PLC 60 F254. 0.5 mm). Commercially available reagents were purchased from Wako, Sigma-Aldrich, TCI and Alfa-aesar chemicals and used as received. Anhydrous solvents were purchased from Sigma Aldrich in SureSeal® bottles. Thin layer chromatography was performed with TLC Silica gel 60 F256 plates, and visualization was affected with short wavelength UV light (254 nm). Compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, Melting Point, IR (ATR) and Mass spectroscopy. (Copies of ^{1}H-NMR and ^{13}C-NMR spectra are provided in the supporting information for all new compounds). Data of known compounds were compared with existing literature characterization data and the references are given. Compounds **1-17** as well as 2-phenylquinolin-4(1*H*)-one, 2-(4-fluorophenyl)quinolin-4(1*H*)-one, 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one, 2-(3-chlorophenyl)quinolin-4(1*H*)-one, 2-(4-chlorophenyl)quinolin-4(1*H*)-one, 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one, 2-(4-methoxyphenyl)quinolin-4(1*H*)-one, 2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one, 2-(benzo[*d*][1,3]dioxol-5-yl)quinolin-4(1*H*)-one, 2-(*p*-tolyl)-quinolin-4(1*H*)-one and 2-(3-(trifluoromethyl)phenyl)quinolin-4(1*H*)-one were previously synthesized and characterized.

4.1.2 | Synthesis of 2-Aryl-4-aryloxyquinolines

General procedure A. In a 10 mL round-bottom flask was added the 2-aryl-4-quinolone (1.00 equiv), sodium methoxide (2.00 equiv) and acetonitrile (0.3 *M*). The round-bottom flask was then placed in a preheated oil bath at 60 °C. After 20 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 on silica gel (100–200) column chromatography to afford the pure aryloxyquinoline.

*4-phenoxy-2-phenylquinoline **(1)***

The following compound was obtained according to the general procedure A, starting from 2-phenylquinolin-4(1*H*)-one and Ph_2IOTf in 92% yield as white solid. R_f = 0.37 (10% AcOEt/hexane). mp= 54-56 °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. The spectroscopic data match with those previously reported.[32]

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

The following compound was obtained according to the general procedure A, starting from 2-(4-fluorophenyl)quinolin-4(1*H*)-one and Ph_2IOTf 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. The spectroscopic data match with those previously reported.[32]

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

The following compound was obtained according to the general procedure A, starting from 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one and Ph_2IOTf 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, CDCl3) 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. The spectroscopic data match with those previously reported.[32]

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

The following compound was obtained according to the general procedure A, starting from 2-(3-chlorophenyl)quinolin-4(1*H*)-one and Ph_2IOTf 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. The spectroscopic data match with those previously reported.[32]

*2-(4-chlorophenyl)-4-phenoxyquinoline **(5)***

The following compound was obtained according to the general procedure A, starting from 2-(4-chlorophenyl)quinolin-4(1*H*)-one and Ph_2IOTf 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. The spectroscopic data match with those previously reported.[32]

*2-(3,4-dichlorophenyl)-4-phenoxyquinoline **(6)***

The following compound was obtained according to the general procedure A, starting from 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one Ph_2IOTf 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. The spectroscopic data match with those previously reported.[32]

2-(4-methoxyphenyl)-4-phenoxyquinoline ***(7)***

The following compound was obtained according to the general procedure A, starting from 2-(4-methoxyphenyl)quinolin-4(1*H*)-one 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. ^1H 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. The spectroscopic data match with those previously reported.[32]

2-(3,4-dimethoxyphenyl)-4-phenoxyquinoline ***(8)***

The following compound was obtained according to the general procedure A, starting from 2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one and Ph_2IOTf 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. ^1H 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. The spectroscopic data match with those previously reported.[32]

2-(benzo[d] [1, 3] dioxol-5-yl)-4-phenoxyquinoline ***(9)***

The following compound was obtained according to the general procedure A, starting from 2-(benzo[*d*][1,3]dioxol-5-yl)quinolin-4(1*H*)-one and Ph_2INOTf 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. ^1H 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. The spectroscopic data match with those previously reported.[32]

4-(4-nitrophenoxy)-2-phenylquinoline ***(10)***

The following compound was obtained according to the general procedure A, starting from 2-phenylquinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. ^1H 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. The spectroscopic data match with those previously reported.[32]

2-(3,5-difluorophenyl)-4-(4-nitrophenoxy)quinolone ***(11)***

The following compound was obtained according to the general procedure A, starting from 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. ^1H NMR (500 MHz, CDCl3) 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. The spectroscopic data match with those previously reported.[32]

4-(4-nitrophenoxy)-2-(3-(trifluoromethyl)phenyl) quinolone ***(12)***

The following compound was obtained according to the general procedure A, starting from 2-(3-(trifluoromethyl)phenyl)quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. ^1H NMR (500 MHz, CDCl3) 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. The spectroscopic data match with those previously reported.[32]

2-(3-chlorophenyl)-4-(4-nitrophenoxy)quinoline ***(13)***

The following compound was obtained according to the general procedure A, starting from 2-(3-chlorophenyl)quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. ^1H 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. The spectroscopic data match with those previously reported.[32]

2-(4-chlorophenyl)-4-(4-nitrophenoxy)quinoline ***(14)***

The following compound was obtained according to the general procedure A, starting from 2-(4-chlorophenyl)quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. ^1H 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. The spectroscopic data match with those previously reported.[32]

2-(3,4-dichlorophenyl)-4-(4-nitrophenoxy)quinoline ***(15)***

The following compound was obtained according to the general procedure A, starting from 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. ^1H NMR (500 MHz, CDCl3) 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. The spectroscopic data match with those previously reported.[32]

4-(4-nitrophenoxy)-2-(p-tolyl)quinoline ***(16)***

The following compound was obtained according to the general procedure A, starting from 2-(*p*-tolyl)-quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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 $C_{22}H_{17}N_2O3$ [M+H] $^+$: 357.1239, found: 357.1227. The spectroscopic data match with those previously reported.[32]

2-(3-chlorophenyl)-4-(4-(trifluoromethyl)phenoxy)quinoline ***(17)***

The following compound was obtained according to the general procedure A, starting from 2-(3-chlorophenyl)quinolin-4(1*H*)-one and 4-NO_2-PhI(OTf)Ph iodonium salt 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. The spectroscopic data match with those previously reported.[32]

4.1.3. | Synthesis of 2-Aryl-4-methoxyquinolines

General procedure B. In 10 mL round-bottom flask were succesively added the 2-aryl-4-quinolone (1.00 equiv), potassium K_2CO_3 (1.5 equiv) and acetone (5 mL) under inert atmosphere. The round-bottom flask was then placed in a pre-heated 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. The 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-methoxyquinolines.

4-methoxy-2-phenylquinoline ***(18)***

This compound was synthesized according to the general procedure B, starting from 2-phenylquinolin-4(1*H*)-one and iodomethane in yield 86% 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. The spectroscopic data match with those previously reported.[38]

2-(4-fluorophenyl)-4-methoxyquinoline ***(19)***

This compound was synthesized according to the general procedure B, starting from 2-(4-fluorophenyl)quinolin-4(1*H*)-one and iodomethane in 84% yield 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. The spectroscopic data match with those previously reported.[38]

2-(3,5-difluorophenyl)-4-methoxyquinoline ***(20)***

This compound was synthesized according to the general procedure B, starting from 2-(3,5-difluorophenyl)quinolin-4(1*H*)-one and iodomethane in 81% yield 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.

4-methoxy-2-(3-(trifluoromethyl)phenyl)quinoline ***(21)***

This compound was synthesized according to the general procedure B, starting from 2-(3-(trifluoromethyl)phenyl)quinolin-4(1*H*)-one and iodomethane in 95% yield 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. The spectroscopic data match with those previously reported.[39]

2-(3,4-dichlorophenyl)-4-methoxyquinoline ***(22)***

This compound was synthesized according to the general procedure B, starting from 2-(3,4-dichlorophenyl)quinolin-4(1*H*)-one and iodomethane in 91% yield 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-(4-chlorophenyl)-4-methoxyquinoline ***(23)***

This compound was synthesized according to the general procedure B, starting from 2-(4-chlorophenyl)quinolin-4(1*H*)-one and iodomethane in 93% yield 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. [38]

4-methoxy-2-(p-tolyl)quinoline ***(24)***

This compound was synthesized according to the general procedure B, starting from 2-(*p*-tolyl)quinolin-4(1*H*)-one and Iodomethane in yield 83% as an amorphous white solid. mp: 94-96 °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); 13C NMR (126 MHz, CDCl3) 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. The spectroscopic data match with those previously reported.[38]

2-(3,4-dimethoxyphenyl)-4-methoxyquinoline ***(25)***

This compound was synthesized according to the general procedure B, starting from 2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one and iodomethane in 75% yield 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. The spectroscopic data match with those previously reported. [40]

4.1.3. │ Synthesis of 2-Aryl-4-methoxyquinolines

General procedure C. Suzuki−Miyaura Cross-Coupling Procedure.

The examples **26**, **27** and **28** were synthesized by Suzuki−Miyaura cross-coupling according to the following procedure. A 50 mL round-bottom flask with a stir bar was fitted with a rubber septum and flame-dried under high vacuum. The flask was purged with argon and successively charged with 2-bromoquinoline (1.00 equiv, 4.80 mmol), $Pd(PPh_3)_4$ (155.5 mg, 0.1 mmol), Na_2CO_3 (580.5 mg, 4.2 mmol), the correponding boronic acid (4.0 mmol), 10.0 mL of toluene and 2 mL of distilled water. The reaction mixture was heated at 80 °C for 8 h. Afterwards, the reaction was allowed to reach room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product were purified by flash chromatography on silica gel.

*2-phenylquinoline **(26)***

This compound was synthesized according to the general procedure C, using phenylboronic acid in 91% yield as an amorphous white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 8.10 (dd, *J* = 8.0, 6.2 Hz, 3H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 6.7 Hz, 1H), 7.63 (d, *J* = 3.4 Hz, 1H), 7.55 – 7.33 (m, 4H). The spectroscopic data match with those previously reported.[41]

*2-(3,5-difluorophenyl)quinoline **(27)***

This compound was synthesized according to the general procedure C, using (3,5-difluorophenyl)boronic acid in 85% yield as an amorphous white solid: ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) 7.97 – 7.92 (m, 2H), 7.70 (dd, *J* = 6.9, 1.5 Hz, 5H), 7.46 (d, *J* = 8.5 Hz, 1H), 6.84 (tt, *J* = 8.7, 2.4 Hz, 1H). Spectral data match with those previously reported.[42]

*2-(3,5-dimethylphenyl)quinoline **(28)***

This compound was synthesized according to the general procedure **B** by using 2-phenylquinoline and (3,5-dimethylphenyl)boronic acid in yield 89% (89 mg) as an amorphous white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (t, *J* = 9.7 Hz, 2H), 7.63 (dd, *J* = 19.5, 8.3 Hz, 2H), 7.56 (s, 2H), 7.51 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.36 – 7.27 (m, 1H), 6.90 (t, *J* = 1.6 Hz, 1H), 2.23 (s, 6H). Spectral data match with those previously reported.[43]

4.2 │ Biology
Fungal strains and cultivation conditions

We used the leucine-requiring *M. circinelloides* strain R7B (ATCC90608)[44] as the wild-type reference strain throughout this study; the M5 strain is a spontaneous allyl alcohol-resistant (Allyr) mutant derived from R7B.[45] Yeast-peptone-glucose (YPG) complete medium was used for the experiments. The strains were maintained, and spores were obtained after growth in YPG medium.

4.3 │ QSAR analysis

The values of the molecular descriptors are shown in Table 2. SPAN, is a geometric descriptor related to the radius of the molecular sphere while the Mor13e, Mor13v and Mor23p descriptors are related to Sanderson's electronegativities, van der Waals atomic volumes and atomic polarisability. The G2m descriptor is related to molecular size, shape, symmetry, and distribution of atoms.

According to the QSAR results, it is evident that geometry plays an important role in the activity so we consider then that the conformation could affect the value of the descriptors and therefore of the activity. If true, information on possible interaction with the recipient would be obtained. Therefore, a conformational analysis using computational methods was performed using the Monte Carlo search method based on molecular mechanics and identifying the lowest energy conformer by means of single point energy calculation with a theory level of B3LYP/6-31G(d). Two main conformers were found: syn and anti with respect to the benzene ring of quinoline. (Figure 1) A very low energy difference was found between the two conformers, which is not significant enough to observe both at room temperature, but it may be important from the point of view of molecular recognition with its receptor because of the well-known topology of interaction of ligands with their molecular targets. A molecular superposition analysis of all analyzed compounds shows the conformational similarity between the syn and *anti*-groups of compounds and it is worth mentioning that, with the exception of compound 1, all of them have preference over the anti geometry with energy difference ranging from 0.25 to 3.25 kcal/mol. This result is interesting because compound 1 is the only one with electrodonator substitutes in the 2-phenyl and is also active despite having electrodonator substituents.

4.4 │ Germination tests

To determine spore germination, aerobic growth was obtained in liquid cultures (5 mL) in YPG medium were grown in 25 mL Erlenmeyer flasks inoculated with spores at a final cell density of 5×10^5/mL and incubated in a shaking at 50 r.p.m. at 28°C for the indicated period of time. Germination percentage under aerobic conditions was calculated from the number of germinules or budding yeasts in at least 1000 cells.

4.5 │ Images analysis

A Carl Zeiss Axiolab 5 microscope equipped with a 40× objective lens and a camera Axiocam 208 was used to capture.

4.6 │ Statistical analysis

In the germination percentage experiments significant difference as assessed by a two-way ANOVA.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

[1] M. Richardson, *CMI.* **2009**, *15*, 2. DOI : 10.1111/j.1469-0691.2009.02972.x
[2] J. A. Ribes, C. L. Vanover-Sams, D. J. Baker, *CMR*. **2000**, *13*, 236. DOI: 10.1128/cmr.13.2.236-301.2000
[3] L. Mendoza, R. Vilela, K. Voelz, A. S. Ibrahim, K. Voigt, S. C. Lee, *Cold. Spring. Harb. Perspect. Med*. **2014**, *5*, 1. DOI: 10.1101/cshperspect.a019562
[4] M. M. Roden, T.E. Zaoutis, W. L. Buchanan, T. A. Knudsen, T. A. Sarkiskova, R. L. Shaufele, M. Sein, T. Sein, C. C. Chiou, J. H. Chu, D. P. Kontoyiannis, T. J. Walsh, *Clin Infect Dis.* **2005**, *41*, 634. DOI: 10.1086/432579
[5] A. Serris, A. F. Danion, F. Lanternier, *J. Fungi*. **2019**, *5*, 23. DOI : 10.3390/jof5010023
[6] R. E. Lewis, S. P. Georgiadou, F. Sampsonas, G. Chamilos, D. P. Kontoyiannis, *Mycoses.* **2013**, *57*, 49. DOI: 10.1111/ myc.12101.
[7] T. J. Walsh, D. R. Hospenthal, V. Petraitis, D. P. Kontoyiannis, *J. Fungi*. **2019**, *5*, 57. DOI: 10.3390/jof5030057
[8] M. Z. R. Gomes, R. E. Lewis, D. P. Kontoyiannis, *Clin. Microbiol. Rev.* **2011**, *24*, 411. DOI: 10.1128/CMR.00056-10
[9] M. Chayakulkeeree, M. A. Ghannoum, J. R. Perfect, *Eur. J. Clin. Microbiol. Infect. Dis*. **2006**. *25*, 215. DOI: 10.1007/s10096-006-0107-1
[10] S. Ibrahim, B. Spellberg. *Zygomycetes as agents of infectious disease in humans, in Molecular Principals of Fungal Pathogenesis* (Eds: J. Heitman, S. Filler, Edwards, Jr. J, A. Mitchell), ASM Press, Washington, **2006,** chapter 29. DOI: 10.1128/9781555815776.ch29
[11] L. Mendoza, R. Vilela, K. Voelz, A. S. Ibrahim, K. Voigt, S. C. Lee, *Cold. Spring. Harb. Perspect. Med*. **2015**, *5:a019562*, 1. DOI : 10.1101/cshperspect.a019562
[12] S. Bartnicki-García, *Bacteriol. Rev.* **1963**, *27*, 293.
[13] C. B. Inderlied, P. S. Sypherd, *J. Bacteriol.* **1978**, *133*, 1282.
[14] M. Orlowski, *Microbiol. Rev.*, **1991**, *55*, 234.
[15] M. McIntyre, J. Breum, J. Arnau, J. Nielsen, *Appl. Microbiol. Biot.* **2002**, *58*, 495. DOI: 10.1007/s00253-001-0916-1
[16] T. L. Lübbehüsen, J. Nielsen, M. Mcintyre, *Mycol. Res.* **2003**, *107*, 223. DOI: 10.1017/s0953756203007299
[17] S. C. Lee, A. Li, S. Calo, J. Heitman, *PLOS Pathog*. **2013**, *9*, 1. DOI: 10.1371/journal.ppat.1003625
[18] R. E. Lewis, D. P. Kontoyiannis, *Future Microbiol.* **2013**, *8*, 1163. DOI: 10.2217/fmb.13.78
[19] T. R. Rogers, *J. Antimicrob. Chemother.* **2008**, *61*, i35. DOI: 10.1093/jac/dkm429.
[20] J. Achan, A.O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana, F. N. Baliraine, P. J. Rosenthal, U. D'Alessandro. *Malar. J.* **2011**, *10*, 1. DOI: 10.1186/1475-2875-10-144
[21] G. Díaz, I. L. Miranda, M. A. Nogueira-Díaz, in *Phytochemicals - Isolation, Characterisation and Role in Human Health*, InTech, **2015**, chapter 6, pag 141. DOI : 10.5772/59819.
[22] V. Sharma V, D. K. Mehta, R. Das. *Mini-Rev Med Chem.* **2017**, *17*, 1557. DOI : 10.2174/1389557517666170510104954
[23] S. Kapishnikov, T. Staalsø, Y. Yang, J. Lee, A. J. Pérez-Berná, E. Pereiro, Y. Yang, S. Werner, P. Guttmann, L. Leiserowitz, J. Als-Nielsen. *PNAS*. **2019**, *116*, 22946. DOI: 10.1073/pnas.1910123116
[24] D. Insuasty, O. Vidal, A. Bernal, A. Marquez, J. Guzman, B. Insuasty, J. Quiroga, L. Svetaz, S. Zacchino, G. Puerto, R. Abonia. *Antibiotics*, **2019**, *8*, 239. DOI: 10.3390/antibiotics8040239
[25] R. Musiol, J. Jampilek, V. Buchta, L. Silva, H. Niedbala, B. Podeszwa, A. Palka, K. Majerz-Maniecka, B. Oleksyn, J. Polanski. *Bioorg. Med. Chem.* **2006**, *14*, 3592. DOI: 10.1016/j.bmc.2006.01.016
[26] L. Senerovic, D. Opsenica, I. Moric, I. Aleksic, M. Spasić M, B. Vasiljevic. *Adv. Exp. Med. Biol.* **2019**, *1282*, 37. DOI: 10.1007/5584_2019_428.
[27] X. F. Shang, S. L. Morris-Natschke, G. Z. Yang, Y. Q. Liu, X. Guo, X. Xu, M. Goto, J. C. Li, J. Y. Zhang, K. H. Lee. *Med. Res. Rev.* **2018**, *38*, 1614. DOI: 10.1002/med.21492
[28] X. F. Shang, S. L. Morris-Natschke, G. Z. Yang, Y. Q. Liu, X. Guo, X. Xu, M. Goto, J. C. Li, J. Y. Zhang, K. H. Lee. *Med. Res. Rev.*, **2018**, *38*, 775. DOI: 10.1002/med.21466
[29] E. G. Tse, M. Korsik, M. H. Todd, *Malar. J.* **2019**, *18*, 93. DOI: 10.1186/s12936-019-2724-z
[30] S. Heeb, M. P. Fletcher, S. R. Chhabra, S. P. Diggle, P. Williams, M. Cámara, *FEMS Microbiol. Rev.* **2011**, *35*, 247. DOI: 10.1111/j.1574-6976.2010.00247.x.
[31] X. M. Chu, C. Wang, W. Liu, L. L. Liang, K. K. Gong, C. Y. Zhao, K. L. Sun, *Eur. J. Med. Chem.* **2018**, *161*, 101. DOI: 10.1016/j.ejmech.2018.10.035.
[32] P. D. Nahide, C. R. Solorio-Alvarado, *Tetrahedron Lett.* **2017**, *58*, 279. DOI: 10.1016/j.tetlet.2016.11.093
[33] R. A. Rangel-Porras, S. P. Díaz-Pérez, J. M. Mendoza-Hernández, P. Romo-Rodríguez, V. Alejandre-Castañeda, M. I. Valle-Maldonado, V. Meza-Carmen, *J. Microbiol.* **2019**, *57*, 606. DOI: 10.1007/s12275-019-8680-z

[34] M. A. Pfaller, D. J. Diekema, D. L. Gibbs, V. A. Newell, D. Ellis, V. Tullio, A. Rodloff, W. Fu, T. A. Ling, Global Antifungal Surveillance Group, *J. Clin. Microbiol.* **2010**, *48*, 1366. DOI: 10.1128/JCM.02117-09.
[35] P. Örtqvist, S. D. Peterson, E. Åkerblom, T. Gossas, Y. A. Sabnis, R. Fransson, G. Linderberg, H. Danielson A. Karlén, A. Sandström, *Bioorg. Med. Chem.* **2007**, *15*, 1448. DOI: 10.1016/j.bmc.2006.11.003
[36] Our procedure fort he synthesis of the more active quinolines **3** and **11** needs of just three-step, while the modern synthesis of fluconazole even at continuous flow involves more. J. Szeto, V. A. Vu, J. P. Malerich, N. Collins, *J. Flow. Chem.* **2019**, *9*, 35. DOI: 10.1007/s41981-018-0019-0
[37] C. P. Jones, K.W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 7968. DOI: 10.1021/jo016038r
[38] J. M. Malose, K. M. Fidelia, T. Mutshutshu, M. H. Sebayitseng, M. M. Richard, *J. Chem. Res.* **1999**, 706. DOI: 10.1039/A906306D
[39] R. Tiago, R. Daniel, K. Jens, S. Petra, S. Gisbert, *Angew. Chem. Int. Ed.* **2015**, *54*, 10516. DOI: 10.1002/anie.201504241
[40] H. K. Kalvi, T. P. Paramasivan, *Tetrahedron*. **2007**, *63*, 9531. DOI: 10.1016/j.tet.2007.06.051
[41] A. I. R. N. A. Barros, A. F. R. Dias, A. M. S. Silva, *Monatsh. Chem.* **2007**, *138*, 584. DOI 10.1007/s00706-007-0647-9
[42] H. Zhibao, D. G. Ilya, Y. Yoshinori, *J. Org. Chem.* **2010**, *75*, 1266. DOI: 10.1021/jo902603v
[43] T. Mamoru, H. Isao, C. Naoto, *J. Am. Chem. Soc.* **2009**, *131*, 12070. DOI: 10.1021/ja9053509
[44] M.I. G. Roncero, *Carlsberg Res. Comm.* **1984**, *49*, 685. DOI: 10.1007/BF02907499
[45] S. P. Díaz-Pérez, J. A. Patiño-Medina, M. I. Valle-Maldonado, A. López-Torres, I. E. Jacome-Galarza, V. Anaya-Martínez, V. Gómez Ruíz, J. Campos -García, R. E. Nuñez -Anita, R. Ortiz -Alvarado, M. I. Ramírez-Díaz, J. F. Gutiérrez-Corona, V. Meza-Carmen, *Infect. Immun.* **2019**, *88*, 1. DOI: 10.1128/IAI.00434-19

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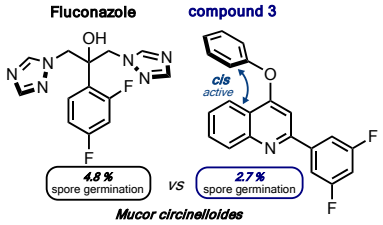

The synthesis and biological evaluation of several 4-phenoxy-2-arylquinolines on the R7B and M5 strains of *Mucor circinelloides,* allowed to the discovery of their fungistatic activity which resulted comparable or better than commercially fluconazole. The QSAR study showed the *cis* conformer as the active. In light of the natural fungus-resistance to antimycotics, here is proposed the compounds **3** and **11** as a potential alternative or iterative treatment.